Industria y Comercio
SUPERINTENDENCIA
República de Colombia
Ministerio de Comercio, Industria y Turismo

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-121953- -00000-0000
Fecha: 2012-07-19 15:09:18 Dep: 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 55

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

SOLICITUD DE

PATENTE DE INVENCION
PCT ENTRADA EN FASE NACIONAL

21. EXPEDIENTE No. _____

54. TITULO: **PIRROLIDINONAS HETEROAROMÁTICAS FUSIONADAS**

52. CLASIFICACION INTERNACIONAL: **C07D 471/04, C07D 487/04, A61K 31/437, A61K 31/519, A61P 7/00, A61P 11/00, A61P 17/00, A61P 19/00, A61P 35/00, A61P 37/00, A61P 29/00**

71. SOLICITANTE: **TAKEDA PHARMACEUTICAL COMPANY LIMITED**

DOMICILIO: **1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi, Osaka 541-0045, JAPON**

74. APODERADO: **Dra. MARGARITA CASTELLANOS A.**

22. BOGOTA, D.C., _____

000001 5

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-121953- -00000-0000
Fecha: 2012-07-19 15:09:18 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 55

DIRECCIÓN DE NUEVAS CREACIONES
SOLICITUD FASE NACIONAL -PCT

1	(12) TIPO DE SOLICITUD	X Patente de invención X Capítulo I	___ Patente de Modelo de Utilidad ___ Capitulo II

2 DATOS SOLICITUD INTERNACIONAL PCT (86)

Solicitud Internacional No.	PCT/US2010/061146	Fecha	17/12/2010
Publicación Internacional No.	WO 2011/079051 A1	Fecha	30/06/2011

3 (54) TÍTULO DE LA INVENCIÓN (200 caracteres o espacios máximos)

PIRROLIDINONAS HETEROAROMATICAS FUSIONADAS

4 CLASIFICACIÓN INTERNACIONAL (51) CIP

C07D 471/04, C07D 487/04, A61K 31/437, A61K 31/519, A61P 7/00, A61P 11/00, A61P 17/00, A61P 19/00, A61P 35/00, A61P 37/00, A61P 29/00

5 (71) SOLICITANTE (S) ___ Esta persona también es inventor. Para datos adicionales utilizar hoja de información complementaria

APELLIDOS O RAZÓN SOCIAL	NOMBRE	IDENTIFICACIÓN	TIPO
TAKEDA PHARMACEUTICAL COMPANY LIMITED			

6 DATOS DEL SOLICITANTE

DIRECCIÓN	**1-1, Doshomachi 4-Chome, Chuo-ku, Osaka-shi**	No. TELÉFONO	
CIUDAD	**Osaka, 541-0045**	E-MAIL	
DEPARTAMENTO/ESTADO		NACIONALIDAD O LUGAR DE CONSTITUCIÓN	**JAPONESA**
PAÍS DE RESIDENCIA	**JAPON**		

7 (72) INVENTOR (ES) Para datos adicionales utilizar hoja de información complementaria

	APELLIDOS	NOMBRES	NACIONALIDAD
1.	**ARIKAWA**	**YASUYOSHI**	**JAPONES**
2.	**JONES**	**BENJAMIN**	**ESTADOUNIDENSE**
3.	**LAM**	**BETTY**	**ESTADOUNIDENSE**
4.	**NIE**	**ZHE**	**CHINA**
5.	**SMITH**	**CHRISTOPHER**	**BRITANICA**

DIRECCIÓN DE CORREO ELECTRÓNICO:

8 DATOS INVENTOR (ES)

	PAÍS RESIDENCIA	DEPARTAMENTO/ESTADO	CIUDAD	DIRECCIÓN
1.	**ESTADOS UNIDOS**	**California 92121**	**San Diego**	**Takeda San Diego, Inc., 10410 Science Center Drive**
2.	**ESTADOS UNIDOS**	**California 92121**	**San Diego**	**Takeda San Diego, Inc., 10410 Science Center Drive**
3.	**ESTADOS UNIDOS**	**California 92121**	**San Diego**	**Takeda San Diego, Inc., 10410 Science Center Drive**
4.	**ESTADOS UNIDOS**	**California 92121**	**San Diego**	**Takeda San Diego, Inc., 10410 Science Center Drive**
5.	**ESTADOS UNIDOS**	**California 92121**	**San Diego**	**Takeda San Diego, Inc., 10410 Science Center Drive**

OTRO(S) SOLICITANTE(S) Y/O (OTRO(S)) INVENTOR(ES)

☐ Los demás solicitantes y/o (demás) inventores se indican en una hoja a continuación.

9 (74) ___ **REPRESENTANTE** X **APODERADO**

APELLIDOS	NOMBRES	IDENTIFICACIÓN
CASTELLANOS ABONDANO	**MARGARITA**	C.C . **39.779.654** T.P . **70.819**

DIRECCIÓN	**CALLE 94 A No. 7 A-09**	No. TELÉFONO	**7560770**
CIUDAD	**BOGOTA**	E-MAIL	**info@castellanosyco.co**
PAÍS	**COLOMBIA**	No. DE PROTOCOLO EN LA OFICINA	

10	(30) DECLARACIONES DE PRIORIDAD	X SI ___ NO		
	(33) PAÍS DE ORIGEN	**CÓDIGO PAÍS**	**(31) NÚMERO**	**(32) FECHA (AAAA/MM/DD)**
	1. ESTADOS UNIDOS	**US**	**61/289.969**	**2009/12/23**
	2. ESTADOS UNIDOS	**US**	**61/386.964**	**2010/09/27**
	3.			

11 DECLARACIÓN SOBRE USO DE RECURSOS GENÉTICOS O BIOLÓGICOS

Declaro que el objeto de la presente solicitud de patente fue obtenido a partir de recursos genéticos o biológicos de los que cualquiera de los países miembros de la Comunidad Andina es país de origen.

___ SI _X_ NO

Nota: En caso afirmativo deberá anexar copia del contrato de acceso de recursos genéticos o productos derivados, o certificado o número de registro, expedido por la Autoridad competente.

12 DECLARACIÓN SOBRE USO DE CONOCIMIENTOS TRADICIONALES

Declaro que el objeto de la presente solicitud de patente fue obtenido a partir de conocimientos tradicionales de comunidades indígenas, afroamericanas o locales de países miembros de la Comunidad Andina.

___ SI _X_ NO

Nota: En caso afirmativo deberá anexar la licencia o autorización de uso de conocimiento tradicional, o certificado, o número de registro expedido por la Autoridad competente.

13 REDUCCIÓN DE TASAS

Declaro que carezco de medios económicos para presentar la solicitud de patente.

___ SI _X_ NO

Nota: En caso de ser persona natural y carecer de medios económicos, y por lo tanto, aplique la reducción de tasas a que se refiere la resolución vigente en tarifas, debe firmar la presente solicitud bajo la gravedad de juramento.

Micro, pequeñas y medianas empresas	**Universidades públicas o privadas**	**Entidades sin ánimo de lucro**
___ Copia simple de la declaración de renta del año inmediatamente anterior, o en su defecto prueba documental idónea. ___ Documento de constancia de cumplimiento con lo establecido en la ley 905 de 2004.	___ Copia acto de reconocimiento institucional emitido por el Ministerio de Educación. Acreditación Colciencias.	___ Copia de registro vigente en Cámara de comercio. ___ Hoja de información complementaria. ___ Otros, especificar

14 AUTORIZACIÓN DE NOTIFICACIÓN EN LÍNEA ___ SI _X_ NO

Manifiesto que he leído y entendido perfectamente los términos y condiciones de uso de medios electrónicos para las notificaciones en linea a través de Internet de los actos administrativos proferidos por la Superintendencia de Industria y Comercio que deben ser notificados personalmente y, en consecuencia, autorizo el servicio de notificación a través de internet.

14	**COMPROBANTE DE PAGO O PAGO ELECTRÓNICO**	**N° 12-00 73145 , 12-00 73146**	**Fecha: Julio 18 de 2012**

15 FIRMA DEL SOLICITANTE, DEL APODERADO O DEL REPRESENTANTE LEGAL

Junto a cada firma, indicar el nombre del firmante y su calidad (si tal calidad no es obvia al leer el petitorio)

MARGARITA CASTELLANOS ABONDANO – APODERADO

16 ORDEN Y RELACIÓN DE DOCUMENTOS QUE ACOMPAÑAN LA SOLICITUD

Documentación Técnica
Solicitud Internacional en castellano

1. _X_ Descripción — N° de folios: **310**
2. _X_ Reivindicaciones — N° Reivindicaciones: **43**
3. __ Dibujos y/o figuras — N° folios:
4. _X_ Resumen.
5. ___ Certificado de depósito de material biológico si fuera el caso.
6. ___ Listado de secuencias de nucleótidos y/o aminoácidos en forma digital si fuera el caso.
7. _X_ Arte final 12 x 12.
8. _X_ Anexo formato digital.

CD-R QUE CONTIENE LOS SIGUIENTES ARCHIVOS:

- **TEXTO EN ESPAÑOL DE LA DESCRIPCION, REIVINDICACIONES Y RESUMEN**
- **TEXTO DE LA PUBLICACION INTERNACIONAL**

Documentación Jurídica

9. _X_ Poderes, si fuera el caso.
10. ___ Documento que legalmente pruebe la cesión del inventor al solicitante o a su causante
11. ___ Copia del contrato de acceso de recursos genéticos o productos derivados, certificado o número de registro, si fuera el caso.
12. ___ Copia de la licencia o autorización de Conocimientos Tradicionales, certificado o número de registro, si fuera el caso.
13. ___ Documento que acredita la existencia y representación legal, cuando el solicitante es persona jurídica
14. _X_ Comprobante de pago de la tasa de presentación de la solicitud.
15. ___ Comprobante de pago por reivindicación de prioridad.
16. ___Comprobante de pago de la tasa por concepto de excedente de palabras en la publicación.
17. _X_ Comprobante de pago por reivindicación adicional a 10.

Industria y Comercio
SUPERINTENDENCIA

HOJA DE INFORMACIÓN COMPLEMENTARIA PCT

1	(12) TIPO DE SOLICITUD	NUMERO DE RADICACIÓN
___ Patente de invención ___ Patente de Modelo de Utilidad		FECHA DE PRESENTACIÓN

4 (71) SOLICITANTE (S)

APELLIDOS O RAZÓN SOCIAL	NOMBRE	IDENTIFICACIÓN	TIPO
2. 3. 4.			

5 DATOS DEL SOLICITANTE

PAÍS DE RESIDENCIA	DEPARTAMENTO/ESTADO	CIUDAD	DIRECCIÓN
2. 3. 4.			

TELÉFONO	FAX	E-MAIL	NACIONALIDAD
2. 3. 4.			

6 (72) INVENTOR (ES)

APELLIDOS	NOMBRE	NACIONALIDAD
6. TAKAHASHI	MASASHI	JAPONES
7. DONG	QING	ESTADOUNIDENSE
8. FEHER	VICTORIA	ESTADOUNIDENSE

7 DATOS INVENTOR (ES)

DIRECCIÓN	CIUDAD	DEPARTAMENTO/ ESTADO	PAÍS RESIDENCIA
6. Takeda San Diego, Inc., 10410 Science Center Drive	San Diego	California 92121	ESTADOS UNIDOS
7. Takeda San Diego, Inc., 10410 Science Center Drive	San Diego	California 92121	ESTADOS UNIDOS
8. Takeda San Diego, Inc., 10410 Science Center Drive	San Diego	California 92121	ESTADOS UNIDOS

9 (30) DECLARACIONES DE PRIORIDAD

PAÍS DE ORIGEN	CÓDIGO PAÍS	NÚMERO	FECHA (AAAA/MM/DD)
4. 5. 6. 7. 8. 9. 10.			

030004

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 12 - 0073145

Bogotá D.C., Julio 18 de 2012 - 14:43:47

RECIBIDO DE : CASTELLANOS Y Y CO NI 800.174.641 RE

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
RECIBO DE CA	999999999	55776	04/06/2012		1.230.000.00
RECIBO DE CA	999999999	64484	26/06/2012		450.000.00
CONSIGNACION	BANCO DE BOGOTA	062754387	449977695	18/07/2012	350.000.00

*** Conceptos Pagados ***

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

==========

SON: **QUINIENTOS NOVENTA MIL PESOS MONEDA CORRIENTE*

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-121953- -00000-0000
Fecha: 2012-07-19 15:09:18 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 55

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 12 - 0073146

Bogotá D.C., Julio 18 de 2012 - 14:43:47

RECIBIDO DE : CASTELLANOS Y Y CO NI 800.174.641 RE

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
RECIBO DE CA	999999999	55776	04/06/2012		1.230.000.00
RECIBO DE CA	999999999	64484	26/06/2012		450.000.00
CONSIGNACION	BANCO DE BOGOTA	062754387	449977695	18/07/2012	350.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
33	50005-01-01 SOLICITUDES	1607 REIVINDICACION UNITARIA ADICIONAL A LAS 10 INICICIALES	30.000.00	990.000.00
				$990.000.00

==========

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

Responsable: _____
-*-
Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-121953- -00000-0000
Fecha: 2012-07-19 15:09:18 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 55

000006

P2115 PP195
3698C00P
TCB

COLOMBIA

PODER

El (los)

TAKEDA PHARMACEUTICAL COMPANY LIMITED

Domiciliados en **1-1, Doshomachi 4-Chome, Chuo-ku, Osaka-shi, Osaka, 541-0045, Japón**

Nombran por el presente a **XIMENA CASTELLANOS A. y/o MARGARITA CASTELLANOS A.** abogadas con oficinas en la Calle 94A No. 7A-09, Bogotá-Colombia para
y para obtener la protección de mi (nuestra) propiedad Industrial e intelectual y con este fin autorizamos a dichos apoderados para que nos representen ante cualesquiera autoridades o personas de los órdenes administrativo, contencioso –administrativo y judicial en todo lo relacionado con los siguientes actos y gestiones:

a) Obtención de patentes de invención, modelos y dibujos industriales; registro de marcas de fabrica, de servicio, colectivas o defensivas y de denominaciones de origen, depósito de nombres y enseñas comerciales; su renovación, prórroga, inscripción de traspaso y cambio de nombre o domicilio, cancelación voluntaria y el registro de licencias de uso de esos derechos;
b) Para la obtención de registros sanitarios;
c) Para la obtención de registros de derechos de autor.
d) Acciones de oposición, observación, cancelación, nulidad, medidas cautelares y en general los juicios civiles, penales, administrativos o contencioso - administrativos que promovamos o se nos promuevan.

Pudiendo en todos los actos y gestiones arriba mencionados sustituir éste mandato entre los apoderados, transigir, desistir, recibir, cancelar, renunciar, aceptar notificaciones y nombrar apoderados judiciales y extra-judiciales. .

Finalmente, este poder ratifica la validez de todos los actos y solicitudes que, a nombre de la poderdante hubieren realizado los apoderados en relación con las facultades anteriormente enumeradas, antes de la suscripción del presente poder

Dado y firmado hoy 01/06/2011

en Kanagawa, Japón

por Takeda Pharmaceutical Company Limited.

(El notario debe suscribir el documento en la pagina siguiente)
(Se requiere legalización consular o mediante apostilla)

POWER OF ATTORNEY

I (we) the undersigned

TAKEDA PHARMACEUTICAL COMPANY LIMITED

Of **1-1, Doshomachi 4-Chome, Chuo-ku, Osaka-shi, Osaka, 541-0045, Japan**

hereby grant(s) Power of Attorney to **XIMENA CASTELLANOS A. and /or MARGARITA CASTELLANOS** a. attorneys residing at Calle 94A No. 7A-09, Bogotá- Colombia, to
and to obtain the protection of my (our) Intellectual Property, for which purpose we authorize the said attorneys to represent us before any authorities, or persons, specially those, administrative, contentious and judicial, in all matters concerning the following:

a) Obtainment of patents, models and designs, registration of trademarks, service, collective and defensive marks, and of designations of origin; the deposit of trade names and ensigns; its renewal, extension, recordal of assignments, change of name or domicile, voluntary cancellation, and the registration of licenses of use of the above rights;
b) For the obtainment of Sanitary registrations;
c) For the obtainment of copyright registrations
d) Actions of opposition, cancellation, nullity, infringement, granting of licenses; and in general the civil, criminal and administrative suits related to those rights; actions and suits instituted by us or against us;

In all the above matters they may substitute this power of attorney within the appointed attorneys, compromise, cancel, receive, withdraw, renounce, accept notifications and appoint attorneys in fact in or out of court.

Finally, this power of attorney ratifies the validity of all acts and applications made by the representatives in the name of the signatory of this power of attorney, with regard to the faculties above given, before the execution of the present power of attorney.

Given and signed this 01/06/2011

in Kanagawa, Japan

by Yoichi Okumura
Yoichi Okumura
General Manager, Intellectual Property Department.
Takeda Pharmaceutical Company Limited

(Notary shall execute on the other side)
(Consular legalization or apostille is required)

CASTELLANOS & Co.
INTELLECTUAL PROPERTY LAW FIRM

CALLE 94 A No. 7 A – 09 / P.O. BOX 6349
PHONE (57 1) 756 07 70 / FAX (57 1) 755 01 58
BOGOTÁ D.C. COLOMBIA
info@castellanosyco.com

000007

平成２３年登簿第　79　号

認　　証

日本国政府大阪法務局の平成２３年４月１８日発行にかかる履歴事項全部証明書により明らかなところであるが、日本国法律により設立され本店が大阪府大阪市中央区道修町４丁目１番１号に所在する武田薬品工業株式会社の知的財産部長奥村洋一は別紙委任状に署名する権限を付与されており、別紙委任状の証書の署名が自己のものに相違ない旨代理人LEVESQUE SON HYUN REGINAを通じ本公証人に対し自認した。　以上

よって、これを認証する。

平成２３年　６月　１　日、本公証人役場において

藤沢市鵠沼石上2丁目11番2号
横浜地方法務局所属
公　証　人
Notary

曾我大三郎

DAISABURO SOGA

証　　明

上記署名は、横浜地方法務局所属公証人の署名に相違ないものであり、かつ、その押印は、真実のものであることを証明する。

平成２３年　６月　１　日

横浜地方法務局長　神尾　衛

APOSTILLE
(Convention de La Haye du 5 octobre 1961)

1. Country : JAPAN
   This public document
2. has been signed by DAISABURO SOGA
3. acting in the capacity of Notary of the Yokohama District Legal Affairs Bureau
4. bears the seal/stamp of DAISABURO SOGA , Notary

Certified

5. at Tokyo　　6. JUN. 1. 2011
7. by the Ministry of Foreign Affairs
8. 11- № 301579
9. Seal/stamp :　　10.Signature :

MINISTRY OF FOREIGN AFFAIRS JAPAN

K. Oyabe

Kazutoyo OYABE
For the Minister for Foreign Affairs

000008

Registered No. 7 9

NOTARIAL CERTIFICATE

This is to certify that LEVESQUE SON HYUN REGINA, an agent of Yoichi OKUMURA, General Manager, Intellectual Property Department of Takeda Pharmaceutical Company Limited , who has been authorized to grant Power of Attorney on behalf of said company organized and existing according to the law of Japan, located at 1-1 , Doshomachi 4-chome, Chuo-ku Osaka-shi Osaka Japan, has stated in my very presence that said Yoichi OKUMURA has acknowledged himself that the signature on the attached document is his own.

The foregoing was duly evidenced by the certified Register of said company issued by the Certificate of All Registered Items dated 18 April, 2011 from Osaka Legal Affairs Bureau for Corporate Number KU250214 and Title Certificate dated April 14, 2011.

Dated this 1st day of June, 2011.

Daisaburo Soga

YOKOHAMA DISTRICT
LEGAL AFFAIRS BUREAU
NOTARY
2-11-2, KUGENUMAISHIGAMI
FUJISAWA-SHI, KANAGAWA-KEN
JAPAN

Daisaburo Soga

Notary

attached to Yokohama District Legal Affairs Bureau

2-11-2, Kugenuma Ishigami Fujisawa-shi

Kanagawa-ken Japan

----------TRADUCCION OFICIAL No. 11-0607----------

De un documento escrito en INGLES, el cual para su identificación lleva el sello y firma de la Traductora e Intérprete Oficial, Res. 2755/68 y 01144/97 de Minjusticia.----------

(Anexos a un documento de Poder de TAKEDA PHARMACEUTICAL COMPANY LIMITED)

Registro No. 79

CERTIFICADO NOTARIAL

La presente es para certificar que LEVESQUE SON HYUN REGINA, agente de Yoichi OKUMURA, Gerente General, Departamento de Propiedad Intelectual de Takeda Pharmaceutical Company Limited, quien ha sido autorizado para otorgar Poder en nombre de dicha compañía, constituida y existente de acuerdo con la ley de Japón, domiciliada en 1-1, Doshomachi 4-chome, Chuo-ku Osaka-shi, Osaka Japòn ha manifestado en mi propia presencia que la firma en el documento adjunto es de éste.

Lo anterior fue debidamente evidenciado por el Certificado de Registro de dicha compañía expedido por el Certificado de Todos los Items Registrados de fecha abril 18 de 2011 de la Oficina de Asuntos Legales de Osaka para Sociedades No. KU250214 y el Certificado de Título de fecha Abril 14, 2011.

Dado hoy dìa primero de Junio de 2011.

(fdo) ilegible

Daisaburo Soga

Notario

Adjunto a la Oficina de Asuntos Legales del Distrito de Yokohama – 2-11-2, Kugenuma Ishigami Fujisawa-shi Kanagawa-ken, Japón

(Sello Notarial): OFICINA DE ASUNTOS LEGALES
DISTRITO DE YOKOHAMA
NOTARIO
2-11-2, Kugenumaishigami
Fujisawa-shi, Kanagawa-ken – Japón

MINISTERIO DE RELACIONES EXTERIORES
JEFE DE LEGALIZACIONES
BOGOTA D.C.
JUN 14 A 8:04

APOSTILLA

(Convención de La Haya de Octubre 5, 1961)

1. País: JAPON

Este documento público

2. ha sido firmado por: DAISABURO SOGA

3. actuando en su carácter de: Notario Público de la Oficina de Asuntos Legales deL Distrito de Yokohama

4. lleva el sello de DAISURO SOGA - Notario

CERTIFICADO:

5. en Tokyo 6. el día 1° de Junio de 2011

7. por el Ministerio de Relaciones Exteriores

8. 11 No. 301579

9. Sello 10. Firma: (fdo) ilegible

NO SE ASUME RESPONSABILIDAD POR EL CONTENIDO DEL DOCUMENTO
LA FIRMA QUE APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS
07 JUN 03

MARIA DORA DUQUE DE BERNAL
TRADUCTORA E INTERPRETE OFICIAL
R.S. 02755/68 Y 01144/97 - MINJUSTICIA
RE. DE COLOMBIA

600011

Kazutoyo OYABE

Por el Ministerio de Relaciones Exteriores (Sello)

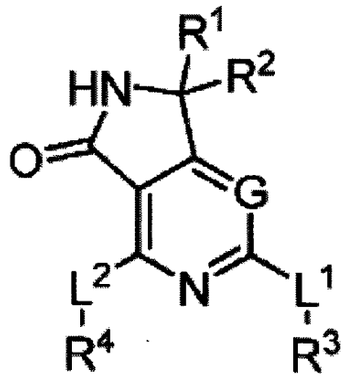
ES TRADUCCION FIEL Y COMPLETA, a la cual me remito,

Bogotá, D. C., Junio 13, 2011

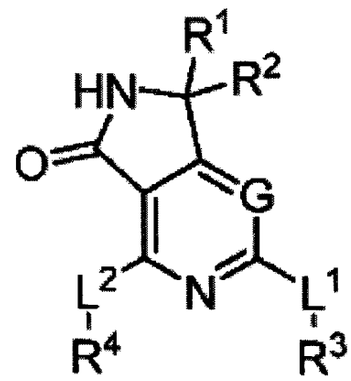
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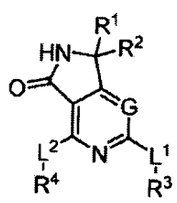
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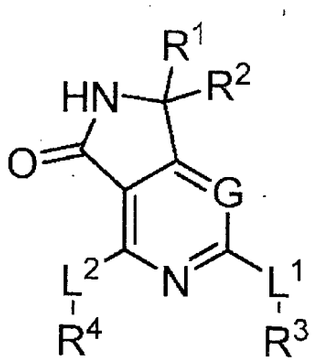
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(54) **Title**: FUSED HETEROAROMATIC PYRROLIDINONES AS SYK INHIBITORS



(I)

(57) **Abstract**: Disclosed are compounds of Formula 1, and pharmaceutically acceptable salts thereof, wherein G, L^1, L^2, R^1, R^2, R^3, and R^4 are defined in the specification. This disclosure also relates to materials and methods for preparing compounds of Formula 1, pharmaceutical compositions containing them, and their use for treating disorders, diseases, and conditions involving the immune system and inflammation, including rheumatoid arthritis, hematological malignancies, epithelial cancers (i.e., carcinomas), and other disorders, diseases, and conditions for which inhibition of SYK is indicated.

WO 2011/079051 A1

FUSED HETEROAROMATIC PYRROLIDINONES AS SYK INHIBITORS

FIELD OF THE INVENTION

[0001] This invention relates to fused heteroaromatic pyrrolidinone compounds, to pharmaceutical compositions containing them, and to the use of the compounds for treating disorders and conditions involving the immune system and inflammation, including rheumatoid arthritis. The heteroaromatic pyrrolidinones are inhibitors of spleen tyrosine kinase.

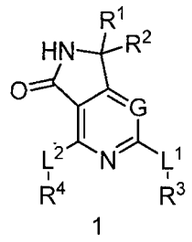
BACKGROUND OF THE INVENTION

[0002] Spleen tyrosine kinase (SYK) is a 72 kDa non-receptor cytoplasmic tyrosine kinase. SYK has a primary amino acid sequence similar to that of zeta-associated protein-70 (ZAP-70) and is involved in receptor-mediated signal transduction. The N-terminal domain of SYK contains two Src-homology 2 (SH2) domains, which bind to diphosphorylated immunoreceptor tyrosine-based activation motifs (ITAMs) found in the cytoplasmic signaling domains of many immunoreceptor complexes. The C-terminus contains the catalytic domain, and includes several catalytic loop autophosphorylation sites that are responsible for receptor-induced SYK activation and subsequent downstream signal propagation. SYK is expressed in many cell types involved in adaptive and innate immunity, including lymphocytes (B cells, T cells, and NK cells), granulocytes (basophils, neutrophils, and eosinophils), monocytes, macrophages, dendritic cells, and mast cells. SYK is expressed in other cell types, including airway epithelium and fibroblasts in the upper respiratory system. See, e.g., Martin Turner et al., *Immunology Today* (2000) 21(3):148-54; and Michael P. Sanderson et al., *Inflammation & Allergy – Drug Targets* (2009) 8:87-95.

[0003] SYK's role in ITAM-dependent signaling and its expression in many cell types suggest that compounds which inhibit SYK activity may be useful for treating disorders involving the immune system and inflammation. Such disorders include Type I hypersensitivity reactions (allergic rhinitis, allergic asthma, and atopic dermatitis); autoimmune diseases (rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, psoriasis, and immune thrombocytopenic purpura); and inflammation of the lung (chronic obstructive pulmonary disease). See, e.g., Brian R. Wong et al., *Expert*

WHAT IS CLAIMED IS:

1. A compound of Formula 1,



1 ,

or a pharmaceutically acceptable salt thereof, wherein:

G is selected from N and $C(R^5)$;

L^1 and L^2 are each independently selected from -NH- and a bond;

R^1 and R^2 are each independently selected from hydrogen, halo, C_{1-3} alkyl, and C_{1-3} haloalkyl, or R^1 and R^2, together with the atom to which they are attached, form a C_{3-6} cycloalkyl;

R^3 is selected from C_{2-6} alkyl, C_{3-8} cycloalkyl, C_{2-5} heterocyclyl, and C_{1-9} heteroaryl, each optionally substituted with from one to five substituents independently selected from halo, oxo, $-NO_2$, -CN, R^6, and R^7;

R^4 is selected from C_{3-8} cycloalkyl, C_{2-5} heterocyclyl, C_{6-14} aryl, and C_{1-9} heteroaryl, each optionally substituted with from one to five substituents independently selected from halo, oxo, -CN, R^6, and R^7;

R^5 is selected from hydrogen, halo, -CN, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-5} heterocyclyl, C_{1-5} heteroaryl, and R^{10}, wherein the alkyl, alkenyl, alkynyl moieties are each optionally substituted with from one to five substituents independently selected from halo, -CN, oxo, and R^{10}, and wherein the heterocyclyl moiety has 3 to 6 ring atoms and the heteroaryl moiety has 5 or 6 ring atoms, and the heterocyclyl and heteroaryl moieties are each optionally substituted with from one to four substituents independently selected from halo, $-NO_2$, -CN, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, and R^{10};

each R^6 is independently selected from $-OR^8$, $-N(R^8)R^9$, $-NR^8C(O)R^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)N(R^8)R^9$, $-C(O)N(R^8)OR^9$, $-C(O)N(R^8)S(O)_2R^9$, $-N(R^8)S(O)_2R^9$, $-S(O)_nR^8$, and $-S(O)_2N(R^8)R^9$;

each R^7 is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl-$(CH_2)_m$-, C_{6-14} aryl-$(CH_2)_m$-, C_{2-5} heterocyclyl-$(CH_2)_m$-, and C_{1-9} heteroaryl-$(CH_2)_m$-, each optionally substituted with from one to five substituents independently selected from halo, oxo, $-NO_2$, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, and R^{10};

each R^8 and R^9 is independently selected from hydrogen or from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl-$(CH_2)_m$-, C_{6-14} aryl-$(CH_2)_m$-, C_{2-5} heterocyclyl-$(CH_2)_m$-, and C_{1-9} heteroaryl-$(CH_2)_m$-, each optionally substituted with from one to five substituents independently selected from halo, oxo, $-NO_2$, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, and R^{10};

each R^{10} is independently selected from $-OR^{11}$, $-N(R^{11})R^{12}$, $-N(R^{11})C(O)R^{12}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-C(O)N(R^{11})R^{12}$, $-C(O)N(R^{11})OR^{12}$, $-C(O)N(R^{11})S(O)_2R^{12}$, $-NR^{11}S(O)_2R^{12}$, $-S(O)_nR^{11}$, and $-S(O)_2N(R^{11})R^{12}$;

each R^{11} and R^{12} is independently selected from hydrogen and C_{1-6} alkyl;

each n is independently selected from 0, 1 and 2; and

each m is independently selected from 0, 1, 2, 3, and 4;

wherein each of the aforementioned heteroaryl moieties has one to four heteroatoms independently selected from N, O, and S, and each of the aforementioned heterocyclyl moieties is saturated or partially unsaturated and has one or two heteroatoms independently selected from N, O, and S.

2. A compound or pharmaceutically acceptable salt according to claim 1, wherein L^1 is -NH-.

3. A compound or pharmaceutically acceptable salt according to claim 1, wherein L^1 is a bond.

4. A compound or pharmaceutically acceptable salt according to any one of the preceding claims, wherein L^2 is -NH-.

5. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 3, wherein L^2 is a bond.

6. A compound or pharmaceutically acceptable salt according to any one of the preceding claims, wherein G is N.

7. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 5, wherein G is $C(R^5)$.

8. A compound or pharmaceutically acceptable salt according to any one of the preceding claims, wherein R^1 and R^2 are both hydrogen.

9. A compound or pharmaceutically acceptable salt according to any one of the preceding claims, wherein R^3 is C_{3-8} cycloalkyl, optionally substituted with from one to five substituents independently selected from halo, oxo, $-NO_2$, -CN, R^6, and R^7.

10. A compound or pharmaceutically acceptable salt according to claim 9, wherein R^3 is 2-amino-C_{3-8} cycloalk-1-yl, optionally substituted with from one to four substituents independently selected from halo, oxo, $-NO_2$, -CN, R^6, and R^7.

11. A compound or pharmaceutically acceptable salt according to claim 10, wherein R^3 is 2-amino-cyclohex-1-yl optionally substituted with from one to four substituents independently selected from halo, oxo, $-NO_2$, -CN, R^6, and R^7.

12. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 8, wherein R^3 is C_{2-6} alkyl optionally substituted with from one to five substituents independently selected from halo, oxo, $-NO_2$, -CN, R^6, and R^7.

13. A compound or pharmaceutically acceptable salt according to claim 12, wherein R^3 is 2-amino-C_{2-6} alk-1-yl optionally substituted with from one to four substituents independently selected from halo, oxo, $-NO_2$, -CN, R^6, and R^7.

14. A compound or pharmaceutically acceptable salt according to claim 13, wherein R^3 is 2-aminoethan-1-yl optionally substituted with from one to four substituents independently selected from halo, oxo, $-NO_2$, -CN, R^6, and R^7.

15. A compound or pharmaceutically acceptable salt according to claim 14, wherein R^3 is 2-amino-2-oxoethan-1-yl optionally substituted with one or two substituents independently selected from halo, oxo, $-NO_2$, -CN, R^6, and R^7.

16. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 8, wherein R^3 is C_{2-5} heterocyclyl optionally substituted with from one to five substituents independently selected from halo, oxo, $-NO_2$, -CN, R^6, and R^7.

17. A compound or pharmaceutically acceptable salt according to claim 16, wherein R^3 is C_{2-5} heterocyclyl substituted with an amino and optionally substituted with from one to four additional substituents independently selected from halo, oxo, $-NO_2$, -CN, R^6, and R^7.

18. A compound or pharmaceutically acceptable salt according to claim 17, wherein R^3 is 3-aminotetrahydro-2*H*-pyran-4-yl optionally substituted with from one to four substituents independently selected from halo, oxo, $-NO_2$, -CN, R^6, and R^7.

19. A compound or pharmaceutically acceptable salt according to any one of claims 1 and 3 to 8, wherein R^3 is C_{2-5} heterocyclyl or an amino-substituted C_{2-5} heterocyclyl, each optionally substituted with from one to five or from one to four substituents, respectively, independently selected from halo, oxo, $-NO_2$, -CN, R^6, and R^7, wherein one of the heteroatoms of the heterocyclyl moiety is directly attached to L^1, and L^1 is a bond.

20. A compound or pharmaceutically acceptable salt according to any one of the preceding claims, wherein R^4 is selected from C_{6-14} aryl and C_{1-9} heteroaryl, each optionally substituted with from one to five substituents independently selected from halo, oxo, -CN, R^6, and R^7.

21. A compound or pharmaceutically acceptable salt according to any one of the preceding claims, wherein R^4 is phenyl optionally substituted with from one to five substituents independently selected from halo, -CN, R^6, and R^7.

22. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 20, wherein R^4 is C_{1-9} heteroaryl optionally substituted with from one to five substituents independently selected from halo, oxo, -CN, R^6, and R^7.

23. A compound or pharmaceutically acceptable salt according to claim 22, wherein R^4 is a monocyclic C_{2-4} heteroaryl optionally substituted with from one to four substituents independently selected from halo, -CN, R^6, and R^7.

24. A compound or pharmaceutically acceptable salt according to claim 23, wherein R^4 is selected from pyrrolyl, furanyl, thiopheneyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isothiazolyl, and thiazolyl, each optionally substituted with from one to three substituents independently selected from halo, -CN, R^6, and R^7.

25. A compound or pharmaceutically acceptable salt according to claim 24, wherein R^4 is selected from thiopheneyl, pyrazolyl, isothiazolyl, and thiazolyl, each optionally substituted with from one to three substituents independently selected from halo, -CN, R^6, and R^7.

26. A compound or pharmaceutically acceptable salt according to claim 25, wherein R^4 is pyrazolyl optionally substituted with from one to three substituents independently selected from halo, -CN, R^6, and R^7.

27. A compound or pharmaceutically acceptable salt according to claim 26, wherein R^4 is pyrazol-4-yl optionally substituted with from one to three substituents independently selected from halo, -CN, R^6, and R^7.

28. A compound or pharmaceutically acceptable salt according to any one of claims 20 to 27, wherein R^4 is substituted with methyl, ethyl, cyclopropyl or C_{1-2} haloalkyl.

29. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 5 and 7 to 28, wherein R^5 is C_{1-5} heteroaryl optionally substituted with from one to four substituents independently selected from halo, $-NO_2$, -CN, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, and R^{10}.

30. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 5 and 7 to 28, wherein R^5 is selected from hydrogen and halo.

31. A compound or pharmaceutically acceptable salt according to claim 30, wherein R^5 is selected from chloro and fluoro.

32. A compound according to claim 1, which is selected from the following compounds:

2-((1*R*,2S)-2-Aminocyclohexylamino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(3-fluorophenylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(3-chlorophenylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

4-(1*H*-Indazol-6-ylamino)-2-((1*R*,2*S*)-2-aminocyclohexylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-aminocyclohexylamino)-4-(3-(trifluoromethyl)phenylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

cis-2-(2-aminocyclohexylamino)-4-(3-(trifluoromethyl)phenylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-(1-Methyl-1*H*-pyrazol-4-yl)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-(4-Ethylpiperazin-1-yl)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-(Cyclohexylamino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

cis-2-(2-Hydroxycyclohexylamino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-(3-Aminopiperidin-1-yl)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-methyl-1*H*-pyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-isobutyl-1*H*-pyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-phenyl-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(benzo[*b*]thiophen-3-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-ethyl-1*H*-pyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-benzyl-1*H*-pyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(imidazo[1,2-*a*]pyridin-3-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-propyl-1*H*-pyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-(2-methoxyethyl)-1*H*-pyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

4-(1*H*-Indazol-6-ylamino)-6-((1*R*,2*S*)-2-aminocyclohexylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(4-fluoro-3-methylphenylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-chloro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(pyrazolo[1,5-*a*]pyridin-3-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

2-(2-(Aminomethyl)piperidin-1-yl)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(3-(methylsulfonyl)phenylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclopentylamino)-4-(3-(methylsulfonyl)phenylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

(*R*)-4-Methyl-2-(4-(3-(methylsulfonyl)phenylamino)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)pentanamide;

(*R*)-4-Methyl-2-(4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)pentanamide;

2-((1*R*,2*S*)-2-(Dimethylamino)cyclohexylamino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-(Methylamino)cyclohexylamino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2'-((1*R*,2*S*)-2-Aminocyclohexylamino)-4'-(*m*-tolylamino)spiro[cyclopropane-1,7'-pyrrolo[3,4-*d*]pyrimidin]-5'(6'*H*)-one;

2-(2-Aminoethylamino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-(2-Amino-2-methylpropylamino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-(5-Oxo-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-2-ylamino)acetamide;

2-((2-Aminoethyl)(methyl)amino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-(Pyrrolidin-2-ylmethylamino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-(3-Aminopyrrolidin-1-yl)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1,5-dimethyl-1*H*-pyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1*H*-indol-2-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1*H*-pyrazol-5-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-(3-Aminopropyl)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(benzofuran-3-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-aminocyclohexylamino)-7-fluoro-4-(imidazo[1,2-*a*]pyridin-3-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-aminocyclohexylamino)-4-(benzo[*b*]thiophen-3-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*S*,2*R*)-2-Aminocyclohexylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(*2H*)-one;

(*R*)-6-(2-Amino-3-ethoxypropylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

(*R*)-6-(2-Amino-3-ethoxypropylamino)-7-fluoro-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-(2-Amino-3,3,3-trifluoropropylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

(*R*)-4-Methyl-2-(3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)pentanamide;

6-(*cis*-4-Aminotetrahydrofuran-3-ylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2H)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-ethyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-ethyl-1*H*-pyrazol-4-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-cyclopropyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-cyclopropyl-1*H*-pyrazol-4-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

cis-6-(2-Aminocyclohexylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-(*cis*-2-Amino-4,4-difluorocyclopentylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-c]pyridin-3(2*H*)-one;

6-(*cis*-2-Amino-3,3-difluorocyclohexylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-(*cis*-2-Amino-3,3-difluorocyclohexylamino)-4-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-(*cis*-2-amino-3,3-difluorocyclohexylamino)-4-(1-cyclopropyl-1H-pyrazol-4-yl)-7-fluoro-1H-pyrrolo[3,4-c]pyridin-3(2H)-one;

(*R*)-2-(7-Fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

(*R*)-2-(4-(1-(Difluoromethyl)-1*H*-pyrazol-4-yl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

(*R*)-2-(4-(1-Cyclopropyl-1*H*-pyrazol-4-yl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

(*R*)-2-(4-(Benzofuran-3-yl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

(*R*)-2-(7-Fluoro-3-oxo-4-(pyrazolo[1,5-*a*]pyridin-3-yl)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-chloro-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile;

(*R*)-6-(2-Amino-3-methoxypropylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

(*R*)-6-(2-Amino-3-methoxypropylamino)-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile;

(*R*)-6-(2-Amino-3-methoxypropylamino)-7-fluoro-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

7-Acryloyl-6-((1*R*,2*S*)-2-aminocyclohexylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-iodo-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-(1*H*-pyrazol-4-yl)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-(*cis*-2-Amino-3,3-difluorocyclohexylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-(1-methyl-1*H*-pyrazol-5-yl)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-4-Aminotetrahydro-2*H*-pyran-3-ylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

tert-Butyl (1*S*,2*R*)-2-(3-oxo-7-phenyl-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-methyl-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-methyl-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

(*R*)-6-(2-Amino-3-methoxypropylamino)-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(pyrazolo[1,5-*a*]pyridin-3-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-4-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-4-(benzofuran-3-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

(*S*)-6-(3-Aminopyrrolidin-1-yl)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

(*S*)-6-(3-Aminopiperidin-1-yl)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(1-isopropyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

7-Fluoro-4,6-bis(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-bromo-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

(*R*)-6-(2-Amino-3-methoxypropylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(thiophen-3-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(4-methylthiophen-2-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(4-methylthiophen-2-yl)-1*H*-pyrrolo[3,4-c]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(thiophen-3-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

(*R*)-2-(7-Fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-*N*,4-dimethylpentanamide;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(5-methylthiophen-2-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

(*R*)-2-(7-Fluoro-4-(4-methylthiophen-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

(*R*)-2-(7-Fluoro-3-oxo-4-(thiophen-3-yl)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

(*R*)-2-(7-Fluoro-4-(5-methylthiophen-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(2-aminothiazol-5-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

(*R*)-2-(7-Fluoro-4-(furan-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

(*R*)-2-(7-Fluoro-4-(furan-3-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

(*R*)-2-(7-Fluoro-4-(furan-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

(*R*)-2-(4-(5-Cyanothiophen-2-yl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

(*R*)-2-(4-(4-Cyanothiophen-2-yl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

(*R*)-2-(7-Fluoro-3-oxo-4-(thiazol-5-yl)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

(*R*)-2-(7-Fluoro-4-(isothiazol-5-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-1,1-dimethyl-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-3-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(2-methylthiazol-5-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(5-methylthiophen-2-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-1-methyl-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

(*R*)-2-(7-Fluoro-3-oxo-4-(thiophen-2-yl)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(thiophen-2-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(thiazol-5-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(thiophen-2-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(4-(trifluoromethyl)-1*H*-imidazol-1-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(4-methyl-1*H*-imidazol-1-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(3-methylisothiazol-5-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(2-methylthiazol-5-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

(*R*)-2-(7-Fluoro-4-(2-methylthiazol-5-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-4-(5-chlorothiophen-2-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-4-(1-cyclopropyl-1*H*-pyrazol-4-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

a stereoisomer of any of the aforementioned compounds; and

a pharmaceutically acceptable salt of any of the aforementioned compounds or stereoisomers.

33. A pharmaceutical composition comprising:

a compound or pharmaceutically acceptable salt as defined in any one of claims 1 to 32; and

a pharmaceutically acceptable excipient.

34. A use of a compound or pharmaceutically acceptable salt as defined in any one of claims 1 to 32, as a medicament.

35. A use of a compound or pharmaceutically acceptable salt as defined in any one of claims 1 to 32, for the manufacture of a medicament for the treatment of a disease or condition for which a SYK inhibitor is indicated.

36. A method of treating a disease or condition in a subject for which a SYK inhibitor is indicated, the method comprising administering to the subject an effective amount of a compound or pharmaceutically acceptable salt as defined in any one of claims 1 to 32.

37. A method of treating a disease or condition in a subject, the method comprising administering to the subject an effective amount of a compound or pharmaceutically acceptable salt as defined in any one of claims 1 to 32, wherein the disease or condition is selected from allergic rhinitis, allergic asthma, atopic dermatitis, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, psoriasis, immune thrombocytopenic purpura, inflammatory bowel disease, chronic obstructive pulmonary disease, and thrombosis.

38. A method of treating a disease or condition in a subject, the method comprising administering to the subject an effective amount of a compound or pharmaceutically acceptable salt as defined in any one of claims 1 to 32, wherein the disease or condition is selected from a hematological malignancy and an epithelial cancer.

39. A method according to claim 38, wherein the hematological malignancy is selected from acute myeloid leukemia, B-cell chronic lymphocytic leukemia, B-cell lymphoma, and T-cell lymphoma.

40. A method according to claim 38, wherein the epithelial cancer is selected from lung cancer, pancreatic cancer, and colon cancer.

41. A combination of an effective amount of a compound or pharmaceutically acceptable salt as defined in any one of claims 1 to 32, and at least one additional pharmacologically active agent.

42. A combination according to claim 41, wherein the additional pharmacologically active agent is a DMARD.

43. A combination according to claim 42, wherein the DMARD is methotrexate.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/061146

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 C07D487/04 A61K31/437 A61K31/519 A61P7/00
A61P11/00 A61P17/00 A61P19/00 A61P35/00 A61P37/00
A61P29/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/070872 A1 (RIGEL PHARMACEUTICALS INC [US]; DING PINGYU [US]; ARGADE ANKUSH [US];) 21 June 2007 (2007-06-21) claims 1, 45-47	1-43
A	RUZZA P ET AL: "Therapeutic prospect of Syk inhibitors", EXPERT OPINION ON THERAPEUTIC PATENTS 2009 INFORMA HEALTHCARE GBR LNKD-DOI:10.1517/13543770903207039, vol. 19, no. 10, October 2009 (2009-10), pages 1361-1376, XP002625888, ISSN: 1354-3776 the whole document	1-43

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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 :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 March 2011	14/03/2011

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PIRROLIDINONAS HETEROAROMÁTICAS FUSIONADAS

Campo de la invención

[0001] Esta invención se refiere a compuestos de pirrolidinona heteroaromáticos fusionados, a composiciones farmacéuticas que los contienen, y al uso de los compuestos para tratar trastornos y afecciones que involucran el sistema inmune y la inflamación, que incluyen la artritis reumatoide. Las pirrolidinonas heteroaromáticas son inhibidores de la tirosina quinasa esplénica

Antecedentes de la invención

[0002] La tirosina quinasa esplénica (SYK) es una tirosina quinasa citoplásmica no receptora de 72 kDa. La SYK tiene una secuencia aminoácida primaria similar a la de la proteína de 70 kD asociada a la cadena zeta (ZAP-70) y está involucrada en la transducción de señal mediada por el receptor. El dominio N-terminal de la SYK contiene dos dominios Src-homología 2 (SH2), que se unen a los motivos de activación en inmunoreceptores difosforilados basados en tirosina (ITAMs) hallados en los dominios de señalización citoplásmica de muchos complejos inmunoreceptores. El C-terminal contiene el dominio catalítico, e incluye varios sitios de autoroforilación de bucle catalítico que son responsables de la activación de la SYK inducida por el receptor y la posterior propagación de la señal corriente abajo. La SYK se expresa en muchos tipos celulares involucradas en la inmunidad adaptativa e innata, que incluyen linfocitos (células B, células T, y células NK), granulocitos (basóficos, neutrófilos, y eosinófilos), monocitos, macrófagos, células dendríticas y mastocitos. La SYK se expresa en otros tipos celulares, que incluyen el epitelio de las vías aéreas y los fibroplastos en el sistema respiratorio superior. Véase, por ej., Martin Turner et al., Immunology Today (2000) 21(3):148-54; y Michael P. Sanderson et al., Inflammation & Allergy – Drug Targets (2009) 8:87-95.

[0003] La función de la SYK en la señalización dependiente del ITAM y su expresión en muchos tipos celulares sugiere que los compuestos que inhiben la actividad de la SYK pueden ser útiles para tratar trastornos que involucran el sistema inmune y la

inflamación. Estos trastornos incluyen las reacciones de hipersensibilidad tipo I (riñitis alérgica, asma alérgico, y dermatitis atópica; enfermedades autoinmunes (artritis reumatoide, esclerosis múltiple, lupus eritematoso sistémico, soriasis, y púrpura trombocitopénica inmune; e inflamación del pulmón (enfermedad pulmonar obstructiva crónica). Véase, por ej., Brian R. Wong et al., Expert Opin. Investig. Drugs (2004) 13(7):743-62; Sanderson et al. 2009); Jane Denyer & Vipul Patel, Drug News Perspective (2009) 22(3):146-50; Esteban S. Masuda & Jochen Schmitz, Pulmonary Pharmacology & Therapeutics (2008) 21:461-67; Malini Bajpai et al., Expert Opin. Investig. Drugs (2008) 17(5):641-59; y Anna Podolanczuk et al., Blood (2009) 113:3154-60. Otros trastornos incluyen malignidades hematológicas, tales como leucemia mieloide aguda, leucemia linfocítica crónica de células B, linfoma de células B (por ej., linfoma de células de la corteza cerebral), y linfoma de células T (por ej., linfoma de células T periféricas); como también cánceres epiteliales, tales como cáncer de pulmón, cáncer pancreático, y cáncer de colon. Véase por ej., Cynthia K. Hahn et al., Cancer Cell (2009) 16:281-294; D. H. Chu et al., Immnol. Rev. (1998) 165:167-180; A. L. Feldman et al., Leukemia (2008) 22:1139-43; A. Rinaldi et al., Br. J. Haematol. (2006) 132:303-316; B. Streubel et al., Leukemia (2006) 20:313-18; Maike Buchner et al., Cancer Research (2009) 69(13):5424-32; A. D. Baudot et al., Oncogene (2009) 28:3261–73; y Anurag Singh et al., Cancer Cell (2009) 15:489-500.

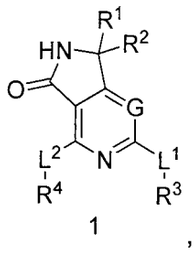
[0004] Varios inhibidores de la SYK han sido descriptos en solicitudes de patentes publicadas. Véase por ej., EP 1184376 A1; WO 01/83485 A1; WO 03/057695 A1; WO 2006/129100 A1; WO 01/09134 A1; WO 03/063794 A1; WO 2005/012294 A1; WO 2004/087699 A2; WO 2009/026107 A1; WO2009136995 A2; y WO2009/145856 A1.

Síntesis de la invención

[0005] Esta invención provee derivados de pirrolidinona heteroaromáticos fusionados, que incluyen las 6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona, 1H-pirrolo[3,4-

REIVINDICACIONES

1. Un compuesto de fórmula 1,



1 ,

o su sal aceptable para uso farmacéutico, donde:

G se selecciona de N y C(R5);

L1 y L2 se seleccionan cada uno de ellos independientemente de NH y un enlace;

R1 y R2 se seleccionan cada uno de ellos independientemente de hidrógeno, halo, alquilo C1-3, y haloalquilo C1-3, o R1 y R2, junto con el átomo al cual están unidos, forman un cicloalquilo C3-6;

R3 se selecciona de alquilo C2-6, cicloalquilo C3-8, heterocicloalquilo C2-5, y heteroarilo C1-9, cada uno opcionalmente sustituido con uno a cinco sustituyentes independientemente seleccionados de halo, oxo, NO2, -CN, R6, y R7;

R4 se selecciona de cicloalquilo C3-8, heterociclilo C2-5, arilo C6-14 y heteroarilo C1-9, cada uno opcionalmente sustituido con uno a cinco sustituyentes independientemente seleccionados de halo, oxo, CN, R6, y R7;

R5 se selecciona de hidrógeno, halo, CN, alquilo C1-4, alquenilo C2-4, alquinilo C2-4, heterociclilo C2-5, heteroarilo C1-5, y R10, donde los restos alquilo, alquenilo, alquinilo están cada uno de ellos opcionalmente sustituidos con uno a cinco sustituyentes seleccionados independientemente de halo, -CN, oxo y R10, y donde el resto heterociclilo tiene 3 a 6 átomos del anillo y el resto heteroarilo tiene 5 o 6 átomos del anillo, y los restos heterociclilo y heteroarilo están cada uno de ellos opcionalmente sustituidos con uno a cuatro sustituyentes seleccionados independientemente de halo, NO2, -CN, alquilo C1-4, alquenilo C2-4, alquinilo C2-4, haloalquilo C1-4, y R10;

cada R6 se selecciona independientemente de OR8, -N(R8)R9, -NR8C(O)R9, -C(O)R8, -C(O)OR8, -C(O)N(R8)R9, -C(O)N(R8)OR9, -C(O)N(R8)S(O)2R9, -N(R8)S(O)2R9, -S(O)nR8, y -S(O)2N(R8)R9;

cada R7 se selecciona independientemente de alquilo C1-6, alquenilo C2-6, alquinilo C2-6, C3-6 cicloalquilo (CH2)m-, C6-14 aril-(CH2)m-, C2-5 heterociclilo (CH2)m-, y C1-9 heteroaril-(CH2)m-, cada uno de ellos opcionalmente sustituido con uno a cinco sustituyentes independientemente seleccionados de halo, oxo, NO2, -CN, alquilo C1-6, haloalquilo C1-6 y R10;

cada R8 y R9 se selecciona independientemente de hidrogeno o de alquilo C1-6, alquenilo C2-6, alquinilo C2-6, C3-6 cicloalquilo (CH2)m-, C6-14 aril-(CH2)m-, C2-5 heterociclilo (CH2)m-, y C1-9 heteroaril-(CH2)m-, cada uno de ellos opcionalmente sustituido con uno a cinco sustituyentes independientemente seleccionados de halo, oxo, NO2, -CN, alquilo C1-6, haloalquilo C1-6 y R10; cada R10 se selecciona independientemente de OR11, -N(R11)R12, -N(R11)C(O)R12, -C(O)R11, -C(O)OR11, -C(O)N(R11)R12, -C(O)N(R11)OR12, -C(O)N(R11)S(O)2R12, -NR11S(O)2R12, -S(O)nR11, y -S(O)2N(R11)R12;

cada R11 y R12 se selecciona independientemente de hidrógeno y alquilo C1-6;

cada n se selecciona independientemente de 0, 1 y 2; y

cada m se selecciona independientemente de 0, 1, 2, 3, y 4;

donde cada uno de los restos heteroarilo antes mencionados tiene uno a cuatro heteroátomos seleccionados independientemente de N, O, y S, y cada uno de los restos heterociclilo antes mencionados está saturado o parcialmente insaturado y tiene uno o dos heteroátomos independientemente seleccionados de N, O y S.

2. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con la reivindicación 1, donde L1 es NH.

3. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con la reivindicación 1, donde L1 es un enlace.

4. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con cualquiera de las reivindicaciones precedentes, donde L2 es NH.

5. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con cualquiera de las reivindicaciones 1 a 3, donde L2 es un enlace.

6. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con cualquiera de las reivindicaciones precedentes, donde G es N.

7. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con cualquiera de las reivindicaciones 1 a 5, donde G es C(R5).

8. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con cualquiera de las reivindicaciones precedentes, donde R1 y R2 son ambos hidrógeno.

9. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con cualquiera de las reivindicaciones precedentes, donde R3 es cicloalquilo C3-8, sustituido opcionalmente con de uno a cinco sustituyentes seleccionados independientemente de halo, oxo, -NO2, -CN, R6, y R7.

10. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con la reivindicación 9, donde R3 es 2-amino-C3-8 cicloalqu-1-ilo, opcionalmente sustituido con uno a cuatro sustituyentes independientemente seleccionados de halo, oxo, -NO2, -CN, R6, y R7.

11. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con la reivindicación 10, donde R3 es 2-amino-ciclohex-1-ilo, opcionalmente sustituido con uno a cuatro sustituyentes independientemente seleccionados de halo, oxo, -NO2, -CN, R6, y R7.

12. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con cualquiera de las reivindicaciones 1 a 8, donde R3 es un alquilo C2-6, opcionalmente sustituido con uno a cinco sustituyentes independientemente seleccionados de halo, oxo, -NO2, -CN, R6, y R7.

13. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con la reivindicación 12, donde R3 es 2-amino-alqu-1-ilo C2-6, opcionalmente sustituido con uno a cuatro sustituyentes independientemente seleccionados de halo, oxo, -NO2, -CN, R6, y R7.

14. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con la reivindicación 13, donde R3 es un 2-aminoetan-1-ilo, opcionalmente sustituido con uno a cuatro sustituyentes independientemente seleccionados de halo, oxo, -NO2, -CN, R6, y R7.

15. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con la reivindicación 14, donde R3 es un 2-amino-2-oxoetan-1-ilo, opcionalmente sustituido con uno a dos sustituyentes independientemente seleccionados de halo, oxo, -NO2, -CN, R6, y R7.

16. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con cualquiera de las reivindicaciones 1 a 8, donde R3 es un heterociclilo C2-5, opcionalmente

sustituido con uno a cinco sustituyentes independientemente seleccionados de halo, oxo, -NO2, -CN, R6, y R7.

17. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con la reivindicación 16, donde R3 es heterociclilo C2-5 sustituido con un amino y opcionalmente sustituido con de uno a cuatro sustituyentes adicionales independientemente seleccionados de halo, oxo, -NO2, -CN, R6, y R7.

18. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con la reivindicación 17, donde R3 es 3-aminotetrahidro-2H-piran-4-ilo, opcionalmente sustituido con uno a cuatro sustituyentes independientemente seleccionados de halo, oxo, -NO2, -CN, R6, y R7.

19. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con cualquiera de las reivindicaciones 1, y 3 a 8, donde R3 es heterociclilo C2-5 o un amino-heterociclilo C2-5 sustituido, cada uno opcionalmente sustituido con uno a cinco o de uno a cuatro sustituyentes respectivamente, independientemente seleccionados de halo, oxo, -NO2, -CN, R6, y R7, donde uno de los heteroátomos del resto heterociclilo se une directamente a L1, y L1 es un enlace.

20. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con cualquiera de las reivindicaciones precedentes, donde R4 se selecciona de arilo C6-14 y heteroarilo C1-9, cada uno opcionalmente sustituido con uno a cinco sustituyentes independientemente seleccionados de halo, oxo, -CN, R6, y R7.

21. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con cualquiera de las reivindicaciones precedentes, donde R4 es fenilo opcionalmente

sustituido con uno a cinco sustituyentes independientemente seleccionados de halo, -CN, R6, y R7.

22. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con cualquiera de las reivindicaciones 1 a 20, donde R4 es un heteroarilo C1-9 opcionalmente sustituido con uno a cinco sustituyentes independientemente seleccionados de halo, oxo, -CN, R6, y R7.

23. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con la reivindicación 22, donde R4 es un heteroarilo C2-4 monocíclico opcionalmente sustituido con uno a cuatro sustituyentes independientemente seleccionados de halo, -CN, R6, y R7.

24. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con la reivindicación 23, donde R4 se selecciona de pirrolilo, furanilo, tiofenilo, pirazolilo, imidazolilo, isoxazolilo, oxazolilo, isotiazolilo, y tiazolilo, cada uno de ellos sustituido opcionalmente con de uno a tres sustituyentes seleccionados independientemente de halo, -CN, R6, y R7.

25. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con la reivindicación 24, donde R4 se selecciona de tiofenilo, pirazolilo, isotiazolilo, y tiazolilo, cada uno de ellos sustituido opcionalmente con de uno a tres sustituyentes seleccionados independientemente de halo, -CN, R6, y R7.

26. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con la reivindicación 25, donde R4 es pirazolilo sustituido opcionalmente con de uno a tres sustituyentes seleccionados independientemente de halo, -CN, R6, y R7.

27. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con la reivindicación 19, donde R4 es pirazol-4-ilo opcionalmente sustituido con uno a tres sustituyentes independientemente seleccionados de halo, -CN, R6, y R7.

28. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con cualquiera de las reivindicaciones 20 a 27, donde R4 está sustituido con metilo, etilo, ciclopropilo o haloalquilo C1-2.

29. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con cualquiera de las reivindicaciones 1 a 5 y 7 a 28, donde R5 es heteroarilo C1-5 , opcionalmente sustituido con uno a cuatro sustituyentes independientemente seleccionados de halo, NO2, -CN, alquilo C1-4, alquenilo C2-4, alquinilo C2-4, haloalquilo C1-4, y R10.

30. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con cualquiera de las reivindicaciones 1 a 5 y 7 a 28, donde R5 se selecciona de hidrógeno y halo.

31. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con la reivindicación 30, donde R5 se selecciona de cloro y flúor.

32. Un compuesto de acuerdo con la reivindicación 1, el cual se selecciona de los siguientes compuestos:

2-((1R,2S)-2-aminociclohexilamino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(3-fluorofenilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(3-clorofenilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

4-(1H-indazol-6-ilamino)-2-((1R,2S)-2-aminociclohexilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(3-trifluorometil)fenilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

cis-2-(2-aminociclohexilamino)-4-(3-(trifluorometil)fenilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-(1-metil-1H-pirazol-4-il)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-(4-etilpiperazin-1-il)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-(ciclohexilamino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

cis-2-(2-hidroxiciclohexilamino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-(3-aminopiperidin-1-il)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

6-((1R,2S)-2-aminociclohexilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(1-metil-1H-pirazol-4-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(1-isobutil-1H-pirazol-4-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-fenil-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(benzo[b]tiofen-3-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(1-etil-1H-pirazol-4-il)-6,7-dihidro-5H-

pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(1-bencil-1H-pirazol-4-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(imidazo[1,2-a]piridin-3-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(1-propil-1H-pirazol-4-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(1-(2-metoxietil)-1H-pirazol-4-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

4-(1H-indazol-6-ilamino)-6-((1R,2S)-2-aminociclohexilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-4-(4-fluoro-3-metilfenilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-7-fluoro-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-aminotetrahidro-2H-piran-4-ilamino)-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-7-cloro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-7-fluoro-4-(pirazolo[1,5-a]piridin-3-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

2-(2-(aminometil)piperidin-1-il)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

6-((1R,2S)-2-aminociclohexilamino)-4-(3-(metilsulfonil)fenilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclopentilamino)-4-(3-(metilsulfonil)fenilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(R)-4-metil-2-(4-(3-(metilsulfonil)fenilamino)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)pentanamida;

(R)-4-metil-2-(4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)pentanamida;

2-((1R,2S)-2-(dimetilamino)ciclohexilamino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-(metilamino)ciclohexilamino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2'-((1R,2S)-2-(aminociclohexilamino)-4'-(m-tolilamino)espiro[ciclopropano-1,7-pirrolo[3,4-d]pirimidin-5'(6'H)-ona;

2-(2-aminoetilamino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-(2-amino-2-metilpropilamino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-(5-oxo-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-2-ilamino)acetamida;

2-((2-aminoetil)(metil)amino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-(pirrolidin-2-ilmetilamino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-(3-aminopirrolidin-1-il)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(1,5-dimetil-1H-pirazol-4-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(1-propil-1H-indol-2-il)-6,7-dihidro-5H-

pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(1H-pirazol-5-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-(3-aminopropil)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

6-((1R,2S)-2-aminociclohexilamino)-4-(benzofuran-3-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-7-fluoro-4-(imidazo[1,2-a]piridin-3-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-4-(benzo[b]tiofen-3-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1S,2R)-2-aminociclohexilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(R)-6-(2-amino-3-etoxipropilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(R)-6-(2-amino-3-etoxipropilamino)-7-fluoro-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-(2-amino-3,3,3-trifluoropropilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(R)-4-metil-2-(3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)pentanamida;

6-(cis-4-aminotetrahidrofuran-3-ilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-4-(1-etil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-4-(1-etil-1H-pirazol-4-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-4-(1-ciclopropil-1H-pirazol-4-il)-1H-pirrolo[3,4-

c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-4-(1-(difluorometil)-1H-pirazol-4-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-4-(1-ciclopropil-1H-pirazol-4-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

cis-6-(2-aminociclohexilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-(cis-2-amino-4,4-difluorociclopentilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-(cis-2-amino-3,3-difluorociclohexilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-(cis-2-amino-3,3-difluorociclohexilamino)-4-(1-(difluorometil)-1H-pirazol-4-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-(cis-2-amino-3,3-difluorociclohexilamino)-4-(1-ciclopropil-1H-pirazol-4-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(R)-2-(7-fluoro-4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

(R)-2-(4-(1-(difluorometil)-1H-pirazol-4-il)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

(R)-2-(4-(1-ciclopropil-1H-pirazol-4-il)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

(R)-2-(4-(benzofuran-3-il)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

(R)-2-(7-fluoro-3-oxo-4-(pirazolo[1,5-a]piridin-3-il)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

6-((1R,2S)-2-aminociclohexilamino)-7-cloro-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-7-carbonitrilo;

(R)-6-(2-amino-3-metoxipropilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(R)-6-(2-amino-3-metoxipropilamino)-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-7-carbonitrilo;

(R)-6-(2-amino-3-metoxipropilamino)-7-fluoro-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

7-acriloil-6-((1R,2S)-2-aminociclohexilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-7-yodo-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-7-(1H-pirazol-4-il)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-(cis-2-amino-3,3-difluorociclohexilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-7-(1-metil-1H-pirazol-5-il)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-aminotetrahidro-2H-piran-4-ilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-4-aminotetrahidro-2H-piran-3-ilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

ter-butilo (1S,2R)-2-(3-oxo-7-fenil-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ;

6-((1R,2S)-2-aminociclohexilamino)-7-metil-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-

3(2H)-ona;

6-((3R,4R)-3-aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-7-metil-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(R)-6-(2-amino-3-metoxipropilamino)-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(pirazolo[1,5-a]piridin-3-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-aminotetrahidro-2H-piran-4-ilamino)-4-(1-(difluorometil)-1H-pirazol-4-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-aminotetrahidro-2H-piran-4-ilamino)-4-(benzofuran-3-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(S)-6-(3-aminopirrolidin-1-il)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(S)-6-(3-aminopiperidin-1-il)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-7-fluoro-4-(1-isopropil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

7-fluoro-4,6-bis(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-7-bromo-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(1-(4-fluorofenil)-1H-pirazol-4-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

(R)-6-(2-amino-3-metoxipropilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(tiofen-3-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(4-metiltiofen-2-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-Aminociclohexilamino)-7-fluoro-4-(4-metiltiofen-2-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-Aminociclohexilamino)-7-fluoro-4-(tiofen-3-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(R)-2-(7-Fluoro-4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-N,4-dimetilpentanamida;

6-((1R,2S)-2-Aminociclohexilamino)-7-fluoro-4-(5-metiltiofen-2-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(R)-2-(7-Fluoro-4-(4-metiltiofen-2-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

(R)-2-(7-Fluoro-3-oxo-4-(tiofen-3-il)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

(R)-2-(7-Fluoro-4-(5-metiltiofen-2-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

6-((1R,2S)-2-Aminociclohexilamino)-4-(2-aminotiazol-5-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(R)-2-(7-Fluoro-4-(furan-2-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

(R)-2-(7-Fluoro-4-(furan-3-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

(R)-2-(7-Fluoro-4-(furan-2-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

(R)-2-(4-(5-Cianotiofen-2-il)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

(R)-2-(4-(4-Cianotiofen-2-il)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

(R)-2-(7-Fluoro-3-oxo-4-(tiazol-5-il)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

(R)-2-(7-Fluoro-4-(isotiazol-5-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

6-((1R,2S)-2-Aminociclohexilamino)-7-fluoro-1,1-dimetil-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

((1R,2S)-2-Aminociclohexilamino)-7-fluoro-4-(1-metil-1H-pirazol-3-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-Aminociclohexilamino)-7-fluoro-4-(2-metiltiazol-5-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(5-metiltiofen-2-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-Aminociclohexilamino)-7-fluoro-1-metil-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(R)-2-(7-Fluoro-3-oxo-4-(tiofen-2-il)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(tiofen-2-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(tiazol-5-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-Aminociclohexilamino)-7-fluoro-4-(tiofen-2-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(4-(trifluorometil)-1H-imidazol-1-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-Aminociclohexilamino)-7-fluoro-4-(4-metil-1H-imidazol-1-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(3-metilisotiazol-5-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(2-metiltiazol-5-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(R)-2-(7-Fluoro-4-(2-metiltiazol-5-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-4-(5-clorotiofen-2-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-4-(1-ciclopropil-1H-pirazol-4-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

un estereoisómero de cualquiera de los compuestos antes mencionados; y

un sal aceptable para uso farmacéutico de cualquiera de los compuestos o estereoisómeros antes mencionados.

33. Una composición farmacéutica que comprende:

un compuesto o sal aceptable para uso farmacéutico según se definió en cualquiera de las reivindicaciones 1 a 32; y

un excipiente aceptable para uso farmacéutico.

34. Un uso de un compuesto o sal aceptable para uso farmacéutico según se definió en cualquiera de las reivindicaciones 1 a 32, como medicamento.

35. Un uso de un compuesto o sal aceptable para uso farmacéutico según se

definió en cualquiera de las reivindicaciones 1 a 32, para la producción de un medicamento para el tratamiento de una enfermedad o afección para la cual se indica un inhibidor de SYK.

36. Un método para tratar una enfermedad o afección en un sujeto para la cual se indica un inhibidor de la SYK, comprendiendo el método la administración al sujeto de una cantidad eficaz de un compuesto o sal aceptable para uso farmacéutico según se define en cualquiera de las reivindicaciones 1 a 32.

37. Un método para el tratamiento de una enfermedad o afección en un sujeto, el método comprende administrar al sujeto una cantidad eficaz de un o sal aceptable para uso farmacéutico según se define en cualquiera de las reivindicaciones 1 a 32, donde la enfermedad o afección se selecciona de riñitis alérgica, asma alérgico, y dermatitis atópica, artritis reumatoide, esclerosis múltiple, lupus eritematoso sistémico, soriasis, púrpura trombocitopénica inmune, enfermedad inflamatoria intestinal, enfermedad pulmonar obstructiva crónica y trombosis.

38. Un método para tratar una enfermedad o afección en un sujeto, el método comprende la administración al sujeto de una cantidad eficaz de un compuesto o sal aceptable para uso farmacéutico según se define en cualquiera de las reivindicaciones 1 a 32, donde la enfermedad o afección se selecciona de una malignidad hematológica y un cáncer epitelial.

39. Un método de acuerdo con la reivindicación 38, donde la malignidad hematológica se selecciona de leucemia mieloide aguda, leucemia linfocítica crónica de las células B, linfoma de las células B, y linfoma de las células T.

40. Un método de acuerdo con la reivindicación 38, donde el cáncer epitelial se selecciona de cáncer de pulmón, cáncer pancreático, y cáncer de colon.

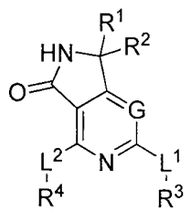
41. Una combinación de una cantidad eficaz de un compuesto o sal aceptable para uso farmacéutico según se define en cualquiera de las reivindicaciones 1 a 32, y al menos un agente farmacológicamente activo adicional.

42. Una combinación de acuerdo con la reivindicación 41, donde el agente farmacológicamente activo adicional es DMARD.

43. Una combinación de acuerdo con la reivindicación 42, donde el DMARD es metotrexato.

RESUMEN

Se divulgan los compuestos de fórmula 1,



1 ,

y sus sales aceptables para uso farmacéutico, donde G, L1, L2, R1, R2, R3, y R4 se definen en la memoria descriptiva. La presente divulgación además se refiere a materiales y métodos para preparar los compuestos de fórmula 1, las composiciones farmacéuticas que los contienen, y su uso para tratar trastornos, enfermedades, y afecciones que involucran el sistema inmune y la inflamación, que incluyen artritis reumatoide, malignidades hematológicas, canceres epiteliales (es decir, carcinomas), y otros trastornos, enfermedades, y afecciones para las cuales se indica la inhibición de la SYK.

Industria y Comercio
SUPERINTENDENCIA

PLANILLA DE RADICACIÓN - DIGITALIZACIÓN DIARIA
RELACIÓN DE ANEXOS

Dependencia:	Fecha:	Recorrido:

Tipo de Radicación: Entrada: Salida: Traslado: Convenio:

Radicador:	Planilla:

ID	No. Radicación	Cons	Item
1	12-121953-0		1
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			

Item	Unidad de Conservación
1	CD
2	Disquetes
3	DVD
4	Fotos
5	Libro
6	Muestra Física
7	Otros
8	Planos
9	Periódico
10	Publicación Periódica
11	Sobre blanco tamaño carta
12	Sobre blanco tamaño oficio
13	Sobre de manila

Observaciones
Folio 53 Sobre con CD.

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
TARJETA ARCHIVO PROPIETARIOS

PATENTE DE INVENCION ____ PCT __X__ MODELO DE UTILIDAD ____ DISEÑO INDUSTRIAL ___

(21) Nº de solicitud: (22) Fecha de solicitud:
(51) Clasificación Internacional :

(71)Solicitante(s) **TAKEDA PHARMACEUTICAL COMPANY LIMITED**

(72) Inventor(es) **ARIKAWA, Yasuyoshi; JONES, Benjamín; LAM, Betty; NIE, Zhe; SMITH, Christopher; TAKAHASHI, Masashi; DONG, Qing; FEHER, Victoria**

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SUPERINTENDENCIA

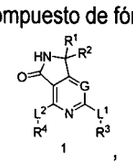
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___ **Patente de Invención** ___ **Patente modelo de utilidad** _X_ **PCT**

(21) No. De solicitud	(51) int. Cl:
(22) Fecha de solicitud	(71) Solicitante (s) **TAKEDA PHARMACEUTICAL COMPANY LIMITED**
(30) Prioridad (31) No. Prioridad **61/289.969** **61/386.964** (32) Fecha **23/12/2009** **27/09/2010** (33) País **US, US**	(72) Interventor (es) **ARIKAWA, Yasuyoshi** **JONES, Benjamin** **LAM, Betty** **NIE, Zhe** **SMITH, Christopher** **TAKAHASHI, Masashi** **DONG, Qing** **FEHER, Victoria** (74) Apoderado (s) **DRA. MARGARITA CASTELLANOS ABONDANO**
(54) Título **PIRROLIDINONAS HETEROAROMÁTICAS FUSIONADAS**	
Las casillas identificadas con 85, 86 y 87 sólo aplican para PCT	
(85) Fecha límite inicio Fase Nacional (86) Datos relativos a la presentación de la solicitud PCT Fecha de presentación de la solicitud **17/12/2010** No. de solicitud **PCT/US2010/061146**	(87) Publicación internacional Fecha **30/06/2011** No. Publicación **WO 2011/079051 A1**

Resumen reivindicación (es):

1. Un compuesto de fórmula 1,



1 ,

o su sal aceptable para uso farmacéutico, donde:

G se selecciona de N y C(R5);

L1 y L2 se seleccionan cada uno de ellos independientemente de NH y un enlace;

R1 y R2 se seleccionan cada uno de ellos independientemente de hidrógeno, halo, alquilo C1-3, y haloalquilo C1-3, o R1 y R2, junto con el átomo al cual están unidos, forman un cicloalquilo C3-6;

R3 se selecciona de alquilo C2-6, cicloalquilo C3-8, heterocicloalquilo C2-5, y heteroarilo C1-9, cada uno opcionalmente sustituido con uno a cinco sustituyentes independientemente seleccionados de halo, oxo, NO2, -CN, R6, y R7;

R4 se selecciona de cicloalquilo C3-8, heterociclilo C2-5, arilo C6-14 y heteroarilo C1-9, cada uno opcionalmente sustituido con uno a cinco sustituyentes independientemente seleccionados de halo, oxo, CN, R6, y R7;

R5 se selecciona de hidrógeno, halo, CN, alquilo C1-4, alquenilo C2-4, alquinilo C2-4, heterociclilo C2-5, heteroarilo C1-5, y R10, donde los restos alquilo, alquenilo, alquinilo están cada uno de ellos opcionalmente sustituidos con uno a cinco sustituyentes seleccionados independientemente de halo, -CN, oxo y R10, y donde el resto heterociclilo tiene 3 a 6 átomos del anillo y el resto heteroarilo tiene 5 o 6 átomos del anillo, y los restos heterociclilo y heteroarilo están cada uno de ellos opcionalmente sustituidos con uno a cuatro sustituyentes seleccionados independientemente de halo, NO2, -CN, alquilo C1-4, alquenilo C2-4, alquinilo C2-4, haloalquilo C1-4, y R10;

cada R6 se selecciona independientemente de OR8, -N(R8)R9, -NR8C(O)R9, -C(O)R8, -C(O)OR8, -C(O)N(R8)R9, -C(O)N(R8)OR9, -C(O)N(R8)S(O)2R9, -N(R8)S(O)2R9, -S(O)nR8, y -S(O)2N(R8)R9;

cada R7 se selecciona independientemente de alquilo C1-6, alquenilo C2-6, alquinilo C2-6, C3-6 cicloalquilo (CH2)m-, C6-14 aril-(CH2)m-, C2-5 heterociclilo (CH2)m-, y C1-9 heteroaril-(CH2)m-, cada uno de ellos opcionalmente sustituido con uno a cinco sustituyentes independientemente seleccionados de halo, oxo, NO2, -CN, alquilo C1-6, haloalquilo C1-6 y R10;

cada R8 y R9 se selecciona independientemente de hidrogeno o de alquilo C1-6, alquenilo C2-6, alquinilo C2-6, C3-6 cicloalquilo (CH2)m-, C6-14 aril-(CH2)m-, C2-5 heterociclilo (CH2)m-, y C1-9 heteroaril-(CH2)m-, cada uno de ellos opcionalmente sustituido con uno a cinco sustituyentes independientemente seleccionados de halo, oxo, NO2, -CN, alquilo C1-6, haloalquilo C1-6 y R10; cada R10 se selecciona independientemente de OR11, -N(R11)R12, -N(R11)C(O)R12, -C(O)R11, -C(O)OR11, -C(O)N(R11)R12, -C(O)N(R11)OR12, -C(O)N(R11)S(O)2R12, -NR11S(O)2R12, -S(O)nR11, y -S(O)2N(R11)R12;

cada R11 y R12 se selecciona independientemente de hidrógeno y alquilo C1-6;

cada n se selecciona independientemente de 0, 1 y 2; y

cada m se selecciona independientemente de 0, 1, 2, 3, y 4;

donde cada uno de los restos heteroarilo antes mencionados tiene uno a cuatro heteroátomos seleccionados independientemente de N, O, y S, y cada uno de los restos heterociclilo antes mencionados está saturado o parcialmente insaturado y tiene uno o dos heteroátomos independientemente seleccionados de N, O y S.

2. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con la reivindicación 1, donde L1 es NH.
3. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con la reivindicación 1, donde L1 es un enlace.
4. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con cualquiera de las reivindicaciones precedentes....

Industria y Comercio
SUPERINTENDENCIA

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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 _X_ **MODELO DE UTILIDAD PCT** ___ **Art.33 Decisión 486/00, Circular Única**

X Indicación que se solicita una PCT
X Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
Dibujos de ser estos pertinentes
X Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa X 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

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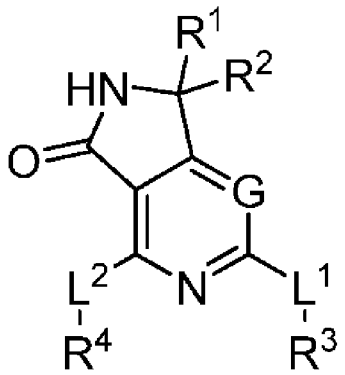
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(54) Title: FUSED HETEROAROMATIC PYRROLIDINONES AS SYK INHIBITORS



(I)

(57) Abstract: Disclosed are compounds of Formula 1, and pharmaceutically acceptable salts thereof, wherein G, L^1, L^2, R^1, R^2, R^3, and R^4 are defined in the specification. This disclosure also relates to materials and methods for preparing compounds of Formula 1, pharmaceutical compositions containing them, and their use for treating disorders, diseases, and conditions involving the immune system and inflammation, including rheumatoid arthritis, hematological malignancies, epithelial cancers (i.e., carcinomas), and other disorders, diseases, and conditions for which inhibition of SYK is indicated.

WO 2011/079051 A1

FUSED HETEROAROMATIC PYRROLIDINONES AS SYK INHIBITORS

FIELD OF THE INVENTION

[0001] This invention relates to fused heteroaromatic pyrrolidinone compounds, to pharmaceutical compositions containing them, and to the use of the compounds for treating disorders and conditions involving the immune system and inflammation, including rheumatoid arthritis. The heteroaromatic pyrrolidinones are inhibitors of spleen tyrosine kinase.

BACKGROUND OF THE INVENTION

[0002] Spleen tyrosine kinase (SYK) is a 72 kDa non-receptor cytoplasmic tyrosine kinase. SYK has a primary amino acid sequence similar to that of zeta-associated protein-70 (ZAP-70) and is involved in receptor-mediated signal transduction. The N-terminal domain of SYK contains two Src-homology 2 (SH2) domains, which bind to diphosphorylated immunoreceptor tyrosine-based activation motifs (ITAMs) found in the cytoplasmic signaling domains of many immunoreceptor complexes. The C-terminus contains the catalytic domain, and includes several catalytic loop autophosphorylation sites that are responsible for receptor-induced SYK activation and subsequent downstream signal propagation. SYK is expressed in many cell types involved in adaptive and innate immunity, including lymphocytes (B cells, T cells, and NK cells), granulocytes (basophils, neutrophils, and eosinophils), monocytes, macrophages, dendritic cells, and mast cells. SYK is expressed in other cell types, including airway epithelium and fibroblasts in the upper respiratory system. See, e.g., Martin Turner et al., *Immunology Today* (2000) 21(3):148-54; and Michael P. Sanderson et al., *Inflammation & Allergy – Drug Targets* (2009) 8:87-95.

[0003] SYK's role in ITAM-dependent signaling and its expression in many cell types suggest that compounds which inhibit SYK activity may be useful for treating disorders involving the immune system and inflammation. Such disorders include Type I hypersensitivity reactions (allergic rhinitis, allergic asthma, and atopic dermatitis); autoimmune diseases (rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, psoriasis, and immune thrombocytopenic purpura); and inflammation of the lung (chronic obstructive pulmonary disease). See, e.g., Brian R. Wong et al., *Expert*

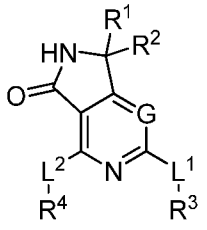
Opin. Investig. Drugs (2004) 13(7):743-62; Sanderson et al. (2009); Jane Denyer & Vipul Patel, *Drug News Perspective* (2009) 22(3):146-50; Esteban S. Masuda & Jochen Schmitz, *Pulmonary Pharmacology & Therapeutics* (2008) 21:461-67; Malini Bajpai et al., *Expert Opin. Investig. Drugs* (2008) 17(5):641-59; and Anna Podolanczuk et al., *Blood* (2009) 113:3154-60. Other disorders include hematological malignancies, such as acute myeloid leukemia, B-cell chronic lymphocytic leukemia, B-cell lymphoma (e.g., mantle cell lymphoma), and T-cell lymphoma (e.g., peripheral T-cell lymphoma); as well as epithelial cancers, such as lung cancer, pancreatic cancer, and colon cancer. See, e.g., Cynthia K. Hahn et al., *Cancer Cell* (2009) 16:281-294; D. H. Chu et al., *Immnol. Rev.* (1998) 165:167-180; A. L. Feldman et al., *Leukemia* (2008) 22:1139-43; A. Rinaldi et al., *Br. J. Haematol.* (2006) 132:303-316; B. Streubel et al., *Leukemia* (2006) 20:313-18; Maike Buchner et al., *Cancer Research* (2009) 69(13):5424-32; A. D. Baudot et al., *Oncogene* (2009) 28:3261–73; and Anurag Singh et al., *Cancer Cell* (2009) 15:489-500.

[0004] Various SYK inhibitors have been described in published patent applications. See, e.g., EP 1184376 A1; WO 01/83485 A1; WO 03/057695 A1; WO 2006/129100 A1; WO 01/09134 A1; WO 03/063794 A1; WO 2005/012294 A1; WO 2004/087699 A2; WO 2009/026107 A1; WO2009136995 A2; and WO2009/145856 A1.

SUMMARY OF THE INVENTION

[0005] This invention provides fused heteroaromatic pyrrolidinone derivatives, including 6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-ones, 1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-ones, and pharmaceutically acceptable complexes, salts, solvates, and hydrates thereof. This invention also provides pharmaceutical compositions containing the heteroaromatic pyrrolidinone derivatives, and uses of the heteroaromatic pyrrolidinone derivatives to treat disorders and conditions involving the immune system and inflammation, including rheumatoid arthritis.

[0006] One aspect of the invention provides compounds of Formula 1:



1 ,

or pharmaceutically acceptable salts thereof, wherein:

G is selected from N and $C(R^5)$;

L^1 and L^2 are each independently selected from -NH- and a bond;

R^1 and R^2 are each independently selected from hydrogen, halo, C_{1-3} alkyl, and C_{1-3} haloalkyl, or R^1 and R^2, together with the atom to which they are attached, form a C_{3-6} cycloalkyl;

R^3 is selected from C_{2-6} alkyl, C_{3-8} cycloalkyl, C_{2-5} heterocyclyl, and C_{1-9} heteroaryl, each optionally substituted with from one to five substituents independently selected from halo, oxo, $-NO_2$, -CN, R^6, and R^7;

R^4 is selected from C_{3-8} cycloalkyl, C_{2-5} heterocyclyl, C_{6-14} aryl, and C_{1-9} heteroaryl, each optionally substituted with from one to five substituents independently selected from halo, oxo, -CN, R^6, and R^7;

R^5 is selected from hydrogen, halo, -CN, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-5} heterocyclyl, C_{1-5} heteroaryl, and R^{10}, wherein the alkyl, alkenyl, alkynyl moieties are each optionally substituted with from one to five substituents independently selected from halo, -CN, oxo, and R^{10}, and wherein the heterocyclyl moiety has 3 to 6 ring atoms and the heteroaryl moiety has 5 or 6 ring atoms, and the heterocyclyl and heteroaryl moieties are each optionally substituted with from one to four substituents independently selected from halo, $-NO_2$, -CN, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, and R^{10};

each R^6 is independently selected from $-OR^8$, $-N(R^8)R^9$, $-NR^8C(O)R^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)N(R^8)R^9$, $-C(O)N(R^8)OR^9$, $-C(O)N(R^8)S(O)_2R^9$, $-N(R^8)S(O)_2R^9$, $-S(O)_nR^8$, and $-S(O)_2N(R^8)R^9$;

each R^7 is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl-$(CH_2)_m$-, C_{6-14} aryl-$(CH_2)_m$-, C_{2-5} heterocyclyl-$(CH_2)_m$-, and C_{1-9} heteroaryl-$(CH_2)_m$-, each optionally substituted with from one to five substituents independently selected from halo, oxo, $-NO_2$, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, and R^{10};

each R^8 and R^9 is independently selected from hydrogen or from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl-$(CH_2)_m$-, C_{6-14} aryl-$(CH_2)_m$-, C_{2-5} heterocyclyl-$(CH_2)_m$-, and C_{1-9} heteroaryl-$(CH_2)_m$-, each optionally

substituted with from one to five substituents independently selected from halo, oxo, $-NO_2$, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, and R^{10};

each R^{10} is independently selected from $-OR^{11}$, $-N(R^{11})R^{12}$, $-N(R^{11})C(O)R^{12}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-C(O)N(R^{11})R^{12}$, $-C(O)N(R^{11})OR^{12}$, $-C(O)N(R^{11})S(O)_2R^{12}$, $-NR^{11}S(O)_2R^{12}$, $-S(O)_nR^{11}$, and $-S(O)_2N(R^{11})R^{12}$;

each R^{11} and R^{12} is independently selected from hydrogen and C_{1-6} alkyl;

each n is independently selected from 0, 1 and 2; and

each m is independently selected from 0, 1, 2, 3, and 4;

wherein each of the aforementioned heteroaryl moieties has one to four heteroatoms independently selected from N, O, and S, and each of the aforementioned heterocyclyl moieties is saturated or partially unsaturated and has one or two heteroatoms independently selected from N, O, and S.

[0007] Another aspect of the invention provides a compound which is selected from the following group of compounds and their pharmaceutically acceptable salts:

2-((1*R*,2S)-2-Aminocyclohexylamino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(3-fluorophenylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(3-chlorophenylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

4-(1*H*-Indazol-6-ylamino)-2-((1*R*,2*S*)-2-aminocyclohexylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-aminocyclohexylamino)-4-(3-(trifluoromethyl)phenylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

cis-2-(2-aminocyclohexylamino)-4-(3-(trifluoromethyl)phenylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-(1-Methyl-1*H*-pyrazol-4-yl)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-(4-Ethylpiperazin-1-yl)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-(Cyclohexylamino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

cis-2-(2-Hydroxycyclohexylamino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-(3-Aminopiperidin-1-yl)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-methyl-1*H*-pyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-isobutyl-1*H*-pyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-phenyl-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(benzo[*b*]thiophen-3-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-ethyl-1*H*-pyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-benzyl-1*H*-pyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(imidazo[1,2-*a*]pyridin-3-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-propyl-1*H*-pyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-(2-methoxyethyl)-1*H*-pyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

4-(1*H*-Indazol-6-ylamino)-6-((1*R*,2*S*)-2-aminocyclohexylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(4-fluoro-3-methylphenylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-chloro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(pyrazolo[1,5-*a*]pyridin-3-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

2-(2-(Aminomethyl)piperidin-1-yl)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(3-(methylsulfonyl)phenylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclopentylamino)-4-(3-(methylsulfonyl)phenylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

(*R*)-4-Methyl-2-(4-(3-(methylsulfonyl)phenylamino)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)pentanamide;

(*R*)-4-Methyl-2-(4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)pentanamide;

2-((1*R*,2*S*)-2-(Dimethylamino)cyclohexylamino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-(Methylamino)cyclohexylamino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2'-((1*R*,2*S*)-2-Aminocyclohexylamino)-4'-(*m*-tolylamino)spiro[cyclopropane-1,7'-pyrrolo[3,4-*d*]pyrimidin]-5'(6'*H*)-one;

2-(2-Aminoethylamino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-(2-Amino-2-methylpropylamino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-(5-Oxo-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-2-ylamino)acetamide;

2-((2-Aminoethyl)(methyl)amino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-(Pyrrolidin-2-ylmethylamino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-(3-Aminopyrrolidin-1-yl)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1,5-dimethyl-1*H*-pyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1*H*-indol-2-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1*H*-pyrazol-5-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-(3-Aminopropyl)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

6-((1R,2S)-2-Aminocyclohexylamino)-4-(benzofuran-3-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-aminocyclohexylamino)-7-fluoro-4-(imidazo[1,2-*a*]pyridin-3-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-aminocyclohexylamino)-4-(benzo[*b*]thiophen-3-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*S*,2*R*)-2-Aminocyclohexylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(*2H*)-one;

(*R*)-6-(2-Amino-3-ethoxypropylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

(*R*)-6-(2-Amino-3-ethoxypropylamino)-7-fluoro-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-(2-Amino-3,3,3-trifluoropropylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

(*R*)-4-Methyl-2-(3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)pentanamide;

6-(*cis*-4-Aminotetrahydrofuran-3-ylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2H)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-ethyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-ethyl-1*H*-pyrazol-4-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-cyclopropyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-cyclopropyl-1*H*-pyrazol-4-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

cis-6-(2-Aminocyclohexylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-(*cis*-2-Amino-4,4-difluorocyclopentylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-c]pyridin-3(2*H*)-one;

6-(*cis*-2-Amino-3,3-difluorocyclohexylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-(*cis*-2-Amino-3,3-difluorocyclohexylamino)-4-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-(*cis*-2-amino-3,3-difluorocyclohexylamino)-4-(1-cyclopropyl-1H-pyrazol-4-yl)-7-fluoro-1H-pyrrolo[3,4-c]pyridin-3(2H)-one;

(*R*)-2-(7-Fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

(*R*)-2-(4-(1-(Difluoromethyl)-1*H*-pyrazol-4-yl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

(*R*)-2-(4-(1-Cyclopropyl-1*H*-pyrazol-4-yl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

(*R*)-2-(4-(Benzofuran-3-yl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

(*R*)-2-(7-Fluoro-3-oxo-4-(pyrazolo[1,5-*a*]pyridin-3-yl)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-chloro-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile;

(*R*)-6-(2-Amino-3-methoxypropylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

(*R*)-6-(2-Amino-3-methoxypropylamino)-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile;

(*R*)-6-(2-Amino-3-methoxypropylamino)-7-fluoro-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

7-Acryloyl-6-((1*R*,2*S*)-2-aminocyclohexylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-iodo-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-(1*H*-pyrazol-4-yl)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-(*cis*-2-Amino-3,3-difluorocyclohexylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-(1-methyl-1*H*-pyrazol-5-yl)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-4-Aminotetrahydro-2*H*-pyran-3-ylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

tert-Butyl (1*S*,2*R*)-2-(3-oxo-7-phenyl-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-methyl-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-methyl-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

(*R*)-6-(2-Amino-3-methoxypropylamino)-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(pyrazolo[1,5-*a*]pyridin-3-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-4-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-4-(benzofuran-3-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

(*S*)-6-(3-Aminopyrrolidin-1-yl)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

(*S*)-6-(3-Aminopiperidin-1-yl)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(1-isopropyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

7-Fluoro-4,6-bis(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-bromo-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

(*R*)-6-(2-Amino-3-methoxypropylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(thiophen-3-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(4-methylthiophen-2-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(4-methylthiophen-2-yl)-1*H*-pyrrolo[3,4-c]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(thiophen-3-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

(*R*)-2-(7-Fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-*N*,4-dimethylpentanamide;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(5-methylthiophen-2-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

(*R*)-2-(7-Fluoro-4-(4-methylthiophen-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

(*R*)-2-(7-Fluoro-3-oxo-4-(thiophen-3-yl)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

(*R*)-2-(7-Fluoro-4-(5-methylthiophen-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(2-aminothiazol-5-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

(*R*)-2-(7-Fluoro-4-(furan-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

(*R*)-2-(7-Fluoro-4-(furan-3-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

(*R*)-2-(7-Fluoro-4-(furan-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

(*R*)-2-(4-(5-Cyanothiophen-2-yl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

(*R*)-2-(4-(4-Cyanothiophen-2-yl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

(*R*)-2-(7-Fluoro-3-oxo-4-(thiazol-5-yl)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

(*R*)-2-(7-Fluoro-4-(isothiazol-5-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-1,1-dimethyl-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-3-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(2-methylthiazol-5-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(5-methylthiophen-2-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-1-methyl-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

(*R*)-2-(7-Fluoro-3-oxo-4-(thiophen-2-yl)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(thiophen-2-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(thiazol-5-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(thiophen-2-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(4-(trifluoromethyl)-1*H*-imidazol-1-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(4-methyl-1*H*-imidazol-1-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(3-methylisothiazol-5-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(2-methylthiazol-5-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

(*R*)-2-(7-Fluoro-4-(2-methylthiazol-5-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-4-(5-chlorothiophen-2-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-4-(1-cyclopropyl-1*H*-pyrazol-4-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one; and

a stereoisomer of any of the aforementioned compounds and their pharmaceutically acceptable salts.

[0008] A further aspect of the invention provides a pharmaceutical composition which includes: a compound of Formula 1, as defined above, or a pharmaceutically acceptable salt thereof, or a compound selected from the group of compounds defined in the preceding paragraph, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable excipient.

[0009] An additional aspect of the invention provides a use as a medicament of a compound of Formula 1, as defined above, or a pharmaceutically acceptable salt thereof,

or a compound selected from the group of compounds defined above, or a pharmaceutically acceptable salt thereof.

[0010] Another aspect of the invention provides a use of a compound of Formula 1, as defined above, or pharmaceutically acceptable salt thereof, or a compound selected from the group of compounds defined above, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of a disease or condition for which a SYK inhibitor is indicated.

[0011] A further aspect of the invention provides a method of treating a disease or condition in a subject for which a SYK inhibitor is indicated, the method comprising administering to the subject an effective amount of a compound of Formula 1, as defined above, or a compound selected from the group of compounds defined above, or a pharmaceutically acceptable salt thereof.

[0012] An additional aspect of the invention provides a method of treating a disease or condition in a subject, the method comprising administering to the subject an effective amount of a compound of Formula 1, as defined above, or a pharmaceutically acceptable salt thereof, or a compound selected from the group of compounds defined above, or a pharmaceutically acceptable salt thereof, wherein the disease or condition is selected from allergic rhinitis, allergic asthma, atopic dermatitis, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, psoriasis, immune thrombocytopenic purpura, inflammatory bowel disease, chronic obstructive pulmonary disease, and thrombosis.

[0013] Another aspect of the invention provides a method of treating a disease or condition in a subject, the method comprising administering to the subject an effective amount of a compound of Formula 1, as defined above, or pharmaceutically acceptable salt thereof, or a compound selected from the group of compounds defined above, or a pharmaceutically acceptable salt thereof, wherein the disease or condition is selected from a hematological malignancy and an epithelial cancer.

[0014] A further aspect of the invention provides a combination of an effective amount of a compound of Formula 1, as defined above, or pharmaceutically acceptable salt thereof, or a compound selected from the group of compounds defined above, or a pharmaceutically acceptable salt thereof, and at least one additional pharmacologically active agent.

DETAILED DESCRIPTION OF THE INVENTION

[0015] Unless indicated otherwise, this disclosure uses definitions given below.

[0016] "Substituted," when used in connection with a chemical substituent or moiety (e.g., an alkyl group), means that one or more hydrogen atoms of the substituent or moiety have been replaced with one or more non-hydrogen atoms or groups, provided that valence requirements are met and that a chemically stable compound results from the substitution.

[0017] "About" or "approximately," when used in connection with a measurable numerical variable, refers to the indicated value of the variable and to all values of the variable that are within the experimental error of the indicated value or within ±10 percent of the indicated value, whichever is greater.

[0018] "Alkyl" refers to straight chain and branched saturated hydrocarbon groups, generally having a specified number of carbon atoms (e.g., C_{1-3} alkyl refers to an alkyl group having 1 to 3 carbon atoms, C_{1-6} alkyl refers to an alkyl group having 1 to 6 carbon atoms, and so on). Examples of alkyl groups include methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *s*-butyl, *i*-butyl, *t*-butyl, pent-1-yl, pent-2-yl, pent-3-yl, 3-methylbut-1-yl, 3-methylbut-2-yl, 2-methylbut-2-yl, 2,2,2-trimethyleth-1-yl, *n*-hexyl, and the like.

[0019] "Alk-1-yl" refers to an alkyl group, as defined above, which is attached to a parent group or substrate through a carbon atom located at the 1 position of the alkyl group.

[0020] "Alkenyl" refers to straight chain and branched hydrocarbon groups having one or more carbon-carbon double bonds, and generally having a specified number of carbon atoms. Examples of alkenyl groups include ethenyl, 1-propen-1-yl, 1-propen-2-yl, 2-propen-1-yl, 1-buten-1-yl, 1-buten-2-yl, 3-buten-1-yl, 3-buten-2-yl, 2-buten-1-yl, 2-buten-2-yl, 2-methyl-1-propen-1-yl, 2-methyl-2-propen-1-yl, 1,3-butadien-1-yl, 1,3-butadien-2-yl, and the like.

[0021] "Alkynyl" refers to straight chain or branched hydrocarbon groups having one or more triple carbon-carbon bonds, and generally having a specified number of carbon atoms. Examples of alkynyl groups include ethynyl, 1-propyn-1-yl, 2-propyn-1-yl, 1-butyn-1-yl, 3-butyn-1-yl, 3-butyn-2-yl, 2-butyn-1-yl, and the like.

[0022] "Halo," "halogen" and "halogeno" may be used interchangeably and refer to fluoro, chloro, bromo, and iodo.

[0023] "Haloalkyl," "haloalkenyl," and "haloalkynyl," refer, respectively, to alkyl, alkenyl, and alkynyl groups substituted with one or more halogen atoms, where alkyl, alkenyl, and alkynyl are defined above, and generally having a specified number of carbon atoms. Examples of haloalkyl groups include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, and the like.

[0024] "Cycloalkyl" refers to saturated monocyclic and bicyclic hydrocarbon groups, generally having a specified number of carbon atoms that comprise the ring or rings (e.g., C_{3-8} cycloalkyl refers to a cycloalkyl group having 3 to 8 carbon atoms as ring members). Bicyclic hydrocarbon groups may include isolated rings (two rings sharing no carbon atoms), spiro rings (two rings sharing one carbon atom), fused rings (two rings sharing two carbon atoms and the bond between the two common carbon atoms), and bridged rings (two rings sharing two carbon atoms, but not a common bond). The cycloalkyl group may be attached to a parent group or to a substrate at any ring atom unless such attachment would violate valence requirements. In addition, the cycloalkyl group may include one or more non-hydrogen substituents unless such substitution would violate valence requirements.

[0025] Examples of monocyclic cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like. Examples of fused bicyclic cycloalkyl groups include bicyclo[2.1.0]pentanyl (i.e., bicyclo[2.1.0]pentan-1-yl, bicyclo[2.1.0]pentan-2-yl, and bicyclo[2.1.0]pentan-5-yl), bicyclo[3.1.0]hexanyl, bicyclo[3.2.0]heptanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.3.0]octanyl, bicyclo[4.2.0]octanyl, bicyclo[4.3.0]nonanyl, bicyclo[4.4.0]decanyl, and the like. Examples of bridged cycloalkyl groups include bicyclo[2.1.1]hexanyl, bicyclo[2.2.1]heptanyl, bicyclo[3.1.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[3.2.1]octanyl, bicyclo[4.1.1]octanyl, bicyclo[3.3.1]nonanyl, bicyclo[4.2.1]nonanyl, bicyclo[3.3.2]decanyl, bicyclo[4.2.2]decanyl, bicyclo[4.3.1]decanyl, bicyclo[3.3.3]undecanyl, bicyclo[4.3.2]undecanyl, bicyclo[4.3.3]dodecanyl, and the like. Examples of spiro cycloalkyl groups include spiro[3.3]heptanyl, spiro[2.4]heptanyl, spiro[3.4]octanyl, spiro[2.5]octanyl, spiro[3.5]nonanyl, and the like. Examples of isolated bicyclic cycloalkyl groups include those derived from bi(cyclobutane), cyclobutanecyclopentane, bi(cyclopentane), cyclobutanecyclohexane, cyclopentanecyclohexane, bi(cyclohexane), etc.

[0026] "Cycloalk-1-yl" refers to a cycloalkyl group, as defined above, which is attached to a parent group or substrate through a carbon atom located at the 1 position of the cycloalkyl group.

[0027] "Cycloalkenyl" refers to partially unsaturated monocyclic and bicyclic hydrocarbon groups, generally having a specified number of carbon atoms that comprise the ring or rings. As with cycloalkyl groups, the bicyclic cycloalkenyl groups may include isolated, spiro, fused, or bridged rings. Similarly, the cycloalkenyl group may be attached to a parent group or to a substrate at any ring atom and may include one or more non-hydrogen substituents unless such attachment or substitution would violate valence requirements. Examples of cycloalkenyl groups include the partially unsaturated analogs of the cycloalkyl groups described above, such as cyclobutenyl (i.e., cyclobuten-1-yl and cyclobuten-3-yl), cyclopentenyl, cyclohexenyl, bicyclo[2.2.1]hept-2-enyl, and the like.

[0028] "Aryl" refers to fully unsaturated monocyclic aromatic hydrocarbons and to polycyclic hydrocarbons having at least one aromatic ring, both monocyclic and polycyclic aryl groups generally having a specified number of carbon atoms that comprise their ring members (e.g., C_{6-14} aryl refers to an aryl group having 6 to 14 carbon atoms as ring members). The aryl group may be attached to a parent group or to a substrate at any ring atom and may include one or more non-hydrogen substituents unless such attachment or substitution would violate valence requirements. Examples of aryl groups include phenyl, biphenyl, cyclobutabenzenyl, indenyl, naphthalenyl, benzocycloheptanyl, biphenylenyl, fluorenyl, groups derived from cycloheptatriene cation, and the like.

[0029] "Heterocycle" and "heterocyclyl" may be used interchangeably and refer to saturated or partially unsaturated monocyclic or bicyclic groups having ring atoms composed of carbon atoms and 1 to 4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. Both the monocyclic and bicyclic groups generally have a specified number of carbon atoms in their ring or rings (e.g., C_{2-5} heterocyclyl refers to a heterocyclyl group having 2 to 5 carbon atoms and 1 to 4 heteroatoms as ring members). As with bicyclic cycloalkyl groups, bicyclic heterocyclyl groups may include isolated rings, spiro rings, fused rings, and bridged rings. The heterocyclyl group may be attached to a parent group or to a substrate at any ring atom and may include one or more non-hydrogen substituents unless such attachment or substitution would violate valence requirements or result in a chemically unstable compound. Examples of monocyclic

heterocyclyl groups include oxiranyl, thiaranyl, aziridinyl (e.g., aziridin-1-yl and aziridin-2-yl), oxetanyl, thiatanyl, azetidinyl, tetrahydrofuranyl, tetrahydrothiopheneyl, pyrrolidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperidinyl, 1,4-dioxanyl, 1,4-oxathianyl, morpholinyl, 1,4-dithianyl, piperazinyl, 1,4-azathianyl, oxepanyl, thiepanyl, azepanyl, 1,4-dioxepanyl, 1,4-oxathiepanyl, 1,4-oxaazepanyl, 1,4-dithiepanyl, 1,4-thiazepanyl, 1,4-diazepanyl, 3,4-dihydro-2*H*-pyranyl, 5,6-dihydro-2*H*-pyranyl, 2*H*-pyranyl, 1,2,3,4-tetrahydropyridinyl, and 1,2,5,6-tetrahydropyridinyl.

[0030] "Heteroaryl" refers to unsaturated monocyclic aromatic groups and to polycyclic groups having at least one aromatic ring, each of the groups having ring atoms composed of carbon atoms and 1 to 4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. Both the monocyclic and polycyclic groups generally have a specified number of carbon atoms as ring members (e.g., C_{1-9} heteroaryl refers to a heteroaryl group having 1 to 9 carbon atoms and 1 to 4 heteroatoms as ring members) and may include any bicyclic group in which any of the above-listed monocyclic heterocycles are fused to a benzene ring. The heteroaryl group may be attached to a parent group or to a substrate at any ring atom and may include one or more non-hydrogen substituents unless such attachment or substitution would violate valence requirements or result in a chemically unstable compound. Examples of heteroaryl groups include monocyclic groups such as pyrrolyl (e.g., pyrrol-1-yl, pyrrol-2-yl, and pyrrol-3-yl), furanyl, thiopheneyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, 1,2,3-triazolyl, 1,3,4-triazolyl, 1-oxa-2,3-diazolyl, 1-oxa-2,4-diazolyl, 1-oxa-2,5-diazolyl, 1-oxa-3,4-diazolyl, 1-thia-2,3-diazolyl, 1-thia-2,4-diazolyl, 1-thia-2,5-diazolyl, 1-thia-3,4-diazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, and pyrazinyl.

[0031] Examples of heteroaryl groups also include bicyclic groups such as benzofuranyl, isobenzofuranyl, benzothiopheneyl, benzo[*c*]thiopheneyl, indolyl, 3*H*-indolyl, isoindolyl, 1*H*-isoindolyl, indolinyl, isoindolinyl, benzimidazolyl, indazolyl, benzotriazolyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, 1*H*-pyrrolo[2,3-*c*]pyridinyl, 1*H*-pyrrolo[3,2-*c*]pyridinyl, 1*H*-pyrrolo[3,2-*b*]pyridinyl, 3*H*-imidazo[4,5-*b*]pyridinyl, 3*H*-imidazo[4,5-*c*]pyridinyl, 1*H*-pyrazolo[4,3-*b*]pyridinyl, 1*H*-pyrazolo[4,3-*c*]pyridinyl, 1*H*-pyrazolo[3,4-*c*]pyridinyl, 1*H*-pyrazolo[3,4-*b*]pyridinyl, 7*H*-purinyl, indolizinyl, imidazo[1,2-*a*]pyridinyl, imidazo[1,5-*a*]pyridinyl, pyrazolo[1,5-*a*]pyridinyl, pyrrolo[1,2-*b*]pyridazinyl, imidazo[1,2-*c*]pyrimidinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl,

quinoxalinyl, phthalazinyl, 1,6-naphthyridinyl, 1,7-naphthyridinyl, 1,8-naphthyridinyl, 1,5-naphthyridinyl, 2,6-naphthyridinyl, 2,7-naphthyridinyl, pyrido[3,2-*d*]pyrimidinyl, pyrido[4,3-*d*]pyrimidinyl, pyrido[3,4-*d*]pyrimidinyl, pyrido[2,3-*d*]pyrimidinyl, pyrido[2,3-*b*]pyrazinyl, pyrido[3,4-*b*]pyrazinyl, pyrimido[5,4-*d*]pyrimidinyl, pyrazino[2,3-*b*]pyrazinyl, and pyrimido[4,5-*d*]pyrimidinyl.

[0032] "Oxo" refers to a double bonded oxygen (=O).

[0033] "Leaving group" refers to any group that leaves a molecule during a fragmentation process, including substitution reactions, elimination reactions, and addition-elimination reactions. Leaving groups may be nucleofugal, in which the group leaves with a pair of electrons that formerly served as the bond between the leaving group and the molecule, or may be electrofugal, in which the group leaves without the pair of electrons. The ability of a nucleofugal leaving group to leave depends on its base strength, with the strongest bases being the poorest leaving groups. Common nucleofugal leaving groups include nitrogen (e.g., from diazonium salts); sulfonates, including alkylsulfonates (e.g., mesylate), fluoroalkylsulfonates (e.g., triflate, hexaflate, nonaflate, and tresylate), and arylsulfonates (e.g., tosylate, brosylate, closylate, and nosylate). Others include carbonates, halide ions, carboxylate anions, phenolate ions, and alkoxides. Some stronger bases, such as NH_2^- and OH^- can be made better leaving groups by treatment with an acid. Common electrofugal leaving groups include the proton, CO_2, and metals.

[0034] "Opposite enantiomer" refers to a molecule that is a non-superimposable mirror image of a reference molecule, which may be obtained by inverting all of the stereogenic centers of the reference molecule. For example, if the reference molecule has *S* absolute stereochemical configuration, then the opposite enantiomer has *R* absolute stereochemical configuration. Likewise, if the reference molecule has *S*,*S* absolute stereochemical configuration, then the opposite enantiomer has *R*,*R* stereochemical configuration, and so on.

[0035] "Stereoisomer" and "stereoisomers" of a compound with given stereochemical configuration refer to the opposite enantiomer of the compound and to any diastereoisomers, including geometrical isomers (*Z*/*E*) of the compound. For example, if a compound has *S*,*R*,*Z* stereochemical configuration, its stereoisomers would include its opposite enantiomer having *R*,*S*,*Z* configuration, and its diastereomers having *S*,*S*,*Z*

configuration, *R*,*R*,*Z* configuration, *S*,*R*,*E* configuration, *R*,*S*,*E* configuration, *S*,*S*,*E* configuration, and *R*,*R*,*E* configuration. If the stereochemical configuration of a compound is not specified, then "stereoisomer" refers to any one of the possible stereochemical configurations of the compound.

[0036] "Substantially pure stereoisomer" and variants thereof refer to a sample containing a compound having a specific stereochemical configuration and which comprises at least about 95% of the sample.

[0037] "Pure stereoisomer" and variants thereof refer to a sample containing a compound having a specific stereochemical configuration and which comprises at least about 99.5% of the sample.

[0038] "Subject" refers to a mammal, including a human.

[0039] "Pharmaceutically acceptable" substances refers to those substances which are within the scope of sound medical judgment suitable for use in contact with the tissues of subjects without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit-to-risk ratio, and effective for their intended use.

[0040] "Treating" refers to reversing, alleviating, inhibiting the progress of, or preventing a disorder, disease or condition to which such term applies, or to reversing, alleviating, inhibiting the progress of, or preventing one or more symptoms of such disorder, disease or condition.

[0041] "Treatment" refers to the act of "treating," as defined immediately above.

[0042] "Drug," "drug substance," "active pharmaceutical ingredient," and the like, refer to a compound (e.g., compounds of Formula 1 and compounds specifically named above) that may be used for treating a subject in need of treatment.

[0043] "Therapeutically effective amount" of a drug refers to the quantity of the drug that may be used for treating a subject and may depend on the weight and age of the subject and the route of administration, among other things.

[0044] "Excipient" refers to any substance that may influence the bioavailability of a drug, but is otherwise pharmacologically inactive.

[0045] "Pharmaceutical composition" refers to the combination of one or more drug substances and one or more excipients.

[0046] "Drug product," "pharmaceutical dosage form," "dosage form," "final dosage form" and the like, refer to a pharmaceutical composition that is administered to a subject

in need of treatment and generally may be in the form of tablets, capsules, sachets containing powder or granules, liquid solutions or suspensions, patches, films, and the like.

[0047] The following abbreviations are used throughout the specification: Ac (acetyl); ACN (acetonitrile); AIBN (azo-bis-isobutyronitrile); API (active pharmaceutical ingredient); aq (aqueous); Boc (*tert*-butoxycarbonyl); BSA (bovine serum albumin); Cbz (carbobenzyloxy); dba (dibenzylideneacetone); DCC (1,3-dicyclohexylcarbodiimide); DCM (dichloromethane); DIPEA (*N*,*N*-diisopropylethyl-amine, Hünig's Base); DMA (*N*,*N*-dimethylacetamide); DMAP (4-dimethylaminopyridine); DMARD (disease modifying antirheumatic drug); DME (1,2-dimethoxyethane); DMF (*N*,*N*-dimethylformamide); DMSO (dimethylsulfoxide); dppf (1,1'-bis(diphenylphosphino)ferrocene); DTT (dithiothreitol); EDA ethoxylated dodecyl alcohol, Brj®35); EDCI (*N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide); EDTA (ethylenediaminetetraacetic acid); ee (enantiomeric excess); eq (equivalents); Et (ethyl); Et_3N (triethyl-amine); EtOAc (ethyl acetate); EtOH (ethanol); FAM (5-carboxyfluorescein); HATU (2-(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate(V)); HEPES (4-(2-hydroxyethyl)piperazine-1-ethanesulfonic acid); HOAc (acetic acid); HOBt (1*H*-benzo[*d*][1,2,3]triazol-1-ol); IC_{50} (concentration at 50% inhibition); IPA (isopropanol); IPAc (isopropyl acetate); IPE (isopropylether); LDA (lithium diisopropylamide); LiHMDS (lithium bis(trimethylsilyl)amide); mCPBA (*m*-chloroperoxybenzoic acid); Me (methyl); MeOH (methanol); MTBE (methyl *tert*-butyl ether); MOI (multiplicity of infection); mp (melting point); NaO*t*-Bu (sodium tertiary butoxide); NBS (*N*-bromosuccinimide); NCS (*N*-chlorosuccinimide); NIS (*N*-iodosuccinimide); PE (petroleum ether); Ph (phenyl); pIC_{50} ($-\log_{10}(IC_{50})$, where IC_{50} is given in molar (M) units); Pr (propyl); *i*-Pr (isopropyl); PTFE (polytetrafluoroethylene); RT (room temperature, approximately 20°C to 25°C); SYK (spleen tyrosine kinase); TCEP (*tris*(2-carboxyethyl)phosphine); TFA (trifluoroacetic acid); TFAA (2,2,2-trifluoroacetic anhydride); THF (tetrahydrofuran); and Tris buffer (2-amino-2-hydroxymethyl-propane-1,3-diol buffer).

[0048] This disclosure concerns compounds of Formula 1, which includes compounds specifically named above, and their pharmaceutically acceptable complexes, salts, solvates and hydrates. This disclosure also concerns materials and methods for preparing

compounds of Formula 1, pharmaceutical compositions containing them, and their use for treating disorders, diseases, and conditions involving the immune system and inflammation, including rheumatoid arthritis, hematological malignancies, epithelial cancers (i.e., carcinomas), and other disorders, diseases, and conditions for which inhibition of SYK is indicated.

[0049] Compounds of Formula 1 include those in which L^1 is a bond and L^2 is –NH-; L^1 is -NH- and L^2 is a bond; L^1 and L^2 are both bonds; or L^1 and L^2 are both -NH-.

[0050] Compounds of Formula 1 also include those in which R^1 is hydrogen and R^2 is C_{1-3} alkyl, in particular, methyl or ethyl; R^1 and R^2 are both C_{1-3} alkyl groups, in particular methyl; R^1 and R^2, together with the carbon atom to which they are attached, form a cyclopropyl group; or R^1 and R^2 are both hydrogen atoms.

[0051] Compounds of Formula 1 include those in which L^1 is -NH- and L^2 is -NH- or a bond; G is N; R^1 and R^2 are both hydrogen; and R^3 is a 2-amino-C_{3-8} cycloalk-1-yl, or more particularly 2-amino-cyclohex-1-yl, optionally substituted with from one to four substituents independently selected from halo, oxo, -NO_2, -CN, R^6, and R^7.

[0052] Compounds of Formula 1 also include those in which L^1 is -NH- and L^2 is -NH- or a bond; G is N; R^1 and R^2 are both hydrogen; and R^3 is a 2-amino-C_{2-6} alk-1-yl, or more particularly 2-aminoethan-1-yl or 2-amino-2-oxoethan-1-yl, optionally substituted with from one to five, from one to four or from one to two substituents, respectively, independently selected from halo, oxo, -NO_2, -CN, R^6, and R^7.

[0053] Compounds of Formula 1 further include those in which L^1 is -NH- and L^2 is -NH- or a bond; G is N; R^1 and R^2 are both hydrogen; and R^3 is a C_{2-5} heterocyclyl, or more particularly an amino-C_{2-5} heterocyclyl such as 3-aminotetrahydro-2*H*-pyran-4-yl, optionally substituted with from one to five or from one to four substituents, respectively, independently selected from halo, oxo, -NO_2, -CN, R^6, and R^7, wherein the heterocyclyl moiety has 5 or 6 ring atoms.

[0054] Compounds of Formula 1 include those in which L^1 is -NH- and L^2 is -NH- or a bond; G is N; R^1 and R^2 are both hydrogen; and R^4 is a C_{6-14} aryl, or more particularly phenyl, optionally substituted with from one to five substituents independently selected from halo, oxo, -CN, R^6, and R^7.

[0055] Compounds of Formula 1 also include those in which L^1 is -NH- and L^2 is -NH- or a bond; G is N; R^1 and R^2 are both hydrogen; and R^4 is a C_{1-9} heteroaryl, or more

particularly a monocyclic C_{2-4} heteroaryl, optionally substituted with from one to five or from one to four substituents, respectively, independently selected from halo, oxo, -CN, R^6, and R^7.

[0056] Compounds of Formula 1 also include those in which L^1 is -NH- and L^2 is -NH- or a bond; G is N; R^1 and R^2 are both hydrogen; and R^4 is a monocyclic C_{2-4} heteroaryl selected from pyrrolyl, furanyl, thiopheneyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isothiazoly, and thiazolyl, or more particularly from thiopheneyl, pyrazolyl, isothiazoly, and thiazolyl, each optionally substituted with from one to three substituents independently selected from halo, -CN, R^6, and R^7.

[0057] Compounds of Formula 1 further include those in which L^1 is -NH- and L^2 is -NH- or a bond; G is N; R^1 and R^2 are both hydrogen; and R^4 is a pyrazole moiety (e.g., pyrazol-4-yl) optionally substituted with from one to three substituents independently selected from halo, -CN, R^6, and R^7.

[0058] Compounds of Formula 1 include those in which L^1 is -NH- and L^2 is -NH- or a bond; G is $C(R^5)$; R^1 and R^2 are both hydrogen; and R^5 is a C_{1-5} heteroaryl optionally substituted with from one to four substituents independently selected from halo, $-NO_2$, -CN, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, and R^{10}.

[0059] Compounds of Formula 1 also include those in which L^1 is -NH- and L^2 is -NH- or a bond; G is $C(R^5)$; R^1 and R^2 are both hydrogen; and R^5 is hydrogen or halo, or more particularly, chloro or fluoro.

[0060] Compounds of Formula 1 include those in which L^1 is -NH- and L^2 is -NH- or a bond; G is $C(R^5)$; R^1 and R^2 are both hydrogen; and R^3 is a 2-amino-C_{3-8} cycloalk-1-yl, or more particularly 2-amino-cyclohex-1-yl, optionally substituted with from one to four substituents independently selected from halo, oxo, $-NO_2$, -CN, R^6, and R^7.

[0061] Compounds of Formula 1 also include those in which L^1 is -NH- and L^2 is -NH- or a bond; G is $C(R^5)$; R^1 and R^2 are both hydrogen; and R^3 is a 2-amino-C_{2-6} alk-1-yl, or more particularly 2-aminoethan-1-yl or 2-amino-2-oxoethan-1-yl, optionally substituted with from one to five, from one to four or from one to two substituents, respectively, independently selected from halo, oxo, $-NO_2$, -CN, R^6, and R^7.

[0062] Compounds of Formula 1 further include those in which L^1 is -NH- and L^2 is -NH- or a bond; G is $C(R^5)$; R^1 and R^2 are both hydrogen; and R^3 is a C_{2-5} heterocyclyl, or more particularly an amino-C_{2-5} heterocyclyl such as 3-aminotetrahydro-2*H*-pyran-4-yl,

optionally substituted with from one to five or from one to four substituents, respectively, independently selected from halo, oxo, $-NO_2$, -CN, R^6, and R^7, wherein the heterocyclyl moiety has 5 or 6 ring atoms.

[0063] Compounds of Formula 1 include those in which L^1 is -NH- and L^2 is -NH- or a bond; G is $C(R^5)$; R^1 and R^2 are both hydrogen; and R^4 is a C_{6-14} aryl, or more particularly phenyl, optionally substituted with from one to five substituents independently selected from halo, oxo, -CN, R^6, and R^7.

[0064] Compounds of Formula 1 also include those in which L^1 is -NH- and L^2 is -NH- or a bond; G is $C(R^5)$; R^1 and R^2 are both hydrogen, and R^4 is a C_{1-9} heteroaryl, or more particularly a monocyclic C_{2-4} heteroaryl, optionally substituted with from one to five or from one to four substituents, respectively, independently selected from halo, oxo, -CN, R^6, and R^7.

[0065] Compounds of Formula 1 also include those in which L^1 is -NH- and L^2 is -NH- or a bond; G is $C(R^5)$; R^1 and R^2 are both hydrogen; and R^4 is a monocyclic C_{2-4} heteroaryl selected from pyrrolyl, furanyl, thiopheneyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isothiazoly, and thiazolyl, or more particularly from thiopheneyl, pyrazolyl, isothiazoly, and thiazolyl, each optionally substituted with from one to three substituents independently selected from halo, -CN, R^6, and R^7.

[0066] Compounds of Formula 1 further include those in which L^1 is -NH- and L^2 is -NH- or a bond; G is $C(R^5)$; R^1 and R^2 are both hydrogen; and R^4 is pyrazole moiety (e.g., pyrazol-4-yl) optionally substituted with from one to three substituents independently selected from halo, -CN, R^6, and R^7.

[0067] Compounds of Formula 1 include those in which L^1 is -NH- and L^2 is -NH- or a bond; G is N; R^1 and R^2 are both hydrogen; R^3 is a 2-amino-C_{3-8} cycloalk-1-yl, or more particularly 2-amino-cyclohex-1-yl, optionally substituted with from one to four substituents independently selected from halo, oxo, $-NO_2$, -CN, R^6, and R^7; and R^4 is a C_{6-14} aryl, or more particularly phenyl, optionally substituted with from one to five substituents independently selected from halo, oxo, -CN, R^6, and R^7.

[0068] Compounds of Formula 1 also include those in which L^1 is -NH- and L^2 is -NH- or a bond; G is N; R^1 and R^2 are both hydrogen; R^3 is a 2-amino-C_{3-8} cycloalk-1-yl, or more particularly 2-amino-cyclohex-1-yl, optionally substituted with from one to four substituents independently selected from halo, oxo, $-NO_2$, -CN, R^6, and R^7; and R^4 is a

C_{1-9} heteroaryl, or more particularly a monocyclic C_{2-4} heteroaryl, optionally substituted with from one to five or from one to four substituents, respectively, independently selected from halo, oxo, -CN, R^6, and R^7.

[0069] Compounds of Formula 1 include those in which L^1 is -NH- and L^2 is -NH- or a bond; G is N; R^1 and R^2 are both hydrogen; R^3 is a 2-amino-C_{3-8} cycloalk-1-yl, or more particularly 2-amino-cyclohex-1-yl, optionally substituted with from one to four substituents independently selected from halo, oxo, -NO_2, -CN, R^6, and R^7; and R^4 is a monocyclic C_{2-4} heteroaryl selected from pyrrolyl, furanyl, thiopheneyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isothiazoly, and thiazolyl, or more particularly from thiopheneyl, pyrazolyl, isothiazoly, and thiazolyl, each optionally substituted with from one to three substituents independently selected from halo, -CN, R^6, and R^7.

[0070] Compounds of Formula 1 further include those in which L^1 is -NH- and L^2 is -NH- or a bond; G is N; R^1 and R^2 are both hydrogen; R^3 is a 2-amino-C_{3-8} cycloalk-1-yl, or more particularly 2-amino-cyclohex-1-yl, optionally substituted with from one to four substituents independently selected from halo, oxo, -NO_2, -CN, R^6, and R^7; and R^4 is a pyrazole moiety (e.g., pyrazol-4-yl) optionally substituted with from one to three substituents independently selected from halo, -CN, R^6, and R^7.

[0071] Compounds of Formula 1 include those in which L^1 is -NH- and L^2 is -NH- or a bond; G is $C(R^5)$; R^1 and R^2 are both hydrogen; R^3 is a 2-amino-C_{3-8} cycloalk-1-yl, or more particularly 2-amino-cyclohex-1-yl, optionally substituted with from one to four substituents independently selected from halo, oxo, -NO_2, -CN, R^6, and R^7; and R^4 is a C_{6-14} aryl, or more particularly phenyl, optionally substituted with from one to five substituents independently selected from halo, oxo, -CN, R^6, and R^7.

[0072] Compounds of Formula 1 also include those in which L^1 is -NH- and L^2 is -NH- or a bond; G is $C(R^5)$; R^1 and R^2 are both hydrogen; R^3 is a 2-amino-C_{3-8} cycloalk-1-yl, or more particularly 2-amino-cyclohex-1-yl, optionally substituted with from one to four substituents independently selected from halo, oxo, -NO_2, -CN, R^6, and R^7; and R^4 is a C_{1-9} heteroaryl, or more particularly a monocyclic C_{2-4} heteroaryl, optionally substituted with from one to five or from one to four substituents, respectively, independently selected from halo, oxo, -CN, R^6, and R^7.

[0073] Compounds of Formula 1 include those in which L^1 is -NH- and L^2 is -NH- or a bond; G is $C(R^5)$; R^1 and R^2 are both hydrogen; R^3 is a 2-amino-C_{3-8} cycloalk-1-yl, or

more particularly 2-amino-cyclohex-1-yl, optionally substituted with from one to four substituents independently selected from halo, oxo, -NO_2, -CN, R^6, and R^7; and R^4 is a monocyclic C_{2-4} heteroaryl selected from pyrrolyl, furanyl, thiopheneyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isothiazoly, and thiazolyl, or more particularly from thiopheneyl, pyrazolyl, isothiazoly, and thiazolyl, each optionally substituted with from one to three substituents independently selected from halo, -CN, R^6, and R^7.

[0074] Compounds of Formula 1 further include those in which L^1 is -NH- and L^2 is -NH- or a bond; G is $C(R^5)$; R^1 and R^2 are both hydrogen; R^3 is a 2-amino-C_{3-8} cycloalk-1-yl, or more particularly 2-amino-cyclohex-1-yl, optionally substituted with from one to four substituents independently selected from halo, oxo, -NO_2, -CN, R^6, and R^7; and R^4 is a pyrazole moiety (e.g., pyrazol-4-yl) optionally substituted with from one to three substituents independently selected from halo, -CN, R^6, and R^7.

[0075] Compounds of Formula 1 include any of the aforementioned embodiments in which L^1 is -NH- and L^2 is a bond.

[0076] Thus, compounds of Formula 1 include those in which L^1 is -NH-; L^2 is a bond; G is $C(R^5)$; R^1 and R^2 are both hydrogen; R^5 is hydrogen or halo, or more particularly, chloro or fluoro; and R^3 is a 2-amino-C_{3-8} cycloalk-1-yl, or more particularly 2-amino-cyclohex-1-yl, optionally substituted with from one to four substituents independently selected from halo, oxo, -NO_2, -CN, R^6, and R^7.

[0077] Compounds of Formula 1 include those in which L^1 is -NH-; L^2 is a bond; G is $C(R^5)$; R^1 and R^2 are both hydrogen; R^5 is hydrogen or halo, or more particularly, chloro or fluoro; and R^3 is a 2-amino-C_{2-6} alk-1-yl, or more particularly 2-aminoethan-1-yl or 2-amino-2-oxoethan-1-yl, optionally substituted with from one to five, from one to four or from two to two substituents, respectively, independently selected from halo, oxo, -NO_2, -CN, R^6, and R^7.

[0078] Compounds of Formula 1 include those in which L^1 is -NH-; L^2 is a bond; G is $C(R^5)$; R^1 and R^2 are both hydrogen; R^5 is hydrogen or halo, or more particularly, chloro or fluoro; and R^3 is a C_{2-5} heterocyclyl, or more particularly an amino-C_{2-5} heterocyclyl such as 3-aminotetrahydro-2*H*-pyran-4-yl, optionally substituted with from one to five or from one to four substituents, respectively, independently selected from halo, oxo, -NO_2, -CN, R^6, and R^7, wherein the heterocyclyl moiety has 5 or 6 ring atoms.

[0079] Compounds of Formula 1 include those in which L^1 is -NH-; L^2 is a bond; G is $C(R^5)$; R^1 and R^2 are both hydrogen; R^5 is hydrogen or halo, or more particularly, chloro or fluoro; and R^4 is a C_{6-14} aryl, or more particularly phenyl, optionally substituted with from one to five substituents independently selected from halo, oxo, -CN, R^6, and R^7.

[0080] Compounds of Formula 1 also include those in which L^1 is -NH-; L^2 is a bond; G is $C(R^5)$; R^1 and R^2 are both hydrogen; R^5 is hydrogen or halo, or more particularly, chloro or fluoro; and R^4 is a C_{1-9} heteroaryl, or more particularly a monocyclic C_{2-4} heteroaryl, optionally substituted with from one to five or from one to four substituents, respectively, independently selected from halo, oxo, -CN, R^6, and R^7.

[0081] Compounds of Formula 1 include those in which L^1 is -NH-; L^2 is a bond; G is $C(R^5)$; R^1 and R^2 are both hydrogen; R^5 is hydrogen or halo, or more particularly, chloro or fluoro; and R^4 is a monocyclic C_{2-4} heteroaryl selected from pyrrolyl, furanyl, thiopheneyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isothiazoly, and thiazolyl, or more particularly from thiopheneyl, pyrazolyl, isothiazoly, and thiazolyl, each optionally substituted with from one to three substituents independently selected from halo, -CN, R^6, and R^7.

[0082] Compounds of Formula 1 include those in which L^1 is -NH-; L^2 is a bond; G is $C(R^5)$; R^1 and R^2 are both hydrogen; R^5 is hydrogen or halo, or more particularly, chloro or fluoro; and R^4 is a pyrazole moiety (e.g., pyrazol-4-yl) optionally substituted with from one to three substituents independently selected from halo, -CN, R^6, and R^7.

[0083] Compounds of Formula 1 include those in which L^1 is -NH-; L^2 is a bond; G is $C(R^5)$; R^1 and R^2 are both hydrogen; R^5 is hydrogen or halo, or more particularly, chloro or fluoro; R^3 is a 2-amino-C_{3-8} cycloalk-1-yl, or more particularly 2-amino-cyclohex-1-yl, optionally substituted with from one to four substituents independently selected from halo, oxo, -NO_2, -CN, R^6, and R^7; and R^4 is a C_{6-14} aryl, or more particularly phenyl, optionally substituted with from one to five substituents independently selected from halo, oxo, -CN, R^6, and R^7.

[0084] Compounds of Formula 1 include those in which L^1 is -NH-; L^2 is a bond; G is $C(R^5)$; R^1 and R^2 are both hydrogen; R^5 is hydrogen or halo, or more particularly, chloro or fluoro; R^3 is a 2-amino-C_{3-8} cycloalk-1-yl, or more particularly 2-amino-cyclohex-1-yl, optionally substituted with from one to four substituents independently selected from halo, oxo, -NO_2, -CN, R^6, and R^7; and R^4 is a C_{1-9} heteroaryl, or more particularly a monocyclic

C_{2-4} heteroaryl, optionally substituted with from one to five or from one to four substituents, respectively, independently selected from halo, oxo, -CN, R^6, and R^7.

[0085] Compounds of Formula 1 include those in which L^1 is -NH-; L^2 is a bond; G is $C(R^5)$; R^1 and R^2 are both hydrogen; R^5 is hydrogen or halo, or more particularly, chloro or fluoro; R^3 is a 2-amino-C_{3-8} cycloalk-1-yl, or more particularly 2-amino-cyclohex-1-yl, optionally substituted with from one to four substituents independently selected from halo, oxo, -NO_2, -CN, R^6, and R^7; and R^4 is a monocyclic C_{2-4} heteroaryl selected from pyrrolyl, furanyl, thiopheneyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isothiazoly, and thiazolyl, or more particularly from thiopheneyl, pyrazolyl, isothiazoly, and thiazolyl, each optionally substituted with from one to three substituents independently selected from halo, -CN, R^6, and R^7.

[0086] Compounds of Formula 1 include those in which L^1 is -NH-; L^2 is a bond; G is $C(R^5)$; R^1 and R^2 are both hydrogen; R^5 is hydrogen or halo, or more particularly, chloro or fluoro; R^3 is a 2-amino-C_{3-8} cycloalk-1-yl, or more particularly 2-amino-cyclohex-1-yl, optionally substituted with from one to four substituents independently selected from halo, oxo, -NO_2, -CN, R^6, and R^7; and R^4 is a pyrazole moiety (e.g., pyrazol-4-yl) optionally substituted with from one to three substituents independently selected from halo, -CN, R^6, and R^7.

[0087] Compounds of Formula 1 also include any of the above embodiments in which one or more of the R^3, R^4, R^5, R^7, R^8, and R^9 substituents have no optional substituents.

[0088] All references to compounds, including compounds of Formula 1 and compounds named in the specification, generally include all complexes, salts, solvates, hydrates, and liquid crystals of the compounds. Likewise, all references to compounds include all complexes, solvates, hydrates, and liquid crystals of the salts of the compounds.

[0089] Compounds of Formula 1, which include compounds specifically named above, may form pharmaceutically acceptable complexes, salts, solvates and hydrates. These salts include acid addition salts (including di-acids) and base salts. Pharmaceutically acceptable acid addition salts include nontoxic salts derived from inorganic acids such as hydrochloric acid, nitric acid, phosphoric acid, sulfuric acid, hydrobromic acid, hydroiodic acid, hydrofluoric acid, and phosphorous acids, as well nontoxic salts derived from organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic

sulfonic acids, etc. Such salts include acetate, adipate, aspartate, benzoate, besylate, bicarbonate, carbonate, bisulfate, sulfate, borate, camsylate, citrate, cyclamate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulfate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate, hydrogen phosphate, dihydrogen phosphate, pyroglutamate, saccharate, stearate, succinate, tannate, tartrate, tosylate, trifluoroacetate and xinofoate salts.

[0090] Pharmaceutically acceptable base salts include nontoxic salts derived from bases, including metal cations, such as an alkali or alkaline earth metal cation, as well as amines. Examples of suitable metal cations include sodium (Na^+), potassium (K^+), magnesium (Mg^{2+}), calcium (Ca^{2+}), zinc (Zn^{2+}), and aluminum (Al^{3+}). Examples of suitable amines include arginine, *N*,*N*'-dibenzylethylenediamine, chloroprocaine, choline, diethylamine, diethanolamine, dicyclohexylamine, ethylenediamine, glycine, lysine, *N*-methylglucamine, olamine, 2-amino-2-hydroxymethyl-propane-1,3-diol, and procaine. For a discussion of useful acid addition and base salts, see S. M. Berge et al., *J. Pharm. Sci.* (1977) 66:1-19; see also Stahl and Wermuth, *Handbook of Pharmaceutical Salts: Properties, Selection, and Use* (2002).

[0091] Pharmaceutically acceptable salts may be prepared using various methods. For example, one may react a compound of Formula 1 with an appropriate acid or base to give the desired salt. One may also react a precursor of the compound of Formula 1 with an acid or base to remove an acid- or base-labile protecting group or to open a lactone or lactam group of the precursor. Additionally, one may convert a salt of the compound of Formula 1 to another salt through treatment with an appropriate acid or base or through contact with an ion exchange resin. Following reaction, one may then isolate the salt by filtration if it precipitates from solution, or by evaporation to recover the salt. The degree of ionization of the salt may vary from completely ionized to almost non-ionized.

[0092] Compounds of Formula 1 may exist in a continuum of solid states ranging from fully amorphous to fully crystalline. The term "amorphous" refers to a state in which the material lacks long range order at the molecular level and, depending upon temperature, may exhibit the physical properties of a solid or a liquid. Typically such materials do not give distinctive X-ray diffraction patterns and, while exhibiting the properties of a solid,

are more formally described as a liquid. Upon heating, a change from solid to liquid properties occurs which is characterized by a change of state, typically second order ("glass transition"). The term "crystalline" refers to a solid phase in which the material has a regular ordered internal structure at the molecular level and gives a distinctive X-ray diffraction pattern with defined peaks. Such materials when heated sufficiently will also exhibit the properties of a liquid, but the change from solid to liquid is characterized by a phase change, typically first order ("melting point").

[0093] Compounds of Formula 1 may also exist in unsolvated and solvated forms. The term "solvate" describes a molecular complex comprising the compound and one or more pharmaceutically acceptable solvent molecules (e.g., EtOH). The term "hydrate" is a solvate in which the solvent is water. Pharmaceutically acceptable solvates include those in which the solvent may be isotopically substituted (e.g., D_2O, acetone-d_6, DMSO-d_6).

[0094] A currently accepted classification system for solvates and hydrates of organic compounds is one that distinguishes between isolated site, channel, and metal-ion coordinated solvates and hydrates. See, e.g., K. R. Morris (H. G. Brittain ed.) *Polymorphism in Pharmaceutical Solids* (1995). Isolated site solvates and hydrates are ones in which the solvent (e.g., water) molecules are isolated from direct contact with each other by intervening molecules of the organic compound. In channel solvates, the solvent molecules lie in lattice channels where they are next to other solvent molecules. In metal-ion coordinated solvates, the solvent molecules are bonded to the metal ion.

[0095] When the solvent or water is tightly bound, the complex will have a well-defined stoichiometry independent of humidity. When, however, the solvent or water is weakly bound, as in channel solvates and in hygroscopic compounds, the water or solvent content will depend on humidity and drying conditions. In such cases, non-stoichiometry will typically be observed.

[0096] Compounds of Formula 1 may also exist as multi-component complexes (other than salts and solvates) in which the compound (drug) and at least one other component are present in stoichiometric or non-stoichiometric amounts. Complexes of this type include clathrates (drug-host inclusion complexes) and co-crystals. The latter are typically defined as crystalline complexes of neutral molecular constituents which are bound together through non-covalent interactions, but could also be a complex of a neutral molecule with a salt. Co-crystals may be prepared by melt crystallization, by

recrystallization from solvents, or by physically grinding the components together. See, e.g., O. Almarsson and M. J. Zaworotko, *Chem. Commun.* (2004) 17:1889-1896. For a general review of multi-component complexes, see J. K. Haleblian, *J. Pharm. Sci.* (1975) 64(8):1269-88.

[0097] When subjected to suitable conditions, compounds of Formula 1 may exist in a mesomorphic state (mesophase or liquid crystal). The mesomorphic state lies between the true crystalline state and the true liquid state (either melt or solution). Mesomorphism arising as the result of a change in temperature is described as "thermotropic" and mesomorphism resulting from the addition of a second component, such as water or another solvent, is described as "lyotropic." Compounds that have the potential to form lyotropic mesophases are described as "amphiphilic" and include molecules which possess a polar ionic moiety (e.g., $-COO^-Na^+$, $-COO^-K^+$, $-SO_3^-Na^+$) or polar non-ionic moiety (such as $-N^-N^+(CH_3)_3$). See, e.g., N. H. Hartshorne and A. Stuart, *Crystals and the Polarizing Microscope* (4th ed, 1970).

[0098] All references to compounds, including compounds of Formula 1 and compounds named in the specification, generally include all polymorphs and crystal habits, prodrugs, metabolites, stereoisomers, and tautomers thereof, as well as all isotopically-labeled compounds thereof.

[0099] "Prodrugs" refer to compounds having little or no pharmacological activity that can, when metabolized *in vivo*, undergo conversion to compounds having desired pharmacological activity. Prodrugs may be prepared by replacing appropriate functionalities present in pharmacologically active compounds with "pro-moieties" as described, for example, in H. Bundgaar, *Design of Prodrugs* (1985). Examples of prodrugs include ester, ether or amide derivatives of compounds of Formula 1 having carboxylic acid, hydroxy, or amino functional groups, respectively. For further discussions of prodrugs, see e.g., T. Higuchi and V. Stella "Pro-drugs as Novel Delivery Systems," *ACS Symposium Series* 14 (1975) and E. B. Roche ed., *Bioreversible Carriers in Drug Design* (1987).

[0100] "Metabolites" refer to compounds formed *in vivo* upon administration of pharmacologically active compounds. Examples include hydroxymethyl, hydroxy, secondary amino, primary amino, phenol, and carboxylic acid derivatives of compounds

of Formula 1 having methyl, alkoxy, tertiary amino, secondary amino, phenyl, and amide groups, respectively.

[0101] Certain compounds described herein may have stereoisomers. These compounds may exist as single enantiomers (enantiopure compounds) or mixtures of enantiomers (enriched and racemic samples), which depending on the relative excess of one enantiomer over another in a sample, may exhibit optical activity. Such stereoisomers, which are non-superimposable mirror images, possess a stereogenic axis or one or more stereogenic centers (i.e., chirality). Other compounds may be stereoisomers that are not mirror images. Such stereoisomers, which are known as diastereoisomers, may be chiral or achiral (contain no stereogenic centers). They include molecules containing an alkenyl or cyclic group, so that *cis*/*trans* (or *Z*/*E*) stereoisomers are possible, or molecules containing two or more stereogenic centers, in which inversion of a single stereogenic center generates a corresponding diastereoisomer. Unless stated or otherwise clear (e.g., through use of stereobonds, stereocenter descriptors, etc.) the scope of the invention and disclosure generally includes the reference compound and its stereoisomers, whether they are each pure (e.g., enantiopure) or mixtures (e.g., enantiomerically enriched or racemic).

[0102] Geometrical (*cis*/*trans*) isomers may be separated by conventional techniques such as chromatography and fractional crystallization.

[0103] Individual enantiomers of compounds may be prepared via chiral synthesis from a suitable optically pure precursor or isolated via resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral HPLC. Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable enantiomerically pure compound (e.g., acid or base) to yield a pair of diastereoisomers, each composed of a single enantiomer, which are separated via, say, fractional recrystallization or chromatography. The desired enantiomer is subsequently regenerated from the appropriate diastereoisomer. Often, the desired enantiomer may be further enriched by recrystallization in a suitable solvent (e.g., ACN) when it is it available in sufficient quantity (e.g., typically not much less than about 85% ee, and in some cases, not much less than about 90% ee). For a further discussion of techniques for separating stereoisomers, see E. L. Eliel and S. H. Wilen, *Stereochemistry of Organic Compounds* (1994).

[0104] "Tautomers" refer to structural isomers that are interconvertible via a low energy barrier. Tautomeric isomerism (tautomerism) may take the form of proton

tautomerism in which the compound contains, for example, an imino, keto, or oxime group, or valence tautomerism in which the compound contains an aromatic moiety.

[0105] Compounds described herein also include all pharmaceutically acceptable isotopic variations, in which at least one atom is replaced by an atom having the same atomic number, but an atomic mass different from the atomic mass usually found in nature. Isotopes suitable for inclusion in compounds of Formula 1 include, for example, isotopes of hydrogen, such as ^{2}H and ^{3}H; isotopes of carbon, such as^{11}C, ^{13}C and ^{14}C; isotopes of nitrogen, such as^{13}N and ^{15}N; isotopes of oxygen, such as ^{15}O, ^{17}O and ^{18}O; isotopes of sulfur, such as ^{35}S; isotopes of fluorine, such as ^{18}F; isotopes of chlorine, such as ^{36}Cl, and isotopes of iodine, such as ^{123}I and ^{125}I. Use of isotopic variations (e.g., deuterium, ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements. Additionally, certain isotopic variations of the disclosed compounds may incorporate a radioactive isotope (e.g., tritium, ^{3}H, or ^{14}C), which may be useful in drug and/or substrate tissue distribution studies. Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, may be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Isotopically-labeled compounds may be prepared by processes analogous to those described elsewhere in the disclosure using an appropriate isotopically-labeled reagent in place of a non-labeled reagent.

[0106] The compounds of Formula 1 may be prepared using the techniques described below. Some of the schemes and examples may omit details of common reactions, including oxidations, reductions, and so on, separation techniques (extraction, evaporation, precipitation, chromatography, filtration, trituration, crystallization, and the like), and analytical procedures, which are known to persons of ordinary skill in the art of organic chemistry. The details of such reactions and techniques can be found in a number of treatises, including Richard Larock, *Comprehensive Organic Transformations* (1999), and the multi-volume series edited by Michael B. Smith and others, *Compendium of Organic Synthetic Methods* (1974 et seq.). Starting materials and reagents may be obtained from commercial sources or may be prepared using literature methods. Some of the reaction schemes may omit minor products resulting from chemical transformations (e.g., an alcohol from the hydrolysis of an ester, CO_2 from the decarboxylation of a diacid, etc.). In

addition, in some instances, reaction intermediates may be used in subsequent steps without isolation or purification (i.e., *in situ*).

[0107] In some of the reaction schemes and examples below, certain compounds can be prepared using protecting groups, which prevent undesirable chemical reaction at otherwise reactive sites. Protecting groups may also be used to enhance solubility or otherwise modify physical properties of a compound. For a discussion of protecting group strategies, a description of materials and methods for installing and removing protecting groups, and a compilation of useful protecting groups for common functional groups, including amines, carboxylic acids, alcohols, ketones, aldehydes, and so on, see T. W. Greene and P. G. Wuts, *Protecting Groups in Organic Chemistry* (1999) and P. Kocienski, *Protective Groups* (2000).

[0108] Generally, the chemical transformations described throughout the specification may be carried out using substantially stoichiometric amounts of reactants, though certain reactions may benefit from using an excess of one or more of the reactants. Additionally, many of the reactions disclosed throughout the specification may be carried out at about room temperature (RT) and ambient pressure, but depending on reaction kinetics, yields, and so on, some reactions may be run at elevated pressures or employ higher temperatures (e.g., reflux conditions) or lower temperatures (e.g., -78°C to 0°C). Any reference in the disclosure to a stoichiometric range, a temperature range, a pH range, etc., whether or not expressly using the word "range," also includes the indicated endpoints.

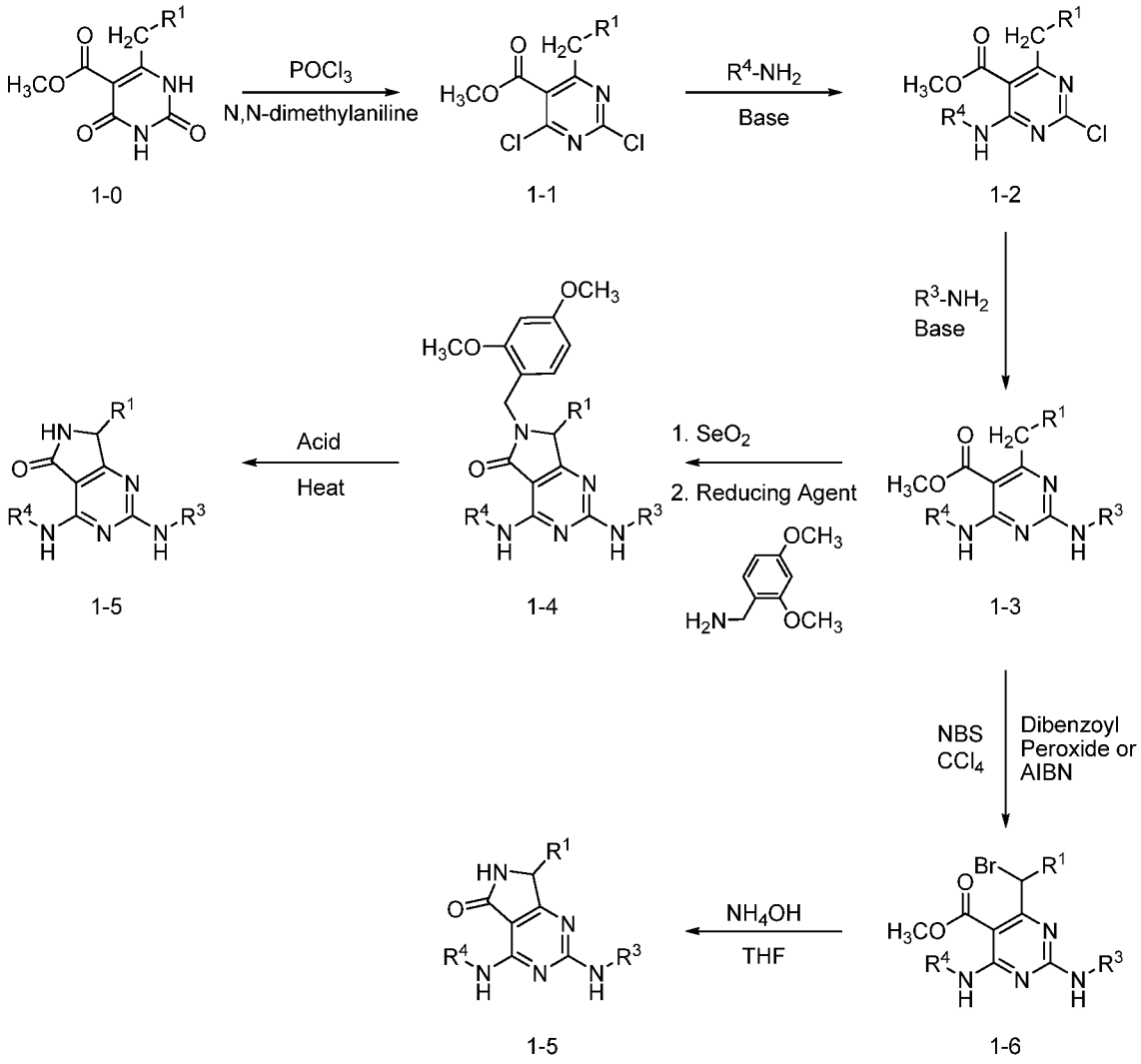
[0109] Many of the chemical transformations may also employ one or more compatible solvents, which may influence the reaction rate and yield. Depending on the nature of the reactants, the one or more solvents may be polar protic solvents (including water), polar aprotic solvents, non-polar solvents, or some combination. Representative solvents include saturated aliphatic hydrocarbons (e.g., *n*-pentane, *n*-hexane, *n*-heptane, *n*-octane); aromatic hydrocarbons (e.g., benzene, toluene, xylenes); halogenated hydrocarbons (e.g., methylene chloride, chloroform, carbon tetrachloride); aliphatic alcohols (e.g., methanol, ethanol, propan-1-ol, propan-2-ol, butan-1-ol, 2-methyl-propan-1-ol, butan-2-ol, 2-methyl-propan-2-ol, pentan-1-ol, 3-methyl-butan-1-ol, hexan-1-ol, 2-methoxy-ethanol, 2-ethoxy-ethanol, 2-butoxy-ethanol, 2-(2-methoxy-ethoxy)-ethanol, 2-(2-ethoxy-ethoxy)-ethanol, 2-(2-butoxy-ethoxy)-ethanol); ethers (e.g., diethyl ether, di-isopropyl ether, dibutyl ether, 1,2-dimethoxy-ethane, 1,2-diethoxy-ethane, 1-methoxy-2-

(2-methoxy-ethoxy)-ethane, 1-ethoxy-2-(2-ethoxy-ethoxy)-ethane, tetrahydrofuran, 1,4-dioxane); ketones (e.g., acetone, methyl ethyl ketone); esters (methyl acetate, ethyl acetate); nitrogen-containing solvents (e.g., formamide, *N*,*N*-dimethylformamide, acetonitrile, *N*-methyl-pyrrolidone, pyridine, quinoline, nitrobenzene); sulfur-containing solvents (e.g., carbon disulfide, dimethyl sulfoxide, tetrahydro-thiophene-1,1,-dioxide); and phosphorus-containing solvents (e.g., hexamethylphosphoric triamide).

[0110] In the schemes, below, substituent identifiers (e.g., R^1, R^3, R^4, R^5, R^7, R^8, R^9, L^1 and L^2) are as defined above for Formula 1. As mentioned earlier, however, some of the starting materials and intermediates may include protecting groups, which are removed prior to the final product. In such cases, the substituent identifier refers to moieties defined in Formula 1 and to those moieties with appropriate protecting groups. For example, a starting material or intermediate in the schemes may include an R^3 that is a moiety having a potentially reactive amine. In such cases, R^3 would include the moiety with or without, say, a Boc or Cbz group attached to the amine.

[0111] Scheme 1 illustrates a method for preparing compound 1-5. Starting material 1-0 (e.g., methyl 6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate) is chlorinated at elevated temperature (e.g., 95-105°C) using phosphoryl trichloride as a reactive solvent, in the presence of a catalytic amount of *N*,*N*-dimethyl aniline to give a methyl pyrimidine carboxylate 1-1. The 2-chloro and 4-chloro groups of intermediate 1-1 are subsequently displaced via treatment with an appropriately-substituted amine. As depicted in Scheme 1, the 2-chloro group is reacted with R^4-NH_2 (e.g. substituted aniline) in a polar aprotic organic solvent (e.g., ACN or THF) and in the presence of a hindered base such as Et_3N or DIPEA (2 eq) to give intermediate 1-2. The reaction may be carried out at elevated temperatures (e.g. 90°C or reflux conditions). In a similar manner, the 4-chloro group is displaced with R^3-NH_2 to give intermediate 1-3. The second displacement is carried out at elevated temperatures (e.g., 90°C or reflux conditions) in a polar aprotic organic solvent (e.g., DMA or DMF) in the presence of a hindered base (e.g., Et_3N or DIPEA).

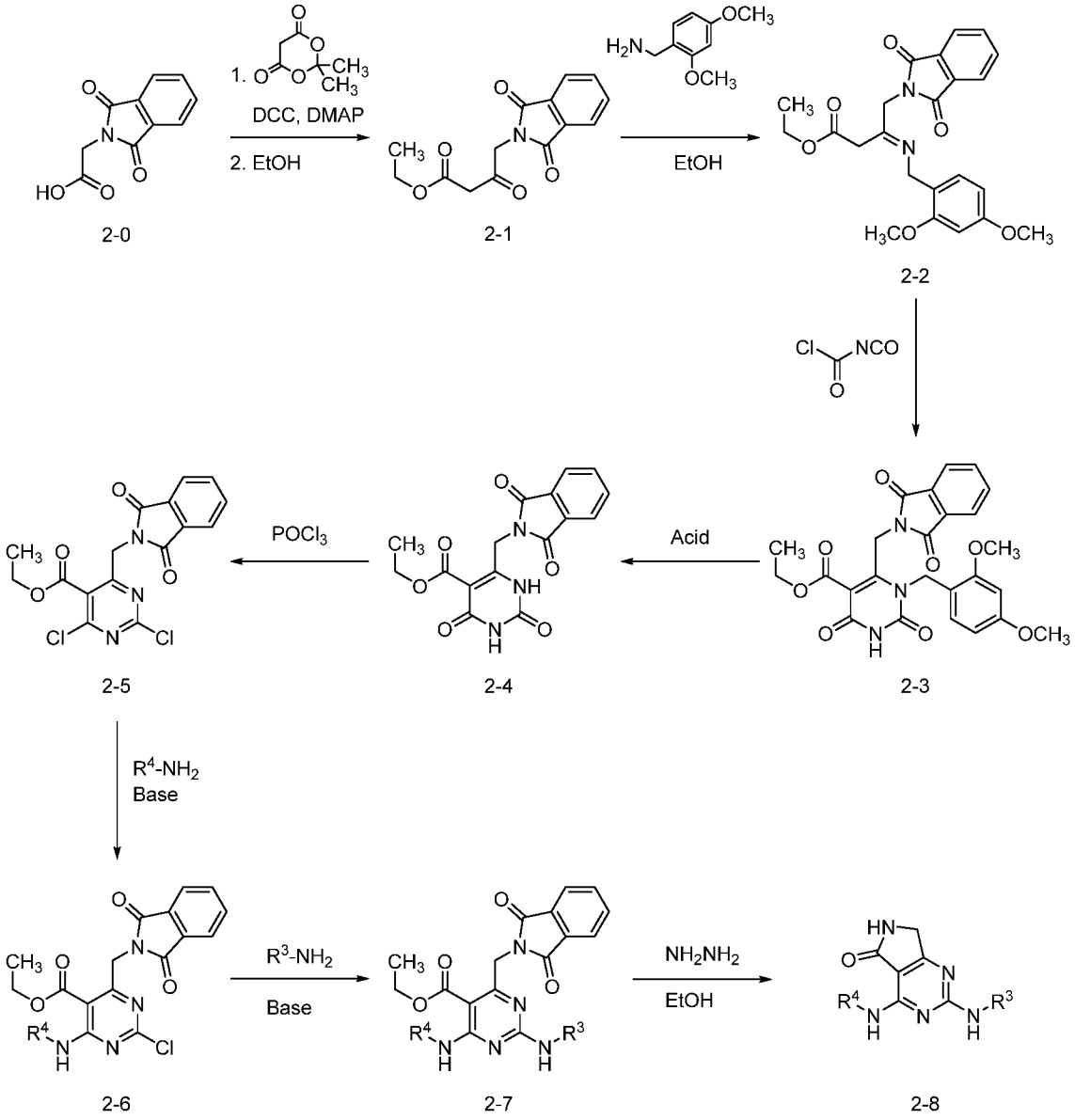
Scheme 1



[0112] Scheme 1 shows two methods for cyclizing intermediate 1-3. In one method, intermediate 1-3 is oxidized with SeO_2 (2-4 eq) in an organic solvent, such as 1,4-dioxane, under reflux conditions (e.g., about 100°C) to give a ketone (or aldehyde) intermediate (not shown). Subsequent reaction with 2,4-dimethoxybenzylamine in the presence of a mild reducing agent, such as sodium cyanoborohydride (1.5 eq) or sodium triacetoxy-borohydride in MeOH, gives via reductive amination, an amino intermediate which cyclizes to 1-4, either immediately or upon heating to about 50°C. The dimethoxybenzyl group can be removed by treating intermediate 1-4 with an acid (e.g., TFA) at about 60°C, which gives the desired compound 1-5. In a second method, intermediate 1-3 is treated with a bromination reagent such as NBS in the presence of an initiator (e.g., dibenzoyl

peroxide or AIBN) in CCl_4. Refluxing the reaction mixture gives intermediate 1-6, which is treated with a source of ammonia (e.g., ammonium hydroxide) in THF to give 1-5.

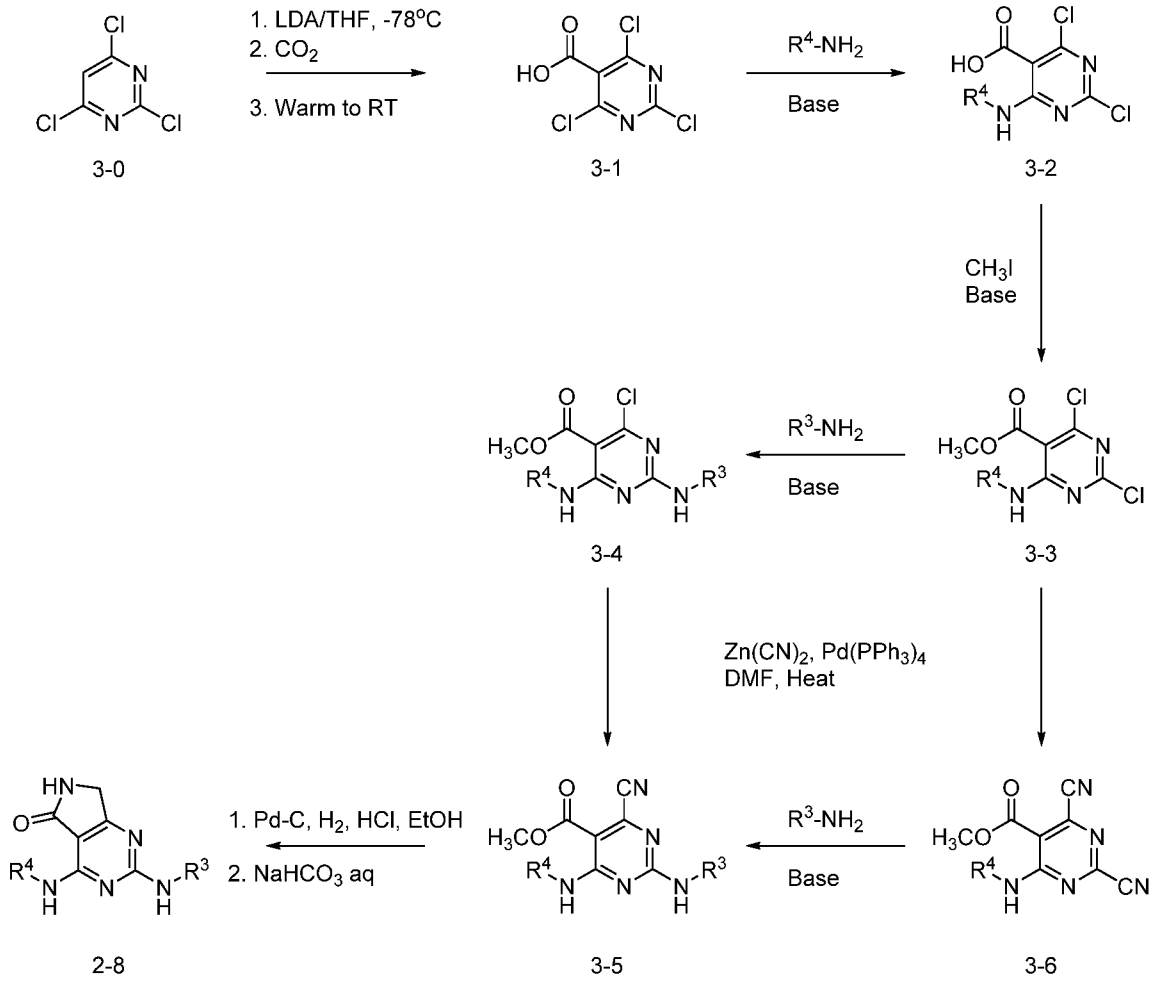
Scheme 2



[0113] Scheme 2 provides a method for preparing compound 2-8. Starting material 2-0 (2-(1,3-dioxoisoindolin-2-yl)acetic acid) is reacted with 2,2-dimethyl-1,3-dioxane-4,6-dione (1-1.5 eq) and 4-dimethylaminopyridine (1-1.5 eq) in the presence of DCC (1-1.5 eq) and an organic solvent such as dichloromethane to give intermediate 2-1. Subsequent treatment of 2-1 with 2,4-dimethoxybenzylamine (1 eq) in EtOH at about 50°C gives an imine 2-2, which is isolated, re-dissolved in an organic solvent (e.g., THF) and treated with an activated carbonylisocyanate (e.g., carbonisocyanatidic chloride, 1 eq) at about

80°C to give intermediate 2-3. Treating 2-3 with an acid (e.g., TFA at RT to 60°C) removes the dimethoxybenzyl group to give intermediate 2-4, which is subsequently reacted with a chlorinating agent (e.g., $POCl_3$) under refluxing conditions (e.g., about 100°C) to give intermediate 2-5. Stepwise displacement of the two chloro groups with appropriately-substituted amines (R^4-NH_2 and R^3-NH_2) gives intermediates 2-6 and 2-7. Treatment of intermediate 2-7 with hydrazine hydrate (4-5 eq) in EtOH with heating (e.g., at about 65°C) gives compound 2-8.

Scheme 3



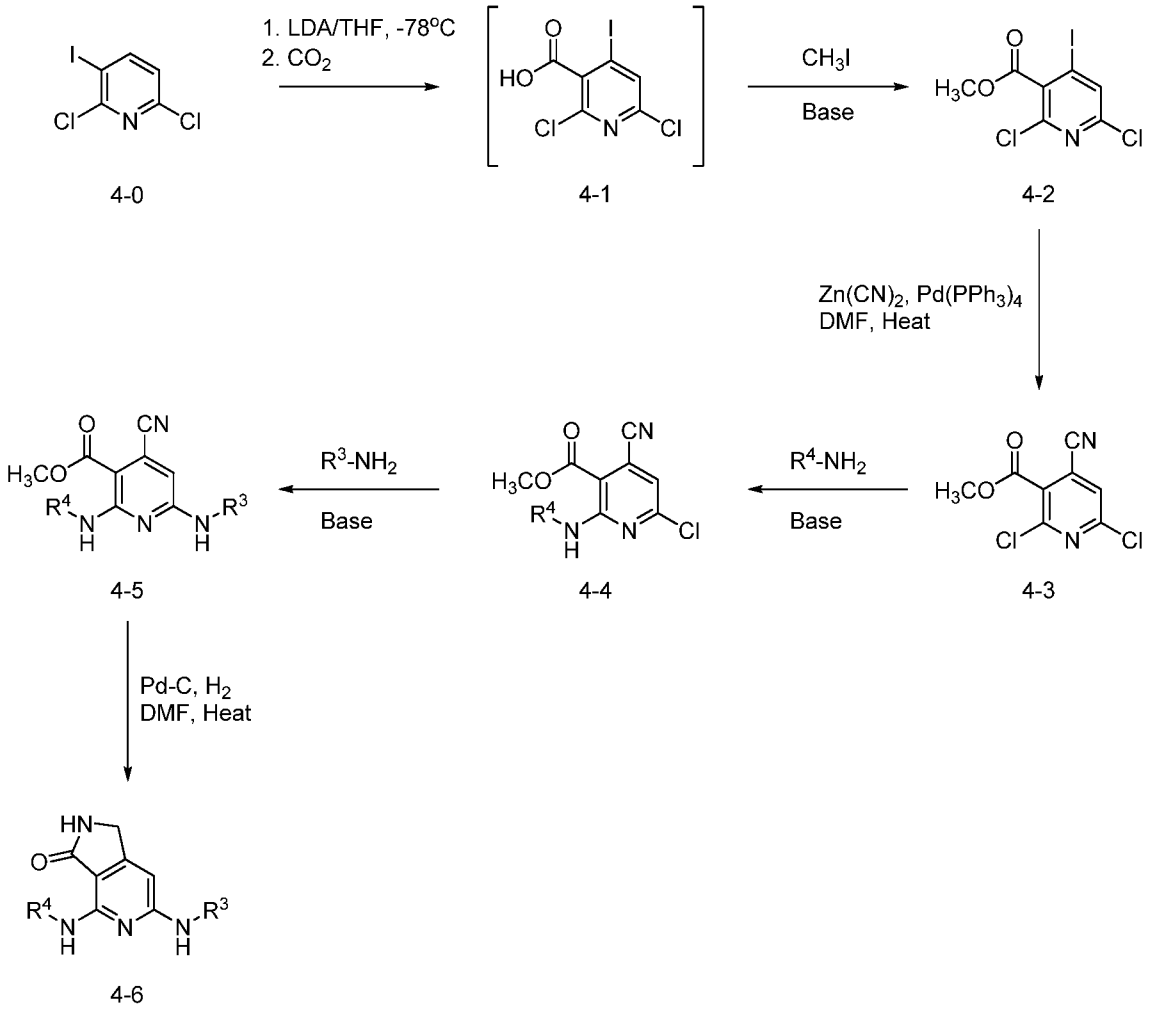
[0114] Scheme 3 provides another method for preparing compound 2-8. Starting material 3-0 (2,4,6-trichloropyrimidine) is treated with a strong base such as LDA (made freshly from diisopropyl amine and *n*-BuLi or purchased) at -78°C in dry THF, followed by quenching with dry ice. Warming the mixture to RT and stirring gives intermediate 3-1. Displacement of a chloro group via treatment with an appropriately-substituted amine (R^4-

NH_2, 1 eq) in the presence of a hindered base (e.g., Et_3N or DIPEA, 2 eq) and a polar aprotic organic solvent (e.g., DMF) gives intermediate 3-2. Subsequent treatment of 3-2 with MeI (1-1.5 eq) and a base (e.g. sodium bicarbonate, 1.5-3 eq) yields an ester 3-3, which may proceed to compound 2-8 through two different routes. In one route, intermediate 3-3 undergoes treatment with an appropriately-substituted amine (R^3-NH_2, 1-1.1 eq) in the presence of a hindered base (e.g., DIPEA) and a polar aprotic organic solvent (e.g., THF) to give intermediate 3-4 and an isomer. Following isolation, intermediate 3-4 is reacted with zinc cyanide (0.5-1 eq) and a catalytic amount (10%) of tetrakis (triphenylphosphine) palladium(0) in DMF at about 90°C to give nitrile 3-5. Reduction of the nitrile group to an amine via hydrogenation using Pd on carbon (5-10%) in EtOH and a catalytic amount of HCl gives, upon treatment with sodium bicarbonate, 2-8.

[0115] In an alternative route, intermediate 3-3 is first converted to nitrile 3-6 via palladium-catalyzed cyanation by heating a mixture of 3-3, zinc cyanide (0.5-1 eq), tetrakis(triphenyl phosphine)palladium(0) (0.1 eq), and a polar aprotic solvent (e.g., DMF) in a microwave oven at about 120°C for about 1 hour. Following isolation, intermediate 3-6 is converted at RT to 3-5 via reaction with an appropriately-substituted amine (R^3-NH_2, 1-1.5 eq) in a polar aprotic solvent (e.g., DMF) and in the presence of a hindered base (e.g., DIPEA). As described above, reduction of the nitrile group of 3-5 and subsequent cyclization gives compound 2-8.

[0116] Scheme 4 shows a method for preparing compound 4-6. Lithiation of starting material 4-0 (2,6-di-halo-3-iodopyridine) via directed ortho-lithiation by LDA in THF at -78°C, followed by quenching with dry ice, gives 4-1, which is subsequently esterified at RT using MeI and a base (e.g., potassium carbonate). As in Scheme 3, the iodo group of intermediate 4-2 is converted to a nitrile group via palladium-catalyzed cyanation to give 4-3. Stepwise displacement of the two chloro groups with appropriately-substituted amines (R^4-NH_2 and R^3-NH_2) gives intermediates 4-4 and 4-5. As in the ring-closure step depicted in Scheme 3, hydrogenation followed by cyclization gives compound 4-6.

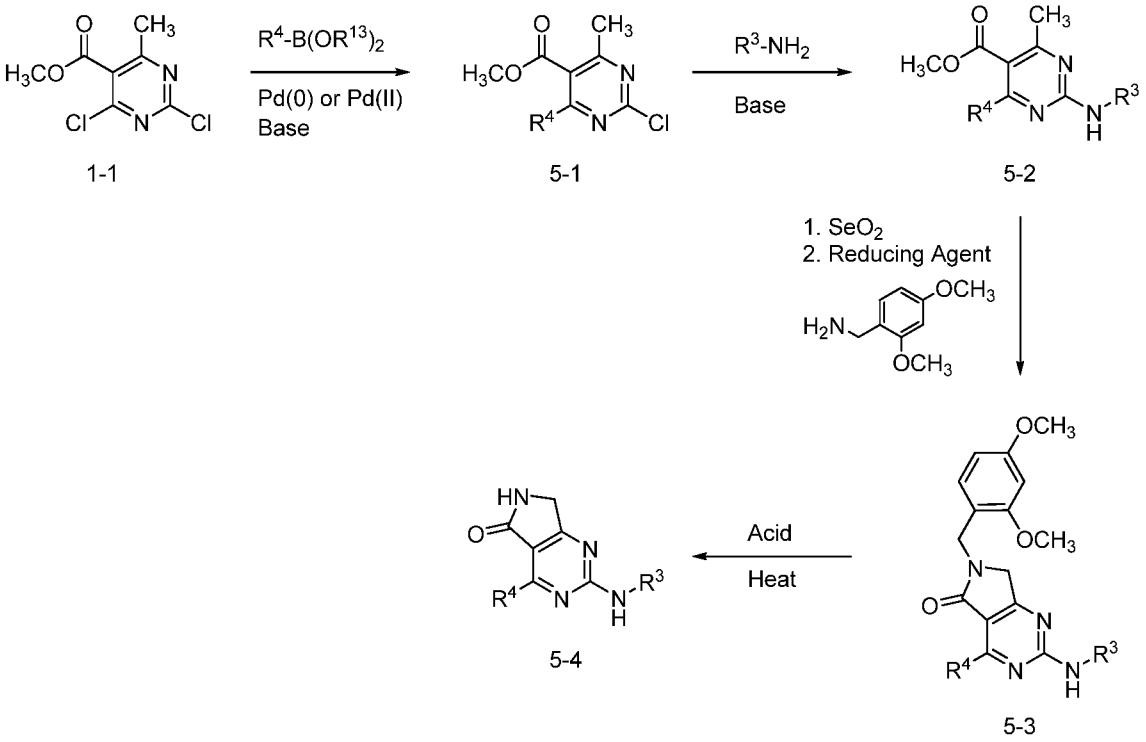
Scheme 4



[0118] Scheme 5 depicts a method for preparing compound 5-4. Starting material 1-1 (methyl 2,4-dichloro-6-methylpyrimidine-5-carboxylate) is reacted with an aromatic boronic acid or borate (e.g., R^4-$B(OR^{13})_2$, where R^4 is C_{6-14} aryl or C_{1-9} heteroaryl, and e.g., each R^{13} is H or C_{1-4} alkyl) in the presence of a palladium catalyst (e.g., $Pd(PPh_3)_4$, $(PPh_3)_2PdCl_2$, etc.), a base (e.g., KF or Na_2CO_3), and an organic solvent (e.g., dioxane, DMF, etc.). The Suzuki-type coupling is carried out at elevated temperature (e.g., about 90°C) and gives intermediate 5-1. Displacement of the chloro group with an appropriately-substituted amine (R^3-NH_2) gives intermediate 5-2. As in Scheme 1, the methyl group on pyrimidine is oxidized with SeO_2 (2-4 eq) in an organic solvent (e.g., 1,4-dioxane) under reflux conditions to give an aldehyde intermediate, which is subsequently reacted with 2,4-dimethoxybenzylamine in the presence of a mild reducing agent (e.g., about 1.5 eq of $NaCNBH_3$ or $NaBH(OAc)_3$) in MeOH, to give, via reductive amination, an amino

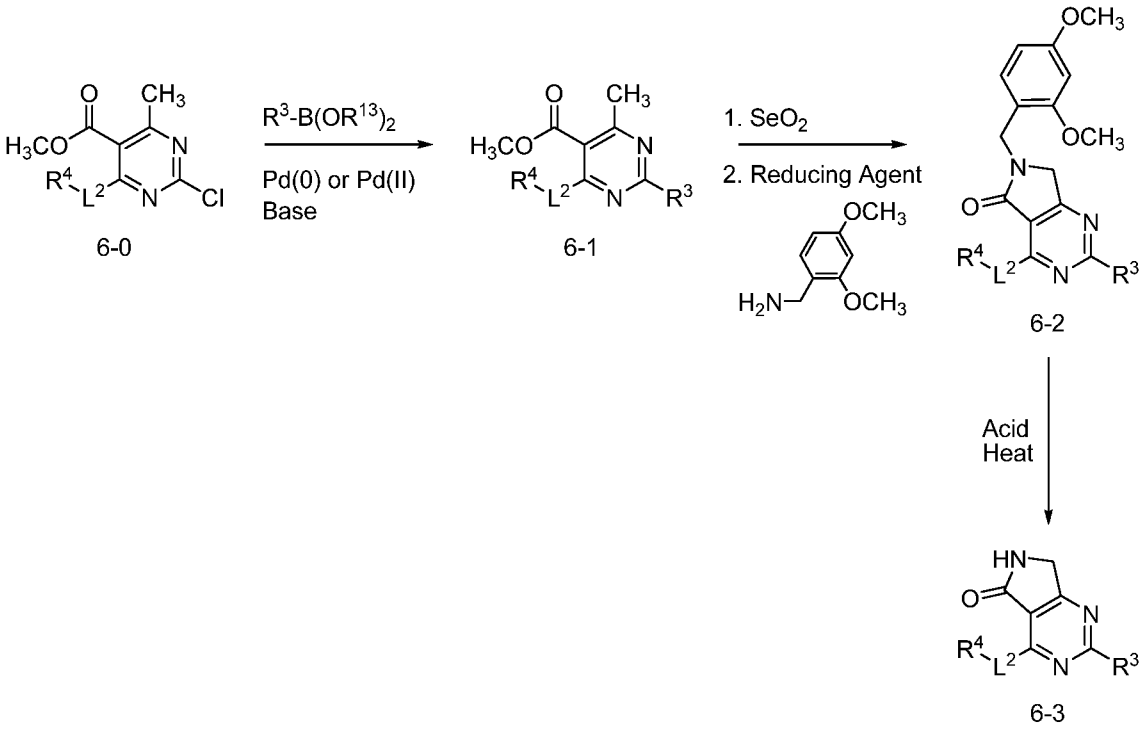
intermediate which cyclizes to 5-3, either immediately or upon heating to about 50°C. Treating intermediate 5-3 with an acid (e.g., TFA) at about 60°C gives compound 5-4.

Scheme 5



[0119] Scheme 6 depicts a method for preparing compound 6-3. Starting material 6-0, which may be prepared from methyl 2,4-dichloro-6-methylpyrimidine-5-carboxylate using the methods described above, is reacted with an aromatic boronic acid or borate (e.g., R^3-$B(OR^{13})_2$, where R^3 is C_{6-14} aryl or C_{1-9} heteroaryl and e.g., R^{13} is H or C_{1-4} alkyl) in the presence of a palladium catalyst (e.g., $Pd(PPh_3)_4$, $(PPh_3)_2PdCl_2$, etc.), a base (e.g., KF or Na_2CO_3), and an organic solvent (e.g., dioxane, DMF, DME, etc.). The Suzuki-type coupling is carried out at elevated temperature (e.g., about 90°C) and gives intermediate 6-1. The methyl group on pyrimidine is oxidized with SeO_2 (2-4 eq) in an organic solvent (e.g., 1,4-dioxane) under reflux conditions to give an aldehyde intermediate, which is subsequently reacted with 2,4-dimethoxybenzylamine in the presence of a mild reducing agent (e.g., about 1.5 eq of $NaCNBH_3$ or $NaBH(OAc)_3$) in MeOH, to give intermediate 6-2. Treating 6-2 with an acid (e.g., TFA) at about 60°C yields compound 6-3.

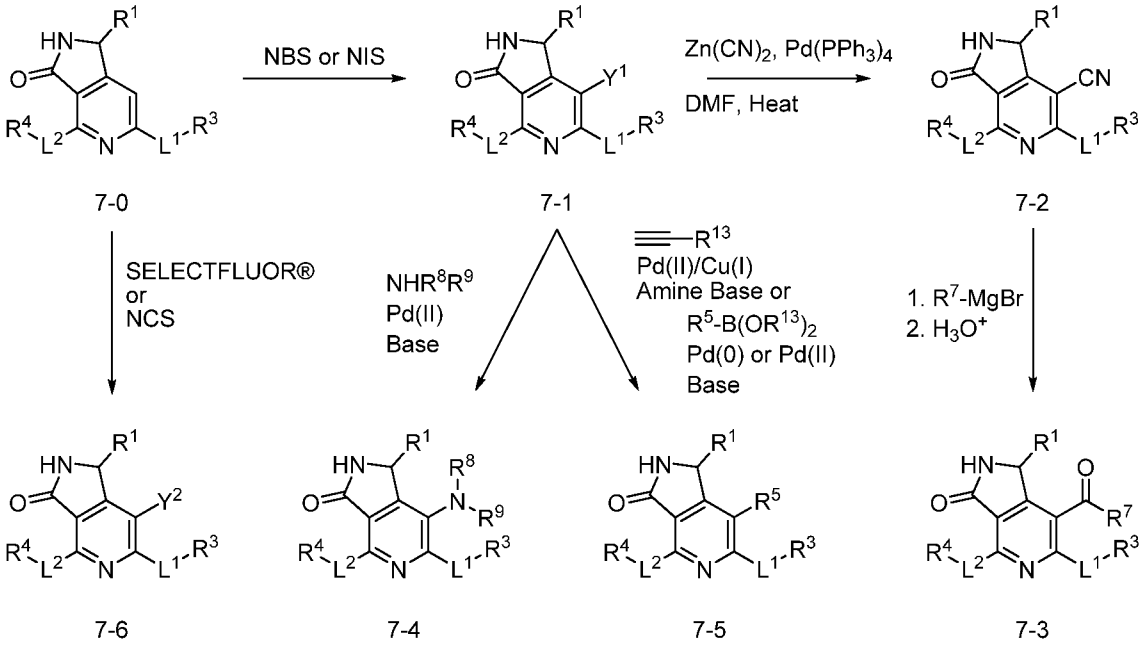
Scheme 6



[0120] Scheme 7 illustrates methods for preparing compounds 7-2, 7-3, 7-4, 7-5, and 7-6. Starting material 7-0, which may be prepared using the methods described above, may be reacted with NBS or NIS to give halo-pyridine intermediate 7-1 (Y^1 is Br or I). As in Scheme 3, the halo group of 7-1 may be converted to a nitrile group via palladium-catalyzed cyanation to give 7-2. Compound 7-2 is subsequently reacted with a Grignard reagent (R^7-MgBr) to give an imine intermediate (not shown), which upon acid hydrolysis, yields compound 7-3. Alternatively, halo-pyridine intermediate 7-1 may be reacted with NHR^8R^9 in the presence of a palladium (II) catalyst (e.g., $PdCl_2$(dppf)), a stoichiometric amount of base (e.g., NaO*t*-Bu), and an organic solvent (e.g., dioxane, toluene, etc.), at elevated temperature (e.g., about 100°C). The Buchwald-Hartwig coupling gives heteroaryl amine 7-4. In addition, 7-1 may be reacted with a terminal alkyne ($HC{\equiv}R^{13}$, e.g., R^{13} is H or C_{1-4} alkyl) in the presence of a palladium(II) catalyst (e.g., $(PPh_3)_2PdCl_2$), a copper(I) co-catalyst (e.g., CuI), and an amine base (e.g. Et_3N), at RT. Following the Sonogashira coupling, reduction of the alkyne moiety yields compound 7-5 with R^5 being, e.g., C_{1-5} alkyl. Compound 7-1 may be reacted with an aromatic boronic acid or borate (e.g., R^5-$B(OR^{13})_2$, where R^5 is C_{1-9} heteroaryl and e.g., R^{13} is H or C_{1-4} alkyl) in the presence of a palladium catalyst (e.g., $Pd(PPh_3)_4$, $(PPh_3)_2PdCl_2$, etc.), a base (e.g., KF or

Na_2CO_3), and an organic solvent (e.g., dioxane, DMF, etc.). The Suzuki-type coupling is carried out at elevated temperature (e.g., about 90°C) and gives compound 7-5 with R^5 being C_{1-9} heteroaryl.

Scheme 7

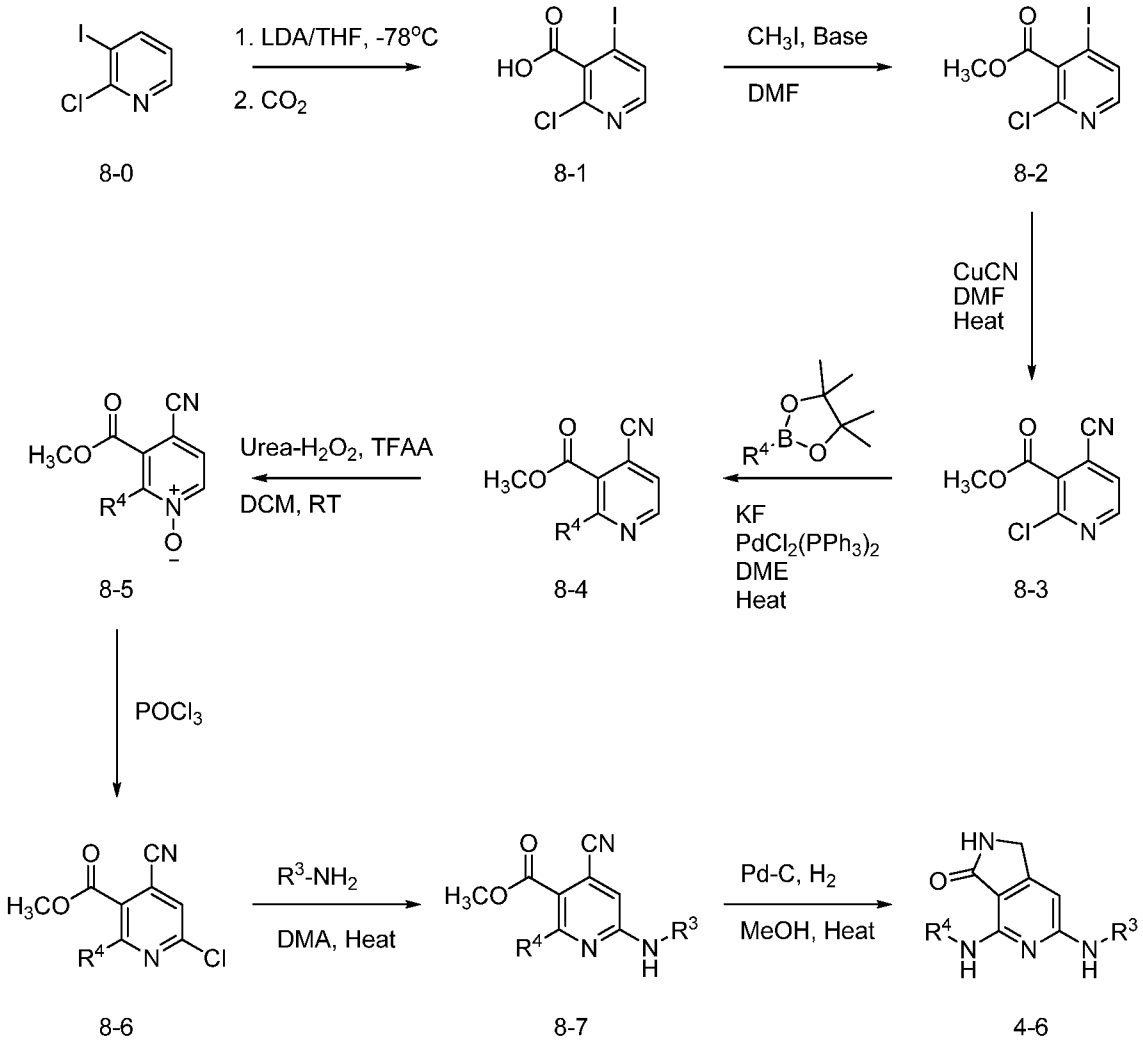


[0121] As shown in Scheme 7, compound 7-0 may alternatively be treated with a fluorinating agent, such as SELECTFLUOR® (1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane ditetrafluoroborate), in an organic solvent (e.g., DCM) or a mixture of organic solvents (e.g., DCM and MeOH), to give a fluoro-pyridine derivative 7-6 (Y^2 is F). Similarly, 7-0 may be treated with a chlorinating agent, such as NCS, in an aprotic solvent (e.g., DCM) to give a chloro-pyridine derivative 7-6 (Y^2 is Cl).

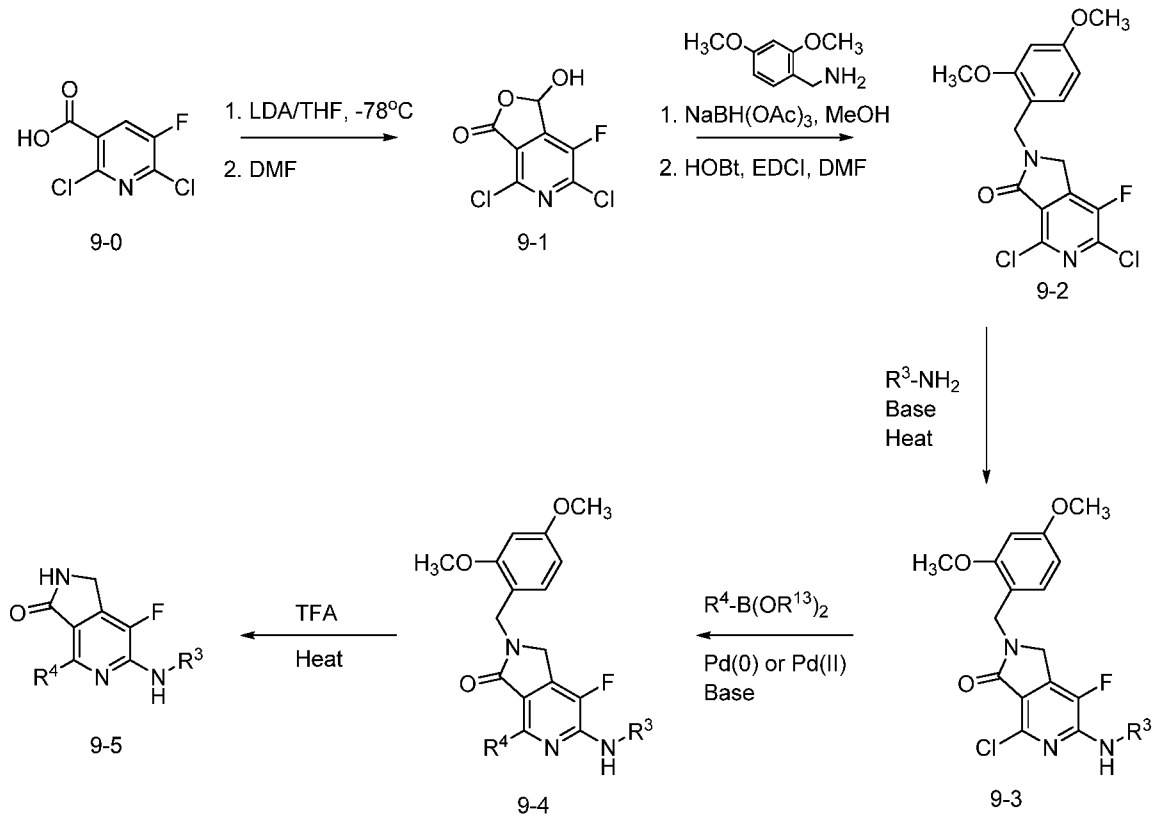
[0122] Scheme 8 shows an alternative method for preparing compound 4-6. Starting material 8-0 (2-chloro-3-iodopyridine) undergoes ortho-directed lithiation via treatment with LDA in THF at -78°C. Quenching with dry ice gives 8-1, which is subsequently esterified at RT using iodomethane and a base (e.g., potassium carbonate). As in Scheme 4, the iodo group of intermediate 8-2 is converted to a nitrile group via palladium-catalyzed cyanation or through treatment with cyanocopper or zinc cyanide in a suitable solvent (e.g., DMF, DMA, etc.) at elevated temperature. The R^4 substituent is installed on 8-3 using a Suzuki reaction, which gives intermediate 8-4. N-oxidation of the pyridine moiety via treatment with hydrogen peroxide/urea complex gives an activated

intermediate 8-5, which is chlorinated through reaction with phosphorus oxychloride at an elevated temperature (e.g., 90-100°C). Displacement of the chloro group on 8-6 via reaction with an appropriately-substituted amine (R^3-NH_2) gives intermediate 8-7. Subsequent reduction through palladium-catalyzed hydrogenation and cyclization gives compound 4-6.

Scheme 8

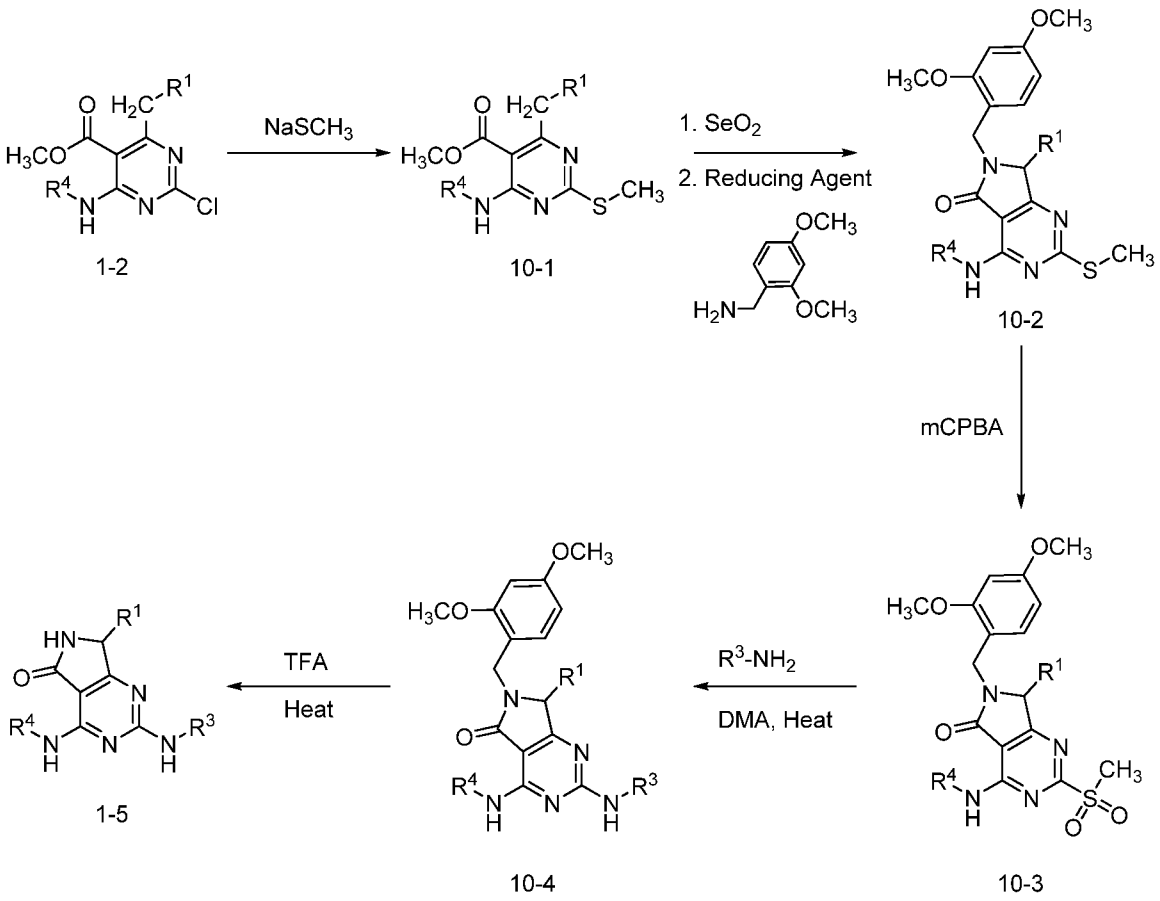


Scheme 9



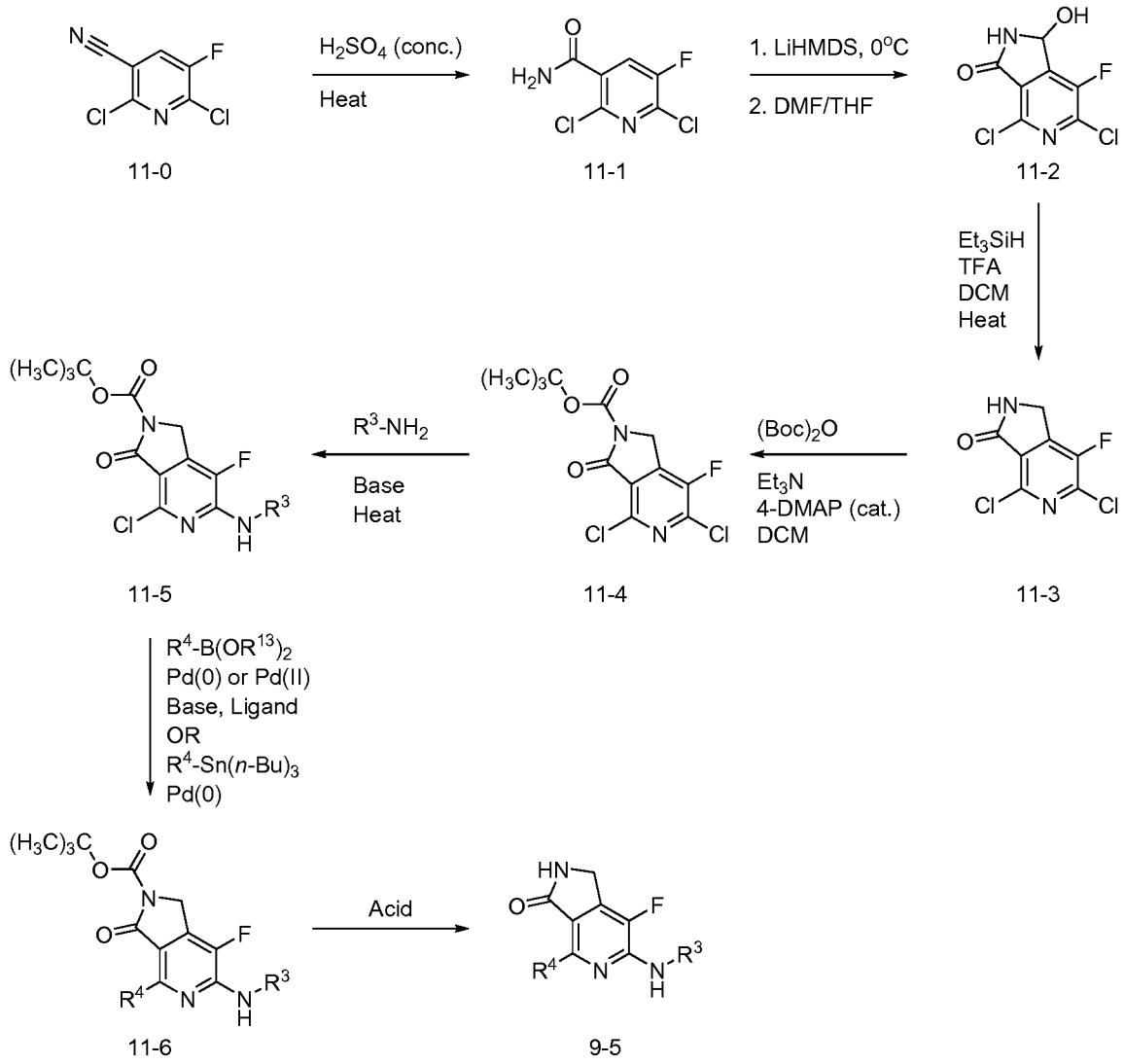
[0123] Scheme 9 depicts the synthesis of compound 9-5. Starting material 9-0 (2,6-dichloro-5-fluoronicotinic acid) is lithiated via treatment with LDA in THF at -78°C. Quenching with DMF gives an aldehyde intermediate 9-1, which undergoes reductive amination through reaction with an amine (e.g., 2,4-dimethoxyphenyl)methanamine) and reducing agent (e.g., $NaBH(OAc)_3$). The resulting amino acid (not shown) is cyclized via amide coupling, which employs a suitable coupling agent (e.g., EDCI, DCC, etc.), catalyst (HOBt, DMAP, etc.), and solvent (e.g., DMF, DMSO, ACN, THF, DCM, etc.). As in previous schemes, displacement of the chloro group of compound 9-2 with an appropriate amine (R^3-NH_2) gives intermediate 9-3, which is subsequently reacted with an aromatic boronic acid or borate (e.g., R^4-$B(OR^{13})_2$ in the presence of a palladium catalyst (e.g., $Pd(PPh_3)_4$, $(PPh_3)_2PdCl_2$, etc.), base (e.g., KF or Na_2CO_3), and organic solvent (e.g., dioxane, DMF, etc.) at elevated temperature (e.g., about 90°C) to give 9-4. Following the Suzuki coupling, treatment of 9-4 with TFA at elevated temperature (e.g., 40-60°C) generates 9-5.

Scheme 10



[0124] Scheme 10 shows another method for preparing compound 1-5. The chloro group of compound 1-2 is first displaced with sodium methanethiolate to give 10-1. As in Scheme 1, intermediate 10-1 is oxidized with SeO_2 to give a ketone (or aldehyde) intermediate (not shown), which is reacted with 2,4-dimethoxybenzylamine in the presence of a reducing agent to give, via reductive amination, an amino acid intermediate which cyclizes to 10-2. The methylthio group is converted to methylsulfonyl using mCPBA (*m*-chloroperoxybenzoic acid), which is displaced with an appropriate amine (R^3-NH_2) to give intermediate 10-4. Treatment of 10-4 with an acid (e.g., TFA) at elevated temperature (e.g., 40-60°C) gives compound 1-5.

Scheme 11



[0125] Scheme 11 depicts an alternate synthesis of compound 9-5. Starting material 11-0 (2,6-dichloro-5-fluoronicotinonitrile) is hydrolyzed by treatment with concentrated sulfuric acid at elevated temperature (e.g., about 65°C) to give amide 11-1, which is lithiated via treatment with LiHMDS at about 0°C or reaction with LDA in THF at -78°C. Quenching with DMF gives aldehyde intermediate 11-2, which is reduced to lactam 11-3 by treatment with a reducing agent (e.g., triethyl silane) and an acid (e.g., TFA) in an organic solvent (e.g., DCM). Following installation of a Boc protecting group on lactam 11-3, displacement of a chloro group on compound 11-4 via reaction with an appropriate amine (R^3-NH_2) gives intermediate 11-5. The intermediate is subsequently reacted with an aromatic boronic acid or borate (e.g., R^4-$B(OR^{13})_2$ in the presence of a palladium catalyst

(e.g., $Pd(PPh_3)_4$, $(PPh_3)_2PdCl_2$, $Pd_2(dba)_3$, etc.), an optional ligand (e.g., 2-(dicyclohexylphosphino)biphenyl), a base (e.g., KF or Na_2CO_3), and an organic solvent (e.g., dioxane, DMF, etc.) to give compound 11-6. The Suzuki reaction is carried out at elevated temperature (e.g., 90-160°C), either by conventional heating or via microwave irradiation. Alternatively, compound 11-5 may be reacted with an aromatic tin reagent (e.g., R^4-Sn(*n*-Bu)$_3$) in the presence of a palladium catalyst (e.g., $Pd(PPh_3)_4$) and an organic solvent (e.g., toluene) at elevated temperature (e.g., about 100°C). Following the Suzuki or Stille coupling, treatment of 11-6 with an acid (e.g., TFA or HCl) at RT or above (e.g., about 20-60°C) generates 9-5.

[0126] Compounds of Formula 1, which include compounds named above, and their pharmaceutically acceptable complexes, salts, solvates and hydrates, should be assessed for their biopharmaceutical properties, such as solubility and solution stability across pH, permeability, and the like, to select an appropriate dosage form and route of administration. Compounds that are intended for pharmaceutical use may be administered as crystalline or amorphous products, and may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, spray drying, evaporative drying, microwave drying, or radio frequency drying.

[0127] Compounds of Formula 1 may be administered alone or in combination with one another or with one or more pharmacologically active compounds which are different than the compounds of Formula 1. Generally, one or more these compounds are administered as a pharmaceutical composition (a formulation) in association with one or more pharmaceutically acceptable excipients. The choice of excipients depends on the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form, among other things. Useful pharmaceutical compositions and methods for their preparation may be found, for example, in A. R. Gennaro (ed.), *Remington: The Science and Practice of Pharmacy* (20th ed., 2000).

[0128] Compounds of Formula 1 may be administered orally. Oral administration may involve swallowing in which case the compound enters the bloodstream via the gastrointestinal tract. Alternatively or additionally, oral administration may involve mucosal administration (e.g., buccal, sublingual, supralingual administration) such that the compound enters the bloodstream through the oral mucosa.

[0129] Formulations suitable for oral administration include solid, semi-solid and liquid systems such as tablets; soft or hard capsules containing multi- or nano-particulates, liquids, or powders; lozenges which may be liquid-filled; chews; gels; fast dispersing dosage forms; films; ovules; sprays; and buccal or mucoadhesive patches. Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules (made, e.g., from gelatin or hydroxypropylmethylcellulose) and typically comprise a carrier (e.g., water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil) and one or more emulsifying agents, suspending agents or both. Liquid formulations may also be prepared by the reconstitution of a solid (e.g., from a sachet).

[0130] Compounds of Formula 1 may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Liang and Chen, *Expert Opinion in Therapeutic Patents* (2001) 11(6):981-986.

[0131] For tablet dosage forms, depending on dose, the active pharmaceutical ingredient (API) may comprise from about 1 wt% to about 80 wt% of the dosage form or more typically from about 5 wt% to about 60 wt% of the dosage form. In addition to the API, tablets may include one or more disintegrants, binders, diluents, surfactants, glidants, lubricants, anti-oxidants, colorants, flavoring agents, preservatives, and taste-masking agents. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, C_{1-6} alkyl-substituted hydroxypropylcellulose, starch, pregelatinized starch, and sodium alginate. Generally, the disintegrant will comprise from about 1 wt% to about 25 wt% or from about 5 wt% to about 20 wt% of the dosage form.

[0132] Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinized starch, hydroxypropylcellulose and hydroxypropylmethylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

[0133] Tablets may also include surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents may comprise from about 0.2 wt% to about 5 wt% of the tablet, and glidants may comprise from about 0.2 wt% to about 1 wt% of the tablet.

[0134] Tablets may also contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulfate. Lubricants may comprise from about 0.25 wt% to about 10 wt% or from about 0.5 wt% to about 3 wt% of the tablet.

[0135] Tablet blends may be compressed directly or by roller compaction to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tableting. If desired, prior to blending one or more of the components may be sized by screening or milling or both. The final dosage form may comprise one or more layers and may be coated, uncoated, or encapsulated. Exemplary tablets may contain up to about 80 wt% of API, from about 10 wt% to about 90 wt% of binder, from about 0 wt% to about 85 wt% of diluent, from about 2 wt% to about 10 wt% of disintegrant, and from about 0.25 wt% to about 10 wt% of lubricant. For a discussion of blending, granulation, milling, screening, tableting, coating, as well as a description of alternative techniques for preparing drug products, see A. R. Gennaro (ed.), *Remington: The Science and Practice of Pharmacy* (20th ed., 2000); H. A. Lieberman et al. (ed.), *Pharmaceutical Dosage Forms: Tablets, Vol. 1-3* (2d ed., 1990); and D. K. Parikh & C. K. Parikh, *Handbook of Pharmaceutical Granulation Technology, Vol. 81* (1997).

[0136] Consumable oral films for human or veterinary use are pliable water-soluble or water-swellable thin film dosage forms which may be rapidly dissolving or mucoadhesive. In addition to the API, a typical film includes one or more film-forming polymers, binders, solvents, humectants, plasticizers, stabilizers or emulsifiers, viscosity-modifying agents, and solvents. Other film ingredients may include anti-oxidants, colorants, flavorants and flavor enhancers, preservatives, salivary stimulating agents, cooling agents, co-solvents (including oils), emollients, bulking agents, anti-foaming agents, surfactants, and taste-masking agents. Some components of the formulation may perform more than one function.

[0137] In addition to dosing requirements, the amount of API in the film may depend on its solubility. If water soluble, the API would typically comprise from about 1 wt% to about 80 wt% of the non-solvent components (solutes) in the film or from about 20 wt% to about 50 wt% of the solutes in the film. A less soluble API may comprise a greater proportion of the composition, typically up to about 88 wt% of the non-solvent components in the film.

[0138] The film-forming polymer may be selected from natural polysaccharides, proteins, or synthetic hydrocolloids and typically comprises from about 0.01 wt% to about 99 wt% or from about 30 wt% to about 80wt% of the film.

[0139] Film dosage forms are typically prepared by evaporative drying of thin aqueous films coated onto a peelable backing support or paper, which may carried out in a drying oven or tunnel (e.g., in a combined coating-drying apparatus), in lyophilization equipment, or in a vacuum oven.

[0140] Useful solid formulations for oral administration may include immediate release formulations and modified release formulations. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted-, and programmed-release. For a general description of suitable modified release formulations, see US Patent No. 6,106,864. For details of other useful release technologies, such as high energy dispersions and osmotic and coated particles, see Verma et al, *Pharmaceutical Technology On-line* (2001) 25(2):1-14.

[0141] Compounds of Formula 1 may also be administered directly into the blood stream, muscle, or an internal organ of the subject. Suitable techniques for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, intrasynovial, and subcutaneous administration. Suitable devices for parenteral administration include needle injectors, including microneedle injectors, needle-free injectors, and infusion devices.

[0142] Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (e.g., pH of from about 3 to about 9). For some applications, however, compounds of Formula 1 may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water. The preparation of parenteral

formulations under sterile conditions (e.g., by lyophilization) may be readily accomplished using standard pharmaceutical techniques.

[0143] The solubility of compounds which are used in the preparation of parenteral solutions may be increased through appropriate formulation techniques, such as the incorporation of solubility-enhancing agents. Formulations for parenteral administration may be formulated to be immediate or modified release. Modified release formulations include delayed, sustained, pulsed, controlled, targeted, and programmed release. Thus, compounds of Formula 1 may be formulated as a suspension, a solid, a semi-solid, or a thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and semi-solids and suspensions comprising drug-loaded poly(DL-lactic-coglycolic)acid (PGLA) microspheres.

[0144] Compounds of Formula 1 may also be administered topically, intradermally, or transdermally to the skin or mucosa. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibers, bandages and microemulsions. Liposomes may also be used. Typical carriers may include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Topical formulations may also include penetration enhancers. See, e.g., Finnin and Morgan, *J. Pharm. Sci.* 88(10):955-958 (1999).

[0145] Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (e.g. Powderject^{TM} and Bioject^{TM}) injection. Formulations for topical administration may be formulated to be immediate or modified release as described above.

[0146] Compounds of Formula 1 may also be administered intranasally or by inhalation, typically in the form of a dry powder, an aerosol spray, or nasal drops. An inhaler may be used to administer the dry powder, which comprises the API alone, a powder blend of the API and a diluent, such as lactose, or a mixed component particle that includes the API and a phospholipid, such as phosphatidylcholine. For intranasal use, the powder may include a bioadhesive agent, e.g., chitosan or cyclodextrin. A pressurized container, pump, sprayer, atomizer, or nebulizer, may be used to generate the aerosol spray from a solution or suspension comprising the API, one or more agents for

dispersing, solubilizing, or extending the release of the API (e.g., EtOH with or without water), one or more solvents (e.g., 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane) which serve as a propellant, and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid. An atomizer using electrohydrodynamics may be used to produce a fine mist.

[0147] Prior to use in a dry powder or suspension formulation, the drug product is usually comminuted to a particle size suitable for delivery by inhalation (typically 90% of the particles, based on volume, having a largest dimension less than 5 microns). This may be achieved by any appropriate size reduction method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing, high pressure homogenization, or spray drying.

[0148] Capsules, blisters and cartridges (made, for example, from gelatin or hydroxypropylmethyl cellulose) for use in an inhaler or insufflator may be formulated to contain a powder mixture of the active compound, a suitable powder base such as lactose or starch, and a performance modifier such as L-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or monohydrated. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose, and trehalose.

[0149] A suitable solution formulation for use in an atomizer using electrohydrodynamics to produce a fine mist may contain from about 1 μg to about 20 mg of the API per actuation and the actuation volume may vary from about 1 μL to about 100 μL. A typical formulation may comprise one or more compounds of Formula 1, propylene glycol, sterile water, EtOH, and NaCl. Alternative solvents, which may be used instead of propylene glycol, include glycerol and polyethylene glycol.

[0150] Formulations for inhaled administration, intranasal administration, or both, may be formulated to be immediate or modified release using, for example, PGLA. Suitable flavors, such as menthol and levomenthol, or sweeteners, such as saccharin or sodium saccharin, may be added to formulations intended for inhaled/intranasal administration.

[0151] In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve that delivers a metered amount. Units are typically arranged to administer a metered dose or "puff" containing from about 10 μg to about 1000 μg of the API. The overall daily dose will typically range from about 100 μg to about 10 mg which

may be administered in a single dose or, more usually, as divided doses throughout the day.

[0152] The active compounds may be administered rectally or vaginally, e.g., in the form of a suppository, pessary, or enema. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate. Formulations for rectal or vaginal administration may be formulated to be immediate or modified release as described above.

[0153] Compounds of Formula 1 may also be administered directly to the eye or ear, typically in the form of drops of a micronized suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, gels, biodegradable implants (e.g. absorbable gel sponges, collagen), non-biodegradable implants (e.g. silicone), wafers, lenses, and particulate or vesicular systems, such as niosomes or liposomes. The formulation may include one or more polymers and a preservative, such as benzalkonium chloride. Typical polymers include crossed-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid, cellulosic polymers (e.g., hydroxypropylmethylcellulose, hydroxyethylcellulose, methyl cellulose), and heteropolysaccharide polymers (e.g., gelan gum). Such formulations may also be delivered by iontophoresis. Formulations for ocular or aural administration may be formulated to be immediate or modified release as described above.

[0154] To improve their solubility, dissolution rate, taste-masking, bioavailability, or stability, compounds of Formula 1 may be combined with soluble macromolecular entities, including cyclodextrin and its derivatives and polyethylene glycol-containing polymers. For example, API-cyclodextrin complexes are generally useful for most dosage forms and routes of administration. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the API, the cyclodextrin may be used as an auxiliary additive, i.e. as a carrier, diluent, or solubilizer. Alpha-, beta- and gamma-cyclodextrins are commonly used for these purposes. See, e.g., WO 91/11172, WO 94/02518, and WO 98/55148.

[0155] As noted above, one or more compounds of Formula 1, including compounds specifically named above, and their pharmaceutically active complexes, salts, solvates and hydrates, may be combined with each other or with one or more other active pharmaceutically active compounds to treat various diseases, conditions and disorders. In such cases, the active compounds may be combined in a single dosage form as described

above or may be provided in the form of a kit which is suitable for coadministration of the compositions. The kit comprises (1) two or more different pharmaceutical compositions, at least one of which contains a compound of Formula 1; and (2) a device for separately retaining the two pharmaceutical compositions, such as a divided bottle or a divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of tablets or capsules. The kit is suitable for administering different types of dosage forms (e.g., oral and parenteral) or for administering different pharmaceutical compositions at separate dosing intervals, or for titrating the different pharmaceutical compositions against one another. To assist with patient compliance, the kit typically comprises directions for administration and may be provided with a memory aid.

[0156] For administration to human patients, the total daily dose of the claimed and disclosed compounds is typically in the range of about 0.1 mg to about 3000 mg depending on the route of administration. For example, oral administration may require a total daily dose of from about 1 mg to about 3000 mg, while an intravenous dose may only require a total daily dose of from about 0.1 mg to about 300 mg. The total daily dose may be administered in single or divided doses and, at the physician's discretion, may fall outside of the typical ranges given above. Although these dosages are based on an average human subject having a mass of about 60 kg to about 70 kg, the physician will be able to determine the appropriate dose for a patient (e.g., an infant) whose mass falls outside of this weight range.

[0157] As noted above, the compounds of Formula 1 may be used to treat disorders, diseases, and conditions for which inhibition of SYK is indicated. Such disorders, diseases, and conditions generally relate to any unhealthy or abnormal state in a subject for which the inhibition of SYK provides a therapeutic benefit. More particularly, such disorders, diseases, and conditions may involve the immune system and inflammation, including Type I hypersensitivity (allergic) reactions (allergic rhinitis, allergic asthma, and atopic dermatitis); autoimmune diseases (rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, psoriasis, and immune thrombocytopenic purpura); inflammation of the lung (chronic obstructive pulmonary disease) and thrombosis. The compounds of Formula 1 may also be used to treat disorders, diseases, and conditions related to abnormal cell growth, including hematological malignancies, such as acute myeloid leukemia, B-cell chronic lymphocytic leukemia, B-cell lymphoma (e.g., mantle cell lymphoma), and T-cell

lymphoma (e.g., peripheral T-cell lymphoma), as well as epithelial cancers (i.e., carcinomas), such as lung cancer (small cell lung cancer and non-small cell lung cancer), pancreatic cancer, and colon cancer.

[0158] In addition to the hematological malignancies and epithelial cancers noted above, the compounds of Formula 1 may also be used to treat other types of cancer, including leukemia (chronic myelogenous leukemia and chronic lymphocytic leukemia); breast cancer, genitourinary cancer, skin cancer, bone cancer, prostate cancer, and liver cancer; brain cancer; cancer of the larynx, gall bladder, rectum, parathyroid, thyroid, adrenal, neural tissue, bladder, head, neck, stomach, bronchi, and kidneys; basal cell carcinoma, squamous cell carcinoma, metastatic skin carcinoma, osteosarcoma, Ewing's sarcoma, veticulum cell sarcoma, and Kaposi's sarcoma; myeloma, giant cell tumor, islet cell tumor, acute and chronic lymphocytic and granulocytic tumors, hairy-cell tumor, adenoma, medullary carcinoma, pheochromocytoma, mucosal neuromas, intestinal ganglioneuromas, hyperplastic corneal nerve tumor, marfanoid habitus tumor, Wilms' tumor, seminoma, ovarian tumor, leiomyomater tumor, cervical dysplasia, neuroblastoma, retinoblastoma, myelodysplastic syndrome, rhabdomyosarcoma, astrocytoma, non-Hodgkin's lymphoma, malignant hypercalcemia, polycythermia vera, adenocarcinoma, glioblastoma multiforma, glioma, lymphomas, and malignant melanomas, among others.

[0159] In addition to cancer, the compounds of Formula 1 may also be used to treat other diseases related to abnormal cell growth, including non-malignant proliferative diseases such as benign prostatic hypertrophy, restinosis, hyperplasia, synovial proliferation disorder, retinopathy or other neovascular disorders of the eye, among others.

[0160] The compounds of Formula 1 may also be used to treat autoimmune disorders in addition to those listed above. Such disorders, diseases, and conditions include Crohns disease, dermatomyositis, diabetes mellitus type 1, Goodpasture's syndrome, Graves' disease, Guillain-Barré syndrome, Hashimoto's disease, mixed connective tissue damage, myasthenia gravis, narcolepsy, pemphigus vulgaris, pernicious anemia, polymyositis, primary biliary cirrhosis, Sjögren's syndrome, temporal arteritis, ulcerative colitis, vasculitis, and Wegener's granulomatosis, among others.

[0161] Furthermore, compounds of Formula 1 may be used to treat inflammatory disorders including asthma, chronic inflammation, chronic prostatitis, glomerulonephritis, hypersensitivities, inflammatory bowel diseases (ulcerative colitis in addition to Crohn's

disease), pelvic inflammatory disease, reperfusion injury, transplant rejection, vasculitis, and systemtic inflammatory response syndrome.

[0162] The compounds of Formula 1 may also be used to treat specific diseases that may fall within one or more general disorders described above, including arthritis. In addition to rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, SLE in children and adolescents, compounds of Formula 1 may also be used to treat other arthritis diseases, including ankylosing spondylitis, avascular necrosis, Bechet's disease, bursitis, calcium pyrophosphate dihyrate crystal deposition disease (pseudo gout), carpal tunnel syndrome, Ehlers-Danlos syndrome, fibromyalgia, Fifth disease, giant cell arteritis, gout, juvenile dermatomyositis, juvenile rheumatoid arthritis, juvenile spondyloarthopathy, Lyme disease, Marfan syndrome, myositis, osteoarthritis, osteogenesis imperfect, osteoporosis, Paget's disease, psoriatic arthritis, Raynaud's phenomenon, reactive arthritis, reflex sympathetic dystrophy syndrome, scleroderma, spinal stenosis, Still's disease, and tendinitis, among others.

[0163] The claimed and disclosed compounds may be combined with one or more other pharmacologically active compounds or therapies for the treatment of one or more disorders, diseases or conditions for which SYK is indicated, including disorders, diseases, and conditions involving the immune system, inflammation, and abnormal cell growth. For example, compounds of Formula 1, which include compounds specifically named above, and their pharmaceutically acceptable complexes, salts, solvates and hydrates, may be administered simultaneously, sequentially or separately in combination with one or more compounds or therapies for treating arthritis, including rheumatoid arthritis and osteoarthritis, or for treating cancer, including hematological malignancies, such as acute myeloid leukemia, B-cell chronic lymphocytic leukemia, B-cell lymphoma, and T-cell lymphoma, and carcinomas, such as lung cancer, pancreatic cancer, and colon cancer. Such combinations may offer significant therapeutic advantages, including fewer side effects, improved ability to treat underserved patient populations, or synergistic activity.

[0164] For example, when used to treat arthritis, the compounds of Formula 1 may be combined with one or more nonsteroidal anti-inflamatory drugs (NSAIDs), analgesics, corticosteroids, biological response modifiers, and protein-A immunoadsorption therapy. Alternatively or additionally, when treating rheumatoid arthritis, the compounds of Formula 1 may be combined with one or more disease modifying antirheumatic drugs

(DMARDs), and when treating osteoarthritis, the compounds of Formula 1 may be combined with one or more osteoporosis agents.

[0165] Representative NSAIDs include apazone, aspirin, celecoxib, diclofenac (with and without misoprostol), diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamate sodium, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, choline and magnesium salicylates, salsalate, and sulindac. Representative analgesics include acetaminophen and morphine sulfate, as well as codeine, hydrocodone, oxycodone, propoxyphene, and tramadol, all with or without acetaminophen. Representative corticosteroids include betamethasone, cortisone acetate, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, and prednisone. Representative biological response modifiers include TNF-α inhibitors, such as adalimumab, etanercept, and infliximab; selective B-cell inhibitors, such as rituximab; IL-1 inhibitors, such as anakinra, and selective costimulation modulators, such as abatacept.

[0166] Representative DMARDs include auranofin (oral gold), azathioprine, chlorambucil, cyclophosamide, cyclosporine, gold sodium thiomalate (injectable gold), hydroxychloroquine, leflunomide, methotrexate, minocycline, myophenolate mofetil, penicillamine, and sulfasalazine. Representative osteoporosis agents include bisphosphonates, such as alendronate, ibandronate, risedronate, and zoledronic acid; selective estrogen receptor modulators, such as droloxifene, lasofoxifene, and raloxifene; hormones, such as calcitonin, estrogens, and parathyroid hormone; and immunosuppressant agents such as azathioprine, cyclosporine, and rapamycin.

[0167] Particularly useful combinations for treating rheumatoid arthritis include a compound of Formula 1 and methotrexate; a compound of Formula 1 and one or more biological response modifiers, such as lefluonomide, etanercept, adalimumab, and infliximab; or a compound of Formula 1, methotrexate, and one or more biological response modifiers, such as lefluonomide, etanercept, adalimumab, and infliximab.

[0168] For the treatment of thrombis and restensosis, the compounds of Formula 1 may be combined with one or more cardiovascular agents such as calcium channel blockers, statins, fibrates, beta-blockers, ACE inhibitors, and platelet aggregation inhibitors.

[0169] The compounds of Formula 1 may also be combined with one or more compounds or therapies for treating cancer. These include chemotherapeutic agents (i.e., cytotoxic or antineoplastic agents) such as alkylating agents, antibiotics, antimetabolic agents, plant-derived agents, and topoisomerase inhibitors, as well as molecularly targeted drugs which block the growth and spread of cancer by interfering with specific molecules involved in tumor growth and progression. Molecularly targeted drugs include both small molecules and biologics.

[0170] Representative alkylating agents include bischloroethylamines (nitrogen mustards, e.g., chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine, melphalan, and uracil mustard); aziridines (e.g., thiotepa); alkyl alkone sulfonates (e.g., busulfan); nitrosoureas (e.g., carmustine, lomustine, and streptozocin); nonclassical alkylating agents (e.g., altretamine, dacarbazine, and procarbazine); and platinum compounds (e.g., carboplatin, cisplatin, nedaplatin, oxaliplatin, satraplatin, and triplatin tetranitrate).

[0171] Representative antibiotic agents include anthracyclines (e.g., aclarubicin, amrubicin, daunorubicin, doxorubicin, epirubicin, idarubicin, pirarubicin, valrubicin, and zorubicin); anthracenediones (e.g., mitoxantrone and pixantrone); and streptomyces (e.g., actinomycin, bleomycin, dactinomycin, mitomycin C, and plicamycin).

[0172] Representative antimetabolic agents include dihydrofolate reductase inhibitors (e.g., aminopterin, methotrexate, and pemetrexed); hymidylate synthase inhibitors (e.g., raltitrexed and pemetrexed); folinic acid (e.g., leucovorin); adenosine deaminase inhibitors (e.g., pentostatin); halogenated/ribonucleotide reductase inhibitors (e.g., cladribine, clofarabine, and fludarabine); thiopurines (e.g, thioguanine and mercaptopurine); thymidylate synthase inhibitors (e.g., fluorouracil, capecitabine, tegafur, carmofur, and floxuridine); DNA polymerase inhibitors (e.g., cytarabine); ribonucleotide reductase inhibitors (e.g., gemcitabine); hypomethylating agent (e.g., azacitidine and decitabine); and ribonucleotide reductase inhibitor (e.g., hydroxyurea); and an asparagine depleter (e.g., asparaginase)

[0173] Representative plant-derived agents include vinca alkaloids (e.g., vincristine, vinblastine, vindesine, vinzolidine, and vinorelbine), podophyllotoxins (e.g., etoposide and teniposide), and taxanes (e.g., docetaxel, larotaxel, ortataxel, paclitaxel, and tesetaxel).

[0174] Representative type I topoisomerase inhibitors include camptothecins, such as belotecan, irinotecan, rubitecan, and topotecan. Representative type II topoisomerase inhibitors include amsacrine, etoposide, etoposide phosphate, and teniposide, which are derivatives of epipodophyllotoxins.

[0175] Molecularly targeted therapies include biologic agents such as cytokines and other immune-regulating agents. Useful cytokines include interleukin-2 (IL-2, aldesleukin), interleukin 4 (IL-4), interleukin 12 (IL-12), and interferon, which includes more than 23 related subtypes. Other cytokines include granulocyte colony stimulating factor (CSF) (filgrastim) and granulocyte macrophage CSF (sargramostim). Other immuno-modulating agents include bacillus Calmette-Guerin, levamisole, and octreotide; monoclonal antibodies against tumor antigens, such as trastruzumab and rituximab; and cancer vaccines, which induce an immune response to tumors.

[0176] In addition, molecularly targeted drugs that interfere with specific molecules involved in tumor growth and progression include inhibitors of epidermal growth factor (EGF), transforming growth factor-alpha (TGF_{α}), TGF_{β}, heregulin, insulin-like growth factor (IGF), fibroblast growth factor (FGF), keratinocyte growth factor (KGF), colony stimulating factor (CSF), erythropoietin (EPO), interleukin-2 (IL-2), nerve growth factor (NGF), platelet-derived growth factor (PDGF), hetaptocyte growth factor (HGF), vascular endothelial growth factor (VEGF), angiopoietin, epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), HER4, insulin-like growth factor 1 receptor (IGF1R), IGF2R, fibroblast growth factor 1 receptor (FGF1R), FGF2R, FGF3R, FGF4R, vascular endothelial growth factor receptor (VEGFR), tyrosine kinase with immunoglobulin-like and epidermal growth factor-like domains 2 (Tie-2), platelet-derived growth factor receptor (PDGFR), Abl, Bcr-Abl, Raf, FMS-like tyrosine kinase 3 (FLT3), c-Kit, Src, protein kinase c (PKC), tropomyosin receptor kinase (Trk), Ret, mammalian target of rapamycin (mTOR), Aurora kinase, polo-like kinase (PLK), mitogen activated protein kinase (MAPK), mesenchymal-epithelial transition factor (c-MET), cyclin-dependant kinase (CDK), Akt, extracellular signal-regulated kinases (ERK), poly(ADP) ribose polymerase (PARP), and the like.

[0177] Specific molecularly targeted drugs include selective estrogen receptor modulators, such as tamoxifen, toremifene, fulvestrant, and raloxifene; antiandrogens,

such as bicalutamide, nilutamide, megestrol, and flutamide; and aromatase inhibitors, such as exemestane, anastrozole, and letrozole. Other specific molecularly targeted drugs include agents which inhibit signal transduction, such as imatinib, dasatinib, nilotinib, trastuzumab, gefitinib, erlotinib, cetuximab, lapatinib, panitumumab, and temsirolimus; agents that induce apoptosis, such as bortezomib; agents that block angiogensis, such as bevacizumab, sorafenib, and sunitinib; agents that help the immune system destroy cancel cells, such as rituximab and alemtuzumab; and monoclonal antibodies which deliver toxic molecules to cancer cells, such as gemtuzumab ozogamicin, tositumomab, 131I-tositumoab, and ibritumomab tiuxetan.

[0178] BIOLOGICAL ACTIVITY: SYK INHIBITION

[0179] The ability of compounds to inhibit SYK activity may be assessed using a variety of methods, including *in vitro* and *in vivo* assays. The following *in vitro* assay measures a test compound's ability to inhibit SYK-mediated phosphorylation of a FAM-labeled SYK-specific substrate (5FAM-KKKKEEIYFFFG-NH_2).

[0180] SYK protein is prepared from cDNA encoding human spleen tyrosine kinase and is expressed in insect cells using a baculovirus expression vector. The cDNA (IMAGE: 3542895) is purchased from Open Biosystems. The SYK kinase domain (residues 356-635) is amplified via PCR and cloned into plasmid pFastBac1 (Invitrogen) at BamHI/XbaI sites. Recombinant plasmid encoding Met-Ala-Lys-SYK(356-635)-HHHHHH is sequenced and transformed into *E.* coli DH10Bac strain. The recombinant bacmid DNA is isolated and transfected into Sf9 insect cells. Recombinant virus is harvested 72 h after transfection. High titer viral stock is prepared by infecting Sf9 cells at a multiplicity of infection (MOI) of approximately 0.01. A suspension of Sf9 cells (10 L) is infected with recombinant virus (MOI=5) and is incubated in a Wave Bioreactor (GE-Healthcare) for 48 h. The cells are harvested and stored at -80°C.

[0181] To purify the expressed protein, the frozen Sf9 cells (10 L) are broken into small (< 1 cm) particles and suspended in a lysis buffer (300 mL) containing 20 mM Tris (pH 7.6), 0.25mM TCEP, 100 mM NaCl, 5% glycerol and a protease inhibitor. The suspension is stirred at RT until completely thawed, lysed an additional 2-4 min on a rotary blade homogenizer, and then centrifuged at 4200 g for 1 h. Following centrifugation, the supernatant is poured through cheese cloth and combined with a nickel chelating resin (Probond Resin™, Invitrogen) which is pre-equilibrated in a wash buffer

containing 10 mM Tris (pH 7.6), 0.25mM TCEP, 300 mM NaCl, 5% glycerol, and 20mM imidazole. The mixture is agitated for 3 h in a cold room and then centrifuged at 900 g for 10 min. The resin is dispersed in wash buffer (50 mL), centrifuged for 10 min at 900 g, re-dispersed in a small amount of wash buffer (5 mL), and then pour into a disposable Poly-Prep chromatography column, through which wash buffer is passed by gravity until no protein is observed in coomassie buffer (about 120 mL of wash buffer). An elution buffer (30 mL) containing 10 mM HEPES (pH 7.4), 150 mM NaCl, 10% glycerol, 5 mM DTT, and 400 mM imidazole is used to elute the SYK protein from the resin. The eluate is concentrated (5 mL) and further purified on a Superdex 200 column (1.2 mL/min for 160 min, 10 mM HEPES (pH 7.4), 10 mM NaCl, 10 mM MgCl, 0.1 mM EDTA, and 0.25 mM TCEP). The chromatographed fractions are run on SDS-PAGE and the requisite fractions are pooled and concentrated. Final delivery buffer is 10 mM HEPES (pH 7.4), 10mM Methione, 150 mM NaCl, 10% glycerol, 5 mM DTT.

[0182] SYK inhibition is determined using a black 384 well plate format in buffer containing 50 mM HEPES, 10 mM NaCl, 10 mM $MgCl_2$, 0.2 mM EDTA, 0.01% EDA (Brij®35), 1 mM DTT, and 0.1 mg/ml BSA at pH 7.3. Each test compound is prepared in DMSO using 2-fold serial dilutions for 11 data points, which are added to the buffer so that each dilution contains 3% DMSO. To each well is added 2 μL of 3 μM 5FAM-KKKKEEIYFFFG-NH_2 (in buffer), 2 μL of diluted test compound (3% DMSO in buffer), and 2 μL of 2.4 nM SYK and 45 μM ATP (in buffer). The reaction mixture is incubated at RT for 60 min, and quenched by adding 50 mM Hepes, 30 mM EDTA, 0.1% Triton X-100 (pH 7.3). To quantify the fluorescent-labeled substrate and product following reaction, the test plate is loaded on a Caliper LC-3000, which measures percent of conversion by microfluidic-based separation. Corresponding IC_{50} values are calculated by non-linear curve fitting of the compound concentrations and percent of inhibition to the standard IC_{50} equation and reported as pIC_{50}, i.e., -log(IC_{50}), where IC_{50} is molar concentration.

EXAMPLES

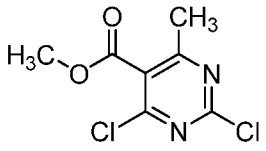
[0183] The following examples are intended to be illustrative and non-limiting, and represent specific embodiments of the present invention.

[0184] ^1H Nuclear magnetic resonance (NMR) spectra were obtained for many of the compounds in the following examples. Characteristic chemical shifts (δ) are given in

parts-per-million downfield from tetramethylsilane using conventional abbreviations for designation of major peaks, including s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), spt (septet) and br (broad). The mass spectra (*m/z*) were recorded using either electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI). The following abbreviations are used for common solvents: $CDCl_3$ (deuterochloroform), DMSO-d_6 (deuterodimethylsulfoxide), CD_3OD (deuteromethanol), and THF-d_8 (deuterotetrahydrofuran). "Ammonia" refers to a concentrated solution of ammonia in water possessing a specific gravity of 0.88.

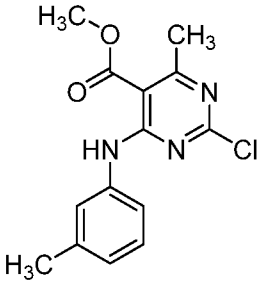
[0185] Where indicated, products of certain preparations and examples are purified by mass-triggered HPLC (e.g., Pump: Waters™ 2525; MS: ZQ™; Software: MassLynx™), flash chromatography or preparative thin layer chromatography (TLC). Preparative HPLC is carried out using either acidic or basic conditions. Acid conditions are typically gradients in Solvent A (water with 0.05% TFA) and Solvent B (acetonitrile with 0.035% TFA); basic conditions are typically gradients in Solvent A (10 mM NH_4HCO_3 in water) and Solvent B (10 mM NH_4HCO_3 in 20/80 (v/v) water/acetonitrile). The mentioned preparative HPLC conditions use acidic conditions unless indicated as basic. Preparative TLC is typically carried out on silica gel 60 F_{254} plates. After isolation by chromatography, the solvent is removed and the product is obtained by drying in a centrifugal evaporator (e.g., GeneVac™), rotary evaporator, evacuated flask, lyophilizer, *etc*. Reactions in an inert (e.g., nitrogen) or reactive (e.g., H_2) atmosphere are typically carried out at a pressure of about 1 atmosphere (14.7 psi) or greater.

[0186] PREPARATION 1: Methyl 2,4-dichloro-6-methylpyrimidine-5-carboxylate



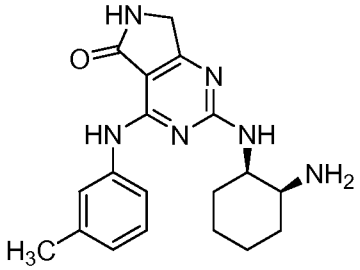
[0187] To a suspension of methyl 6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1 g, 5.43 mmol) in $POCl_3$ (10 mL) was added 10 drops of *N*,*N*-dimethylaniline. The reaction mixture was heated at 105°C for 6 h until it became a clear solution. It was then cooled, concentrated under reduced pressure, poured over ice, and extracted with EtOAc. The organic extract was washed with water and brine, dried and concentrated under reduced pressure to give the title compound as greenish-yellow solid (940 mg, 78%). [M+H] calc'd for $C_7H_6Cl_2N_2O_2$, 222; found, 221, 223.

[0188] PREPARATION 2: Methyl 2-chloro-4-methyl-6-(*m*-tolylamino)pyrimidine-5-carboxylate.

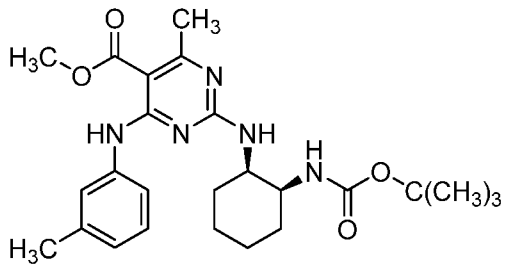


[0189] A mixture of methyl 2,4-dichloro-6-methylpyrimidine-5-carboxylate (940 mg, 4.25 mmol), *m*-toluidine (0.461 mL, 4.25 mmol) and *N*-ethyldiisopropylamine (1.481 mL, 8.51 mmol) in CH_3CN (30 mL) was heated under reflux for 3 h. The mixture was diluted with EtOAc, and was washed with brine and water. The organic extract was dried and concentrated under reduced pressure to give the title compound as a light yellow solid (1.2 g, 97%). [M+H] calc'd for $C_{14}H_{14}N_3ClO_2$, 292; found, 292.

[0190] EXAMPLE 1: 2-((1*R*,2S)-2-Aminocyclohexylamino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one



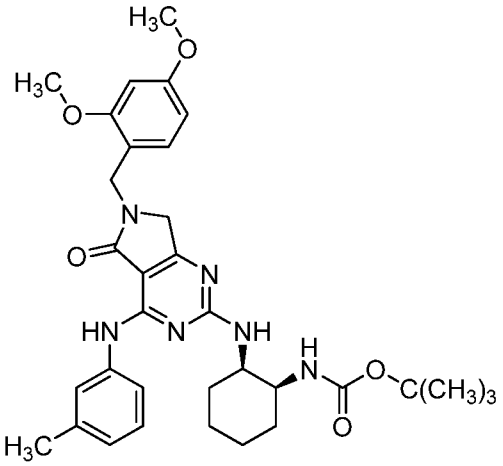
[0191] A. Methyl 2-((1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclohexylamino)-4-methyl-6-(*m*-tolylamino)pyrimidine-5-carboxylate



[0192] A solution of methyl 2-chloro-4-methyl-6-(*m*-tolylamino)pyrimidine-5-carboxylate (1.2 g, 4.11 mmol), *tert*-butyl (1*S*,2*R*)-2-aminocyclohexylcarbamate (0.882 g, 4.11 mmol) and triethylamine (1.720 mL, 12.34 mmol) in DMA (10 mL) was heated at 90°C for 4 h. The solution was then diluted with EtOAc, washed with brine and water. The

organic extract was dried and concentrated under reduced pressure to give a light yellow residue; white crystals were formed upon triturating with ACN (5 mL). The resultant solid was filtered, washed with ACN, and dried to give the title compound as white solid (1.2 g, 62%). [M+H] calc'd for $C_{25}H_{35}N_5O_4$, 470; found, 470.

[0193] B. *tert*-Butyl (1*S*,2*R*)-2-(6-(2,4-dimethoxybenzyl)-5-oxo-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-2-ylamino)cyclohexylcarbamate

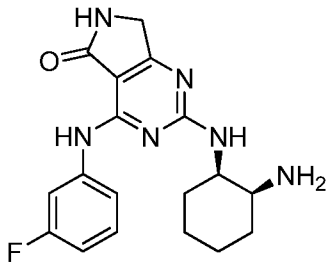


[0194] A mixture of methyl 2-((1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclohexylamino)-4-methyl-6-(*m*-tolylamino)pyrimidine-5-carboxylate (500 mg, 1.065 mmol) and selenium dioxide (236 mg, 2.130 mmol) in dioxane (10 mL) was heated at 100°C for 24 h. The solution was subsequently cooled and filtered. The filtrate was concentrated under reduced pressure and dried to give a brown foam (534 mg; dihydroxyl form was observed via mass spectroscopy), which was used directly in the next step without further purification. A mixture of the unpurified intermediate (534 mg, 1.065 mmol) and (2,4-dimethoxyphenyl)methanamine (0.160 mL, 1.065 mmol) in MeOH (10 mL) was stirred at RT for 10 min, after which sodium cyanoborohydride (100 mg, 1.597 mmol) was added, and the reaction mixture was stirred at RT for 20 h. The reaction mixture was warmed to 50°C and stirred for an additional 2 h to complete the reaction. The mixture was cooled to RT and the solid filtered and washed with MeOH to give the title compound as a pinkish solid (237 mg, 37%). [M+H] calc'd for $C_{33}H_{42}N_6O_5$, 603; found, 603.

[0195] C. 2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one

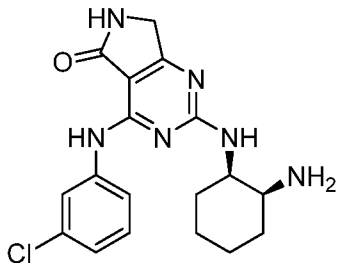
[0196] A mixture of crude *tert*-butyl (1*S*,2*R*)-2-(6-(2,4-dimethoxybenzyl)-5-oxo-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-2-ylamino)cyclohexylcarbamate (235 mg, 0.390 mmol) in TFA (5 mL) was stirred at 60°C for 2 h and was then purified by reverse phase preparative HPLC. The fractions were collected, concentrated under reduced pressure, diluted in EtOAc, and basified with an aqueous saturated solution of $NaHCO_3$. The organic extract was dried and concentrated under reduced pressure to give the title compound as a white solid (60 mg, 44%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33-1.60 (m, 10 H), 2.32 (s, 3 H), 3.16 (m, 2 H), 3.92 (br s, 1 H), 4.14 (s, 2 H), 6.88 (d, *J*=7.07 Hz, 1 H), 7.13 (br s, 1 H), 7.22 (t, *J*=7.45 Hz, 1 H), 7.34 - 7.55 (m, 1 H), 7.70 (br s, 1 H), 8.01 (br s, 1 H), 8.58 (br s, 1 H). [M+H] calc'd for $C_{19}H_{24}N_6O$, 353; found, 353.

[0197] EXAMPLE 2: 2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(3-fluorophenylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one



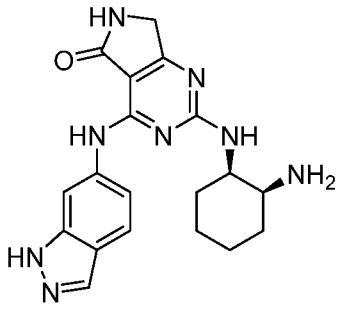
[0198] The title compound was prepared in a manner similar to EXAMPLE 1 by reacting methyl 2,4-dichloro-6-methylpyrimidine-5-carboxylate with 3-fluoroaniline instead of *m*-toluidine. The final product was purified via reverse phase preparative HPLC. Lyophilization gave a TFA salt of the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 - 1.56 (m, 2 H), 1.56 - 1.73 (m, 4 H), 1.77 -1.85 (br s, 2 H), 4.22 (br s, 4 H), 6.90 (br s, 1 H), 7.25 - 7.44 (m, 2 H), 7.48 (br s, 1 H), 7.77 (br s, 3 H), 8.20 (d, *J*=13.64 Hz, 1 H), 8.83 (d, *J*=14.40 Hz, 1 H). [M+H] calc'd for $C_{18}H_{21}FN_6O$, 357; found, 357.

[0199] EXAMPLE 3: 2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(3-chlorophenylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one



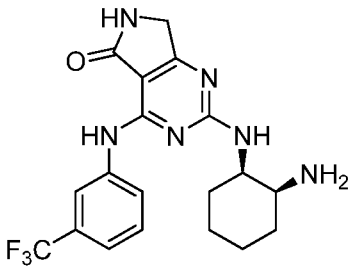
[0200] The title compound was prepared in a manner similar to EXAMPLE 1 by reacting methyl 2,4-dichloro-6-methylpyrimidine-5-carboxylate with 3-chloroaniline instead of *m*-toluidine. The final product was purified via reverse phase preparative HPLC. Lyophilization gave a TFA salt of the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.43 (br s, 2 H), 1.67-1.96 (m, 6 H), 4.20 (br s, 3 H), 7.13 (d, *J*=7.33 Hz, 1 H), 7.36 (t, *J*=8.08 Hz, 1 H), 7.48 (br s, 1 H), 7.75 (br s, 2 H), 8.16 (br s, 1 H), 8.82 (br s, 1 H). [M+H] calc'd for $C_{18}H_{21}ClN_6O$, 373; found, 373.

[0201] EXAMPLE 4: 4-(1*H*-Indazol-6-ylamino)-2-((1*R*,2*S*)-2-aminocyclohexylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one

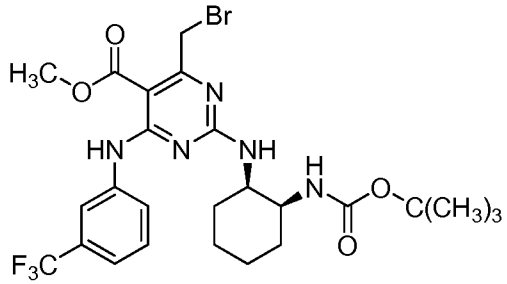


[0202] The title compound was prepared in a manner similar to EXAMPLE 1 by reacting methyl 2,4-dichloro-6-methylpyrimidine-5-carboxylate with 1*H*-indazol-6-amine instead of *m*-toluidine. The final product was purified via reverse phase preparative HPLC. Lyophilization gave a TFA salt of the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.43-1.92 (br s, 8 H), 2.33 (s, 1 H), 3.57 (m, 1 H), 4.21 (br s, 2 H), 6.94 (s, 1 H), 7.07 (s, 1 H), 7.14 - 7.31 (m, 1 H), 7.43 (m, 1 H), 7.71 (d, *J*=8.59 Hz, 2 H), 8.01 (s, 1 H), 8.14 (br s, 1 H), 8.84 (s, 1 H), 12.99 (br s, 1 H). [M+H] calc'd for $C_{19}H_{22}N_8O$, 379; found, 379.

[0203] EXAMPLE 5: 2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(3-(trifluoromethyl)phenylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one

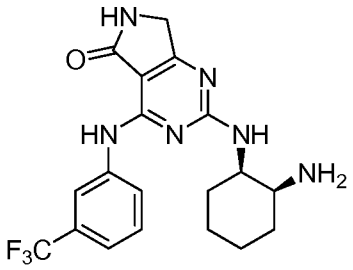


[0204] A. Methyl 4-(bromomethyl)-2-((1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclohexylamino)-6-(3-(trifluoromethyl)phenylamino)pyrimidine-5-carboxylate



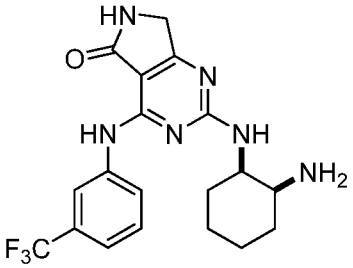
[0205] Methyl 2-((1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclohexylamino)-4-methyl-6-(3-(trifluoromethyl)phenylamino)pyrimidine-5-carboxylate (104 mg, 0.199 mmol), which was prepared in a manner similar to methyl 2-((1*R*,2*S*)-2-(*tert*-butoxycarbonyl-amino)cyclohexylamino)-4-methyl-6-(*m*-tolylamino)pyrimidine-5-carboxylate in step B of EXAMPLE 1 using 3-(trifluoromethyl)aniline in place of *m*-toluidine in step A of the example, was combined with 1-bromopyrrolidine-2,5-dione (53.0 mg, 0.298 mmol) and benzoic peroxyanhydride (48.1 mg, 0.199 mmol) in CCl_4 (10 mL), and the resulting mixture was stirred at 70°C for 18 h. The reaction was stopped. The mixture was concentrated under reduced pressure, separated between water and EtOAc. The organic extract was dried and concentrated under reduced pressure to give the title compound, which was used in the next step without further purification. [M+H] calc'd for $C_{25}H_{31}BrN_5O_4$, 603; found, 604.

[0206] B. 2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(3-(trifluoromethyl)phenylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one



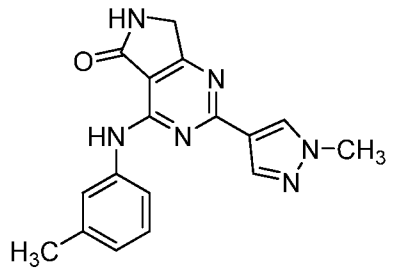
[0207] A mixture of methyl 4-(bromomethyl)-2-((1*R*,2*S*)-2-(*tert*-butoxycarbonyl-amino)cyclohexylamino)-6-(3-(trifluoromethyl)phenylamino)pyrimidine-5-carboxylate (120 mg, 0.199 mmol) in THF was treated with ammonium hydroxide. The reaction mixture was stirred at RT overnight, and subsequently worked up and purified by reverse phase preparative HPLC. The fractions were collected and concentrated under reduced pressure to give a residue, which was treated with TFA/DCM. The final product was purified again by preparative HPLC. Lyophilization gave a TFA salt of the title compound as a white solid (2.6 mg, 3%). [M+H] calc'd for $C_{19}H_{21}F_3N_6O$, 407; found, 407.

[0208] EXAMPLE 6: *cis*-2-(2-Aminocyclohexylamino)-4-(3-(trifluoromethyl)phenylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one



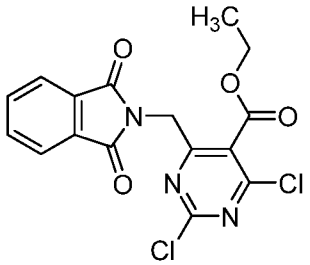
[0209] The title compound was prepared in a manner similar to EXAMPLE 5 using methyl *cis*-2-(2-(*tert*-butoxycarbonylamino)cyclohexylamino)-4-methyl-6-(3-(trifluoromethyl)phenylamino)pyrimidine-5-carboxylate in place of methyl 2-((1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclohexylamino)-4-methyl-6-(3-(trifluoromethyl)phenyl-amino)pyrimidine-5-carboxylate. The final product was purified via reverse phase preparative HPLC. Lyophilization gave a TFA salt of the title compound as a white solid. [M+H] calc'd for $C_{19}H_{21}F_3N_6O$, 407; found, 407.

[0210] EXAMPLE 7: 2-(1-Methyl-1*H*-pyrazol-4-yl)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one

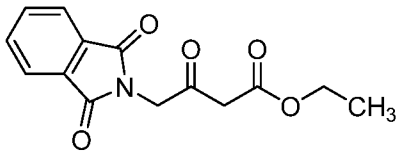


[0211] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 1 using 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole in place of *tert*-butyl (1*S*,2*R*)-2-aminocyclohexylcarbamate. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.37 (s, 3 H), 3.93 (s, 3 H), 4.39 (s, 2 H), 6.95 (d, J = 7.32 Hz, 1 H), 7.32 (t, J = 7.81 Hz, 1 H), 7.62 (s, 1 H), 7.77 (d, J = 8.30 Hz, 1 H), 8.03 (s, 1 H), 8.37 (s, 1 H), 8.65 (s, 1 H), 8.82 (s, 1 H). [M+H] calc'd for $C_{17}H_{16}N_6O$, 321; found, 321.

[0212] PREPARATION 3: Ethyl 2,4-dichloro-6-((1,3-dioxoisoindolin-2-yl)methyl)pyrimidine-5-carboxylate



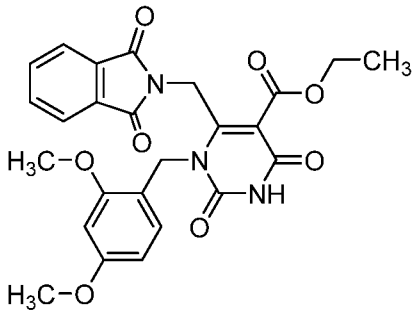
[0213] A. Ethyl 4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-3-oxobutanoate



[0214] To a solution of 2-(1,3-dioxoisoindolin-2-yl)acetic acid (3.01 g, 14.67 mmol), 2,2-dimethyl-1,3-dioxane-4,6-dione (2.23 g, 15.47 mmol) and 4-dimethylaminopyridine (2.73 g, 22.35 mmol) in dichloromethane (150 mL) was added a solution of DCC (3.36 g, 16.28 mmol) in DCM (50 mL) at 0°C. The mixture was stirred at RT for 16 h. The insoluble materials were filtered off, and the filtrate was washed with 5% $NaHSO_4$ aqueous solution. The organic phase was dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was treated with EtOH (200 mL) and the resulting mixture was stirred at 70°C for 4 h and then concentrated under reduced pressure. Water was added to the residue and the mixture was extracted with

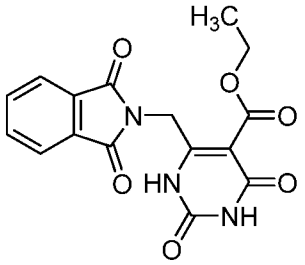
EtOAc. The organic layers were washed with water and brine, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure and the residue was washed with IPE to give the title compound as a colorless solid (3.43 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.31 (t, *J*=6.8Hz, 3H,), 3.58 (s, 2H), 4.24 (q, *J*=6.8 Hz, 2H), 4.67 (s, 2H), 7.73 - 7.78 (m, 2H), 7.86 - 7.91 (m, 2H).

[0215] B. Ethyl 1-(2,4-dimethoxybenzyl)-6-((1,3-dioxoisoindolin-2-yl)methyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate



[0216] A mixture of ethyl 4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-3-oxobutanoate (249.8 mg, 0.908 mmol) and (2,4-dimethoxyphenyl)methanamine (152 mg, 0.908 mmol) in EtOH (4 mL) was stirred at 50°C for 16 h. The obtained solid was isolated by filtration to give a colorless solid (51.7 mg). To a suspension of the solid in THF (4 mL) was added carbonisocyanatidic chloride (96 mg, 0.908 mmol) and the mixture was stirred at 80°C for 1 h. After cooling to RT, water (10 mL) was added and the mixture was extracted with EtOAc. The organic layers were washed with brine, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (SiO_2, hexane/EtOAc=1/1) to give the title compound (56.2 mg, 13%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.28 (t, *J*=7.2Hz, 3H), 3.63 (s, 3H), 3.81 (s, 3H), 4.22 (q, *J*=7.2Hz, 2H), 4.95 (s, 2H), 5.12 (s, 2H), 6.18 (dd, *J*=8.4, 6.4Hz, 1H), 6.23 (d, *J*=6.4Hz, 1H), 6.75 (d, *J*=8.4Hz, 1H), 7.63 - 7.72 (m, 4H), 8.23 (br s, 1H).

[0217] C. Ethyl 6-((1,3-dioxoisoindolin-2-yl)methyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

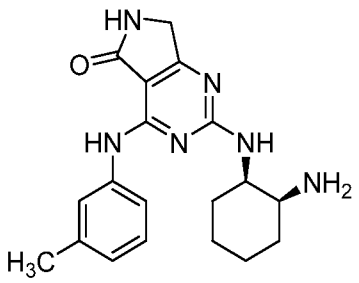


[0218] To trifluoroacetic acid (2 mL, 26.0 mmol) was added ethyl 1-(2,4-dimethoxybenzyl)-6-((1,3-dioxoisoindolin-2-yl)methyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (198.9 mg, 0.403 mmol) at 0°C. The mixture was stirred at 0°C for 1 h, then at RT for 6 h. The mixture was concentrated under reduced pressure, and the residue was washed with IPE (5 mL) to give the title compound (183.3 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.42 (t, *J*=7.2Hz, 3H), 4.45 (q, *J*=7.2Hz, 2H), 4.98 (s, 2H), 7.78 - 7.81 (m, 2H), 7.91 - 7.93 (m, 2H), 8.19 (br s, 1H), 8.96 (br s, 1H).

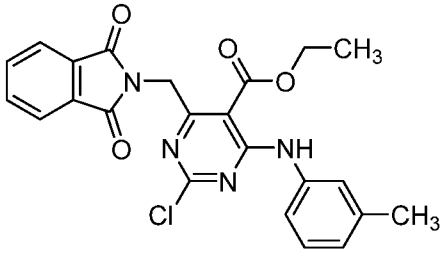
[0219] D. Ethyl 2,4-dichloro-6-((1,3-dioxoisoindolin-2-yl)methyl)pyrimidine-5-carboxylate

[0220] A mixture of ethyl 6-((1,3-dioxoisoindolin-2-yl)methyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (96.1 mg, 0.280 mmol) and phosphorus oxychloride (1 mL, 10.92 mmol) was stirred at 100°C for 12 h and allowed to cool. The mixture was concentrated under reduced pressure to remove excess $POCl_3$. The residue was treated with saturated aq $NaHCO_3$ and extracted with EtOAc. The organic phase was washed with saturated aqueous $NaHCO_3$, water, and brine, was dried over anhydrous Na_2SO_4, and then filtered through SiO_2. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/EtOAc=4/1) to give the title compound (46.0 mg, 43%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.42 (t, *J*=7.2Hz, 3H), 4.45 (q, *J*=7.2Hz, 2H), 5.05 (s, 2H), 7.76 - 7.80 (m, 2H), 7.89 - 7.93 (m, 2H).

[0221] EXAMPLE 8: 2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(3-(trifluoromethyl)phenylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one (free base)

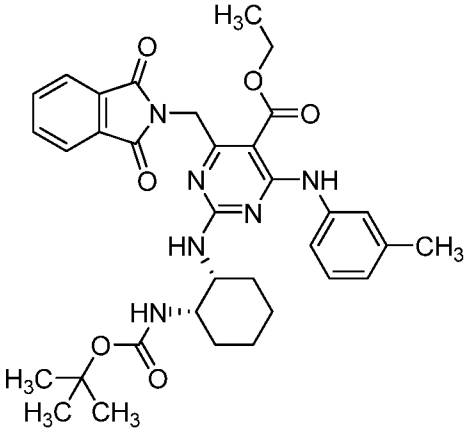


[0222] A. Ethyl 2-chloro-4-((1,3-dioxoisoindolin-2-yl)methyl)-6-(*m*-tolylamino)pyrimidine-5-carboxylate



[0223] To a solution of ethyl 2,4-dichloro-6-((1,3-dioxoisoindolin-2-yl)methyl)pyrimidine-5-carboxylate (45.3 mg, 0.119 mmol) in MeCN (1 mL) was added *m*-toluidine (0.020 mL, 0.187 mmol) and *N*,*N*-diisopropylethylamine (0.037 mL, 0.212 mmol). The mixture was stirred at RT for 12 h. Saturated aq $NaHCO_3$ was added to the mixture, which was subsequently extracted with EtOAc. The organic layers were washed again with saturated aq $NaHCO_3$, water, and brine, were dried over anhydrous Na_2SO_4, and then filtered through SiO_2. The filtrate was concentrated under reduced pressure and the residue was washed with IPE to give the title compound as a pale brown solid (37.1 mg, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.50 (t, *J*=7.2Hz, 3H), 2.36 (s, 3H), 4.52 (q, *J*=7.2Hz, 2H), 5.20 (s, 2H), 6.97 - 6.98 (m, 1H), 7.23 - 7.27 (m, 1H), 7.33 (br s, 1H), 7.45 - 7.47 (m, 1H), 7.73 - 7.78 (m, 2H), 7.89 - 7.94 (m, 2H), 10.67 (br s, 1H).

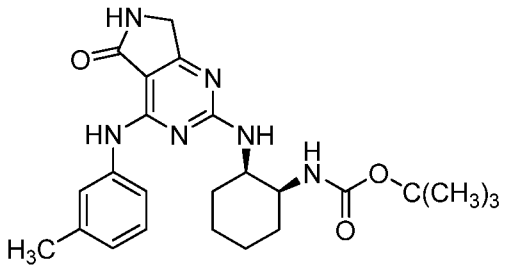
[0224] B. Ethyl 2-((1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclohexylamino)-4-((1,3-dioxoisoindolin-2-yl)methyl)-6-(*m*-tolylamino)pyrimidine-5-carboxylate



[0225] A mixture of ethyl 2-chloro-4-((1,3-dioxoisoindolin-2-yl)methyl)-6-(*m*-tolylamino)pyrimidine-5-carboxylate (96.3 mg, 0.214 mmol), *tert*-butyl (1*S*,2*R*)-2-aminocyclohexylcarbamate (58.14 mg, 0.271 mmol) and Et_3N (0.030 mL, 0.214 mmol) in

DMA (2 mL) was stirred at 80°C for 3 h. Saturated aq $NaHCO_3$ was added to the mixture, which was extracted with EtOAc. The combined organic layers were washed with aqueous $NaHCO_3$, water, and brine, were dried over anhydrous Na_2SO_4, and then filtered through SiO_2. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/EtOAc=3/1) to give the title compound as a yellow oil (123.8 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.12 - 1.71 (m, 20H), 2.33 (s, 3H), 3.39 - 3.57 (m, 1H), 3.84 - 3.99 (m, 1H), 4.42 (q, *J*=7.2Hz, 2H), 4.55 - 4.79 (m, 1H), 5.16 (s, 2H), 5.41 (br s, 1H), 6.87 - 6.89 (m, 1H), 7.16 - 7.49 (m, 3H), 7.74 - 7.75 (m, 2H), 7.90 - 7.91 (m, 2H), 10.68 - 10.81 (m, 1H). [M+H] calc'd for $C_{34}H_{41}N_6O_6$, 629; found, 629.

[0226] C. *tert*-Butyl (1*S*,2*R*)-2-(5-oxo-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-2-ylamino)cyclohexylcarbamate

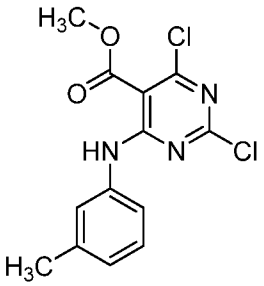


[0227] A mixture of ethyl 2-((1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclohexylamino)-4-((1,3-dioxoisoindolin-2-yl)methyl)-6-(*m*-tolylamino)pyrimidine-5-carboxylate (109 mg, 0.174 mmol) and hydrazine hydrate (36.5 mg, 0.729 mmol) in EtOH (2 mL) was stirred at 65°C for 12 h. After cooling, the mixture was concentrated under reduced pressure and the residue was treated with water and extracted with EtOAc. The combined organic layers were washed with aqueous $NaHCO_3$, water, and brine, were filtered through SiO_2, and the filtrate was concentrated under reduced pressure. The residue was recrystallized from EtOAc/hexanes and filtered to give the title compound (34.8 mg). The filtrate was concentrated and triturated with IPE to give a second batch (20.3 mg) of the title compound (total 65.1 mg, 83%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.24 - 1.79 (m, 17H), 2.32 (s, 3H), 3.84 (br s, 1H), 4.06 (br s, 1H), 4.14 (s, 2H), 6.55 - 6.70 (m, 1H), 6.87 - 7.04 (m, 2H), 7.20 - 7.24 (m, 1H), 7.40 - 7.48 (m, 1H), 7.68 - 7.80 (m, 1H), 8.01 - 8.06 (m, 1H), 8.56 - 8.59 (m, 1H). [M+H] calc'd for $C_{24}H_{33}N_6O_3$, 453; found, 453.

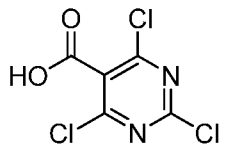
[0228] D. 2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(3-(trifluoromethyl)phenylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one

[0229] To a solution of *tert*-butyl (1*S*,2*R*)-2-(5-oxo-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-2-ylamino)cyclohexylcarbamate (50.4 mg, 0.111 mmol) in HOAc (2 mL) was added hydrochloric acid (0.5 mL, 16.46 mmol). The mixture was stirred at RT for 30 min and then concentrated under reduced pressure. The residue was treated with saturated aq $NaHCO_3$ and extracted with EtOAc. The organic layers were washed with saturated aq $NaHCO_3$, water, and brine, were dried over anhydrous Na_2SO_4, and then filtered. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (SiO_2, EtOAc/MeOH=20/1) to give the title compound as a white powder (11.3 mg, 29%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.48 - 1.80 (m, 10H), 2.37 (s, 3H), 3.24 (br s, 1H), 4.07 (br s, 1H), 4.20 (s, 2H), 5.55 (br s, 1H), 5.89 (br s, 1H), 6.89 - 6.91 (m, 1H), 7.22 - 7.24 (m, 1H), 7.53 - 7.63 (m, 2H), 8.49 (br s, 1H). [M+H] calc'd for $C_{19}H_{25}N_6O$, 353; found, 353.

[0230] PREPARATION 4: Methyl 2,4-dichloro-6-(*m*-tolylamino)pyrimidine-5-carboxylate



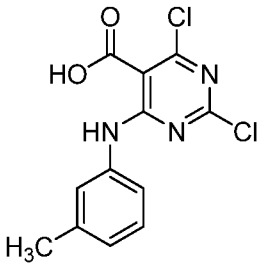
[0231] A. 2,4,6-Trichloropyrimidine-5-carboxylic acid



[0232] To a solution of diisopropylamine (23.42 mL, 164 mmol) in THF (200 mL) was slowly added butyllithium (100 mL, 160 mmol) at -78°C. The mixture was stirred at -78°C for 15 min. To this mixture was slowly added a solution of 2,4,6-trichloropyrimidine (20.06 g, 109 mmol) in THF (50 mL) at -78°C. The mixture was stirred for 1 h. Dry ice was added and the mixture was stirred at RT for 1 h. To the mixture was added 1N HCl, which was subsequently extracted with EtOAc. The organic layers were basified with

aqueous $NaHCO_3$, and washed with EtOAc. The aqueous layer was then acidified with 1N HCl, and extracted with EtOAc. The organic layers were washed with 1N HCl, water, and brine, were dried over anhydrous $MgSO_4$, and then filtered. The filtrate was concentrated under reduced pressure. The residue was washed with hexane to give the desired product as a pale brown solid (12.28 g, 49%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.65 (br s, 1H).

[0233] B. 2,4-Dichloro-6-(*m*-tolylamino)pyrimidine-5-carboxylic acid



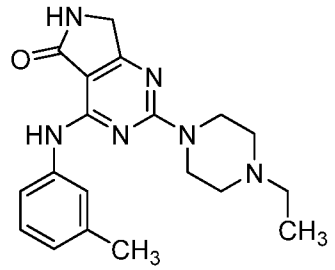
[0234] To a solution of 2,4,6-trichloropyrimidine-5-carboxylic acid (5.69 g, 25.02 mmol) in DMF (60 mL) was added Et_3N (8 mL, 57.4 mmol) and *m*-toluidine (3.2 mL, 29.5 mmol) at 0°C. The mixture was stirred at RT for 12 h. To the mixture was added 1N HCl. The mixture was extracted with EtOAc. The organic layers were basified with saturated aq $NaHCO_3$ and the aqueous layers were washed with EtOAc. The washed aqueous layer was acidified with 1N HCl and extracted with EtOAc. The combined organic layers were washed with 1N HCl, water, and brine, were dried over anhydrous Na_2SO_4, and then filtered. The filtrate was concentrated under reduced pressure, triturated with hexane, and filtered to give a first batch of the title compound (4.36 g). The filtrate was concentrated, triturated with hexane, and filtered to give a second batch (0.36 g) of the title compound (total 4.72g, 63%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.30 (s, 3H), 7.00 - 7.02 (m, 1H), 7.25 - 7.28 (m, 2H), 7.33 - 7.35 (m, 2H), 10.13 (s, 1H), 1H not detected. [M+H] calc'd for $C_{12}H_{10}Cl_2N_3O_2$, 298; found, 298.

[0235] C. Methyl 2,4-dichloro-6-(*m*-tolylamino)pyrimidine-5-carboxylate

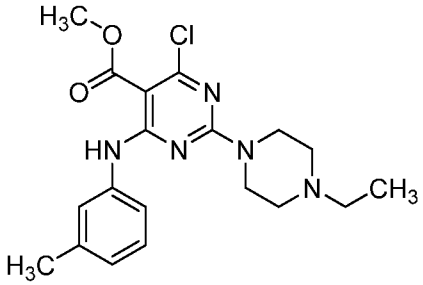
[0236] To a solution of 2,4-dichloro-6-(*m*-tolylamino)pyrimidine-5-carboxylic acid (7.67 g, 25.7 mmol) in DMF (80 mL) was added $NaHCO_3$ (3.30 g, 39.3 mmol) and iodomethane (1.605 mL, 25.7 mmol) at 0°C. The mixture was stirred at RT for 14 h, after which saturated aq $NaHCO_3$ was added. The mixture was extracted with EtOAc. The organic layers were washed with aqueous $NaHOC_3$, water, and brine, were dried over anhydrous Na_2SO_4, and then filtered through SiO_2. The filtrate was concentrated under

reduced pressure. The residue was triturated with isopropyl ether and filtered to give a first batch (5.28 g) of the title compound. The filtrate was concentrated, triturated with IPE, and filtered to give a second batch (0.66 g) of the title compound as a yellow solid (total 5.94 g, 74%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.38 (s, 3H), 4.00 (s, 3H), 7.02 - 7.03 (m, 1H), 7.27 - 7.33 (m, 2H), 7.44 - 7.46 (m, 1H), 10.30 (br s, 1H). [M+H] calc'd for $C_{13}H_{12}Cl_2N_3O_2$, 312; found, 312.

[0237] EXAMPLE 9: 2-(4-Ethylpiperazin-1-yl)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one

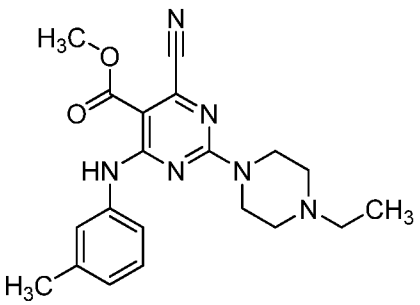


[0238] A. Methyl 4-chloro-2-(4-ethylpiperazin-1-yl)-6-(*m*-tolylamino)pyrimidine-5-carboxylate



[0239] A mixture of methyl 2,4-dichloro-6-(*m*-tolylamino)pyrimidine-5-carboxylate (502.6 mg, 1.610 mmol), *N*-ethyldiisopropylamine (0.3 mL, 1.718 mmol) and *N*-ethylpiperazine (0.21 mL, 1.653 mmol) in THF (8 mL) was stirred at RT for 12 h. Saturated aq $NaHCO_3$ was added and the resulting mixture was extracted with EtOAc. The organic layers were washed with saturated aq $NaHCO_3$, water, and brine, were dried over anhydrous Na_2SO_4, and then filtered through SiO_2. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/EtOAc=4/1) to give the title compound (152.6 mg, 24%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.12 (t, *J*=6.5Hz, 3H), 2.35 (s, 3H), 2.48 (br s, 6H), 3.82 - 3.97 (m, 7H), 6.92 - 6.93 (m, 1H), 7.21 - 7.22 (m, 1H), 7.37 - 7.42 (m, 2H), 10.45 (s, 1H). [M+H] calc'd for $C_{19}H_{25}ClN_5O_2$, 390; found, 390.

[0240] B. Methyl 4-cyano-2-(4-ethylpiperazin-1-yl)-6-(*m*-tolylamino)pyrimidine-5-carboxylate



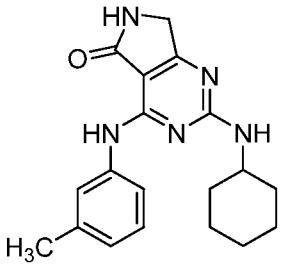
[0241] A mixture of methyl 4-chloro-2-(4-ethylpiperazin-1-yl)-6-(*m*-tolylamino)pyrimidine-5-carboxylate (152.6 mg, 0.391 mmol), tetrakis(triphenylphosphine)palladium (40.8 mg, 0.035 mmol) and zinc(II) cyanide (25.2 mg, 0.215 mmol) in DMF (3 mL) was stirred at 90°C for 3 h. Water was added and the resulting mixture was extracted with EtOAc. The organic layers were washed with aq $NaHCO_3$, water, and brine, were dried over anhydrous Na_2SO_4, and then filtered through SiO_2. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (SiO_2 hexanes/EtOAc=5/1) to give the title compound as a yellow oil (51.1 mg, 34%). ^1H NMR (500 MHz, $CDCl_3$) δ ppm 1.12 (t, *J*=7.5Hz, 3H), 2.35 (s, 3H), 2.44 - 2.49 (m, 6H), 3.81 - 3.98 (m, 7H), 6.95 - 6.96 (m, 1H), 7.23 - 7.26 (m, 1H), 7.37 - 7.47 (m, 2H), 10.46 (s, 1H). [M+H] calc'd for $C_{20}H_{25}N_6O_2$, 381; found, 381.

[0242] C. 2-(4-Ethylpiperazin-1-yl)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one

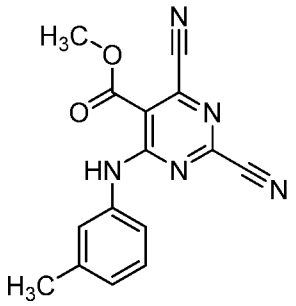
[0243] A mixture of methyl 4-cyano-2-(4-ethylpiperazin-1-yl)-6-(*m*-tolylamino)pyrimidine-5-carboxylate (49.8 mg, 0.131 mmol) and palladium on carbon (10.1 mg) in EtOH (3 mL) and 1N HCl (3 mL) was stirred at RT for 2 h under a hydrogen atmosphere. The insoluble materials were filtered off, and the filtrate was concentrated under reduced pressure. The residue was treated with saturated aq $NaHCO_3$ and EtOAc for 3 h. The mixture was extracted with EtOAc. The organic layers were washed with aq $NaHCO_3$, water, and brine, were dried over anhydrous Na_2SO_4, and then filtered. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography twice (SiO_2, EtOAc then DM1020 EtOAc/MeOH=20/1) to give the title compound as a white solid (19.8 mg, 43%). ^1H NMR (500 MHz, $CDCl_3$) δ ppm 1.19 (br s, 3H), 2.36 (s, 3H), 2.5 (br s, 6H), 4.08 (br s, 4H), 4.23 (s, 2H), 5.50 (s, 1H), 6.91 - 6.92 (m,

1H), 7.22 - 7.26 (m, 1H), 7.49 - 7.54 (m, 2H), 8.44 (s, 1H). [M+H] calc'd for $C_{19}H_{25}N_6O$, 353; found, 353.

[0244] EXAMPLE 10: 2-(Cyclohexylamino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one

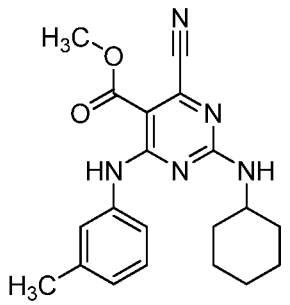


[0245] A. Methyl 2,4-dicyano-6-(*m*-tolylamino)pyrimidine-5-carboxylate



[0246] A mixture of methyl 2,4-dichloro-6-(*m*-tolylamino)pyrimidine-5-carboxylate (500.5 mg, 1.603 mmol), zinc(II) cyanide (100.7 mg, 0.857 mmol) and tetrakis(triphenylphosphine)palladium (187.3 mg, 0.162 mmol) in DMF (5 mL) was stirred at 120°C for 1 h in a microwave oven. After cooling, saturated aq $NaHCO_3$ was added and the mixture was extracted with EtOAc. The organic layers were washed with aq $NaHCO_3$, water, and brine, were dried over anhydrous Na_2SO_4, and then filtered through SiO_2. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/EtOAc=4/1) to afford a yellow solid (182.5 mg), which was washed with IPE to give the title compound (117.5 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.41 (s, 3H), 4.12 (s, 3H), 7.10 - 7.12 (m, 1H), 7.31 - 7.35 (m, 2H), 7.42 - 7.43 (m, 1H), 10.65 (br s, 1H). [M+H] calc'd for $C_{15}H_{12}N_5O_2$, 294; found, 294.

[0247] B. Methyl 4-cyano-2-(cyclohexylamino)-6-(*m*-tolylamino)pyrimidine-5-carboxylate



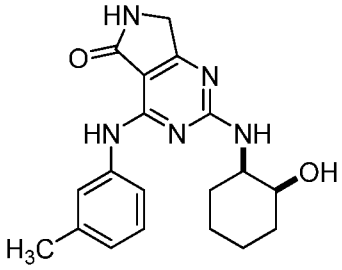
[0248] A mixture of methyl 2,4-dicyano-6-(*m*-tolylamino)pyrimidine-5-carboxylate (102.3 mg, 0.349 mmol), *N*,*N*-diisopropylethylamine (0.075 mL, 0.429 mmol) and cyclohexylamine (0.05 mL, 0.437 mmol) in DMF (2 mL) was stirred at RT for 14 h. Saturated aq $NaHCO_3$ was added and the mixture was extracted with EtOAc. The organic layers were washed with aq $NaHCO_3$, water, and brine, and were filtered through SiO_2. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/EtOAc=4/1) to give the title compound as a yellow oil (114.7 mg, 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.19 - 1.45 (m, 5H), 1.64 - 1.67 (m, 1H), 1.73 - 1.80 (m, 2H), 2.00 - 2.05 (m, 2H), 2.38 (s, 3H), 3.75 - 3.82 (m, 1H), 3.98 (s, 3H), 5.57 - 5.58 (br d, *J*=7.9Hz, 1H), 6.97 - 6.98 (m, 1H), 7.27 - 7.29 (m, 1H), 7.46 - 7.51 (m, 2H), 10.62 (br s, 1H). [M+H] calc'd for $C_{20}H_{24}N_5O_2$, 366; found, 366.

[0249] C. 2-(Cyclohexylamino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one

[0250] A mixture of methyl 4-cyano-2-(cyclohexylamino)-6-(*m*-tolylamino)pyrimidine-5-carboxylate (112.6 mg, 0.308 mmol) and palladium on carbon (26.4 mg, 0.248 mmol) in MeOH (2 mL) and HCl (1N, 2 mL) was stirred at RT for 4 h under a hydrogen atmosphere. Saturated aq $NaHCO_3$ was added and the mixture was stirred for 12 h. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was extracted with EtOAc. The organic layers were washed with aq $NaHCO_3$, water, and brine, were dried over anhydrous Na_2SO_4, and then filtered through SiO_2. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (SiO_2, EtOAc) to give a white solid (72.2 mg, 69%). The white solid was recrystallized from EtOH gave the title compound (35.2 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.14 - 1.17 (m, 1H), 1.24 - 1.34 (m, 4H), 1.62 - 1.63 (m, 1H), 1.73 - 1.78 (m, 2H), 1.89 - 1.97 (m, 2H), 2.33 (s, 3H), 3.74 - 3.83 (m, 1H), 4.12 - 4.17 (m,

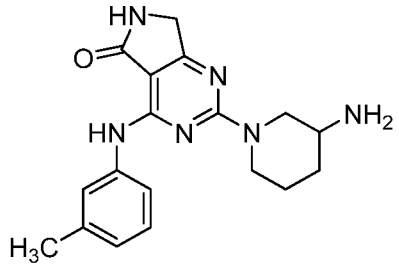
2H), 6.86 - 6.88 (m, 1H), 7.20 - 7.23 (m, 1H), 7.42 - 7.52 (m, 2H), 7.76 (s, 1H), 8.00 - 8.05 (m, 1H), 8.53 - 8.57 (m, 1H). [M+H] calc'd for $C_{19}H_{24}N_5O$, 338; found, 338.

[0251] EXAMPLE 11: *cis*-2-(2-Hydroxycyclohexylamino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one



[0252] The above compound was prepared in a manner similar to EXAMPLE 10 using *cis*-2-aminocyclohexanol in place of cyclohexylamine. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.31 - 1.37 (m, 2H), 1.46 - 1.78 (m, 6H), 2.32 (s, 3H), 3.82 - 3.96 (m, 2H), 4.13 - 4.17 (m, 2H), 4.66 - 4.71 (m, 1H), 6.86 - 6.92 (m, 2H), 7.20 - 7.23 (m, 1H), 7.46 - 7.50 (m, 1H), 7.71 - 7.77 (m, 1H), 8.03 - 8.08 (m, 1H), 8.58 - 8.59 (m, 1H). [M+H] calc'd for $C_{19}H_{24}N_5O_2$, 354; found, 354.

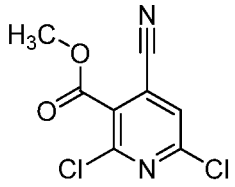
[0253] EXAMPLE 12: 2-(3-Aminopiperidin-1-yl)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one



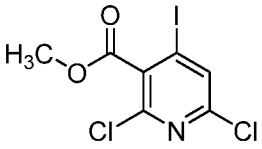
[0254] The above compound was prepared in a manner similar to EXAMPLE 10 using *tert*-butyl piperidin-3-ylcarbamate in place of cyclohexylamine. Following cyclization, *tert*-butyl 1-(5-oxo-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-2-yl)piperidin-3-ylcarbamate (20.00 mg, 0.046 mmol) was treated with 4M HCl in dioxane (2 mL, 8.00 mmol) at RT for 5 h to deprotect the Boc group. The mixture was subsequently basified with 2N NaOH, extracted with EtOAc, washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by recrystallization (EtOH-Hexane) to give the title compound as white solid (10 mg, 64.8 % yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.99 – 2.03 (m, 4 H), 2.30 (s, 3 H), 2.57 – 3.07 (m, 3 H), 4.16 (s,

2 H), 4.26 – 4.86 (m, 2 H), 6.88 (d, J=5.6 Hz, 1 H), 7.23 (s, 1 H), 7.42 – 7.55 (m, 1 H), 7.59 (s, 1 H), 8.08 (s, 1 H), 8.55 (s, 1 H). [M+H] calc'd for $C_{18}H_{22}N_6O$, 339; found, 339.

[0255] PREPARATION 5: Methyl 2,6-dichloro-4-cyanonicotinate



[0256] A. Methyl 2,6-dichloro-4-iodonicotinate



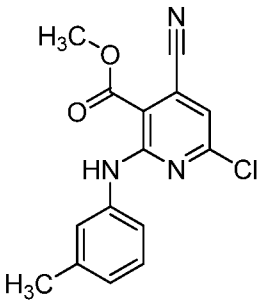
[0257] A solution of *n*-butyllithium in hexane (1.6M, 120 mL, 192 mmol) was added dropwise to a solution of diisopropylamine (31.2 mL, 219 mmol) in THF (200 mL) at -78°C and the mixture was stirred for 30 min. A solution of 2,6-dichloro-3-iodopyridine (50.0 g, 183 mmol) in THF (100 mL) was added dropwise to the reaction mixture at -78°C and the resulting mixture was stirred at -78°C for 2 h. After adding dry ice to the reaction mixture, the mixture was warmed to RT and stirred overnight. The resulting mixture was quenched with H_2O and the organic phase was washed with H_2O. The combined aqueous phase was acidified with HCl and extracted with $CHCl_3$ (3 x). The organic phases were combined, washed with brine, dried over $MgSO_4$, and evaporated. After the residue was dissolved into DMF (500 mL), K_2CO_3 (39.2 g, 284 mmol) and CH_3I (17.73 mL, 284 mmol) were added. The reaction mixture was stirred at RT for 3 h. To the resulting mixture was added 1N HCl and Et_2O. The aqueous phase was extracted with Et_2O and the combined organic layers were washed with H_2O and brine, dried over $MgSO_4$ and evaporated. The residue was purified by chromatography on SiO_2 to give the title compound as a white solid (7.24 g, 11%). ^1H NMR (500 MHz, $CDCl_3$) δ ppm 3.99 (s, 3 H), 7.77 (s, 1H). [M+H] calc'd for $C_7H_4ClINO_2$, 332; found, 332.

[0258] B. Methyl 2,6-dichloro-4-cyanonicotinate

[0259] A mixture of tetrakis(triphenylphosphine)palladium (34.8 mg, 0.03 mmol), methyl 2,6-dichloro-4-iodonicotinate (100 mg, 0.301 mmol) and dicyanozinc (38.9 mg, 0.331 mmol) in DMF (2 mL) was stirred at 100°C overnight under N_2 atmosphere. To the resulting mixture were added H_2O and EtOAc. The aqueous phase was extracted with

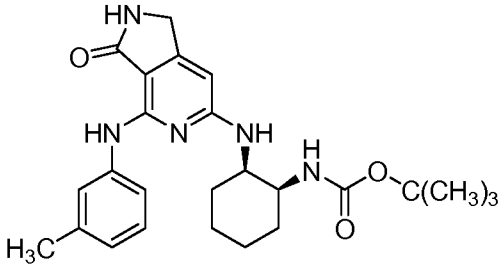
EtOAc, and the combined organic layers were washed with H_2O and brine, dried over $MgSO_4$ and evaporated. The residue was purified by chromatography on SiO_2 to give the title compound as a white solid (28 mg, 40%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 3.99 (s, 3 H), 8.44 (s, 1H).

[0260] PREPARATION 6: Methyl 6-chloro-4-cyano-2-(*m*-tolylamino)nicotinate

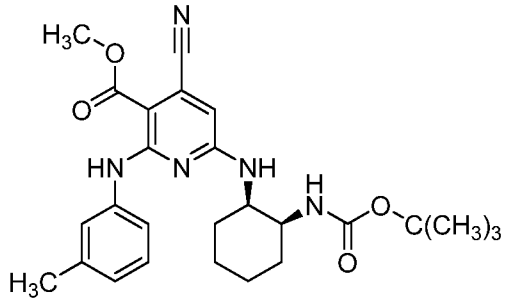


[0261] A solution of methyl 2,6-dichloro-4-cyanonicotinate (455 mg, 1.97 mmol), triethylamine (0.549 mL, 3.94 mmol) and *m*-toluidine (0.32 mL, 2.95 mmol) in THF (10 mL) was stirred at RT for 3 days. Water was added to the resulting mixture, and the aqueous phase was extracted with EtOAc. The organic phases were combined, washed with H_2O and brine, dried over $MgSO_4$, and evaporated. The residue was purified by chromatography on SiO_2 to give the title compound as a yellow solid (198 mg, 33.3%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.40 (s, 3 H), 3.99 (s, 3H), 6.92 (s, 1H), 7.05 - 7.14 (m, 4H), 7.33 (t, *J*=7.81 Hz, 1H).

[0262] PREPARATION 7: *tert*-Butyl (1*S*,2*R*)-2-(3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate



[0263] A. Methyl 6-((1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclohexylamino)-4-cyano-2-(*m*-tolylamino)nicotinate

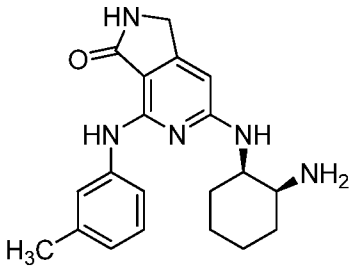


[0264] A solution of methyl 6-chloro-4-cyano-2-(*m*-tolylamino)nicotinate (198 mg, 0.656 mmol), *tert*-butyl (1*S*,2*R*)-2-aminocyclohexylcarbamate (562 mg, 2.62 mmol) and Et_3N (0.402 mL, 2.89 mmol) was stirred at reflux overnight. To the resulting mixture were added H_2O and EtOAc. The aqueous phase was extracted with EtOAc. The organic layers were combined, washed with brine, dried over $MgSO_4$, and evaporated. The residue was triturated with EtOAc. The resulting solid was filtered, rinsed with EtOAc, and dried to give the title compound as a yellow solid (250 mg, 79 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.23 - 1.77 (m, 17 H), 2.34 (s, 3 H), 3.94 (br s, 3 H), 3.98 (br s, 1H), 4.80 (s, 1H), 6.15 (s, 1 H), 6.91 (d, *J*=5.37 Hz, 1 H), 7.21 (t, *J*=7.81 Hz, 1H), 7.29 (s, 1H), 7.47 - 7.55 (m, 1 H), 10.64 (br s, 1 H).

[0265] B. *tert*-Butyl (1*S*,2*R*)-2-(3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate

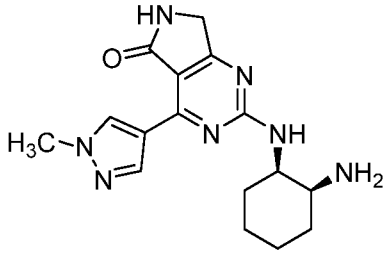
[0266] Methyl 6-((1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclohexylamino)-4-cyano-2-(*m*-tolylamino)nicotinate (100 mg, 0.209 mmol) was dissolved into DMF (5 mL). To the solution was added palladium on carbon (22.19 mg, 0.209 mmol) and the resulting mixture was stirred at 80°C overnight under H_2 atmosphere. The mixture was filtered, the filtrate was evaporated, and the residue was diluted with H_2O and EtOAc. The aqueous phase was extracted with EtOAc. The organic phases were combined, washed with H_2O and brine, dried over $MgSO_4$, and evaporated. The residue was purified by recrystallization (EtOH-Hexane) to give the title compound as a white solid (70 mg, 74.3 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.03 - 2.10 (m, 17 H), 2.34 (s, 3 H), 3.81 - 4.29 (m, 4 H), 5.03 (s, 1 H), 5.32 (s, 1 H), 5.81 (s, 1 H), 6.20 (s, 1 H), 6.81 (s, 1 H), 7.18 (s, 1 H), 7.49 (s, 1 H), 7.64 (s, 1 H), 8.77 (s, 1 H). [M+H] calc'd for $C_{25}H_{33}N_5O_3$, 452; found, 452.

[0267] EXAMPLE 13: 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

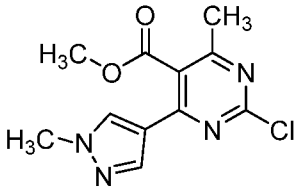


[0268] A mixture of tert-butyl (1*S*,2*R*)-2-(3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (50.0 mg, 0.111 mmol) and 4N HCl in dioxane (2 mL, 8.00 mmol) was stirred at RT for 2 h. The reaction mixture was concentrated under reduced pressure, the residue was purified by reverse phase preparative HPLC. The fractions were collected, concentrated, diluted with EtOAc, and basified with saturated aq $NaHCO_3$ solution. The organic extract was dried and evaporated to give the title compound as a white solid (10 mg, 25.7 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.19 - 1.77 (m, 8 H), 2.29 (s, 3 H), 3.20 (br s, 1 H), 3.99 (br s, 1 H), 4.19 (s, 2 H), 6.06 (s, 1 H), 6.75 (d, *J*=7.32 Hz, 2 H), 7.14 (t, *J*=7.81 Hz, 1 H), 7.48 (d, *J*=7.32 Hz, 1 H), 7.60 (s, 1 H), 7.90 (s, 1 H), 8.87 (s, 1 H). [M+H] calc'd for $C_{20}H_{25}N_5O$, 352; found, 352.

[0269] EXAMPLE 14: 2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-methyl-1*H*-pyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one



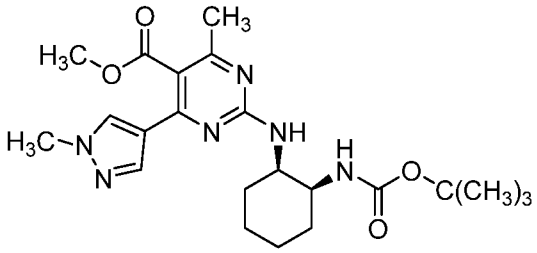
[0270] A. Methyl 2-chloro-4-methyl-6-(1-methyl-1*H*-pyrazol-4-yl)pyrimidine-5-carboxylate



[0271] A mixture of methyl 2,4-dichloro-6-methylpyrimidine-5-carboxylate (0.79 g, 3.57 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (0.595 g, 2.86 mmol) and bis(triphenylphosphine)palladium chloride (0.050 g, 0.071 mmol) in dioxane (5 mL) was stirred at RT for 10 min, after which potassium fluoride (1.038 g,

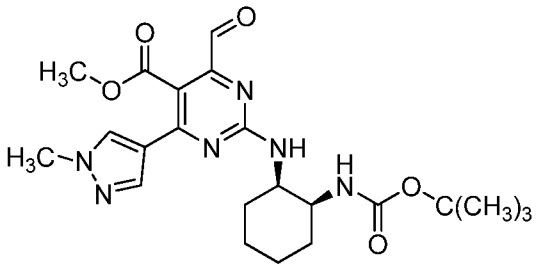
17.87 mmol) was added. The mixture was stirred under a nitrogen atmosphere and heated at 90°C for 12 h. The reaction mixture was filtered through a bed of Celite 545, rinsed with DCM and a small amount of MeOH. Following solvent removal, the residue was dispersed in DMSO/MeOH (1/1) and purified via reverse phase preparative HPLC to give the title compound (237 mg, 25%). [M+H] calc'd for $C_{11}H_{11}ClN_4O_2$, 267; found, 267.

[0272] B. Methyl 2-((1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclohexylamino)-4-methyl-6-(1-methyl-1*H*-pyrazol-4-yl)pyrimidine-5-carboxylate



[0273] To a mixture of methyl 2-chloro-4-methyl-6-(1-methyl-1*H*-pyrazol-4-yl)pyrimidine-5-carboxylate (0.227 g, 0.851 mmol) and *tert*-butyl (1*S*,2*R*)-2-aminocyclohexylcarbamate (0.182 g, 0.851 mmol) in DMA (3 mL) was added Et_3N (0.356 mL, 2.55 mmol). The reaction mixture was heated at 90°C for 4 h. The reaction mixture was cooled to RT and poured onto ice. The solid was filtered and dried under high vacuum to yield the title compound as an off-white foam (170 mg). [M+H] calc'd for $C_{22}H_{32}N_6O_4$, 445; found, 445.

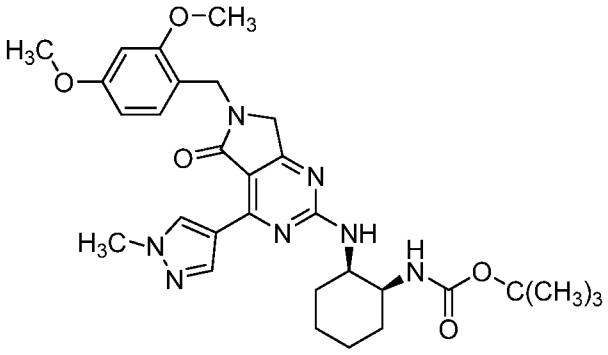
[0274] C. Methyl 2-((1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclohexylamino)-4-formyl-6-(1-methyl-1*H*-pyrazol-4-yl)pyrimidine-5-carboxylate



[0275] To a 25 mL round bottom flask was added methyl 2-((1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclohexylamino)-4-methyl-6-(1-methyl-1*H*-pyrazol-4-yl)pyrimidine-5-carboxylate (0.17 g, 0.382 mmol), selenium dioxide (0.085 g, 0.765 mmol) and dioxane. The reaction mixture was heated at 100°C overnight, cooled to RT, and filtered through a bed of Celite 545, which was rinsed with MeOH. The solvent was

removed to give the title compound as yellowish-brown foam, which was used in the next step without further purification (245 mg).

[0276] D. *tert*-Butyl (1*S*,2*R*)-2-(6-(2,4-dimethoxybenzyl)-4-(1-methyl-1*H*-pyrazol-4-yl)-5-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-2-ylamino)cyclohexylcarbamate



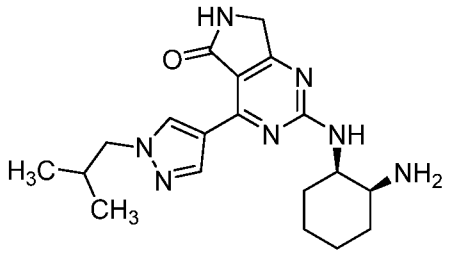
[0277] Methyl 2-((1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclohexylamino)-4-formyl-6-(1-methyl-1*H*-pyrazol-4-yl)pyrimidine-5-carboxylate (0.175 g, 0.382 mmol) was dissolved in DCM (2 mL) and MeOH (1 mL). To this mixture was added (2,4-dimethoxyphenyl)methanamine (0.057 mL, 0.382 mmol) and sodium acetate (0.094 g, 1.145 mmol). The mixture was stirred in a capped 20 mL vial for 1 h, after which sodium cyanoborohydride (0.060 g, 0.954 mmol) was added. The reaction mixture was stirred at RT overnight. After the solvent was removed under reduced pressure, the residue was dissolved in DMSO/MeOH (1/1) solution. An off-white solid precipitate was initially formed, which was isolated by vacuum filtration, rinsed with MeOH, and air dried to give a first batch of the title compound (6.7 mg). The mother liquor was purified via preparative HPLC. The fractions were concentrated under reduced pressure until an off-white solid precipitate was formed, which was collected by vacuum filtration and air dried to give a second batch (46 mg) of the title compound (total 62.5 mg, 28%). [M+H] calc'd for $C_{30}H_{39}N_7O_5$, 578; found, 578.

[0278] E. 2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-methyl-1*H*-pyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one

[0279] *tert*-Butyl (1*S*,2*R*)-2-(6-(2,4-dimethoxybenzyl)-4-(1-methyl-1*H*-pyrazol-4-yl)-5-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-2-ylamino)cyclohexylcarbamate (0.0625 g, 0.108 mmol) was dissolved in TFA (2 mL) and heated at 70°C for 1 h. The solvent was removed under reduced pressure and the resulting residue was dispersed in DMSO/MeOH (1/1) solution. A pale purple precipitate was formed and was separated by filtration. The

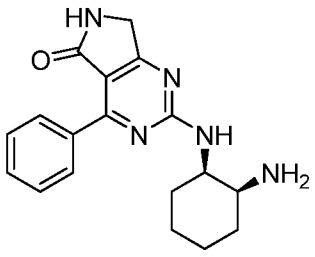
filtrate, which contained the product, was purified via reverse phase preparative HPLC. Lyophilized fractions gave a TFA salt of the title compound as a white solid (21 mg, 59%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.28 - 1.52 (m, 2 H) 1.51 - 1.94 (m, 6 H) 3.93 (s, 3 H) 4.14 - 4.30 (m, 2 H) 4.29 - 4.58 (m, 1 H) 7.51 (d, *J*=6.83 Hz, 1 H) 7.71 (br s, 2 H) 8.29 (s, 1 H) 8.34 - 8.69 (m, 1 H) 9.11 (d, *J*=17.09 Hz, 1 H). [M+H] calc'd for $C_{16}H_{21}N_7O$, 328; found, 328.

[0280] EXAMPLE 15: 2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-isobutyl-1*H*-pyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one



[0281] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 14 using 1-isobutyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole in place of 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 0.92 (d, *J*=1.00 Hz, 6 H), 0.87 - 1.00 (m, 6 H), 1.45 - 1.70 (m, 2 H), 1.46 - 1.70 (m, 2 H), 1.70 - 2.00 (m, 6 H), 2.22 (spt, *J*=13.70 Hz, 1 H), 3.64 (br s, 1 H), 4.02 (d, *J*=6.83 Hz, 2 H), 4.30 (s, 2 H), 4.63 (d, *J*=3.91 Hz, 1 H), 8.54 (s, 1 H), 9.12 (br s, 1 H). [M+H] calc'd for $C_{19}H_{27}N_7O$, 370; found, 370.

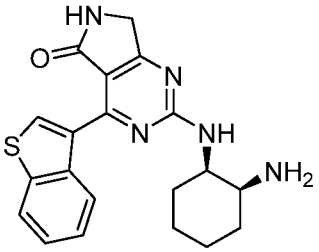
[0282] EXAMPLE 16: 2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-phenyl-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one



[0283] The title compound was prepared in a manner similar to EXAMPLE 14 using phenylboronic acid in place of 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole. The final product was purified via reverse phase preparative HPLC. The fractions were collected, concentrated, neutralized with saturated aq $NaHCO_3$, and extracted into EtOAc. The organic phase was dried over anhydrous Na_2SO_4 and the

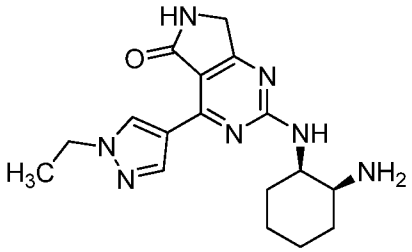
solvent removed *in vacuo* to give the title compound as an off-white film. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.40 - 1.95 (m, 8 H), 3.27 (br s, 1 H), 4.18 - 4.54 (m, 3 H), 7.35 - 7.59 (m, 3 H), 8.12 (br s, 2 H). [M+H] calc'd for $C_{18}H_{21}N_5O$, 324; found, 324.

[0284] EXAMPLE 17: 2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(benzo[*b*]thiophen-3-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one



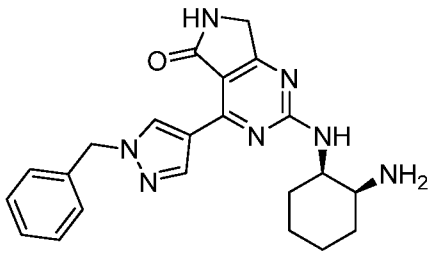
[0285] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 14 using benzo[*b*]thiophen-3-ylboronic acid in place of 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.44 - 2.02 (m, 8 H), 3.53 - 3.84 (m, 1 H), 4.25 - 4.43 (m, 2 H), 4.54 - 4.72 (m, 1 H), 7.32 - 7.55 (m, 2 H), 7.84 - 8.03 (m, 1 H), 8.40 - 8.88 (m, 1 H), 8.86 - 9.10 (m, 1 H). [M+H] calc'd for $C_{20}H_{21}N_5OS$, 380; found, 380.

[0286] EXAMPLE 18: 2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-ethyl-1*H*-pyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one



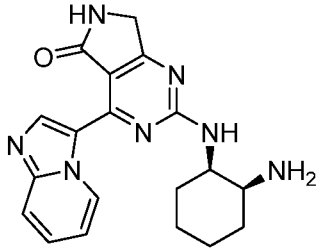
[0287] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 14 using 1-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole in place of 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.47 - 1.55 (m, 3 H), 1.54 - 1.99 (m, 8 H), 3.64 (br s, 1 H), 4.26 (q, *J*=7.32 Hz, 2 H), 4.30 (s, 2 H), 4.63 (br s, 1 H), 8.54 (br s, 1 H), 9.14 (s, 1 H). [M+H] calc'd for $C_{17}H_{23}N_7O$, 342; found, 342.

[0288] EXAMPLE 19: 2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-benzyl-1*H*-pyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one



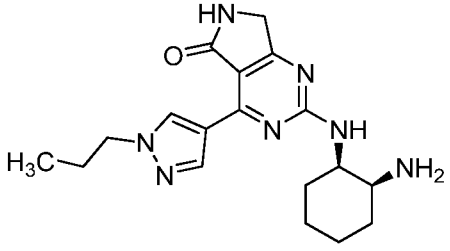
[0289] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 14 using 1-benzyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole in place of 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.45 - 1.69 (m, 2 H), 1.69 - 2.00 (m, 6 H), 3.63 (br s, 1 H), 4.29 (s, 2 H), 4.61 (br s, 1 H), 5.40 (s, 2 H), 7.22 - 7.41 (m, 5 H), 8.58 (s, 1 H), 9.16 (br s, 1 H). [M+H] calc'd for $C_{22}H_{25}N_7O$, 404; found, 404.

[0290] EXAMPLE 20: 2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(imidazo[1,2-*a*]pyridin-3-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one



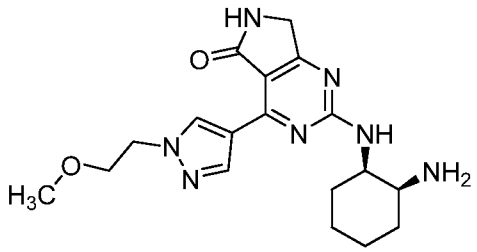
[0291] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 14 using imidazo[1,2-*a*]pyridin-3-ylboronic acid in place of 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.47 - 1.73 (m, 2 H), 1.74 - 2.03 (m, 6 H), 3.68 (br s, 1 H), 4.27 - 4.54 (m, 2 H), 4.58 - 4.75 (m, 1 H), 7.52 - 7.79 (m, 1 H), 8.00 - 8.12 (m, 1 H), 8.14 (t, *J*=7.57 Hz, 1 H), 10.23 (br s, 1 H), 10.81 (d, *J*=5.86 Hz, 1 H). [M+H] calc'd for $C_{19}H_{21}N_7O$, 364; found, 364.

[0292] EXAMPLE 21: 2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-propyl-1*H*-pyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one



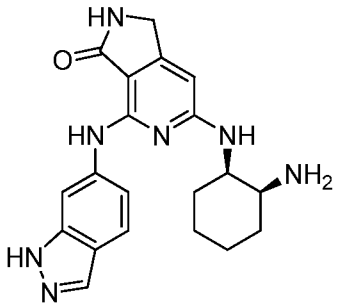
[0293] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 14 using 1-propyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole in place of 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 0.92 (t, *J*=1.00 Hz, 3 H), 1.43 - 1.70 (m, 2 H), 1.69 - 2.14 (m, 8 H), 3.62 (br s, 1 H), 4.18 (t, *J*=6.83 Hz, 2 H), 4.24 - 4.41 (m, 2 H), 4.63 (br s, 1 H), 8.56 (br s, 1 H), 9.13 (br s, 1 H). [M+H] calc'd for $C_{18}H_{25}N_7O$, 356; found, 356.

[0294] EXAMPLE 22: 2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-(2-methoxyethyl)-1*H*-pyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one

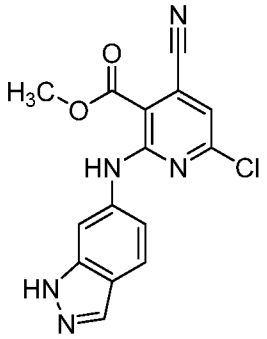


[0295] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 14 using 1-(2-methoxyethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole in place of 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.45 - 1.70 (m, 2 H), 1.70 - 2.05 (m, 6 H), 3.33 - 3.35 (m, 3 H), 3.63 (br s, 1 H), 3.73 - 3.90 (m, 2 H), 4.30 (s, 2 H), 4.33 - 4.47 (m, 2 H), 4.63 (br s, 1 H), 8.58 (br s, 1 H), 9.13 (br s, 1 H). [M+H] calc'd for $C_{18}H_{25}N_7O_2$, 372; found, 372.

[0296] EXAMPLE 23: 4-(1*H*-Indazol-6-ylamino)-6-((1*R*,2*S*)-2-aminocyclohexylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

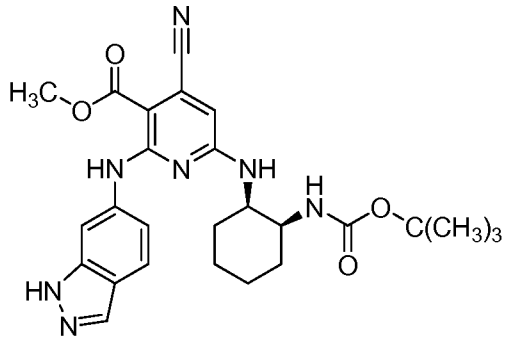


[0297] A. Methyl 2-(1*H*-indazol-6-ylamino)-6-chloro-4-cyanonicotinate



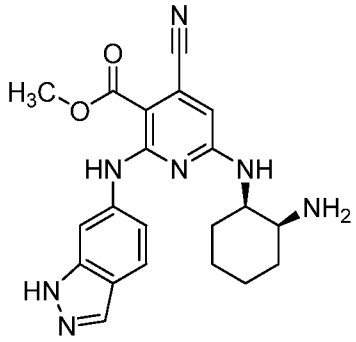
[0298] A mixture of methyl 2,6-dichloro-4-cyanonicotinate (250 mg, 1.082 mmol), 1*H*-indazol-6-amine (173 mg, 1.299 mmol) and Et_3N (0.226 mL, 1.623 mmol) in THF (10 mL) was stirred at 80°C overnight. Water and EtOAc were added to the mixture. The organic phase was washed with H_2O and brine, dried over $MgSO_4$, and evaporated. The residue was purified by chromatography on SiO_2 (Hexane/EtOAc=5/1) to give the title compound as a yellow solid (120 mg, 38.5%).

[0299] B. Methyl 2-(1*H*-indazol-6-ylamino)-6-((1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclohexylamino)-4-cyanonicotinate



[0300] A solution of methyl 2-(1*H*-indazol-6-ylamino)-6-chloro-4-cyanonicotinate (115 mg, 0.351 mmol), *tert*-butyl (1*S*,2*R*)-2-aminocyclohexylcarbamate (90 mg, 0.421 mmol) and Et_3N (0.073 mL, 0.526 mmol) in THF (1 mL) was stirred at reflux overnight. Water and EtOAc were added to the mixture. The aqueous phase was extracted with EtOAc. The organic phases were combined, washed with H_2O and brine, dried over $MgSO_4$, and evaporated. The residue was rinsed with EtOAc to give the title compound as yellow solid (110 mg, 62.0%). ^1H NMR (500 MHz, $CDCl_3$) δ ppm 1.00 – 1.86 (m, 17 H), 3.84 (s, 3 H), 3.91 (br s, 1 H), 4.12 (br s, 1H), 6.51 (s, 1 H), 6.63 (d, *J*=8.79 Hz, 1 H), 7.13 (d, *J*=8.30 Hz, 1 H), 7.97 (s, 1H), 8.03 (br s, 1 H), 10.71 (br s, 1 H), 12.87 (br s, 1 H).

[0301] C. Methyl 2-(1*H*-indazol-6-ylamino)-6-((1*R*,2*S*)-2-aminocyclohexylamino)-4-cyanonicotinate

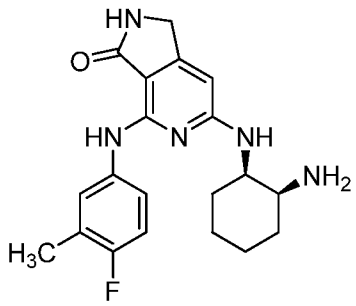


[0302] A solution of methyl 2-(1*H*-indazol-6-ylamino)-6-((1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclohexylamino)-4-cyanonicotinate (110 mg, 0.218 mmol) and TFA (2 mL, 26.9 mmol) in DCM (1 mL) was stirred at room temperature for 3 h. Following reaction, the mixture was concentrated *in vacuo* to give the title compound, which was used in the next step without further purification.

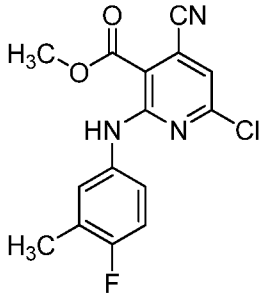
[0303] D. 4-(1*H*-Indazol-6-ylamino)-6-((1*R*,2*S*)-2-aminocyclohexylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

[0304] To a solution of methyl 2-(1*H*-indazol-6-ylamino)-6-((1*R*,2*S*)-2-aminocyclohexylamino)-4-cyanonicotinate (88 mg, 218 mmol) in MeOH (2 mL) was added palladium on carbon, and the resulting mixture was stirred at room temperature overnight under H_2 atmosphere. The mixture was subsequently filtered to remove the catalyst and the filtrate was evaporated. The residue was diluted with saturated aq $NaHCO_3$ and MeOH, and the mixture was stirred at RT for 30 min. The resulting suspension was filtered and the precipitate was washed with EtOAc and dried to give the title compound as a white solid (15 mg, 18.2%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.22 – 1.74 (m, 8 H), 3.13 (br s, 1H), 3.94 – 4.07 (m, 1 H), 4.21 (s, 2 H), 6.02 – 6.14 (m, 1 H), 6.70 (br s, 1 H), 7.13 (d, *J*=8.30 Hz, 1 H), 7.63 (d, *J*=8.30 Hz, 1 H), 7.94 (d, *J*=2.93 Hz, 2 H), 8.23 (s, 1 H), 9.08 (s, 1 H), 12.84 (br s, 1 H). [M+H] calc'd for $C_{20}H_{23}N_7O$, 378; found, 378.

[0305] EXAMPLE 24: 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(4-fluoro-3-methylphenylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

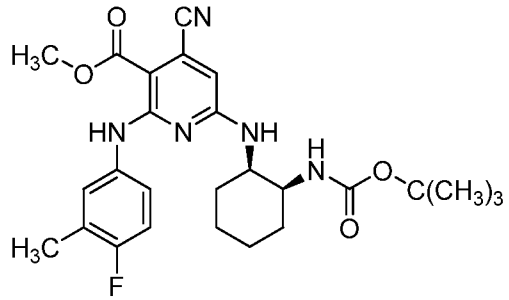


[0306] A. Methyl 6-chloro-4-cyano-2-(4-fluoro-3-ethylphenylamino)nicotinate



[0307] A solution of methyl 2,6-dichloro-4-cyanonicotinate (500 mg, 2.164 mmol), 4-fluoro-3-methylaniline (325 mg, 2.60 mmol) and Et_3N (0.452 mL, 3.25 mmol) in ACN (5 mL) was stirred at 50°C for 24 h. Water and EtOAc were added to the mixture and the aqueous phase was extracted with EtOAc. The organic phases were combined, washed with H_2O and brine, dried over $MgSO_4$, and evaporated. The residue was purified by chromatography on SiO_2 to give the title compound, which contains some starting material and was used without further purification (390 mg). [M+H] calc'd for $C_{15}H_{11}ClFN_3O_2$, 320; found, 320.

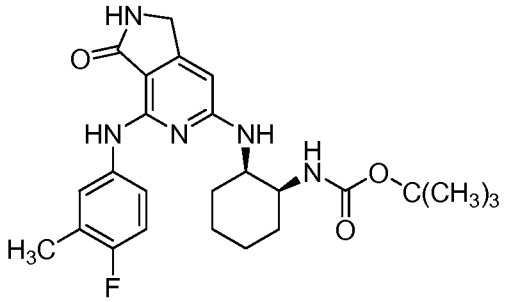
[0308] B. Methyl 6-((1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclohexylamino)-4-cyano-2-(4-fluoro-3-methylphenylamino)nicotinate



[0309] A mixture of methyl 6-chloro-4-cyano-2-(4-fluoro-3-methylphenylamino)nicotinate (390 mg, 1.220 mmol), Et_3N (0.204 mL, 1.464 mmol) and *tert*-butyl (1*S*,2*R*)-2-aminocyclohexylcarbamate (392 mg, 1.830 mmol) in THF (5 mL)

was stirred at 80°C overnight. Water and EtOAc were subsequently added to the mixture and the aqueous phase was extracted with EtOAc. The organic phases were combined, washed with H_2O and brine, dried over $MgSO_4$, and evaporated. The residue was diluted with EtOAc and filtered to give the title compound as a yellow solid (75 mg, 12.36%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.03 – 1.71 (m, 17 H), 2.22 (d, *J*=0.98 Hz, 3 H), 3.80 – 3.82 (m, 3 H), 3.83 (br s, 1 H), 4.01 – 4.09 (m, 1 H), 6.48 (s, 1 H), 6.62 (d, *J*=7.81 Hz, 1 H), 7.06 (t, *J*=9.03, 1 H), 7.39 (d, *J*=4.39 Hz, 1 H), 7.50 – 7.68 (m, 1 H), 10.41 (br s, 1 H).

[0310] C. *tert*-Butyl (1*S*,2*R*)-2-(4-(4-fluoro-3-methylphenylamino)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate

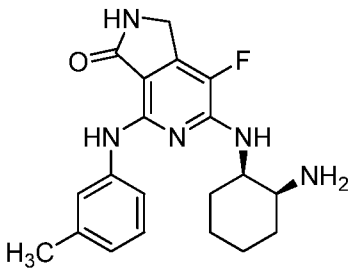


[0311] A mixture of methyl 6-((1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclohexylamino)-4-cyano-2-(4-fluoro-3-methylphenylamino)nicotinate (75 mg, 0.151 mmol) and platinum oxide (34.2 mg, 0.151 mmol) in DCM (2 mL) and HOAc (0.5 mL) was stirred at RT under H_2 atmosphere. The mixture was subsequently filtered through Celite. The filtrate was concentrated and the residue was purified by preparative HPLC to give the title compound (50 mg, 70.6%). [M+H] calc'd for $C_{25}H_{32}FN_5O_3$, 470; found, 470.

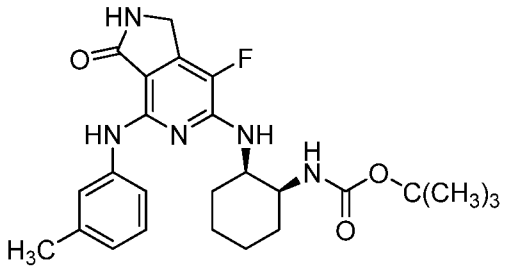
[0312] D. 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(4-fluoro-3-methylphenylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

[0313] A solution of *tert*-butyl (1*S*,2*R*)-2-(4-(4-fluoro-3-methylphenylamino)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (50.0 mg, 0.106 mmol) and TFA (1 mL, 12.98 mmol) in DCM (0.5 mL) was stirred at RT for 1 hr. The resulting mixture was concentrated and the residue was purified by preparative HPLC to give the title compound as a white solid (1 mg, 2.54%). ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.14 – 1.95 (m, 8 H), 2.28 (s, 3 H), 3.73 (br s, 1 H), 4.30 (s, 2H), 4.38 (s, 1 H), 6.17 (s, 1 H), 7.00 (t, *J*=9.03 Hz, 1 H), 7.41 – 7.54 (m, 2 H).

[0314] EXAMPLE 25: 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



[0315] A. *tert*-Butyl (1*S*,2*R*)-2-(7-fluoro-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate



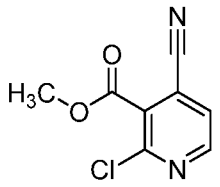
[0316] A solution of *tert*-butyl (1*S*,2R)-2-(3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (94 mg, 0.208 mmol) and SELECTFLUOR® (73.7 mg, 0.208 mmol) was stirred at 0°C for 5 h and at RT for 1 h. The mixture was filtered and the filtrate was purified by preparative HPLC. The fractions were collected and concentrated. The residue was washed with saturated aq $NaHCO_3$ solution, extracted with EtOAc, washed with brine, dried over $MgSO_4$, and evaporated to give the title compound as yellow solid (45 mg, 46.0%). [M+H] calc'd for $C_{25}H_{32}FN_5O_3$, 470; found, 470.

[0317] B. 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

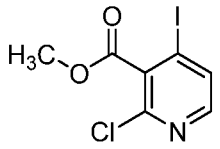
[0318] A solution of *tert*-butyl (1*S*,2*R*)-2-(7-fluoro-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (40.0 mg, 0.085 mmol) and TFA (2 mL, 26.0 mmol) in DCM (1 mL) was stirred at RT for 1 h. The mixture was concentrated and the resulting residue was purified by preparative HPLC to give the title compound as a white solid (20 mg, 63.5%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm1.36 – 1.97 (m, 8 H), 2.30 (s, 3 H), 3.70 (br s, 1 H), 4.27 (br s, 1 H), 4.33 – 4.46 (m, 2 H), 6.73 (d, *J*=6.35 Hz, 1 H), 6.79 (d, *J*=7.32 Hz, 1 H), 7.17 (t, *J*=7.57 Hz, 1 H), 7.43 (d, *J*=7.81 Hz, 1

H), 7.46 (s, 1 H), 7.76 (br s, 2 H), 8.29 (s, 1 H), 8.79 (s, 1 H). [M+H] calc'd for $C_{20}H_{24}FN_5O$, 370; found, 370.

[0319] PREPARATION 8: Methyl 2-chloro-4-cyanonicotinate

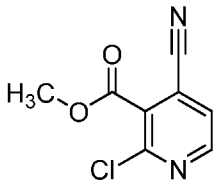


[0320] A. Methyl 2-chloro-4-iodonicotinate



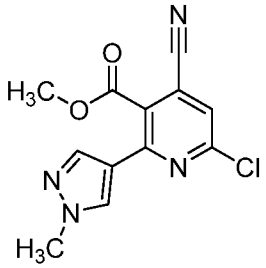
[0321] Butyllithium in hexane solution (1.6 M, 13.70 mL, 21.93 mmol) was added drop wise to a solution of diisopropylamine (3.57 mL, 25.06 mmol) in THF (100 mL) at -78°C and the mixture was stirred for 30 min. A solution of 2-chloro-3-iodopyridine (5.00 g, 20.88 mmol) in THF (50 mL) was added drop wise to the reaction mixture at -78°C and the resulting mixture was stirred at -78°C for 2 h. Dry ice was added to the reaction mixture, which was warmed to room temperature and stirred overnight. The resulting mixture was quenched with H_2O and the organic phase was washed with H_2O. The combined aqueous phase was acidified with concentrated HCl and extracted with EtOAc. The organic phases were combined, washed with brine, dried over $MgSO_4$, and evaporated to yield crude 2-chloro-4-iodonicotinic acid, which was combined with potassium carbonate (5.77 g, 41.8 mmol) and iodomethane (1.567 mL, 25.06 mmol) in DMF (70 mL). The mixture was stirred at room temperature for 1 h, which was followed by the addition of Et_2O and H_2O. The organic phase was washed with H_2O and brine, dried over $MgSO_4$, and evaporated. The residue was purified by chromatography on SiO_2 to give the title compound as a white solid (3.23 g, 52.0%). ^1H NMR (500 MHz, $CDCl_3$) δ ppm 4.01 (s, 3 H), 7.68 – 7.76 (m, 1 H), 7.97 – 8.11 (m, 1 H). [M+H] calc'd for $C_7H_5ClINO_2$, 298; found, 298.

[0322] B. Methyl 2-chloro-4-cyanonicotinate

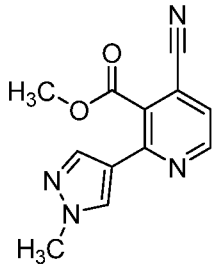


[0323] A solution of methyl 2-chloro-4-iodonicotinate (3.20 g, 10.76 mmol) and cyanocopper (0.963 g, 10.76 mmol) in DMA (40 mL) was stirred at 140°C overnight. Following reaction, the mixture was filtered through Celite and the filtrate was diluted with H_2O and EtOAc. The aqueous phase was extracted with EtOAc. The organic phases were combined, washed with H_2O and brine, dried over $MgSO_4$, and evaporated. The residue was purified by chromatography on SiO_2 (Hexane/EtOAc=10/1) to give the title compound as a white solid (730 mg, 34.5%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 4.07 (s, 3 H), 7.57 (d, *J*=5.37 Hz, 1 H), 8.66 (d, *J*=4.88 Hz, 1 H).

[0324] PREPARATION 9: Methyl 6-chloro-4-cyano-2-(1-methyl-1*H*-pyrazol-4-yl)nicotinate



[0325] A. Methyl 4-cyano-2-(1-methyl-1*H*-pyrazol-4-yl)nicotinate



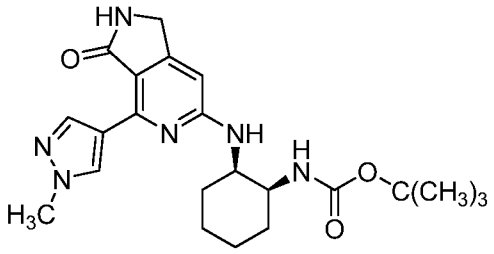
[0326] A mixture of methyl 2-chloro-4-cyanonicotinate (730 mg, 3.71 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (927 mg, 4.46 mmol), *trans*-dichlorobis(triphenylphosphine)palladium (261 mg, 0.371 mmol) and potassium fluoride (2697 mg, 14.85 mmol) in DME (15 mL) was stirred at 120°C for 1 h under microwave irradiation. The mixture was filtered through Celite, and the filtrate was diluted with H_2O and EtOAc. The organic phase was washed with H_2O and brine, dried

over $MgSO_4$, and evaporated. The residue was purified by chromatography on SiO_2 to give the title compound as a pale yellow solid (470 mg, 52.3%). ^1H NMR (500 MHz, $CDCl_3$) δ ppm 3.97 (s, 3 H), 4.03 (s, 3 H), 7.41 (d, *J*=4.88 Hz, 1 H), 7.82 (s, 1 H), 7.91 (s, 1 H), 8.79 (d, *J*=4.88 Hz, 1 H). [M+H] calc'd for $C_{12}H_{10}N_4O_2$, 243; found, 243.

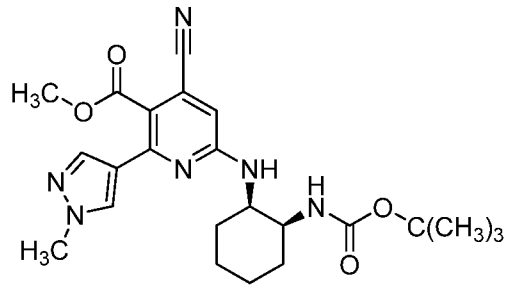
[0327] B. Methyl 6-chloro-4-cyano-2-(1-methyl-1*H*-pyrazol-4-yl)nicotinate

[0328] To a mixture of methyl 4-cyano-2-(1-methyl-1*H*-pyrazol-4-yl)nicotinate (470 mg, 1.940 mmol) in DCM (10 mL) was added urea-hydrogen peroxide compound (1/1, 913 mg, 9.70 mmol), and 2,2,2-trifluoroacetic anhydride (1.370 mL, 9.70 mmol) at 0°C. The mixture was stirred at room temperature for 4 h. More urea-hydrogen peroxide compound (1/1, 400 mg) was added and the mixture was stirred at RT for an additional 3 h after which was added saturated aq $NaHCO_3$ solution and $CHCl_3$. The aqueous phase was extracted with $CHCl_3$ (3 x), and the combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated to obtain crude 4-cyano-3-(methoxycarbonyl)-2-(1-methyl-1*H*-pyrazol-4-yl)pyridine 1-oxide, which was combined with phosphorus oxychloride (2 mL, 21.46 mmol). The resulting mixture was stirred at 80°C for 5 h and then concentrated to a residue, which was neutralized with 2N NaOH. The organic phase was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by chromatography on SiO_2 (Hexane/EtOAc=1/1) to give the title compound as a white solid (155 mg, 41.3%). ^1H NMR (500 MHz, $CDCl_3$) δ ppm 3.96 (s, 3 H), 4.03 (s, 3 H), 7.41 (s, 1 H), 7.81 (s, 1 H), 7.94 (s, 1 H). [M+H] calc'd for $C_{12}H_9ClN_4O_2$, 277; found, 277.

[0329] PREPARATION 10: *tert*-Butyl (1*S*,2*R*)-2-(4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate



[0330] A. Methyl 6-((1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclohexylamino)-4-cyano-2-(1-methyl-1*H*-pyrazol-4-yl)nicotinate

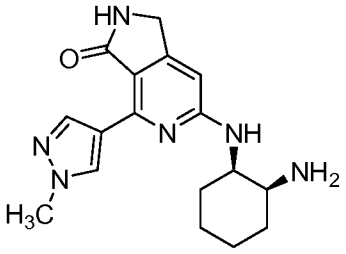


[0331] A mixture of methyl 6-chloro-4-cyano-2-(1-methyl-1*H*-pyrazol-4-yl)nicotinate (155 mg, 0.560 mmol) and *tert*-butyl (1*S*,2*R*)-2-aminocyclohexylcarbamate (144 mg, 0.672 mmol) in DMA (2 mL) was stirred at 150°C for 1 h under microwave irradiation. To the resulting mixture were added H_2O and EtOAc. The organic phase was washed with H_2O (3 x) and brine, dried over $MgSO_4$, and evaporated. The residue was purified by chromatography on SiO_2 to give the title compound as a yellow oil (100 mg, 39.3%). ^1H NMR (500 MHz, $CDCl_3$) δ ppm 1.34 – 1.95 (m, 17 H), 3.92 (s, 3 H), 3.93 (s, 3 H), 4.87 (br s, 1 H), 5.66 (br s, 1 H), 6.52 (s, 1 H), 7.78 – 7.83 (m, 2 H). [M+H] calc'd for $C_{23}H_{30}N_6O_4$, 455; found, 455.

[0332] B. *tert*-Butyl (1*S*,2*R*)-2-(4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate

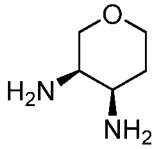
[0333] A solution of methyl 6-((1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclohexylamino)-4-cyano-2-(1-methyl-1*H*-pyrazol-4-yl)nicotinate (110 mg, 0.242 mmol) and palladium on carbon (2.58 mg, 0.024 mmol) in MeOH (5 mL) and HOAc (1 mL) was stirred at RT overnight under H_2 atmosphere. After reaction, the mixture was filtered through Celite, the filtrate was evaporated, and the residue was diluted with MeOH and sat aq $NaHCO_3$. The mixture was stirred at RT for 30 min and extracted with EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by chromatography on SiO_2 and preparative HPLC to give the title compound (60 mg, 58.1%). ^1H NMR (500 MHz, $CDCl_3$) δ ppm 1.26 – 1.87 (m, 17 H), 3.91 (s, 3 H), 4.25 (br s, 2 H), 5.16 – 5.49 (m 2 H), 6.23 (br s, 1 H), 6.75 (br s, 1 H), 8.18 – 8.44 (m, 1 H), 8.76 – 9.05 (m, 1 H).

[0334] EXAMPLE 26: 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

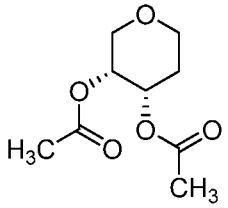


[0335] A mixture of *tert*-butyl (1*S*,2*R*)-2-(4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (94 mg, 0.22 mmol) and TFA (1 mL, 12.98 mmol) in DCM (1 mL) was stirred at RT for 2 h. The mixture was subsequently concentrated. The residue was purified by preparative HPLC (01-25; 5.45 min) and basified to give the title compound as a yellow solid (10 mg, 14%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 122 – 1.61 (m, 8 H), 3.63 (s, 3 H), 4.19 (s, 2 H), 6.46 (br s, 1 H), 7.98 (s, 1 H), 8.29 (s, 1 H), 8.85 (s, 1 H). [M+H] calc'd for $C_{17}H_{22}N_6O$, 327; found, 327.

[0336] PREPARATION 11: (3*R*,4*R*)-Tetrahydro-2*H*-pyran-3,4-diamine

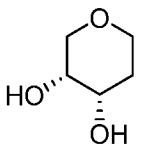


[0337] A. (3*R*,4*S*)-Tetrahydro-2*H*-pyran-3,4-diyl diacetate



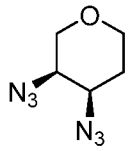
[0338] A mixture of (3*R*,4*S*)-3,4-dihydro-2*H*-pyran-3,4-diyl diacetate (8 g, 40 mmol) and Pd/C (10%, 5.0 g) in MeOH was stirred at RT for 12 h under H_2 atmosphere (50 psi). After filtration, the residue was concentrated to give the title compound, which was used without further purification (7.5 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.06 (s, 6 H), 3.95-4.03 (m, 2 H), 4.84 (t, *J*=4.0 Hz, 1 H), 5.15-5.20 (m, 1 H), 5.43 (t, *J*=4.0 Hz, 1 H), 6.49 (d, *J*=4.0 Hz, 1 H).

[0339] B. (3*R*,4*S*)-Tetrahydro-2*H*-pyran-3,4-diol



[0340] (3*R*,4*S*)-Tetrahydro-2*H*-pyran-3,4-diyl diacetate (7.5 g, 0.4 mmol) and sodium methylate (8.64 g, 0.16 mol) in MeOH was stirred overnight at RT. The reaction mixture was subsequently quenched with 6 N HCl in an ice bath. The mixture was concentrated to dryness. The residue was treated with EtOAc (500 mL) and vigorously stirred at 45°C for 30 min. After filtration, the filtrate was concentrated to give the title compound, which was used without further purification (4.4 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.79-1.84 (m, 1 H), 2.00 (s, 6 H), 3.56-3.67 (m, 2 H), 3.88-3.97 (m, 2 H), 5.09-5.14 (m, 2 H).

[0341] C. (3*R*,4*R*)-3,4-Diazidotetrahydro-2*H*-pyran

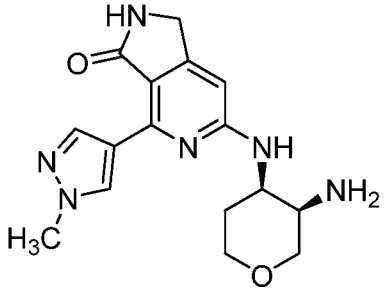


[0342] (3*R*,4*S*)-Tetrahydro-2*H*-pyran-3,4-diol (5.0 g, 42.4 mmol) was dissolved in DCM (50 mL). To the mixture was added pyridine (2.5 eq), and in an ice bath, trifluoromethanesulfonic anhydride (21.5 g, 94.3 mmol). The reaction was complete in 15 min. To the mixture was added DMF (50 mL) and hexamethylphosphoramide (1 mL), followed by sodium azide (25.0 g, 385.0 mmol). The reaction mixture was stirred at 50°C for 3 h. DCM was removed under reduced pressure. Water was added and the mixture was extracted with EtOAc (3 x 30 mL). The organic layer was washed with water, dried over Na_2SO_4, and concentrated to give the title compound, which was used without further purification (1.88 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.85-1.90 (m, 1 H), 2.05-2.09 (m, 1 H), 3.54-3.60 (m, 1 H), 3.65-3.72 (m, 1 H), 3.81-3.89 (m, 1 H), 3.91-3.95 (m, 1 H).

[0343] D. (3*R*,4*R*)-Tetrahydro-2*H*-pyran-3,4-diamine

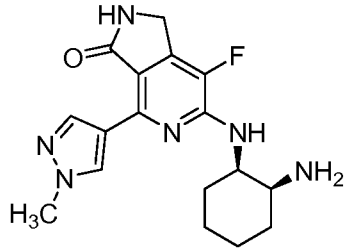
[0344] A mixture of (3*R*,4*R*)-3,4-diazidotetrahydro-2*H*-pyran (1.0 g, 5.9 mmol), di-*tert*-butyl pyrocarbonate (2.8 g, 12.9 mmol) and Pd/C (10%, 1.0 g) in MeOH was stirred at RT for 12 h under H_2 atmosphere (50 psi). After filtration, the residue was concentrated and purified by column chromatography eluting with EtOAc and petroleum ether (EtOAc/PE = 1/3) to give the intermediate di-*tert*-butyl *N*,*N*-((3*R*,4*R*)-tetrahydro-2*H*-pyran-3,4-diyl)-biscarbamate (1.2 g). The intermediate was dissolved in 1 M HCl-EtOAc and stirred at RT overnight to give the title compound (400 mg, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.93-1.97 (m, 1 H), 2.12-2.22 (m, 1 H), 3.60-3.66 (m, 1 H), 3.76-3.79 (m, 2 H), 3.86-3.92 (m, 1 H), 4.04-4.15 (m, 1 H). [M+H] calc'd for $C_5H_{12}N_2O$, 117; found, 117.

[0345] EXAMPLE 27: 6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

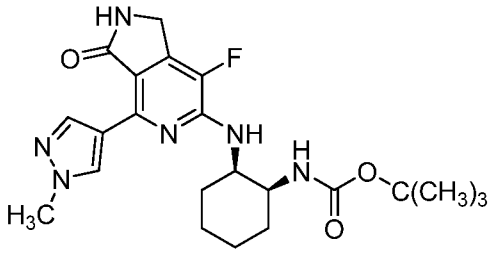


[0346] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 26 using (3*R*,4*R*)-tetrahydro-2*H*-pyran-3,4-diamine in place of *tert*-butyl (1*S*,2*R*)-2-aminocyclohexylcarbamate. The desired stereoisomer was isolated using preparative HPLC. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 3.52 (m, 2 H), 3.78 - 4.01 (m & s, 10 H), 4.21 - 4.42 (m & s, 3 H), 6.50 (s, 1 H), 7.91 (br s, 2 H), 8.29 - 8.39 (m, 1 H), 8.88 - 8.96 (m, 1 H). [M+H] calc'd for $C_{16}H_{20}N_6O_2$, 329; found, 329.

[0347] EXAMPLE 28: 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



[0348] A. *tert*-Butyl (1*S*,2*R*)-2-(7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate



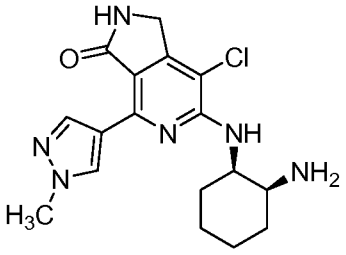
[0349] A solution of *tert*-butyl (1*S*,2*R*)-2-(4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (150 mg, 0.352 mmol) and SELECTFLUOR® (150 mg, 0.422 mmol) in DCM (1 mL) and MeOH (1 mL) was stirred at RT overnight. Water was subsequently added and the mixture was extracted with

$CHCl_3$ (3 x). The organic phases were combined, washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by preparative HPLC to give the title compound (15 mg, 9.60%). [M+H] calc'd for $C_{22}H_{29}FN_6O_3$, 445; found, 445.

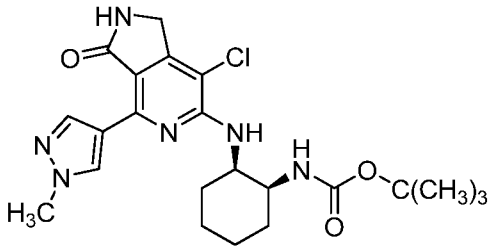
[0350] B. 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

[0351] A solution of *tert*-butyl (1*S*,2*R*)-2-(7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (15 mg, 0.034 mmol) and TFA (0.5 mL, 6.49 mmol) in DCM (0.5 mL) was stirred at RT for 30 min. The reaction mixture was concentrated and the resulting residue was purified by preparative HPLC to give a TFA salt of the title compound (7 mg, 60.2%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.37 – 2.01 (m, 8 H), 3.67 (br s, 1 H), 3.89 (s, 3 H), 4.32 – 4.43 (m, 2 H), 4.45 (br s, 1 H), 6.77 (d, *J*=6.35 Hz, 1 H), 7.93 (br s, 3 H), 8.30 (s, 1 H), 8.36 (s, 1 H), 8.84 (s, 1 H). [M+H] calc'd for $C_{17}H_{21}FN_6O$, 345; found, 345.

[0352] EXAMPLE 29: 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-chloro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



[0353] A. *tert*-Butyl (1*S*,2*R*)-2-(7-chloro-4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate



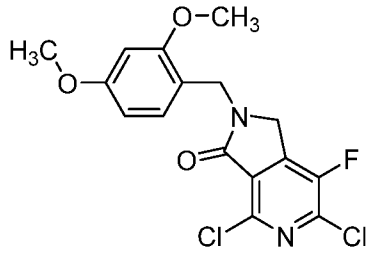
[0354] A solution of *tert*-butyl (1*S*,2*R*)-2-(4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (30 mg, 0.070 mmol) and *N*-chlorosuccinimide (9.86 mg, 0.074 mmol) in DCM (1 mL) was stirred at RT overnight. Additional *N*-chlorosuccinimide (1 eq) was added and the mixture was stirred at

RT for 3 h. Water and $CHCl_3$ were added to the mixture and the organic phase was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by preparative HPLC to give the title compound (20 mg, 61.7%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.18 – 2.09 (m, 17 H), 4.02 (s, 3 H), 4.28 – 4.45 (m, 2 H), 5.80 (br s, 1 H), 8.39 (br s, 1 H), 9.03 (br s, 1 H). [M+H] calc'd for $C_{22}H_{29}ClN_6O_3$, 461; found, 461.

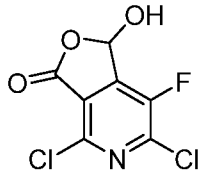
[0355] B. 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-chloro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

[0356] A solution of *tert*-butyl (1*S*,2*R*)-2-(7-chloro-4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (10.00 mg, 0.022 mmol) in HCl (0.5 mL, 16.46 mmol) and HOAc (1 mL) was stirred at RT for 30 min. The reaction mixture was concentrated and the resulting residue was washed with IPE to give the HCl salt of the title compound (5 mg, 63.9%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.48 – 1.97 (m, 8 H), 3.72 – 3.78 (m, 1 H), 3.96 (br s, 3 H), 4.35 (d, *J*=4.88 Hz, 2 H), 4.57 (br s, 1 H), 6.29 (d, *J*=6.83 Hz, 1 H), 7.93 (br s, 2 H), 8.40 – 8.45 (m, 1 H), 8.49 (s, 1 H), 8.98 (s, 1 H). [M+H] calc'd for $C_{17}H_{21}ClN_6O$, 361; found, 361.

[0357] PREPARATION 12: 4,6-Dichloro-2-(2,4-dimethoxybenzyl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



[0358] A. 4,6-Dichloro-7-fluoro-1-hydroxyfuro[3,4-*c*]pyridin-3(1*H*)-one



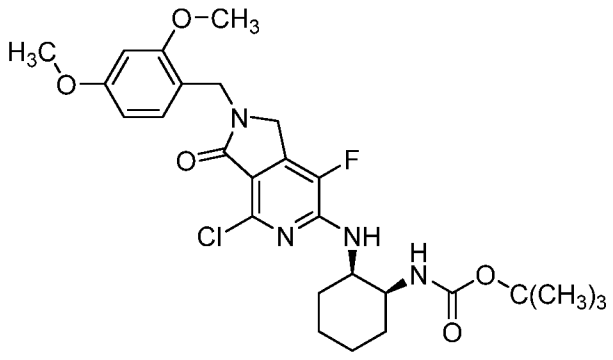
[0359] To a butyllithium-hexane solution (100 mL, 160 mmol) in THF (200 mL) was slowly added diisopropylamine (27.4 mL, 192 mmol) in THF (15 mL) at -78°C. The mixture was stirred at the same temperature for 15 min. A solution of 2,6-dichloro-5-fluoronicotinic acid (14.98 g, 71.4 mmol) in THF (15 mL) was added and the mixture was stirred for 2 h. Next, DMF (29.3 mL, 378 mmol) was added and the mixture was stirred

for 1 h. Hydrochloric acid (1N, 400 mL) was added and the mixture was subsequently extracted with EtOAc (2 x 300 mL). The organic phase was basified with saturated aq $NaHCO_3$ solution and the aqueous phase was separated. The aqueous phase was re-acidified with 1N HCl (300 mL) and extracted with EtOAc (2 x 300 mL). The organic phase was washed with H_2O (200 mL) and brine (200 mL), dried over $MgSO_4$, and evaporated. The residue was washed with Hexane/EtOAc (1/8) to give the title compound as a white solid (11.5 g, 67.7%). ^1H NMR (500 MHz, DMSO-d_6) δ ppm 6.85 (br s, 1 H), 8.82 (br s, 1 H).

[0360] B. 4,6-Dichloro-2-(2,4-dimethoxybenzyl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

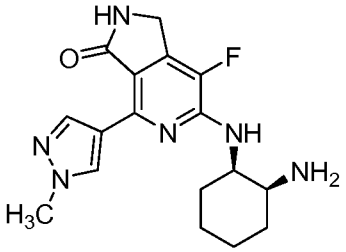
[0361] A mixture of 4,6-dichloro-7-fluoro-1-hydroxyfuro[3,4-*c*]pyridin-3(1*H*)-one (25.8 g, 108 mmol) and (2,4-dimethoxyphenyl)methanamine (34.2 mL, 228 mmol) in MeOH (400 mL) was stirred at RT for 2h. Sodium triacetoxyhydroborate (22.98 g, 108 mmol) was added to the mixture, which was stirred at RT for 2 h. Next, HCl (2N, 120 mL) was added and the resulting solid (17.3 g) was isolated by filtration. A mixture of the solid, *N*1-((ethylimino)methylene)-*N*3,*N*3-dimethylpropane-1,3-diamine hydrochloride (10.35 g, 54 mmol) and 1*H*-benzo[*d*][1,2,3]triazol-1-ol hydrate (8.27 g, 54 mmol) in DMF (200 mL) was stirred at room temperature for 2 h. Next, water was added and the mixture was extracted with EtOAc (2 x 300 mL). The organic phases were combined, washed with saturated aq $NaHCO_3$ solution (300 mL), H_2O (300 mL), and brine (300 mL), dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure and the residue was washed with EtOAc to give the title compound as a pale yellow solid (6.7 g, 16.7%). [M+H] calc'd for $C_{16}H_{13}Cl_2FN_2O_3$, 371; found, 371.

[0362] PREPARATION 13: *tert*-Butyl (1*S*,2*R*)-2-(4-chloro-2-(2,4-dimethoxybenzyl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate

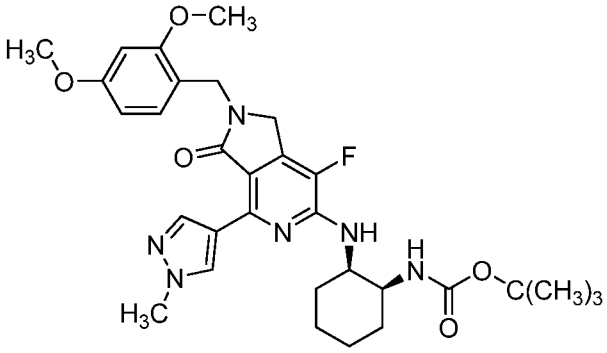


[0363] A mixture of 4,6-dichloro-2-(2,4-dimethoxybenzyl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one (4.8 g, 12.93 mmol) and *tert*-butyl (1*S*,2*R*)-2-aminocyclohexylcarbamate (4.16 g, 19.40 mmol) and diisopropylethylamine (3.39 mL, 19.40 mmol) in ACN (20 mL) was stirred at 100°C for 3 days. Water and EtOAc were added and the aqueous phase was extracted with EtOAc. The organic phases were combined, washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by chromatography on SiO_2 (Hexane/EtOAc=1/1) to give the title compound as a brown amorphous solid (3.31 g, 46.6%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.35 – 2.02 (m, 17 H), 3.80 (s, 3 H), 3.84 (s, 3 H), 4.01 (br s, 1 H), 4.20 (s, 2H), 4.23 (br s, 1 H), 4.66 (s, 2 H), 4.91 (br s, 1 H), 6.40 – 6.52 (m, 2 H), 7.20 -7.28 (m, 1 H). [M+H] calc'd for $C_{27}H_{34}ClFN_4O_5$, 549; found, 549.

[0364] EXAMPLE 30: 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one (HCl salt)



[0365] A. *tert*-Butyl (1*S*,2*R*)-2-(2-(2,4-dimethoxybenzyl)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate



[0366] A mixture of *tert*-butyl (1*S*,2*R*)-2-(4-chloro-2-(2,4-dimethoxybenzyl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (200 mg, 0.364 mmol), sodium carbonate (77 mg, 0.729 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (91 mg, 0.437 mmol) and

bis(triphenylphosphine)palladium chloride (25.6 mg, 0.036 mmol) in DME (2 mL) and H_2O (0.667 mL) was stirred at 85°C for 2 h. To the resulting mixture was added EtOAc. The aqueous phase was extracted with EtOAc. The organic phases were combined, washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by chromatography on SiO_2 (Hexane/EtOAc=2/3) to give the title compound as a yellow oil (88 mg, 40.6%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.28 – 2.01 (m, 17 H), 3.80 (d, *J*=2.93 Hz, 3 H), 3.85 (s, 3 H), 3.91 – 4.01 (m, 4 H), 4.23 (br s, 2 H), 4.41 (br s, 1 H), 4.68 (d, *J*=1.95 Hz, 2 H), 5.36 (br s, 1 H), 6.36 – 6.54 (m, 2 H), 7.15 – 7.21 (m, 1 H), 8.26 (br s, 1 H), 9.02 (br s, 1 H). [M+H] calc'd for $C_{31}H_{39}FN_6O_5$, 595; found, 595.

[0367] B. 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

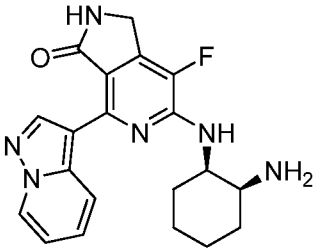
A solution of *tert*-butyl (1*S*,2*R*)-2-(2-(2,4-dimethoxybenzyl)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (2.4 g, 4.04 mmol) and TFA (5 mL, 64.9 mmol) was stirred at 80°C for 30 min. The resulting suspension was diluted with EtOAc (5 mL) and filtered. The filtrate was evaporated *in vacuo*. The residue was diluted with H_2O (300 mL) and EtOAc (100 mL) and filtered. The precipitate was washed with EtOAc and dried to give the title compound as a TFA salt (900 mg). The filtrate was extracted with EtOAc (200 mL). The aqueous phase was neutralized with saturated aq $NaHCO_3$ solution and extracted with EtOAc (2 x 400 mL) and THF (2 x 200 mL). The organic phases were combined, dried over $MgSO_4$, and evaporated. The residue was washed with EtOAc to give a first crop (400 mg) of the title compound as the free base. The TFA salt obtained above was diluted with saturated aq $NaHCO_3$ solution (20 mL) and stirred at RT overnight. The resulting suspension was filtered and the solids were washed with EtOAc to give a second crop (700 mg) of the title compound as the free base (1.1 g, 79%).

[0368] C. 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one (HCl salt)

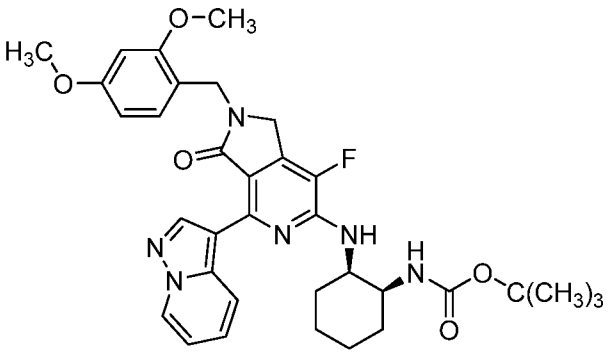
[0369] To a solution of 6-((1*R*,2*S*)-2-aminocyclohexylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one (2.300 g, 6.68 mmol) in THF (300 mL) was added 1N HCl in EtOAc (20 mL, 20.0 mmol) dropwise and the mixture was stirred at room temperature for 30 min. The resulting suspension was filtered and the precipitate was collected and washed with EtOAc (10 mL) to afford crude HCl salt of the

title compound (2.55 g). The crude compound was recrystallized from EtOH (60mL) and H_2O (16 mL) to give the HCl salt of the title compound as a white solid (1.5 g, 59.0%). ^1H NMR (500 MHz, DMSO-d_6) δ ppm 1.34 – 1.99 (m, 8 H), 3.67 (br s, 3 H), 3.89 (br s, 3 H), 4.32 – 4.43 (m, 2 H), 4.45 (br s, 1 H), 6.76 (d, *J*=5.86 Hz, 1 H), 7.88 (br s, 3 H), 8.29 (d, *J*=4.88 Hz, 1 H), 8.36 (s, 1 H), 8.84 (s, 1 H). [M+H] calc'd for $C_{17}H_{21}FN_6O$, 345; found, 345.

[0370] EXAMPLE 31: 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(pyrazolo[1,5-*a*]pyridin-3-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



[0371] A. *tert*-butyl (1*S*,2*R*)-2-(2-(2,4-dimethoxybenzyl)-7-fluoro-3-oxo-4-(pyrazolo[1,5-*a*]pyridin-3-yl)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate



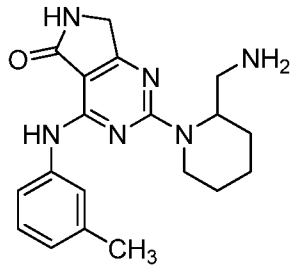
[0372] A mixture of *tert*-butyl (1*S*,2*R*)-2-(4-chloro-2-(2,4-dimethoxybenzyl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (100 mg, 0.182 mmol), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-*a*]pyridine (53.4 mg, 0.219 mmol), sodium carbonate (48.3 mg, 0.455 mmol) and tetrakis(triphenylphosphine)palladium (21.05 mg, 0.018 mmol) in DME (1 mL) and H_2O (0.333 mL) was stirred at 85°C for 3 h. Following reaction, the mixture was filtered and the filtrate was diluted with EtOAc and H_2O. The aqueous phase was extracted with EtOAc. The organic phases were combined, washed with brine, dried over $MgSO_4$, and

evaporated. The residue was purified by chromatography on SiO_2 to give the title compound (53 mg, 46.1%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.17 – 2.03 (m, 17 H), 3.74 – 3.81(m, 3 H), 3.84 – 3.89 (m, 3 H), 4.04 (br s, 1 H), 4.26 (br s, 2 H), 4.46 (br s, 1 H), 4.71 (br s, 2 H), 6.36 – 6.55 (m, 2 H), 6.83 (d, *J*=5.86 Hz, 1 H), 7.18 – 7.31 (m, 2 H), 8.42 (br s, 1 H), 8.47 – 8.57 (m, 1 H), 9.42 (br s, 1 H).

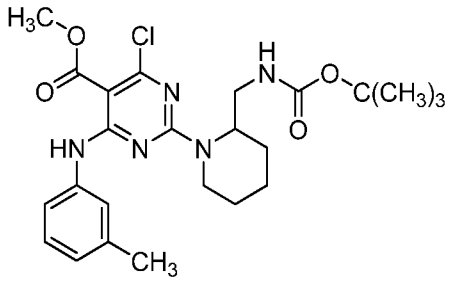
[0373] B. 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(pyrazolo[1,5-*a*]pyridin-3-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

[0374] A mixture of *tert*-butyl (1*S*,2*R*)-2-(2-(2,4-dimethoxybenzyl)-7-fluoro-3-oxo-4-(pyrazolo[1,5-*a*]pyridin-3-yl)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (52 mg, 0.082 mmol) and TFA (1 mL, 12.98 mmol) was stirred at 65°C for 30 min. The mixture was concentrated and the residue was purified by preparative HPLC to give the title compound as a white solid (15 mg, 47.8%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.21 – 2.07 (m, 8 H), 3.31 (br s, 1 H), 4.18 – 4.26 (m, 1 H), 4.46 (br s, 2 H), 6.61 (br s, 1 H), 7.09 (d, *J*=6.35 Hz, 1 H), 7.49 (d, *J*=7.32, 1 H), 8.36 (br s, 1 H), 8.59 (d, *J*= 7.81 Hz, 1 H), 8.83 (d, *J*=6.83 Hz, 1 H), 9.56 (br s, 1 H). [M+H] calc'd for $C_{20}H_{21}FN_6O$, 381; found, 381.

[0375] EXAMPLE 32: 2-(2-(Aminomethyl)piperidin-1-yl)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one

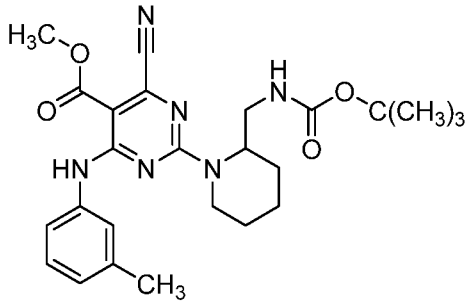


[0376] A. Methyl 2-(2-((*tert*-butoxycarbonylamino)methyl)piperidin-1-yl)-4-chloro-6-(*m*-tolylamino)pyrimidine-5-carboxylate



[0377] A mixture of methyl 2,4-dichloro-6-(m-tolylamino)pyrimidine-5-carboxylate (600.6 mg, 1.924 mmol), *tert*-butyl piperidin-2-ylmethylcarbamate (500.9 mg, 2.337 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (0.4 mL, 2.296 mmol) in DMF (10 mL) was stirred at 0°C for 3 h. Water (50 mL) was added to the mixture, which was extracted with EtOAc (2 x 40 mL). The organic layers were washed with saturated aq $NaHCO_3$ (20 mL), water (20 mL) and brine (20 mL), were dried over anhydrous Na_2SO_4, and then filtered (DM1020). The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/EtOAc=4/1) to give the title compound as a clear oil (310.5 mg). ^1H NMR (500 MHz, $CDCl_3$) δ ppm 1.34-1.74 (m, 15H), 2.35-2.37 (m, 3H), 3.03-3.21 (m, 2H), 3.60-3.71 (m, 1H), 3.90 (s, 3H), 4.43-5.04 (m, 3H), 6.94-6.98 (m, 1H), 7.23-7.46 (m, 3H), 10.13-10.43 (m, 1H). [M+H] calc'd for $C_{24}H_{33}ClN_5O_4$, 490; found, 490.

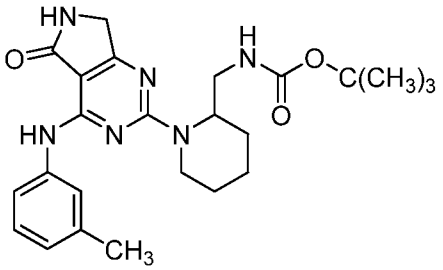
[0378] B. Methyl 2-(2-((*tert*-butoxycarbonylamino)methyl)piperidin-1-yl)-4-cyano-6-(*m*-tolylamino)pyrimidine-5-carboxylate



[0379] A mixture of methyl 2-(2-((*tert*-butoxycarbonylamino)methyl)piperidin-1-yl)-4-chloro-6-(*m*-tolylamino)pyrimidine-5-carboxylate (399.7 mg, 0.816 mmol), tetrakis(triphenylphosphine)palladium(0) (96.3 mg, 0.083 mmol), and zinc cyanide (53.2 mg, 0.453 mmol) in DMF (5 mL) was stirred at 120°C for 1 h under microwave irradiation. Water (50 mL) was added and the mixture was extracted with EtOAc (2 x 100 mL). The organic layers were washed with saturated aq $NaHCO_3$ (50 mL), water (50 mL), and brine (50 mL), were dried over anhydrous Na_2SO_4, and then filtered (DM1020). The filtrate was concentrated under reduced pressure and was purified by column chromatography (SiO_2, hexanes/EtOAc=4/1) to give the title compound as a colorless oil (315.0 mg, 80%). ^1H NMR (500 MHz, $CDCl_3$) δ ppm 1.34-1.77 (m, 15H), 2.36-2.39 (m, 3H), 3.00-3.21 (m, 2H), 3.49-3.69 (m, 1H), 3.97 (s, 3H), 4.49-5.10 (m, 3H), 6.96-7.02 (m,

1H), 7.24-7.41 (m, 3H), 10.14-10.45 (m, 1H). [M+H] calc'd for $C_{25}H_{33}N_6O_4$, 481; found, 481.

[0380] C. *tert*-Butyl (1-(5-oxo-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-2-yl)piperidin-2-yl)methylcarbamate



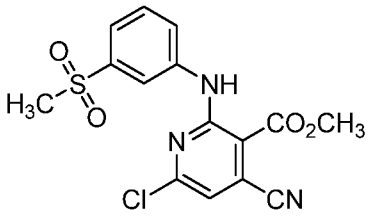
[0381] A mixture of methyl 2-(2-((*tert*-butoxycarbonylamino)methyl)piperidin-1-yl)-4-cyano-6-(*m*-tolylamino)pyrimidine-5-carboxylate (310.1 mg, 0.645 mmol), palladium on carbon (72.4 mg, 0.680 mmol) in EtOH (8 mL), and 1N HCl (4 mL) was stirred at RT for 16 h. The mixture was filtered to remove the catalyst. The filtrate was treated with saturated aq $NaHCO_3$ (20 mL) for 3 h. The mixture was concentrated under reduced pressure and the residue was extracted with EtOAc (2 x 40 mL). The organic layers were washed with saturated aq $NaHCO_3$ (20 mL), water (20 mL), and brine (20 mL), were dried over anhydrous Na_2SO_4, and then filtered through SiO_2. The filtrate was concentrated under reduced pressure to give the title compound as a colorless solid (213.4 mg, 73%). ^{1}H-NMR (DMSO-d_6) δ ppm 1.28 (s, 9H), 1.35 (br s, 1H), 1.49-1.56 (m, 2H), 1.67-1.69 (m, 3H), 2.31 (s, 3H), 3.06 (br s, 1H), 3.24 (br s, 2H), 4.16 (s, 2H), 4.67 (br s, 1H), 5.08 (br s, 1H), 6.77 (br s, 1H), 6.87 (d, 1H, J=7.0Hz), 7.23-7.25 (m, 1H), 7.53 (br s, 2h), 8.07 (s, 1H), 8.55 (s, 1H). [M+H] calc'd for $C_{24}H_{33}N_6O_3$, 453; found, 453.5.

[0382] D. 2-(2-(Aminomethyl)piperidin-1-yl)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one

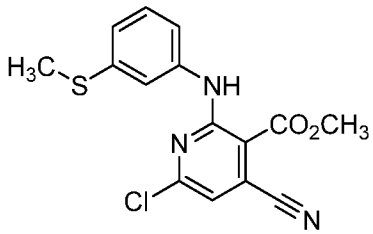
[0383] To a solution of *tert*-butyl (1-(5-oxo-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-2-yl)piperidin-2-yl)methylcarbamate (207.1 mg, 0.458 mmol) in HOAc (3 mL) was added HCl (1 mL, 32.9 mmol). The mixture was stirred at RT for 1 h and then concentrated under reduced pressure. The residue was treated with saturated aq $NaHCO_3$ (50 mL) and was extracted with EtOAc-THF(1/1, 2 x 40 mL). The organic layers were washed with saturated aq NaHCO3 (20 mL), water (20 mL), and brine (20 mL), were dried over anhydrous Na_2SO_4, and then filtered. The filtrate was concentrated under

reduced pressure and the residue was washed with EtOH to give the title compound as a pale yellow solid (27.4 mg, 17%). ^{1}H-NMR (DMSO-d_6) δ ppm 1.32-1.70 (m, 7H), 1.89-1.92 (m, 1H), 2.31 (s, 3H), 2.74-2.87 (m, 1H), 2.81-2.85 (m, 1H), 2.94 (br s, 1H), 4.17 (s, 2H), 4.68-4.79 (m, 2H), 6.88 (d, 1H, J=7.5 Hz), 7.22- 7.25(m, 1H), 7.49-7.50 (m, 1H), 7.60 (s, 1H), 8.06 (s, 1H), 8.58 (s, 1H). [M+H] calc'd for $C_{19}H_{25}N_6O$, 353; found, 353.5.

[0384] PREPARATION 14: Methyl 6-chloro-4-cyano-2-(3-(methylsulfonyl)phenylamino)nicotinate



[0385] A. Methyl 6-chloro-4-cyano-2-(3-(methylthio)phenylamino)nicotinate

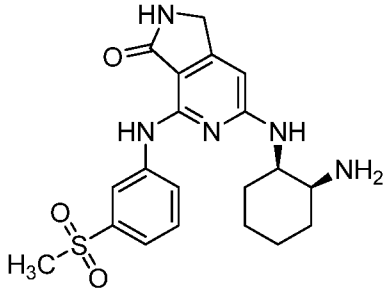


[0386] A mixture of methyl 2,6-dichloro-4-cyanonicotinate (340.8 mg, 1.475 mmol), DIPEA (0.3 mL, 1.718 mmol) and 3-(methylthio)aniline (234.8 mg, 1.687 mmol) in CH_3CN (5 mL) was stirred at 60°C for 2 days. After the mixture was cooled, saturated aq $NaHCO_3$ (30 mL) was added and the mixture was extracted with EtOAc (2 x 30 mL). The organic layers were washed with saturated aq $NaHCO_3$ (20 mL), water (20 mL) and brine (20 mL), were dried over anhydrous Na_2SO_4, and then filtered through SiO_2. The filtrate was concentrated under reduced pressure and the residue was washed with IPE and filtered to give the title compound as a yellow solid (157.8 mg). The filtrate was purified by column chromatography (SiO_2, hexanes/EtOAc=8/1) to give another crop (135.5 mg) of the title compound as a yellow oil of (total 293 mg, 60%). ^{1}H-NMR ($CDCl_3$) δ ppm 2.52 (s, 3H), 4.05 (s, 3H), 7.00 (s, 1H), 7.03-7.05 (m, 1H), 7.25-7.32 (m, 2H), 7.66-7.67 (m, 1H), 10.51 (br s, 1H). [M+H] calc'd for $C_{15}H_{13}ClN_3O_2S$, 334; found, 334.

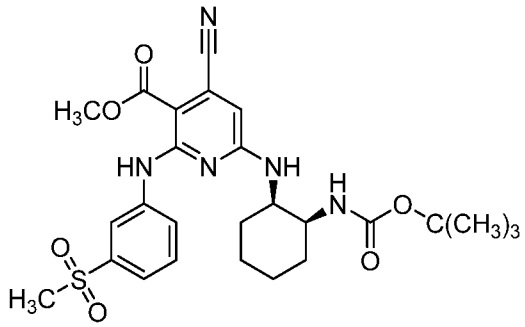
[0387] B. Methyl 6-chloro-4-cyano-2-(3-(methylsulfonyl)phenylamino)nicotinate

[0388] To a solution of methyl 6-chloro-4-cyano-2-(3-(methylthio)phenylamino)nicotinate (291.1 mg, 0.872 mmol) in DMF (10 mL) was added *m*-chloroperoxybenzoic acid (538.9 mg, 2.405 mmol) at 0°C. The mixture was stirred at RT for 16 h. Aqueous $Na_2S_2O_3$ (30 mL) was added and the mixture was extracted with EtOAc (2 x 30 mL). The organic layers were washed with saturated aq $NaHCO_3$ (20 mL), water (20 mL) and brine (20 mL), were dried over anhydrous Na_2SO_4, and then filtered (DM1020). The filtrate was concentrated under reduced pressure and the residue was washed with IPE to give the title compound as a yellow solid (158.2 mg, 50%). ^{1}H-NMR ($CDCl_3$) δ ppm 3.11 (s, 3H), 4.07 (s, 3H), 7.10 (s, 1H), 7.57-7.60 (m, 1H), 7.70-7.72 (m, 1H), 7.91-7.93 (m, 1H), 8.25-8.26 (m, 1H), 10.73 (s, 1H).

[0389] EXAMPLE 33: 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(3-(methylsulfonyl)phenylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



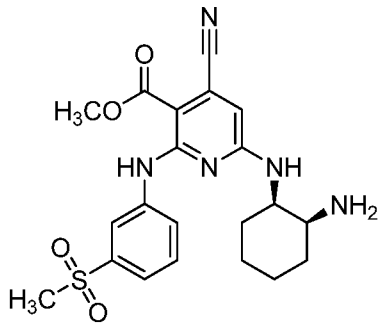
[0390] A. Methyl 6-((1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclohexylamino)-4-cyano-2-(3-(methylsulfonyl)phenylamino)nicotinate



[0391] A mixture of methyl 6-chloro-4-cyano-2-(3-(methylsulfonyl)phenylamino)nicotinate (162.8 mg, 0.445 mmol), *tert*-butyl (1*S*,2*R*)-2-aminocyclohexylcarbamate (111.6 mg, 0.521 mmol) and Et_3N (0.1 mL, 0.717 mmol) in THF (6 mL) and DMF (6.00 mL) was stirred at 60°C for 12 h. After the mixture was cooled, saturated aq $NaHCO_3$ (30 mL) was added and the mixture was extracted with EtOAc (2 x 30 mL). The organic layers were washed with saturated aq $NaHCO_3$ (15 mL),

water (15 mL) and brine (15 mL), were dried over anhydrous Na_2SO_4, and filtered through SiO_2. The filtrate was concentrated under reduced pressure and the residue was washed with IPE to give the title compound as a yellow solid (182.2 mg, 75%). ^{1}H-NMR ($CDCl_3$) δ ppm 1.42-1.67 (m, 15H), 1.84-1.91 (m, 2H), 3.07 (s, 3H), 3.95-3.97 (m, 4H), 4.16-4.17 (m, 1H), 4.77 (s, 1H), 6.24 (s, 1H), 7.48-7.51 (m, 1H), 7.58-7.61 (m, 1H), 7.77-7.78 (m, 1H), 8.41 (s, 1H), 10.99 (s, 1H), 1H not detected.

[0392] B. Methyl 6-((1*R*,2*S*)-2-aminocyclohexylamino)-4-cyano-2-(3-(methylsulfonyl)phenylamino)nicotinate

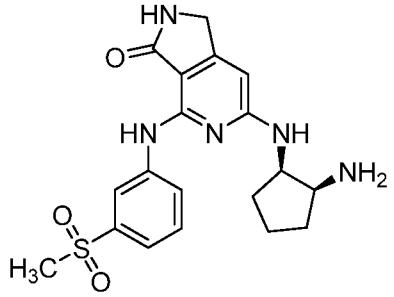


[0393] To a solution of methyl 6-((1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclohexylamino)-4-cyano-2-(3-(methylsulfonyl)phenylamino)nicotinate (178.3 mg, 0.328 mmol) in HOAc (4 mL) was added HCl (4 mL, 132 mmol). The mixture was stirred at RT for 4 h and then concentrated under reduced pressure. Water (15 mL) and 1M HCl (15 mL) were added to the concentrate and the aqueous layer was washed with EtOAc (10 mL). The washed aqueous layer was basified with saturated aqueous $NaHCO_3$ (50 mL) and extracted with EtOAc (2 x 30 mL). The organic layers were combined, washed with saturated aq $NaHCO_3$ (20 mL), water (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give the title compound as a brown solid (123.2 mg, 85%). ^{1}H-NMR($CDCl_3$) δ ppm 1.45-16.4 (m, 6H), 1.77-1.79 (m, 4H), 3.06 (s, 3H), 3.17-3.18 (m, 1H), 3.94 (s, 3H), 4.10-4.14 (m, 1H), 6.03-6.05 (m, 1H), 6.29 (s, 1H), 7.48-7.51 (m, 1H), 7.58-7.60 (m, 1H), 7.71-7.72 (m, 1H), 8.53 (s, 1H), 11.01 (s, 1H).

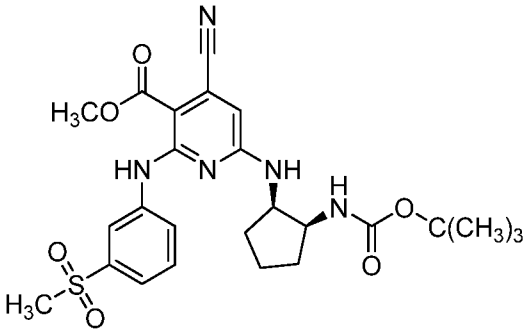
[0394] C. 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(3-(methylsulfonyl)phenylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

[0395] A mixture of methyl 6-((1*R*,2*S*)-2-aminocyclohexylamino)-4-cyano-2-(3-(methylsulfonyl)phenylamino)nicotinate (117.3 mg, 0.264 mmol) and palladium on carbon (23.6 mg, 0.222 mmol) in MeOH (4 mL) and 1N HCl (4 mL) was stirred at RT for 16 h under a hydrogen atmosphere. The mixture was filtered to remove the catalyst and the filtrate was treated with saturated aq $NaHCO_3$ (20 mL) and stirred at RT for 20 h. The mixture was concentrated under reduced pressure and the residue was extracted with EtOAc/THF (2/1, 2 x 30 mL). The organic layers were washed with saturated aq $NaHCO_3$ (15 mL), water (15 mL) and brine (15 mL), were dried over anhydrous Na_2SO_4, and then filtered. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (DM1020, EtOAc/MeOH=20/1) to give the desired product (37.2 mg, 34%). The product was recrystallized from EtOH to give the title compound as a colorless solid (13.2 mg, 12%). ^{1}H-NMR (DMSO-d_6) δ ppm 1.31-1.41 (m, 4H), 1.55-1.68 (m, 6H), 3.05 (s, 1H), 3.21 (s, 3H), 4.08 (s, 1H), 4.23 (s, 2H), 6.17 (s, 1H), 6.78-6.79 (m, 1H), 7.46-7.47 (m, 1H), 7.53-7.56 (m, 1H), 7.96-7.99 (m, 2H), 8.49 (s, 1H), 9.18 (s, 1H).

[0396] EXAMPLE 34: 6-((1*R*,2*S*)-2-Aminocyclopentylamino)-4-(3-(methylsulfonyl)phenylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one (HCl salt)

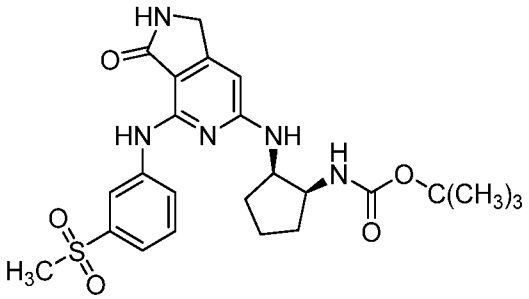


[0397] A. Methyl 6-((1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclopentylamino)-4-cyano-2-(3-(methylsulfonyl)phenylamino)nicotinate



[0398] A mixture of methyl 6-chloro-4-cyano-2-(3-(methylsulfonyl)phenylamino)nicotinate (165.0 mg, 0.451 mmol), Et_3N (0.15 mL, 1.076 mmol), and *tert*-butyl (1*S*,2*R*)-2-aminocyclopentylcarbamate (142.0 mg, 0.709 mmol) in DMF (6 mL) was stirred at 60°C for 12 h. Saturated aq $NaHCO_3$ (20 mL) was added to the mixture, which was subsequently extracted with EtOAc (2 x 30 mL). The organic layers were washed with saturated aq $NaHCO_3$ (20 mL), water (20 mL) and brine (20 mL), were dried over anhydrous Na_2SO_4, and filtered (DM1020). The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexanes/EtOAc=1/1) and then triturated with IPE to provide the title compound (147 mg).

[0399] B. *tert*-Butyl (1*S*,2*R*)-2-(4-(3-(methylsulfonyl)phenylamino)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclopentylcarbamate

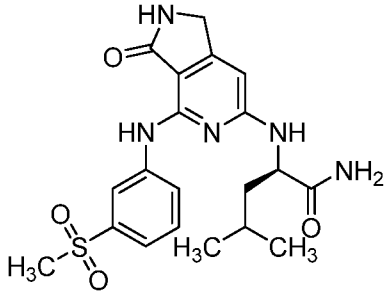


[0400] A mixture of methyl 6-((1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclopentylamino)-4-cyano-2-(3-(methylsulfonyl)phenylamino)nicotinate (141.1 mg, 0.266 mmol) and palladium hydroxide on carbon (43.2 mg, 0.308 mmol) in MeOH (10 mL) and HOAc (10 mL) was stirred at RT for 12 h under a hydrogen atmosphere. The mixture was filtered to remove the catalyst and the filtrate was concentrated under reduced pressure. The residue was treated with saturated aq $NaHCO_3$ (20 mL) and MeOH (20 mL). The mixture was stirred at RT for 6 h and then concentrated under reduced pressure. The residue was treated with saturated aq $NaHCO_3$ (30 mL) and extracted with EtOAc (2 x 50 mL). The organic layers were washed with saturated aq $NaHCO_3$ (20 mL), water (20 mL) and brine (20 mL), were dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (DM1020, EtOAc) to give the desired product (46.5 mg). The product was washed with IPE/EtOAc to give the title compound as a pale brown solid (34.7 mg, 26%).

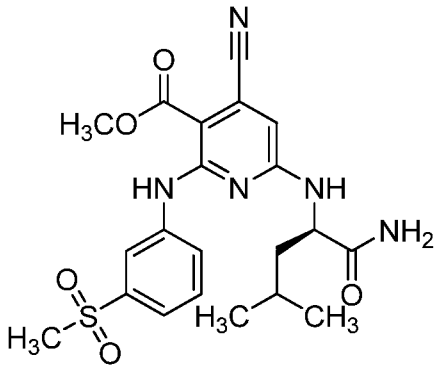
[0401] C. 6-((1*R*,2*S*)-2-Aminocyclopentylamino)-4-(3-(methylsulfonyl)phenylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one (HCl salt)

[0402] A mixture of *tert*-butyl (1*S*,2*R*)-2-(4-(3-(methylsulfonyl)phenylamino)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclopentylcarbamate (16.5 mg, 0.329 mmol) and HCl (1 mL, 32.9 mmol) in HOAc (2 mL) was stirred at RT for 3 h. The mixture was concentrated under reduced pressure and the residue was recrystalized from EtOH-H_2O to give the title compound (9.6 mg, 67%). ^{1}H-NMR (DMSO-d_6) δ ppm 1.63-1.79 (m, 4H), 20.3-2.06 (m, 1H), 2.19-2.20 (m, 1H), 3.32 (s, 3H), 3.74 (br s, 1H), 4.23-4.28 (m, 2H), 4.45 (br s, 1H), 6.22 (s, 1H), 7.34-7.35 (m, 1H), 7.51-7.58 (m, 3H), 7.73 (br s, 3H), 8.13 (s, 1H), 8.82 (s, 1H), 9.26 (s, 1H).

[0403] EXAMPLE 35: (*R*)-4-Methyl-2-(4-(3-(methylsulfonyl)phenylamino)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)pentanamide



[0404] A. (*R*)-Methyl 6-(1-amino-4-methyl-1-oxopentan-2-ylamino)-4-cyano-2-(3-(methylsulfonyl)phenylamino)nicotinate



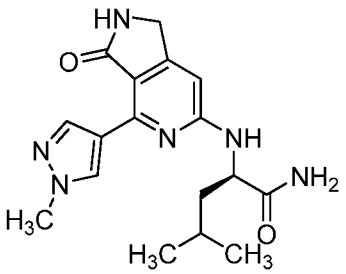
[0405] A mixture of methyl 6-chloro-4-cyano-2-(3-(methylsulfonyl)phenylamino)nicotinate (120.7 mg, 0.330 mmol), (*R*)-2-amino-4-methylpentanamide (67.1 mg, 0.515 mmol), and Et_3N (0.1 mL, 0.717 mmol) in DMF (4 mL) was stirred at 60°C for 14 h. Saturated aq $NaHCO_3$ (20 mL) was added to the mixture, which was subsequently extracted with EtOAc (2 x 30 mL). The organic layers

were washed with saturated aq $NaHCO_3$ (20 mL), water (20 mL) and brine (20 mL), were dried over anhydrous Na_2SO_4, and filtered (DM1020). The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexanes/EtOAc=1/2) and then triturated with IPE to give the title compound (76 mg, 50%).

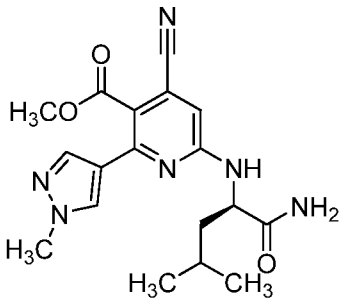
[0406] B. (*R*)-4-Methyl-2-(4-(3-(methylsulfonyl)phenylamino)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)pentanamide

[0407] A mixture of (*R*)-methyl 6-(1-amino-4-methyl-1-oxopentan-2-ylamino)-4-cyano-2-(3-(methylsulfonyl)phenylamino)nicotinate (73.2 mg, 0.159 mmol) and palladium hydroxide on carbon (23.2 mg, 0.165 mmol) in MeOH (6 mL) and HOAc (3 mL) was stirred at RT for 12 h under a hydrogen atmosphere. The mixture was filtered to remove the catalyst and the filtrate was concentrated under reduced pressure. The residue was treated with saturated aq $NaHCO_3$ (20 mL) and MeOH (20 mL). The resulting mixture was stirred at RT for 16 h and then concentrated under reduced pressure. The residue was treated with saturated aq $NaHCO_3$ (30 mL) and extracted with EtOAc (2 x 50 mL). The organic layers were washed with saturated aq $NaHCO_3$ (20 mL), water (20 mL) and brine (20 mL), were dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure and the residue was recrystallized from EtOH to give the title compound as a white solid (18.8 mg, 27%). ^{1}H-NMR (DMSO-d_6) δ ppm 0.87-0.94 (m, 6H), 1.54-1.63 (m, 2H), 1.76 (br s, 1H), 3.32 (s, 3H), 4.24 (s, 2H), 4.50 (br s, 1H), 6.17 (s, 1H), 7.00-7.04 (m, 2H), 7.22 (br s, 1H), 7.47-7.57 (m, 2H), 8.01 (br s, 1H), 8.06 (s, 1H), 8.45 (br s, 1H), 9.23 (s, 1H). [M+H] calc'd for $C_{20}H_{26}N_5O_4S$, 432; found, 432.5.

[0408] EXAMPLE 36: (*R*)-4-Methyl-2-(4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)pentanamide



[0409] A. (*R*)-Methyl 6-(1-amino-4-methyl-1-oxopentan-2-ylamino)-4-cyano-2-(1-methyl-1*H*-pyrazol-4-yl)nicotinate

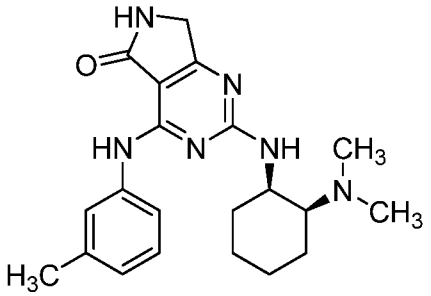


[0410] A mixture of methyl 6-chloro-4-cyano-2-(1-methyl-1*H*-pyrazol-4-yl)nicotinate (82.9 mg, 0.300 mmol) and (*R*)-2-amino-4-methylpentanamide (39.0 mg, 0.300 mmol) in DMA (2 mL) was stirred at 150°C for 12 h. Water was subsequently added and the mixture was extracted with EtOAc. The organic layers were washed with saturated aq $NaHCO_3$, water, and brine, were dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, EtOAc) to give the title compound as a yellow oil (11.7 mg, 11%).

[0411] B. (*R*)-4-Methyl-2-(4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)pentanamide

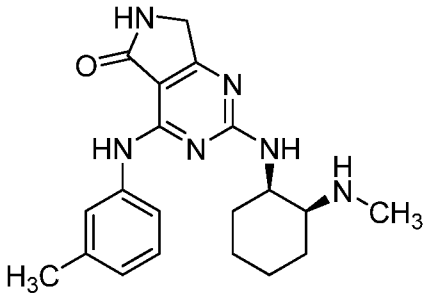
[0412] A mixture of (*R*)-methyl 6-(1-amino-4-methyl-1-oxopentan-2-ylamino)-4-cyano-2-(1-methyl-1*H*-pyrazol-4-yl)nicotinate (20.3 mg, 0.055 mmol) and palladium hydroxide (10 mg, 0.094 mmol) in MeOH (2 mL) and HOAc (2 mL) was stirred at RT for 3 h under a hydrogen atmosphere. The mixture was filtered to remove the catalyst and the filtrate was concentrated under reduced pressure. The residue was treated with saturated aq $NaHCO_3$ (20 mL) and EtOAc (20 mL) for 12 h. The mixture was extracted with EtOAc (2 x 20 mL). The organic layers were washed with saturated aq $NaHCO_3$ (20 mL), water (20 mL) and brine (20 mL), were dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (DM1020, EtOAc/MeOH=15/1-10/1) to give the title compound as a white solid (10.2 mg, 54%). ^{1}H-NMR (DMSO-d_6) δ ppm 0.88-0.95 (m, 6H), 1.52-1.60 (m, 2H), 1.73-1.76 (m, 1H), 3.88 (s, 3H), 4.21 (s, 2H), 4.48 (br s, 1H), 6.43 (s, 1H), 6.90 (s, 1H), 7.03 (br s, 1H), 7.42 (s, 1H), 8.01 (s, 1H), 8.41 (s, 1H), 8.92 (s, 1H). [M+H] calc'd for $C_{17}H_{23}N_6O_2$, 343; found, 343.

[0413] EXAMPLE 37: 2-((1*R*,2*S*)-2-(Dimethylamino)cyclohexylamino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one



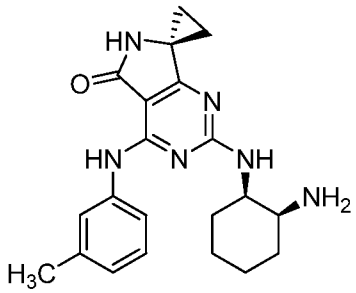
[0414] A solution of 2-((1*R*,2*S*)-2-aminocyclohexylamino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one (10 mg, 0.028 mmol), paraformaldehyde (0.852 mg, 0.028 mmol) in MeOH (2 mL) was stirred at RT for 10 min. Sodium cyanotrihydroborate (1.783 mg, 0.028 mmol) was added and the reaction mixture was stirred at RT overnight. The mixture was purified by reverse phase preparative HPLC to give the TFA salt of the title compound (5 mg, 46%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.44 -1.57 (m, 4 H), 1.85 (br s, 4 H), 2.32 (s, 3 H), 2.64 - 2.87 (2s, 6 H), 4.20 (d, *J*=4.55 Hz, 2 H), 6.91 (d, *J*=7.07 Hz, 1 H), 7.00 (s, 1 H), 7.13 (s, 1 H), 7.17 - 7.34 (m, 2 H), 8.19 (br s, 1 H), 8.68 (br s, 1 H). [M+H] calc'd for $C_{21}H_{28}N_6O$, 381; found, 381.

[0415] EXAMPLE 38: 2-((1*R*,2*S*)-2-(Methylamino)cyclohexylamino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one

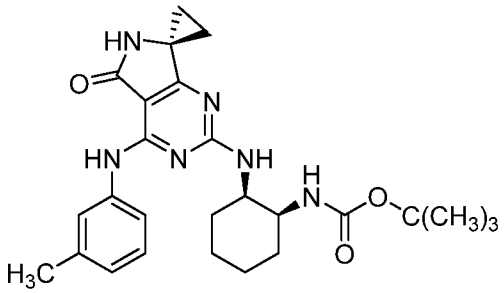


[0416] A solution of 2-((1*R*,2S)-2-Aminocyclohexylamino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one (17.7 mg, 0.050 mmol), paraformaldehyde (1.508 mg, 0.050 mmol) in MeOH (2 mL) was stirred at RT for 10 min. Sodium cyanotrihydroborate (3.16 mg, 0.050 mmol) was added and the reaction mixture was stirred at RT for 4 h. The reaction was stopped and the mixture was purified by reverse phase preparative HPLC to give the TFA salt of the title compound (5 mg, 27%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.35-1.79 (m, 8 H), 2.32 (s, 3 H), 4.20 (br s, 2 H), 6.52 (br s, 2 H), 6.91 (d, *J*=7.33 Hz, 1 H), 7.24 (t, *J*=7.71 Hz, 2 H), 8.03 (br s, 1 H), 8.16 (br s, 2 H), 8.40 (br s, 1 H), 8.66 (br s, 1 H). [M+H] calc'd for $C_{20}H_{26}N_6O$, 367; found, 367.

[0417] EXAMPLE 39: 2'-((1*R*,2*S*)-2-Aminocyclohexylamino)-4'-(*m*-tolylamino)spiro[cyclopropane-1,7'-pyrrolo[3,4-*d*]pyrimidin]-5'(6'*H*)-one



[0418] A. *tert*-Butyl (1*S*,2*R*)-2-(5'-oxo-4'-(*m*-tolylamino)-5',6'-dihydrospiro[cyclopropane-1,7'-pyrrolo[3,4-*d*]pyrimidine]-2'-ylamino)cyclohexylcarbamate



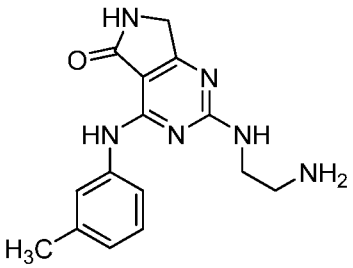
[0419] Ethylmagnesium bromide (0.069 mL, 0.208 mmol) was added at RT to a solution of methyl 2-((1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclohexylamino)-4-cyano-6-(*m*-tolylamino)pyrimidine-5-carboxylate (50 mg, 0.104 mmol) and tetraisopropylorthotitanate (0.091 mL, 0.312 mmol) in Et_2O (5 mL). The reaction mixture was stirred at RT for 20 h and was subsequently diluted with EtOAc. The organic phase was washed with saturated aq $NaHCO_3$, brine and water, was dried then concentrated to give a pink residue, which was purified by reverse phase preparative HPLC. The fractions were collected and concentrated to a residue, which was used in next step. [M+H] calc'd for $C_{26}H_{34}N_6O_3$, 479; found, 479.

[0420] B. 2'-((1*R*,2*S*)-2-Aminocyclohexylamino)-4'-(*m*-tolylamino)spiro[cyclopropane-1,7'-pyrrolo[3,4-*d*]pyrimidin]-5' (6'*H*)-one

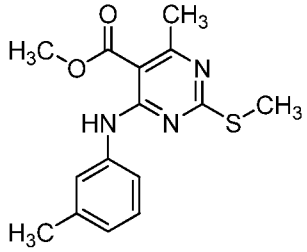
[0421] A solution of *tert*-Butyl (1*S*,2*R*)-2-(5'-oxo-4'-(*m*-tolylamino)-5',6'-dihydrospiro[cyclopropane-1,7'-pyrrolo[3,4-*d*]pyrimidine]-2'-ylamino)cyclohexylcarbamate (50 mg, 0.104 mmol) in DCM (5 mL) was treated with TFA (2 mL) for 1 h and was purified by reverse phase preparative HPLC. The collected

fractions were lyophilized to give the TFA salt of the title compound (4 mg, 10% in two steps). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.12 - 1.31 (m, 1 H), 1.42 (m, 6 H), 1.63 (m, 3 H), 1.86 (m, 2 H), 2.33 (s, 3 H), 3.62 (br s, 1 H), 4.18 (br s, 1 H), 6.91 (d, *J*=7.33 Hz, 1 H), 7.24 (t, *J*=7.71 Hz, 1 H), 7.36 - 7.56 (m, 1 H), 7.60 (br s, 1 H), 7.73 (br s, 2 H), 8.33 (br s, 1 H), 8.65 (br s, 1 H). [M+H] calc'd for $C_{21}H_{26}N_6O$, 379; found, 379.

[0422] EXAMPLE 40: 2-(2-Aminoethylamino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one

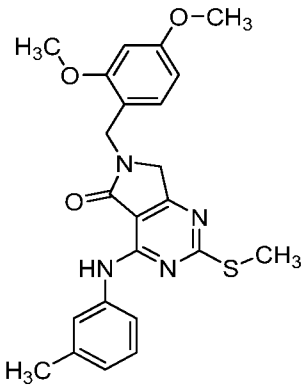


[0423] A. Methyl 4-methyl-2-(methylthio)-6-(*m*-tolylamino)pyrimidine-5-carboxylate



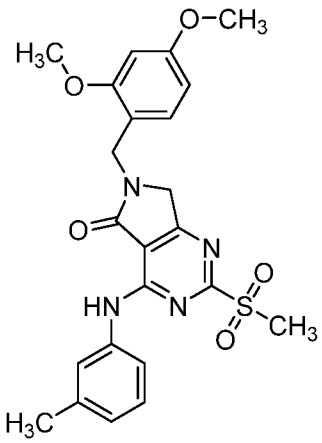
[0424] Methyl 2-chloro-4-methyl-6-(m-tolylamino)pyrimidine-5-carboxylate (0.078 g, 0.267 mmol) was dissoloved in DMF (3 mL). Sodium thiomethoxide (0.019 g, 0.267 mmol) was added and the reaction mixture was allowed to stir at RT for 1 h. The reaction mixture was poured onto ice. The pH was adjusted to 7 with 1 N HCl. The title compound was isolated as a yellow solid by vacuum filtration (72.8 mg, 90%). [M+H] calc'd for $C_{15}H_{17}N_3O_2S$, 304; found, 304.

[0425] B. 6-(2,4-Dimethoxybenzyl)-2-(methylthio)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one



[0426] A mixture methyl 4-methyl-2-(methylthio)-6-(*m*-tolylamino)pyrimidine-5-carboxylate (0.44 g, 1.45 mmol) and selenium dioxide (0.32 g, 2.89 mmol) in dioxane (12 mL) was heated at 100°C for 24 h. The reaction mixture was subsequently cooled and filtered. The filtrate was concentrated and dried to give a brown foam (0.459 g) which was dispersed in (2,4-dimethoxyphenyl)methanamine (0.217 mL, 1.446 mmol) in DCM (6 mL) and MeOH (3 mL). The resulting mixture was stirred at RT for 30 min. Sodium cyanoborohydride (0.227 g, 3.62 mmol) was added and the reaction mixture was stirred at RT for 20 h. The solid phase was filtered and washed with MeOH to give the title compound as a yellow solid (0.537 g, 85%). [M+H] calc'd for $C_{23}H_{24}N_4O_3S$, 437; found, 437.

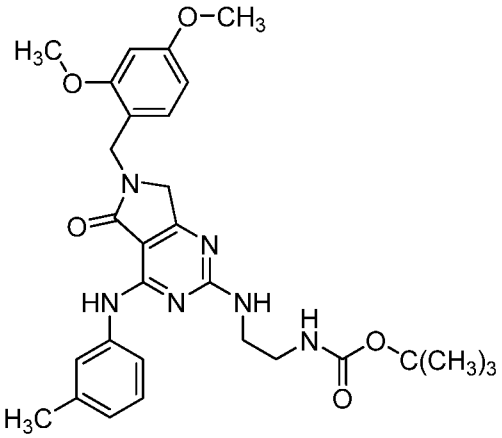
[0427] C. 6-(2,4-dimethoxybenzyl)-2-(methylsulfonyl)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one



[0428] 6-(2,4-Dimethoxybenzyl)-2-(methylthio)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one (0.432 g, 0.990 mmol) was dissolved in DCM (10 mL). The solution was chilled in an ice bath and *m*-chloroperoxybenzoic acid (0.256 g, 1.484 mmol) was added. The reaction was allowed to warm to RT with stirring for 3 h. A second

aliquot of *m*-chloroperoxybenzoic acid (0.170 g, 0.990 mmol) was added to the reaction mixture, which was stirred for 1 h. A third aliquot of *m*-chloroperoxybenzoic acid (0.100 g, 0.579 mmol) was added. The reaction mixture was stirred for 30 min, diluted with DCM (20 mL), and quenched with saturated aq $NaHCO_3$ (20 mL). The organic phase was washed with saturated aq $NaHCO_3$ (20 mL) and brine (20 mL), and was dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* to give the title compound as a light brown glassy solid (330 mg, 71%). [M+H] calc'd for $C_{23}H_{24}N_4O_5S$, 469; found, 469.

[0429] D. *tert*-Butyl 2-(6-(2,4-dimethoxybenzyl)-5-oxo-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-2-ylamino)ethylcarbamate



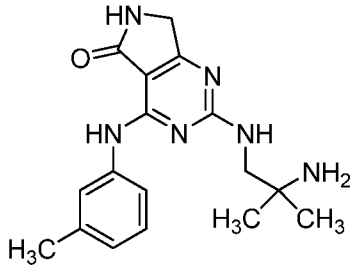
[0430] A mixture of 6-(2,4-dimethoxybenzyl)-2-(methylsulfonyl)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one (0.07 g, 0.149 mmol), *tert*-butyl 2-aminoethylcarbamate (0.024 g, 0.149 mmol), and Et_3N (0.104 mL, 0.747 mmol) in DMA (2 mL) was heated in a sealed tube at 90°C for 4 h. The reaction mixture was poured slowly onto ice and its pH adjusted to about 7 through addition of 1 N HCl, resulting in precipitation of a tan solid. The solid was isolated by vacuum filtration, washed with water, and dried under vacuum to give the title compound as a tan brown solid (55 mg, 67%). [M+H] calc'd for $C_{29}H_{36}N_6O_5$, 549; found, 549.

[0431] E. 2-(2-Aminoethylamino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one

[0432] A mixture of *tert*-butyl 2-(6-(2,4-dimethoxybenzyl)-5-oxo-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-2-ylamino)ethylcarbamate (0.055 g, 0.100 mmol) in TFA (2 mL) was stirred at 70°C for 1.5 h. Following reaction, the solvent was removed and the resulting residue was dispersed into a solution of DMSO and MeOH (1/1). The

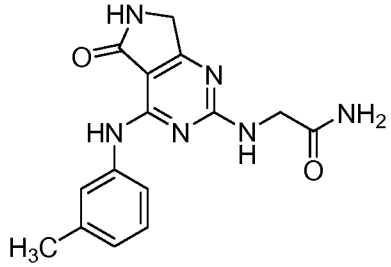
mixture was filtered and the filtrate was purified by preparative HPLC. The fractions were collected and dried *in vacuo* to give a TFA salt of the title compound as an off-white solid (28 mg, 93%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.21 - 2.40 (m, 3 H) 2.90 - 3.21 (m, 2 H) 3.57 (q, *J*=5.86 Hz, 2 H) 4.19 (br s, 2 H) 6.90 (br s, 1 H) 7.13 - 7.34 (m, 1 H) 7.54 (br s, 1 H) 7.56 - 7.74 (m, 2 H) 7.80 (br s, 2 H) 8.18 (d, *J*=13.67 Hz, 1 H) 8.54 - 8.82 (m, 1 H). [M+H] calc'd for $C_{15}H_{18}N_6O$, 299; found, 299.

[0433] EXAMPLE 41: 2-(2-Amino-2-methylpropylamino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one



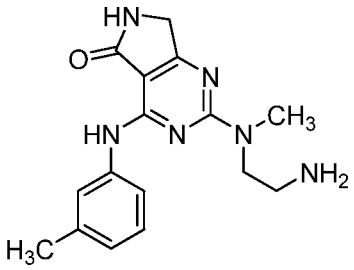
[0434] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 40 using *tert*-butyl 1-amino-2-methylpropan-2-ylcarbamate in place of *tert*-butyl 2-aminoethylcarbamate. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.14 - 1.53 (m, 6 H), 2.37 (br s, 3 H), 3.62 (br s, 2 H), 4.12 - 4.47 (m, 2 H), 6.77 - 7.15 (m, 1 H), 7.13 - 7.40 (m, 1 H), 7.40 - 7.79 (m, 2 H). [M+H] calc'd for $C_{17}H_{22}N_6O$, 327; found, 327.

[0435] EXAMPLE 42: 2-(5-Oxo-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-2-ylamino)acetamide



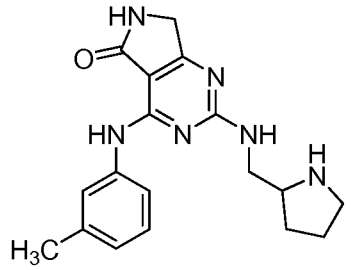
[0436] The title compound was prepared in a manner similar to EXAMPLE 40 using glycinamide hydrochloride in place of *tert*-butyl 2-aminoethylcarbamate. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 2.38 (s, 3 H), 4.11 (br s, 2 H), 4.41 (br s, 2 H), 7.02 (br s, 1 H), 7.27 (br s, 1 H), 7.51 (br s, 2 H). [M+H] calc'd for $C_{15}H_{16}N_6O_2$, 313; found, 313.

[0437] EXAMPLE 43: 2-((2-Aminoethyl)(methyl)amino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one



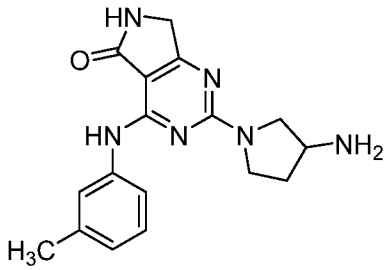
[0438] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 40 using *tert*-butyl 2-(methylamino)ethylcarbamate hydrochloride in place of *tert*-butyl 2-aminoethylcarbamate. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 2.35 (s, 3 H), 3.26 (t, *J*=5.86 Hz, 2 H), 3.30 (s, 3 H), 3.89 - 4.04 (m, 2 H), 4.24 (s, 2 H), 6.94 (d, *J*=7.32 Hz, 1 H), 7.23 (t, *J*=7.81 Hz, 1 H), 7.55 (d, *J*=7.81 Hz, 2 H). [M+H] calc'd for $C_{16}H_{20}N_6O$, 313; found, 313.

[0439] EXAMPLE 44: 2-(Pyrrolidin-2-ylmethylamino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one



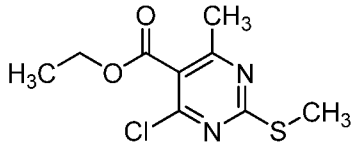
[0440] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 40 using *tert*-butyl 2-(aminomethyl)pyrrolidine-1-carboxylate in place of *tert*-butyl 2-aminoethylcarbamate. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.80 (br s, 1 H), 1.91 - 2.26 (m, 3 H), 2.38 (br s, 3 H), 3.19 (br s, 1 H), 3.63 (d, *J*=7.32 Hz, 1 H), 3.71 - 4.03 (m, 2 H), 4.15 - 4.51 (m, 2 H), 6.74 - 7.16 (m, 1 H), 7.13 - 7.76 (m, 3 H). [M+H] calc'd for $C_{18}H_{22}N_6O$, 339; found, 339.

[0441] EXAMPLE 45: 2-(3-Aminopyrrolidin-1-yl)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one



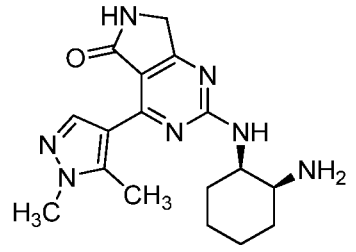
[0442] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 40 using *tert*-butyl pyrrolidin-3-ylcarbamate in place of *tert*-butyl 2-aminoethylcarbamate. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 2.13 - 2.28 (m, 1 H), 2.35 (s, 3 H), 2.51 (dd, J=13.42, 6.10 Hz, 1 H), 3.69 - 4.12 (m, 5 H), 4.22 (d, *J*=18.06 Hz, 2 H), 6.93 (d, *J*=7.32 Hz, 1 H), 7.21 (t, *J*=7.81 Hz, 1 H), 7.46 - 7.69 (m, 2 H). [M+H] calc'd for $C_{17}H_{20}N_6O$, 325; found, 325.

[0443] PREPARATION 15: Ethyl 4-chloro-6-methyl-2-(methylthio)pyrimidine-5-carboxylate

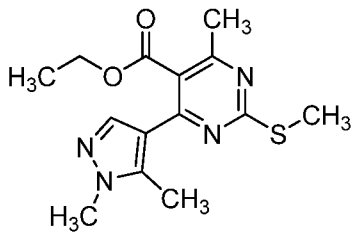


[0444] Ethyl 4-hydroxy-6-methyl-2-(methylthio)pyrimidine-5-carboxylate (0.2 g, 0.876 mmol), tetraethylammonium chloride (0.145 g, 0.876 mmol), and *N*,*N*-dimethylaniline (0.112 mL, 0.876 mmol) were dispersed in acetonitrile (10 mL). The reaction mixture was stirred briefly followed by the addition of phosphorous oxychloride (0.204 mL, 2.190 mmol). The reaction was heated at 100°C for 4 h. The solvent was subsequently removed *in vacuo*. The residue was poured onto ice to give an off-white oil, which was extracted with DCM (2 x 15 mL), and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* to give the title compound as a yellowish-green oil (0.179 g, 83%). [M+H] calc'd for $C_9H_{11}ClN_2O_2S$, 247; found, 247.

[0445] EXAMPLE 46: 2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1,5-dimethyl-1*H*-pyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one

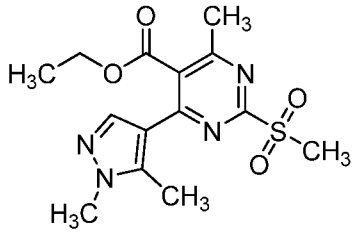


[0446] A. Ethyl 4-(1,5-dimethyl-1*H*-pyrazol-4-yl)-6-methyl-2-(methylthio)pyrimidine-5-carboxylate



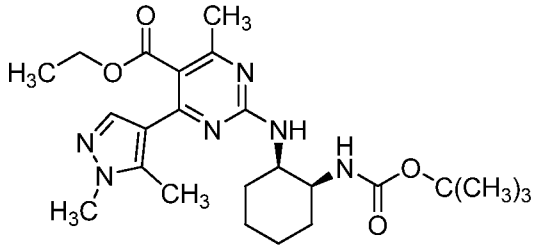
[0447] Ethyl 4-chloro-6-methyl-2-(methylthio)pyrimidine-5-carboxylate (0.179 g, 0.726 mmol), 1,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (0.242 g, 1.088 mmol), and $PdCl_2$(dppf) (0.106 g, 0.145 mmol) were dispersed in DMA (2 mL). After 10 min, 2 N sodium carbonate (1.814 mL, 3.63 mmol) was added to the reaction mixture. The reaction mixture was purged with nitrogen, sealed in a vial, and then heated at 80°C for 5 h. The mixture was subsequently filtered through a pad of Celite, rinsed with MeOH, and the filtrate was purified via reverse phase preparative HPLC. The fractions were concentrated *in vacuo* to give the title compound as tan needles (0.159 g, 71%). [M+H] calc'd for $C_{14}H_{18}N_4O_2S$, 307; found, 307.

[0448] B. Ethyl 4-(1,5-dimethyl-1*H*-pyrazol-4-yl)-6-methyl-2-(methylsulfonyl)pyrimidine-5-carboxylate



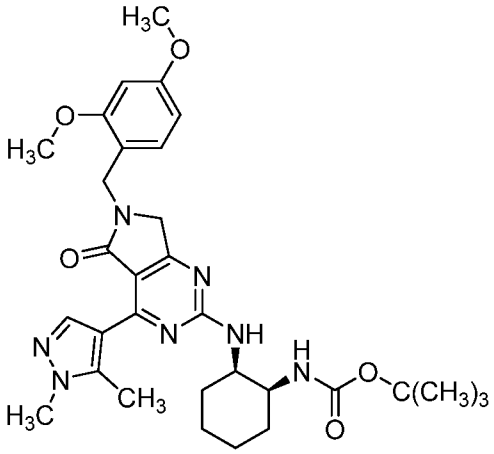
[0449] Ethyl 4-(1,5-dimethyl-1*H*-pyrazol-4-yl)-6-methyl-2-(methylthio)pyrimidine-5-carboxylate (0.159 g, 0.519 mmol) was dissolved in DCM (10 mL). The solution was chilled in an ice bath and *m*-chloroperoxybenzoic acid (0.134 g, 0.778 mmol) was added. The reaction was allowed to warm to RT over a 30 min period with stirring. Another aliquot of *m*-chloroperoxybenzoic acid (0.159 g, 0.519 mmol) was added to the reaction mixture and it was stirred for an additional 45 min. The reaction mixture was subsequently diluted with DCM (10 mL) and was quenched with saturated aq $NaHCO_3$ (10 mL). The organic phase was washed with saturated aq $NaHCO_3$ (5 mL) and brine (5 mL) and was dried over anhydrous Na_2SO_4. The solvents were removed *in vacuo* to give the title compound as a yellow oil (173 mg, 98%). [M+H] calc'd for $C_{14}H_{18}N_4O_4S$, 339; found, 339.

[0450] C. Ethyl 2-((1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclohexylamino)-4-(1,5-dimethyl-1*H*-pyrazol-4-yl)-6-methylpyrimidine-5-carboxylate



[0451] A solution of ethyl 4-(1,5-dimethyl-1*H*-pyrazol-4-yl)-6-methyl-2-(methylsulfonyl)pyrimidine-5-carboxylate (0.07 g, 0.207 mmol), *tert*-butyl (1*S*,2*R*)-2-aminocyclohexylcarbamate (0.089 g, 0.414 mmol) and Et_3N (0.115 mL, 0.827 mmol) in DMA (3 mL) was heated in a sealed tube at 90°C for 8 h. The reaction mixture was poured slowly onto ice to yield a pale yellow precipitate, which was isolated by vacuum filtration, washed with water, and dried under vacuum to give the title compound. [M+H] calc'd for $C_{24}H_{36}N_6O_4$, 473; found, 473.

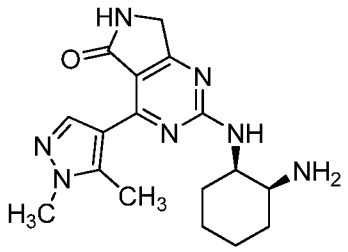
[0452] D. *tert*-Butyl (1*S*,2*R*)-2-(6-(2,4-dimethoxybenzyl)-4-(1,5-dimethyl-1*H*-pyrazol-4-yl)-5-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-2-ylamino)cyclohexylcarbamate



[0453] A mixture ethyl 2-((1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclohexylamino)-4-(1,5-dimethyl-1*H*-pyrazol-4-yl)-6-methylpyrimidine-5-carboxylate (0.098 g, 0.207 mmol) and selenium dioxide (0.046 g, 0.415 mmol) in dioxane (2 mL) was heated at 100°C for 24 h. The mixture was subsequently cooled and filtered. The filtrate was concentrated and dried to give a brown foam (0.1 g, 0.206 mmol) which was combined with sodium acetate (0.051 g, 0.617 mmol) and (2,4-dimethoxyphenyl)methanamine (0.031 mL, 0.206 mmol) in DCM (2 mL) and MeOH (1 mL). The mixture was stirred at RT for 30 min, after which

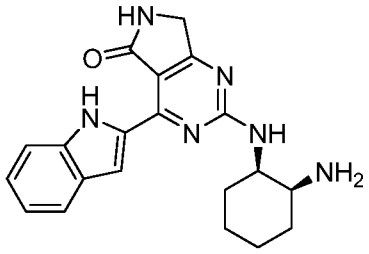
sodium cyanoborohydride (0.032 g, 0.514 mmol) was added. The reaction mixture was stirred at RT for 20 h, and then filtered through a pad of Celite, which was rinsed with MeOH. The filtrate was purified by reverse phase preparative HPLC and the fractions concentrated *in vacuo* to give the title compound as a tan solid. [M+H] calc'd for $C_{31}H_{41}N_7O_5$, 592; found, 592.

[0454] E. 2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1,5-dimethyl-1*H*-pyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one



[0455] A mixture of *tert*-butyl (1*S*,2*R*)-2-(6-(2,4-dimethoxybenzyl)-4-(1,5-dimethyl-1*H*-pyrazol-4-yl)-5-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-2-ylamino)cyclohexylcarbamate obtained above in TFA (2 mL) was stirred at 70°C for 2 h. The mixture was subsequently purified by reverse phase preparative HPLC. The fractions were collected and concentrated to give a TFA salt of the title compound as a white solid (0.5 mg). ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.59 (br s, 2 H), 1.67 - 2.02 (m, 6 H), 2.66 - 2.72 (m, 3 H), 3.67 (br s, 1 H), 3.85 (s, 3 H), 4.29 (s, 2 H), 4.50 - 4.64 (m, 1 H), 8.64 (br s, 1 H). [M+H] calc'd for $C_{17}H_{23}N_7O$, 342; found, 342.

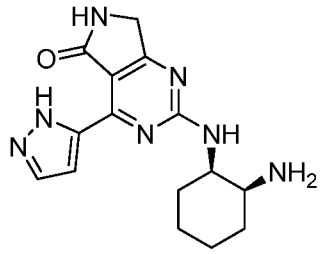
[0456] EXAMPLE 47: 2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1*H*-indol-2-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one



[0457] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 46 using 1-(*tert*-butoxycarbonyl)-1*H*-indol-2-ylboronic acid in place of 1,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.46 - 1.72 (m, 2 H), 1.72 - 2.06 (m, 6 H), 3.56 - 3.89 (m, 1 H), 4.36

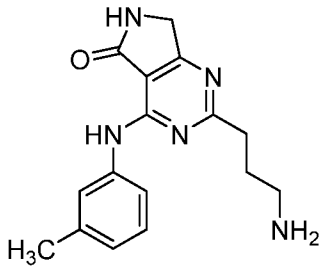
(s, 2 H), 4.52 - 4.77 (m, 1 H), 7.08 (t, *J*=7.57 Hz, 1 H), 7.25 (t, *J*=7.57 Hz, 1 H), 7.47 (d, *J*=8.30 Hz, 1 H), 7.58 - 7.79 (m, 2 H). [M+H] calc'd for $C_{20}H_{22}N_6O$, 363; found, 363.

[0458] EXAMPLE 48: 2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1*H*-pyrazol-5-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one

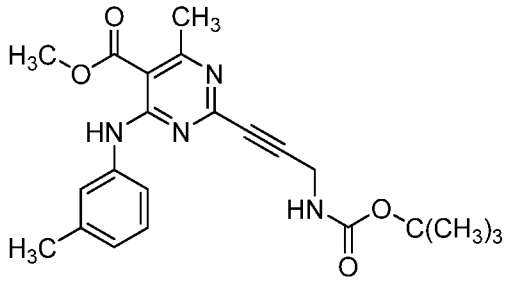


[0459] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 46 using *tert*-butyl 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1*H*-pyrazole-1-carboxylate in place of 1,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.44 - 1.69 (m, 2 H), 1.68 - 1.94 (m, 6 H), 3.64 (br s, 1 H), 4.41 (s, 2 H), 4.65 (br s, 1 H), 7.11 - 7.55 (m, 1 H), 7.69 (d, *J*=1.77 Hz, 1 H). [M+H] calc'd for $C_{15}H_{19}N_7O$, 314; found, 314.

[0460] EXAMPLE 49: 2-(3-Aminopropyl)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one



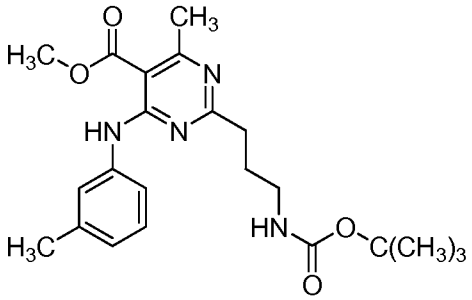
[0461] A. Methyl 2-(3-(*tert*-butoxycarbonylamino)prop-1-ynyl)-4-methyl-6-(*m*-tolylamino)pyrimidine-5-carboxylate



[0462] Methyl 2-chloro-4-methyl-6-(*m*-tolylamino)pyrimidine-5-carboxylate (0.4 g, 1.371 mmol), *tert*-butyl prop-2-ynylcarbamate (0.426 g, 2.74 mmol),

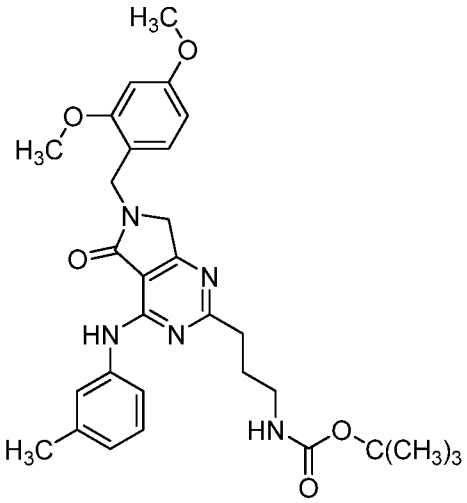
tetrakis(triphenylphosphine)palladium (0.032 g, 0.027 mmol), and copper (I) iodide (0.026 g, 0.137 mmol) was dispersed in DMA (5 mL). Triethylamine (0.382 mL, 2.74 mmol) was added and the mixture was degassed with nitrogen for 5 min. The reaction mixture was placed in a sealed tube and heated at 90°C for 4 h, after which it was filtered through a pad of Celite, which was rinsed with MeOH. The filtrate was purified via reverse phase preparative HPLC and the fractions were concentrated *in vacuo* to give the title compound as a brown oil (0.190 g, 34%). [M+H] calc'd for $C_{22}H_{26}N_4O_4$, 411; found, 411.

[0463] B. Methyl 2-(3-(*tert*-butoxycarbonylamino)propyl)-4-methyl-6-(*m*-tolylamino)pyrimidine-5-carboxylate



[0464] Methyl 2-(3-(*tert*-butoxycarbonylamino)prop-1-ynyl)-4-methyl-6-(*m*-tolylamino)pyrimidine-5-carboxylate (0.190 g, 0.463 mmol) was dissolved in EtOH (4 mL). To this solution was added palladium on carbon (0.049 g, 0.046 mmol) and the resulting mixture was stirred overnight at RT under H_2 atmosphere. The mixture was filtered through a pad of Celite, and the filtrate was evaporated to give the title compound as a brown oil, which was used in next step without further purification. [M+H] calc'd for $C_{22}H_{30}N_4O_4$, 415; found, 415.

[0465] C. *tert*-Butyl 3-(6-(2,4-dimethoxybenzyl)-5-oxo-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-2-yl)propylcarbamate

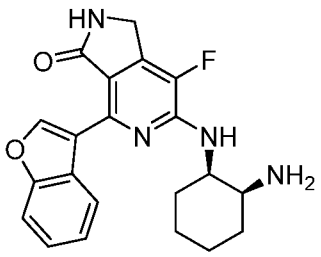


[0466] A mixture methyl 2-(3-(*tert*-butoxycarbonylamino)propyl)-4-methyl-6-(*m*-tolylamino)pyrimidine-5-carboxylate (0.124 g, 0.299 mmol) and selenium dioxide (0.033 g, 0.299 mmol) in dioxane (2 mL) was heated at 100°C for 24 h. The reaction mixture was subsequently cooled and filtered. The filtrate was concentrated and dried to give a brown foam (0.128 g, 0.299 mmol), which was combined with (2,4-dimethoxyphenyl)methanamine (0.045 mL, 0.299 mmol), DCM (2 mL) and MeOH (1 mL). The mixture was stirred at RT for 30 min, after which sodium cyanoborohydride (0.047 g, 0.747 mmol) was added. The reaction mixture was stirred at RT for 20 h, and then filtered through a pad of Celite, which was rinsed with MeOH. The filtrate was purified via reverse phase preparative HPLC. The fractions were collected and concentrated *in vacuo* to yield the title compound as a tan solid (1.7 mg, 1%). [M+H] calc'd for $C_{30}H_{37}N_5O_5$, 548; found, 548.

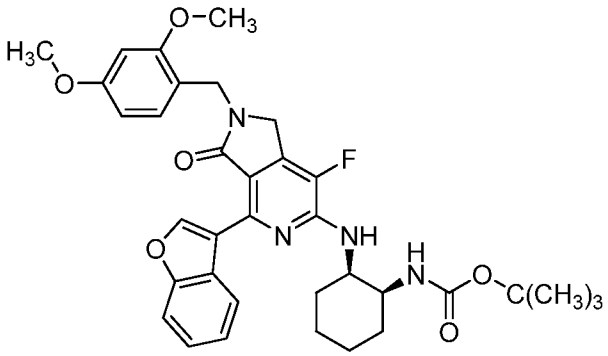
[0467] D. 2-(3-Aminopropyl)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one

[0468] A mixture of *tert*-butyl 3-(6-(2,4-dimethoxybenzyl)-5-oxo-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-2-yl)propylcarbamate (1.7 mg, 0.003 mmol) in TFA (2 mL) was stirred at 70°C for 2 h. The mixture was purified by reverse phase preparative HPLC. The fractions were collected and concentrated to give a TFA salt of the title compound as a white solid (0.6 mg, 65%). ^{1}H NMR (500 MHz, CD_3OD) δ ppm 2.11 - 2.26 (m, 2 H), 2.30 - 2.45 (m, 3 H), 2.92 - 3.09 (m, 4 H), 4.39 (s, 2 H), 6.98 (d, *J*=8.34 Hz, 1 H), 7.16 - 7.35 (m, 1 H), 7.51 (s, 1 H), 7.65 (d, *J*=8.59 Hz, 1 H). [M+H] calc'd for $C_{16}H_{19}N_5O$, 298; found, 298.

[0469] EXAMPLE 50: 6-((1R,2S)-2-Aminocyclohexylamino)-4-(benzofuran-3-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



[0470] A. *tert*-Butyl (1*S*,2*R*)-2-(4-(benzofuran-3-yl)-2-(2,4-dimethoxybenzyl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate



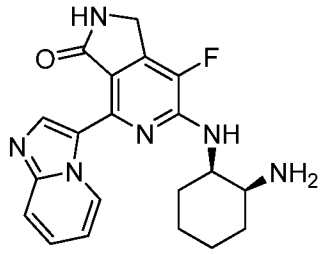
[0471] A mixture of *tert*-butyl (1*S*,2*R*)-2-(4-chloro-2-(2,4-dimethoxybenzyl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (65 mg, 0.118 mmol), aqueous sodium carbonate (2 N, 0.237 mL, 0.474 mmol), 2-(benzofuran-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (43 mg, 0.178 mmol) and bis(triphenylphosphine)palladium chloride (17 mg, 0.024 mmol) in DME (2 mL) was placed in a vial. The vial was purged with nitrogen, sealed, and the reaction mixture heated at 120°C for 1 h. The mixture was filtered through a pad of Celite, which was rinsed with MeOH. The solvent was removed *in vacuo* and the residue diluted with MeOH, passed through a microfiltration frit, and purified via preparative HPLC. The fractions were collected and concentrated *in vacuo* to give the title compound as a tan oil (36.3 mg, 48%). [M+H] calc'd for $C_{35}H_{39}FN_4O_6$, 632; found, 632.

[0472] B. 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(benzofuran-3-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

[0473] A mixture of *tert*-butyl (1*S*,2*R*)-2-(4-(benzofuran-3-yl)-2-(2,4-dimethoxybenzyl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (75 mg, 0.119 mmol) and TFA (2 mL) was placed in a vial

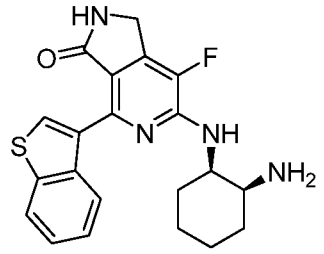
and heated at 125°C for 3 h. The solvent was subsequently removed *in vacuo* to give a residue which was dispersed in DMSO and MeOH (1/1), passed through a microfiltration frit, and purified via preparative HPLC. The fractions were collected and the solvent removed *in vacuo* to give a TFA salt of the title compound as a gray solid (9.2 mg, 20%). ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.67 (br s, 3 H), 1.79 - 2.05 (m, 5 H), 3.98 (br s, 1 H), 4.50 (s, 2 H), 4.69 (br s, 1 H), 7.28 - 7.47 (m, 2 H), 7.56 (d, *J*=7.81 Hz, 1 H), 8.31 (d, *J*=6.83 Hz, 1 H), 9.08 (s, 1 H). [M+H] calc'd for $C_{21}H_{21}FN_4O_2$, 381; found, 381.

[0474] EXAMPLE 51: 6-((1*R*,2*S*)-2-aminocyclohexylamino)-7-fluoro-4-(imidazo[1,2-*a*]pyridin-3-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



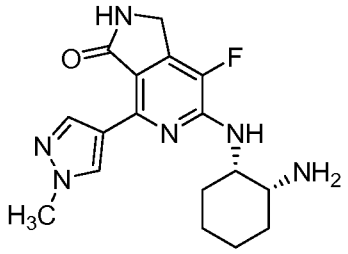
[0475] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 50 using imidazo[1,2-*a*]pyridin-3-ylboronic acid in place of 2-(benzofuran-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.50 - 1.75 (m, 3 H), 1.74 - 1.98 (m, 5 H), 3.78 (br s, 1 H), 4.58 (br s, 3 H), 7.57 (t, J = 6.35 Hz, 1 H), 7.93 - 8.21 (m, 2 H), 8.78 (br s, 1 H), 9.45 (d, *J*=6.35 Hz, 1 H). [M+H] calc'd for $C_{20}H_{21}FN_6O$, 381; found, 381.

[0476] EXAMPLE 52: 6-((1*R*,2*S*)-2-aminocyclohexylamino)-4-(benzo[*b*]thiophen-3-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

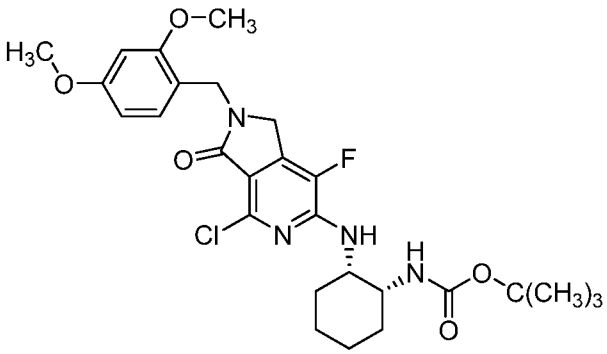


[0477] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 50 using benzo[*b*]thiophen-3-ylboronic acid in place of 2-(benzofuran-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.50 - 1.93 (m, 8 H), 3.80 (br s, 1 H), 4.42 - 4.68 (m, 3 H), 7.38 (m, *J*=4.40 Hz, 2 H), 7.94 (br s, 1 H), 8.00 - 8.20 (m, 2 H). [M+H] calc'd for $C_{21}H_{21}FN_4OS$, 397; found, 397.

[0478] EXAMPLE 53: 6-((1*S*,2*R*)-2-Aminocyclohexylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(*2H*)-one

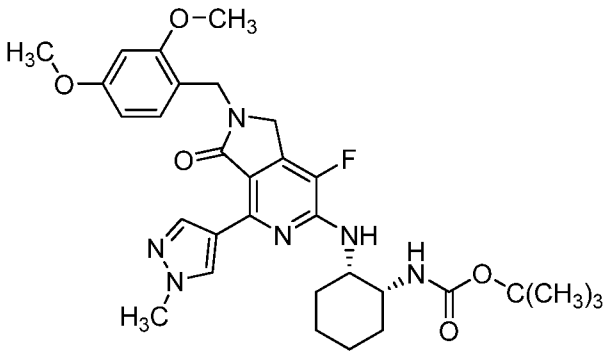


[0479] A. *tert*-Butyl (1*R*,2*S*)-2-(4-chloro-2-(2,4-dimethoxybenzyl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate



[0480] To a mixture of 4,6-dichloro-2-(2,4-dimethoxybenzyl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one (200 mg, 0.539 mmol) and *tert*-butyl (1*R*,2*S*)-2-aminocyclohexylcarbamate (173 mg, 0.808 mmol) in ACN (5 mL) was added *N*,*N*-diisopropylethylamine (0.141 mL, 0.808 mmol). The reaction mixture was heated in a sealed vial at 100°C for several hours after which additional amine (0.5 eq) was added. The mixture was heated overnight and the solvent was subsequently removed *in vacuo*. The residue was dispersed in DMSO and MeOH (1/1) and the resulting mixture was filtered. The filtrate was purified via preparative HPLC. The fractions were collected and dried *in vacuo* to give the title compound as a tan solid (60.7 mg, 21%). [M+H] calc'd for $C_{27}H_{34}ClFN_4O_5$, 550; found, 550

[0481] B. *tert*-Butyl (1*R*,2*S*)-2-(2-(2,4-dimethoxybenzyl)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate

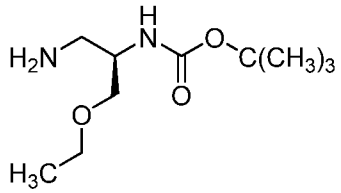


[0482] A mixture of *tert*-butyl (1*R*,2*S*)-2-(4-chloro-2-(2,4-dimethoxybenzyl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (60 mg, 0.109 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (34 mg, 0.164 mmol) and bis(triphenylphosphine)palladium chloride (15 mg, 0.022 mmol) in DME (1 mL) was placed in a vial. The vial was purged with nitrogen and aqueous sodium carbonate (2 N, 0.219 mL, 0.437 mmol) was added. The vial was sealed and the reaction mixture heated in an oil bath at 85°C for 3 h. The reaction mixture was filtered through a pad of Celite, which was rinsed with MeOH and DCM. The solvent was removed *in vacuo* and the residue was diluted with DMSO and MeOH (1/1). The resulting mixture was filtered to recover a white precipitate (31.3 mg). The mother liquor was purified via preparative HPLC. The fractions were collected and dried *in vacuo* to recover an additional white solid (10.2 mg). The two crops were combined to give the title compound as a white solid (41.5 mg, 64%). [M+H] calc'd for $C_{31}H_{39}FN_6O_5$, 595; found, 595.

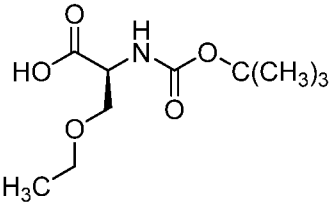
[0483] C. 6-((1*S*,2*R*)-2-Aminocyclohexylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(*2H*)-one

[0484] A mixture of *tert*-butyl (1*R*,2*S*)-2-(2-(2,4-dimethoxybenzyl)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (41.5 mg, 0.070 mmol) and TFA (2 mL) was heated at 65°C for 3 h. Following reaction, the solvent was removed *in vacuo*. The residue was diluted with DMSO and MeOH (1/1), passed through a microfiltration frit, and purified via preparative HPLC. The fractions were collected and dried *in vacuo* to give a TFA salt of the title compound as a white solid (22 mg, 92%). ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.56 - 2.01 (m, 8 H), 3.85 (br s, 1 H), 3.94 (br s, 3 H), 4.45 (br s, 2 H), 4.67 (br s, 1 H), 8.31 (br s, 1 H), 8.81 (br s, 1 H). [M+H] calc'd for $C_{17}H_{21}FN_6O$, 345; found, 345.

[0485] PREPARATION 16: (*R*)-*tert*-Butyl 1-amino-3-ethoxypropan-2-ylcarbamate

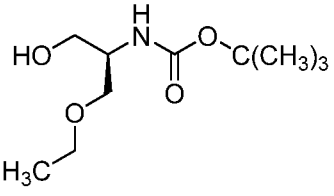


[0486] A. (*S*)-2-(*tert*-Butoxycarbonylamino)-3-ethoxypropanoic acid



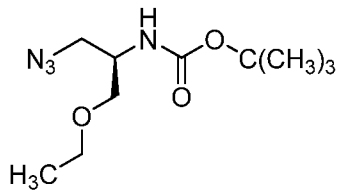
[0487] To a suspension of sodium hydride (17.73 g, 702 mmol) in THF (600 mL) at 0°C was added MeOH (18 mL) dropwise. The mixture was stirred at RT for 1 h to yield a sodium methanolate solution. Iodoethane (25.5 mL, 316 mmol) and a portion of the sodium methanolate solution (120 mL) were added to a solution of (*S*)-2-(*tert*-butoxycarbonylamino)-3-hydroxypropanoic acid (18 g, 88 mmol) in THF (600 mL). After stirring at RT for 1 h, the remaining sodium methanolate solution (480 mL) was added, followed by additional iodoethane (9.9 mL, 123 mmol). The mixture was stirred at RT overnight. The mixture was subsequently concentrated and the residue was dissolved in water. The aqueous layer was washed with ether (250 mL), acidified to pH 2 using 1N HCl, and extracted with EtOAc (3 x 300 mL). The combined organic layers were washed with 1M $Na_2S_2O_3$ (300mL), dried, and concentrated. The resulting crude material was reconstituted in MeOH, DCM and DMF (total volume: 50 mL) and purified via reverse phase preparative HPLC. The fractions were collected and the ACN was removed via rotary evaporation. The resulting aq solution was neutralized with saturated aq $NaHCO_3$, washed with EtOAc (2 x 200 mL), dried over Na_2SO_4, filtered, and the organic phase stripped to dryness via rotary evaporation to yield the title compound as a clear oil (1.81 g, 9%). [M+H] calc'd for $C_{10}H_{19}NO_5$, 234; found, 234.

[0488] B. (*R*)-*tert*-Butyl 1-ethoxy-3-hydroxypropan-2-ylcarbamate



[0489] To a solution of (*S*)-2-(*tert*-butoxycarbonylamino)-3-ethoxypropanoic acid (1.81 g, 7.76 mmol) in THF (20 mL) at -15°C was added isobutyl chloroformate (1.015 mL, 7.76 mmol) in THF (5 mL) and 4-methylmorpholine (0.853 mL, 7.76 mmol) in THF (5 mL). After stirring for 10 min at -15°C, the mixture was slowly added to a solution of sodium borohydride (0.881 g, 23.28 mmol) in H_2O (7 mL). The mixture was stirred at -15°C for 30 min and was diluted with EtOAc. The organic layer was washed with saturated aq $NaHCO_3$ and brine and dried. The residue was carried to next step without further purification (1.6 g, 94%). [M+H] calc'd for $C_{10}H_{21}NO_4$, 220; found, 220.

[0490] C. (*R*)-*tert*-Butyl 1-azido-3-ethoxypropan-2-ylcarbamate

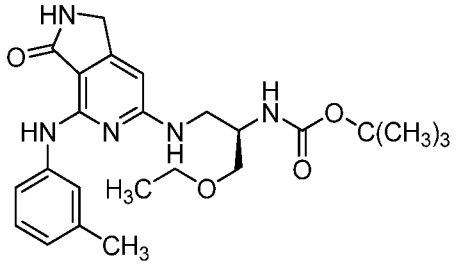


[0491] Methanesulfonyl chloride (0.851 mL, 10.95 mmol) in DCM (1 mL) was added to a solution of (*R*)-*tert*-butyl 1-ethoxy-3-hydroxypropan-2-ylcarbamate (1.6g, 7.30 mmol) and Et_3N (1.538 mL, 10.95 mmol) in DCM (10 mL) at 0°C. After stirring at RT for 1 h, the mixture was diluted with EtOAc. The organic layer was washed with saturated aq $NaHCO_3$ solution, dried, and concentrated *in vacuo*. The residue was dissolved in DMF (10.00 mL). Sodium azide (2.372 g, 36.5 mmol) and tetrabutylammonium iodide (0.270 g, 0.730 mmol) were added, and the reaction mixture was stirred at 75°C for 4 h. After cooling to RT, the mixture was diluted with EtOAc. The organic layer was washed with saturated aq $NaHCO_3$, dried, and concentrated *in vacuo* to give the title compound (1.2 g, 67%). [M+H] calc'd for $C_{10}H_{20}N_4O_3$, 245; found, 245.

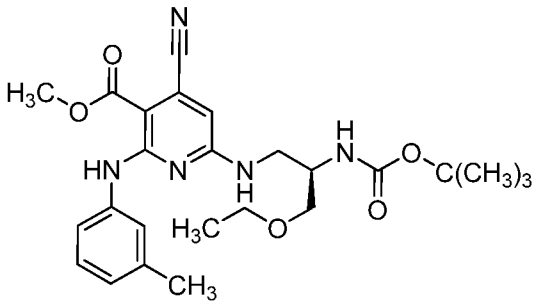
[0492] D. (*R*)-*tert*-Butyl 1-amino-3-ethoxypropan-2-ylcarbamate

[0493] A mixture of (*R*)-*tert*-butyl 1-azido-3-ethoxypropan-2-ylcarbamate (1.2 g, 4.91 mmol) in MeOH (10 mL) was added palladium on carbon (0.523 g, 4.91 mmol). The mixture was stirred under hydrogen atmosphere overnight at RT. The resulting crude material was reconstituted in MeOH (1.0 mL) and purified via reverse phase preparative HPLC. The fractions were collected and solvent was stripped to dryness via rotary evaporation to give the title compound as clear oil (722 mg, 67%). [M+H] calc'd for $C_{10}H_{22}N_2O_3$, 219; found, 219.

[0494] PREPARATION 17: (*R*)-*tert*-Butyl 1-ethoxy-3-(3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)propan-2-ylcarbamate



[0495] A. (*R*)-Methyl 6-(2-(*tert*-butoxycarbonylamino)-3-ethoxypropylamino)-4-cyano-2-(*m*-tolylamino)nicotinate



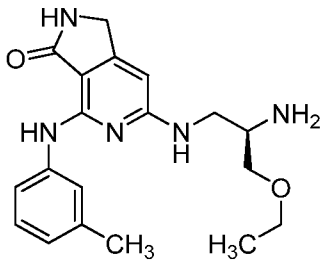
[0496] To a solution of methyl 6-chloro-4-cyano-2-(*m*-tolylamino)nicotinate (200 mg, 0.663 mmol) in DMF (5 mL) was added DIPEA (0.232 mL, 1.326 mmol) and (*R*)-*tert*-butyl 1-amino-3-ethoxypropan-2-ylcarbamate (174 mg, 0.795 mmol). The reaction mixture was stirred at RT overnight. Additional (*R*)-*tert*-butyl 1-amino-3-ethoxypropan-2-ylcarbamate (231.25 mg, 1.061 mmol) was added and the mixture was heated at 65°C for 1 h. After cooling to RT, the reaction mixture was diluted with EtOAc (30 mL) and washed with water (2 x 20 mL) and brine (20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to thick yellow oil. The crude product was used in the next step without further purification (415 mg). [M+H] calc'd for $C_{25}H_{33}N_5O_5$, 484; found, 484.

[0497] B. (*R*)-*tert*-Butyl 1-ethoxy-3-(3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)propan-2-ylcarbamate

[0498] In a flask containing (*R*)-methyl 6-(2-(*tert*-butoxycarbonylamino)-3-ethoxypropylamino)-4-cyano-2-(*m*-tolylamino)nicotinate (400mg, 0.827 mmol) in HOAc (0.25 mL) and DCM (1 mL) was added platinum(IV) oxide (18.78 mg, 0.083 mmol). The flask was evacuated and filled with H_2 three times, and the reaction mixture was stirred

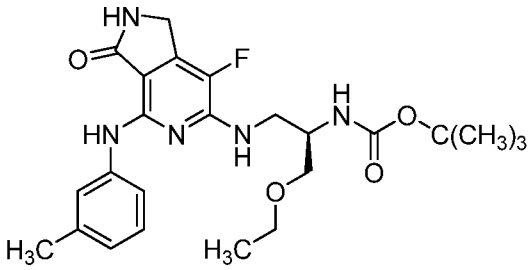
vigorously at RT under H_2 atmosphere for 3-4 h. The mixture was subsequently filtered through Celite, and the solvent was removed *in vacuo*. The residue was kept under vacuum overnight to remove excess HOAc. The crude residue was dissolved in anhydrous DCM (20 mL). Potassium carbonate (572 mg, 4.14 mmol) was added, and the mixture was stirred at RT for 8 h. The mixture was filtered through Celite and concentrated *in vacuo*. The residue was reconstituted in a MeOH/DCM solution (1/1, 5 mL) and purified via reverse phase preparative HPLC. The collected fractions were concentrated *in vacuo* to give the title compound as a TFA salt (109 mg, 28.9%). [M+H] calc'd for $C_{24}H_{33}N_5O_4$, 456; found, 456.

[0499] EXAMPLE 54: (*R*)-6-(2-Amino-3-ethoxypropylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



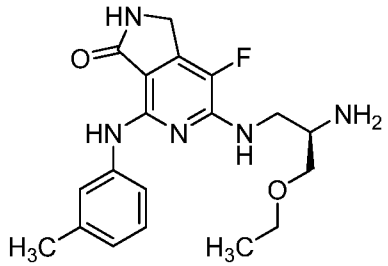
[0500] To a solution of (*R*)-*tert*-butyl 1-ethoxy-3-(3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)propan-2-ylcarbamate (109 mg, 0.239 mmol) in DCM (1 mL) was added a TFA/DCM solution (1/1, 10 mL). The mixture was stirred at RT for 2 h. After removal of the solvent, the resulting crude material was reconstituted in a solution of MeOH/DCM (1/1, 5 mL) and was purified via reverse phase preparative HPLC. The fractions were collected, and ACN was removed via rotary evaporation. The resulting aq solution was neutralized with saturated aq $NaHCO_3$, washed with EtOAc (2 x 200 mL), dried over Na_2SO_4, and filtered. The organic phase was stripped to dryness via rotary evaporation to give the title compound (11 mg, 13%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.08 - 1.18 (m, 3 H), 1.25 - 1.44 (m, 4 H), 2.26 - 2.32 (m, 3 H), 4.07 - 4.17 (m, 3 H), 4.19 - 4.29 (m, 2 H), 6.03 (s, 1 H), 6.78 (d, *J*=7.83 Hz, 1 H), 7.06 (br s, 1 H), 7.12 - 7.22 (m, 1 H), 7.48 (s, 1 H), 7.60 (d, *J*=7.83 Hz, 1 H), 7.66 - 7.75 (m, 2 H), 7.99 (s, 1 H), 8.83 - 8.97 (m, 1 H). [M+H] calc'd for $C_{19}H_{25}N_5O_2$, 356; found, 356.

[0501] PREPARATION 18: (*R*)-*tert*-Butyl 1-ethoxy-3-(7-fluoro-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)propan-2-ylcarbamate



[0502] To a chilled solution of (R)-tert-butyl 1-ethoxy-3-(3-oxo-4-(m-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)propan-2-ylcarbamate (94.7 mg, 0.208 mmol) in CH_2Cl_2 (5 mL) at 0°C was added SELECTFLUOR® (73.6 mg, 0.208 mmol). The mixture was left stirring in an ice bath and warmed slowly to RT for 6 h. Afterwards, the mixture was diluted with EtOAc (10 mL) and washed with saturated aq $NaHCO_3$ (5 mL) followed by water (5 mL) and brine (5 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated to a brown residue. The resulting crude material was reconstituted in MeOH/DCM (5 mL) and purified via preparative HPLC. The collected fractions were collected and ACN was removed via rotary evaporation. The resulting aq solution was neutralized with saturated aq $NaHCO_3$ and washed with EtOAc (2 x 200 mL), dried over Na_2SO_4, filtered, and the organic phase stripped to dryness via rotary evaporation to yield the title compound. [M+H] calc'd for $C_{24}H_{32}FN_5O_4$, 474; found, 474.

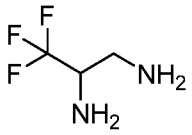
[0503] EXAMPLE 55: (*R*)-6-(2-Amino-3-ethoxypropylamino)-7-fluoro-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



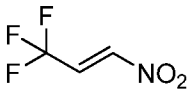
[0504] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 54 using (*R*)-*tert*-butyl 1-ethoxy-3-(7-fluoro-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)propan-2-ylcarbamate in place of (*R*)-*tert*-butyl 1-ethoxy-3-(3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)propan-2-ylcarbamate. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.08 - 1.19 (m, 3 H), 2.25 - 2.36 (m, 3 H), 3.38 - 3.77 (m, 7 H), 4.40 (s, 2 H), 6.80 (d, *J*=7.58 Hz, 1 H), 7.07

- 7.25 (m, 2 H), 7.38 (s, 1 H), 7.54 (d, *J*=7.58 Hz, 1 H), 7.92 (br s, 2 H), 8.28 (s, 1 H), 8.83 (s, 1 H). [M+H] calc'd for $C_{19}H_{24}FN_5O_2$, 374; found, 374.

[0505] PREPARATION 19: 3,3,3-Trifluoropropane-1,2-diamine

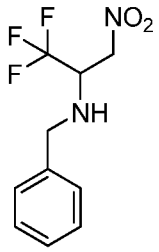


[0506] A. 3,3,3-Trifluoro-1-nitroprop-1-ene



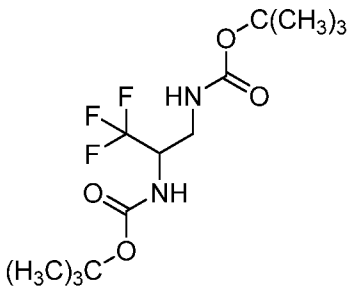
[0507] A mixture of 2,2,2-trifluoroethane-1,1-diol (75% aq solution, 20 g, 0.13 mol), CH_3NO_2 (24 g, 0.39 mol) and Na_2CO_3 (0.85 g, 8 mmol) was stirred overnight at RT. Water (50 mL) was added and the mixture was extracted with diethyl ether (3 x 30 mL) and dried over Na_2SO_4. After concentrating the organic extract at low temperature and under reduced pressure, P_2O_5 (20.0 g, 0.14 mol) was added to the residue oil, which was distilled at atmospheric pressure to give a green-yellow oil (4 g, 50% purity, 10% yield). Boiling point 85-90°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.09-7.17 (m, 1 H), 7.50 (dd, *J*=2.0 Hz, 12.0 Hz, 1 H).

[0508] B. *N*-Benzyl-1,1,1-trifluoro-3-nitropropan-2-amine



[0509] A mixture of 3,3,3-trifluoro-1-nitroprop-1-ene (4 g, 28.4 mmol) and benzylamine (3.2 g, 30.0 mmol) in toluene (50 mL) was stirred for RT or 1 h. The mixture was concentrated and the residue was purified by column chromatography (EtOAc/PE = 1/10) to give the title compound (5.5 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.91-3.95 (m, 1 H), 4.06-4.14 (m, 1 H), 4.45-4.51 (m, 1 H), 4.63-4.67 (m, 1 H), 7.30-7.39 (m, 5 H).

[0510] C. Di-*tert*-butyl *N*,*N*-(3,3,3-trifluoropropane-1,2-diyl)-biscarbamate

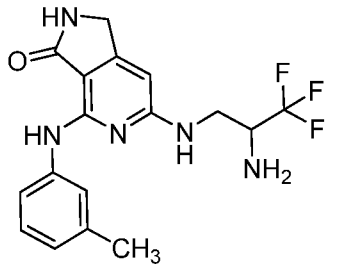


[0511] A mixture of *N*-benzyl-1,1,1-trifluoro-3-nitropropan-2-amine (5.5 g, 22.0 mmol) and Pd/C (3.0 g) in MeOH was stirred at RT overnight under H_2 atmosphere. The mixture was subsequently filtered and concentrated to afford an oil, which was combined with di-*tert*-butyl pyrocarbonate (11.0 g, 50.0 mmol) and Et_3N (5.0 g, 50.0 mmol) in DCM (100 mL). The mixture was stirred overnight and then concentrated. The residue was purified by column chromatography (EtOAc/PE = 1/7) to give the title compound as a white solid (5.5 g).

[0512] D. 3,3,3-Trifluoropropane-1,2-diamine

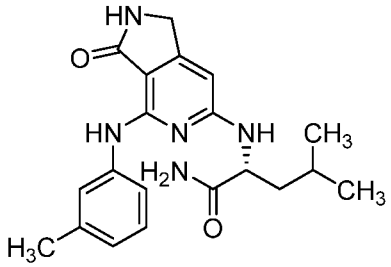
[0513] A mixture of di-*tert*-butyl *N*,*N*-(3,3,3-trifluoropropane-1,2-diyl)-biscarbamate and 1.0 M HCl-EtOAc was stirred at RT overnight to give the title compound (1.5 g, 54%). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 3.50-3.55 (m, 1 H), 3.61-3.66 (m, 1 H), 4.58-4.63 (m, 1 H). [M+H] calc'd for $C_3H_7F_3N_2$, 129; found, 129.

[0514] EXAMPLE 56: 6-(2-Amino-3,3,3-trifluoropropylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



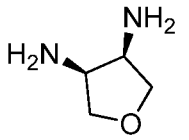
[0515] The title compound was prepared in a manner similar to EXAMPLE 54 using 3,3,3-trifluoropropane-1,2-diamine in place of (*R*)-*tert*-butyl 1-amino-3-ethoxypropan-2-ylcarbamate. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.12 - 1.39 (m, 2 H), 1.91 - 2.15 (m, 1 H), 2.22 - 2.40 (m, 3 H), 3.47 - 3.66 (m, 1 H), 3.66 - 3.86 (m, 1 H), 4.14 - 4.27 (m, 1 H), 4.33 - 4.46 (m, 1 H), 4.74 - 4.89 (m, 1 H), 5.96 - 6.13 (m, 1 H), 6.71 - 6.86 (m, 1 H), 7.08 - 7.26 (m, 1 H), 7.38 - 7.70 (m, 2 H), 8.79 - 9.07 (m, 1 H). [M+H] calc'd for $C_{17}H_{18}F_3N_5O$, 366; found, 366.

[0516] EXAMPLE 57: (*R*)-4-Methyl-2-(3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)pentanamide

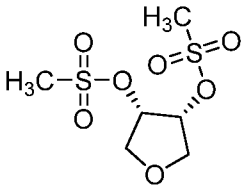


[0517] The title compound was prepared in a manner similar to EXAMPLE 54 using (*R*)-2-amino-4-methylpentanamide (64.7 mg, 0.497 mmol) in place of (*R*)-*tert*-butyl 1-amino-3-ethoxypropan-2-ylcarbamate. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.82 - 0.88 (m, 3 H), 0.91 - 0.96 (m, 3 H), 1.18 - 1.32 (m, 1 H), 1.61 (t, *J*=7.33 Hz, 2 H), 1.69 - 1.83 (m, 1 H), 2.24 - 2.34 (m, 3 H), 4.21 (s, 1 H), 4.37 (s, 1 H), 6.00 - 6.17 (m, 1 H), 6.69 - 6.80 (m, 1 H), 6.96 (br s, 1 H), 7.04 (d, *J*=7.83 Hz, 1 H), 7.10 - 7.26 (m, 2 H), 7.49 (s, 1 H), 7.58 (d, *J*=7.33 Hz, 1 H), 7.95 (s, 1 H), 8.82 - 8.97 (m, 1 H). [M+H] calc'd for $C_{20}H_{25}N_5O_2$, 368; found, 368.

[0518] PREPARATION 20: (3*R*,4*S*)-Tetrahydrofuran-3,4-diamine

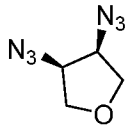


[0519] A. (3*R*,4*S*)-tetrahydrofuran-3,4-diyl dimethanesulfonate



[0520] Methanesulfonyl chloride (1.642 mL, 21.13 mmol) in DCM (5 mL) was added to a solution of (3*R*,4*S*)-tetrahydrofuran-3,4-diol (0.787 mL, 9.61 mmol) and Et_3N (4.05 mL, 28.8 mmol) in DCM (10 mL) at 0°C. After stirring at 0°C for 1 h, the mixture was diluted with DCM. The organic layer was washed with saturated aqueous $NaHCO_3$, dried, and concentrated *in vacuo* to give the title compound as a yellowish white solid (2.5 g, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.09 - 3.20 (m, 6 H), 3.90 - 4.07 (m, 2 H), 4.10 - 4.22 (m, 2 H), 5.19 (ddd, J=5.31, 3.54, 1.77 Hz, 2 H).

[0521] B. (3*R*,4*S*)-3,4-Diazidotetrahydrofuran

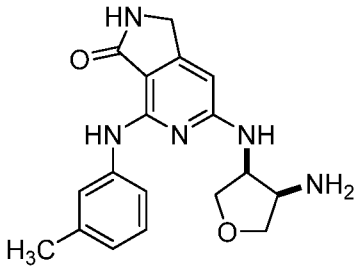


[0522] To a solution of (3*R*,4*S*)-tetrahydrofuran-3,4-diyl dimethanesulfonate (2.5 g, 9.60 mmol) in DMF (50 mL) was added sodium azide (3.75 g, 57.6 mmol) and tetrabutylammonium iodide (0.355 g, 0.960 mmol). The reaction mixture was heated at 100°C overnight. After cooling to RT, the mixture was diluted with EtOAc, and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was dispersed in toluene and the mixture was evaporated *in vacuo* to remove excess DMF and to give the title compound as brown oil which was used in the next step without further purification (2.2 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.72 - 3.87 (m, 2 H), 3.94 - 4.46 (m, 4 H).

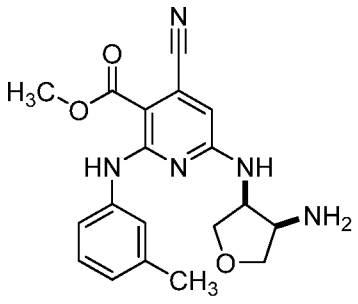
[0523] C. (3*R*,4*S*)-Tetrahydrofuran-3,4-diamine

[0524] To a mixture of (3*R*,4*S*)-3,4-diazidotetrahydrofuran (2.2 g, 14.27 mmol) dispersed in MeOH (10 mL) and DCM (8 mL) was added palladium on carbon (1.519 g, 14.27 mmol). The reaction mixture was stirred under H_2 atmosphere overnight. Following hydrogenation, the mixture was filtered through Celite and the solvent was removed *in vacuo* to yield the title compound which was used without further purification (1.54 g).

[0525] EXAMPLE 58: 6-(*cis*-4-Aminotetrahydrofuran-3-ylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



[0526] A. Methyl 6-(*cis*-4-Aminotetrahydrofuran-3-ylamino)-4-cyano-2-(*m*-tolylamino)nicotinate



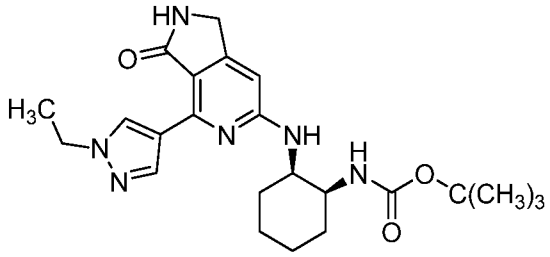
[0527] To a solution of methyl 6-chloro-4-cyano-2-(*m*-tolylamino)nicotinate (40 mg, 0.133 mmol) in DMF (1 mL) was added DIPEA (0.046 mL, 0.265 mmol) and (3*R*,4*S*)-tetrahydrofuran-3,4-diamine (13.54 mg, 0.133 mmol). The mixture was stirred at RT overnight. Additional amine was added and the reaction mixture was stirred at RT for an additional day. The reaction mixture was diluted in MeOH (10 mL) and purified by reverse phase preparative HPLC. The fractions were collected and ACN was removed via rotary evaporation. The resulting aq solution was neutralized with saturated aq $NaHCO_3$ and washed with EtOAc (2 x 200 mL), dried over Na_2SO_4, and filtered. The organic phase was stripped to dryness via rotary evaporation to yield the title compound (35.5 mg, 73%). [M+H] calc'd for $C_{19}H_{21}N_5O_3$, 368; found, 368.

[0528] B. 6-(*cis*-4-Aminotetrahydrofuran-3-ylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

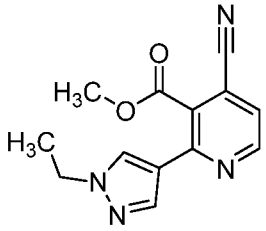
[0529] To a vessel containing methyl 6-(*cis*-4-aminotetrahydrofuran-3-ylamino)-4-cyano-2-(*m*-tolylamino)nicotinate (35.5 mg, 0.097 mmol) in MeOH (5 mL) and HOAc (2.5 mL) was added palladium on carbon (1.028 mg, 9.66 μmol). The vessel was evacuated and filled with H_2 three times, and the mixture was then stirred vigorously at RT under H_2 atmosphere overnight. The mixture was subsequently filtered through Celite, and the solvent was removed *in vacuo*. The residue was dissolved in DCM (10mL) and MeOH (5mL) and potassium carbonate (26.7 mg, 0.193 mmol) was added. The mixture was stirred at RT overnight. Additional potassium carbonate (40.1 mg, 0.290 mmol) was added and the reaction mixture was stirred for 4 h at RT, and then heated at 50°C for 30 min. The mixture was filtered to remove solid K_2CO_3 and the filtrate was diluted with MeOH (10 mL) and purified by reverse phase preparative HPLC. The fractions were collected and concentrated *in vacuo* to give a TFA salt of the title compound (4.5 mg, 13.7%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.30 (s, 3 H), 2.52 - 2.58 (m, 2 H), 3.67 - 3.83 (m, 2 H), 3.90 (br s, 1 H), 3.98 - 4.14 (m, 2 H), 4.20 - 4.30 (m, 2 H), 4.58 (br s, 1 H),

6.16 (s, 1 H), 6.81 (d, *J*=7.32 Hz, 1 H), 7.11 - 7.27 (m, 2 H), 7.46 (d, *J*=7.32 Hz, 1 H), 7.59 (br s, 1 H), 8.08 (s, 1 H), 8.94 (s, 1 H). [M+H] calc'd for $C_{18}H_{21}N_5O_2$, 340; found, 340.

[0530] PREPARATION 21: *tert*-Butyl (1*S*,2*R*)-2-(4-(1-ethyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate

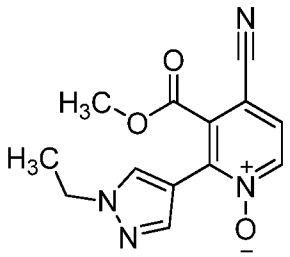


[0531] A. Methyl 4-cyano-2-(1-ethyl-1*H*-pyrazol-4-yl)nicotinate



[0532] A mixture of methyl 2-chloro-4-cyanonicotinate (207 mg, 1.053 mmol), 1-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (201 mg, 0.905 mmol) and tetrakis(triphenylphosphine)palladium(0) (122 mg, 0.105 mmol) in DME (2 mL), and saturated aq Na_2CO_3 (2 mL) was stirred at 80°C for 3 h under N_2 atmosphere. Water and EtOAc were subsequently added. The organic phase was washed with H_2O and brine, dried over $MgSO_4$, and evaporated to yield the title compound (265.3 mg, 98%). [M+H] calc'd for $C_{13}H_{12}N_4O_2$, 257; found, 257.

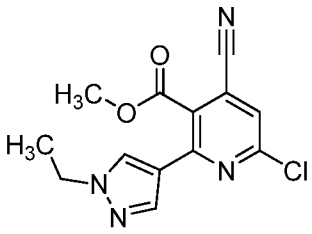
[0533] B. 4-Cyano-2-(1-ethyl-1*H*-pyrazol-4-yl)-3-(methoxycarbonyl)pyridine 1-oxide



[0534] To a mixture of methyl 4-cyano-2-(1-ethyl-1*H*-pyrazol-4-yl)nicotinate (207 mg, 0.808 mmol) in ACN (2 mL) was added urea hydrogen peroxide (380 mg, 4.04 mmol) and trifluoroacetic anhydride (0.456 mL, 3.23 mmol) at 0°C. The resulting mixture was stirred at RT overnight. Next, saturated aq $NaHCO_3$ solution and chloroform were added.

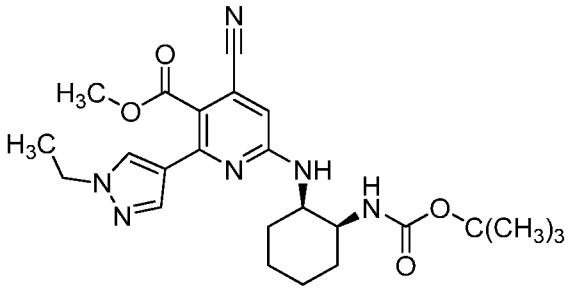
The aqueous phase was extracted with chloroform (3 x 200 mL). The organic layers were combined and washed with brine, dried over $MgSO_4$, and evaporated to give the title compound which was used without further purification (210 mg, 95%). [M+H] calc'd for $C_{13}H_{12}N_4O_3$, 273.5; found, 273.5.

[0535] C. Methyl 6-chloro-4-cyano-2-(1-ethyl-1*H*-pyrazol-4-yl)nicotinate



[0536] A solution of 4-cyano-2-(1-ethyl-1*H*-pyrazol-4-yl)-3-(methoxycarbonyl)pyridine 1-oxide (210 mg, 0.771 mmol) in $POCl_3$ (2 mL) was heated at 80°C for 3-4 h. The mixture was concentrated and purified by flash chromatography (SiO_2, 10-100% EtOAc in Hexane). The fractions were collected and the solvent was removed *in vacuo* to give the title compound (201 mg, 90%).

[0537] D. Methyl 6-((1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclohexylamino)-4-cyano-2-(1-ethyl-1*H*-pyrazol-4-yl)nicotinate



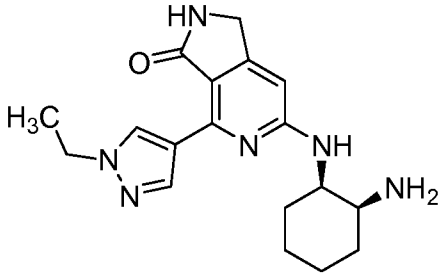
[0538] To a solution of methyl 6-chloro-4-cyano-2-(1-ethyl-1*H*-pyrazol-4-yl)nicotinate (201 mg, 0.691 mmol) in DMF (1 mL) was added DIPEA (0.242 mL, 1.383 mmol) and *tert*-butyl (1*S*,2*R*)-2-aminocyclohexylcarbamate (237 mg, 1.106 mmol). The reaction mixture was stirred at 100°C overnight, after which the solvent was removed, and the resulting crude material was diluted in MeOH (5.0 mL) and purified via reverse phase preparative HPLC. The collected fractions were collected and ACN was removed via rotary evaporation. The resulting aq solution was neutralized with saturated aq $NaHCO_3$ and washed with EtOAc (2 x 200 mL), dried over Na_2SO_4, and filtered. The organic phase

was stripped to dryness via rotary evaporation to yield the title compound (62 mg, 19%). [M+H] calc'd for $C_{24}H_{32}N_6O_4$, 469; found, 469.

[0539] E. *tert*-Butyl (1*S*,2*R*)-2-(4-(1-ethyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate

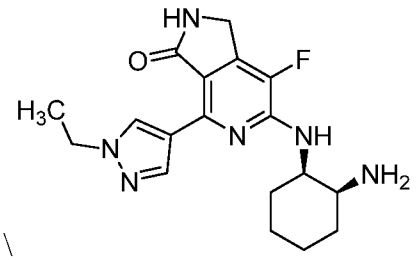
[0540] To a flask containing methyl 6-((1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclohexylamino)-4-cyano-2-(1-ethyl-1*H*-pyrazol-4-yl)nicotinate (62 mg, 0.132 mmol) in MeOH (2 mL) was added HOAc (1 mL) to give a yellow solution. Palladium on carbon was added (14.08 mg, 0.132 mmol). The flask was evacuated and filled with H_2 three times, after which the mixture was stirred vigorously at RT under a H_2 atmosphere overnight. The mixture was filtered through Celite, and the solvent was removed *in vacuo* to give a residue, which was dissolved in DCM (10mL) and MeOH (10mL). Potassium carbonate was added and the mixture was stirred for 5 h. The solids were filtered out and the filtrate concentrated to give the title compound (50 mg, 86%). [M+H] calc'd for $C_{23}H_{32}N_6O_3$, 441; found, 441.

[0541] EXAMPLE 59: 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-ethyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

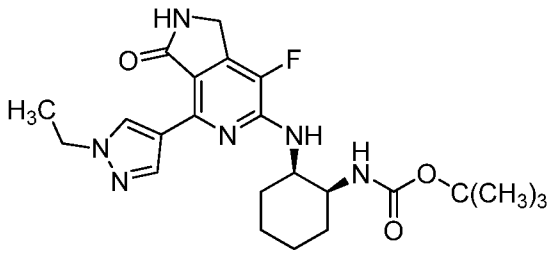


[0542] To a solution of *tert*-butyl (1*S*,2*R*)-2-(4-(1-ethyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (50 mg, 0.113 mmol) in DCM (1 mL) was added DCM/TFA (1/1, 2 mL). The mixture was stirred at RT for 2 h. After removal of solvent, the resulting crude material was reconstituted in MeOH (5.0 mL) and was purified by preparative HPLC. The fractions were collected and the solvent stripped to dryness via rotary evaporation to yield the title compound as a TFA salt (10.5 mg, 27%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.31 - 1.55 (m, 6 H), 1.58 - 1.86 (m, 8 H), 4.20 - 4.31 (m, 3 H), 6.56 (s, 1 H), 6.84 (d, *J*=7.32 Hz, 1 H), 7.56 - 7.76 (m, 2 H), 8.10 (s, 1 H), 8.38 (s, 1 H), 8.96 (s, 1 H). [M+H] calc'd for $C_{18}H_{24}N_6O$, 341; found, 341.

[0543] EXAMPLE 60: 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-ethyl-1*H*-pyrazol-4-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



[0544] A. *tert*-Butyl (1*S*,2*R*)-2-(4-(1-ethyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino



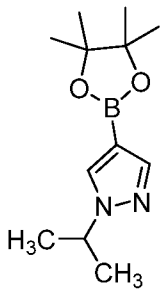
[0545] A solution of *tert*-Butyl (1*S*,2*R*)-2-(4-(1-ethyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (69.7mg, 0.158 mmol) in DCM (5 mL) was cooled to 0°C. SELECTFLUOR® (84 mg, 0.237 mmol) was added. The mixture was left stirring in an ice bath and was allowed to warm slowly to RT with stirring overnight. Additional SELECTFLUOR® (2 eq) was added and the reaction was stopped after 2 h. After removal of solvent, the residue was diluted with EtOAc (10 mL) and washed with saturated aq $NaHCO_3$ (5 mL), water (5 mL), and brine (5 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated to a brown residue. The resulting crude material was reconstituted in MeOH/DCM (6 mL) and was purified via preparative HPLC. The fractions were collected and ACN was removed via rotary evaporation. The resulting aq solution was neutralized with saturated aq $NaHCO_3$, washed with EtOAc (2 x 200 mL), dried over Na_2SO_4, and filtered. The organic phase was stripped to dryness via rotary evaporation to yield the title compound (20 mg, 28%).[M+H] calc'd for $C_{23}H_{31}FN_6O_3$, 459; found, 459.

[0546] B. 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-ethyl-1*H*-pyrazol-4-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

[0547] To a solution of *tert*-butyl (1*S*,2*R*)-2-(4-(1-ethyl-1*H*-pyrazol-4-yl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (20 mg, 0.044

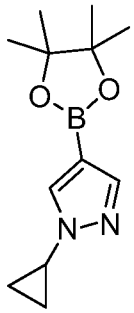
mmol) in DCM (1 mL) was added DCM/TFA (1/1, 2 mL). The mixture was stirred at RT for 2 h. After removal of solvent, the resulting crude material was reconstituted in MeOH (5.0 mL) and was purified by preparative HPLC. The fractions were collected and solvent stripped to dryness via rotary evaporation to yield the title compound as a TFA salt (7 mg, 45%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.40 (t, J=7.08 Hz, 4 H), 1.54 - 1.72 (m, 2 H), 1.75 - 1.97 (m, 2 H), 3.47 - 3.60 (m, 2 H), 3.69 (br s, 1 H), 4.18 (q, J=7.32 Hz, 2 H), 4.33 - 4.52 (m, 3 H), 6.74 (d, J=6.83 Hz, 1 H), 7.77 (br s, 3 H), 8.26 - 8.44 (m, 2 H), 8.88 (s, 1 H). [M+H] calc'd for $C_{18}H_{23}FN_6O$, 359; found, 359.

[0548] PREPARATION 22: 1-Isopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole



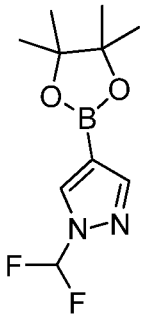
[0549] In a microwave vial, a solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (1 g, 5.15 mmol) in DMF (10 mL) was added cesium carbonate (5.04 g, 15.46 mmol) and 2-iodopropane (2.58 mL, 25.8 mmol). The mixture was heated at 100°C overnight. After cooling to RT, H_2O (300 mL) was added and the aqueous layer was extracted with EtOAC (2 x 200 mL). The organic extracts were combined, dried over Na_2SO_4, filtered, and solvent was removed in vacuo. The resulting crude material was reconstituted in MeOH (1.0 mL) and purified by HPLC. The fractions were collected and stripped to dryness via rotary evaporation to yield the title compound. [M+H] calc'd for $C_{12}H_{21}BN_2O_2$, 237; found 237.

[0550] PREPARATION 23: 1-Cyclopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole



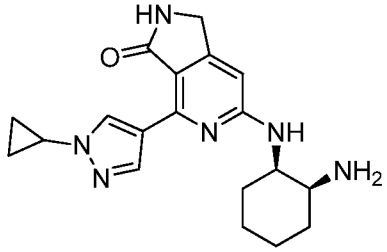
[0551] The title compound was prepared in a manner similar to PREPARATION 22 using bromocyclopropane in place of iodopropane. [M+H] calc'd for $C_{12}H_{19}BN_2O_2$, 234; found, 234.

[0552] PREPARATION 24: 1-(Difluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole



[0553] The title compound was prepared in a manner similar to PREPARATION 22 using difluoroiodomethane in place of iodopropane and carrying out the reaction at 90°C. [M+H] calc'd for $C_{10}H_{15}BF_2N_2O_2$, 245; found, 245.

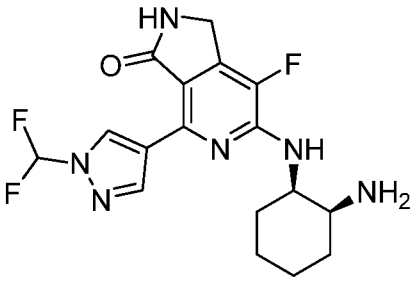
[0554] EXAMPLE 61: 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-cyclopropyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



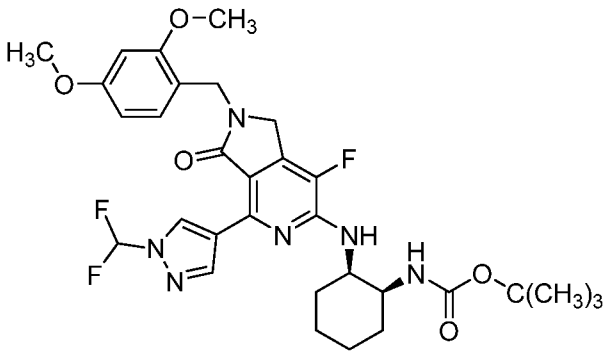
[0555] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 59 using 1-cyclopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole in place of 1-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.47 - 1.67 (m, 4 H), 1.69 - 1.95 (m, 8 H), 3.63 - 3.74

(m, 3 H), 4.35 (s, 2 H), 6.65 (s, 1 H), 8.35 (s, 1 H), 8.96 (s, 1 H). [M+H] calc'd for $C_{19}H_{24}N_6O$, 353; found, 353.

[0556] EXAMPLE 62: 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



[0557] A. *tert*-Butyl (1*S*,2*R*)-2-(4-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-2-(2,4-dimethoxybenzyl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate

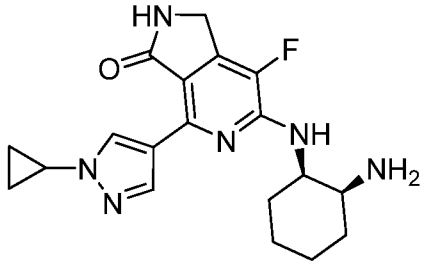


[0558] A solution of *tert*-butyl (1*S*,2*R*)-2-(4-chloro-2-(2,4-dimethoxybenzyl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (35 mg, 0.064 mmol), 1-(difluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (18.67 mg, 0.076 mmol) and bis(triphenylphosphine)palladium chloride (44.7 mg, 0.064 mmol) in dioxane (500 μL) and saturated aq Na_2CO_3 (500 μL) was heated at 85°C for 2 h. After filtering out the solids, the solvent was removed and the residue was dissolved in MeOH and DCM and purified by preparative HPLC. The fractions were collected and ACN was removed via rotary evaporation. The resulting aq solution was neutralized with saturated aq $NaHCO_3$, washed with EtOAc (2 x 200 mL), dried over Na_2SO_4, and filtered. The organic phase was stripped to dryness via rotary evaporation to yield the title compound (36 mg, 90%). [M+H] calc'd for $C_{31}H_{37}F_3N_6O_5$, 631; found, 631.

[0559] B. 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

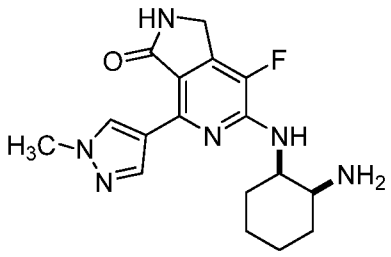
[0560] A solution of *tert*-butyl (1*S*,2*R*)-2-(4-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-2-(2,4-dimethoxybenzyl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (36 mg, 0.057 mmol) in TFA (2 mL) was heated at 60°C for 2 h. After removal of the solvent, the residue was diluted in MeOH (2 mL) and was purified by preparative HPLC. The fractions were collected and stripped to dryness via rotary evaporation to yield the title compound as a TFA salt (18.7 mg, 86%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.40 - 1.52 (m, 2 H), 1.58 - 1.76 (m, 3 H), 1.75 - 1.94 (m, 3 H), 3.67 (br s, 1 H), 4.44 (d, *J*=4.88 Hz, 2 H), 4.53 (br s, 1 H), 6.86 (d, *J*=6.83 Hz, 1 H), 7.71 (br s, 2 H), 7.79 - 8.12 (m, 1 H), 8.53 (s, 2 H), 9.41 (s, 1 H). [M+H] calc'd for $C_{17}H_{19}F_3N_6O$, 381; found, 381.

[0561] EXAMPLE 63: 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-cyclopropyl-1*H*-pyrazol-4-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

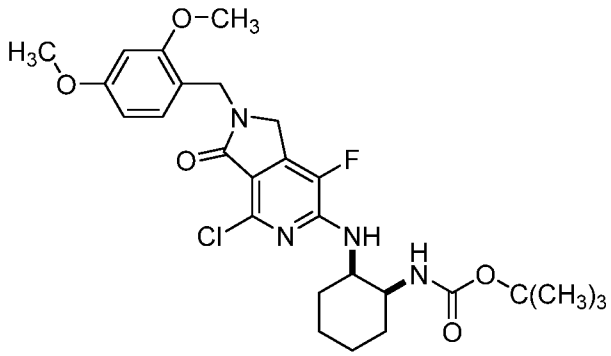


[0562] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 62 using 1-cyclopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole in place of 1-(difluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.94 - 1.11 (m, 4 H), 1.47 (d, *J*=6.35 Hz, 2 H), 1.56 - 1.97 (m, 6 H), 3.60 - 3.85 (m, 2 H), 4.28 - 4.53 (m, 3 H), 6.74 (d, *J*=6.35 Hz, 1 H), 7.70 (br s, 2 H), 8.25 (s, 1 H), 8.38 (s, 1 H), 8.94 (s, 1 H). [M+H] calc'd for $C_{19}H_{23}FN_6O$, 371; found, 371.

[0563] EXAMPLE 64: *cis*-6-(2-Aminocyclohexylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

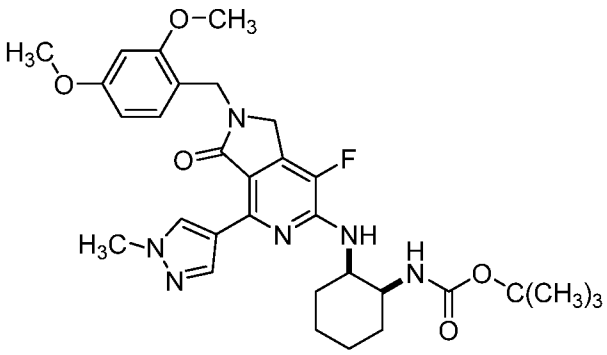


[0564] A. *cis-tert*-Butyl 2-(4-chloro-2-(2,4-dimethoxybenzyl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate



[0565] A mixture of 4,6-dichloro-2-(2,4-dimethoxybenzyl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one (316 mg, 0.851 mmol) and *cis-tert*-butyl 2-aminocyclohexylcarbamate (365 mg, 1.703 mmol) and DIPEA (0.743 mL, 4.26 mmol) in ACN (2 mL) was stirred at 85°C for 3 d. The resulting crude material was reconstituted in MeOH (1 mL) and purified by preparative HPLC. The fractions were collected and stripped to dryness via rotary evaporation to yield the title compound (161 mg, 34%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.35 (br s, 10 H), 1.58 (br s, 2 H), 1.76 (br s, 2 H), 3.71 - 3.90 (m, 11 H), 4.33 (br s, 2 H), 4.51 (br s, 2 H), 6.43 - 6.72 (m, 3 H), 6.87 (br s, 1 H), 7.07 (br s, 1 H). [M+H] calc'd for $C_{27}H_{34}ClFN_4O_5$, 549; found, 549.

[0566] B. *cis-tert*-Butyl 2-(2-(2,4-dimethoxybenzyl)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate

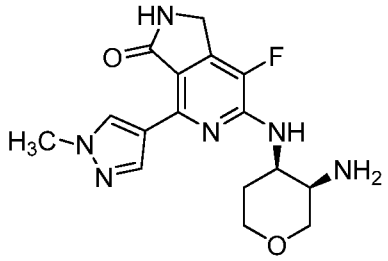


[0567] A solution of *cis-tert*-butyl 2-(4-chloro-2-(2,4-dimethoxybenzyl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (135.8 mg, 0.247 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (154 mg, 0.742 mmol) and bis(triphenylphosphine)palladium chloride (174 mg, 0.247 mmol) in dioxane (2 mL) and saturated aq Na_2CO_3 (2 mL) was heated at 120°C for 30 min. After filtering out the solids, the solvent was removed and the residue was dissolved in MeOH and DCM and the mixture was purified by preparative HPLC. The fractions were collected and the solvent was stripped to dryness via rotary evaporation to give the title compound (109 mg, 74%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.97 - 1.98 (m, 10 H), 2.28 - 2.44 (m, 3 H), 2.56 - 2.72 (m, 4 H), 3.63 - 3.99 (m, 11 H), 4.36 (d, *J*=18.06 Hz, 2 H), 4.56 (br s, 2 H), 6.50 (br s, 1 H), 6.61 (br s, 1 H), 6.65 - 6.81 (m, 1 H), 7.08 (br s, 1 H), 7.70 (br s, 1 H), 8.30 (br s, 1 H), 8.75 - 9.02 (m, 1 H). [M+H] calc'd for $C_{31}H_{39}FN_6O_5$, 595; found, 595.

[0568] C. *cis*-6-(2-Aminocyclohexylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

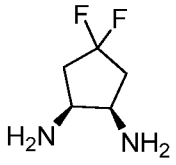
[0569] A solution of *cis-tert*-butyl 2-(2-(2,4-dimethoxybenzyl)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (109 mg, 0.183 mmol) in TFA (5 mL) was heated at 60°C for 2 h. After removal of the solvent, the residue was diluted in MeOH (2 mL) and was purified by preparative HPLC. The fractions were collected and stripped to dryness via rotary evaporation to give the title compound as a TFA salt. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.47 (br s, 2 H), 1.57 - 1.75 (m, 3 H), 1.84 (br s, 2 H), 3.12 - 3.23 (m, 2 H), 3.87 - 3.94 (m, 3 H), 4.35 - 4.50 (m, 3 H), 6.73 (br s, 1 H), 7.71 (br s, 2 H), 8.28 - 8.44 (m, 2 H), 8.84 (d, *J*=3.91 Hz, 1 H). [M+H] calc'd for $C_{17}H_{21}FN_6O$, 345; found, 345.

[0570] EXAMPLE 65: 6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



[0571] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 64 using (3*R*,4*R*)-tetrahydro-2*H*-pyran-3,4-diamine dihydrochloride in place of *cis*-*tert*-butyl 2-aminocyclohexylcarbamate. The desired stereoisomer was isolated using preparative HPLC. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.29 (br s, 2 H), 1.86 - 1.99 (m, 1 H), 3.84 - 3.99 (m, 4 H), 4.03 - 4.17 (m, 1 H), 4.45 (br s, 2 H), 8.29 (br s, 1 H), 8.79 (br s, 1 H). [M+H] calc'd for $C_{16}H_{19}FN_6O_{20}$, 347; found, 347.

[0572] PREPARATION 25: *cis*-4,4-Difluorocyclopentane-1,2-diamine

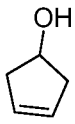


[0573] A. Cyclopenta-1,3-diene



[0574] A flask containing dicyclopentadiene was flushed with N_2 for 1 min and was then heated by oil bath to approximately 180°C. Cyclopentadiene distilled slowly at 40-45°C. The title compound (100 g) was collected and kept at –70°C under N_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.02 (t, *J*=1.4 Hz, 2 H), 6.49-6.51 (m, 2 H), 6.61-6.62 (m, 2 H).

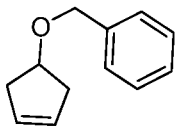
[0575] B. Cyclopent-3-enol



[0576] To cooled alpha-pinene (225.0 g, 1.65 mol) at 0°C was added dropwise BH_3-THF (1 M, 750 mL) over a 30 min period under N_2 atmosphere. The reaction mixture was stirred for 3.5 h at 0°C. Distilled cyclopenta-1,3-diene (99.0 g, 1.50 mol) was added dropwise at 0°C over a 40 min period. The resulting mixture was slowly warmed to RT and stirred for 20 h. Excess hydride was decomposed by adding water (30 mL) at a temperature below 10°C. Aqueous NaOH (3N, 300 mL) was added at a temperature below

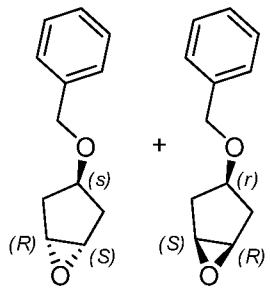
5°C, followed by H_2O_2 (30%, 250 mL). The aqueous layer was salted out with NaCl, and the organic layer was separated and dried over Na_2SO_4. The product was distilled at 65°C under a reduced pressure of 20mm Hg to give the title compound as an oil (30.4 g, 24%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.29 (d, *J*=17.6 Hz, 2 H), 2.61 (dd, *J*=6.0, 16.4 Hz, 2 H), 4.82 (s, 1 H), 5.68 (s, 2 H).

[0577] C. ((Cyclopent-3-enyloxy)methyl)benzene



[0578] To a cooled solution of cyclopent-3-enol (30.40 g, 0.36 mol) in THF (300 mL) at 0°C was added NaH (18.82 g, 0.47 mol, 60% in mineral oil). After effervescence had ceased, benzyl bromide (80.45 g, 0.47 mol) was added dropwise at 0°C over a 45 min period. The reaction mixture was allowed to warm to RT over a 6 h period. Excess NaH was quenched with MeOH (120 mL) at a temperature below 5°C. The mixture was warmed to RT, diluted with H_2O, and the two layers were separated. The aqueous layer was extracted with EtOAc. The organic layers were combined, concentrated, and purified by column chromatography eluting with petroleum ether and EtOAc (PE/EA = 40/1 to 30/1) to give the title compound as an oil (45.28 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.38-2.41 (m, 2 H), 2.49-2.54 (m, 2 H), 4.20-4.24 (m, 1 H), 4.42 (s, 2 H), 5.62 (s, 2 H), 7.17-7.28 (m, 5 H).

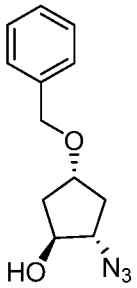
[0579] D. (1*R*,3*s*,5*S*)-3-(Benzyloxy)-6-oxabicyclo[3.1.0]hexane and (1*R*,3*r*,5*S*)-3-(Benzyloxy)-6-oxabicyclo[3.1.0]hexane



[0580] To a cooled solution of ((cyclopent-3-enyloxy)methyl)benzene (45.28 g, 260 mmol) in DCM (300 mL) at 0°C was added *m*-chloroperoxybenzoic acid (111.9 g, 520 mmol) in one portion. The mixture was stirred at a temperature from 0°C to RT overnight. The reaction mixture was filtered and excess *m*-chloroperoxybenzoic acid was reduced by

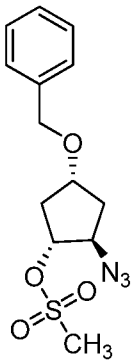
the addition of saturated aq $Na_2S_2O_3$ until a negative starch iodide test was observed. The mixture was neutralized with saturated $NaHCO_3$ to pH 8 -9 and filtered. The filtrate was separated with DCM, washed with brine, dried over Na_2SO_4, and purified by column chromatography eluting with petroleum ether and EtOAc (PE/EtOAc = 30/1, 20/1 to 10/1) to give the title compounds as oils ((1*R*,3*s*,5*S*): 14.41 g, 76 mmol; ((1*R*,3*r*,5*S*): 21.38 g, 113 mmol). ^{1}H NMR of (1*R*,3*s*,5*S*) (400MHz, $CDCl_3$) δ ppm 1.69 (*dd*, *J*=6.8, 14.0 Hz, 2 H), 2.49 (dd, *J*=7.2, 14.0 Hz, 2 H), 3.49 (s, 2 H), 3.85 (quintet *J*=7.0 Hz, 1 H), 4.43 (s, 2 H), 7.25-7.34 (m, 5 H); ^{1}H NMR of (1*R*,3*r*,5*S*) (400 MHz, $CDCl_3$) δ ppm 1.99 (dd, *J*=7.6, 15.6 Hz, 2 H), 2.23 (d, *J*=16.6 Hz, 2 H), 3.55 (s, 2 H), 4.08 (t, *J*=7.2 Hz, 1 H), 4.49 (s, 2 H), 7.27-7.35 (m, 5 H).

[0581] E. (1*S*,2*S*,4*R*)-2-Azido-4-(benzyloxy)cyclopentanol



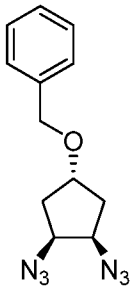
[0582] To a solution of (1*R*,3*s*,5*S*)-3-(benzyloxy)-6-oxabicyclo[3.1.0]hexane (14.41 g, 76 mmol) in EtOH/H_2O (550 mL/160mL) was added NH_4Cl (15.06 g, 284 mmol) and sodium azide (18.47 g, 284 mmol), The mixture was refluxed overnight and then cooled to RT. After removing EtOH, water was added and the residue was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and purified by column chromatography eluting with petroleum ether and EtOAc (PE/EtOAc = 20/1, 10/1 to 6/1) to give the title compound as an oil (18.24 g, 78.3 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.65-1.79 (m, 2 H), 2.01-2.07 (m, 1 H), 2.30-2.37 (m, 1 H), 3.49-3.54 (m 1 H), 3.97-4.06 (m, 2 H), 4.11-4.13 (br, 1 H), 4.33-4.40 (m, 2 H), 7.18-7.27 (m, 5 H).

[0583] F. (1*R*,2*R*,4*R*)-2-Azido-4-(benzyloxy)cyclopentyl methanesulfonate



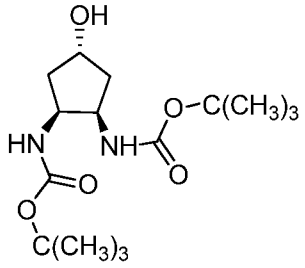
[0584] To a cooled mixture of Et_3N (9.49 g, 94.0 mmol) and (1*S*,2*S*,4*R*)-2-azido-4-(benzyloxy)cyclopentanol (18.25 g, 78.3 mmol) in DCM (500 mL) was added dropwise methanesulfonyl chloride (9.87 g, 86.2 mmol) in DCM (50 mL) at 0°C. The mixture was stirred overnight at a temperature of 0°C to RT. After complete conversion, aq $NaHCO_3$ (5%, 300 mL) was added. The mixture was extracted with DCM, washed with brine, and dried over Na_2SO_4 to give the title compound as an oil (23.58 g, 75.8 mmol). ^1H NMR (400MHz, $CDCl_3$) δ ppm 1.83-1.89 (m, 1 H), 2.06-2.13 (m, 1 H), 2.34-2.49 (m, 2 H), 3.04 (s, 3 H), 3.94-3.99 (m, 1 H), 4.08-4.13 (m, 1 H), 4.64 (s, 2 H), 4.93-4.98 (q, *J*=5.6/7.0 Hz, 1 H), 7.25-7.36 (m, 5 H).

[0585] G. (((1*s*,3*R*,4*S*)-3,4-Diazidocyclopentyloxy)methyl)benzene



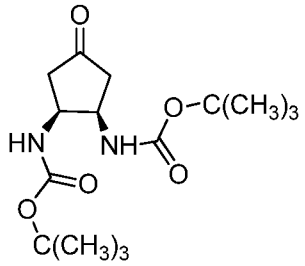
[0586] To a mixture of (1*R*,2*R*,4*R*)-2-azido-4-(benzyloxy)cyclopentyl methanesulfonate (23.58 g 75.8 mmol), pyridine (25 mL), water (140 mL), and DMA (350 mL) was added NaN_3 (10.84 g, 166.8 mmol). The mixture was heated at 130°C under N_2 atmosphere overnight. The reaction mixture was cooled to RT and quenched with cold water (300 mL). The mixture was extracted with EtOAc, washed with H_2O (several times) and with brine, dried over Na_2SO_4, and purified by column chromatography eluting with petroleum ether and EtOAc (PE/EA = 40/1 to 30/1) to give the title compound as an oil (15.35 g, 59.5 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.99-2.08 (m. 2 H), 2.23-2.30 (m, 2 H), 3.75-3.80 (m, 2 H), 3.99-4.04 (m, 1 H), 4.49 (s, 2 H), 7.26-7.35 (m, 5 H).

[0587] H. Di-*tert*-butyl *N*,*N*-((1*R*,2*S*,4*s*)-4-hydroxycyclopentane-1,2-diyl)-biscarbamate



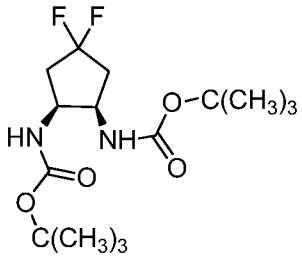
[0588] To a solution of (((1*s*,3*R*,4*S*)-3,4-diazidocyclopentyloxy)methyl)benzene (15.35g, 59.5 mmol) and di-*tert*-butyl pyrocarbonate (31.69 g, 145.4 mmol) in MeOH (200 mL) was added Pd/C (50% wet, 8.0 g) in an autoclave. The autoclave was charged with H_2 to 2.2 MPa. The reaction mixture was stirred at RT overnight. After conversion, the mixture was filtered and solvent removed to give the title compound, which was used without further purification (14.8 g, 46.8 mmol). ^{1}H NMR (400MHz, $CDCl_3$) δ ppm 1.45 (s, 18 H), 1.72-1.75 (m, 2 H), 2.20 (m, 2 H), 4.04 (br, 2 H), 4.34-4.37 (m, 1 H), 4.45 (br, 2 H), 5.21 (br, 1H).

[0589] I. Di-*tert*-butyl *N*,*N*-(*cis*-4-oxocyclopentane-1,2-diyl)-biscarbamate



[0590] To a cooled solution of di-*tert*-butyl *N*,*N*-((1*R*,2*S*,4*s*)-4-hydroxycyclopentane-1,2-diyl)-biscarbamate (5.35 g, 16.9 mmol) in DCM 90 (mL) at 0°C was added Dess-Martin periodinane reagent (24.4 g, 57.6 mmol). The mixture was stirred from 0°C to RT for 1.5 h. After the reaction was completed, the mixture was filtered and the residue was purified by column chromatography eluting with petroleum ether and EtOAc (PE/EtOAc = 6/1 to 2/1) to give the title compound as a solid (5.03 g, 15.9 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.38 (s, 18 H), 2.30-2.50 (m, 4 H), 4.29 (s, 2 H).

[0591] J. Di-*tert*-butyl *N*,*N*-(*cis*-4,4-difluorocyclopentane-1,2-diyl)-biscarbamate

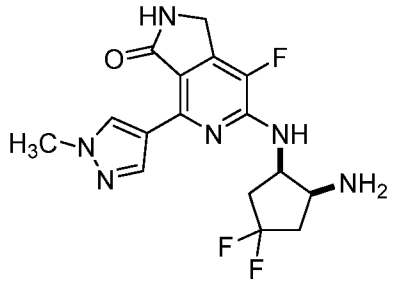


[0592] To a cooled solution of di-*tert*-butyl *N*,*N*-(*cis*-4-oxocyclopentane-1,2-diyl)-biscarbamate (5.00 g, 15.9 mmol) in DCM (100 mL) was added dropwise a mixture of diethylaminosulfur trifluoride (12.82 g, 79.6 mmol) in DCM (10 mL) at 0°C. The mixture was stirred at a temperature of from 0°C to RT overnight. The mixture was subsequently cooled to 0°C and its pH adjusted to 9-10 with saturated aq K_2CO_3, while maintaining the temperature of the mixture below 5°C. Di-*tert*-butyl pyrocarbonate (7.60 g, 2.2 eq) was added and the mixture was stirred at a temperature of from 0°C to RT for 3 h. After removing DCM, the residue was purified by column chromatography eluting with petroleum ether and EtOAc (PE/EtOAc = 20/1 to 15/1 to 12/1) to give the title compound as a solid (2.40 g, 7.10 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.45 (br, 18 H), 2.15-2.19 (m, 2 H), 2.47-2.52 (m, 2 H), 4.22 (br, 2 H), 4.87 (br, 2 H).

[0593] K. *cis*-4,4-Difluorocyclopentane-1,2-diamine

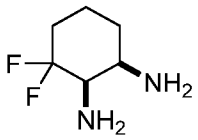
[0594] To a cooled solution of di-*tert*-butyl *N*,*N*-(*cis*-4,4-difluorocyclopentane-1,2-diyl)-biscarbamate (2.40 g, 7.10 mmol) in EtOAc (30 mL) at 0°C was added 1N HCl-EtOAc (10 mL) while maintaining the temperature of the mixture below 5°C. The mixture was stirred at RT overnight. The mixture was subsequently filtered, washed with EtOAc several times, and dried *in vacuo* to give a hydrochloride salt of the title compound as a solid (0.98 g, 4.7 mmol). ^{1}H NMR (400 MHz, CD_3OD,) δ ppm 2.63-2.67 (m, 2 H), 2.76-2.86 (m, 2 H), 4.15-4.17 (m, 2 H). [M+H] calc'd for $C_5H_{10}F_2N_2$, 137; found 137.

[0595] EXAMPLE 66: 6-(*cis*-2-Amino-4,4-difluorocyclopentylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-c]pyridin-3(2*H*)-one

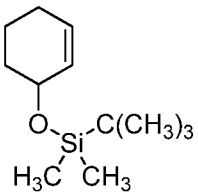


[0596] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 64 using *cis*-4,4-difluorocyclopentane-1,2-diamine in place of *cis-tert*-butyl 2-aminocyclohexylcarbamate. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.62 - 2.69 (m, 2 H), 2.87 (td, *J*=16.84, 8.79 Hz, 2 H), 3.89 (s, 3 H), 4.14 (br s, 1 H), 4.32 - 4.48 (m, 2 H), 4.79 (d, *J*=9.76 Hz, 1 H), 7.28 (d, *J*=5.37 Hz, 1 H), 7.93 (br s, 2 H), 8.41 (d, *J*=7.32 Hz, 2 H), 8.87 (s, 1 H). [M+H] calc'd for $C_{16}H_{17}F_3N_6O$, 367; found, 367.

[0597] PREPARATION 26: *cis*-3,3-Difluorocyclohexane-1,2-diamine

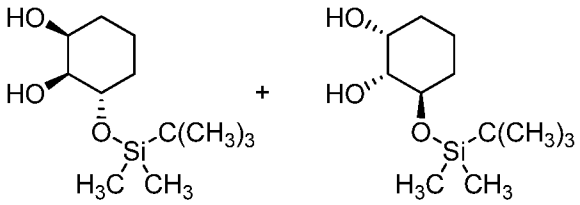


[0598] A. *tert*-Butyl(cyclohex-2-enyloxy)dimethylsilane



[0599] Pyridine (4.74 g, 60 mmol) and *tert*-butyldimethylsilyl chloride (4.83 g, 32 mmol) were added to a solution of cyclohex-2-enol (1.96 g, 20 mmol) in DCM (40 mL). The reaction mixture was stirred at RT overnight. The mixture was concentrated and the residue was dispersed in EtOAc and water. The organic phase was separated and washed with brine, dried over anhydrous Na_2SO_4, concentrated, and purified by silica flash chromatography eluting with EtOAc and petroleum ether (5-10% EtOAc) to give the title compound as an oil (4.1 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.06-0.09 (m, 6 H), 0.92 (s, 9 H), 1.50-1.57 (m, 2 H), 1.74-1.89 (m, 2 H), 1.93-2.03 (m, 2 H), 4.21-4.23 (m, 1 H), 5.61 -5.64 (m, 1 H), 5.72-5.76 (m, 1 H).

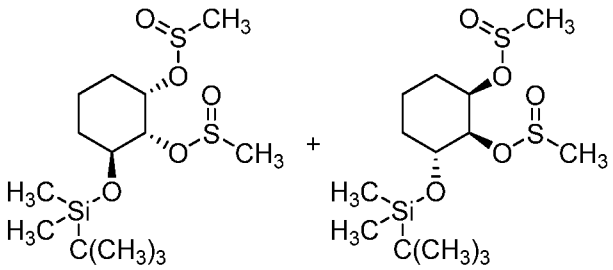
[0600] B. (1*S*,2*S*,3*S*)-3-(*tert*-Butyldimethylsilyloxy)cyclohexane-1,2-diol and (1*R*,2*R*,3*R*)-3-(*tert*-butyldimethylsilyloxy)cyclohexane-1,2-diol



[0601] *tert*-Butyl(cyclohex-2-enyloxy)dimethylsilane (12.72 g, 60 mmol) was dissolved in CH_3CN (100 mL). A solution of *N*-methylmorpholine-*N*-oxide (14 g, 120

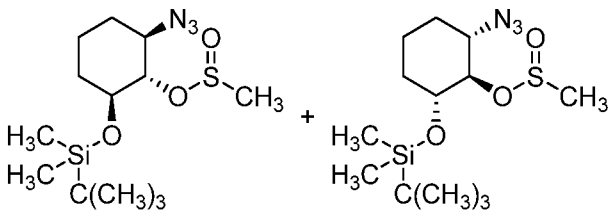
mmol) in H_2O (20 mL) and OsO_4 (0.5 g) in acetone (5 mL) was added, and the mixture was stirred at RT overnight. The mixture was then diluted with EtOAc (800 mL), washed with brine and saturated aq $NaHCO_3$, dried over anhydrous Na_2SO_4, concentrated, and purified by silica flash chromatography eluting with EtOAC and petroleum ether (20-40% EtOAc) to give the title compounds as an oil (12.8 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$,) δ ppm 0.06-0.09 (m, 6 H), 0.90 (s, 9 H), 1.25-1.28 (m, 2 H), 1.44-1.62 (m, 2 H), 1.80-1.84 (m, 2 H), 2.28 (s, 1 H), 2.51 (s, 1 H),3.40-3.44 (m, 1 H), 3.77-3.82 (m, 1 H), 4.08-4.11 (m, 1 H).

[0602] C. (1*S*,2*R*,3*S*)-3-(*tert*-Butyldimethylsilyloxy)cyclohexane-1,2-diyl dimethanesulfinate and (1*R*,2*S*,3*R*)-3-(*tert*-Butyldimethylsilyloxy)cyclohexane-1,2-diyl dimethanesulfinate



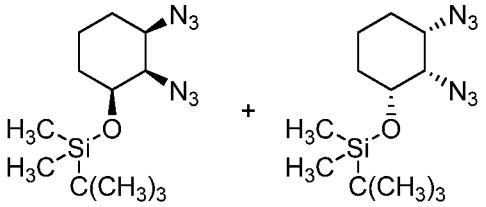
[0603] (1*S*,2*S*,3*S*)/(1*R*,2*R*,3*R*)-3-(*tert*-Butyldimethylsilyloxy)cyclohexane-1,2-diol (1.9 g, 7.7 mmol) was dissolved in DCM (40 mL). The mixture was placed in an ice bath. Pyridine (3.1 mL, 38.5 mmol) and methanesulfonyl chloride (1.44 mL, 18.5 mmol) were added and the reaction mixture was stirred at RT overnight. Next, the mixture was diluted with DCM, washed with brine, dried over anhydrous Na_2SO_4, concentrated, and purified by silica flash chromatography eluting with EtOAC and petroleum ether (20-30% EtOAc) to give the title compounds as an oil (2.6 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.06-0.09 (m, 6 H), 0.90 (s, 9 H), 1.58-1.64 (m, 2 H), 1.70-1.78 (m, 2 H), 1.85-1.90(m, 2 H), 3.12 (s, 6 H), 4.08-4.12 (m, 1 H), 4.51-4.55 (m, 1 H), 5.06-5.10 (m, 1 H).

[0604] D. (1*S*,2*R*,6*S*)-2-Azido-6-(*tert*-butyldimethylsilyloxy)cyclohexyl methanesulfonate and (1*R*,2*S*,6*R*)-2-Azido-6-(*tert*-butyldimethylsilyloxy)cyclohexyl methanesulfinate



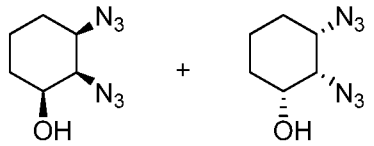
[0605] (1*S*,2*R*,3*S*)/(1*R*,2*S*,3*R*)-3-(*tert*-Butyldimethylsilyloxy)cyclohexane-1,2-diyl dimethanesulfinate (12.0 g, 29.8 mmol) was dissolved in DMF (80 mL) and hexamethylphosphoramide (20 mL). Sodium azide (10.0 g, 154 mmol) was added and the mixture was stirred at 75°C overnight. The mixture was diluted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated. The solid was washed petroleum ether and dried *in vacuo* to give the title compounds (7 g, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.06-0.09 (m, 6 H), 0.90 (s, 9 H), 1.32-1.47 (m,3 H), 1.76-1.81 (m, 1 H), 1.97-2.01(m, 1 H), 2.10-2.14 (m, 1 H), 3.14 (s, 3 H), 3.33-3.39 (m, 1 H), 3.55-3.61 (m, 1 H), 4.23-4.28 (m, 1H).

[0606] E. *tert*-Butyl((1*S*,2*R*,3*R*)-2,3-diazidocyclohexyloxy)dimethylsilane and *tert*-Butyl((1*R*,2*S*,3*S*)-2,3-diazidocyclohexyloxy)dimethylsilane



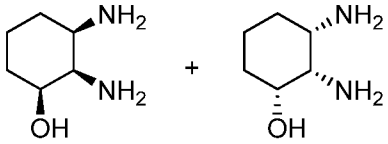
[0607] (1*S*,2*R*,6*S*)/(1*R*,2*S*,6*R*)-2-Azido-6-(*tert*-butyldimethylsilyloxy)cyclohexyl methanesulfonate (7 g, 20 mmol) was dissolved in DMF (80 mL) and hexamethylphosphoramide (20 mL). Sodium azide (15.0 g, 230 mmol) was added and the mixture was stirred at 120°C for 24 h. The mixture was diluted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, concentrated, and purified by silica flash chromatography eluting with EtOAc and petroleum ether (3% EtOAc) to give the title compounds as an oil (3.52 g, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.06-0.09 (m, 6 H), 0.90 (s, 9 H), 1.66-1.70 (m, 2 H), 1.72-1.76 (m, 2 H), 1.80-1.85 (m, 2 H), 3.16-3.21 (m, 1 H), 3.71-3.76 (m, 1 H), 3.80-3.85 (m, 1 H).

[0608] F. (1*S*,2*R*,3*R*)-2,3-Diazidocyclohexanol and (1*R*,2*S*,3*S*)-2,3-Diazidocyclohexanol



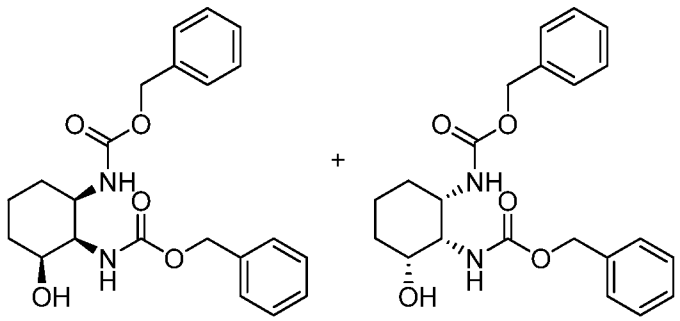
[0609] Tetrabutylammonium fluoride (16.0 g, 61.3 mmol) dissolved in THF was added to *tert*-butyl((1*S*,2*R*,3*R*)/(1*R*,2*S*,3*S*)-2,3-diazidocyclohexyloxy)dimethylsilane (12.0 g, 40.5 mmol) in THF (300 mL). The reaction mixture was stirred at RT for 3 h and was then quenched with MeOH. The mixture was concentrated and the residue was purified by column chromatography (EtOAc/PE = 4/1) to give the title compounds as an oil (5 g, 68%).

[0610] G. (1*S*,2*R*,3*R*)-2,3-Diaminocyclohexanol and (1*R*,2*S*,3*S*)-2,3-Diaminocyclohexanol



[0611] A mixture of (1*S*,2*R*,3*R*)/(1*R*,2*S*,3*S*)-2,3-diazidocyclohexanol (5.0 g, 27.5 mmol) and Pd/C (2.0 g) in MeOH was stirred at RT overnight under H_2 atmosphere. Following reaction, the mixture was filtered and concentrated to give the title compounds as an oil, which was used without further purification (3.18 g).

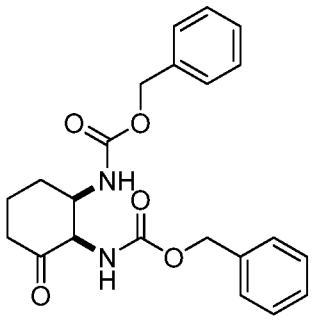
[0612] H. Dibenzyl *N*,*N*-((1*R*,2*R*,3*S*)-3-hydroxycyclohexane-1,2-diyl)-biscarbamate and Dibenzyl *N*,*N*-((1*S*,2*S*,3*R*)-3-hydroxycyclohexane-1,2-diyl)-biscarbamate



[0613] To a solution of (1*S*,2*R*,3*R*)/(1*R*,2*S*,3*S*)-2,3-diaminocyclohexanol (3.1 g, 24.5 mmol) and Et_3N (7.4 g, 73.5 mmol) in DCM (50 mL) at -10°C was added benzyl carbonochloridate (9.6 g, 56.3 mmol). The progress of the reaction was monitored by TLC and LCMS. Following completion of the reaction, the mixture was washed with water, dried over Na_2SO_4, and concentrated. The residue was purified by column

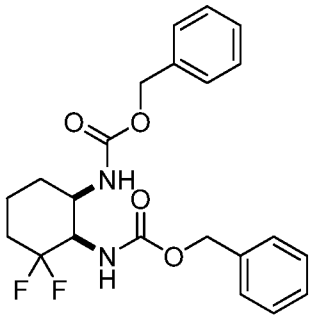
chromatography (EtOAc/PE = 2/1) to give the title compounds as an oil (2.2 g, 22%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.59-1.84 (m, 6 H), 3.80 (br, 1 H), 4.05-4.16 (m, 2 H), 5.12 (s, 4 H), 5.4 (s, 1 H), 6.4 (s, 1 H), 7.33-7.37 (m, 10 H).

[0614] I. Dibenzyl *N*,*N*-(*cis*-3-oxocyclohexane-1,2-diyl)-biscarbamate



[0615] To a solution of dibenzyl *N*,*N*-((1*R*,2*R*,3*S*)/(1*S*,2*S*,3*R*)-3-hydroxycyclohexane-1,2-diyl)-biscarbamate (2.2 g, 5.5 mmol) in DCM (30 mL) at -0°C was added Dess-Martin periodinane reagent (5.9 g, 13.8 mmol). The suspension was stirred at RT for 3 h. The mixture was concentrated and the residue was purified by column chromatography (EtOAc/PE = 2/1) to give the title compound as a solid (2.0 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.60-1.70 (m, 3 H), 2.00-2.04 (m, 1 H), 2.35-2.58 (m, 2 H), 4.27-4.31 (m, 1 H), 5.12 (s, 4 H), 5.82-5.92 (m, 1 H), 7.33-7.38 (m, 10 H).

[0616] J. Dibenzyl *N*,*N*-(*cis*-3,3-difluorocyclohexane-1,2-diyl)-biscarbamate

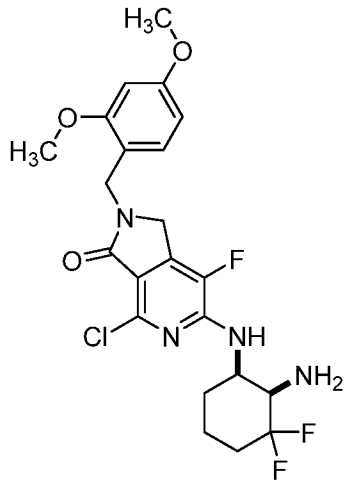


[0617] To a solution of dibenzyl *N*,*N*-(*cis*-3-oxocyclohexane-1,2-diyl)-biscarbamate (2.0 g, 5.1 mmol) in DCM (30 mL) at -0°C was added diethylaminosulfur trifluoride (4 mL, 1.22 g/cm^3). The reaction mixture was stirred at -0°C overnight. The reaction mixture was neutralized with sodium bicarbonate, concentrated, and the residue was purified by column chromatography (EtOAc/PE = 2/1) to give the title compound as a solid (1.0 g, 47%). ^{1}H NMR (400 MHz, CD_3OD,) δ ppm 1.43-2.01 (m, 6 H), 3.83-3.84 (m, 1 H), 4.23-4.24 (m, 1 H), 4.97 (s, 4 H), 7.16-7.24 (m, 10 H).

[0618] K. *cis*-3,3-Difluorocyclohexane-1,2-diamine

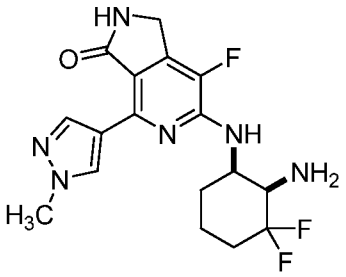
[0619] A mixture of dibenzyl *N*,*N*-(*cis*-3,3-difluorocyclohexane-1,2-diyl)-biscarbamate (1.0 g, 2.4 mmol) and Pd/C (0.9 g) in MeOH was stirred at RT overnight under H_2 atmosphere. Following reaction, the mixture was filtered and concentrated to an oil, which was reacted with EtOAc-HCl to give a hydrochloride salt of the title compound as a white solid (280mg, 77%). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.84-2.31 (m, 6 H), 4.01 (m, 1 H), 4.20-4.26 (m, 1 H). [M+H] calc'd for $C_6H_{12}F_2N_2$, 151; found, 151.

[0620] PREPARATION 27: 6-(*cis*-2-Amino-3,3-difluorocyclohexylamino)-4-chloro-2-(2,4-dimethoxybenzyl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

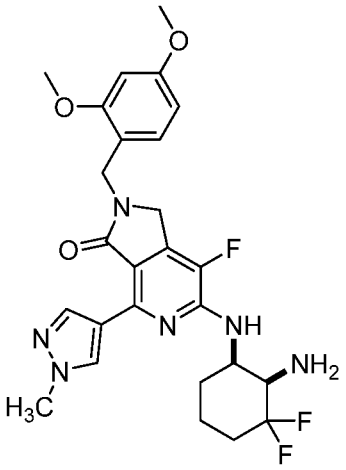


[0621] A mixture of 4,6-dichloro-2-(2,4-dimethoxybenzyl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one (100 mg, 0.269 mmol) and *cis*-3,3-difluorocyclohexane-1,2-diamine hydrochloride (75 mg, 0.404 mmol) and DIPEA (118 µL, 0.674 mmol) in acetonitrile (449 µL) was stirred at 100°C for 3 d. The reaction mixture was concentrated to a brown oil and reconstituted in DMF (1 mL). The residue was purified by preparative HPLC, the appropriate fraction was collected, and excess acetonitrile was evaporated. The residue was treated with saturated aq sodium carbonate and extracted with EtOAc (3 x 20 mL). The organic layers were combined, dried over sodium sulfate, and concentrated to give the title compound as a colorless residue (13.7 mg, 10%). [M+H] calc'd for $C_{22}H_{24}ClF_3N_4O_3$, 485; found, 485.

[0622] EXAMPLE 67: 6-(*cis*-2-Amino-3,3-difluorocyclohexylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



[0623] A. 6-(*cis*-2-Amino-3,3-difluorocyclohexylamino)-2-(2,4-dimethoxybenzyl)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

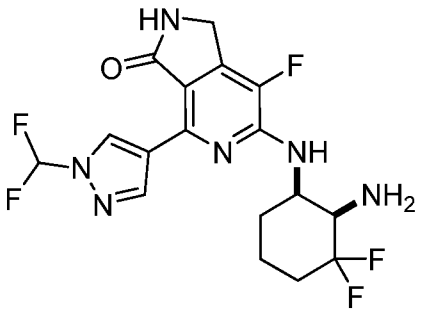


[0624] A microwave vial was charged with 6-(*cis*-2-amino-3,3-difluorocyclohexylamino)-4-chloro-2-(2,4-dimethoxybenzyl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one (13.7 mg, 0.028 mmol) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (8.82 mg, 0.042 mmol) and bis(triphenylphosphine)palladium chloride (3.97 mg, 5.65 μmol) and placed under an inert environment. DME (283 μL) was added to the mixture and the resulting yellow slurry was degassed for 5 min. Sodium carbonate was added (56.5 μL, 0.113 mmol) and the slurry degassed for an additional 3 min. The vessel was capped and the mixture was heated at 80°C for 4 h, cooled to ambient temperature, diluted with EtOAc (5 mL), and washed with water (3 mL) and brine (3 mL). The organic layer was collected, dried over sodium sulfate, and concentrated to give the title compound as a dark brown residue which was used in the next step without further purification (21 mg). [M+H] calc'd for $C_{26}H_{29}F_3N_6O_3$, 531; found, 531.

[0625] B. 6-(*cis*-2-Amino-3,3-difluorocyclohexylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

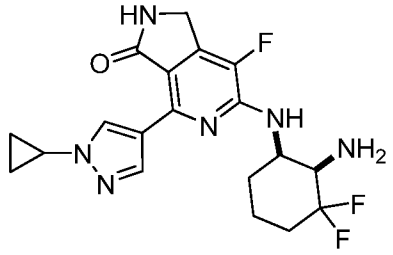
[0626] To a solution of 6-(*cis*-2-amino-3,3-difluorocyclohexylamino)-2-(2,4-dimethoxybenzyl)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one (21 mg, 0.040 mmol) in DCM (300 μL) was added TFA (500 μL, 6.49 mmol). The reaction mixture was stirred at ambient temperature for 12 h then an additional 3 h at 50°C. The mixture was subsequently concentrated to a dark oil and diluted with DMF (1 mL) which was purified via preparative HPLC and lyophilized to give a TFA salt of the title compound as a fluffy white solid (3.6 mg, 19%). ^{1}H NMR (400MHz ,DMSO-d_6) δ ppm 8.89 (s, 1 H), 8.43 (s, 3 H), 8.16 (s, 1 H), 6.89 (br s, 1 H), 6.54 (br s, 1 H), 4.65 - 4.52 (m, 1 H), 4.49 - 4.32 (m, 2 H), 4.17 (br s, 1 H), 3.89 (s, 3 H), 2.37 - 2.03 (m, 2 H), 1.84 (br s, 3 H), 1.63 (br s, 1 H). [M+H] calc'd for $C_{17}H_{19}F_3N_6O$, 381; found, 381.

[0627] EXAMPLE 68: 6-(*cis*-2-Amino-3,3-difluorocyclohexylamino)-4-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



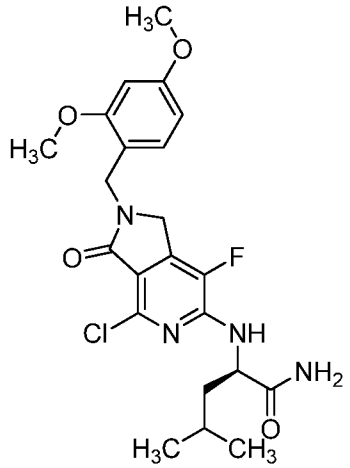
[0628] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 67 using 1-(difluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole in place of 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.64 (br s, 1 H), 1.83 (br s, 3 H), 2.00 - 2.29 (m, 2 H), 2.33 (t, *J*=1.77 Hz, 1 H), 2.63 - 2.72 (m, 1 H), 4.11 (br s, 1 H), 4.40 - 4.50 (m, 2 H), 4.62 (br s, 1 H), 6.93 (d, *J*=5.31 Hz, 1 H), 7.74 - 8.14 (m, 1 H), 8.45 (s, 1 H), 8.56 (s, 1 H), 9.40 (s, 1 H). [M+H] calc'd for $C_{17}H_{17}F_5N_6O$, 417; found, 417.

[0629] EXAMPLE 69: 6-(*cis*-2-amino-3,3-difluorocyclohexylamino)-4-(1-cyclopropyl-1H-pyrazol-4-yl)-7-fluoro-1H-pyrrolo[3,4-c]pyridin-3(2H)-one



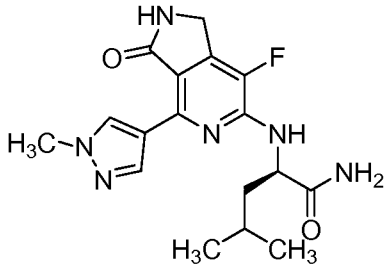
[0630] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 67 using 1-cyclopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole in place of 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.63 (br s, 1 H), 1.75 - 1.92 (m, 3 H), 2.00 - 2.29 (m, 2 H), 2.33 (dt, *J*=3.73, 1.80 Hz, 1 H), 2.62 - 2.74 (m, 1 H), 4.34 - 4.46 (m, 2 H), 4.57 (br s, 1 H), 4.81 (d, *J*=5.56 Hz, 2 H), 5.08 - 5.30 (m, 2 H), 5.93 - 6.10 (m, 1 H), 6.83 (d, *J*=6.06 Hz, 1 H), 8.22 (s, 1 H), 8.39 (s, 2 H), 8.84 - 9.05 (m, 1 H). [M+H] calc'd for $C_{19}H_{21}F_3N_6O$, 407; found, 407.

[0631] PREPARATION 28: (*R*)-2-(4-Chloro-2-(2,4-dimethoxybenzyl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide

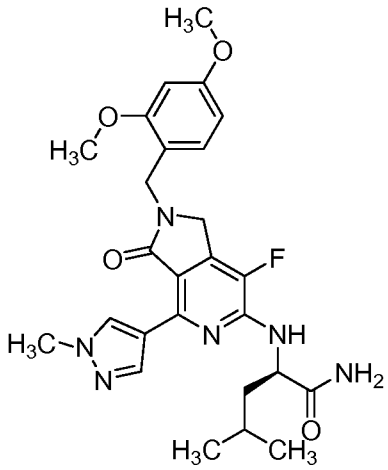


[0632] A mixture of 4,6-dichloro-2-(2,4-dimethoxybenzyl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one (200 mg, 0.539 mmol), (*R*)-2-amino-4-methylpentanamide (140 mg, 1.078 mmol), and *N*-isopropyl-*N*-methylpropan-2-amine (310 mg, 2.69 mmol) in acetonitrile (2 mL) was stirred at 85°C for 3 d. The resulting crude material was reconstituted in MeOH/DCM/DMF (10.0 mL) and purified via preparative HPLC. The fractions were collected and stripped to dryness via rotary evaporation to yield the title compound (83 mg, 33%). [M+H] calc'd for $C_{22}H_{26}ClFN_4O_4$, 465; found, 465.

[0633] EXAMPLE 70: (*R*)-2-(7-Fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide



[0634] A. (*R*)-2-(2-(2,4-dimethoxybenzyl)-7-fluoro-4-(1-methyl-1H-pyrazol-4-yl)-3-oxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-ylamino)-4-methylpentanamide



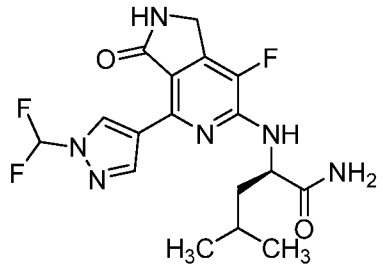
[0635] A solution of (*R*)-2-(4-chloro-2-(2,4-dimethoxybenzyl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide (83 mg, 0.179 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (111 mg, 0.536 mmol), and bis(triphenylphosphine)palladium chloride (12.53 mg, 0.018 mmol) in dioxane (2 mL) and saturated aq Na_2CO_3 (2 mL) was heated at 120°C for 30 min. After filtering off the solid, the solvent was removed, and the residue was dissolved in MeOH and DCM and was purified by preparative HPLC. The fractions were collected and the solvent was stripped to dryness via rotary evaporation to yield the title compound (40 mg, 44%). [M+H] calc'd for $C_{26}H_{31}FN_6O_4$, 511; found, 511.

[0636] B. (*R*)-2-(7-Fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide

[0637] A solution of (*R*)-2-(2-(2,4-dimethoxybenzyl)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide (39.8 mg, 0.078 mmol) in TFA (5 mL) was heated at 60°C for 2 h. After removal of solvent, the residue was diluted in MeOH (2 mL) and was purified by preparative HPLC. The fractions were collected and the solvent stripped to dryness via

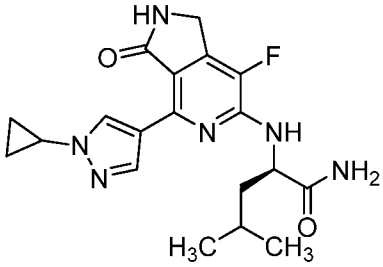
rotary evaporation to yield the title compound (12.8 mg, 46%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.82 - 1.00 (m, 6 H), 1.45 - 1.60 (m, 1 H), 1.67 - 1.83 (m, 2 H), 3.87 (s, 3 H), 4.36 (s, 2 H), 4.50 - 4.64 (m, 1 H), 6.88 - 7.02 (m, 2 H), 7.44 (s, 1 H), 8.28 (s, 2 H), 8.83 (s, 1 H). [M+H] calc'd for $C_{17}H_{21}FN_6O_2$, 361; found, 361.

[0638] EXAMPLE 71: (*R*)-2-(4-(1-(Difluoromethyl)-1*H*-pyrazol-4-yl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide



[0639] The title compound was prepared in a manner similar to EXAMPLE 70 using 1-(difluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole in place of 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.63 (br s, 1 H), 1.75 - 1.92 (m, 3 H), 2.00 - 2.29 (m, 2 H), 2.33 (dt, *J*=3.73, 1.80 Hz, 1 H), 2.62 - 2.74 (m, 1 H), 4.34 - 4.46 (m, 2 H), 4.57 (br s, 1 H), 4.81 (d, *J*=5.56 Hz, 2 H), 5.08 - 5.30 (m, 2 H), 5.93 - 6.10 (m, 1 H), 6.83 (d, *J*=6.06 Hz, 1 H), 8.22 (s, 1 H), 8.39 (s, 2 H), 8.84 - 9.05 (m, 1 H). [M+H] calc'd for $C_{17}H_{19}F_3N_6O_2$, 397; found, 397.

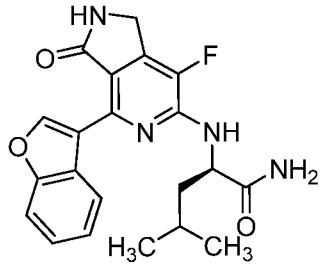
[0640] EXAMPLE 72: (*R*)-2-(4-(1-Cyclopropyl-1*H*-pyrazol-4-yl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide



[0641] The title compound was prepared in a manner similar to EXAMPLE 70 using 1-cyclopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole in place of 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.70 - 1.07 (m, 7 H), 1.15 - 1.35 (m, 1 H), 1.48 - 1.64 (m, 1 H), 1.67 - 1.93 (m, 2 H), 4.25 - 4.43 (m, 2 H), 4.54 (d, *J*=9.60 Hz, 1 H), 4.79 (d, *J*=5.81 Hz, 1 H),

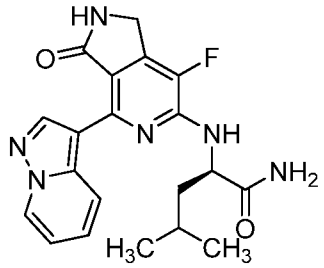
5.11 - 5.31 (m, 1 H), 5.91 - 6.16 (m, 1 H), 6.80 - 7.07 (m, 2 H), 7.42 (br s, 1 H), 8.25 (s, 1 H), 8.34 - 8.43 (m, 1 H), 8.83 - 8.97 (m, 1 H). [M+H] calc'd for $C_{19}H_{23}FN_6O_2$, 387; found, 387.

[0642] EXAMPLE 73: (*R*)-2-(4-(Benzofuran-3-yl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide



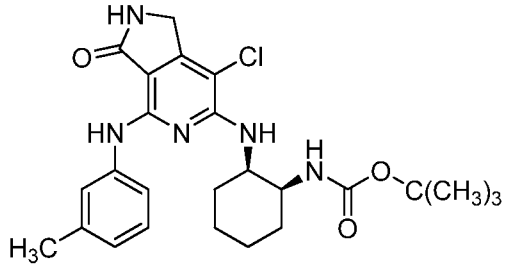
[0643] The title compound was prepared in a manner similar to EXAMPLE 70 using 2-(benzofuran-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane in place of 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.73 - 0.96 (m, 6 H), 1.57 - 1.91 (m, 3 H), 4.42 (s, 2 H), 4.63 - 4.77 (m, 1 H), 6.99 - 7.17 (m, 2 H), 7.24 - 7.42 (m, 3 H), 7.62 (d, *J*=7.83 Hz, 1 H), 8.32 - 8.48 (m, 2 H), 9.28 (s, 1 H). [M+H] calc'd for $C_{21}H_{21}FN_4O_3$, 397; found, 397.

[0644] EXAMPLE 74: (*R*)-2-(7-Fluoro-3-oxo-4-(pyrazolo[1,5-*a*]pyridin-3-yl)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide



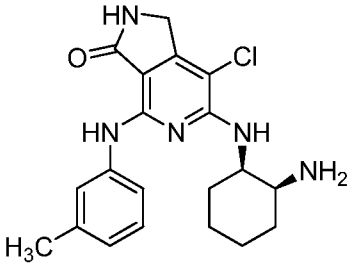
[0645] The title compound was prepared in a manner similar to EXAMPLE 70 using 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-*a*]pyridine in place of 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.77 - 0.99 (m, 6 H), 1.57 - 1.70 (m, 1 H), 1.71 - 1.90 (m, 2 H), 4.33 - 4.45 (m, 2 H), 4.56 - 4.68 (m, 1 H), 6.93 - 7.12 (m, 3 H), 7.27 - 7.42 (m, 2 H), 8.27 (s, 1 H), 8.47 (d, *J*=8.84 Hz, 1 H), 8.72 (d, *J*=6.82 Hz, 1 H), 9.30 (s, 1 H). [M+H] calc'd for $C_{20}H_{21}FN_6O_2$, 397; found, 397.

[0646] PREPARATION 29: *tert*-Butyl (1*S*,2*R*)-2-(7-chloro-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate



[0647] A vial was charged with *tert*-butyl (1*S*,2*R*)-2-(3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (63 mg, 0.140 mmol) and *N*-chlorosuccinimide (18.63 mg, 0.140 mmol) in DCM (1.4 mL) to give a yellow solution. The solution was stirred for 1 h at RT. The crude reaction mixture was diluted with DCM (20 mL) and washed with saturated aq $NaHCO_3$ (2 x 10 mL) followed by water (10 mL) and brine (10 mL). The organic layers were combined, dried over sodium sulfate, and concentrated to a residue which was purified by flash column chromatography. The collected fractions were concentrated to a brown residue to give the title compound as a cream colored solid upon drying (38.1 mg, 56%). [M+H] calc'd for $C_{25}H_{32}ClN_5O_3$, 486; found, 486.

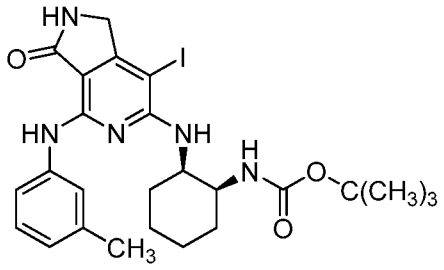
[0648] EXAMPLE 75: 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-chloro-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



[0649] To a solution of *tert*-butyl (1*S*,2*R*)-2-(7-chloro-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (20 mg, 0.041 mmol) in DCM (0.8 mL) was added trifluoroacetic acid (0.31 mL). The reaction mixture was stirred at RT for 1 h, then concentrated to a brown residue which was diluted in MeOH (2 mL) and purified via preparative HPLC to give a TFA salt of the title compound as a fluffy white solid (12.3 mg, 61.9%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.85 (s, 1 H), 8.36 (s, 1 H), 7.83 (br s, 3 H), 7.39 - 7.57 (m, 2 H), 7.12 - 7.32 (m, 1 H), 6.84 (d, *J*=7.6 Hz,

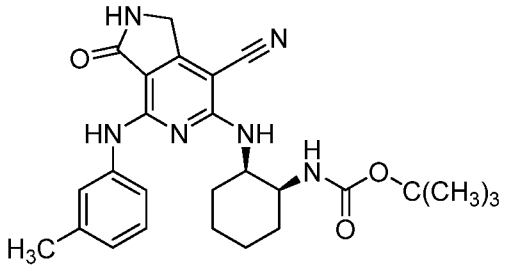
1 H), 6.22 (d, *J*=6.8 Hz, 1 H), 4.19 - 4.43 (m, 3 H), 3.71 (br s, 1 H), 2.32 (s, 3 H), 1.37 - 1.99 (m, 8 H). [M+H] calc'd for $C_{20}H_{24}ClN_5O$, 386; found, 386.

[0650] PREPARATION 30: *tert*-Butyl (1*S*,2*R*)-2-(7-iodo-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate



[0651] To a screw-top vial was added *tert*-butyl (1*S*,2*R*)-2-(3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (73 mg, 0.162 mmol) and 1-iodopyrrolidine-2,5-dione (36.4 mg, 0.162 mmol) in DCM (1.6 mL) to give a yellow solution. The reaction was stirred 0.5 h at RT. The reaction mixture was diluted with DCM (10 mL) and washed with saturated aq $NaHCO_3$ (10 mL), water (10 mL), and brine (10 mL). The collected organic layers were dried with sodium sulfate and concentrated to give the title compound as a brown solid, which was used without further purification (85.7 mg, 92%). [M+H] calc'd for $C_{25}H_{32}IN_5O_3$, 578; found, 578.

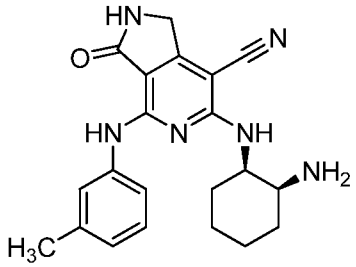
[0652] PREPARATION 31: *tert*-Butyl (1*S*,2*R*)-2-(7-cyano-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate



[0653] To an oven-dried microwave vial was added *tert*-butyl (1*S*,2*R*)-2-(7-iodo-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (47.0 mg, 0.081 mmol), dicyanozinc (5.74 mg, 0.049 mmol), zinc powder (0.532 mg, 8.14 μmol), dppf (0.451 mg, 0.814 μmol), and $Pd_2(dba)_3$ (0.745 mg, 0.814 μmol). *N*,*N*-Dimethylacetamide (814 μL) was added and the resulting dark brown solution was degassed with nitrogen for 3 min. The vial was capped and heated at 80°C with stirring for 1 h. The temperature was increased to 110°C, and the

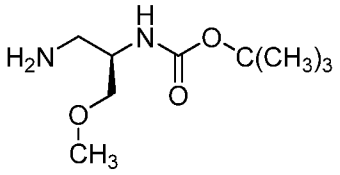
mixture was stirred for an additional 3 h, then cooled to RT, diluted with EtOAc (10 mL), and washed with water (2 x10 mL) and brine (10 mL). The organic phase was dried with sodium sulfate and concentrated to give the title compound as a brown residue, which was used without further purification (40mg, 103%). [M+H] calc'd for $C_{26}H_{32}N_6O_3$, 477; found, 477.

[0654] EXAMPLE 76: 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile

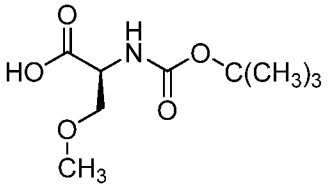


[0655] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 75 using *tert*-butyl (1*S*,2*R*)-2-(7-cyano-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate in place of *tert*-butyl (1*S*,2*R*)-2-(7-chloro-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.22 (s, 1 H), 8.48 (s, 1 H), 7.80 (br s, 3 H), 7.40 - 7.59 (m, 2 H), 7.26 (t, *J*=7.7 Hz, 1 H), 6.91 (dd, *J*=13.0, 6.9 Hz, 2 H), 4.43 (s, 2 H), 4.26 - 4.38 (m, 1 H), 3.68 (br s, 1 H), 2.33 (s, 3 H), 1.78 - 1.96 (m, 2 H), 1.35 - 1.79 (m, 6 H). [M+H] calc'd for $C_{21}H_{24}N_6O$, 377; found, 377.

[0656] PREPARATION 32: (*R*)-*tert*-Butyl 1-amino-3-methoxypropan-2-ylcarbamate



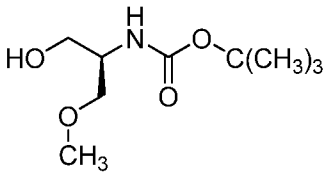
[0657] A. (*S*)-2-(*tert*-Butoxycarbonylamino)-3-methoxypropanoic acid



[0658] A sodium methanolate (NaOMe) solution was prepared by slowly adding MeOH (50 mL) to a suspension of sodium hydride (60% in mineral oil, 28 g, 0.71 mol) in

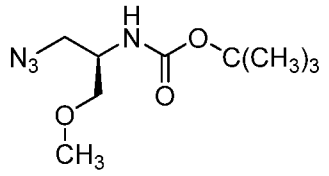
dry THF (1.2 L) at 0°C. The resulting mixture was stirred at RT for 2 h. A portion of the NaOMe solution (320 mL) was added to (*S*)-2-(*tert*-butoxycarbonylamino)-3-hydroxypropanoic acid (36 g, 175 mmol) in dry THF (1.6 L), and the mixture was stirred at RT for 1 h. Methyl iodine (16 mL) was then added and the mixture was stirred at RT for 1 h. Another aliquot of NaOMe solution (540 mL) was added and the reaction mixture stirred at RT for 1 h. Additional methyl iodine (38 mL) in THF (200 mL) was added and the reaction mixture was stirred at RT for 36 h. Following reaction, the mixture was concentrated and the residue was dissolved in water and washed with diethyl ether (2 x 100 mL). The aqueous layer was acidified to pH 2 by the addition of solid citric acid and was extracted with EtOAc (3 x 200 mL) and dried over Na_2SO_4. The organic phase was concentrated, and the residue was dissolved in water and extracted with DCM (4 x 150 mL). The organic layers were combined and concentrated to give the title compound as an oil, which was used without further purification (10.9 g, 28%).

[0659] B. (*R*)-*tert*-Butyl 1-hydroxy-3-methoxypropan-2-ylcarbamate



[0660] To a mixture of (*S*)-2-(*tert*-butoxycarbonylamino)-3-methoxypropanoic acid (10.9 g) and *N*-methylmorpholine (5.6 g, 55 mmol) in THF (50 mL) was added 2-methylpropylchloroformate (7.48 g, 55 mmol) in THF at -15°C. The reaction mixture was stirred -15°C for 15 min, after which $NaBH_4$ (6.0 g, 159 mmol) in water (10 mL) was added. The reaction mixture was stirred for 30 min, then diluted with EtOAc, and neutralized with dilute HCl. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel eluting with EtOAc and petroleum ether (EtOAc/PE = 1.5/1) to give the title compound (6.0 g, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.23 (s, 1 H), 3.80 (d, *J*=8.0 Hz, 2 H), 3.72-3.68 (m, 1 H), 3.60-3.52 (m, 2 H), 3.38 (s, 3 H), 2.85 (s, 1 H), 1.47 (s, 9 H).

[0661] C. (*R*)-*tert*-Butyl 1-azido-3-methoxypropan-2-ylcarbamate

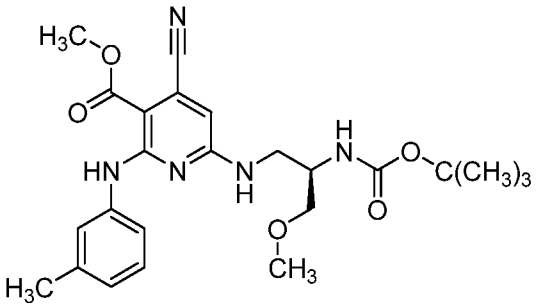


[0662] Methanesulfonyl chloride (4.0 g, 35 mmol) in DCM (50 mL) was slowly added to a solution of (*R*)-*tert*-butyl 1-hydroxy-3-methoxypropan-2-ylcarbamate (6.0 g, 29 mmol) and Et_3N (3.64 g, 36 mmol) in DCM (150 mL) at 0°C. The reaction mixture was stirred at RT for 2 h. The organic phase was washed with water and saturated aq $NaHCO_3$, concentrated, and dissolved in DMF. Sodium azide (2.34 g, 36.0 mmol) was added, and the reaction mixture was stirred at 75°C for 4 h. The reaction mixture was diluted by EtOAc and washed with water. The crude product was purified by column chromatography on silica gel eluting with EtOAc and petroleum ether (EtOAc/PE = 2/1) to give the title compound (4.3 g, 64%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 4.92 (s, 1 H), 3.91 (m, 1 H), 3.53-3.48 (m, 2 H), 3.45-3.40 (m, 2 H), 3.38 (s, 3 H), 1.47 (s, 9 H).

[0663] D. (*R*)-*tert*-Butyl 1-amino-3-methoxypropan-2-ylcarbamate

[0664] A mixture of (*R*)-*tert*-butyl 1-azido-3-methoxypropan-2-ylcarbamate (4.3 g, 18.7 mmol) and 10% Pd/C (1.5 g) in MeOH was stirred at RT under H_2 atmosphere overnight. After filtration, the crude product was purified by amino-protected silica gel chromatography eluting with EtOAc and petroleum ether (EtOAc/PE = 1/1) to give the title compound (740 mg, 19.4%). ^1H NMR (400 MHz, CD_3OD) δ ppm 5.00 (s, 1 H), 3.67-3.66 (m, 1 H), 3.51-3.47 (m, 1 H), 3.42-3.38 (m, 1 H), 3.35 (s, 1 H), 2.82-2.78 (m, 2 H), 1.46 (s, 9 H). [M+H] calc'd for $C_9H_{20}N_2O_3$, 205; found, 205.

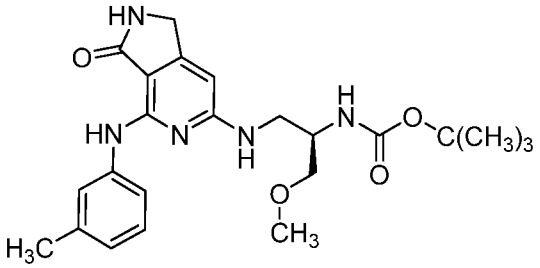
[0665] PREPARATION 33: (*R*)-Methyl 6-(2-(*tert*-butoxycarbonylamino)-3-methoxypropylamino)-4-cyano-2-(*m*-tolylamino)nicotinate



[0666] To a screw-top vial was added methyl 6-chloro-4-cyano-2-(m-tolylamino)nicotinate (0.28 g, 0.928 mmol), (*R*)-*tert*-Butyl 1-amino-3-methoxypropan-2-ylcarbamate (0.227 g, 1.114 mmol), and DIPEA (0.211 mL, 1.206 mmol) in DMF (3 mL). The resulting yellow solution was stirred at RT for 12 h, diluted with EtOAc (30 mL) and washed with water (2 x 20 mL) and brine (20 mL). The organic phase was dried with

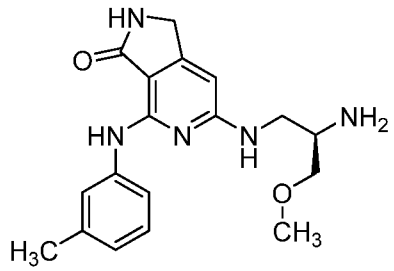
Na_2SO_4 and concentrated to give the title compound as thick yellow oil, which was used without further purification (470 mg). [M+H] calc'd for $C_{24}H_{31}N_5O_5$, 470; found, 470.

[0667] PREPARATION 34: (*R*)-*tert*-Butyl 1-methoxy-3-(3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)propan-2-ylcarbamate



[0668] To a round-bottomed flask was added (*R*)-methyl 6-(2-(*tert*-butoxycarbonylamino)-3-methoxypropylamino)-4-cyano-2-(*m*-tolylamino)nicotinate (84.5 mg, 0.180 mmol) in acetic acid (3 mL) and DCM (10 mL). To the resulting yellow solution was added platinum(IV) oxide (4.09 mg, 0.018 mmol). The flask was evacuated and back filled with hydrogen (3 x 1 atm). The reaction mixture was stirred vigorously at RT for 16 h, subsequently diluted with DCM (10 mL), and filtered through Celite. The filtrate was concentrated to an oil, which was diluted with DCM (10 mL). Potassium carbonate (24.87 mg, 0.180 mmol) was added and the reaction mixture was stirred at RT for 12 h. The crude reaction was diluted with DCM (10 mL), filtered through Celite, and concentrated to give the title compound as a thick yellow oil, which was used without further purification (26.5 mg, 33.4%). [M+H] calc'd for $C_{23}H_{31}N_5O_4$, 442; found, 442.

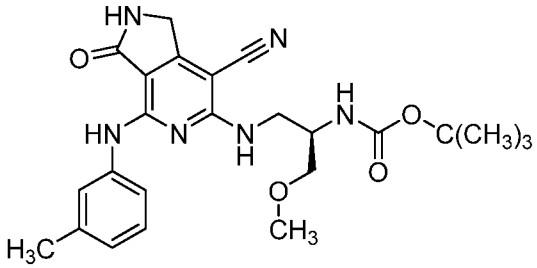
[0669] EXAMPLE 77: (*R*)-6-(2-Amino-3-methoxypropylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



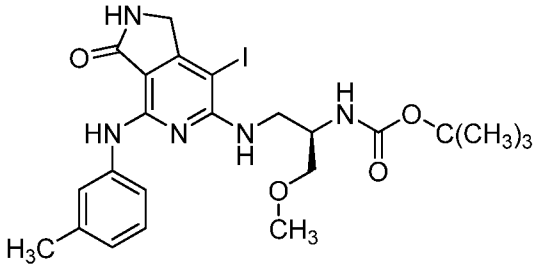
[0670] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 75 using (*R*)-*tert*-butyl 1-methoxy-3-(3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)propan-2-ylcarbamate in place of *tert*-butyl (1*S*,2*R*)-2-(7-chloro-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-

ylamino)cyclohexylcarbamate. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.57 (d, *J*=8.3 Hz, 1 H), 7.36 (s, 1 H), 7.22 (t, *J*=7.8 Hz, 1 H), 6.87 (d, *J*=7.3 Hz, 1 H), 6.07 (s, 1 H), 4.30 (s, 2 H), 3.70 - 3.82 (m, 2 H), 3.50 - 3.65 (m, 3 H), 3.40 (s, 3 H), 2.35 (s, 3 H). [M+H] calc'd for $C_{18}H_{23}N_5O_2$, 342; found, 342.

[0671] PREPARATION 35: (*R*)-*tert*-Butyl 1-(7-cyano-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-3-methoxypropan-2-ylcarbamate



[0672] A. (*R*)-*tert*-Butyl 1-(7-iodo-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-3-methoxypropan-2-ylcarbamate

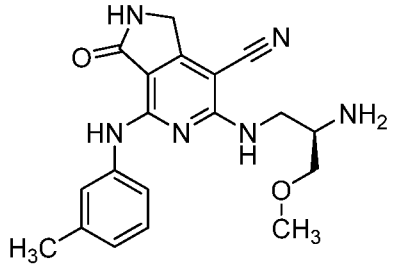


[0673] The title compound was prepared in a manner similar to PREPARATION 30 using (*R*)-*tert*-butyl 1-methoxy-3-(3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)propan-2-ylcarbamate in place of *tert*-butyl (1*S*,2*R*)-2-(3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate. [M+H] calc'd for $C_{23}H_{30}IN_5O_4$, 568; found, 568.

[0674] B. (*R*)-*tert*-Butyl 1-(7-cyano-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-3-methoxypropan-2-ylcarbamate

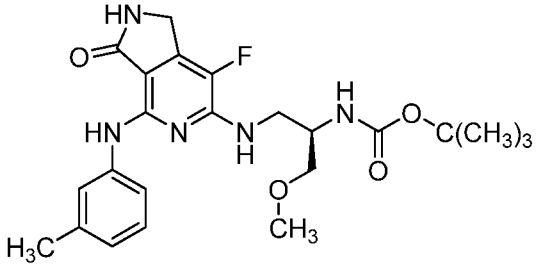
[0675] The title compound was prepared in a manner similar to PREPARATION 31 using (*R*)-*tert*-butyl 1-(7-iodo-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-3-methoxypropan-2-ylcarbamate in place of *tert*-butyl (1*S*,2*R*)-2-(7-iodo-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate. [M+H] calc'd for $C_{24}H_{30}N_6O_4$, 467; found, 467.

[0676] EXAMPLE 78: (*R*)-6-(2-Amino-3-methoxypropylamino)-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile



[0677] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 75 using (*R*)-*tert*-butyl 1-(7-cyano-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-3-methoxypropan-2-ylcarbamate in place of *tert*-butyl (1*S*,2*R*)-2-(7-chloro-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.25 (s, 1 H), 8.47 (s, 1 H), 7.93 (br s, 3 H), 7.58 (d, *J*=7.8 Hz, 1 H), 7.51 (t, *J*=5.4 Hz, 1 H), 7.42 (s, 1 H), 7.27 (t, *J*=7.8 Hz, 1 H), 6.93 (d, *J*=7.3 Hz, 1 H), 4.43 (s, 2 H), 3.71 - 3.80 (m, 1 H), 3.60 - 3.70 (m, 1 H), 3.44 - 3.60 (m, 3 H), 3.29 (s, 3 H), 2.33 (s, 3 H). [M+H] calc'd for $C_{19}H_{22}N_6O_2$, 367; found, 367.

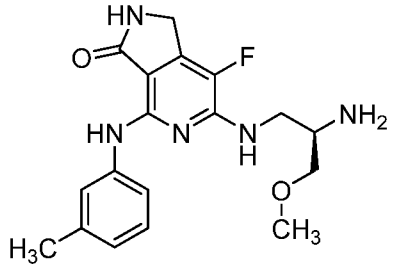
[0678] PREPARATION 36: (*R*)-*tert*-Butyl 1-(7-fluoro-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-3-methoxypropan-2-ylcarbamate



[0679] To a screw-top vial was added (*R*)-*tert*-butyl 1-methoxy-3-(3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)propan-2-ylcarbamate (27 mg, 0.061 mmol) in a mixture of DCM and MeOH (1/1, 1.2 mL). The resulting colorless solution was cooled to 0°C. SELECTFLUOR® (21.66 mg, 0.061 mmol) was added and the reaction mixture was stirred at 0°C for 2 h. Next, the reaction mixture was diluted with EtOAc (10 mL) and washed with saturated aq sodium bicarbonate (5 mL), water (5 mL), and brine (5 mL). The organic layer was collected, dried over Na_2SO_4, and concentrated to

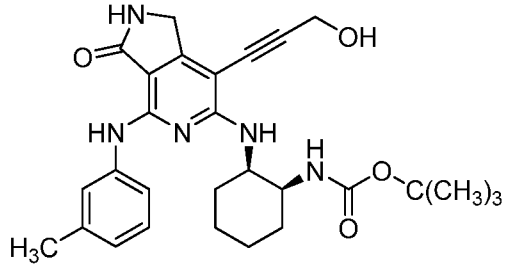
give the title compound as a brown residue, which was used without further purification (32 mg, 114%). [M+H] calc'd for $C_{23}H_{30}FN_5O_4$, 460; found, 460.

[0680] EXAMPLE 79: (*R*)-6-(2-Amino-3-methoxypropylamino)-7-fluoro-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



[0681] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 75 using (*R*)-*tert*-butyl 1-(7-fluoro-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-3-methoxypropan-2-ylcarbamate in place of *tert*-butyl (1*S*,2*R*)-2-(7-chloro-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.84 (s, 1 H), 8.28 (s, 1 H), 7.97 (br s, 3 H), 7.47 - 7.62 (m, 1 H), 7.40 (s, 1 H), 7.11 - 7.29 (m, 2 H), 6.80 (d, *J*=7.6 Hz, 1 H), 4.40 (s, 2 H), 3.62 - 3.78 (m, 2 H), 3.46 - 3.61 (m, 3 H), 3.31 (s, 3 H), 2.31 (s, 3 H). [M+H] calc'd for $C_{18}H_{22}FN_5O_2$, 360; found, 360.

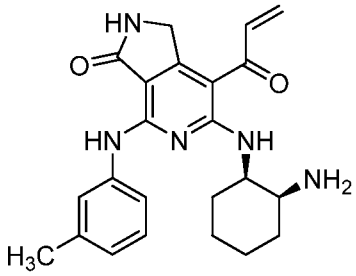
[0682] PREPARATION 37: *tert*-Butyl (1*S*,2*R*)-2-(7-(3-hydroxyprop-1-ynyl)-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate



[0683] To an oven dried glass pressure vessel was added *tert*-butyl (1*S*,2*R*)-2-(7-iodo-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (25 mg, 0.043 mmol), copper(I) iodide (12.37 mg, 0.065 mmol), bis(triphenylphosphine) palladium(II)chloride (9.12 mg, 0.013 mmol), butylated hydroxytoluene (one granule), THF (866 μL), and Et_3N (121 μL, 0.866 mmol). The mixture was degassed 3 min with nitrogen. Propargyl alcohol (31 μL, 0.520 mmol) was added and the vessel was capped and heated at 80°C with stirring for 2 h and then at RT

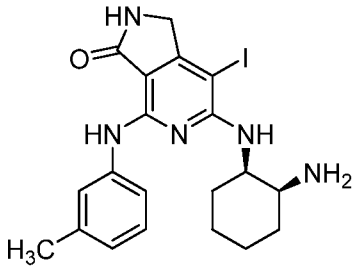
for 12 h. The reaction mixture was diluted with EtOAc (10 mL) and washed with water (5mL) and brine (5 mL). The organic layer was collected, dried with Na_2SO_4, and concentrated to give the title compound as a brown residue, which was used without further purification (22 mg, 101%). [M+H] calc'd for $C_{28}H_{35}N_5O_4$, 506; found, 506.

[0684] EXAMPLE 80: 7-Acryloyl-6-((1*R*,2*S*)-2-aminocyclohexylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



[0685] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 75 using *tert*-butyl (1*S*,2*R*)-2-(7-(3-hydroxyprop-1-ynyl)-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate in place of *tert*-butyl (1*S*,2*R*)-2-(7-chloro-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.53 (d, *J*=7.8 Hz, 1 H), 9.81 (s, 1 H), 8.65 (s, 1 H), 7.85 (br s, 3 H), 7.60 (s, 1 H), 7.51 (s, 1 H), 7.27 (t, *J*=7.8 Hz, 1 H), 7.08 (dd, *J*=16.5, 10.5 Hz, 1 H), 6.93 (d, *J*=7.6 Hz, 1 H), 6.19 (dd, *J*=16.7, 2.0 Hz, 1 H), 5.68 - 5.90 (m, 1 H), 4.50 - 4.80 (m, 3 H), 3.65 (br s, 1 H), 2.34 (s, 3 H), 1.78 - 2.01 (m, 2 H), 1.75 (s, 3 H), 1.43 - 1.58 (m, 3 H). [M+H] calc'd for $C_{23}H_{27}N_5O_2$, 406; found, 406.

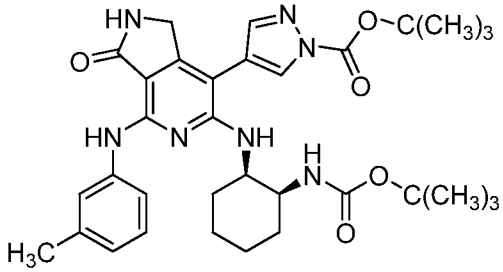
[0686] EXAMPLE 81: 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-iodo-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



[0687] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 75 using *tert*-butyl (1*S*,2*R*)-2-(7-iodo-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate in place of *tert*-butyl (1*S*,2*R*)-2-

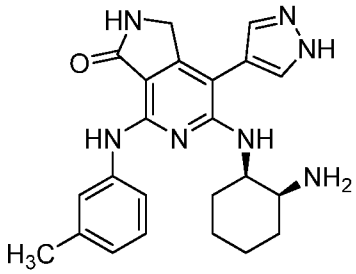
(7-chloro-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.48 (d, *J*=8.1 Hz, 1 H), 7.39 (s, 1 H), 7.23 (t, *J*=7.8 Hz, 1 H), 6.90 (d, *J*=7.6 Hz, 1 H), 4.47 (d, *J*=9.1 Hz, 1 H), 4.18 (d, *J*=3.0 Hz, 2 H), 3.80 - 3.87 (m, 1 H), 2.36 (s, 3 H), 1.87 (d, *J*=5.6 Hz, 4 H), 1.66 (br s, 4 H). [M+H] calc'd for $C_{20}H_{24}IN_5O$, 478; found, 478.

[0688] PREPARATION 38: *tert*-Butyl 4-(6-((1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclohexylamino)-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-7-yl)-1*H*-pyrazole-1-carboxylate



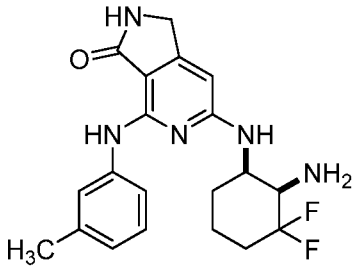
[0689] To an oven dried vial was added *tert*-butyl (1*S*,2*R*)-2-(7-iodo-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (40 mg, 0.069 mmol), *tert*-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole-1-carboxylate (30.6 mg, 0.104 mmol), and sodium carbonate (0.104 mL, 0.208 mmol) in DMF (1 mL). The resulting tan mixture was degassed 15 min. Bis(triphenylphosphine) palladium(II)chloride (4.86 mg, 6.93 μmol) was added and the mixture was degassed an additional 5 min. The vial was capped and was heated at 80°C for 12 h. The reaction mixture was diluted with EtOAc (10 mL) and washed with water (5 mL) and brine (5mL). The organic layer was collected, dried with Na_2SO_4 and concentrated to give a brown residue, which was used without further purification (55 mg). LCMS indicated the desired mass less one of the Boc protecting groups. [M+H-Boc] calc'd for $C_{33}H_{43}N_7O_5$, 518; found, 518.

[0690] EXAMPLE 82: 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-(1*H*-pyrazol-4-yl)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

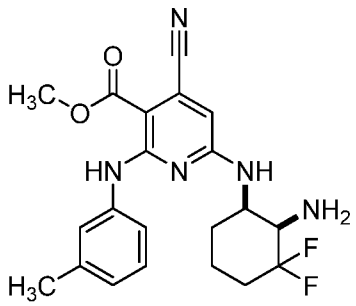


[0691] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 75 using *tert*-Butyl 4-(6-((1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclohexylamino)-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-7-yl)-1*H*-pyrazole-1-carboxylate in place of *tert*-butyl (1*S*,2*R*)-2-(7-chloro-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.13 (br s, 1 H), 8.97 (s, 1 H), 8.19 (s, 1 H), 8.06 (br s, 1 H), 7.75 (br s, 4 H), 7.42 - 7.58 (m, 2 H), 7.21 (t, *J*=8.1 Hz, 1 H), 6.81 (d, *J*=7.3 Hz, 1 H), 5.55 (d, *J*=6.6 Hz, 1 H), 4.25 (s, 3 H), 3.77 (br s, 1 H), 2.32 (s, 3 H), 1.63 - 1.89 (m, 4 H), 1.36 - 1.63 (m, 4 H). [M+H] calc'd for C23H27N7O, 418; found, 418.

[0692] EXAMPLE 83: 6-(*cis*-2-Amino-3,3-difluorocyclohexylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



[0693] A. Methyl 6-(*cis*-2-Amino-3,3-difluorocyclohexylamino)-4-cyano-2-(*m*-tolylamino)nicotinate

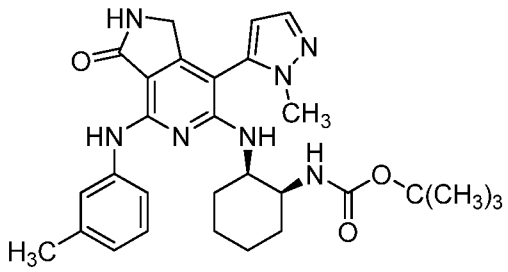


[0694] To a screw-cap vial was added methyl 6-chloro-4-cyano-2-(*m*-tolylamino)nicotinate (200 mg, 0.663 mmol), *cis*-3,3-difluorocyclohexane-1,2-diamine hydrochloride (148 mg, 0.795 mmol), and DIPEA (347 μL, 1.989 mmol) in DMF (3.9 mL). The resulting brownish-yellow mixture was stirred at RT for 2 h and then at 60°C for 12 h. The reaction mixture was cooled to RT, diluted with EtOAc (30 mL) and washed with water (2 x 10 mL) and brine (20 mL). The organic layer was collected, dried over Na_2SO_4, and concentrated to give a thick brown oil, which included the title compound and isomers (328 mg, 119%). The crude product was used without further purification. [M+H] calc'd for $C_{21}H_{23}F_2N_5O_2$, 416; found, 416.

[0695] B. 6-(*cis*-2-Amino-3,3-difluorocyclohexylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

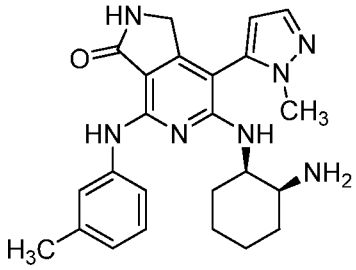
[0696] A round-bottomed flask was charged with methyl 6-(*cis*-2-amino-3,3-difluorocyclohexylamino)-4-cyano-2-(*m*-tolylamino)nicotinate (275 mg, 0.662 mmol) in HOAc (2.6 mL) and DCM (10.6 mL). To the resulting brown solution was added platinum(IV) oxide (15.03 mg, 0.066 mmol). The flask was evacuated and back filled with hydrogen (3 x 1 atm). The reaction mixture was stirred vigorously under H_2 atmosphere (1 atm) at RT for 16 h and then filtered through Celite. The filtrate was washed with DCM (20 mL) and concentrated to a residue, which was diluted in MeOH (3 mL) and purified via preparative HPLC to give a TFA salt of the title compound as a light green solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.97 (s, 1 H), 8.48 (br s, 3 H), 8.09 (s, 1 H), 7.62 (d, *J*=8.8 Hz, 1 H), 7.32 (s, 1 H), 7.14 (t, *J*=7.8 Hz, 1 H), 6.87 (br s, 1 H), 6.79 (d, *J*=7.3 Hz, 1 H), 6.15 (s, 1 H), 4.45 (br s, 1 H), 4.24 (d, 2 H), 4.15 (br s, 1 H), 2.29 (s, 3 H), 2.01 - 2.25 (m, 2 H), 1.74 - 1.89 (m, 3 H), 1.60 (d, *J*=10 Hz, 1 H). [M+H] calc'd for $C_{20}H_{23}F_2N_5O$, 388; found, 388.

[0697] PREPARATION 39: *tert*-Butyl (1*S*,2*R*)-2-(7-(1-methyl-1*H*-pyrazol-5-yl)-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate



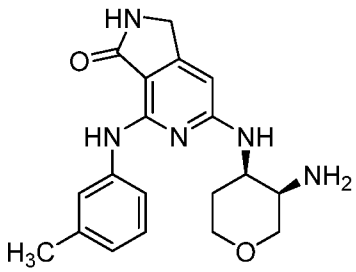
[0698] The title compound was prepared in a manner similar to PREPARATION 36 using 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole in place of *tert*-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole-1-carboxylate. [M+H] calc'd for $C_{29}H_{37}N_7O_3$, 532; found, 532.

[0699] EXAMPLE 84: 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-(1-methyl-1*H*-pyrazol-5-yl)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

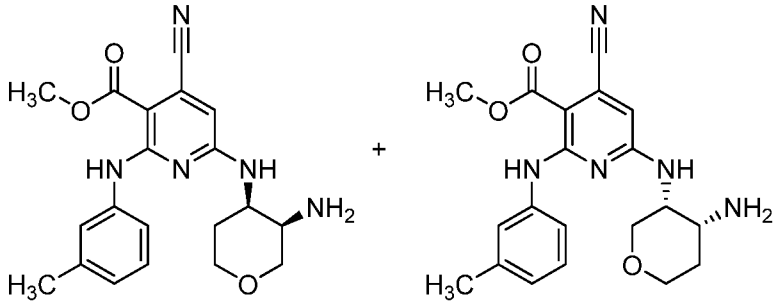


[0700] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 75 using *tert*-butyl (1*S*,2*R*)-2-(7-(1-methyl-1*H*-pyrazol-5-yl)-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate in place of *tert*-butyl (1*S*,2*R*)-2-(7-chloro-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.33 (d, *J*=1.26 Hz, 3 H), 3.64 (d, *J*=14.15 Hz, 3 H), 3.89 - 4.00 (m, 1 H), 4.02 - 4.21 (m, 1 H), 5.23 - 5.58 (m, 1 H), 6.29 - 6.47 (m, 1 H), 6.85 (d, *J*=7.58 Hz, 1 H), 7.23 (td, *J*=7.77, 4.93 Hz, 1 H), 7.47 - 7.56 (m, 2 H), 7.58 (dd, *J*=9.35, 1.77 Hz, 1 H), 7.64 - 7.83 (m, 2 H), 8.21 (d, *J*=2.27 Hz, 1 H), 9.04 (s, 1 H). [M+H] calc'd for $C_{24}H_{29}N_7O$, 432; found, 432.

[0701] EXAMPLE 85: 6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



[0702] A. Methyl 6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-4-cyano-2-(*m*-tolylamino)nicotinate and Methyl 6-((3*R*,4*R*)-4-Aminotetrahydro-2*H*-pyran-3-ylamino)-4-cyano-2-(*m*-tolylamino)nicotinate



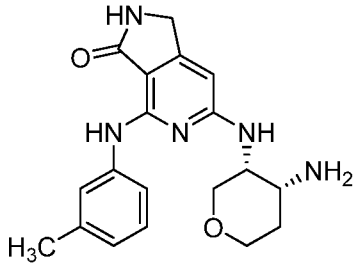
[0703] To a screw-cap vial was added methyl 6-chloro-4-cyano-2-(*m*-tolylamino)nicotinate (500 mg, 1.657 mmol), (3*R*,4*R*)-tetrahydro-2*H*-pyran-3,4-diamine hydrochloride (303.0 mg, 1.989 mmol), and DIPEA (868 μL, 4.97 mmol) in DMF (9748 μL). The resulting yellow suspension, which became a solution upon adding base, was stirred at 50°C for 12 h. The reaction mixture was cooled to RT, diluted with EtOAc (30 mL), and washed with water (20 mL) and brine (20 mL). The organic layer was collected, dried with Na_2SO_4, and concentrated to give a yellow oil, which included the title compounds (350 mg, 55.4%). The crude product was used in the next step without further purification. [M+H] calc'd for $C_{20}H_{23}N_5O_3$, 382; found, 382.

[0704] B. 6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

[0705] To a 50 mL round-bottomed flask was added a mixture of methyl 6-((3*R*,4*R*)-3-aminotetrahydro-2*H*-pyran-4-ylamino)-4-cyano-2-(*m*-tolylamino)nicotinate and methyl 6-((3*R*,4*R*)-4-aminotetrahydro-2*H*-pyran-3-ylamino)-4-cyano-2-(*m*-tolylamino)nicotinate (100 mg, 0.262 mmol) and platinum(IV) oxide (11.91 mg, 0.052 mmol) in DCM (4195 μL) and HOAc (1049 μL). The vessel was evacuated and back filled with hydrogen (1 atm) and the mixture was stirred at RT for 12 h. The reaction mixture was diluted with

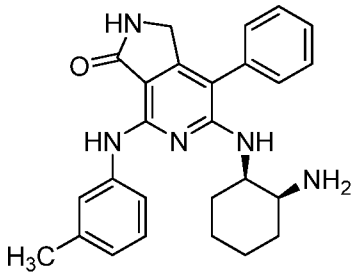
DCM (10 mL) and MeOH (20 mL), filtered through Celite, and concentrated to a residue, which was diluted with DCM (50 mL). Potassium carbonate (217 mg, 1.573 mmol) was added and the mixture was stirred at RT for 12 h. The mixture was filtered through Celite, concentrated to a residue, diluted with a mixture of DMF and MeOH (1/1, 3mL), and purified via preparative HPLC. The appropriate isomer peak was collected and lyophilized to give a TFA salt of the title compound as a light grey solid (20.3 mg, 21.9%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.92 (s, 1 H), 8.05 (s, 1 H), 7.95 (br s, 3 H), 7.50 (d, *J*=8.1 Hz, 1 H), 7.43 (s, 1 H), 7.21 (t, *J*=7.8 Hz, 1 H), 7.09 (d, *J*=4.8 Hz, 1 H), 6.80 (d, *J*=7.6 Hz, 1 H), 6.11 (s, 1 H), 4.20 - 4.32 (m, 3 H), 3.91 - 4.06 (m, 2 H), 3.76 (br s, 1 H), 3.53 - 3.72 (m, 2 H), 2.31 (s, 3 H), 1.99 (qd, *J*=12.6, 4.7 Hz, 1 H), 1.70 - 1.80 (m, 1 H). [M+H] calc'd for $C_{19}H_{23}N_5O_2$, 354; found, 354.

[0706] EXAMPLE 86: 6-((3*R*,4*R*)-4-Aminotetrahydro-2*H*-pyran-3-ylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



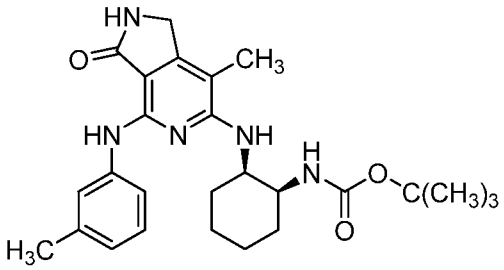
[0707] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 85, collecting the fractions corresponding to 6-((3*R*,4*R*)-4-aminotetrahydro-2*H*-pyran-3-ylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one in place 6-((3*R*,4*R*)-3-aminotetrahydro-2*H*-pyran-4-ylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.91 (s, 1 H), 7.94 - 8.15 (m, 4 H), 7.52 (s, 1 H), 7.43 (d, *J*=8.3 Hz, 1 H), 7.18 (t, *J*=7.8 Hz, 1 H), 7.03 (d, *J*=8.3 Hz, 1 H), 6.79 (d, *J*=7.6 Hz, 1 H), 6.21 (s, 1 H), 4.44 (br s, 1 H), 4.20 - 4.30 (m, 2 H), 3.84 - 3.95 (m, 2 H), 3.67 - 3.81 (m, 1 H), 3.62 (dd, *J*=11.6, 1.8 Hz, 1 H), 3.50 (td, *J*=11.2, 2.4 Hz, 1 H), 2.30 (s, 3 H), 1.98 - 2.13 (m, 1 H), 1.71 - 1.82 (m, 1 H). [M+H] calc'd for $C_{19}H_{23}N_5O_2$, 354; found, 354.

[0708] EXAMPLE 87: *tert*-Butyl (1*S*,2*R*)-2-(3-oxo-7-phenyl-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate



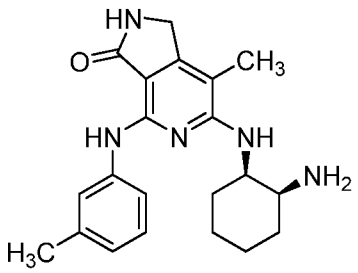
[0709] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 82 using phenylboronic acid in place of *tert*-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole-1-carboxylate. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.03 (s, 1 H), 8.15 (s, 1 H), 7.72 (br s, 3 H), 7.51 (d, *J*=4.5 Hz, 6 H), 7.35 - 7.45 (m, 1 H), 7.22 (dd, *J*=8.7, 7.5 Hz, 1 H), 6.83 (d, *J*=7.6 Hz, 1 H), 5.33 (d, *J*=6.8 Hz, 1 H), 4.30 (br s, 1 H), 4.17 - 4.27 (m, 1 H), 4.04 (d, *J*=17.7 Hz, 1 H), 3.76 (br s, 1 H), 2.33 (s, 3 H), 1.59 - 1.85 (m, 4 H), 1.37 - 1.59 (m, 4 H). [M+H] calc'd for $C_{26}H_{29}N_5O$, 428; found, 428.

[0710] PREPARATION 40: *tert*-Butyl (1*S*,2*R*)-2-(7-methyl-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate



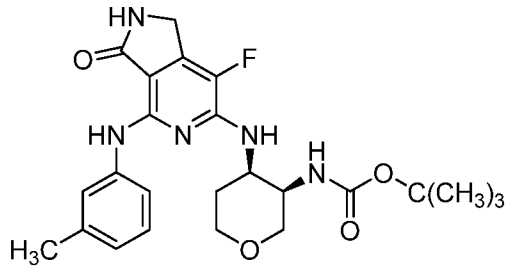
[0711] To an oven dry flask was added *tert*-butyl (1*S*,2*R*)-2-(7-bromo-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (40 mg, 0.075 mmol), 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (20.99 μL, 0.151 mmol), and potassium carbonate (31.3 mg, 0.226 mmol) in dioxane (1959 μL) and water (196 μL). The resulting tan solution was degassed with nitrogen for 5 min. Palladium chloride (dppf) (5.52 mg, 7.54 μmol) was added and the mixture was degassed for an additional 2 min. The vessel was capped and the reaction mixture was heated at 100°C with stirring overnight. The reaction mixture was cooled to RT, diluted with EtOAc (5 mL), and washed with water (5 mL) and brine (5 mL). The organic layer was collected, dried over Na_2SO_4 and concentrated to give the title compound as a brown viscous oil, which was used without purification (45 mg). [M+H] calc'd for $C_{26}H_{35}N_5O_3$, 466; found, 466.

[0712] EXAMPLE 88: 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-methyl-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

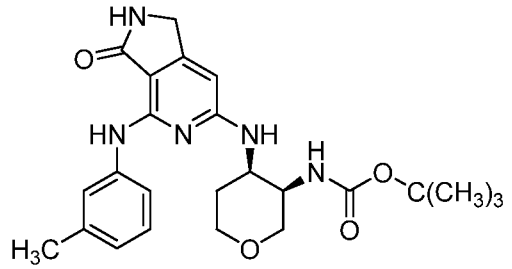


[0713] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 75 using *tert*-butyl (1*S*,2*R*)-2-(7-methyl-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate in place of *tert*-butyl (1*S*,2*R*)-2-(7-chloro-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.79 (s, 1 H), 8.10 (s, 1 H), 7.73 (br s, 3 H), 7.48 (d, *J*=2.0 Hz, 2 H), 7.14 - 7.21 (m, 1 H), 6.77 (d, *J*=7.6 Hz, 1 H), 5.69 (d, *J*=6.6 Hz, 1 H), 4.36 (br s, 1 H), 4.18 - 4.29 (m, 2 H), 3.72 (br s, 1 H), 2.31 (s, 3 H), 2.01 (s, 3 H), 1.88 (d, *J*=9.1 Hz, 2 H), 1.55 - 1.79 (m, 4 H), 1.39 - 1.55 (m, 2 H). [M+H] calc'd for $C_{21}H_{27}N_5O$, 366; found, 366.

[0714] PREPARATION 41: *tert*-Butyl (3*R*,4*R*)-4-(7-fluoro-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)tetrahydro-2*H*-pyran-3-ylcarbamate



[0715] A. *tert*-Butyl (3*R*,4*R*)-4-(3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)tetrahydro-2*H*-pyran-3-ylcarbamate

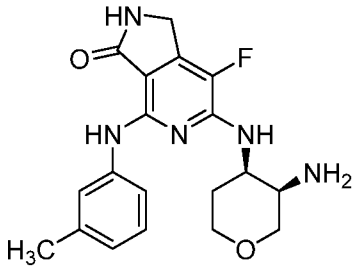


[0716] To a suspension of 6-((3*R*,4*R*)-3-aminotetrahydro-2*H*-pyran-4-ylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one (13.0 mg, 0.037 mmol) in DCM (368 μL) was added Et_3N (6.05 μL, 0.043 mmol) and di-*tert*-butyl dicarbonate (Boc anhydride) (39.0 μL, 0.039 mmol). The suspension was sonicated for 5 min and then stirred at RT for 12 h. The solution was diluted with DCM (15 mL) and washed with water (10 mL) and brine (10 mL). The organic layer was collected, dried over Na_2SO_4 and concentrated to give the title compound as a light yellow residue, which was used without further purification (15.2 mg, 91%). [M+H] calc'd for $C_{24}H_{31}N_5O_4$, 454; found, 454.

[0717] B. *tert*-Butyl (3*R*,4*R*)-4-(7-fluoro-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)tetrahydro-2*H*-pyran-3-ylcarbamate

[0718] To a screw-cap vial was added *tert*-butyl (3*R*,4*R*)-4-(3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)tetrahydro-2*H*-pyran-3-ylcarbamate (15.2 mg, 0.034 mmol) and SELECTFLUOR® (11.87 mg, 0.034 mmol) in DCM (335 μL) and MeOH (335 μL). The reaction mixture was stirred at RT for 2 h, diluted with EtOAc (10 mL) and washed with saturated aq $NaHCO_3$ (5 mL), water (5 mL), and brine (5 mL). The organic layer was collected, concentrated to a residue, and purified via preparative HPLC. The appropriate fractions were collected and concentrated to yield a TFA salt of the title compound as a colorless residue (4.2 mg, 26.6%). [M+H] calc'd for $C_{24}H_{30}FN_5O_4$, 472; found, 472.

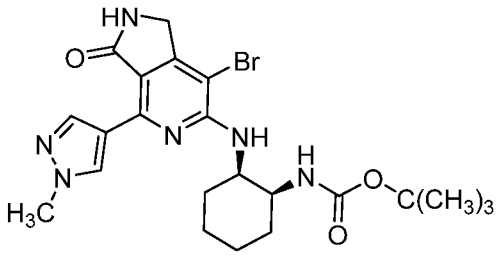
[0719] EXAMPLE 89: 6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



[0720] A solution of *tert*-butyl (3*R*,4*R*)-4-(7-fluoro-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)tetrahydro-2*H*-pyran-3-ylcarbamate (4.5 mg, 9.54 μmol) in 4 M HCl-dioxane (2 mL) was stirred for 0.5 h at RT. The reaction mixture was concentrated to a residue, which was diluted in DMF (1 mL) and purified via preparative HPLC. The appropriate fractions were collected and lyophilized to give a TFA

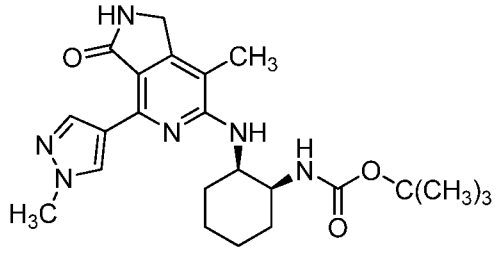
salt of the title compound as a white solid (2.6 mg, 73%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.81 (s, 1 H), 8.25 (s, 1 H), 7.57 (s, 1 H), 7.40 (d, *J*=8.1 Hz, 1 H), 7.04 - 7.28 (m, 2 H), 6.79 (d, *J*=7.3 Hz, 1 H), 6.62 - 6.76 (m, 2 H), 4.26 - 4.46 (m, 3 H), 3.85 - 3.96 (m, 2 H), 2.32 (s, 3 H), 1.94 - 2.13 (m, 1 H), 1.59 - 1.70 (m, 1 H), 1.07 - 1.28 (m, 4 H). [M+H] calc'd for $C_{19}H_{22}FN_5O_2$, 372; found, 372.

[0721] PREPARATION 42: *tert*-Butyl (1*S*,2*R*)-2-(7-bromo-4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate



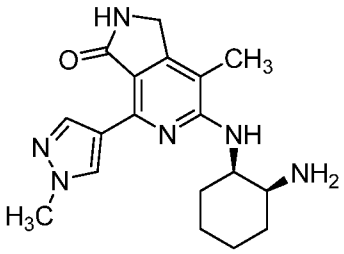
[0722] To a round bottomed flask was added *tert*-butyl (1*S*,2*R*)-2-(4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (124 mg, 0.291 mmol) in DCM (30 mL). The resulting white suspension was heated with a heat gun while stirring until all the starting material was dissolved. The solution was cooled to 0°C, and while stirring, 1-bromopyrrolidine-2,5-dione (51.7 mg, 0.291 mmol) was added. The reaction mixture was allowed to warm to RT and was stirred for 30 min. The solution was diluted with DCM (20 mL) and was washed with saturated aq $NaHCO_3$ (20 mL), water (20 mL), and brine (20 mL). The organic layer was collected and concentrated to an orange solid, which was treated with Et_2O (5 mL). Solids began to precipitate after the solution was allowed to sit undisturbed for 5 min. The mixture was allowed to sit for 1 h and was then filtered through paper. The solids were washed with Et_2O (5 mL) and collected to give the title compound as a tan solid (137.3 mg, 93%). [M+H] calc'd for $C_{22}H_{29}BrN6O_3$, 505; found, 505.

[0723] PREPARATION 43: *tert*-Butyl (1*S*,2*R*)-2-(7-methyl-4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate



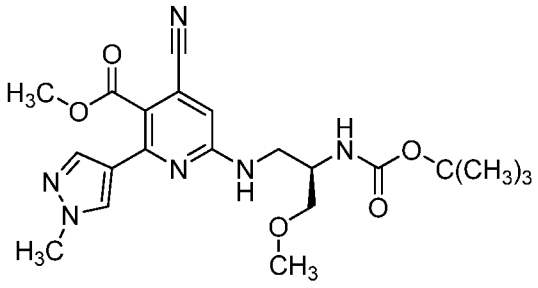
[0724] The title compound was prepared in a manner similar to PREPARATION 40 using *tert*-butyl (1*S*,2*R*)-2-(7-bromo-4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate in place of *tert*-butyl (1*S*,2*R*)-2-(7-bromo-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate. [M+H] calc'd for $C_{23}H_{32}N_6O_3$, 441; found, 441.

[0725] EXAMPLE 90: 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-methyl-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



[0726] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 89 using *tert*-butyl (1*S*,2*R*)-2-(7-methyl-4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate in place of *tert*-butyl (3*R*,4*R*)-4-(7-fluoro-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)tetrahydro-2*H*-pyran-3-ylcarbamate. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.87 (s, 1 H), 8.30 (s, 1 H), 8.17 (s, 1 H), 7.71 (br s, 3 H), 5.71 (d, *J*=6.3 Hz, 1 H), 4.49 (d, *J*=2.8 Hz, 1 H), 4.24 (s, 2 H), 3.91 (br s, 3 H), 3.71 (br s, 1 H), 2.08 (s, 3 H), 1.77 - 1.93 (m, 3 H), 1.69 (d, *J*=8.6 Hz, 3 H), 1.40 - 1.53 (m, 2 H). [M+H] calc'd for $C_{18}H_{24}N_6O$, 341; found, 341.

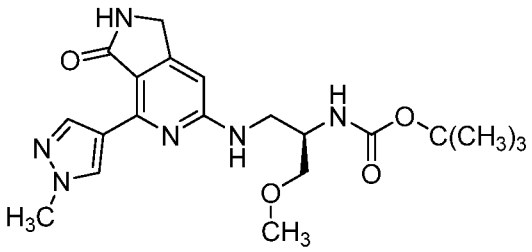
[0727] PREPARATION 44: (*R*)-Methyl 6-(2-(*tert*-butoxycarbonylamino)-3-methoxypropylamino)-4-cyano-2-(1-methyl-1*H*-pyrazol-4-yl)nicotinate



[0728] To a screw-top vial was added methyl 6-chloro-4-cyano-2-(1-methyl-1*H*-pyrazol-4-yl)nicotinate (115 mg, 0.416 mmol), (*R*)-*tert*-butyl 1-amino-3-methoxypropan-2-ylcarbamate (93 mg, 0.457 mmol), and DIPEA (87 μL, 0.499 mmol) in DMF (308 μL).

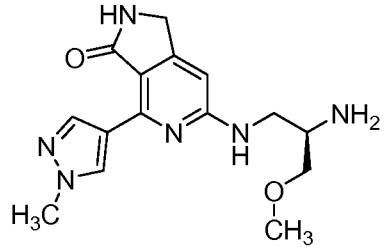
The resulting yellow solution was stirred for 12 h at 45°C and then at 50°C for 6 h. The reaction mixture was diluted with EtOAc (20 mL) and was washed with water (10 mL) and brine (20 mL). The organic layer was collected and dried over Na_2SO_4 and was concentrated to a yellow oil. The concentrate was purified via standard phase column chromatography eluting with EtOAc and hexanes (50-100% EtOAc gradient) to give the title compound as a light yellow residue (36.5 mg, 20%). [M+H] calc'd for $C_{21}H_{28}N_6O_5$, 445; found, 445.

[0729] PREPARATION 45: (*R*)-*tert*-Butyl 1-methoxy-3-(4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)propan-2-ylcarbamate



[0730] The title compound was prepared in a manner similar to PREPARATION 34 using (*R*)-methyl 6-(2-(*tert*-butoxycarbonylamino)-3-methoxypropylamino)-4-cyano-2-(1-methyl-1*H*-pyrazol-4-yl)nicotinate in place of (*R*)-methyl 6-(2-(*tert*-butoxycarbonylamino)-3-methoxypropylamino)-4-cyano-2-(*m*-tolylamino)nicotinate (84.5 mg, 0.180 mmol). [M+H] calc'd for $C_{20}H_{28}N_6O_4$, 417; found, 417.

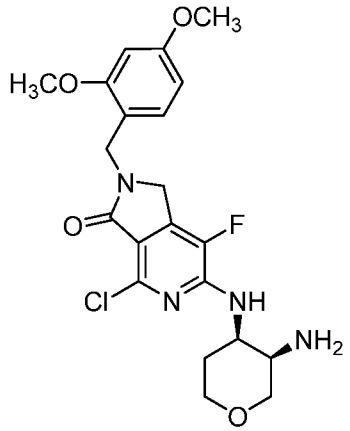
[0731] EXAMPLE 91: (*R*)-6-(2-Amino-3-methoxypropylamino)-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



[0732] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 89 using (*R*)-*tert*-butyl 1-methoxy-3-(4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)propan-2-ylcarbamate in place of *tert*-butyl (3*R*,4*R*)-4-(7-fluoro-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)tetrahydro-2*H*-pyran-3-ylcarbamate. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.97 (s, 1 H), 8.40 (s, 1 H), 8.09 (s, 1 H), 8.00 (br s, 3 H), 7.17 - 7.26 (m, 1 H), 6.42 (s, 1

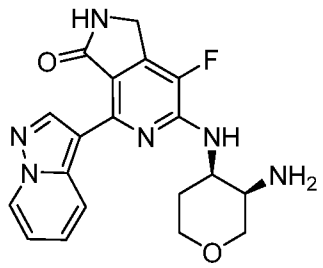
H), 4.24 (s, 2 H), 3.89 (s, 3 H), 3.54 - 3.60 (m, 5 H), 3.33 (s, 3H). [M+H] calc'd for $C_{15}H_{20}N_6O_2$, 317; found, 317.

[0733] PREPARATION 46: 6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-4-chloro-2-(2,4-dimethoxybenzyl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

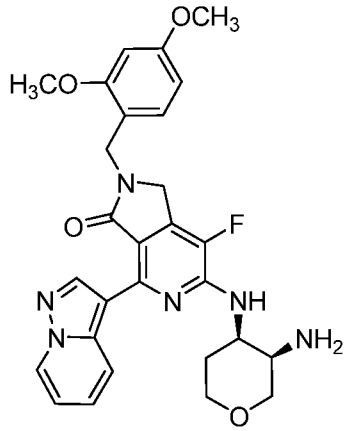


[0734] A mixture of 4,6-dichloro-2-(2,4-dimethoxybenzyl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one (2.5 g, 6.74 mmol), (3*R*,4*R*)-tetrahydro-2*H*-pyran-3,4-diamine (0.711 g, 6.12 mmol), and DIPEA (5.35 mL, 30.6 mmol) in ACN (30 mL) was stirred at 85°C for 3 d in a sealed tube. Additional (3*R*,4*R*)-tetrahydro-2*H*-pyran-3,4-diamine (0.356 g, 3.06 mmol) and DIPEA (2.14 mL, 12.2 mmol) were added and the mixture was heated at 100°C overnight. The mixture was concentrated and purified via preparative HPLC. The fractions corresponding to the desired regioisomer were collected to give the title compound (265 mg, 9.60%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.64-1.65 (m, 1 H), 1.80-1.82 (s, 1 H), 3.40 (td, *J*=11.47, 2.44 Hz, 1 H), 3.53 (dd, *J*=11.23, 1.95 Hz, 1 H), 3.67 (dd, *J*=11.47, 2.20 Hz, 1 H), 3.71-3.73 (m, 1 H), 3.75 (s, 3 H), 3.77-3.79 (m, 1 H), 3.81 (s, 3 H), 4.09-4.11 (m, 1 H), 4.33 (s, 2 H), 4.50 (s, 2 H), 6.48 (dd, *J*=8.30, 2.44 Hz, 1 H), 6.58 (d, J=2.44, 1 H), 6.90 (br s, 1 H), 7.06 (d, *J*=8.30 Hz, 1 H). [M+H] calc'd for $C_{21}H_{24}ClFN_4O_4$, 451; found, 451.

[0735] EXAMPLE 92: 6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(pyrazolo[1,5-*a*]pyridin-3-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



[0736] A. 6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-2-(2,4-dimethoxybenzyl)-7-fluoro-4-(pyrazolo[1,5-*a*]pyridin-3-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2H)-one

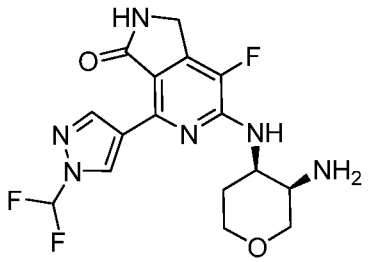


[0737] To a 5 mL microwave vial with a stir bar was added bis(triphenylphosphine)palladium chloride (11.68 mg, 0.017 mmol), 6-((3*R*,4*R*)-3-aminotetrahydro-2*H*-pyran-4-ylamino)-4-chloro-2-(2,4-dimethoxybenzyl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one (75 mg, 0.166 mmol), pyrazolo[1,5-*a*]pyridin-3-ylboronic acid (135 mg, 0.832 mmol) in dioxane (2 mL), and saturated aq $NaHCO_3$ (2 mL). The mixture was heated in a Biotage Initiator microwave at 120°C for 30 min. The mixture was concentrated and purified via preparative HPLC to give the title compound (89 mg, 100%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.82-1.84 (m, 1 H), 2.10-2.12 (m, 1 H), 3.68-3.72 (m, 3 H), 3.75 (s, 3 H), 3.82 (s, 3 H), 3.92-3.95 (m, 1 H), 4.01-4.02 (m, 1 H), 4.39 (s, 2 H), 4.55-4.58 (m, 1 H), 4.59 (s, 2 H), 6.50 (dd, *J*=8.30, 1.95 Hz, 1 H), 6.60 (d, *J*=2.44, 1 H), 7.04-7.08 (m, 2 H), 7.16 (d, *J*=5.86 Hz, 1 H), 7.48-7.51 (m, 1 H), 7.93 (br s, 1 H), 8.37 (d, *J*=9.27 Hz, 1 H), 8.79 (d, *J*=6.83 Hz, 1 H), 9.36 (s, 1 H). [M+H] calc'd for $C_{28}H_{29}FN_6O_4$, 533; found, 533.

[0738] B. 6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(pyrazolo[1,5-*a*]pyridin-3-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

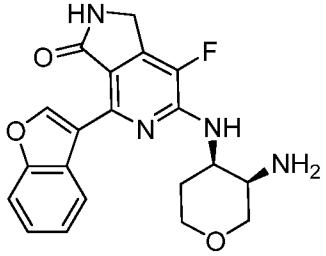
[0739] To a 25 mL round bottom flask with a stir bar was added 6-((3*R*,4*R*)-3-aminotetrahydro-2*H*-pyran-4-ylamino)-2-(2,4-dimethoxybenzyl)-7-fluoro-4-(pyrazolo[1,5-*a*]pyridin-3-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one (85 mg, 0.160 mmol) in TFA (5 mL). The mixture was heated at 60°C for 1.5 h and then cooled to RT. The mixture was concentrated and purified via preparative HPLC to give a TFA salt of the title compound as a white solid (27 mg, 44.2%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.83-1.85 (m, 1 H), 2.12-2.14 (m, 1 H), 3.65-3.73 (m, 2 H), 3.81-3.82 (m, 1 H), 3.93-3.95 (m, 1 H), 4.01-4.03 (m, 1 H), 4.43 (s, 2 H), 4.53-4.55 (m, 1 H), 7.04 (t, *J*=6.83 Hz, 1 H), 7.13 (d, *J*=4.88 Hz, 1 H), 7.49 (t, *J*=8.05 Hz, 1 H), 7.94 (br s, 1 H), 8.36-8.42 (m, 2 H), 8.78 (d, *J*=6.83 Hz, 1 H), 9.33 (s, 1 H). [M+H] calc'd for $C_{19}H_{19}FN_6O_2$, 383; found, 383.

[0740] EXAMPLE 93: 6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-4-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



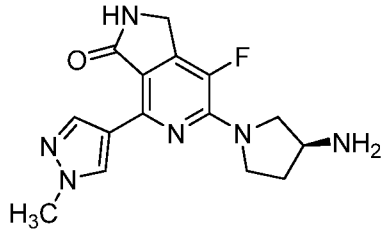
[0741] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 92 using 1-(difluoromethyl)-1*H*-pyrazol-4-ylboronic acid in place of pyrazolo[1,5-*a*]pyridin-3-ylboronic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.75-1.77 (m, 1 H), 2.09-2.12 (m, 1 H), 3.60-3.63 (m, 1 H), 3.76-3.77 (m, 1 H), 3.88-3.98 (m, 3 H), 4.44 (d, *J*=6.35 Hz, 2 H), 4.54-4.55 (m, 1 H), 7.17 (d, *J*=5.86 Hz, 1 H), 7.89 (br s, 1 H), 8.54 (s, 1 H), 8.58 (s, 1 H), 9.43 (s, 1 H). [M+H] calc'd for $C_{16}H_{17}F_3N_6O_2$, 383; found, 383.

[0742] EXAMPLE 94: 6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-4-(benzofuran-3-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

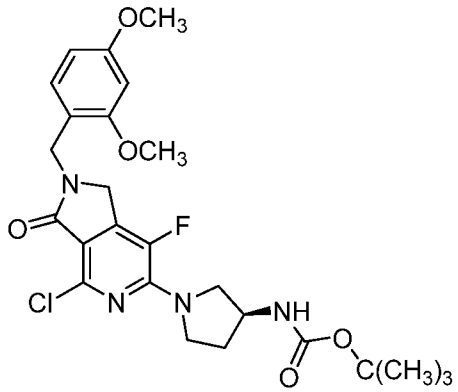


[0743] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 92 using benzofuran-3-ylboronic acid in place of pyrazolo[1,5-*a*]pyridin-3-ylboronic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.84-1.88 (m, 2 H), 3.68-3.73 (m, 1 H), 3.76-4.02 (m, 4 H), 4.47 (s, 2 H), 4.58-4.59 (m, 1 H), 7.25 (d, *J*=6.35 Hz, 1 H), 7.40-7.42 (m, 2 H), 7.67-7.69 (m, 1 H), 7.93 (br s, 1 H), 8.33 (d, *J*=9.76 Hz, 1 H), 8.56 (s, 1 H), 9.38 (s, 1 H). [M+H] calc'd for $C_{20}H_{19}FN_4O_3$, 383; found, 383.

[0744] EXAMPLE 95: (*S*)-6-(3-Aminopyrrolidin-1-yl)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



[0745] A. (*S*)-*tert*-Butyl 1-(4-chloro-2-(2,4-dimethoxybenzyl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-yl)pyrrolidin-3-ylcarbamate

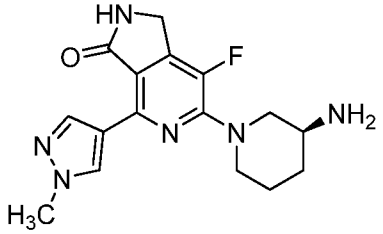


[0746] A tube containing 4,6-dichloro-2-(2,4-dimethoxybenzyl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one (300 mg, 0.808 mmol) and (*S*)-*tert*-butyl pyrrolidin-3-ylcarbamate (301 mg, 1.616 mmol) dissolved in ACN (4 mL) was sealed and heated at 100°C for 2 d. The reaction mixture was concentrated and dissolved in EtOAc (20 mL) and washed with saturated aq $NaHCO_3$ (10 mL) and brine (10 mL). The organic extracts were dried over Na_2SO_4 and evaporated to give a crude product, which was purified via preparative HPLC. Pure fractions were collected and evaporated to give the title compound (235 mg, 55.8%). [M+H] calc'd for $C_{25}H_{30}ClFN_4O_5$, 521; found, 521.

[0747] B. (*S*)-6-(3-Aminopyrrolidin-1-yl)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

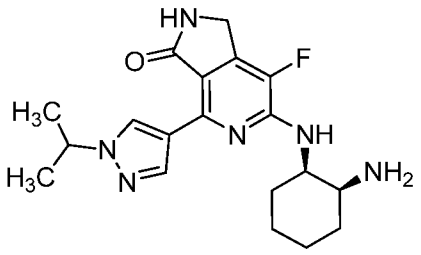
[0748] To a 30 mL tube charged with (*S*)-*tert*-butyl 1-(4-chloro-2-(2,4-dimethoxybenzyl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-yl)pyrrolidin-3-ylcarbamate (225 mg, 0.43 mmol) 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (145 mg, 0.695 mmol), and $PdCl_2(PPh_3)$ dispersed in dioxane (5 mL) was added 2 N Na_2CO_3 (0.5 mL). The tube was sealed and the reaction mixture was heated at 85°C for 4 h. The mixture was diluted with water (5 mL) and extracted into EtOAc (2 x 30 mL). The organic layer was dried over Na_2SO_4 and evaporated to afford a residue, which was treated with TFA (1 mL) and heated at 85°C for 1 h to remove the protecting groups. TFA was evaporated and the mixture was dissolved in DMSO (8 mL) and purified via preparative HPLC. Pure fractions were collected, evaporated to a minimal volume, and lyophilized to give a TFA salt of the title compound as a pale yellow solid (46 mg, 27.2%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.05 - 2.39 (m, 3 H), 3.75 - 4.04 (m, 6 H), 3.89 (s, 3 H), 4.38 (s, 2 H), 8.02 (br s, 2 H), 8.26 (d, *J*=0.51 Hz, 1 H), 8.39 (s, 1 H), 8.85 (s, 1 H);). [M+H] calc'd for $C_{15}H_{17}FN_6O$, 317; found, 317.

[0749] EXAMPLE 96: (*S*)-6-(3-Aminopiperidin-1-yl)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



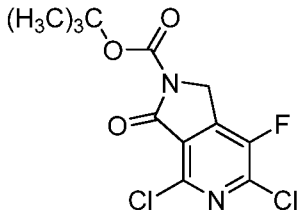
[0750] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 95 using (*S*)-*tert*-butyl piperidin-3-ylcarbamate in place of (*S*)-*tert*-butyl pyrrolidin-3-ylcarbamate. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.61 (m, 2 H), 1.83 (d, *J*=8.34 Hz, 1 H), 2.03 (br s, 1 H), 2.53 - 2.55 (m, 2 H), 3.16 - 3.35 (m, 3 H), 3.90 (s, 3 H), 3.92 (m, 1 H), 4.33 (m, 1H), 4.39 (s, 2 H), 8.04 (br s, 3 H), 8.36 (s, 1 H), 8.51 (s, 1 H), 8.90 (s, 1 H). [M+H] calc'd for $C_{16}H_{19}FN_6O$, 331; found, 331.

[0751] EXAMPLE 97: 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(1-isopropyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

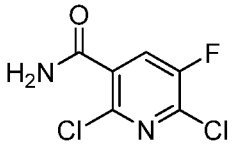


[0752] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 62 using 1-isopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole in place of 1-(difluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.14 - 1.33 (m, 6 H), 1.47 - 1.64 (m, 8 H), 1.76 (br. s., 2 H), 1.94 - 2.01 (m, 2 H), 3.86 (br. s., 1 H), 4.36 (s, 2 H), 4.53 (d, *J*=6.83 Hz, 2 H), 8.15 (s, 1 H), 8.88 (s, 1 H). [M+H] calc'd for $C_{19}H_{25}FN_6O$, 373; found, 373.

[0753] PREPARATION 47: *tert*-Butyl 4,6-dichloro-7-fluoro-3-oxo-1*H*-pyrrolo[3,4-*c*]pyridine-2(3*H*)-carboxylate



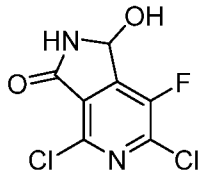
[0754] A. 2,6-Dichloro-5-fluoronicotinamide



[0755] A 12-L 3-neck round bottom flask equipped with overhead stirrer, refluxing condenser, and N_2 inlet/outlet was charged with 2,6-dichloro-5-fluoronicotinonitrile (2.0 kg, 1.0 eq). Concentrated sulfuric acid (4.93 L) was added and the mixture was stirred at RT until most of the brown solids had dissolved. Next, the reaction mixture was stirred at 65°C for 1 h. The dark-brown solution was cooled to a temperature < 10°C using an ice bath. The reaction mixture was added to a 50-L round bottom flask, which contained de-ionized water (24.7 L) that had been cooled to a temperature < 10°C, using a peristaltic pump. The reaction mixture was added to the water quench over a 2.3 h period, which kept the internal temperature of the mixture below 21°C. The resulting slurry was filtered through a Buchner funnel fitted with a Sharkskin filter paper. The 50-L RBF was rinsed with water (3 x 4 L) and the rinses were used to wash the filter cake. The filter cake was

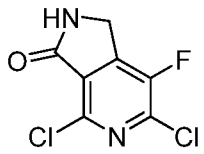
conditioned for 50 min, transferred to a drying tray, and was dried under high vacuum at 40–50°C for 24 h and then at 20–25°C for 18 h to give the title compound as a beige solid (896.4 g, 82%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.94 (s, 1 H), 8.10 (s, 1 H), 8.24 (d, 1 H). [M+H] calc'd for $C_6H_3Cl_2FN_2O$, 209; found, 209.

[0756] B. 4,6-Dichloro-7-fluoro-1-hydroxy-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



[0757] A 22-L multi-neck RBF equipped with an overhead stirrer, temperature probe, and N_2 inlet/outlet was charged with LiHMDS (10.65 L, 2.5 eq) by N_2 pressure. The orange solution was cooled to < 0°C using an ice/brine bath. A separate 12-L RBF was sequentially charged with 2,6-dichloro-5-fluoronicotinamide (890 g, 1.0 eq), anhydrous THF (6.0 L), and anhydrous DMF (1.0 L, 3.0 eq). The resulting solution was added to the LiHMDS solution via a peristaltic pump over a 1 h period, which kept the internal temperature below 5°C. The 12-L flask was rinsed with THF (1.6 L), and the rinse was transferred to the reaction mixture. The mixture was stirred at a temperature < 5°C for 1 h, and the reaction was added to a pre-cooled 2N HCl aq solution via a peristaltic pump at a rate that kept the temperature of the mixture below 22°C. Following the quench, IPAc (14 L) was added and the mixture was stirred for 10 min. The biphasic mixture was separated and the organic layer was stored in a carboy at RT overnight. The organic layer was subsequently washed with water (8.9 L) and was concentrated under reduced pressure to a volume of about 4.5 L. The distillation was continued the next day. Isopropyl acetate (16 L) was added to the slurry and the distillation was continued until about 4.5 L of material remained. The off-white slurry was transferred into a 50-L multi-neck RBF to which was charged heptanes (18 L) via a peristaltic pump over a 45 min period. The resultant slurry was stirred at RT overnight and then filtered through a Buchner funnel with a Sharkskin filter paper. The filter cake was washed with heptanes (2 x 4.5 L) and then dried under high vacuum at RT for 24 h to afford title compound (913.0 g,90%). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 6.11 (dd, *J*=9.3 Hz, 1.5 Hz, 1 H), 6.95 (d, *J*=9.3 Hz, 1 H), 9.54 (s, 1 H). [M+H] calc'd for $C_7H_3Cl_2FN_2O_2$, 237; found, 237.

[0758] C. 4,6-Dichloro-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

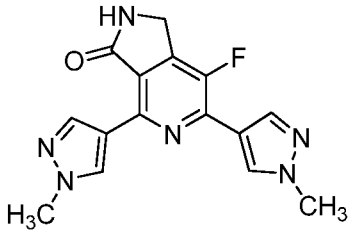


[0759] A 22-L 3-neck RBF equipped with overhead stirrer, refluxing condenser, and N_2 inlet/outlet, and having all glass or PTFE-coated parts, was sequentially charged with 4,6-dichloro-7-fluoro-1-hydroxy-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one (908 g), DCM (4.55 L), and TFA (3.46 L, 11.76 eq). Agitation was started and Et_3SiH (3.05 L, 4.97 eq) was added. The cloudy mixture was heated to reflux, resulting in a clear solution that was stirred at refluxing conditions for 24 h. The mixture was cooled to RT and stirred overnight. The orange solution was cooled to < 10°C using an ice bath. Methyl *tert*-butyl ether (14.0 L) was added via a peristaltic pump within a 1 h period. The resultant slurry was stirred at < 10°C for 1 h and then filtered through a coarse fritted glass funnel. The filter cake was washed with MTBE (2 x 4 L). The solid was dried under high vacuum at RT for 19 h to afford the title compound (802 g, 94%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 4.55 (s, 2 H), 9.15 (s, 1 H). [M+H] calc'd for $C_7H_3Cl_2FN_2O$, 221; found, 221.

[0760] D. *tert*-Butyl 4,6-dichloro-7-fluoro-3-oxo-1*H*-pyrrolo[3,4-*c*]pyridine-2(3*H*)-carboxylate

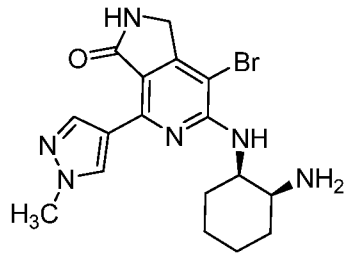
[0761] A 12 L 3-neck RBF was charged with 4,6-dichloro-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one (745.0 g, 1.0 eq), DCM (3.0 L), Et_3N (940 mL, 2.0 eq), and DMAP (20.59 g, 0.05 eq). To a separate 2-L flask containing di-*tert*-butyl dicarbonate (882.8 g, 1.2 eq) was added DCM (0.75 L), and the resulting clear solution was added dropwise to the reaction mixture over a 20 min period via a peristaltic pump. The 2-L flask was rinsed with DCM (0.75 L) and the rinse was added to the reaction mixture, which was stirred at RT for 28 min. Ethanol (7.5 L) was added and the mixture was concentrated under reduced pressure to a volume of about 4.5 L. A second volume of EtOH (7.5 L) was added to the mixture and distillation was continued until about 4.5 L of the material remained. The resultant slurry was stirred at 15–20°C for 10 min and was then filtered through a Buchner funnel. The filter cake was washed with EtOH (3 x 1.5 L) and dried under high vacuum at RT overnight to give the title compound as a pink solid (873 g, 81% yield). ^{1}H (300 MHz, $CDCl_3$) δ ppm 1.61 (s, 9 H), 4.82 (d, *J*=0.9 Hz, 2 H), ^{19}F NMR (282 MHz, $CDCl_3$) δ ppm -128.36. [M-H] calc'd for $C_{12}H_{11}Cl_2FN_2O_3$, 319; found, 319.

[0762] EXAMPLE 98: 7-Fluoro-4,6-bis(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



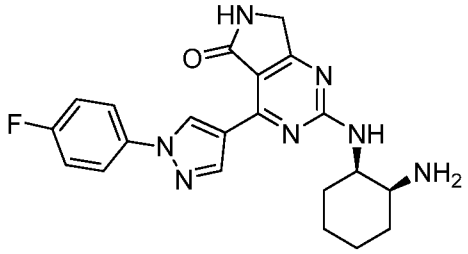
[0763] A mixture of *tert*-butyl 4,6-dichloro-7-fluoro-3-oxo-1*H*-pyrrolo[3,4-*c*]pyridine-2(3*H*)-carboxylate (30.0 mg, 0.093 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (19.4 mg, 0.093 mmol), tris(dibenzylideneacetone)dipalladium (3.42 mg, 0.003 mmol), tricyclohexylphosphine (3.90 mg, 0.001 mmol) and potassium phosphate (35.7 mg, 0.168 mmol) in dioxane (1 mL) and deionized water (0.3 mL) were heated at 120°C in a microwave for 20 min. The mixture was concentrated and purified via preparative HPLC to give a TFA salt of the title compound as a pale yellow solid (4.1 mg, 14%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.92 (s, 3 H), 3.96 (s, 3 H), 4.53 (s, 2 H), 8.17 (s, 1 H), 8.49 (s, 1 H), 8.50 (s, 1 H), 8.81 (s, 1 H), 8.92 (s, 1 H). [M+H] calc'd for $C_{15}H_{13}FN_6O$, 313; found, 313.

[0764] EXAMPLE 99: 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-bromo-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



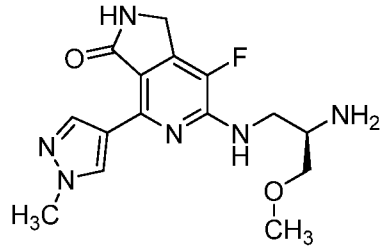
[0765] A solution of *tert*-butyl (1*S*,2*R*)-2-(7-bromo-4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (10 mg, 0.020 mmol) in HCl-dioxane (999 μL, 4.00 mmol) was stirred at RT for 2 h. The mixture was concentrated to a residue, diluted with Et_2O (3 mL), and sonicated to yield a white precipitate, which was filtered and dried overnight in a lyophilizer to give an HCl salt of the title compound as a white solid (1.8 mg, 21%). [M+H] calc'd for $C_{17}H_{21}BrN_6O$, 406; found, 406.

[0766] EXAMPLE 100: 2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one



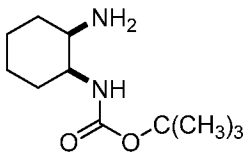
[0767] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 14 using 1-(4-fluorophenyl)-1*H*-pyrazol-4-ylboronic acid in place of 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.43 (br s, 2 H), 1.55 - 1.98 (m, 6 H), 4.10 - 4.35 (m, 2 H), 4.34 - 4.70 (m, 1 H), 7.43 (t, *J*=8.79 Hz, 2 H), 7.65 (d, *J*=7.81 Hz, 1 H), 7.68 - 7.83 (m, 3 H), 7.87 (br s, 2 H), 8.39 (s, 1 H), 8.58 - 9.00 (m, 1 H), 9.62 - 9.86 (m, 1 H). [M+H] calc'd for $C_{21}H_{22}FN_7O$, 408; found, 408.

[0768] EXAMPLE 101: (*R*)-6-(2-Amino-3-methoxypropylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

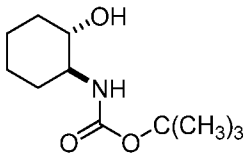


[0769] To a 20 mL round-bottomed flask was added (*R*)-*tert*-butyl 1-methoxy-3-(4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)propan-2-ylcarbamate (19.7 mg, 0.047 mmol) and SELECTFLUOR® (21.78 mg, 0.061 mmol) in DCM (473 μL) and MeOH (473 μL). The resulting yellow solution was stirred at RT for 3 h and concentrated to a residue, which was dissolved in 4 N HCl-dioxane (2 mL) and stirred at RT for 2 h. The mixture was concentrated, dissolved in DMF (1 mL) and purified via preparative HPLC to give a TFA salt of the title compound. [M+H] calc'd for $C_{15}H_{19}FN_6O_2$, 335; found, 335.

[0770] PREPARATION 48: *cis*-*tert*-butyl 2-aminocyclohexylcarbamate

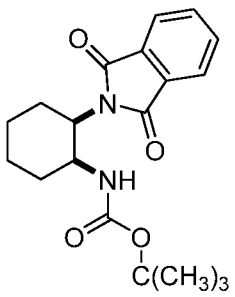


[0771] A. *trans-tert*-Butyl 2-hydroxycyclohexylcarbamate



[0772] To a stirred slurry of *trans*-2-aminohexanol hydrochloride (15.0 g, 98.92 mmol) in EtOAc (75 mL) was added a solution of NaOH (9.1 g, 0.227 mol) in water (150 mL). A solution of di-*tert*-butyl dicarbonate (25.9 g, 118.70 mmol) in EtOAc (75 mL) was added in one portion and the mixture was heated to 45°C and stirred for 16 h. The phases were separated and the aqueous phase was extracted with EtOAc (60 mL). The combined organic extracts were washed with water (45 mL) and phase separated. The organic phase was distilled at atmospheric pressure until approximately 75 mL of solution remained. Heptane (90 mL) was added and the solution was distilled until approximately 75 mL of solution remained. Heptane (150 mL) was added and the mixture was heated to 98–100°C. The heat was switched off and the mixture was allowed to cool to RT. Seeds of pure product were added at 70°C and crystallization occurred at about 65°C. Once the slurry reached RT, the mixture was cooled to about 5°C and was stirred for 30 min. The solids were filtered, washed with heptane (2 x 45 mL), and dried to give the title compound as a white crystalline solid (19.6 g, 92%).

[0773] B. *cis-tert*-Butyl 2-(1,3-dioxoisoindolin-2-yl)cyclohexylcarbamate



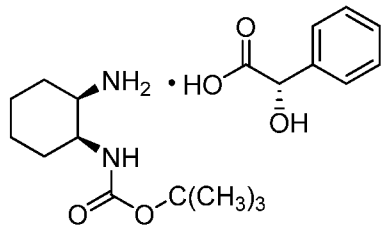
[0774] To a stirred slurry of *trans-tert*-butyl 2-hydroxycyclohexylcarbamate (1.00 g, 4.64 mmol), PPh_3 (1.34 g, 5.10 mmol) and phthalimide (1.50 g, 10.20 mmol) in a 2:1 mixture of toluene and THF (15 mL) was added diisopropyl azodicarboxylate (1.0 mL, 5.10 mmol) dropwise over a period of 1 h. Once the addition was complete, the mixture

was stirred at about 0°C for 7 h and was then warmed slowly to 7°C over a period of 14 h. The mixture was filtered, and the filtrate was concentrated under reduced pressure to give the title compound as a yellow oil (3.90 g). The crude product was used in the next step without further purification.

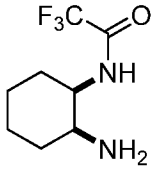
[0775] C. *cis-tert*-Butyl 2-aminocyclohexylcarbamate

[0776] Crude *cis-tert*-butyl 2-(1,3-dioxoisoindolin-2-yl)cyclohexylcarbamate (3.90g) was dissolved in toluene (20 mL) and charged to a round bottom flask. Hydrazine hydrate (0.70 mL) was added and the mixture was heated to 80°C for 2 h whereupon TLC analysis indicated the reaction was complete. The reaction was cooled to RT and the solids were filtered and washed with toluene (2 x 5 mL). The filtrates were washed with 2 N NaOH aq (10 mL) and phase separated. The aqueous phase was extracted with toluene (2 x 5 mL) and the combined organic extracts were washed with 10% HOAc aq (2 x 10 mL). The combined aqueous washes were basified with 2 N NaOH aq (13 mL). The product was extracted with IPAc (2 x 10 mL) and the combined organic extracts were washed with water (5 mL). The organic phase was concentrated to dryness to give 0.78 g of crude product. The oil was re-dissolved in IPAc (12 mL), heated to about 75°C, and maleic acid (423 mg) was added. Precipitation of solids occurred immediately and the thick mixture was diluted with IPAc (5 mL). The slurry was cooled to RT and allowed to stand for 20 min. The solids were filtered, washed with IPAc (10 mL), and dried to give a maleic acid salt of the title compound as white crystalline solid (730 mg, 44%). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.34-1.42 (m, 2 H), 1.50 (s, 9 H), 1.50-1.64 (m, 6 H), 3.22 (m, 1 H), 3.83 (br s, 1 H), 6.02 (s, 2 H), 6.86 (d, *J*=7.5 Hz, 1 H), 7.68 (br s, 3 H).

[0777] PREPARATION 49: *tert*-Butyl (1*S*,2*R*)-2-aminocyclohexylcarbamate, (*S*)-mandelic acid salt

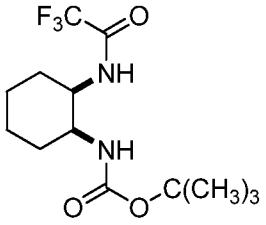


[0778] A. *cis-N*-(2-Aminocyclohexyl)-2,2,2-trifluoroacetamide



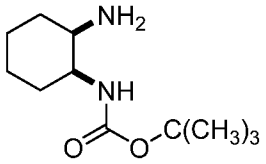
[0779] *cis*-Cyclohexane-1,2-diamine (5.00 g, 43.9 mmol, 1.00 eq) was charged to a 250 mL three-neck round bottom flask equipped with an overhead stirrer and a thermocouple. Ethanol (50 mL) was added and the solution was cooled to < 0°C using an ice-brine bath. A solution of ethyl trifluoroacetate (6.23 g, 1.00 eq) in EtOH (25 mL) was added via a syringe pump over a one hour period. Once the addition was complete, the cooling bath was removed and the solution was slowly warmed to RT and stirred for 3.5 hours to afford the title compound in EtOH. Half (41 mL, about 21.9 mmol) of the total solution (about 82 mL) was carried into the next step.

[0780] B. *cis-tert*-Butyl 2-(2,2,2-trifluoroacetamido)cyclohexylcarbamate



[0781] Triethylamine (3.1 mL, 22.05 mmol, 1.0 eq) was added to a solution of *cis-N*-(2-aminocyclohexyl)-2,2,2-trifluoroacetamide in EtOH (41 mL, 21.9 mmol). Di-*tert*-butyl dicarbonate (5.74 g, 26.3 mmol, 1.2 eq) was added in one portion at RT. An ice bath was used to control a modest exotherm and the internal reaction temperature was maintained at < 25°C. Once the exotherm subsided the ice bath was removed, and the mixture was stirred at RT for 16 h to give the title compound in EtOH.

[0782] C. *cis-tert*-Butyl 2-aminocyclohexylcarbamate



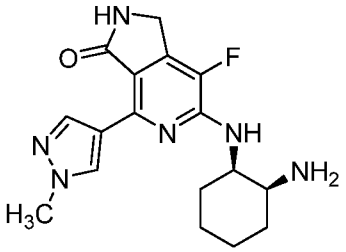
[0783] Aqueous sodium hydroxide (50%, 10 g, 0.125 mole, 5.7 eq) was added to a solution of *cis-tert*-butyl 2-(2,2,2-trifluoroacetamido)cyclohexylcarbamate in EtOH (about 21.9 mmol). An exotherm from 20 to 37°C was observed and a fine white slurry formed. The reaction mixture was stirred overnight, during which further solids precipitated out of

solution. The solvent volume was concentrated under reduced pressure to about 10 to 15 mL and then IPAc (40 mL) and water (30 mL) were added to form a clean bi-phasic solution. Following phase separation the aqueous phase was extracted with IPAc (15 mL) and the organic extracts were combined and washed with water (15 mL) to give the title compound as a crude racemic product in IPAc.

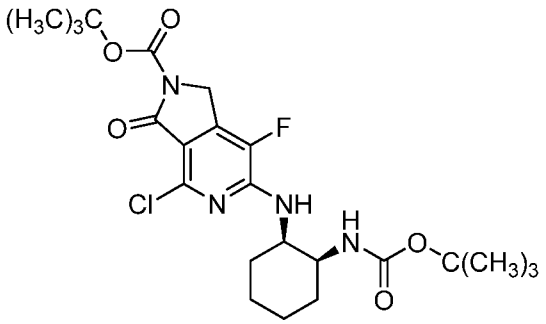
[0784] D. *tert*-Butyl (1*S*,2*R*)-2-aminocyclohexylcarbamate

[0785] Crude *cis*-*tert*-butyl 2-aminocyclohexylcarbamate in IPAc (70 mL, about 21.9 mmol) was charged to a 100 mL three-neck RBF equipped with a short-path distillation unit, thermocouple, and stir bar. Vacuum was applied and the solution was heated and the solvent volume was distilled at 43-44°C until the volume reached about 45 mL (10 volumes relative to theoretical crude yield of racemic product). Karl Fisher analysis indicated a water content of 4.9%. The vacuum was released and the solution was heated to 60°C. The solution was then slowly cooled to RT and seeds of *tert*-butyl (1*S*,2*R*)-2-aminocyclohexylcarbamate, (*S*)-mandelic acid salt (from small scale resolution experiments) were added at 5°C intervals. All the seeds dissolved while cooling, but remained when RT was reached. The solution was cooled in an ice-brine bath (–15°C) for 30 min. The solution was reheated, and following the addition of IPAc (40 mL), was redistilled under vacuum at 45-46°C to about 45 mL of volume. The reaction was cooled to RT and stirred overnight. The solids were filtered, washed with IPAc (2 x 12.5 mL) and dried to afford an (*S*)-mandelic acid salt of the title compound as a white solid (2.21 g, 28%, 98% ee). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.24-1.30 (m, 2 H), 1.35 (s, 9 H), 1.35-1.64 (m, 6 H), 3.15 (m, 1 H), 3.71 (br s, 1 H), 4.55 (s, 1 H), 6.85-7.11 (br s, 3 H), 6.95 (br d, 1 H, *J*=7.5 Hz), 7.15 (m 1 H), 7.23 (m, 2 H), 7.37 (m, 2 H).

[0786] EXAMPLE 102: 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one (HCl salt)

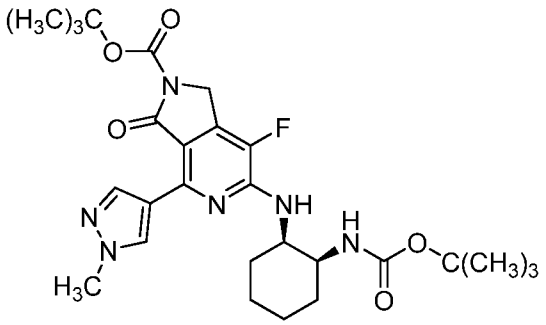


[0787] A. *tert*-Butyl 6-((1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclohexylamino)-4-chloro-7-fluoro-3-oxo-1*H*-pyrrolo[3,4-*c*]pyridine-2(3*H*)-carboxylate



[0788] To a stirred suspension of *tert*-butyl 4,6-dichloro-7-fluoro-3-oxo-1*H*-pyrrolo[3,4-*c*]pyridine-2(3*H*)-carboxylate (12.5 g, 38.9 mmol) in 2-propanol (72 mL) was added a solution of *tert*-butyl (1*S*,2*R*)-2-aminocyclohexylcarbamate (10.01 g, 46.7 mmol) in DMSO (12.00 mL) and DIPEA (8.84 mL, 50.6 mmol). The reaction mixture was heated to 90°C for 16 h at which point it was cooled to 50°C and water (50 mL) was added dropwise to give a precipitate. The suspension was stirred at 50°C for 1 h then cooled to RT. The suspension was reheated to 50°C for 15 min and cooled to RT for two more cycles. The solids were subsequently filtered and washed with isopropanol (20 mL) and dried on a filter to give the title compound (9.538 g, 49%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.18 - 1.76 (br m, 26 H), 3.83 (br s, 1 H), 4.12 (br s, 1 H), 4.72 (s, 2 H), 6.71 (d, *J*=7.58 Hz, 1 H), 7.22 (d, *J*=6.32 Hz, 1 H).

[0789] B. *tert*-Butyl 6-((1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclohexylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-1*H*-pyrrolo[3,4-*c*]pyridine-2(3*H*)-carboxylate



[0790] A 50 mL, 2-neck round bottom flask was charged with *tert*-butyl 6-((1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclohexylamino)-4-chloro-7-fluoro-3-oxo-1*H*-pyrrolo[3,4-*c*]pyridine-2(3*H*)-carboxylate (520 mg, 1.042 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (282 mg, 1.355 mmol), potassium carbonate (504 mg, 3.65 mmol), and DMA (3 mL). The reaction flask was degassed followed by addition of 1,1-bis (di-*tert*-butylphosphino)ferrocene palladium chloride (21 mg, 0.032 mmol).

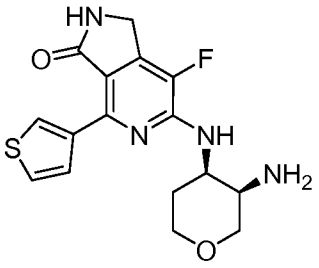
Under N_2 atmosphere, the reaction mixture was heated in an oil bath at 80°C for 2.5 h and then allowed to cool to RT. In a separate 50 mL recovery flask was added de-ionized H_2O (12 mL) and the vessel was cooled in an ice/water bath. When the internal temperature of the water reached 2°C, the reaction mixture was transferred to the recovery flask at a rate which kept the internal temperature below 10°C. Following the addition, the reaction vessel was rinsed with DMA (1 mL). The rinse was added to the recovery flask and the resulting aqueous slurry was stirred in an ice bath for 10 min and was then allowed to warm to RT with stirring. When the internal temperature reached 22°C, the mixture was filtered. The filter cake was rinsed with de-ionized H_2O (2 x 5 mL) and air-dried under suction. The solids were re-suspended in glacial acetic acid (3 mL) and stirred at RT for 1 h. Isopropanol (1 mL) was added and the mixture was stirred at RT. De-ionized water (3.4 mL) was added to induce crystallization. Precipitation occurred, but some solids were sticky, so the mixture was heated in a 40°C oil bath, with stirring, for 20 min. The mixture was allowed to cool to RT with stirring and then filtered. The filter cake was rinsed with a 3:3:1 mixture of HOAc/H_2O/IPA (2.1 mL), briefly air-dried under suction, and then dried in a vacuum oven at 60°C to give the title compound as a tan solid (352 mg, 62%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.35 (s, 9 H), 1.53 (s, 9 H), 1.65 (m, 3 H), 1.76 (m, 3 H), 3.94 (s, 3 H), 4.03 (br s, 1 H), 4.38 (br s, 1 H), 4.67 (s, 2 H), 5.12 (br s, 1 H), 5.77 (br s, 1 H), 8.25 (br s, 1 H), 8.96 (br s, 1 H). [M+H] calc'd for $C_{27}H_{37}FN_6O_5$, 545; found, 545.

[0791] C. 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

[0792] A suspension of *tert*-butyl 6-((1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclohexylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-1*H*-pyrrolo[3,4-*c*]pyridine-2(3*H*)-carboxylate (2.148 g, 3.94 mmol) in IPA (21 mL) was heated to 70°C at which point 2M HCl aq (9.86 mL, 19.72mmol) was added. The reaction mixture was heated at 65°C for approximately 3 h, cooled in an ice water bath for 1 h, and then filtered. The solids were rinsed with cold IPA (15 mL) and then dried in a 50°C vacuum oven overnight to give an HCL salt of the title compound as a light yellow solid (1.404 g, 3.37 mmol) having 1.5 - 2 eq of associated water (by ^{1}H NMR). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.46 (d, *J*=7.07 Hz, 2 H), 1.57 - 1.76 (m, 3 H), 1.76 - 2.04 (m, 3 H), 3.31 (s, 3 H), 3.67 (br s, 1 H), 3.90 (s, 3 H), 4.39 (d, *J*=2.53 Hz, 2 H), 4.41 - 4.60 (m, 1

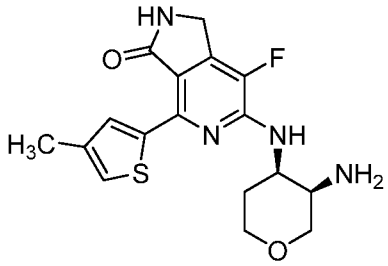
H), 6.75 (d, *J*=6.57 Hz, 1 H), 7.96 (br s, 3 H), 8.22 - 8.31 (m, 1 H), 8.34 (s, 1 H), 8.84 (s, 1 H). [M+H] calc'd for $C_{17}H_{21}FN_6O$, 345; found 345.

[0793] EXAMPLE 103: 6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(thiophen-3-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



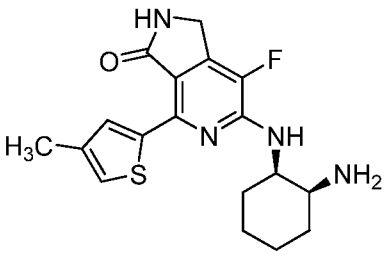
[0794] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 92 using thiophene-3-boronic acid in place of pyrazolo[1,5-*a*]pyridin-3-ylboronic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.16-3.17 (m, 2H), 3.61-3.63 (m, 1H), 3.77-3.79 (m, 2 H), 3.81-3.83 (m, 2 H), 4.41-4.43 (m, 2 H), 4.49-5.10 (m, 1 H), 7.12-7.13 (m, 1 H), 7.52-7.54 (m, 1 H), 7.90-7.97 (m, 3 H), 8.48 (s, 1 H), 8.88 (s, 1 H). [M+H] calc'd for $C_{16}H_{17}FN_4O_2S$, 349; found, 349.

[0795] EXAMPLE 104: 6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(4-methylthiophen-2-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



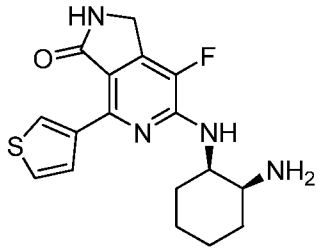
[0796] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 92 using 4-methylthiophene-2-boronic acid in place of pyrazolo[1,5-*a*]pyridin-3-ylboronic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.24 (s, 3 H), 3.17 (d, *J*=4.04 Hz, 2 H), 3.35-3.39 (m, 1 H), 3.62-3.64 (m, 1 H), 3.74-3.75 (m, 2 H), 4.00-4.03 (m, 2 H), 4.42 (d, *J*=11.62 Hz, 2 H), 6.46 (s, 1 H), 7.20-7.22 (m, 3 H), 8.46 (s, 1 H), 8.85 (s, 1 H). [M+H] calc'd for $C_{17}H_{19}FN_4O_2S$, 363; found, 363.

[0797] EXAMPLE 105: 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(4-methylthiophen-2-yl)-1*H*-pyrrolo[3,4-c]pyridin-3(2*H*)-one



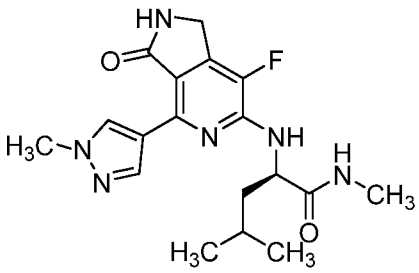
[0798] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 62 using 4,4,5,5-tetramethyl-2-(4-methylthiophen-2-yl)-1,3,2-dioxaborolane in place of 1-(difluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.31 - 2.04 (m, 8 H), 2.24 (s, 3 H), 3.83 (br s, 1 H), 4.22 (br s, 1 H), 4.36 - 4.49 (m, 2 H), 6.98 (d, *J*=5.37 Hz, 1 H), 7.22 (s, 1 H), 7.75 (br s, 2 H), 8.47 (s, 1 H), 8.85 (s, 1 H). [M+H] calc'd for $C_{18}H_{21}FN_4OS$, 361; found, 361.

[0799] EXAMPLE 106: 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(thiophen-3-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

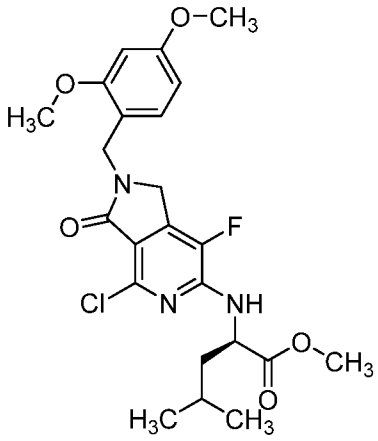


[0800] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 62 using 4,4,5,5-tetramethyl-2-(thiophen-3-yl)-1,3,2-dioxaborolane in place of 1-(difluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.31 - 2.05 (m, 8 H), 3.84 (br s, 1 H), 4.25 (d, *J*=3.42 Hz, 1 H), 4.36 - 4.50 (m, 2 H), 7.01 (d, *J*=5.86 Hz, 1 H), 7.15 (dd, *J*=5.37, 3.91 Hz, 1 H), 7.64 (dd, *J*=4.88, 0.98 Hz, 1 H), 7.75 (br s, 2 H), 8.50 (s, 1 H), 8.95 - 9.07 (m, 1 H). [M+H] calc'd for $C_{17}H_{19}FN_4OS$, 347; found, 347.

[0801] EXAMPLE 107: (*R*)-2-(7-Fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-*N*,4-dimethylpentanamide

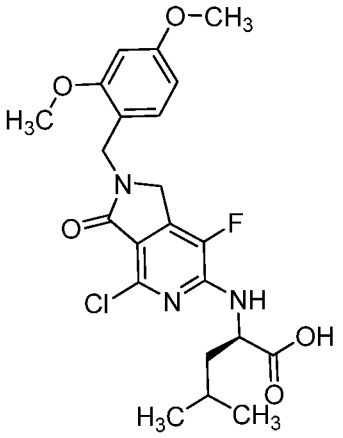


[0802] A. (*R*)-Methyl 2-(4-chloro-2-(2,4-dimethoxybenzyl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanoate



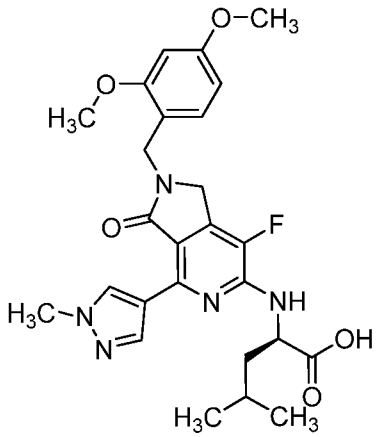
[0803] A mixture of 4,6-dichloro-2-(2,4-dimethoxybenzyl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one (3 g, 8.08 mmol), (*S*)-methyl 2-amino-4-methylpentanoate hydrochloride (2.94g, 16.16 mmol), and *N*-isopropyl-*N*-methylpropan-2-amine (3.76 mL, 24.25 mmol) in ACN (50 mL) was stirred at 100°C for 3 d. The solvent was removed and the resulting residue was used in the next step without further purification. [M+H] calc'd for $C_{23}H_{27}ClFN_3O_5$, 480; found, 480.

[0804] B. (*R*)-2-(4-Chloro-2-(2,4-dimethoxybenzyl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanoic acid



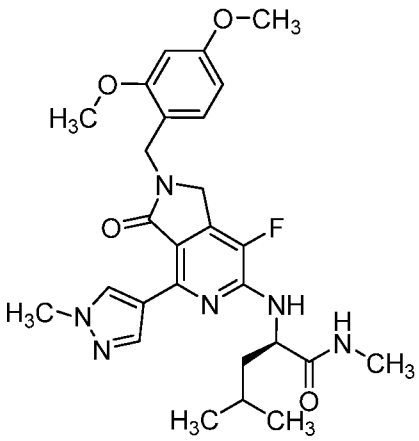
[0805] A mixture of (*R*)-methyl 2-(4-chloro-2-(2,4-dimethoxybenzyl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanoate (2.9 g, 6.04 mmol) in MeOH (10 mL) and 1N NaOH (40.0 mL) was stirred at 50°C for 2 h. UPLC showed 30% starting material remained. Additional saturated NaOH solution (5 mL) was added and the reaction mixture was stirred for 3 h at 50°C. The solvent was removed and the resulting residue was dispersed in H_2O (100 mL) and acidified to pH 3 using HCl. After stirring at RT for 2 h, the solid was filtered to give the title compound. [M+H] calc'd for $C_{22}H_{25}ClFN_3O_5$, 466; found, 466.

[0806] C. (*R*)-2-(2-(2,4-Dimethoxybenzyl)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanoic acid



[0807] A solution of (*R*)-2-(4-chloro-2-(2,4-dimethoxybenzyl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanoic acid (1.1 g, 2.361 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (2.456 g, 11.81 mmol) and bis(triphenylphosphine)palladium chloride (1.657 g, 2.361 mmol) in dioxane (10 mL)and saturated aq Na_2CO_3 (10.00 mL) was heated to 120°C for 30 min. After filtering out the solids, the solvent was removed from the filtrate. The resulting residue was dissolved in MeOH and DCM and was purified via preparative HPLC eluting with water (0.05% TFA) and ACN (40-70% gradient, 0.035 % TFA). The collected fractions were combined and the solvent stripped to dryness via rotary evaporation to yield the title compound. [M+H] calc'd for $C_{26}H_{30}FN_5O_5$, 512; found, 512.

[0808] D. (*R*)-2-(2-(2,4-Dimethoxybenzyl)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-*N*,4-dimethylpentanamide



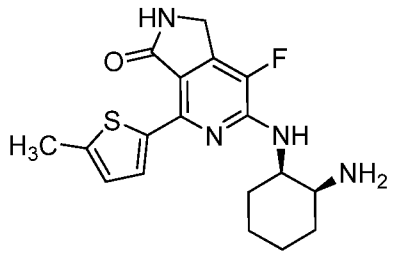
[0809] A solution of (*R*)-2-(2-(2,4-dimethoxybenzyl)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanoic acid (48 mg, 0.094 mmol), methylamine hydrochloride (31.7 mg, 0.469 mmol) and DIPEA (49.2 μL, 0.281 mmol) in DMF (1 mL) was stirred at RT for 10 min. HATU (71.4 mg, 0.188 mmol) was added and the mixture was stirred at RT for 1 h, after which UPLC showed about 80% starting material remained. Additional methylamine (58.4 μL, 0.469 mmol, 33% in EtOH) was added, which resulted in little conversion of the starting material. The solvent was stripped off and the residue was dissolved in DMF (1 mL). To this solution was added EDCI hydrochloride (54.0 mg, 0.281 mmol), HOBT monohydrate (43.1 mg, 0.281 mmol), and methylamine hydrochloride (31.7 mg, 0.469 mmol). The reaction mixture was heated to 60°C for 4 h. UPLC subsequently showed the reaction mixture contained 95% of desired product. The reaction mixture was allowed to cool to RT. Water (50 mL) was added and the mixture was extracted with DCM (3 x 50 mL). The organic layers were collected, dried over Na_2SO_4, filtered, and the solvent was stripped to dryness via rotary evaporation to yield the title compound, which was used without further purification. [M+H] calc'd for $C_{27}H_{33}FN_6O_4$, 525; found, 525.

[0810] E. (*R*)-2-(7-Fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-*N*,4-dimethylpentanamide

[0811] A solution of (*R*)-2-(2-(2,4-dimethoxybenzyl)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-*N*,4-dimethylpentanamide (38 mg, 0.072 mmol) in TFA (5 mL) was heated to 65°C for 4 h. After removal of the solvent, the residue was diluted in MeOH (2 mL) and was purified by preparative HPLC eluting with water (0.05% TFA) and ACN (25-30%, gradient, 0.035%

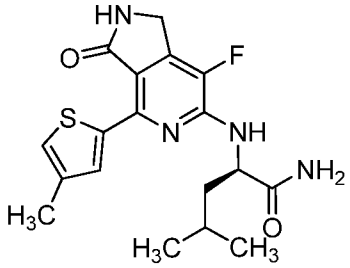
TFA). The collected fractions were stripped to dryness to give the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.84 - 0.93 (m, 6 H), 1.63 - 1.81 (m, 2 H), 2.57 (d, *J*=4.39 Hz, 3 H), 3.88 (s, 3 H), 4.04 - 4.19 (m, 2 H), 4.36 (s, 2 H), 6.99 (d, *J*=7.32 Hz, 1 H), 7.61 - 7.76 (m, 1 H), 7.93 (d, *J*=4.39 Hz, 1 H), 8.30 (s, 1 H), 8.83 (s, 1 H). [M+H] calc'd for $C_{18}H_{23}FN_6O_2$, 375; found, 375.

[0812] EXAMPLE 108: 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(5-methylthiophen-2-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



[0813] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 62 using 4,4,5,5-tetramethyl-2-(5-methylthiophen-2-yl)-1,3,2-dioxaborolane in place of 1-(difluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 - 2.01 (m, 8 H), 2.46 (d, *J*=0.51 Hz, 3 H), 3.80 (br s, 1 H), 4.25 (d, *J*=4.55 Hz, 1 H), 4.36 - 4.50 (m, 2 H), 6.83 (dd, *J*=3.79, 1.01 Hz, 1 H), 6.91 (d, *J*=6.06 Hz, 1 H), 7.73 (br s, 2 H), 8.43 (s, 1 H), 8.82 (d, *J*=3.54 Hz, 1 H). [M+H] calc'd for $C_{18}H_{21}FN_4OS$, 361; found, 361.

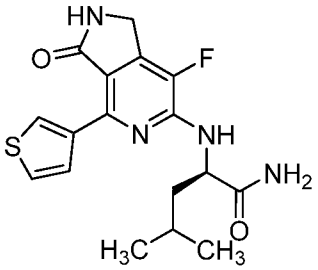
[0814] EXAMPLE 109: (*R*)-2-(7-Fluoro-4-(4-methylthiophen-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide



[0815] The title compound was prepared in a manner similar to EXAMPLE 70 using 4,4,5,5-tetramethyl-2-(4-methylthiophen-2-yl)-1,3,2-dioxaborolane in place of 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.82 - 0.95 (m, 6 H), 1.20 - 1.32 (m, 2 H), 2.23 (s, 3 H), 4.38 (s, 2 H), 4.59 - 4.72 (m, 2 H), 6.94 - 6.99 (m, 1 H), 7.02 - 7.08 (m, 1 H), 7.15 - 7.23 (m, 1 H), 7.27 - 7.34

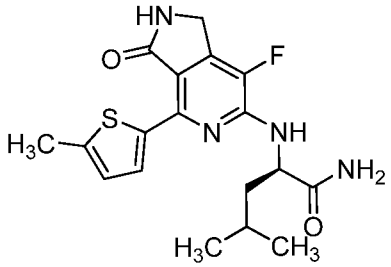
(m, 1 H), 8.35 (s, 1 H), 8.78 (d, *J*=1.26 Hz, 1 H). [M+H] calc'd for $C_{18}H_{21}FN_4O_2S$, 377; found, 377.

[0816] EXAMPLE 110: (*R*)-2-(7-Fluoro-3-oxo-4-(thiophen-3-yl)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide



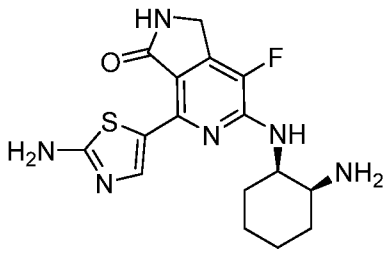
[0817] The title compound was prepared in a manner similar to EXAMPLE 70 using 4,4,5,5-tetramethyl-2-(thiophen-3-yl)-1,3,2-dioxaborolane in place of 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.75 - 1.00 (m, 6 H), 1.50 - 1.63 (m, 1 H), 1.69 - 1.83 (m, 2 H), 4.39 (s, 2 H), 4.52 - 4.61 (m, 1 H), 6.93 (br s, 1 H), 7.01 (d, *J*=7.58 Hz, 1 H), 7.38 (br s, 1 H), 7.49 (dd, *J*=5.05, 3.03 Hz, 1 H), 8.04 (dd, *J*=5.05, 1.26 Hz, 1 H), 8.36 (s, 1 H), 8.94 (dd, *J*=3.03, 1.01 Hz, 1 H). [M+H] calc'd for $C_{17}H_{19}FN_4O_2S$, 363; found, 363.

[0818] EXAMPLE 111: (*R*)-2-(7-Fluoro-4-(5-methylthiophen-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide

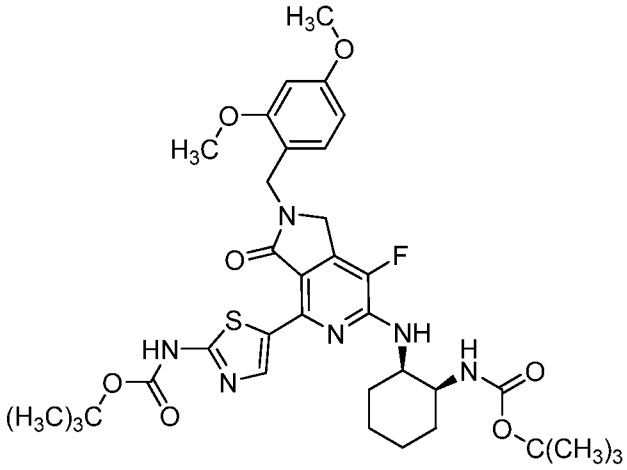


[0819] The title compound was prepared in a manner similar to EXAMPLE 70 using 4,4,5,5-tetramethyl-2-(5-methylthiophen-2-yl)-1,3,2-dioxaborolane in place of 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.71 - 0.96 (m, 6 H), 1.52 - 1.85 (m, 3 H), 2.45 (s, 3 H), 4.38 (s, 2 H), 4.56 - 4.74 (m, 1 H), 6.80 (dd, *J*=3.66, 1.14 Hz, 1 H), 6.93 - 7.10 (m, 2 H), 7.30 (br s, 1 H), 8.32 (s, 1 H), 8.78 (d, *J*=3.79 Hz, 1 H). [M+H] calc'd for $C_{18}H_{21}FN_4O_2S$, 377; found, 377.

[0820] EXAMPLE 112: 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(2-aminothiazol-5-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



[0821] A. *tert*-Butyl (5-(6-(((1*R*,2*S*)-2-((*tert*-butoxycarbonyl)amino)cyclohexyl)amino)-2-(2,4-dimethoxybenzyl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-4-yl)-1,3-thiazol-2-yl)carbamate



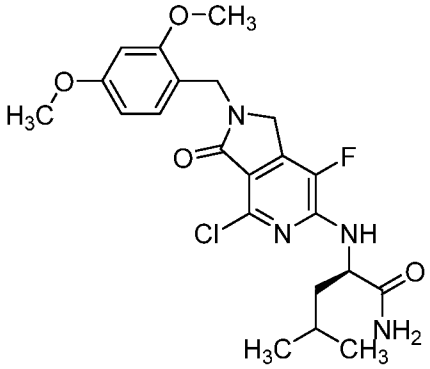
[0822] A solution of *tert*-butyl (1*S*,2*R*)-2-(4-chloro-2-(2,4-dimethoxybenzyl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (50 mg, 0.091 mmol), *tert*-butyl 5-(tributylstannyl)thiazol-2-ylcarbamate (53.5 mg, 0.109 mmol), and tetrakis(triphenylphosphine)palladium(0) (105 mg, 0.091 mmol) in toluene (1 mL) was heated to 102°C for 24 h. After removal of the solvent, the resulting crude material was reconstituted in MeOH/DMF (6.0 mL) and purified via preparative HPLC eluting with water (0.05% TFA) and ACN (70-75% gradient, 0.035% TFA). The collected fractions were stripped to dryness via rotary evaporation to yield the title compound (42 mg, 64%). [M+H] calc'd for $C_{35}H_{45}FN_6O_7S$, 713; found, 713.

[0823] B. 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(2-aminothiazol-5-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

[0824] A solution of *tert*-butyl (5-(6-(((1*R*,2*S*)-2-((*tert*-butoxycarbonyl)amino)cyclohexyl)amino)-2-(2,4-dimethoxybenzyl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-4-yl)-1,3-thiazol-2-yl)carbamate (41.5mg, 0.058 mmol) in TFA (5 mL) was heated to 65°C for 3 h. After removal of the solvent, the resulting crude material was

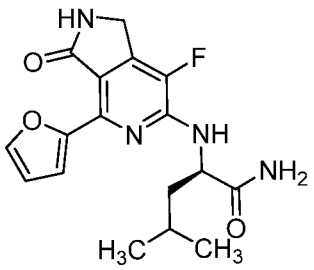
reconstituted in MeOH/DMF (6.0 mL) and purified via preparative HPLC eluting with water (0.05% TFA) and ACN (10-20% gradient, 0.035% TFA). The collected fractions were stripped to dryness via rotary evaporation to yield the title compound as a TFA salt (6.7 mg, 32%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.12 - 2.11 (m, 9 H), 3.73 (br s, 2 H), 4.19 (d, *J*=3.79 Hz, 1 H), 4.41 (d, *J*=3.03 Hz, 2 H), 6.95 (d, *J*=3.03 Hz, 1 H), 7.77 (br s, 2 H), 8.44 (s, 1 H), 8.93 (s, 1 H). [M+H] calc'd for $C_{16}H_{19}FN_6OS$, 363; found, 363.

[0825] PREPARATION 50. (*R*)-2-(4-Chloro-2-(2,4-dimethoxybenzyl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide

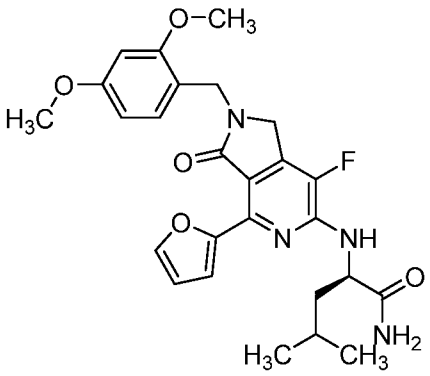


[0826] A mixture of 4,6-dichloro-2-(2,4-dimethoxybenzyl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one (7 g, 18.86 mmol), *N*-isopropyl-*N*-methylpropan-2-amine (14.64 mL, 94 mmol), and *N*-isopropyl-*N*-methylpropan-2-amine (14.64 ml, 94 mmol) in ACN (100 mL) was stirred at 100°C for 3 d. UPLC showed about 10% starting material remained. The reaction was stopped, the solvent was removed, and the crude product was reconstituted in MeOH/DCM and dispersed on silica gel (10 g). The solvent was evaporated and the residue was purified on a silica gel column eluting with 1-3% MeOH in DCM over a 45 min period. The collected fractions were combined and stripped to dryness via rotary evaporation to yield the title compound (5.3 g, 61%). [M+H] calc'd for $C_{22}H_{26}ClFN_4O_4$, 465; found 465.

[0827] EXAMPLE 113: (*R*)-2-(7-Fluoro-4-(furan-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide



[0828] A. (*R*)-2-(2-(2,4-Dimethoxybenzyl)-7-fluoro-4-(furan-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide



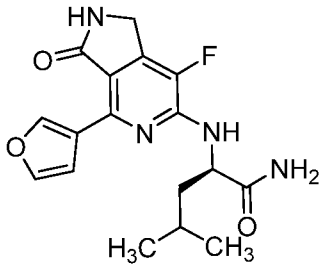
[0829] A solution of (*R*)-2-(4-chloro-2-(2,4-dimethoxybenzyl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide (150 mg, 0.323 mmol), tributyl(furan-2-yl)stannane (138 mg, 0.387 mmol), and tetrakis(triphenylphosphine)palladium(0) (373 mg, 0.323 mmol) in toluene (1 mL) was heated to 102°C overnight. After removal of the solvent, the residue was diluted in MeOH/DCM (10 mL) and was purified via preparative HPLC eluting with water (0.05% TFA) and ACN (45-60% gradient, 0.035 % TFA). The collected fractions were stripped to dryness via rotary evaporation to give the title compound (93.1 mg, 58%). [M+H] calc'd for $C_{26}H_{29}FN_4O_5$, 498; found 498.

[0830] B. (*R*)-2-(7-Fluoro-4-(furan-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide

[0831] A solution of (*R*)-2-(2-(2,4-dimethoxybenzyl)-7-fluoro-4-(furan-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide (93.1 mg, 0.188 mmol) in TFA (5 mL) was heated to 65°C for 3 h. The solvent was removed and the resulting residue was diluted in MeOH/DCM (10 mL) and was purified via preparative HPLC eluting with water (0.05% TFA) and ACN (30%, 0.035 % TFA). The collected fractions were stripped to dryness via rotary evaporation to afford the title compound. ^{1}H

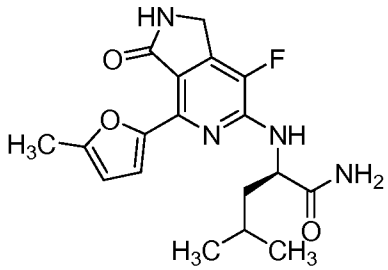
NMR (400 MHz, DMSO-d_6) δ ppm 0.79 - 0.97 (m, 6 H), 1.52 - 1.87 (m, 3 H), 4.38 (s, 2 H), 4.66 - 4.85 (m, 1 H), 6.61 (dd, *J*=3.54, 1.77 Hz, 1 H), 6.92 - 7.07 (m, 2 H), 7.36 (br s, 1 H), 7.79 (dd, *J*=1.64, 0.63 Hz, 1 H), 8.04 (dd, *J*=3.54, 0.51 Hz, 1 H), 8.32 (s, 1 H). [M+H] calc'd for $C_{17}H_{19}FN_4O_3$, 347; found, 347.

[0832] EXAMPLE 114: (*R*)-2-(7-Fluoro-4-(furan-3-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide



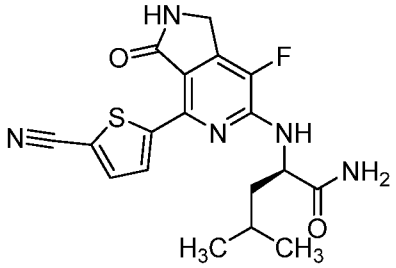
[0833] The title compound was prepared in a manner similar to EXAMPLE 70 using 2-(furan-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane in place of 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.80 - 0.99 (m, 6 H), 1.21 - 1.33 (m, 1 H), 1.50 - 1.60 (m, 1 H), 1.74 - 1.81 (m, 1 H), 4.38 (s, 2 H), 4.47 - 4.61 (m, 1 H), 6.89 - 6.98 (m, 1 H), 7.03 (d, *J*=7.81 Hz, 1 H), 7.35 (s, 1 H), 7.42 (s, 1 H), 7.68 (s, 1 H), 8.35 (s, 1 H), 8.98 (s, 1 H). [M+H] calc'd for $C_{17}H_{19}FN_4O_3$, 347; found, 347.

[0834] EXAMPLE 115: (*R*)-2-(7-Fluoro-4-(furan-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide

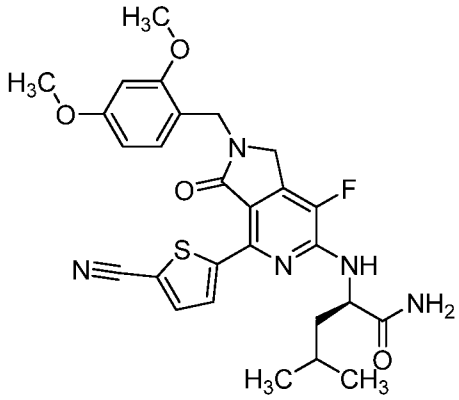


[0835] The title compound was prepared in a manner similar to EXAMPLE 113 using tributyl(5-methylfuran-2-yl)stannane *tert*-butyl in place of tributyl(furan-2-yl)stannane. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.84 - 0.97 (m, 6 H), 1.51 - 1.78 (m, 3 H), 2.29 - 2.36 (m, 3 H), 4.36 (s, 2 H), 4.64 - 4.86 (m, 1 H), 6.22 (dd, *J*=3.28, 1.01 Hz, 1 H), 6.92 (d, *J*=8.08 Hz, 1 H), 7.01 (br s, 1 H), 7.41 (br s, 1 H), 7.97 (d, *J*=3.03 Hz, 1 H), 8.26 (s, 1 H). [M+H] calc'd for $C_{18}H_{21}FN_4O_3$, 361; found, 361.

[0836] EXAMPLE 116: (*R*)-2-(4-(5-Cyanothiophen-2-yl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide



[0837] A. (*R*)-2-(4-(5-Cyanothiophen-2-yl)-2-(2,4-dimethoxybenzyl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide

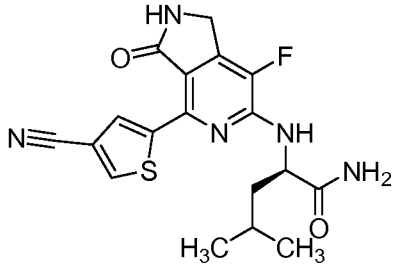


[0838] A solution of (*R*)-2-(4-chloro-2-(2,4-dimethoxybenzyl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide (114 mg, 0.245 mmol), 5-cyanothiophen-2-ylboronic acid (113 mg, 0.736 mmol), tris(dibenzylideneacetone)dipalladium(0) (13.47 mg, 0.015 mmol), and 2-(dicyclohexylphosphino)biphenyl (5.16 mg, 0.015 mmol) in dioxane (2 mL) and DMF (0.5 mL) was heated to 160°C under microwave irradiation for 45 min. UPLC showed 50% conversion. The reaction mixture was subsequently heated at 160°C under microwave irradiation for 45 min. Additional 5-cyanothiophen-2-ylboronic acid (113 mg, 0.736 mmol) was added and the reaction mixture was heated at 160°C under microwave irradiation for 60 min. After removal of the solvent, the resulting crude material was reconstituted in MeOH/DMF (6.0 mL) and purified via preparative HPLC eluting with water (0.05% TFA) and ACN (40-80% gradient, 0.035% TFA). The collected fractions were stripped to dryness via rotary evaporation to yield the title compound. [M+H] calc'd for $C_{27}H_{28}FN_5O_4S$, 538; found, 538.

[0839] B. (*R*)-2-(4-(5-Cyanothiophen-2-yl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide

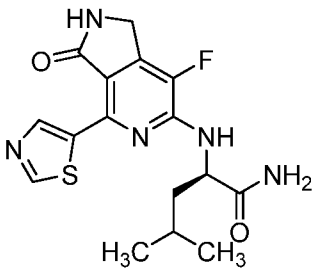
[0840] A solution of (*R*)-2-(4-(5-cyanothiophen-2-yl)-2-(2,4-dimethoxybenzyl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridin-6-ylamino)-4-methylpentanamide (68 mg, 0.126 mmol) in TFA (2 mL) was heated to 65°C for 3 h. After removal of the solvent, the resulting crude material was reconstituted in MeOH/DCM (3.0 mL) and purified via preparative HPLC eluting with water (0.05% TFA) and ACN (40%, 0.035% TFA). The collected fractions were combined and the solvent was removed via rotary evaporation to yield the title compound (8.3 mg, 17%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.86 - 0.96 (m, 6 H), 1.53 - 1.62 (m, 1 H), 1.67 - 1.88 (m, 2 H), 4.45 (s, 2 H), 4.50 - 4.57 (m, 1 H), 6.96 - 7.06 (m, 1 H), 7.32 - 7.54 (m, 2 H), 7.86 - 8.02 (m, 1 H), 8.61 (s, 1 H), 9.00 - 9.15 (m, 1 H). [M+H] calc'd for $C_{18}H_{18}FN_5O_2S$, 388; found, 388.

[0841] EXAMPLE 117: (*R*)-2-(4-(4-Cyanothiophen-2-yl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide



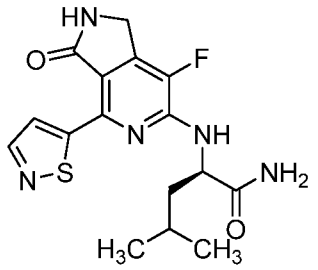
[0842] The title compound was prepared in a manner similar to EXAMPLE 116 using 4-cyanothiophen-2-ylboronic acid in place of 5-cyanothiophen-2-ylboronic acid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.80 - 0.96 (m, 6 H), 1.55 - 1.66 (m, 1 H), 1.65 - 1.86 (m, 2 H), 4.44 (s, 2 H), 4.51 - 4.64 (m, 1 H), 6.99 (s, 1 H), 7.04 - 7.20 (m, 1 H), 7.32 (d, *J*=8.30 Hz, 1 H), 7.37 (s, 1 H), 8.53 - 8.68 (m, 1 H), 9.24 (s, 1 H). [M+H] calc'd for $C_{18}H_{18}FN_5O_2S$, 388; found, 388.

[0843] EXAMPLE 118: (*R*)-2-(7-Fluoro-3-oxo-4-(thiazol-5-yl)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide



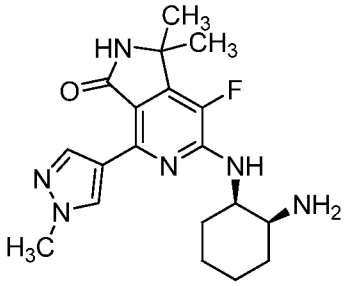
[0844] The title compound was prepared in a manner similar to EXAMPLE 113 using 5-(tributylstannyl)thiazole in place of tributyl(furan-2-yl)stannane. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.77 - 0.98 (m, 6 H), 1.53 - 1.68 (m, 1 H), 1.71 - 1.84 (m, 2 H), 4.42 (s, 2 H), 4.52 - 4.66 (m, 1 H), 6.95 (br s, 1 H), 7.18 (d, *J*=8.59 Hz, 1 H), 7.34 (br s, 1 H), 8.46 (s, 1 H), 9.11 (s, 1 H), 9.46 (s, 1 H). [M+H] calc'd for $C_{16}H_{18}FN_5O_2S$, 364; found, 364.

[0845] EXAMPLE 119: (*R*)-2-(7-Fluoro-4-(isothiazol-5-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide

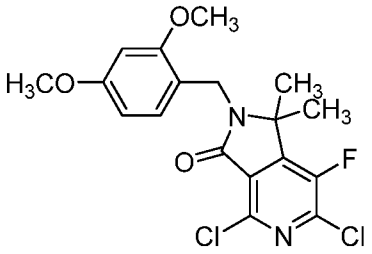


[0846] The title compound was prepared in a manner similar to EXAMPLE 116 using 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isothiazole in place of 5-cyanothiophen-2-ylboronic acid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.77 - 0.97 (m, 6 H), 1.56 - 1.64 (m, 1 H), 1.67 - 1.86 (m, 2 H), 4.45 (s, 2 H), 4.49 - 4.62 (m, 1 H), 7.00 (s, 1 H), 7.33 (d, *J*=8.30 Hz, 1 H), 7.44 (s, 1 H), 8.53 - 8.65 (m, 2 H), 8.91 (d, *J*=1.46 Hz, 1 H). [M+H] calc'd for $C_{16}H_{18}FN_5O_2S$, 364; found, 364.

[0847] EXAMPLE 120: 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-1,1-dimethyl-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

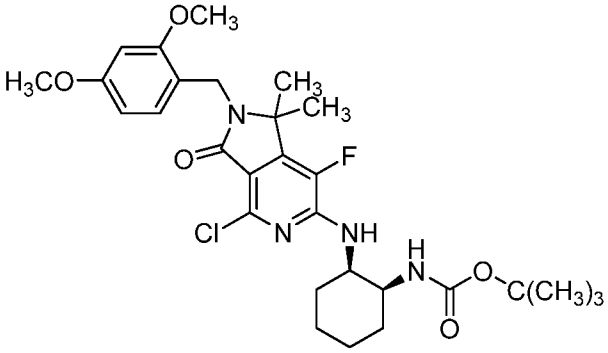


[0848] A. 4,6-Dichloro-2-(2,4-dimethoxybenzyl)-7-fluoro-1,1-dimethyl-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



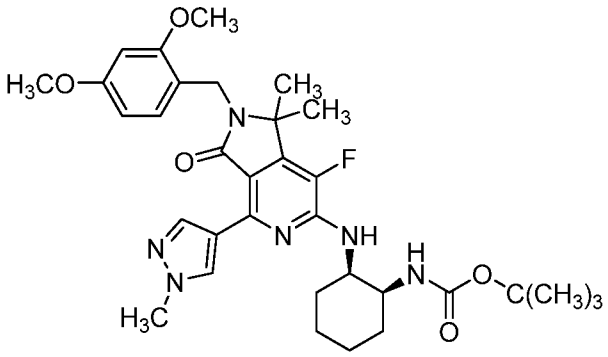
[0849] To a solution of 4,6-dichloro-2-(2,4-dimethoxybenzyl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one (500 mg, 1.347 mmol) in DMF (5 mL) at 0°C was added sodium hydride (53.9 mg, 1.347 mmol) and iodomethane (0.084 mL, 1.347 mmol). The mixture was stirred at 0°C for 1 h, then diluted to EtOAc (200 mL) and washed with brine (200 mL) and water (200 mL). The organic phase was dried and concentrated to a residue, which was purified by reverse phase preparative HPLC to give the title compound as one of the products (50 mg, 9%, mono-methylated product was observed). [M+H] calc'd for $C_{18}H_{17}Cl_2FN_2O_3$, 400.2; found, 399.4.

[0850] B. *tert*-Butyl (1*S*,2*R*)-2-(4-chloro-2-(2,4-dimethoxybenzyl)-7-fluoro-1,1-dimethyl-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate



[0851] In a 10 mL sealed cap glass vial, 4,6-dichloro-2-(2,4-dimethoxybenzyl)-7-fluoro-1,1-dimethyl-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one (50 mg, 0.125 mmol) and *tert*-butyl (1*S*,2*R*)-2-aminocyclohexylcarbamate (53.2 mg, 0.250 mmol) were dissolved in ACN (2 mL). *N*-ethyldiisopropylamine (0.033 mL, 0.188 mmol) was added, the cap was sealed, and the reaction mixture heated at 95°C for 72 h. The reaction mixture was subsequently purified by preparative HPLC and basified to give the title compound as a light yellow solid (40 mg, 55%). [M+H] calc'd for $C_{29}H_{38}ClFN_4O_5$, 578.1; found, 577.4.

[0852] C. *tert*-Butyl (1*S*,2*R*)-2-(2-(2,4-dimethoxybenzyl)-7-fluoro-1,1-dimethyl-4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate

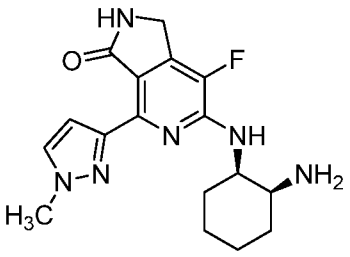


[0853] In a sealed tube, a mixture of *tert*-butyl (1*S*,2*R*)-2-(4-chloro-2-(2,4-dimethoxybenzyl)-7-fluoro-1,1-dimethyl-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (30 mg, 0.052 mmol), Na_2CO_3 aq (2M, 0.065 mL, 0.130 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (12.98 mg, 0.062 mmol), bis(triphenylphosphine)palladium chloride (3.65 mg, 5.20 μmol), and DMF (1 mL) was heated at 160°C for 0.5 h in a microwave oven. The reaction mixture was then heated at 160°C for an additional 4 h in a microwave oven and was subsequently purified by preparative HPLC to give the title compound as a light yellow solid (5 mg, 18%). [M+H] calc'd for $C_{28}H_{35}FN_6O_3$, 524; found 524.

[0854] D. 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-1,1-dimethyl-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

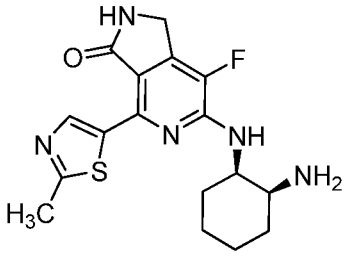
[0855] A solution of *tert*-butyl (1*S*,2*R*)-2-(2-(2,4-dimethoxybenzyl)-7-fluoro-1,1-dimethyl-4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (5 mg, 9.57 μmol) in TFA (1 mL) was heated at 60°C for 0.5 h. The reaction mixture was subsequently purified by preparative HPLC and the product lyophilized to give the title compound as a TFA salt (2 mg, 56%). [M+H] calc'd for $C_{19}H_{25}FN_6$, 374; found, 374.

[0856] EXAMPLE 121: ((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-3-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

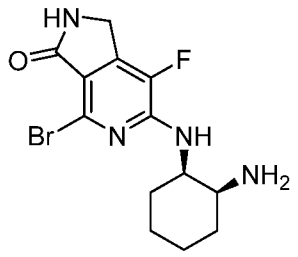


[0857] In a 30 mL sealed cap glass vial, *tert*-butyl (1*S*,2*R*)-2-(4-chloro-2-(2,4-dimethoxybenzyl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (350 mg, 0.637 mmol), 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (172 mg, 0.829 mmol) and $PdCl_2(PPh_3)_2$ (44.7 mg, 0.064 mmol) were dissolved in dioxane (5 mL). An aqueous solution of Na_2CO_3 (2M, 0.5 mL) was added and the cap was sealed. The reaction mixture was heated at 85°C for 4 h, then diluted with water (5 mL), and extracted with EtOAc (2 x 30 mL). The organic phase was dried over Na_2SO_4 and the solvent evaporated. The resulting residue was treated with TFA (4 mL) and heated at 80°C for 1.5 h to remove the protecting groups. Next, TFA was evaporated and the product was dissolved in DMSO (8 mL) and purified by preparative HPLC. The pure fractions were combined, concentrated, and lyophilized to give a TFA salt of the title compound as a white solid (52.3 mg, 24%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.40 - 1.95 (m, 8 H), 3.64 (br s, 1 H), 3.92 (s, 2 H), 4.28 - 4.49 (m, 3 H), 6.76 (d, *J*=5.31 Hz, 1 H), 7.42 (d, *J*=2.27 Hz, 1 H), 7.72 (d, *J*=2.27 Hz, 1 H), 7.98 (br s, 3 H), 8.39 (s, 1 H). [M+H] calc'd for $C_{17}H_{21}FN_6O$, 345; found, 345.

[0858] EXAMPLE 122: 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(2-methylthiazol-5-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



[0859] A. 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-bromo-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

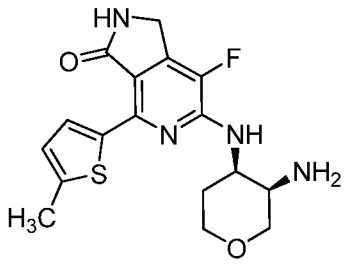


[0860] A mixture of *tert*-butyl (1*S*,2*R*)-2-(4-chloro-2-(2,4-dimethoxybenzyl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (200 mg, 0.364 mmol) and hydrobromic acid in HOAc (10 mL) was stirred at 90°C for 6 h. The mixture was concentrated under reduced pressure, and the resulting crude material was reconstituted in MeOH (1.0 mL) and was purified via preparative HPLC eluting with water (0.05% TFA) and ACN (15-30% gradient, 0.035% TFA). The collected fractions were combined and ACN was removed via rotary evaporation. The resulting aqueous solution was neutralized with saturated aqueous $NaHCO_3$, washed with EtOAc (2 x 200 mL), dried over Na_2SO_4, and filtered. The organic phase was stripped to dryness via rotary evaporation to yield the title compound (38 mg, 30%). [M+H] calc'd for $C_{13}H_{16}BrFN_4O$, 343; found, 343.

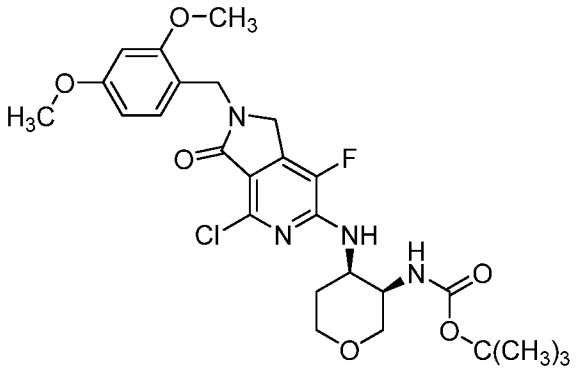
[0861] B. 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(2-methylthiazol-5-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

[0862] A solution of 6-((1*R*,2*S*)-2-aminocyclohexylamino)-4-bromo-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one (38 mg, 0.111 mmol), 2-methylthiazole-5-carboxylic acid (15.85 mg, 0.111 mmol), silver(I) acetate (18.48 mg, 0.111 mmol), and copper(II) chloride (14.89 mg, 0.111 mmol) in toluene (1.8 mL) and DMA (0.2 mL) was heated to 135°C overnight. The reaction mixture was filtered through a pad of Celite and the solvent was removed *in vacuo*. The resulting crude material was reconstituted in MeOH/DMF (10.0 mL) and purified via preparative HPLC eluting with water (0.05% TFA) and ACN (50-90% gradient, 0.035% TFA). The collected fractions were combined and the solvent was stripped to dryness via rotary evaporation to yield the title compound as a TFA salt (2.3 mg, 6%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.37 - 1.85 (m, 8 H) 2.93 (s, 2 H) 2.97 - 3.08 (m, 3 H) 4.22 - 4.42 (m, 2 H) 6.52 (s, 1 H) 7.53 (d, *J*=4.39 Hz, 1 H) 7.72 (br s, 1 H) 8.08 (br s, 1 H) 8.27 (s, 1 H) [M+H] calc'd for $C_{17}H_{20}FN_5OS$, 362; found, 362.

[0863] EXAMPLE 123: 6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(5-methylthiophen-2-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

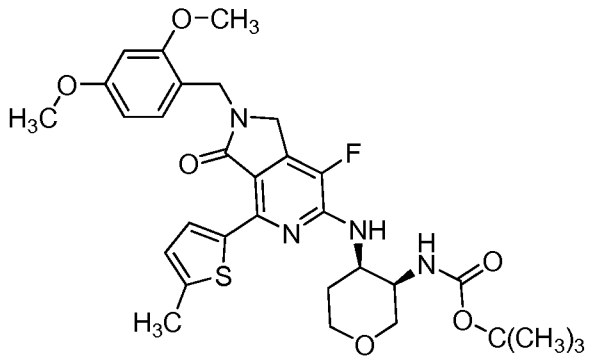


[0864] A. *tert*-Butyl (3*R*,4*R*)-4-(4-chloro-2-(2,4-dimethoxybenzyl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)tetrahydro-2*H*-pyran-3-ylcarbamate



[0865] A mixture of 4,6-dichloro-2-(2,4-dimethoxybenzyl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one (320 mg, 0.862 mmol), *tert*-butyl (3*R*,4*R*)-4-aminotetrahydro-2*H*-pyran-3-ylcarbamate (280 mg, 1.293 mmol) and DIPEA (0.226 mL, 1.293 mmol) in ACN (5 mL) was stirred at 85°C overnight. UPLC indicated the presence of starting material, so the mixture was stirred at 85°C overnight. UPLC showed about 50% conversion. Additional stirring at 85°C for 3 d and at 100°C overnight did not appreciably increase the conversion, so the reaction was stopped and the solvent was removed. The resulting crude material was reconstituted in MeOH/DMF (10 mL) and purified via preparative HPLC eluting with water (0.05% TFA) and ACN (50%, 0.035% TFA). The collected fractions were combined and the ACN was removed via rotary evaporation. The resulting aqueous solution was neutralized with saturated aqueous $NaHCO_3$, washed with EtOAc (2 x 200 mL), dried over Na_2SO_4, and filtered. The organic phase was stripped to dryness via rotary evaporation to give the title compound (51 mg, 11%). [M+H] calc'd for $C_{26}H_{32}ClFN_4O_6$, 552; found, 552.

[0866] B. *tert*-Butyl (3*R*,4*R*)-4-(2-(2,4-dimethoxybenzyl)-7-fluoro-4-(5-methylthiophen-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)tetrahydro-2*H*-pyran-3-ylcarbamate

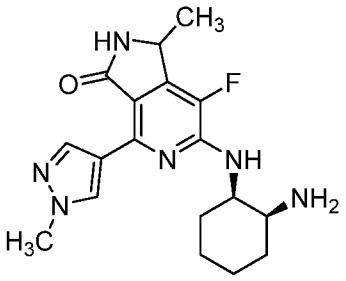


[0867] A solution of *tert*-butyl (3*R*,4*R*)-4-(4-chloro-2-(2,4-dimethoxybenzyl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)tetrahydro-2*H*-pyran-3-ylcarbamate (51 mg, 0.093 mmol), 4,4,5,5-tetramethyl-2-(5-methylthiophen-2-yl)-1,3,2-dioxaborolane (104 mg, 0.463 mmol), and bis(triphenylphosphine)palladium chloride (65.0 mg, 0.093 mmol) in dioxane (1 mL) and saturated Na_2CO_3 aq (1 mL) was heated to 140°C for 40 min. After filtering out the solids, the solvent was removed from the filtrate. The resulting residue was dissolved in MeOH and DCM (10 mL) and was purified via preparative HPLC eluting with water (0.05% TFA) and ACN (80%, 0.035 %TFA). The collected fractions were combined and solvent was stripped to dryness via rotary evaporation to give the title compound (31 mg, 55%). [M+H] calc'd for$C_{31}H_{37}FN_4O_6S$, 613; found, 613.

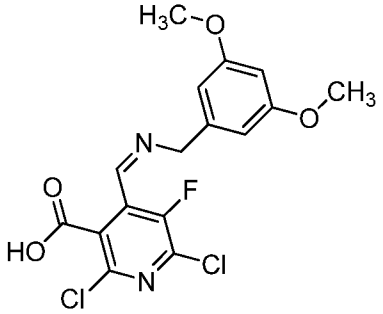
[0868] C. 6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(5-methylthiophen-2-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

[0869] A solution of *tert*-butyl (3*R*,4*R*)-4-(2-(2,4-dimethoxybenzyl)-7-fluoro-4-(5-methylthiophen-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)tetrahydro-2*H*-pyran-3-ylcarbamate (31 mg, 0.051 mmol) in TFA (10 mL) was heated to 80°C for 1 h. After the solvent was removed, the residue was dissolved in MeOH and DCM (8 mL) and was purified via preparative HPLC eluting with water (0.05% TFA) and ACN (15-30% gradient, 0.035% TFA). The collected fractions were combined and the solvent was stripped to dryness via rotary evaporation to give the title compound as a TFA salt (13.5 mg, 74%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.78 (d, *J*=13.18 Hz, 1 H), 2.03 - 2.18 (m, 1 H), 2.46 (s, 3 H), 3.17 (d, *J*=4.88 Hz, 1 H), 3.55 - 3.65 (m, 1 H), 3.75 (d, *J*=13.18 Hz, 1 H), 3.85 (br s, 1 H), 3.96 - 4.06 (m, 2 H), 4.41 (d, *J*=7.81 Hz, 2 H), 6.84 (d, *J*=2.44 Hz, 1 H), 7.22 (d, *J*=4.88 Hz, 1 H), 7.92 (br s, 2 H), 8.47 (s, 1 H), 8.83 (d, *J*=3.42 Hz, 1 H). [M+H] calc'd for $C_{17}H_{19}FN_4O_2S$, 363; found, 363.

[0870] EXAMPLE 124: 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-1-methyl-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

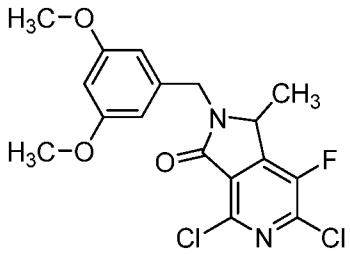


[0871] A. 2,6-Dichloro-4-((3,5-dimethoxybenzylimino)methyl)-5-fluoronicotinic acid



[0872] A. To a solution of (2,4-dimethoxyphenyl)methanamine (4.4 g, 26.6 mmol) in MeOH (50 mL) was added 4,6-dichloro-7-fluoro-1-hydroxyfuro[3,4-*c*]pyridin-3(1*H*)-one (6.0 g, 25.3 mmol). The mixture was stirred for 0.5 h, filtered, and washed with petroleum ether to give the title compound as a white solid (5.8 g, 60%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.75 (s, 3 H), 3.79 (s, 3 H), 3.93 (s, 2 H), 6.30 (s, 1 H), 6.40-6.42 (m, 2 H), 7.12 (d, *J*=8.4 Hz, 1 H).

[0873] B. 4,6-Dichloro-2-(3,5-dimethoxybenzyl)-7-fluoro-1-methyl-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



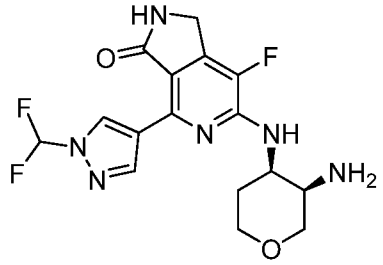
[0874] To a mixture of 2,6-dichloro-4-((3,5-dimethoxybenzylimino)methyl)-5-fluoronicotinic acid (5.8 g, 25.3 mmol) in THF (120 mL) was added methyl-lithium (60.0 mL, 126.6 mmol) drop wise at -78°C. After the addition was completed, the mixture was stirred for an additional 2 h. The reaction mixture was acidified with 1N HCl to pH 7 and

THF was removed under reduced pressure. The mixture was extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, and purified by silica gel chromatography eluting with PE-EtOAc (5:1) to give the title compound as a white solid (0.93 g, 16%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.58 (d, *J*=6.8 Hz, 3 H), 3.79 (s, 3 H), 3.84 (s, 3 H), 4.35 (d, *J*=14.4 Hz, 1 H), 4.52 (q, *J*=6.8 Hz, 1 H), 5.07 (d, *J*=14.4 Hz, 1 H), 6.43-6.45 (m, 2 H), 7.28 (d, *J*=9.2 Hz, 1 H). [M+H] calc'd for $C_{17}H_{15}Cl_2FN_2O_3$, 386; found, 385.

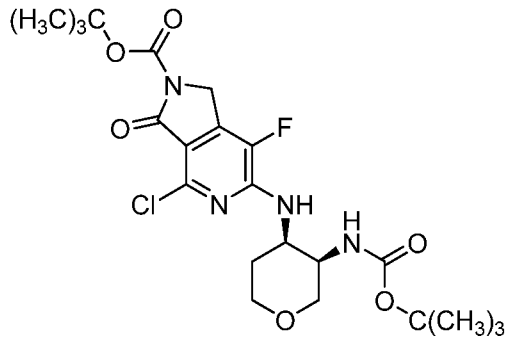
[0875] C. 6-((*1R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-1-methyl-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

[0876] A mixture of 6-((1*R*,2*S*)-2-aminocyclohexylamino)-2-(2,4-dimethoxybenzyl)-7-fluoro-1-methyl-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one (20 mg, 0.039 mmol) and TFA (1 mL) was heated at 60°C for 2 h. Following reaction, the mixture was purified by preparative HPLC eluting with water (0.05% TFA) and ACN (15-25% gradient, 0.035% TFA) to give the title compound as a TFA salt (10 mg, 71%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.41 (d, *J*=6.59 Hz, 3 H), 1.46 (d, *J*=7.02 Hz, 2 H), 1.60-1.84 (m, 5 H), 3.68 (br s, 1 H), 3.89 (s, 2 H), 4.44 (br s, 1 H), 4.71 (q, *J*=6.65 Hz, 1 H), 6.52 (br s, 1 H), 6.73 (d, *J*=6.53 Hz, 1 H), 7.72 (br s, 2 H), 8.24 - 8.32 (m, 1 H), 8.46 (s, 1 H), 8.82 (s, 1 H). [M+H] calc'd for $C_{18}H_{23}FN_6O$, 359; found, 359.

[0877] EXAMPLE 125: 6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-4-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

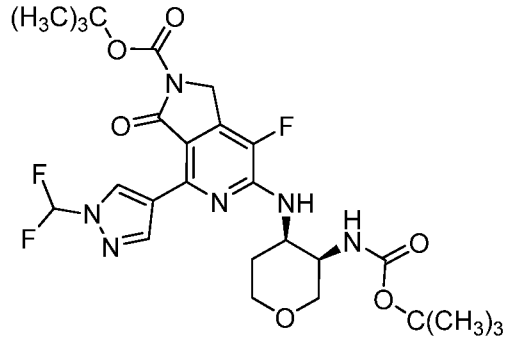


[0878] A. *tert*-Butyl 6-((3*R*,4*R*)-3-(*tert*-butoxycarbonylamino)tetrahydro-2*H*-pyran-4-ylamino)-4-chloro-7-fluoro-3-oxo-1*H*-pyrrolo[3,4-*c*]pyridine-2(3*H*)-carboxylate



[0879] A mixture of *tert*-butyl 4,6-dichloro-7-fluoro-3-oxo-1*H*-pyrrolo[3,4-*c*]pyridine-2(3*H*)-carboxylate (1.42 g, 4.43 mmol), *tert*-butyl (3*R*,4*R*)-4-aminotetrahydro-2*H*-pyran-3-ylcarbamate (1.15 g, 5.52 mmol), diisopropylethylamine (3.87 mL, 22.16 mmol) in DMSO (10 mL) and 2-propanol (40 mL) were heated to 100°C in an oil bath for 20 h. The solution was then concentrated and the resulting oil was dissolved in water (50 mL) and heated in an oil bath to 50°C for 1 h then allowed to cool to RT. The solution was subsequently heated to 50°C for 15 min, allowed to cool to RT, again heated to 50°C for 15 min, and allowed to cool to RT. The resulting precipitate was filtered and rinsed with water to give the title compound as a pale pinkish-white solid (1.90 g, 86%, 4:1 mixture with regioisomer) which was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.36 (s, 9 H), 1.50 (s, 3 H), 1.59-1.61 (m, 1 H), 1.97-1.99 (m, 1 H), 1.97-1.99 (m, 1 H), 3.46-3.49 (m, 2 H), 3.80-3.83 (m, 3 H), 4.31-4.33 (m, 1 H), 4.73 (s, 1 H), 6.59 (d, *J*=7.30 Hz, 1 H), 7.43 (d, *J*=7.30 Hz, 1 H). [M+H] calc'd for $C_{22}H_{30}ClFN_4O_6$, 501; found, 501.

[0880] B. *tert*-Butyl 6-((3*R*,4*R*)-3-(*tert*-butoxycarbonylamino)tetrahydro-2*H*-pyran-4-ylamino)-4-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-7-fluoro-3-oxo-1*H*-pyrrolo[3,4-*c*]pyridine-2(3*H*)-carboxylate



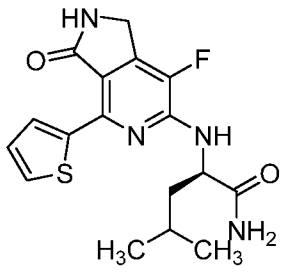
[0881] A mixture of *tert*-butyl 6-((3*R*,4*R*)-3-(*tert*-butoxycarbonylamino)tetrahydro-2*H*-pyran-4-ylamino)-4-chloro-7-fluoro-3-oxo-1*H*-pyrrolo[3,4-*c*]pyridine-2(3*H*)-

carboxylate (500 mg, 0.998 mmol), 1-(difluoromethyl)-1*H*-pyrazol-4-ylboronic acid (808 mg, 4.99 mmol), bis(triphenylphosphine)palladium chloride (70.1 mg, 0.100 mmol) in dioxane (15 mL) and 2M saturated sodium carbonate (2 mL) were heated to 100°C in a microwave for 30 min. The solution was concentrated and was purified by preparatory HPLC eluting with water (10 mM NH_4HCO_3) and ACN/water (80/20 v/v, 15-30% gradient, 10 mM NH_4HCO_3) to give the title compound as a white solid (132 mg, 23%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.35 (s, 9 H), 1.52 (s, 9 H), 1.55-1.56 (m, 1 H), 2.46-2.47 (m, 1 H), 3.57-3.59 (m, 2 H), 3.81-3.84 (m, 3 H), 4.61-4.62 (m, 1 H), 4.78 (s, 2 H), 6.61 (d, *J*=6.35 Hz, 1 H), 7.15 (d, *J*=6.83 Hz, 1 H), 7.97 (s, 1 H), 8.54 (s, 1 H), 9.24 (s, 1 H). [M+H] calc'd for $C_{26}H_{33}F_3N_6O_6$, 583; found, 583.

[0882] C. 6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-4-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

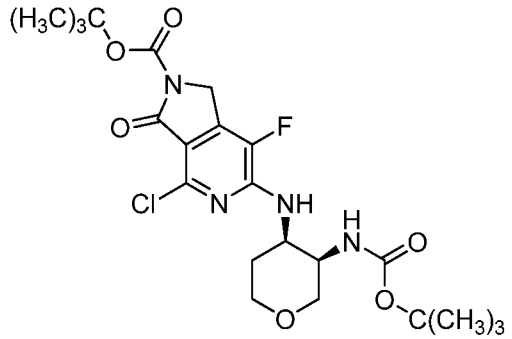
[0883] *tert*-Butyl 6-((3*R*,4*R*)-3-(*tert*-butoxycarbonylamino)tetrahydro-2*H*-pyran-4-ylamino)-4-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-7-fluoro-3-oxo-1*H*-pyrrolo[3,4-*c*]pyridine-2(3*H*)-carboxylate (126 mg, 0.998 mmol) was dissolved in 2-propanol (5 mL) and the solution was heated to 75°C with a heating block. Then 2M HCl (2.5 mL) was added, the temperature was lowered to 65°C, and the reaction mixture was stirred for 3 h. The solution was concentrated and purified by preparatory HPLC eluting with water (10 mM NH_4HCO_3) and ACN/water (80/20 v/v, 10-50% gradient, 10 mM NH_4HCO_3) to give the title compound as a white solid (79 mg, 96%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.75-1.77 (m, 1 H), 2.09-2.12 (m, 1 H), 3.60-3.63 (m, 1 H), 3.76-3.77 (m, 1 H), 3.88-3.98 (m, 3 H), 4.44 (d, *J*=6.35 Hz, 2 H), 4.54-4.55 (m, 1 H), 7.17 (d, *J*=5.86 Hz, 1 H), 7.89 (br s, 1 H), 8.54 (s, 1 H), 8.58 (s, 1 H), 9.43 (s, 1 H). [M+H] calc'd for $C_{16}H_{17}F_3N_6O_2$, 383; found, 383.

[0884] EXAMPLE 126: (*R*)-2-(7-Fluoro-3-oxo-4-(thiophen-2-yl)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide



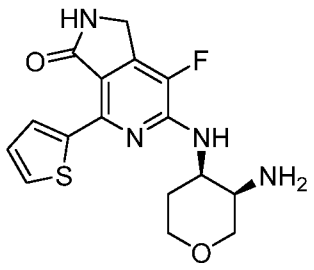
[0885] The title compound was prepared in a manner similar to EXAMPLE 113 using tributyl(thiophen-2-yl)stannane in place of tributyl(furan-2-yl)stannane. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.80 - 0.99 (m, 6 H), 1.51 - 1.84 (m, 3 H), 4.40 (s, 2 H), 4.59 - 4.76 (m, 1 H), 6.99 (br s, 1 H), 7.06 - 7.17 (m, 2 H), 7.34 (br s, 1 H), 7.61 (d, *J*=4.88 Hz, 1 H), 8.40 (s, 1 H), 8.93 - 9.05 (m, 1 H). [M+H] calc'd for $C_{17}H_{19}FN_4O_2S$, 363; found, 363.

[0886] PREPARATION 51: *tert*-Butyl 6-((3*R*,4*R*)-3-(*tert*-butoxycarbonylamino)tetrahydro-2*H*-pyran-4-ylamino)-4-chloro-7-fluoro-3-oxo-1*H*-pyrrolo[3,4-*c*]pyridine-2(3*H*)-carboxylate

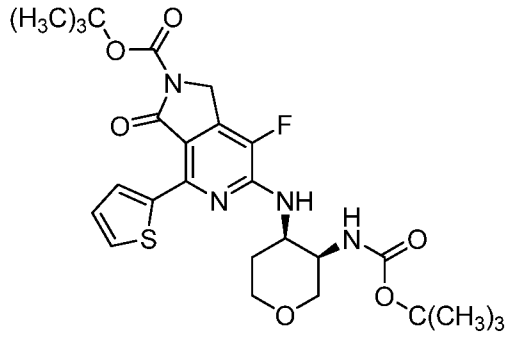


[0887] A mixture of *tert*-butyl 4,6-dichloro-7-fluoro-3-oxo-1*H*-pyrrolo[3,4-*c*]pyridine-2(3*H*)-carboxylate (1.24 g, 3.85 mmol), *tert*-butyl (3*R*,4*R*)-4-aminotetrahydro-2*H*-pyran-3-ylcarbamate (1.00 g, 4.62 mmol), diisopropylethylamine (3.36 mL, 19.27 mmol) in DMSO (10 mL) and 2-propanol (40 mL) were heated to 100°C in an oil bath for 20 h. The reaction was repeated on the same scale and both reaction solutions were combined and concentrated. The mixture was purified via silica gel flash chromatography eluting with EtOAc and hexanes (10-50% EtOAc gradient) to give the title compound as a pale pinkish-white solid (510 mg, 13%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.36 (s, 9 H), 1.50 (s, 3 H), 1.59-1.61 (m, 1 H), 1.97-1.99 (m, 1 H), 1.97-1.99 (m, 1 H), 3.46-3.49 (m, 2 H), 3.80-3.83 (m, 3 H), 4.31-4.33 (m, 1 H), 4.73 (s, 1 H), 6.59 (d, *J*=7.30 Hz, 1 H), 7.43 (d, *J*=7.30 Hz, 1 H). [M+H] calc'd for $C_{22}H_{30}ClFN_4O_6$, 501; found, 501.

[0888] EXAMPLE 127: 6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(thiophen-2-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



[0889] A. *tert*-Butyl 6-((3*R*,4*R*)-3-(*tert*-butoxycarbonylamino)tetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-3-oxo-4-(thiophen-2-yl)-1*H*-pyrrolo[3,4-*c*]pyridine-2(3*H*)-carboxylate



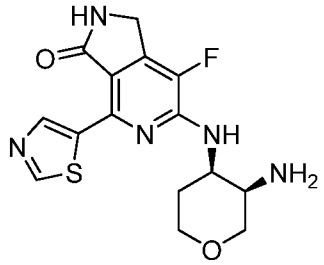
[0890] A solution of *tert*-butyl 6-((3*R*,4*R*)-3-(*tert*-butoxycarbonylamino)tetrahydro-2*H*-pyran-4-ylamino)-4-chloro-7-fluoro-3-oxo-1*H*-pyrrolo[3,4-*c*]pyridine-2(3*H*)-carboxylate (50 mg, 0.1 mmol), tributyl(thiophen-2-yl)stannane (44.7 mg, 0.12 mmol) and tetrakis(triphenylphosphine)palladium(0) (115 mg, 0.1 mmol) in toluene (3 mL) was heated to 102°C for 24 h. The solid was filtered though a pad of Celite, and resulting crude material was reconstituted in MeOH/DCM (20 mL) and purified via preparative HPLC. The collected fractions were combined and stripped to dryness via rotary evaporation to yield the title compound (30 mg, 55%).

[0891] B. 6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(thiophen-2-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

[0892] A solution of *tert*-butyl 6-((3*R*,4*R*)-3-(*tert*-butoxycarbonylamino)tetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-3-oxo-4-(thiophen-2-yl)-1*H*-pyrrolo[3,4-*c*]pyridine-2(3*H*)-carboxylate (30 mg, 0.055 mmol) in TFA/DCM (1:1, 10 mL) was stirred at RT for 2 h. The solvent was removed and the resulting crude material was reconstituted in MeOH/DCM (20 mL) and purified via preparative HPLC. The collected fractions were combined and stripped to dryness via rotary evaporation to yield the title compound (16 mg, 85%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.79 (d, *J*=9.76 Hz, 1 H), 2.12 (qd, *J*=12.94, 5.13 Hz, 1 H), 3.56 - 3.68 (m, 1 H), 3.75 (d, *J*=11.72 Hz, 1 H), 3.89 (br s, 1 H),

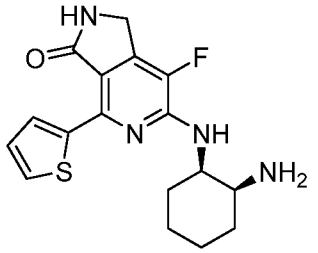
4.02 (d, *J*=11.72 Hz, 2 H), 4.28 - 4.37 (m, 1 H), 4.38 - 4.49 (m, 2 H), 7.10 - 7.20 (m, 1 H), 7.28 (d, *J*=4.88 Hz, 1 H), 7.59 - 7.70 (m, 1 H), 7.93 (br s, 2 H), 8.52 (s, 1 H), 9.02 (dd, *J*=3.91, 0.98 Hz, 1 H). [M+H] calc'd for $C_{16}H_{17}FN_4O_2S$, 349; found, 349.

[0893] EXAMPLE 128: 6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(thiazol-5-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



[0894] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 127 using 5-(tributylstannyl)thiazole in place of tributyl(thiophen-2-yl)stannane. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.78 (dd, *J*=13.67, 4.39 Hz, 1 H), 2.04 - 2.20 (m, 1 H), 3.53 - 3.66 (m, 1 H), 3.69 - 3.85 (m, 2 H), 4.01 (d, *J*=11.72 Hz, 2 H), 4.25 - 4.38 (m, 1 H), 4.41 - 4.55 (m, 2 H), 7.38 (s, 1 H), 7.94 (br s, 2 H), 8.62 (s, 1 H), 9.15 (s, 1 H), 9.52 (s, 1 H). [M+H] calc'd for $C_{15}H_{16}FN_5O_2S$, 350; found, 350.

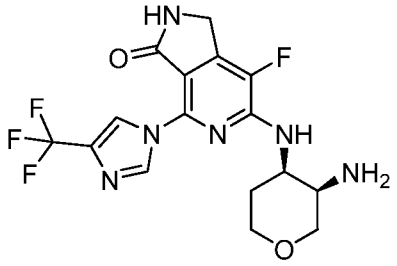
[0895] EXAMPLE 129: 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(thiophen-2-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



[0896] In a 30 mL sealed cap glass vial, *tert*-butyl (1*S*,2*R*)-2-(4-chloro-2-(2,4-dimethoxybenzyl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (300 mg, 0.546 mmol), 4,4,5,5-tetramethyl-2-(thiophen-2-yl)-1,3,2-dioxaborolane (172 mg, 0.820 mmol), and trans-dichloro-bis(triphenylphosphine)palladium-II (38.4 mg, 0.055 mmol) were dissolved in dioxane (5 mL). An aqueous solution of 2N Na_2CO_3 (0.5 mL) was added, the cap was sealed, and the mixture was allowed to react at 85°C for 3 h. The reaction mixture was subsequently diluted with water (5 mL) and extracted into EtOAc (2 x 30 mL). The organic layer was dried over sodium sulfate and evaporated. The resulting residue was treated with TFA (4

mL) and heated at 80°C for 1 h to remove the protecting groups. Next, TFA was evaporated from the reaction mixture. The product was reconstituted in DMSO (8 mL) and was then purified via preparative HPLC eluting with water (0.05% TFA) and ACN (15-45% gradient, 0.035% TFA). The pure fractions were combined and evaporated to a minimal volume. Saturated aq $NaHCO_3$ (10 mL) was added and the mixture was extracted with EtOAc (3 x 25 mL). The organic layers were combined, dried over sodium sulfate, and evaporated to give the title compound as a pale yellow solid (83 mg, 44%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.16 - 1.80 (m, 8 H), 3.18 (br s, 1 H), 3.86 - 4.11 (m, 1 H), 4.39 (s, 2 H), 6.60 (d, *J*=6.57 Hz, 1 H), 7.13 (dd, *J*=5.05, 3.79 Hz, 1 H), 7.60 (dd, *J*=5.18, 1.14 Hz, 1 H), 8.39 (s, 1 H), 9.00 (dd, *J*=3.79, 1.01 Hz, 1 H). [M+H] calc'd for $C_{17}H_{19}FN_4OS$, 347; found, 347.

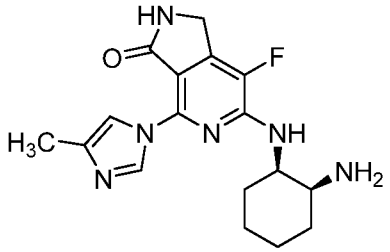
[0897] EXAMPLE 130: 6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(4-(trifluoromethyl)-1*H*-imidazol-1-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



[0898] In a 10 mL sealed cap glass vial, *tert*-butyl 6-((3*R*,4*R*)-3-(*tert*-butoxycarbonylamino)tetrahydro-2*H*-pyran-4-ylamino)-4-chloro-7-fluoro-3-oxo-1*H*-pyrrolo[3,4-*c*]pyridine-2(3*H*)-carboxylate (60 mg, 0.120 mmol), 4-(trifluoromethyl)-1*H*-imidazole (48.9 mg, 0.359 mmol) and K_2CO_3 (66.2 mg, 0.479 mmol) were dissolved in ACN (2 mL). The cap was sealed and the mixture was reacted at 100°C for 16 h. The reaction mixture was subsequently filtered through a Buchner funnel to remove un-dissolved K_2CO_3. The solids were washed with ACN (2 x 5 mL) and the filtrate was evaporated to give a residue, which was treated with TFA (2 mL) at RT for 20 min to remove the protecting groups. Next, TFA was evaporated from the reaction mixture. The product was reconstituted in DMSO (5 mL) and was then purified by preparative HPLC eluting with water (0.05% TFA) and ACN (15-45% gradient, 0.035% TFA). The pure fractions were combined, evaporated to a minimal volume, and lyophilized to give a TFA salt of the title compound as a brown solid (4.2 mg, 8.8%). ^{1}H NMR (400 MHz, DMSO-

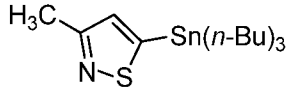
d_6) δ ppm 1.67 (m, 1 H), 2.05 (td, *J*=12.88, 7.33 Hz, 1 H), 3.30 - 3.90 (m, 4 H), 3.78 - 3.99 (m, 2 H), 4.44 (s, 2 H), 6.49 (br s, 2 H), 7.54 (d, *J*=5.56 Hz, 1 H), 7.85 (br s, 2 H), 8.67 - 8.80 (m, 2 H). [M+H] calc'd for $C_{16}H_{16}F_4N_6O_2$, 401; found, 401.

[0899] EXAMPLE 131: 6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(4-methyl-1*H*-imidazol-1-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



[0900] In a 10 mL sealed cap glass vial, *tert*-butyl (1*S*,2*R*)-2-(4-chloro-2-(2,4-dimethoxybenzyl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate (50 mg, 0.091 mmol), 4-methyl-1*H*-imidazole (22.43 mg, 0.273 mmol) and K_2CO_3 (50.3 mg, 0.364 mmol) were dissolved in ACN (2 mL). The cap was sealed and the mixture was reacted at 100°C for 16 h. The reaction mixture was subsequently filtered through a Buchner funnel to remove un-dissolved solids. The solids were washed with ACN (2 x 5 mL) and the filtrate was evaporated to give a residue, which was treated with TFA (4 mL) and heated at 80°C for 1 h to remove the protecting groups. Next, TFA was evaporated from the reaction mixture. The resulting residue was reconstituted in DMSO (5 mL) and purified via preparative HPLC eluting with water (0.05% TFA) and ACN (15-65% gradient, 0.035% TFA). The pure fractions were combined, evaporated to a minimal volume, and lyophilized to give a TFA salt of the title compound as a white solid (7.2 mg, 23%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.20-1.65 (m., 8 H), 3.65 - 3.79 (m, 5 H), 4.15 (s, 2 H), 6.40 (d, 1 H), 6.51 (d, 1 H), 6.73 (m, 1 H), 6.97 (d, 1 H), 7.26 (d, 1 H), 8.68 (br s, 1 H). [M+H] calc'd for $C_{17}H_{21}FN_6O$, 345; found, 345.

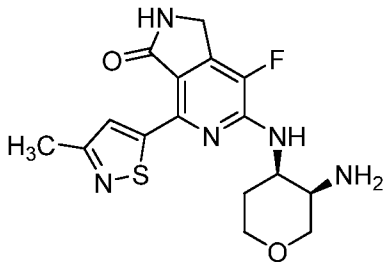
[0901] PREPARATION 52: 3-Methyl-5-(tributylstannyl)isothiazole



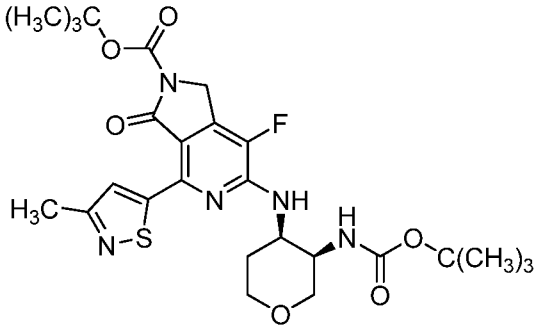
[0902] To a cold (-78°C) solution of 3-methylisothiazole (100 mg, 1.0 mmol) in anhydrous THF (2.0 mL) was added *n*-butyllithium (0.693 mL, 1.1 mmol) dropwise. After stirring for 60 min at -78°C, a solution of tributylchlorostannane (0.326 mL, 1.210 mmol)

in anhydrous THF (0.5 mL) was added to the reaction mixture. The reaction mixture was stirred for 30 min at -78°C and then allowed to warm to RT over a 2 to 3 h period. Saturated aq $NaHCO_3$ was added and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (9:1 Hexane/EtOAc, Flash 60 column) to give the title compound. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 0.86 - 0.94 (m, 9 H), 1.05 - 1.21 (m, 6 H), 1.26 - 1.38 (m, 6 H), 1.44 - 1.65 (m, 6 H), 2.56 (s, 3 H), 6.97 - 7.04 (m, 1 H).

[0903] EXAMPLE 132: 6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(3-methylisothiazol-5-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



[0904] A. *tert*-Butyl 6-((3*R*,4*R*)-3-(*tert*-butoxycarbonylamino)tetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(3-methylisothiazol-5-yl)-3-oxo-1*H*-pyrrolo[3,4-*c*]pyridine-2(3*H*)-carboxylate



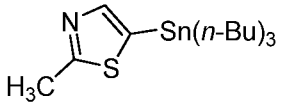
[0905] A solution of *tert*-butyl 6-((3*R*,4*R*)-3-(*tert*-butoxycarbonylamino)tetrahydro-2*H*-pyran-4-ylamino)-4-chloro-7-fluoro-3-oxo-1*H*-pyrrolo[3,4-*c*]pyridine-2(3*H*)-carboxylate (10 mg, 0.02 mmol), 3-methyl-5-(tributylstannyl)isothiazole (23.25 mg, 0.06 mmol) and tetrakis(triphenylphosphine)palladium(0) (23.07 mg, 0.02 mmol) in toluene (3 mL) was heated to 120°C for 45 min under microwave irradiation. The reaction mixture was poured into water and extracted with EtOAc. The organic extracts were dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo*. After removal of solvent, the

resulting crude material was reconstituted in DMF and purified via preparative HPLC eluting with water (0.05% TFA) and ACN (55-80% gradient, 0.035 % TFA). The collected fractions were combined and ACN was removed via rotary evaporation. The resulting aq solution was neutralized with saturated aq $NaHCO_3$ and washed with EtOAc (2 x 50 mL), dried over anhydrous Na_2SO_4, filtered, and the organic phase stripped to dryness via rotary evaporation to give the title compound. [M+H] calc'd for $C_{26}H_{34}FN_5O_6S$, 564; found, 564.

[0906] B. 6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(3-methylisothiazol-5-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

[0907] To a solution of *tert*-butyl 6-((3*R*,4*R*)-3-(*tert*-butoxycarbonylamino)tetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(3-methylisothiazol-5-yl)-3-oxo-1*H*-pyrrolo[3,4-*c*]pyridine-2(3*H*)-carboxylate (5.5 mg, 9.76 μmol) in DCM (2.0 mL) was added TFA (2.0 mL, 26.0 mmol). The reaction mixture was stirred at RT for 1 h, and concentrated *in vacuo*. The resulting crude material was reconstituted in DMF and purified via preparative HPLC eluting with water (0.05% TFA) and ACN (55-80% gradient, 0.035 % TFA). The collected fractions were combined and the ACN was removed via rotary evaporation. The resulting aq solution was neutralized with saturated aq $NaHCO_3$, washed with EtOAc (2 x 50 mL), dried over anhydrous Na_2SO_4, filtered, and the organic phase stripped to dryness via rotary evaporation. The residue was recrystallized from THF/hexane to give a TFA salt of the title compound. [M+H] calc'd for $C_{16}H_{18}FN_5O_2S$, 364; found, 364.

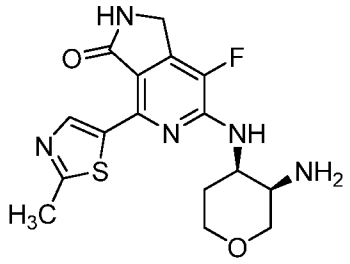
[0908] PREPARATION 53: 1: 2-Methyl-5-(tributylstannyl)thiazole



[0909] To a cold (-78°C) solution of 2-methylthiazole (2.80 g, 28.2 mmol) in anhydrous THF (100 mL) was added butyllithium (19.41 mL, 31.1 mmol) dropwise. After stirring for 60 min at -78°C, a solution of tributylchlorostannane (9.14 mL, 33.9 mmol) in anhydrous THF was added to the reaction mixture. The reaction mixture was stirred for 30 min at -78°C and then allowed to warm to RT over a 2 to 3 h period. Saturated aq $NaHCO_3$ was added and the aqueous phase was extracted with ether (3 x 200 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo*. The crude product was purified on a silica gel column eluting with 10-50% EtOAc

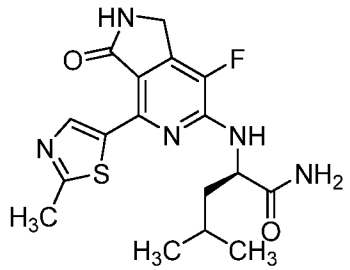
in Hexane over a 60 min period. The fractions were collected and solvent was removed *in vacuo* to give the title compound as a yellow oil (72%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.71 - 0.92 (m, 9 H), 0.96 - 1.18 (m, 6 H), 1.23 - 1.38 (m, 6 H), 1.40 - 1.64 (m, 6 H), 2.69 (s, 3 H), 7.56 (d, *J*=12.69 Hz, 1 H).

[0910] EXAMPLE 133: 6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(2-methylthiazol-5-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



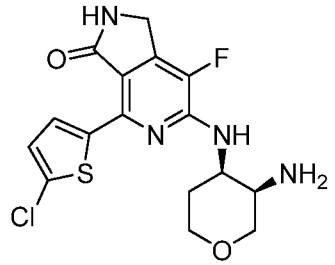
[0911] A TFA salt of the title compound was prepared in a manner similar to EXAMPLE 132 using 2-methyl-5-(tributylstannyl)thiazole in place of 3-methyl-5-(tributylstannyl)isothiazole. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.24 (s, 1 H), 1.73 (d, *J*=12.69 Hz, 1 H), 1.93 - 2.03 (m, 1 H), 2.57 - 2.71 (m, 4 H), 3.38 - 3.44 (m, 1 H), 3.48 - 3.55 (m, 1 H), 3.67 (d, *J*=11.72 Hz, 1 H), 3.82 - 3.97 (m, 2 H), 4.22 (br s, 1 H), 4.43 (s, 2 H), 7.06 (br s, 1 H), 8.52 (s, 1 H), 9.21 - 9.34 (m, 1 H). [M+H] calc'd for $C_{16}H_{18}FN_5O_2S$, 364; found, 364.

[0912] EXAMPLE 134: (*R*)-2-(7-Fluoro-4-(2-methylthiazol-5-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide



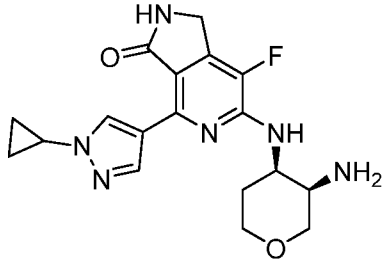
[0913] The title compound was prepared in a manner similar to EXAMPLE 113 using 2-methyl-5-(tributylstannyl)thiazole in place of tributyl(furan-2-yl)stannane. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.74 - 0.98 (m, 6 H), 1.54 - 1.63 (m, 1 H), 1.64 - 1.83 (m, 2 H), 2.61 - 2.68 (m, 3 H), 4.41 (s, 2 H), 4.56 (ddd, *J*=10.50, 8.30, 4.15 Hz, 1 H), 6.97 (s, 1 H), 7.19 (d, *J*=7.81 Hz, 1 H), 7.35 (s, 1 H), 8.45 (s, 1 H), 9.22 (s, 1 H). [M+H] calc'd for $C_{17}H_{20}FN_5O_2S$, 378; found, 378.

[0914] EXAMPLE 135: 6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-4-(5-chlorothiophen-2-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



[0915] To a solution of 6-((3*R*,4*R*)-3-aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(thiophen-2-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one (12 mg, 0.034 mmol) in DCM (3 mL) was added pyridine (8.17 mg, 0.103 mmol) and 1-chloropyrrolidine-2,5-dione (4.60 mg, 0.034 mmol). The reaction mixture was stirred at RT for 3 h. The reaction mixture was subsequently diluted with MeOH (3 mL) and was purified via preparative HPLC eluting with water (0.05% TFA) and ACN (45-70% gradient, 0.035 % TFA). The collected fractions were combined and the solvent was removed via rotary evaporation. The resulting product was purified a second time using a gradient eluent of 15-45% ACN in 0.035% TFA (aq). The collected fractions were combined and the solvent was removed via rotary evaporation to yield a TFA salt of the title compound (2 mg, 15%). ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.92 (d, *J*=13.18 Hz, 1 H), 2.14 (dd, *J*=12.69, 4.88 Hz, 1 H), 3.56 - 3.66 (m, 2 H), 3.65 - 3.78 (m, 1 H), 3.90 (d, *J*=12.20 Hz, 1 H), 4.04 - 4.19 (m, 3 H), 4.37 - 4.47 (m, 1 H), 6.99 (d, *J*=3.91 Hz, 1 H), 8.80 (d, *J*=3.91 Hz, 1 H). [M+H] calc'd for $C_{16}H_{16}ClFN_4O_2S$, 383; found, 383.

[0916] EXAMPLE 136: 6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-4-(1-cyclopropyl-1*H*-pyrazol-4-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one



[0917] A 2 mL microwave vial was charged with *tert*-butyl 6-((3*R*,4*R*)-3-(*tert*-butoxycarbonylamino)tetrahydro-2*H*-pyran-4-ylamino)-4-chloro-7-fluoro-3-oxo-1*H*-pyrrolo[3,4-*c*]pyridine-2(3*H*)-carboxylate (55 mg, 0.11 mmol), 1-cyclopropyl-4-(4,4,5,5-

tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (77 mg, 0.329 mmol), and bis(triphenylphosphine)palladium chloride (15.41 mg, 0.022 mmol) and placed under an inert environment. Dioxane (1.1 mL) was added and the yellow slurry was degassed for 5 min. To the slurry was then added Na_2CO_3 (220 μL, 0.439 mmol) which caused the reaction slurry to turn orange. The mixture was degassed an additional 3 min. The vessel was capped and the reaction mixture was heated to 80°C for 4 h. The reaction mixture was subsequently diluted with EtOAc (10 mL) and washed with water (8 mL) followed by brine (8 mL). The organic phase was collected, dried over Na_2SO_4, and concentrated to an oil, which was diluted with DCM (2 mL) and treated with HCl (4 M in dioxane, 1 mL). The mixture was stirred for 1 h at RT, and then concentrated. The residue was diluted with MeOH (2 mL) and was purified via preparative HPLC to give a TFA salt of the title compound as a white solid. . ^{1}H NMR (DMSO-d_6) δ ppm 1.75 (t, 1 H), 2.03 - 2.17 (m, 1 H), 3.57 - 3.67 (m, 1 H), 3.78 (br s, 1 H), 3.82 - 3.88 (m, 1 H), 3.93 - 4.02 (m, 2 H), 4.39 (d, *J*=5.3 Hz, 2 H), 4.45 - 4.54 (m, 1 H), 4.82 (d, *J*=5.8 Hz, 2H), 5.15 (dd, *J*=17.2, 1.5 Hz, 1H), 5.22 (dd, *J*=10.2, 1.4 Hz, 1 H), 6.04 (dddd, *J*=16.8, 10.6, 5.8, 5.7 Hz, 1 H), 7.09 (d, *J*=5.3 Hz, 1 H), 7.93 (d, *J*=4.3 Hz, 3 H), 8.32 (s, 1 H), 8.40 (s, 1 H), 8.85 - 9.03 (m, 1 H). [M+H] calc'd for $C_{18}H_{21}FN_6O_2$, 373; found, 373.

[0918] TABLE 1, below, lists SYK inhibition data for many of the compounds described in the examples, where larger pIC_{50} values represent higher potency. The compounds were tested in accordance with the assay described on page 60 of the specification.

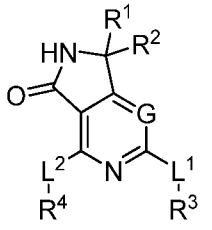
TABLE 1: SYK Inhibition (pIC_{50}) for Example (Ex) Compounds

Ex	pIC_{50}	Ex	pIC_{50}	Ex	pIC_{50}	Ex	pIC_{50}	Ex	pIC_{50}	Ex	pIC_{50}	Ex	pIC_{50}
1	8.1	21	6.3	41	5.9	61	7.2	81	8.5	101	7.2	121	5.4
2	6.9	22	5.7	42	6.8	62	8.0	82	9.2	102	8.4	122	6.2
3	7.6	23	8.7	43	5.3	63	8.1	83	6.6	103	6.9	123	8.1
4	7.8	24	7.6	44	6.2	64	8.0	84	7.7	104	8.7	124	7.6
5	6.2	25	9.0	45	6.1	65	8.0	85	8.4	105	9.0	125	8.0
6	6.3	26	7.5	46	5.8	66	6.3	86	5.6	106	8.6	126	8.1
7	6.0	27	7.4	47	8.6	67	7.4	87	7.2	107	6.3	127	8.2
8	8.1	28	8.6	48	6.1	68	7.0	88	8.5	108	8.6	128	7.7
9	5.1	29	8.5	49	<4.7	69	6.8	89	8.4	109	8.5	129	8.4
10	<4.7	30	8.4	50	8.6	70	8.8	90	8.0	110	7.3	130	5.0
11	5.9	31	8.6	51	7.2	71	8.1	91	6.6	111	8.1	131	<4.7
12	5.7	32	5.4	52	7.2	72	7.5	92	7.9	112	8.7	132	8.4
13	8.7	33	7.3	53	5.8	73	8.1	93	8.0	113	6.7	133	7.6
14	6.9	34	6.5	54	6.6	74	8.3	94	8.5	114	6.6	134	
15	6.0	35	7.3	55	7.8	75	9.1	95	5.4	115	6.5	135	
16	5.5	36	7.6	56	5.6	76	9.3	96	6.7	116	8.1	136	7.5
17	7.4	37	6.0	57	7.8	77	7.5	97	6.8	117	7.9		
18	7.1	38	6.2	58	5.8	78	8.4	98	5.7	118	7.9		
19	6.6	39	5.5	59	7.1	79	7.7	99	8.5	119	7.8		
20	6.7	40	6.6	60	7.8	80	5.5	100	6.8	120	6.6		

[0919] As used in this specification and the appended claims, singular articles such as "a," "an," and "the," may refer to a single object or to a plurality of objects unless the context clearly indicates otherwise. Thus, for example, reference to a composition containing "a compound" may include a single compound or two or more compounds. It is to be understood that the above description is intended to be illustrative and not restrictive. Many embodiments will be apparent to those of skill in the art upon reading the above description. Therefore, the scope of the invention should be determined with reference to the appended claims and includes the full scope of equivalents to which such claims are entitled. The disclosures of all articles and references, including patents, patent applications and publications, are herein incorporated by reference in their entirety and for all purposes.

WHAT IS CLAIMED IS:

1. A compound of Formula 1,



1

,

or a pharmaceutically acceptable salt thereof, wherein:

G is selected from N and $C(R^5)$;

L^1 and L^2 are each independently selected from -NH- and a bond;

R^1 and R^2 are each independently selected from hydrogen, halo, C_{1-3} alkyl, and C_{1-3} haloalkyl, or R^1 and R^2, together with the atom to which they are attached, form a C_{3-6} cycloalkyl;

R^3 is selected from C_{2-6} alkyl, C_{3-8} cycloalkyl, C_{2-5} heterocyclyl, and C_{1-9} heteroaryl, each optionally substituted with from one to five substituents independently selected from halo, oxo, $-NO_2$, -CN, R^6, and R^7;

R^4 is selected from C_{3-8} cycloalkyl, C_{2-5} heterocyclyl, C_{6-14} aryl, and C_{1-9} heteroaryl, each optionally substituted with from one to five substituents independently selected from halo, oxo, -CN, R^6, and R^7;

R^5 is selected from hydrogen, halo, -CN, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-5} heterocyclyl, C_{1-5} heteroaryl, and R^{10}, wherein the alkyl, alkenyl, alkynyl moieties are each optionally substituted with from one to five substituents independently selected from halo, -CN, oxo, and R^{10}, and wherein the heterocyclyl moiety has 3 to 6 ring atoms and the heteroaryl moiety has 5 or 6 ring atoms, and the heterocyclyl and heteroaryl moieties are each optionally substituted with from one to four substituents independently selected from halo, $-NO_2$, -CN, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, and R^{10};

each R^6 is independently selected from $-OR^8$, $-N(R^8)R^9$, $-NR^8C(O)R^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)N(R^8)R^9$, $-C(O)N(R^8)OR^9$, $-C(O)N(R^8)S(O)_2R^9$, $-N(R^8)S(O)_2R^9$, $-S(O)_nR^8$, and $-S(O)_2N(R^8)R^9$;

each R^7 is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl-$(CH_2)_m$-, C_{6-14} aryl-$(CH_2)_m$-, C_{2-5} heterocyclyl-$(CH_2)_m$-, and C_{1-9} heteroaryl-$(CH_2)_m$-, each optionally substituted with from one to five substituents independently selected from halo, oxo, $-NO_2$, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, and R^{10};

each R^8 and R^9 is independently selected from hydrogen or from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl-$(CH_2)_m$-, C_{6-14} aryl-$(CH_2)_m$-, C_{2-5} heterocyclyl-$(CH_2)_m$-, and C_{1-9} heteroaryl-$(CH_2)_m$-, each optionally substituted with from one to five substituents independently selected from halo, oxo, $-NO_2$, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, and R^{10};

each R^{10} is independently selected from $-OR^{11}$, $-N(R^{11})R^{12}$, $-N(R^{11})C(O)R^{12}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-C(O)N(R^{11})R^{12}$, $-C(O)N(R^{11})OR^{12}$, $-C(O)N(R^{11})S(O)_2R^{12}$, $-NR^{11}S(O)_2R^{12}$, $-S(O)_nR^{11}$, and $-S(O)_2N(R^{11})R^{12}$;

each R^{11} and R^{12} is independently selected from hydrogen and C_{1-6} alkyl;

each n is independently selected from 0, 1 and 2; and

each m is independently selected from 0, 1, 2, 3, and 4;

wherein each of the aforementioned heteroaryl moieties has one to four heteroatoms independently selected from N, O, and S, and each of the aforementioned heterocyclyl moieties is saturated or partially unsaturated and has one or two heteroatoms independently selected from N, O, and S.

2. A compound or pharmaceutically acceptable salt according to claim 1, wherein L^1 is -NH-.

3. A compound or pharmaceutically acceptable salt according to claim 1, wherein L^1 is a bond.

4. A compound or pharmaceutically acceptable salt according to any one of the preceding claims, wherein L^2 is -NH-.

5. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 3, wherein L^2 is a bond.

6. A compound or pharmaceutically acceptable salt according to any one of the preceding claims, wherein G is N.

7. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 5, wherein G is $C(R^5)$.

8. A compound or pharmaceutically acceptable salt according to any one of the preceding claims, wherein R^1 and R^2 are both hydrogen.

9. A compound or pharmaceutically acceptable salt according to any one of the preceding claims, wherein R^3 is C_{3-8} cycloalkyl, optionally substituted with from one to five substituents independently selected from halo, oxo, $-NO_2$, -CN, R^6, and R^7.

10. A compound or pharmaceutically acceptable salt according to claim 9, wherein R^3 is 2-amino-C_{3-8} cycloalk-1-yl, optionally substituted with from one to four substituents independently selected from halo, oxo, $-NO_2$, -CN, R^6, and R^7.

11. A compound or pharmaceutically acceptable salt according to claim 10, wherein R^3 is 2-amino-cyclohex-1-yl optionally substituted with from one to four substituents independently selected from halo, oxo, $-NO_2$, -CN, R^6, and R^7.

12. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 8, wherein R^3 is C_{2-6} alkyl optionally substituted with from one to five substituents independently selected from halo, oxo, $-NO_2$, -CN, R^6, and R^7.

13. A compound or pharmaceutically acceptable salt according to claim 12, wherein R^3 is 2-amino-C_{2-6} alk-1-yl optionally substituted with from one to four substituents independently selected from halo, oxo, $-NO_2$, -CN, R^6, and R^7.

14. A compound or pharmaceutically acceptable salt according to claim 13, wherein R^3 is 2-aminoethan-1-yl optionally substituted with from one to four substituents independently selected from halo, oxo, $-NO_2$, -CN, R^6, and R^7.

15. A compound or pharmaceutically acceptable salt according to claim 14, wherein R^3 is 2-amino-2-oxoethan-1-yl optionally substituted with one or two substituents independently selected from halo, oxo, $-NO_2$, -CN, R^6, and R^7.

16. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 8, wherein R^3 is C_{2-5} heterocyclyl optionally substituted with from one to five substituents independently selected from halo, oxo, $-NO_2$, -CN, R^6, and R^7.

17. A compound or pharmaceutically acceptable salt according to claim 16, wherein R^3 is C_{2-5} heterocyclyl substituted with an amino and optionally substituted with from one to four additional substituents independently selected from halo, oxo, $-NO_2$, -CN, R^6, and R^7.

18. A compound or pharmaceutically acceptable salt according to claim 17, wherein R^3 is 3-aminotetrahydro-2*H*-pyran-4-yl optionally substituted with from one to four substituents independently selected from halo, oxo, $-NO_2$, -CN, R^6, and R^7.

19. A compound or pharmaceutically acceptable salt according to any one of claims 1 and 3 to 8, wherein R^3 is C_{2-5} heterocyclyl or an amino-substituted C_{2-5} heterocyclyl, each optionally substituted with from one to five or from one to four substituents, respectively, independently selected from halo, oxo, $-NO_2$, -CN, R^6, and R^7, wherein one of the heteroatoms of the heterocyclyl moiety is directly attached to L^1, and L^1 is a bond.

20. A compound or pharmaceutically acceptable salt according to any one of the preceding claims, wherein R^4 is selected from C_{6-14} aryl and C_{1-9} heteroaryl, each optionally substituted with from one to five substituents independently selected from halo, oxo, -CN, R^6, and R^7.

21. A compound or pharmaceutically acceptable salt according to any one of the preceding claims, wherein R^4 is phenyl optionally substituted with from one to five substituents independently selected from halo, -CN, R^6, and R^7.

22. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 20, wherein R^4 is C_{1-9} heteroaryl optionally substituted with from one to five substituents independently selected from halo, oxo, -CN, R^6, and R^7.

23. A compound or pharmaceutically acceptable salt according to claim 22, wherein R^4 is a monocyclic C_{2-4} heteroaryl optionally substituted with from one to four substituents independently selected from halo, -CN, R^6, and R^7.

24. A compound or pharmaceutically acceptable salt according to claim 23, wherein R^4 is selected from pyrrolyl, furanyl, thiopheneyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isothiazolyl, and thiazolyl, each optionally substituted with from one to three substituents independently selected from halo, -CN, R^6, and R^7.

25. A compound or pharmaceutically acceptable salt according to claim 24, wherein R^4 is selected from thiopheneyl, pyrazolyl, isothiazolyl, and thiazolyl, each optionally substituted with from one to three substituents independently selected from halo, -CN, R^6, and R^7.

26. A compound or pharmaceutically acceptable salt according to claim 25, wherein R^4 is pyrazolyl optionally substituted with from one to three substituents independently selected from halo, -CN, R^6, and R^7.

27. A compound or pharmaceutically acceptable salt according to claim 26, wherein R^4 is pyrazol-4-yl optionally substituted with from one to three substituents independently selected from halo, -CN, R^6, and R^7.

28. A compound or pharmaceutically acceptable salt according to any one of claims 20 to 27, wherein R^4 is substituted with methyl, ethyl, cyclopropyl or C_{1-2} haloalkyl.

29. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 5 and 7 to 28, wherein R^5 is C_{1-5} heteroaryl optionally substituted with from one to four substituents independently selected from halo, $-NO_2$, -CN, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, and R^{10}.

30. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 5 and 7 to 28, wherein R^5 is selected from hydrogen and halo.

31. A compound or pharmaceutically acceptable salt according to claim 30, wherein R^5 is selected from chloro and fluoro.

32. A compound according to claim 1, which is selected from the following compounds:

2-((1*R*,2S)-2-Aminocyclohexylamino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(3-fluorophenylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(3-chlorophenylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

4-(1*H*-Indazol-6-ylamino)-2-((1*R*,2*S*)-2-aminocyclohexylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-aminocyclohexylamino)-4-(3-(trifluoromethyl)phenylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

cis-2-(2-aminocyclohexylamino)-4-(3-(trifluoromethyl)phenylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-(1-Methyl-1*H*-pyrazol-4-yl)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-(4-Ethylpiperazin-1-yl)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-(Cyclohexylamino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

cis-2-(2-Hydroxycyclohexylamino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-(3-Aminopiperidin-1-yl)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-methyl-1*H*-pyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-isobutyl-1*H*-pyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-phenyl-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(benzo[*b*]thiophen-3-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-ethyl-1*H*-pyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-benzyl-1*H*-pyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(imidazo[1,2-*a*]pyridin-3-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-propyl-1*H*-pyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-(2-methoxyethyl)-1*H*-pyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

4-(1*H*-Indazol-6-ylamino)-6-((1*R*,2*S*)-2-aminocyclohexylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(4-fluoro-3-methylphenylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-chloro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(pyrazolo[1,5-*a*]pyridin-3-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

2-(2-(Aminomethyl)piperidin-1-yl)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(3-(methylsulfonyl)phenylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclopentylamino)-4-(3-(methylsulfonyl)phenylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

(*R*)-4-Methyl-2-(4-(3-(methylsulfonyl)phenylamino)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)pentanamide;

(*R*)-4-Methyl-2-(4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)pentanamide;

2-((1*R*,2*S*)-2-(Dimethylamino)cyclohexylamino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-(Methylamino)cyclohexylamino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2'-((1*R*,2*S*)-2-Aminocyclohexylamino)-4'-(*m*-tolylamino)spiro[cyclopropane-1,7'-pyrrolo[3,4-*d*]pyrimidin]-5'(6'*H*)-one;

2-(2-Aminoethylamino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-(2-Amino-2-methylpropylamino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-(5-Oxo-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-2-ylamino)acetamide;

2-((2-Aminoethyl)(methyl)amino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-(Pyrrolidin-2-ylmethylamino)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-(3-Aminopyrrolidin-1-yl)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1,5-dimethyl-1*H*-pyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1*H*-indol-2-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1*H*-pyrazol-5-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

2-(3-Aminopropyl)-4-(*m*-tolylamino)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(benzofuran-3-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-aminocyclohexylamino)-7-fluoro-4-(imidazo[1,2-*a*]pyridin-3-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-aminocyclohexylamino)-4-(benzo[*b*]thiophen-3-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*S*,2*R*)-2-Aminocyclohexylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(*2H*)-one;

(*R*)-6-(2-Amino-3-ethoxypropylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

(*R*)-6-(2-Amino-3-ethoxypropylamino)-7-fluoro-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-(2-Amino-3,3,3-trifluoropropylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

(*R*)-4-Methyl-2-(3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)pentanamide;

6-(*cis*-4-Aminotetrahydrofuran-3-ylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2H)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-ethyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-ethyl-1*H*-pyrazol-4-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-cyclopropyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-cyclopropyl-1*H*-pyrazol-4-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

cis-6-(2-Aminocyclohexylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-(*cis*-2-Amino-4,4-difluorocyclopentylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-c]pyridin-3(2*H*)-one;

6-(*cis*-2-Amino-3,3-difluorocyclohexylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-(*cis*-2-Amino-3,3-difluorocyclohexylamino)-4-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-(*cis*-2-amino-3,3-difluorocyclohexylamino)-4-(1-cyclopropyl-1H-pyrazol-4-yl)-7-fluoro-1H-pyrrolo[3,4-c]pyridin-3(2H)-one;

(*R*)-2-(7-Fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

(*R*)-2-(4-(1-(Difluoromethyl)-1*H*-pyrazol-4-yl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

(*R*)-2-(4-(1-Cyclopropyl-1*H*-pyrazol-4-yl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

(*R*)-2-(4-(Benzofuran-3-yl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

(*R*)-2-(7-Fluoro-3-oxo-4-(pyrazolo[1,5-*a*]pyridin-3-yl)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-chloro-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile;

(*R*)-6-(2-Amino-3-methoxypropylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

(*R*)-6-(2-Amino-3-methoxypropylamino)-3-oxo-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile;

(*R*)-6-(2-Amino-3-methoxypropylamino)-7-fluoro-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

7-Acryloyl-6-((1*R*,2*S*)-2-aminocyclohexylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-iodo-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-(1*H*-pyrazol-4-yl)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-(*cis*-2-Amino-3,3-difluorocyclohexylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-(1-methyl-1*H*-pyrazol-5-yl)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-4-Aminotetrahydro-2*H*-pyran-3-ylamino)-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

tert-Butyl (1*S*,2*R*)-2-(3-oxo-7-phenyl-4-(*m*-tolylamino)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)cyclohexylcarbamate;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-methyl-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(*m*-tolylamino)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-methyl-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

(*R*)-6-(2-Amino-3-methoxypropylamino)-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(pyrazolo[1,5-*a*]pyridin-3-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-4-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-4-(benzofuran-3-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

(*S*)-6-(3-Aminopyrrolidin-1-yl)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

(*S*)-6-(3-Aminopiperidin-1-yl)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(1-isopropyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

7-Fluoro-4,6-bis(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-bromo-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

2-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(1-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-5-one;

(*R*)-6-(2-Amino-3-methoxypropylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(thiophen-3-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(4-methylthiophen-2-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(4-methylthiophen-2-yl)-1*H*-pyrrolo[3,4-c]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(thiophen-3-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

(*R*)-2-(7-Fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-*N*,4-dimethylpentanamide;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(5-methylthiophen-2-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

(*R*)-2-(7-Fluoro-4-(4-methylthiophen-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

(*R*)-2-(7-Fluoro-3-oxo-4-(thiophen-3-yl)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

(*R*)-2-(7-Fluoro-4-(5-methylthiophen-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-4-(2-aminothiazol-5-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

(*R*)-2-(7-Fluoro-4-(furan-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

(*R*)-2-(7-Fluoro-4-(furan-3-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

(*R*)-2-(7-Fluoro-4-(furan-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

(*R*)-2-(4-(5-Cyanothiophen-2-yl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

(*R*)-2-(4-(4-Cyanothiophen-2-yl)-7-fluoro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

(*R*)-2-(7-Fluoro-3-oxo-4-(thiazol-5-yl)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

(*R*)-2-(7-Fluoro-4-(isothiazol-5-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-1,1-dimethyl-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(1-methyl-1*H*-pyrazol-3-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(2-methylthiazol-5-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(5-methylthiophen-2-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-1-methyl-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

(*R*)-2-(7-Fluoro-3-oxo-4-(thiophen-2-yl)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(thiophen-2-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(thiazol-5-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(thiophen-2-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(4-(trifluoromethyl)-1*H*-imidazol-1-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((1*R*,2*S*)-2-Aminocyclohexylamino)-7-fluoro-4-(4-methyl-1*H*-imidazol-1-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(3-methylisothiazol-5-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-7-fluoro-4-(2-methylthiazol-5-yl)-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

(*R*)-2-(7-Fluoro-4-(2-methylthiazol-5-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-ylamino)-4-methylpentanamide;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-4-(5-chlorothiophen-2-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

6-((3*R*,4*R*)-3-Aminotetrahydro-2*H*-pyran-4-ylamino)-4-(1-cyclopropyl-1*H*-pyrazol-4-yl)-7-fluoro-1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one;

a stereoisomer of any of the aforementioned compounds; and

a pharmaceutically acceptable salt of any of the aforementioned compounds or stereoisomers.

33. A pharmaceutical composition comprising:

a compound or pharmaceutically acceptable salt as defined in any one of claims 1 to 32; and

a pharmaceutically acceptable excipient.

34. A use of a compound or pharmaceutically acceptable salt as defined in any one of claims 1 to 32, as a medicament.

35. A use of a compound or pharmaceutically acceptable salt as defined in any one of claims 1 to 32, for the manufacture of a medicament for the treatment of a disease or condition for which a SYK inhibitor is indicated.

36. A method of treating a disease or condition in a subject for which a SYK inhibitor is indicated, the method comprising administering to the subject an effective amount of a compound or pharmaceutically acceptable salt as defined in any one of claims 1 to 32.

37. A method of treating a disease or condition in a subject, the method comprising administering to the subject an effective amount of a compound or pharmaceutically acceptable salt as defined in any one of claims 1 to 32, wherein the disease or condition is selected from allergic rhinitis, allergic asthma, atopic dermatitis, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, psoriasis, immune thrombocytopenic purpura, inflammatory bowel disease, chronic obstructive pulmonary disease, and thrombosis.

38. A method of treating a disease or condition in a subject, the method comprising administering to the subject an effective amount of a compound or pharmaceutically acceptable salt as defined in any one of claims 1 to 32, wherein the disease or condition is selected from a hematological malignancy and an epithelial cancer.

39. A method according to claim 38, wherein the hematological malignancy is selected from acute myeloid leukemia, B-cell chronic lymphocytic leukemia, B-cell lymphoma, and T-cell lymphoma.

40. A method according to claim 38, wherein the epithelial cancer is selected from lung cancer, pancreatic cancer, and colon cancer.

41. A combination of an effective amount of a compound or pharmaceutically acceptable salt as defined in any one of claims 1 to 32, and at least one additional pharmacologically active agent.

42. A combination according to claim 41, wherein the additional pharmacologically active agent is a DMARD.

43. A combination according to claim 42, wherein the DMARD is methotrexate.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/061146

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 C07D487/04 A61K31/437 A61K31/519 A61P7/00
A61P11/00 A61P17/00 A61P19/00 A61P35/00 A61P37/00
A61P29/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/070872 A1 (RIGEL PHARMACEUTICALS INC [US]; DING PINGYU [US]; ARGADE ANKUSH [US];) 21 June 2007 (2007-06-21) claims 1, 45-47	1-43
A	RUZZA P ET AL: "Therapeutic prospect of Syk inhibitors", EXPERT OPINION ON THERAPEUTIC PATENTS 2009 INFORMA HEALTHCARE GBR LNKD-DOI:10.1517/13543770903207039, vol. 19, no. 10, October 2009 (2009-10), pages 1361-1376, XP002625888, ISSN: 1354-3776 the whole document	1-43

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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 :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 March 2011	14/03/2011

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	Marzi, Elena

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/061146

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/09134 A1 (NOVARTIS AG [CH]; NOVARTIS ERFIND VERWALT GMBH [AT]; COLLINGWOOD STEPH) 8 February 2001 (2001-02-08) claims 1-11	1-43
A	EP 1 880 993 A1 (KYOWA HAKKO KOGYO KK [JP] KYOWA HAKKO KIRIN CO LTD [JP]) 23 January 2008 (2008-01-23) page 3, paragraph 1 claims 1-20	1-43

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2010/061146

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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PIRROLIDINONAS HETEROAROMÁTICAS FUSIONADAS

Campo de la invención

[0001] Esta invención se refiere a compuestos de pirrolidinona heteroaromáticos fusionados, a composiciones farmacéuticas que los contienen, y al uso de los compuestos para tratar trastornos y afecciones que involucran el sistema inmune y la inflamación, que incluyen la artritis reumatoide. Las pirrolidinonas heteroaromáticas son inhibidores de la tirosina quinasa esplénica

Antecedentes de la invención

[0002] La tirosina quinasa esplénica (SYK) es una tirosina quinasa citoplásmica no receptora de 72 kDa. La SYK tiene una secuencia aminoácida primaria similar a la de la proteína de 70 kD asociada a la cadena zeta (ZAP-70) y está involucrada en la transducción de señal mediada por el receptor. El dominio N-terminal de la SYK contiene dos dominios Src-homología 2 (SH2), que se unen a los motivos de activación en inmunoreceptores difosforilados basados en tirosina (ITAMs) hallados en los dominios de señalización citoplásmica de muchos complejos inmunoreceptores. El C-terminal contiene el dominio catalítico, e incluye varios sitios de autoroforilación de bucle catalítico que son responsables de la activación de la SYK inducida por el receptor y la posterior propagación de la señal corriente abajo. La SYK se expresa en muchos tipos celulares involucradas en la inmunidad adaptativa e innata, que incluyen linfocitos (células B, células T, y células NK), granulocitos (basóficos, neutrófilos, y eosinófilos), monocitos, macrófagos, células dendríticas y mastocitos. La SYK se expresa en otros tipos celulares, que incluyen el epitelio de las vías aéreas y los fibroplastos en el sistema respiratorio superior. Véase, por ej., Martin Turner et al., Immunology Today (2000) 21(3):148-54; y Michael P. Sanderson et al., Inflammation & Allergy – Drug Targets (2009) 8:87-95.

[0003] La función de la SYK en la señalización dependiente del ITAM y su expresión en muchos tipos celulares sugiere que los compuestos que inhiben la actividad de la SYK pueden ser útiles para tratar trastornos que involucran el sistema inmune y la

inflamación. Estos trastornos incluyen las reacciones de hipersensibilidad tipo I (riñitis alérgica, asma alérgico, y dermatitis atópica; enfermedades autoinmunes (artritis reumatoide, esclerosis múltiple, lupus eritematoso sistémico, soriasis, y púrpura trombocitopénica inmune; e inflamación del pulmón (enfermedad pulmonar obstructiva crónica). Véase, por ej., Brian R. Wong et al., Expert Opin. Investig. Drugs (2004) 13(7):743-62; Sanderson et al. 2009); Jane Denyer & Vipul Patel, Drug News Perspective (2009) 22(3):146-50; Esteban S. Masuda & Jochen Schmitz, Pulmonary Pharmacology & Therapeutics (2008) 21:461-67; Malini Bajpai et al., Expert Opin. Investig. Drugs (2008) 17(5):641-59; y Anna Podolanczuk et al., Blood (2009) 113:3154-60. Otros trastornos incluyen malignidades hematológicas, tales como leucemia mieloide aguda, leucemia linfocítica crónica de células B, linfoma de células B (por ej., linfoma de células de la corteza cerebral), y linfoma de células T (por ej., linfoma de células T periféricas); como también cánceres epiteliales, tales como cáncer de pulmón, cáncer pancreático, y cáncer de colon. Véase por ej., Cynthia K. Hahn et al., Cancer Cell (2009) 16:281-294; D. H. Chu et al., Immnol. Rev. (1998) 165:167-180; A. L. Feldman et al., Leukemia (2008) 22:1139-43; A. Rinaldi et al., Br. J. Haematol. (2006) 132:303-316; B. Streubel et al., Leukemia (2006) 20:313-18; Maike Buchner et al., Cancer Research (2009) 69(13):5424-32; A. D. Baudot et al., Oncogene (2009) 28:3261–73; y Anurag Singh et al., Cancer Cell (2009) 15:489-500.

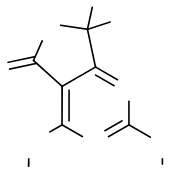
[0004] Varios inhibidores de la SYK han sido descriptos en solicitudes de patentes publicadas. Véase por ej., EP 1184376 A1; WO 01/83485 A1; WO 03/057695 A1; WO 2006/129100 A1; WO 01/09134 A1; WO 03/063794 A1; WO 2005/012294 A1; WO 2004/087699 A2; WO 2009/026107 A1; WO2009136995 A2; y WO2009/145856 A1.

Síntesis de la invención

[0005] Esta invención provee derivados de pirrolidinona heteroaromáticos fusionados, que incluyen las 6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona, 1H-pirrolo[3,4-

c]piridin-3(2H)-ona, y sus complejos, sales, solvatos, e hidratos aceptables para uso farmacéutico. Esta invención además provee composiciones farmacéuticas que contienen los derivados de pirrolidinona heteroaromáticos, y los usos de los derivados de pirrolidinona heteroaromáticos para tratar trastornos y afecciones que involucran el sistema inmune y la inflamación, que incluyen la artritis reumatoide.

[0006] Un aspecto de la invención provee compuestos de Fórmula 1:



,

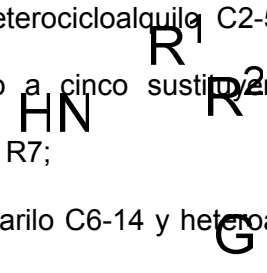
o sus sales aceptables para uso farmacéutico, donde:

G se selecciona de N y C(R5);

L1 y L2 se seleccionan cada uno de ellos independientemente de NH y un enlace;

R1 y R2 se seleccionan cada uno de ellos independientemente de hidrógeno, halo, alquilo C1-3, y haloalquilo C1-3, o R1 y R2, junto con el átomo al cual están unidos, forman un cicloalquilo C3-6;

R3 se selecciona de alquilo C2-6, cicloalquilo C3-8, heterocicloalquilo C2-5, y heteroarilo C1-9, cada uno opcionalmente sustituido con uno a cinco sustituyentes independientemente seleccionados de halo, oxo, NO2, -CN, R6, y R7;



R4 se selecciona de cicloalquilo C3-8, heterociclilo C2-5, arilo C6-14 y heteroarilo C1-9, cada uno opcionalmente sustituido con uno a cinco sustituyentes independientemente seleccionados de halo, oxo, CN, R6, y R7;

R5 se selecciona de hidrógeno, halo, CN, alquilo C1-4, alquenilo C2-4, alquinilo C2-4, heterociclilo C2-5, heteroarilo C1-5, y R10, donde los restos alquilo, alquenilo, alquinilo están cada uno de ellos opcionalmente sustituidos con de uno a cinco sustituyentes seleccionados independientemente de halo, -CN, oxo, y R10, y donde el

resto heterociclilo tiene 3 a 6 átomos del anillo y el resto heteroarilo tiene 5 o 6 átomos del anillo, y los restos heterociclilo y heteroarilo están cada uno de ellos opcionalmente sustituidos con uno a cuatro sustituyentes seleccionados independientemente de halo, NO2, -CN, alquilo C1-4, alquenilo C2-4, alquinilo C2-4, haloalquilo C1-4, y R10;

cada R6 se selecciona independientemente de OR8, -N(R8)R9, -NR8C(O)R9, -C(O)R8, -C(O)OR8, -C(O)N(R8)R9, -C(O)N(R8)OR9, -C(O)N(R8)S(O)2R9, -N(R8)S(O)2R9, -S(O)nR8, y -S(O)2N(R8)R9;

cada R7 se selecciona independientemente de alquilo C1-6, alquenilo C2-6, alquinilo C2-6, C3-6 cicloalquilo (CH2)m-, C6-14 aril-(CH2)m-, C2-5 heterociclilo (CH2)m-, y C1-9 heteroaril-(CH2)m-, cada uno de ellos opcionalmente sustituido con uno a cinco sustituyentes independientemente seleccionados de halo, oxo, NO2, -CN, alquilo C1-6, haloalquilo C1-6 y R10;

cada R8 y R9 se selecciona independientemente de alquilo C1-6, alquenilo C2-6, alquinilo C2-6, C3-6 cicloalquilo (CH2)m-, C6-14 aril-(CH2)m-, C2-5 heterociclilo (CH2)m-, y C1-9 heteroaril-(CH2)m-, cada uno de ellos opcionalmente sustituido con uno a cinco sustituyentes independientemente seleccionados de halo, oxo, NO2, -CN, alquilo C1-6, haloalquilo C1-6 y R10;

cada R10 se selecciona independientemente de OR11, -N(R11)R12, -N(R11)C(O)R12, -C(O)R11, -C(O)OR11, -C(O)N(R11)R12, -C(O)N(R11)OR12, -C(O)N(R11)S(O)2R12, -NR11S(O)2R12, -S(O)nR11, y -S(O)2N(R11)R12;

cada R11 y R12 se selecciona independientemente de hidrógeno y alquilo C1-6;

cada n se selecciona independientemente de 0, 1 y 2; y

cada m se selecciona independientemente de 0, 1, 2, 3, y 4;

donde cada uno de los restos heteroarilo antes mencionados tiene uno a cuatro heteroátomos seleccionados independientemente de N, O, y S, y cada uno de los restos heterociclilo antes mencionados está saturado o parcialmente insaturado y tiene uno o dos heteroátomos independientemente seleccionados de N, O y S.

[0007] Otro aspecto de la invención provee un compuesto que se selecciona del siguiente grupo de compuestos y sus sales aceptables para uso farmacéutico:

2-((1R,2S)-2-aminociclohexilamino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(3-fluorofenilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(3-clorofenilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

4-(1H-indazol-6-ilamino)-2-((1R,2S)-2-aminociclohexilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(3-trifluorometil)fenilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

cis-2-(2-aminociclohexilamino)-4-(3-(trifluorometil)fenilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-(1-metil-1H-pirazol-4-il)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-(4-etilpiperazin-1-il)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-(ciclohexilamino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

cis-2-(2-hidroxiciclohexilamino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-(3-aminopiperidin-1-il)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

6-((1R,2S)-2-aminociclohexilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(1-metil-1H-pirazol-4-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(1-isobutil-1H-pirazol-4-il)-6,7-dihidro-5H-

pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-fenil-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(benzo[b]tiofen-3-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(1-etil-1H-pirazol-4-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(1-bencil-1H-pirazol-4-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(imidazo[1,2-a]piridin-3-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(1-propil-1H-pirazol-4-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(1-(2-metoxietil)-1H-pirazol-4-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

4-(1H-indazol-6-ilamino)-6-((1R,2S)-2-aminociclohexilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-4-(4-fluoro-3-metilfenilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-7-fluoro-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-aminotetrahidro-2H-piran-4-ilamino)-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-7-cloro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-7-fluoro-4-(pirazolo[1,5-a]piridin-3-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

2-(2-(aminometil)piperidin-1-il)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

6-((1R,2S)-2-aminociclohexilamino)-4-(3-(metilsulfonil)fenilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclopentilamino)-4-(3-(metilsulfonil)fenilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(R)-4-metil-2-(4-(3-(metilsulfonil)fenilamino)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)pentanamida;

(R)-4-metil-2-(4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)pentanamida;

2-((1R,2S)-2-(dimetilamino)ciclohexilamino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-(metilamino)ciclohexilamino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2’-((1R,2S)-2-(aminociclohexilamino)-4'-(m-tolilamino)espiro[ciclopropano-1,7-pirrolo[3,4-d]pirimidin-5’(6’H)-ona;

2-(2-aminoetilamino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-(2-amino-2-metilpropilamino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-(5-oxo-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-2-ilamino)acetamida;

2-((2-aminoetil)(metil)amino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-(pirrolidin-2-ilmetilamino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-(3-aminopirrolidin-1-il)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(1,5-dimetil-1H-pirazol-4-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(1-propil-1H-indol-2-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(1H-pirazol-5-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-(3-aminopropil)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

6-((1R,2S)-2-aminociclohexilamino)-4-(benzofuran-3-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-7-fluoro-4-(imidazo[1,2-a]piridin-3-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-4-(benzo[b]tiofen-3-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1S,2R)-2-aminociclohexilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(R)-6-(2-amino-3-etoxipropilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(R)-6-(2-amino-3-etoxipropilamino)-7-fluoro-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-(2-amino-3,3,3-trifluoropropilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(R)-4-metil-2-(3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)pentanamida;

6-(cis-4-aminotetrahidrofuran-3-ilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-4-(1-etil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-4-(1-etil-1H-pirazol-4-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-4-(1-ciclopropil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-4-(1-(difluorometil)-1H-pirazol-4-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-4-(1-ciclopropil-1H-pirazol-4-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

cis-6-(2-aminociclohexilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-(cis-2-amino-4,4-difluorociclopentilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-(cis-2-amino-3,3-difluorociclohexilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-(cis-2-amino-3,3-difluorociclohexilamino)-4-(1-(difluorometil)-1H-pirazol-4-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-(cis-2-amino-3,3-difluorociclohexilamino)-4-(1-ciclopropil-1H-pirazol-4-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(R)-2-(7-fluoro-4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

(R)-2-(4-(1-(difluorometil)-1H-pirazol-4-il)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-

c]piridin-6-ilamino)-4-metilpentanamida;

(R)-2-(4-(1-ciclopropil-1H-pirazol-4-il)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

(R)-2-(4-(benzofuran-3-il)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

(R)-2-(7-fluoro-3-oxo-4-(pirazolo[1,5-a]piridin-3-il)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

6-((1R,2S)-2-aminociclohexilamino)-7-cloro-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-7-carbonitrilo;

(R)-6-(2-amino-3-metoxipropilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(R)-6-(2-amino-3-metoxipropilamino)-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-7-carbonitrilo;

(R)-6-(2-amino-3-metoxipropilamino)-7-fluoro-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

7-acriloil-6-((1R,2S)-2-aminociclohexilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-7-yodo-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-7-(1H-pirazol-4-il)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-(cis-2-amino-3,3-difluorociclohexilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-7-(1-metil-1H-pirazol-5-il)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-aminotetrahidro-2H-piran-4-ilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-4-aminotetrahidro-2H-piran-3-ilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

ter-butilo (1S,2R)-2-(3-oxo-7-fenil-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ;

6-((1R,2S)-2-aminociclohexilamino)-7-metil-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-7-metil-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(R)-6-(2-amino-3-metoxipropilamino)-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(pirazolo[1,5-a]piridin-3-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-aminotetrahidro-2H-piran-4-ilamino)-4-(1-(difluorometil)-1H-pirazol-4-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-aminotetrahidro-2H-piran-4-ilamino)-4-(benzofuran-3-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(S)-6-(3-aminopirrolidin-1-il)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(S)-6-(3-aminopiperidin-1-il)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-7-fluoro-4-(1-isopropil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

7-fluoro-4,6-bis(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-7-bromo-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(1-(4-fluorofenil)-1H-pirazol-4-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

(R)-6-(2-amino-3-metoxipropilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(tiofen-3-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(4-metiltiofen-2-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-Aminociclohexilamino)-7-fluoro-4-(4-metiltiofen-2-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-Aminociclohexilamino)-7-fluoro-4-(tiofen-3-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(R)-2-(7-Fluoro-4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-N,4-dimetilpentanamida;

6-((1R,2S)-2-Aminociclohexilamino)-7-fluoro-4-(5-metiltiofen-2-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(R)-2-(7-Fluoro-4-(4-metiltiofen-2-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

(R)-2-(7-Fluoro-3-oxo-4-(tiofen-3-il)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

(R)-2-(7-Fluoro-4-(5-metiltiofen-2-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

6-((1R,2S)-2-Aminociclohexilamino)-4-(2-aminotiazol-5-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(R)-2-(7-Fluoro-4-(furan-2-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

(R)-2-(7-Fluoro-4-(furan-3-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

(R)-2-(7-Fluoro-4-(furan-2-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

(R)-2-(4-(5-Cianotiofen-2-il)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

(R)-2-(4-(4-Cianotiofen-2-il)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

(R)-2-(7-Fluoro-3-oxo-4-(tiazol-5-il)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

(R)-2-(7-Fluoro-4-(isotiazol-5-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

6-((1R,2S)-2-Aminociclohexilamino)-7-fluoro-1,1-dimetil-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

((1R,2S)-2-Aminociclohexilamino)-7-fluoro-4-(1-metil-1H-pirazol-3-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-Aminociclohexilamino)-7-fluoro-4-(2-metiltiazol-5-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(5-metiltiofen-2-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-Aminociclohexilamino)-7-fluoro-1-metil-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(R)-2-(7-Fluoro-3-oxo-4-(tiofen-2-il)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(tiofen-2-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(tiazol-5-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-Aminociclohexilamino)-7-fluoro-4-(tiofen-2-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(4-(trifluorometil)-1H-imidazol-1-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-Aminociclohexilamino)-7-fluoro-4-(4-metil-1H-imidazol-1-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(3-metilisotiazol-5-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(2-metiltiazol-5-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(R)-2-(7-Fluoro-4-(2-metiltiazol-5-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-4-(5-clorotiofen-2-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-4-(1-ciclopropil-1H-pirazol-4-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona; y

un estereoisómero de cualquiera de los compuestos antes mencionados y sus sales aceptables para uso farmacéutico.

[0008] Otro aspecto de la invención provee una composición farmacéutica que incluye: un compuesto de fórmula 1, como se definió anteriormente, o su sal aceptable para uso farmacéutico, o un compuesto seleccionado del grupo de compuestos que se definen en el párrafo precedente, o su sal aceptable para uso farmacéutico; y un excipiente aceptable para uso farmacéutico.

[0009] Un aspecto adicional de la invención provee el uso como medicamento de un compuesto de fórmula 1, como se definió anteriormente, o su sal aceptable para uso farmacéutico, o un compuesto seleccionado del grupo de compuestos que se definieron anteriormente, o su sal aceptable para uso farmacéutico.

[0010] Otro aspecto de la invención provee el uso de un compuesto de fórmula 1, como se definió anteriormente, o su sal aceptable para uso farmacéutico, o un compuesto seleccionado del grupo de compuestos que se definieron anteriormente, o su sal aceptable para uso farmacéutico, para la producción de un medicamento para el tratamiento de una enfermedad o afección para la cual se indica un inhibidor de SYK.

[0011] Otro aspecto de la invención provee un método para el tratamiento de una enfermedad o afección en un sujeto para la cual se indica un inhibidor de SYK, el método comprende administrar al sujeto una cantidad eficaz de un compuesto de fórmula 1, como se definió anteriormente, o un compuesto seleccionado del grupo de compuestos que se definió anteriormente, o su sal aceptable para uso farmacéutico.

[0012] Un aspecto adicional de la invención provee un método para el tratamiento de una enfermedad o afección en un sujeto, el método comprende administrar al sujeto una cantidad eficaz de un compuesto de fórmula 1, como se definió anteriormente, o su sal aceptable para uso farmacéutico, o un compuesto seleccionado del grupo de compuestos que se definió anteriormente, o su sal aceptable para uso farmacéutico, donde la enfermedad o afección se selecciona de riñitis alérgica, asma alérgico, y dermatitis atópica, artritis reumatoide, esclerosis múltiple, lupus eritematoso sistémico, soriasis, púrpura trombocitopénica inmune, enfermedad inflamatoria intestinal, enfermedad pulmonar obstructiva crónica y trombosis.

[0013] Otro aspecto de la invención provee un método para el tratamiento de una enfermedad o afección en un sujeto, el método comprende administrar al sujeto una cantidad eficaz de un compuesto de fórmula 1, como se definió anteriormente, o su sal aceptable para uso farmacéutico, o un compuesto seleccionado del grupo de compuestos

que se definió anteriormente, o su sal aceptable para uso farmacéutico, donde la enfermedad o afección se selecciona de un malignidad hematológica o un cáncer epitelial.

[0014] Otro aspecto de la invención provee una combinación de una cantidad eficaz de un compuesto de fórmula 1, como se definió anteriormente, o su sal aceptable para uso farmacéutico, o un compuesto seleccionado del grupo de compuestos que se definieron anteriormente, o su sal aceptable para uso farmacéutico, y al menos un agente farmacológicamente activo adicional.

Descripción detallada de la invención

[0015] A menos que se indique lo contrario, esta divulgación utiliza las definiciones que se mencionan a continuación.

[0016] "Sustituido", cuando se utiliza con relación a un sustituyente o resto químico (por ej., un grupo alquilo), significa que uno o más átomos de hidrógeno del sustituyente o resto han sido reemplazados con uno o más átomos o grupos no hidrógeno, siempre que los requerimientos de valencia se reúnan y que un compuesto químicamente estable surja del a sustitución.

[0017] "Aproximadamente", cuando se utiliza con relación a una variable numérica medible, se refiere al valor indicado de la variable y a todos los valores de la variable que están dentro del error experimental del valor indicado o dentro ±10 por ciento del valor indicado, cualquiera sea el mayor.

[0018] "Alquilo" se refiere a grupos hidrocarbonados saturados de cadena recta y ramificada, que tienen en general un número específico de átomos de carbono (por ej., alquilo C1-3 se refiere a un grupo alquilo que tiene 1 a 3 átomos de carbono, alquilo C1-6 se refiere a un grupo alquilo que tiene 1 a 6 átomos de carbono, etc.). Ejemplos de grupos alquilo incluyen metilo, etilo, n-propilo, i-propilo, n-butilo, s-butilo, i-butilo, t-butilo, pent-1-ilo, pent-2-ilo, pent-3-ilo, 3-metilbut-1-ilo, 3-metilbut-2-ilo, 2-metilbut-2-ilo, 2,2,2-trimetilet-1-ilo, n-hexilo, y similares.

[0019] "Alqu-1-ilo" se refiere a un grupo alquilo, como se definió anteriormente, que se une a un grupo principal o sustrato a través de un átomo de carbono localizado en la posición 1 del grupo alquilo.

[0020] "Alquenilo" se refiere a grupos hidrocarbonados de cadena recta y ramificada que tiene uno o más enlaces doble carbono-carbono, y en general tiene un número específico de átomos de carbono. Ejemplos de grupos alquenilo incluyen etenilo, 1-propen-1-ilo, 1-propen-2-ilo, 2-propen-1-ilo, 1-buten-1-ilo, 1-buten-2-ilo, 3-buten-1-ilo, 3-buten-2-ilo, 2-buten-1-ilo, 2-buten-2-ilo, 2-metil-1-propen-1-ilo, 2-metil-2-propen-1-ilo, 1,3-butadien-1-ilo, 1,3-butadien-2-ilo, y similares.

[0021] "Alquinilo" se refiere a grupos hidrocarbonados de cadena recta o ramificada que tiene uno o más enlaces triple carbono-carbono, y en general tiene un número específico de átomos de carbono. Ejemplo de grupos alquinilo incluyen etinilo, 1-propin-1-ilo, 2-propin-1-ilo, 1-butin-1-ilo, 3-butin-1-ilo, 3-butin-2-ilo, 2-butin-1-ilo, y similares.

[0022] "Halo," y "halógeno" se pueden utilizar intercambiablemente y se refieren a flúor, cloro, bromo, y yodo.

[0023] "HaloalquilO", "haloalquenilo", y "haloalquinilO", se refieren, respectivamente, a grupos alquilo, alquenilo y alquinilo sustituidos con uno o más átomos de halógeno, donde alquilo, alquenilo y alquinilo se definieron anteriormente, y en general tienen un número específico de átomos de carbono. Ejemplos de grupos haloalquilo incluyen fluorometilo, difluorometilo, trifluorometilo, clorometilo, diclorometilo, triclorometilo, y similares.

[0024] "Cicloalquilo" se refiere a grupos hidrocarbonados monocíclicos o bicíclicos saturados, que tienen en general un número específico de átomos de carbono que comprenden el anillo o los anillos (por ej., cicloalquilo C3-8 se refiere a un grupo cicloalquilo que tiene 3 a 8 átomos de carbono como miembros del anillo). Los grupos hidrocarbonados bicíclicos pueden incluir anillos aislados (dos anillos que no comparten

átomos de carbono), anillos espiro (dos anillos que comparten un átomo de carbono), anillos fusionados (dos anillos que comparten dos átomos de carbono y el enlace entre los dos átomos de carbono comunes), y anillos puenteados (dos anillos que comparten dos átomos de carbono, pero no un enlace común). El grupo cicloalquilo puede estar unido a un grupo principal o a un sustrato en cualquier átomo del anillo a menos que dicha unión violase los requerimientos de valencia. Además, el grupo cicloalquilo puede incluir uno o más sustituyentes no hidrógeno a menos que dicha sustitución violase los requerimientos de valencia.

[0025] Ejemplos de grupos cicloalquilo monocíclicos incluyen ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, y similares. Ejemplos de grupos cicloalquilo bicíclico fusionado incluyen grupos biciclo[2.1.0]pentanilo (i.e., biciclo[2.1.0]pentan-1-ilo, biciclo[2.1.0]pentan-2-ilo, y biciclo[2.1.0]pentan-5-ilo), biciclo[3.1.0]hexanilo, biciclo[3.2.0]heptanilo, biciclo[4.1.0]heptanilo, biciclo[3.3.0]octanilo, biciclo[4.2.0]octanilo, biciclo[4.3.0]nonanilo, biciclo[4.4.0]decanilo, y similares. Ejemplo de grupos cicloalquilo puenteados incluyen biciclo[2.1.1]hexanilo, biciclo[2.2.1]heptanilo, biciclo[3.1.1]heptanilo, biciclo[2.2.2]octanilo, biciclo[3.2.1]octanilo, biciclo[4.1.1]octanilo, biciclo[3.3.1]nonanilo, biciclo[4.2.1]nonanilo, biciclo[3.3.2]decanilo, biciclo[4.2.2]decanilo, biciclo[4.3.1]decanilo, biciclo[3.3.3]undecanilo, biciclo[4.3.2]undecanilo, biciclo[4.3.3]dodecanilo, y similares. Ejemplo de grupos espiro cicloalquilo incluyen espiro[3.3]heptanilo, espiro[2.4]heptanilo, espiro[3.4]octanilo, espiro[2.5]octanilo, espiro[3.5]nonanilo, y similares. Ejemplos de grupos cicloalquilo bicíclicos aislados incluyen los que derivan de bi(ciclobutano), ciclobutanociclopentano, bi(ciclopentano), ciclobutanociclohexano, ciclopentanociclohexano, bi(ciclohexano), etc.

[0026] "Cicloalqu-1-ilo" se refiere a un grupo cicloalquilo, como se definió anteriormente, que se une a un grupo principal o sustrato a través de un átomo de carbono localizado en la posición 1 del grupo cicloalquilo.

[0027] "Cicloalquenilo" se refiere a grupos hidrocarbonados monocíclicos y

bicíclicos parcialmente insaturados, que tienen en general un número específico de átomos de carbono que comprenden el anillo o los anillos. Como con los grupos cicloalquilo, los grupos cicloalquenilo bicíclicos pueden incluir anillos espiro, fusionados, o puenteados aislados. De manera similar, el grupo cicloalquenilo puede estar unido a un grupo principal, o a un sustrato en cualquier átomo de anillo y puede incluir uno o más sustituyentes no hidrógeno a menos que dicha unión o sustitución violase los requerimientos de valencia. Ejemplos de grupos cicloalquenilo incluyen los análogos parcialmente insaturados de los grupos cicloalquilo que se describieron anteriormente, tales como ciclobutenilo (es decir, ciclobuten-1-il y ciclobuten-3-il), ciclopentenilo, ciclohexenilo, biciclo[2.2.1]hept-2-enilo, y similares.

[0028] "Arilo" se refiere a hidrocarburos aromáticos monocíclicos totalmente insaturados y a hidrocarburos policíclicos que tienen al menos un anillo aromático, ambos grupos arilo monocíclicos y bicíclicos que tienen en general un número específico de átomos de carbono que comprenden sus miembros anulares (por ej., arilo C6-14 se refiere a un grupo arilo que tiene 6 a 14 átomos de carbono como miembros del anillo). El grupo arilo puede estar unido a un grupo principal, o a un sustrato en cualquier átomo de anillo y puede incluir uno o más sustituyentes no hidrógeno a menos que dicha unión o sustitución violase los requerimientos de valencia. Ejemplos de grupos arilo incluyen grupos fenilo, bifenilo, ciclobutanbencenilo, indenilo, naftalenilo, benzocicloheptanilo, bifenilenilo, fluorenilo que derivan del catión cicloheptatrieno, y similares.

[0029] "Heterociclo" y "heterociclilo" se pueden utilizar intercambiablemente y se refieren a grupos monocíclicos o bicíclicos saturados o parcialmente insaturados que tienen átomos del anillo compuestos de átomos de carbono y 1 a 4 heteroátomos seleccionados independientemente de nitrógeno, oxígeno, y azufre. Ambos grupos monocíclico y bicíclico tienen en general un número específico de átomos de carbono en su anillo o anillos (por ej., heterociclilo C2-5 se refiere a un grupo heterociclilo que tiene 2 a 5 átomos de carbono y 1 a 4 heteroátomos como miembros del anillo). Como con los

grupos cicloalquilo bicíclico, los grupos heterociclilo bicíclico pueden incluir anillos aislados, anillos espiro, anillos fusionados y anillos puenteados. El grupo heterociclilo puede estar unido a un grupo principal, o a un sustrato en cualquier átomo de anillo y puede incluir uno o más sustituyentes no hidrógeno a menos que dicha unión o sustitución violase los requerimientos de valencia o resultase en un compuesto químicamente inestable. Ejemplo de grupos heterociclilo monocíclico incluyen oxiranilo, tiaranilo, aziridinilo (por ej., aziridin-1-ilo y aziridin-2-ilo), oxetanilo, tiatanilo, azetidinilo, tetrahidrofuranilo, tetrahidrotiofenilo, pirrolidinilo, tetrahidropiranilo, tetrahidrotiopiranilo, piperidinilo, 1,4-dioxanilo, 1,4-oxatianilo, morfolinilo, 1,4-ditianilo, piperazinilo, 1,4-azatianilo, oxepanilo, tiepanilo, azepanilo, 1,4-dioxepanilo, 1,4-oxatiepanilo, 1,4-oxaazepanilo, 1,4-ditiepanilo, 1,4-tiazepanilo, 1,4-diazepanilo, 3,4-dihidro-2H-piranilo, 5,6-dihidro-2H-piranilo, 2H-piranilo, 1,2,3,4-tetrahidropiridinilo, y 1,2,5,6-tetrahidropiridinilo.

[0030] "Heteroarilo" se refiere a grupos aromáticos monocíclicos insaturados y a grupos policíclicos que tienen al menos un anillo aromático, cada uno de los grupos tiene átomos del anillo compuestos de átomos de carbono y 1 a 4 heteroátomos independientemente seleccionados de nitrógeno, oxígeno y azufre. Ambos grupos monocíclicos y policíclicos tienen en general un número específico de átomos de carbono como miembros del anillo (por ej., heteroarilo C1-9 se refiere a un grupo heteroarilo que tiene 1 a 9 átomos de carbono y 1 a 4 heteroátomos como miembros del anillo) y pueden incluir cualquier grupo bicíclico en el cual cualquiera de los heterociclos monocíclicos mencionados anteriormente están fusionados a un anillo benceno. El grupo heteroarilo puede estar unido a un grupo principal, o a un sustrato en cualquier átomo de anillo y puede incluir uno o más sustituyentes no hidrógeno a menos que dicha unión o sustitución violase los requerimientos de valencia o resultase en un compuesto químicamente inestable. Ejemplos de grupos heteroarilo incluyen grupos monocíclicos como pirrolilo (por ej. pirrol-1-ilo, pirrol-2-ilo, y pirrol-3-ilo), furanilo, tiofenilo, pirazolilo, imidazolilo, isoxazolilo, oxazolilo, isotiazolilo, tiazolilo, 1,2,3-triazolilo, 1,3,4-triazolilo, 1-oxa-2,3-diazolilo, 1-oxa-

2,4-diazolilo, 1-oxa-2,5-diazolilo, 1-oxa-3,4-diazolilo, 1-tia-2,3-diazolilo, 1-tia-2,4-diazolilo, 1-tia-2,5-diazolilo, 1-tia-3,4-diazolilo, tetrazolilo, piridinilo, piridazinilo, pirimidinilo, y pirazinilo.

[0031] Ejemplos de grupos heteroarilo además incluyen grupos bicíclicos como benzofuranilo, isobenzofuranilo, benzotiofenilo, benzo[c]tiofenilo, indolilo, 3H-indolilo, isoindolilo, 1H-isoindolilo, indolinilo, isoindolinilo, bencimidazolilo, indazolilo, benzotriazolilo, 1H-pirrolo[2,3-b]piridinilo, 1H-pirrolo[2,3-c]piridinilo, 1H-pirrolo[3,2-c]piridinilo, 1H-pirrolo[3,2-b]piridinilo, 3H-imidazo[4,5-b]piridinilo, 3H-imidazo[4,5-c]piridinilo, 1H-pirazolo[4,3-b]piridinilo, 1H-pirazolo[4,3-c]piridinilo, 1H-pirazolo[3,4-c]piridinilo, 1H-pirazolo[3,4-b]piridinilo, 7H-purina, indolizinilo, imidazo[1,2-a]piridinilo, imidazo[1,5-a]piridinilo, pirazolo[1,5-a]piridinilo, pirrolo[1,2-b]piridazinilo, imidazo[1,2-c]pirimidinilo, quinolinilo, isoquinolinilo, cinnolinilo, quinazolinilo, quinoxalinilo, ftalazinilo, 1,6-naftiridinilo, 1,7-naftiridinilo, 1,8-naftiridinilo, 1,5-naftiridinilo, 2,6-naftiridinilo, 2,7-naftiridinilo, pirido[3,2-d]pirimidinilo, pirido[4,3-d]pirimidinilo, pirido[3,4-d]pirimidinilo, pirido[2,3-d]pirimidinilo, pirido[2,3-b]pirazinilo, pirido[3,4-b]pirazinilo, pirimido[5,4-d]pirimidinilo, pirazino[2,3-b]pirazinilo, y pirimido[4,5-d]pirimidinilo.

[0032] "Oxo" se refiere a un oxígeno enlazado doble (=O).

[0033] "Grupo saliente" se refiere a cualquier grupo que sale de una molécula durante un proceso de fragmentación, que incluye las reacciones de sustitución, reacciones de eliminación, y reacciones de adición-eliminación. Los grupos salientes pueden nucleofugal, en el cual el grupo sale con un par de electrones que sirven inicialmente como enlace entre el grupo saliente y la molécula, o puede ser electrofugal, en el cual el grupo sale sin el par de electrones. La capacidad de un grupo saliente nucleofugal de salir depende de su resistencia base, siendo las bases más fuertes los grupos salientes más pobres. Los grupos salientes nucleofugales comunes incluyen nitrógeno (por ej., de sales de diazonio); sulfonatos, que incluyen alquilsulfonatos (por ej., mesilato), fluoroalquilsulfonatos (por ej., triflato, hexaflato, nonaflato, y tresilato), y

arilsulfonatos (por ej., tosilado, brosilato, closilato, y nosilato). Otros incluyen carbonatos, iones de haluro, aniones de carboxilato, iones de fenolato, y alcóxidos. Algunas bases más fuertes, tales como NH2- y OH- se pueden resultar mejores grupos salientes mediante el tratamiento con un ácido. Los grupos salientes electrofugales comunes incluyen el protón, CO2, y metales.

[0034] "Enantiómero opuesto" se refiere a una molécula que es una imagen refleja no superimponente de una molécula de referencia, que se puede obtener invirtiendo todos los centros estereogénicos de la molécula de referencia. Por ejemplo, si la molécula de referencia tiene configuración estereoquímica absoluta S, entonces el enantiómero opuesto tiene configuración estereoquímica absoluta R. De igual modo, si la molécula de referencia tiene configuración estereoquímica absoluta S,S, entonces el enantiómero opuesto tiene configuración estereoquímica R,R, etc.

[0035] "Estereoisómero" y "estereoisómeros" de un compuesto con configuración estereoquímica dada se refiere al enantiómero opuesto del compuesto a cualquier diastereoisómero, que incluye isómeros geométricos (Z/E) del compuesto. Por ejemplo, si un compuesto tiene configuración estereoquímica S,R,Z, sus estereoisómeros incluirían su enantiómero opuesto que tiene configuración R,S,Z, y sus diastereómeros que tienen configuración S,S,Z, configuración R,R,Z, configuración S,R,E, configuración R,S,E, configuración S,S,E, y configuración R,R,E. Si la configuración estereoquímica de un compuesto no es específica, entonces el "estereoisómero" se refiere a cualquiera de las configuraciones estereoquímicas posibles del compuesto.

[0036] "Estereoisómero sustancialmente puro" y sus variantes se refieren a una muestra que contiene un compuesto que tiene una configuración estereoquímica específica y que comprende al menos aproximadamente 95% de la muestra.

[0037] "Estereoisómero puro" y sus variantes se refieren a una muestra que contiene un compuesto que tiene una configuración estereoquímica específica y que comprende al menos aproximadamente 99,5% de la muestra.

[0038] "Sujeto" se refiere a un mamífero, que incluye un ser humano.

[0039] Sustancias "aceptables para uso farmacéutico" se refiere a las sustancias que están dentro del alcance del criterio médico adecuado para su uso en contacto con los tejidos de los sujetos sin la indebida toxicidad, irritación, respuesta alérgica, y similares, en proporción con una relación beneficio-riesgo razonable, y eficaz para el uso destinado.

[0040] "Que trata" se refiere a la inversión, alivio, inhibición del avance de, o a la prevención de un trastorno, enfermedad o afección a la cual se aplica dicho término, a la inversión, alivio, inhibición del avance de, o a la prevención de uno o más síntomas de dicho trastorno, enfermedad o afección.

[0041] "Tratamiento" se refiere al acto de "tratar", como se definió inmediatamente antes.

[0042] "Fármaco", "sustancia del fármaco", "principio farmacéutico activo", y similares, se refieren a un compuesto (por ej., compuestos de fórmula 1 y compuestos específicamente mencionados anteriormente) que se pueden utilizar para tratar a un sujeto que necesita el tratamiento.

[0043] "Cantidad eficaz para uso terapéutico" de un fármaco se refiere a la cantidad del fármaco que se puede utilizar para tratar a un sujeto y puede depender del peso y la edad del sujeto y la vía de administración, entre otras cosas.

[0044] "Excipiente" se refiere a cualquier sustancia que puede influir en la biodisponibilidad de un fármaco, pero de otro modo es farmacológicamente inactiva.

[0045] "Composición farmacéutica" se refiere a la combinación de una o más sustancias del fármaco y uno o más excipientes.

[0046] "Producto del fármaco", "forma de dosificación farmacéutica", "forma de dosificación", "forma de dosificación final" y similares, se refieren a una composición farmacéutica que se administra a un sujeto que necesita el tratamiento y en general puede tener la forma de comprimidos, cápsulas, saches que contienen polvo o gránulos,

soluciones líquidas o suspensiones, parches, películas, y similares.

[0047] Las siguientes abreviaturas se utilizan a lo largo de la memoria descriptiva:

Ac (acetilo); ACN (acetonitrilo); AIBN (azo-bis-isobutironitrilo); API (principio farmacéutico activo); ac (acuoso); Boc (ter-butoxicarbonilo); BSA (albúmina suero bovino); Cbz (carbobenciloxi); dba (dibencilidenacetona); DCC (1,3-diciclohexilcarbodiimida)

DCM (diclorometano); DIPEA (N,N-diisopropiletilamina, base de Hünig); DMA ((N,N-dimetilacetamida); DMAP (4-dimetilaminopiridina); DMARD (fármaco antirreumático que modifica la enfermedad); DME (1,2-dimetoxietano); DMF (N,N-dimetilformamida); DMSO (dimetilsulfóxido); dppf (1,1'-bis(difenilfosfino)ferroceno); DTT (ditiotreitol); EDA dodecil alcohol etoxilado, Brj®35); EDCI (N-(3-dimetilaminopropil)-N'-etilcarbodiimide); EDTA (ácido etilendiaminatetraacético); ee (exceso enantiomérico); eq (equivalentes); Et (etilo); Et3N (trietilamina); EtOAc (acetato de etilo); EtOH (etanol); FAM (5-carboxifluoresceína); HATU (hexafluorofosfato(V) de (2-(3H-[1,2,3]triazolo[4,5-b]piridin-3-il)-1,1,3,3-tetrametiluronio); HEPES (4-(ácido 2-hidroxietil)piperazina-1-etanosulfónico); HOAc (ácido acético); HOBt (1H-benzo[d][1,2,3]triazol-1-ol); IC50 (concentración a 50% de inhibición); IPA (isopropanol); IPAc (acetato de isopropilo); IPE (isopropiléter); LDA (litio diisopropilamida); LiHMDS (bis(trimetilsilil)amida de litio); mCPBA (ácido m-cloroperoxibenzoico); Me (metilo); MeOH (metanol); MTBE (metil ter-butil éter); MOI (multiplicidad de infección); pf (punto de fusión); NaOt-Bu (ter-butóxido de sodio); NBS (N-bromosuccinimida); NCS (N-clorosuccinimida); NIS (N-yodosuccinimida); PE (éter petróleo); f (fenilo); pIC50 (-log10(IC50), donde IC50 se menciona en unidades molares (M)); Pr (propilo); i-Pr (isopropilo); PTFE (politetrafluoroetileno); RT (temperatura ambiente, aproximadamente 20°C a 25°C); (SyK (tirosina quinasa esplénica); TCEP (tris(2-carboxietil)fosfina); TFA (ácido trifluoroacético); TFAA (anhídrido 2,2,2-trifluoroacético); tF (tetrahidrofurano); y buffer Tris (buffer 2-amino-2-hidroximetil-propano-1,3-diol).

[0048] Esta divulgación se refiere a compuestos de fórmula 1, que incluye los

compuestos específicamente mencionados anteriormente, y sus complejos, sales, solvatos e hidrato aceptables para uso farmacéutico. La presente divulgación además se refiere a materiales y métodos para preparar los compuestos de fórmula 1, las composiciones farmacéuticas que los contienen, y su uso para tratar trastornos, enfermedades, y afecciones que involucran el sistema inmune y la inflamación, que incluyen artritis reumatoide, malignidades hematológicas, canceres epiteliales (es decir, carcinomas), y otros trastornos, enfermedades, y afecciones para las cuales se indica la inhibición de la SYK.

[0049] Los compuestos de fórmula 1 incluyen aquéllos en los cuales L1 es un enlace y L2 es –Nº; L1 es -NH- y L2 es un enlace; L1 y L2 son ambos enlaces; o L1 y L2 son ambos -NH-.

[0050] Los compuestos de fórmula 1 incluyen además aquéllos en los cuales R1 es hidrógeno y R2 es alquilo C1-3, en particular, metilo o etilo, R1 y R2 son ambos grupos alquilo C1-3, en particular metilo; R1 y R2, junto con el átomo de carbono al cual están unidos, forman un grupo ciclopropilo; o R1 y R2 son ambos átomos de hidrógeno.

[0051] Los compuestos de fórmula 1 incluyen aquéllos en los cuales L1 es -NH- y L2 es -NH- o un enlace; G es N; R1 y R2 son ambos hidrógeno; y R3 es un 2-amino-C3-8 cicloalqu-1-ilo, o más en particular 2-amino-ciclohex-1-ilo, opcionalmente sustituido con uno a cuatro sustituyentes independientemente seleccionados de halo, oxo, NO2, -CN, R6, y R7.

[0052] Los compuestos de fórmula 1 incluyen aquéllos en los cuales L1 es -NH- y L2 es -NH- o un enlace; G es N; R1 y R2 son ambos hidrógeno; y R3 es un 2-amino-C26 alqu-1-ilo, o más en particular 2-aminoetan-1-ilo o 2-amino-2-oxoetan-1-ilo, opcionalmente sustituido con uno a cinco, de uno a cuatro o de uno a dos sustituyentes, respectivamente, independientemente seleccionados de halo, oxo, NO2, -CN, R6, y R7.

[0053] Los compuestos de fórmula 1 además incluyen aquéllos en los cuales L1 es -NH- y L2 es -NH- o un enlace; G es N; R1 y R2 son ambos hidrógeno; y R3 es un

heterociclilo C2-5, o más en particular un amino heterociclilo C2-5 como 3-aminotetrahidro-2H-piran-4-ilo, opcionalmente sustituido con uno a cinco o de uno a cuatro sustituyentes, respectivamente, independientemente seleccionados de halo, oxo, NO2, -CN, R6, y R7, donde el resto heterociclilo tiene 5 o 6 átomos del anillo.

[0054] Los compuestos de fórmula 1 incluyen aquéllos en los cuales L1 es -NH- y L2 es -NH- o un enlace; G es N; R1 y R2 son ambos hidrógeno; y R4 es arilo C6-14, o más en particular fenilo, opcionalmente sustituido con uno a cinco sustituyentes independientemente seleccionados de halo, oxo, CN, R6, y R7.

[0055] Los compuestos de fórmula 1 incluyen aquéllos en los cuales L1 es -NH- y L2 es -NH- o un enlace; G es N; R1 y R2 son ambos hidrógeno; y R4 es heteroarilo C1-9, o más en particular un heteroarilo C2-4 monocíclico, opcionalmente sustituido con uno a cinco o de uno a cuatro sustituyentes, respectivamente, independientemente seleccionados de halo, oxo, CN, R6, y R7.

[0056] Los compuestos de Fórmula 1 también incluyen aquellos en los que L1 es –NH- y L2 es –NH- o un enlace; G es N; R1 y R2 son ambos hidrógeno, y R4 es un heteroarilo C2-4 monocíclico seleccionado de pirrolilo, furanilo tiofenilo, pirazolilo, imidazolilo, isoxazolilo, oxazolilo, isotiazolilo y tiazolilo, o más particularmente de tiofenilo, pirazolilo, isotiazolilo y tiazolilo, cada uno opcionalmente sustituido con de uno a tres sustituyentes seleccionados independientemente entre halo, -CN, R6 y R7.

[0057] Los compuestos de fórmula 1 incluyen aquéllos en los cuales L1 es -NH- y L2 es -NH- o un enlace; G es N; R1 y R2 son ambos hidrógeno; y R4 es un resto pirazol (por ejemplo, pirazol-4-ilo) opcionalmente sustituido con uno a tres sustituyentes independientemente seleccionados de halo, R6, y R7.

[0058] Los compuestos de fórmula 1 incluyen aquéllos en los cuales L1 es NH y L2 es NH o un enlace; G es C(R5); R1 y R2 son ambos hidrógeno; y R5 es un heteroarilo C1-5 opcionalmente sustituido con uno a cuatro sustituyentes independientemente seleccionados de halo, NO2, - CN, alquilo C1-4, alquenilo C2-4, alquinilo C24, haloalquilo

C14, y R10.

[0059] Los compuestos de fórmula 1 además incluyen aquéllos en los cuales L1 es NH y L2 es NH o un enlace; G es C(R5); R1 y R2 son ambos hidrógeno; y R5 es hidrógeno o halo, o más en particular, cloro o flúor.

[0060] Los compuestos de fórmula 1 incluyen aquéllos en los cuales L1 es -NH- y L2 es -NH- o un enlace; G es C(R5); R1 y R2 son ambos hidrógeno; y R3 es un 2-amino-C3-8 cicloalqu-1-ilo, o más en particular 2-amino-ciclohex-1-ilo, opcionalmente sustituido con uno a cuatro sustituyentes independientemente seleccionados de halo, oxo, NO2, -CN, R6, y R7.

[0061] Los compuestos de fórmula 1 incluyen aquéllos en los cuales L1 es -NH- y L2 es -NH- o un enlace; G es C(R5); R1 y R2 son ambos hidrógeno; y R3 es un 2-amino-C26 alqu-1-ilo, o más en particular 2-aminoetan-1-ilo o 2-amino-2-oxoetan-1-ilo, opcionalmente sustituido con uno a cinco, de uno a cuatro o de uno a dos sustituyentes, respectivamente independientemente seleccionados de halo, oxo, NO2, -CN, R6, y R7.

[0062] Los compuestos de fórmula 1 además incluyen aquéllos en los cuales L1 es -NH- y L2 es -NH- o un enlace; G es C(R5); R1 y R2 son ambos hidrógeno; y R3 es un heterociclilo C2-5, o más en particular un amino heterociclilo C2-5 como 3-aminotetrahidro-2H-piran-4-ilo, opcionalmente sustituido con uno a cinco o de uno a cuatro sustituyentes, respectivamente, independientemente seleccionados de halo, oxo, NO2, -CN, R6, y R7, donde el resto heterociclilo tiene 5 o 6 átomos del anillo.

[0063] Los compuestos de fórmula 1 incluyen aquéllos en los cuales L1 es -NH- y L2 es -NH- o un enlace; G es C(R5); R1 y R2 son ambos hidrógeno; y R4 es arilo C6-14, o más en particular fenilo, opcionalmente sustituido con uno a cinco sustituyentes independientemente seleccionados de halo, oxo, CN, R6, y R7.

[0064] Los compuestos de fórmula 1 incluyen aquéllos en los cuales L1 es -NH- y L2 es -NH- o un enlace; G es C(R5); R1 y R2 son ambos hidrógeno; y R4 es arilo C1-9, o más en particular un heteroarilo C2-4, opcionalmente sustituido con uno a cinco o de uno

a cuatro sustituyentes, respectivamente, independientemente seleccionados de halo, oxo, CN, R6, y R7.

[0065] Los compuestos de Fórmula 1 también incluyen aquellos en los que L1 es –NH- y L2 es –NH- o un enlace; G es C (R5); R1 y R2 son ambos hidrógeno, y R4 es un heteroarilo C2-4 monocíclico seleccionado de pirrolilo, furanilo, tiofenilo, pirazolilo, imidazolilo, isoxazolilo, oxazolilo, isotiazolilo, y tiazolilo, o más particularmente de tiofenilo, pirazolilo, isotiazolilo, y tiazolilo, cada uno opcionalmente sustituido con de uno a tres sustituyentes seleccionados independientemente de halo, -CN, R6 y R7.

[0066] Los compuestos de fórmula 1 incluyen aquéllos en los cuales L1 es -NH- y L2 es -NH- o un enlace; G es C(R5); R1 y R2 son ambos hidrógeno; y R4 es un resto pirazol (por ejemplo, pirazol-4-ilo) opcionalmente sustituido con uno a tres sustituyentes independientemente seleccionados de halo, CN, R6, y R7.

[0067] Los compuestos de fórmula 1 incluyen aquéllos en los cuales L1 es -NH- y L2 es -NH- o un enlace; G es N; R1 y R2 son ambos hidrógeno; R3es un 2-amino-C3-8 cicloalqu-1-ilo, o más en particular 2-amino-ciclohex-1-ilo, opcionalmente sustituido con uno a cuatro sustituyentes independientemente seleccionados de halo, oxo, NO2, CN, R6, y R7; y R4 es un arilo C6-14, o más en particular fenilo, opcionalmente sustituido con uno a cinco sustituyentes independientemente seleccionados de halo, oxo, CN, R6, y R7.

[0068] Los compuestos de fórmula 1 incluyen aquéllos en los cuales L1 es -NH- y L2 es -NH- o un enlace; G es N; R1 y R2 son ambos hidrógeno; R3es un 2-amino-C3-8 cicloalqu-1-ilo, o más en particular 2-amino-ciclohex-1-ilo, opcionalmente sustituido con uno a cuatro sustituyentes independientemente seleccionados de halo, oxo, NO2, CN, R6, y R7; y R4 es un heteroarilo C1-9, o más en particular un heteroarilo C2-4 monocíclico, opcionalmente sustituido con uno a cinco o de uno a cuatro sustituyentes, respectivamente independientemente seleccionados de halo, oxo, CN, R6, y R7.

[0069] Los compuestos de Fórmula 1 incluyen aquellos en los cuales L1 es NH y L2 es NH o un enlace; G es N; R1 y R2 son ambos hidrógeno; R3 es un 2-amino-

cicloalqu-1-ilo C3-8, o más particularmente 2-amino-ciclohex-1-ilo, opcionalmente sustituido con de uno a cuatro sustituyentes seleccionados independientemente de halo, oxo, NO2, CN, R6, R7; y R4 es un heteroarilo C2-4 monocíclico seleccionado de pirrolilo, furanilo, tiofenilo, pirazolilo , imidazolilo, isoxazolilo, oxazolilo, isotiazolilo, y tiazolilo, o más particularmente de tiofenilo, pirazolilo, isotiazolilo, y tiazolilo, cada uno opcionalmente sustituido con de uno a tres sustituyentes seleccionados independientemente de halo, CN, R6, y R7.

[0070] Los compuestos de Fórmula 1 incluyen aquellos en los cuales L1 es NH y L2 es NH o un enlace; G es N; R1 y R2 son ambos hidrógeno; R3 es un 2-amino-cicloalqu-1-ilo C3-8, o más particularmente 2-amino-ciclohex-1-ilo, opcionalmente sustituido con de uno a cuatro sustituyentes seleccionados independientemente de halo, oxo, NO2, CN, R6, y R7; y R4 es un resto pirazol (por ejemplo, pirazol-4-ilo) sustituido con de uno a tres sustituyentes seleccionados independientemente de halo, CN, R6, y R7.

[0071] Los compuestos de fórmula 1 incluyen aquéllos en los cuales L1 es -NH- y L2 es -NH- o un enlace; G es C(R5); R1 y R2 son ambos hidrógeno; R3es un 2-amino-C3-8 cicloalqu-1-ilo, o más en particular 2-amino-ciclohex-1-ilo, opcionalmente sustituido con uno a cuatro sustituyentes independientemente seleccionados de halo, oxo, NO2, CN, R6, y R7; y R4 es un arilo C6-14, o más en particular fenilo, opcionalmente sustituido con uno a cinco sustituyentes independientemente seleccionados de halo, oxo, CN, R6, y R7.

[0072] Los compuestos de fórmula 1 además incluyen aquéllos en los cuales L1 es -NH- y L2 es -NH- o un enlace; G es C(R5); R1 y R2 son ambos hidrógeno; R3es un 2-amino-C3-8 cicloalqu-1-ilo, o más en particular 2-amino-ciclohex-1-ilo, opcionalmente sustituido con uno a cuatro sustituyentes independientemente seleccionados de halo, oxo, NO2, CN, R6, y R7; y R4 es un heteroarilo C1-9, o más en particular un heteroarilo C2-4 monocíclico, opcionalmente sustituido con uno a cinco o de uno a cuatro sustituyentes , respectivamente, independientemente seleccionados de halo, oxo, CN, R6, y R7.

[0073] Los compuestos de Fórmula 1 incluyen aquellos en los cuales L1 es NH y

L2 es NH o un enlace; G es C(R5); R1 y R2 son ambos hidrógeno; R3 es un 2-amino-cicloalqu-1-ilo C3-8, o más particularmente 2-amino-ciclohex-1-ilo, opcionalmente sustituido con de uno a cuatro sustituyentes seleccionados independientemente de halo, oxo, NO2, CN, R6, y R7; y R4 es un heteroarilo C2-4 monocíclico seleccionado de pirrolilo, furanilo, tiofenilo, pirazolilo , imidazolilo, isoxazolilo, oxazolilo, isotiazolilo, y tiazolilo, o más particularmente de tiofenilo, pirazolilo, isotiazolilo, y tiazolilo, cada uno opcionalmente sustituido con de uno a tres sustituyentes seleccionados independientemente de halo, CN, R6, y R7.

[0074] Los compuestos de Fórmula 1 incluyen aquellos en los cuales L1 es NH y L2 es NH o un enlace; G es C(R5); R1 y R2 son ambos hidrógeno; R3 es un 2-amino-cicloalqu-1-ilo C3-8, o más particularmente 2-amino-ciclohex-1-ilo, opcionalmente sustituido con de uno a cuatro sustituyentes seleccionados independientemente de halo, oxo, NO2, CN, R6, y R7; y R4 es un resto pirazol (por ejemplo, pirazol-4-ilo) sustituido con de uno a tres sustituyentes seleccionados independientemente de halo, CN, R6, y R7.

[0075] Los compuestos de fórmula 1 incluyen cualquiera de las realizaciones antes mencionadas en las cuales L1 es -NH- y L2 es un enlace.

[0076] De este modo, los compuestos de fórmula 1 incluyen aquéllos en los cuales L1 es -NH; L2 es -un enlace; G es C(R5); R1 y R2 son ambos hidrógeno; R5 es hidrógeno o halo, o más en particular, cloro o flúor; y R3 es un 2-amino-C3-8 cicloalqu-1-ilo, o más en particular 2-amino-ciclohex-1-ilo, opcionalmente sustituido con uno a cuatro sustituyentes independientemente seleccionados de halo, oxo, NO2, -CN, R6, y R7.

[0077] Los compuestos de fórmula 1 incluyen aquéllos en los cuales L1 es -NH; L2 es -un enlace; G es C(R5); R1 y R2 son ambos hidrógeno; R5 es hidrógeno o halo, o más en particular, cloro o flúor; y R3 es un 2-amino-C26 alqu-1-ilo, o más en particular 2-aminoetan-1-ilo o 2-amino-2-oxoetan-1-ilo, opcionalmente sustituido con uno a cinco, de uno a cuatro o de uno a dos sustituyentes, respectivamente, independientemente seleccionados de halo, oxo, NO2, -CN, R6, y R7.

[0078] Los compuestos de fórmula 1 además incluyen aquéllos en los cuales L1 es -NH-; L2 es un enlace; G es C(R5); R1 y R2 son ambos hidrógeno; R5 es hidrógeno o halo, o más en particular, cloro o flúor; y R3 es un heterociclilo C2-5, o más en particular un amino heterociclilo C2-5 como 3-aminotetrahidro-2H-piran-4-ilo, opcionalmente sustituido con uno a cinco o de uno a cuatro sustituyentes, respectivamente, independientemente seleccionados de halo, oxo, NO2, -CN, R6, y R7, donde el resto heterociclilo tiene 5 o 6 átomos del anillo.

[0079] Los compuestos de fórmula 1 incluyen aquéllos en los cuales L1 es -NH; L2 es -un enlace; G es C(R5); R1 y R2 son ambos hidrógeno; R5 es hidrógeno o halo, o más en particular, cloro o flúor; y R4 es un arilo C6-14, o más en particular fenilo, opcionalmente sustituido con uno a cinco sustituyentes independientemente seleccionados de halo, oxo, CN, R6, y R7.

[0080] Los compuestos de fórmula 1 también incluyen aquéllos en los cuales L1 es -NH; L2 es -un enlace; G es C(R5); R1 y R2 son ambos hidrógeno; R5 es hidrógeno o halo, o más en particular, cloro o flúor; y R4 es un heteroarilo C1-9, o más en particular un heteroarilo C2-4 monocíclico, opcionalmente sustituido con uno a cinco sustituyentes o de uno a cuatro sustituyentes, respectivamente, independientemente seleccionados de halo, oxo, CN, R6, y R7.

[0081] Los compuestos de fórmula 1 incluyen aquéllos en los cuales L1 es -NH; L2 es -un enlace; G es C(R5); R1 y R2 son ambos hidrógeno; R5 es hidrógeno o halo, o más en particular, cloro o flúor; y R4 es un heteroarilo C2-4 monocíclico seleccionado de pirrolilo, furanilo tiofenilo, pirazolilo, imidazolilo, isoxazolilo, oxazolilo, isotiazolilo y tiazolilo, o más particularmente de tiofenilo, pirazolilo, isotiazolilo y tiazolilo, cada uno opcionalmente sustituido con de uno a tres sustituyentes seleccionados independientemente entre halo, -CN, R6 y R7.

[0082] Los compuestos de fórmula 1 incluyen aquéllos en los cuales L1 es -NH; L2 es -un enlace; G es C(R5); R1 y R2 son ambos hidrógeno; R5 es hidrógeno o halo, o más

en particular, cloro o flúor; y R4 es un resto pirazol (por ejemplo, pirazol-4-ilo) opcionalmente sustituido con uno a tres sustituyentes independientemente seleccionados de halo, CN, R6, y R7.

[0083] Los compuestos de fórmula 1 incluyen aquéllos en los cuales L1 es -NH; L2 es -un enlace; G es C(R5); R1 y R2 son ambos hidrógeno; R5 es hidrógeno o halo, o más en particular, cloro o flúor; R3es un 2-amino-C3-8 cicloalqu-1-ilo, o más en particular 2-amino-ciclohex-1-ilo, opcionalmente sustituido con uno a cuatro sustituyentes independientemente seleccionados de halo, oxo, NO2, CN, R6, y R7; y R4 es un arilo C6-14, o más en particular fenilo, opcionalmente sustituido con uno a cinco sustituyentes independientemente seleccionados de halo, oxo, CN, R6, y R7.

[0084] Los compuestos de fórmula 1 incluyen aquéllos en los cuales L1 es -NH; L2 es -un enlace; G es C(R5); R1 y R2 son ambos hidrógeno; R5 es hidrógeno o halo, o más en particular, cloro o flúor; R3es un 2-amino-C3-8 cicloalqu-1-ilo, o más en particular 2-amino-ciclohex-1-ilo, opcionalmente sustituido con uno a cuatro sustituyentes independientemente seleccionados de halo, oxo, NO2, CN, R6, y R7; y R4 es un heteroarilo C1-9, o más en particular un heteroarilo C2-4 monocíclico, opcionalmente sustituido con uno a cinco o de uno a cuatro sustituyentes, respectivamente, independientemente seleccionados de halo, oxo, CN, R6, y R7.

[0085] Los compuestos de Fórmula 1 incluyen aquellos en los cuales L1 es NH y L2 es NH o un enlace; G es C(R5); R1 y R2 son ambos hidrógeno; R3 es un 2-amino-cicloalqu-1-ilo C3-8, o más particularmente 2-amino-ciclohex-1-ilo, opcionalmente sustituido con de uno a cuatro sustituyentes seleccionados independientemente de halo, oxo, NO2, CN, R6, R7; y R4 es un heteroarilo C2-4 monocíclico seleccionado de pirrolilo, furanilo, tiofenilo, pirazolilo , imidazolilo, isoxazolilo, oxazolilo, isotiazolilo, y tiazolilo, o más particularmente de tiofenilo, pirazolilo, isotiazolilo, y tiazolilo, cada uno opcionalmente sustituido con de uno a tres sustituyentes seleccionados independientemente de halo, CN, R6, y R7.

[0086] Los compuestos de Fórmula 1 incluyen aquellos en los cuales L1 es NH y L2 es NH o un enlace; G es N; R1 y R2 son ambos hidrógeno; R5 es hidrógeno o halo, o más particularmente, cloro o flúor; R3 es un 2-amino-cicloalqu-1-ilo C3-8, o más particularmente 2-amino-ciclohex-1-ilo, opcionalmente sustituido con de uno a cuatro sustituyentes seleccionados independientemente de halo, oxo, NO2, CN, R6, y R7; y R4 es un resto pirazol (por ejemplo, pirazol-4-ilo) sustituido con de uno a tres sustituyentes seleccionados independientemente de halo, CN, R6, y R7.

[0087] Los compuestos de Fórmula 1 también incluyen cualquiera de las realizaciones anteriores en las que uno o más de los sustituyentes R3, R4, R5, R7, R8 y R9 no tienen sustituyentes opcionales.

[0088] Todas las referencias a los compuestos, incluyendo los compuestos de fórmula 1y los compuestos mencionados en la memoria descriptiva, en general incluyen todos los complejos, sales, solvatos, hidratos y cristales líquidos de los compuestos. De igual modo, todas las referencias a los compuestos incluyen todos los complejos, solvatos, hidratos y cristales líquidos de las sales de los compuestos.

[0089] Los compuestos de fórmula 1, que incluye los compuestos específicamente mencionados anteriormente, y sus complejos, sales, solvatos e hidrato aceptables para uso farmacéutico. Estas sales incluyen sales de adición de ácido (que incluyen diácidos) y sales de base. Las sales de adición de ácido aceptables para uso farmacéutico incluyen sales no tóxicas de ácido inorgánicos tales como ácido clorhídrico, ácido nítrico, ácido fosfórico, ácido sulfúrico, ácido bromhídrico, ácido yodhídrico, ácido hidrofluórico, y ácidos fosforosos, como también sales no tóxicas que derivan de ácidos orgánicos, tales como ácido alifáticos mono y dicarboxílicos, ácidos alcanoicos sustituidos con fenilo, ácidos hidroxi alcanoicos, ácidos alcanodioicos, ácidos aromáticos, ácidos sulfónicos alifáticos y aromáticos, etc. Estas sales incluyen acetato adipato, aspartato, benzoato, besilato, bicarbonato, carbonato, bisulfato, sulfato, borato, camsilato, citrato, ciclamato, edisilato, esilato, formato, fumarato, gluceptato, gluconato, glucuronato,

hexafluorofosfato, hibenzato, clorhidrato/cloruro, bromhidrato/bromuro, yohidrato/yoduro, isetionato, lactato, malato, maleato, malonato, mesilato, metilsulfato, naftilato, 2-napsilato, nicotinato, nitrato, orotato, oxalato, palmitato, pamoato, fosfato, fosfato hidrógeno, fosfato dihidrógeno, piroglutamato, saccharato, estearato, succinato, tannato, tartrato, tosilato, trifluoroacetato y sales xinofoato.

[0090] Las sales base aceptables para uso farmacéutico incluyen sales no tóxicas que derivan de bases, que incluyen cationes metálicos, tales como catión de metal alcalino o alcalinotérreo, como también aminas. Ejemplos de cationes metálicos adecuados incluyen (Na+) de sodio, (K+) de potasio, (Mg2+) de magnesio, (Ca2+) de calcio, (Zn2+) de zinc, y (Al3+) de aluminio.. Ejemplos de aminas adecuadas incluyen arginina, N,N'-dibenciletilendiamina, cloroprocaína, colina, dietilamina, dietanolamina, diciclohexilamina, etilendiamina, glicina, lisina, N-metilglucamina, olamina, 2-amino-2-hidroximetil-propano-1,3-diol, y procaína. Para una discusión de sales de base y adición de ácido útiles, véase S. M. Berge et al., J. Pharm. Sci. (1977) 66:1-19; véase además Stahl y Wermuth, Handbook of Pharmaceutical Salts: Properties, Selection, and Use (2002).

[0091] Las sales aceptables para uso farmacéutico se pueden preparar utilizando varios métodos. Por ejemplo, se puede hacer reaccionar un compuesto de fórmula 1 con un ácido o base apropiada para dar la sal deseada. Además se puede hacer reaccionar un precursor del compuesto de fórmula 1 con un ácido o base para eliminar un grupo protector lábil de ácido o base o para abrir una lactona o grupo lactamo del precursor. Además, se puede convertir una sal del compuesto de fórmula 1 a otra sal a través del tratamiento con un ácido o base apropiada o a través del contacto con una resina de intercambio iónico. Siguiendo la reacción, a continuación se puede aislar la sal por filtración si precipita de la solución, o por evaporación para recuperar la sal. El grado de ionización de la sal puede variar de completamente ionizado a casi no ionizado.

[0092] Los compuestos de fórmula 1 pueden existir en un continuum de estados

sólidos que oscilan desde totalmente amorfos a completamente cristalinos. El término "amorfo" se refiere a un estado en el cual el material carece de orden de largo rango en el nivel molecular y, dependiendo de la temperatura, puede exhibir las propiedades físicas de un sólido o un líquido. Típicamente estos materiales no dan patrones de difracción de rayos X distintivos y, mientras exhiben las propiedades de un sólido, se describen más formalmente como un líquido Al cabo del calentamiento, se produce un cambio de propiedades sólidas a líquidas que se caracteriza por un cambio de estado, típicamente de segundo orden ("transición vítrea"). El término "cristalino" se refiere a una fase sólida en la cual el material tiene una estructura interna ordenada regular en el nivel molecular y da un patrón de difracción de rayos X distintivo con picos definidos. Estos materiales cuando se calientan lo suficiente exhibirán además las propiedades de un líquido, pero el cambio de sólido a líquido se caracteriza por un cambio de fase, típicamente de primer orden ("punto de fusión").

[0093] Los compuestos de fórmula 1 pueden existir además en formas solvatadas y no solvatadas. El término "solvato" describe un complejo molecular que comprende el compuesto y una o más moléculas de solvente aceptables para uso farmacéutico (por ej., EtOH). El término "hidrato" es un solvato en el cual el solvente es agua. Los solvatos aceptables para uso farmacéutico incluyen aquéllos en los cuales el solvente puede ser sustituido isotópicamente (por ej., D2O, d6-acetona, d6-DMSO).

[0094] Un sistema de clasificación normalmente aceptado para solvatos e hidratos de compuestos orgánicos es uno que distingue entre sitio aislado, canal, y solvatos e hidratos coordinados de metal-ion. Véase, por ej., K. R. Morris (H. G. Brittain ed.) Polymorphism in Pharmaceutical Solids (1995). Los solvatos e hidratos de sitio aislados son aquéllos en los cuales las moléculas de solvente (por ej., agua) se aíslan del contacto directo entre sí mediante moléculas intervinientes del compuesto orgánico. En los solvatos de canal, las moléculas de solvente se encuentran en canales de red cristalina donde están próximas a otras moléculas de solvente. En los solventes coordenados de metal-

ion, las moléculas de solvente se unen al ion metálico.

[0095] Cuando el solvente o el agua se unen con firmeza, el complejo tendrá una estoiquiometría bien definida independiente de la humedad. Cuando, sin embargo, el solvente o el agua se unen débilmente, como en los solvatos de canales y en los compuestos higroscópicos, el contenido de agua o solvente dependerá de la humedad y las condiciones de secado. En estos casos, la no-estoiquiometría será típicamente observada.

[0096] Los compuestos de fórmula 1 además pueden existir como complejos de múltiples componentes (que no son sales ni solvatos) en los cuales el compuesto (fármaco) y al menos otro componente están presentes en cantidades estoiquiométricas o no estoiquiométricas. Los complejos de este tipo incluyen clatratos (complejos de inclusión de fármaco-hospedante) y co-cristales. Éstos últimos se definen típicamente como complejos cristalinos de constituyentes moleculares neutros que se unen a través de interacciones no covalentes, pero además podrían ser un complejo de una molécula neutra con una sal. Los co-cristales se pueden preparar por cristalización de fusión, por recristalización de solventes, o por molido físico de los componentes. Véase, por ej., O. Almarsson y M. J. Zaworotko, Chem. Commun. (2004) 17:1889-1896. Para una revisión general de complejos de múltiples componentes, véase J. K. Haleblian, J. Pharm. Sci. (1975) 64(8):1269-88.

[0097] Cuando se someten a condiciones adecuadas, los compuestos de fórmula 1 pueden existir en un estado mesomórfico (mesofase o cristal líquido). El estado mesomórfico se encuentra entre el estado cristalino verdadero y el estado líquido verdadero (ya sea fusión o solución). El mesomorfismo que surge como resultado de un cambio en temperatura se describe como "termotrópico" y el mesomorfismo que surge de la adición de un segundo componente, tal como agua u otro solvente, se describe como "liotrópico". Los compuestos que tienen el potencial para formar mesofases liotrópicas se describen como "amfifilicos" e incluyen moléculas que poseen un resto iónico polar (por

ej., COO^-Na+, $-COO^-K+$, $-SO3^-Na+$) o resto no iónico polar (tal como $N^-N+(CH3)3$). Véase, por ej., N. H. Hartshorne y A. Stuart, Crystals and the Polarizing Microscope (4º ed, 1970).

[0098] Todas las referencias a compuestos, que incluyen los compuestos de fórmula 1 y los compuestos mencionados en la memoria descriptiva, incluyen en general todos los polimorfos y hábitos cristalinos, profármacos, metabolitos, estereoisómeros, y tautómeros de los mismos, como también todos sus compuestos isotópicamente marcados.

[0099] "Profármacos" se refiere a compuestos que tienen poca o ninguna actividad farmacológica que pueden, cuando se metabolizan in vivo, someterse a conversión a compuestos que tiene la actividad farmacológica deseada. Los profármacos se pueden preparar reemplazando las funcionalidades apropiadas presentes en los compuestos farmacológicamente activos con "pro-restos" como se describe, por ejemplo, en H. Bundgaar, Design of Prodrugs (1985). Ejemplos de profármacos incluyen, derivados de éster, éter o amida de los compuestos de fórmula 1 que tienen grupos funcionales de ácido carboxílico, hidroxi, o amino, respectivamente. Para mayor discusión sobre los profármacos, véase por ej., T. Higuchi y V. Stella “Pro-drugs as Novel Delivery Systems,” ACS Symposium Series 14 (1975) and E. B. Roche ed., Bioreversible Carriers in Drug Design (1987).

[00100]"Metabolitos" se refieren a compuestos que se forman in vivo al cabo de la administración de compuestos farmacológicamente activos. Ejemplos incluyen hidroximetilo, hidroxi, amino secundario, amino primario, fenol, y derivados de ácido carboxílico de los compuestos de fórmula 1 que tienen metilo, alcoxi, amino terciario, amino secundario, fenilo, y grupos amida, respectivamente.

[00101]Ciertos compuestos que se describen en la presente pueden tener estereoisómeros. Estos compuestos pueden existir como enantiómeros simples (compuestos enantiopuros) o mezclas de enantiómeros (muestras enriquecidas y

racémicas), que dependen del exceso relativo de un enantiómero sobre otro en una muestra, pueden exhibir actividad óptica. Estos estereoisómeros, que son imágenes reflejas superimponentes, poseen un eje estereogénico o uno o más centros estereogénicos (es decir, quiralidad). Otros compuestos pueden ser estereoisómeros que no son imágenes reflejas. Estos estereoisómeros, que son conocidos como diastereoisómeros, pueden ser quirales o aquirales (no contienen centros estereogénicos). Ellos incluyen moléculas que contienen un grupo alquenilo o cíclico, de modo que estereoisómeros cis/trans (o Z/E) son posibles, o moléculas que contienen dos o más centros estereogénicos, en los cuales la inversión de un centro estereogénico simple genera un diastereoisómero correspondiente. A menos que se establezca o se aclare de otro modo (por ej., a través del uso de estereoenlaces, descriptores estereocentrales, etc.) el alcance de la invención y la divulgación incluye en general el compuesto de referencia, y sus esteroisómeros, ya sea que sean cada uno de ellos puros (por ej., enantiopuro) o mezclas (por ej, enantioméricamente enriquecidas o racémicas).

[00102]Los isómeros geométricos (cis/trans)) se pueden separar por técnicas convencionales tales como cromatografía y cristalización fraccional.

[00103]Los enantiómeros individuales de los compuestos se pueden preparar mediante síntesis quiral a partir de un precursor ópticamente puro adecuado o aislarse mediante resolución del racemato (o el racemato de una sal o derivado) utilizando, por ejemplo, HPLC quiral. En forma alternativa, el racemato (o un precurso racémico) se puede hacer reaccionar con un compuesto enantioméricamente puro adecuado (por ej., ácido o base) para dar un par de diastereoisómeros, cada uno compuesto de un enantiómero simple, que se separan mediante, digamos, recristalización fraccional o cromatografía. El enantiómero deseado se regenera a continuación a partir del diastereoisómero apropiado. A menudo, el enantiómero deseado puede enriquecerse posteriormente mediante recristalización en un solvente adecuado (por ej., ACN) cuando está disponible en cantidad suficiente (por ej., típicamente no menos de aproximadamente

85% ee, y en algunos casos, no menos de aproximadamente 90% ee). Para una posterior discusión de técnicas para separar estereoisómeros, véase E. L. Eliel y S. H. Wilen, Stereochemistry of Organic Compounds (1994).

[00104]"Tautómeros" se refiere a isómeros estructurales que son interconvertibles mediante una barrera de baja energía. El isomerismo tautomérico (tautomerismo) puede tomar la forma de tautomerismo de protones en los cuales el compuesto contiene, por ejemplo, un grupo imino, ceto, o oxima, o tautomerismo de valencia en el cual el compuesto contiene un resto aromático.

[00105]Los compuestos que se describen en la presente además incluyen todas las variantes isotópicas aceptables para uso farmacéutico, en las cuales al menos un átomo se reemplaza con un átomo que tiene el mismo número atómico, pero una masa atómica diferente de la masa atómica usualmente hallada en la naturaleza. Los isótopos adecuados para su inclusión en los compuestos de fórmula 1 incluyen, por ejemplo, isótopos de hidrógeno, tales como 2H y 3H; isótopos de carbono, tales como 11C, 13C y 14C; isótopos de nitrógeno, tales como 13N and 15N; isótopos de oxígeno, tales como 15O, 17O y 18O; isótopos de azufre, tal como 35S; isótopos de flúor, tal como 18F; isótopos de cloro, tal como 36Cl, e isótopos de yodo, tales como 123I y 125I. El uso de variantes isotópicas (por ej., deuterismo, 2H) puede dar ciertas ventajas terapéuticas que surgen de una mayor estabilidad metabólica, por ejemplo, tiempo de vida medio in vivo aumentado o requerimientos de dosificación reducidos. Además, ciertas variaciones isotópicas de los compuestos divulgados pueden incorporar un isótopo radioactivo (por ej., tritio, 3H, o 14C), que puede ser útil en los estudios de distribución de tejido de sustrato y/o fármaco. La sustitución con isótopos de emisión de positrones, tales como 11C, 18F, 15O and 13N, puede ser útil en los estudios de topografía de emisión de positrones (PET) para examinar la ocupación del receptor del sustrato. Los compuestos isotópicamente marcados se pueden preparar mediante procesos análogos a los que se describen en cualquier parte en la divulgación utilizando un reactivo isotópicamente

marcado apropiado en lugar de un reactivo no marcado.

[00106]Los compuestos de fórmula 1 se pueden preparar utilizando las técnicas que se describen a continuación. Algunos de los esquemas y ejemplos pueden omitir detalles de reacciones comunes, que incluyen oxidaciones, reducciones, etc., técnicas de separación (extracción, evaporación, precipitación, cromatografía, filtración, trituración, cristalización, y similares), y procedimientos analíticos, que son conocidos para los expertos en la técnica de la química orgánica. Los detalles de estas reacciones y técnicas se pueden hallar en un número de tratados, que incluyen Richard Larock, Comprehensive Organic Transformations (1999), y la serie de múltiples volúmenes editada por Michael B. Smith y otros, Compendium of Organic Synthetic Methods (1974 et seq.). Los materiales de partida y los reactivos se pueden obtener a partir de fuentes comerciales o se pueden preparar utilizando métodos de literatura. Algunos de los esquemas de reacción pueden omitir productos menores que surgen de transformaciones químicas (por ej., un alcohol a partir de la hidrólisis de un éster, CO2 a partir de la decarboxilación de un diácido, etc.). Además, en algunos casos, los intermediarios de reacción se pueden utilizar en pasos subsiguientes sin el aislamiento o la purificación (es decir, in situ).

[00107]En algunos de los esquemas de reacción y en los ejemplos a continuación, ciertos compuestos se pueden preparar utilizando grupos protectores, que previenen la reacción química indeseable en cualquiera de los sitios reactivos. Los grupos protectores se pueden utilizar además para mejorar la solubilidad o modificar de otro modo las propiedades físicas de un compuesto. Para una discusión de las estrategias del grupo protector, una descripción de los materiales y métodos para instalar y eliminar los grupos protectores, y una compilación de grupos protectores útiles para los grupos funcionales comunes, que incluyen aminas, ácidos carboxílicos, alcoholes, cetonas, aldehídos, etc., véase T. W. Greene y P. G. Wuts, Protecting Groups in Organic Chemistry (1999) y P. Kocienski, Protective Groups (2000).

[00108]En general, las transformaciones químicas que se describen en la memoria

descriptiva se pueden llevar a cabo utilizando cantidades sustancialmente estoiquiométricas de reactivos, si bien ciertas reacciones pueden beneficiarse a partir del uso de un exceso de uno o más de los reactivos. Además, muchos de las reacciones que se divulgan en la memoria descriptiva se pueden llevar a cabo a aproximadamente temperatura ambiente (TA) y presión ambiente, pero depende de la cinética de la reacción, los rendimientos, etc., algunas reacciones se pueden correr a presiones elevadas o emplear temperaturas más altas (por ej., condiciones de reflujo) o temperaturas más bajas (por ej., 78°C a 0°C). Cualquier referencia en la divulgación a un rango estoiquiométrico, un rango de temperatura, un rango de pH, etc., sea o no expresamente utilizando la palabra "rango", además incluye los puntos finales indicados.

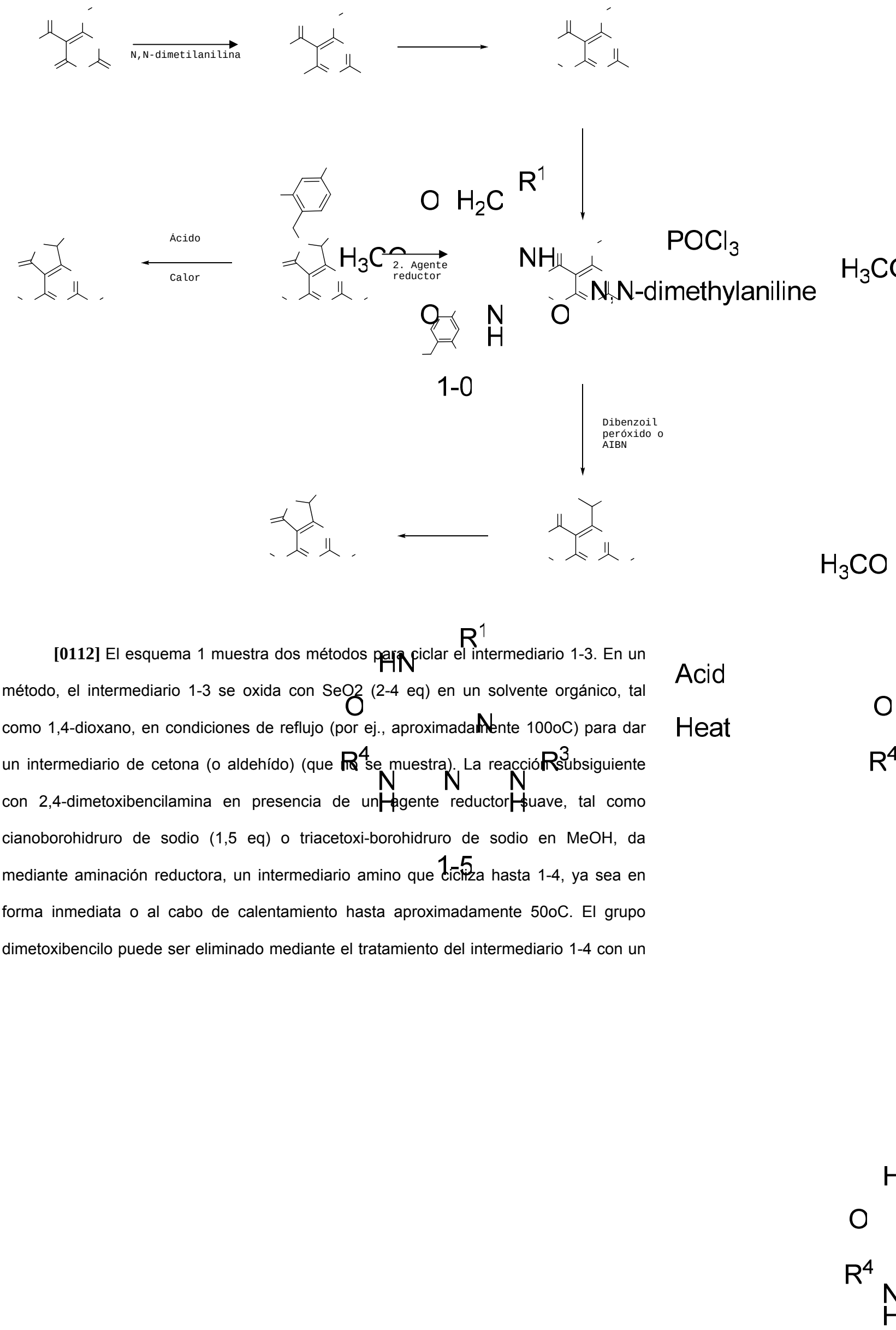
[0109] Muchas de las transformaciones químicas además pueden emplear uno o más solventes compatibles, que pueden influenciar la velocidad de reacción y el rendimiento. Dependiendo de la naturaleza de los reactivos, uno o más solventes pueden ser solventes próticos polares (incluyendo el agua), solventes apróticos polares, solventes no polares, o alguna combinación. Los solventes representativos incluyen hidrocarburos alifáticos saturados (por ej., n-pentano, n-hexano, n-heptano, n-octano); hidrocarburos aromáticos (por ej., benceno, tolueno, xilenos); hidrocarburos halogenados (por ej., metileno cloruro, cloroformo, tetracloruro de carbono); alcoholes alifáticos (por ej., metanol, etanol, propan-1-ol, propan-2-ol, butan-1-ol, 2-metil-propan-1-ol, butan-2-ol, 2-metil-propan-2-ol, pentan-1-ol, 3-metil-butan-1-ol, hexan-1-ol, 2-metoxi-etanol, 2-etoxi-etanol, 2-butoxi-etanol, 2-(2-metoxi-etoxi)-etanol, 2-(2-etoxi-etoxi)-etanol, 2-(2-butoxi-etoxi)-etanol); éteres (por ej., éter dietílico, di-isopropil éter, dibutil éter, 1,2-dimetoxi-etano, 1,2-dietoxi-etano, 1-metoxi-2-(2-metoxi-etoxi)-etano, 1-etoxi-2-(2-etoxi-etoxi)-etano, tetrahidrofurano, 1,4-dioxano); cetonas (por ej., acetona, metil etil cetona); ésteres (acetato de metilo, acetato de etilo); solventes que contienen nitrógeno (por ej., formamida, N,N-dimetilformamida, acetonitrilo, N-metil-pirrolidona, piridina, quinolina, nitrobenceno); solventes que contienen azufre (por ej., disulfuro de carbono, dimetil

sulfóxido, tetrahidro-tiofeno-1,1,-dióxido); y solventes que contienen fósforo (por ej., triamida hexametilfosfórica).

[0110] En los esquemas, a continuación, los identificadores sustituyentes (por ejemplo, R1, R3, R4, R5, R7, R8, L1 y L2) son como se definieron anteriormente para la fórmula 1. Como se mencionó anteriormente, sin embargo, algunos de los materiales de partida e intermediarios pueden incluir grupos protectores, que se eliminan antes del producto final. En estos casos, el identificador sustituyente se refiere a restos que se definen en la fórmula 1 y a aquellos restos con grupos protectores apropiados. Por ejemplo, un material de partida o intermediario en los esquemas puede incluir un R3 que es un resto que tiene una amina potencialmente reactiva. En estos casos, R3 incluiría el resto con o sin, digamos, un grupo Boc o Cbz unido al mismo.

[0111] El esquema 1 ilustra un método para preparar el compuesto 1-5. El material de partida 1-0 (por ej., 6-metil-2,4-dioxo-1,2,3,4-tetrahidropirimidin-5-carboxilato de metilo) se clorina a temperatura elevada (por ej., 95-105oC) utilizando fosforil tricloruro como solvente reactivo, en presencia de una cantidad catalítica de N,N-dimetil anilina para dar un pirimidin carboxilato de metilo 1-1. Los grupos 2-cloro y 4-cloro del intermediario 1-1 se desplazan posteriormente mediante tratamiento con una mina sustituida en forma apropiada. Como se describe en el esquema 1, el grupo 2-cloro se hace reaccionar con R4-NH2 (por ej., anilina sustituida) en un solvente orgánico aprótico polar (por ej. ACN o THF) y en presencia de una base impedida tal como Et3N o DIPEA (2 eq) para dar el intermediario 1-2. La reacción se puede llevar a cabo a temperaturas elevadas (por ej., 90oC o condiciones de reflujo). De manera similar, el grupo 4-cloro se desplaza con R3-NH2 para dar el intermediario 1-3. El segundo desplazamiento se lleva a cabo a temperatura elevada (por ej., 90oC o condiciones de reflujo) en un solvente orgánico aprótico polar (por ej., DMA o DMF) en presencia de una base impedida (por ej., Et3N o DIPEA).

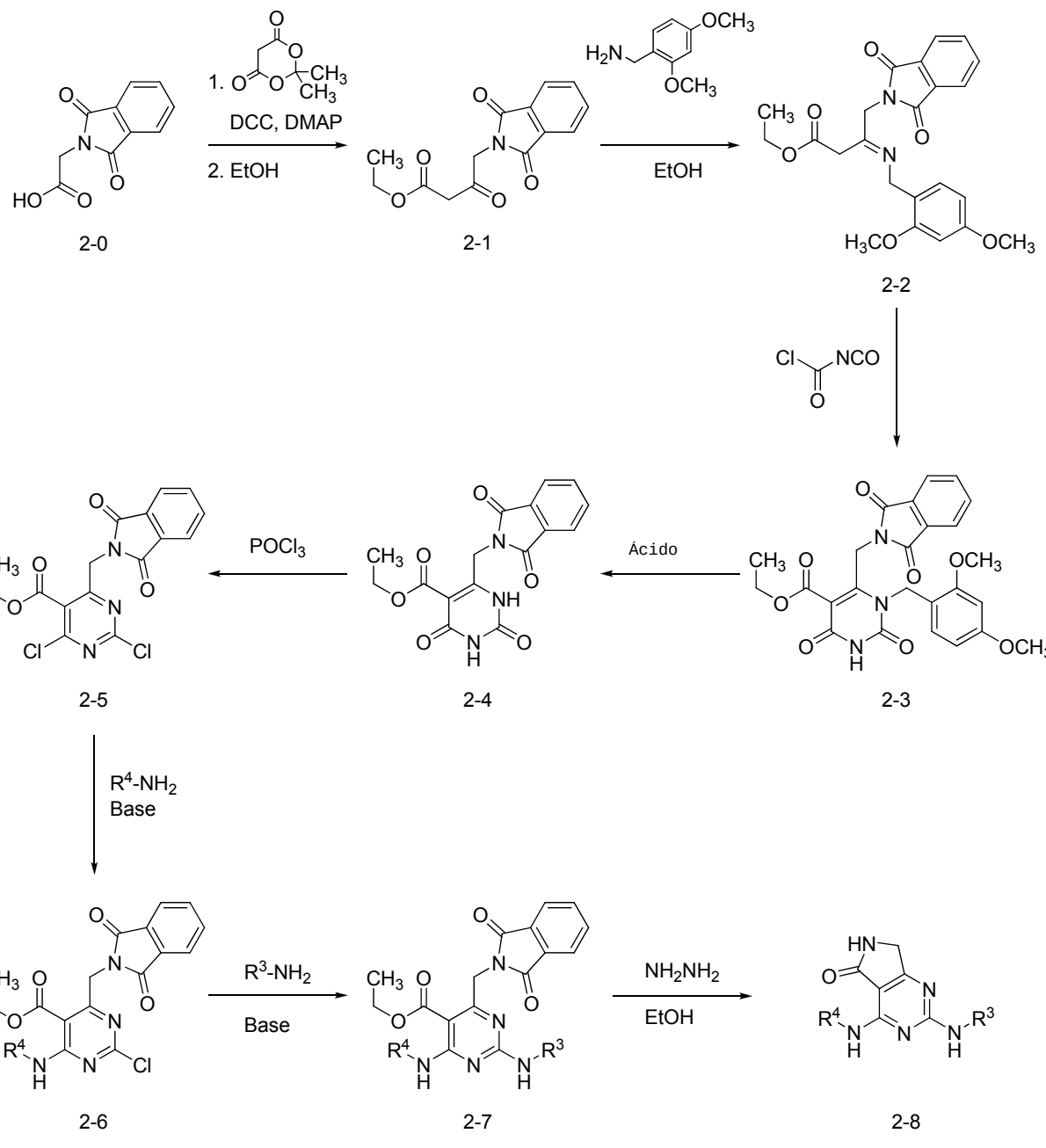
Esquema 1



[0112] El esquema 1 muestra dos métodos para ciclar el intermediario 1-3. En un método, el intermediario 1-3 se oxida con SeO2 (2-4 eq) en un solvente orgánico, tal como 1,4-dioxano, en condiciones de reflujo (por ej., aproximadamente 100oC) para dar un intermediario de cetona (o aldehído) (que no se muestra). La reacción subsiguiente con 2,4-dimetoxibencilamina en presencia de un agente reductor suave, tal como cianoborohidruro de sodio (1,5 eq) o triacetoxi-borohidruro de sodio en MeOH, da mediante aminación reductora, un intermediario amino que cicliza hasta 1-4, ya sea en forma inmediata o al cabo de calentamiento hasta aproximadamente 50oC. El grupo dimetoxibencilo puede ser eliminado mediante el tratamiento del intermediario 1-4 con un

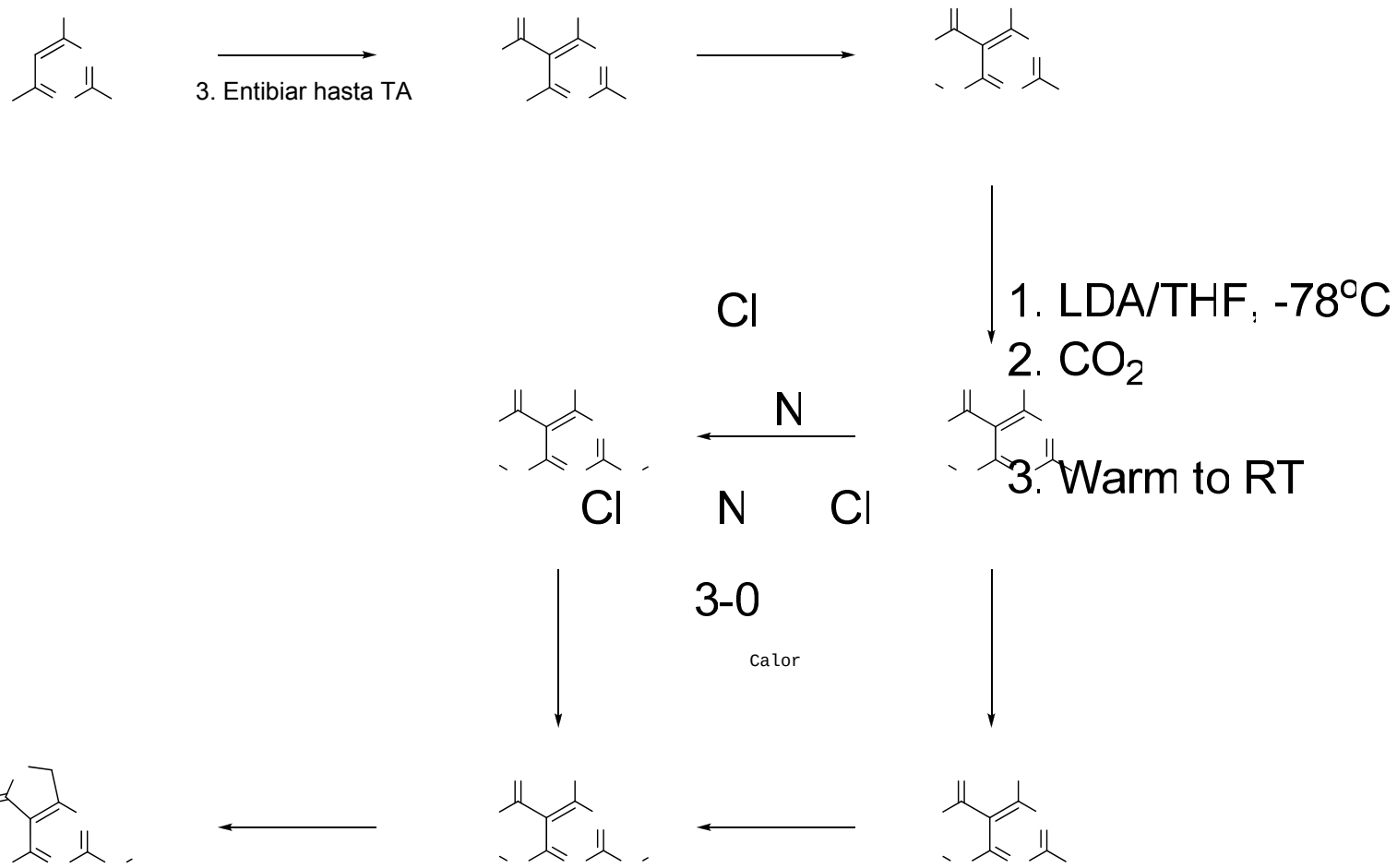
ácido (por ej., TFA) a aproximadamente 60oC, lo cual da el compuesto 1-5 deseado. En un segundo método, el intermediario 1-3 se trata con un reactivo de bromination tal como NBS en presencia de un iniciador (por ej., dibenzoíl peróxido o AIBN) en CCl4. El reflujo de la mezcla de reacción da el intermediario 1-6, que se trata con una fuente de amoníaco (por ej., hidróxido de amonio) en THF para dar 1-5.

Esquema 2

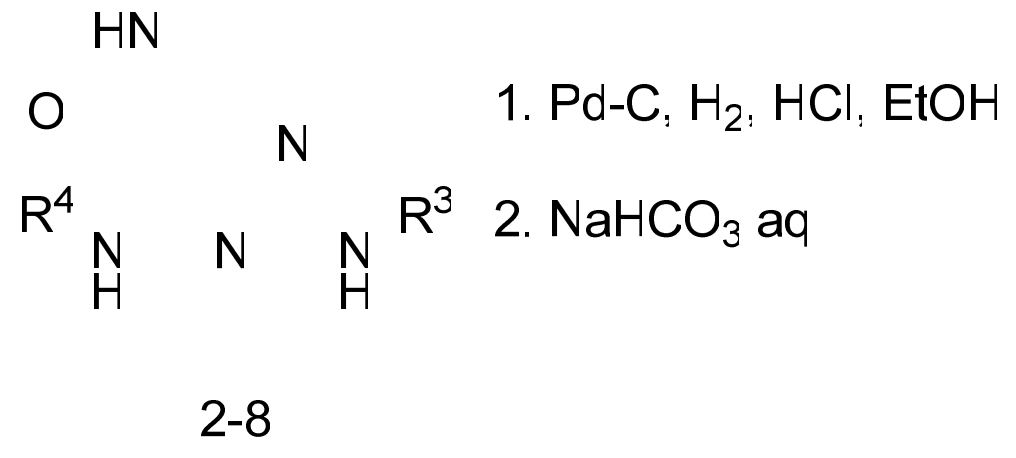


[0113] El esquema 2 provee un método para preparar el compuesto 2-8. El material de partida 2-0 (ácido 2-(1,3-dioxoisoindolin-2-il)acético) se hace reaccionar con 2,2-dimetil-1,3-dioxano-4,6-diona (1-1,5 eq) y 4-dimetilaminopiridina (1-1,5 eq) en presencia de DCC (1-1,5 eq) y un solvente orgánico tal como diclorometano para dar el intermediario 2-1. El tratamiento posterior de 2-1 con 2,4-dimetoxibencilamina (1 eq) en EtOH a aproximadamente 50oC da una imina 2-2, la cual se aísla, se redisuelve en un solvente orgánico (por ej., THF) y se trata con un carbonilisocianato activado (por ej., cloruro carbonisocianatidico, 1 eq) a aproximadamente 80oC para dar el intermediario 2-3. El tratamiento de 2-3 con un ácido (por ej., TFA a TA hasta 60oC) elimina el grupo dimetoxibencilo para dar el intermediario 2-4, el cual se hace reaccionar posteriormente con un agente de cloración (por ej., POCl3) en condiciones de reflujo (por ej., aproximadamente 100oC) para dar el intermediario 2-5. El desplazamiento en pasos de los dos grupos cloro con las aminas sustituidas en forma apropiada (R4-NH2 y R3-NH2) da los intermediarios 2-6 y 2-7. El tratamiento del intermediario 2-7 con hidrato hidrazina (4-5 eq) en EtOH con calentamiento (por ej, a aproximadamente 65oC) da el compuesto 2-8.

Esquema 3



[0114] El esquema 3 provee otro método para preparar el compuesto 2-8- El material de partida 3-0 (2,4,6-tricloropirimidina) se trata con una base fuerte tal como LDA (recién preparada a partir de diisopropilamina y n-BuLi o adquirida) a -78oC en THF seco, seguido de templado con hielo seco. El calentamiento de la mezcla a temperatura ambiente y la agitación dan el intermediario 3-1. El desplazamiento de un grupo cloro mediante el tratamiento con una amina sustituida en forma apropiada (R4-NH2, 1 eq) en presencia de una base impedida (por ej., Et3N o DIPEA, 2 eq) y un solvente orgánico aprótico polar (por ej., DMF) da el intermediario 3-2. El tratamiento posterior de 3-2 con MeI (1-1,5 eq) y una base (por ej., bicarbonato de sodio, 1,5-3 eq) da un éster 3-3, que puede proceder al compuesto 2-8 a través de dos vías diferentes. En una ruta, el intermediario 3-3 se somete al tratamiento con una amina sustituida en forma apropiada



2-8

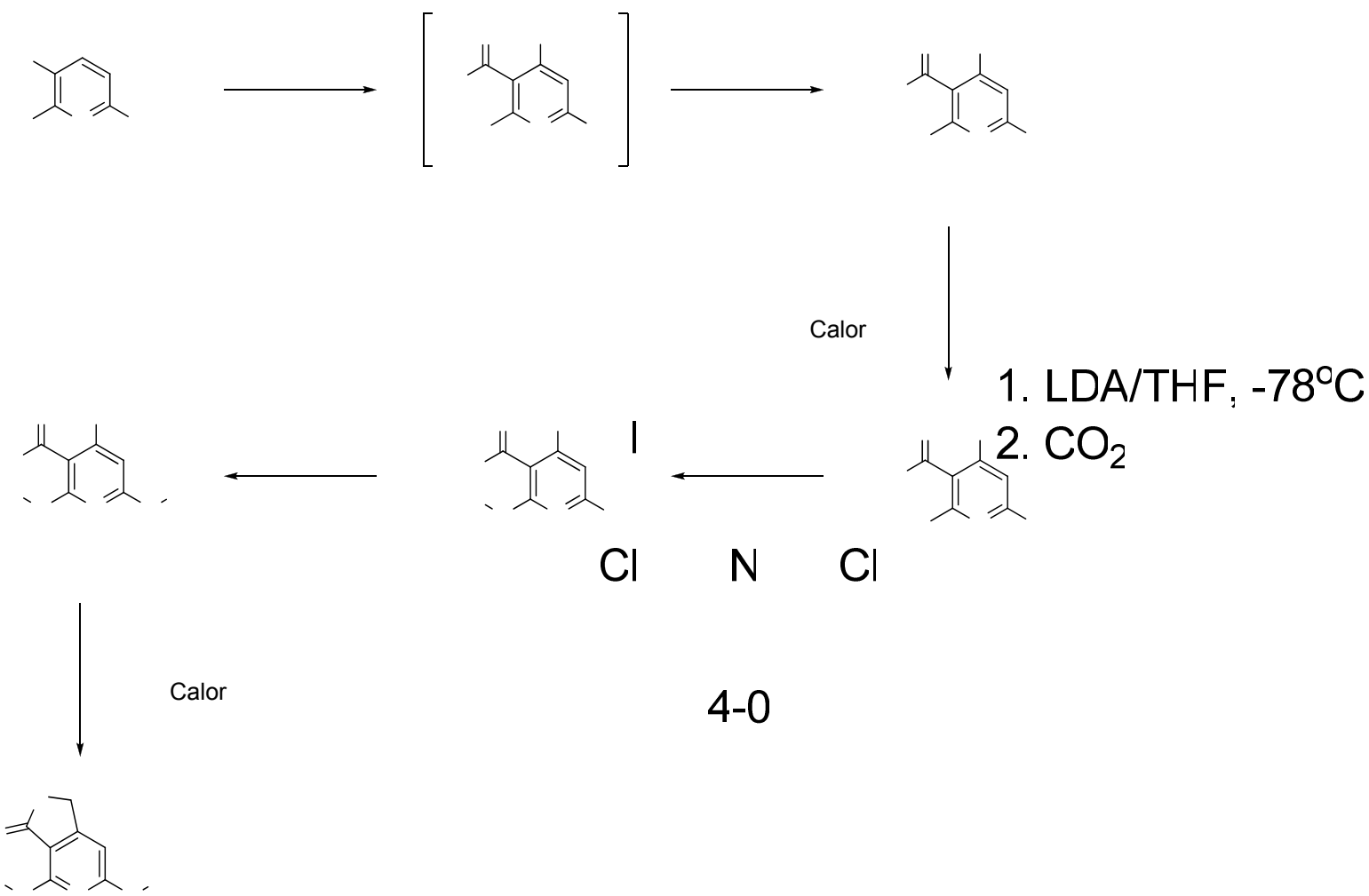
(R3-NH2, 1-1,1 eq) en presencia de una base impedida (por ej., DIPEA) y un solvente orgánico aprótico polar (por ej, THF) para dar el intermediario 3-4 y un isómero. A continuación del aislamiento, el intermediario 3-4 se hace reaccionar con cianuro de zinc (0,5-1 eq) y una cantidad catalítica (10%) de tetrakis (trifenilfosfina) paladio (0) en DMF a aproximadamente 90oC para dar nitrilo 3-5. La reducción del grupo nitrilo a una amina mediante hidrogenación utilizando Pd sobre carbono (5-10%) en EtOH y una cantidad catalítica de HCl da, al cabo del tratamiento con bicarbonato de sodio, 2-8.

[0115] En una vía alternativa, el intermediario 3-3 se convierte primero a nitrilo 3-6 mediante cianación catalizada con paladio calentando una mezcla de 3-3, cianuro de zinc (0,5-1 eq), tetrakis(trifenil fosfina)paladio (0) (0,1 eq), y un solvente aprótico polar (por ej., DMF) en un horno de microondas a aproximadamente 120oC durante aproximadamente 1 hora. A continuación del aislamiento, el intermediario 3-6 se convierte a temperatura ambiente hasta 3-5 mediante reacción con una amina sustituida en forma apropiada (R3-NH2, 1-1,5 eq) en un solvente aprótico polar (por ej., DMF) y en presencia de una base impedida (por ej., DIPEA). Como se describió anteriormente, la reducción del grupo nitrilo de 3-5 y la posterior ciclización da el compuesto 2-8.

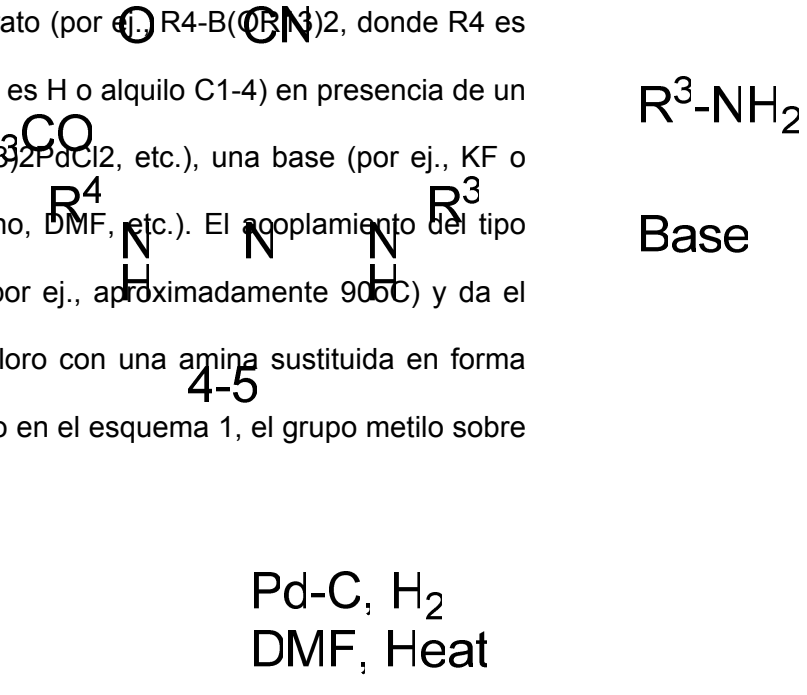
[0116] El esquema 4 muestra un método para preparar el compuesto 4-6. La litiación del material de partida 4-0 (2,6-di-halo-3-yodopiridina) mediante orto-litiación dirigida por LDA en THF a -78oC, seguido del templado con hielo seco, da 4-1, que se esterifica posteriormente a temperatura ambiente utilizando MeI y una base (por ej., carbonato de potasio). Como en el esquema 3, el grupo yodo del intermediario 4-2 se convierte a un grupo nitrilo a través de la cianación catalizada con paladio para dar 4-3. El desplazamiento en pasos de los dos grupos cloro con las aminas sustituidas en forma apropiada (R4-NH2 y R3-NH2) da los intermediarios 4-4 y 4-5. Como en el paso de cierre del anillo descripto en el esquema 3, la hidrogenación seguida de ciclización da el compuesto 4-6.

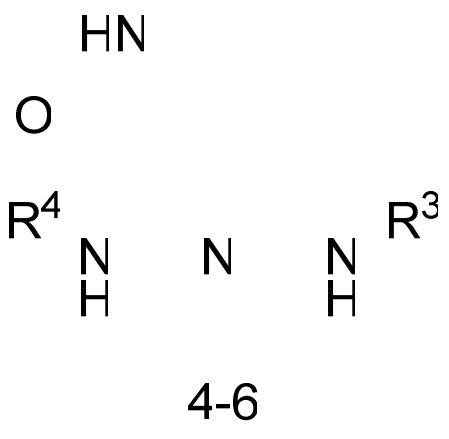
[0117]

Esquema 4



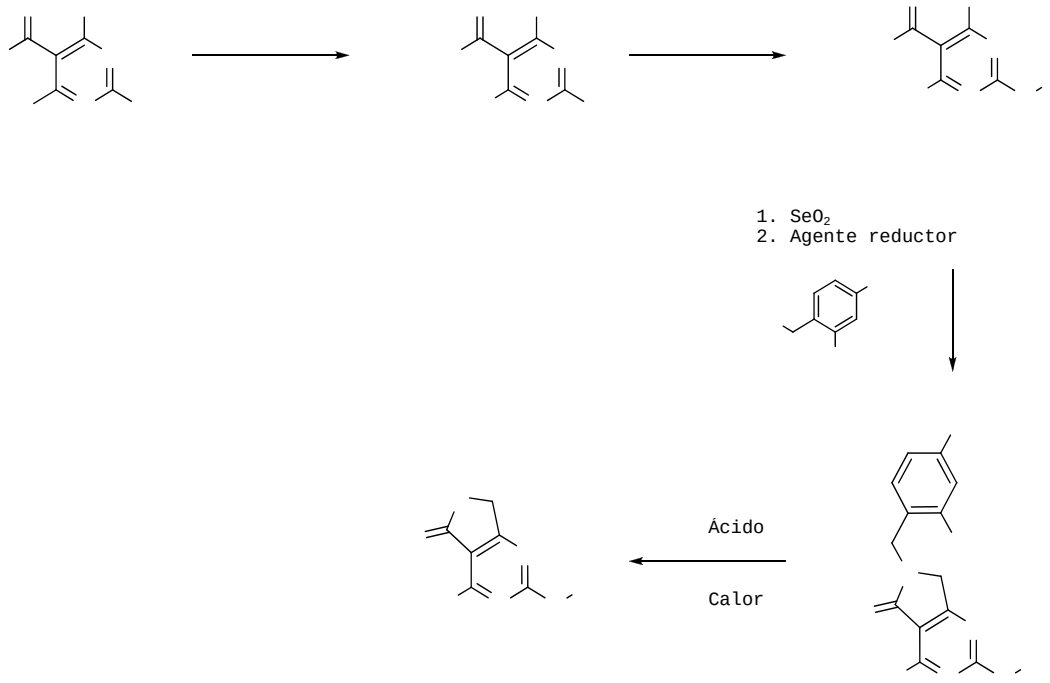
[0118] El esquema 5 describe un método para preparar el compuesto 5-4. El material de partida 1-1 (2,4-dicloro-6-metilpirimidin-5-carboxilato de metilo) se hace reaccionar con un ácido borónico aromático o borato (por ej., R4-B(OR13)2, donde R4 es arilo C6-14 o heteroarilo C1-9, y por ej., cada R13 es H o alquilo C1-4) en presencia de un catalizador de paladio (por ej., Pd(PPh3)4, (PPh3)2PdCl2, etc.), una base (por ej., KF o Na2CO3), y un solvente orgánico (por ej., dioxano, DMF, etc.). El acoplamiento del tipo Suzuki se lleva a cabo a temperatura elevada (por ej., aproximadamente 90°C) y da el intermediario 5-1. El desplazamiento del grupo cloro con una amina sustituida en forma apropiada (R3-NH2) da el intermediario 5-2. Como en el esquema 1, el grupo metilo sobre



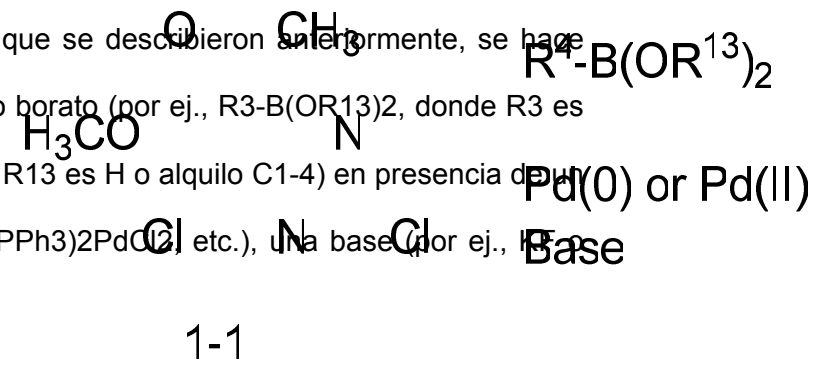


pirimidina se oxida con SeO2 (2-4 eq) en un solvente orgánico (por ej., 1,4-dioxano) en condiciones de reflujo para dar un intermediario aldehído, el cual se hace reaccionar posteriormente con 2,4-dimetoxibencilamina en presencia de un agente reductor suave (por ej., aproximadamente 1,5 eq de NaCNBH3 o NaBH(OAc)3) en MeOH, para dar, mediante aminación reductora, un intermediario amino que cicliza hasta 5-3, ya sea en forma inmediata o al cabo del calentamiento hasta aproximadamente 50oC. El tratamiento del intermediario 5-3 con un ácido (por ej., TFA) a aproximadamente 60oC da el compuesto 5-4.

Esquema 5



[0119] El esquema 6 describe un método para preparar el compuesto 6-3. El material de partida 6-0, el cual se puede preparar a partir de 2,4-dicloro-6-metilpirimidin-5-carboxilato de metilo utilizando los métodos que se describieron anteriormente, se hace reaccionar con un ácido borónico aromático o borato (por ej., R3-B(OR13)2, donde R3 es arilo C6-14 o heteroarilo C1-9, y por ej., cada R13 es H o alquilo C1-4) en presencia de un catalizador de paladio (por ej., Pd(PPh3)4, (PPh3)2PdCl2, etc.), una base (por ej., KF o

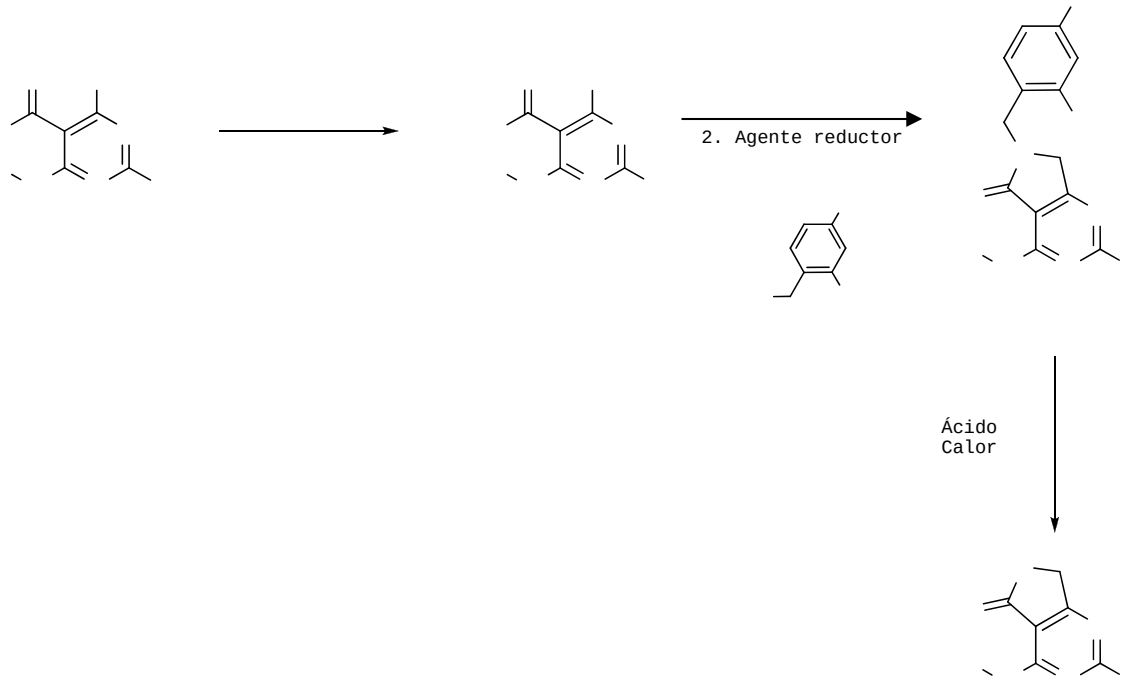


1-1

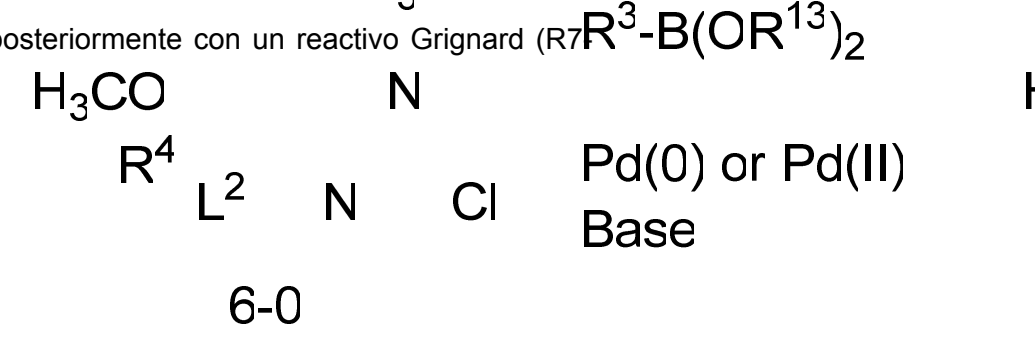


Na2CO3), y un solvente orgánico (por ej., dioxano, DMF, DME, etc.). El acoplamiento del tipo Suzuki se lleva a cabo a temperatura elevada (por ej., aproximadamente 90oC) y da el intermediario 6-1. El grupo metilo sobre pirimidina se oxida con SeO2 (2-4 eq) en un solvente orgánico (por ej., 1,4-dioxano) en condiciones de reflujo para dar un intermediario aldehído, el cual se hace reaccionar posteriormente con 2,4-dimetoxibencilamina en presencia de un agente reductor suave (por ej., aproximadamente 1,5 eq de NaCNBH3 o NaBH(OAc)3) en MeOH, para dar el intermediario 6-2. El tratamiento de 6-2 con un ácido (por ej., TFA) a aproximadamente 60oC da el compuesto 6-3.

Esquema 6

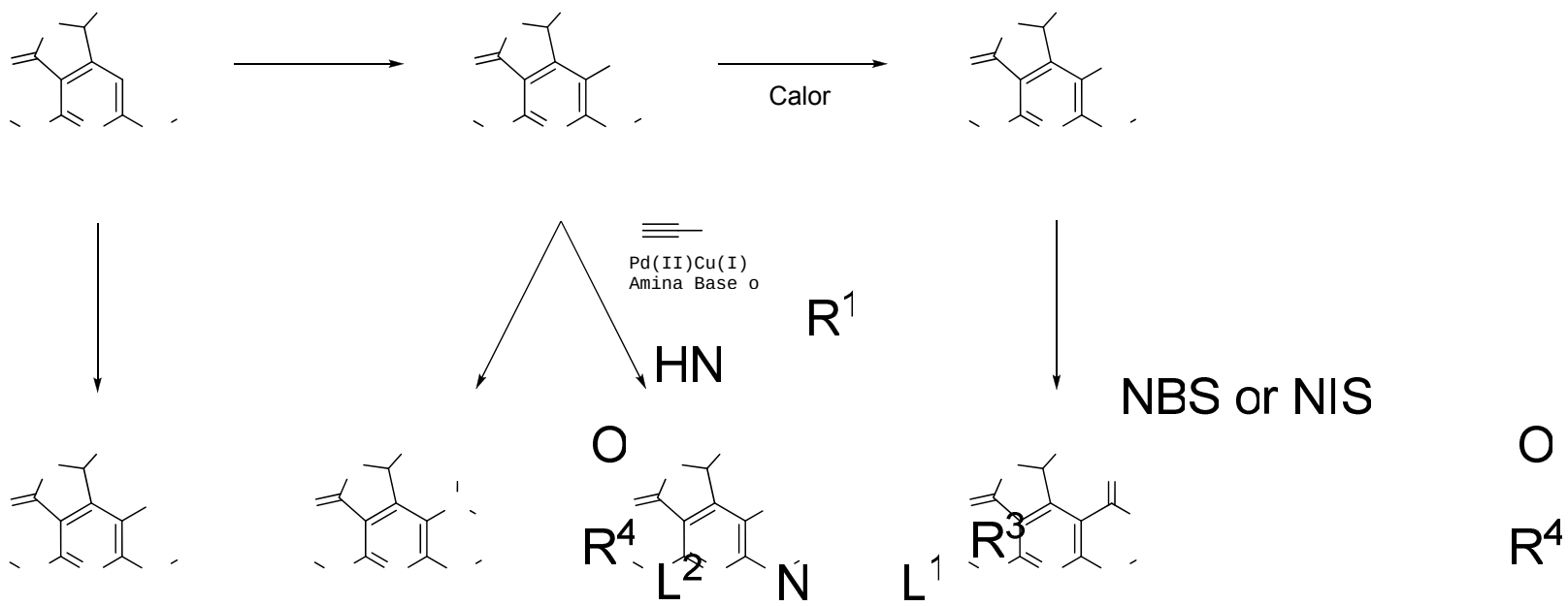


[0120] El esquema 7 ilustra los métodos para preparar los compuestos 7-2, 7-3, 7-4, 7-5, y 7-6. El material de partida 7-0, el cual se puede preparar utilizando los métodos que se describieron anteriormente, se puede hacer reaccionar con NBS o NIS para dar el intermediario halo-piridina 7-1 (Y1 es Br o I). Como en el esquema 3, el grupo halo de 7-1 puede convertirse a un grupo nitrilo a través de cianación catalizada con paladio para dar 7-2. El compuesto 7-2 se hace reaccionar posteriormente con un reactivo Grignard (R7-



MgBr) para dar un intermediario imina (que no se muestra), el cual al cabo de la hidrólisis ácida, da el compuesto 7-3. En forma alternativa, el intermediario halo-piridina 7-1 se puede hacer reaccionar con NHR8R9 en presencia de un catalizador de paladio (II) (por ej., PdCl2(dppf)), una cantidad estoiquiométrica de base (por ej., NaOt-Bu), y un solvente orgánico (por ej., dioxano, tolueno, etc.), a temperatura elevada (por ej., aproximadamente 100oC). El acoplamiento Buchwald-Hartwig da heteroaril amina 7-4. Además, 7-1 se puede hacer reaccionar con un terminal alquino (HC≡R13, por ej., R13 es H o alquilo C1-4) en presencia de un catalizador de paladio (II) (por ej., (PPh3)2PdCl2), un co-catalizador de cobre (I) (por ej., CuI), y una base amina (por ej., Et3N), a TA. Siguiendo el acoplamiento Sonogashira, la reducción del resto alquino da el compuesto 7-5 siendo R5, por ej., alquilo C1-5. El compuesto 7-1 se puede hacer reaccionar con un ácido borónico aromático o borato (por ej., R5-B(OR13)2, donde R5 es heteroarilo C1-9 y por ej., R13 es H o alquilo C1-4) en presencia de un catalizador de paladio (por ej., Pd(PPh3)4, (PPh3)2PdCl2, etc.), una base (por ej., KF o Na2CO3), y un solvente orgánico (por ej., dioxano, DMF, etc.). El acoplamiento del tipo Suzuki se lleva a cabo a temperatura elevada (por ej., aproximadamente 90oC) y da el compuesto 7-5 siendo R5 heteroarilo C1-9.

Esquema 7

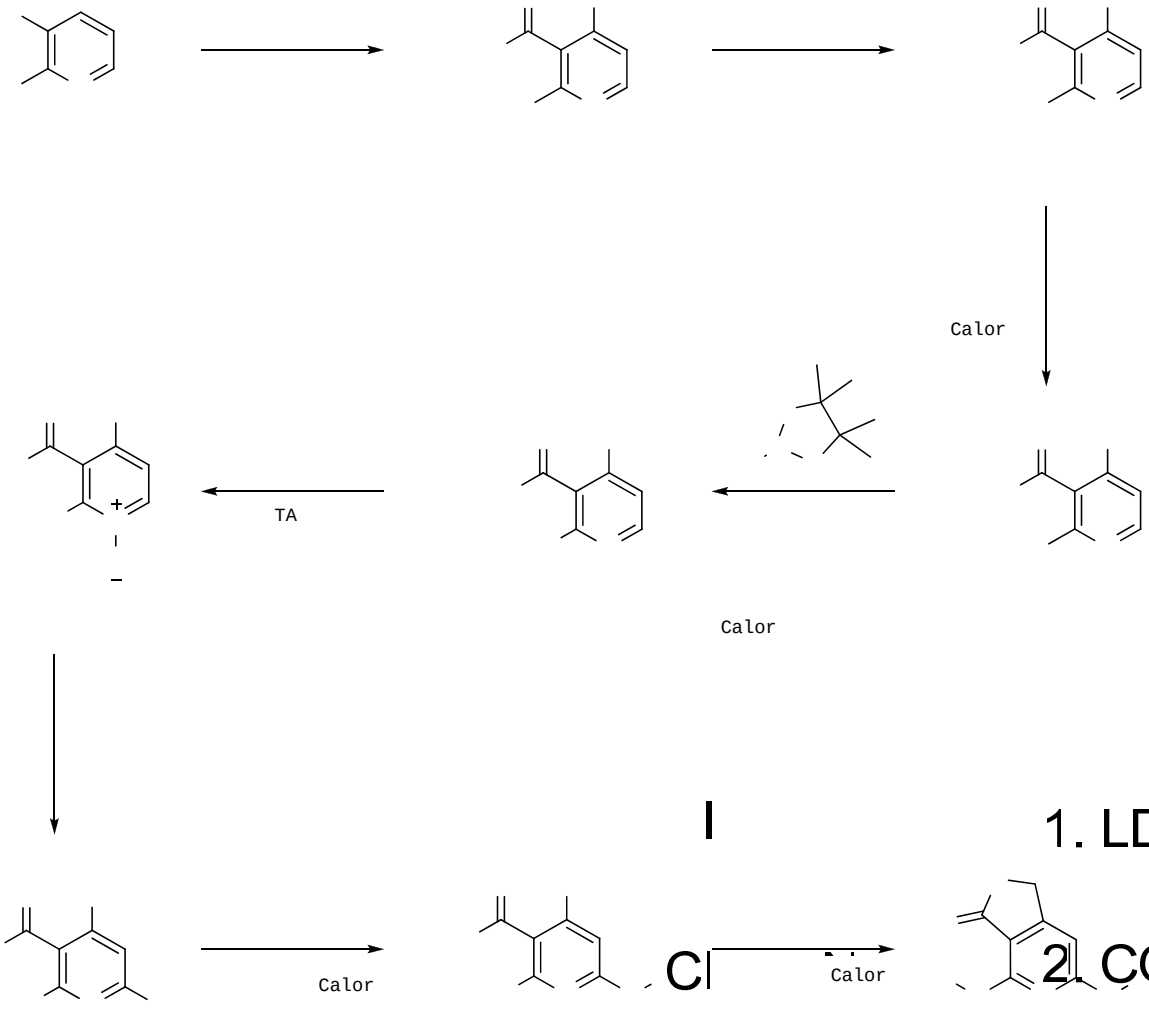


[0121] Como se muestra en el esquema 7, el compuesto 7-0 se puede tratar en forma alternativa con un agente de fluoración, tal como SELECTFLUOR® (1-(clorometil)-4-fluoro-1,4-diazoniabiciclo[2.2.2]octano ditetrafluoroborato), en un solvente orgánico (por ej., DCM) o una mezcla de solventes orgánicos (por ej., DCM y MeOH), para dar un derivado fluoro-piridina 7-6 (Y2 es F). De manera similar, 7-0 se puede tratar con un agente de cloración, tal como NCS, en un solvente aprótico (por ej., DCM) para dar un derivado cloro-piridina 7-6 (Y2 es Cl).

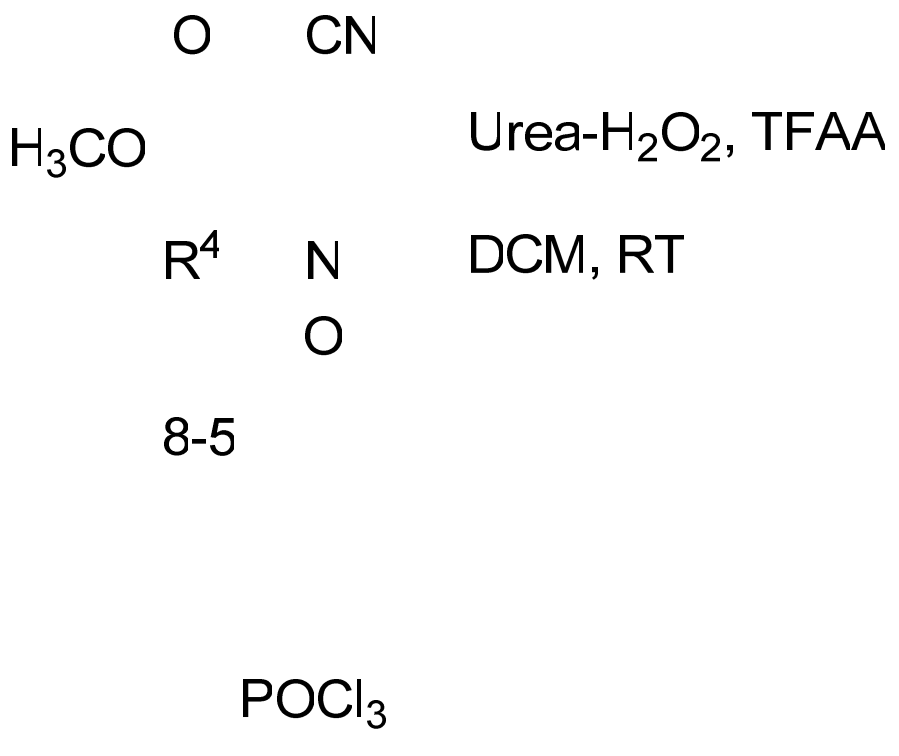
[0122] El esquema 8 muestra un método alternativo para preparar el compuesto 4-6. El material de partida 8-0 (2-cloro-3-yodopiridina) se somete a orto-litiación dirigida mediante tratamiento con LDA en THF a -78oC. El templado con hielo seco da 8-1, que se esterifica posteriormente a temperatura ambiente utilizando yodometano y una base (por ej., carbonato de potasio). Como en el esquema 4, el grupo yodo del intermediario 8-2 se convierte a un grupo nitrilo por cianación catalizada por paladio o a través del tratamiento con cianocobre o cianuro de zinc en un solvente adecuado (por ej., DMF, DMA, etc.) a temperatura elevada. El sustituyente R4 se instala en 8-3 utilizando una reacción Suzuki, la cual da el intermediario 8-4. La N-oxidación del resto piridina mediante tratamiento con

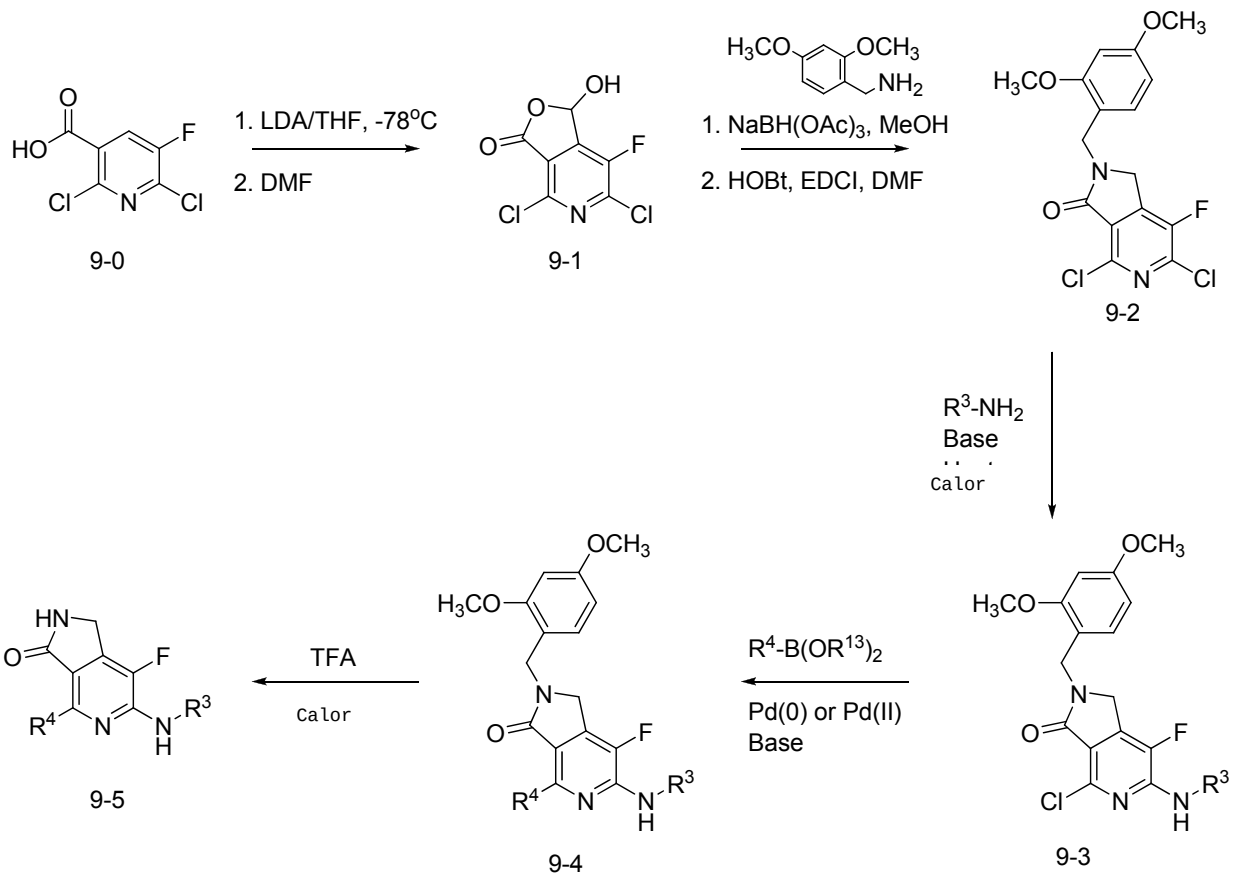
peróxido de hidrógeno/complejo de urea da un intermediario activado 8-5, el cual se clorina a través de la reacción con oxicloruro de fósforo a una temperatura elevada (por ej., 90-100oC). El desplazamiento del grupo cloro sobre 8-6 mediante reacción con una amina sustituida en forma apropiada (R3-NH2) da el intermediario 8-7. La reducción posterior a través de hidrogenación catalizada con paladio y ciclización da el compuesto 4-6.

Esquema 8



Esquema 9

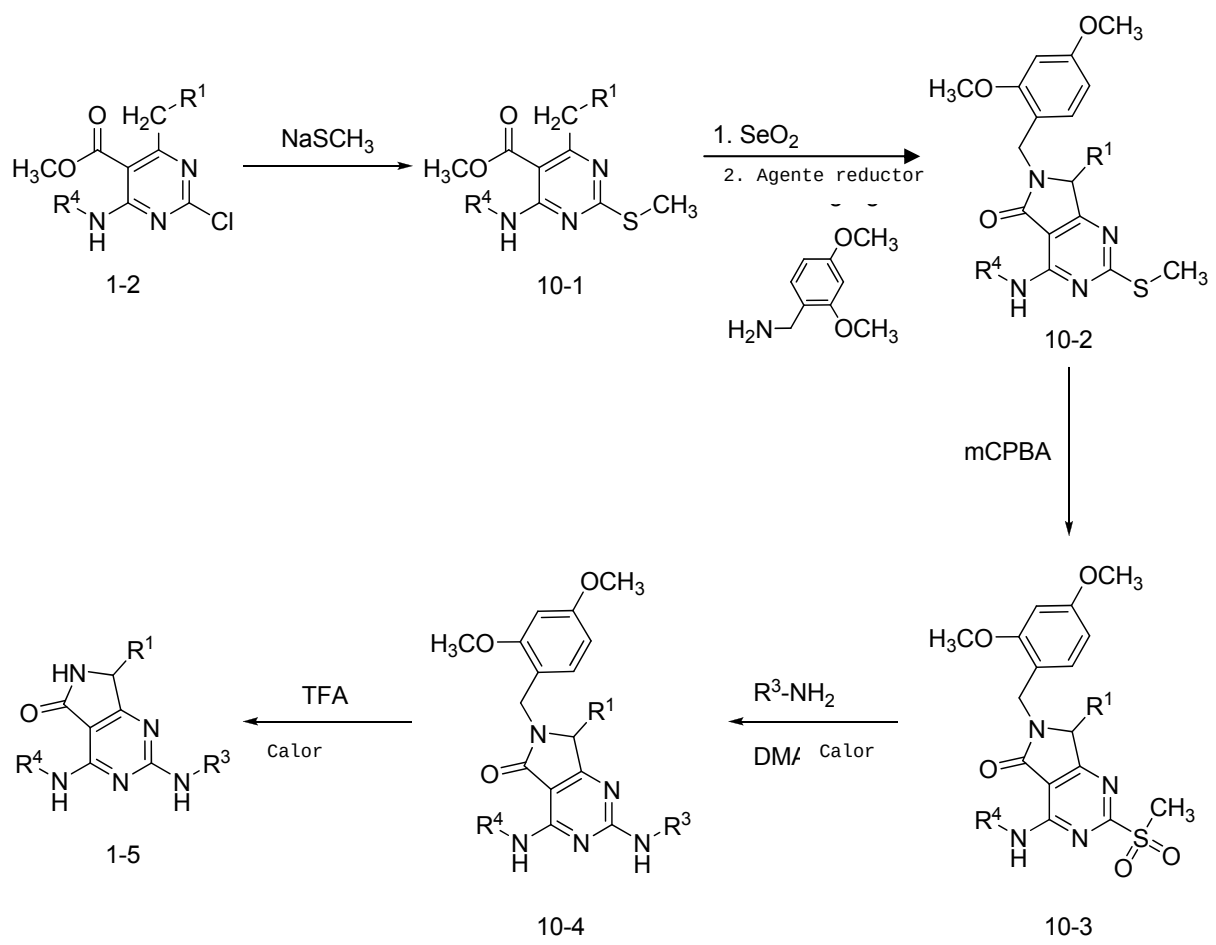




[0123] El esquema 9 describe la síntesis del compuesto 9-5. El material de partida 9-0 (ácido 2,6-dicloro-5-fluoronicotínico) se litia mediante tratamiento con LDA en THF a 78oC. El templado con DMF da un intermediario aldehído 9-1, que se somete a aminación reductora a través de la reacción con amina (por ej., 2,4-dimetoxifenil)metanamina) y el agente reductor (por ej., NaBH(OAc)3). El aminoácido resultante (que no se muestra) se cicla mediante acoplamiento de amida, que emplea un agente de acoplamiento adecuado (por ej., EDCI, DCC, etc.) catalizador (HOBt, DMAP, etc.), y solvente (por ej., DMF, DMSO, ACN, THF, DCM, etc.). Como en los esquemas previos, el desplazamiento del grupo cloro del compuesto 9-2 con una amina apropiada (R3-NH2) da el intermediario 9-3, que se hace reaccionar posteriormente con un ácido borónico aromático o borato (por ej., R4-B(OR13)2 en presencia de un catalizador de paladio (por ej., Pd(PPh3)4, (PPh3)2PdCl2, etc.), base (por ej., KF o Na2CO3), y solvente orgánico (por ej., dioxano, DMF, etc.) a temperatura elevada (por ej., aproximadamente 90oC) para dar 9-4.

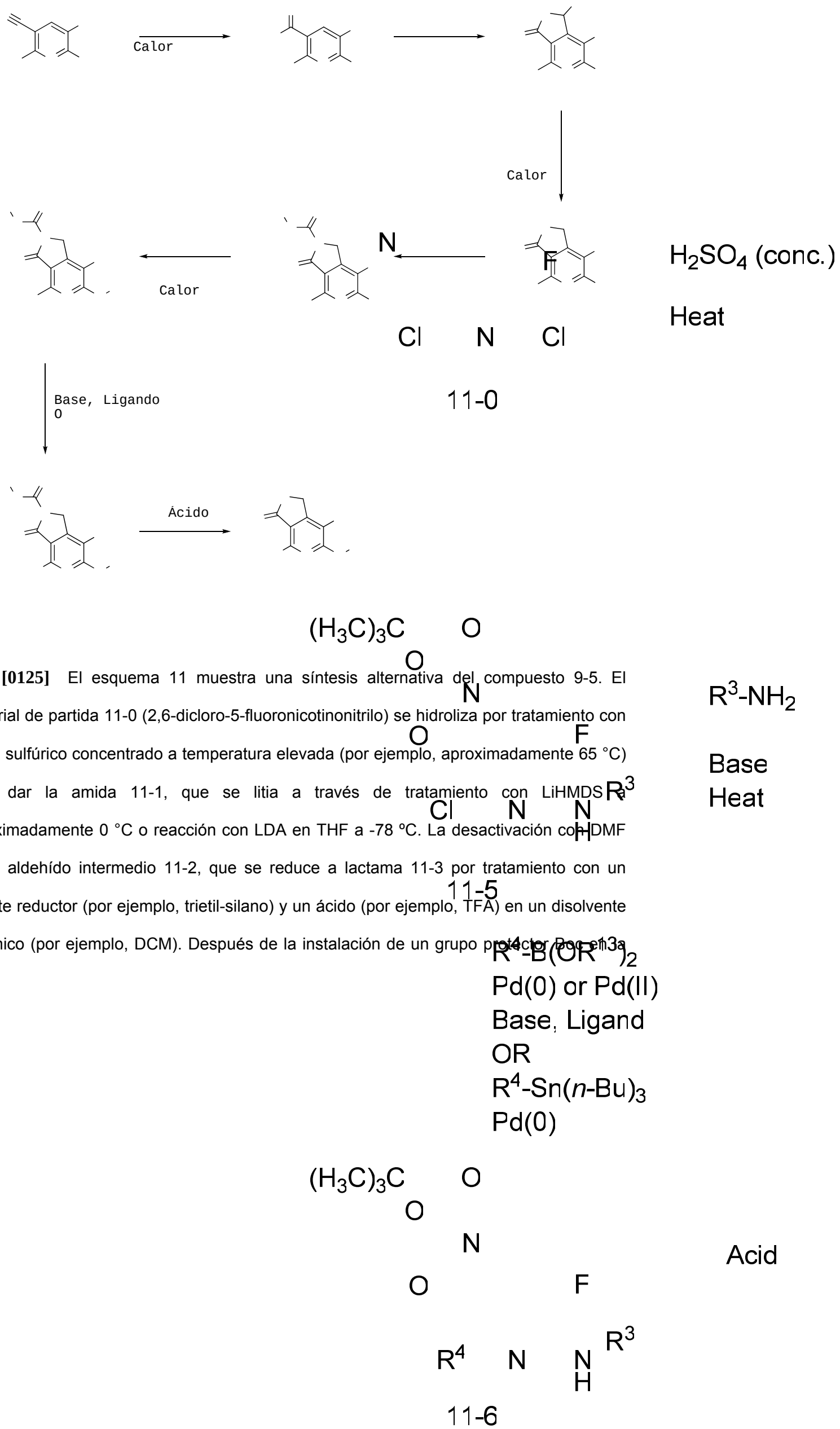
Siguiendo el acoplamiento Suzuki, el tratamiento de 9-4 con TFA a temperatura elevada (por ej., 40-60oC) genera 9-5.

Esquema 10



[0124] El esquema 10 muestra otro método para preparar el compuesto 1-5. El grupo cloro del compuesto 1-2 primero se desplaza con metanotiolato de sodio para dar 10-1. Como en el esquema 1, el intermediario 10-1 se oxida con SeO2 para dar un intermediario cetona (o aldehído) (que no se muestra), el cual se hace reaccionar con 2,4-dimetoxibencilamino en presencia de un agente reductor para dar, mediante aminación reductora, un intermediario aminoácido que cicliza 10-2. El grupo metiltio se convierte a metilsulfonilo utilizando mCPBA (ácido m-cloroperoxibenzoico), el cual se desplaza con una amina apropiada (R3-NH2) para dar el intermediario 10-4. El tratamiento de 10-4 con un ácido (por ej. TFA) a temperatura elevada (por ej., 40-60oC) da el compuesto 1-5.

Esquema 11



[0125] El esquema 11 muestra una síntesis alternativa del compuesto 9-5. El material de partida 11-0 (2,6-dicloro-5-fluoronicotinonitrilo) se hidroliza por tratamiento con ácido sulfúrico concentrado a temperatura elevada (por ejemplo, aproximadamente 65 °C) para dar la amida 11-1, que se litia a través de tratamiento con LiHMDS a aproximadamente 0 °C o reacción con LDA en THF a -78 ºC. La desactivación con DMF da el aldehído intermedio 11-2, que se reduce a lactama 11-3 por tratamiento con un agente reductor (por ejemplo, trietil-silano) y un ácido (por ejemplo, TFA) en un disolvente orgánico (por ejemplo, DCM). Después de la instalación de un grupo protector Boc en 3a

lactama 11-3, el desplazamiento de un grupo cloro en el compuesto 11-4 a través de la reacción con una amina apropiada (R3-NH2) da el intermediario 11-5. El intermedio se hace reaccionar posteriormente con un ácido borónico o borato aromático (por ejemplo, R4-B(OR13)2 en presencia de un catalizador de paladio (por ejemplo, Pd(PPh3)4, (PPh3)2PdCl2, Pd2(dba)3, etc.), un ligando opcional (por ejemplo, 2-(diciclohexilfosfino)bifenilo), una base (por ejemplo, KF o Na2CO3), y un disolvente orgánico (por ejemplo, dioxano, DMF, etc.) para dar el compuesto 11-6. La reacción de Suzuki se lleva a cabo a temperatura elevada (por ejemplo, 90-160 °C), ya sea por calentamiento convencional o mediante irradiación de microondas. Alternativamente, el compuesto 11-5 puede hacerse reaccionar con un reactivo de estaño aromático (por ejemplo, R4-Sn(n-Bu)3) en presencia de un catalizador de paladio (por ejemplo, Pd(PPh3)4) y un disolvente orgánico (por ejemplo, tolueno) a temperatura elevada (por ejemplo, aproximadamente 100 °C). Luego del acoplamiento de Suzuki o de Stille, el tratamiento de 11-6 con un ácido (por ejemplo, TFA o HCl) a temperatura ambiente o superior (por ejemplo, aproximadamente 20-60 °C) genera 9-5.

[0126] Los compuestos de fórmula 1, que incluyen los compuestos mencionados anteriormente, y sus complejos, sales, solvatos e hidratos aceptables para uso farmacéutico, deben ser evaluados por sus propiedades biofarmaceúticas, tales como solubilidad y estabilidad de la solución a través del pH, permeabilidad, y similares, para seleccionar una forma de dosificación apropiada y la vía de administración. Los compuestos que están destinados para uso farmacéutico pueden ser administrados como productos cristalinos o amorfos, y se pueden obtener, por ejemplo, como tapones sólidos, polvos, o películas mediante métodos tales como precipitación, cristalización, liofilización, secado por aspersión, secado por evaporación, secado por microondas, o secado por radiofrecuencia.

[0127] Los compuestos de fórmula 1 se pueden administrar solos o en combinación con otro o con uno o más compuestos activos para uso farmacológico que

son diferentes a los compuestos de fórmula 1. En general, uno o más de estos compuestos se administran en forma de una composición farmacéutica (una formulación) en asociación con uno o más excipientes aceptables para uso farmacéutico. La elección de excipientes depende del modo particular de administración, el efecto del excipiente sobre la solubilidad y la estabilidad, y la naturaleza de la forma de dosificación, entre otras cosas. Las composiciones farmacéuticas útiles y los métodos para su preparación se pueden hallar, por ejemplo, en A. R. Gennaro (ed.), Remington: The Science and Practice of Pharmacy (20º ed., 2000).

[0128] Los compuestos de fórmula 1 se pueden administrar por vía oral. La administración oral puede involucrar la masticación en cuyo caso el compuesto ingresa a la corriente sanguínea a través del tracto gastrointestinal. En forma alternativa o además, la administración oral puede involucrar la administración mucosal (por ej., administración bucal, sublingual, supralingual) de modo que el compuesto ingresa al corriente sanguíneo a través de la mucosa oral.

[0129] Las formulaciones adecuadas para administración oral incluyen sistemas sólidos, semisólidos y líquidos tales como comprimidos, cápsulas blandas o duras que contienen múltiples partículas o nano-partículas, líquidos, o polvos; pastillas que pueden estar rellenas con líquido; masticables; formas de dosificación de dispersión rápida; películas; óvulos; pulverizaciones; y parches bucales o mucoadhesivos. Las formulaciones líquidas incluyen suspensiones, soluciones, jarabes y elixires. Estas formulaciones se pueden emplear como rellenos en cápsulas blandas o duras (producidas, por ej., a partir de gelatina o hidroxipropilmetilcelulosa) y típicamente comprenden un vehículo (por ej., agua, etanol, polietilenglicol, propilenglicol, metilcelulosa, o un aceite adecuado) y uno o más agentes emulsionantes, agentes de suspensión o ambos. Las formulaciones líquidas se pueden preparar además mediante la reconstitución de un sólido (por ej., de un sache).

[0130] Los compuestos de fórmula 1 además se pueden utilizar en formas de

dosificación de rápida desintegración y rápida disolución tales como los que se describen en Liang y Chen, Expert Opinion in Therapeutic Patents (2001) 11(6):981-986.

[0131] Para las formas de dosificación en comprimidos, dependiendo de la dosis, el principio farmacéutico activo (PFA) puede comprender desde aproximadamente 1% en peso hasta aproximadamente 80% en peso de la forma de dosificación o más típicamente desde aproximadamente 5% en peso hasta aproximadamente 60% en peso de la forma de dosificación. Además del PFA, los comprimidos pueden incluir uno o más desintegrantes, aglutinantes, diluyentes, surfactantes, deslizantes, lubricantes, antioxidantes, colorantes, agentes saborizantes, conservantes, y agentes enmascaradores del sabor. Ejemplos de desintegrantes incluyen glicolato de almidón sódico, carboximetil celulosa sódica, carboximetil celulosa de calcio, croscarmelosa sódica, cropovidona, polivinilpirrolidona, metil celulosa, celulosa microcristalina, hidroxipropilcelulosa sustituida con alquilo C1-6, almidón, almidón pregelatinizado, y alginato sódico. En general, el desintegrante comprenderá desde aproximadamente 1% en peso hasta aproximadamente 25% en peso o desde aproximadamente 5% en peso hasta aproximadamente 20% en peso de la forma de dosificación.

[0132] Los aglutinantes se utilizan en general para impartir cualidades cohesivas a una formulación de comprimidos. Los aglutinantes adecuados incluyen celulosa microcristalina, gelatina, azúcares, polietilenglicol, gomas naturales y sintéticas, polivinilpirrolidona, almidón pregelatinizado, hidroxipropilcelulosa e hidroxipropilmetilcelulosa. Los comprimidos además pueden contener diluyentes, tales como lactosa (monohidrato, monohidrato secado por aspersión, anhidro), manitol, xilitol, dextrosa, sacarosa, sorbitol, celulosa microcristalina, almidón y dihidrato fosfato de calcio dibásico.

[0133] Los comprimidos además pueden incluir agentes tensioactivos, tales como lauril sulfato sódico y polisorbato 80, y deslizantes tales como dióxido de silicio y talco. Cuando están presentes, los agentes tensioactivos pueden comprender desde

aproximadamente 0,2% en peso hasta aproximadamente 5% en peso del comprimido, y los deslizantes pueden comprender desde aproximadamente 0,2% en peso hasta aproximadamente 1% en peso del comprimido.

[0134] Los comprimidos además pueden contener lubricantes tales como estearato de magnesio, estearato de calcio, estearato de zinc, estearil fumarato de sodio, y mezclas de estearato de magnesio con lauril sulfato sódico. Los lubricantes pueden comprender desde aproximadamente 0,25% en peso hasta aproximadamente 10% en peso o desde aproximadamente 0,5% en peso hasta aproximadamente 3% en peso del comprimido.

[0135] Las mezclas de comprimidos pueden ser comprimidas directamente o por compactación por rodillo para formar los comprimidos Las mezclas de comprimidos o las porciones de las mezclas pueden ser alternativamente granuladas por humedad, en seco o por fusión, congeladas por fusión, o extrudidas antes de la compresión. Si se desea, antes del mezclado uno o más de los componentes se pueden aprestar por cribaje o molido o ambos. La forma de dosificación final puede comprender una o más capas y pueden estar recubiertas, sin recubrimiento, o encapsuladas. Los ejemplos de comprimidos pueden contener hasta aproximadamente 80% en peso de PFA, desde aproximadamente 10% en peso hasta aproximadamente 90% en peso de aglutinante, desde aproximadamente 0% en peso hasta aproximadamente 85% en peso de diluyente, desde aproximadamente 2% en peso hasta aproximadamente 10% en peso de desintegrante, y desde aproximadamente 0,25% en peso hasta aproximadamente 10% en peso de lubricante. Para una discusión de mezclado, granulación, molienda, cribaje, compresión, recubrimiento como también una descripción de las técnicas alternativas para preparar los fármacos, véase A. R. Gennaro (ed.), Remington: The Science and Practice of Pharmacy (20th ed., 2000); H. A. Lieberman et al. (ed.), Pharmaceutical Dosage Forms: Tablets, Vol. 1-3 (2d ed., 1990); y D. K. Parikh & C. K. Parikh, Handbook of Pharmaceutical Granulation Technology, Vol. 81 (1997).

[0136] Las películas orales consumibles para uso humano o veterinario son formas de dosificación de películas delgadas hidrosolubles flexibles o hinchables en agua que se pueden disolver rápidamente o mucoadhesivas. Además del PFA, una película típica incluye uno o más polímeros formadores de películas, aglutinantes, solventes, humectantes, plastificantes, estabilizantes o emulsionantes, agentes modificadores de la viscosidad, y solventes. Otras principios para películas pueden incluir antioxidantes, colorantes, saborizantes y mejoradores del sabor, conservantes, agentes estimulantes salivares, agentes de enfriamiento, cosolventes (incluyendo aceites), emolientes, agentes de carga, agentes antiespumantes, tensioactivos, y agentes enmascaradores del gusto. Algunos componentes de la formulación pueden cumplir más de una función.

[0137] Además de los requerimientos de dosificación, la cantidad del PFA en la película puede depender de su solubilidad. Si son hidrosolubles, el PFA comprendería típicamente desde aproximadamente 1% en peso hasta aproximadamente 80% en peso de los componentes no solventes (solutos) en la película o desde aproximadamente 20% en peso hasta aproximadamente 50% en peso de los solutos en la película. Un PFA menos soluble puede comprende una proporción mayor de la composición, típicamente hasta aproximadamente 88% en peso de los componentes no solventes en la película.

[0138] El polímero formador de películas puede seleccionarse a partir de polisacáridos naturales, proteínas, o hidrocoloides sintéticos y típicamente comprende desde aproximadamente 0,01% en peso hasta aproximadamente 99% en peso o desde aproximadamente 30% en peso hasta aproximadamente 80% en peso de la película.

[0139] Las formas de dosificación de la película se preparan típicamente por secado por evaporación de las películas acuosas delgadas recubiertas sobre un soporte de respaldo desprendible o papel, que puede llevarse a cabo en un horno o túnel de secado (por ej., en un aparato de secado por recubrimiento combinado), en un equipo de liofilización, o en un horno de vacío.

[0140] Las formulaciones sólidas útiles para la administración oral pueden incluir

formulaciones de liberación inmediata y formulaciones de liberación modificada. Las formulaciones de liberación modificada incluyen liberación retardada, sostenida, pulsada, controlada, específica y programada. Para una descripción general de las formulaciones de liberación modificada, véase la patente estadounidense no. 6.106.864. Para detalles de otras tecnologías de liberación, útiles, tales como dispersiones de energía elevada y partículas osmóticas y recubiertas, véase Verma et al, Pharmaceutical Technology On-line (2001) 25(2):1-14.

[0141] Los compuestos de fórmula 1 además se pueden administrar directamente en la corriente sanguínea, o un órgano interno del sujeto. Las técnicas adecuadas para administración parenteral incluyen administración intravenosa, intraarterial, intraperitoneal, intratecal, intraventricular, intrauretral, intraesternal, intracraniana intramuscular, intrasinovial, y subcutánea. Los dispositivos adecuados para administración parenteral incluyen inyectores de agujas, que incluyen inyectores de micro agujas, inyectores libres de agujas, y dispositivos de infusión.

[0142] Las formulaciones parenterales son típicamente soluciones acuosas que pueden contener excipientes tales como sales, carbohidratos y agentes de buffer (por ej., pH desde aproximadamente 3 hasta aproximadamente 9). Para algunas aplicaciones, sin embargo, los compuestos de fórmula 1 pueden ser formulados en forma más adecuada como una solución no acuosa estéril o en forma seca para ser utilizada junto con un vehículo adecuado tales como agua libre de pirógeno estéril. La preparación de las formulaciones parenterales en condiciones estériles (por ej., por liofilización) puede lograrse fácilmente utilizando técnicas farmacéuticas estándares.

[0143] La solubilidad de los compuestos que se utilizan en la preparación de soluciones parenterales puede ser incrementada a través de las técnicas de formulación apropiada, tal como la incorporación de agentes mejoradores de la solubilidad. Las formulacioens para administración parenteral se pueden formular para una liberación inmediata o modificada. Las formulaciones de liberación modificada incluyen liberación

retardada, sostenida, pulsada, controlada, específica y programada. De este modo, los compuestos de fórmula 1 se pueden formular en forma de una suspensión, un sólido, un semisólido, o un líquido tixotrópico para administración en forma de una acumulación implantada que provee liberación modificada del compuesto activo. Ejemplos de estas formulaciones incluyen stents recubiertos con fármaco y semisólidos y suspensiones que comprenden microesferas de ácido poli(DL-láctico-coglicólico) (PGLA).

[0144] Los compuestos de fórmula 1 además se pueden administrar por vía tópica, intradérmica, o transdérmica a la piel o la mucosa. Las formulaciones típicas para este fin incluyen geles, hidrogeles, lociones, soluciones, cremas, ungüentos, polvos, apósitos, espumas, películas, parches cutáneos, obleas, implantes, esponjas, fibras, vendajes y microemulsiones. Además se pueden utilizar liposomas. Los vehículos típicos pueden incluir alcohol, agua, aceite mineral, petrolato líquido, petrolato blanco, glicerina, polietilenglicol y propilenglicol. Las formulaciones típicas además pueden incluir mejoradores de la penetración. Véase, por ej., Finnin y Morgan, J. Pharm. Sci. 88(10):955-958 (1999).

[0145] Otros medios de administración tópica incluyen administración por electroporación, iontoforesis, fonoforesis, sonoforesis e inyección por micro agujas o libres de agujas (por ej., PowderjectTM y BiojectTM). Las formulaciones para administración tópica se pueden formular para una liberación inmediata o modificada como se describió anteriormente.

[0146] Los compuestos de fórmula 1 se pueden administrar además por vía intranasal o por inhalación, típicamente en la forma de un polvo seco, un aerosol, o gotas nasales. Un inhalador se puede utilizar para administrar el polvo seco, que comprende el PFA solo, una mezcla de polvo del PFA y un diluyente, tal como lactosa, o una mezcla de partículas de componentes que incluye el PFA y un fosfolípido, tal como fosfatidilcolina. Para uso intranasal, el polvo puede incluir un agente bioadhesivo, por ej., quitosan o ciclodextrina. Un contenedor presurizado, bomba, pulverizador, atomizador o nebulizador,

se puede utilizar para generar el pulverizado en aerosol a partir de una solución o suspensión que comprende el PFA, uno o más agentes para dispersión, solubilización, o extensión de la liberación del PFA (por ej., EtOH con o sin agua), uno o más solventes (por ej., 1,1,1,2-tetrafluoroetano o 1,1,1,2,3,3,3-heptafluoropropano) que sirven como propulsores, y un tensioactivo opcional, tal como sorbitán trioleato, ácido oleico o un ácido oligoláctico. Un atomizador que utiliza electrohidrodinámica se puede utilizar para producir una neblina fina.

[0147] Antes del uso en una formulación en polvo o suspensión, el fármaco usualmente se tritura a un tamaño de partícula adecuado para la administración por inhalación (típicamente 90% de las partículas, basado en el volumen, que tiene una dimensión más grande inferior a 5 micrones). Esto puede obtenerse mediante cualquier método de reducción de tamaño apropiado, tal como molienda a chorro en espiral, molienda a chorro en lecho fluido, procesamiento del fluido supercrítico, homogenización de presión alta, o secado por aspersión.

[0148] Las cápsulas, los blisteres y cartuchos (producidos, por ejemplo, de gelatina o hidroxipropilmetil celulosa) para su uso en un inhalador o insuflador se pueden formular para que contengan una mezcla de polvo del compuesto activo, una base de polvo adecuada tal como lactosa o almidón, y un modificador del rendimiento tal como L-leucina, manitol, o estearato de magnesio. La lactosa puede ser anhidra o monohidratada. Otros excipientes adecuados incluyen dextran, glucosa, maltosa, sorbitol, xilitol, fructosa, sacarosa, y trehalosa.

[0149] Una formulación de solución adecuada para su uso en un atomizador que utiliza electrohidrodinámica para producir una fina niebla puede contener desde aproximadamente 1 μg hasta aproximadamente 20 mg del PFA por activación y el volumen de activación puede variar desde 1 μl hasta aproximadamente 100 μl. Una formulación típica puede comprender uno o más compuestos de fórmula 1, propilenglicol, agua estéril, EtOH, y NaCl. Los solventes alternativos, que se pueden utilizar en lugar de

propilenglicol, incluyen glicerol y polietilenglicol.

[0150] Las formulaciones para administración inhalada, administración intranasal, o ambos, se pueden formular para ser de liberación inmediata o modificada que utiliza, por ejemplo, PGLA. Los saborizantes adecuados, tales como mentol y levo mentol, o los endulzantes, tales como sacarina o sacarina sódica, se pueden agregar a formulaciones destinadas a la administración inhalada/intranasal.

[0151] En el caso de inhaladores de polvo seco y aerosoles, la unidad de dosificación se determina por medio de una válvula que administra una cantidad medida. Las unidades se disponen típicamente para administrar una dosis medida o "puff" que contiene desde aproximadamente 10 µg hasta aproximadamente 1000 µg del PFA. La dosis diaria total oscilará típicamente desde aproximadamente 100 µg hasta aproximadamente 10 mg que se pueden administrar en una sola dosis o, usualmente, como dosis divididas a lo largo del día.

[0152] Los compuestos activos se pueden administrar por vía rectal o vaginal, por ej., en la forma de un supositorio, óvulos o enema. La manteca cacao es una base de supositorio tradicional, pero se pueden utilizar varias alternativas como base apropiada. Las formulaciones para administración rectal o vaginal se pueden formular para una liberación inmediata o modificada como se describió anteriormente.

[0153] Los compuestos de fórmula 1 se pueden administrar además directamente al ojo o al oído, típicamente en la forma de gotas de una suspensión micronizada o solución en solución salina isotónica, ajustada por pH, estéril. Otras formulaciones adecuadas para administración ocular y auditiva incluyen ungüentos, geles, implantes biodegradables (por ej., esponjas de gel absorbibles, colágeno), implantes biodegradables (por ej., silicona), obleas, lentes, y sistemas particulados o vesiculares, tales como niosomas o liposomas. La formulación puede incluir uno o más polímeros y un conservante, tal como cloruro de benzalconio. Los polímeros típicos incluyen ácido poliacrílico entrecruzado, alcohol polivinílico, ácido hialurónico, polímeros celulósicos (por

ej., hidroxipropilmetilcelulosa, hidroxietilcelulosa, metil celulosa), y polímeros heteropolisacáridos (por ej., goma gelan). Estas formulaciones además pueden administrarse por iontoforesis. Las formulaciones para administración ocular o auditiva se pueden formular para una liberación inmediata o modificada como se describió anteriormente.

[0154] Para mejorar su solubilidad, la velocidad de disolución, el enmascaramiento del sabor, la biodisponibilidad, o la estabilidad, los compuestos de fórmula 1 se pueden combinar con entidades macromoleculares solubles, que incluyen ciclodextrina y sus derivados y polímeros que contienen polietilenglicol. Por ejemplo, los complejos de PFA-ciclodextrina son útiles en general para la mayoría de las formas de dosificación y las vías de administración. Se pueden utilizar tanto complejos de inclusión como de no inclusión. Como alternativa a la complejación directa con el PFA, la ciclodextrina se puede utilizar como aditivo auxiliar, es decir, en forma de un vehículo, diluyente o solubilizante. Las ciclodextrinas alfa, beta y gamma se utilizan normalmente para estos fines. Véase por ej., WO 91/11172, WO 94/02518, y WO 98/55148.

[0155] Como se observó anteriormente, uno o más compuestos de fórmula 1, que incluyen los compuestos específicamente mencionados anteriormente, y sus complejos activos, sales, solvato e hidratos para uso farmacéutico, se pueden combinar entre sí o con uno o más de otros compuestos activos para uso farmacéutico para tratar varias enfermedades, afecciones y trastornos. En estos casos, los compuestos activos se pueden combinar en una forma de dosificación simple como se describió anteriormente o se pueden proveer en la forma de un kit que es adecuado para la coadministración de las composiciones. El kit comprende (1) dos o más diferentes composiciones farmacéuticas, al menos una de las cuales contiene un compuesto de fórmula 1; y (2) un dispositivo para retener en forma separada dos composiciones farmacéuticas, tales como un botella dividida o un paquete de aluminio dividido. Un ejemplo de este tipo de kit es el paquete de blister familiar que se utiliza para el envasado de comprimidos o cápsulas. El kit es

adecuado para administrar diferentes tipo de formas de dosificación (por ej., oral y parenteral) o para administrar diferentes composiciones farmacéuticas a intervalos de dosificación separados, o para titular las diferentes composiciones farmacéuticas una contra otra. Para asistir con el cumplimiento del paciente, el kit comprende típicamente direcciones para administración y se pueden proveer con una ayuda memoria.

[0156] Para la administración a pacientes humanos, la dosis diaria total de los compuestos reivindicados y divulgados oscila típicamente desde aproximadamente 0,1 mg hasta aproximadamente 3.000 mg dependiendo de la vía de administración. Por ejemplo, la administración oral puede requerir una dosis diaria total desde aproximadamente 1 mg hasta aproximadamente 3.000 mg, mientras que una dosis intravenosa puede sólo requerir una dosis diaria total desde aproximadamente 0,1 mg hasta aproximadamente 300 mg. La dosis diaria total se puede administrar en dosis simples o divididas y, a criterio del profesional actuante, puede estar fuera de los rangos típicos especificados anteriormente. Si bien estas dosificaciones se basan en un sujeto humano promedio que tiene una masa corporal de aproximadamente 60 Kg. hasta aproximadamente 70 Kg., el profesional actuante podrá determinar la dosis apropiada para un paciente (por ej., un niño) cuya masa corporal está fuera de este rango de peso.

[0157] Como se observó anteriormente, los compuestos de fórmula 1 se pueden utilizar para tratar trastornos, enfermedades, y afecciones para las cuales se indica la inhibición de la SYK. Estos trastornos, enfermedades y afecciones en general se refieren a cualquier estado no saludable o anormal en un sujeto para lo cual la inhibición de la SYK provee un beneficio terapéutico. En particular, estos trastornos, enfermedades y afecciones pueden involucrar el sistema inmune y la inflamación, que incluyen las reacciones de hipersensibilidad tipo I (riñitis alérgica, asma alérgico, y dermatitis atópica; enfermedades autoinmunes (artritis reumatoide, esclerosis múltiple, lupus eritematoso sistémico, soriasis, y púrpura trombocitopénica inmune; inflamación del pulmón (enfermedad pulmonar obstructiva crónica) y trombosis. Los compuestos de fórmula 1

además se pueden utilizar para tratar trastornos enfermedades y afecciones relacionadas con el crecimiento celular anormal, que incluye malignidades hematológicas, tales como leucemia mieloide aguda, leucemia linfocítica crónica de las células B, linfoma de células B (por ej., linfoma de células de la corteza cerebral), y linfoma de células T (por ej., linfoma de células T periféricas); como también cánceres epiteliales (es decir, carcinomas), tales como cáncer de pulmón (cáncer de pulmón de células pequeñas y cáncer de pulmón de células no pequeñas), cáncer pancreático, y cáncer de colon.

[0158] Además de las malignidades hematológicas y de los cánceres epiteliales mencionados anteriormente, los compuestos de fórmula 1 se pueden utilizar además para tratar otros tipos de cáncer, que incluyen leucemia (leucemia mielógena crónica y leucemia linfocítica crónica); cáncer de pecho, cáncer genitourinario, cáncer de piel, cáncer de huesos, cáncer de próstata, y cáncer de hígado; cáncer cerebral, cáncer de la laringe, vesícula biliar, recto, paratiroides, tiroides, suprarrenal, tejido neural, vesícula, cabeza, cuello, estómago, bronquios, y riñones; carcinoma de células basales, carcinoma de células escamosas, carcinoma de piel metastático, osteosarcoma, sarcoma de Ewing, sarcoma de células del veticulum, y sarcoma de Kaposi; mieloma, tumor de células gigantes, tumor de las células de los islotes, tumores linfocíticos y granulocíticos agudos y crónicos, tumor de los tricoleucitos, adenoma, carcinoma medular, feocromocitoma, neuromas mucosales, ganglioneuromas intestinales, tumor del nervio corneal hiperplásico, tumor del hábito marfanoide, tumor de Wilms, seminoma, tumor de ovarios, tumor eliomiomater, displasia cervical, neuroblastoma, retinoblastoma, síndrome mielodisplásico, rabdomiosarcoma, astrocitoma, linfoma de no Hodgkin, hipercalcemia maligna, policitermia vera, adenocarcinoma, glioblastoma multiforma, glioma, linfomas, y melanomas malignos, entre otros.

[0159] Además del cáncer, los compuestos de fórmula 1 se pueden utilizar para tratar otras enfermedades relacionadas con el crecimiento celular anormal, que incluye enfermedades proliferativas tales como hipertrofia prostática benigna, restinosis,

hiperplasia, trastorno de proliferación sinovial, retinopatía u otros trastornos neovasculares del ojo, entre otros.

[0160] Los compuestos de fórmula 1 además se pueden utilizar para tratar trastornos autoinmunes además de los mencionados anteriormente. Estos trastornos, enfermedades y afecciones incluyen enfermedad de Crohn, dermatomiositis, diabetes mellitus tipo 1, síndrome de Goodpasture, enfermedad de Graves, síndrome de Guilllain-Barré, enfermedad de Hashimoto, daño del tejido conectivo mixto, miastenia gravis, narcolepsia, pénfigo vulgaris, anemia perniciosa, polimiositis, cirrosis biliar primaria, síndrome de Sjödren, arteritis temporal, colitis ulcerativa, vasculitis, y granulomatosis de Wegener, entre otros.

[0161] Más aún, los compuestos de fórmula 1 se pueden utilizar para tratar trastornos inflamatorios que incluyen asma, inflamación crónica, prostatitis crónica, glomerulonefritis, hipersensibilidades, enfermedades inflamatorias del intestino (colitis ulcerativa además de la enfermedad de Crohn), enfermedad inflamatoria pélvica, lesión de reperfusión, rechazo al trasplante, y síndrome de respuesta inflamatoria sistémica.

[0162] Los compuestos de fórmula 1 se pueden utilizar además para tratar enfermedades específicas que pueden estar dentro de uno o más trastornos generales que se describieron anteriormente, que incluyen la artritis. Además de la artritis reumatoide, el síndrome de Sjödren, el lupus eritematoso sistémica, SLE en niños y adolescentes, los compuestos de fórmula 1 además se pueden utilizar para tratar otras enfermedades de artritis, que incluyen la espondilitis anquilosante, necrosis vascular, enfermedad de Bechet, bursitis, pirofosfato de calcio, enfermedad de deposición cristal dihirato (seudo gota), síndrome del túnel carpiano, síndrome de Ehlers-Danlos, fibromialgia, quinta enfermedad, arteritis de células gigantes, gota, dermatomiositis juvenil, artritis reumatoide juvenil, espondiloartopatía juvenil, enfermedad de Lyme, síndrome Marfan, miositis, osteoartritis, osteogénesis imperfecta, osteoporosis, enfermedad de Paget, artritis soriásica, fenómeno de Raynaud, artritis reactiva, síndrome de distrofia

simpática refleja, escleroderma, estenosis espinal, enfermedad de Still, y tendinitis, entre otras.

[0163] Los compuestos reivindicados y divulgados se pueden combinar con uno o más compuestos farmacológicamente activos o terapias para el tratamiento de uno o más trastornos, enfermedades y afecciones para las cuales se indica la SYK, que incluyen trastornos, enfermedades y afecciones que involucran el sistema inmune, la inflamación, y el crecimiento celular anormal. Por ejemplo, los compuestos de fórmula 1, que incluyen los compuestos específicamente mencionados anteriormente, y sus complejos, sales, solvatos e hidratos aceptables para uso farmacéutico, se pueden administrar en forma simultánea, secuencial o separada en combinación con uno o más compuestos o terapias para tratar la artritis, que incluyen la artritis reumatoide y la osteoartritis, o para tratar el cáncer, que incluye malignidades hematológicas, tales como leucemia mieloide aguda, leucemia linfocítica crónica de las células B, linfoma de las células B, y linfoma de las células T, y carcinomas, tales como cáncer de pulmón, cáncer pancreático, y cáncer de colon. Estas combinaciones pueden ofrecer ventajas terapéuticas significativas, que incluyen menores efectos colaterales, capacidad mejorada para tratar poblaciones de pacientes de bajos recursos, o actividad sinergística.

[0164] Por ejemplo, cuando se utilizan para tratar la artritis, los compuestos de fórmula 1 se pueden combinar con uno o más fármacos antiinflamatorios no esteroides (NSAIDs), analgésicos, corticosteroides, modificadores de la respuesta biológica, y terapia de inmunoadsorción de la proteína A. En forma alternativa o además, cuando se trata la artritis reumatoide, los compuestos de fórmula 1 se pueden combinar con uno o más fármacos antirreumáticos modificadores de la enfermedad (DMARDs), y cuando se trata la osteoartritis, los compuestos de fórmula 1 se pueden combinar con uno o más agentes de la osteoporosis.

[0165] Los NSAIDs representativos incluyen apazona, aspirina, celecoxib, diclofenac (con y sin misoprostol), diflunisal, etodolac, fenoprofeno, flurbiprofeno,

ibuprofeno, indometacin, cetoprofeno, meclofenamato sódico, ácido mefenámico, meloxicam, nabumetona, naproxeno, oxaprozin, fenilbutazona, piroxicam, colina y salicilatos de magnesio, salsalato, y sulindac. Los analgésicos representativos incluyen acetaminofeno y morfina sulfato, como también codeína, hidrocodona, oxicodona, propoxifeno, y tramadol, todos con o sin acetaminofeno. Los corticosteroides representativos incluyen betametasona, acetato de cortisona, dexametasona, hidrocortisona, metilprednisolona, prednisolona, y prednisona. Los modificadores de respuesta biológica representativos incluyen inhibidores de TNF-α, tales como adalimumab, etanercept, e infliximab; inhibidores de células B selectivas, tales como rituximab; inhibidores de IL-1, tales como anakinra, y moduladores de coestimulación selectiva, tal como abatacept.

[0166] Los DMARDs representativos incluyen auranofin (oro oral), azatioprina, clorambucil, ciclofosfamida, ciclosporina, tiomalato de sodio dorado (oro inyectable), hidroxicloroquina, leflunomida, metotrexato, minociclina, miofenolato mofetil, penicilamina, y sulfasalazina. Los agentes de la osteoporosis representativos incluyen bisfosfonatos, tales como alendronato, ibandronato, risedronato y ácido zoledrónico; los moduladores del receptor de estrógenos selectivos, tales como droloxifeno, lasofoxifeno, y raoxifeno; las hormonas, tales como calcitonina, estrógenos, y hormona paratiroide; y agentes inmunosupresores tales como azatioprina, ciclosporina, y rapamicina.

[0167] Las combinaciones útiles en particular para tratar la artritis reumatoide incluyen un compuesto de fórmula 1 y metotrexato; un compuesto de fórmula 1 y uno o más modificadores de la respuesta biológica, tales como lefluonomida, etanercept, adalimumab, e infliximab; o un compuesto de fórmula 1, metotrexato y uno o más modificadores de la respuesta biológica, tales como lefluonomida, etanercept, adalimumab, e infliximab.

[0168] Para el tratamiento de la trombosis y la restenosis, los compuestos de fórmula 1 se pueden combinar con uno o más agentes cardiovasculares tales como

bloqueadores del canal de calcio, estatinas, fibratos, beta-bloqueadores, inhibidores de ACE, e inhibidores de la agregación plaquetaria.

[0169] Los compuestos de fórmula 1 se pueden combinar además con uno o más compuestos o terapias para tratar el cáncer. Estos incluyen agentes quimioterapéuticos (es decir, agentes citotóxicos y antineoplásicos) tales como agentes alquilantes, antibióticos, agentes antimetabólicos, agentes derivados de plantas, e inhibidores de topoisomerasa, como también fármacos molecularmente específicos que bloquean el crecimiento y la dispersión del cáncer interfiriendo con las moléculas específicas que están involucradas en el desarrollo y avance del tumor. Los fármacos molecularmente focalizados incluyen tanto moléculas como biológicos.

[0170] Los agentes alquilantes representativos incluyen biscloroetilaminas (mostazas de nitrógeno, por ej., clorambucilo, ciclofosfamida, ifosfamida, mecloretamina, melfalan, y mostaza uracilo); azirdinas (por ej., tiotepa); sulfonatos de alquil alcona (por ej., busulfan); nitrosoureas (por ej., carmustina, lamustina, y estreptozocina); agentes alquilantes no clásicos (por ej., aretamina, dacarbazina, y procarbazina); y compuestos de platino (por ej., carboplatino, cisplatino, nedaplatino, oxaliplatino, satraplatino, y triplatino tetranitrato).

[0171] Los agentes antibióticos representativos incluyen antraciclinas (por ej., aclarubicin, amrubicin, daunorubicin, doxorubicin, epirubicin, idarubicin, pirarubicin, valrubicin, y zorubicin); antracenodionas (por ej., mitoxantrona y pixantrona); y estreptomices (por ej., actinomicin, bleomicin, dactinomicin, mitomicin C y plicamicin).

[0172] Los agentes antimetabólicos incluyen inhibidores de la dihidrofolato reductasa (por ej., aminopterin, metotrexato, y pemetrexed); inhibidores de himidilato sintasa (por ej., raltitrexed y pemetrexed); ácido folínico (por ej., leucovorin); inhibidores de adenosin deaminasa (por ej., pentostatina); inhibidores halogenados/ribonucleótido reductasa (por ej., cladribina, clofarabina, y fludarabina); tiopurinas (por ej., tioguanina y mercaptopurina); inhibidores de timidilato sintasa (por ej., fluorouracilo, capecitabina,

tegafur, carmofur, y floxuridina); inhibidores de ADN polimerasa (por ej., citarabina); inhibidores de ribonucleótido reductasa (por ej., gemcitabina); agentes hipometilantes (por ej., azacitidina y decitabina); e inhibidor de la ribonucleótido reductasa (por ej., hidroxiurea); y un supresor de asparagina (por ej., asparaginasa).

[0173] Los agentes derivados de plantas representativos incluyen vinca alcaloides (por ej., vincristina, vinblastina, vindesina, vinzolidina, and vinorelbina), podofilotoxinas (por ej., etoposida y teniposida), y taxanos (por ej., docetaxel, larotaxel, ortataxel, paclitaxel, y tesetaxel).

[0174] Los inhibidores de topoisomerasa tipo I representativos incluyen camtotecinas, tales como belotecan, irinotecan, rubitecan, y topotecan. Los inhibidores de topoisomerasa tipo II representativos incluyen amsacrina, etoposida, etoposida fosfato, y teniposida, que son derivados de las epipodofilotoxinas.

[0175] Las terapias focalizadas molecularmente incluyen agentes biológicos tales como citoquinas y otros agentes inmunoreguladores. Las citoquinas útiles incluyen la interleuquina-2 (IL-2, aldesleuquina), interleuquina 4 (IL-4), interleuquina 12 (IL-12), y el interferón, que incluye más de 23 subtipos relacionados. Otras citoquinas incluyen el factor de estimulación de la colonia granulocítica (CSF) (filgrastim) y el macrófago granulocito (CSF (sargramostim). Otros agentes inmunomoduladores incluyen acillus Calmette-Guerin, levamisol, y octreotida; anticuerpos monoclonales contra antígenos del tumor, tales como trastruzumab y rituximab; y vacunas contra el cáncer, que inducen una respuesta inmune a los tumores.

[0176] Además, los fármacos focalizados molecularmente que interfieren con las moléculas específicas involucradas en el crecimiento y el desarrollo del tumor incluyen inhibidores del factor de crecimiento epidérmico (EGF), que transforman el factor de crecimiento alfa (TGFα), TGFβ, heregulin, factor de crecimiento del tipo insulina (IGF), factor de crecimiento del fibroplasto (FGF), factor de crecimiento del queeratinocito (KGF), factor de estimulación de las colonias (CSF), eritropoyetina (EPO), interleuquina-2

(IL-2), factor de crecimiento del nervio (NGF), factor de crecimiento derivado de plaquetas (PDGF), factor de crecimiento de hepatocitos (HGF), factor de crecimiento endotelial vascular (VEGF), angiopoyetina, receptor del factor de crecimiento epidérmico (EGFR), receptor del factor de crecimiento epidérmico humano 2 (HER2), HER4, receptor del factor de crecimiento del tipo insulina 1 (IGF1R), receptor del factor de crecimiento del fibroplasto 1 (FGR1R), FGF2R, FGF3R, FGF4R, receptor del factor de crecimiento endotelial vascular (VEGFR), tirosina quinasa con dominios del tipo inmunoglobulina y del tipo del factor de crecimiento epidérmico 2 (Tie-2), receptor del factor de crecimiento derivado de las plaquetas (PDGFR), tirosina quinasa 3 del tipo Abl, Bcr-Abl, Raf, FMS (FLT3), c-Kit, Src, proteína quinasa c (PKC), tropomiosina receptor quinasa (Trk), Ret, blanco mamífero de rapamicina (mTOR), Aurora quinas, quinasa del tipo polo (PLK), proteína quinasa activada por mitotéennos (MARPK), factor de transición epitelial mesenquimal (c-MET), quinasa dependiente de ciclina (CDK), Akt, quinasas reguladas por la señal extracelular (ERK), poli(ADP) ribosa polimerasa (PARP), y similares.

[0177] Los fármacos específicos focalizados molecularmente incluyen los moduladores del receptor de estrógenos selectivo, tales como tamoxifeno, toremifeno, fulvestrant, y raloxifeno; antiandrógenos, tales como bicalutamida, nilutamida, megestrol, y flutamida; e inhibidores de aromatasa, tales como exemestano, anastrozol, y letrozol. Otros fármacos específicos focalizados molecularmente incluyen agentes que inhiben la transducción de señal, tales como imatinib, dasatinib, nilotinib, trastuzumab, gefitinib, erlotinib, cetuximab, lapatinib, panitumumab, y temsirolimus; agentes que inducen la apoptosis, tales como bortezomib; agentes que bloquean la angiogénesis, tales como bevacizumab, sorafenib, y sunitinib; agentes que colaboran con el sistema inmune a destruir y retirar células, tales como rituximab y alemtuzumab; y anticuerpos monoclonales que administran moléculas tóxicas a células cancerígenas, tales como gemtuzumab ozogamicin, tositumomab, 131I-tositumoab, e ibritumomab tiuxetan.

[0178] Actividad biológica: Inhibición de la SYK

[0179] La capacidad de los compuestos para inhibir la actividad de la SYK puede evaluarse utilizando una variedad de métodos, que incluyen ensayos in vitro e in vivo El siguiente ensayo in vitro mide la capacidad de un compuesto de ensayo de inhibir la fosforilación mediada por la SYK de un sustrato específico de la SYK marcado con FAM (5FAM-KKKKEEIYFFFG-NH2).

[0180] La proteína SYK se prepara a partir de la tirosina quinasa esplénica humana que codifica el ADNc y se expresa en células de insectos utilizando un vector de expresión del baculovirus. El ADNc (IMAGE: 3542895) se adquiere de Open Biosystems. El dominio de la SYK quinasa (residuos 356-635) se amplifica mediante PCR y se clona en el plásmido pFastBac1 (Invitrogen) en los sitios BamHI/XbaI. El plásmido recombinante que codifica Met-Ala-Lys-SYK(356-635)-HHHHHH se secuencia y se transforma en la cepa de la E. coli DH10Bac El ADN bacmido recombinante se aísla y se transfecta en las células de insecto Sf9. El virus recombinante se cosecha 72 horas después de la transfección. La reserva viral de título alto se prepara infectando las células Sf9 a una multiplicidad de infección (MOI) de aproximadamente 0,01. Una suspensión de células Sf9 (10 l) se infecta con virus recombinantes (MOI=5) y se incuba en un Bioreactor Wave (GE-Healthcare) durante 48 horas. Las células se cosechan y se almacenan a -80ºC.

[0181] Para purificar la proteína expresada, las células Sf9 congeladas (10 l) se quiebran en pequeñas partículas (< 1 cm.) y se suspenden en un buffer de lisis (300 ml) que contiene 20 mM de Tris (pH 7,6), 0.25mM de TCEP, 100 mM de NaCl, 5% glicerol y un inhibidor de proteasa. La suspensión se agita a TA hasta descongelarse completamente, se lisan otros 2 a 4 minutos en un homogenizador de pala rotativa, y a continuación se centrifuga a 4200 g durante 1 hora. A continuación de la centrifugación, el sobrenadante se vierte a través de la tela de queso y se combina con una resina quelante de níquel (Probond ResinTM, Invitrogen) que se pre-equilibra en un buffer de lavado que contiene 10 mM de Tris (pH 7,6), 0.25mM de TCEP, 300 mM de NaCl, 5% de glicerol, y 20mM de imidazol. La mezcla se agita durante 3 horas en un cuarto frío y a continuación

se centrifuga a 900 g durante 10 min. La resina se dispersa en buffer de lavado (50 ml), se centrifuga durante 10 min. a 900 g, se redispersa en una pequeña cantidad de buffer de lavado (5 ml), y a continuación se vierte en una columna de cromatografía Poly-Prep desechable, a través de la cual se pasa buffer de lavado por gravedad hasta que no se observan proteínas en el buffer de coomassie (aproximadamente 120 ml de buffer de lavado). Un buffer de elución (30 ml) que contiene 10 mM de HEPES (pH 7,4), 150 de mM NaCl, 10% de glicerol, 5 mM DTT, y 400 mM de imidazol se utiliza para eluir la proteína SYK de la resina. El eluado se concentra (5 ml) y posteriormente se purifica sobre una columna Superdex 200 (1,2 ml/min. durante 160 min., 10 mM de HEPES (pH 7,4), 10 mM de NaCl, 10 mM de MgCl, 0,1 mM de EDTA, y 0.25 mM de TCEP). Las fracciones cromatografiadas se corren sobre SDS-PAGE y la fracciones necesarias se reúnen y se concentran. El buffer de administración final es 10 mM de HEPES (pH 7,4), 10mM de metiona, 150 mM de NaCl, 10% de glicerol, 5 mM de DTT.

[0182] La inhibición de SYK se determina utilizando un formato de placa de 384 pocillos negra en buffer que contiene 50 mM de HEPES, 10 mM de NaCl, 10 mM de MgCl2, 0,2 mM de EDTA, 0,01% de EDA (Brij®35), 1 mM de DTT, y 0,1 mg/ml de BSA a pH 7,3. Cada compuesto de ensayo se prepara en DMSO utilizando diluciones de serie de 2 veces para 11 puntos de datos, que se agregan al buffer de modo que cada dilución contiene 3% de DMSO. A cada pocillo se agrega 2 µL de3 µM 5FAM-KKKKEEIYFFFG-NH2 (en buffer), 2 µL de compuesto de ensayo diluido (3% de DMSO en buffer), y 2 µL de 2,4 nM de SYK y 45 µM de ATP (en buffer). La mezcla de reacción se incuba a temperatura ambiente durante 60 min., y se templa agregando 50 mM de Hepes, 30 mM de EDTA, 0,1% de Triton X-100 (pH 7.3). Para cuantificar el sustrato marcado fluorescente y el producto siguiente a la reacción, la placa de ensayo se carga sobre un Caliper LC-3000, que mide el porcentaje de la conversión por separación basada en microfluídico. Los valores de IC50 correspondientes se calculan por ajuste de la curva no lineal de las concentraciones del compuesto y el porcentaje de inhibición a la ecuación de

IC50 estándar y se informa como pIC50, es decir, -log(IC50), donde IC50 es concentración molar.

Ejemplos

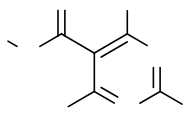
[0183] Los siguientes ejemplos intentan ser ilustrativos y no limitantes, y representan las realizaciones específicas de la presente invención.

[0184] Los espectros de resonancia magnética nuclear 1H (RMN) se obtuvieron para muchos de los compuestos en los siguientes ejemplos. Los desplazamientos químicos característicos (δ) se mencionan en partes por millón corriente abajo de tetrametilsilano utilizando abreviaturas convencionales para la designación de los picos principales, que incluyen s (singulete), d (doblete), t (triplete), q (cuarteto), m (multiplete), spt (septeto) y br (ancho). Los espectros de masa (m/z) se registraron utilizando ya se ionización por electroaspersión (ESI) o ionización química por presión atmosférica (APCI). Las siguientes abreviaturas se utilizan para solventes comunes: CDCl3 (deuterocloroformo), DMSO-d6 (deuterodimetilsulfóxido), CD3OD (deuterometanol), y THF-d8 (deuterotetrahidrofurano). "Amoníaco" se refiere a una solución concentrada de amoníaco en agua que posee una gravedad específica de 0,88.

[0185] Donde se indica, los productos de ciertas preparaciones y ejemplos se purifican por HPLC disparada por masa (por ej., Bomba: WatersTM 2525; EM: ZQTM; Software: MassLynxTM), cromatografía flash o cromatografía de capa delgada preparativa (TLC). La HPLC preparativa se lleva a cabo utilizando ya sea condiciones ácidas o básicas. Las condiciones ácidas son típicamente gradientes en solvente A (agua con 0,05% de TFA) y solvente B (acetonitrilo con 0,035% de TFA); las condiciones básicas son típicamente gradientes en solvente A (10 mM de NH4HCO3 en agua) y solvente B (10 mM NH4HCO3 en 20/80 (v/v) agua/acetonitrilo). Las condiciones de HPLC preparativa mencionadas utilizan condiciones ácidas a menos que se indiquen como básicas. La TLC preparativa se lleva a cabo típicamente sobre placas de gel de sílice 60 F254. Después del aislamiento por cromatografía, el solvente se elimina y el producto se obtiene por

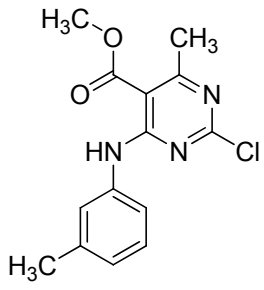
secado en un evaporador centrífugo (por ej., GeneVacTM), evaporador rotativo, matraz evacuado, liofilizador, etc. Las reacciones en una atmósfera inerte (por ej., nitrógeno) o reactiva (por ej., H2) se llevan a cabo típicamente a una presión de aproximadamente 1 atmósfera (14,7 psi) o mayor.

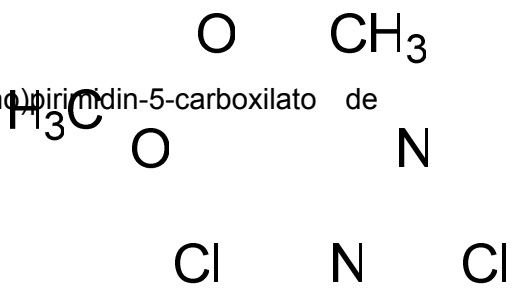
[0186] Preparación 1: 2,4-dicloro-6-metilpirimidin-5-carboxilato de metilo



[0187] A una suspensión de 6-metil-2,4-dioxo-1,2,3,4-tetrahidropirimidin-5-carboxilato de metilo (1 g, 5,43 mmoles) en POCl3 (10 ml) se agregó 10 gotas de N,N-dimetilanilina. La mezcla de reacción se calentó a 105ºC durante 6 horas hasta que se tornó una solución transparente. A continuación se enfrió, se concentró a presión reducida, se vertió sobre hielo, y se extrajo con EtOAc. El extracto orgánico se lavó con agua y salmuera, se secó y se concentró a presión reducida para dar el compuesto del título en forma de un sólido verdoso-amarillo (940 mg, 78%). [M+H] calc para C7H6Cl2N2O2, 222; experimental, 221, 223.

[0188] Preparación 2: 2-cloro-4-metil-6-(m-tolilamino)pirimidin-5-carboxilato de metilo.

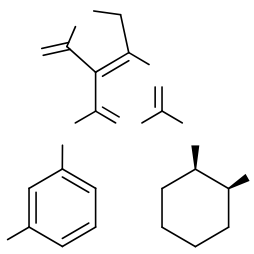




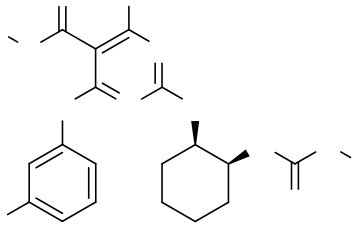
[0189] Una mezcla de 2,4-dicloro-6-metilpirimidin-5-carboxilato de metilo (940 mg, 4,25 mmoles), m-toluidina (0,461 ml, 4,25 mmoles) y N-etildiisopropilamina (1,481 ml, 8,51 mmoles) en CH3CN (30 ml) se calentó a reflujo durante 3 horas. La mezcla se diluyó con EtOAc, y se lavó con salmuera y agua. El extracto orgánico se secó y se concentró a

presión reducida para dar el compuesto del título en forma de un sólido color amarillo claro (1,2 g, 97%). [M+H] calc para C14H14N3ClO2, 292; experimental, 292.

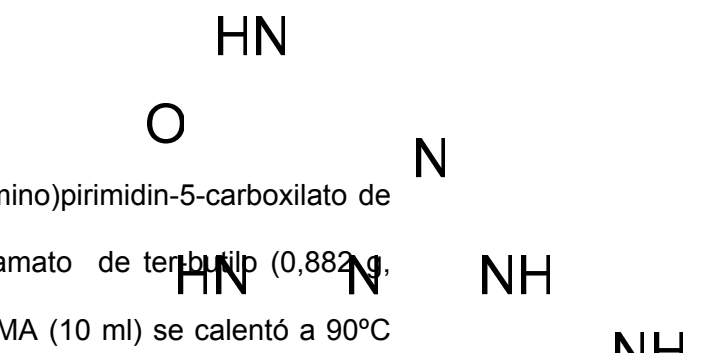
[0190] Ejemplo 1: 2-((1R,2S)-2-aminociclohexilamino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona



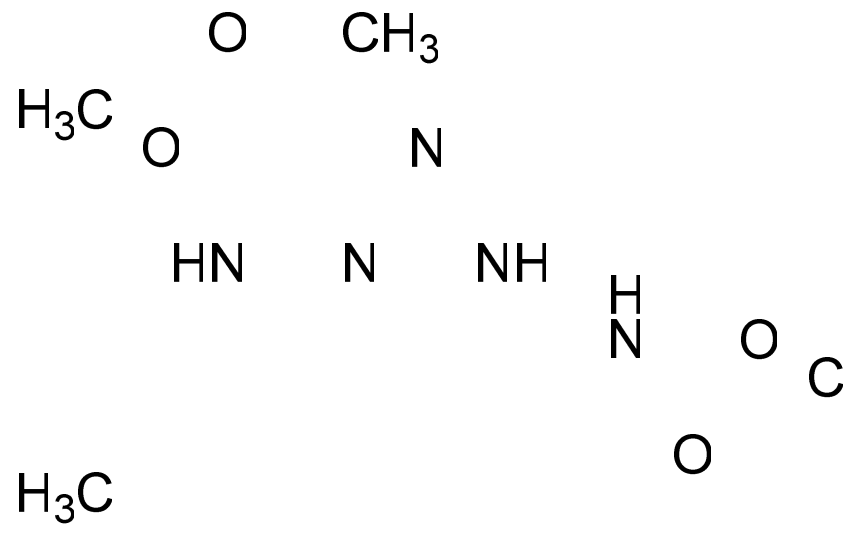
[0191] A. 2-((1R,2S)-2-(ter-butoxicarbonilamino) ciclohexilamino)-4-metil-6-(m-tolilamino)pirimidin-5-carboxilato de metilo.

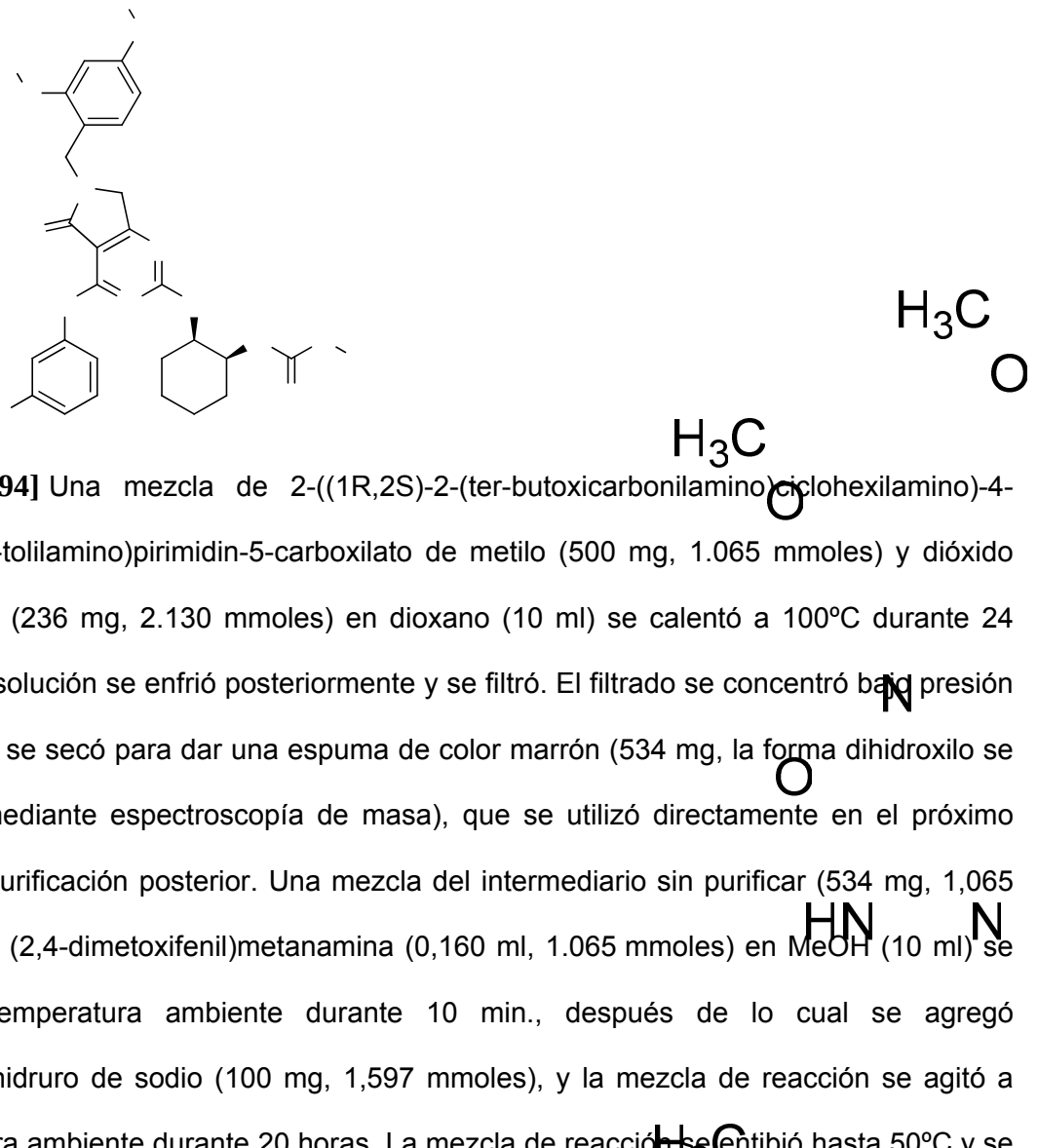


[0192] Una solución de 2-cloro-4-metil-6-(m-tolesilamino)pirimidin-5-carboxilato de metilo (1,2 g, 4,11 mmoles), (1S,2R)-2-aminociclohexilcarbamato de terbutilo (0,882 g, 4,11 mmoles) y trietilamina (1,720 ml, 12,34 mmoles) en DMA (10 ml) se calentó a 90ºC durante 4 horas. La solución se diluyó a continuación con EtOAc, se lavó con salmuera y agua. El extracto orgánico se secó y se concentró a presión reducida para dar un residuo de color amarillo claro; los cristales de color blanco se formaron al cabo de la trituración con ACN (5 ml). El sólido resultante se filtró, se lavó con ACN, y se secó para dar el compuesto del título en forma de un sólido de color blanco (1,2 g, 62%). [M+H] calc para C25H35N5CO4, 470; experimental, 470.



[0193] B. (1S,2R)-2-(6-(2,4-dimetoxibencil)-5-oxo-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-2-ilamino)ciclohexilcarbamato de ter-butilo





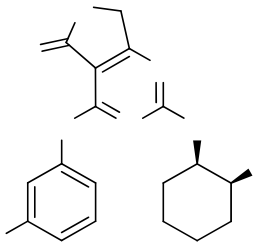
[0194] Una mezcla de 2-((1R,2S)-2-(ter-butoxicarbonilamino)ciclohexilamino)-4-metil-6-(m-tolilamino)pirimidin-5-carboxilato de metilo (500 mg, 1.065 mmoles) y dióxido de selenio (236 mg, 2.130 mmoles) en dioxano (10 ml) se calentó a 100ºC durante 24 horas. La solución se enfrió posteriormente y se filtró. El filtrado se concentró bajo presión reducida y se secó para dar una espuma de color marrón (534 mg, la forma dihidroxilo se observó mediante espectroscopía de masa), que se utilizó directamente en el próximo paso sin purificación posterior. Una mezcla del intermediario sin purificar (534 mg, 1,065 mmoles) y (2,4-dimetoxifenil)metanamina (0,160 ml, 1.065 mmoles) en MeOH (10 ml) se agitó a temperatura ambiente durante 10 min., después de lo cual se agregó cianoborohidruro de sodio (100 mg, 1,597 mmoles), y la mezcla de reacción se agitó a temperatura ambiente durante 20 horas. La mezcla de reacción se entibió hasta 50ºC y se agitó durante otras 2 horas adicionales para completar la reacción. La mezcla se enfrió hasta temperatura ambiente y el sólido se filtró y se lavó con MeOH para dar el compuesto del título en forma de un sólido rosado (237 mg, 37%). [M+H] calc para C33H42N6CO5, 603; experimental, 603.

[0195] C. 2-((1R,2S)-2-aminociclohexilamino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona.

[0196] Una mezcla de (1S,2R)-2-(6-(2,4-dimetoxibencil)-5-oxo-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-2-ilamino)ciclohexilcarbamato de ter-butilo (235 mg,

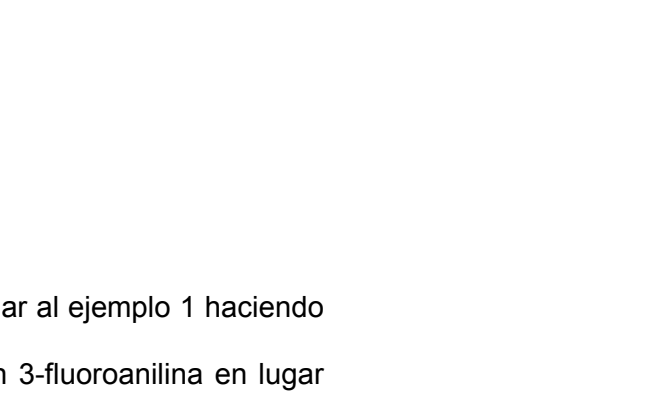
0,390 mmoles) en TFA (5 ml) se agitó a 60ºC durante 2 horas y a continuación se purificó por HPLC preparativa de fase inversa. Las fracciones e recolectaron, se concentraron a presión reducida, se diluyeron en EtOAc, y se basificaron con solución acuosa saturada de NaHCO3. El extracto orgánico se secó y se concentró a presión reducida para dar el compuesto del título en forma de un sólido color blanco (60 mg, 44%). 1H RMN (400 MHz, DMSO-d6) δ ppm 1,33-1,60 (m, 10 H), 2,32 (s, 3 H), 3,16 (m, 2 H), 3,92 (br s, 1 H), 4,14 (s, 2 H), 6,88 (d, J=7,07 Hz, 1 H), 7,13 (br s, 1 H), 7,22 (t, J=7,45 Hz, 1 H), 7,34 - 7,55 (m, 1 H), 7,70 (br s, 1 H), 8,01 (br s, 1 H), 8,58 (br s, 1 H). [M+H] calc para C19H24N6CO353; experimental, 353.

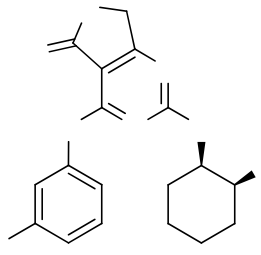
[0197] Ejemplo 2: 2-((1R,2S)-2-aminociclohexilamino)-4-(3-fluorofenilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona



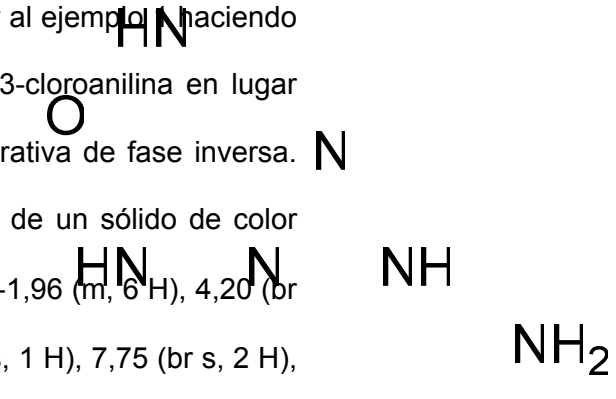
[0198] El compuesto del título se preparó de manera similar al ejemplo 1 haciendo reaccionar 2,4-dicloro-6-metilpirimidin-5-carboxilato de metilo con 3-fluoroanilina en lugar de m-toluidina. El producto final se purificó mediante HPLC preparativa de fase inversa. La liofilización dio una sal TFA del compuesto del título en forma de un sólido de color blanco. 1H RMN (400 MHz, DMSO-d6) δ ppm 1,29 - 1,56 (m, 2 H), 1,56 - 1,73 (m, 4 H), 1,77 -1,85 (br s, 2 H), 4,22 (br s, 4 H), 6,90 (br s, 1 H), 7,25 - 7,44 (m, 2 H), 7,48 (br s, 1 H), 7,77 (br s, 3 H), 8,20 (d, J=13,64 Hz, 1 H), 8,83 (d, J=14,40 Hz, 1 H). [M+H] calc para C18H21FN6O357; experimental, 357.

[0199] Ejemplo 3: 2-((1R,2S)-2-aminociclohexilamino)-4-(3-clorofenilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona

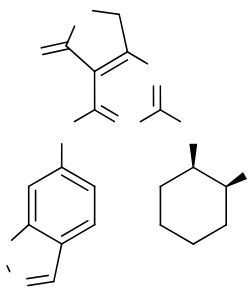




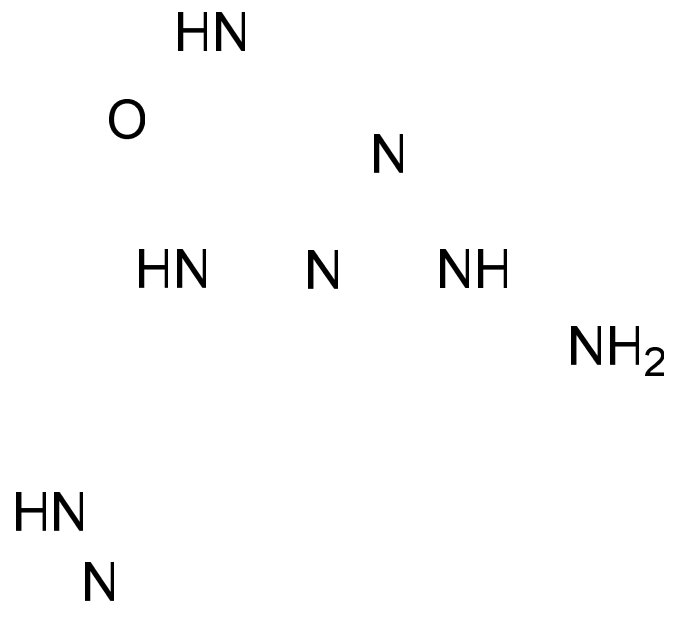
[0200] El compuesto del título se preparó de manera similar al ejemplo 1 haciendo reaccionar 2,4-dicloro-6-metilpirimidin-5-carboxilato de metilo con 3-cloroanilina en lugar de m-toluidina. El producto final se purificó mediante HPLC preparativa de fase inversa. La liofilización dio una sal TFA del compuesto del título en forma de un sólido de color blanco. 1H RMN (400 MHz, DMSO-d6) δ ppm 1,43 (br s, 2 H), 1,67-1,96 (m, 6 H), 4,20 (br s, 3 H), 7,13 (d, J=7,33 Hz, 1 H), 7,36 (t, J=8,08 Hz, 1 H), 7,48 (br s, 1 H), 7,75 (br s, 2 H), 8,16 (br s, 1 H), 8,82 (br s, 1 H). [M+H] calc para C18H21ClN6O373; experimental, 373.



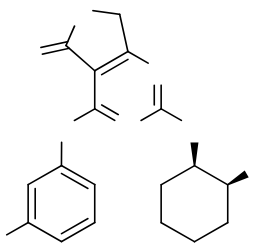
[0201] Ejemplo 4: 4-(1H-indazol-6-ilamino)-2-((1R,2S)-2-aminociclohexilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona



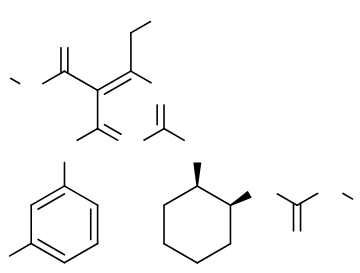
[0202] El compuesto del título se preparó de manera similar al ejemplo 1 haciendo reaccionar 2,4-dicloro-6-metilpirimidin-5-carboxilato de metilo con 1H-indazol-6-amina en lugar de m-toluidina. El producto final se purificó mediante HPLC preparativa de fase inversa. La liofilización dio una sal TFA del compuesto del título en forma de un sólido de color blanco. 1H RMN (400 MHz, DMSO-d6) δ ppm 1,43-1,92 (br s, 8 H), 2,33 (s, 1 H), 3,57 (m, 1 H), 4,21 (br s, 2 H), 6,94 (s, 1 H), 7,07 (s, 1 H), 7,14 - 7,31 (m, 1 H), 7,43 (m, 1 H), 7,71 (d, J=8,59 Hz, 2 H), 8,01 (s, 1 H), 8,14 (br s, 1 H), 8,84 (s, 1 H), 12,99 (br s, 1 H). [M+H] calc para C19H22N8CO379; experimental, 379.



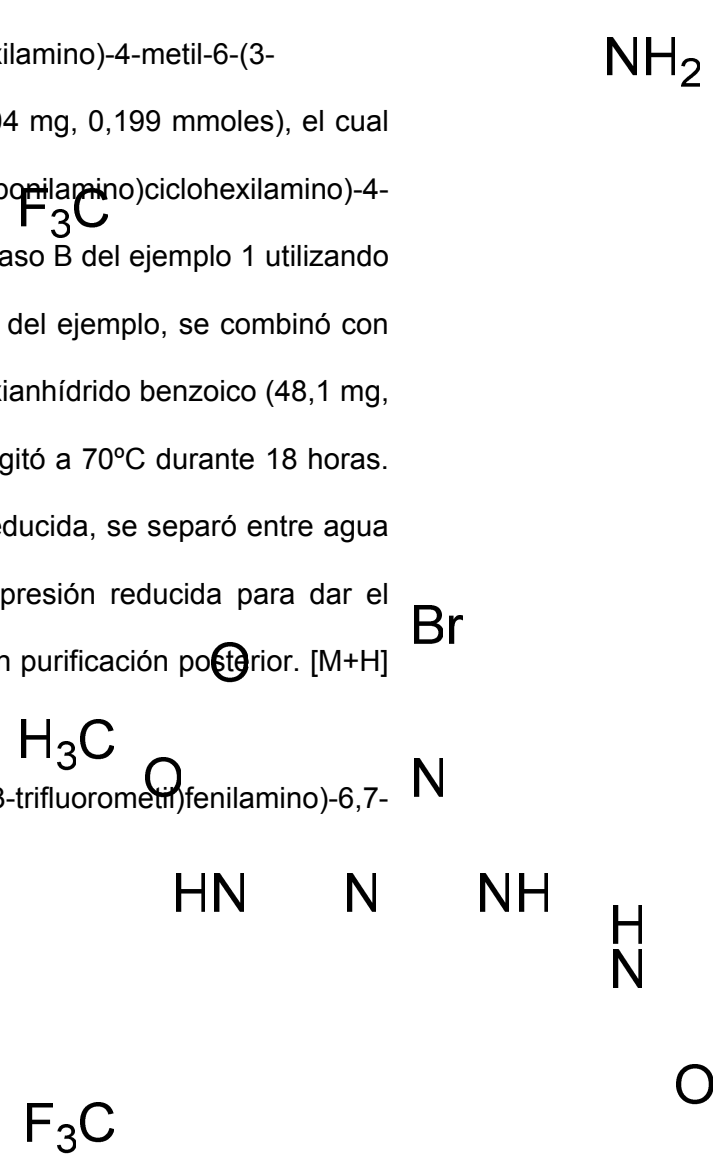
[0203] Ejemplo 5: 2-((1R,2S)-2-aminociclohexilamino)-4-(3-trifluorometil)fenilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona



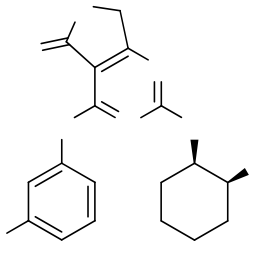
[0204] A. 4-(bromometil)-2-((1R,2S)-2-(ter-butoxicarbonilamino)ciclohexilamino)-6-(3-(trifluorometil)fenilamino)pirimidin-5-carboxilato de metilo



[0205] 2-((1R,2S)-2-(ter-butoxicarbonilamino)ciclohexilamino)-4-metil-6-(3-(trifluorometil)fenilamino)pirimidin-5-carboxilato de metilo (104 mg, 0,199 mmoles), el cual se preparó de manera similar a 2-((1R,2S)-2-(ter-butoxicarbonilamino)ciclohexilamino)-4-metil-6-(m-tolilamino)pirimidin-5-carboxilato de metilo en el paso B del ejemplo 1 utilizando 3-(trifluorometil)anilina en lugar de m-toluidina en el paso A del ejemplo, se combinó con 1-bromopirrolidin-2,5-diona (53,0 mg, 0,298 mmoles) y peroxianhídrido benzoico (48,1 mg, 0.199 mmoles) en CCl4 (10 ml), y la mezcla resultante se agitó a 70ºC durante 18 horas. La reacción se detuvo. La mezcla se concentró a presión reducida, se separó entre agua y EtOAc. El extracto orgánico se secó y se concentró a presión reducida para dar el compuesto del título, el cual se utilizó en el próximo paso sin purificación posterior. [M+H] calc para C25H31BrN5CO4, 603; experimental, 604.

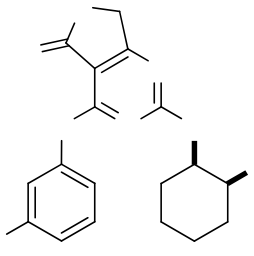


[0206] B. 2-((1R,2S)-2-aminociclohexilamino)-4-(3-trifluorometil)fenilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona

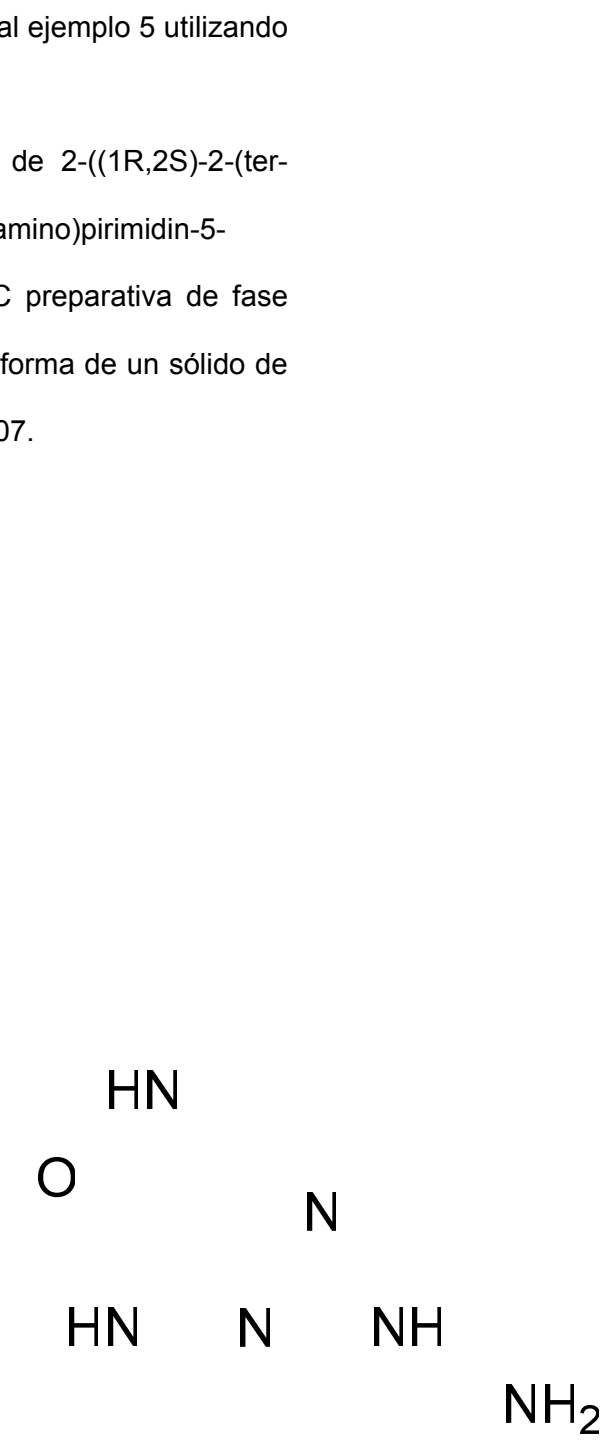


[0207] Una mezcla de 4-(bromometil)-2-((1R,2S)-2-(ter-butoxicarbonilamino)ciclohexilamino)-6-(3-(trifluorometil)fenilamino)pirimidin-5-carboxilato de metilo (120 mg, 0,199 mmoles) en THF se trató con hidróxido de amonio. La mezcla de reacción se agitó a temperatura ambiente durante toda la noche, y posteriormente se elaboró y se purificó por HPLC preparativa de fase inversa. Las fracciones e recolectaron, se concentraron a presión reducida para dar un residuo, el cual se trató con TFA/DCM. El producto final se purificó mediante HPLC preparativa. La liofilización dio una sal TFA del compuesto del título en forma de un sólido de color blanco (26 mg, 3%). [M+H] calc para C19H21N3N6O, 407; experimental, 407.

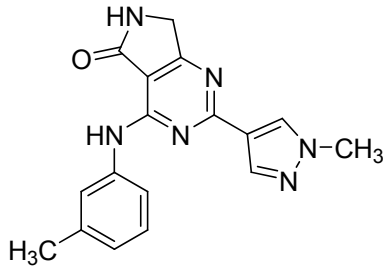
[0208] Ejemplo 6: cis-2-(2-aminociclohexilamino)-4-(3-(trifluorometil)fenilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona



[0209] El compuesto del título se preparó de manera similar al ejemplo 5 utilizando cis-2-(2-(ter-butoxicarbonilamino)ciclohexilamino)-4-metil-6-(3-(trifluorometil)fenilamino)pirimidin-5-carboxilato de metilo en lugar de 2-((1R,2S)-2-(ter-butoxicarbonilamino)ciclohexilamino)-4-metil-6-(3-(trifluorometil)fenilamino)pirimidin-5-carboxilato de metilo. El producto final se purificó mediante HPLC preparativa de fase inversa. La liofilización dio una sal TFA del compuesto del título en forma de un sólido de color blanco. [M+H] calc para C19H21N3N6O, 407; experimental, 407.

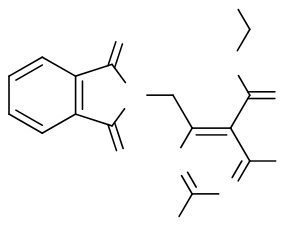


[0210] Ejemplo 7: 2-(1-metil-1H-pirazol-4-il)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona

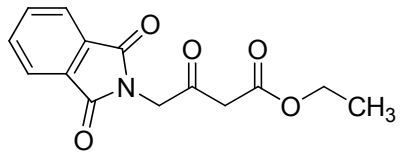


[0211] Una sal TFA del compuesto del título se preparó de manera similar al ejemplo 1 utilizando 1-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol en lugar de (1S,2R)-2-aminociclohexilcarbamato de ter-butilo. 1H RMN (500 MHz, DMSO-d6) δ ppm 2,37 (s, 3 H), 3,93 (s, 3 H), 4,39 (s, 2 H), 6,95 (d, J = 7,32 Hz, 1 H), 7,32 (t, J = 7,81 Hz, 1 H), 7,62 (s, 1 H), 7,77 (d, J = 8,30 Hz, 1 H), 8,03 (s, 1 H), 8,37 (s, 1 H), 8,65 (s, 1 H), 8,82 (s, 1 H). [M+H] calc para C17H16N6O, 321; experimental, 321.

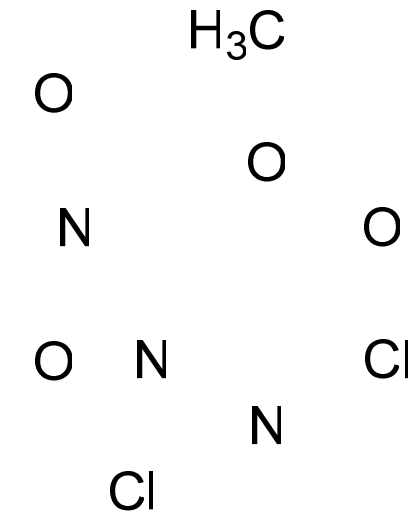
[0212] Preparación 3: 2,4-dicloro-6-((1,3-dioxoisoindolin-2-il)metil)pirimidin-5-carboxilato de etilo



[0213] A. 4-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-3-oxobutanoato de etilo

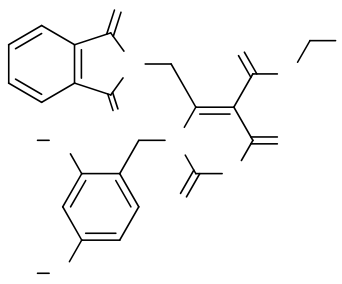


[0214] A una solución del ácido 2-(1,3-dioxoisoindolin-2-il)acético (3,01 g, 14,67 mmoles), 2,2-dimetil-1,3-dioxano-4,6-diona (2.23 g, 15.47 mmoles) y 4-dimetilaminopiridina (2.73 g, 22.35 mmoles) en diclorometano (150 ml) se agregó una solución de DCC (3.36 g, 16.28 mmoles) en DCM (50 ml) a 0ºC. La mezcla se agitó a

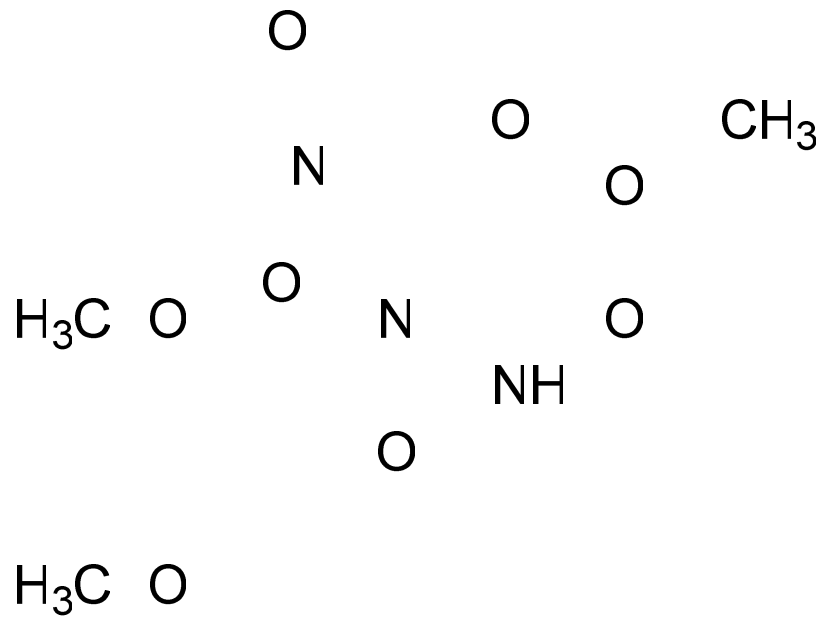


temperatura ambiente durante 16 horas. Los materiales insolubles se filtraron, y el filtrado se lavó con 5% de solución acuosa de NaHSO4 La fase orgánica se secó sobre Na2SO4 anhidro, se filtró y el filtrado se concentró bajo presión reducida. El residuo se trató con EtOH (200 ml) y la mezcla resultante se agitó a 70ºC durante 4 horas y a continuación se concentró a presión reducida. Se agregó agua al residuo y la mezcla se extrajo con EtOAc. Las capas orgánicas se lavaron con agua y salmuera, se secaron sobre MgSO4 anhidro, y se filtraron. El filtrado se concentró a presión reducida y el residuo se lavó con IPE para dar el compuesto del título en forma de un sólido incoloro (3,43 g, 85%).. 1H RMN (400 MHz, CDCl3) δ ppm 1,31 (t, J=6,8Hz, 3H,), 3,58 (s, 2H), 4,24 (q, J=6,8 Hz, 2H), 4,67 (s, 2H), 7,73 - 7,78 (m, 2H), 7,86 - 7,91 (m, 2H).

[0215] B.1-(2,4-dimetoxibencil)-6-((1,3-dioxoisoindolin-2-il)metil)-2,4-dioxo-1,2,3,4-tetrahidropirimidin-5-carboxilato de etilo

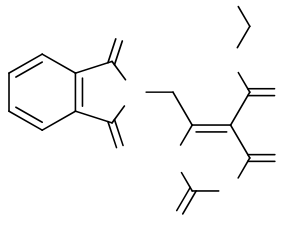


[0216] Una mezcla de 4-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-3-oxobutanoato de etilo (249,8 mg, 0,908 mmoles) y (2,4-dimetoxifenil)metanamina (152 mg, 0,908 mmoles) en EtOH (4 ml) se agitó a 50ºC durante 16 horas. El sólido obtenido se aisló por filtración para dar un sólido incoloro (51,7 mg). A una suspensión del sólido en THF (4 ml) se agregó cloruro de carbonisocianatídico (96 mg, 0,908 mmoles) y la mezcla se agitó a 80ºC durante 1 hora. Después de enfriar hasta temperatura ambiente, se agregó agua (10 ml) y la mezcla se extrajo con EtOAc. Las capas orgánicas se lavaron con salmuera, se secaron sobre Na2SO4 anhidro, y se filtraron. El filtrado se concentró a presión reducida y el residuo se purificó por cromatografía de columna (SiO2, hexano/EtOAc=1/1) para dar el compuesto del título (56,2 mg, 13%). 1H RMN (400 MHz, CDCl3) δ ppm 1,28 (t, J=7,2Hz,



3H), 3,63 (s, 3H), 3,81 (s, 3H), 4,22 (q, J=7,2Hz, 2H), 4,95 (s, 2H), 5,12 (s, 2H), 6,18 (dd, J=8,4, 6,4Hz, 1H), 6,23 (d, J=6,4Hz, 1H), 6,75 (d, J=8,4Hz, 1H), 7,63 - 7,72 (m, 4H), 8,23 (br s, 1H).

[0217] C.6-(6-((1,3-dioxoisoindolin-2-il)metil)-2,4-dioxo-1,2,3,4-tetrahidropirimidin-5-carboxilato de etilo



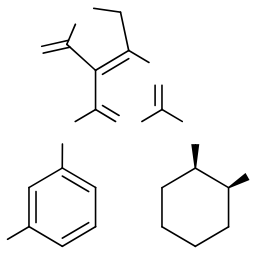
[0218] Al ácido trifluoroacético (2 ml, 26,0 mmoles) se agregó 1-(2,4-dimetoxibencil)-6-((1,3-dioxoisoindolin-2-il)metil)-2,4-dioxo-1,2,3,4-tetrahidropirimidin-5-carboxilato de etilo (198,9 mg, 0,403 mmoles) a 0ºC. La mezcla se agitó a 01C durante 1 hora, a continuación a temperatura ambiente durante 6 horas. La mezcla se concentró a presión reducida, y el residuo se lavó con IPE (5 ml) para dar el compuesto del título (183,3 mg). 1H RMN (400 MHz, CDCl3) δ ppm 1,42 (t, J=7,2Hz, 3H), 4,45 (q, J=7,2Hz, 2H), 4,98 (s, 2H), 7,78 - 7,81 (m, 2H), 7,91 - 7,93 (m, 2H), 8,19 (br s, 1H), 8,96 (br s, 1H).

[0219] D. 2,4-dicloro-6-((1,3-dioxoisoindolin-2-il)metil)pirimidin-5-carboxilato de etilo

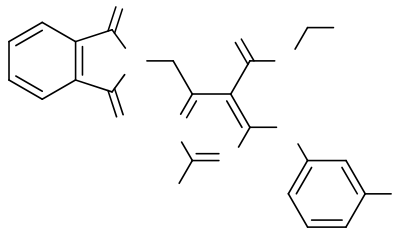
[0220] Una mezcla de 6-((1,3-dioxoisoindolin-2-il)metil)-2,4-dioxo-1,2,3,4-tetrahidropirimidin-5-carboxilato de etilo (96,1 mg, 0,280 mmoles) y oxicloruro fosforeso (1 ml, 10,92 mmoles) se agitó a 100ºC durante 12 horas y se dejó enfriar. La mezcla se concentró bajo presión reducida para eliminar el exceso de POCl3. El residuo se trató con NaHCO3 acuoso saturado y se extrajo con EtOAc. La fase orgánica se lavó con NaHCO3 acuoso saturado, agua, y salmuera, se secó sobre Na2SO4 anhidro, y a continuación se filtró a través de SiO2. El filtrado se concentró a presión reducida y el residuo se purificó por cromatografía de columna (SiO2, hexano/EtOAc=4/1) para dar el compuesto del título

(46,0 mg, 43%). 1H RMN (400 MHz, CDCl3) δ ppm 1,42 (t, J=7,2Hz, 3H), 4,45 (q, J=7,2Hz, 2H), 5,05 (s, 2H), 7,76 - 7,80 (m, 2H), 7,89 - 7,93 (m, 2H).

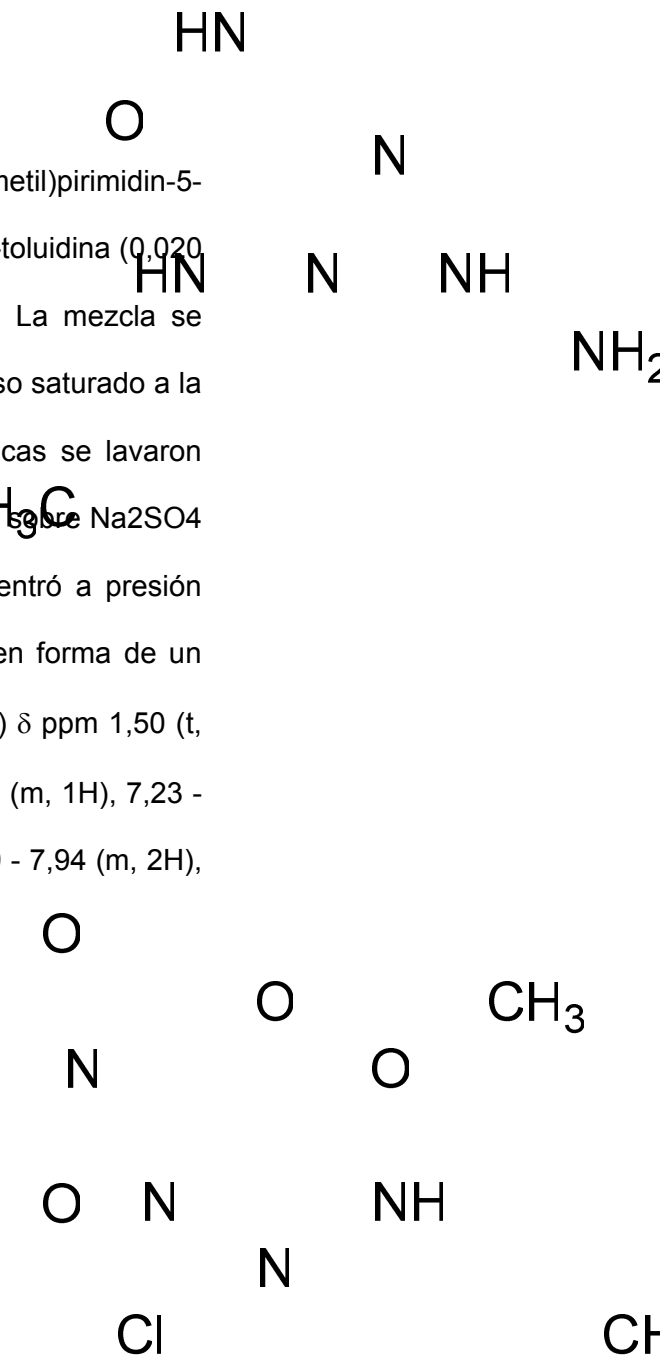
[0221] Ejemplo 8: 2-((1R,2S)-2-aminociclohexilamino)-4-(3-trifluorometil)fenilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona (base libre)



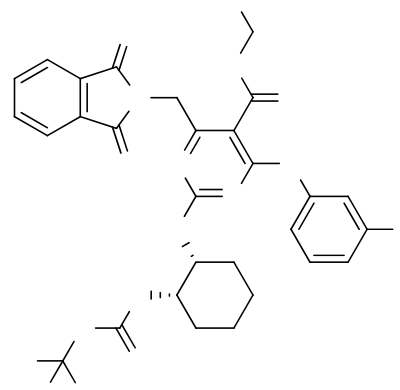
[0222] A. 2-cloro-4-((1,3-dioxoisoindolin-2-il)metil)-6-(m-tolilamino)pirimidin-5-carboxilato de etilo



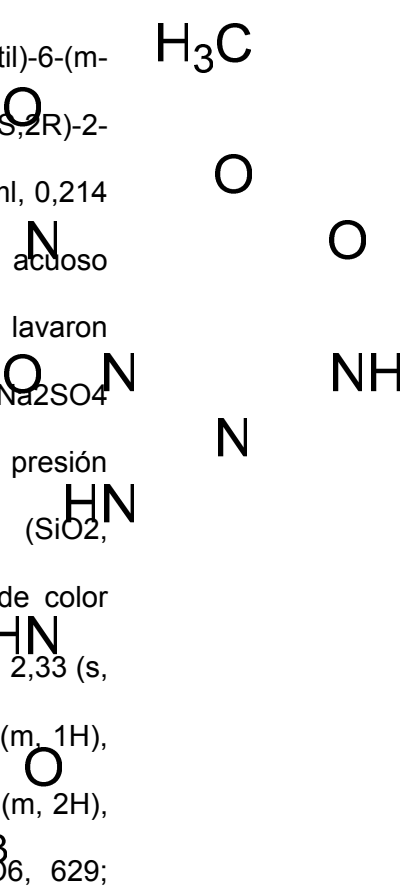
[0223] A una solución de 2,4-dicloro-6-((1,3-dioxoisoindolin-2-il)metil)pirimidin-5-carboxilato de etilo (45,3 mg, 0,119 mmoles) en MeCN (1 ml) se agregó m-toluidina (0,020 ml, 0.187 mmoles) y N,N-diisopropiletilamina (0,037 ml, 0,212 mmoles). La mezcla se agitó a temperatura ambiente durante 12 horas. Se agregó NaHCO3 acuoso saturado a la mezcla, la cual se extrajo posteriormente con EtOAc. Las capas orgánicas se lavaron nuevamente con NaHCO3 acuoso saturado, agua, y salmuera, se secaron sobre Na2SO4 anhidro, y a continuación se filtró a través de SiO2. El filtrado se concentró a presión reducida y el residuo se lavó con IPE para dar el compuesto del título en forma de un sólido de color marrón pálido (37,1 mg, 69%). 1H RMN (400 MHz, CDCl3) δ ppm 1,50 (t, J=7,2Hz, 3H), 2,36 (s, 3H), 4,52 (q, J=7,2Hz, 2H), 5,20 (s, 2H), 6,97 - 6,98 (m, 1H), 7,23 - 7,27 (m, 1H), 7,33 (br s, 1H), 7,45 - 7,47 (m, 1H), 7,73 - 7,78 (m, 2H), 7,89 - 7,94 (m, 2H), 10,67 (br s, 1H).



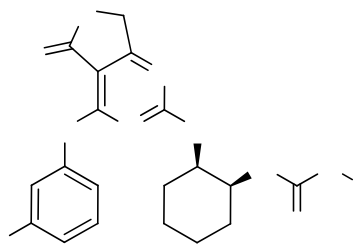
[0224] B. 2-((1R,2S)-2-(ter-butoxicarbonilamino)ciclohexilamino)-4-((1,3-dioxoisoindolin-2-il)metil)-6-(m-tolilamino)pirimidin-5-carboxilato de etilo



[0225] Una mezcla de 2-cloro-4-((1,3-dioxoisoindolin-2-il)metil)-6-(m-tolilamino)pirimidin-5-carboxilato de etilo ((96,3 mg, 0,214 mmoles), (1S,2R)-2-aminociclohexilcarbamato de ter-butilo (58,14 mg, 0,271 mmoles) y Et3N (0,030 ml, 0,214 mmoles) en DMA (2 ml) se agitó a 80ºC durante 3 horas, Se agregó NaHCO3 acuoso saturado, el cual se extrajo con EtOAc. Las capas orgánicas combinadas se lavaron nuevamente con NaHCO3 acuoso saturado, agua, y salmuera, se secaron sobre Na2SO4 anhidro, y a continuación se filtró a través de SiO2. El filtrado se concentró a presión reducida y el residuo se purificó por cromatografía de columna (SiO2, hexanos/EtOAc=3/1) para dar el compuesto del título en forma de un aceite de color amarillo (123,8 mg, 92%). 1H RMN (400 MHz, CDCl3) δ ppm 1,12 - 1,71 (m, 20H), 2,33 (s, 3H), 3,39 - 3,57 (m, 1H), 3,84 - 3,99 (m, 1H), 4,42 (q, J=7,2Hz, 2H), 4,55 - 4,79 (m, 1H), 5,16 (s, 2H), 5,41 (br s, 1H), 6,87 - 6,89 (m, 1H), 7,16 - 7,49 (m, 3H), 7,74 - 7,75 (m, 2H), 7,90 - 7,91 (m, 2H), 10,68 - 10,81 (m, 1H). [M+H] calc para C34H41N6O6, 629; experimental, 629.



[0226] C. (1S,2R)-2-(5-oxo-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-2-ilamino)ciclohexilcarbamato de ter-butilo



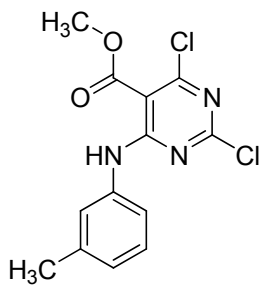
[0227] Una mezcla de 2-((1R,2S)-2-(ter-butoxicarbonilamino)ciclohexilamino)-4-((1,3-dioxoisoindolin-2-il)metil)-6-(m-tolilamino)pirimidin-5-carboxilato de etilo (109 mg, 0,174 mmoles) e hidrato hidrazina (36,5 mg, 0,729 mmoles) en EtOH (2 ml) se agitó a 65ºC durante 12 horas. Después de enfriar, la mezcla se concentró a presión reducida y el residuo se trató con agua y se extrajo con EtOAc. Las capas orgánicas combinadas se lavaron con NaHCO3 acuoso, agua, y salmuera, se filtraron a través de SiO2, y el filtrado se concentró bajo presión reducida. El residuo se recristalizó a partir de EtOAc/hexanos y se filtró para dar el compuesto del título (34,8 mg). El filtrado se concentró y se trituró con IPE para dar un segundo lote (20,3 mg) del compuesto del título (total 65,1 mg, 83%). 1H RMN (400 MHz, DMSO-d6) δ ppm 1,24 - 1,79 (m, 17H), 2,32 (s, 3H), 3,84 (br s, 1H), 4,06 (br s, 1H), 4,14 (s, 2H), 6,55 - 6,70 (m, 1H), 6,87 - 7,04 (m, 2H), 7,20 - 7,24 (m, 1H), 7,40 - 7,48 (m, 1H), 7,68 - 7,80 (m, 1H), 8,01 - 8,06 (m, 1H), 8,56 - 8,59 (m, 1H). [M+H] calc para C24H33N6O3, 453; experimental, 453.

[0228] D. 2-((1R,2S)-2-aminociclohexilamino)-4-(3-(trifluorometil)fenilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona

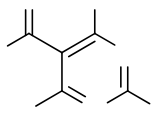
[0229] A una solución de (1S,2R)-2-(5-oxo-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-2-ilamino)ciclohexilcarbamato de ter-butilo (50,4 mg, 0,111 mmoles) en HOAc (2 ml) se agregó ácido clorhídrico (0,5 ml, 16,46 mmoles). La mezcla se agitó a temperatura ambiente durante 30 min. y a continuación se concentró a presión reducida. El residuo se trató con NaHCO3 acuoso saturado y se extrajo con EtOAc. Las capas orgánicas se lavaron nuevamente con NaHCO3 acuoso saturado, agua, y salmuera, se secaron sobre Na2SO4 anhidro, y a continuación se filtró. El filtrado se concentró a

presión reducida y el residuo se purificó por cromatografía de columna (SiO2, EtOAc/MeOH=20/1) para dar el compuesto del título en forma de un polvo de color blanco (11,3 mg, 29%). 1H RMN (400 MHz, CDCl3) δ ppm 1,48 - 1,80 (m, 10H), 2,37 (s, 3H), 3,24 (br s, 1H), 4,07 (br s, 1H), 4,20 (s, 2H), 5,55 (br s, 1H), 5,89 (br s, 1H), 6,89 - 6,91 (m, 1H), 7,22 - 7,24 (m, 1H), 7,53 - 7,63 (m, 2H), 8,49 (br s, 1H). [M+H] calc para C19H25N6O, 353; experimental, 353.

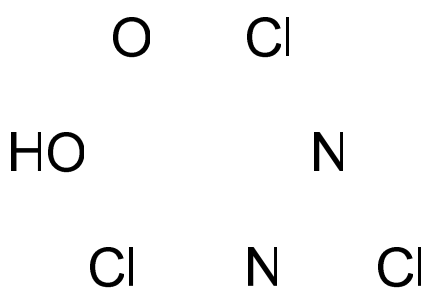
[0230] Preparación 4: 2,4-dicloro-6-(m-tolilamino)pirimidin-5-carboxilato de metilo.



[0231] A. Ácido 2,4,6-tricloropirimidin5-carboxílico

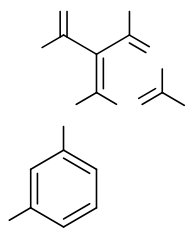


[0232] A una solución de diisopropilamina (23,42 ml, 164 mmoles) en THF (200 ml) se agregó lentamente butillitio (100 ml, 160 mmoles) a -78ºC. La mezcla se agitó a -78ºC durante 15 min. A esta mezcla se agregó lentamente una solución de 2,4,6-tricloropirimidina (20,06 g, 109 mmoles) en THF (50 ml) a 78ºC. La mezcla se agitó durante 1 hora. Se agregó hielo seco y la mezcla se agitó a temperatura ambiente durante 1 hora. A la mezcla se agregó HCl 1N, la cual se extrajo posteriormente con EtOAc. Las capas orgánicas se basificaron con NaHCO3 acuoso, y se lavaron con EtOAc. La capa acuosa se acidificó a continuación con HCl 1N, y se extrajo con EtOAc. Las capas orgánicas se lavaron con HCl 1N, agua, y salmuera, se secaron sobre MgSO4 anhidro, y a continuación se filtraron. El filtrado se concentró bajo presión reducida. El residuo se lavó con hexano para dar el producto deseado en forma de un sólido de color marrón

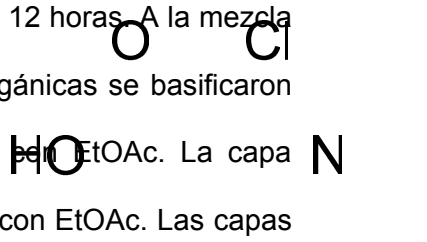


pálido (12,28 g, 49%). 1H RMN (500 MHz, CDCl3) δ ppm 7,65 (br s, 1H).

[0233] B. Ácido 2,4-dicloro-6-(m-tolilamino)pirimidin-5-carboxílico



[0234] A una solución del ácido 2,4,6-tricloropirimidin-5-carboxílico (5,69 g, 25,02 mmoles) en DMF (60 ml) se agregó Et3N (8 ml, 57.4 mmoles) y m-toluidina (3,2 ml, 29,5 mmoles) a 0°C. La mezcla se agitó a temperatura ambiente durante 12 horas. A la mezcla se agregó HCl 1N. La mezcla se extrajo con EtOAc. Las capas orgánicas se basificaron con NaHCO3 acuoso saturado, y las capas acuosas se lavaron con EtOAc. La capa acuosa lavada se acidificó a continuación con HCl 1N, y se extrajo con EtOAc. Las capas orgánicas combinadas se lavaron con HCl 1N, agua, y salmuera, se secaron sobre Na2SO4 anhidro, y a continuación se filtraron. El filtrado se concentró a presión reducida, se trituró con hexano, y se filtró para dar un primer lote del compuesto del título (4,36 g). El filtrado se concentró, se trituró con hexano, y se filtró para dar un segundo lote (0,36 g) del compuesto del título (total 4,72g, 63%). 1H RMN (500 MHz, DMSO-d6) δ ppm 2,30 (s, 3H), 7,00 - 7,02 (m, 1H), 7,25 - 7,28 (m, 2H), 7,33 - 7,35 (m, 2H), 10,13 (s, 1H), 1H no detectado. [M+H] calc para C12H10Cl2N3O2, 298; experimental, 298.

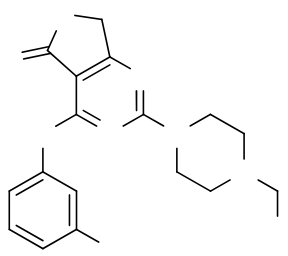


[0235] C. 2,4-dicloro-6-(m-tolilamino)pirimidin-5-carboxilato de metilo.

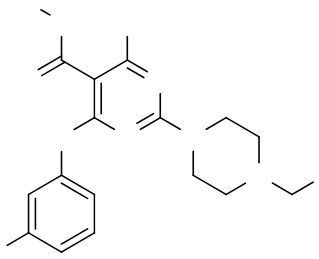
[0236] A una solución del ácido 2,4-dicloro-6-(m-tolilamino)pirimidin-5-carboxílico (7,67 g, 25,7 mmoles) en DMF (80 ml) se agregó NaHCO3 (3,30 g, 39,3 mmoles) y yodometano (1,605 ml, 25,7 mmoles) a 0ºC. La mezcla se agitó a temperatura ambiente durante 14 horas, después de lo cual se agregó NaHCO3 acuoso saturado. La mezcla se extrajo con EtOAc. Las capas orgánicas se lavaron nuevamente con NaHOC3 acuoso saturado, agua, y salmuera, se secaron sobre Na2SO4 anhidro, y a continuación se

filtraron a través de SiO2. El filtrado se concentró bajo presión reducida. El residuo se trituró con éter isopropílico y se filtró para dar un primer lote (5,28 g) del compuesto del título. El filtrado se concentró, se trituró con hexano, y se filtró para dar un segundo lote (0,66 g) del compuesto del título en forma de un sólido de color amarillo (total 5,94 g, 74%). 1H RMN (500 MHz, CDCl3) δ ppm 2,38 (s, 3H), 4,00 (s, 3H), 7,02 - 7,03 (m, 1H), 7,27 - 7,33 (m, 2H), 7,44 - 7,46 (m, 1H), 10,30 (br s, 1H). [M+H] calc para C12H12Cl2N3O2, 312; experimental, 312.

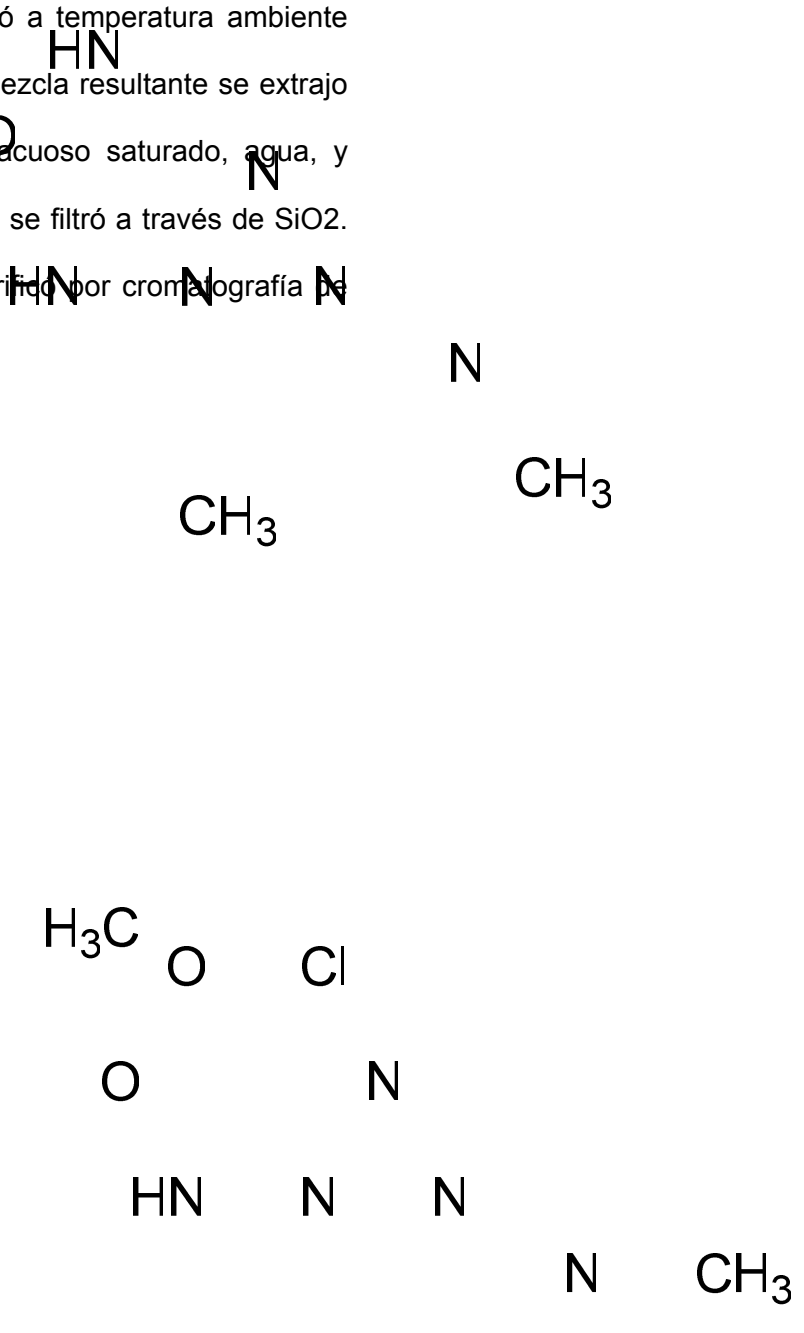
[0237] Ejemplo 9: 2-(4-etilpiperazin-1-il)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona



[0238] A. 4-cloro-4-2-(4-etilpiperazin-1-il)-6-(m-tolilamino)pirimidin-5-carboxilato de metilo

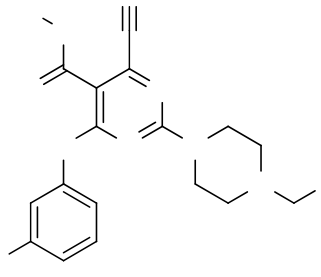


[0239] Una mezcla de 2,4-dicloro-6-(m-tolilamino)pirimidin-5-carboxilato de metilo (502,6 mg, 1,610 mmoles), N-etildiisopropilamina (0,3 ml, 1,718 mmoles) y N-etilpiperazina (0,21 ml, 1,653 mmoles) en THF (8 ml) se agitó a temperatura ambiente durante 12 horas. Se agregó NaHCO3 acuoso saturado y la mezcla resultante se extrajo con EtOAc. Las capas orgánicas se lavaron con NaHCO3 acuoso saturado, agua, y salmuera, se secaron sobre Na2SO4 anhidro, y a continuación se filtró a través de SiO2. El filtrado se concentró a presión reducida y el residuo se purificó por cromatografía de

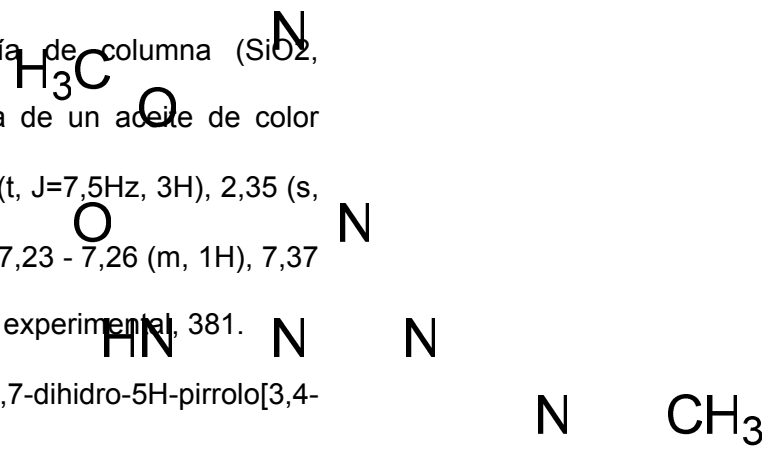


columna (SiO2, hexano/EtOAc=4/1) para dar el compuesto del título (152,6 mg, 24%). 1H RMN (500 MHz, CDCl3) δ ppm 1,12 (t, J=6,5Hz, 3H), 2,35 (s, 3H), 2,48 (br s, 6H), 3,82 - 3,97 (m, 7H), 6,92 - 6,93 (m, 1H), 7,21 - 7,22 (m, 1H), 7,37 - 7,42 (m, 2H), 10,45 (s, 1H). [M+H] calc para C19H25ClN5O2, 390; experimental, 390.

[0240] B. 4-ciano-4-2-(4-etilpiperazin-1-il)-6-(m-tolilamino)pirimidin-5-carboxilato de metilo



[0241] Una mezcla de 4-cloro-4-2-(4-etilpiperazin-1-il)-6-(m-tolilamino)pirimidin-5-carboxilato de metilo (152,6 mg, 0,391 mmoles), tetrakis(trifenilfosfina)paladio (40,8 mg, 0,035 mmoles) y cianuro de zinc (II) (25,2 mg, 0,215 mmoles) en DMF (3 ml) se agitó a 90ºC durante 3 horas. Se agregó agua y la mezcla resultante se extrajo con EtOAc. Las capas orgánicas se lavaron con NaHCO3 acuoso, agua, y salmuera, se secaron sobre Na2SO4 anhidro, y a continuación se filtró a través de SiO2. El filtrado se concentró a presión reducida y el residuo se purificó por cromatografía de columna (SiO2, hexanos/EtOAc=5/1) para dar el compuesto del título en forma de un aceite de color amarillo (51,1 mg, 34%). 1H RMN (500 MHz, CDCl3) δ ppm 1,12 (t, J=7,5Hz, 3H), 2,35 (s, 3H), 2,44 - 2,49 (m, 6H), 3,81 - 3,98 (m, 7H), 6,95 - 6,96 (m, 1H), 7,23 - 7,26 (m, 1H), 7,37 - 7,47 (m, 2H), 10,46 (s, 1H). [M+H] calc para C20H25N6O2, 381; experimental, 381.

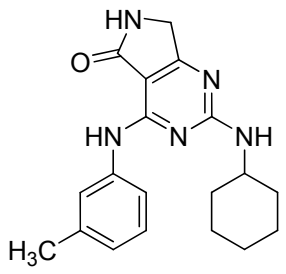


[0242] C. 2-(4-etilpiperazin-1-il)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona

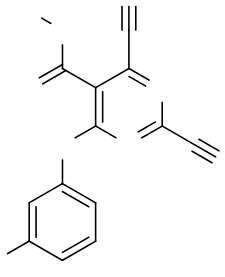
[0243] Una mezcla de 4-ciano-4-2-(4-etilpiperazin-1-il)-6-(m-tolilamino)pirimidin-5-carboxilato de metilo (49,8 mg, 0,131 mmoles) y paladio sobre carbono (10,1 mg) en EtOH (3 ml) y HCl 1N (3 ml) se agitó a temperatura ambiente durante 2 horas en una

atmósfera de hidrógeno. Los materiales insolubles se filtraron y el filtrado se concentró a presión reducida. El residuo se trató con NaHCO3 acuoso y EtOAc durante 3 horas. La mezcla se extrajo con EtOAc. Las capas orgánicas se lavaron con NaHCO3 acuoso saturado, agua, y salmuera, se secaron sobre Na2SO4 anhidro, y a continuación se filtró. El filtrado se concentró a presión reducida y el residuo se purificó por cromatografía de columna (SiO2, EtOAc a continuación DM1020 EtOAc/MeOH=20/1) para dar el compuesto del título en forma de un sólido de color blanco (19,8 mg, 43%). 1H RMN (500 MHz, CDCl3) δ ppm 1,19 (br s, 3H), 2,36 (s, 3H), 2,5 (br s, 6H), 4,08 (br s, 4H), 4,23 (s, 2H), 5,50 (s, 1H), 6,91 - 6,92 (m, 1H), 7,22 - 7,26 (m, 1H), 7,49 - 7,54 (m, 2H), 8,44 (s, 1H). [M+H] calc para C19H25N6O, 353; experimental, 353.

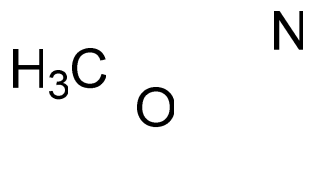
[0244] Ejemplo 10: 2-(ciclohexilamino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona



[0245] A. 2,4-diciano-6-(m-tolilamino)pirimidin-5-carboxilato de metilo.

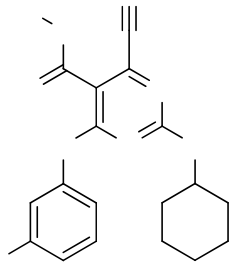


[0246] Una mezcla de 2,4-dicloro-6-(m-tolilamino)pirimidin-5-carboxilato de metilo (500,5 mg, 1,603 mmoles), cianuro de zinc (II) (100,7 mg, 0,857 mmoles y tetrakis(trifenilfosfina)paladio (187,3 mg, 0,162 mmoles) en DMF (5 ml) se agitó a 120ºC durante 1 hora en un horno de microondas. Después de enfriar, se agregó NaHCO3

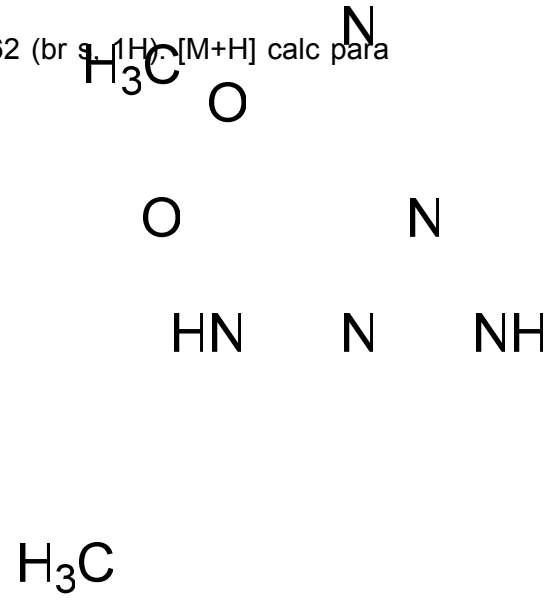


acuoso saturado y la mezcla se extrajo con EtOAc. Las capas orgánicas se lavaron con NaHCO3 acuoso, agua, y salmuera, se secaron sobre Na2SO4 anhidro, y a continuación se filtró a través de SiO2. El filtrado se concentró a presión reducida y el residuo se purificó por cromatografía de columna (SiO2, hexanos/EtOAc=4/1) para dar el compuesto del título en forma de un sólido de color amarillo (182,5 mg), el cual se lavó con IPE para dar el compuesto del título (117,5 mg). 1H RMN (500 MHz, CDCl3) δ ppm 2,41 (s, 3H), 4,12 (s, 3H), 7,10 - 7,12 (m, 1H), 7,31 - 7,35 (m, 2H), 7,42 - 7,43 (m, 1H), 10,65 (br s, 1H). [M+H] calc para C15H12N5O2, 294; experimental, 294.

[0247] B. 4-ciano-4-2-(ciclohexilamino)-6-(m-tolilamino)pirimidin-5-carboxilato de metilo



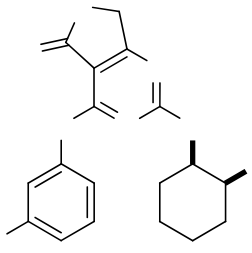
[0248] Una mezcla de 2,4-dicloro-6-(m-tolilamino)pirimidin-5-carboxilato de metilo (102,3 mg, 0,349 mmoles), N,N-diisopropilamina (0,075 ml, 0,429 mmoles) y ciclohexilamina (0,05 ml, 0,437 mmoles) en DMF (2 ml) se agitó a temperatura ambiente durante 14 horas. Se agregó NaHCO3 acuoso saturado y la mezcla resultante se extrajo con EtOAc. Las capas orgánicas se lavaron con NaHCO3 acuoso, agua, y salmuera, y se filtraron a través de SiO2. El filtrado se concentró a presión reducida y el residuo se purificó por cromatografía de columna (SiO2, hexanos/EtOAc=4/1) para dar el compuesto del título en forma de un aceite de color amarillo (114,7 mg, 90%). 1H RMN (500 MHz, CDCl3) δ ppm 1,19 - 1,45 (m, 5H), 1,64 - 1,67 (m, 1H), 1,73 - 1,80 (m, 2H), 2,00 - 2,05 (m, 2H), 2,38 (s, 3H), 3,75 - 3,82 (m, 1H), 3,98 (s, 3H), 5,57 - 5,58 (br d, J=7,9Hz, 1H), 6,97 - 6,98 (m, 1H), 7,27 - 7,29 (m, 1H), 7,46 - 7,51 (m, 2H), 10,62 (br s, 1H). [M+H] calc para C20H24N5O2, 366; experimental, 366.



[0249] C. 2-(ciclohexilamino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona

[0250] Una mezcla de 4-ciano-2-(ciclohexilamino)-6-(m-tolilamino)pirimidin-5-carboxilato de metilo (112,6 mg, 0,308 mmoles) y paladio sobre carbono (26,4 mg, 0,248 mmoles) en MeOH (2 ml) y HCl (1N, 2 ml) se agitó a temperatura ambiente durante 4 horas en una atmósfera de hidrógeno. Se agregó NaHCO3 acuoso saturado y la mezcla se agitó durante 12 horas. La mezcla se filtró y el filtrado se concentró a presión reducida. El residuo se extrajo con EtOAc. Las capas orgánicas se lavaron con NaHCO3 acuoso, agua, y salmuera, se secaron sobre Na2SO4 anhidro, y a continuación se filtró a través de SiO2. El filtrado se concentró a presión reducida y el residuo se purificó por cromatografía de columna (SiO2, EtOAc) para dar un sólido de color blanco (72,2 mg, 69%). El sólido de color blanco se recristalizó a partir de EtOH y dio el compuesto del título (35,2 mg). 1H RMN (500 MHz, DMSO-d6) δ ppm 1,14 - 1,17 (m, 1H), 1,24 - 1,34 (m, 4H), 1,62 - 1,63 (m, 1H), 1,73 - 1,78 (m, 2H), 1,89 - 1,97 (m, 2H), 2,33 (s, 3H), 3,74 - 3,83 (m, 1H), 4,12 - 4,17 (m, 2H), 6,86 - 6,88 (m, 1H), 7,20 - 7,23 (m, 1H), 7,42 - 7,52 (m, 2H), 7,76 (s, 1H), 8,00 - 8,05 (m, 1H), 8,53 - 8,57 (m, 1H). [M+H] calc para C19H24N5O, 338; experimental, 338.

[0251] Ejemplo 11: cis-2-(2-hidroxiciclohexilamino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona

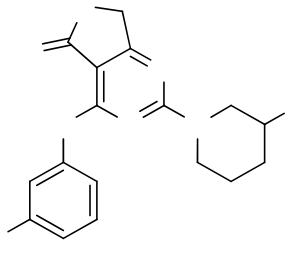


[0252] El compuesto anterior se preparó de manera similar al ejemplo 10 utilizando cis-2-aminociclohexanol en lugar de ciclohexilamina. 1H RMN (500 MHz, DMSO-d6) δ ppm 1,31 - 1,37 (m, 2H), 1,46 - 1,78 (m, 6H), 2,32 (s, 3H), 3,82 - 3,96 (m, 2H), 4,13 - 4,17 (m, 2H), 4,66 - 4,71 (m, 1H), 6,86 - 6,92 (m, 2H), 7,20 - 7,23 (m, 1H), 7,46

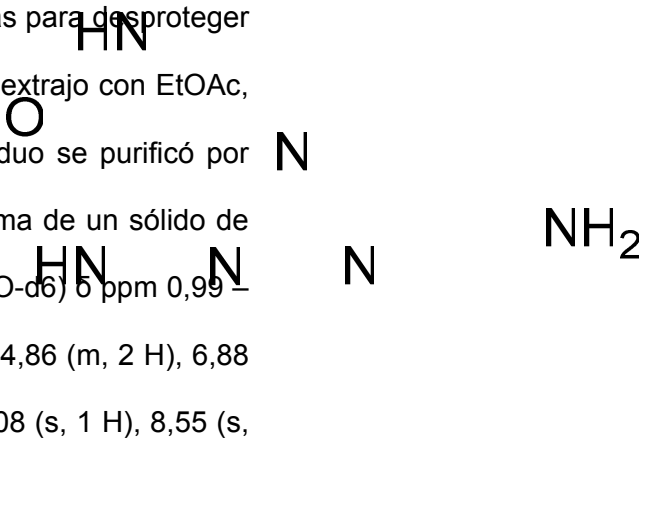
HN

- 7,50 (m, 1H), 7,71 - 7,77 (m, 1H), 8,03 - 8,08 (m, 1H), 8,58 - 8,59 (m, 1H). [M+H] calc para C19H24N5O2, 354; experimental, 354.

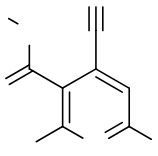
[0253] Ejemplo 12: 2-(3-aminopiperidin-1-il)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona



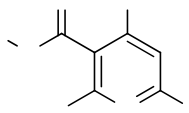
[0254] El compuesto anterior se preparó de manera similar al ejemplo 10 utilizando piperidin-3-ilcarbamato de en lugar de ter-butilo en lugar de ciclohexilamina. Siguiendo la ciclización, 1-(5-oxo-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-2-il)piperidin-3-ilcarbamato de ter-butilo (20,00 mg, 0,046 mmoles) se trató con 4M de HCl en dioxano (2 ml, 8,00 mmoles) a temperatura ambiente durante 5 horas para desproteger el grupo Boc. La mezcla se basificó posteriormente con NaOH 2N, se extrajo con EtOAc, se lavó con salmuera, se secó sobre MgSO4, y se evaporó. El residuo se purificó por recristalización (EtOH-hexano) para dar el compuesto del título en forma de un sólido de color blanco (10 mg, 64,8% de rendimiento). 1H RMN (500 MHz, DMSO-d6) δ ppm 0,99 – 2,03 (m, 4 H), 2,30 (s, 3 H), 2,57 – 3,07 (m, 3 H), 4,16 (s, 2 H), 4,26 – 4,86 (m, 2 H), 6,88 (d, J=5,6 Hz, 1 H), 7,23 (s, 1 H), 7,42 – 7,55 (m, 1 H), 7,59 (s, 1 H), 8,08 (s, 1 H), 8,55 (s, 1 H). [M+H] calc para C18H22N6O, 339; experimental, 339.



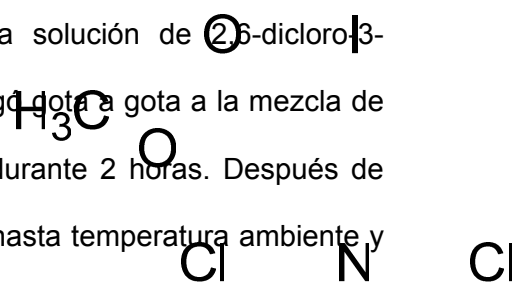
[0255] Preparación 5: 2,6-dicloro-4-cianonicotinato de metilo



[0256] 2,6-dicloro-4-yodonicotinato de metilo



[0257] Una solución de n-butillitio en hexano (1,6M, 120 ml, 192 mmoles) se agregó gota a gota a una solución de diisopropilamina (31,2 ml, 219 mmoles) en THF (200 ml) a -78ºC y la mezcla se agitó durante 30 min. Una solución de 2,6-dicloro-3-yodopiridina (50,0 g, 183 mmoles) en THF (100 ml) se agregó gota a gota a la mezcla de reacción a -78ºC y la mezcla resultante se agitó a -78ºC durante 2 horas. Después de agregar hielo a la mezcla de reacción, la mezcla se entibió hasta temperatura ambiente y se agitó durante toda la noche. La mezcla resultante se templó con H2O y la fase orgánica se lavó con H2O. La fase acuosa combinada se acidificó con HCl y se extrajo con CHCl3 (3 x). Las fases orgánicas se combinaron, se lavaron con salmuera, se secaron sobre MgSO4, y se evaporaron. Después que el residuo se disolvió en DMF (500 ml), se agregaron K2CO3 (39,2 g, 284 mmoles) y CH3I (17,73 ml, 284 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 3 horas. A la mezcla resultante se agregó HCl 1N y Et2O. La fase acuosa se extrajo con Et2O y las capas orgánicas combinadas se lavaron con H2O y salmuera, se secaron sobre MgSO4 y se evaporaron. El residuo se purificó por cromatografía sobre SiO2 para dar el compuesto del título en forma de un sólido de color blanco (7,24 g, 11%). 1H RMN (500 MHz, CDCl3) δ ppm 3,99 (s, 3 H), 7,77 (s, 1H). [M+H] calc para C7H4ClINO2O, 332; experimental, 332.

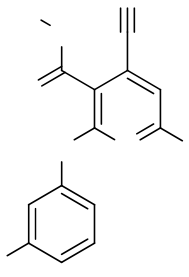


[0258] B. 2,6-dicloro-4-cianonicotinato de metilo

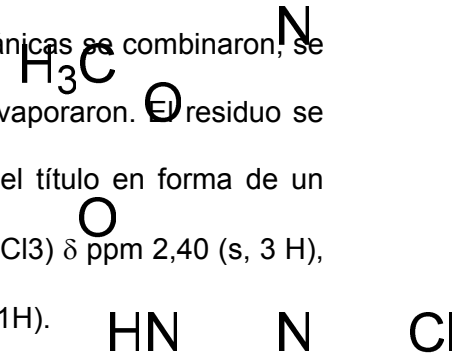
[0259] Una mezcla de tetrakis(trifenilfosfina)paladio (34,8 mg, 0,03 mmoles), 2,6-dicloro-4-yodonicotinato de metilo (100 mg, 0,301 mmoles) y dicianozinc (38,9 mg, 0,331 mmoles) en DMF (2 ml) se agitó a 100ºC durante toda la noche en atmósfera de N2. A la mezcla resultante se agregaron H2O y EtOAc. La fase acuosa se extrajo con EtOAC, y las capas orgánicas combinadas se lavaron con H2O y salmuera, se secaron sobre MgSO4 y se evaporaron El residuo se purificó por cromatografía sobre SiO2 para dar el compuesto

del título en forma de un sólido de color blanco (28 mg, 40%). 1H RMN (500 MHz, DMSO-d6) δ ppm 3,99 (s, 3 H), 8,44 (s, 1H).

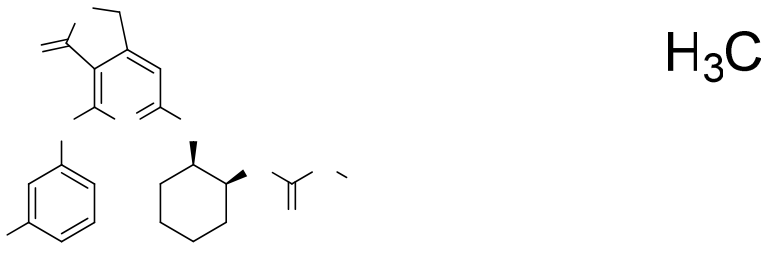
[0260] Preparación 6: 6-cloro-4-ciano-2-(m-tolilamino)nicotinato de metilo.



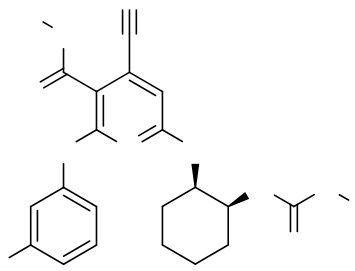
[0261] Una solución de 2,6-dicloro-4-cianonicotinato de metilo (455 mg, 1,97 mmoles), trietilamina (0,549 ml, 3,94 mmoles) y m-toluidina (0,32 ml, 2,95 mmoles en THF (10 ml) se agitó a temperatura ambiente durante 3 días. Se agregó agua a la mezcla resultante, y la fase acuosa se extrajo con EtOAc. Las fases orgánicas se combinaron, se lavaron con H2O y salmuera, se secaron sobre MgSO4, y se evaporaron. El residuo se purificó por cromatografía sobre SiO2 para dar el compuesto del título en forma de un sólido de color amarillo (198 mg, 33,3%). 1H RMN (500 MHz, CDCl3) δ ppm 2,40 (s, 3 H), 3,99 (s, 3H), 6,92 (s, 1H), 7,05 - 7,14 (m, 4H), 7,33 (t, J=7,81 Hz, 1H).



[0262] Preparación 7: (1S,2R)-2-(3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo



[0263] A. 6-((1R,2S)-2-(ter-butoxicarbonilamino)ciclohexilamino)-4-ciano-2-(m-tolilamino)nicotinato de metilo.



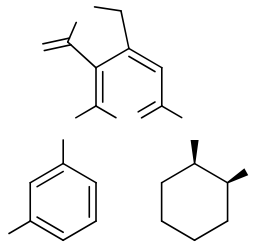
[0264] Una solución de 6-cloro-4-ciano-2-(m-tolilamino)nicotinato de metilo (198 mg, 0,656 mmoles), (1S,2R)-2-aminociclohexilcarbamato de ter-butilo (562 mg, 2,62 mmoles) y Et3N (0,402 ml, 2,89 mmoles) se agitó a reflujo durante toda la noche. A la mezcla resultante se agregaron H2O y EtOAc. La fase acuosa se extrajo con EtOAc. Las capas orgánicas se combinaron, se lavaron con salmuera, se secaron sobre MgSO4, y se evaporaron. El residuo se trituró con EtOAc. El sólido resultante se filtró, se enjuagó con EtOAc, y se secó para dar el compuesto del título en forma de un sólido de color amarillo (250 mg, 79 %). 1H RMN (500 MHz, CDCl3) δ ppm 1,23 - 1,77 (m, 17 H), 2,34 (s, 3 H), 3,94 (br s, 3 H), 3,98 (br s, 1H), 4,80 (s, 1H), 6,15 (s, 1 H), 6,91 (d, J=5,37 Hz, 1 H), 7,21 (t, J=7,81 Hz, 1H), 7,29 (s, 1H), 7,47 - 7,55 (m, 1 H), 10,64 (br s, 1 H).

[0265] B. (1S,2R)-2-(3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo

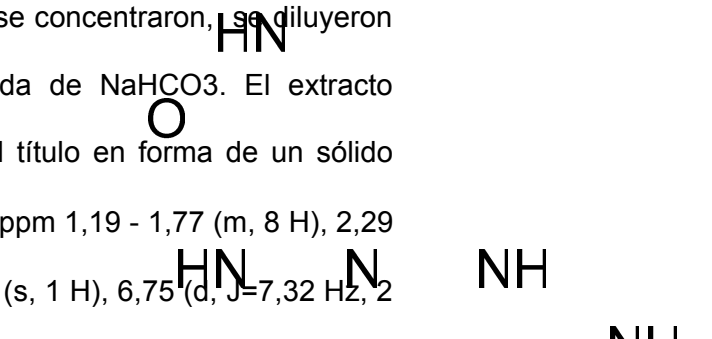
[0266] 6-((1R,2S)-2-(ter-butoxicarbonilamino)ciclohexilamino)-4-ciano-2-(m-tolilamino)nicotinato de metilo (100 mg, 0,209 mmoles) se disolvió en DMF (5 ml). A la solución se agregó paladio sobre carbono (22,19 mg, 0,209 mmoles) y la mezcla resultante se agitó a 80ºC durante toda la noche en atmósfera de H2. La mezcla se filtró, el filtrado se evaporó, y el residuo se diluyó con H2O y EtOAc. La fase acuosa se extrajo con EtOAc. Las fases orgánicas se combinaron, se lavaron con H2O y salmuera, se secaron sobre MgSO4, y se evaporaron. El residuo se purificó por recristalización (EtOH-hexano) para dar el compuesto del título en forma de un sólido de color blanco (70 mg, 74,3 %). 1H RMN (500 MHz, CDCl3) δ ppm 1,03 - 2,10 (m, 17 H), 2,34 (s, 3 H), 3,81 - 4,29 (m, 4 H), 5,03 (s, 1 H), 5,32 (s, 1 H), 5,81 (s, 1 H), 6,20 (s, 1 H), 6,81 (s, 1 H), 7,18 (s, 1

H), 7,49 (s, 1 H), 7,64 (s, 1 H), 8,77 (s, 1 H). [M+H] calc para C25H33N5O3, 452; experimental, 452.

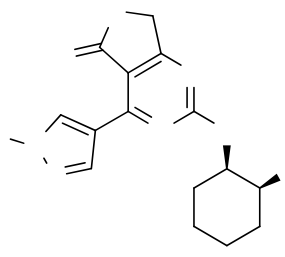
[0267] Ejemplo 13: 6-((1R,2S)-2-aminociclohexilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



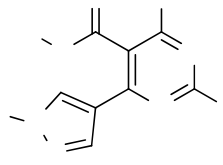
[0268] Una mezcla de (1S,2R)-2-(3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo (50,0 mg, 0,111 mmoles) y HCl 4N en dioxano (2 ml, 8,00 mmoles) se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se concentró a presión reducida, el residuo se purificó por HPLC preparativa de fase inversa. Las fracciones e recolectaron, se concentraron, se diluyeron en EtOAc, y se basificaron con solución acuosa saturada de NaHCO3. El extracto orgánico se secó y se evaporó para dar el compuesto del título en forma de un sólido color blanco (10 mg, 25,7 %). 1H RMN (500 MHz, CDCl3) δ ppm 1,19 - 1,77 (m, 8 H), 2,29 (s, 3 H), 3,20 (br s, 1 H), 3,99 (br s, 1 H), 4,19 (s, 2 H), 6,06 (s, 1 H), 6,75 (d, J=7,32 Hz, 2 H), 7,14 (t, J=7,81 Hz, 1 H), 7,48 (d, J=7,32 Hz, 1 H), 7,60 (s, 1 H), 7,90 (s, 1 H), 8,87 (s, 1 H). [M+H] calc para C20H25N5O, 352; experimental, 352.



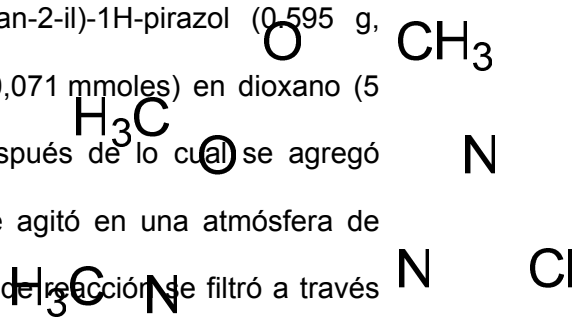
[0269] Ejemplo 14: 2-((1R,2S)-2-aminociclohexilamino)-4-(1-metil-1H-pirazol-4-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona



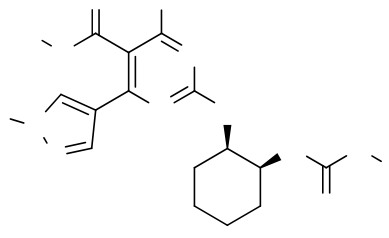
[0270] A. 2-cloro-4-metil-6-(1-metil-1H-pirazol-4-il)pirimidin-5-carboxilato de metilo



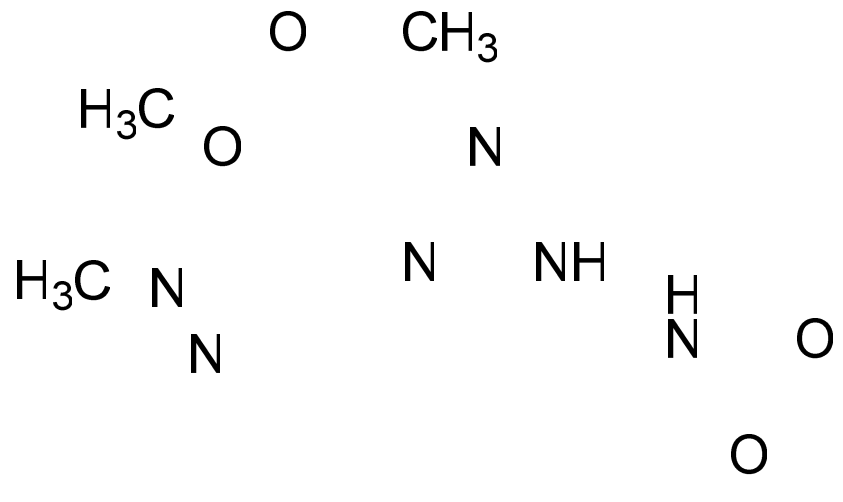
[0271] Una mezcla de 2,4-dicloro-6-metilpirimidin-5-carboxilato de metilo (0,79 g, 3,57 mmoles), 1-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (0,595 g, 2.86 mmoles) y bis(trifenilfosfina)paladio cloruro (0,050 g, 0,071 mmoles) en dioxano (5 ml) se agitó a temperatura ambiente durante 10 min., después de lo cual se agregó fluoruro de potasio (1,038 g, 17,87 mmoles). La mezcla se agitó en una atmósfera de nitrógeno y se calentó a 90ºC durante 12 horas. La mezcla de reacción se filtró a través de un lecho de celite 545, se enjuagó con DCM y una pequeña cantidad de MeOH. A continuación de la eliminación del solvente, el residuo se dispersó en DMSO/MeOH (1/1) y se purificó mediante HPLC preparativa de fase inversa para dar el compuesto del título (237 mg, 25%). [M+H] calc para C11H11ClN4O2, 267; experimental, 267.



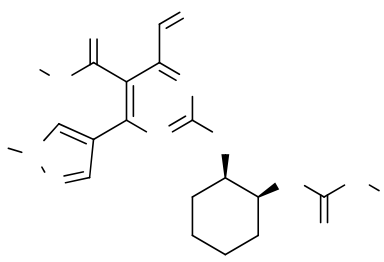
[0272] B. 2-((1R,2S)-2-(ter-butoxicarbonilamino)ciclohexilamino)-4-metil-6-(1-metil-1H-pirazol-4-il)pirimidin-5-carboxilato de metilo



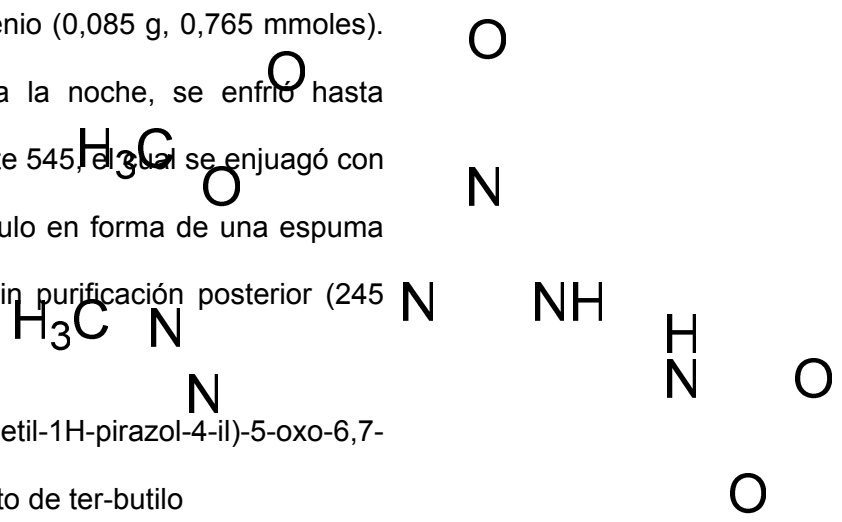
[0273] A una mezcla de 2-cloro-4-metil-6-(1-metil-1H-pirazol-4-il)pirimidin-5-carboxilato de metilo ((0,227 g, 0,851 mmoles) y (1S,2R)-2-aminociclohexilcarbamato de ter-butilo (0,182 g, 0,851 mmoles) en DMA (3 ml) se agregó Et3N (0,356 ml, 2,55 mmoles). La mezcla de reacción se calentó a 90ºC durante 4 horas. La mezcla de reacción se enfrió hasta temperatura ambiente y se vertió en hielo. El sólido se filtró y se secó a alto vacío para dar el compuesto del título en forma de una espuma blancuzca (170 mg). [M+H] calc para C22H32N6O4, 445; experimental, 445.



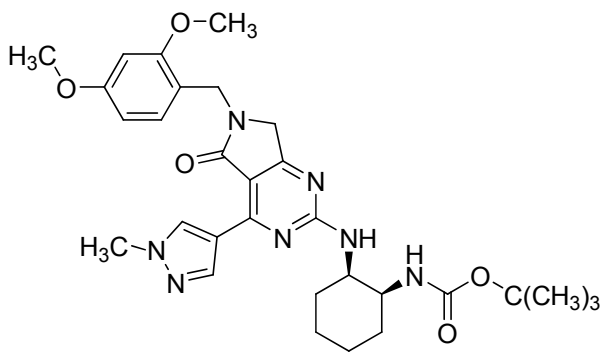
[0274] C. 2-((1R,2S)-2-(ter-butoxicarbonilamino)ciclohexilamino)-4-formil-6-(1-metil-1H-pirazol-4-il)pirimidin-5-carboxilato de metilo



[0275] A un matraz de base redonda de 25 ml se agregó 2-((1R,2S)-2-(ter-butoxicarbonilamino)ciclohexilamino)-4-metil-6-(1-metil-1H-pirazol-4-il)pirimidin-5-carboxilato de metilo(0,17 g, 0,382 mmoles), dióxido de selenio (0,085 g, 0,765 mmoles). La mezcla de reacción se calentó a 100ºC durante toda la noche, se enfrió hasta temperatura ambiente, y se filtró a través de un lecho de celite 545, el cual se enjuagó con MeOH. El solvente se eliminó para dar el compuesto del título en forma de una espuma amarillenta-marrón, la cual se utilizó en el próximo paso sin purificación posterior (245 mg).



[0276] D. (1S,2R)-2-(6-(2,4-dimetoxibencil)-4-(1-metil-1H-pirazol-4-il)-5-oxo-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-2-ilamino)ciclohexilcarbamato de ter-butilo



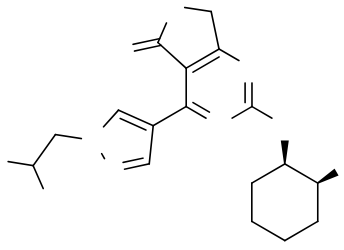
[0277] Se disolvió 2-((1R,2S)-2-(ter-butoxicarbonilamino)ciclohexilamino)-4-formil-6-(1-metil-1H-pirazol-4-il)pirimidin-5-carboxilato de metilo (0,175 g, 0, 382 mmoles) en DCM (2 ml) y MeOH (1 ml). A esta mezcla se agregó (2,4-dimetoxifenil)metanamina (0,057 ml, 0,382 mmoles) y acetato de sodio (0,094 g, 1,145 mmoles). La mezcla se agitó en un recipiente de 20 ml tapado durante 1 hora, después de lo cual se agregó

cianoborohidruro de sodio (0,060 g, 0,954 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante toda la noche. Después de que el solvente se eliminó a presión reducida, el residuo se disolvió en una solución de DMSO/MeOH (1/1). Un precipitado sólido blancuzco se formó inicialmente, el cual se aisló por filtración al vacío, se enjuagó con MeOH, y se secó al aire para dar un primer lote del compuesto del título (6,7 mg). La lejía madre se purificó por HPLC preparativa. Las fracciones se concentraron a presión reducida hasta que se formó un precipitado sólido blancuzco, el cual se recolectó por filtración al vacío y se secó al aire para dar un segundo lote (46 mg) del compuesto del título (total 62,5 mg, 28%). [M+H] calc para C30H39N7O5, 578; experimental, 578.

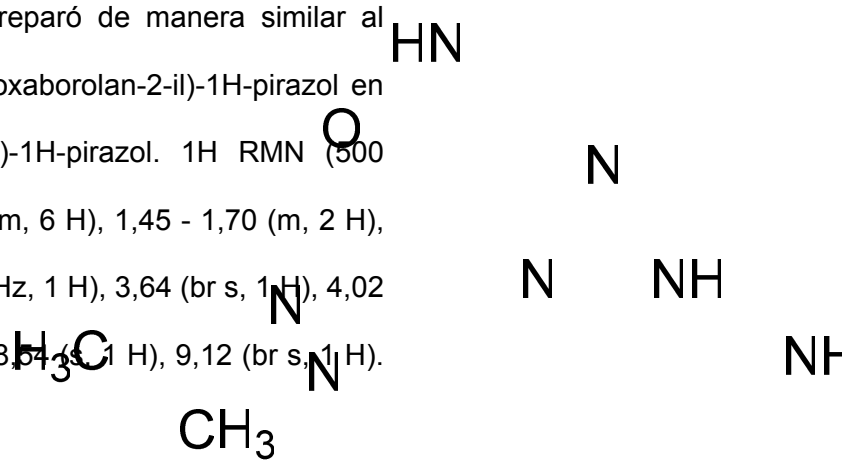
[0278] E. 2-((R,2S)-2-aminociclohexilamino)-4-(1-metil-1H-pirazol-4-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona

[0279] Se disolvió (1S,2R)-2-(6-(2,4-dimetoxibencil)-4-(1-metil-1H-pirazol-4-il)-5-oxo-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-2-ciclohexilcarbamato de ter-butilo (0,0625 g, 0,108 mmoles) en TFA (2 ml) y se calentó a 70ºC durante 1 hora. El solvente se eliminó a presión reducida y el residuo resultante se dispersó en solución de DMSO/MeOH (1/1). Un precipitado de color púrpura pálido se formó y se separó por filtración. El filtrado, que contenía el producto se purificó mediante HPLC preparativa de fase inversa. Las fracciones liofilizadas dieron una sal TFA del compuesto del título en forma de un sólido de color blanco (21 mg, 59%). 1H RMN (500 MHz, DMSO-d6) δ ppm 1,28 - 1,52 (m, 2 H) 1,51 - 1,94 (m, 6 H) 3,93 (s, 3 H) 4,14 - 4,30 (m, 2 H) 4,29 - 4,58 (m, 1 H) 7,51 (d, J=6,83 Hz, 1 H) 7,71 (br s, 2 H) 8,29 (s, 1 H) 8,34 - 8,69 (m, 1 H) 9,11 (d, J=17,09 Hz, 1 H). [M+H] calc para C16H21N7O, 328; experimental, 328.

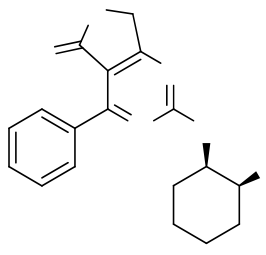
[0280] Ejemplo 15: 2-((1R,2S)-2-aminociclohexilamino)-4-(1-isobutil-1H-pirazol-4-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona



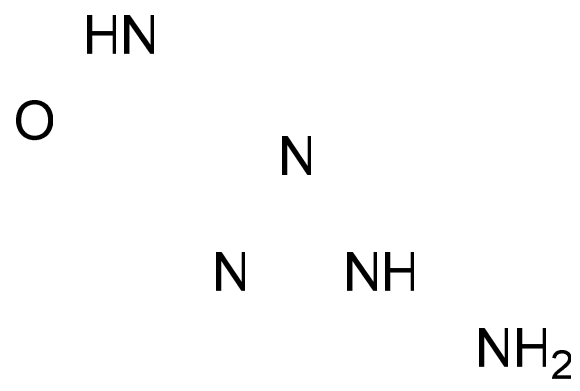
[0281] Una sal TFA del compuesto del título se preparó de manera similar al ejemplo 14 utilizando 1-isobutil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol en lugar de 1-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol. 1H RMN (500 MHz, CD3OD) δ ppm 0,92 (d, J=1,00 Hz, 6 H), 0,87 - 1,00 (m, 6 H), 1,45 - 1,70 (m, 2 H), 1,46 - 1,70 (m, 2 H), 1,70 - 2,00 (m, 6 H), 2,22 (spt, J=13,70 Hz, 1 H), 3,64 (br s, 1 H), 4,02 (d, J=6,83 Hz, 2 H), 4,30 (s, 2 H), 4,63 (d, J=3,91 Hz, 1 H), 8,54 (s, 1 H), 9,12 (br s, 1 H). [M+H] calc para C19H27N7O, 370; experimental, 370.



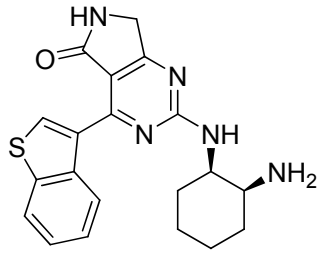
[0282] Ejemplo 16: 2-((1R,2S)-2-aminociclohexilamino)-4-fenil-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona



[0283] El compuesto del título se preparó de manera similar al ejemplo 14 utilizando ácido fenilborónico en lugar de 1-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol. El producto final se purificó mediante HPLC preparativa de fase inversa. Las fracciones e recolectaron, se concentraron, se neutralizaron con NaHCO3 acuoso saturado, y se extrajeron en EtOAc. La fase orgánica se secó sobre Na2SO4 anhidro y el solvente se eliminó in vacuo para dar el compuesto del título en forma de una película blancuzca. 1H RMN (400 MHz, CD3OD) δ ppm 1,40 - 1,95 (m, 8 H), 3,27 (br s, 1 H), 4,18 - 4,54 (m, 3 H), 7,35 - 7,59 (m, 3 H), 8,12 (br s, 2 H). [M+H] calc para C18H21N5O, 324; experimental, 324.

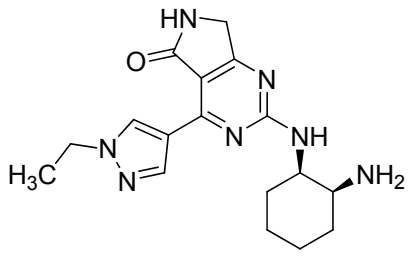


[0284] Ejemplo 17: 2-((1R,2S)-2-aminociclohexilamino)-4-(benzo[b]tiofen-3-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona



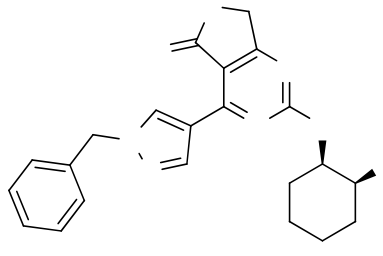
[0285] Una sal TFA del título se preparó de manera similar al ejemplo 14 utilizando ácido benzo[b]tiofen-3-ilborónico en lugar de 1-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol. 1H RMN (400 MHz, CD3OD) δ ppm 1,44 - 2,02 (m, 8 H), 3,53 - 3,84 (m, 1 H), 4,25 - 4,43 (m, 2 H), 4,54 - 4,72 (m, 1 H), 7,32 - 7,55 (m, 2 H), 7,84 - 8,03 (m, 1 H), 8,40 - 8,88 (m, 1 H), 8,86 - 9,10 (m, 1 H). [M+H] calc para C20H21N5OS, 380; experimental, 380.

[0286] Ejemplo 18: 2-((1R,2S)-2-aminociclohexilamino)-4-(1-etil-1H-pirazol-4-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona

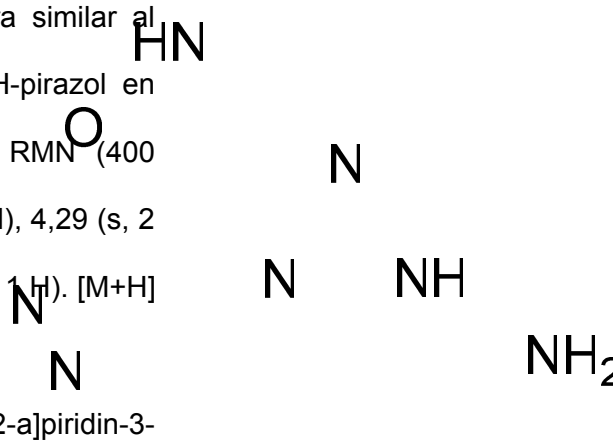


[0287] Una sal TFA del compuesto del título se preparó de manera similar al ejemplo 14 utilizando 1-etil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol en lugar de 1-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol. 1H RMN (400 MHz, CD3OD) δ ppm 1,47 - 1,55 (m, 3 H), 1,54 - 1,99 (m, 8 H), 3,64 (br s, 1 H), 4,26 (q, J=7,32 Hz, 2 H), 4,30 (s, 2 H), 4,63 (br s, 1 H), 8,54 (br s, 1 H), 9,14 (s, 1 H). [M+H] calc para C17H23N7O, 342; experimental, 342.

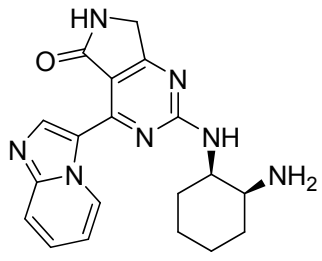
[0288] Ejemplo 19: 2-((1R,2S)-2-aminociclohexilamino)-4-(1-bencil-1H-pirazol-4-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona



[0289] Una sal TFA del compuesto del título se preparó de manera similar al ejemplo 14 utilizando 1-bencil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol en lugar de 1-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol. 1H RMN (400 MHz, CD3OD) δ ppm 1,45 - 1,69 (m, 2 H), 1,69 - 2,00 (m, 6 H), 3,63 (br s, 1 H), 4,29 (s, 2 H), 4,61 (br s, 1 H), 5,40 (s, 2 H), 7,22 - 7,41 (m, 5 H), 8,58 (s, 1 H), 9,16 (br s, 1 H). [M+H] calc para C22H25N7O, 404; experimental, 404.

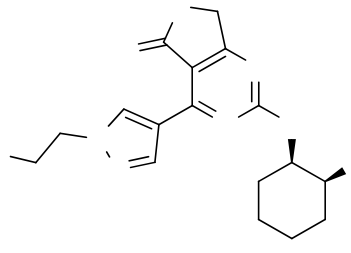


[0290] Ejemplo 20: 2-((1R,2S)-2-aminociclohexilamino)-4-(imidazo[1,2-a]piridin-3-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona

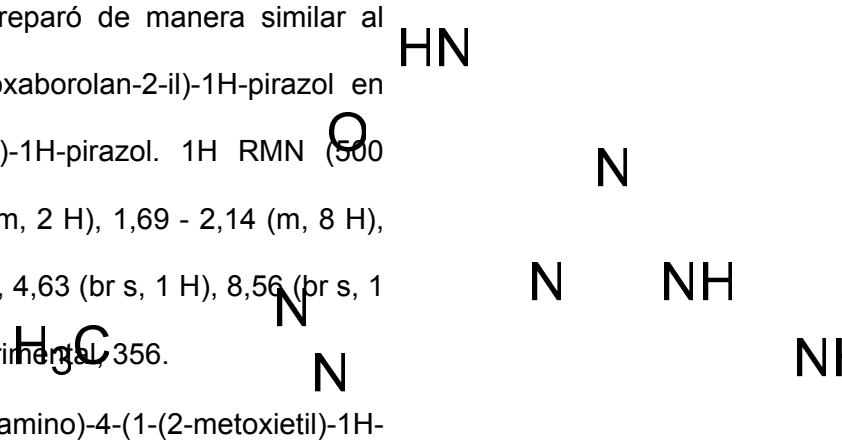


[0291] Una sal TFA del título se preparó de manera similar al ejemplo 14 utilizando ácido imidazo[1,2-a]piridin-3-ilborónico en lugar de 1-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol. 1H RMN (500 MHz, CD3OD) δ ppm 1,47 - 1,73 (m, 2 H), 1,74 - 2,03 (m, 6 H), 3,68 (br s, 1 H), 4,27 - 4,54 (m, 2 H), 4,58 - 4,75 (m, 1 H), 7,52 - 7,79 (m, 1 H), 8,00 - 8,12 (m, 1 H), 8,14 (t, J=7,57 Hz, 1 H), 10,23 (br s, 1 H), 10,81 (d, J=5,86 Hz, 1 H). [M+H] calc para C19H21N7O, 364; experimental, 364.

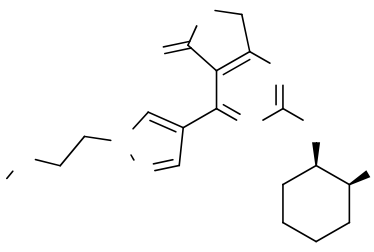
[0292] Ejemplo 21: 2-((1R,2S)-2-aminociclohexilamino)-4-(1-propil-1H-pirazol-4-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona



[0293] Una sal TFA del compuesto del título se preparó de manera similar al ejemplo 14 utilizando 1-propil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol en lugar de 1-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol. 1H RMN (500 MHz, CD3OD) δ ppm 0,92 (t, J=1,00 Hz, 3 H), 1,43 - 1,70 (m, 2 H), 1,69 - 2,14 (m, 8 H), 3,62 (br s, 1 H), 4,18 (t, J=6,83 Hz, 2 H), 4,24 - 4,41 (m, 2 H), 4,63 (br s, 1 H), 8,56 (br s, 1 H), 9,13 (br s, 1 H). [M+H] calc para C18H25N7O, 356; experimental, 356.

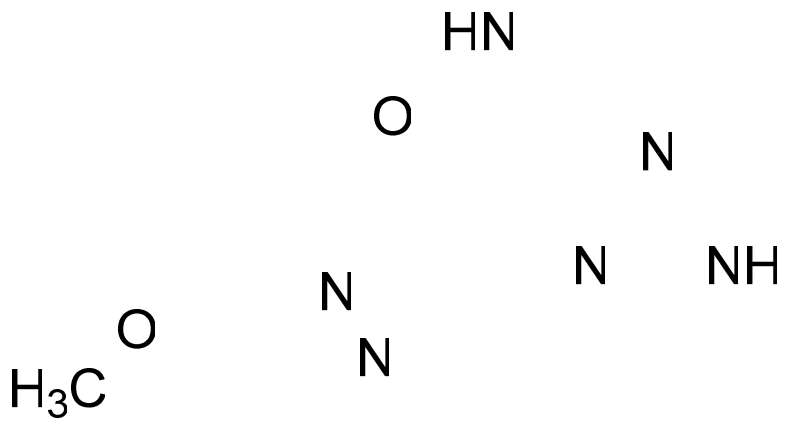


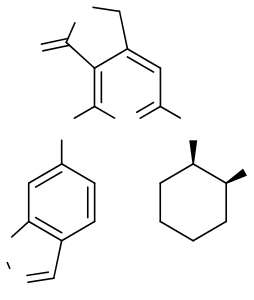
[0294] Ejemplo 22: 2-((1R,2S)-2-aminociclohexilamino)-4-(1-(2-metoxietil)-1H-pirazol-4-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;



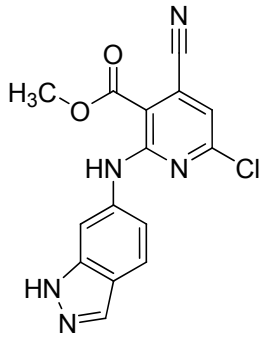
[0295] Una sal TFA del compuesto del título se preparó de manera similar al ejemplo 14 utilizando 1-(2-metoxietil)-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol en lugar de 1-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol. 1H RMN (500 MHz, CD3OD) δ ppm 1,45 - 1,70 (m, 2 H), 1,70 - 2,05 (m, 6 H), 3,33 - 3,35 (m, 3 H), 3,63 (br s, 1 H), 3,73 - 3,90 (m, 2 H), 4,30 (s, 2 H), 4,33 - 4,47 (m, 2 H), 4,63 (br s, 1 H), 8,58 (br s, 1 H), 9,13 (br s, 1 H). [M+H] calc para C18H25N7O2, 372; experimental, 372.

[0296] Ejemplo 23: 4-(1H-indazol-6-ilamino)-6-((1R,2S)-2-aminociclohexilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



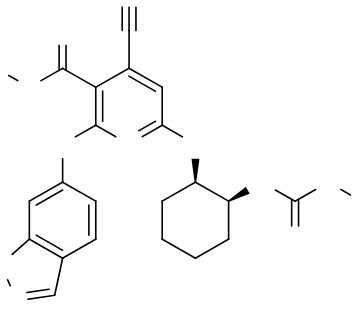


[0297] A. 2-(1H-indazol-6-ilamino)-6-cloro-4-cianonicotinato de metilo



[0298] Una mezcla de 2,6-dicloro-4-cianonicotinato de metilo (250 mg, 1,082 mmoles), 1H-indazol-6-amina (173 mg, 1,299 mmoles) y Et3N (0,226 ml, 1.623 mmoles) en THF (10 ml) se agitó a 80ºC durante toda la noche. Se agregaron agua y EtOAc a la mezcla. La fase orgánica se lavó con H2O y salmuera, se secó sobre MgSO4, y se evaporó. El residuo se purificó por cromatografía sobre SiO2 (hexano/EtOAc=5/1) para dar el compuesto del título en forma de un sólido de color amarillo (120 mg, 38,5%).

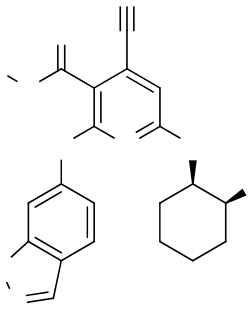
[0299] B. 2-(1H-indazol-6-ilamino)-6-((1R,2S)-2-(ter-butoxicarbonilamino)ciclohexilamino)-4-cianonicotinato de metilo



[0300] Una solución de 2-(1H-indazol-6-ilamino)-6-cloro-4-cianonicotinato de metilo (115 mg, 0,351 mmoles), (1S,2R)-2-aminociclohexilcarbamato de ter-butilo (90 mg,

0,421 mmoles) y Et3N (0,073 ml, 0,526 mmoles) en THF (1 ml) se agitó a reflujo durante toda la noche. Se agregaron agua y EtOAc a la mezcla. La fase acuosa se extrajo con EtOAc. Las fases orgánicas se combinaron, se lavaron con H2O y salmuera, se secaron sobre MgSO4, y se evaporaron. El residuo se enjuagó con EtOAc para dar el compuesto del título en forma de un sólido de color amarillo (110 mg, 62,0%). 1H RMN (500 MHz, CDCl3) δ ppm 1,00 – 1,86 (m, 17 H), 3,84 (s, 3 H), 3,91 (br s, 1 H), 4,12 (br s, 1H), 6,51 (s, 1 H), 6,63 (d, J=8,79 Hz, 1 H), 7,13 (d, J=8,30 Hz, 1 H), 7,97 (s, 1H), 8,03 (br s, 1 H), 10,71 (br s, 1 H), 12,87 (br s, 1 H).

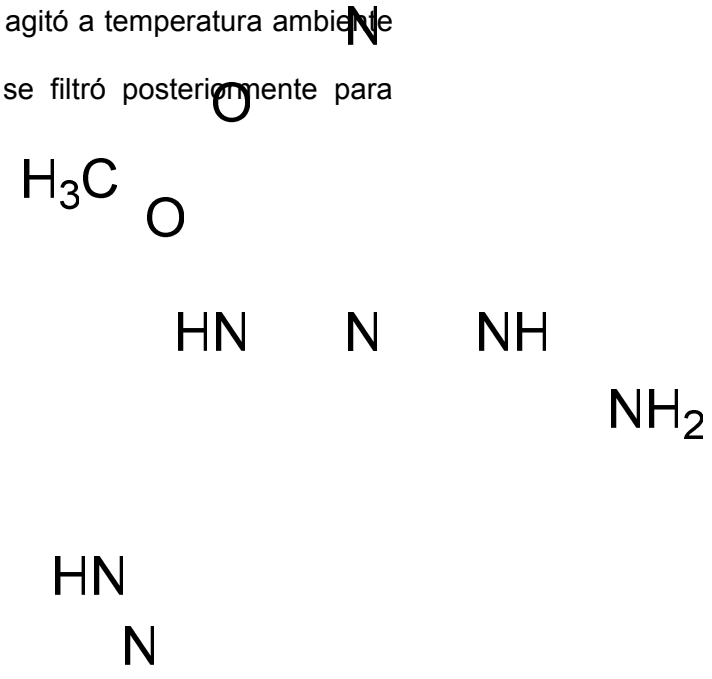
[0301] C. 2-(1H-indazol-6-ilamino)-6-((1R,2S)-2-aminociclohexilamino)-4-cianonicotinato de metilo



[0302] Una solución de 2-(1H-indazol-6-ilamino)-6-((1R,2S)-2-(ter-butoxicarbonilamino)ciclohexilamino)-4-cianonicotinato de metilo (110 mg, 0,218 mmoles) y TFA (2 ml, 26,9 mmoles) en DCM (1 ml) se agitó a temperatura ambiente durante 3 horas. A continuación de la reacción, la mezcla se concentró in vacuo para dar el compuesto del título, el cual se utilizó en el próximo paso sin purificación posterior.

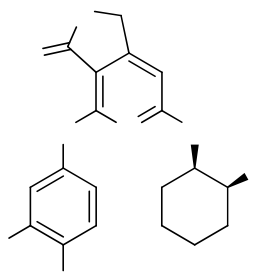
[0303] D. 4-(1H-indazol-6-ilamino)-6-((1R,2S)-2-aminociclohexilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona

[0304] A una solución de 2-(1H-indazol-6-ilamino)-6-((1R,2S)-2-aminociclohexilamino)-4-cianonicotinato de metilo (88 mg, 218 mmoles) en MeOH (2 ml) se agregó paladio sobre carbono, y la mezcla resultante se agitó a temperatura ambiente durante toda la noche en atmósfera de H2. La mezcla se filtró posteriormente para

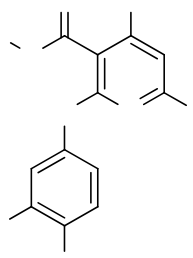


eliminar el catalizador y el filtrado se evaporó. El residuo se diluyó con NaHCO3 saturado acuoso y MeOH, y la mezcla se agitó a temperatura ambiente durante 30 min. La suspensión resultante se filtró y el precipitado se lavó con EtOAc y se secó para dar el compuesto del título en forma de un sólido de color blanco (15 mg, 18,2%). 1H RMN (500 MHz, DMSO-d6) δ ppm 1,22 – 1,74 (m, 8 H), 3,13 (br s, 1H), 3,94 – 4,07 (m, 1 H), 4,21 (s, 2 H), 6,02 – 6,14 (m, 1 H), 6,70 (br s, 1 H), 7,13 (d, J=8,30 Hz, 1 H), 7,63 (d, J=8,30 Hz, 1 H), 7,94 (d, J=2,93 Hz, 2 H), 8,23 (s, 1 H), 9,08 (s, 1 H), 12,84 (br s, 1 H). [M+H] calc para C20H23N7O, 378; experimental, 378.

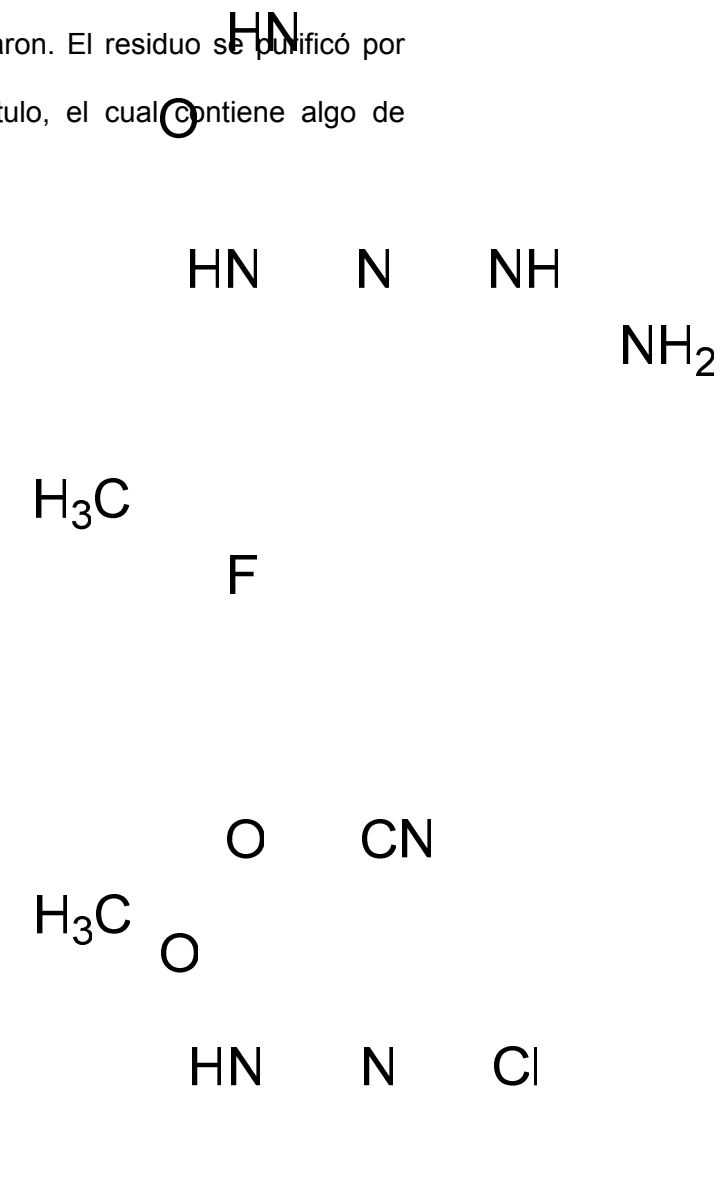
[0305] Ejemplo 24: 6-((1R,2S)-2-aminociclohexilamino)-4-(4-fluoro-3-metilfenilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



[0306] A.6-cloro-4-ciano-2-(4-fluoro-3-etilfenilamino)nicotinato de metilo

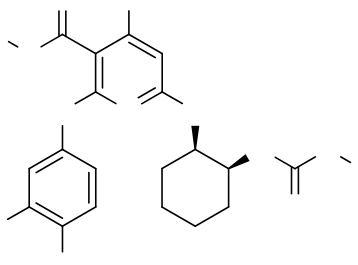


[0307] Una solución de 2,6-dicloro-4-cianonicotinato de metilo (500 mg, 2,164 mmoles, 4-fluoro-3-metilanilina (325 mg, 2,60 mmoles) y Et3N (0,452 ml, 3,25 mmoles) en ACN (5 ml) se agitó a 50ºC durante 24 horas. Se agregaron agua y EtOAc a la mezcla y la fase acuosa se extrajo con EtOAc. Las fases orgánicas se combinaron, se lavaron con H2O y salmuera, se secaron sobre MgSO4, y se evaporaron. El residuo se purificó por cromatografía sobre SiO2 para dar el compuesto del título, el cual contiene algo de

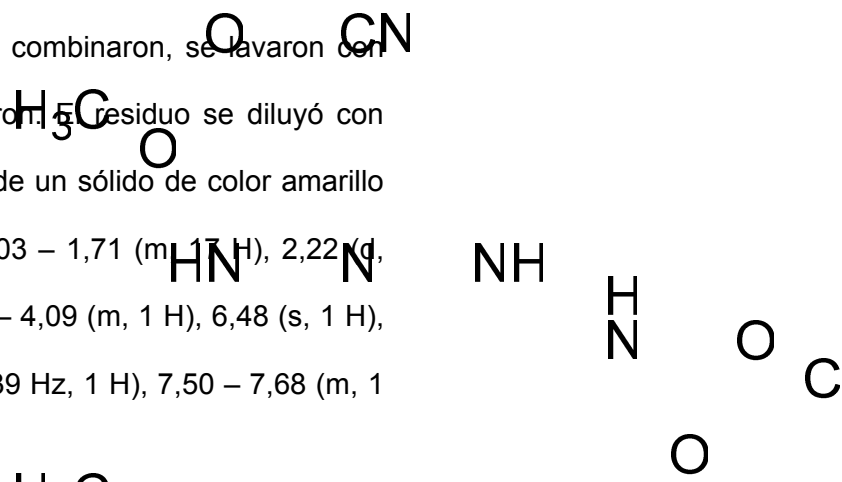


material de partida y se utilizó sin purificación posterior (390 mg). [M+H] calc para C15H11ClFN3O2, 320; experimental, 320.

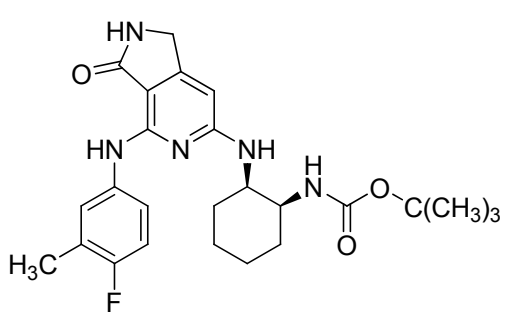
[0308] B. 6-((1R,2S)-2-(ter-butoxicarbonilamino)ciclohexilamino)-4-ciano-2-(4-fluoro-3-metilfenilamino)nicotinato de metilo



[0309] Una mezcla de 6-cloro-4-ciano-2-(4-fluoro-3-metilfenilamino)nicotinato de metilo (390 mg, 1,220 mmoles), Et3N (0,204 ml, 1,464 mmoles) y (1S,2R)-2-aminociclohexilcarbamato de ter-butilo (392 mg, 1,830 mmoles) en THF (5 ml) se agitó a 80ºC durante toda la noche. Se agregaron posteriormente agua y EtOAc a la mezcla y la fase acuosa se extrajo con EtOAc. Las fases orgánicas se combinaron, se lavaron con H2O y salmuera, se secaron sobre MgSO4, y se evaporaron. El residuo se diluyó con EtOAc y se filtró para dar el compuesto del título en forma de un sólido de color amarillo (75 mg, 12,36%). 1H RMN (500 MHz, DMSO-d6) δ ppm 1,03 – 1,71 (m, 17 H), 2,22 (d, J=0,98 Hz, 3 H), 3,80 – 3,82 (m, 3 H), 3,83 (br s, 1 H), 4,01 – 4,09 (m, 1 H), 6,48 (s, 1 H), 6,62 (d, J=7,81 Hz, 1 H), 7,06 (t, J=9,03, 1 H), 7,39 (d, J=4,39 Hz, 1 H), 7,50 – 7,68 (m, 1 H), 10,41 (br s, 1 H).



[0310] C. (1S,2R)-2-(4-(4-fluoro-3-metilfenilamino)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo

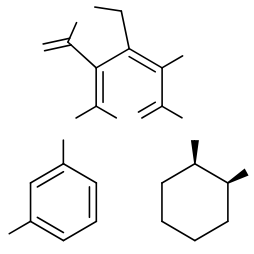


[0311] Una mezcla de 6-((1R,2S)-2-(ter-butoxicarbonilamino)ciclohexilamino)-4-ciano-2-(4-fluoro-3-metilfenilamino)nicotinato de metilo (75 mg, 0,151 mmoles) y óxido de platino (34,2 mg, 0,151 mmoles) en DCM (2 ml) y HOAc (0,5 ml) se agitó a temperatura ambiente en una atmósfera de H2. La mezcla se filtró posteriormente a través de celite. El filtrado se concentró y el residuo se purificó por HPLC preparativa para dar el compuesto del título (50 mg, 70,6%). [M+H] calc para C25H32FN5O3, 470; experimental, 470.

[0312] D. 6-((1R,2S)-2-aminociclohexilamino)-4-(4-fluoro-3-metilfenilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona

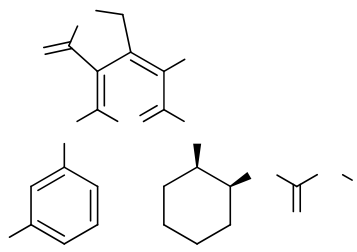
[0313] Una solución de (1S,2R)-2-(4-(4-fluoro-3-metilfenilamino)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo (50,0 mg, 0,106 mmoles) y TFA (1 ml, 12,98 mmoles) en DCM (0,5 ml) se agitó a temperatura ambiente durante 1 hora. La mezcla resultante se concentró y el residuo se purificó por HPLC preparativa para dar el compuesto del título en forma de un sólido de color blanco (1 mg, 2,54%). 1H RMN (500 MHz, CD3OD) δ ppm 1,14 – 1,95 (m, 8 H), 2,28 (s, 3 H), 3,73 (br s, 1 H), 4,30 (s, 2H), 4,38 (s, 1 H), 6,17 (s, 1 H), 7,00 (t, J=9,03 Hz, 1 H), 7,41 – 7,54 (m, 2 H).

[0314] Ejemplo 25: 6-((1R,2S)-2-aminociclohexilamino)-7-fluoro-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona

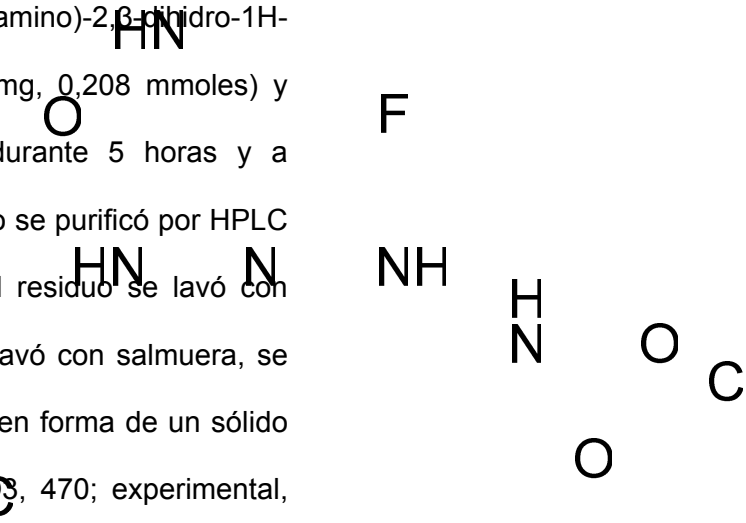


[0315] A. (1S,2R)-2-(7-fluoro-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo





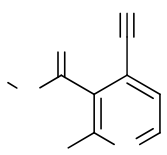
[0316] Una solución de (1S,2R)-2-(3-oxo-7-fenil-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo (94 mg, 0,208 mmoles) y SELECTFLUOR® (73,7 mg, 0,208 mmoles) se agitó a 0ºC durante 5 horas y a temperatura ambiente durante 1 hora. La mezcla se filtró y el filtrado se purificó por HPLC preparativa. Las fracciones se recolectaron y se concentraron. El residuo se lavó con solución de NaHCO3 acuoso saturado, se extrajo con EtOAc, se lavó con salmuera, se secó sobre MgSO4, y se evaporó para dar el compuesto del título en forma de un sólido de color amarillo (45 mg, 46,0%). [M+H] calc para C25H32FN5O3, 470; experimental, 470.



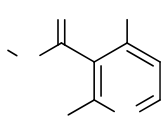
[0317] B. 6-((1R,2S)-2-aminociclohexilamino)-7-fluoro-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona

[0318] Una solución de (1S,2R)-2-(7-fluoro-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo (40,0 mg, 0,085 mmoles) y TFA (2 ml, 26,0 mmoles) en DCM (1 ml) se agitó a temperatura ambiente durante 1 hora. La mezcla se concentró y el residuo resultante se purificó por HPLC preparativa para dar el compuesto del título en forma de un sólido de color blanco (20 mg, 63,5%). 1H RMN (500 MHz, DMSO-d6) δ ppm1,36 – 1,97 (m, 8 H), 2,30 (s, 3 H), 3,70 (br s, 1 H), 4,27 (br s, 1 H), 4,33 – 4,46 (m, 2 H), 6,73 (d, J=6,35 Hz, 1 H), 6,79 (d, J=7,32 Hz, 1 H), 7,17 (t, J=7,57 Hz, 1 H), 7,43 (d, J=7,81 Hz, 1 H), 7,46 (s, 1 H), 7,76 (br s, 2 H), 8,29 (s, 1 H), 8,79 (s, 1 H). [M+H] calc para C20H24FN5O, 370; experimental, 370.

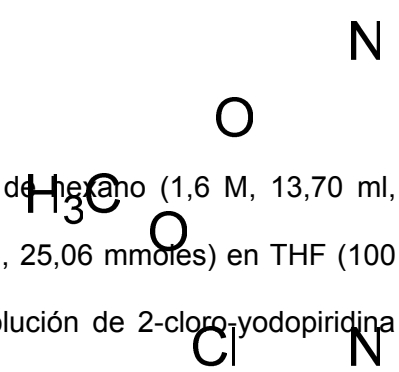
[0319] Preparación 8: 2-cloro-4-cianonicotinato de metilo

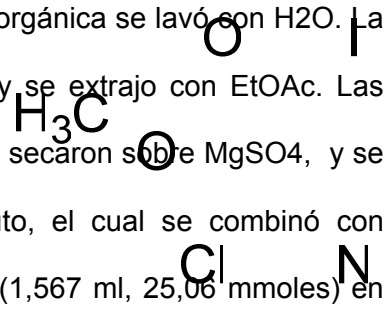


[0320] A: 2-cloro-4-yodonicotinato de metilo

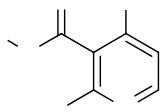


[0321] Se agregó gota a gota butilitio en solución de hexano (1,6 M, 13,70 ml, 21,93 mmoles) a una solución de diisopropilamina (3,57 ml, 25,06 mmoles) en THF (100 ml) a -78ºC y la mezcla se agitó durante 30 min. Una solución de 2-cloro-yodopiridina (5,00 g, 20,88 mmoles) en THF (50 ml) se agregó gota a gota a la mezcla de reacción a -78ºC y la mezcla resultante se agitó a -78ºC durante 2 horas. Se agregó hielo seco a la mezcla de reacción, la cual se entibió hasta temperatura ambiente y se agitó durante toda la noche. La mezcla resultante se templó con H2O y la fase orgánica se lavó con H2O. La fase acuosa combinada se acidificó con HCl concentrado y se extrajo con EtOAc. Las fases orgánicas se combinaron, se lavaron con salmuera, se secaron sobre MgSO4, y se evaporaron para dar el ácido 2-cloro-4-yodonicotínico bruto, el cual se combinó con carbonato de potasio (5,77 g, 41,8 mmoles) y yodometano (1,567 ml, 25,06 mmoles) en DMF (70 ml). La mezcla se agitó a temperatura ambiente durante 1 hora, lo cual fue seguido de la adición de Et2O y H2O. La fase orgánica se lavó con H2O y salmuera, se secó sobre MgSO4, y se evaporó. El residuo se purificó por cromatografía sobre SiO2 para dar el compuesto del título en forma de un sólido de color blanco (3,23 g, 52,0%). 1H RMN (500 MHz, CDCl3) δ ppm 4,01 (s, 3 H), 7,68 – 7,76 (m, 1 H), 7,97 – 8,11 (m, 1 H). [M+H] calc para C7H5ClINO2O, 298; experimental, 298.

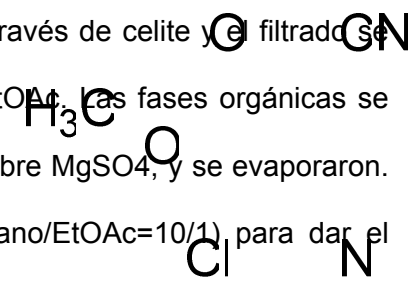




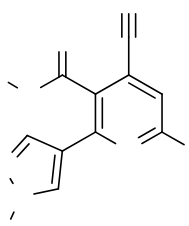
[0322] B. 2-cloro-4-cianonicotinato de metilo



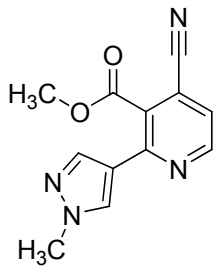
[0323] Una solución de 2-cloro-4-yodonicotinato de metilo (3,20 g, 10,76 mmoles) y cianocobre (0,963 g, 10,76 mmoles) en DMA (40 ml) se agitó a 140ºC durante toda la noche. A continuación de la reacción, la mezcla se filtró a través de celite y el filtrado se diluyó con H2O y EtOAc. La fase acuosa se extrajo con EtOAc. Las fases orgánicas se combinaron, se lavaron con H2O y salmuera, se secaron sobre MgSO4, y se evaporaron. El residuo se purificó por cromatografía sobre SiO2 (hexano/EtOAc=10/1) para dar el compuesto del título en forma de un sólido de color blanco (730 mg, 34,5%). 1H RMN (500 MHz, CDCl3) δ ppm 4,07 (s, 3 H), 7,57 (d, J=5,37 Hz, 1 H), 8,66 (d, J=4,88 Hz, 1 H).



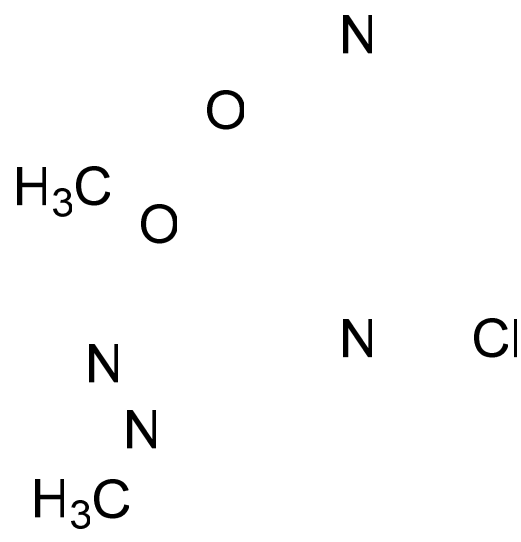
[0324] Preparación 9: 6-cloro-4-ciano-2-(1-metil-1H-pirazol-4-il)nicotinato de metilo



[0325] A. 4-ciano-2-(1-metil-1H-pirazol-4-il)nicotinato de metilo



[0326] Una mezcla de 2-cloro-4-cianonicotinato de metilo (730 mg, 3,71 mmoles), 1-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (927 mg, 4,46 mmoles), trans-diclorobis(trifenilfosfina)paladio (261 mg, 0,371 mmoles) y fluoruro de potasio (2697 mg, 14,85 mmoles) en DME (15 ml) se agitó a 120ºC durante 1 hora bajo irradiación de microondas. La reacción, la mezcla se filtró a través de celite y el filtrado se diluyó con

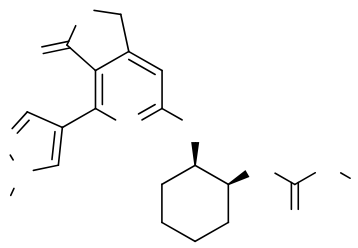


H2O y EtOAc. La fase orgánica se lavó con H2O y salmuera, se secó sobre MgSO4, y se evaporó. El residuo se purificó por cromatografía sobre SiO2 para dar el compuesto del título en forma de un sólido de color amarillo pálido (470 mg, 52,3%). 1H RMN (500 MHz, CDCl3) δ ppm 3,97 (s, 3 H), 4,03 (s, 3 H), 7,41 (d, J=4,88 Hz, 1 H), 7,82 (s, 1 H), 7,91 (s, 1 H), 8,79 (d, J=4,88 Hz, 1 H). [M+H] calc para C12H10N4O2, 243; experimental, 243.

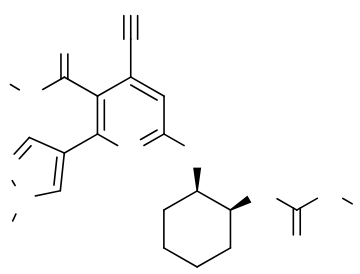
[0327] B. 6-cloro-4-ciano-2-(1-metil-1H-pirazol-4-il)nicotinato de metilo

[0328] A una mezcla de 4-ciano-4-ciano-2-(1-metil-1H-pirazol-4-il)nicotinato de metilo (470 mg, 1,940 mmoles) en DCM (10 ml) se agregó compuesto peróxido de hidrógeno-urea (1/1, 913 mg, 9,70 mmoles), y anhídrido 2,2,2-trifluoroacético (1,370 ml, 9,70 mmoles) a 0ºC. La mezcla se agitó a temperatura ambiente durante 4 horas. Más compuesto peróxido de hidrógeno-urea (1/1, 400 mg) se agregó y la mezcla se agitó a temperatura ambiente durante otras 3 horas después de los cual se agregó solución de NaHCO3 acuoso saturado y CHCl3. La fase acuosa se extrajo con CHCl3 (3 x), y las capas orgánicas se combinaron, se lavaron con salmuera, se secaron sobre MgSO4, y se evaporaron para obtener 4-ciano-3-(metoxicarbonil)-2-(1-metil-1H-pirazol-4-il)piridin 1-óxido, el cual se combinó con oxicloruro de fósforo (2 ml, 21,46 mmoles). La mezcla resultante se agitó a 80ºC durante 5 horas y a continuación se concentró hasta un residuo, el cual se neutralizó con NaOH 2N. La fase orgánica se lavó con salmuera, se secó sobre MgSO4, y se evaporó. El residuo se purificó por cromatografía sobre SiO2 (hexano/EtOAc=1/1) para dar el compuesto del título en forma de un sólido de color blanco (155 mg, 41,3%). 1H RMN (500 MHz, CDCl3) δ ppm 3,96 (s, 3 H), 4,03 (s, 3 H), 7,41 (s, 1 H), 7,81 (s, 1 H), 7,94 (s, 1 H). [M+H] calc para C12H9ClN4O2, 277; experimental, 277.

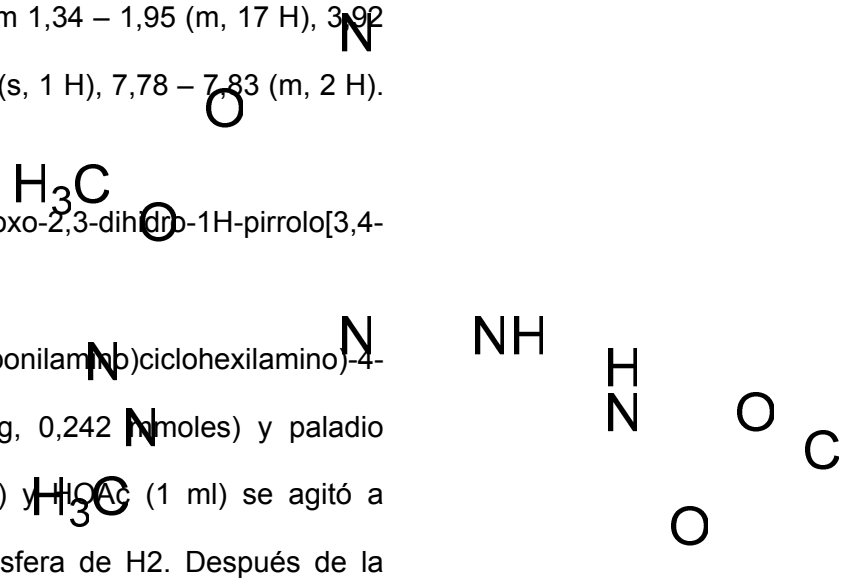
[0329] Preparación 10: (1S,2R)-2-(4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo



[0330] A. 6-((1R,2S)-2-(ter-butoxicarbonilamino)ciclohexilamino)-4-ciano-2-(1-metil-1H-pirazol-4-il)nicotinato de metilo



[0331] Una mezcla de 6-cloro-4-ciano-2-(1-metil-1H-pirazol-4-il)nicotinato de metilo ((155 mg, 0,560 mmoles) y (1S,2R)-2-aminociclohexilcarbamato de ter-butilo (144 mg, 0,672 mmoles) en DMA (2 ml) se agitó a 150ºC durante 1 hora bajo irradiación de microondas. A la mezcla resultante se agregaron H2O y EtOAc. La fase orgánica se lavó con H2O (3 x) y salmuera, se secó sobre MgSO4, y se evaporó. El residuo se purificó por cromatografía sobre SiO2 para dar el compuesto del título en forma de un aceite de color amarillo (100 mg, 39,3%). 1H RMN (500 MHz, CDCl3) δ ppm 1,34 – 1,95 (m, 17 H), 3,92 (s, 3 H), 3,93 (s, 3 H), 4,87 (br s, 1 H), 5,66 (br s, 1 H), 6,52 (s, 1 H), 7,78 – 7,83 (m, 2 H). [M+H] calc para C23H30N6O4, 455; experimental, 455.

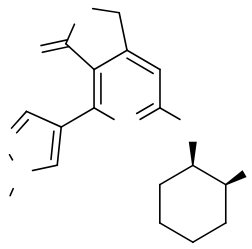


[0332] B. (1S,2R)-2-(4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo

[0333] Una solución de 6-((1R,2S)-2-(ter-butoxicarbonilamino)ciclohexilamino)-4-ciano-2-(1-metil-1H-pirazol-4-il)nicotinato de metilo (110 mg, 0,242 mmoles) y paladio sobre carbono (2,58 mg, 0,024 mmoles) en MeOH (5 ml) y HOAc (1 ml) se agitó a temperatura ambiente durante toda la noche en una atmósfera de H2. Después de la reacción, la mezcla se filtró a través de celite, el filtrado se evaporó, y el residuo se diluyó

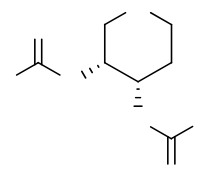
con MeOH y NaHCO3 acuoso saturado. La mezcla se agitó a temperatura ambiente durante 30 min. y se extrajo con EtOAc. La fase orgánica se lavó con salmuera, se secó sobre MgSO4, y se evaporó. El residuo se purificó por cromatografía sobre SiO2 y HPLC preparativa para dar el compuesto del título (60 mg, 58,1%). 1H RMN (500 MHz, CDCl3) δ ppm 1,26 – 1,87 (m, 17 H), 3,91 (s, 3 H), 4,25 (br s, 2 H), 5,16 – 5,49 (m 2 H), 6,23 (br s, 1 H), 6,75 (br s, 1 H), 8,18 – 8,44 (m, 1 H), 8,76 – 9,05 (m, 1 H).

[0334] Ejemplo 26: 6-((1R,2S)-2-aminociclohexilamino)-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona

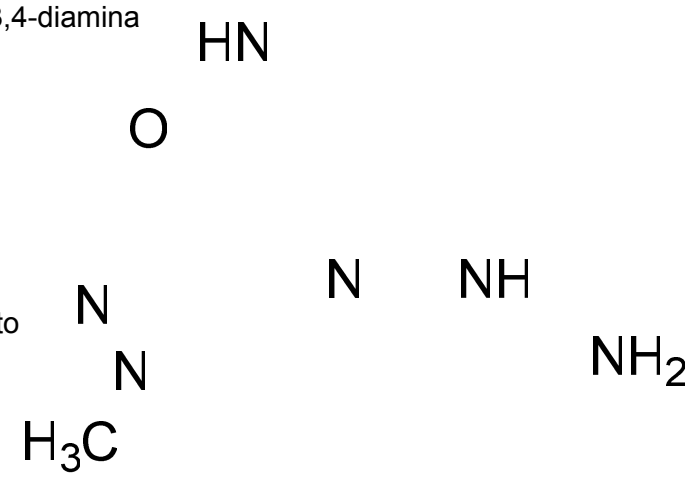


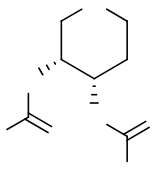
[0335] Una mezcla de (1S,2R)-2-(4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo (94 mg, 0,22 mmoles) y TFA (1 ml, 12,98 mmoles) en DCM (1 ml) se agitó a temperatura ambiente durante 2 horas. Posteriormente la mezcla se concentró. El residuo se purificó por HPLC preparativa (01-25; 5,45 min.) y se basificó para dar el compuesto del título en forma de un sólido de color amarillo (10 mg, 14%). 1H RMN (500 MHz, DMSO-d6) δ ppm 122 – 1,61 (m, 8 H), 3,63 (s, 3 H), 4,19 (s, 2 H), 6,46 (br s, 1 H), 7,98 (s, 1 H), 8,29 (s, 1 H), 8,85 (s, 1 H). [M+H] calc para C17H22N6O, 327; experimental, 327.

[0336] Preparación 11: (3R,4R)-tetrahidro-2H-piran-3,4-diamina

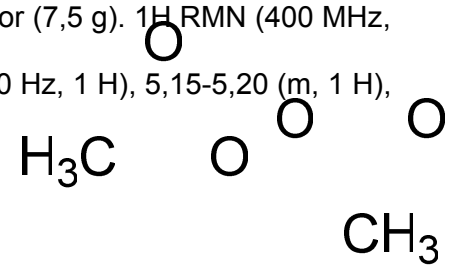


[0337] A. (3R,4S)-tetrahidro-2H-piran-3,4-diil diacetato

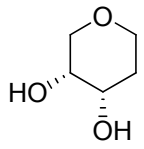




[0338] Una mezcla de (3R,4S)-3,4-dihidro-2H-piran-3,4-diil diacetato (8 g, 40 mmoles) y Pd/C (10%, 5,0 g) en MeOH se agitó a temperatura ambiente durante 12 horas en atmósfera de H2 (50 psi). Después de la filtración, el residuo se concentró para dar el compuesto del título, el cual se utilizó sin purificación posterior (7,5 g). 1H RMN (400 MHz, CDCl3) δ ppm 2,06 (s, 6 H), 3,95-4,03 (m, 2 H), 4,84 (t, J=4,0 Hz, 1 H), 5,15-5,20 (m, 1 H), 5,43 (t, J=4,0 Hz, 1 H), 6,49 (d, J=4,0 Hz, 1 H).

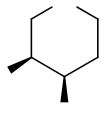


[0339] B. (3R,4S)-tetrahidro-2H-piran-3,4-diol



[0340] Se agitaron (3R,4S)-tetrahidro-2H-piran-3,4-diil diacetato (7,5 g, 0,4 mmoles) y metilato de sodio (8,64 g, 0,16 moles) en MeOH, durante toda la noche a temperatura ambiente, La mezcla de reacción se templó posteriormente con HCl 6N en un baño helado. La mezcla se concentró hasta sequedad. El residuo se trató con EtOAc (500 ml) y se agitó vigorosamente a 45ºC durante 30 min. Después de la filtración, el filtrado se concentró para dar el compuesto del título, el cual se utilizó sin purificación posterior (4,4 g). 1H RMN (400 MHz, CDCl3) δ ppm 1,79-1,84 (m, 1 H), 2,00 (s, 6 H), 3,56-3,67 (m, 2 H), 3,88-3,97 (m, 2 H), 5,09-5,14 (m, 2 H).

[0341] C. (3R,4R)-3,4-diazidotetrahidro-2H-piran



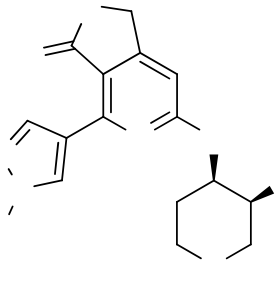
[0342] Se disolvió (3R,4S)-tetrahidro-2H-piran-3,4-diol (5,0 g, 42,4 mmoles) en DCM (50 ml). A la mezcla se agregó piridina (2,5 eq), y en un baño helado, anhídrido

trifluorometanosulfónico (21,5 g, 94,3 mmoles). La reacción se completó en 15 min. A la mezcla se agregó DMF (50 ml) y hexametilfosforamida (1 ml), seguido de azida de sodio (25,0 g, 385,0 mmoles). La mezcla de reacción se agitó a 50ºC durante 3 horas. Se eliminó DCM a presión reducida. Se agregó agua y la mezcla se extrajo con EtOAc (3 x 30 ml). La capa orgánica se lavó con agua, se secó sobre Na2SO4, y se concentró para dar el compuesto del título, el cual se utilizó sin purificación posterior (1,88 g). 1H RMN (400 MHz, CDCl3) δ ppm 1,85-1,90 (m, 1 H), 2,05-2,09 (m, 1 H), 3,54-3,60 (m, 1 H), 3,65-3,72 (m, 1 H), 3,81-3,89 (m, 1 H), 3,91-3,95 (m, 1 H).

[0343] D. (3R,4R)-tetrahidro-2H-piran-3,4-diamina

[0344] Una mezcla de (3R,4R)-3,4-diazidotetrahidro-2H-piran (1,0 g, 5,9 mmoles), di-ter-butil pirocarbonato (2,8 g, 12,9 mmoles) y Pd/C (10%, 1,0 g) en MeOH se agitó a temperatura ambiente durante 12 horas en atmósfera de H2 (50 psi). Después de la filtración, el residuo se concentró y se purificó por cromatografía de columna eluyendo con EtOAc y éter de petróleo (EtOAc/PE = 1/3) para dar el intermediario N,N-((3R,4R)-tetrahidro-2H-piran-3,4-diil)-biscarbamato de di-ter-butilo (1,2 g). El intermediario se disolvió en 1 M de HCl-EtOAc y se agitó a temperatura ambiente durante toda la noche para dar el compuesto del título (400 mg, 58%). 1H RMN (400 MHz, CDCl3) δ ppm 1,93-1,97 (m, 1 H), 2,12-2,22 (m, 1 H), 3,60-3,66 (m, 1 H), 3,76-3,79 (m, 2 H), 3,86-3,92 (m, 1 H), 4,04-4,15 (m, 1 H). [M+H] calc para C5H12N2O, 117; experimental, 117.

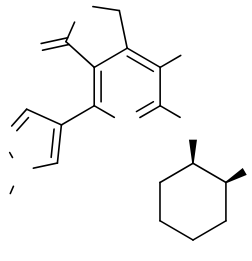
[0345] Ejemplo 27: 6-((3R,4R)-3-aminotetrahidro-2H-piran-4-ilamino)-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



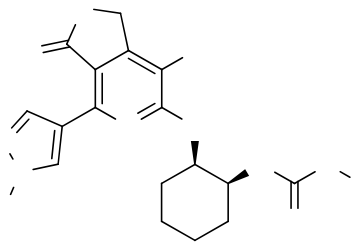
[0346] Una sal TFA del compuesto del título se preparó de manera similar al

ejemplo 26 utilizando (3R,4R)-tetrahidro-2H-piran-3,4-diamina en lugar de (1S,2R)-2-aminocilohexilcarbamato de ter-butilo. El estereoisómero deseado se aisló utilizando HPLC preparativa. 1H RMN (500 MHz, DMSO-d6) δ ppm 3,52 (m, 2 H), 3,78 - 4,01 (m & s, 10 H), 4,21 - 4,42 (m & s, 3 H), 6,50 (s, 1 H), 7,91 (br s, 2 H), 8,29 - 8,39 (m, 1 H), 8,88 - 8,96 (m, 1 H). [M+H] calc para C16H20N6O2, 329; experimental, 329.

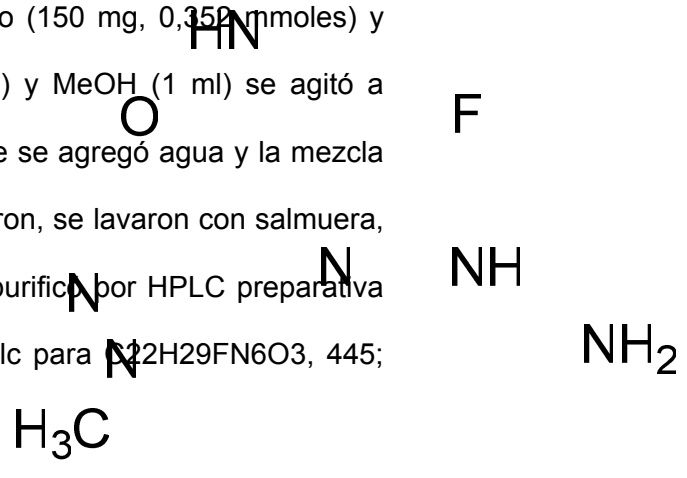
[0347] Ejemplo 28: 6-((1R,2S)-2-aminociclohexilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;



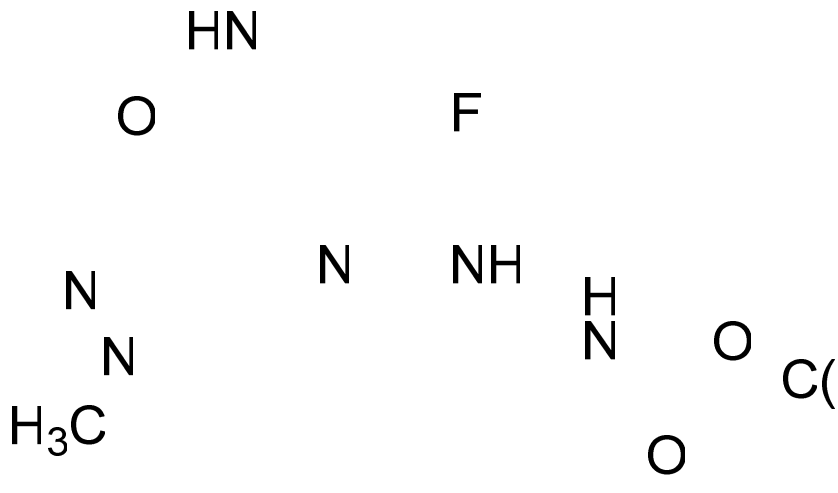
[0348] A. (1S,2R)-2-(7-fluoro-4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo



[0349] Una solución de (1S,2R)-2-(4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo (150 mg, 0,352 mmoles) y SELECTFLUOR® (150 mg, 0,422 mmoles) en DCM (1 ml) y MeOH (1 ml) se agitó a temperatura ambiente durante toda la noche. Posteriormente se agregó agua y la mezcla se extrajo con CHCl3 (3 x). Las fases orgánicas se combinaron, se lavaron con salmuera, se secaron sobre MgSO4, y se evaporaron. El residuo se purificó por HPLC preparativa para dar el compuesto del título (15 mg, 9,60%). [M+H] calc para C22H29FN6O3, 445; experimental, 445.



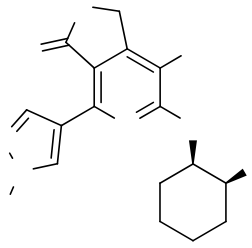
[0350] B. 6-((1R,2S)-2-aminociclohexilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-



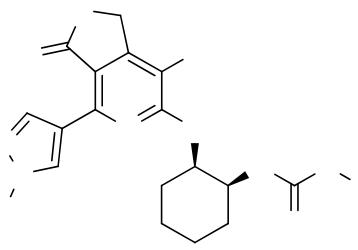
1H-pirrolo[3,4-c]piridin-3(2H)-ona

[0351] Una solución de (1S,2R)-2-(7-fluoro-4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo (15 mg, 0,034 mmoles) y TFA (0,5 ml, 6,49 mmoles) en DCM (0,5 ml) se agitó a temperatura ambiente durante 30 min. La mezcla se concentró y el residuo resultante se purificó por HPLC preparativa para dar una sal TFA del compuesto del título (7 mg, 60,2%). 1H RMN (500 MHz, DMSO-d6) δ ppm 1,37 – 2,01 (m, 8 H), 3,67 (br s, 1 H), 3,89 (s, 3 H), 4,32 – 4,43 (m, 2 H), 4,45 (br s, 1 H), 6,77 (d, J=6,35 Hz, 1 H), 7,93 (br s, 3 H), 8,30 (s, 1 H), 8,36 (s, 1 H), 8,84 (s, 1 H). [M+H] calc para C17H21FN6O, 345; experimental, 345.

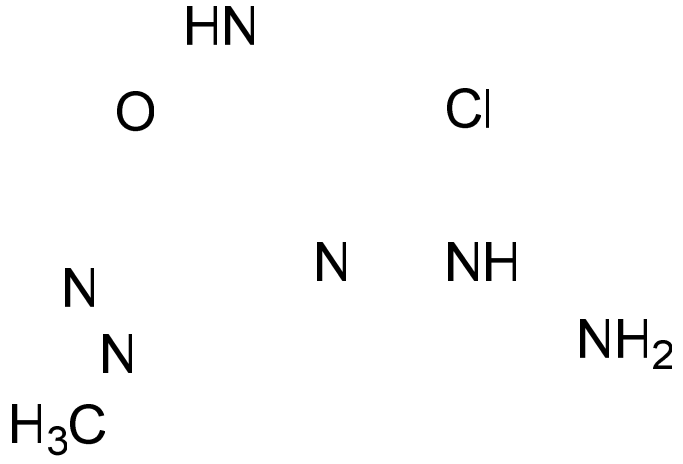
[0352] Ejemplo 29: 6-((1R,2S)-2-aminociclohexilamino)-7-cloro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

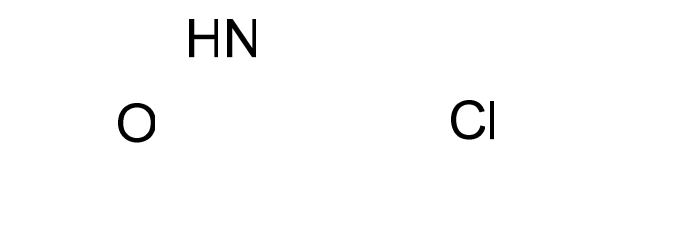


[0353] A. (1S,2R)-2-(7-cloro-4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo



[0354] Una solución de (1S,2R)-2-(4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo (30 mg, 0,070 mmoles) y N-clorosuccinimida (9,86 mg, 0,074 mmoles) en DCM (1 ml) se agitó a temperatura ambiente durante toda la noche. Se agregó más N-clorosuccinimida (1 eq) y la mezcla se agitó a temperatura ambiente durante 3 horas. Se agregaron agua y CHCl3 a la mezcla y



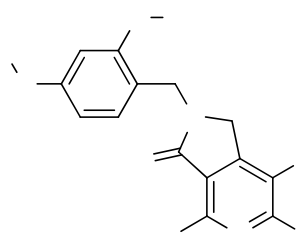


la fase orgánica se lavó con salmuera, se secó sobre MgSO4, y se evaporó. El residuo se purificó por HPLC preparativa para dar el compuesto del título (20 mg, 61,7%). 1H RMN (500 MHz, CDCl3) δ ppm 1,18 – 2,09 (m, 17 H), 4,02 (s, 3 H), 4,28 – 4,45 (m, 2 H), 5,80 (br s, 1 H), 8,39 (br s, 1 H), 9,03 (br s, 1 H). [M+H] calc para C22H29ClN6O3, 461; experimental, 461.

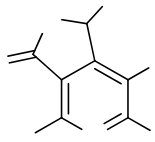
[0355] B. 6-((1R,2S)-2-aminociclohexilamino)-7-cloro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona

[0356] Una solución de (1S,2R)-2-(7-cloro-4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo (10,00 mg, 0,022 mmoles) en HCl (0,5 ml, 16,46 mmoles) y HOAc (1 ml) se agitó a temperatura ambiente durante 30 min. La mezcla de reacción se concentró y el residuo resultante se lavó con IPE para dar la sal HCl del compuesto del título (5 mg, 63,9%). 1H RMN (500 MHz, DMSO-d6) δ ppm 1,48 – 1,97 (m, 8 H), 3,72 – 3,78 (m, 1 H), 3,96 (br s, 3 H), 4,35 (d, J=4,88 Hz, 2 H), 4,57 (br s, 1 H), 6,29 (d, J=6,83 Hz, 1 H), 7,93 (br s, 2 H), 8,40 – 8,45 (m, 1 H), 8,49 (s, 1 H), 8,98 (s, 1 H). [M+H] calc para C17H21ClN6O, 361; experimental, 361.

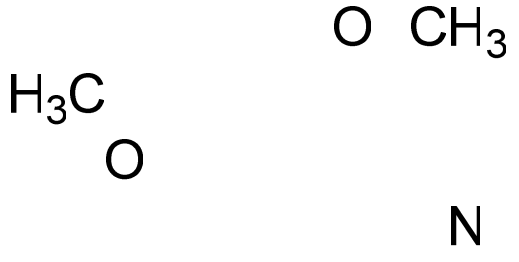
[0357] Preparación 12: 4,6-dicloro-2-(2,4-dimetoxibencil)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona



[0358] A. 4,6-dicloro-7-fluoro-1-hidroxifluoro[3,4-c]piridin-3(1H)-ona



[0359] A una solución de butillitio-hexano (100 ml; 160 mmoles) en THF (200 ml) se agregó lentamente diisopropilamina (27,4 ml, 192 mmoles) en THF (15 ml) a -78ºC. La



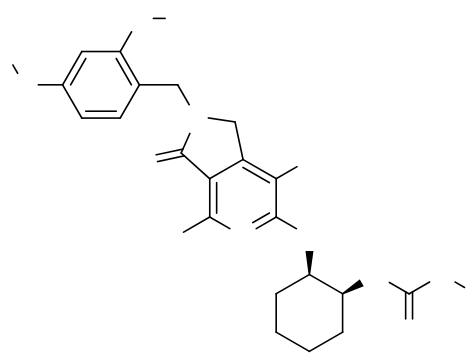
mezcla se agitó a la misma temperatura durante 15 min. Una solución del ácido 2,6-dicloro-5-fluoronicotínico (14,98 g, 71,4 mmoles) en THF (15 ml) se agregó y la mezcal se agitó durante 2 horas. A continuación, se agregó DMF (29,3 ml, 378 mmoles) y la mezcla se agitó durante 1 hora. Se agregó ácido clorhídrico (1N, 400 ml) y la mezcla se extrajo posteriormente con EtOAc (2 x 300 ml). La fase orgánica se basificó con solución de NaHCO3 acuoso saturado y la fase acuosa se separó. La fase acuosa se re-acidificó con HCl 1N (300 ml) y se extrajo con EtOAc (2 x 300 ml). La fase orgánica se lavó con H2O (200 ml) y salmuera (200 ml), se secó sobre MgSO4, y se evaporó. El residuo se lavó con hexano/EtOAc para dar el compuesto del título en forma de un sólido de color blanco (11,5 g, 67,7%). 1H RMN (500 MHz, DMSO-d6) δ ppm 6,85 (br s, 1 H), 8,82 (br s, 1 H).

[0360] B. 4,6-dicloro-2-(2,4-dimetoxibencil)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona

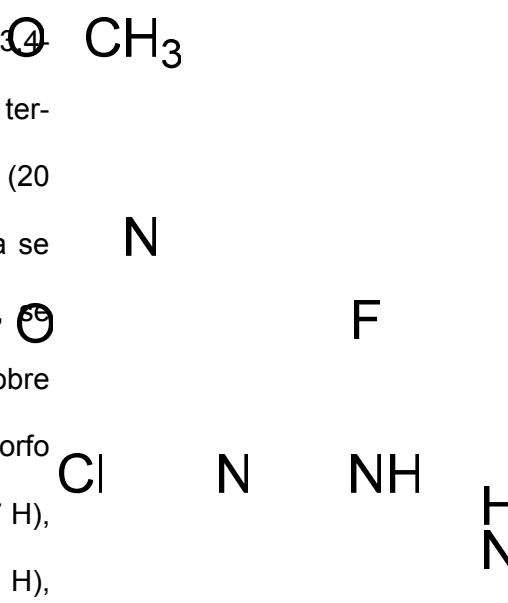
[0361] Una mezcla de 4,6-dicloro-7-fluoro-1-hidroxifluoro[3,4-c]piridin-3(1H)-ona (25,8 g, 108 mmoles) y (2,4-dimetoxifenil)metanamina (34,2 ml, 228 mmoles) en MeOH (400 ml) se agitó a temperatura ambiente durante 2 horas. Se agregó triacetoxihidroborato de sodio (22,98 g, 108 mmoles) a la mezcla, la cual se agitó a temperatura ambiente durante 2 horas. A continuación, se agregó HCl (2N, 120 ml) y el sólido resultante (17,3 g) se aisló por filtración. Una mezcla del sólido, clorhidrato N1-((etilimino)metileno)-N3,N3-dimetilpropano-1,3-diamina (10,35 g, 54 mmoles) y 1H-benzo[d][1,2,3]triazol-1-ol hidrato (8,27 g, 54 mmoles) en DMF (200 ml) se agitó a temperatura ambiente durante 2 horas, A continuación, se agregó agua y la mezcla se extrajo con EtOAc (2 x 300 ml). Las fases orgánicas se combinaron, se lavaron con solución de NaHCO3 acuoso saturado (300 ml), H2O (300 ml), y salmuera (300 ml), se secaron sobre Na2SO4 anhidro, y se filtraron. El filtrado se concentró a presión reducida y el residuo se lavó con EtOAc para dar el compuesto del título en forma de un sólido de color amarillo pálido (6,7 g, 16,7%). [M+H] calc para C16H13Cl2FN2O3, 371; experimental, 371.

[0362] Preparación 13: (1S,2R)-2-(4-cloro-2-(2,4-dimetoxibencil)-7-fluoro-3-oxo-

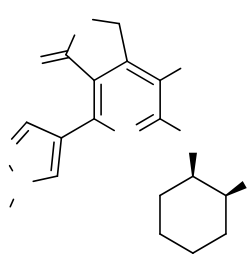
2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo



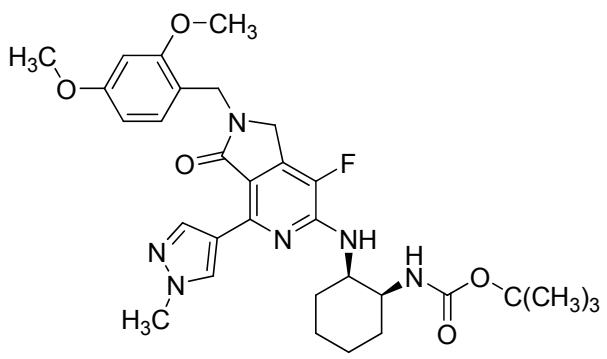
[0363] Una mezcla de 4,6-dicloro-2-(2,4-dimetoxibencil)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona (4,8 g, 12,93 mmoles) y (1S,2R)-2-aminociclohexilcarbamato de ter-butilo (4,16 g, 19,40 mmoles) y diisopropiletilamina (3,39 ml, 19,40 mmoles) en ACN (20 ml) se agitó a 100ºC durante 3 días. Se agregaron agua y EtOAc y la fase acuosa se extrajo con EtOAc. Las fases orgánicas se combinaron, se lavaron con salmuera, se secaron sobre MgSO4, y se evaporaron. El residuo se purificó por cromatografía sobre SiO2 (hexano/EtOAc=1/1) para dar el compuesto del título en forma de un sólido amorfo de color marrón (3,31 g, 46,6%). 1H RMN (500 MHz, CDCl3) δ ppm 1,35 – 2,02 (m, 17 H), 3,80 (s, 3 H), 3,84 (s, 3 H), 4,01 (br s, 1 H), 4,20 (s, 2H), 4,23 (br s, 1 H), 4,66 (s, 2 H), 4,91 (br s, 1 H), 6,40 – 6,52 (m, 2 H), 7,20 -7,28 (m, 1 H). [M+H] calc para C27H34ClFN4O5, 549; experimental, 549.



[0364] Ejemplo 30: 6-((1R,2S)-2-aminociclohexilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona (sal HCl).



[0365] A. (1S,2R)-2-(2-(2,4-dimetoxibencil)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo



[0366] Una mezcla de (1S,2R)-2-(4-cloro-2-(2,4-dimetoxibencil)-7-fluoro3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo (200 mg, 0,364 mmoles), carbonato de sodio (77 mg, 0,729 mmoles), 1-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (91 mg, 0,437 mmoles) y bis(trifenilfosfina)paladio cloruro (25,6 mg, 0,036 mmoles) en DME (2 ml) y H2O (0,667 ml) se agitó a 85ºC durante 2 horas, A la mezcla resultante se agregó EtOAc. La fase acuosa se extrajo con EtOAc. Las fases orgánicas se combinaron, se lavaron con salmuera, se secaron sobre MgSO4, y se evaporaron. El residuo se purificó por cromatografía sobre SiO2 (hexano/EtOAc=2/3) para dar el compuesto del título en forma de un aceite de color amarillo (88 mg, 40.6%). 1H RMN (500 MHz, CDCl3) δ ppm 1,28 – 2,01 (m, 17 H), 3,80 (d, J=2,93 Hz, 3 H), 3,85 (s, 3 H), 3,91 – 4,01 (m, 4 H), 4,23 (br s, 2 H), 4,41 (br s, 1 H), 4,68 (d, J=1,95 Hz, 2 H), 5,36 (br s, 1 H), 6,36 – 6,54 (m, 2 H), 7,15 – 7,21 (m, 1 H), 8,26 (br s, 1 H), 9,02 (br s, 1 H). [M+H] calc para C31H39FN6O5, 595; experimental, 595.

[0367] B. 6-((1R,2S)-2-aminociclohexilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona

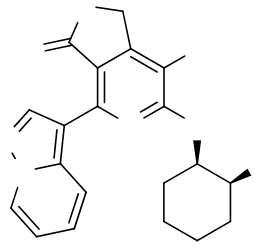
Una solución de (1S,2R)-2-(2-(2,4-dimetoxibencil)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo (2,4 g, 4,04 mmoles) y TFA (1 ml, 64,9 mmoles) se agitó a t80ºC durante 30 min. La suspensión resultante se diluyó con EtOAc (5 ml) y se filtró. El filtrado se evaporó in vacuo. El residuo se diluyó con H2O (300 ml) y EtOAc (100 ml) y se filtró. El precipitado se lavó con EtOAc y se secó para dar el compuesto del título en forma de una sal TFA

(900 mg). El filtrado se extrajo con EtOAc (200 ml). La fase acuosa se neutralizó con solución de NaHCO3 acuoso saturado y se extrajo con EtOAc (2 x 400 ml) y THF (2 x 200 ml). Las fases orgánicas se combinaron, se secaron sobre MgSO4, y se evaporaron. El residuo se lavó con EtOAc para dar un primer cultivo (400 ml) del compuesto del título en forma de base libre. La sal TFA obtenida anteriormente se diluyó con solución de NaHCO3 acuoso saturado (20 ml) y se agitó a temperatura ambiente durante toda la noche. La suspensión resultante se filtró y los sólidos se lavaron con EtOAc para dar un segundo cultivo (700 mg) del compuesto del título como la base libre (1,1 g, 79%).

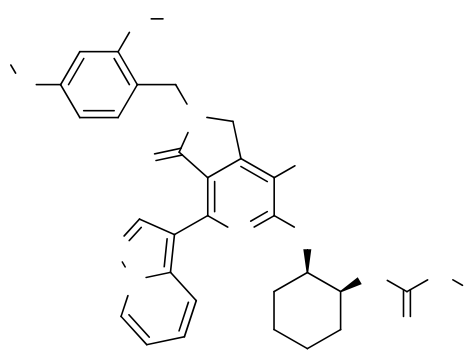
[0368] C. 6-((1R,2S)-2-aminociclohexilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona (sal HCl).

[0369] A una solución de 6-((1R,2S)-2-aminociclohexilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona (2,300 g, 6,68 mmoles) en THF (300 ml) se agregó HCl 1N en EtOAc (20 ml, 20,0 mmoles) gota a gota y la mezcla se agitó a temperatura ambiente durante 30 min. La suspensión resultante se filtró y el precipitado se recolectó y se lavó con EtOAc (10 ml) para dar la sal HCl bruta del compuesto del título (2,55 g). El compuesto bruto se recristalizó a partir de EtOH (60 ml) y H2O (16 ml) para dar la sal HCl del compuesto del título en forma de un sólido de color blanco (1,5 g, 59,0%). 1H RMN (500 MHz, DMSO-d6) δ ppm 1,34 – 1,99 (m, 8 H), 3,67 (br s, 3 H), 3,89 (br s, 3 H), 4,32 – 4,43 (m, 2 H), 4,45 (br s, 1 H), 6,76 (d, J=5,86 Hz, 1 H), 7,88 (br s, 3 H), 8,29 (d, J=4,88 Hz, 1 H), 8,36 (s, 1 H), 8,84 (s, 1 H). [M+H] calc para C17H21FN6O, 345; experimental, 345.

[0370] Ejemplo 31: 6-((1R,2S)-2-aminociclohexilamino)-7-fluoro-4-(pirazolo[1,5-a]piridin-3-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



[0371] A. (1S,2R)-2-(2-(2,4-dimetoxibencil)-7-fluoro-3-oxo-4-(pirazolo[1,5-a]piridin-3-il)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo



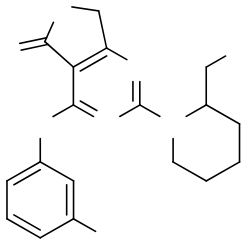
[0372] Una mezcla de (1S,2R)-2-(4-cloro-2-(2,4-dimetoxibencil)-7-fluoro3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo (100 mg, 0,182 mmoles), 3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)pirazolo[1,5-a]piridina (53,4 mg, 0,219 mmoles) carbonato de sodio (48,3 mg, 0,455 mmoles) y tetrakis(trifenilfosfina)paladio (21,05 mg, 0,018 mmoles) en DME (1 ml) y H2O (0,333 ml) se agitó a 85ºC durante 3 horas. A continuación de la reacción, la mezcla se filtró y el filtrado se diluyó con EtOAc y H2O. La fase acuosa se extrajo con EtOAc. Las fases orgánicas se combinaron, se lavaron con salmuera, se secaron sobre MgSO4, y se evaporaron. El residuo se purificó por cromatografía sobre SiO2 para dar el compuesto del título (53 mg, 46,1%). 1H RMN (500 MHz, CDCl3) δ ppm 1,17 – 2,03 (m, 17 H), 3,74 – 3,81(m, 3 H), 3,84 – 3,89 (m, 3 H), 4,04 (br s, 1 H), 4,26 (br s, 2 H), 4,46 (br s, 1 H), 4,71 (br s, 2 H), 6,36 – 6,55 (m, 2 H), 6,83 (d, J=5,86 Hz, 1 H), 7,18 – 7,31 (m, 2 H), 8,42 (br s, 1 H), 8,47 – 8,57 (m, 1 H), 9,42 (br s, 1 H).

[0373] B. 6-((1R,2S)-2-aminociclohexilamino)-7-fluoro-4-(pirazolo[1,5-a]piridin-3-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona

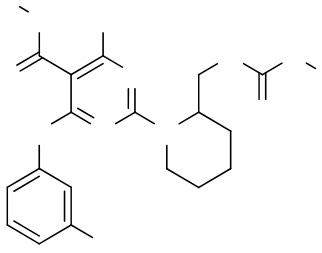
[0374] Una mezcla de (1S,2R)-2-(2-(2,4-dimetoxibencil)-7-fluoro-3-oxo-4-(pirazolo[1,5-a]piridin-3-il)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo (52 mg, 0,082 mmoles) y TFA (1 ml, 12,98 mmoles) se agitó a 65ºC durante 30 min. La mezcla se concentró y el residuo se purificó por HPLC preparativa para dar el

compuesto del título en forma de un sólido de color blanco (15 mg, 47,8%). 1H RMN (500 MHz, DMSO-d6) δ ppm 1,21 – 2,07 (m, 8 H), 3,31 (br s, 1 H), 4,18 – 4,26 (m, 1 H), 4,46 (br s, 2 H), 6,61 (br s, 1 H), 7,09 (d, J=6,35 Hz, 1 H), 7,49 (d, J=7,32, 1 H), 8,36 (br s, 1 H), 8,59 (d, J= 7,81 Hz, 1 H), 8,83 (d, J=6,83 Hz, 1 H), 9,56 (br s, 1 H). [M+H] calc para C20H21FN6O, 381; experimental, 381.

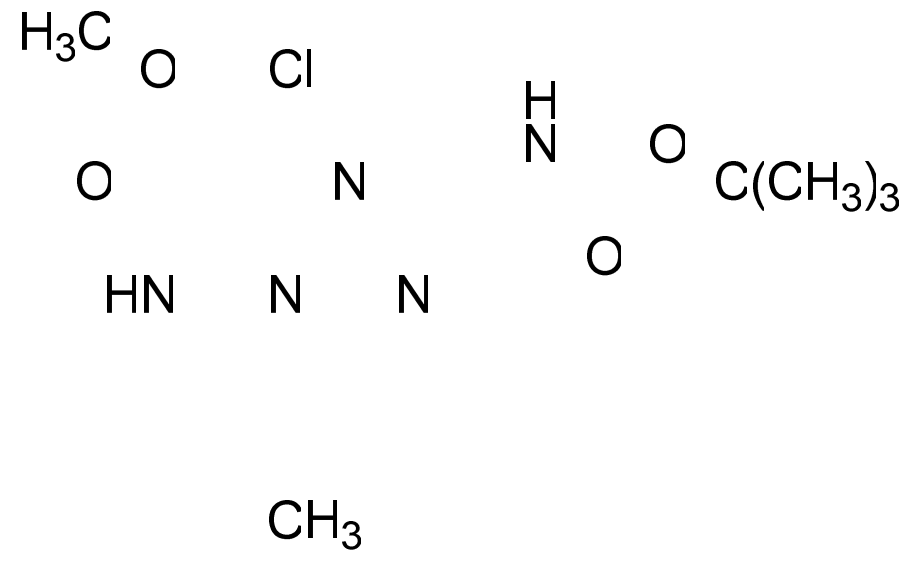
[0375] Ejemplo 32: 2-(2-(aminometil)piperidin-1-il)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona



[0376] A. 2-(2-((ter-butoxicarbonilamino)metil)piperidin-1-il)-4-cloro-6-(m-tolilamino)pirimidin-5-carboxilato de metilo

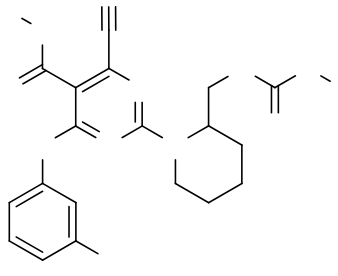


[0377] Una mezcla de 2,4-dicloro-6-(m-tolilamino)pirimidin-5-carboxilato de metilo (600,6 mg, 1,924 mmoles), piperidin-2-ilmetilcarbamato de ter-butilo (500,9 mg, 2,337 mmoles) y N-etil-N-isopropilpropan-2-amina (0,4 ml, 2,296 mmoles) en DMF (10 ml) se agitó a 0ºC durante 3 horas. Se agregó agua (50 ml) a la mezcla, la cual se extrajo con EtOAc (2 x 40 ml). Las capas orgánicas se lavaron con NaHCO3 acuoso saturado (20 ml), agua (20 ml), y salmuera (20 ml), se secaron sobre Na2SO4 anhidro, y a continuación se filtraron (DM1020). El filtrado se concentró a presión reducida y el residuo se purificó por cromatografía de columna (SiO2, hexanos/EtOAc=4/1) para dar el compuesto del título en

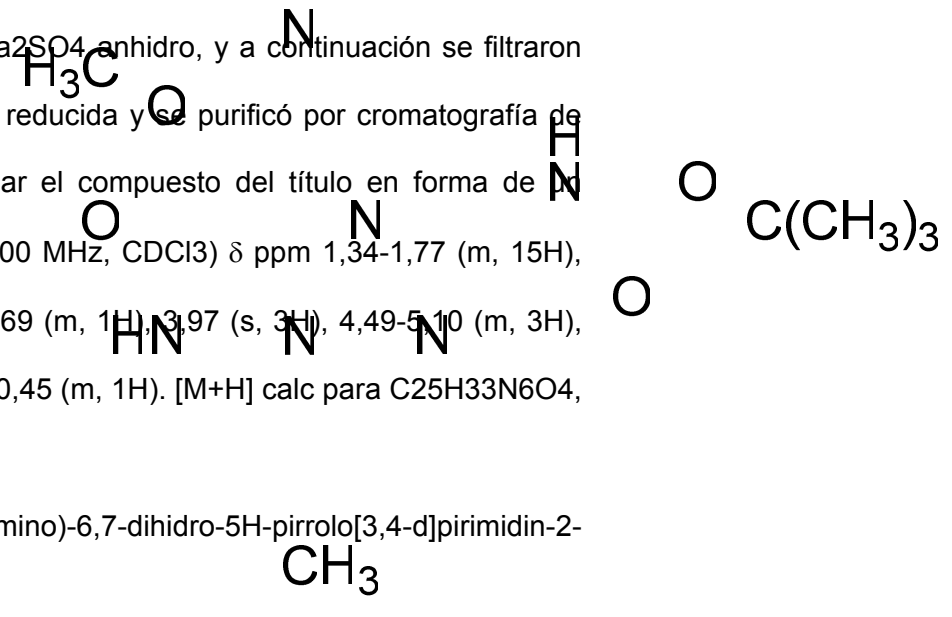


forma de un aceite transparente (310,5 mg). 1H RMN (500 MHz, CDCl3) δ ppm 1,34-1,74 (m, 15H), 2,35-2,37 (m, 3H), 3,03-3,21 (m, 2H), 3,60-3,71 (m, 1H), 3,90 (s, 3H), 4,43-5,04 (m, 3H), 6,94-6,98 (m, 1H), 7,23-7,46 (m, 3H), 10,13-10,43 (m, 1H). [M+H] calc para C24H33ClN5O4, 490; experimental, 490.

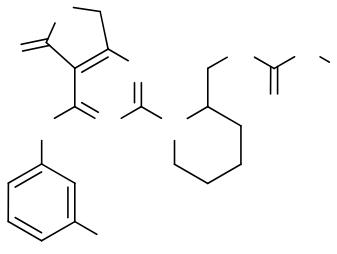
[0378] B. 2-(2-((ter-butoxicarbonilamino)metil)piperidin-1-il)-4-ciano-6-(m-tolilamino)pirimidin-5-carboxilato de metilo



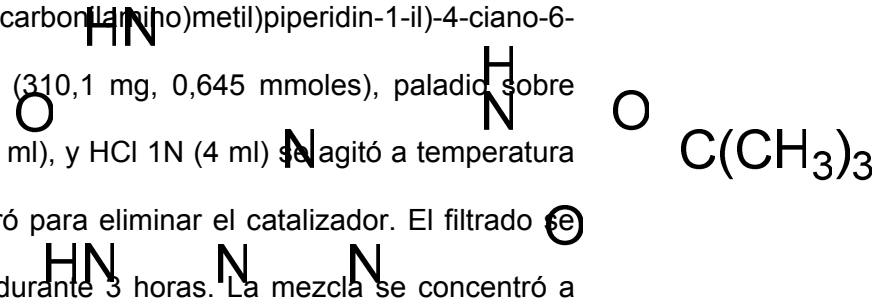
[0379] Una mezcla de 2-(2-((ter-butoxicarbonilamino)metil)piperidin-1-il)-4-cloro-6-(m-tolilamino)pirimidin-5-carboxilato de metilo (399,7 mg, 0,816 mmoles), tetrakis(trifenilfosfina)paladio (0) (96,3 mg, 0,083 mmoles), y cianuro de zinc (53,2 mg, 0,453 mmoles) en DMF (5 ml) se agitó a 120ºC durante 1 hora bajo irradiación de microondas. Se agregó agua (50 ml) y la mezcla se extrajo con EtOAc (2 x 100 ml). Las capas orgánicas se lavaron nuevamente con NaHCO3 acuoso saturado (50 ml), agua (50 ml), y salmuera (50 ml), se secaron sobre Na2SO4 anhidro, y a continuación se filtraron (DM1020). El filtrado se concentró a presión reducida y se purificó por cromatografía de columna (SiO2, hexanos/EtOAc=4/1) para dar el compuesto del título en forma de un aceite incoloro (315,0 mg, 80%). 1H RMN (500 MHz, CDCl3) δ ppm 1,34-1,77 (m, 15H), 2,36-2,39 (m, 3H), 3,00-3,21 (m, 2H), 3,49-3,69 (m, 1H), 3,97 (s, 3H), 4,49-5,10 (m, 3H), 6,96-7,02 (m, 1H), 7,24-7,41 (m, 3H), 10,14-10,45 (m, 1H). [M+H] calc para C25H33N6O4, 481; experimental, 481.



[0380] C. (1-(5-oxo-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-2-il)piperidin-2-il)metilcarbamato de ter-butilo



[0381] Una mezcla de 2-(2-((ter-butoxicarbonilamino)metil)piperidin-1-il)-4-ciano-6-(m-tolilamino)pirimidin-5-carboxilato de metilo (310,1 mg, 0,645 mmoles), paladio sobre carbono (72,4 mg, 0,680 mmoles) en EtOH (8 ml), y HCl 1N (4 ml) se agitó a temperatura ambiente durante 16 horas. La mezcla se filtró para eliminar el catalizador. El filtrado se trató con NaHCO3 acuoso saturado (20 ml) durante 3 horas. La mezcla se concentró a presión reducida y el residuo se extrajo con EtOAc (2 x 40 ml). Las capas orgánicas se lavaron nuevamente con NaHCO3 acuoso saturado (20 ml), agua (20 ml), y salmuera (20 ml), se secaron sobre Na2SO4 anhidro, y a continuación se filtraron a través de SiO2 El filtrado se concentró a presión reducida para dar el compuesto del título en forma de un sólido incoloro (213,4 mg, 73%). 1H-RMN (DMSO-d6) δ ppm 1,28 (s, 9H), 1,35 (br s, 1H), 1,49-1,56 (m, 2H), 1,67-1,69 (m, 3H), 2,31 (s, 3H), 3,06 (br s, 1H), 3,24 (br s, 2H), 4,16 (s, 2H), 4,67 (br s, 1H), 5,08 (br s, 1H), 6,77 (br s, 1H), 6,87 (d, 1H, J=7,0Hz), 7,23-7,25 (m, 1H), 7,53 (br s, 2h), 8,07 (s, 1H), 8,55 (s, 1H). [M+H] calc para C24H33N6O3, 453; experimental, 453,5.

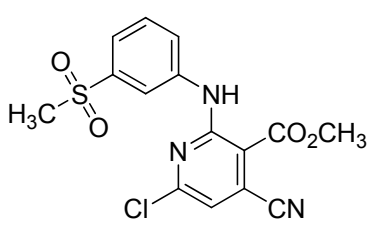


[0382] D. 2-(2-(aminometil)piperidin-1-il)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona

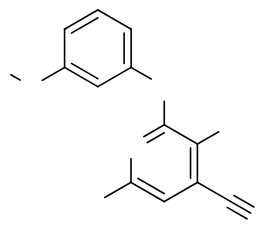
[0383] A una solución de (1-(5-oxo-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-2-il)piperidin-2-il)metilcarbamato de ter-butilo (207,1 mg, 0,458 mmoles) en HOAc (3 ml) se agregó HCl (1 ml, 32,9 mmoles). La mezcla se agitó a temperatura ambiente durante 1 hora y a continuación se concentró a presión reducida. El residuo se trató con NaHCO3 acuoso saturado (50 ml) y se extrajo con EtOAc-THF (1/1, 2x 40 ml). Las capas orgánicas se lavaron nuevamente con NaHCO3 acuoso saturado (20 ml), agua

(20 ml), y salmuera (20 ml), se secaron sobre Na2SO4 anhidro, y a continuación se filtraron. El filtrado se concentró a presión reducida y el residuo se lavó con EtOH para dar el compuesto del título en forma de un sólido de color amarillo pálido (27,4 mg, 17%). 1H-RMN (DMSO-d6) δ ppm 1,32-1,70 (m, 7H), 1,89-1,92 (m, 1H), 2,31 (s, 3H), 2,74-2,87 (m, 1H), 2,81-2,85 (m, 1H), 2,94 (br s, 1H), 4,17 (s, 2H), 4,68-4,79 (m, 2H), 6,88 (d, 1H, J=7,5 Hz), 7,22- 7,25(m, 1H), 7,49-7,50 (m, 1H), 7,60 (s, 1H), 8,06 (s, 1H), 8,58 (s, 1H). [M+H] calc para C19H25N6O, 353; experimental, 353,5.

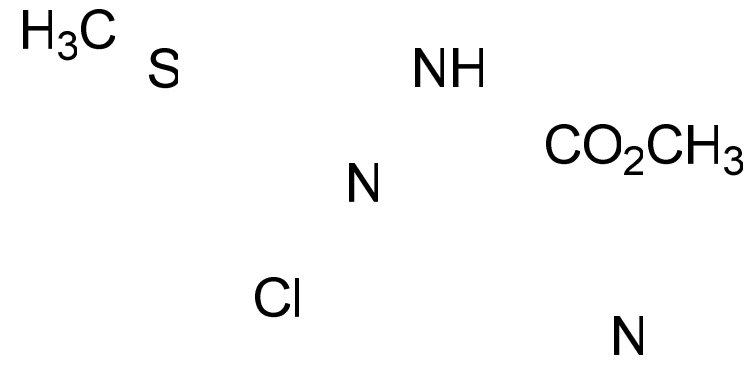
[0384] Preparación 14: 6-cloro-4-ciano-2-(3-(metilsulfonil)fenilamino)nicotinato de metilo.



[0385] A. 6-cloro-4-ciano-2-(3-(metiltiol)fenilamino)nicotinato de metilo.



[0386] Una mezcla de 2,6-dicloro-4-cianonicotinato de metilo (340,8 mg, 1,475mmoles), DIPEA (0,3 ml, 1,718 mmoles) y 3-(metiltio)anilina (234,8 mg, 1,687 mmoles) en CH3CN (5 ml) se agitó a 60ºC durante 2 días. Después de que se enfrió la mezcla, se agregó NaHCO3 acuoso saturado (30 ml) y la mezcla se extrajo con EtOAc (2 x 30 ml). Las capas orgánicas se lavaron nuevamente con NaHCO3 acuoso saturado (20 ml), agua (20 ml), y salmuera (20 ml), se secaron sobre Na2SO4 anhidro, y a continuación se filtraron a través de SiO2 El filtrado se concentró a presión reducida y el residuo se lavó con IPE y se filtró para dar el compuesto del título en forma de un sólido de color amarillo (157,8 mg, 85%).. El filtrado se purificó por cromatografía sobre SiO2

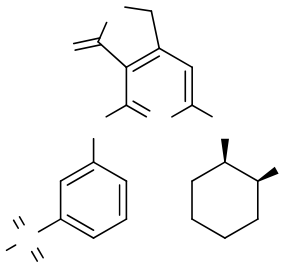


(hexano/EtOAc=8/1) para dar otro cultivo (135,5 mg) del compuesto del título en forma de un aceite de color amarillo (293 mg, 60%). 1H-RMN (CDCl3) δ ppm 2,52 (s, 3H), 4,05 (s, 3H), 7,00 (s, 1H), 7,03-7,05 (m, 1H), 7,25-7,32 (m, 2H), 7,66-7,67 (m, 1H), 10,51 (br s, 1H). [M+H] calc para C15H13ClN3O2S, 334; experimental, 334.

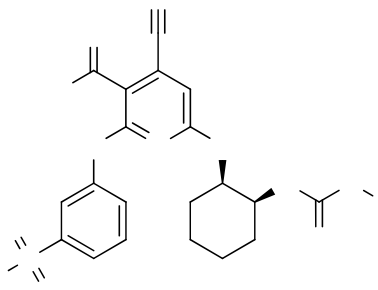
[0387] B. 6-cloro-4-ciano-2-(3-(metilsulfonil)fenilamino)nicotinato de metilo.

[0388] A una solución de 6-cloro-4-ciano-2-(3-(metiltiol)fenilamino)nicotinato de metilo (291,1 mg, 0,872 mmoles) en DMF (10 ml) se agregó el ácido m-cloroperoxibenzoico (538,9 mg, 2,405 mmoles) a 0ºC. La mezcla se agitó a temperatura ambiente durante 16 horas. Se agregó Na2S2O3 acuoso (30 ml) y la mezcla se extrajo con EtOAc (2 x 30 ml). Las capas orgánicas se lavaron con NaHCO3 acuoso saturado (20 ml), agua (20 ml), y salmuera (20 ml), se secaron sobre Na2SO4 anhidro, y a continuación se filtraron (DM1020). El filtrado se concentró a presión reducida y el residuo se lavó con IPE para dar el compuesto del título en forma de un sólido de color amarillo (158,2 mg, 50%).. 1H-RMN (CDCl3) δ ppm 3,11 (s, 3H), 4,07 (s, 3H), 7,10 (s, 1H), 7,57-7,60 (m, 1H), 7,70-7,72 (m, 1H), 7,91-7,93 (m, 1H), 8,25-8,26 (m, 1H), 10,73 (s, 1H).

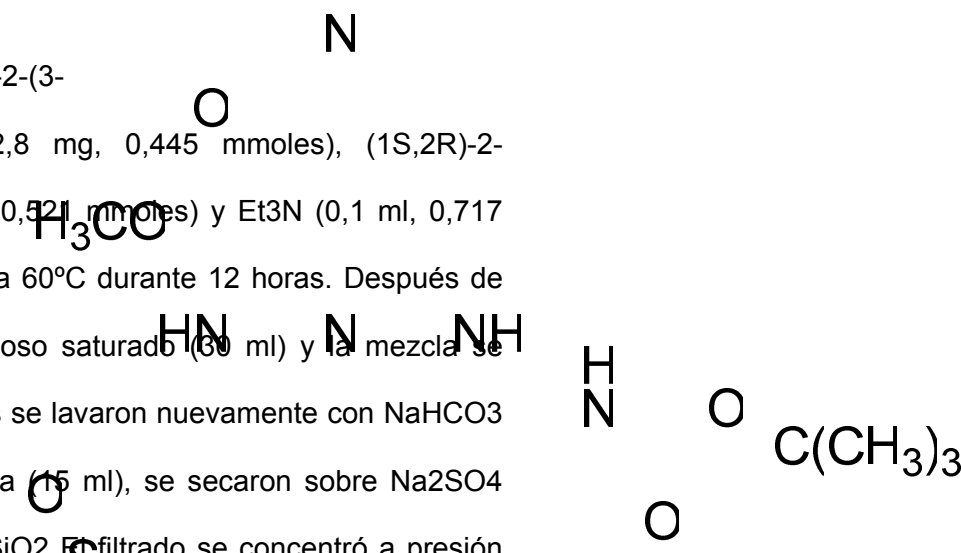
[0389] Ejemplo 33: 6-((1R,2S)-2-aminociclohexilamino)-4-(3-(metilsulfonil)fenilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



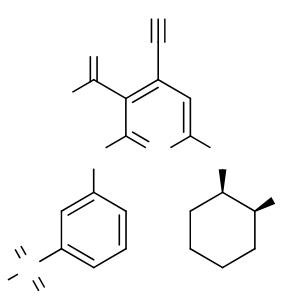
[0390] A. 6-((1R,2S)-2-(ter-butoxicarbonilamino)ciclohexilamino)-4-ciano-2-(3-(metilsulfonil)fenilamino)nicotinato de metilo



[0391] Una mezcla de 6-cloro-4-ciano-2-(3-(metilsulfonil)fenilamino)nicotinato de metilo (162,8 mg, 0,445 mmoles), (1S,2R)-2-aminociclohexilcarbamato de ter-butilo (111,6 mg, 0,521 mmoles) y Et3N (0,1 ml, 0,717 mmoles) en THF (6 ml) y DMF (6,00 ml) se agitó a 60ºC durante 12 horas. Después de que se enfrió la mezcla, se agregó NaHCO3 acuoso saturado (30 ml) y la mezcla se extrajo con EtOAc (2 x 30 ml). Las capas orgánicas se lavaron nuevamente con NaHCO3 acuoso saturado (15 ml), agua (15 ml), y salmuera (15 ml), se secaron sobre Na2SO4 anhidro, y a continuación se filtraron a través de SiO2 El filtrado se concentró a presión reducida y el residuo se lavó con IPE para dar el compuesto del título en forma de un sólido de color amarillo (182,2 mg, 75%).. 1H-RMN (CDCl3) δ ppm 1,42-1,67 (m, 15H), 1,84-1,91 (m, 2H), 3,07 (s, 3H), 3,95-3,97 (m, 4H), 4,16-4,17 (m, 1H), 4,77 (s, 1H), 6,24 (s, 1H), 7,48-7,51 (m, 1H), 7,58-7,61 (m, 1H), 7,77-7,78 (m, 1H), 8,41 (s, 1H), 10,99 (s, 1H), 1H no detectado.



[0392] B. 6-((1R,2S)-2-aminociclohexilamino)-4-ciano-2-(3-(metilsulfonil)fenilamino)nicotinato de metilo



[0393] A una solución de 6-((1R,2S)-2-(ter-butoxicarbonilamino)ciclohexilamino)-4-

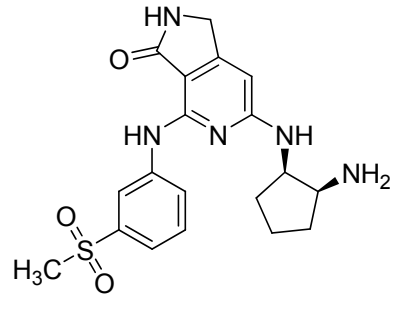
ciano-2-(3-(metilsulfonil)fenilamino)nicotinato de metilo (178,3 mg, 0,328 mmoles) en HOAc (4 ml) se agregó HCl (4 ml, 132 mmoles). La mezcla se agitó a temperatura ambiente durante 4 hora y a continuación se concentró a presión reducida. Se agregaron agua (15 ml) y 1M de HCl (15 ml) al concentrado y la capa acuosa se lavó con EtOAc (10 ml). La capa acuosa lavada se basificó con NaHCO3 acuoso saturado (50 ml) y se extrajo con EtOAc (2 x 30 ml). Las capas orgánicas se combinaron, se lavaron con NaHCO3 acuoso saturado (20 ml), agua (20 ml), y salmuera (20 ml), se secaron sobre Na2SO4 anhidro, y se filtraron. El filtrado se concentró a presión reducida para dar el compuesto del título en forma de un sólido de color marrón (123,2 mg, 85%). 1H-RMN (CDCl3) δ ppm 1,45-16,4 (m, 6H), 1,77-1,79 (m, 4H), 3,06 (s, 3H), 3,17-3,18 (m, 1H), 3,94 (s, 3H), 4,10-4,14 (m, 1H), 6,03-6,05 (m, 1H), 6,29 (s, 1H), 7,48-7,51 (m, 1H), 7,58-7,60 (m, 1H), 7,71-7,72 (m, 1H), 8,53 (s, 1H), 11,01 (s, 1H).

[0394] C. 6-((1R,2S)-2-aminociclohexilamino)-4-(3-(metilsulfonil)fenilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona

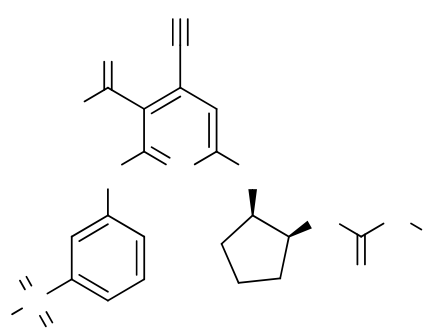
[0395] Una mezcla de 6-((1R,2S)-2-aminociclohexilamino)-4-ciano-2-(3-(metilsulfonil)fenilamino)nicotinato de metilo (117,3 mg, 0,264 mmoles) y paladio sobre carbono (23,6 mg, 0,222 mmoles) en MeOH (4 ml) y HCl 1N (4 ml) se agitó a temperatura ambiente durante 16 horas en una atmósfera de hidrógeno. La mezcla se filtró para eliminar el catalizador y el filtrado se trató con NaHCO3 acuoso saturado (20 ml) y se agitó a temperatura ambiente durante 20 horas. La mezcla se concentró a presión reducida y el residuo se extrajo con EtOAc/THF (2/1, 2 x 30 ml). Las capas orgánicas se lavaron con NaHCO3 acuoso saturado (15 ml), agua (15 ml), y salmuera (15 ml), se secaron sobre Na2SO4 anhidro, y a continuación se filtraron. El filtrado se concentró a presión reducida y el residuo se purificó por cromatografía de columna (DM1020, EtOAc/MeOH=20/1) para dar el producto deseado (37,2 mg, 34%). El producto se recristalizó a partir de EtOH para dar el compuesto del título en forma de un sólido incoloro (13,2 mg, 12%). 1H-RMN (DMSO-d6) δ ppm 1,31-1,41 (m, 4H), 1,55-1,68 (m,

6H), 3,05 (s, 1H), 3,21 (s, 3H), 4,08 (s, 1H), 4,23 (s, 2H), 6,17 (s, 1H), 6,78-6,79 (m, 1H), 7,46-7,47 (m, 1H), 7,53-7,56 (m, 1H), 7,96-7,99 (m, 2H), 8,49 (s, 1H), 9,18 (s, 1H).

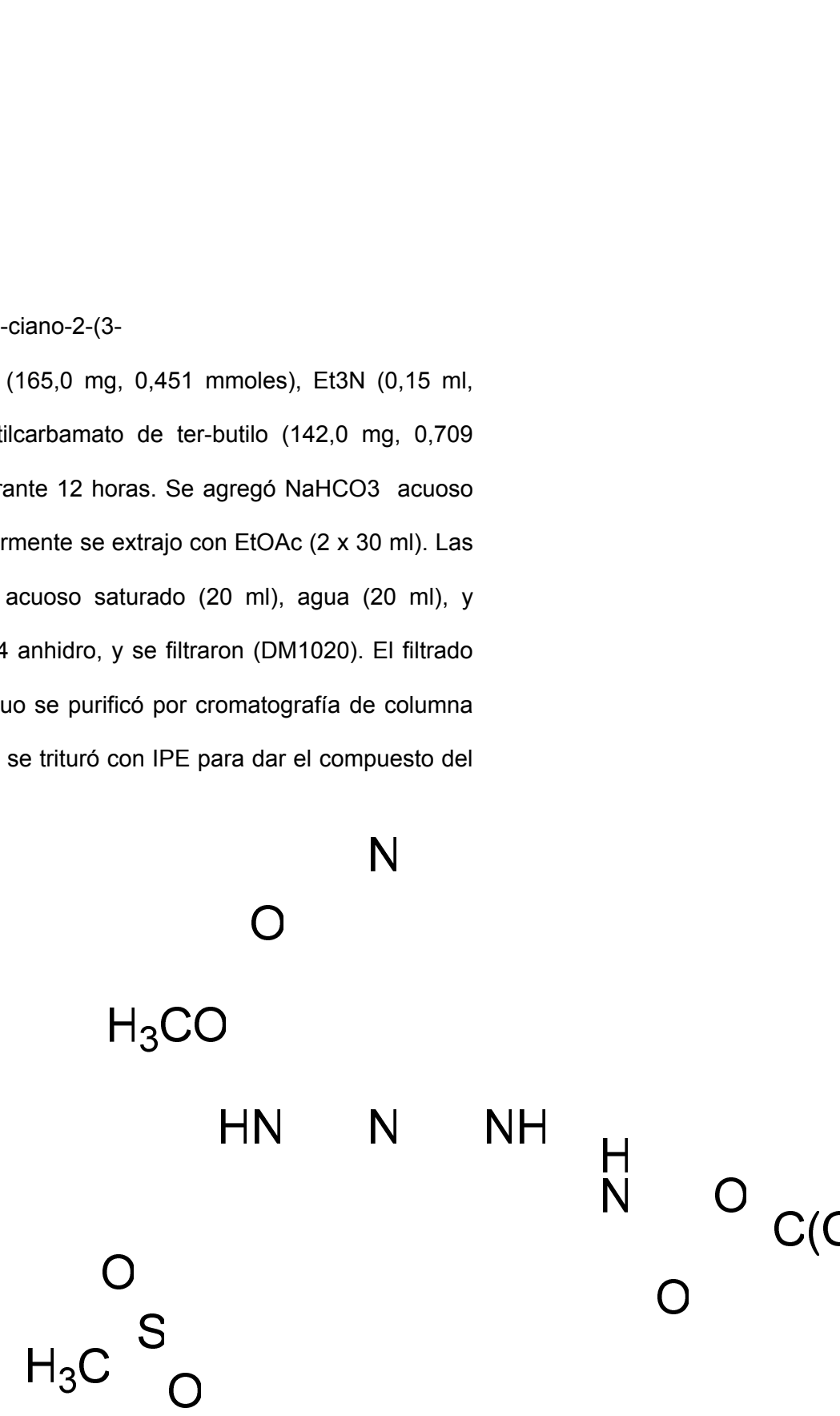
[0396] Ejemplo 34: 6-((1R,2S)-2-aminociclopentilamino)-4-(3-(metilsulfonil)fenilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona (sal HCl)



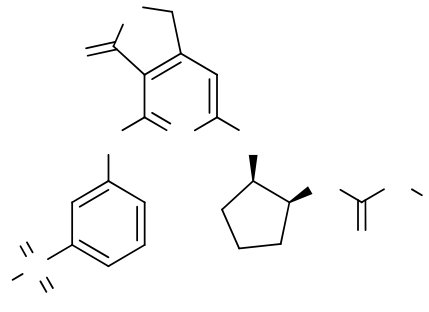
[0397] A. 6-((1R,2S)-2-(ter-butoxicarbonilamino)ciclopentilamino)-4-ciano-2-(3-(metilsulfonil)fenilamino)nicotinato de metilo



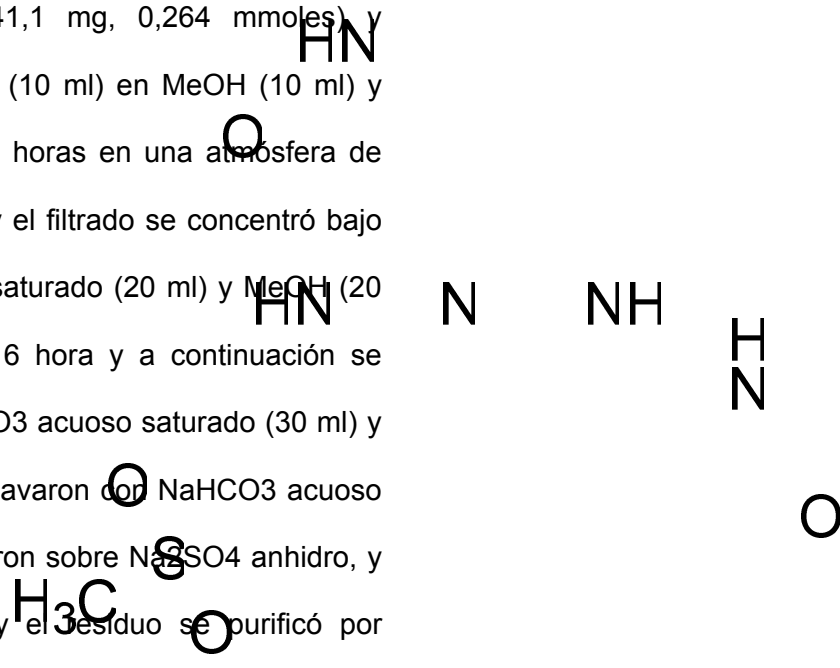
[0398] Una mezcla de 6-cloro-4-ciano-2-(3-(metilsulfonil)fenilamino)nicotinato de metilo (165,0 mg, 0,451 mmoles), Et3N (0,15 ml, 1,076 mmoles), y (1S,2R)-2-aminociclopentilcarbamato de ter-butilo (142,0 mg, 0,709 mmoles) en DMF (6 ml) se agitó a 60ºC durante 12 horas. Se agregó NaHCO3 acuoso saturado (20 ml) a la mezcla, la cual posteriormente se extrajo con EtOAc (2 x 30 ml). Las capas orgánicas se lavaron con NaHCO3 acuoso saturado (20 ml), agua (20 ml), y salmuera (20 ml), se secaron sobre Na2SO4 anhidro, y se filtraron (DM1020). El filtrado se concentró bajo presión reducida. El residuo se purificó por cromatografía de columna (SiO2, hexanos/EtOAc=1/1) y a continuación se trituró con IPE para dar el compuesto del título (147 mg).



[0399] B. (1S,2R)-2-(4-(3-metilsulfonil)fenilamino)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclopentilcarbamato de ter-butilo



[0400] Una mezcla de 6-((1R,2S)-2-(ter-butoxicarbonilamino)ciclopentilamino)-4-ciano-2-(3-(metilsulfonil)fenilamino)nicotinato de metilo (141,1 mg, 0,264 mmoles) y paladio sobre carbono (43,2 mg, 0,308 mmoles) en MeOH (10 ml) en MeOH (10 ml) y HOAc (10 ml) se agitó a temperatura ambiente durante 12 horas en una atmósfera de hidrógeno. La mezcla se filtró para eliminar el catalizador y el filtrado se concentró bajo presión reducida. El residuo se trató con NaHCO3 acuoso saturado (20 ml) y MeOH (20 ml). La mezcla se agitó a temperatura ambiente durante 6 hora y a continuación se concentró a presión reducida. El residuo se trató con NaHCO3 acuoso saturado (30 ml) y se extrajo con EtOAc (2 x 50 ml). Las capas orgánicas se lavaron con NaHCO3 acuoso saturado (20 ml), agua (20 ml), y salmuera (20 ml), se secaron sobre Na2SO4 anhidro, y se filtraron. El filtrado se concentró a presión reducida y el residuo se purificó por cromatografía de columna (DM1020, EtOAc) para dar el producto deseado (46,5 mg). El producto se lavó con IPE/EtOAc para dar el compuesto del título en forma de un sólido de color marrón pálido (34,7 mg, 26%).

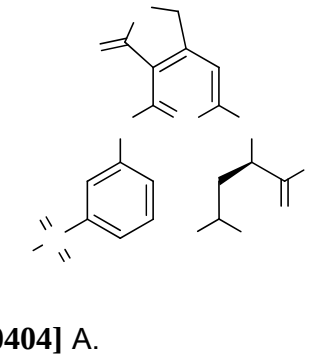


[0401] C. 6-((1R,2S)-2-aminociclopentilamino)-4-(3-(metilsulfonil)fenilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona (sal HCl).

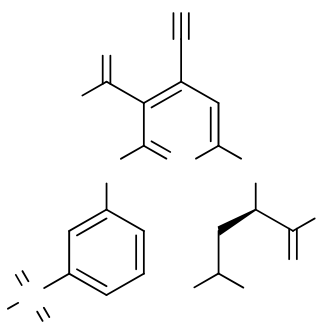
[0402] Una mezcla de (1S,2R)-2-(4-(3-metilsulfonil)fenilamino)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclopentilcarbamato de ter-butilo (16,5 mg, 0,329 mmoles)y HCl (1 ml, 32,9 mmoles) en HOAc (2 ml) se agitó a temperatura ambiente

durante 3 horas. La mezcla se concentró a presión reducida y el residuo se recristalizó a partir de EtOH-H2O para dar el compuesto del título (9,6 mg, 67%). 1H-RMN (DMSO-d6) δ ppm 1,63-1,79 (m, 4H), 20,3-2,06 (m, 1H), 2,19-2,20 (m, 1H), 3,32 (s, 3H), 3,74 (br s, 1H), 4,23-4,28 (m, 2H), 4,45 (br s, 1H), 6,22 (s, 1H), 7,34-7,35 (m, 1H), 7,51-7,58 (m, 3H), 7,73 (br s, 3H), 8,13 (s, 1H), 8,82 (s, 1H), 9,26 (s, 1H).

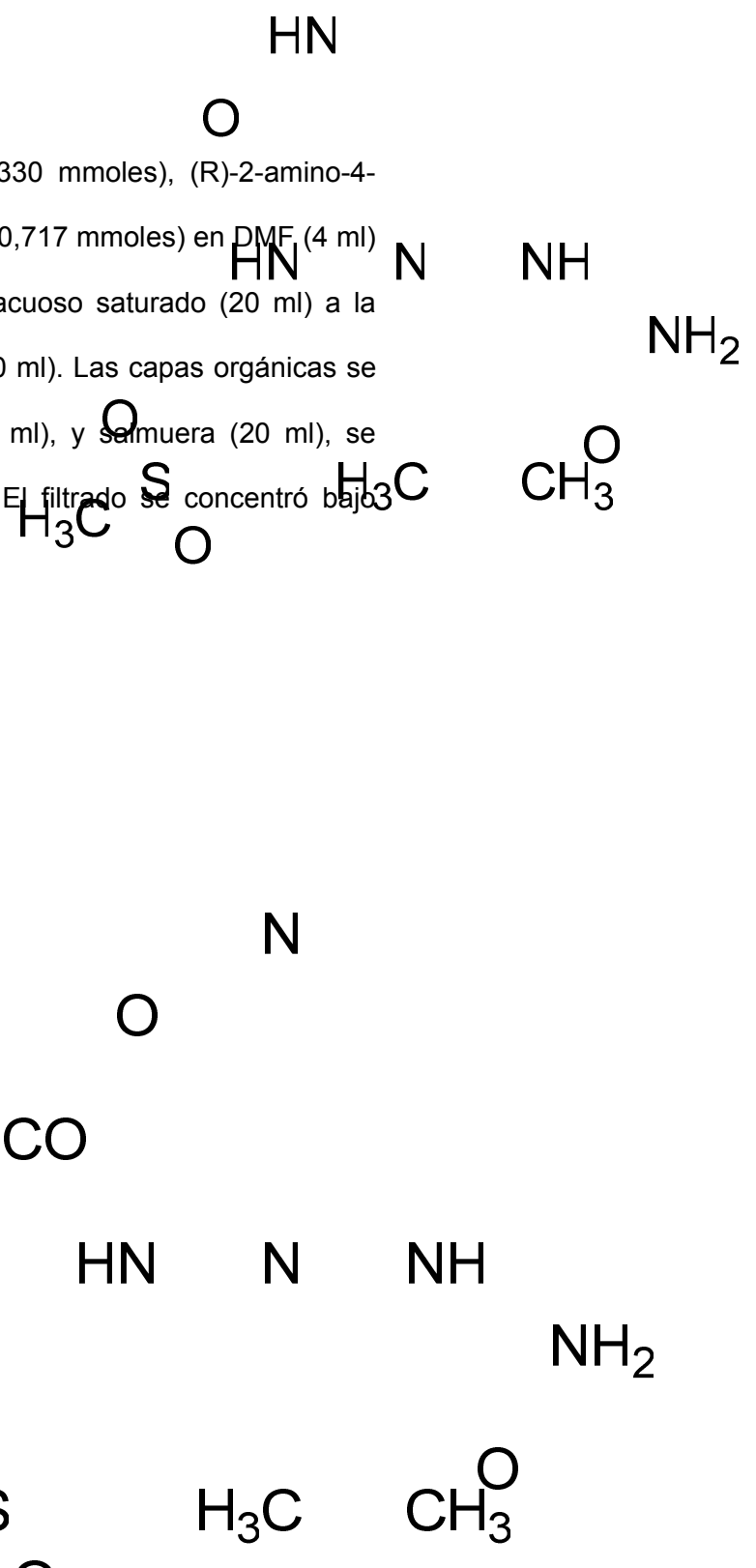
[0403] Ejemplo 35: (R)-4-metil-2-(4-(3-(metilsulfonil)fenilamino)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)pentanamida



[0404] A. 6-(1-amino-4-metil-1-oxopentan-2-ilamino)-4-ciano-2-(3-(metilsulfonil)fenilamino)nicotinato de (R)-metilo



[0405] Una mezcla de 6-cloro-4-ciano-2-(3-(metilsulfonil)fenilamino)nicotinato de metilo (120,7 mg, 0,330 mmoles), (R)-2-amino-4-metilpentanamida (67,1 mg, 0,515 mmoles), y Et3N (0,1 ml, 0,717 mmoles) en DMF (4 ml) se agitó a 60ºC durante 14 horas. Se agregó NaHCO3 acuoso saturado (20 ml) a la mezcla, la cual posteriormente se extrajo con EtOAc (2 x 30 ml). Las capas orgánicas se lavaron con NaHCO3 acuoso saturado (20 ml), agua (20 ml), y salmuera (20 ml), se secaron sobre Na2SO4 anhidro, y se filtraron (DM1020). El filtrado se concentró bajo

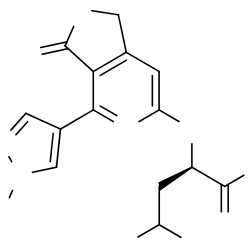


presión reducida. El residuo se purificó por cromatografía de columna (SiO2, hexanos/EtOAc=1/2) y a continuación se trituró con IPE para dar el compuesto del título (76 mg, 50%).

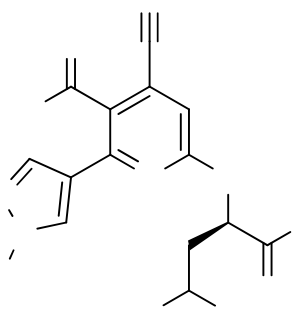
[0406] B. (R)-4-metil-2-(4-(3-(metilsulfonil)fenilamino)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)pentanamida

[0407] Una mezcla de 6-(1-amino-4-metil-1-oxopentan-2-ilamino)-4-ciano-2-(3-(metilsulfonil)fenilamino)nicotinato de (R)-metilo (73,2 mg, 0,159 mmoles) y paladio sobre carbono (23,2 mg, 0,165 mmoles) en MeOH (6 ml) en HOAc (3 ml) se agitó a temperatura ambiente durante 12 horas en una atmósfera de hidrógeno. La mezcla se filtró para eliminar el catalizador y el filtrado se concentró bajo presión reducida. El residuo se trató con NaHCO3 acuoso saturado (20 ml) y MeOH (20 ml). La mezcla resultante se agitó a temperatura ambiente durante 16 horas y a continuación se concentró a presión reducida. El residuo se trató con NaHCO3 acuoso saturado (30 ml) y se extrajo con EtOAc (2 x 50 ml). Las capas orgánicas se lavaron con NaHCO3 acuoso saturado (20 ml), agua (20 ml), y salmuera (20 ml), se secaron sobre Na2SO4 anhidro, y se filtraron. El filtrado se concentró a presión reducida y el residuo se recristalizó a partir de EtOH para dar el compuesto del título en forma de un sólido de color blanco (18,8 mg, 27%).. 1H-RMN (DMSO-d6) δ ppm 0,87-0,94 (m, 6H), 1,54-1,63 (m, 2H), 1,76 (br s, 1H), 3,32 (s, 3H), 4,24 (s, 2H), 4,50 (br s, 1H), 6,17 (s, 1H), 7,00-7,04 (m, 2H), 7,22 (br s, 1H), 7,47-7,57 (m, 2H), 8,01 (br s, 1H), 8,06 (s, 1H), 8,45 (br s, 1H), 9,23 (s, 1H). [M+H] calc para C20H26N4O3S, 432; experimental, 432,5.

[0408] Ejemplo 36: (R)-4-metil-2-(4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)pentanamida

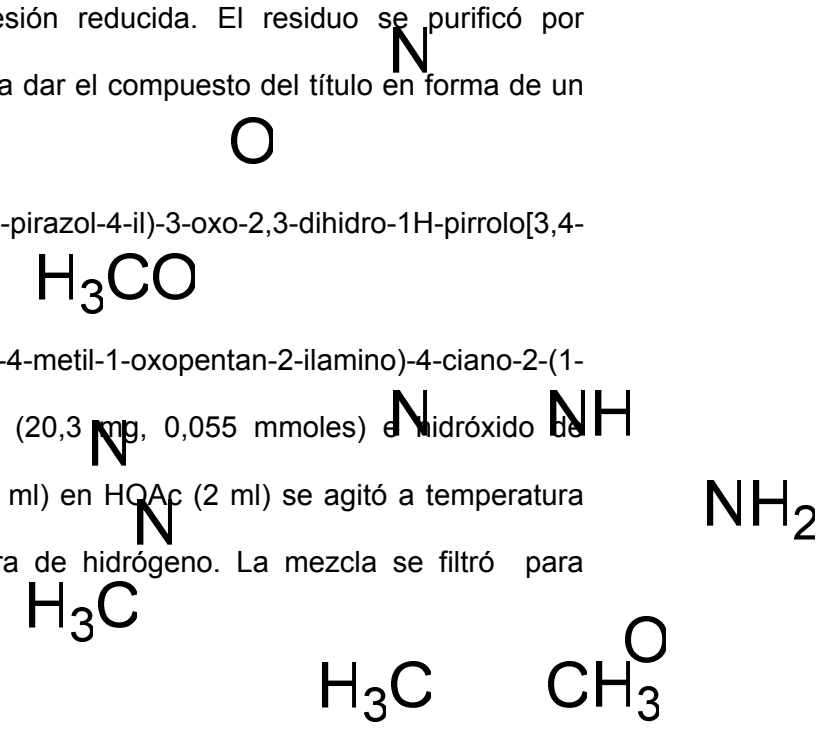


[0409] A. 6-(1-amino-4-metil-1-oxopentan-2-ilamino)-4-ciano-2-(1-metil-1H-pirazol-4-il)nicotinato de (R)-metilo



[0410] Una mezcla de 6-cloro-4-ciano-2-(1-metil-1H-pirazol-4-il)nicotinato de metilo (82,9 mg, 0,300 mmoles) y (R)-2-amino-4-metilpentanamida (39,0 mg, 0,300 mmoles) en DMA (2 ml) se agitó a 150ºC durante 12 horas. Se agregó posteriormente agua y la mezcla se extrajo con EtOAc. Las capas orgánicas se lavaron nuevamente con NaHCO3 acuoso saturado, agua, y salmuera, se secaron sobre Na2SO4 anhidro, y a continuación se filtró. El filtrado se concentró bajo presión reducida. El residuo se purificó por cromatografía de columna (SiO2, EtOAc) para dar el compuesto del título en forma de un aceite de color amarillo (11,7 mg, 11%).

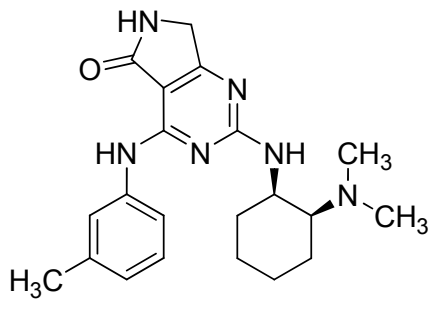
[0411] B. R)-4-metil-2-(4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)pentanamida



[0412] Una mezcla de 6-(1-amino-4-metil-1-oxopentan-2-ilamino)-4-ciano-2-(1-(metil-1H-pirazol-4-il)nicotinato de (R)-metilo (20,3 mg, 0,055 mmoles) e hidróxido de paladio (10 mg, 0,094 mmoles) en MeOH (2 ml) en HOAc (2 ml) se agitó a temperatura ambiente durante 3 horas en una atmósfera de hidrógeno. La mezcla se filtró para

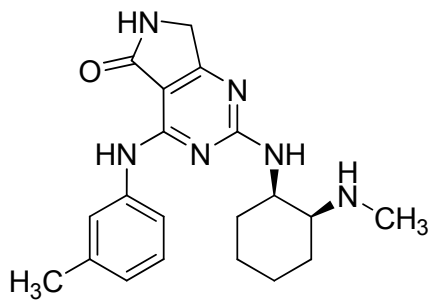
eliminar el catalizador y el filtrado se concentró bajo presión reducida. El residuo se trató con NaHCO3 acuoso saturado (20 ml) y EtOAc (20 ml) durante 12 horas. La mezcla se extrajo con EtOAc (2 x 20 ml). Las capas orgánicas se lavaron con NaHCO3 acuoso saturado (20 ml), agua (20 ml), y salmuera (20 ml), se secaron sobre Na2SO4 anhidro, y se filtraron. El filtrado se concentró a presión reducida y el residuo se purificó por cromatografía de columna (DM1020, EtOAc/MeOH=15/1-10/1) para dar el compuesto del título en forma de un sólido de color blanco (10,2 mg, 54%). 1H-RMN (DMSO-d6) δ ppm 0,88-0,95 (m, 6H), 1,52-1,60 (m, 2H), 1,73-1,76 (m, 1H), 3,88 (s, 3H), 4,21 (s, 2H), 4,48 (br s, 1H), 6,43 (s, 1H), 6,90 (s, 1H), 7,03 (br s, 1H), 7,42 (s, 1H), 8,01 (s, 1H), 8,41 (s, 1H), 8,92 (s, 1H). [M+H] calc para C17H23N6O2, 343; experimental, 343.

[0413] Ejemplo 37: 2-((1R,2S)-2-(dimetilamino)ciclohexilamino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona



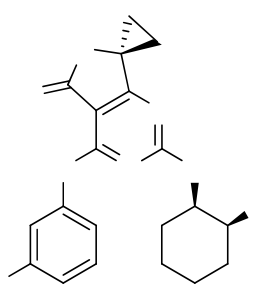
[0414] Una solución de 2-((1R,2S)-2-aminociclohexilamino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona (10 mg, 0.028 mmoles), paraformaldehído (0.852 mg, 0.028 mmoles) in MeOH (2 ml) se agitó a temperatura ambiente durante 10 min. Se agregó cianotrihidroborato de sodio (1,783 mg, 0,028 mmoles) y la mezcla de reacción se agitó a temperatura ambiente durante toda la noche. La mezcla se purificó por HPLC preparativa de fase inversa para dar la sal TFA del compuesto del título (5 mg, 46%). 1H RMN (400 MHz, DMSO-d6) δ ppm 1,44 -1,57 (m, 4 H), 1,85 (br s, 4 H), 2,32 (s, 3 H), 2,64 - 2,87 (2s, 6 H), 4,20 (d, J=4,55 Hz, 2 H), 6,91 (d, J=7,07 Hz, 1 H), 7,00 (s, 1 H), 7,13 (s, 1 H), 7,17 - 7,34 (m, 2 H), 8,19 (br s, 1 H), 8,68 (br s, 1 H). [M+H] calc para C21H28N6O, 381; experimental, 381.

[0415] Ejemplo 38: 2-((1R,2S)-2-(metilamino)ciclohexilamino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona

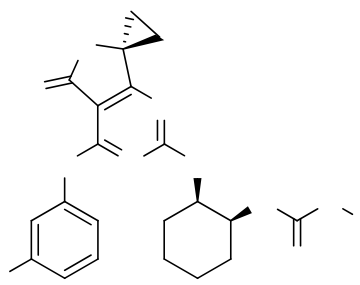


[0416] Una solución de 2-((1R,2S)-2-aminociclohexilamino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona (17,7 mg, 0,050 mmoles), paraformaldehído (1,508 mg, 0,050 mmoles) en MeOH (2 ml) se agitó a temperatura ambiente durante 10 min. Se agregó cianotrihidroborato de sodio (3,16 mg, 0,050 mmoles) y la mezcla de reacción se agitó a temperatura ambiente durante 4 horas. La reacción se detuvo y la mezcla se purificó por HPLC preparativa de fase inversa para dar la sal TFA del compuesto del título (5 mg, 27%). 1H RMN (400 MHz, DMSO-d6) δ ppm 1,35-1,79 (m, 8 H), 2,32 (s, 3 H), 4,20 (br s, 2 H), 6,52 (br s, 2 H), 6,91 (d, J=7,33 Hz, 1 H), 7,24 (t, J=7,71 Hz, 2 H), 8,03 (br s, 1 H), 8,16 (br s, 2 H), 8,40 (br s, 1 H), 8,66 (br s, 1 H). [M+H] calc para C20H26N6O, 367; experimental, 367.

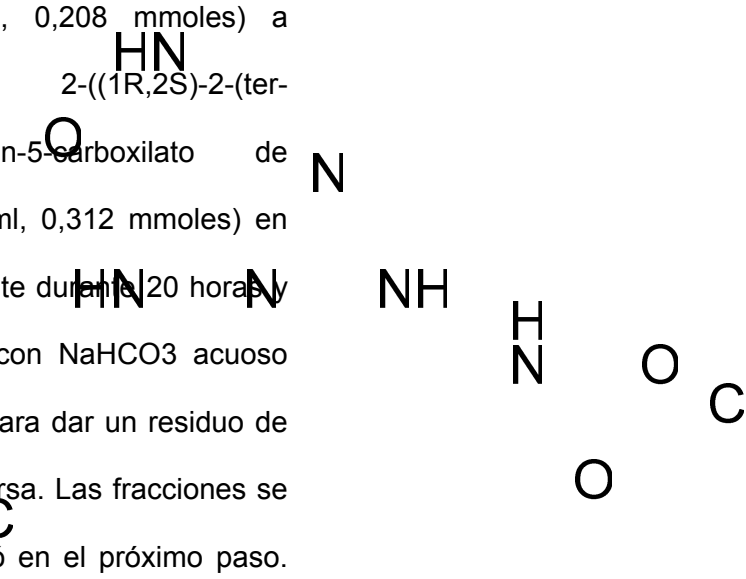
[0417] Ejemplo 39: 2'-((1R,2S)-2-(aminociclohexilamino)-4'-(m-tolilamino)espiro[ciclopropano-1,7-pirrolo[3,4-d]pirimidin-5'(6'H)-ona



[0418] A. (1S,2R)-2-(5'-oxo-4'-(m-tolilamino)-5',6'-dihidroespiro[ciclopropano-1,7'-pirrolo[3,4-d]pirimidina]-2'-ilamino)ciclohexilcarbamato de ter-butilo



[0419] Se agregó bromuro de etilmagnesio (0,069 ml, 0,208 mmoles) a temperatura ambiente a una solución de 2-((1R,2S)-2-(ter-butoxicarbonilamino)ciclohexilamino)-4-ciano-6-(m-tolilamino)pirimidin-5-carboxilato de metilo (50 mg, 0,104 mmoles) y tetraisopropilortotitanato (0,091 ml, 0,312 mmoles) en Et2O (5 ml). La mezcla de reacción se agitó a temperatura ambiente durante 20 horas y se diluyó posteriormente con EtOAc. La fase orgánica se lavó con NaHCO3 acuoso saturado, agua, y salmuera, se secó, a continuación s concentró para dar un residuo de color rosado, el cual se purificó por HPLC preparativa de fase inversa. Las fracciones se recolectaron y se concentraron hasta un residuo, el cual se utilizó en el próximo paso. [M+H] calc para C26H34N6O3, 479; experimental, 479.

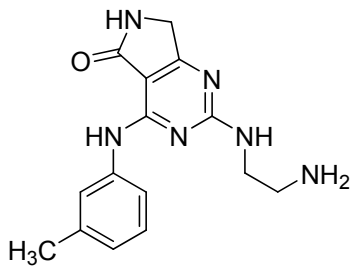


[0420] B. 2'-((1R,2S)-2-aminociclohexilamino)-4'-(m-tolilamino)espiro[ciclopropano-1,7'-pirrolo[3,4-d]pirimidin]-5'(6'H)-ona

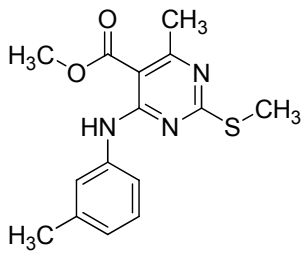
[0421] Una solución de (1S,2R)-2-(5'-oxo-4'-(m-tolilamino)-5',6'-dihidroespiro[ciclopropano-1,7'-pirrolo[3,4-d]pirimidina]-2'-ilamino)ciclohexilcarbamato de ter-butilo (50 mg, 0,104 mmoles) en DCM (5 ml) se trató con TFA (2 ml) durante 1 hora y se purificó por HPLC preparativo de fase inversa. Las fracciones recolectadas se liofilizaron para dar la sal TFA del compuesto del título (4 mg, 10% en dos pasos). 1H RMN (400 MHz, DMSO-d6) δ ppm 1,12 - 1,31 (m, 1 H), 1,42 (m, 6 H), 1,63 (m, 3 H), 1,86 (m, 2 H), 2,33 (s, 3 H), 3,62 (br s, 1 H), 4,18 (br s, 1 H), 6,91 (d, J=7,33 Hz, 1 H), 7,24 (t, J=7,71 Hz, 1 H), 7,36 - 7,56 (m, 1 H), 7,60 (br s, 1 H), 7,73 (br s, 2 H), 8,33 (br s, 1 H), 8,65 (br s, 1 H). [M+H] calc para C21H26N6O, 379; experimental, 379.

[0422] Ejemplo 40: 2-(2-aminoetilamino)-4-(m-tolilamino)-6,7-dihidro-5H-

pirrolo[3,4-d]pirimidin-5-ona

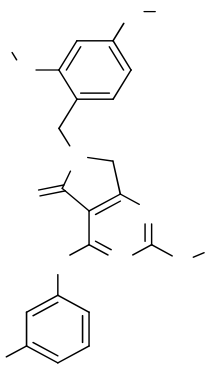


[0423] A. 4-metil-2-(metiltio)-6-(m-tolilamino)pirimidin-5-carboxilato de metilo



[0424] Se disolvió 2-cloro-4-metil-6-(m-tolilamino)pirimidin-5-carboxilato de metilo (0,078 g, 0,267 mmoles) en DMF (3 ml). Se agregó tiometóxido de sodio (0,019 g, 0,267 mmoles) y la mezcla de reacción se dejó agitar a temperatura ambiente durante 1 hora. La mezcla de reacción se vertió sobre hielo. El pH se ajustó hasta 7 con HCl 1N. El compuesto del título se aisló en forma de un sólido de color amarillo por filtración al vacío (72,8 mg, 90%). [M+H] calc para C15H17N4O3S, 304; experimental, 304.

[0425] B. 6-(2,4-dimetoxibencil)-2-(metiltio)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona

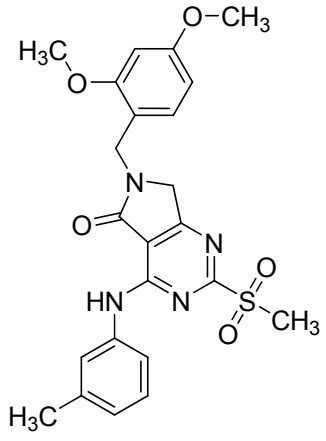


[0426] Una mezcla de 4-metil-2-(metiltio)-6-(m-tolilamino)pirimidin-5-carboxilato de metilo (0,44 g, 1,45 mmoles) y dióxido de selenio (0,32 g, 2,89 mmoles) en dioxano (12



ml) se calentó a 100ºC durante 24 horas. La mezcla de reacción se agrupó posteriormente y se filtró. El filtrado se concentró y se secó para dar una espuma de color marrón (0,459 g) la cual se dispersó en (2,4-dimetoxifenil)metanamina (0,217 ml, 1,446 mmoles) en DCM (6 ml) y MeOH (3 ml). La mezcla resultante se agitó a temperatura ambiente durante 30 min. Se agregó cianoborohidruro de sodio (0,227 g, 3,62 mmoles) y la mezcla de reacción se agitó a temperatura ambiente durante 20 horas. La fase sólida se filtró y se lavó con MeOH para dar el compuesto del título en forma de un sólido de color amarillo (0,537 g, 85%). [M+H] calc para C23H24N4O3S, 437; experimental, 437.

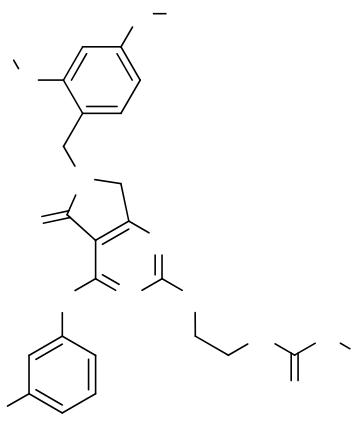
[0427] C. 6-(2,4-dimetoxibencil)-2-(metilsulfonil)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona



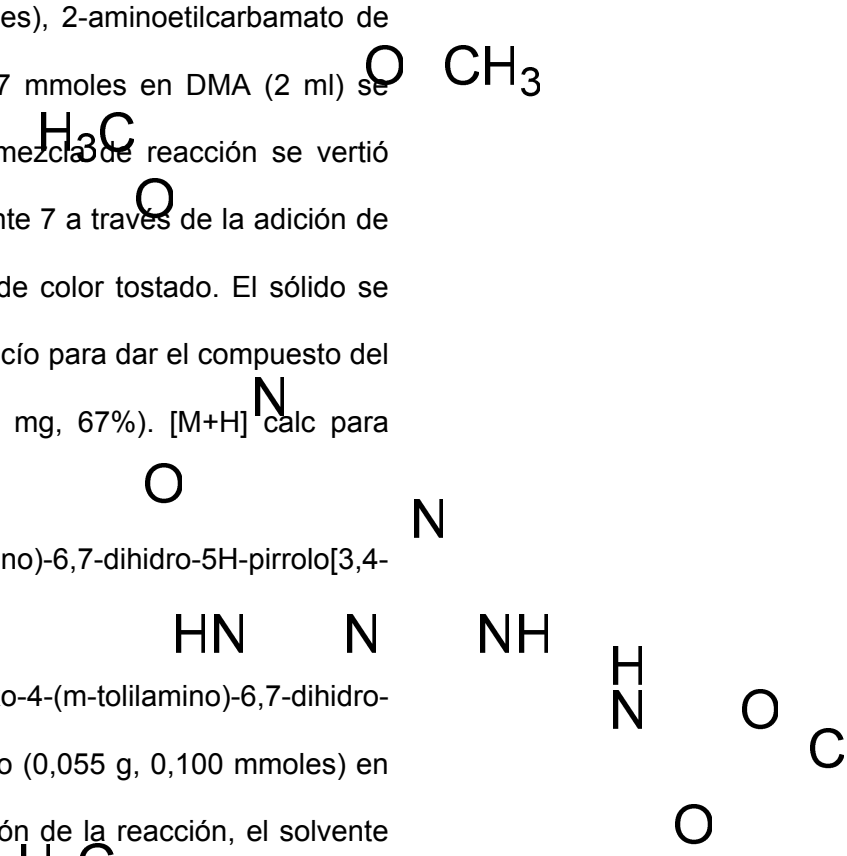
[0428] Se disolvió 6-(2,4-dimetoxibencil)-2-(metiltio)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona (0,432 g, 0,990 mmoles) en DCM (10 ml). La solución se enfrió en un baño helado y se agregó el ácido m-cloroperoxibenzoico (0,256 g, 1,484 mmoles). La reacción se dejó entibiar hasta temperatura ambiente con agitación durante 3 horas. Una segunda alícuota del ácido m-clorperoxibenzoico (0,170 g, 0,990 mmoles) se agregó a la mezcla de reacción, la cual se agitó durante 1 hora. Una tercera alícuota del ácido m-cloroperoxibenzoico (0,100 g, 0,579 mmoles). La mezcla de reacción se agitó durante 30 min., se diluyó con DCM (20 ml), y se templó con NaHCO3 acuoso saturado (20 ml). La fase orgánica se lavó con NaHCO3 acuoso saturado (20 ml) y salmuera (20 ml), y se secó sobre Na2SO4 anhidro. El solvente se eliminó in vacuo para dar el

compuesto del título en forma de un sólido vidrioso de color marrón claro (330 mg, 71%). [M+H] calc para C23H24N4O5S, 469; experimental, 469.

[0429] D. (2-(6-(2,4-dimetoxibencil)-5-oxo-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-2-ilamino)etilcarbamato de ter-butilo



[0430] Una mezcla de 6-(2,4-dimetoxibencil)-2-(metilsulfonil)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona (0,07 g, 0,149 mmoles), 2-aminoetilcarbamato de ter-butilo (0,024 g, 0,149 mmoles) y Et3N (0,104 ml, 0,747 mmoles en DMA (2 ml) se calentó en un tubo cerrado a 90ºC durante 4 horas. La mezcla de reacción se vertió lentamente en hielo y su pH se ajustó hasta aproximadamente 7 a través de la adición de HCl 1N, dando por resultado la precipitación de un sólido de color tostado. El sólido se aisló por filtración al vacío, se lavó con agua, y se secó al vacío para dar el compuesto del título en forma de un sólido de color marrón tostado (55 mg, 67%). [M+H] calc para C29H36N6O5, 549; experimental, 549.

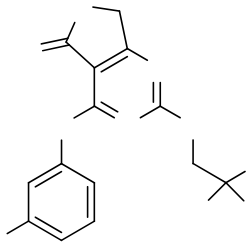


[0431] E. 2-(2-aminoetilamino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona

[0432] Una mezcla de (2-(6-(2,4-dimetoxibencil)-5-oxo-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-2-ilamino)etilcarbamato de ter-butilo (0,055 g, 0,100 mmoles) en TFA (2 ml) se agitó a 70ºC durante 1,5 horas. A continuación de la reacción, el solvente se eliminó y el residuo resultante se dispersó en una solución de DMSO y MeOH (1/1). La mezcla se filtró y el filtrado se purificó por HPLC preparativa. Las fracciones se

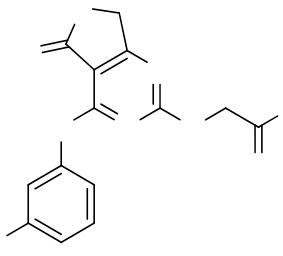
recolectaron y se secaron in vacuo para dar una sal TFA del compuesto del título en forma de un sólido blancuzco (28 mg, 93%). 1H RMN (500 MHz, DMSO-d6) δ ppm 2,21 - 2,40 (m, 3 H) 2,90 - 3,21 (m, 2 H) 3,57 (q, J=5,86 Hz, 2 H) 4,19 (br s, 2 H) 6,90 (br s, 1 H) 7,13 - 7,34 (m, 1 H) 7,54 (br s, 1 H) 7,56 - 7,74 (m, 2 H) 7,80 (br s, 2 H) 8,18 (d, J=13,67 Hz, 1 H) 8,54 - 8,82 (m, 1 H). [M+H] calc para C15H18N6O, 299; experimental, 299.

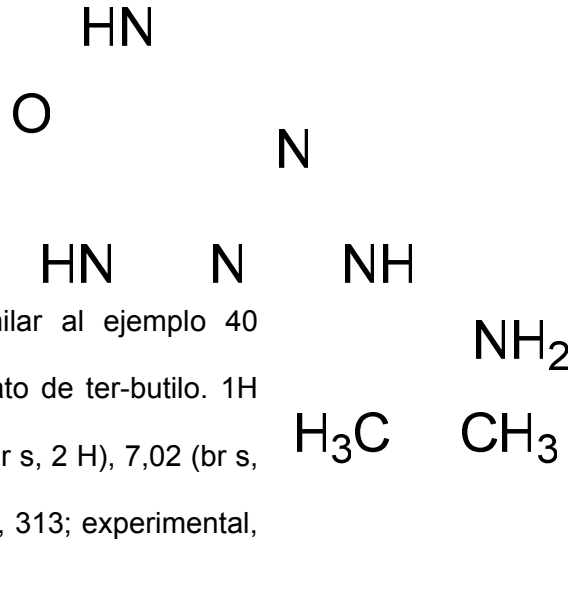
[0433] Ejemplo 41: 2-(2-amino-2-metilpropilamino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona



[0434] Una sal TFA del compuesto del título se preparó de manera similar al ejemplo 40 utilizando 1-amino-2-metilpropan-2-ilcarbamato de ter-butilo en lugar de 2-aminoetilcarbamato de ter-butilo. 1H RMN (500 MHz, CD3OD) δ ppm 1,14 - 1,53 (m, 6 H), 2,37 (br s, 3 H), 3,62 (br s, 2 H), 4,12 - 4,47 (m, 2 H), 6,77 - 7,15 (m, 1 H), 7,13 - 7,40 (m, 1 H), 7,40 - 7,79 (m, 2 H). [M+H] calc para C17H22N6O, 327; experimental, 327.

[0435] Ejemplo 42: 2-(5-oxo-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-2-ilamino)acetamida



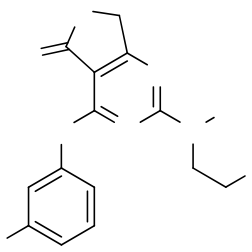


[0436] El compuesto del título se preparó de manera similar al ejemplo 40 utilizando clorhidrato de glicina mida en lugar de 2-aminoetilcarbamato de ter-butilo. 1H RMN (500 MHz, CD3OD) δ ppm 2,38 (s, 3 H), 4,11 (br s, 2 H), 4,41 (br s, 2 H), 7,02 (br s, 1 H), 7,27 (br s, 1 H), 7,51 (br s, 2 H). [M+H] calc para C15H16N6O2, 313; experimental,



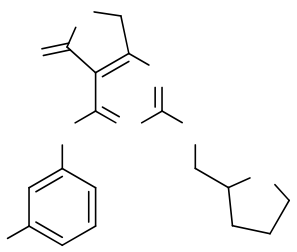
313.

[0437] Ejemplo 43: 2-((2-aminoetil)(metil)amino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona



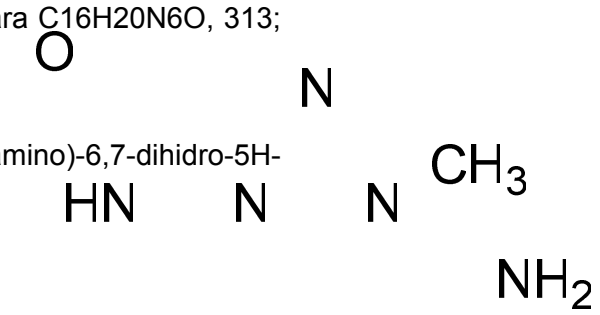
[0438] Una sal TFA del compuesto del título se preparó de manera similar al ejemplo 40 utilizando clorhidrato de 2-(metilamino)etilcarbamato de ter-butilo en lugar de 2-aminoetilcarbamato de ter-butilo. 1H RMN (500 MHz, CD3OD) δ ppm 2,35 (s, 3 H), 3,26 (t, J=5,86 Hz, 2 H), 3,30 (s, 3 H), 3,89 - 4,04 (m, 2 H), 4,24 (s, 2 H), 6,94 (d, J=7,32 Hz, 1 H), 7,23 (t, J=7,81 Hz, 1 H), 7,55 (d, J=7,81 Hz, 2 H). [M+H] calc para C16H20N6O, 313; experimental, 313.

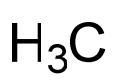
[0439] Ejemplo 44: 2-(pirrolidin-2-ilmetilamino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona

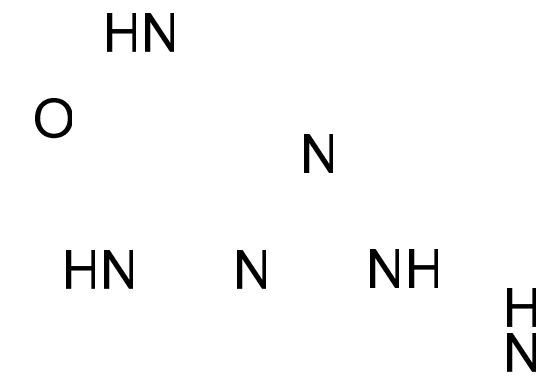


[0440] Una sal TFA del compuesto del título se preparó de manera similar al ejemplo 40 utilizando 2-(aminometil)pirrolidin-1-carboxilato de ter-butilo en lugar de 2-aminoetilcarbamato de ter-butilo. 1H RMN (500 MHz, CD3OD) δ ppm 1,80 (br s, 1 H), 1,91 - 2,26 (m, 3 H), 2,38 (br s, 3 H), 3,19 (br s, 1 H), 3,63 (d, J=7,32 Hz, 1 H), 3,71 - 4,03 (m, 2 H), 4,15 - 4,51 (m, 2 H), 6,74 - 7,16 (m, 1 H), 7,13 - 7,76 (m, 3 H). [M+H] calc para C18H22N6O, 339; experimental, 339.

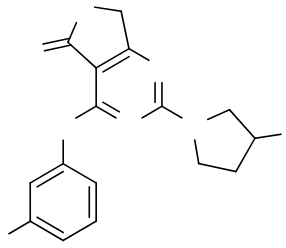
[0441] Ejemplo 45: 2-(3-aminopirrolidin-1-il)-4-(m-tolilamino)-6,7-dihidro-5H-



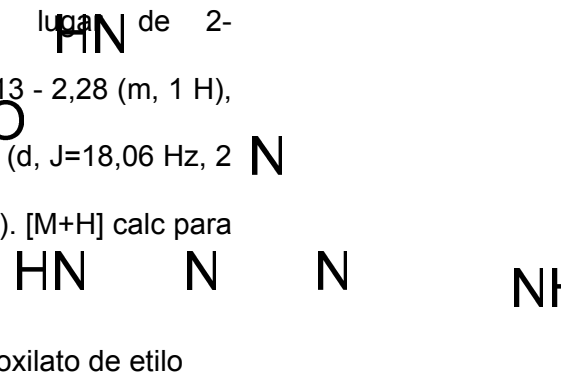




pirrolo[3,4-d]pirimidin-5-ona



[0442] Una sal TFA del compuesto del título se preparó de manera similar al ejemplo 40 utilizando pirrolidin-3-ilcarbamato de ter-butilo en lugar de 2-aminoetilcarbamato de ter-butilo. 1H RMN (500 MHz, CD3OD) δ ppm 2,13 - 2,28 (m, 1 H), 2,35 (s, 3 H), 2,51 (dd, J=13,42, 6,10 Hz, 1 H), 3,69 - 4,12 (m, 5 H), 4,22 (d, J=18,06 Hz, 2 H), 6,93 (d, J=7,32 Hz, 1 H), 7,21 (t, J=7,81 Hz, 1 H), 7,46 - 7,69 (m, 2 H). [M+H] calc para C17H20N6O, 325; experimental, 325.

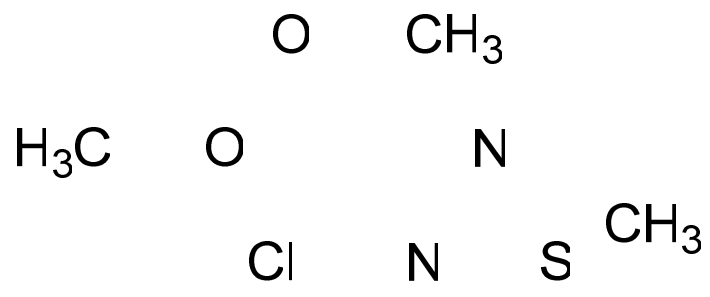


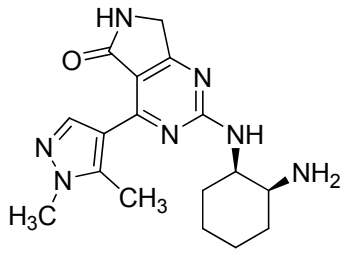
[0443] Preparación 15: 4-cloro-6-metil-2-(metiltio)pirimidin-5-carboxilato de etilo



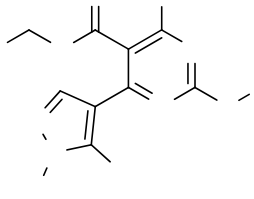
[0444] Se dispersaron 4-hidroxi-6-metil-2-(metiltio)pirimidin-5-carboxilato de etilo (0,2 g, 0,876 mmoles), cloruro de tetraetilamonio (0,145 g, 0,876 mmoles), y N,N-dimetilanilina (0,112 ml, 0,876 mmoles) en acetonitrilo (10 ml). La mezcla de reacción se agitó brevemente seguido de la adición de oxicloruro de fósforo (0,204 ml, 2,190 mmoles). La reacción se calentó a 100ºC durante 4 horas. El solvente se eliminó posteriormente in vacuo. El residuo se vertió en hielo para dar un aceite blancuzco, el cual se extrajo con DCM (2 x 15 ml), y se secó sobre Na2SO4 anhidro. El solvente se eliminó in vacuo para dar el compuesto del título en forma de un aceite de color verde amarillento (0,179 g, 83%). [M+H] calc para C9H11ClN2O2S, 247; experimental, 247.

[0445] Ejemplo 46: 2-((1R,2S)-2-aminociclohexilamino)-4-(1,5-dimetil-1H-pirazol-4-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona

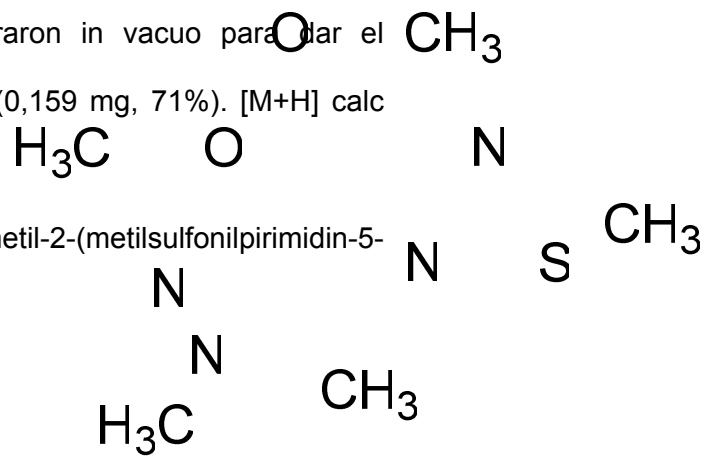




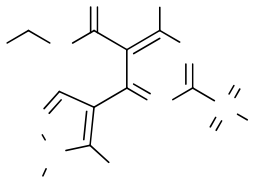
[0446] A. 4-(1,5-dimetil-1H-pirazol-4-il)-6-metil-2-(metiltio)pirimidin-5-carboxilato de etilo



[0447] Se dispersaron 4-cloro-6-metil-2-(metiltio)pirimidin-5-carboxilato de etilo (0,179 g, 0,726 mmoles), 1-dimetil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (0,242 g, 1,088 mmoles), y PdCl2(dppf) (0,106 g, 0,145 mmoles) en DMA (2 ml). Después de 10 min., se agregó carbonato de sodio 2N (1,814 ml, 3,63 mmoles) a la mezcla de reacción. La mezcla de reacción se purgó con nitrógeno, se cerró en un recipiente, y a continuación se calentó a 80ºC durante 5 horas. La mezcla se filtró posteriormente a través de un taco de celite, se enjuagó con MeOH, y el filtrado se purificó mediante HPLC preparativa de fase inversa. Las fracciones se concentraron in vacuo para dar el compuesto del título en forma de agujas de color tostado (0,159 mg, 71%). [M+H] calc para C14H18N4O2S, 307; experimental, 307.



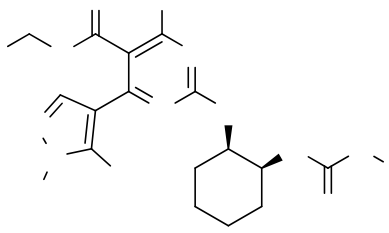
[0448] B. 4-(1,5-dimetil-1H-pirazol-4-il)-6-metil-2-(metilsulfonilpirimidin-5-carboxilato de etilo



[0449] Se disolvió 4-(1,5-dimetil-1H-pirazol-4-il)-6-metil-2-(metiltio)pirimidin-5-

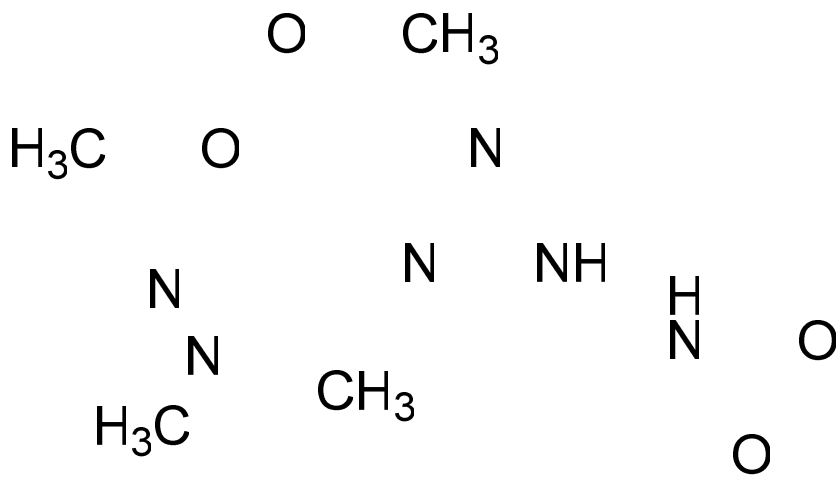
carboxilato de etilo (0,159 g, 0,519 mmoles) en DCM (10 ml). La solución se enfrió en un baño helado y se agregó el ácido m-cloroperoxibenzoico (0,134 g, 0,778 mmoles). La reacción se dejó entibiar hasta temperatura ambiente durante un período de 30 min. mientras se agitaba. Otra alícuota del ácido m-cloroperoxibenzoico (0,159 g, 0,519 mmoles) se agregó a la mezcla de reacción y se agitó durante otros 45 min. La mezcla de reacción se diluyó posteriormente con DCM (10 ml) y se templó con NaHCO3 acuoso saturado (10 ml). La fase orgánica se lavó con NaHCO3 acuoso saturado (5 ml) y salmuera (5 ml), y se secó sobre Na2SO4 anhidro. Los solventes se eliminaron in vacuo para dar el compuesto del título en forma de un aceite de color amarillo (173 mg, 98%). [M+H] calc para C14H18N4O4S, 339; experimental, 339.

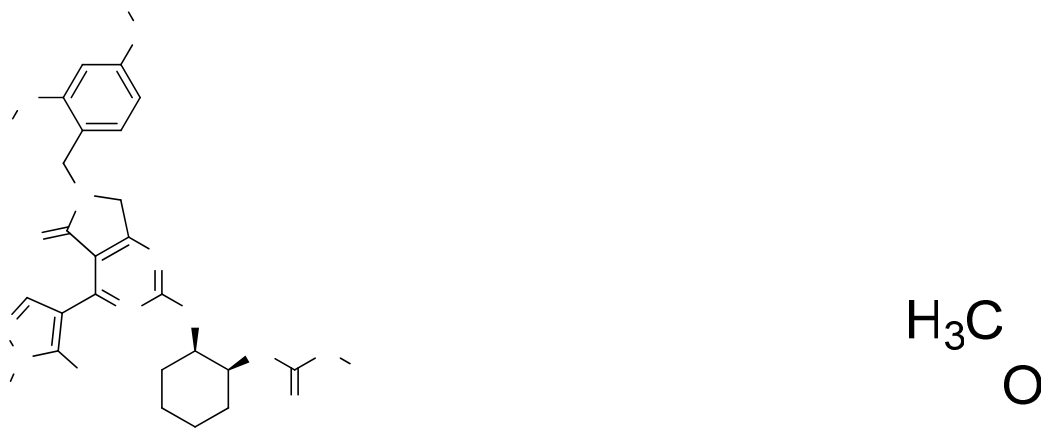
[0450] C. 2-((1R,2S)-2-(ter-butoxicarbonilamino)ciclohexilamino)-4-formil-6-(1,5-dimetil-1H-pirazol-4-il)-6-metilpirimidin-5-carboxilato de etilo



[0451] Una solución de 4-(1,5-dimetil-1H-pirazol-4-il)-6-metil-2-(metilsulfonilpirimidin-5-carboxilato de etilo (0,07 g, 0,207 mmoles), ter-butilo (1S,2R)-2-aminociclohexilcarbamato de (0,089 g, 0,414 mmoles) y Et3N (0,115 ml, 0,827 mmoles) en DMA (3 ml) se calentó en un tubo cerrado a 90ºC durante 8 horas. La mezcla de reacción se vertió lentamente en hielo para dar un precipitado de color amarillo pálido, el cual se aisló por filtración al vacío, se lavó con agua, y se secó al vacío para dar el compuesto del título. [M+H] calc para C24H36N6CO4, 473; experimental, 473.

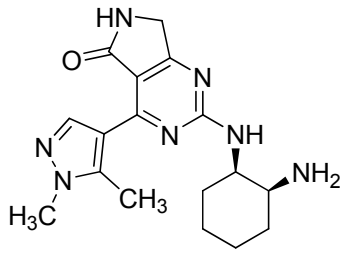
[0452] D. ter-butilo (1S,2R)-2-(6-(2,4-dimetoxibencil)-4-(1,5-dimetil-1H-pirazol-4-il)-5-oxo-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-2-ilamino)ciclohexilcarbamato de





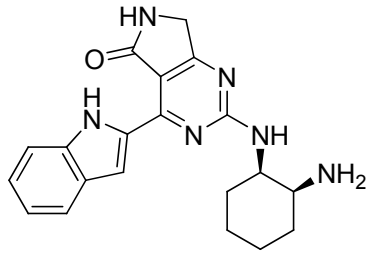
[0453] Una mezcla de 2-((1R,2S)-2-(ter-butoxicarbonilamino)ciclohexilamino)-4-(1,5-dimetil-1H-pirazol-4-il)-6-metilpirimidin-5-carboxilato de etilo (0,098 g, 0,207 mmoles) y dióxido de selenio (0,046 g, 0,415 mmoles) en dioxano (2 ml) se calentó a 100ºC durante 24 horas. La solución se enfrió posteriormente y se filtró. El filtrado se concentró y se secó para dar una espuma de color marrón (0,1 g, 0,206 mmoles) la cual se combinó con acetato de sodio (0,051 g, 0,617 mmoles) y (2,4-dimetoxifenil)metanamina (0,031 ml, 0,206 mmoles), en DCM (2 ml) y MeOH (1 ml). La mezcla se agitó a temperatura ambiente durante 30 min., después de lo cual se agregó cianoborohidruro de sodio (0,032 g, 0,514 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 20 horas, y a continuación se filtró a través de un taco de celite, el cual se enjuagó con MeOH. El filtrado se purificó mediante HPLC preparativa de fase inversa y las fracciones se concentraron in vacuo para dar el compuesto del título en forma de un sólido de color tostado. [M+H] calc para C31H41N7CO5, 592; experimental, 592.

[0454] E. 2-((R,2S)-2-aminociclohexilamino)-4-(1,5-dimetil-1H-pirazol-4-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona



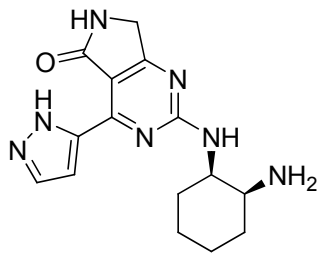
[0455] Una mezcla de ter-butilo(1S,2R)-2-(6-(2,4-dimetoxibencil)-4-(1,5-dimetil-1H-pirazol-4-il)-5-oxo-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-2-ilamino)ciclohexilcarbamato de obtenido anteriormente en TFA (2 ml) se agitó a 70ºC durante 2 horas. A continuación la mezcla se purificó por HPLC preparativa de fase inversa. Las fracciones se recolectaron y se concentraron para dar una sal TFA del compuesto del título en forma de un sólido de color blanco (0,5 mg). 1H RMN (500 MHz, CD3OD) δ ppm 1,59 (br s, 2 H), 1,67 - 2,02 (m, 6 H), 2,66 - 2,72 (m, 3 H), 3,67 (br s, 1 H), 3,85 (s, 3 H), 4,29 (s, 2 H), 4,50 - 4,64 (m, 1 H), 8,64 (br s, 1 H). [M+H] calc para C17H23N7O, 342; experimental, 342.

[0456] Ejemplo 47: 2-((1R,2S)-2-aminociclohexilamino)-4-(1-propil-1H-indol-2-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona



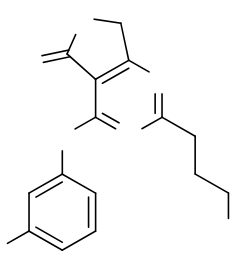
[0457] Una sal TFA del compuesto del título se preparó de manera similar al ejemplo 46 utilizando El ácido 11-(ter-butoxicarbonil)-1H-indol-2-ilborónico en lugar de 1,5-dimetil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol. 1H RMN (500 MHz, CD3OD) δ ppm 1,46 - 1,72 (m, 2 H), 1,72 - 2,06 (m, 6 H), 3,56 - 3,89 (m, 1 H), 4,36 (s, 2 H), 4,52 - 4,77 (m, 1 H), 7,08 (t, J=7,57 Hz, 1 H), 7,25 (t, J=7,57 Hz, 1 H), 7,47 (d, J=8,30 Hz, 1 H), 7,58 - 7,79 (m, 2 H). [M+H] calc para C20H22N6O, 363; experimental, 363.

[0458] Ejemplo 48: 2-((1R,2S)-2-aminociclohexilamino)-4-(1H-pirazol-5-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona

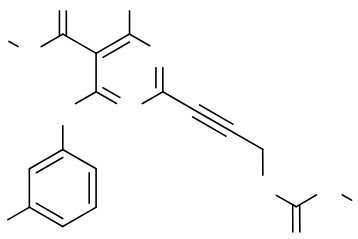


[0459] Una sal TFA del compuesto del título se preparó de manera similar al ejemplo 14 utilizando 5-(5,5-dimetil-1,3,2-dioxaborinan-2-il)-1H-pirazol-1-carboxilato de ter-butilo en lugar de 1,5-dimetil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol. 1H RMN (500 MHz, CD3OD) δ ppm 1,44 - 1,69 (m, 2 H), 1,68 - 1,94 (m, 6 H), 3,64 (br s, 1 H), 4,41 (s, 2 H), 4,65 (br s, 1 H), 7,11 - 7,55 (m, 1 H), 7,69 (d, J=1,77 Hz, 1 H). [M+H] calc para C15H19N7O, 314; experimental, 314.

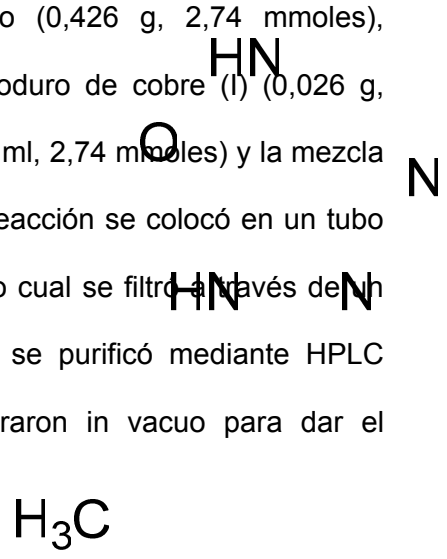
[0460] Ejemplo 49: 2-(3-aminopropil)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona

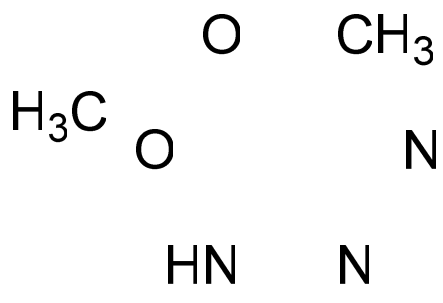


[0461] A. 2-(3-((ter-butoxicarbonilamino)prop-1-inil)-4-metil-6-(m-tolilamino)pirimidin-5-carboxilato de metilo



[0462] Se dispersó 2-cloro-4-metil-6-(m-tolilamino)pirimidin-5-carboxilato de metilo (0,4 g, 1,371 mmoles), prop-2-inilcarbamato de ter-butilo (0,426 g, 2,74 mmoles), tetrakis(trifenilfosfina)paladio (0,032 g, 0,027 mmoles), y yoduro de cobre (I) (0,026 g, 0,137 mmoles) en DMA (5 ml). Se agregó trietilamina (0,382 ml, 2,74 mmoles) y la mezcla se desgasificó con nitrógeno durante 5 min. La mezcla de reacción se colocó en un tubo cerrado y se calentó a 90ºC durante 4 horas, después de lo cual se filtró a través de un taco de celite, el cual se enjuagó con MeOH. El filtrado se purificó mediante HPLC preparativa de fase inversa y las fracciones se concentraron in vacuo para dar el

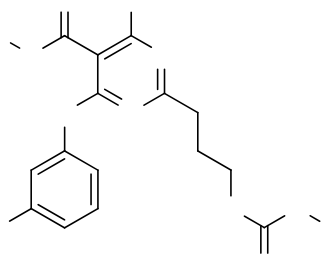






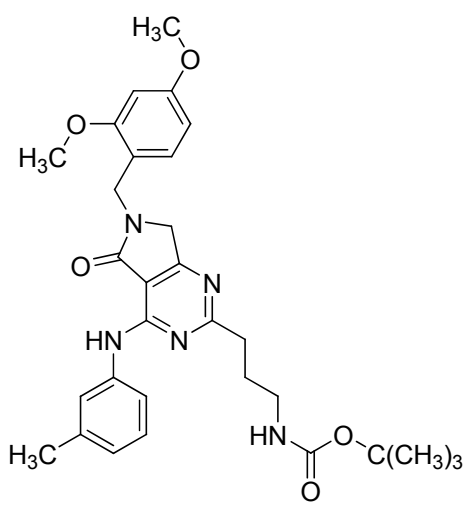
compuesto del título en forma de un aceite de color marrón (0,190 g, 34%). [M+H] calc para C22H26N4O4, 411; experimental, 411.

[0463] B. 2-(3-(ter-butoxicarbonilamino)propil)-4-metil-6-(m-tolilamino)pirimidin-5-carboxilato de metilo



[0464] A. Se disolvió 2-(3-((ter-butoxicarbonilamino)prop-1-inil)-4-metil-6-(m-tolilamino)pirimidin-5-carboxilato de metilo (0,190 g, 0,463 mmoles) en EtOH (4 ml). A esta solución se agregó paladio sobre carbono (0,049 g, 0,046 mmoles) y la mezcla resultante se agitó durante toda la noche a temperatura ambiente en atmósfera de H2 . La mezcla se filtró a través de un taco de celite, y el filtrado se evaporó para dar el compuesto del título en forma de un aceite de color marrón, el cual se utilizó en el próximo paso sin purificación posterior. [M+H] calc para C22H30N4O4, 415; experimental, 415.

[0465] C. (3-(6-(2,4-dimetoxibencil)-5-oxo-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-2-il)propilcarbamato de ter-butilo



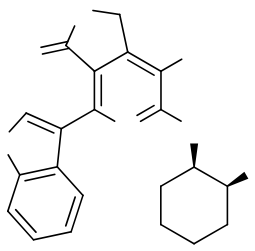
[0466] Una mezcla de 2-(3-((ter-butoxicarbonilamino)propil)-4-metil-6-(m-

tolilamino)pirimidin-5-carboxilato de metilo (0,124 g, 0,299 mmoles) y dióxido de selenio (0,033 g, 0,299 mmoles) en dioxano (2 ml) se calentó a 100ºC durante 24 horas. La mezcla de reacción se agrupó posteriormente y se filtró. El filtrado se concentró y se secó para dar una espuma de color marrón (0,128 g, 0,299 mmoles) la cual se combinó con (2,4-dimetoxifenil)metanamina (0,045 ml, 0,299 mmoles), DCM (2 ml) y MeOH (1 ml). La mezcla se agitó a temperatura ambiente durante 30 min., después de lo cual se agregó cianoborohidruro de sodio (0,047 g, 0,747 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 20 horas, y a continuación se filtró a través de un taco de celite, el cual se enjuagó con MeOH. El filtrado se purificó mediante HPLC preparativa de fase inversa. Las fracciones se recolectaron y se concentraron in vacuo para dar el compuesto del título en forma de un sólido de color tostado (1,7 mg, 1%). [M+H] calc para C30H37N5O5, 548; experimental, 548.

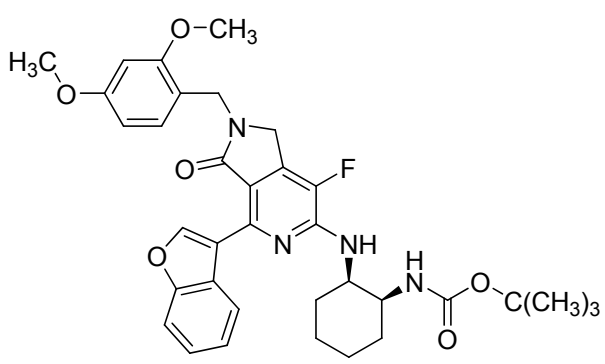
[0467] D. 2-(3-aminopropil)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona

[0468] Una mezcla de (3-(6-(2,4-dimetoxibencil)-5-oxo-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-2-ilamino)ciclohexilcarbamato de ter-butilo (1,7 mg, 0,003 mmoles) en TFA (2 ml) se agitó a 70ºC durante 2 horas. La mezcla se purificó por HPLC preparativa de fase inversa. Las fracciones se recolectaron y se concentraron para dar una sal TFA del compuesto del título en forma de un sólido de color blanco (0,6 mg, 65%). 1H RMN (500 MHz, CD3OD) δ ppm 2,11 - 2,26 (m, 2 H), 2,30 - 2,45 (m, 3 H), 2,92 - 3,09 (m, 4 H), 4,39 (s, 2 H), 6,98 (d, J=8,34 Hz, 1 H), 7,16 - 7,35 (m, 1 H), 7,51 (s, 1 H), 7,65 (d, J=8,59 Hz, 1 H). [M+H] calc para C16H19N5O, 298; experimental, 298.

[0469] Ejemplo 50: 6-((1R,2S)-2-aminociclohexilamino)-4-(benzofuran-3-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona



[0470] A. (1S,2R)-2-(4-cloro-2-(4-benzofuran-3-il)-2-(2,4-dimetoxibencil)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piriditi-6-ilamino)ciclohexilcarbamato de ter-butilo



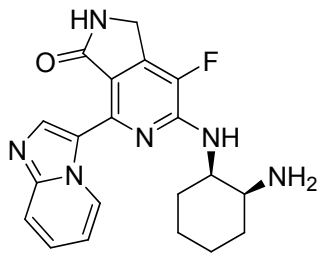
[0471] Una mezcla de (1S,2R)-2-(4-cloro-2-(2,4-dimetoxibencil)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo (65 mg, 0,118 mmoles), carbonato de sodio acuoso (2N, 0,237 ml, 0,474 mmoles), 2-(benzofuran-3-il)-4,4,5,5-tetrametil-1,3,2-dioxaborolano (43 mg, 0,178 mmoles) y cloruro de bis(trifenilfosfina)paladio (17 mg, 0,024 mmoles) en DME (2 ml) se colocó en un recipiente. El recipiente se purgó con nitrógeno, se cerró, y la mezcla de reacción se calentó a 120ºC durante 1 hora. La mezcla se filtró a través de un taco de celite, el cual se enjuagó con MeOH. El solvente se eliminó in vacuo y el residuo se diluyó con MeOH, se pasó a través de una frita de micro filtración, y se purificó mediante HPLC preparativa. Las fracciones se recolectaron y se concentraron in vacuo para dar el compuesto del título en forma de un aceite de color tostado (36,3 mg, 48%). [M+H] calc para C35H39FN4O6, 632; experimental, 632.

[0472] B. 6-((1R,2S)-2-aminociclohexilamino)-4-(benzofuran-3-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona

[0473] Una mezcla de (1S,2R)-2-(4-(benzofuran-3-il)-2-(2,4-dimetoxibencil)-7-

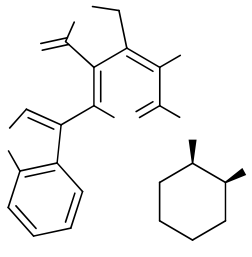
fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo (75 mg, 0,119 mmoles) y TFA (2 ml) se colocó en un recipiente y se calentó a 125ºC durante 3 horas. El solvente se eliminó posteriormente in vacuo para dar un residuo el cual se dispersó en DMSO y MeOH (1/1), se pasó a través de una frita de micro filtración, y se purificó mediante HPLC preparativa. Las fracciones se recolectaron y el solvente se eliminó in vacuo para dar una sal TFA del compuesto del título en forma de un sólido de color gris (9,2 mg, 20%). 1H RMN (500 MHz, CD3OD) δ ppm 1,67 (br s, 3 H), 1,79 - 2,05 (m, 5 H), 3,98 (br s, 1 H), 4,50 (s, 2 H), 4,69 (br s, 1 H), 7,28 - 7,47 (m, 2 H), 7,56 (d, J=7,81 Hz, 1 H), 8,31 (d, J=6,83 Hz, 1 H), 9,08 (s, 1 H). [M+H] calc para C21H21FN4O2, 381; experimental, 381.

[0474] Ejemplo 51: 6-((1R,2S)-2-aminociclohexilamino)-7-fluoro-4-(imidazo[1,2-a]piridin-3-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona

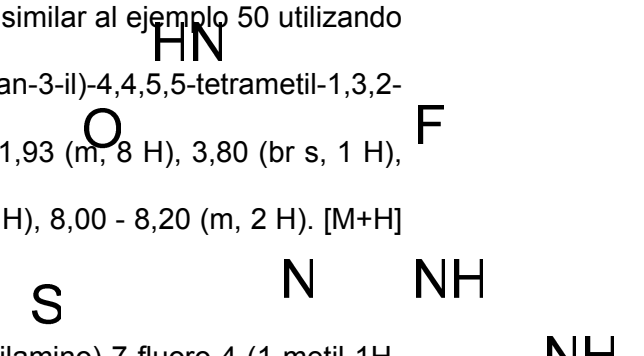


[0475] Una sal TFA del título se preparó de manera similar al ejemplo 50 utilizando ácido imidazo[1,2-a]piridin-3-ilborónico en lugar de 2-(benzofuran-3-il)-4,4,5,5-tetrametil-1,3,2-dioxaborolano. 1H RMN (500 MHz, CD3OD) δ ppm 1,50 - 1,75 (m, 3 H), 1,74 - 1,98 (m, 5 H), 3,78 (br s, 1 H), 4,58 (br s, 3 H), 7,57 (t, J = 6,35 Hz, 1 H), 7,93 - 8,21 (m, 2 H), 8,78 (br s, 1 H), 9,45 (d, J=6,35 Hz, 1 H). [M+H] calc para C20H21FN6O, 381; experimental, 381.

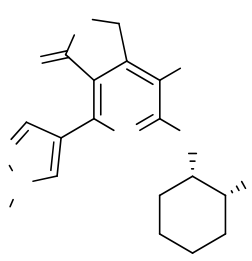
[0476] Ejemplo 52: 6-((1R,2S)-2-aminociclohexilamino)-4-(benzo[b]tiofen-3-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona



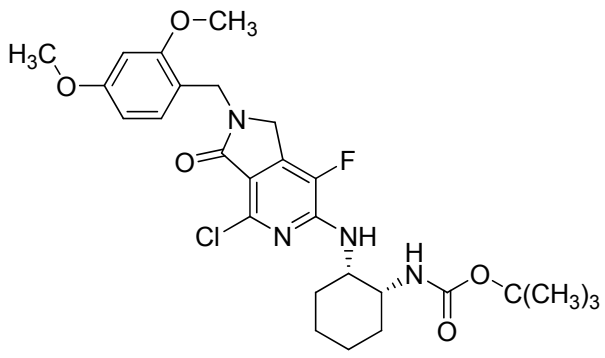
[0477] Una sal TFA del título se preparó de manera similar al ejemplo 50 utilizando ácido benzo[b]tiofen-3-ilborónico en lugar de 2-(benzofuran-3-il)-4,4,5,5-tetrametil-1,3,2-dioxaborolano. 1H RMN (500 MHz, CD3OD) δ ppm 1,50 - 1,93 (m, 8 H), 3,80 (br s, 1 H), 4,42 - 4,68 (m, 3 H), 7,38 (m, J=4,40 Hz, 2 H), 7,94 (br s, 1 H), 8,00 - 8,20 (m, 2 H). [M+H] calc para C21H21FN4OS, 397; experimental, 397.



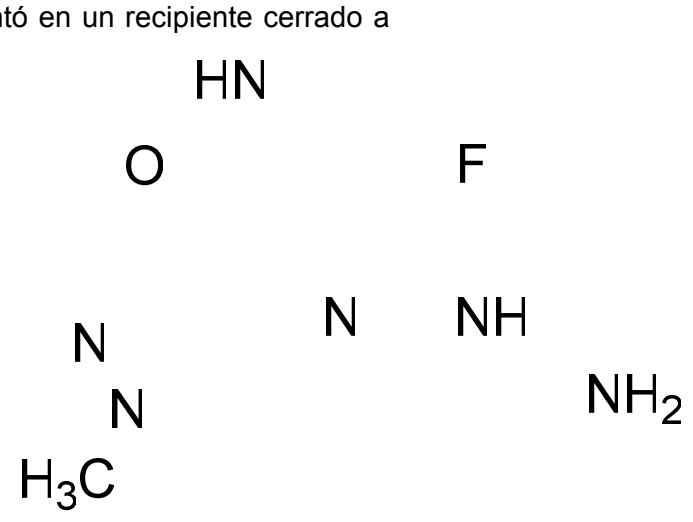
[0478] Ejemplo 53: 6-((1S,2R)-2-aminociclohexilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



[0479] (1R,2S)-2-(4-cloro-2-(2,4-dimetoxibencil)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo

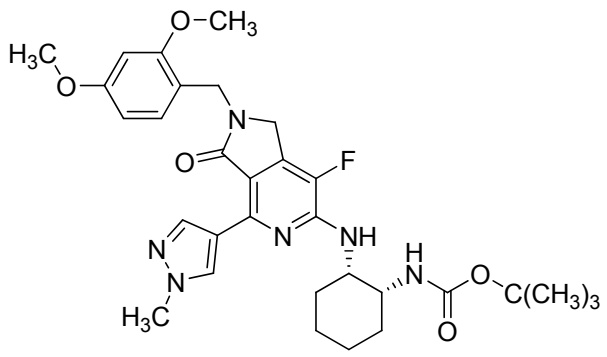


[0480] A una mezcla de 4,6-dicloro-2-(2,4-dimetoxibencil)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona (200 mg, 10,539 mmoles) y (1R,2S)-2-aminociclohexilcarbamato de ter-butilo (173 mg, 0,808 mmoles) en ACN (5 ml) se agregó N,N-diisopropiletilamina (0,141 ml, 0,808 mmoles). La mezcla de reacción se calentó en un recipiente cerrado a



100ºC durante varias horas después de lo cual se agregó amina adicional (0,5 eq). La mezcla se calentó durante toda la noche y el solvente se eliminó posteriormente in vacuo. El residuo se dispersó en DMSO y MeOH (1/1) y la mezcla resultante se filtró. El filtrado se purificó mediante HPLC preparativa. Las fracciones se recolectaron y se secaron in vacuo para dar el compuesto del título en forma de un sólido de color tostado (60,7 mg, 21%). [M+H] calc para C27H34ClFN4O5, 550; experimental, 550.

[0481] B. (1R,2S)-2-(2-(2,4-dimetoxibencil)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo



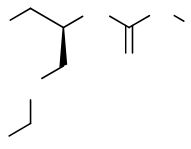
[0482] Una mezcla de (1S,2R)-2-(4-cloro-2-(2,4-dimetoxibencil)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo (60 mg, 0,109 mmoles), 1-metil-4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (34 mg, 0,164 mmoles) y cloruro de bis(trifenilfosfina)paladio (15 mg, 0,022 mmoles) en DME (1 ml) se colocó en un recipiente. El recipiente se purgó con nitrógeno y se agregó carbonato de sodio acuoso (2 N, 0,219 ml, 0,437 mmoles). El recipiente se cerró y la mezcla de reacción se calentó en un baño de aceite a 85ºC durante 3 horas. La mezcla de reacción se filtró a través de un taco de celite, el cual se enjuagó con MeOH y DCM. El solvente se eliminó in vacuo y el residuo se diluyó con DMSO y MeOH (1/1). La mezcla resultante se filtró para recuperar un precipitado de color blanco (31,3 mg). La lejía madre se purificó por HPLC preparativa. Las fracciones se recolectaron y se secaron in vacuo para recuperar un sólido de color blanco adicional (10,2 mg). Los dos cultivos se combinaron para dar el compuesto del título en forma de un sólido de color blanco (41,5 mg, 64%).

[M+H] calc para C31H39FN6O5, 595; experimental, 595.

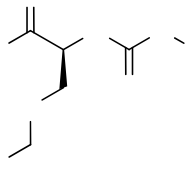
[0483] C. 6-((1S,2R)-2-aminociclohexilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona

[0484] Una mezcla de (1R,2S)-2-(2-(2,4-dimetoxibencil)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo (41,5 mg, 0,070 mmoles) y TFA (2 ml) se calentó a 65ºC durante 3 horas. A continuación de la reacción, el solvente se eliminó in vacuo. El residuo se diluyó con DMSO y MeOH (1/1), se pasó a través de una frita de micro filtración, y se purificó mediante HPLC preparativa. Las fracciones se recolectaron y se secaron in vacuo para dar una sal TFA del compuesto del título en forma de un sólido ce color blanco (22 mg, 92%). 1H RMN (500 MHz, CD3OD) δ ppm 1,56 - 2,01 (m, 8 H), 3,85 (br s, 1 H), 3,94 (br s, 3 H), 4,45 (br s, 2 H), 4,67 (br s, 1 H), 8,31 (br s, 1 H), 8,81 (br s, 1 H). [M+H] calc para C17H21FN6O, 345; experimental, 345.

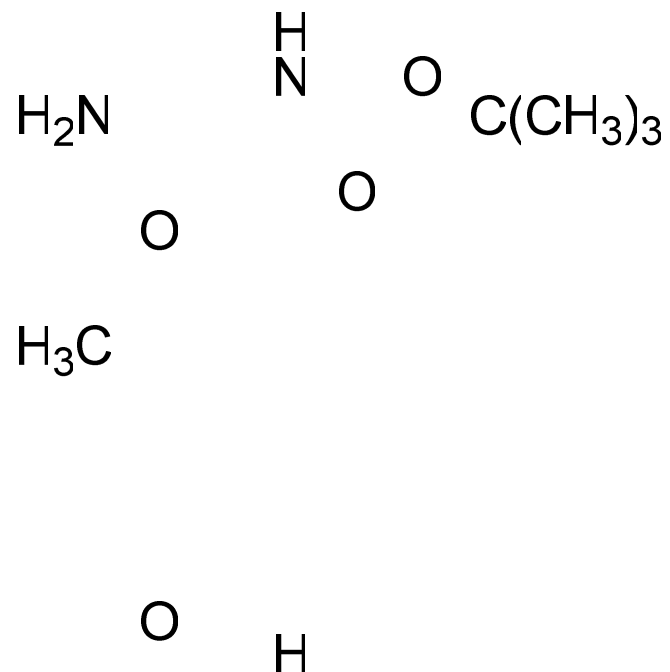
[0485] Preparación 16: (1-amino-3-etoxipropan-2-ilcarbamato de R)-ter-butilo



[0486] A. Ácido (S)-2-(ter-butoxicarbonilamino)-3-etoxipropanoico

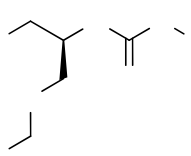


[0487] A una suspensión de hidruro de sodio (17,73 g, 702 mmoles) en THF (600 ml) a 0ºC se agregó MeOH (18 ml) gota a gota. La mezcla se agitó a temperatura ambiente durante 1 hora para dar una solución de metanolato de sodio. Se agregaron yodoetano (25,5 ml, 316 mmoles) y una porción de la solución de metanolato de sodio (120 ml) a una solución del ácido (S)-2-(ter-butoxicarbonilamino)-3-hidroxipropanoico (18

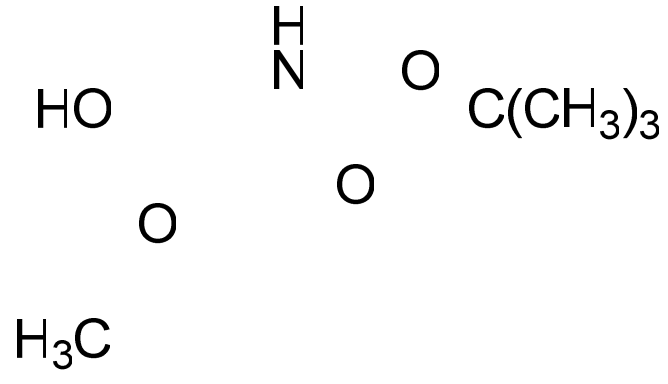


g, 88 mmoles) en THF (600 ml). Después de agitar a temperatura ambiente durante 1 hora, se agregó la solución restante de metanolato de sodio (480 ml), seguido de yodoetano adicional (9,9 ml, 123 mmoles). La mezcla se agitó a temperatura ambiente durante toda la noche. La mezcla se concentró posteriormente y el residuo se disolvió en agua. La capa acuosa se lavó con éter (250 ml), se acidificó hasta pH 2 utilizando HCl 1N, y se extrajo con EtOAc (3 x 300 ml). Las capas orgánicas combinadas se lavaron con 1M de Na2S2O3 (300ml), se secaron y se concentraron. El material bruto resultante se reconstituyó en MeOH, DCM y DMF (volumen total: 50 ml)y se purificó mediante HPLC preparativa de fase inversa. Las fracciones se recolectaron y el ACN se eliminó mediante evaporación rotativa. La solución acuosa resultante se neutralizó con NaHCO3 acuoso saturado, se lavó con EtOAc (2 x 200 ml), se secó sobre Na2SO4, se filtró, y la fase acuosa se despojó hasta sequedad mediante evaporación rotativa para dar el compuesto del título en forma de un aceite transparente (1,81 g, 9%). [M+H] calc para C10H19NO5O, 234; experimental, 234.

[0488] B. 1-etoxi-3-hidroxipropan-2-ilcarbamato de R)-ter-butilo

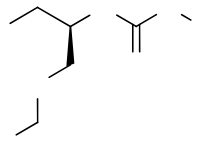


[0489] A una solución del ácido (S)-2-(ter-butoxicarbonilamino)-3-etoxipropanoico (1,81 g, 7,76 mmoles) en THF (20 ml) a -15ºC se agregó cloroformiato de isobutilo (1,015 ml, 7,76 mmoles) en THF (5 ml) y 4-metilmorfolina (0,853 ml, 7,76 mmoles) en THF (5 ml). Después de agitar durante 10 min. a -15ºC, la mezcla se agregó lentamente a una solución de borohidruro de sodio (0,881 g, 23,28 mmoles) en H2O (7 ml). La mezcla se agitó a t-15ºC durante 30 min. y se extrajo con EtOAc. La capa orgánica se lavó con NaHCO3 acuoso saturado y salmuera y se secó. El residuo se transportó al próximo paso sin purificación posterior (1,6 g, 94%). [M+H] calc para C10H21NO4O, 220; experimental,

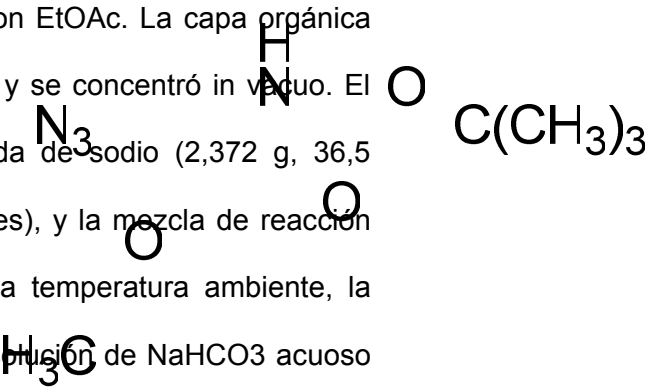


220.

[0490] C. 1-azido-3-etoxipropan-2-ilcarbamato de R)-ter-butilo



[0491] Se agregó cloruro de metanosulfonilo (0,851 ml, 10,95 mmoles) en DCM (1 ml) a una solución de 1-etoxi-3-hidroxipropan-2-ilcarbamato de R)-ter-butilo (1,6g, 7,30 mmoles) y Et3N (1,538 ml, 10,95 mmoles) en DCM (10 ml) a 0ºC. Después de agitar a temperatura ambiente durante 1 hora, la mezcla se diluyó con EtOAc. La capa orgánica se lavó con solución de NaHCO3 acuoso saturado, se secó y se concentró in vacuo. El residuo se disolvió en DMF (10,00 ml). Se agregaron azida de sodio (2,372 g, 36,5 mmoles) y yoduro de tetrabutilamonio (0,270 g, 0,730 mmoles), y la mezcla de reacción se agitó a 75ºC durante 4 horas. Después de enfriar hasta temperatura ambiente, la mezcla se diluyó con EtOAc. La capa orgánica se lavó con solución de NaHCO3 acuoso saturado, se secó y se concentró in vacuo para dar el compuesto del título (1,2 g, 67%). [M+H] calc para C10H20N4O3, 245; experimental, 245.

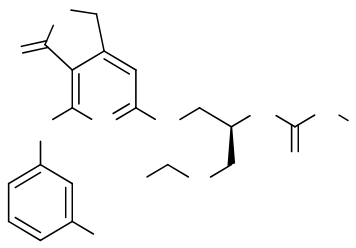


[0492] D. 1-amino-3-etoxipropan-2-ilcarbamato de (R)-ter-butilo

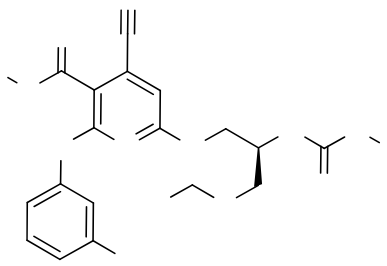
[0493] Una mezcla de 1-azido-3-etoxipropan-2-ilcarbamato de RR)-ter-butilo (1,2 g, 4,91 mmoles) en MeOH (10 ml) se agregó paladio sobre carbono (0,523 g, 4,91 mmoles). La mezcla se agitó en atmósfera de hidrógeno durante toda la noche a temperatura ambiente. El material bruto resultante se reconstituyó en MeOH (1,0 ml) y se purificó mediante HPLC preparativa de fase inversa. Las fracciones se recolectaron y el solvente se despojó hasta sequedad mediante evaporación rotativa para dar el compuesto del título en forma de un aceite transparente (722 mg, 67%). [M+H] calc para C10H22N2O3, 219; experimental, 219.

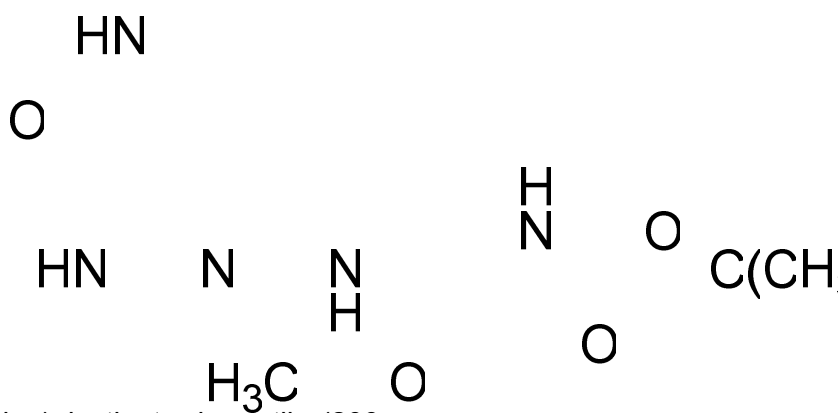
[0494] Preparación 17: (1-etoxi-3-(3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-

pirrolo[3,4-c]piridin-6-ilamino)propan-2-ilcarbamato de (R)-ter-butilo

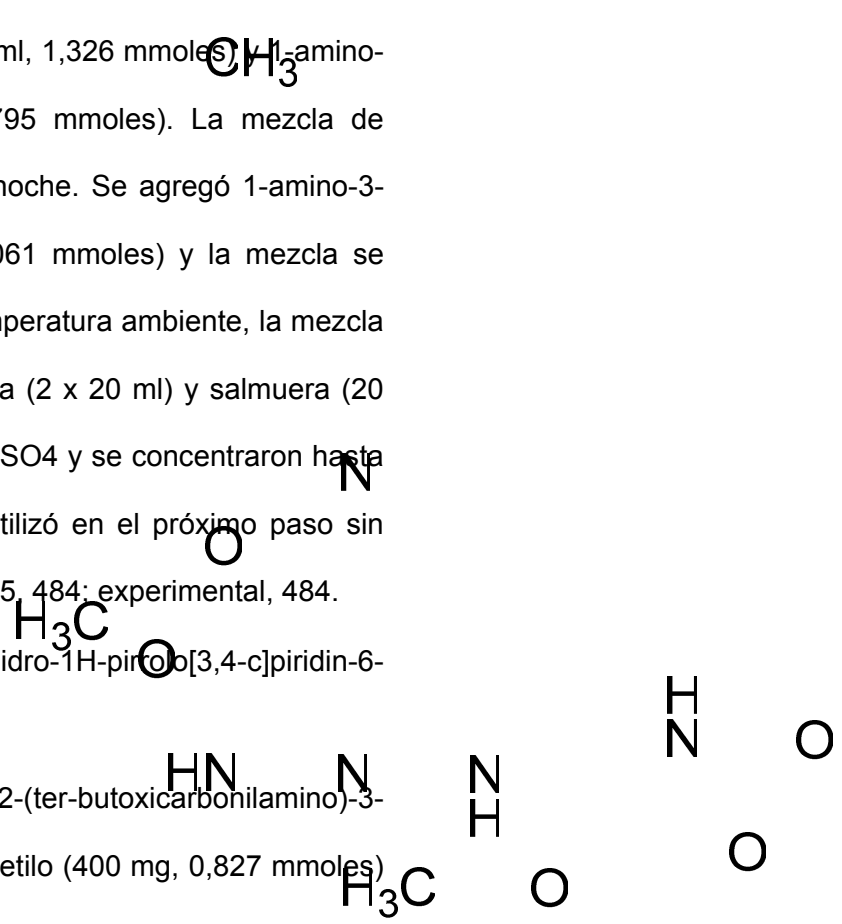


[0495] A. 6-(2-(ter-butoxicarbonilamino)-3-etoxipropilamino)-4-ciano-2-(m-tolilamino)nicotinato de (R)-metilo



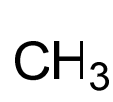


[0496] A una solución de 6-cloro-4-ciano-2-(m-tolilamino)nicotinato de metilo (200 mg, 0,663 mmoles) en DMF (5 ml) se agregó DIPEA (0,232 ml, 1,326 mmoles) y 1-amino-3-etoxipropan-2-ilcarbamato de (R)-ter-butilo (174 mg, 0,795 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante toda la noche. Se agregó 1-amino-3-etoxipropan-2-ilcarbamato de (R)-ter-butilo (231,25 mg, 1,061 mmoles) y la mezcla se calentó a 65ºC durante 1 hora. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se diluyó con EtOAc (30 ml) y se lavó con agua (2 x 20 ml) y salmuera (20 ml). Las capas orgánicas combinadas se secaron sobre Na2SO4 y se concentraron hasta un aceite de color amarillo espeso. El producto bruto se utilizó en el próximo paso sin purificación posterior (415 mg). [M+H] calc para C25H33N5O5, 484; experimental, 484.



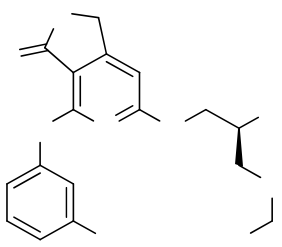
[0497] B. 1-etoxi-3-(3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)propan-2-ilcarbamato de (R)-ter-butilo

[0498] En un matraz que contiene 6-(2-(ter-butoxicarbonilamino)-3-etoxipropilamino)-4-ciano-2-(m-tolilamino)nicotinato de (R)-metilo (400 mg, 0,827 mmoles)

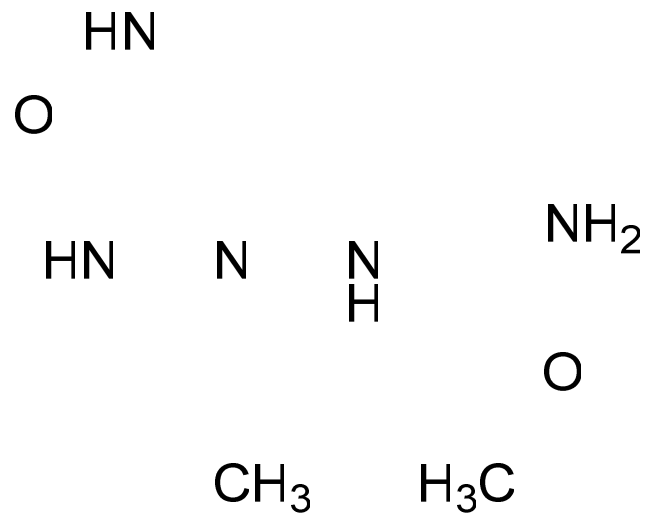


en HOAc (0,25 ml) y DCM (1 ml) se agregó óxido de platino (IV) (18,78 mg, 0,083 mmoles). El matraz se evacuó y se rellenó con H2 tres veces, y la mezcla de reacción se agitó vigorosamente a temperatura ambiente en atmósfera de H2 durante 3 a 4 horas. La mezcla se filtró posteriormente a través de celite, y el solvente se eliminó in vacuo. El residuo se mantuvo al vacío durante toda la noche para eliminar el HOAc en exceso. El residuo bruto se disolvió en DCM anhidro (20 ml). Se agregó carbonato de potasio (572 mg, 4,14 mmoles), y la mezcla se agitó a temperatura ambiente durante 8 horas. La mezcla se filtró a través de celite y se concentró in vacuo. El residuo se reconstituyó en una solución de MeOH/DCM (1/1,5 ml) y se purificó mediante HPLC preparativa de fase inversa. Las fracciones recolectadas se concentraron in vacuo para dar el compuesto del título en forma de una sal TFA (109 mg, 28,9%). [M+H] calc para C24H33N5O4, 456; experimental, 456.

[0499] Ejemplo 54: (R)-6-(2-amino-3-etoxipropilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona

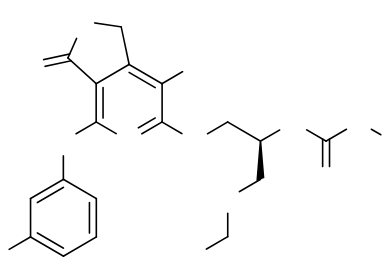


[0500] A un solución de 1-etoxi-3-(3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)propan-2-ilcarbamato de (R)-ter-butilo (109 mg, 0,239 mmoles) en DCM (1 ml) se agregó una solución de TFA/DCM (1/1, 10 ml). La mezcla se agitó a temperatura ambiente durante 2 horas. Después de la eliminación del solvente, el material bruto resultante se reconstituyó en una solución de MeOH/DCM (1/1, 5 ml) y se purificó mediante HPLC preparativa de fase inversa. Las fracciones se recolectaron, y el ACN se eliminó mediante evaporación rotativa. La solución acuosa resultante se neutralizó con NaHCO3 acuoso saturado, se lavó con EtOAc (2 x 200 ml), se secó sobre

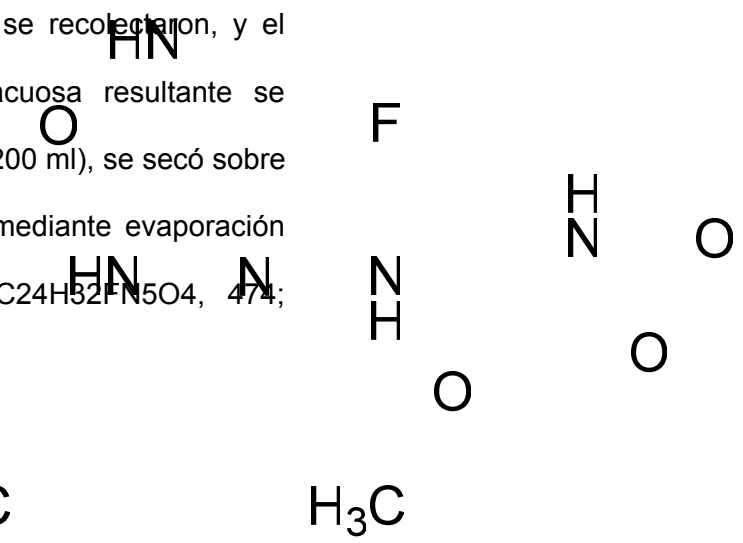


Na2SO4, y se filtró. La fase acuosa se despojó hasta sequedad mediante evaporación rotativa para dar el compuesto del título (11 mg, 13%). 1H RMN (400 MHz, DMSO-d6) δ ppm 1,08 - 1,18 (m, 3 H), 1,25 - 1,44 (m, 4 H), 2,26 - 2,32 (m, 3 H), 4,07 - 4,17 (m, 3 H), 4,19 - 4,29 (m, 2 H), 6,03 (s, 1 H), 6,78 (d, J=7,83 Hz, 1 H), 7,06 (br s, 1 H), 7,12 - 7,22 (m, 1 H), 7,48 (s, 1 H), 7,60 (d, J=7,83 Hz, 1 H), 7,66 - 7,75 (m, 2 H), 7,99 (s, 1 H), 8,83 - 8,97 (m, 1 H). [M+H] calc para C19H25N5O2, 356; experimental, 356.

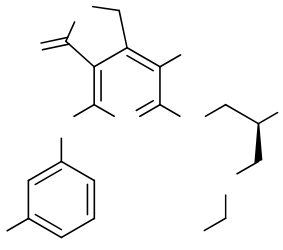
[0501] Preparación 18: (1-etoxi-3-(7-fluoro-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)propan-2-ilcarbamato de (R)-ter-butilo



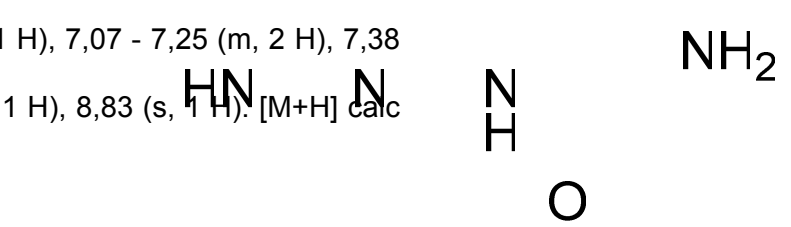
[0502] A una solución enfriada de 1-etoxi-3-(3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)propan-2-ilcarbamato de (R)-ter-butilo (94,7 mg, 0,208 mmoles) en CH2Cl2 (5 ml) a 0ºC se agregó SELECTFLUOR® (73,6 mg, 0,208 mmoles). La mezcla se dejó agitar en un baño helado y se entibió lentamente a temperatura ambiente durante 6 horas. Después, la mezcla se diluyó con EtOAc (10 ml) y se lavó con NaHCO3 acuoso saturado (5 ml) seguido de agua (5 ml) y salmuera (5 ml). Las capas orgánicas se combinaron, se secaron sobre Na2SO4 y se concentraron hasta un residuo de color marrón. El material bruto resultante se reconstituyó en MeOH/DCM (5 ml) y se purificó mediante HPLC preparativa. Las fracciones recolectadas se recolectaron, y el ACN se eliminó mediante evaporación rotativa. La solución acuosa resultante se neutralizó con NaHCO3 acuoso saturado, y se lavó con EtOAc (2 x 200 ml), se secó sobre Na2SO4, se filtró, y la fase acuosa se despojó hasta sequedad mediante evaporación rotativa para dar el compuesto del título. [M+H] calc para C24H32FN5O4, 474; experimental, 474.



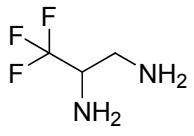
[0503] Ejemplo 55: (R)-6-(2-amino-3-etoxipropilamino)-7-fluoro-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



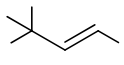
[0504] Una sal TFA del compuesto del título se preparó de manera similar al Ejemplo 54 usando (R)-1-etoxi-3-(7-fluoro-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)propan-2-ilcarbamato de ter-butilo en lugar de (R)-1-etoxi-3-(3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)propan-2-ilcarbamato de ter-butilo. 1H RMN (400 MHz, DMSO-d6) δ ppm 1,08 - 1,19 (m, 3 H), 2,25 - 2,36 (m, 3 H), 3,38 - 3,77 (m, 7 H), 4,40 (s, 2 H), 6,80 (d, J=7,58 Hz, 1 H), 7,07 - 7,25 (m, 2 H), 7,38 (s, 1 H), 7,54 (d, J=7,58 Hz, 1 H), 7,92 (br s, 2 H), 8,28 (s, 1 H), 8,83 (s, 1 H). [M+H] calc para C19H24FN5O2, 374; experimental, 374.



[0505] Preparación 19: 3,3,3-trifluoropropano-1,2-diamina



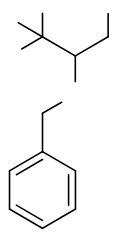
[0506] A. 3,3,3-trifluoro-1-nitroprop-1-eno



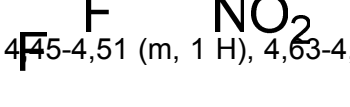
[0507] Una mezcla de 2,2,2-trifluoroetano-1,1-diol (75% de solución acuosa, 20 g, 0,13 moles), CH3NO2 (24 g, 0,39 moles) y Na2CO3 (0,85 g, 8 mmoles) se agitó durante toda la noche a temperatura ambiente. Se agregó agua (50 ml) y la mezcla se extrajo con éter dietílico (3 x 30 ml) y se secó sobre Na2SO4. Después de concentrar el extracto orgánico a baja temperatura y a presión reducida, se agregó P2O5 (20,0 g, 0,14 moles) al aceite residual, el cual se destiló a presión atmosférica para dar un aceite verde-amarillo

(4 g, 50% de pureza, 10% de rendimiento). Punto de ebullición 85-90°C; 1H RMN (400 MHz, CDCl3) δ ppm 7,09-7,17 (m, 1 H), 7,50 (dd, J=2,0 Hz, 12,0 Hz, 1 H).

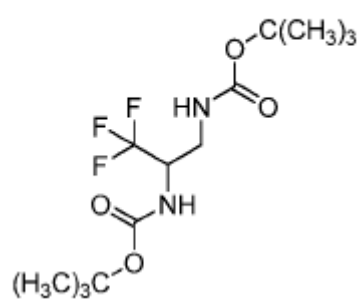
[0508] B. N-bencil-1,1,1-trifluoro-3-nitropropan-2-amina



[0509] Una mezcla de 3,3,3-trifluoro-1-nitroprop-1-eno (4 g, 28,4 mmoles) y bencilamina (3,2 g, 30,0 mmoles) en tolueno (50 ml) se agitó a temperatura ambiente durante 1 hora. la mezcla se concentró y el residuo se purificó por cromatografía de columna (EtOAc/PE = 1/10) para dar el compuesto del título (5,5 g, 78%). 1H RMN (400 MHz, CDCl3) δ ppm 3,91-3,95 (m, 1 H), 4,06-4,14 (m, 1 H), 4,45-4,51 (m, 1 H), 4,63-4,67 (m, 1 H), 7,30-7,39 (m, 5 H).



[0510] C. N,N-(3,3,3-trifluoropropan-1,2-diil)-biscarbamato de di-ter-butilo

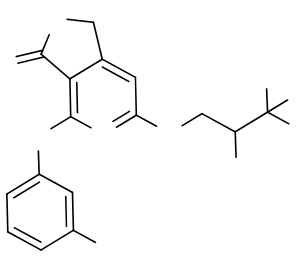


[0511] Una mezcla de N-bencil-1,1,1-trifluoro-3-nitropropan-2-amina (5,5 g, 22,0 mmoles) y Pd/C (3.0 g) en MeOH se agitó a temperatura ambiente durante toda la noche en atmósfera de H2. La mezcla se filtró posteriormente y se concentró para dar un aceite, el cual se combinó con pirocarbonato de di-ter-butilo (11,0 g, 50,0 mmoles) y Et3N (5,0 g, 50,0 mmoles) en DCM (100 ml). La mezcla se agitó durante toda la noche y a continuación se concentró. El residuo se purificó por cromatografía de columna (EtOA/PE = 1/7) para dar el compuesto del título en forma de un sólido de color blanco (5,5 g).

[0512] D. 3,3,3-trifluoropropano-1,2-diamina

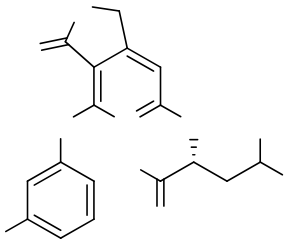
[0513] Una mezcla de N,N-(3,3,3-trifluoropropano-1,2-diil)-biscarbamato de di-ter-butilo y 1,0 M de HCl-EtOAc se agitó a temperatura ambiente durante toda la noche para dar el compuesto del título (1,5 g, 54%). 1H RMN (400 MHz, CD3OD) δ ppm 3,50-3,55 (m, 1 H), 3,61-3,66 (m, 1 H), 4,58-4,63 (m, 1 H). [M+H] calc para C3H7N3O2, 129; experimental, 129.

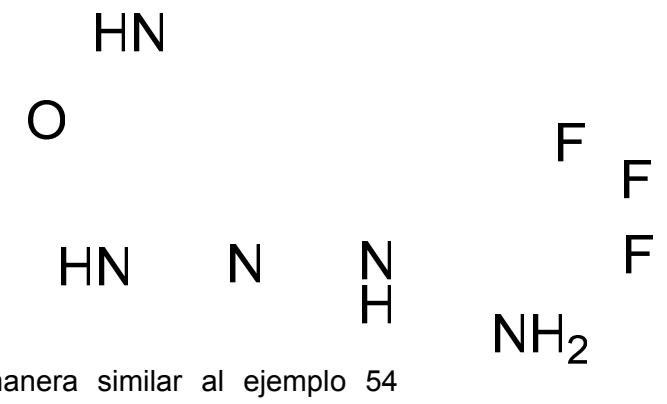
[0514] Ejemplo 56: 6-(2-amino-3,3,3-trifluoropropilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



[0515] El compuesto del título se preparó de manera similar al ejemplo 54 utilizando 3,3,3-trifluoropropano-1,2-diamina en lugar de 1-amino-3-etoxipropan-2-ilcarbamato de (R)-ter-butilo. 1H RMN(400 MHz, DMSO-d6) δ ppm 1,12 - 1,39 (m, 2 H), 1,91 - 2,15 (m, 1 H), 2,22 - 2,40 (m, 3 H), 3,47 - 3,66 (m, 1 H), 3,66 - 3,86 (m, 1 H), 4,14 - 4,27 (m, 1 H), 4,33 - 4,46 (m, 1 H), 4,74 - 4,89 (m, 1 H), 5,96 - 6,13 (m, 1 H), 6,71 - 6,86 (m, 1 H), 7,08 - 7,26 (m, 1 H), 7,38 - 7,70 (m, 2 H), 8,79 - 9,07 (m, 1 H). [M+H] calc para C17H18F3N5O, 366; experimental, 366.

[0516] Ejemplo 57: (R)-4-metil-2-(3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)pentanamida



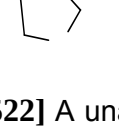


[0517] El compuesto del título se preparó de manera similar al ejemplo 54

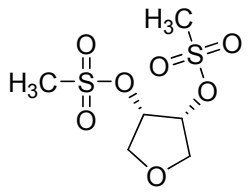


utilizando (R)-2-amino-4-metilpentanamida (64,7 mg, 0,497 mmoles) en lugar de 1-amino-3-etoxipropan-2-ilcarbamato de (R)-ter-butilo. 1H RMN (400 MHz, DMSO-d6) δ ppm 0,82 - 0,88 (m, 3 H), 0,91 - 0,96 (m, 3 H), 1,18 - 1,32 (m, 1 H), 1,61 (t, J=7,33 Hz, 2 H), 1,69 - 1,83 (m, 1 H), 2,24 - 2,34 (m, 3 H), 4,21 (s, 1 H), 4,37 (s, 1 H), 6,00 - 6,17 (m, 1 H), 6,69 - 6,80 (m, 1 H), 6,96 (br s, 1 H), 7,04 (d, J=7,83 Hz, 1 H), 7,10 - 7,26 (m, 2 H), 7,49 (s, 1 H), 7,58 (d, J=7,33 Hz, 1 H), 7,95 (s, 1 H), 8,82 - 8,97 (m, 1 H). [M+H] calc para C20H25N5O2, 368; experimental, 368.

[0518] Preparación 20: (3R,4S)-tetrahidrofuran-3,4-diamina



[0519] A. (3R,4S)-tetrahidrofuran-3,4-diil dimetanosulfonato



[0520] Se agregó cloruro de metanosulfonilo (1,642 ml, 21,13 mmoles) en DCM (5 ml) a una solución de (3R,4S)-tetrahidrofuran-3,4-diol (0,787 ml, 9,61 mmoles) y Et3N (4,05 ml, 28,8 mmoles) en DCM (10 ml) a 0ºC. Después de agitar a 0ºC durante 1 hora, la mezcla se diluyó con DCM. La capa orgánica se lavó con NaHCO3 acuoso saturado, se secó y se concentró in vacuo para dar el compuesto del título en forma de un sólido de color amarillento (2,5 g, 100%). 1H RMN (400 MHz, CDCl3) δ ppm 3,09 - 3,20 (m, 6 H), 3,90 - 4,07 (m, 2 H), 4,10 - 4,22 (m, 2 H), 5,19 (ddd, J=5,31, 3,54, 1,77 Hz, 2 H).

[0521] B. (3R,4S)-3,4-diazidotetrahidrofurano



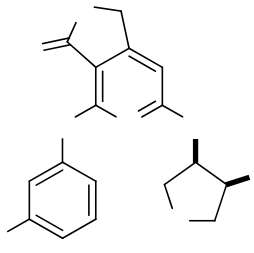
[0522] A una solución de (3R,4S)-tetrahidrofuran-3,4-diil dimetanosulfonato (2,5 g, 9,60 mmoles) en DMF (50 ml) se agregó azida de sodio (3,75 g, 57,6 mmoles) y yoduro

de tetrabutilamonio (0,355 g, 0,960 mmoles). La mezcla de reacción se calentó a 100ºC durante toda la noche. Después de enfriar a temperatura ambiente, la mezcla se diluyó con EtOAc, y la capa orgánica se lavó con salmuera, se secó sobre Na2SO4, y se concentró in vacuo. El residuo se dispersó en tolueno y la mezcla se evaporó in vacuo para eliminar DMF en exceso y para dar el compuesto del título en forma de un aceite de color marrón el cual se utilizó en el próximo paso sin purificación posterior (2,2 g). 1H RMN (400 MHz, CDCl3) δ ppm 3,72 - 3,87 (m, 2 H), 3,94 - 4,46 (m, 4 H).

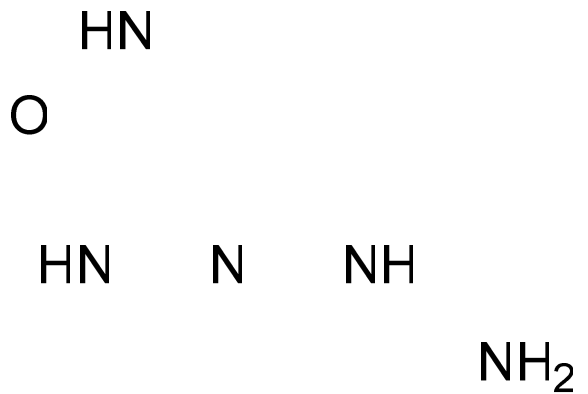
[0523] C. (3R,4S)-tetrahidrofuran-3,4-diamina

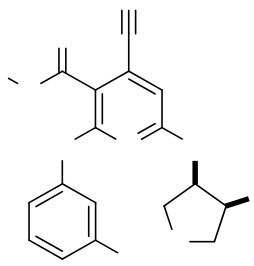
[0524] A una mezcla de (3R,4S)-3,4-diazidotetrahidrofurano (2,2 g, 14,27 mmoles) dispersa en MeOH (10 ml) y DCM (8 ml) se agregó paladio sobre carbono (1,519 g, 14,27 mmoles). La mezcla de reacción se agitó en atmósfera de H2 durante toda la noche. A continuación de la hidrogenación, la mezcla se filtró a través de celite y el solvente se eliminó in vacuo para dar el compuesto del título el cual se utilizó sin purificación posterior (1,54 g).

[0525] Ejemplo 58: 6-(cis-4-aminotetrahidrofuran-3-ilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



[0526] A. 6-(cis-4-aminotetrahidrofuran-3-ilamino)-4-ciano-2-(m-tolilamino)nicotinato de metilo





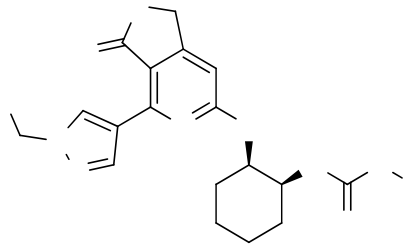
[0527] A una solución de 6-cloro-4-ciano-2-(m-tolilamino)nicotinato de metilo (40 mg, 0,133 mmoles) en DMF (1 ml) se agregó DIPEA (0,046 ml, 0,265 mmoles) y (3R,4S)-tetrahidrofuran-3,4-diamina (13,54 mg, 0,133 mmoles). La mezcla se agitó a temperatura ambiente durante toda la noche. Se agregó amina adicional y la mezcla de reacción se agitó a temperatura ambiente durante otro día. La mezcla de reacción se diluyó en MeOH (10 ml) y se purificó por HPLC preparativa de fase inversa. Las fracciones se recolectaron y el ACN se eliminó mediante evaporación rotativa. La solución acuosa resultante se neutralizó con NaHCO3 acuoso saturado y se lavó con EtOAc (2 x 200 ml), se secó sobre Na2SO4, y se filtró. La fase acuosa se despojó hasta sequedad mediante evaporación rotativa para dar el compuesto del título (35,5 mg, 73%). [M+H] calc para C19H21N5O3, 368; experimental, 368.

[0528] B. 6-(cis-4-aminotetrahidrofuran-3-ilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona

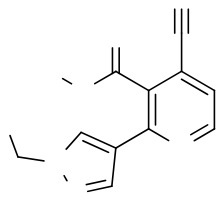
[0529] A un recipiente que contiene 6-(cis-4-aminotetrahidrofuran-3-ilamino)-4-ciano-2-(m-tolilamino)nicotinato de metilo (35,5 mg, 0,097 mmoles) en MeOH (5 ml) y HOAc (2,5 ml) se agregó paladio sobre carbono (1,028 mg, 9,66 µmoles). El recipiente se evacuó y se rellenó con H2 tres veces, y la mezcla se agitó a continuación vigorosamente a temperatura ambiente en atmósfera de H2 durante toda la noche. La mezcla se filtró posteriormente a través de celite, y el solvente se eliminó posteriormente in vacuo. El residuo se disolvió en DCM (10 ml) y MeOH (5 ml) y se agregó carbonato de potasio (26,7 mg, 0,193 mmoles). La mezcla se agitó a temperatura ambiente durante toda la noche. Se agregó carbonato de potasio adicional (40,1 mg, 0,290 mmoles) y la mezcla de reacción

se agitó durante 4 horas a temperatura ambiente, y a continuación se calentó a 50ºC durante 30 min. La mezcla se filtró para eliminar K2CO3 sólido y el filtrado se diluyó con MeOH (10 ml) y se purificó por HPLC preparativa de fase inversa. Las fracciones se recolectaron y se concentraron in vacuo para dar la sal TFA del compuesto del título (4,5 mg, 13,7%). 1H RMN (500 MHz, DMSO-d6) δ ppm 2,30 (s, 3 H), 2,52 - 2,58 (m, 2 H), 3,67 - 3,83 (m, 2 H), 3,90 (br s, 1 H), 3,98 - 4,14 (m, 2 H), 4,20 - 4,30 (m, 2 H), 4,58 (br s, 1 H), 6,16 (s, 1 H), 6,81 (d, J=7,32 Hz, 1 H), 7,11 - 7,27 (m, 2 H), 7,46 (d, J=7,32 Hz, 1 H), 7,59 (br s, 1 H), 8,08 (s, 1 H), 8,94 (s, 1 H). [M+H] calc para C18H21N5O2, 340; experimental, 340.

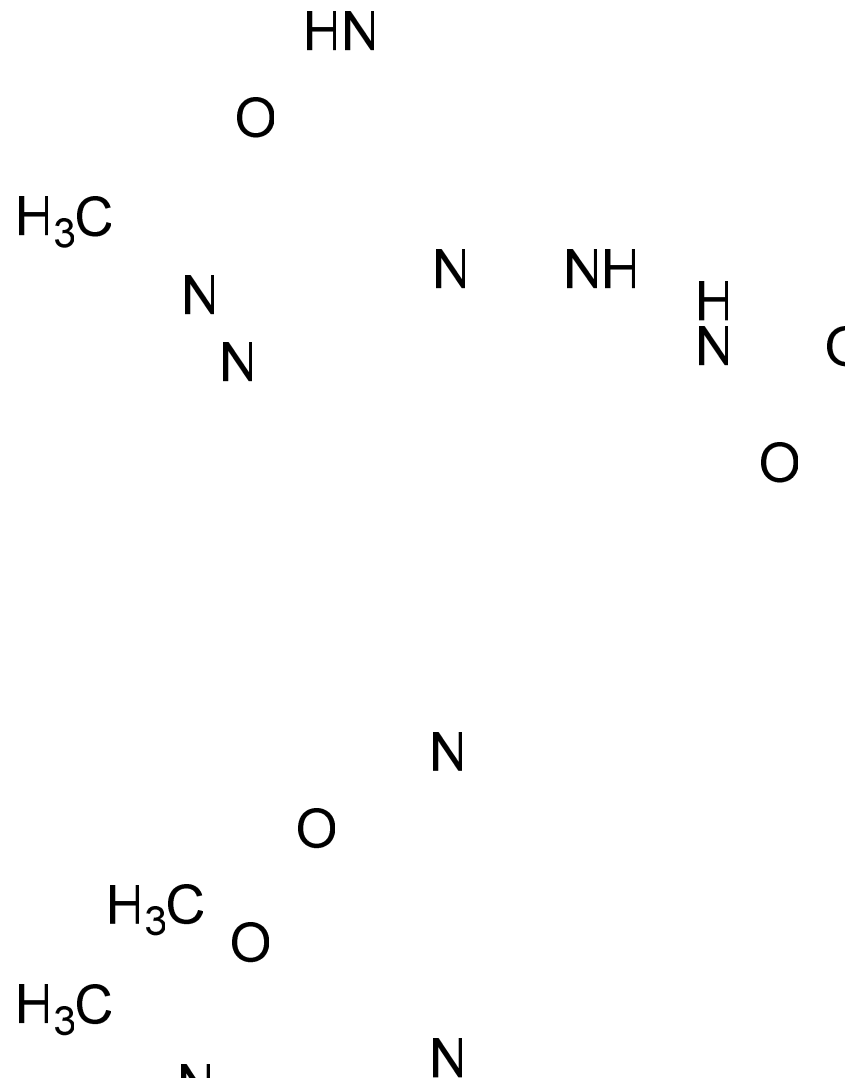
[0530] Preparación 21: (1S,2R)-2-(4-(1-etil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo



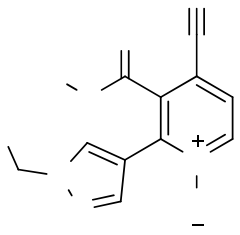
[0531] A. 4-ciano-2-(1-metil-1H-pirazol-4-il)nicotinato de metilo



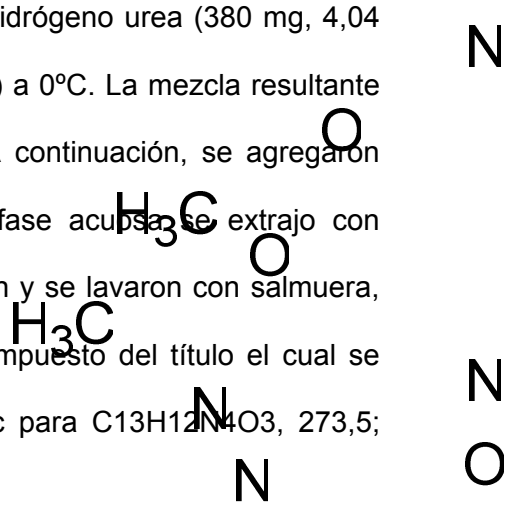
[0532] Una mezcla de 2-cloro-4-cianonicotinato de metilo (207 mg, 1,053 mmoles), 1-etil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (201 mg, 0,905 mmoles) y tetrakis(trifenilfosfina)paladio (0) (122 mg, 0,105 mmoles) en DME (2 ml), y Na2CO3 acuoso saturado (2 ml) se agitó a 80ºC durante 3 horas en atmósfera de N2. Se agregaron posteriormente agua y EtOAc. La fase orgánica se lavó con H2O y salmuera, se secó sobre MgSO4, y se evaporó para dar el compuesto del título (265,3 mg, 98%). [M+H] calc para C13H12N4O2, 257; experimental, 257.



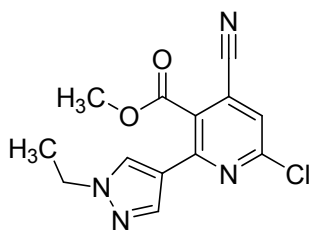
[0533] B. 4-ciano-2-(1-etil-1H-pirazol-4-il)-3-(metoxicarbonil)piridina 1-óxido



[0534] A una mezcla de 4-ciano-2-(1-metil-1H-pirazol-4-il)nicotinato de metilo (207 mg, 0,808 mmoles) en ACN (2 ml) se agregó peróxido de hidrógeno urea (380 mg, 4,04 mmoles) y anhídrido trifluoroacético (0,456 ml, 3,23 mmoles) a 0ºC. La mezcla resultante se agitó a temperatura ambiente durante toda la noche. A continuación, se agregaron solución de NaHCO3 acuoso saturado y cloroformo. La fase acuosa se extrajo con cloroformo (3 x 200 ml). Las capas orgánicas se combinaron y se lavaron con salmuera, se secaron sobre MgSO4, y se evaporaron para dar el compuesto del título el cual se utilizó sin purificación posterior (210 mg, 95%). [M+H] calc para C13H12N4O3, 273,5; experimental, 273,5.

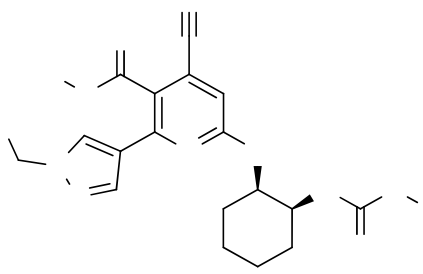


[0535] C. 6-cloro-4-ciano-2-(1-etil-1H-pirazol-4-il)nicotinato de metilo

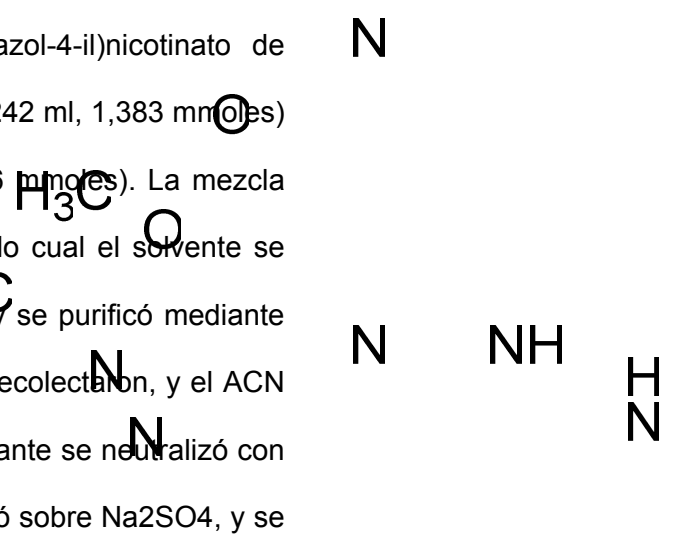


[0536] Una solución de 4-ciano-2-(1-etil-1H-pirazol-4-il)-3-(metoxicarbonil)piridina 1-óxido (210 mg, 0,771 mmoles) en POCl3 (2 ml) se calentó a 80ºC durante 3 a 4 horas. La mezcla se concentró y se purificó por cromatografía flash (SiO2, 10-100% EtOAc en hexano). Las fracciones se recolectaron y el solvente se eliminó in vacuo para dar el compuesto del título (201 mg, 90%).

[0537] D. 6-((1R,2S)-2-(ter-butoxicarbonilamino)ciclohexilamino)-4-ciano-2-(1-etil-1H-pirazol-4-il)nicotinato de metilo



[0538] A una solución de 6-cloro-4-ciano-2-(1-etil-1-H-pirazol-4-il)nicotinato de metilo (201 mg, 0,691 mmoles) en DMF (1 ml) se agregó DIPEA (0,242 ml, 1,383 mmoles) y (1S,2R)-2-aminociclohexilcarbamato de ter-butilo (237 mg, 1,106 mmoles). La mezcla de reacción se agitó a 100ºC durante toda la noche, después de lo cual el solvente se eliminó, y el material bruto resultante se diluyó en MeOH (5,0 ml) y se purificó mediante HPLC preparativa de fase inversa. Las fracciones recolectadas se recolectaron, y el ACN se eliminó mediante evaporación rotativa. La solución acuosa resultante se neutralizó con NaHCO3 acuoso saturado y se lavó con EtOAc (2 x 200 ml), se secó sobre Na2SO4, y se filtró. La fase acuosa se despojó hasta sequedad mediante evaporación rotativa para dar el compuesto del título (62 mg, 19%). [M+H] calc para C24H32N6O4, 469; experimental, 469.

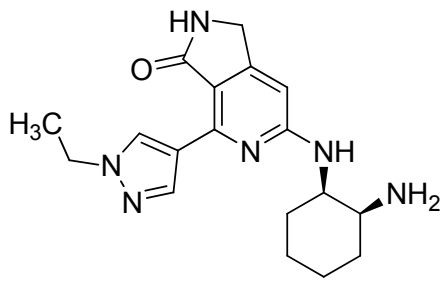


[0539] E. (1S,2R)-2-(4-(1-etil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo

[0540] A un matraz que contiene 6-((1R,2S)-2-(ter-butoxicarbonilamino)ciclohexilamino)-4-ciano-2-(1-etil-1H-pirazol-4-il)nicotinato de metilo (62 mg, 0,132 mmoles) en MeOH (2 ml) se agregó HOAc (1 ml) para dar una solución de color amarillo. Se agregó paladio sobre carbono (14,08 mg, 0,132 mmoles). El matraz se evacuó y se rellenó con H2 tres veces, después de lo cual la mezcla se agitó a continuación vigorosamente a temperatura ambiente en atmósfera de H2 durante toda la noche. La mezcla se filtró a través de celite, y el solvente se eliminó in vacuo para dar un residuo, el cual se disolvió en DCM (10 ml) y MeOH (10 ml). Se agregó carbonato de potasio y la mezcla se agitó durante 5 horas. Los sólidos se filtraron y el filtrado se

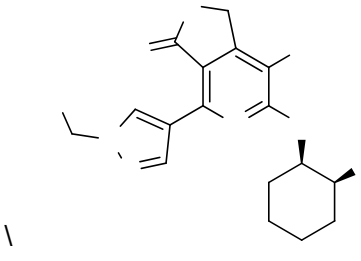
concentró para dar el compuesto del título (50 mg, 86%). [M+H] calc para C23H32N6O3, 441; experimental, 441.

[0541] Ejemplo 59: 6-((1R,2S)-2-aminociclohexilamino)-4-(1-etil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona

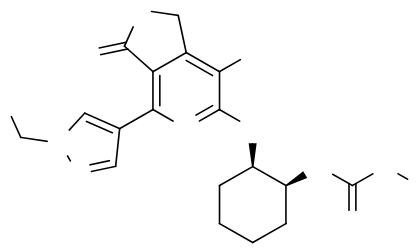


[0542] A una solución de (1S,2R)-2-(4-(1-etil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo (50 mg, 0,113 mmoles) en DCM (1 ml) se agregó DCM/TFA (1/1, 2 ml). La mezcla se agitó a temperatura ambiente durante 2 horas. Después de la eliminación del solvente, el material bruto resultante se reconstituyó en MeOH (5,0 ml) y se purificó por HPLC preparativa. Las fracciones se recolectaron y el solvente se despojó hasta sequedad mediante evaporación rotativa para dar el compuesto del título en forma de una sal TFA (10,5 mg, 27%). 1H RMN (500 MHz, DMSO-d6) δ ppm 1,31 - 1,55 (m, 6 H), 1,58 - 1,86 (m, 8 H), 4,20 - 4,31 (m, 3 H), 6,56 (s, 1 H), 6,84 (d, J=7,32 Hz, 1 H), 7,56 - 7,76 (m, 2 H), 8,10 (s, 1 H), 8,38 (s, 1 H), 8,96 (s, 1 H). [M+H] calc para C18H24N6O, 341; experimental, 341.

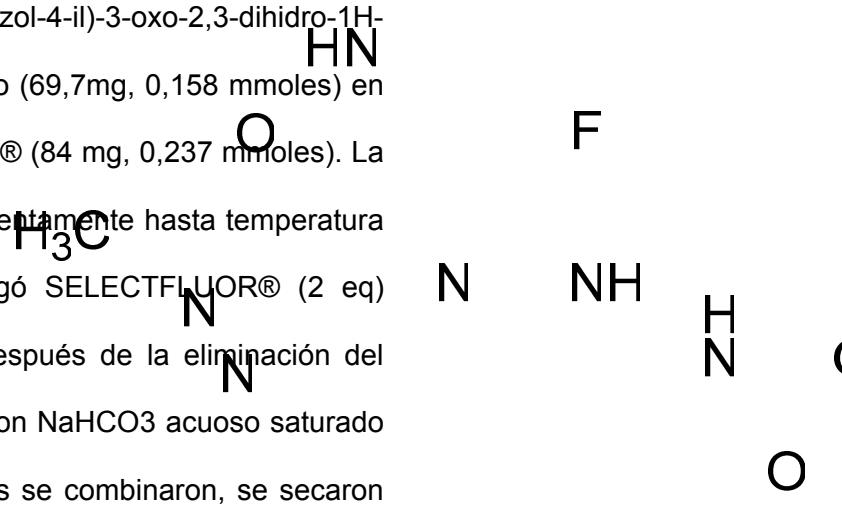
[0543] Ejemplo 60: 6-((1R,2S)-2-aminociclohexilamino)-4-(1-etil-1H-pirazol-4-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona



[0544] A. (1S,2R)-2-(4-(1-etil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino de ter-butilo



[0545] Una solución de (1S,2R)-2-(4-(1-etil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo (69,7mg, 0,158 mmoles) en DCM (5 ml) se enfrió hasta 0ºC. Se agregó SELECTFLUOR® (84 mg, 0,237 mmoles). La mezcla se dejó agitar en un baño helado y se dejó entibiar lentamente hasta temperatura ambiente con agitación durante toda la noche. Se agregó SELECTFLUOR® (2 eq) adicional y la reacción se detuvo después de 2 horas. Después de la eliminación del solvente, el residuo se diluyó con EtOAc (10 ml) y se lavó con NaHCO3 acuoso saturado (5 ml), agua (5 ml), y salmuera (5 ml). Las capas orgánicas se combinaron, se secaron sobre Na2SO4 y se concentraron hasta un residuo de color marrón. El material bruto resultante se reconstituyó en MeOH/DCM (6 ml) y se purificó mediante HPLC preparativa. Las fracciones se recolectaron y el ACN se eliminó mediante evaporación rotativa. La solución acuosa resultante se neutralizó con NaHCO3 acuoso saturado, se lavó con EtOAc (2 x 200 ml), se secó sobre Na2SO4, y se filtró. La fase orgánica se despojó hasta sequedad mediante evaporación rotativa para dar el compuesto del título (20 mg, 28%). [M+H] calc para C23H31FN6O3, 459; experimental, 459.

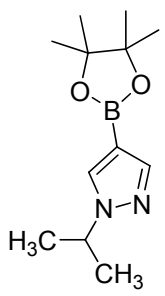


[0546] B. 6-((1R,2S)-2-aminociclohexilamino)-4-(1-etil-1H-pirazol-4-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona

[0547] A una solución de (1S,2R)-2-(4-(1-etil-1H-pirazol-4-il)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo (20 mg, 0,044 mmoles) en DCM (1 ml) se agregó DCM/TFA (1/1, 2 ml). La mezcla se agitó a temperatura ambiente durante 2 horas. Después de la eliminación del solvente, el material bruto resultante se reconstituyó en MeOH (5,0 ml) y se purificó por HPLC preparativa. Las fracciones se recolectaron y el solvente se despojó hasta sequedad mediante evaporación

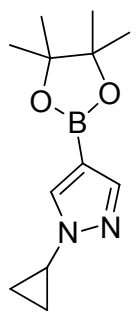
rotativa para dar el compuesto del título en forma de una sal TFA (7 mg, 45%). 1H RMN (500 MHz, DMSO-d6) δ ppm 1,40 (t, J=7,08 Hz, 4 H), 1,54 - 1,72 (m, 2 H), 1,75 - 1,97 (m, 2 H), 3,47 - 3,60 (m, 2 H), 3,69 (br s, 1 H), 4,18 (q, J=7,32 Hz, 2 H), 4,33 - 4,52 (m, 3 H), 6,74 (d, J=6,83 Hz, 1 H), 7,77 (br s, 3 H), 8,26 - 8,44 (m, 2 H), 8,88 (s, 1 H). [M+H] calc para C18H23FN6O, 359; experimental, 359.

[0548] Preparación 22: 1-isopropil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol



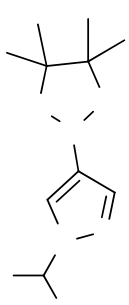
[0549] En un recipiente de microondas, una solución de 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (1 g, 5,15 mmoles) en DMF (10 ml) se agregó carbonato de cesio (5,04 g, 15,46 mmoles) y 2-yodopropano (2,58 ml, 25,8 mmoles). La mezcla de reacción se calentó a 100ºC durante toda la noche. Después de enfriar hasta temperatura ambiente, se agregó H2O (300 ml) y la capa acuosa se lavó con EtOAc (2 x 200 ml). Los extractos orgánicos se combinaron, se secaron sobre Na2SO4, se filtraron y el solvente se eliminó al vacío. El material bruto resultante se reconstituyó en MeOH (1,0 ml) y se purificó mediante HPLC. Las fracciones se recolectaron y se despojaron hasta sequedad mediante evaporación rotativa para dar el compuesto del título. [M+H] calc para C12H21BN2O2, 237; experimental, 237.

[0550] Preparación 23: 1-ciclopropil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol



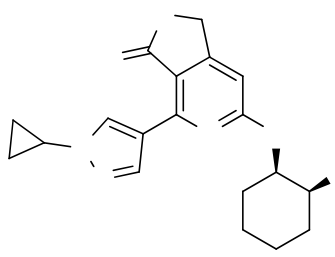
[0551] El compuesto del título se preparó de manera similar a la Preparación 22 utilizando bromociclopropano en lugar de yodopropano. [M+H] calc para C12H19BN2O2, 234; experimental, 234.

[0552] Preparación 24: 1-(difluorometil)-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol

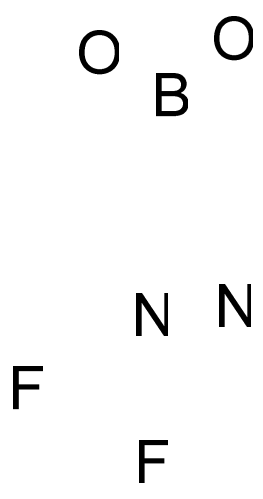


[0553] El compuesto del título se preparó de manera similar a la preparación 22 utilizando difluoroyodometano en lugar de yodopropano y llevando a cabo la reacción a 90ºC [M+H] calc para C10H15BF2N2O2, 245; experimental, 245.

[0554] Ejemplo 61: 6-((1R,2S)-2-aminociclohexilamino)-4-(1-ciclopropil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona

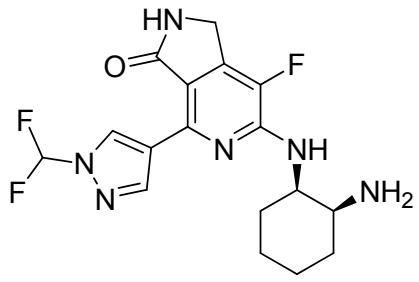


[0555] Una sal TFA del compuesto del título se preparó de manera similar al Ejemplo 59 utilizando 1-ciclopropil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol

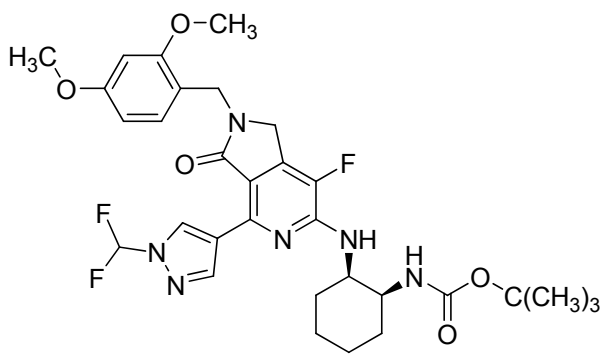


en lugar de 1-etil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol. 1H RMN (500 MHz, CD3OD) δ ppm 1,47 - 1,67 (m, 4 H), 1,69 - 1,95 (m, 8 H), 3,63 - 3,74 (m, 3 H), 4,35 (s, 2 H), 6,65 (s, 1 H), 8,35 (s, 1 H), 8,96 (s, 1 H). [M+H] calc para C19H24N6O, 353; experimental, 353.

[0556] Ejemplo 62: 6-((1R,2S)-2-aminociclohexilamino)-4-(1-(difluorometil)-1H-pirazol-4-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona



[0557] A. (1S,2R)-2-(4-1-(difluorometil)-1H-pirazol-4-il)-2-(2,4-dimetoxibencil)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo



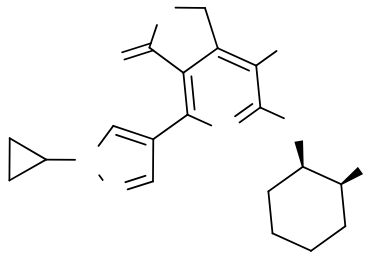
[0558] Una solución de (1S,2R)-2-(4-cloro-2-(2,4-dimetoxibencil)-7-fluoro3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo (35 mg, 0,064 mmoles), 1-(difluorometil)-4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (18,67 mg, 0,076 mmoles) y cloruro de bis(trifenilfosfina)paladio (44,7 mg, 0,064 mmoles) en dioxano (500 µl) y Na2CO3 acuoso saturado (500 µL) y se calentó a 85ºC durante 2 horas. Después de filtrar los sólidos, el solvente se eliminó y el residuo se disolvió en MeOH y DCM y se purificó por HPLC preparativa. Las fracciones se recolectaron y el ACN se eliminó mediante evaporación rotativa. La solución acuosa resultante se neutralizó con NaHCO3 acuoso saturado, se lavó con EtOAc (2 x 200 ml), se secó sobre Na2SO4, y se

filtró. La fase acuosa se despojó hasta sequedad mediante evaporación rotativa para dar el compuesto del título (36 mg, 90%). [M+H] calc para C31H37F3N5O2, 631; experimental, 631.

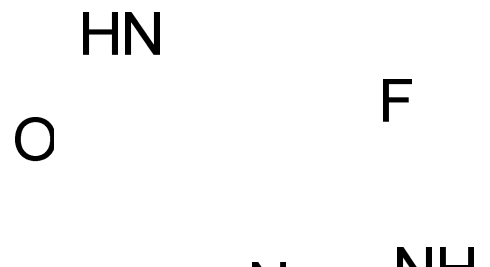
[0559] B. 6-((1R,2S)-2-aminociclohexilamino)-4-(1-(difluorometil)-1H-pirazol-4-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona

[0560] Una solución de (1S,2R)-2-(4-(2,4-dimetoxibencil)-1H-pirazol-4-il)-2-(2,4-dimetoxibencil)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo (36 mg, 0,057 mmoles) y TFA (2 ml) se calentó a 60ºC durante 2 horas. Después de la eliminación del solvente, el residuo se diluyó en MeOH (2 ml) y se purificó por HPLC preparativa. Las fracciones se recolectaron y se despojaron hasta sequedad mediante evaporación rotativa para dar el compuesto del título en forma de una sal TFA (18,7 mg, 86%). 1H RMN (500 MHz, DMSO-d6) δ ppm 1,40 - 1,52 (m, 2 H), 1,58 - 1,76 (m, 3 H), 1,75 - 1,94 (m, 3 H), 3,67 (br s, 1 H), 4,44 (d, J=4,88 Hz, 2 H), 4,53 (br s, 1 H), 6,86 (d, J=6,83 Hz, 1 H), 7,71 (br s, 2 H), 7,79 - 8,12 (m, 1 H), 8,53 (s, 2 H), 9,41 (s, 1 H). [M+H] calc para C17H19F3N6O, 381; experimental, 381.

[0561] Ejemplo 63: 6-((1R,2S)-2-aminociclohexilamino)-4-(1-ciclopropil-1H-pirazol-4-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona

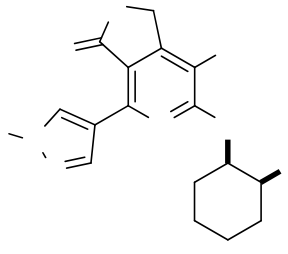


[0562] Una sal TFA del compuesto del título se preparó de manera similar al ejemplo 62 utilizando 1-ciclopropil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol en lugar de 1-(difluorometil)-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol. 1H RMN (500 MHz, DMSO-d6) δ ppm 0,94 - 1,11 (m, 4 H), 1,47 (d, J=6,35 Hz, 2 H), 1,56 - 1,97 (m, 6 H), 3,60 - 3,85 (m, 2 H), 4,28 - 4,53 (m, 3 H), 6,74 (d, J=6,35 Hz, 1 H), 7,70 (br

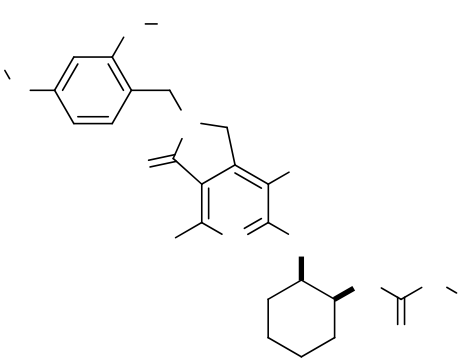


s, 2 H), 8,25 (s, 1 H), 8,38 (s, 1 H), 8,94 (s, 1 H). [M+H] calc para C19H23FN6O, 371; experimental, 371.

[0563] Ejemplo 64: cis-6-(2-aminociclohexilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



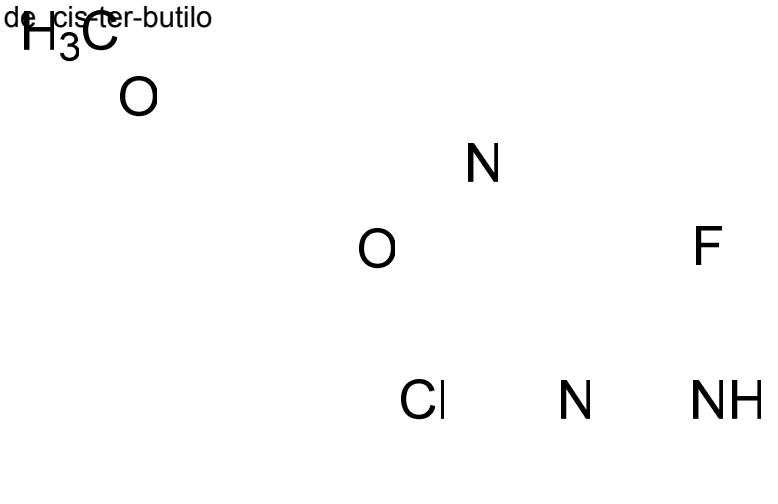
[0564] A. 2-(4-cloro-2-(2,4-dimetoxibencil)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de cis-ter-butilo

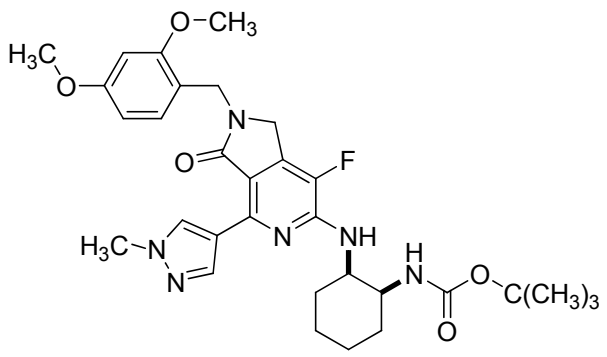


[0565] Una mezcla de 4,6-dicloro-2-(2,4-dimetoxibencil)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona (316 mg, 0,851 mmoles) y 2-aminociclohexilcarbamato de cis-ter-butilo (365 mg, 1,703 mmoles) y DIPEA (0,743 ml, 4,26 mmoles) en ACN (2 ml) se agitó a 85ºC durante 3 días. El material bruto resultante se reconstituyó en MeOH (1 ml) y se purificó por HPLC preparativa. Las fracciones se recolectaron y se despojaron hasta sequedad mediante evaporación rotativa para dar el compuesto del título (161 mg, 34%). 1H RMN (500 MHz, DMSO-d6) δ ppm 1,35 (br s, 10 H), 1,58 (br s, 2 H), 1,76 (br s, 2 H), 3,71 - 3,90 (m, 11 H), 4,33 (br s, 2 H), 4,51 (br s, 2 H), 6,43 - 6,72 (m, 3 H), 6,87 (br s, 1 H), 7,07 (br s, 1 H). [M+H] calc para C27H34ClFN4O5, 549; experimental, 549.



[0566] B. 2-(2-(2,4-dimetoxibencil)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de cis-ter-butilo





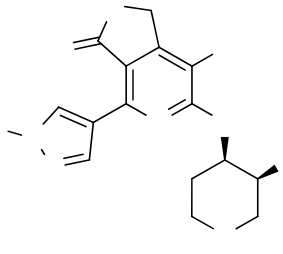
[0567] Una solución de 2-(4-cloro-2-(2,4-dimetoxibencil)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de cis-ter-butilo (135,8 mg, 0,247 mmoles), 1-metil-4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (154 mg, 0,742 mmoles) y cloruro de bis(trifenilfosfina)paladio (174 mg, 0,247 mmoles) en dioxano (2 ml) y Na2CO3 acuoso saturado (2 ml) y se calentó a 120ºC durante 30 min. Después de filtrar los sólidos, el solvente se eliminó y el residuo se disolvió en MeOH y DCM y la mezcla se purificó por HPLC preparativa. Las fracciones se recolectaron y el solvente se despojó hasta sequedad mediante evaporación rotativa para dar el compuesto del título (109 mg, 74%). 1H RMN (500 MHz, DMSO-d6) δ ppm 0,97 - 1,98 (m, 10 H), 2,28 - 2,44 (m, 3 H), 2,56 - 2,72 (m, 4 H), 3,63 - 3,99 (m, 11 H), 4,36 (d, J=18,06 Hz, 2 H), 4,56 (br s, 2 H), 6,50 (br s, 1 H), 6,61 (br s, 1 H), 6,65 - 6,81 (m, 1 H), 7,08 (br s, 1 H), 7,70 (br s, 1 H), 8,30 (br s, 1 H), 8,75 - 9,02 (m, 1 H). [M+H] calc para C31H39FN6O5, 595; experimental, 595.

[0568] C. cis-6-(2-aminociclohexilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona

[0569] Una solución de 2-(4-(2,4-dimetoxibencil)--7-fluoro-4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de cis-ter-butilo (109 mg, 0,183 mmoles) y TFA (5 ml) se calentó a 60ºC durante 2 horas. Después de la eliminación del solvente, el residuo se diluyó en MeOH (2 ml) y se purificó por HPLC preparativa. Las fracciones se recolectaron y se despojaron hasta sequedad mediante evaporación rotativa para dar el compuesto del título en forma de una sal TFA. 1H RMN

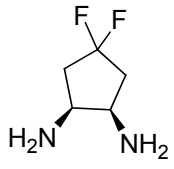
(500 MHz, DMSO-d6) δ ppm 1,47 (br s, 2 H), 1,57 - 1,75 (m, 3 H), 1,84 (br s, 2 H), 3,12 - 3,23 (m, 2 H), 3,87 - 3,94 (m, 3 H), 4,35 - 4,50 (m, 3 H), 6,73 (br s, 1 H), 7,71 (br s, 2 H), 8,28 - 8,44 (m, 2 H), 8,84 (d, J=3,91 Hz, 1 H). [M+H] calc para C17H21FN6O, 345; experimental, 345.

[0570] Ejemplo 65: 6-((3R,4R)-3-aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



[0571] Una sal TFA del compuesto del título se preparó de manera similar al ejemplo 64 utilizando diclorhidrato de (3R,4R)-tetrahiro-2H-piran-3,4-diamina en lugar de 2-aminociclohexilcarbamato de cis-ter-butilo. El estereoisómero deseado se aisló utilizando HPLC preparativa. 1H RMN (500 MHz, CD3OD) δ ppm 1,29 (br s, 2 H), 1,86 - 1,99 (m, 1 H), 3,84 - 3,99 (m, 4 H), 4,03 - 4,17 (m, 1 H), 4,45 (br s, 2 H), 8,29 (br s, 1 H), 8,79 (br s, 1 H). [M+H] calc para C16H19FN6O20, 347; experimental, 347.

[0572] Preparación 25: cis-4,4-difluorociclopentano-1,2-diamina



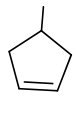
[0573] A. ciclopenta-1,3-dieno



[0574] Un matraz que contiene diciclopentadieno se burbujeó con N2 durante 1 min. y se calentó a continuación mediante un baño de aceite hasta aproximadamente 180ºC. Se destiló lentamente ciclopentadieno a 40-45ºC. El compuesto del título (100 g) se recolectó y se mantuvo a -70ºC en N2. 1H RMN (400 MHz, CDCl3) δ ppm 3,02 (t,

J=1,4 Hz, 2 H), 6,49-6,51 (m, 2 H), 6,61-6,62 (m, 2 H).

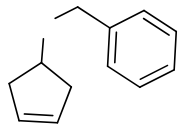
[0575] B. Ciclopent-3-enol



[0576] A alfa-pineno enfriado (225,0 g, 1,65 moles) a 0ºC se agregó gota a gota BH3-THF (1 M, 750 ml) durante un período de 30 min. en atmósfera de N2. La mezcla de reacción se agitó durante 3,5 horas a 0ºC. Se agregó gota a gota ciclopenta-1,3-dieno destilado (99,0 g, 1,50 moles) gota a gota a 0ºC durante un período de 40 min. La mezcla resultante se entibió lentamente a temperatura ambiente y se agitó durante 20 horas. El exceso de hidruro se descompuso agregando agua (30 ml) a una temperatura por debajo de 10ºC. Se agregó NaOH acuoso (3N, 300 ml) a una temperatura por debajo de 5ºC, seguido de H2O2 (30%, 250 ml). La capa acuosa se saló con NaCl, y la capa orgánica se separó y se secó sobre Na2SO4. El producto se destiló a 65ºC a una presión reducida de 20mm Hg para dar el compuesto del título en forma de un aceite (30,4, 24%). 1H RMN (400 MHz, CDCl3) δ ppm 2,29 (d, J=17,6 Hz, 2 H), 2,61 (dd, J=6,0, 16,4 Hz, 2 H), 4,82 (s, 1 H), 5,68 (s, 2 H).

OH

[0577] C. ((Ciclopent-3-eniloxi)metil)benceno

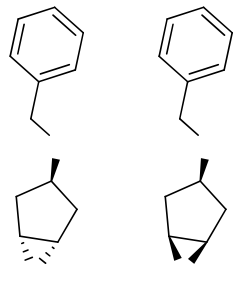


[0578] A una solución enfriada de ciclopent-3-eno (30,40 g, 0,36 moles) en THF ((300 ml) a 0ºC se agregó NaH (18,82 g, 0,47 moles, 60% en aceite mineral). Después de que cesó la efervescencia, se agregó bromuro de bencilo (80,45 g, 0,47 moles) gota a gota a 0ºC durante un período de 45 min. La mezcla de reacción se dejó entibiar a temperatura ambiente durante un período de 6 horas. El exceso de NaH se templó con MeOH (120 ml) a una temperatura por debajo de 5ºC. La mezcla se entibió a temperatura ambiente, se diluyó con H2O, y las dos capas se separaron. La capa acuosa se extrajo

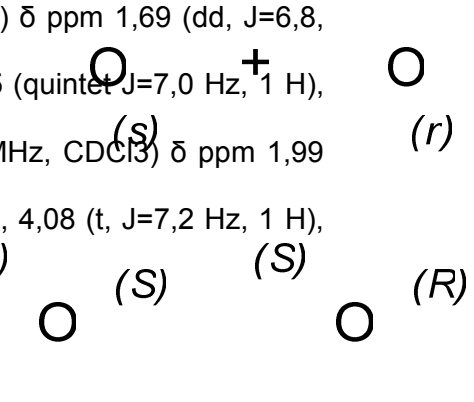
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con EtOAc. Las capas orgánicas se combinaron, se concentraron, y se purificaron por cromatografía de columna, eluyendo con éter de petróleo y EtOAc (PE/EA = 40/1 hasta 30/1) para dar el compuesto del título en forma de un aceite (45,48 g, 72%). 1H RMN (400 MHz, CDCl3) δ ppm 2,38-2,41 (m, 2 H), 2,49-2,54 (m, 2 H), 4,20-4,24 (m, 1 H), 4,42 (s, 2 H), 5,62 (s, 2 H), 7,17-7,28 (m, 5 H).

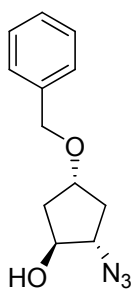
[0579] D. (1R,3s,5S)-3-(benciloxi)-6-oxabiciclo[3.1.0]hexano y (1R,3r,5S)-3-(benciloxi)-6-oxabiciclo[3.1.0]hexano



[0580] A una solución enfriada de ((ciclopent-3-eniloxi)metil)benceno (45,28 g, 260 mmoles) en DCM (300 ml) a 0ºc se agregó el ácido m-cloroperoxibenzoico (111,9 g, 520 mmoles) en una porción. La mezcla se agitó a una temperatura desde 0ºC hasta temperatura ambiente durante toda la noche. La mezcla de reacción se filtró y el exceso de ácido m-cloroperoxibenzoico se redujo por la adición de Na2S2O3 acuoso saturado hasta que se observó un ensayo de yoduro de almidón negativo. La mezcla se neutralizó con NaHCO3 saturado hasta pH 8 - 9 y se filtró. El filtrado se separó con DCM, se lavó con salmuera, se secó sobre Na2SO4, y se purificó por cromatografía de columna eluyendo con éter de petróleo y EtOAc (PE/EtOAc = 30/1, 20/1 a 10/1) para dar los compuestos del título en forma de aceites ((1R,3s,5S): 14,41 g, 76 mmoles; ((1R,3r,5S): 21,38 g, 113 mmoles). 1H RMN de (1R,3s,5S) (400MHz, CDCl3) δ ppm 1,69 (dd, J=6,8, 14,0 Hz, 2 H), 2,49 (dd, J=7,2, 14,0 Hz, 2 H), 3,49 (s, 2 H), 3,85 (quintet J=7,0 Hz, 1 H), 4,43 (s, 2 H), 7,25-7,34 (m, 5 H); 1H NMR of (1R,3r,5S) (400 MHz, CDCl3) δ ppm 1,99 (dd, J=7,6, 15,6 Hz, 2 H), 2,23 (d, J=16,6 Hz, 2 H), 3,55 (s, 2 H), 4,08 (t, J=7,2 Hz, 1 H), 4,49 (s, 2 H), 7,27-7,35 (m, 5 H).

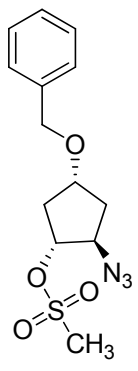


[0581] E. (1S,2S,4R)-2-azido-4-(benciloxi)ciclopentanol



[0582] A una solución de (1R,3s,5S)-3-(benciloxi)-6-oxabiciclo[3.1.0]hexano (14,41 g, 76 mmoles) en EtOH/H2O (550 ml160ml) se agregó NH4Cl (15,06 g, 284 mmoles) y azida de sodio ((18,47 g, 284 mmoles), la mezcla se reflujó durante toda la noche y a continuación se enfrió hasta TA. Después de eliminar EtOH, se agregó agua y el residuo se extrajo con EtOAc. La capa orgánica se lavó con salmuera , se secó sobre a2SO4, y se purificó por cromatografía de columna, eluyendo con éter de petróleo y EtOAc (PE/EtOAc = 20/1, 10/1 hasta 6/1) para dar el compuesto del título en forma de un aceite (18,24 g, 78,3 mmoles). 1H RMN (400 MHz, CDCl3) δ ppm 1,65-1,79 (m, 2 H), 2,01-2,07 (m, 1 H), 2,30-2,37 (m, 1 H), 3,49-3,54 (m 1 H), 3,97-4,06 (m, 2 H), 4,11-4,13 (br, 1 H), 4,33-4,40 (m, 2 H), 7,18-7,27 (m, 5 H).

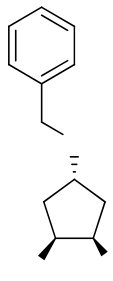
[0583] F. (1R,2R,4R)-2-azido-4-(benciloxi)ciclopentil metanosulfonato



[0584] A una mezcla enfriada de Et3N (9,49 g, 94,0 mmoles) y (1S,2S,4R)-2-azido-4-(benciloxi)ciclopentanol (18,25 g, 78,3 mmoles) en DCM (500 ml) se agregó gota a gota cloruro de metanosulfonilo (9,87 g, 86,2 mmoles) en DCM (50 ml) a 0ºC. La mezcla se agitó durante toda la noche a una temperatura de 0ºC hasta temperatura ambiente.

Después de la conversión completa, se agregó NaHCO3 acuoso (5%, 300 ml). La mezcla se extrajo con DCM, se lavó con salmuera, y se secó sobre Na2SO4 para dar el compuesto del título en forma de un aceite (23,58 g, 75,8 mmoles). 1H RMN (400MHz, CDCl3) δ ppm 1,83-1,89 (m, 1 H), 2,06-2,13 (m, 1 H), 2,34-2,49 (m, 2 H), 3,04 (s, 3 H), 3,94-3,99 (m, 1 H), 4,08-4,13 (m, 1 H), 4,64 (s, 2 H), 4,93-4,98 (q, J=5,6/7,0 Hz, 1 H), 7,25-7,36 (m, 5 H).

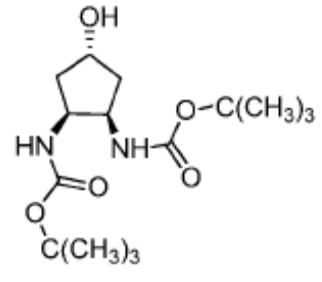
[0585] G. (((1s,3R,4S)-3,4-diazidociclopentiloxi)metil)benceno



[0586] A una mezcla de (1R,2R,4R)-2-azido-4-(benciloxi)ciclopentil metanosulfonato (23,58 g, 75,8 mmoles), piridina (25 ml), agua (140 ml), y DMA (350 ml) se agregó NaN3 (10,84 g, 166,8 mmoles). La mezcla se calentó a 130ºC en atmósfera de N2 durante toda la noche. La mezcla de reacción se enfrió hasta temperatura ambiente y se templó con agua fría (300 ml). La mezcla se extrajo con EtOAc, se lavó con H2O (varias veces) y con salmuera, se secó sobre Na2SO4, y se purificó por cromatografía de columna, eluyendo con éter de petróleo y EtOAc (PE/EA = 40/1 hasta 30/1) para dar el compuesto del título en forma de un aceite (15,35 g, 59,5 mmoles). 1H RMN (400 MHz, CDCl3) δ ppm 1,99-2,08 (m, 2 H), 2,23-2,30 (m, 2 H), 3,75-3,80 (m, 2 H), 3,99-4,04 (m, 1 H), 4,49 (s, 2 H), 7,26-7,35 (m, 5 H).

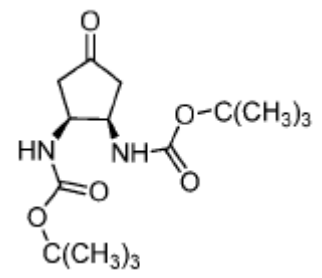
[0587] H. N,N-((1R,2S,4s)-4-hidroxiciclopentano-1,2-diil)-biscarbamato de di-ter-butilo





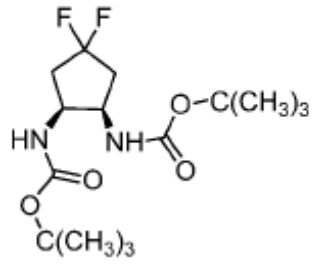
[0588] A una solución de (((1s,3R,4S)-3,4-diazidopentiloxi)metil)benceno (15,35g, 59,5 mmoles) y pirocarbonato de di-ter-butilo (31,69 g, 145,4 mmoles) en MeOH (200 ml) se agregó Pd/C (50% húmedo, 8,0 g) en un autoclave. El autoclave se cargó con H2 hasta 2,2 MPa. La mezcla de reacción se agitó a temperatura ambiente durante toda la noche. Después de la conversión, la mezcla se filtró y el solvente se eliminó para dar el compuesto del título, el cual se utilizó sin purificación posterior (14,8 g, 46,8 mmoles). 1H RMN (400MHz, CDCl3) δ ppm 1,45 (s, 18 H), 1,72-1,75 (m, 2 H), 2,20 (m, 2 H), 4,04 (br, 2 H), 4,34-4,37 (m, 1 H), 4,45 (br, 2 H), 5,21 (br, 1H).

[0589] I. N,N-(cis-4-oxociclopentano-1,2-diil)-biscarbamato de di-ter-butilo



[0590] A una solución enfriada de N,N-((1R,2S,4s)-4-hidroxiciclopentano-1,2-diil)-biscarbamato de di-ter-butilo (5,35 g, 16,9 mmoles) en DCM (90 ml) a 0ºC se agregó reactivo de periodinano Dess-Martin (24,4 g, 57,6 mmoles). La mezcla se agitó desde 0ºC hasta temperatura ambiente durante 1,5 horas. Después de que se completó la reacción, la mezcla se filtró y el residuo se purificó por cromatografía de columna eluyendo con éter de petróleo y EtOAc (PE/EtOAc = 6/1 hasta 2/1) para dar el compuesto del título en forma de un sólido (5,03 g, 15,9 mmoles). 1H RMN (400 MHz, CDCl3) δ ppm 1,38 (s, 18 H), 2,30-2,50 (m, 4 H), 4,29 (s, 2 H).

[0591] J. N,N-(cis-4,4-difluorociclopentano-1,2-diil)-biscarbamato de di-ter-butilo



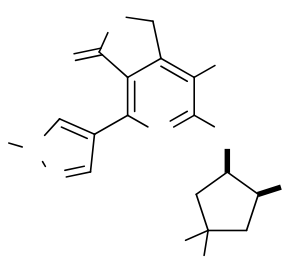
[0592] A una solución enfriada de N,N-(cis-4-oxociclopentano-1,2-diil)-biscarbamato de di-ter-butilo (5,00 g, 15,9 mmoles) en DCM (100 ml) se agregó gota a gota una mezcla de trifluoruro de dietilaminoazufre (12,82 g, 79,6 mmoles) en DCM (10 ml) a 0ºC. La mezcla se agitó a una temperatura desde 0ºC hasta temperatura ambiente durante toda la noche. Posteriormente la mezcla se enfrió hasta 0ºC y su pH se ajustó hasta 9-10 con K2CO3 acuoso saturado, mientras se mantiene la temperatura de la mezcla por debajo de 5ºC. Se agregó pirocarbonato de di-ter-butilo (7,60 g, 2,2 eq) y la mezcla se agitó a una temperatura desde 0ºC hasta temperatura ambiente durante 3 horas. Después de eliminar DCM, el residuo se purificó por cromatografía de columna eluyendo con éter de petróleo y EtOAc (PE/EtOAc = 20/1 hasta 15/1 hasta 12/1) para dar el compuesto del título en forma de un sólido (2,40 g, 7,10 mmoles). 1H RMN (400 MHz, CDCl3) δ ppm 1,45 (br, 18 H), 2,15-2,19 (m, 2 H), 2,47-2,52 (m, 2 H), 4,22 (br, 2 H), 4,87 (br, 2 H).

[0593] K. cis-4,4-difluorociclopentano-1,2-diamina

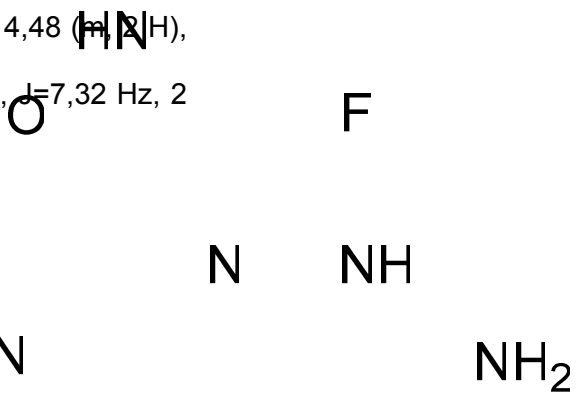
[0594] A una solución enfriada de N,N-(cis-4,4-difluorociclopentano-1,2-diil)-biscarbamato de di-ter-butilo (2,40 g, 7,10 mmoles) en EtOAc (30 ml) a 0ºC se agregó HCl 1N-EtOAc (10 ml) mientras se mantiene la temperatura de la mezcla por debajo de 5ºC. La mezcla se agitó a temperatura ambiente durante toda la noche. La mezcla se filtró posteriormente, se lavó con EtOAc varias veces, y se secó in vacuo para dar una sal clorhidrato del compuesto del título en forma de un sólido (0,98 g, 4,7 mmoles). 1H RMN (400 MHz, CD3OD,) δ ppm 2,63-2,67 (m, 2 H), 2,76-2,86 (m, 2 H), 4,15-4,17 (m, 2 H).

[M+H] calc para C5H10N2N2, 137; experimental, 137.

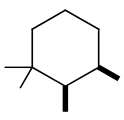
[0595] Ejemplo 66: 6-(cis-2-amino-4,4-difluorociclopentilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



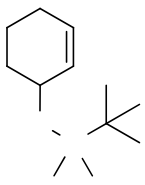
[0596] Una sal TFA del compuesto del título se preparó de manera similar al ejemplo 64 utilizando cis-4,4-difluorociclopentano-1,2-diamina en lugar de 2-aminoetilcarbamato de cis-ter-butilo. 1H RMN (500 MHz, DMSO-d6) δ ppm 2,62 - 2,69 (m, 2 H), 2,87 (td, J=16,84, 8,79 Hz, 2 H), 3,89 (s, 3 H), 4,14 (br s, 1 H), 4,32 - 4,48 (m, 2 H), 4,79 (d, J=9,76 Hz, 1 H), 7,28 (d, J=5,37 Hz, 1 H), 7,93 (br s, 2 H), 8,41 (d, J=7,32 Hz, 2 H), 8,87 (s, 1 H). [M+H] calc para C16H17F3N6O, 367; experimental, 367.



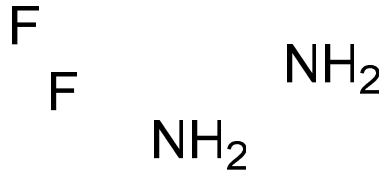
[0597] Preparación 26: cis-3,3-difluorociclohexano-1,2-diamina



[0598] A. ter-butil(ciclohex-2-eniloxi)dimetilsilano

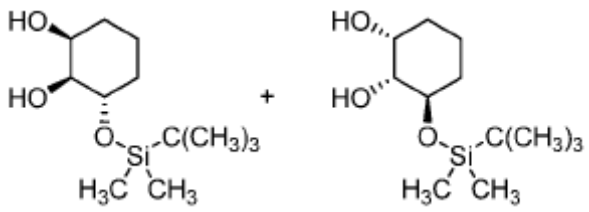


[0599] Se agregaron piridina (4,74 g, 60 mmoles) y cloruro de ter-butildimetilsilil (4,83 g, 32 mmoles) a una solución de ciclohex-2-enol (1,96 g, 20 mmoles) en DCM (40 ml). La mezcla de reacción se agitó a temperatura ambiente durante toda la noche. La mezcla se concentró y el residuo se dispersó en EtOAc y agua. La fase orgánica se separó y se lavó con salmuera, se secó sobre Na2SO4 anhidro, se concentró, y se



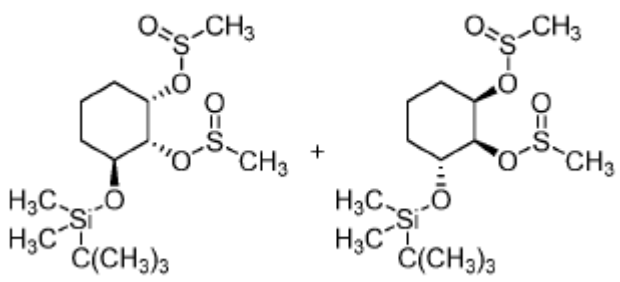
purificó por cromatografía de flash de sílice, eluyendo con EtOAc y éter de petróleo (5-10% EtOAc) para dar el compuesto del título en forma de un aceite (4,1 g, 97%). 1H RMN (400 MHz, CDCl3) δ ppm 0,06-0,09 (m, 6 H), 0,92 (s, 9 H), 1,50-1,57 (m, 2 H), 1,74-1,89 (m, 2 H), 1,93-2,03 (m, 2 H), 4,21-4,23 (m, 1 H), 5,61 -5,64 (m, 1 H), 5,72-5,76 (m, 1 H).

[0600] B. (1S,2S,3S)-3-(ter-butildimetilsililoxi)ciclohexano-1,2-diol and (1R,2R,3R)-3-(ter-butildimetilsililoxi)ciclohexano-1,2-diol



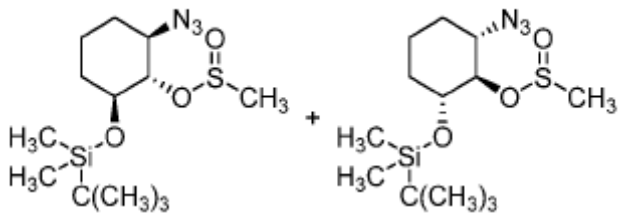
[0601] Se disolvió ter-butil(ciclohex-2-eniloxi)dimetilsilano (12,72 g, 60 mmoles) en CH3CN (100 ml). Una solución de N-metilmorfolin-N-óxido (14 g, 120 mmoles) en H2O (20 ml) y OsO4 (0,5 g) en acetona (5 ml) se agregó, y la mezcla se agitó a temperatura ambiente durante toda la noche. A continuación la mezcla se diluyó con EtOAc (800 ml), se lavó con salmuera y NaHCO3 acuoso saturado, se secó sobre Na2SO4 anhidro, se concentró y se purificó por cromatografía flash de sílice eluyendo con EtOAc y éter de petróleo (20-40% EtOAc) para dar los compuestos del título en forma de un aceite (12,8 g, 87%). 1H RMN (400 MHz, CDCl3,) δ ppm 0,06-0,09 (m, 6 H), 0,90 (s, 9 H), 1,25-1,28 (m, 2 H), 1,44-1,62 (m, 2 H), 1,80-1,84 (m, 2 H), 2,28 (s, 1 H), 2,51 (s, 1 H),3,40-3,44 (m, 1 H), 3,77-3,82 (m, 1 H), 4,08-4,11 (m, 1 H).

[0602] C. (1S,2S,3S)-3-(ter-butildimetilsililoxi)ciclohexano-1,2-diil dimetanosulfinato y (1R,2R,3R)-3-(ter-butildimetilsililoxi)ciclohexano-1,2-diil dimetanosulfinato



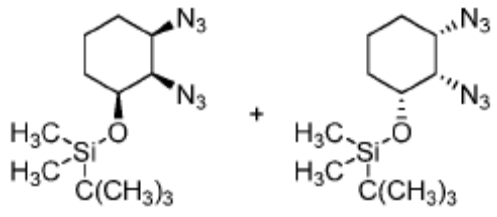
[0603] (1Se disolvió S,2S,3S)/(1R,2R,3R)-3-(ter-butildimetilsililoxi)ciclohexano-1,2-diol (1,9 g, 7,7 mmoles) en DCM (40 ml). La mezcla se colocó en un baño de hielo. Se agregaron piridina (3,1 ml, 38,5 mmoles) y cloruro de metanosulfonilo (1,44 ml, 18,5 mmoles) y la mezcla de reacción se agitó a temperatura ambiente durante toda la noche. A continuación, la mezcla se diluyó con DCM, se lavó con salmuera, se secó sobre Na2SO4 anhidro, se concentró, y se purificó por cromatografía de flash de sílice, eluyendo con EtOAc y éter de petróleo (20-30% EtOAc) para dar los compuestos del título en forma de un aceite (2,6 g, 84%). 1H RMN (400 MHz, CDCl3) δ ppm 0,06-0,09 (m, 6 H), 0,90 (s, 9 H), 1,58-1,64 (m, 2 H), 1,70-1,78 (m, 2 H), 1,85-1,90(m, 2 H), 3,12 (s, 6 H), 4,08-4,12 (m, 1 H), 4,51-4,55 (m, 1 H), 5,06-5,10 (m, 1 H).

[0604] D. (1S,2R,6S)-2-azido-6-(ter-butildimetilsililoxi)ciclohexil metanosulfonato y (1R,2S,6R)-2-azido-6-(ter-butildimetilsililoxi)ciclohexil metanosulfinato



[0605] (1Se disolvió S,2S,3S)/(1R,2R,3R)-3-(ter-butildimetilsililoxi)ciclohexano-1,2-diil dimetanosulfinato (12,0 g, 29,8 mmoles) en DCM (80 ml) y hexametilfosforamida (20 ml). Se agregó azida de sodio (10,0 g, 154 mmoles) y la mezcla se agitó a 75ºC durante toda la noche. La mezcla se diluyó con EtOAc, se lavó con agua y salmuera, se secó sobre Na2SO4 anhidro, y se concentró. El sólido se lavó con éter de petróleo y se secó in vacuo para dar los compuestos del título (7 g, 68%). 1H RMN (400 MHz, CDCl3) δ ppm 0,06-0,09 (m, 6 H), 0,90 (s, 9 H), 1,32-1,47 (m,3 H), 1,76-1,81 (m, 1 H), 1,97-2,01(m, 1 H), 2,10-2,14 (m, 1 H), 3,14 (s, 3 H), 3,33-3,39 (m, 1 H), 3,55-3,61 (m, 1 H), 4,23-4,28 (m, 1H).

[0606] E. ter-butil((1S,2R,3R)-2,3-diazidociclohexiloxi)dimetilsilano y ter-butil((1R,2S,3S)-2,3-diazidociclohexiloxi)dimetilsilano



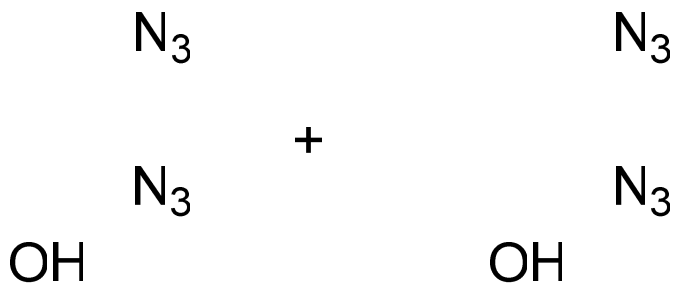
[0607] (1Se disolvió S,2R,6S)/(1R,2S,6R)-2-azido-6-(ter-butildimetilsililoxi)ciclohexil metanosulfonato (7 g, 20 mmoles) en DMF (80 ml) y hexametilfosforamida (20 ml). Se agregó azida de sodio (15,0 g, 230 mmoles) y la mezcla se agitó a 120ºC durante 24 horas. La mezcla se diluyó con EtOAc, se lavó con agua y salmuera, se secó sobre Na2SO4 anhidro, se concentró, y se purificó por cromatografía de flash de sílice eluyendo con EtOAc y éter de petróleo (3% EtOAc) para dar los compuestos del título en forma de un aceite (3,52 g, 60%). 1H RMN (400 MHz, CDCl3) δ ppm 0,06-0,09 (m, 6 H), 0,90 (s, 9 H), 1,66-1,70 (m, 2 H), 1,72-1,76 (m, 2 H), 1,80-1,85 (m, 2 H), 3,16-3,21 (m, 1 H), 3,71 -3,76 (m, 1 H), 3,80-3,85 (m, 1 H).

[0608] F. (1S,2R,3R)-2,3-diazidociclohexanol y (1R,2S,3S)-2,3-diazidociclohexanol



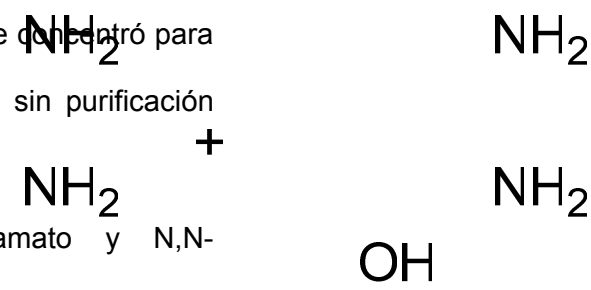
[0609] Se agregó tetrabutilamonio fluoruro (16,0 g, 61,3 mmoles) disuelto en THF ter-butil((1S,2R,3R)/(1R,2S,3S)-2,3-diazidociclohexiloxi)dimetilsilano (12,0 g, 40,5 mmoles) en THF (300 ml). La mezcla de reacción se agitó a temperatura ambiente durante 3 horas y se templó a continuación con MeOH. La mezcla se concentró y el residuo se purificó por cromatografía de columna (EtOAc/PE = 4/1) para dar los compuestos del título en forma de un aceite (5 g, 68%).

[0610] G. (1S,2R,3R)-2,3-diaminociclohexanol y (1R,2S,3S)-2,3-diaminociclohexanol

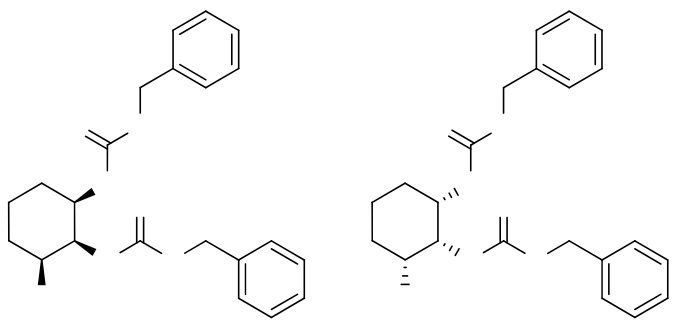




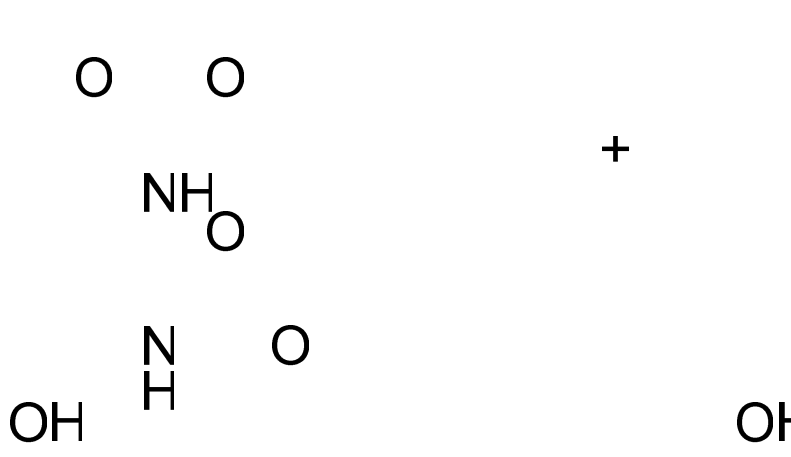
[0611] Una mezcla de (1S,2R,3R)/(1R,2S,3S)-2,3-diazidociclohexanol (5,0 g, 27,5 mmoles) y Pd/C (2,0 g) en MeOH se agitó a temperatura ambiente durante toda la noche en atmósfera de H2. A continuación de la reacción, la mezcla se filtró y se concentró para dar los compuestos del título en forma de un aceite, el cual se utilizó sin purificación posterior (3,18 g).



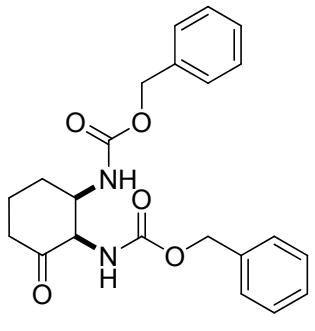
[0612] H. N,N-((1R,2R,3S)-3-hidroxiciclohexano-1,2-diil)-biscarbamato y N,N-((1S,2S,3R)-3-hidroxiciclohexano-1,2-diil)-biscarbamato de dibencilo



[0613] A una solución de (1S,2R,3R)/(1R,2S,3S)-2,3-diaminociclohexanol (3,1 g, 24,5 mmoles) y Et3N (7,4 g, 73,5 mmoles) en DCM (50 ml) a -10°C se agregó carbonocloridrato de bencilo (9,6 g, 56,3 mmoles). El avance de la reacción se monitoreó por TLC y LCMS. A continuación de la terminación de la reacción, la mezcla se lavó con agua, se secó sobre Na2SO4, y se concentró. El residuo se purificó por cromatografía de columna (EtOA/PE = 2/1) para dar los compuestos del título en forma de un aceite (2,2 g, 22%). 1H RMN (400 MHz, CDCl3) δ ppm 1,59-1,84 (m, 6 H), 3,80 (br, 1 H), 4,05-4,16 (m, 2 H), 5,12 (s, 4 H), 5,4 (s, 1 H), 6,4 (s, 1 H), 7,33-7,37 (m, 10 H).

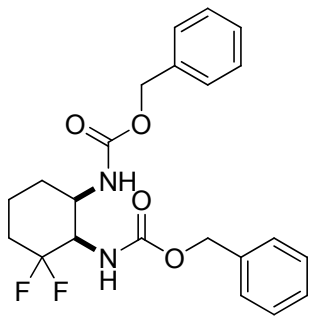


[0614] I. N,N-(cis-3-oxociclohexano-1,2-diil)-biscarbamato de dibencilo



[0615] A una solución de N,N-((1R,2R,3S)/(1S,2S,3R)-3-hidroxiciclohexano-1,2-diil)-biscarbamato de dibencilo (2,2 g, 5,5 mmoles) en DCM (30 ml) a -0°C se agregó reactivo Dess-Martin periodinano (5,9 g, 13,8 mmoles). La suspensión se agitó a temperatura ambiente durante 3 horas. La mezcla se concentró y el residuo se purificó por cromatografía de columna (EtOAc/PE = 2/1) para dar el compuesto del título en forma de un sólido (2,0 g, 93%). 1H RMN (400 MHz, CDCl3) δ ppm 1,60-1,70 (m, 3 H), 2,00-2,04 (m, 1 H), 2,35-2,58 (m, 2 H), 4,27-4,31 (m, 1 H), 5,12 (s, 4 H), 5,82-5,92 (m, 1 H), 7,33-7,38 (m, 10 H).

[0616] J. N,N-(cis-3,3-difluorociclohexano-1,2-diil)-biscarbamato de dibencilo



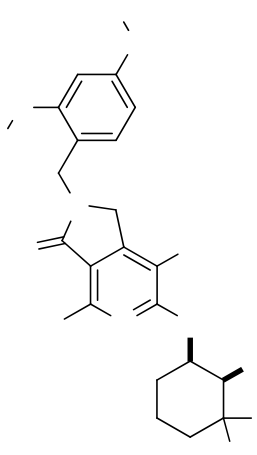
[0617] A una solución de N,N-(cis-3-oxociclohexano-1,2-diil)-biscarbamato de dibencilo (2,0 g, 5,1 mmoles) en DCM (30 ml) a -0ºC se agregó dietilaminoazufre trifluoruro (4 ml, 1,22 g/cm3). La mezcla de reacción se agitó a -0ºC durante toda la noche. La mezcla de reacción se neutralizó con bicarbonato de sodio, se concentró, y el residuo se purificó por cromatografía de columna (EtOAc/PE = 2/1) para dar los compuestos del título en forma de un aceite (1,0 g, 47%). 1H RMN (400 MHz, CD3OD,) δ ppm 1,43-2,01 (m, 6 H), 3,83-3,84 (m, 1 H), 4,23-4,24 (m, 1 H), 4,97 (s, 4 H), 7,16-7,24

(m, 10 H).

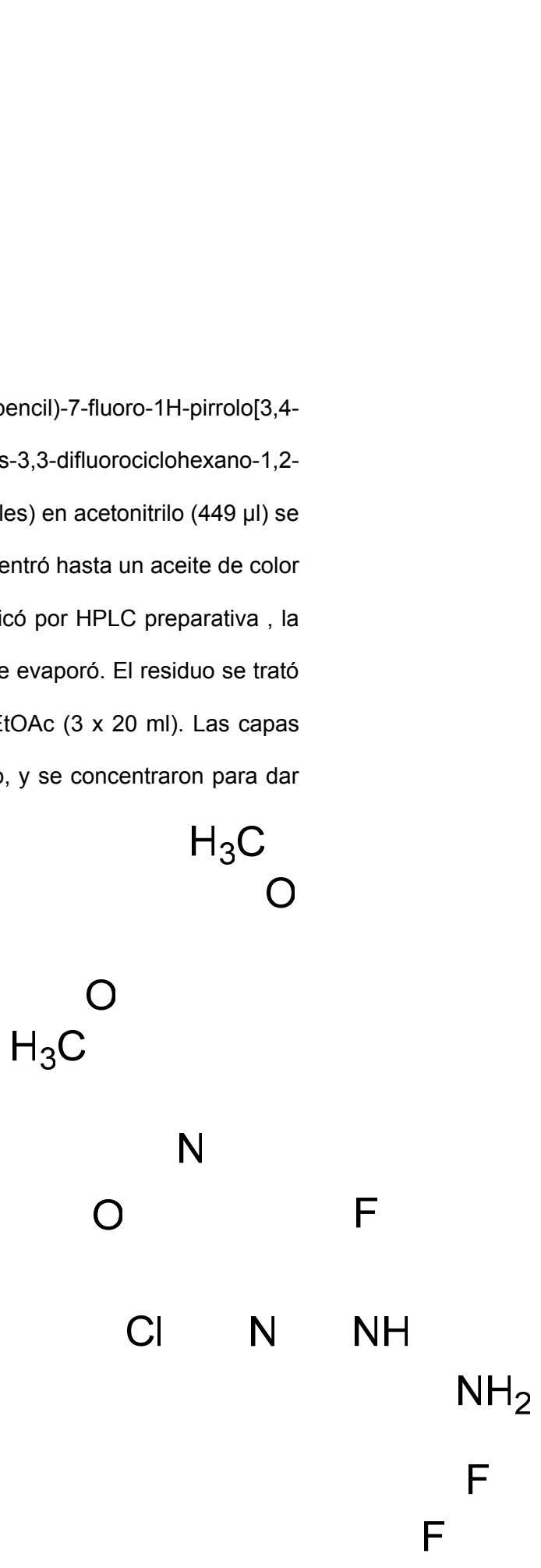
[0618] K. cis-3,3-difluorociclohexano-1,2-diamina

[0619] Una mezcla de N,N-(cis-3,3-difluorociclohexano-1,2-diil)-biscarbamato de dibencilo (1,0 g, 2,4 mmoles) y Pd/C (0,9 g) en MeOH se agitó a temperatura ambiente durante toda la noche en atmósfera de H2. A continuación de la reacción, la mezcla se filtró y se concentró hasta un aceite, el cual se hizo reaccionar con EOAc-HCl para dar sal clorhidrato del compuesto del título en forma de un sólido de color blanco (280mg, 77%). 1H RMN (400 MHz, CD3OD) δ ppm 1,84-2,31 (m, 6 H), 4,01 (m, 1 H), 4,20-4,26 (m, 1 H). [M+H] calc para C6H12N2O2, 151; experimental, 151.

[0620] Preparación 27: 6-(cis-2-amino-3,3-difluorociclohexilamino)-4-cloro-2-(2,4-dimetoxibencil)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona

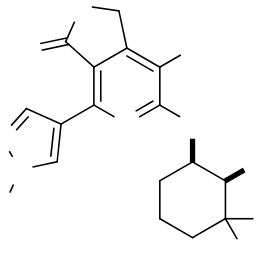


[0621] Una mezcla de 4,6-dicloro-2-(2,4-dimetoxibencil)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona (100 mg, 0,269 mmoles) y clorhidrato cis-3,3-difluorociclohexano-1,2-diamina (75 mg, 0,404 mmoles) y DIPEA (118 µl, 0,674 mmoles) en acetonitrilo (449 µl) se agitó a 100ºC durante 3 días. La mezcla de reacción se concentró hasta un aceite de color marrón y se reconstituyó en DMF (1 ml). El residuo se purificó por HPLC preparativa , la fracción apropiada se recolectó, y el exceso de acetonitrilo se evaporó. El residuo se trató con carbonato de sodio acuoso saturado y se extrajo con EtOAc (3 x 20 ml). Las capas orgánicas se combinaron, se secaron sobre sulfato de sodio, y se concentraron para dar

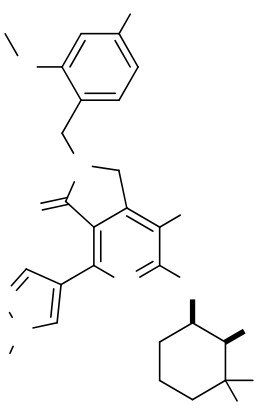


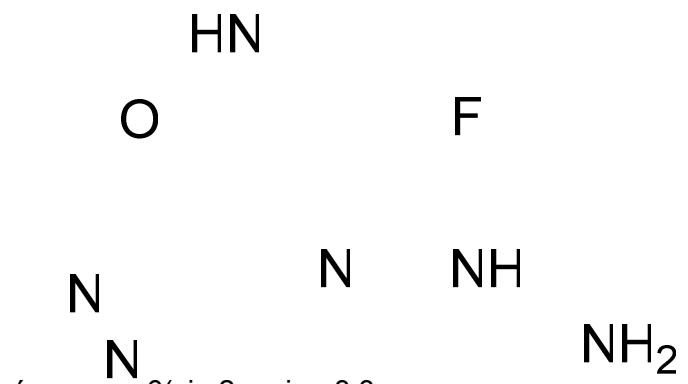
el compuesto del título en forma de un residuo incoloro (13,7 mg, 10%). [M+H] calc para C22H24ClF3N4O3, 485; experimental, 485.

[0622] Ejemplo 67: 6-(cis-2-amino-3,3-difluorociclohexilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona

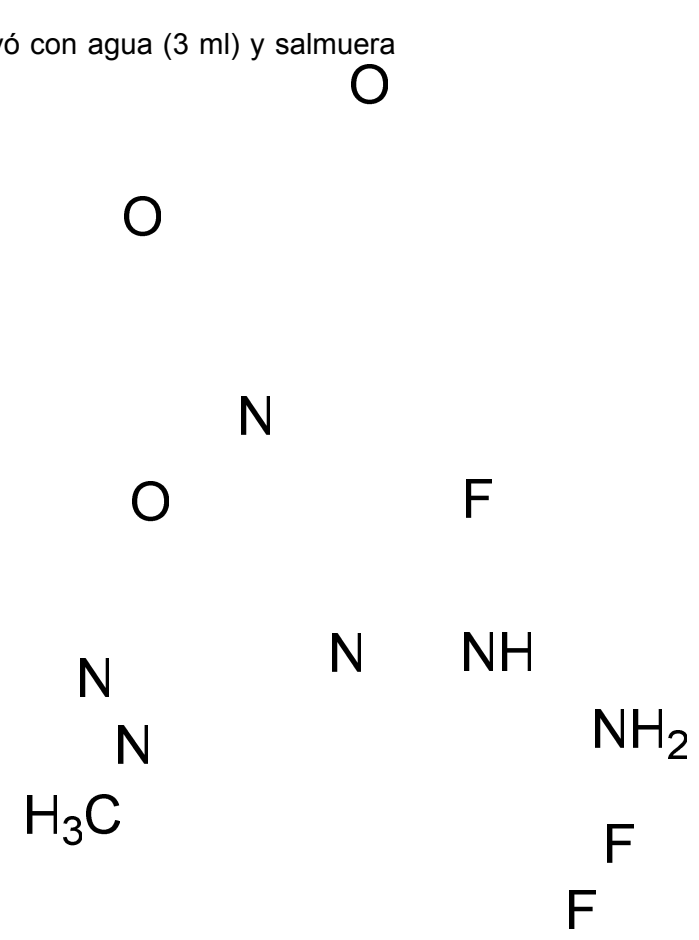


[0623] A, 6-(cis-2-amino-3,3-difluorociclohexilamino)-2-(2,4-dimetoxibencil)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona





[0624] Un recipiente de microondas se cargó con 6(cis-2-amino-3,3-difluorociclohexilamino)-4-cloro-2-(2,4-dimetoxibencil)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona (13,7 mg, 0,028 mmoles) y 1-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (8,82 mg, 0,042 mmoles) y cloruro de bis(trifenilfosfina)paladio (3,97 mg, 5,65 µmoles) y se colocó en un ambiente inerte. Se agregó DME (283 µl) a la mezcla y la suspensión de color amarillo resultante se desgasificó durante 5 min. Se agregó carbonato de sodio (56,5 µl, 0,113 mmoles) y la suspensión se desgasificó durante otros 3 min. El recipiente se tapó y la mezcla se calentó a 80ºC durante 4 horas, se enfrió hasta temperatura ambiente, se diluyó con EtOAc (5 ml), y se lavó con agua (3 ml) y salmuera

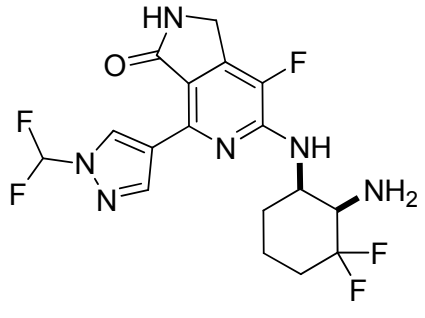


(3 ml). La capa orgánica se recolectó, se secó sobre sulfato de sodio, y se concentró para dar el compuesto del título en forma de un residuo de color marrón oscuro el cual se utilizó en el próximo paso sin purificación posterior (21 mg). [M+H] calc para C26H29F3N3O2, 531; experimental, 531.

[0625] B. 6-(cis-2-amino-3,3-difluorociclohexilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona

[0626] A un solución de 6-(cis-2-amino-3,3-difluorociclohexilamino)-2-(2,4-dimetoxibencil)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona (21 mg, 0,040 mmoles) en DCM (300 µl) se agregó TFA (500 µl, 6,49 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 12 horas, a continuación 3 horas a 50ºC. Posteriormente la mezcla se concentró hasta un aceite oscuro y se diluyó con DMF (1 ml) el cual se purificó por HPLC preparativa y se liofilizó para dar una sal TFA del compuesto del título en forma de un sólido de color blanco suave y sedoso (3,6 mg, 19%). 1H RMN (400MHz ,DMSO-d6) δ ppm 8,89 (s, 1 H), 8,43 (s, 3 H), 8,16 (s, 1 H), 6,89 (br s, 1 H), 6,54 (br s, 1 H), 4,65 - 4,52 (m, 1 H), 4,49 - 4,32 (m, 2 H), 4,17 (br s, 1 H), 3,89 (s, 3 H), 2,37 - 2,03 (m, 2 H), 1,84 (br s, 3 H), 1,63 (br s, 1 H). [M+H] calc para C17H19F3N6O, 381; experimental, 381.

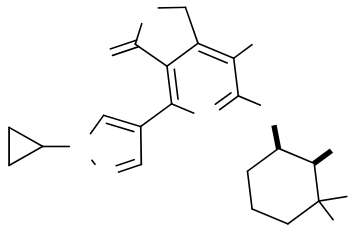
[0627] Ejemplo 68: 6-(cis-2-amino-3,3-difluorociclohexilamino)-4-(1-(difluorometil)-1H-pirazol-4-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona



[0628] Una sal TFA del compuesto del título se preparó de manera similar al ejemplo 67 utilizando 1-(difluorometil)-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol en lugar de 1-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol. 1H

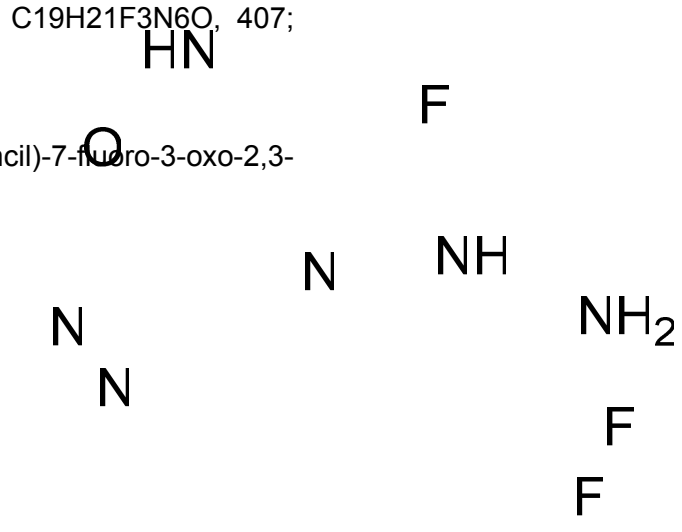
RMN (400 MHz, DMSO-d6) δ ppm 1,64 (br s, 1 H), 1,83 (br s, 3 H), 2,00 - 2,29 (m, 2 H), 2,33 (t, J=1,77 Hz, 1 H), 2,63 - 2,72 (m, 1 H), 4,11 (br s, 1 H), 4,40 - 4,50 (m, 2 H), 4,62 (br s, 1 H), 6,93 (d, J=5,31 Hz, 1 H), 7,74 - 8,14 (m, 1 H), 8,45 (s, 1 H), 8,56 (s, 1 H), 9,40 (s, 1 H). [M+H] calc para C17H17F5N6O, 417; experimental, 417.

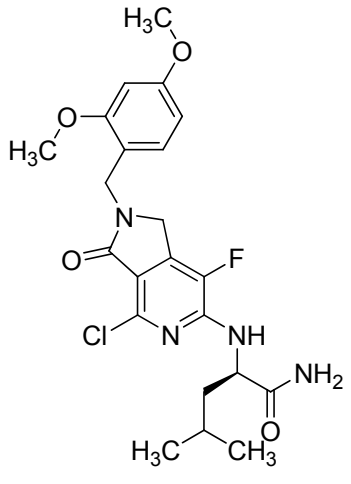
[0629] Ejemplo 69: 6-(cis-2-amino-3,3-difluorociclohexilamino)-4-(1-ciclopropil-1H-pirazol-4-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona



[0630] Una sal TFA del compuesto del título se preparó de manera similar al ejemplo 67 utilizando 1-ciclopropil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol en lugar de 1-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol. 1H RMN (400 MHz, DMSO-d6) δ ppm 1,63 (br s, 1 H), 1,75 - 1,92 (m, 3 H), 2,00 - 2,29 (m, 2 H), 2,33 (dt, J=3,73, 1,80 Hz, 1 H), 2,62 - 2,74 (m, 1 H), 4,34 - 4,46 (m, 2 H), 4,57 (br s, 1 H), 4,81 (d, J=5,56 Hz, 2 H), 5,08 - 5,30 (m, 2 H), 5,93 - 6,10 (m, 1 H), 6,83 (d, J=6,06 Hz, 1 H), 8,22 (s, 1 H), 8,39 (s, 2 H), 8,84 - 9,05 (m, 1 H). [M+H] calc para C19H21F3N6O, 407; experimental, 407.

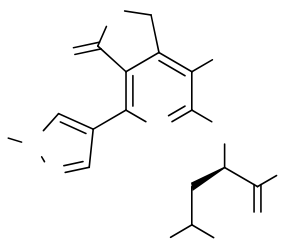
[0631] Preparación 28: (R)-2-(4-cloro-2-(2,4-dimetoxibencil)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida





[0632] Una mezcla de 4,6-dicloro-2-(2,4-dimetoxibencil)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona (200 mg, 0,5391 mmoles) y (R)-2-amino-4-metilpentanamida (140 mg, 1,078 mmoles) y N-isopropil-N-metilpropan-2-amina (310 mg, 2,69 mmoles) en acetonitrilo (2 ml) se agitó a 85ºC durante 3 días. El material bruto resultante se reconstituyó en MeOH/DCM/DMF (10,0 ml) y se purificó por HPLC preparativa. Las fracciones se recolectaron y se despojaron hasta sequedad mediante evaporación rotativa para dar el compuesto del título (83 mg, 33%). [M+H] calc para C22H26ClFN4O4, 465; experimental, 465.

[0633] Ejemplo 70: (R)-2-(7-fluoro-4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida



[0634] A. (R)-2-(2-(2,4-dimetoxibencil)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida





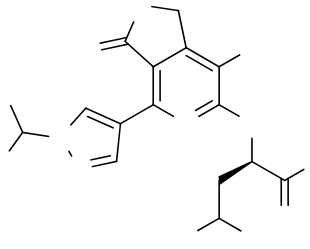
[0635] Una solución de (R)-2-(4-cloro-2-(2,4-dimetoxibencil)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida (83 mg, 0,179 mmoles), 1-metil-4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (111 mg, 0,536 mmoles) y cloruro de bis(trifenilfosfina)paladio (12,53 mg, 0,018 mmoles) en dioxano (2 ml) y Na2CO3 acuoso saturado (2 ml) se calentó a 120ºC durante 30 min. Después de filtrar los sólidos, el solvente se eliminó y el residuo se disolvió en MeOH y DCM y la mezcla se purificó por HPLC preparativa. Las fracciones se recolectaron y el solvente se despojó hasta sequedad mediante evaporación rotativa para dar el compuesto del título (40 mg, 44%). [M+H] calc para C26H31FN6O4, 511; experimental, 511.

[0636] B. (R)-2-(7-fluoro-4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida

[0637] Una solución de (R)-2-(4-(2,4-dimetoxibencil)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida (39,8 mg, 0,078 mmoles) en TFA (5 ml) se calentó a 60ºC durante 2 horas. Después de la eliminación del solvente, el residuo se diluyó en MeOH (2 ml) y se purificó por HPLC preparativa. Las fracciones se recolectaron y el solvente se despojó hasta sequedad mediante evaporación rotativa para dar el compuesto del título en forma de una sal TFA (12,8 mg, 46%). 1H RMN (500 MHz, DMSO-d6) δ ppm 0,82 - 1,00 (m, 6 H), 1,45 - 1,60 (m, 1 H), 1,67 - 1,83 (m, 2 H), 3,87 (s, 3 H), 4,36 (s, 2 H), 4,50 - 4,64 (m, 1 H), 6,88 - 7,02

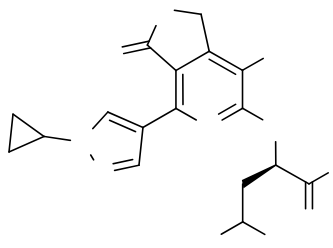
(m, 2 H), 7,44 (s, 1 H), 8,28 (s, 2 H), 8,83 (s, 1 H). [M+H] calc para C17H21FN6O2, 361; experimental, 361.

[0638] Ejemplo 71: (R)-2-(4-(1-(difluorometil)-1H-pirazol-4-il)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida



[0639] El compuesto del título se preparó de manera similar al ejemplo 70 utilizando 1-(difluorometil)-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol en lugar de 1-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol. 1H RMN (400 MHz, DMSO-d6) δ ppm 1,63 (br s, 1 H), 1,75 - 1,92 (m, 3 H), 2,00 - 2,29 (m, 2 H), 2,33 (dt, J=3,73, 1,80 Hz, 1 H), 2,62 - 2,74 (m, 1 H), 4,34 - 4,46 (m, 2 H), 4,57 (br s, 1 H), 4,81 (d, J=5,56 Hz, 2 H), 5,08 - 5,30 (m, 2 H), 5,93 - 6,10 (m, 1 H), 6,83 (d, J=6,06 Hz, 1 H), 8,22 (s, 1 H), 8,39 (s, 2 H), 8,84 - 9,05 (m, 1 H). [M+H] calc para C17H19F3N2O2, 397; experimental, 397.

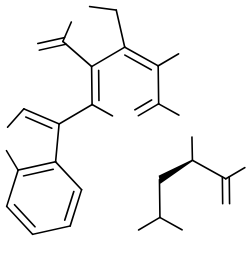
[0640] Ejemplo 72: (R)-2-(4-(1-(ciclopropil)-1H-pirazol-4-il)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida



[0641] El compuesto del título se preparó de manera similar al ejemplo 70 utilizando 1-ciclopropil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol en lugar de 1-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol. 1H RMN (400 MHz, DMSO-d6) δ ppm 0,70 - 1,07 (m, 7 H), 1,15 - 1,35 (m, 1 H), 1,48 - 1,64 (m, 1 H), 1,67 -

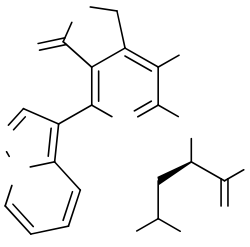
1,93 (m, 2 H), 4,25 - 4,43 (m, 2 H), 4,54 (d, J=9,60 Hz, 1 H), 4,79 (d, J=5,81 Hz, 1 H), 5,11 - 5,31 (m, 1 H), 5,91 - 6,16 (m, 1 H), 6,80 - 7,07 (m, 2 H), 7,42 (br s, 1 H), 8,25 (s, 1 H), 8,34 - 8,43 (m, 1 H), 8,83 - 8,97 (m, 1 H). [M+H] calc para C19H23FN6O2, 387; experimental, 387.

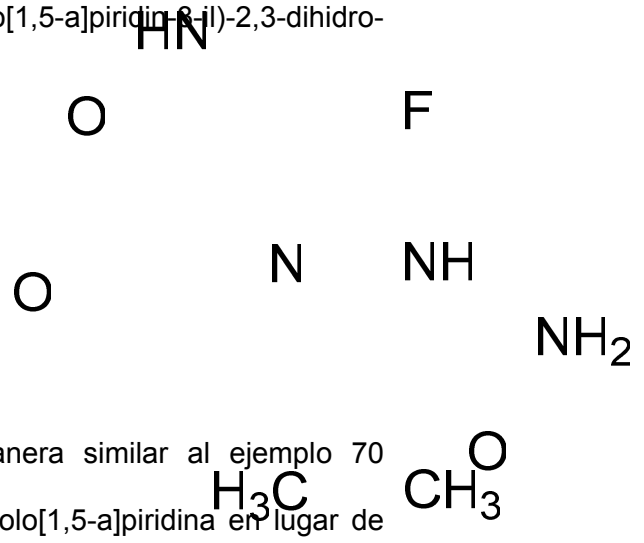
[0642] Ejemplo 73: (R)-2-(4-(benzofuran-3-il)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida



[0643] El compuesto del título se preparó de manera similar al ejemplo 70 utilizando 2-(benzofuran-3-il)-4,4,5,5-tetrametil-1,3,2-dioxaborolano en lugar de 1-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol. 1H RMN (400 MHz, DMSO-d6) δ ppm 0,73 - 0,96 (m, 6 H), 1,57 - 1,91 (m, 3 H), 4,42 (s, 2 H), 4,63 - 4,77 (m, 1 H), 6,99 - 7,17 (m, 2 H), 7,24 - 7,42 (m, 3 H), 7,62 (d, J=7,83 Hz, 1 H), 8,32 - 8,48 (m, 2 H), 9,28 (s, 1 H). [M+H] calc para C21H21FN4O3, 397; experimental, 397.

[0644] Ejemplo 74: (R)-2-(7-fluoro-3-oxo-4-(pirazolo[1,5-a]piridin-3-il)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida



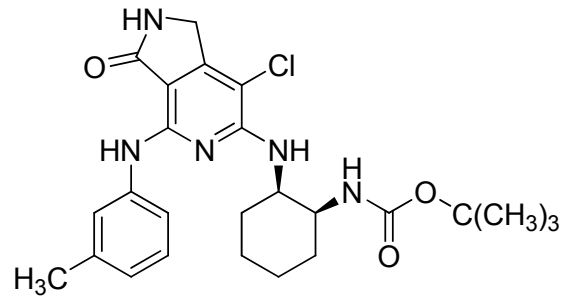


[0645] El compuesto del título se preparó de manera similar al ejemplo 70 utilizando 3-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)pirazolo[1,5-a]piridina en lugar de 1-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)1,5H-pirazol. 1H RMN (400 MHz, DMSO-d6) δ ppm 0,77 - 0,99 (m, 6 H), 1,57 - 1,70 (m, 1 H), 1,71 - 1,90 (m, 2 H), 4,33 -



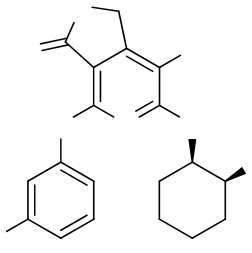
4,45 (m, 2 H), 4,56 - 4,68 (m, 1 H), 6,93 - 7,12 (m, 3 H), 7,27 - 7,42 (m, 2 H), 8,27 (s, 1 H), 8,47 (d, J=8,84 Hz, 1 H), 8,72 (d, J=6,82 Hz, 1 H), 9,30 (s, 1 H). [M+H] calc para C20H21FN6O2, 397; experimental, 397.

[0646] Preparación 29: A. (1S,2R)-2-(7-cloro-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo



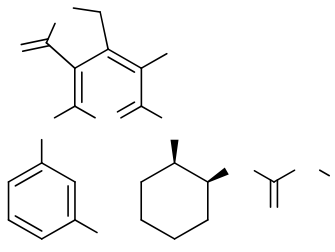
[0647] Un recipiente se cargó con (1S,2R)-2-(3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo (63 mg, 0,140 mmoles) y N-clorosuccinimida (18,63 mg, 0,140 mmoles) en DCM (1,4 ml) para dar una solución de color amarillo. La solución se agitó durante 1 hora a temperatura ambiente. La mezcla de reacción bruta se diluyó con DCM (20 ml) y se lavó con NaHCO3 acuoso saturado (2 x 10 ml) seguido de agua (10 ml) y salmuera (10 ml). Las capas orgánicas se combinaron, se secaron sobre sulfato de sodio, y se concentraron hasta un residuo el cual se purificó por cromatografía de columna flash. Las fracciones recolectadas se concentraron hasta un residuo de color marrón para dar el compuesto del título en forma de un sólido de color crema al cabo del secado (38,1 mg, 56%). [M+H] calc para C25H32ClN5CO3, 486; experimental, 486.

[0648] Ejemplo 75: 6-((1R,2S)-2-aminociclohexilamino)-7-cloro-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



[0649] A una solución de (1S,2R)-2-(7-cloro-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-d]pirimidin-6-ilamino)ciclohexilcarbamato de ter-butilo (20 mg, 0,041 mmoles) en DCM (0,8 ml) se agregó ácido trifluoroacético (0,31 ml). La mezcla de reacción se agitó a temperatura ambiente durante 1 hora, a continuación se concentró hasta un residuo de color marrón el cual se diluyó en MeOH (2 ml) y se purificó por HPLC preparativa para dar una sal TFA del compuesto del título en forma de un sólido de color blanco suave y sedoso (12,3 mg, 61,9%). [M+H] calc para C20H24ClN5O, 386; experimental, 386. 1H RMN (400 MHz, DMSO-d6) δ ppm 8,85 (s, 1 H), 8,36 (s, 1 H), 7,83 (br s, 3 H), 7,39 - 7,57 (m, 2 H), 7,12 - 7,32 (m, 1 H), 6,84 (d, J=7,6 Hz, 1 H), 6,22 (d, J=6,8 Hz, 1 H), 4,19 - 4,43 (m, 3 H), 3,71 (br s, 1 H), 2,32 (s, 3 H), 1,37 - 1,99 (m, 8 H). [M+H] calc'd para C20H24ClN5O, 386; encontrado, 386.

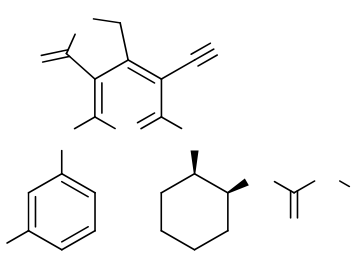
[0650] Preparación 30: A. (1S,2R)-2-(7-yodo-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo



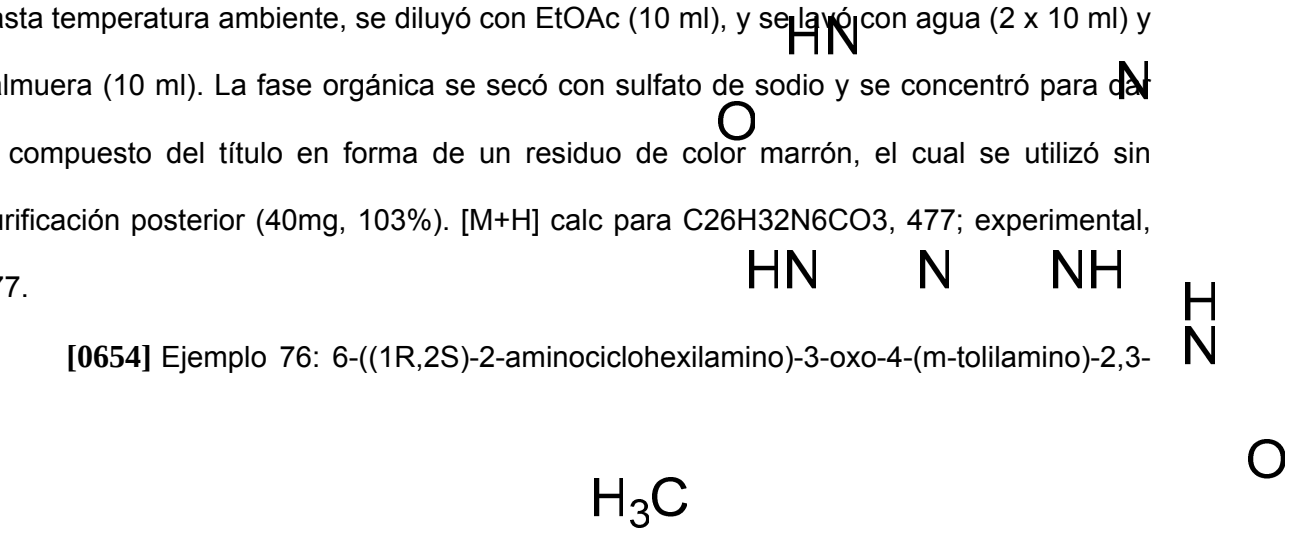
[0651] A un recipiente con rosca superior se agregó (1S,2R)-2-(3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo (73 mg, 0,162 mmoles) y 1-yodopirrolidina-2,5-diona (36,4 mg, 0,162 mmoles) en DCM (1,6 ml) para dar una solución de color amarillo. La reacción se agitó durante 0,5 hora a

temperatura ambiente. La mezcla de reacción bruta se diluyó con DCM (10 ml) y se lavó con NaHCO3 acuoso saturado (10 ml), agua (10 ml) y salmuera (10 ml). Las capas orgánicas recolectadas se secaron con sulfato de sodio y se concentraron para dar el compuesto del título en forma de un sólido de color marrón, el cual se utilizó sin purificación posterior (85,7 mg, 92%). [M+H] calc para C25H32IN5CO3, 578; experimental, 578.

[0652] Preparación 31: A. (1S,2R)-2-(7-ciano-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo

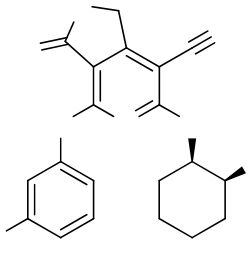


[0653] A un recipiente de microondas secado en horno se agregó (1S,2R)-2-(7-yodo-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo (47,0 mg, 0,081 mmoles), dicianozinc (5,74 mg, 0,049 mmoles), polvo de zinc (0,532 mg, 8,14 µmoles), dppf (0,451 mg, 0,814 µmoles), y Pd2(dba)3 (0,745 mg, 0,814 µmoles). Se agregó N,N-dimetilacetamida (814 µl) y la solución de color marrón oscuro resultante se desgasificó con nitrógeno durante 3 min. El recipiente se tapó y se calentó a 80ºC con agitación durante 1 hora. La temperatura se incrementó hasta 100ºC y la mezcla se agitó durante otras 3 horas, a continuación s enfrió hasta temperatura ambiente, se diluyó con EtOAc (10 ml), y se lavó con agua (2 x 10 ml) y salmuera (10 ml). La fase orgánica se secó con sulfato de sodio y se concentró para dar el compuesto del título en forma de un residuo de color marrón, el cual se utilizó sin purificación posterior (40mg, 103%). [M+H] calc para C26H32N6CO3, 477; experimental, 477.

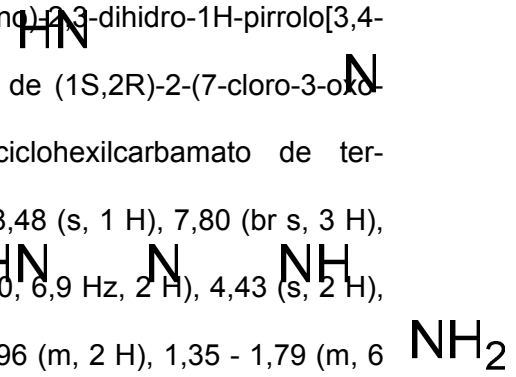


[0654] Ejemplo 76: 6-((1R,2S)-2-aminociclohexilamino)-3-oxo-4-(m-tolilamino)-2,3-

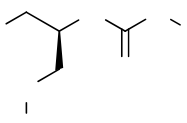
dihidro-1H-pirrolo[3,4-c]piridin-7-carbonitrilo



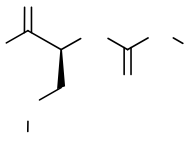
[0655] Una sal TFA del compuesto del título se preparó de manera similar al ejemplo 75 utilizando (1S,2R)-2-(7-ciano-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo en lugar de (1S,2R)-2-(7-cloro-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo. 1H RMN (400 MHz, DMSO-d6) δ ppm 9,22 (s, 1 H), 8,48 (s, 1 H), 7,80 (br s, 3 H), 7,40 - 7,59 (m, 2 H), 7,26 (t, J=7,7 Hz, 1 H), 6,91 (dd, J=13,0, 6,9 Hz, 2 H), 4,43 (s, 2 H), 4,26 - 4,38 (m, 1 H), 3,68 (br s, 1 H), 2,33 (s, 3 H), 1,78 - 1,96 (m, 2 H), 1,35 - 1,79 (m, 6 H). [M+H] calc para C21H24N6CO377; experimental, 377.



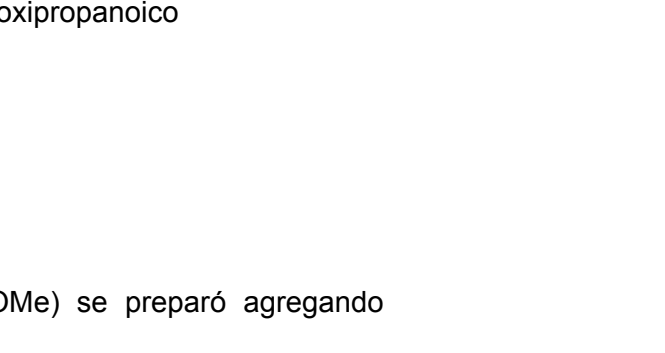
[0656] Preparación 32: (1-amino-3-metoxipropan-2-ilcarbamato de (R)-ter-butilo



[0657] A. Ácido (S)-2-(ter-butoxicarbonilamino)-3-metoxipropanoico



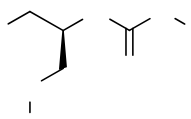
[0658] Una solución de matanolato de sodio (NaOMe) se preparó agregando lentamente MeOH (50 ml) a una suspensión de hidruro de sodio (60% en aceite mineral, 28 g, 0,71 moles) en THF seco (1,2 l) a 0ºC. La mezcla resultante se agitó a temperatura ambiente durante 2 horas. Una porción de la solución de NaOMe (320 ml) se agregó al ácido (S)-2-(ter-butoxicarbonilamino)-3-hidroxipropanoico (36 g, 175 mmoles) en THF





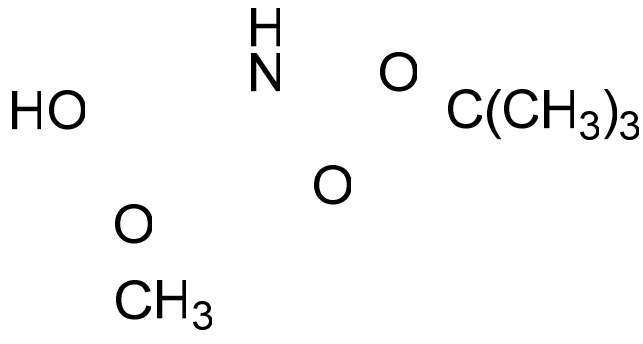
seco (1,6 l), y la mezcla se agitó a temperatura ambiente durante 1 hora. A continuación se agregó metil yodina (16 ml) y la mezcla se agitó a temperatura ambiente durante 1 hora. Otra alícuota de la solución de NaOMe (540 ml) se agregó y la mezcla de reacción se agitó a temperatura ambiente durante 1 hora. Se agregó yodina de metilo adicional (38 ml) en THF (200 ml) y la mezcla de reacción se agitó a temperatura ambiente durante 36 horas. A continuación de la reacción, la mezcla se concentró y el residuo se disolvió en agua y se lavó con éter dietílico (2 x 100 ml). La capa acuosa se acidificó hasta pH 2 por la adición de ácido cítrico sólido y se extrajo con EtOAc (3 x 200 ml) y se secó sobre Na2SO4. La fase orgánica se concentró, y el residuo se disolvió en agua y se extrajo con DCM (4 x 150 ml). Las capas orgánicas se combinaron y se concentraron para dar el compuesto del título en forma de un aceite, el cual se utilizó sin purificación posterior (10,9 g, 28%).

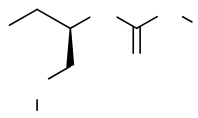
[0659] B. 1-hidroxi-3-metoxipropan-2-ilcarbamato de (R)-ter-butilo.



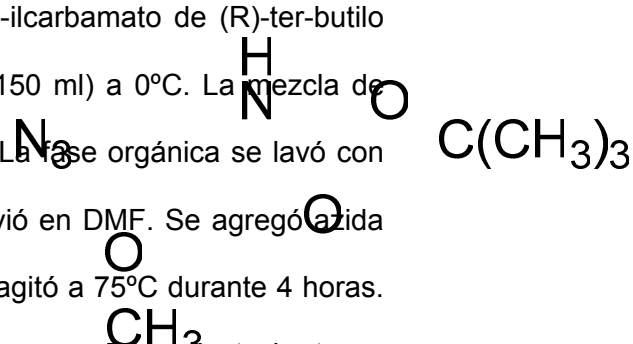
[0660] A una mezcla del ácido (S)-2-(ter-butoxicarbonilamino)-3-metoxipropanoico (10,9 g) y N-metilmorfolina (5,6 g, 55 mmoles) en THF (50 ml) se agregó 2-metilpropilcloroformiato (7,48 g, 55 mmoles) en THF a -15ºC. La mezcla de reacción se agitó a -15ºC durante 15 min., después de lo cual se agregó NaBH4 (6.0 g, 159 mmoles) en agua (10 ml). La mezcla de reacción se agitó durante 30 min., a continuación se diluyó con EtOAc, y se neutralizó con HCl diluido. La capa orgánica se secó sobre Na2SO4 y se concentró. El residuo se purificó por cromatografía de columna de columna sobre gel de sílice eluyendo con EtOAC y éter de petróleo (EtOAc/PE = 1.5/1) para dar el compuesto del título (6,0 g, 58%). 1H RMN (400 MHz, CDCl3) δ ppm 5,23 (s, 1 H), 3,80 (d, J=8,0 Hz, 2 H), 3,72-3,68 (m, 1 H), 3,60-3,52 (m, 2 H), 3,38 (s, 3 H), 2,85 (s, 1 H), 1,47 (s, 9 H).

[0661] C. 1-azido-3-metoxipropan-2-ilcarbamato de (R)-ter-butilo





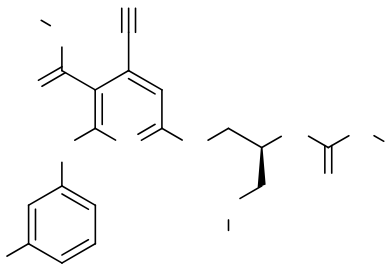
[0662] Se agregó lentamente cloruro de metanosulfonilo (4,0 g, 35 mmoles) en DCM (50 ml) a una solución de 1-hidroxi-3-metoxipropan-2-ilcarbamato de (R)-ter-butilo (6,0 g, 29 mmoles) y Et3N (3,64 g, 36 mmoles) en DCM (150 ml) a 0ºC. La mezcla de reacción se agitó a temperatura ambiente durante 2 horas. La fase orgánica se lavó con agua y NaHCO3 acuoso saturado, se concentró, y se disolvió en DMF. Se agregó azida de sodio (2,34 g, 36,0 mmoles), y la mezcla de reacción se agitó a 75ºC durante 4 horas. La mezcla de reacción se diluyó por EtOAc y se lavó con agua. El producto bruto se purificó por cromatografía de columna de columna sobre gel de sílice eluyendo con EtOAC y éter de petróleo (EtOAc/PE = 2/1) para dar el compuesto del título (4,3 g, 64%). 1H RMN (400 MHz, CDCl3) δ ppm 4,92 (s, 1 H), 3,91 (m, 1 H), 3,53-3,48 (m, 2 H), 3,45-3,40 (m, 2 H), 3,38 (s, 3 H), 1,47 (s, 9 H).



[0663] D. 1-amino-3-metoxipropan-2-ilcarbamato de (R)-ter-butilo

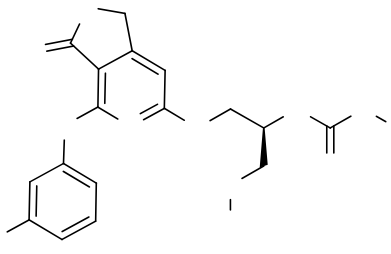
[0664] Una mezcla de 1-azido-3-metoxipropan-2-ilcarbamato de (RR)-ter-butilo (4,3 g, 18,7 mmoles) y 10% de Pd/C (1,5 g) en MeOH se agitó a temperatura ambiente en atmósfera de H2 durante toda la noche. Después de la filtración, el producto bruto se purificó por cromatografía de gel de sílice protegido con amino eluyendo con EtOAC y éter de petróleo (EtOAc/PE = 1/1) para dar el compuesto del título (740 mg, 19,4%). 1H RMN (400 MHz, CD3OD) δ ppm 5,00 (s, 1 H), 3,67-3,66 (m, 1 H), 3,51-3,47 (m, 1 H), 3,42-3,38 (m, 1 H), 3,35 (s, 1 H), 2,82-2,78 (m, 2 H), 1,46 (s, 9 H). [M+H] calc para C9H20N2O3, 205; experimental, 205.

[0665] Preparación 33: (6-(2-(ter-butoxicarbonilamino)-3-metoxipropilamino)-4-ciano-2-(m-tolilamino)nicotinato de (R)-metilo

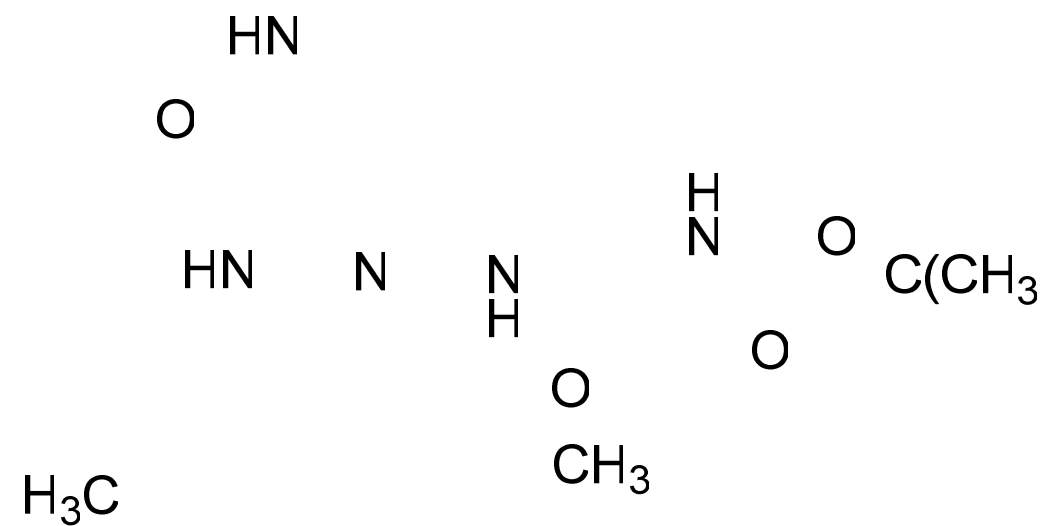


[0666] A un recipiente con rosca superior se agregó 6-cloro-4-ciano-2-(m-tolilamino)nicotinato de metilo (0,28 g, 0,928 mmoles), 1-amino-3-metoxipropan-2-ilcarbamato de (RR)-ter-butilo (0,227 g, 1,114 mmoles), y DIPEA (0,211 ml, 1,206 mmoles) en DMF (3 ml). La solución de color amarillo resultante se agitó a temperatura ambiente durante 12 horas, se diluyó con EtOAc (30 ml) y se lavó con agua (2 x 20 ml) y salmuera (20 ml). La fase orgánica se secó con Na2SO4 y se concentró para dar el compuesto del título en forma de un aceite de color amarillo espeso, el cual se utilizó sin purificación posterior (470 mg). [M+H] calc para C24H31N5CO5, 470; experimental, 470

[0667] Preparación 34: (1-metoxi-3-(3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)propan-2-ilcarbamato de (R)-ter-butilo

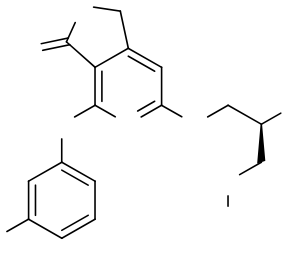


[0668] A un matraz de base redonda se agregó 6-(2-(ter-butoxicarbonilamino)-3-metoxipropilamino)-4-ciano-2-(m-tolilamino)nicotinato de (R)-metilo (84,5 mg, 0,180 mmoles) en ácido acético (3 ml) y DCM (10 ml). A la solución de color amarillo resultante se agregó óxido de platino (IV) (4,09 mg, 0,018 mmoles). El matraz se evacuó y retrollenó con hidrógeno (3 x 1 atm). La mezcla de reacción se agitó vigorosamente a temperatura ambiente durante 16 horas, posteriormente se diluyó con DCM (10 ml), y se filtró a través de celite. El filtrado se concentró hasta un aceite, el cual se diluyó con DCM (10 ml). Se



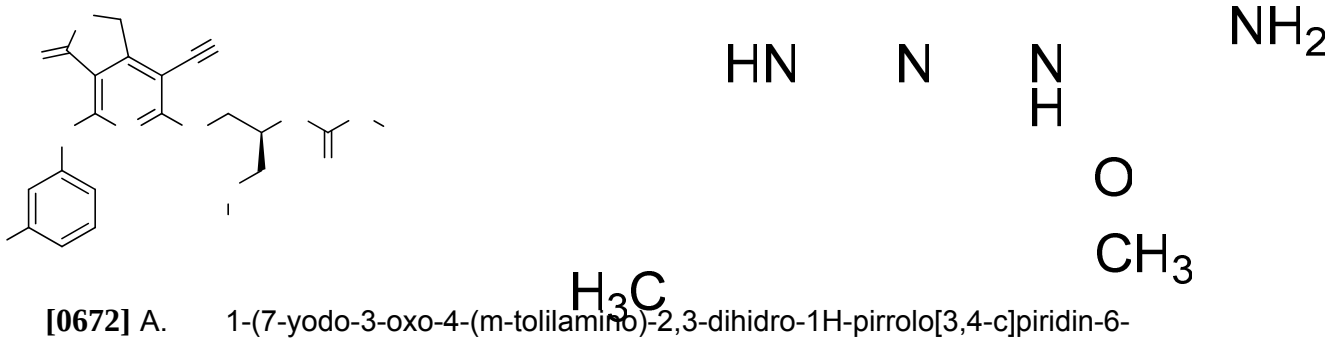
agregó carbonato de potasio (24,87 mg, 0,180 mmoles) y la mezcla de reacción se agitó a temperatura ambiente durante 12 horas. La reacción bruta se diluyó con DCM (10 ml), se filtró a través de celite, y se concentró para dar el compuesto del título en forma de un aceite de color amarillo espeso, el cual se utilizó sin purificación posterior (26,5 mg, 33,4%). [M+H] calc para C23H31N5CO4, 442; experimental, 442.

[0669] Ejemplo 77: (R)-6-(2-amino-3-metoxipropilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



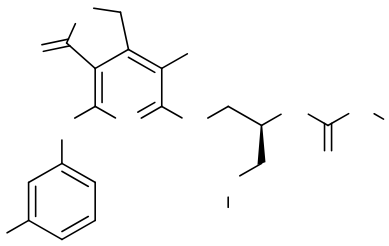
[0670] Una sal TFA del compuesto del título se preparó de manera similar al ejemplo 75 utilizando 1-metoxi-3-(3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)propan-2-ilcarbamato de (R)-ter-butilo en lugar de (1S,2R)-2-(7-cloro-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo. 1H RMN (400 MHz, CD3OD) δ ppm 7,57 (d, J=8,3 Hz, 1 H), 7,36 (s, 1 H), 7,22 (t, J=7,8 Hz, 1 H), 6,87 (d, J=7,3 Hz, 1 H), 6,07 (s, 1 H), 4,30 (s, 2 H), 3,70 - 3,82 (m, 2 H), 3,50 - 3,65 (m, 3 H), 3,40 (s, 3 H), 2,35 (s, 3 H). [M+H] calc para C18H23N5O2, 342; experimental, 342.

[0671] Preparación 35: (1-(7-ciano-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-3-metoxipropan-2-ilcarbamato de R)-ter-butilo



[0672] A. 1-(7-yodo-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-

ilamino)-3-metoxipropan-2-ilcarbamato de R)-ter-butilo

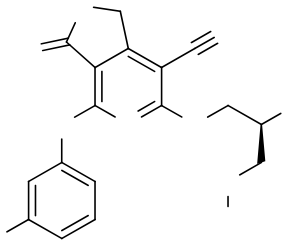


[0673] El compuesto del título se preparó de manera similar al ejemplo 30 utilizando 1-metoxi-3-(3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)propan-2-ilcarbamato de (R)-ter-butilo en lugar de (1S,2R)-2-(3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo. [M+H] calc para C23H30IN5O4, 568; experimental, 568.

[0674] B. 1-(7-ciano-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-3-metoxipropan-2-ilcarbamato de R)-ter-butilo

[0675] El compuesto del título se preparó de manera similar al ejemplo 31 utilizando 1-(7-yodo-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)propan-3-metoxipropan-2-ilcarbamato de (R)-ter-butilo en lugar de (1S,2R)-2-(7-yodo-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo. [M+H] calc para C24H30N6O4, 467; experimental, 467.

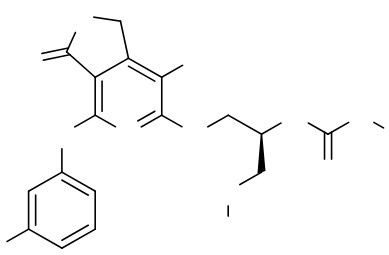
[0676] Ejemplo 78: (R)-6-(2-amino-3-metoxipropilamino)-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-7-carbonitrilo



[0677] Una sal TFA del compuesto del título se preparó de manera similar al ejemplo 75 utilizando 1-(7-ciano-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-

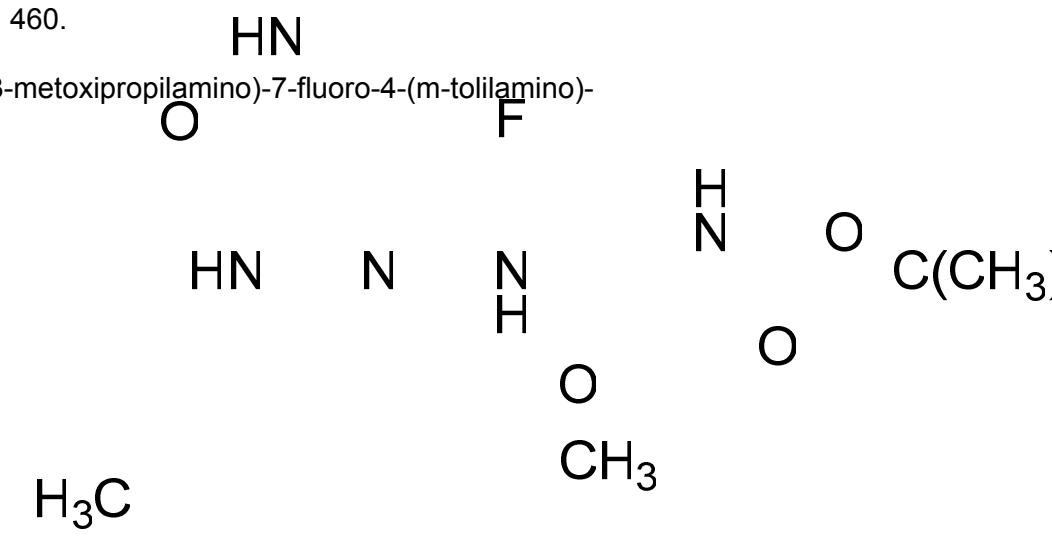
6-ilamino)propan-3-metoxipropan-2-ilcarbamato de (R)-ter-butilo en lugar de (1S,2R)-2-(7-cloro-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo. 1H RMN (400 MHz, DMSO-d6) δ ppm 9,25 (s, 1 H), 8,47 (s, 1 H), 7,93 (br s, 3 H), 7,58 (d, J=7,8 Hz, 1 H), 7,51 (t, J=5,4 Hz, 1 H), 7,42 (s, 1 H), 7,27 (t, J=7,8 Hz, 1 H), 6,93 (d, J=7,3 Hz, 1 H), 4,43 (s, 2 H), 3,71 - 3,80 (m, 1 H), 3,60 - 3,70 (m, 1 H), 3,44 - 3,60 (m, 3 H), 3,29 (s, 3 H), 2,33 (s, 3 H). [M+H] calc para C19H22N6O2, 367; experimental, 367.

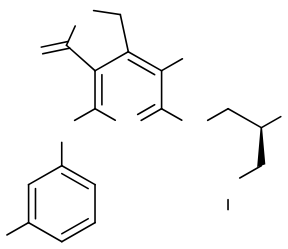
[0678] Preparación 36: (1-(7-fluoro-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-3-metoxipropan-2-ilcarbamato de R)-ter-butilo



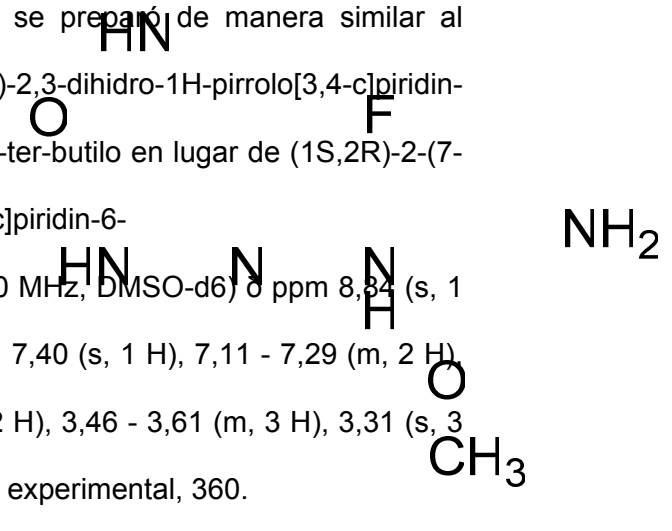
[0679] A un recipiente con tapa superior se agregó 1-metoxi-3-(3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)propan-2-ilcarbamato de (R)-ter-butilo (27 mg, 0,061 mmoles) en una mezcla de DCM y MeOH (1/1, 1,2 ml). La solución incolora resultante se enfrió hasta 0ºC. Se agregó SELECTFLUOR® (21,66 mg, 0,061 mmoles) y la mezcla de reacción se agitó a 0ºC durante 2 horas. A continuación, la mezcla de reacción se diluyó con EtOAc (10 ml) y se lavó con bicarbonato de sodio acuoso saturado (5 ml), agua (5 ml), y salmuera (5 ml). La capa orgánica se recolectó, se secó sobre Na2SO4, y se concentró para dar el compuesto del título en forma de un residuo de color marrón, el cual se utilizó sin purificación posterior (32 mg, 114%. [M+H] calc para C23H30FN5O4, 460; experimental, 460.

[0680] Ejemplo 79: (R)-6-(2-amino-3-metoxipropilamino)-7-fluoro-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona

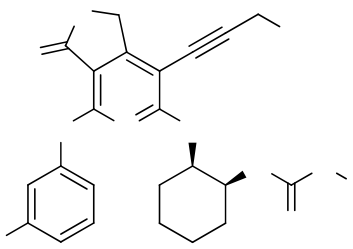




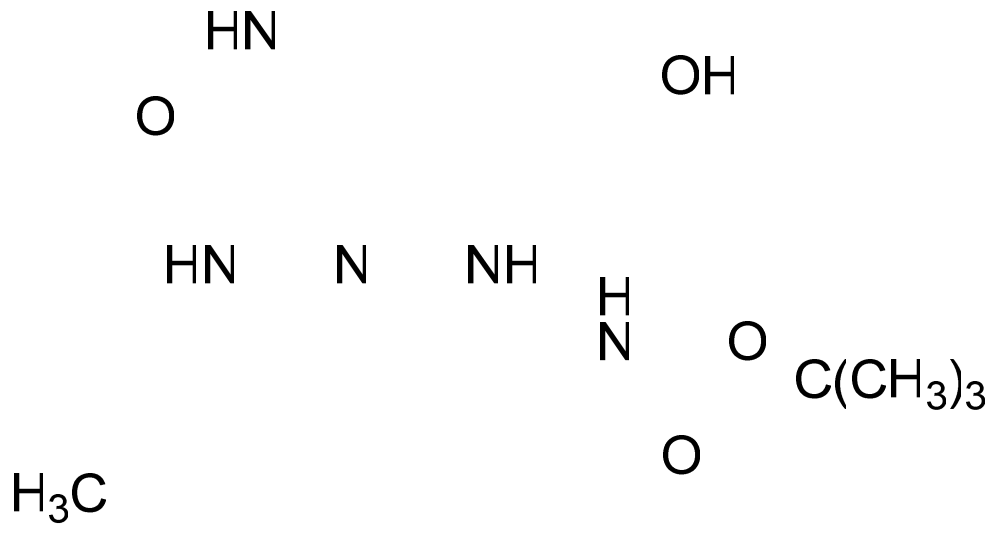
[0681] Una sal TFA del compuesto del título se preparó de manera similar al ejemplo 75 utilizando 1-(7-fluoro-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)propan-3-metoxipropan-2-ilcarbamato de (R)-ter-butilo en lugar de (1S,2R)-2-(7-cloro-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo. 1H RMN (400 MHz, DMSO-d6) δ ppm 8,34 (s, 1 H), 8,28 (s, 1 H), 7,97 (br s, 3 H), 7,47 - 7,62 (m, 1 H), 7,40 (s, 1 H), 7,11 - 7,29 (m, 2 H), 6,80 (d, J=7,6 Hz, 1 H), 4,40 (s, 2 H), 3,62 - 3,78 (m, 2 H), 3,46 - 3,61 (m, 3 H), 3,31 (s, 3 H), 2,31 (s, 3 H). [M+H] calc para C18H22FN5O2, 360, experimental, 360.



[0682] Preparación 37: A. (1S,2R)-2-(7-(3-hidroxiprop-1-inil)-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo

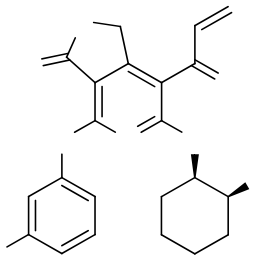


[0683] A un recipiente de presión de vidrio secado en horno se agregó (1S,2R)-2-(7-yodo-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo (25 mg, 0,043 mmoles), yoduro de cobre (I) (12,37 mg, 0,065 mmoles), cloruro de bis(trifenilfosfina)paladio (II) (9,12 mg, 0,013 mmoles), hidroxitolueno butilado (un gránulo), THF (866 µl), y Et3N (121 µl, 0,866 mmoles). La mezcla se desgasificó 3 min. con nitrógeno. Se agregó alcohol propargílico (31 µl, 0,520 mmoles) y el recipiente se tapó y se calentó a 80ºC con agitación durante 2 horas y a continuación a temperatura ambiente durante 12 horas. La mezcla de reacción



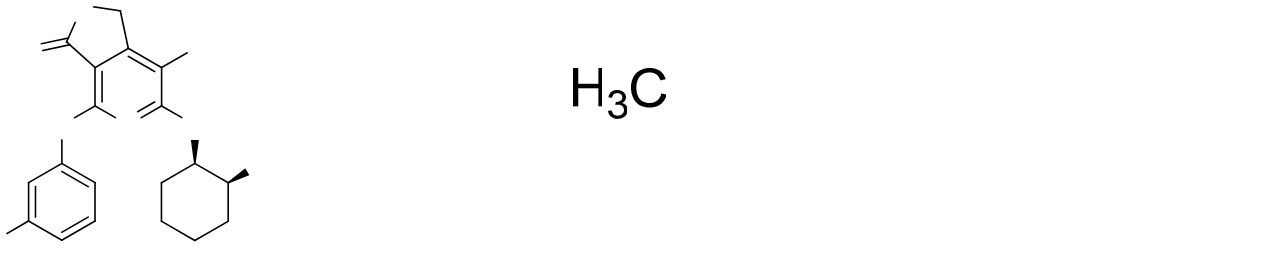
se diluyó con EtOAc (10 ml) y se lavó con agua (5 ml) y salmuera (5 ml). La capa orgánica se recolectó, se secó con Na2SO4, y se concentró para dar el compuesto del título en forma de un residuo de color marrón, el cual se utilizó sin purificación posterior (22 mg, 101%. [M+H] calc para C28H35N5O4, 506; experimental, 506.

[0684] Ejemplo 80: 7-acriloil-6-((1R,2S)-2-aminociclohexilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



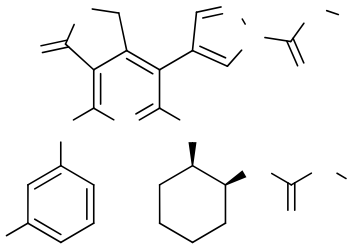
[0685] Una sal TFA del compuesto del título se preparó de manera similar al ejemplo 75 utilizando (1S,2R)-2-(7-(3-hidroxiprop-1-inil)-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo en lugar de (1S,2R)-2-(7-cloro-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo. 1H RMN (400 MHz, DMSO-d6) δ ppm 10,53 (d, J=7,8 Hz, 1 H), 9,81 (s, 1 H), 8,65 (s, 1 H), 7,85 (br s, 3 H), 7,60 (s, 1 H), 7,51 (s, 1 H), 7,27 (t, J=7,8 Hz, 1 H), 7,08 (dd, J=16,5, 10,5 Hz, 1 H), 6,93 (d, J=7,6 Hz, 1 H), 6,19 (dd, J=16,7, 2,0 Hz, 1 H), 5,68 - 5,90 (m, 1 H), 4,50 - 4,80 (m, 3 H), 3,65 (br s, 1 H), 2,34 (s, 3 H), 1,78 - 2,01 (m, 2 H), 1,75 (s, 3 H), 1,43 - 1,58 (m, 3 H). [M+H] calc para C23H27N5O2, 406; experimental, 406.

[0686] Ejemplo 81: 6-((1R,2S)-2-aminociclohexilamino)-7-yodo-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona

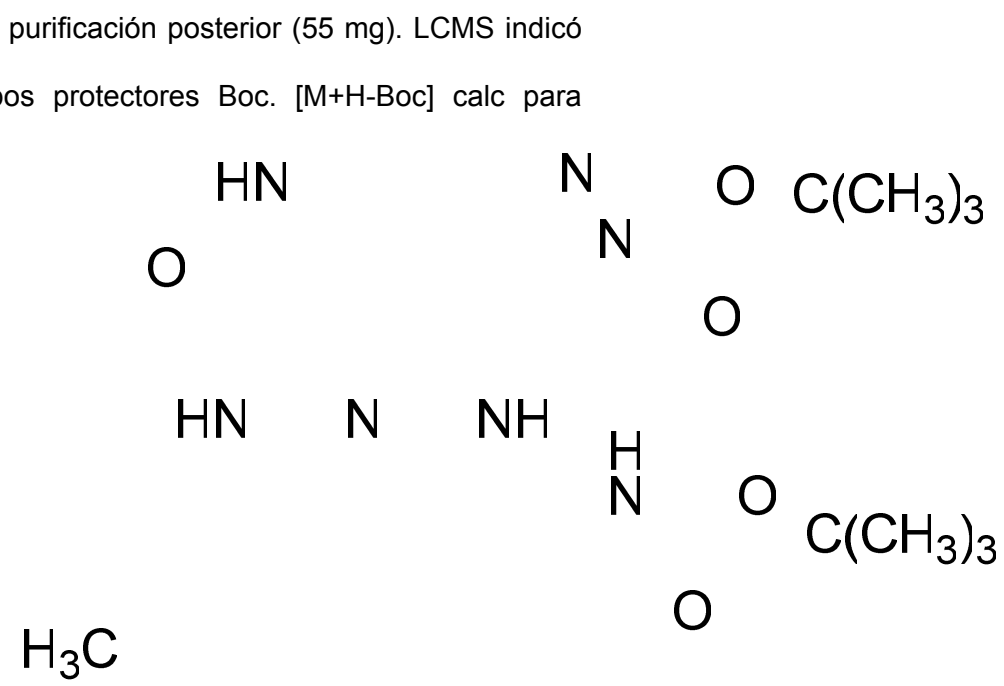


[0687] Una sal TFA del compuesto del título se preparó de manera similar al ejemplo 75 utilizando (1S,2R)-2-(7-yodo-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo en lugar de (1S,2R)-2-(7-cloro-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo. 1H RMN (400 MHz, CD3OD) δ ppm 7,48 (d, J=8,1 Hz, 1 H), 7,39 (s, 1 H), 7,23 (t, J=7,8 Hz, 1 H), 6,90 (d, J=7,6 Hz, 1 H), 4,47 (d, J=9,1 Hz, 1 H), 4,18 (d, J=3,0 Hz, 2 H), 3,80 - 3,87 (m, 1 H), 2,36 (s, 3 H), 1,87 (d, J=5,6 Hz, 4 H), 1,66 (br s, 4 H). [M+H] calc para C20H24IN5O, 478; experimental, 478.

[0688] Preparación 38: 4-(6-((1R,2S)-2-(ter-butoxicarbonilamino)ciclohexilamino)-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-7-il)-1H-pirazol-1-carboxilato de ter-butilo

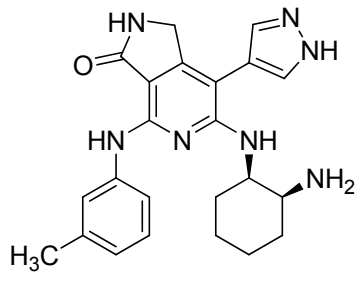


[0689] A un recipiente secado en horno se agregó (1S,2R)-2-(7-yodo-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo (40 mg, 0,069 mmoles), 3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol-1-carboxilato de ter-butilo (30,6 mg, 0,104 mmoles), y carbonato de sodio (0,104 ml, 0,208 mmoles) en DMF (1 ml). La mezcla de color tostado resultante se desgasificó 15 min. Se agregó cloruro de bis(trifenilfosfina)paladio (II) (4,86 mg, 6,93 µmoles) y la mezcla se desgasificó 5 min. adicionales. El recipiente se tapó y se calentó a 80ºC durante 12 horas. La mezcla de reacción se diluyó con EtOAc (10 ml) y se lavó con agua (5 ml) y salmuera (5 ml). La capa orgánica se recolectó, se secó con Na2SO4, y se concentró para dar un residuo de color marrón, el cual se utilizó sin purificación posterior (55 mg). LCMS indicó la masa deseada menos uno de los grupos protectores Boc. [M+H-Boc] calc para



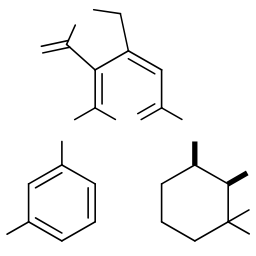
C33H43N7O5, 518; experimental, 518.

[0690] Ejemplo 82: 6-((1R,2S)-2-aminociclohexilamino)-7-(1H-pirazol-4-il)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



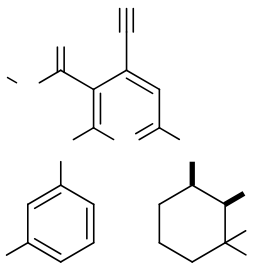
[0691] Una sal TFA del compuesto del título se preparó de manera similar al ejemplo 75 utilizando 4-(6-((1R,2S)-2-(ter-butoxicarbonilamino)ciclohexilamino)-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-7-il)-1H-pirazol-1-carboxilato de ter-butilo en lugar de (1S,2R)-2-(7-cloro-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo. 1H RMN (400 MHz, DMSO-d6) δ ppm 13,13 (br s, 1 H), 8,97 (s, 1 H), 8,19 (s, 1 H), 8,06 (br s, 1 H), 7,75 (br s, 4 H), 7,42 - 7,58 (m, 2 H), 7,21 (t, J=8,1 Hz, 1 H), 6,81 (d, J=7,3 Hz, 1 H), 5,55 (d, J=6,6 Hz, 1 H), 4,25 (s, 3 H), 3,77 (br s, 1 H), 2,32 (s, 3 H), 1,63 - 1,89 (m, 4 H), 1,36 - 1,63 (m, 4 H). [M+H] calc para C23H27N7O, 418; experimental, 418.

[0692] Ejemplo 83: 6-(cis-2-amino-3,3-difluorociclohexilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona

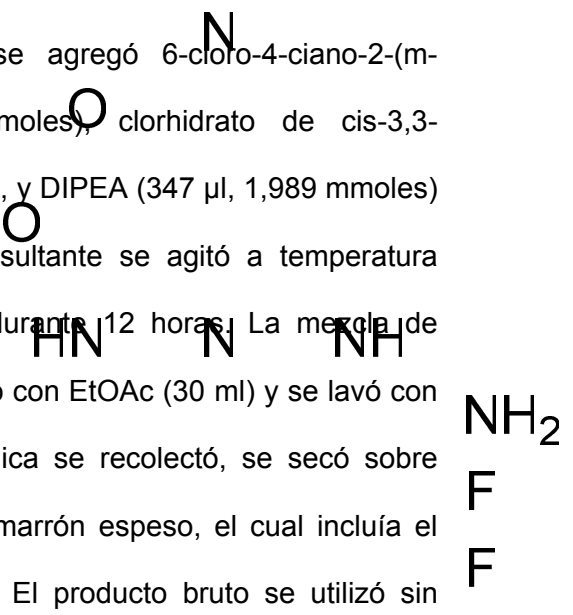


[0693] A. 6-(cis-2-amino-3,3-difluorociclohexilamino)-4-ciano-2-(m-tolilamino)nicotinato de metilo





[0694] A un recipiente con rosca superior se agregó 6-cloro-4-ciano-2-(m-tolilamino)nicotinato de metilo (200 mg, 0,663 mmoles), clorhidrato de cis-3,3-difluorociclohexano-1,2-diamina (148 mg, 0,795 mmoles), y DIPEA (347 µl, 1,989 mmoles) en DMF (3,9 ml). La mezcla amarilla amarronada resultante se agitó a temperatura ambiente durante 2 horas y a continuación a 60ºC durante 12 horas. La mezcla de reacción se enfrió hasta temperatura ambiente, se diluyó con EtOAc (30 ml) y se lavó con agua (2 x 10 ml) y salmuera (20 ml). La capa orgánica se recolectó, se secó sobre Na2SO4, y se concentró para dar un aceite de color marrón espeso, el cual incluía el compuesto del título y los isómeros (328 mg, 119%). El producto bruto se utilizó sin purificación posterior. [M+H] calc para C21H23F2N5O2, 416; experimental, 416.

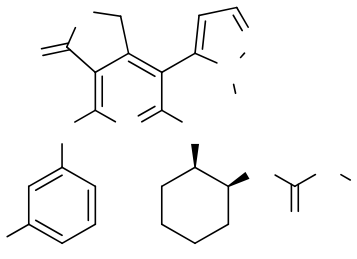


[0695] B. 6-(cis-2-amino-3,3-difluorociclohexilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona

[0696] Un matraz de base redonda se cargó con 6-(cis-2-amino-3,3-difluorociclohexilamino)-4-ciano-2-(m-tolilamino)nicotinato de metilo (275 mg, 0,662 mmoles) en HOAc (2,6 ml) y DCM (10,6 ml). A la solución de color marrón resultante se agregó óxido de platino (IV) (15,03 mg, 0,066 mmoles). El matraz se evacuó y retrollenó con hidrógeno (3 x 1 atm). La mezcla de reacción se agitó vigorosamente en atmósfera de H2 (1 atm) a temperatura ambiente durante 16 horas y a continuación se filtró a través de celite. El filtrado se lavó con DCM (20 ml) y se concentró hasta un residuo, el cual se diluyó en MeOH (3 ml) y se purificó mediante HPLC preparativa para dar una sal TFA del compuesto del título en forma de un sólido de color verde claro. 1H RMN (400 MHz, DMSO-d6) δ ppm 8,97 (s, 1 H), 8,48 (br s, 3 H), 8,09 (s, 1 H), 7,62 (d, J=8,8 Hz, 1 H), 7,32

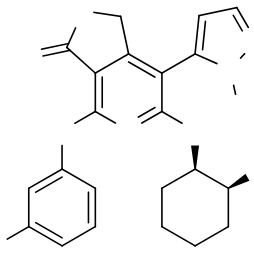
(s, 1 H), 7,14 (t, J=7,8 Hz, 1 H), 6,87 (br s, 1 H), 6,79 (d, J=7,3 Hz, 1 H), 6,15 (s, 1 H), 4,45 (br s, 1 H), 4,24 (d, 2 H), 4,15 (br s, 1 H), 2,29 (s, 3 H), 2,01 - 2,25 (m, 2 H), 1,74 - 1,89 (m, 3 H), 1,60 (d, J=10 Hz, 1 H). [M+H] calc para C20H23F2N5O, 388; experimental, 388.

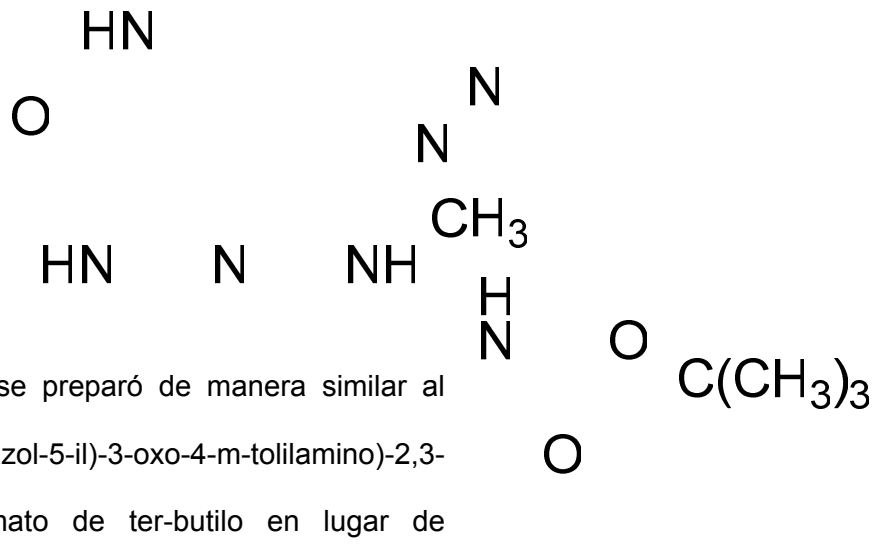
[0697] Preparación 39: (1S,2R)-2-(7-(1-metil-1H-pirazol-5-il)-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo



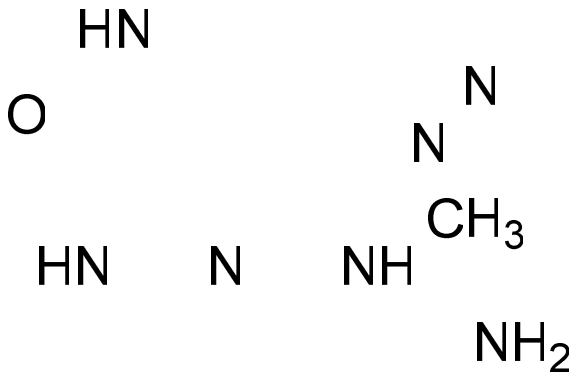
[0698] El compuesto del título se preparó de manera similar al ejemplo 36 utilizando 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol en lugar de 1-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol-1-carboxilato de ter-butilo. [M+H] calc para C29H37N7O3, 532; experimental, 532.

[0699] Ejemplo 84: 6-((1R,2S)-2-aminociclohexilamino)-7-(1-metil-1H-pirazol-5-il)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



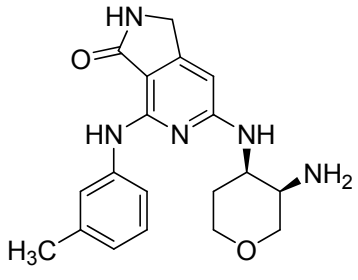


[0700] Una sal TFA del compuesto del título se preparó de manera similar al ejemplo 75 utilizando (1S,2R)-2-(7-(1-metil-1-H-pirazol-5-il)-3-oxo-4-m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo en lugar de (1S,2R)-2-(7-cloro-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo. 1H RMN (400 MHz, DMSO-d6) δ ppm 2,33 (d, J=1,26 Hz, 3 H), 3,64 (d, J=14,15 Hz, 3 H), 3,89 - 4,00 (m, 1 H), 4,02 - 4,21 (m, 1 H), 5,23 - 5,58 (m, 1 H), 6,29 - 6,47 (m, 1 H), 6,85 (d, J=7,58 Hz, 1 H), 7,23 (td, J=7,77, 4,93 Hz, 1

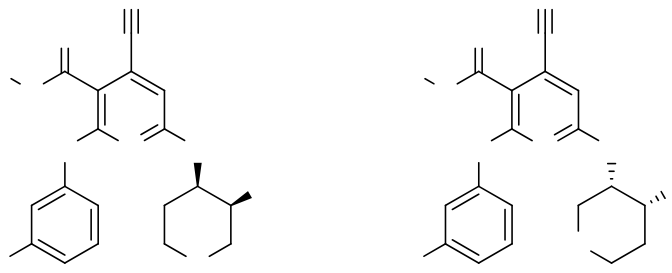


H), 7,47 - 7,56 (m, 2 H), 7,58 (dd, J=9,35, 1,77 Hz, 1 H), 7,64 - 7,83 (m, 2 H), 8,21 (d, J=2,27 Hz, 1 H), 9,04 (s, 1 H). [M+H] calc para C24H29N7O, 432; experimental, 432.

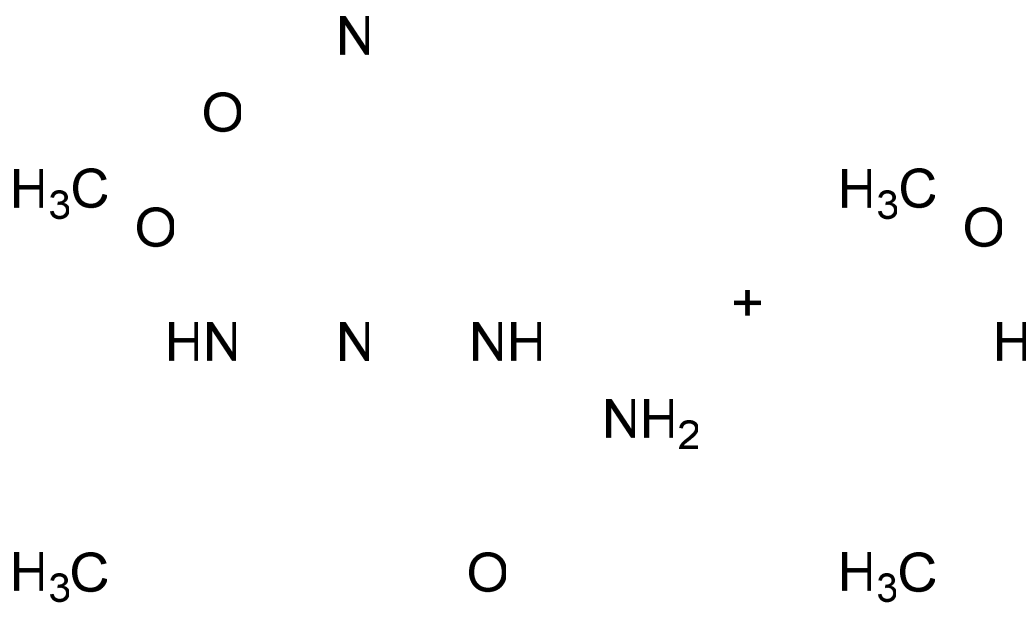
[0701] Ejemplo 85: 6-((3R,4R)-3-aminotetrahidro-2H-piran-4-ilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



[0702] A. 6-((3R,4R)-3-aminotetrahidro-2H-piran-4-ilamino)-4-ciano-2-(m-tolilamino)nicotinato de metilo y 6-((3R,4R)-4-aminotetrahidro-2H-piran-3-ilamino)-4-ciano-2-(m-tolilamino)nicotinato de metilo



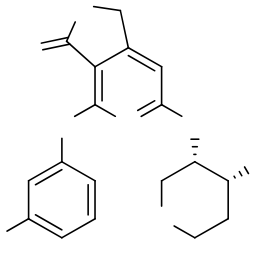
[0703] A un recipiente con tapa a rosca se agregó 6-cloro-4-ciano-2-(m-tolilamino)nicotinato de metilo (500 mg, 1,657 mmoles), clorhidrato de (3R,4R)-tetrahidro-2H-piran-3,4-diamina (303,0 mg, 1,989 mmoles), y DIPEA (868 µL, 4,97 mmoles) en DMF (9748 µL). La suspensión de color amarillo resultante, la cual se tornó una solución al cabo de agregar la base, se agitó a 50ºC durante 12 horas. La mezcla de reacción se enfrió hasta temperatura ambiente, se diluyó con EtOAc (30 ml), y se lavó con agua (20 ml) y salmuera (20 ml). La capa orgánica se recolectó, se secó con Na2SO4, y se concentró para dar un aceite de color marrón espeso, el cual incluía los compuestos del título (350 mg, 55,4%). El producto bruto se utilizó en el próximo paso sin purificación posterior. [M+H] calc para C20H23N5O3, 382; experimental, 382.



[0704] B. 6-((3R,4R)-3-aminotetrahidro-2H-piran-4-ilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona

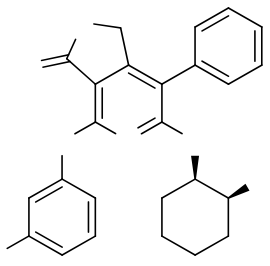
[0705] A un matraz de base redonda de 50 ml se agregó una mezcla de 6-((3R,4R)-3-aminotetrahidro-2H-piran-4-ilamino)-4-ciano-2-(m-tolilamino)nicotinato de metilo y 6-((3R,4R)-4-aminotetrahidro-2H-piran-3-ilamino)-4-ciano-2-(m-tolilamino)nicotinato de metilo (100 mg, 0,262 mmoles) y óxido de platino (IV) (11,91 mg, 0,052 mmoles) en DCM (4195 µL) y HOAc (1049 µL). El recipiente se evacuó y retrollenó con hidrógeno (1 atm) y la mezcla se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se diluyó con DCM (10 ml) y MeOH (20 ml), se filtró a través de celite, y se concentró hasta un residuo, el cual se diluyó con DCM (50 ml). Se agregó carbonato de potasio (217 mg, 1,573 mmoles) y la mezcla se agitó a temperatura ambiente durante 12 horas. La mezcla se filtró a través de celite, se concentró hasta un residuo, se diluyó con una mezcla de DMF y MeOH (1/1, 3 ml), y se purificó mediante HPLC preparativa. El pico de isómero apropiado se recolectó y se liofilizó para dar una sal TFA del compuesto del título en forma de un sólido color gris claro (20,3 mg, 21,9%). 1H RMN (400 MHz, DMSO-d6) δ ppm 8,92 (s, 1 H), 8,05 (s, 1 H), 7,95 (br s, 3 H), 7,50 (d, J=8,1 Hz, 1 H), 7,43 (s, 1 H), 7,21 (t, J=7,8 Hz, 1 H), 7,09 (d, J=4,8 Hz, 1 H), 6,80 (d, J=7,6 Hz, 1 H), 6,11 (s, 1 H), 4,20 - 4,32 (m, 3 H), 3,91 - 4,06 (m, 2 H), 3,76 (br s, 1 H), 3,53 - 3,72 (m, 2 H), 2,31 (s, 3 H), 1,99 (qd, J=12,6, 4,7 Hz, 1 H), 1,70 - 1,80 (m, 1 H). [M+H] calc para C19H23N5O2, 354; experimental, 354.

[0706] Ejemplo 86: 6-((3R,4R)-4-aminotetrahidro-2H-piran-3-ilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



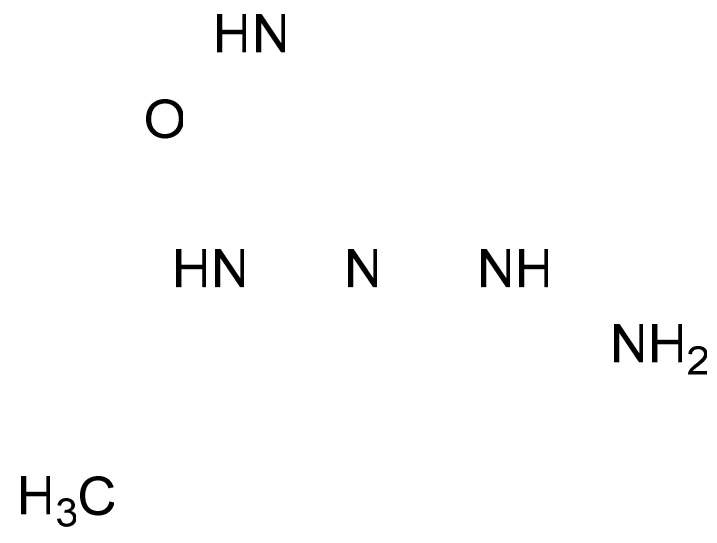
[0707] Una sal TFA del compuesto del título se preparó de manera similar al ejemplo 85, recolectando las fracciones correspondientes a 6-((3R,4R)-4-aminotetrahidro-2H-piran-3-ilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona en lugar de 6-((3R,4R)-3-aminotetrahidro-2H-piran-4-ilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona. 1H RMN (400 MHz, DMSO-d6) δ ppm 8,91 (s, 1 H), 7,94 - 8,15 (m, 4 H), 7,52 (s, 1 H), 7,43 (d, J=8,3 Hz, 1 H), 7,18 (t, J=7,8 Hz, 1 H), 7,03 (d, J=8,3 Hz, 1 H), 6,79 (d, J=7,6 Hz, 1 H), 6,21 (s, 1 H), 4,44 (br s, 1 H), 4,20 - 4,30 (m, 2 H), 3,84 - 3,95 (m, 2 H), 3,67 - 3,81 (m, 1 H), 3,62 (dd, J=11,6, 1,8 Hz, 1 H), 3,50 (td, J=11,2, 2,4 Hz, 1 H), 2,30 (s, 3 H), 1,98 - 2,13 (m, 1 H), 1,71 - 1,82 (m, 1 H). [M+H] calc para C19H23N5O2, 354; experimental, 354.

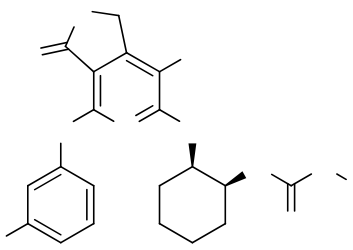
[0708] Ejemplo 87: (1S,2R)-2-(3-oxo-7-fenil-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo



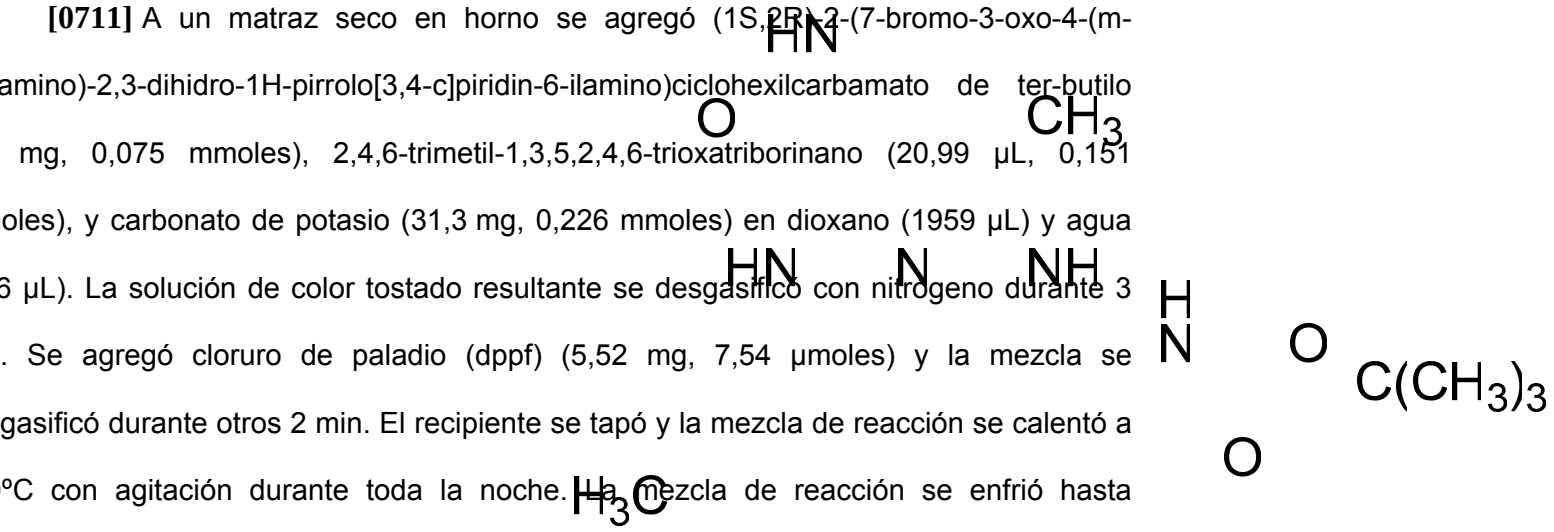
[0709] Una sal TFA del compuesto del título se preparó de manera similar al ejemplo 82 utilizando ácido fenilborónico en lugar de 3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol-1-carboxilato de ter-butilo. 1H RMN (400 MHz, DMSO-d6) δ ppm 9,03 (s, 1 H), 8,15 (s, 1 H), 7,72 (br s, 3 H), 7,51 (d, J=4,5 Hz, 6 H), 7,35 - 7,45 (m, 1 H), 7,22 (dd, J=8,7, 7,5 Hz, 1 H), 6,83 (d, J=7,6 Hz, 1 H), 5,33 (d, J=6,8 Hz, 1 H), 4,30 (br s, 1 H), 4,17 - 4,27 (m, 1 H), 4,04 (d, J=17,7 Hz, 1 H), 3,76 (br s, 1 H), 2,33 (s, 3 H), 1,59 - 1,85 (m, 4 H), 1,37 - 1,59 (m, 4 H). [M+H] calc para C26H29N5O, 428; experimental, 428.

[0710] Preparación 40: A. (1S,2R)-2-(7-metil-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo

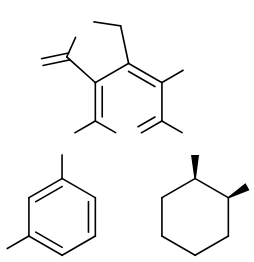




[0711] A un matraz seco en horno se agregó (1S,2R)-2-(7-bromo-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo (40 mg, 0,075 mmoles), 2,4,6-trimetil-1,3,5,2,4,6-trioxatriborinano (20,99 µL, 0,151 mmoles), y carbonato de potasio (31,3 mg, 0,226 mmoles) en dioxano (1959 µL) y agua (196 µL). La solución de color tostado resultante se desgasificó con nitrógeno durante 3 min. Se agregó cloruro de paladio (dppf) (5,52 mg, 7,54 µmoles) y la mezcla se desgasificó durante otros 2 min. El recipiente se tapó y la mezcla de reacción se calentó a 100ºC con agitación durante toda la noche. La mezcla de reacción se enfrió hasta temperatura ambiente, se diluyó con EtOAc (5 ml), y se lavó con agua (5 ml) y salmuera (5 ml). La capa orgánica se recolectó, se secó sobre Na2SO4, y se concentró para dar el compuesto del título en forma de un aceite viscoso de color marrón, el cual se utilizó sin purificación posterior (45 mg). [M+H] calc para C26H35N5O3, 466; experimental, 466.



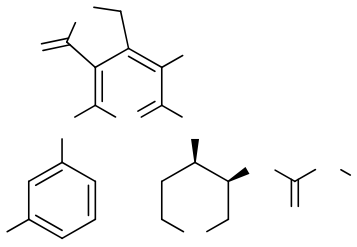
[0712] Ejemplo 88: 6-((1R,2S)-2-aminociclohexilamino)-7-metil-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



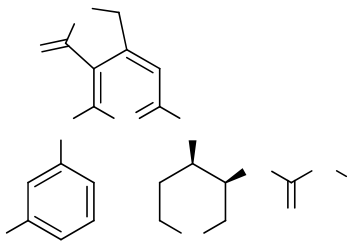
[0713] Una sal TFA del compuesto del título se preparó de manera similar al ejemplo 75 utilizando (1S,2R)-2-(7-metil-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo en lugar de (1S,2R)-2-(7-cloro-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-

butilo. 1H RMN (400 MHz, DMSO-d6) δ ppm 8,79 (s, 1 H), 8,10 (s, 1 H), 7,73 (br s, 3 H), 7,48 (d, J=2,0 Hz, 2 H), 7,14 - 7,21 (m, 1 H), 6,77 (d, J=7,6 Hz, 1 H), 5,69 (d, J=6,6 Hz, 1 H), 4,36 (br s, 1 H), 4,18 - 4,29 (m, 2 H), 3,72 (br s, 1 H), 2,31 (s, 3 H), 2,01 (s, 3 H), 1,88 (d, J=9,1 Hz, 2 H), 1,55 - 1,79 (m, 4 H), 1,39 - 1,55 (m, 2 H). [M+H] calc para C21H27N5O, 366; experimental, 366.

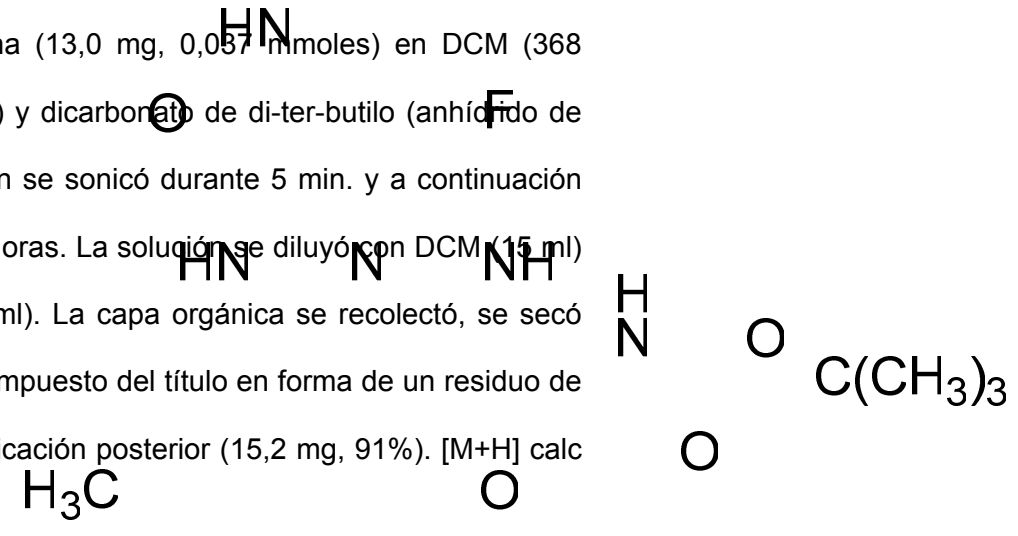
[0714] Preparación 41: (3R,4R)-4-(7-fluoro-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)tetrahidro-2H-piran-3-ilcarbamato de ter-butilo

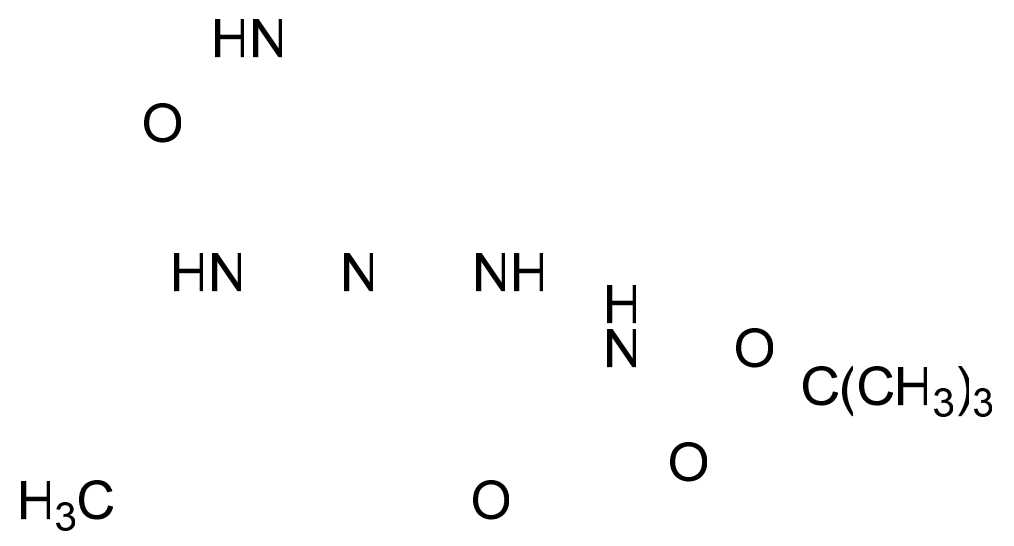


[0715] A. (3R,4R)-4-(3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)tetrahidro-2H-piran-3-ilcarbamato de ter-butilo



[0716] A una suspensión de 6-((3R,4R)-3-aminotetrahidro-2H-piran-4-ilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona (13,0 mg, 0,037 mmoles) en DCM (368 µL) se agregó Et3N (6,05 µL, 0,043 mmoles) y dicarbonato de di-ter-butilo (anhídrido de Boc) (39,0 µL, 0,039 mmoles). La suspensión se sonicó durante 5 min. y a continuación se agitó a temperatura ambiente durante 12 horas. La solución se diluyó con DCM (15 ml) y se lavó con agua (10 ml) y salmuera (10 ml). La capa orgánica se recolectó, se secó sobre Na2SO4, y se concentró para dar el compuesto del título en forma de un residuo de color amarillo claro, el cual se utilizó sin purificación posterior (15,2 mg, 91%). [M+H] calc para C24H31N5O4, 454; experimental, 454.

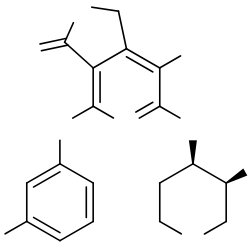




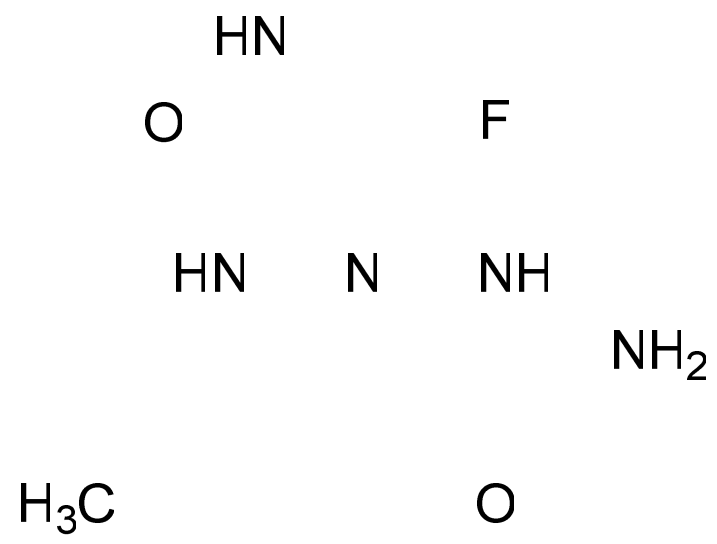
[0717] B. (3R,4R)-4-(7-fluoro-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)tetrahidro-2H-piran-3-ilcarbamato de ter-butilo

[0718] A un recipiente con tapa a rosca se agregó (3R,4R)-4-(3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)tetrahidro-2H-piran-3-ilcarbamato de ter-butilo (15,2 mg, 0,034 mmoles) y selectfluor® (11,87 mg, 0,034 mmoles) en DCM (335 µL) y MeOH (335 µL). La mezcla de reacción se agitó a temperatura ambiente durante 2 horas, se diluyó con EtOAc (10 ml) y se lavó con NaHCO3 acuoso saturado (5 ml), agua (5 ml) y salmuera (5 ml). La capa orgánica se recolectó, se concentró hasta un residuo, y se purificó mediante HPLC preparativa. Las fracciones apropiadas se recolectaron y se concentraron para dar una sal TFA del compuesto del título en forma de un residuo incoloro (4,2 mg, 26,6%). [M+H] calc para C24H30FN5O4, 472; experimental, 472.

[0719] Ejemplo 89: 6-((3R,4R)-3-aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona

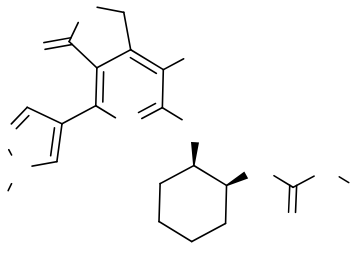


[0720] Una solución de (3R,4R)-4-(7-fluoro-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)tetrahidro-2H-piran-3-ilcarbamato de ter-butilo (4,5 mg, 9,54 µmoles) en 4 M HCl-dioxano (2 ml) se agitó durante 0,5 horas a temperatura ambiente. La mezcla de reacción se concentró hasta un residuo, la cual se diluyó en DMF (1 ml) y se purificó mediante HPLC preparativa. Las fracciones apropiadas se recolectaron y se liofilizaron para dar una sal TFA del compuesto del título en forma de un sólido de color blanco (2,6 mg, 73%). 1H RMN (400 MHz, DMSO-d6) δ ppm 8,81 (s, 1 H), 8,25 (s, 1 H), 7,57 (s, 1 H), 7,40 (d, J=8,1 Hz, 1 H), 7,04 - 7,28 (m, 2 H), 6,79 (d, J=7,3 Hz, 1 H), 6,62 -

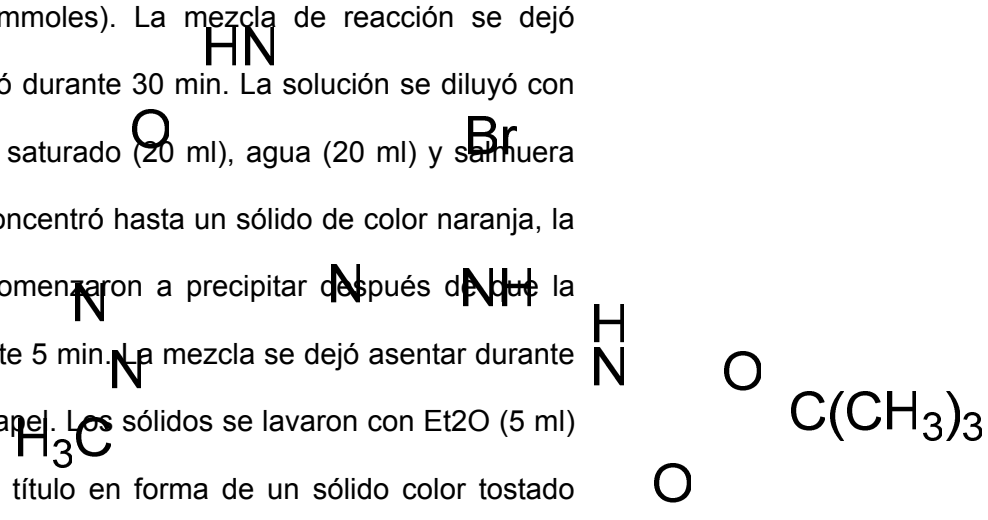


6,76 (m, 2 H), 4,26 - 4,46 (m, 3 H), 3,85 - 3,96 (m, 2 H), 2,32 (s, 3 H), 1,94 - 2,13 (m, 1 H), 1,59 - 1,70 (m, 1 H), 1,07 - 1,28 (m, 4 H). [M+H] calc para C19H22FN5O2, 372; experimental, 372.

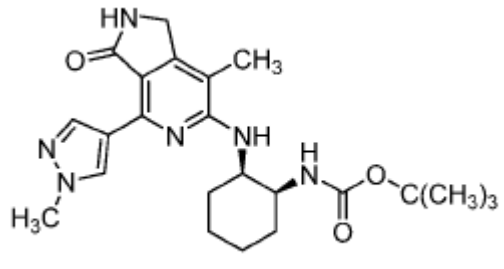
[0721] Preparación 42: (1S,2R)-2-(7-bromo-4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo



[0722] A una matraz de base redonda se agregó (1S,2R)-2-(4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo (124 mg, 0,291 mmoles) en DCM (30 ml). La suspensión de color blanco resultante se calentó con una pistola de calor mientras se agita hasta que se disolvió el material de partida. La solución se enfrió hasta 0ºC, y mientras se agitaba, se agregó 1-bromopirrolidina-2,5-diona (51,7 mg, 0,291 mmoles). La mezcla de reacción se dejó entibiar hasta temperatura ambiente y se agitó durante 30 min. La solución se diluyó con DCM (20 ml) y se lavó con NaHCO3 acuoso saturado (20 ml), agua (20 ml) y salmuera (20 ml). La capa orgánica se recolectó y se concentró hasta un sólido de color naranja, la cual se trató con Et2O (5 ml). Los sólidos comenzaron a precipitar después de que la solución se dejó asentar sin disturbarse durante 5 min. La mezcla se dejó asentar durante 1 hora y se filtró a continuación a través del papel. Los sólidos se lavaron con Et2O (5 ml) y se recolectaron para dar el compuesto del título en forma de un sólido color tostado (137,3 mg, 93%). [M+H] calc para C22H29BrN6O3, 505; experimental, 505.



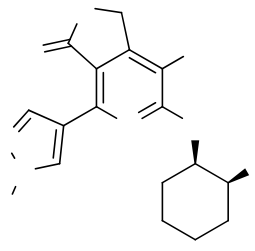
[0723] Preparación 43: (1S,2R)-2-(7-metil-4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo



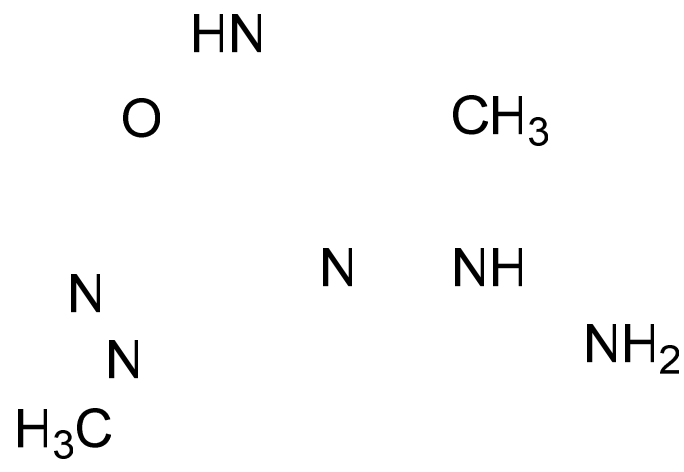
195

[0724] Una sal TFA del compuesto del título se preparó de manera similar a la preparación 40 utilizando (1S,2R)-2-(7-bromo-4-(1-metil-1H-pirazol-e-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo en lugar de (1S,2R)-2-(7-bromo-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo. [M+H] calc para C23H32N6O3, 441; experimental, 441.

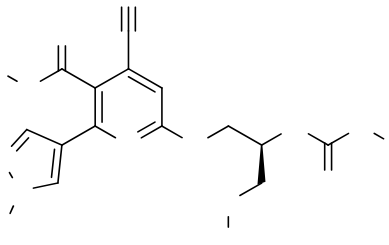
[0725] Ejemplo 90: 6-((1R,2S)-2-aminociclohexilamino)-7-metil-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



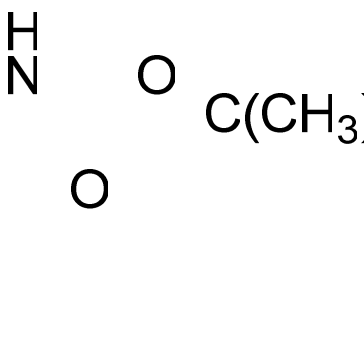
[0726] Una sal TFA del compuesto del título se preparó de manera similar al ejemplo 89 utilizando (1S,2R)-2-(7-metil-4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo en lugar de (3R,4R)-4-(7-fluoro-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)tetrahidro-2H-piran-3-ilcarbamato de ter-butilo. 1H RMN (400 MHz, DMSO-d6) δ ppm 8,87 (s, 1 H), 8,30 (s, 1 H), 8,17 (s, 1 H), 7,71 (br s, 3 H), 5,71 (d, J=6,3 Hz, 1 H), 4,49 (d, J=2,8 Hz, 1 H), 4,24 (s, 2 H), 3,91 (br s, 3 H), 3,71 (br s, 1 H), 2,08 (s, 3 H), 1,77 - 1,93 (m, 3 H), 1,69 (d, J=8,6 Hz, 3 H), 1,40 - 1,53 (m, 2 H). [M+H] calc para C18H24N6O, 341; experimental, 341.



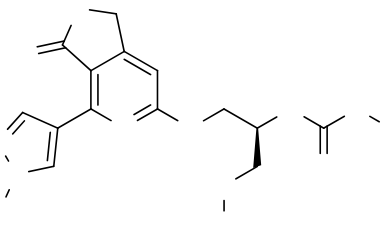
[0727] Preparación 44: (6-(2-(ter-butoxicarbonilamino)-3-metoxipropilamino)-4-ciano-2-(1-metil-1H-pirazol-4-il)nicotinato de (R)-metilo



[0728] A un recipiente con rosca superior se agregó 6-cloro-4-ciano-2-(1-metil-1H-pirazol-4-il)nicotinato de metilo (115 mg, 0,416 mmoles), 1-amino-3-metoxipropan-2-ilcarbamato de (RR)-ter-butilo (93 mg, 0,457 mmoles), y DIPEA (87 µL, 0,499 mmoles) en DMF (308 µL). La solución de color amarillo resultante se agitó durante 12 horas a 45ºC y a continuación a 50ºC durante 6 horas. La mezcla de reacción se diluyó con EtOAc (20 ml) y se lavó con agua (10 ml) y salmuera (20 ml). La capa orgánica se recolectó y se secó sobre Na2SO4 y se concentró hasta un aceite de color amarillo. El concentrado se purificó mediante cromatografía de columna de fase estándar eluyendo con EtOAc y hexanos (gradiente 50-100% EtOAc) para dar el compuesto del título en forma de un residuo de color amarillo claro (36,5 mg, 20%). [M+H] calc para C21H28N6O5, 445; experimental, 445.



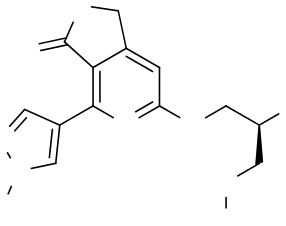
[0729] Preparación 45: (1-metoxi-3-(4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)propan-2-ilcarbamato de (R)-ter-butilo



[0730] El compuesto del título se preparó de manera similar a la preparación 34 utilizando 6-(2-(ter-butoxicarbonilamino)-3-metoxipropilamino)-4-ciano-2-(1-metil-1H-pirazol-4-il)nicotinato de (R)-metilo en lugar de 6-(2-(ter-butoxicarbonilamino)-3-

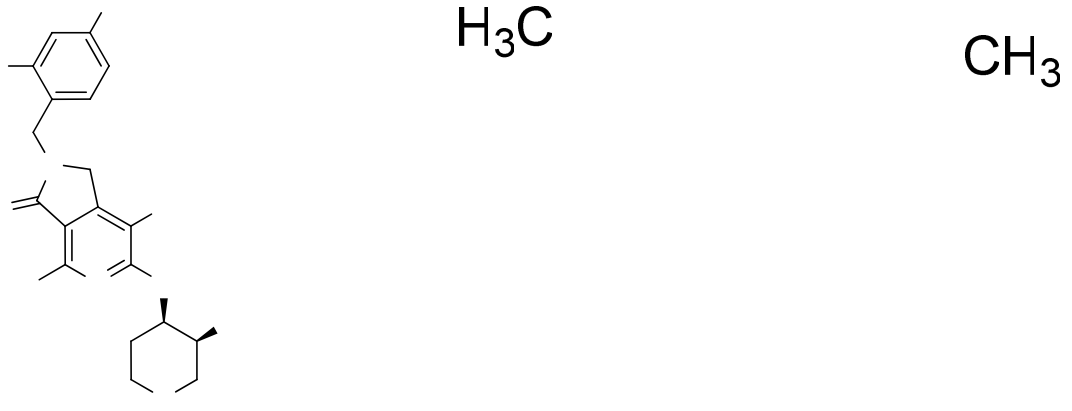
metoxipropilamino)-4-ciano-2-(m-tolilamino)nicotinato de (R)-metilo (84,5 mg, 0,180 mmoles). [M+H] calc para C20H28N6O4, 417; experimental, 417.

[0731] Ejemplo 91: (R)-6-(2-amino-3-metoxipropilamino)-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



[0732] Una sal TFA del compuesto del título se preparó de manera similar a los ejemplo 89 utilizando 1-metoxi-3-(4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)propan-2-ilcarbamato de (R)-ter-butilo en lugar de (3R,4R)-4-(7-fluoro-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)tetrahidro-2H-piran-3-ilcarbamato de ter-butilo. 1H RMN (400 MHz, DMSO-d6) δ ppm 8,97 (s, 1 H), 8,40 (s, 1 H), 8,09 (s, 1 H), 8,00 (br s, 3 H), 7,17 - 7,26 (m, 1 H), 6,42 (s, 1 H), 4,24 (s, 2 H), 3,89 (s, 3 H), 3,54 - 3,60 (m, 5 H), 3,33 (s, 3H). [M+H] calc para C15H20N6O2, 317; experimental, 317.

[0733] Preparación 46: 6-((3R,4R)-3-aminotetrahidro-2H-piran-4-ilamino)-4-cloro-2-(2,4-dimetoxibencil)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona

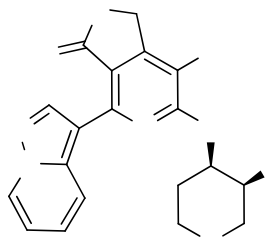


[0734] Una mezcla de 4,6-dicloro-2-(2,4-dimetoxibencil)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona (2,5 g, 6,74 mmoles) y (3R,4R)-tetrahidro-2H-piran-3,4-diamina (0,711

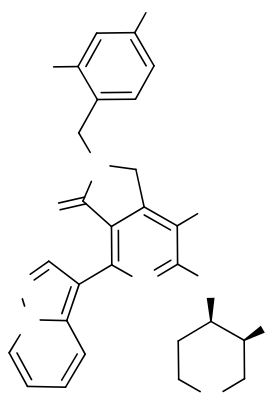


g, 6,12 mmoles) y DIPEA (5,35 ml, 30,6 mmoles) en ACN (30 ml) se agitó a 85ºC durante 3 días en un tubo cerrado. Se agregaron (3R,4R)-tetrahidro-2H-piran-3,4-diamina (0,356 g, 3,06 mmoles) y DIPEA (2,14 ml, 12,2 mmoles) y la mezcla se calentó a 100ºC durante toda la noche. El filtrado se concentró y se purificó mediante HPLC preparativa. Las fracciones correspondientes al regioisómero deseado se recolectaron para dar el compuesto del título (265 mg, 9,60%). 1H RMN (400 MHz, DMSO-d6) δ ppm 1,64-1,65 (m, 1 H), 1,80-1,82 (s, 1 H), 3,40 (td, J=11,47, 2,44 Hz, 1 H), 3,53 (dd, J=11,23, 1,95 Hz, 1 H), 3,67 (dd, J=11,47, 2,20 Hz, 1 H), 3,71-3,73 (m, 1 H), 3,75 (s, 3 H), 3,77-3,79 (m, 1 H), 3,81 (s, 3 H), 4,09-4,11 (m, 1 H), 4,33 (s, 2 H), 4,50 (s, 2 H), 6,48 (dd, J=8,30, 2,44 Hz, 1 H), 6,58 (d, J=2,44, 1 H), 6,90 (br s, 1 H), 7,06 (d, J=8,30 Hz, 1 H). [M+H] calc para C21H24ClFN4O4, 451; experimental, 451.

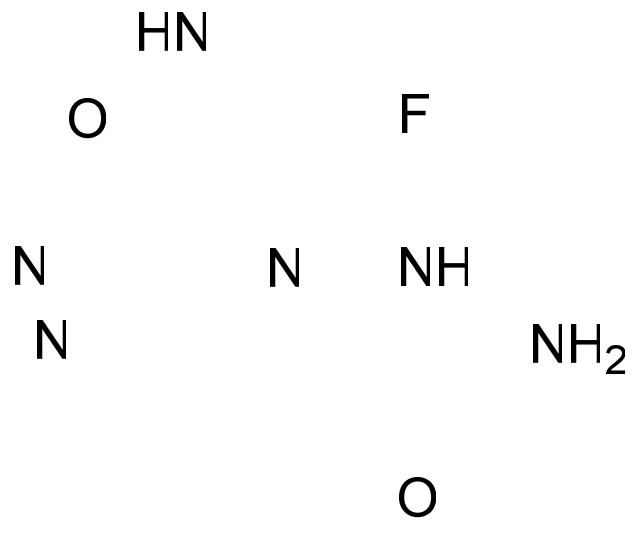
[0735] Ejemplo 92: 6-((3R,4R)-3-aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(pirazolo[1,5-a]piridin-3-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



[0736] A. 6-((3R,4R)-3-aminotetrahidro-2H-piran-4-ilamino)-2-(2,4-dimetoxibencil)-7-fluoro-4-(pirazolo[1,5-a]piridin-3-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



[0737] A un recipientes de microondas de 5 ml con una barra de agitación se

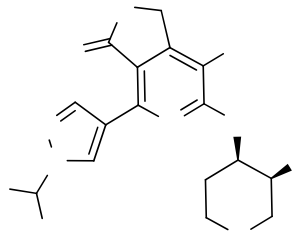


agregó cloruro de bis(trifenilfosfina)paladio (11,68 mg, 0,017 mmoles), 6-((3R,4R)-3-aminotetrahidro-2H-piran-4-ilamino)-4-cloro-2-(2,4-dimetoxibencil)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona (75 mg, 0,166 mmoles), ácido pirazolo[1,5-a]piridin-3-ilborónico (135 mg, 0,832 mmoles) en dioxano (2 ml), y NaHCO3 acuoso saturado (2 ml). La mezcla se calentó en un microondas Biotage Initiator a 120ºC durante 30 min. La mezcla se concentró y se purificó mediante HPLC preparativa para dar el compuesto del título (89 mg, 100%). 1H RMN (400 MHz, DMSO-d6) δ ppm 1,82-1,84 (m, 1 H), 2,10-2,12 (m, 1 H), 3,68-3,72 (m, 3 H), 3,75 (s, 3 H), 3,82 (s, 3 H), 3,92-3,95 (m, 1 H), 4,01-4,02 (m, 1 H), 4,39 (s, 2 H), 4,55-4,58 (m, 1 H), 4,59 (s, 2 H), 6,50 (dd, J=8,30, 1,95 Hz, 1 H), 6,60 (d, J=2,44, 1 H), 7,04-7,08 (m, 2 H), 7,16 (d, J=5,86 Hz, 1 H), 7,48-7,51 (m, 1 H), 7,93 (br s, 1 H), 8,37 (d, J=9,27 Hz, 1 H), 8,79 (d, J=6,83 Hz, 1 H), 9,36 (s, 1 H). [M+H] calc para C28H29FN6O4, 533; experimental, 533.

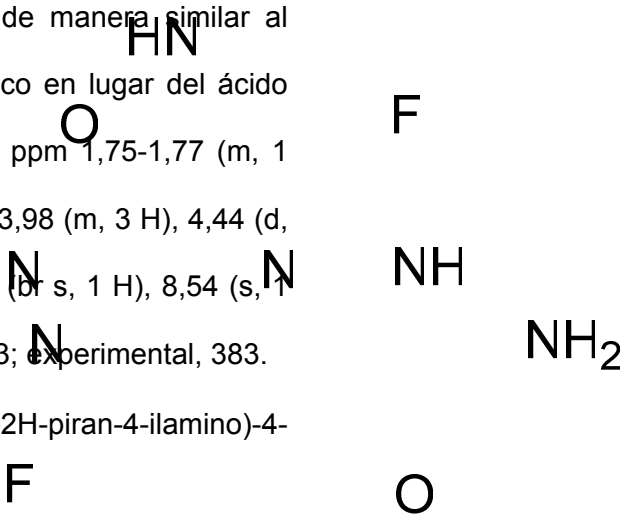
[0738] B. 6-((3R,4R)-3-aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(pirazolo[1,5-a]piridin-3-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona

[0739] A un matraz de base redonda de 25 ml con una barra de agitación se agregó 6-((3R,4R)-3-aminotetrahidro-2H-piran-4-ilamino)-2-(2,4-dimetoxibencil)-7-fluoro-4-(pirazolo[1,5-a]piridin-3-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona (85 mg, 0,160 mmoles) en TFA (5 ml). La mezcla se calentó a 60ºC durante 1,5 hora y a continuación se enfrió hasta temperatura ambiente. La mezcla se concentró y se purificó mediante HPLC preparativa para dar una sal TFA del compuesto del título en forma de un sólido de color blanco (27 mg, 44,2%). 1H RMN (400 MHz, DMSO-d6) δ ppm 1,83-1,85 (m, 1 H), 2,12-2,14 (m, 1 H), 3,65-3,73 (m, 2 H), 3,81-3,82 (m, 1 H), 3,93-3,95 (m, 1 H), 4,01-4,03 (m, 1 H), 4,43 (s, 2 H), 4,53-4,55 (m, 1 H), 7,04 (t, J=6,83 Hz, 1 H), 7,13 (d, J=4,88 Hz, 1 H), 7,49 (t, J=8,05 Hz, 1 H), 7,94 (br s, 1 H), 8,36-8,42 (m, 2 H), 8,78 (d, J=6,83 Hz, 1 H), 9,33 (s, 1 H). [M+H] calc para C19H19FN6O2, 383; experimental, 383.

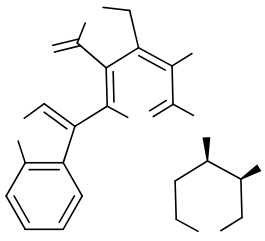
[0740] Ejemplo 93: 6-((3R,4R)-3-aminotetrahidro-2H-piran-4-ilamino)-4-(1-difluorometil)-1H-pirazol-4-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona



[0741] Una sal TFA del compuesto del título se preparó de manera similar al ejemplo 70 utilizando el ácido 1-(difluorometil)-1H-pirazol-4-ilborónico en lugar del ácido pirazolo[1,5-a]piridin-3-ilborónico 1H RMN (400 MHz, DMSO-d6) δ ppm 1,75-1,77 (m, 1 H), 2,09-2,12 (m, 1 H), 3,60-3,63 (m, 1 H), 3,76-3,77 (m, 1 H), 3,88-3,98 (m, 3 H), 4,44 (d, J=6,35 Hz, 2 H), 4,54-4,55 (m, 1 H), 7,17 (d, J=5,86 Hz, 1 H), 7,89 (br s, 1 H), 8,54 (s, 1 H), 8,58 (s, 1 H), 9,43 (s, 1 H). [M+H] calc para C16H17F3N2O2, 383; experimental, 383.

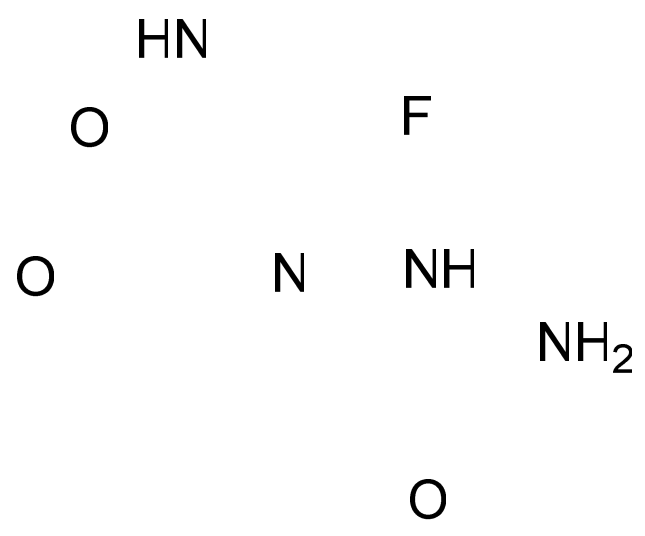


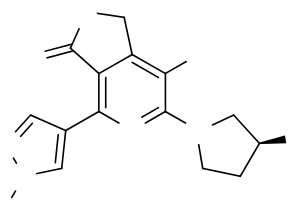
[0742] Ejemplo 94: 6-((3R,4R)-3-aminotetrahidro-2H-piran-4-ilamino)-4-(benzofuran-3-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona



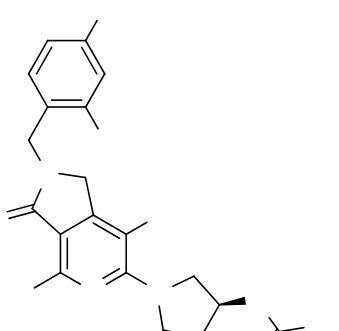
[0743] Una sal TFA del compuesto del título se preparó de manera similar al ejemplo 70 utilizando el ácido benzofuran-3-ilborónico en lugar del ácido pirazolo[1,5-a]piridin-3-ilborónico. 1H RMN (400 MHz, DMSO-d6) δ ppm 1,84-1,88 (m, 2 H), 3,68-3,73 (m, 1 H), 3,76-4,02 (m, 4 H), 4,47 (s, 2 H), 4,58-4,59 (m, 1 H), 7,25 (d, J=6,35 Hz, 1 H), 7,40-7,42 (m, 2 H), 7,67-7,69 (m, 1 H), 7,93 (br s, 1 H), 8,33 (d, J=9,76 Hz, 1 H), 8,56 (s, 1 H), 9,38 (s, 1 H). [M+H] calc para C20H19FN4O3, 383; experimental, 383.

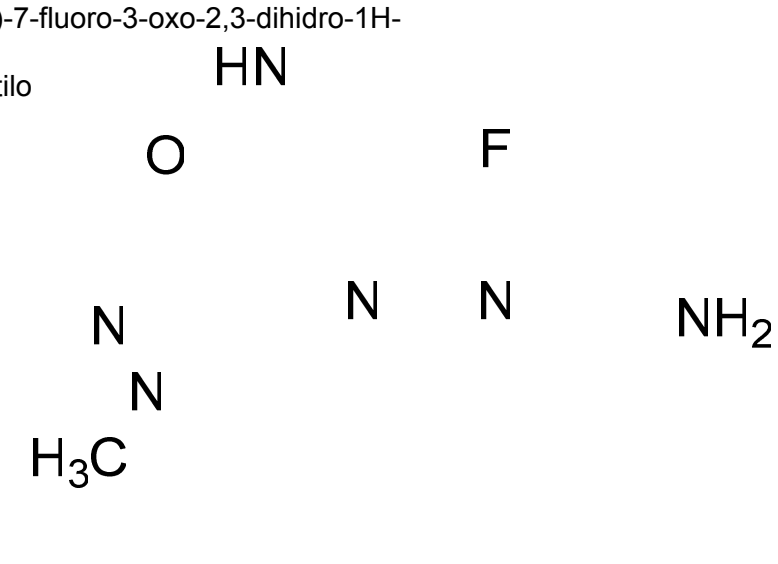
[0744] Ejemplo 95: (S)-6-(3-aminopirrolidin-1-il)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona





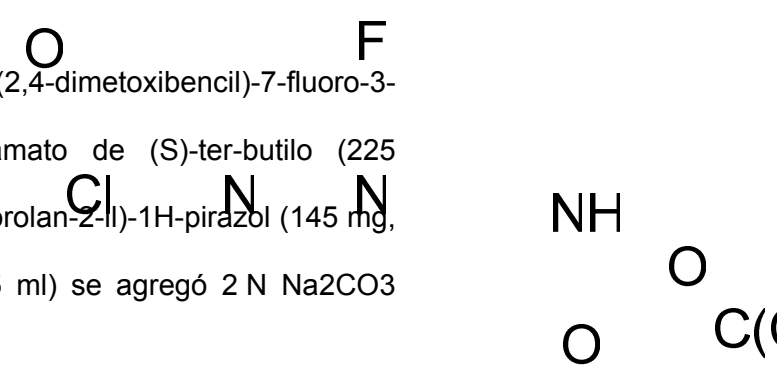
[0745] A. 1-(4-cloro-2-(2,4-dimetoxibencil)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-il)pirrolidin-3-ilcarbamato de (S)-ter-butilo





[0746] Un tubo que contiene 4,6-dicloro-2-(2,4-dimetoxibencil)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona (300 mg, 0,808 mmoles) y pirrolidin-3-ilcarbamato de (S)-ter-butilo (301 mg, 1,616 mmoles) disuelto en ACN (4 ml) se cerró y se calentó a 100ºC durante 2 días. La mezcla de reacción se concentró y se disolvió en EtOAc (20 ml) y se lavó con NaHCO3 acuoso saturado (10 ml) y salmuera (10 ml). Los extractos orgánicos se secaron sobre Na2SO4 y se evaporaron para dar un producto bruto, el cual se purificó mediante HPLC preparativa. Las fracciones puras se recolectaron y se evaporaron para dar el compuesto del título (235 mg, 55,8%). [M+H] calc para C25H30ClFN4O5, 521; experimental, 521.

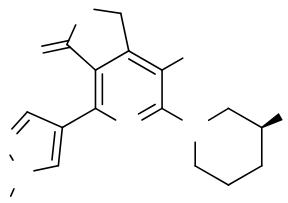
[0747] B. (S)-6-(3-aminopirrolidin-1-il)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



[0748] A un tubo de 30 ml cargado con 1-(4-cloro-2-(2,4-dimetoxibencil)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-il)pirrolidin-3-ilcarbamato de (S)-ter-butilo (225 mg, 0,43 mmoles) 1-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (145 mg, 0,695 mmoles), and PdCl2(PPh3) disperso en dioxano (5 ml) se agregó 2 N Na2CO3

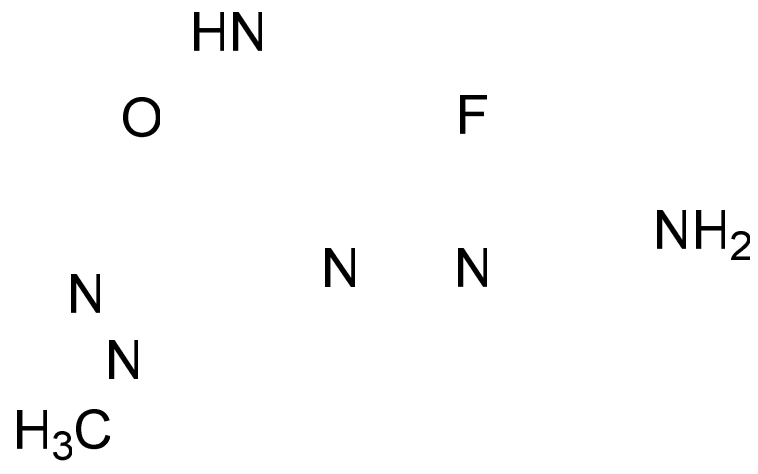
(0,5 ml). El tubo se cerró y la mezcla de reacción se calentó a 85ºC durante 4 horas. La mezcla se diluyó con agua (5 ml) y se extrajo en EtOAc (2 x 30 ml). La capa orgánica se secó sobre Na2SO4 y se evaporó para dar un residuo, el cual se trató con TFA (1 ml) y se calentó a 85ºC durante 1 hora para eliminar los grupos protectores. Se evaporó TFA y la mezcla se disolvió en DMSO (8 ml) y se purificó mediante HPLC preparativa. Las fracciones puras se recolectaron, se evaporaron hasta un volumen mínimo, y se liofilizaron para dar una sal TFA del compuesto del título en forma de un sólido de color amarillo pálido (46 mg, 27,2%). 1H RMN (400 MHz, DMSO-d6) δ ppm 2,05 - 2,39 (m, 3 H), 3,75 - 4,04 (m, 6 H), 3,89 (s, 3 H), 4,38 (s, 2 H), 8,02 (br s, 2 H), 8,26 (d, J=0,51 Hz, 1 H), 8,39 (s, 1 H), 8,85 (s, 1 H);). [M+H] calc para C15H17FN6O, 317; experimental, 317.

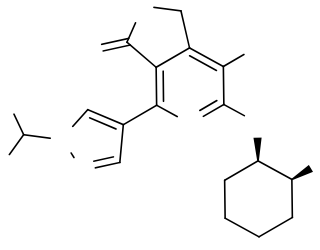
[0749] Ejemplo 96: (S)-6-(3-aminopiperidin-1-il)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



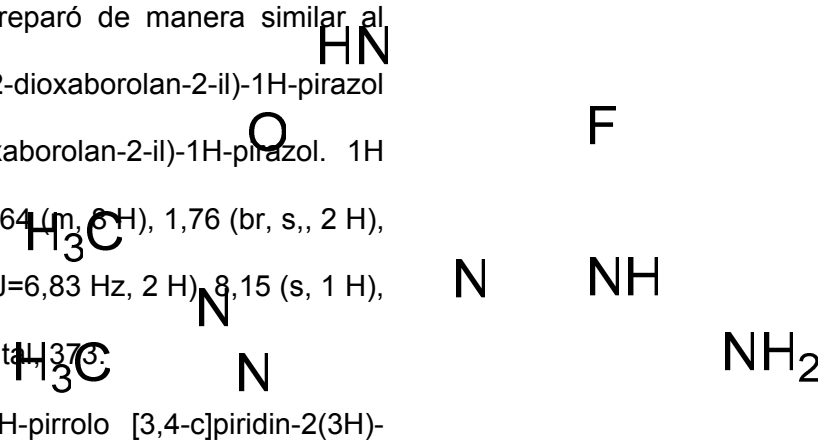
[0750] Una sal TFA del compuesto del título se preparó de manera similar al ejemplo 95 utilizando piperidin-3-ilcarbamato de (S)-ter-butilo en lugar de pirrolidin-3-ilcarbamato de (S)-ter-butilo. 1H RMN (400 MHz, DMSO-d6) δ ppm 1,61 (m, 2 H), 1,83 (d, J=8,34 Hz, 1 H), 2,03 (br s, 1 H), 2,53 - 2,55 (m, 2 H), 3,16 - 3,35 (m, 3 H), 3,90 (s, 3 H), 3,92 (m, 1 H), 4,33 (m, 1H), 4,39 (s, 2 H), 8,04 (br s, 3 H), 8,36 (s, 1 H), 8,51 (s, 1 H), 8,90 (s, 1 H). [M+H] calc para C16H19FN6O, 331; experimental, 331.

[0751] Ejemplo 97: 6-((1R,2S)-2-aminociclohexilamino)-7-fluoro-4-(1-isopropil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

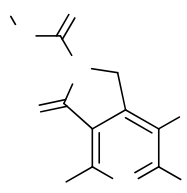




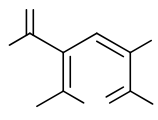
[0752] Una sal TFA del compuesto del título se preparó de manera similar al ejemplo 62 utilizando 1-isopropil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol en lugar de 1-(difluorometil)-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol. 1H RMN (500 MHz, CDCl3) δ ppm 1,14 - 1,33 (m, 6 H), 1,47 - 1,64 (m, 6 H), 1,76 (br, s,, 2 H), 1,94 - 2,01 (m, 2 H), 3,86 (br, s,, 1 H), 4,36 (s, 2 H), 4,53 (d, J=6,83 Hz, 2 H), 8,15 (s, 1 H), 8,88 (s, 1 H). [M+H] calc para C19H25FN6O, 373; experimental 373.



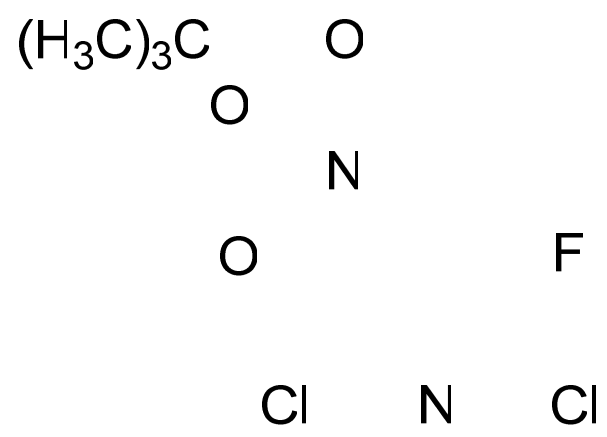
[0753] Preparación 47: 4,6-Dicloro-7-fluoro-3-oxo-1H-pirrolo [3,4-c]piridin-2(3H)-carboxilato de ter-butilo

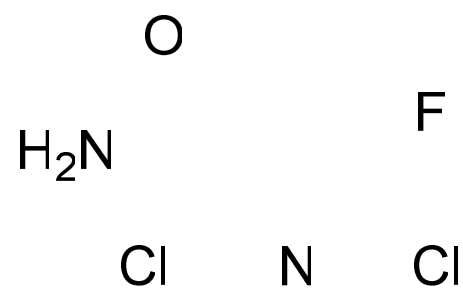


[0754] A. 2,6-Dicloro-5-fluoronicotinamida



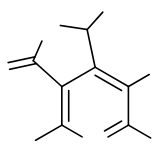
[0755] Un matraz de fondo redondo, de tres bocas, de 12 L, equipado con agitador superior, condensador de reflujo, y entrada/salida de N2, se cargó con 2,6-dicloro-5-fluoronicotinonitrilo (2,0 kg, 1,0 eq). Se añadió ácido sulfúrico concentrado (4,93 L) y la mezcla se agitó a temperatura ambiente hasta que la mayoría de los sólidos de color marrón se habían disuelto. A continuación, la mezcla de reacción se agitó a 65 °C durante 1 h. La solución de color marrón oscuro se enfrió a una temperatura <10 °C usando un baño de hielo. La mezcla de reacción se añadió a un matraz de fondo redondo de 50 L,



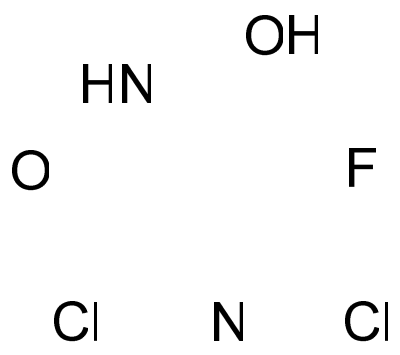


que contenía agua desionizada (24,7 L) que había sido enfriada a una temperatura <10 °C, utilizando una bomba peristáltica. La mezcla de reacción se añadió al agua enfriada durante un período de 2,3 h, lo que mantuvo la temperatura interna de la mezcla por debajo de 21 °C. La suspensión resultante se filtró a través de un embudo Buchner equipado con un papel de filtro Sharkskin. El matraz de fondo redondo de 50 L se enjuagó con agua (3 x 4 L) y los enjuagues se utilizaron para lavar la torta del filtro. La torta del filtro se acondicionó durante 50 min, se transfirió a una bandeja de secado, y se secó a alto vacío a 40-50 °C durante 24 horas y después a 20-25 °C durante 18 h para dar el compuesto del título como un sólido de color beige (896,4 g, 82%). 1H RMN (500 MHz, DMSO-d6) δ ppm 7,94 (s, 1 H), 8,10 (s, 1 H), 8,24 (d, 1 H). [M+H] calculado para C6H3Cl2FN2O, 209; experimental, 209.

[0756] B. 4,6-Dicloro-7-fluoro-1-hidroxi-1H-pirrolo[3,4-c]piridin-3(2H)-ona

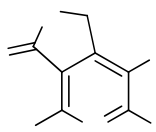


[0757] Un matraz de fondo redondo, de varias bocas, de 22 L, equipado con agitador superior, sonda de temperatura, y entrada/salida de N2, se cargó con LiHMDS (10,65 L, 2,5 eq) por presión de N2. La solución de color naranja se enfrió a <0 °C usando un baño de hielo/salmuera. Otro matraz de fondo redondo de 12 L se cargó secuencialmente con 2,6-dicloro-5-fluoronicotinamida (890 g, 1,0 eq), THF anhidro (6,0 L), y DMF anhidro (1,0 L, 3,0 eq). La solución resultante se añadió a la solución de LiHMDS a través de una bomba peristáltica durante un período de 1 h, lo que mantuvo la temperatura interna por debajo de 5 °C. El matraz de 12 L se enjuagó con THF (1,6 L), y el enjuague se transfirió a la mezcla de reacción. La mezcla se agitó a una temperatura <5 °C durante 1 h, y la reacción se añadió a una solución pre-enfriada de HCl 2N acuoso a través de una bomba peristáltica a una velocidad que mantenía la temperatura de la mezcla por debajo de 22 °C. Luego del enfriamiento, se añadió IPAc (14 L) y la mezcla se

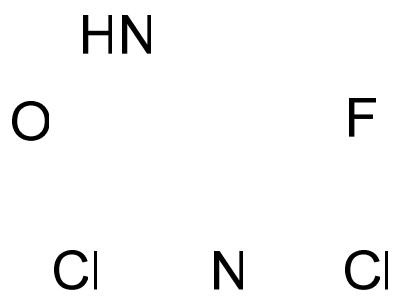


agitó durante 10 min. La mezcla bifásica se separó y la capa orgánica se almacenó en una bombona a temperatura ambiente durante una noche. La capa orgánica se lavó posteriormente con agua (8,9 L) y se concentró bajo presión reducida hasta un volumen de aproximadamente 4,5 L. La destilación se continuó el día siguiente. Se añadió acetato de isopropilo (16 L) a la suspensión y la destilación se continuó hasta alrededor de 4,5 L de material remanente. La suspensión de color blanquecino se transfirió a un matraz de fondo redondo de varias bocas, de 50 L al que se cargó heptano (18 L) a través de una bomba peristáltica durante un período de 45 min. La suspensión resultante se agitó a temperatura ambiente durante una noche y luego se filtró a través de un embudo Buchner con un papel de filtro Sharkskin. La torta del filtro se lavó con heptano (2 x 4,5 L) y después se secó a alto vacío a temperatura ambiente durante 24 h para dar el compuesto del título (913.0 g,90%). 1H RMN (300 MHz, DMSO-d6) δ ppm 6,11 (dd, J=9,3 Hz, 1,5 Hz, 1 H), 6,95 (d, J=9,3 Hz, 1 H), 9,54 (s, 1 H). [M+H] calculado para C7H3Cl2FN2O2, 237; experimental, 237.

[0758] C. 4,6-Dicloro-7-fluoro-1H-pirrolo[3,4-c]piridin-3-(2H)-ona



[0759] Un matraz de fondo redondo de tres bocas, de 22 L, equipado con agitador superior, condensador de reflujo, y entrada/salida de N2, y con todas sus partes recubiertas con vidrio o PTFE, se cargó secuencialmente con 4,6-dicloro-7-fluoro-1-hidroxi-1H-pirrolo[3,4-c]piridin-3(2H)-ona (908 g), DCM (4,55 L), y TFA (3,46 L, 11,76 eq). Se inició la agitación y se añadió Et3SiH (3,05 L, 4,97 eq). La mezcla turbia se calentó a reflujo, lo que resultó en una solución clara que se agitó en condiciones de reflujo durante 24 h. La mezcla se enfrió a temperatura ambiente y se agitó durante una noche. La solución de color naranja se enfrió a <10 °C usando un baño de hielo. Se añadió metil ter-butil éter (14,0 L) a través de una bomba peristáltica dentro de un período de 1 h. La

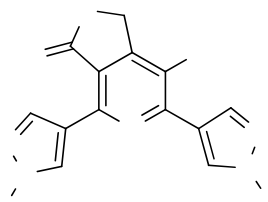


suspensión resultante se agitó a <10 °C durante 1 y después se filtró a través de un embudo de vidrio fritado grueso. La torta del filtro se lavó con MTBE (2 x 4 L). El sólido se secó a alto vacío a temperatura ambiente durante 19 h para dar el compuesto del título ((802 g, 94%). 1H RMN (500 MHz, DMSO-d6) δ ppm 4,55 (s, 2 H), 9,15 (s, 1 H). [M+H] calculado para C7H3Cl2FN2O, 221; experimental, 221.

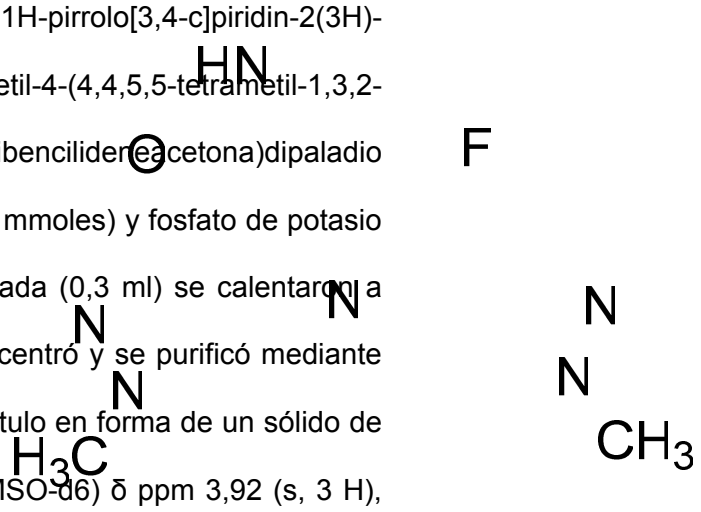
[0760] D. 4,6-Dicloro-7-fluoro-3-oxo-1H-pirrolo[3,4-c]piridin-2(3H)-carboxilato de ter-butilo

[0761] Un matraz de fondo redondo de tres bocas, de 12 L, se cargó con 4,6-dicloro-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona (745,0 g, 1,0 eq), DCM (3,0 L), Et3N (940 ml, 2,0 eq) y DMAP (20,59 g, 0,05 eq). En un matraz de 2 L separado que contenía carbonato de di-ter-butilo (882,8 g, 1,2 eq) se añadió DCM (0,75 L), y la solución clara resultante se añadió gota a gota a la mezcla de reacción durante un período de 20 min a través de una bomba peristáltica. El matraz de 2 L se enjuagó con DCM (0,75 L) y el enjuague se añadió a la mezcla de reacción, que se agitó a temperatura ambiente durante 28 min. Se añadió etanol (7,5 L) y la mezcla se concentró a presión reducida hasta un volumen de aproximadamente 4,5 L. Se añadió un segundo volumen de EtOH (7,5 L) a la mezcla y la destilación se continuó hasta alrededor de 4,5 L de material remanente. La suspensión resultante se agitó a 15-20 °C durante 10 min y se filtró luego a través de un embudo Buchner. La torta del filtro se lavó con EtOH (3 x 1,5 L) y se secó a alto vacío a temperatura ambiente durante una noche para dar el compuesto del título como un sólido de color rosado (873 g, rendimiento 81%). 1H (300 MHz, CDCl3) δ ppm 1,61 (s, 9 H), 4,82 (d, J=0,9 Hz, 2 H), 19F RMN (282 MHz, CDCl3) δ ppm -128,36. [M-H] calculado para C12H11Cl2FN2O3, 319; experimental, 319.

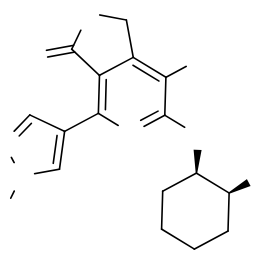
[0762] Ejemplo 98: 7-fluoro-4,6-bis(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



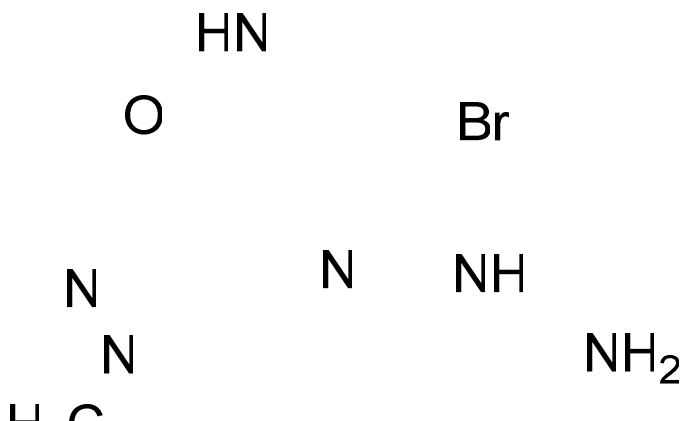
[0763] Una mezcla de 4,6-dicloro-7-fluoro-3-oxo-1H-pirrolo[3,4-c]piridin-2(3H)-carboxilato de ter-butilo (30,0 mg, 0,093 mmoles), 1-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (19,4 mg, 0,093 mmoles), tris(dibencilideneacetona)dipaladio (3,42 mg, 0,003 mmoles), triciclohexilfosfina (3,90 mg, 0,001 mmoles) y fosfato de potasio (35,7 mg, 0,168 mmoles) en dioxano (1 ml) y agua deionizada (0,3 ml) se calentaron a 120ºC en un microondas durante 20 min. La mezcla se concentró y se purificó mediante HPLC preparativa para dar una sal TFA del compuesto del título en forma de un sólido de color amarillo pálido (4,1 mg, 14%). 1H RMN (400 MHz, DMSO-d6) δ ppm 3,92 (s, 3 H), 3,96 (s, 3 H), 4,53 (s, 2 H), 8,17 (s, 1 H), 8,49 (s, 1 H), 8,50 (s, 1 H), 8,81 (s, 1 H), 8,92 (s, 1 H). [M+H] calc para C15H13FN6O, 313; experimental, 313.



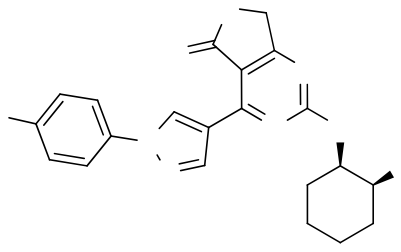
[0764] Ejemplo 99: 6-((1R,2S)-2-aminociclohexilamino)-7-bromo-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;



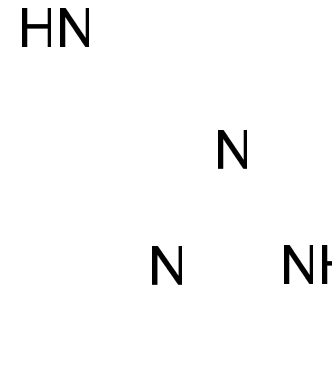
[0765] Una solución de (1S,2R)-2-(7-bromo-4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo (10 mg, 0,020 mmoles) en HCl-dioxano (999 µL, 4,00 mmoles) se agitó a temperatura ambiente durante 2 horas. La mezcla se concentró hasta un residuo, se diluyó con Et2O (3 ml), y se sonicó para dar un precipitado de color blanco, el cual se filtró y se secó durante toda la noche en un liofilizador para dar una sal HCl del compuesto del título en forma de un sólido de color blanco (1,8 mg, 21%). [M+H] calc para C17H21BrN6O, 406; experimental, 406.



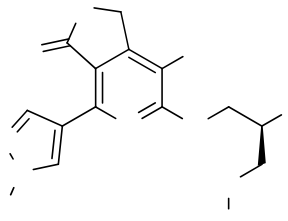
[0766] Ejemplo 100: 2-((1R,2S)-2-aminociclohexilamino)-4-(1-(4-fluorofenil)-1H-pirazol-4-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona



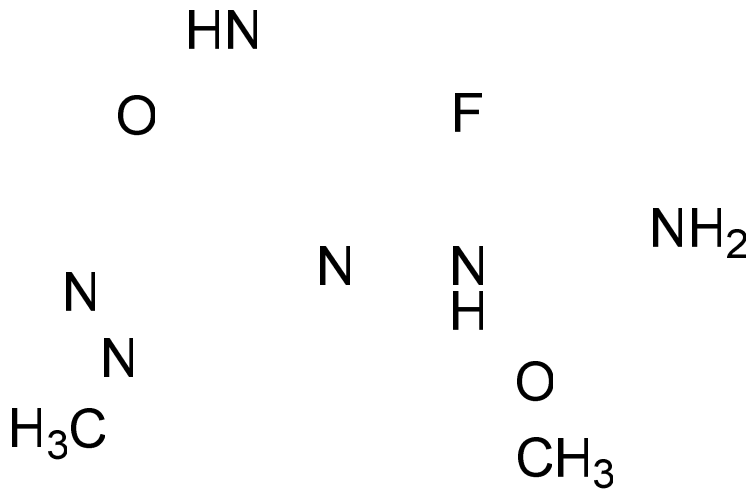
[0767] Una sal TFA del título se preparó de manera similar al ejemplo 14 utilizando ácido 1-(4-fluorofenil)-1H-pirazol-4-ilborónico en lugar de 1-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol. 1H RMN (500 MHz, DMSO-d6) δ ppm 1,43 (br s, 2 H), 1,55 - 1,98 (m, 6 H), 4,10 - 4,35 (m, 2 H), 4,34 - 4,70 (m, 1 H), 7,43 (t, J=8,79 Hz, 2 H), 7,65 (d, J=7,81 Hz, 1 H), 7,68 - 7,83 (m, 3 H), 7,87 (br s, 2 H), 8,39 (s, 1 H), 8,58 - 9,06 (m, 1 H), 9,62 - 9,86 (m, 1 H). [M+H] calc para C21H22FN7O, 408; experimental, 408.



[0768] Ejemplo 101: (R)-6-(2-amino-3-metoxipropilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona

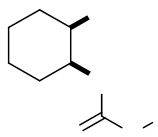


[0769] A un matraz de base redonda de 20 ml se agregó 1-metoxi-3-(4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)propan-2-ilcarbamato de (R)-ter-butilo (19,7 mg, 0,047 mmoles) y SELECTFLUOR® (21,78 mg, 0,061 mmoles) en DCM (473 µL) y MeOH (473 µL). La solución de color amarillo resultante se agitó a temperatura ambiente durante 3 horas y se concentró hasta un residuo, el cual se disolvió en HCl 4N-dioxano (2 ml) y se agitó a temperatura ambiente durante 2 horas. La mezcla se concentró, se disolvió en DMF (1 ml) y se purificó mediante HPLC preparativa para dar una sal TFA del compuesto del título. [M+H] calc para C15H19FN6O2, 335; experimental,

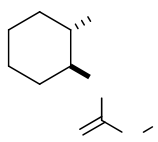


335.

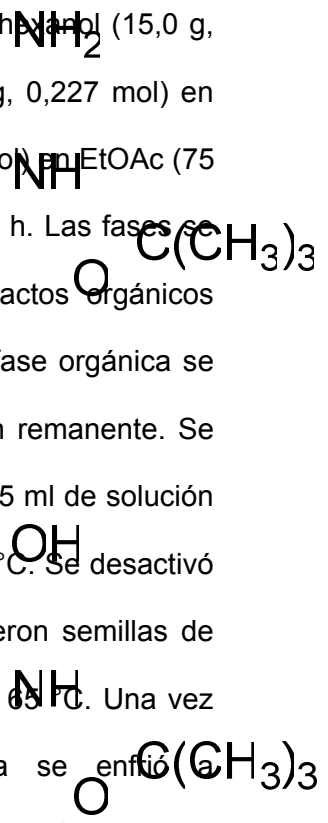
[0770] Preparación 48: cis-2-Aminociclohexilcarbamato de ter-butilo



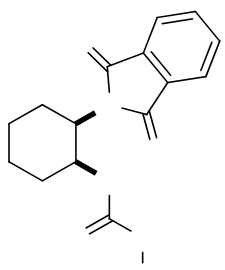
[0771] A. trans-2-Hidroxiciclohexilcarbamato de ter-butilo



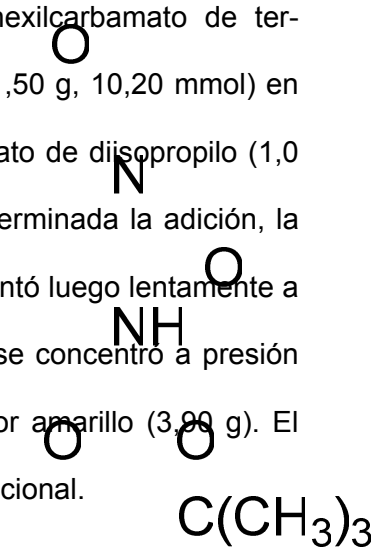
[0772] A una suspensión agitada de clorhidrato de trans-2-aminohexanol (15,0 g, 98,92 mmol) en EtOAc (75 ml) se añadió una solución de NaOH (9,1 g, 0,227 mol) en agua (150 ml). Se añadió una solución de di-ter-butilo (25,9 g, 118,70 mmol) en EtOAc (75 ml) en una porción y la mezcla se calentó a 45 °C y se agitó durante 16 h. Las fases se separaron y la fase acuosa se extrajo con EtOAc (60 ml). Los extractos orgánicos combinados se lavaron con agua (45 ml) y se separaron las fases. La fase orgánica se destiló a presión atmosférica hasta aproximadamente 75 ml de solución remanente. Se añadió heptano (90 ml) y la solución se destiló hasta aproximadamente 75 ml de solución remanente. Se añadió heptano (150 ml) y la mezcla se calentó a 98-100 °C. Se desactivó el calor y la mezcla se dejó enfriar a temperatura ambiente. Se añadieron semillas de producto puro a 70 °C y se produjo la cristalización a aproximadamente 65 °C. Una vez que la suspensión alcanzó la temperatura ambiente, la mezcla se enfrió a aproximadamente 5 °C y se agitó durante 30 min. Los sólidos se filtraron, se lavaron con heptano (2 x 45 ml), y se secaron para dar el compuesto del título como un sólido cristalino de color blanco (19,6 g, 92%).



[0773] B. cis-2-(1,3-Dioxoisoindolin-2-il)ciclohexilcarbamato de ter-butilo



[0774] A una suspensión agitada de trans-2-hidroxiciclohexilcarbamato de ter-butilo (1,00 g, 4,64 mmol), PPh3 (1,34 g, 5,10 mmol) y ftalimida (1,50 g, 10,20 mmol) en una mezcla 2:1 de tolueno y THF (15 ml) se añadió azodicarboxilato de diisopropilo (1,0 ml, 5,10 mmol) gota a gota durante un período de 1 h. Una vez terminada la adición, la mezcla se agitó a aproximadamente 0 °C durante 7 horas y se calentó luego lentamente a 7 °C durante un período de 14 h. La mezcla se filtró y el filtrado se concentró a presión reducida para dar el compuesto del título como un aceite de color amarillo (3,90 g). El producto en bruto se utilizó en la siguiente etapa sin purificación adicional.

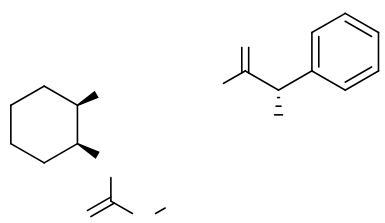


[0775] C. cis-2-Aminociclohexilcarbamato de ter-butilo

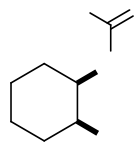
[0776] Se disolvió cis-2-(1,3-dioxoisoindolin-2-il) ciclohexilcarbamato de ter-butilo (3,90g) en tolueno (20 ml) y se cargó a un matraz de fondo redondo. Se añadió hidrato de hidrazina (0,70 ml) y la mezcla se calentó a 80 °C durante 2 h después de lo cual el análisis por TLC indicó que la reacción era completa. La reacción se enfrió a temperatura ambiente y los sólidos se filtraron y se lavaron con tolueno (2 x 5 ml). Los filtrados se lavaron con NaOH acuoso 2 N (10 ml) y se separaron las fases. La fase acuosa se extrajo con tolueno (2 x 5 ml) y los extractos orgánicos combinados se lavaron con HOAc acuoso al 10% (2 x 10 ml). Los lavados acuosos combinados se alcalinizaron con NaOH acuoso 2 N (13 ml). El producto se extrajo con IPAc (2 x 10 ml) y los extractos orgánicos combinados se lavaron con agua (5 ml). La fase orgánica se concentró a sequedad para dar 0,78 g de producto en bruto. Se re-disolvió el aceite en IPAc (12 ml), se calentó a aproximadamente 75 °C, y se añadió ácido maleico (423 mg). La precipitación de los sólidos se produjo inmediatamente y la mezcla espesa se diluyó con IPAc (5 ml). La

suspensión se enfrió a temperatura ambiente y se dejó reposar durante 20 min. Los sólidos se filtraron, se lavaron con IPAc (10 ml), y se secaron para dar una sal de ácido maleico del compuesto del título como un sólido cristalino de color blanco (730 mg, 44%). 1H RMN (300 MHz, DMSO-d6) δ ppm 1,34-1,42 (m, 2 H), 1,50 (s, 9 H), 1,50-1,64 (m, 6 H), 3,22 (m, 1 H), 3,83 (br s, 1 H), 6,02 (s, 2 H), 6,86 (d, J=7,5 Hz, 1 H), 7,68 (br s, 3 H).

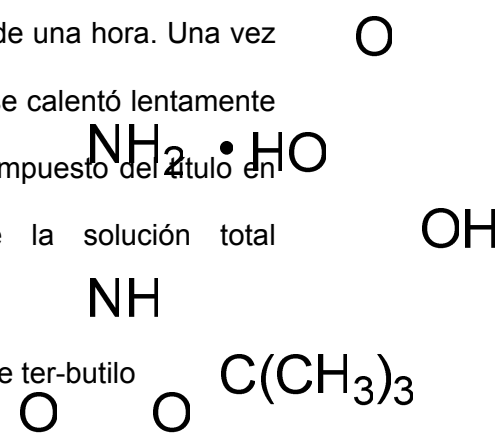
[0777] Preparación 49: (1S,2R)-2-Aminociclohexilcarbamato de ter-butilo, sal de ácido (S)-mandélico



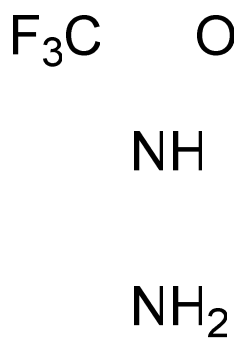
[0778] A. cis-N-(2-aminociclohexil)-2,2,2-trifluoroacetamida

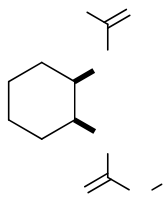


[0779] Se cargó cis-ciclohexano-1,2-diamina (5,00 g, 43,9 mmol, 1,00 eq) a un matraz de fondo redondo, de tres bocas, de 250 ml, equipado con un agitador superior y un termopar. Se añadió etanol (50 ml) y la solución se enfrió a <0 °C usando un baño de hielo-salmuera. Se añadió una solución de trifluoroacetato de etilo (6,23 g, 1,00 eq) en EtOH (25 ml) a través de una bomba de jeringa durante un período de una hora. Una vez terminada la adición, se retiró el baño de enfriamiento y la solución se calentó lentamente a temperatura ambiente y se agitó durante 3,5 horas para dar el compuesto del título en EtOH. La mitad (41 ml, aproximadamente 21,9 mmol) de la solución total (aproximadamente 82 ml) se llevó a la etapa siguiente.

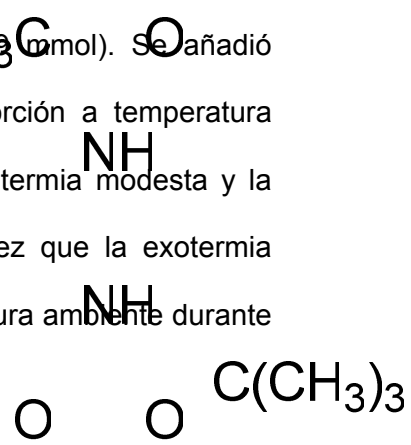


[0780] B. cis-2-(2,2,2-Trifluoracetamido)ciclohexilcarbamato de ter-butilo

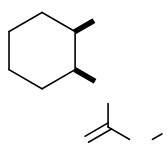




[0781] Se añadió trietilamina (3,1 ml, 22,05 mmoles, 1,0 eq) a una solución de cis-N-(2-aminociclohexil)-2,2,2-trifluoroacetamida en EtOH (41 ml, 21,9 mmol). Se añadió carbonato de di-ter-butilo (5,74 g, 26,3 mmol, 1,2 eq) en una porción a temperatura ambiente. Se usó un baño de hielo se usa para controlar una exotermia modesta y la temperatura interna de la reacción se mantuvo a <25 °C. Una vez que la exotermia disminuyó, se retiró el baño de hielo, y la mezcla se agitó a temperatura ambiente durante 16 h para dar el compuesto del título en EtOH.



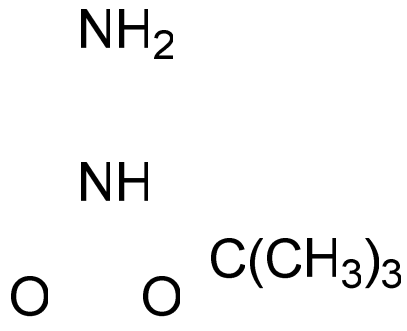
[0782] C. cis-2-Aminociclohexilcarbamato de ter-butilo



[0783] Se añadió hidróxido de sodio acuoso (50%, 10 g, 0,125 moles, 5,7 eq) a una solución de cis-2-(2,2,2-trifluoracetamido) ciclohexilcarbamato de ter-butilo en EtOH (aproximadamente 21,9 mmol). Se observó exotermia de 20 a 37 °C y se formó una suspensión blanca y fina. La mezcla de reacción se agitó durante una noche, durante la cual precipitaron más sólidos de la solución. El volumen de disolvente se concentró a presión reducida a aproximadamente 10 a 15 ml y luego se añadieron IPAc (40 ml) y agua (30 ml) para formar una solución bifásica limpia. Luego de la separación de fases la fase acuosa se extrajo con IPAc (15 ml) y los extractos orgánicos se combinaron y se lavaron con agua (15 ml) para dar el compuesto del título como un producto racémico en bruto en IPAc.

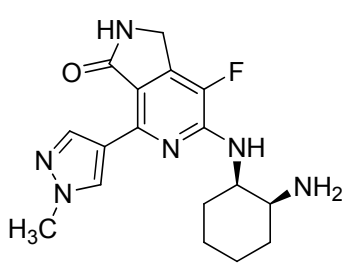
[0784] D. (1S,2R)-2-Aminociclohexilcarbamato de ter-butilo

[0785] Se cargó cis-2-aminociclohexilcarbamato de ter-butilo en bruto en IPAc (70

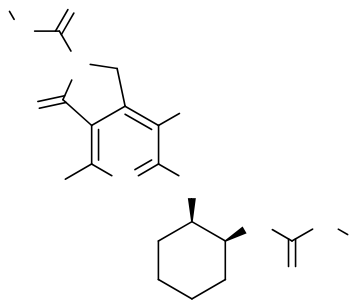


ml, aproximadamente 21,9 milimoles) a un matraz de fondo redondo, de tres bocas, de 100 ml, equipado con una unidad de paso corto, termopar, y una barra de agitación. Se aplicó vacío y la solución se calentó y se destiló el volumen de disolvente a 43-44 °C hasta que el volumen alcanzó aproximadamente 45 ml (10 volúmenes en relación con el rendimiento teórico en bruto del producto racémico). El análisis por Karl Fisher indicó un contenido de agua de 4,9%. Se liberó el vacío y la solución se calentó a 60 °C. La solución se enfrió luego lentamente a temperatura ambiente y se añadieron semillas de (1S,2R)-2-aminociclohexilcarbamato de ter-butilo, sal de ácido (S)-mandélico (de experimentos de resolución a pequeña escala) a intervalos de 5 °C. Todas las semillas se disolvieron durante el enfriamiento, pero permanecieron cuando se llegó a la temperatura ambiente. La solución se enfrió en un baño de hielo-salmuera (-15 °C) durante 30 min. La solución se recalentó, y luego de la adición de IPAc (40 ml), se redestiló bajo vacío a 45-46 °C a aproximadamente 45 ml de volumen. La reacción se enfrió a temperatura ambiente y se agitó durante una noche. Los sólidos se filtraron, se lavaron con IPAc (2 x 12,5 ml) y se secaron para dar una sal de ácido (S)-mandélico del compuesto del título como un sólido de color blanco (2,21 g, 28%, 98% ee). 1H RMN (500 MHz, DMSO-d6) δ ppm 1,24-1,30 (m, 2 H), 1,35 (s, 9 H), 1,35-1,64 (m, 6 H), 3,15 (m, 1 H), 3,71 (br s, 1 H), 4,55 (s, 1 H), 6,85-7,11 (br s, 3 H), 6,95 (br d, 1 H, J=7,5 Hz), 7,15 (m 1 H), 7,23 (m, 2 H), 7,37 (m, 2 H).

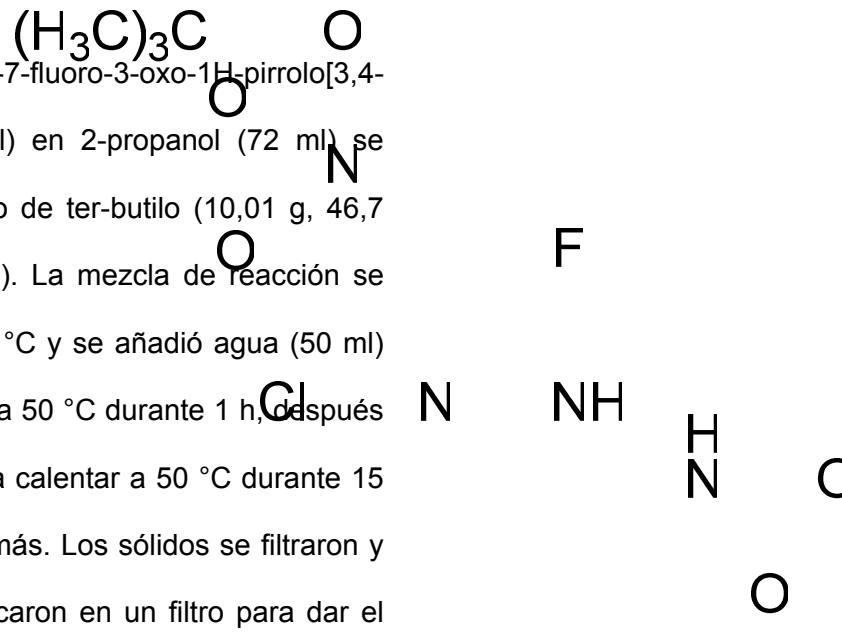
[0786] Ejemplo 102: 6-((1R,2S)-2-Aminociclohexilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona (sal de HCl)



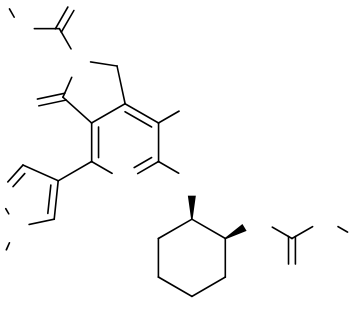
[0787] A. 6-((1R,2S)-2-(ter-butoxicarbonilamino)ciclohexilamino)-4-cloro-7-fluoro-3-oxo-1H-pirrolo[3,4-c]piridin-2(3H)-carboxilato de ter-butilo



[0788] A una suspensión agitada de 4,6-dicloro-7-fluoro-3-oxo-1H-pirrolo[3,4-c]piridin-2(3H)-carboxilato de ter-butilo (12,5 g, 38,9 mmol) en 2-propanol (72 ml) se añadió una solución de (1S,2R)-2-aminociclohexilcarbamato de ter-butilo (10,01 g, 46,7 mmol) en DMSO (12,00 ml) y DIPEA (8,84 ml, 50,6 mmol). La mezcla de reacción se calentó a 90 °C durante 16 h en cuyo punto se enfrió a 50 °C y se añadió agua (50 ml) gota a gota para dar un precipitado. La suspensión se agitó a 50 °C durante 1 h, después se enfrió a temperatura ambiente. La suspensión se volvió a calentar a 50 °C durante 15 min y se enfrió a temperatura ambiente durante dos ciclos más. Los sólidos se filtraron y posteriormente se lavaron con isopropanol (20 ml) y se secaron en un filtro para dar el compuesto del título (9,538 g, 49%). 1H RMN (400 MHz, DMSO-d6) δ ppm 1,18 - 1,76 (br m, 26 H), 3,83 (br s, 1 H), 4,12 (br s, 1 H), 4,72 (s, 2 H), 6,71 (d, J=7,58 Hz, 1 H), 7,22 (d, J=6,32 Hz, 1 H).



[0789] B. 6-((1R,2S)-2-(ter-Butoxicarbonilamino)ciclohexilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-3-oxo-1H-pirrolo[3,4-c]piridin-2(3H)-carboxilato de ter-butilo



[0790] Un matraz de fondo redondo de dos bocas, de 50 ml, se cargó con 6-((1R,2S)-2-(ter-butoxicarbonilamino)ciclohexilamino)-4-cloro-7-fluoro-3-oxo-1H-pirrolo[3,4-

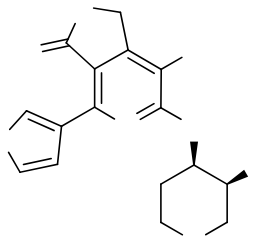
c]piridin-2(3H)-carboxilato de ter-butilo (520 mg, 1,042 mmol), 1-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (282 mg, 1,355 mmol), carbonato de potasio (504 mg, 3,65 mmol) y DMA (3 ml). El matraz de reacción se desgasificó seguido por la adición de cloruro de 1,1-bis(di-ter-butilfosfino)ferroceno paladio (21 mg, 0,032 mmol). Bajo una atmósfera de N2, la mezcla de reacción se calentó en un baño de aceite a 80 °C durante 2,5 horas y después se dejó enfriar a temperatura ambiente. En un matraz de recuperación de 50 ml separado se añadió H2O desionizada (12 ml) y el recipiente se enfrió en un baño de hielo/agua. Cuando la temperatura interna del agua llegó a 2 °C, la mezcla de reacción se transfirió al matraz de recuperación a una velocidad que mantenía la temperatura interna por debajo de 10 °C. Después de la adición, el recipiente de reacción se enjuagó con DMA (1 ml). El enjuague se añadió al matraz de recuperación y la suspensión acuosa resultante se agitó en un baño de hielo durante 10 min y después se dejó calentar a temperatura ambiente con agitación. Cuando la temperatura interna alcanzó 22 °C, la mezcla se filtró. La torta del filtro se enjuagó con H2O desionizada (2 x 5 ml) y se secó al aire bajo succión. Los sólidos se re-suspendieron en ácido acético glacial (3 ml) y se agitaron a temperatura ambiente durante 1 h. Se añadió isopropanol (1 ml) y la mezcla se agitó a temperatura ambiente. Se añadió agua desionizada (3,4 ml) para inducir la cristalización. Se produjo la precipitación, pero algunos sólidos eran pegajosos, por lo que la mezcla se calentó en un baño de aceite a 40 °C, con agitación, durante 20 min. La mezcla se dejó enfriar a temperatura ambiente con agitación y luego se filtró. La torta del filtro se lavó con una mezcla de 03:03:01 de HOAc/H2O/IPA (2,1 ml), se secó al aire brevemente bajo succión, y luego se secó en una estufa de vacío a 60 °C para dar el compuesto del título como un sólido de color tostado (352 mg, 62%). 1H RMN (400 MHz, DMSO-d6) δ ppm 1,35 (s, 9 H), 1,53 (s, 9 H), 1,65 (m, 3 H), 1,76 (m, 3 H), 3,94 (s, 3 H), 4,03 (br s, 1 H), 4,38 (br s, 1 H), 4,67 (s, 2 H), 5,12 (br s, 1 H), 5,77 (br s, 1 H), 8,25 (br s, 1 H), 8,96 (br s, 1 H). [M+H] calculado para C27H37FN6O5, 545; experimental, 545.

[0791] C. 6-((1R,2S)-2-Aminociclohexilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-

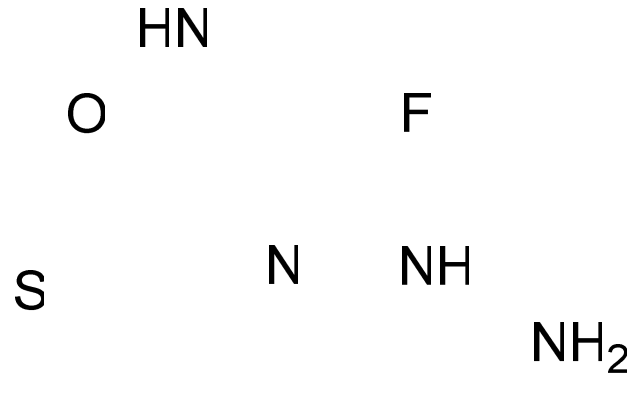
1H-pirrolo[3,4-c]piridin-3(2H)-ona

[0792] Una suspensión de 6-((1R,2S)-2-(ter-butoxicarbonilamino)ciclohexilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-3-oxo-1H-pirrolo[3,4-c]piridin-2(3H)-carboxilato de ter-butilo (2,148 g, 3,94 mmol) en IPA (21 ml) se calentó a 70 °C, en cuyo punto se añadió HCl acuoso 2M (9,86 ml, 19,72 mmol). La mezcla de reacción se calentó a 65 °C durante aproximadamente 3 horas, se enfrió en un baño de agua con hielo durante 1 h, y luego se filtró. Los sólidos se lavaron con IPA frío (15 ml) y después se secaron en un horno de vacío a 50 °C durante una noche para dar una sal de HCl del compuesto del título como un sólido de color amarillo claro (1,404 g, 3,37 mmol) con 1,5 a 2 eq de agua asociada (por 1H RMN). 1H RMN (400 MHz, DMSO-d6) δ ppm 1,46 (d, J=7,07 Hz, 2 H), 1,57 - 1,76 (m, 3 H), 1,76 - 2,04 (m, 3 H), 3,31 (s, 3 H), 3,67 (br s, 1 H), 3,90 (s, 3 H), 4,39 (d, J=2,53 Hz, 2 H), 4,41 - 4,60 (m, 1 H), 6,75 (d, J=6,57 Hz, 1 H), 7,96 (br s, 3 H), 8,22 - 8,31 (m, 1 H), 8,34 (s, 1 H), 8,84 (s, 1 H). [M+H] calculado para C17H21FN6O, 345; experimental 345.

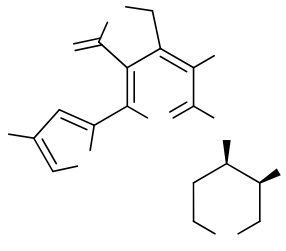
[0793] Ejemplo 103: 6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(tiofen-3-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



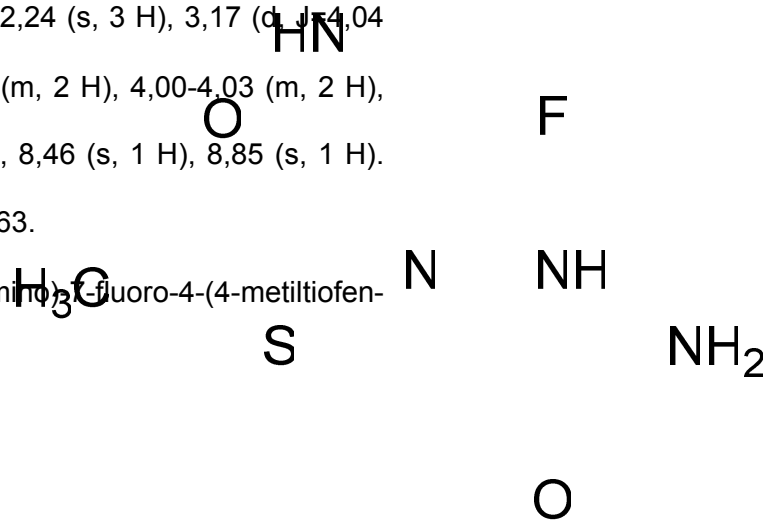
[0794] Se preparó una sal de TFA del compuesto del título de una manera similar al Ejemplo 92 usando ácido tiofeno-3-borónico en lugar de ácido pirazolo[1,5-a]piridin-3-ilborónico. 1H RMN (400 MHz, DMSO-d6) δ ppm 3,16-3,17 (m, 2H), 3,61-3,63 (m, 1H), 3,77-3,79 (m, 2 H), 3,81-3,83 (m, 2 H), 4,41-4,43 (m, 2 H), 4,49-5,10 (m, 1 H), 7,12-7,13 (m, 1 H), 7,52-7,54 (m, 1 H), 7,90-7,97 (m, 3 H), 8,48 (s, 1 H), 8,88 (s, 1 H). [M+H] calculado para C16H17FN4O2S, 349; experimental, 349.



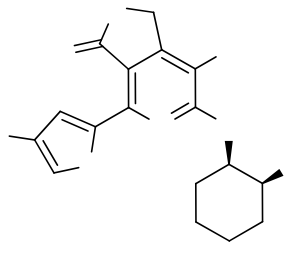
[0795] Ejemplo 104: 6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(4-metiltiofen-2-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



[0796] Se preparó una sal de TFA del compuesto del título de una manera similar al Ejemplo 92 utilizando ácido 4-metiltiofeno-2-borónico en lugar de ácido pirazolo[1,5-a]piridin-3-ilborónico. 1H RMN (400 MHz, DMSO-d6) δ ppm 2,24 (s, 3 H), 3,17 (d, J=4,04 Hz, 2 H), 3,35-3,39 (m, 1 H), 3,62-3,64 (m, 1 H), 3,74-3,75 (m, 2 H), 4,00-4,03 (m, 2 H), 4,42 (d, J=11,62 Hz, 2 H), 6,46 (s, 1 H), 7,20-7,22 (m, 3 H), 8,46 (s, 1 H), 8,85 (s, 1 H). [M+H] calculado para C17H19FN4O2S, 363; experimental, 363.

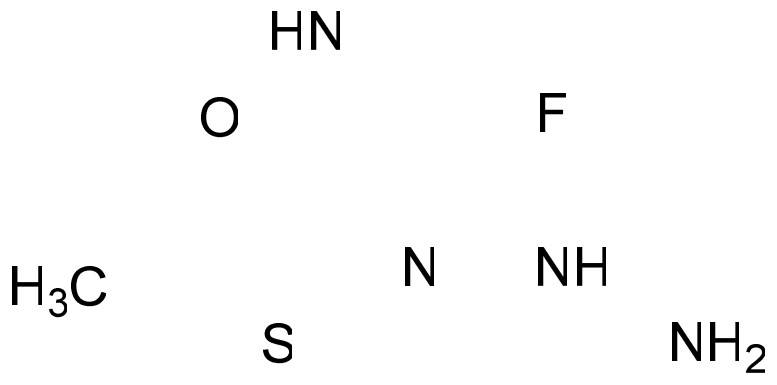


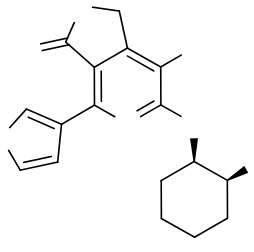
[0797] Ejemplo 105: 6-((1R,2S)-2-Aminociclohexilamino)-7-fluoro-4-(4-metiltiofen-2-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



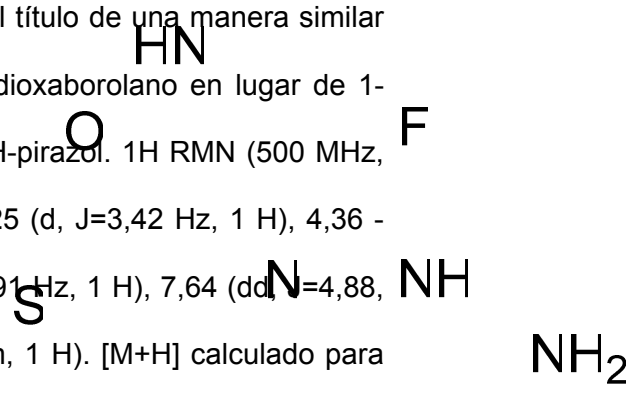
[0798] Se preparó una sal de TFA del compuesto del título de una manera similar al Ejemplo 62 usando 4,4,5,5-tetrametil-2-(4-metiltiofen-2-il)-1,3,2-dioxaborolano en lugar de 1-(difluorometil)-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol. 1H RMN (500 MHz, DMSO-d6) δ ppm 1,31 - 2,04 (m, 8 H), 2,24 (s, 3 H), 3,83 (br s, 1 H), 4,22 (br s, 1 H), 4,36 - 4,49 (m, 2 H), 6,98 (d, J=5,37 Hz, 1 H), 7,22 (s, 1 H), 7,75 (br s, 2 H), 8,47 (s, 1 H), 8,85 (s, 1 H). [M+H] calculado para C18H21FN4OS, 361; experimental, 361.

[0799] Ejemplo 106: 6-((1R,2S)-2-Aminociclohexilamino)-7-fluoro-4-(tiofen-3-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona

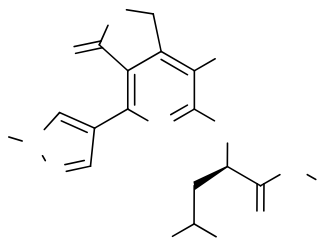




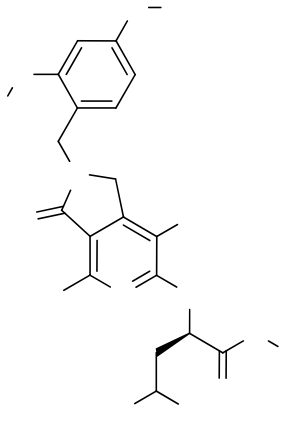
[0800] Se preparó una sal de TFA del compuesto del título de una manera similar al Ejemplo 62 usando 4,4,5,5-tetrametil-2-(tiofen-3-il)-1,3,2-dioxaborolano en lugar de 1-(difluorometil)-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol. 1H RMN (500 MHz, DMSO-d6) δ ppm 1,31 - 2,05 (m, 8 H), 3,84 (br s, 1 H), 4,25 (d, J=3,42 Hz, 1 H), 4,36 - 4,50 (m, 2 H), 7,01 (d, J=5,86 Hz, 1 H), 7,15 (dd, J=5,37, 3,91 Hz, 1 H), 7,64 (dd, J=4,88, 0,98 Hz, 1 H), 7,75 (br s, 2 H), 8,50 (s, 1 H), 8,95 - 9,07 (m, 1 H). [M+H] calculado para C17H19FN4OS, 347; experimental, 347.

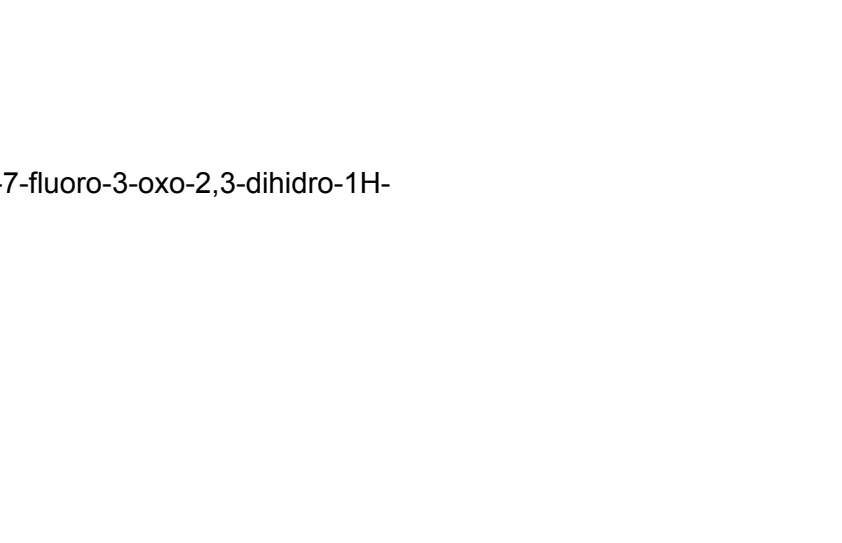


[0801] Ejemplo 107: (R)-2-(7-Fluoro-4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-N,4-dimetilpentanamida



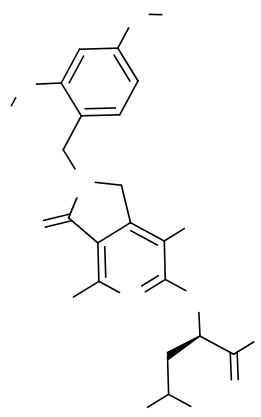
[0802] A. (R)-2-(4-cloro-2-(2,4-dimetoxibencil)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanoato de metilo





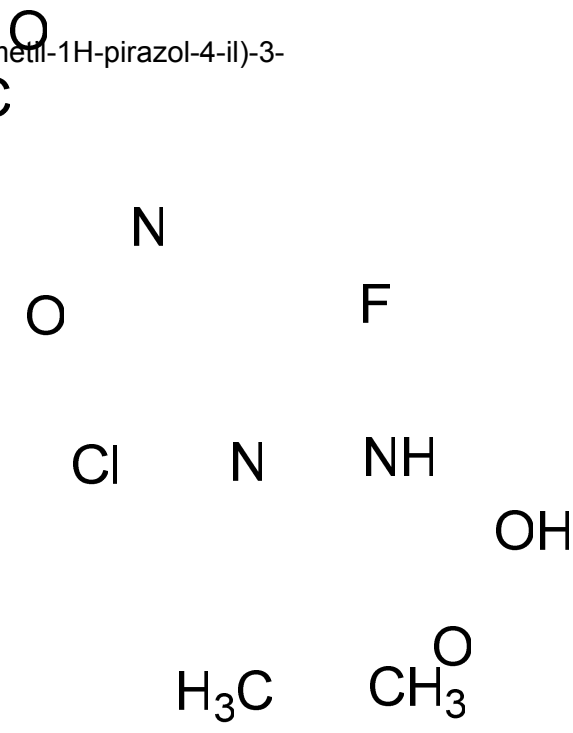
[0803] Una mezcla de 4,6-dicloro-2-(2,4-dimetoxibencil)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona (3 g, 8,08 mmol), clorhidrato de (S)-2-amino-4-metilpentanoato de metilo (2,94 g, 16,16 mmol) y N-isopropil-N-metil-2-amina (3,76 ml, 24,25 mmol) en ACN (50 ml) se agitó a 100 °C durante 3 días. Se eliminó el disolvente y el residuo resultante se utilizó en la siguiente etapa sin purificación adicional. [M+H] calculado para C23H27ClFN3O5, 480; experimental, 480.

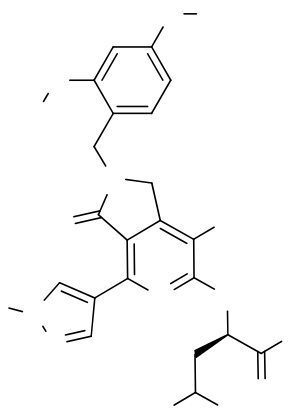
[0804] B. Ácido (R)-2-(4-cloro-2-(2,4-dimetoxibencil)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanoico



[0805] Una mezcla de R)-2-(4-cloro-2-(2,4-dimetoxibencil)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanoato de metilo (2,9 g, 6,04 mmol) en MeOH (10 ml) y NaOH 1N (40,0 ml) se agitó a 50 °C durante 2 h. Una UPLC mostró que se mantuvo el 30% material de partida. Se añadió solución saturada de NaOH adicional (5 ml) y la mezcla de reacción se agitó durante 3 horas a 50 °C. Se eliminó el disolvente y el residuo resultante se dispersó en H2O (100 ml) y se acidificó a pH 3 con HCl. Después de agitar a temperatura ambiente durante 2 h, el sólido se filtró para dar el compuesto del título. [M+H] calculado para C22H25ClFN3O5, 466; experimental, 466.

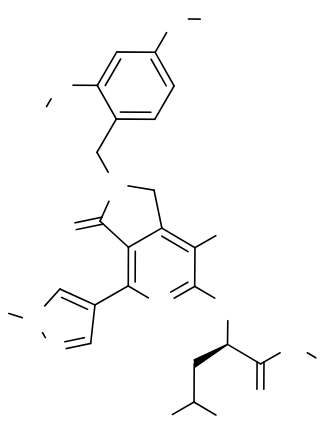
[0806] C. Ácido (R)-2-(2-(2,4-Dimetoxibencil)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanoico





[0807] Una solución de ácido (R)-2-(4-cloro-2-(2,4-dimetoxibencil)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanoico (1,1 g, 2,361 mmol), 1-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (2,456 g, 11,81 mmol) y cloruro de bis(trifenilfosfina)paladio (1,657 g, 2,361 mmol) en dioxano (10 ml) y Na2CO3 acuoso saturado (10,00 ml) se calentó a 120 °C durante 30 min. Después de filtrar los sólidos, el disolvente se eliminó del filtrado. El residuo resultante se disolvió en MeOH y DCM y se purificó mediante HPLC preparativa eluyendo con agua (0,05% de TFA) y ACN (gradiente 40-70%, 0,035% de TFA). Las fracciones recolectadas se combinaron y el disolvente se evaporó a sequedad por evaporación rotativa para dar el compuesto del título. [M+H] calculado para C26H30FN5O5, 512; experimental, 512.

[0808] D. (R)-2-(2-(2,4-Dimetoxibencil)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-N,4-dimetilpentanamida



[0809] Una solución de ácido (R)-2-(2-(2,4-dimetoxibencil)-7-fluoro-4-(1-metil-1H-

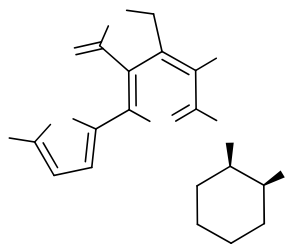
pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanoico (48 mg, 0,094 mmol), clorhidrato de metilamina (31,7 mg, 0,469 mmol) y DIPEA (49,2 µl, 0,281 mmol) en DMF (1 ml) se agitó a temperatura ambiente durante 10 min. Se añadió HATU (71,4 mg, 0,188 mmol) y la mezcla se agitó a temperatura ambiente durante 1 h, después de lo cual una UPLC mostró que se mantuvo aproximadamente el 80% material de partida. Se añadió metilamina adicional (58,4 µl, 0,469 mmol, 33% en EtOH), lo que resultó en una pequeña conversión del material de partida. Se eliminó el disolvente y el residuo se disolvió en DMF (1 ml). A esta solución se añadió clorhidrato de EDCI (54,0 mg, 0,281 mmol), HOBT monohidrato (43,1 mg, 0,281 mmol), y clorhidrato de metilamina (31,7 mg, 0,469 mmol). La mezcla de reacción se calentó a 60 °C durante 4 h. Una UPLC mostró posteriormente que la mezcla de reacción contenía 95% del producto deseado. La mezcla de reacción se dejó enfriar a temperatura ambiente. Se añadió agua (50 ml) y la mezcla se extrajo con DCM (3 x 50 ml). Se recolectaron las capas orgánicas, se secaron sobre Na2SO4, se filtraron y el disolvente se evaporó a sequedad por evaporación rotativa para dar el compuesto del título, que se utilizó sin purificación adicional. [M+H] calculado para C27H33FN6O4, 525; experimental, 525.

[0810] E. (R)-2-(7-Fluoro-4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-N,4-dimetilpentanamida

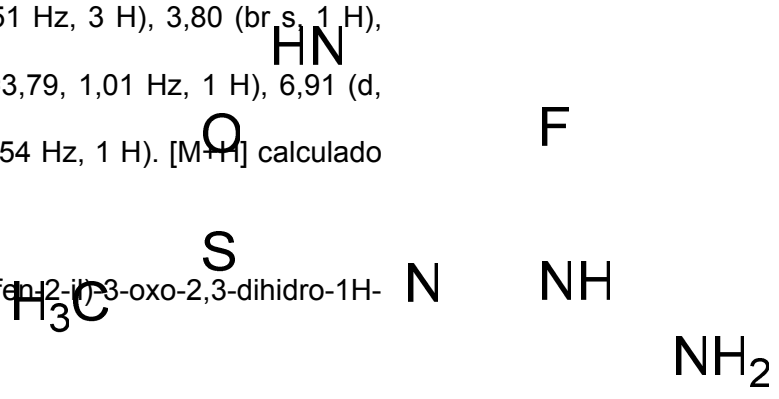
[0811] Una solución de (R)-2-(2-(2,4-dimetoxibencil)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-N,4-dimetilpentanamida (38 mg, 0,072 mmol) en TFA (5 ml) se calentó a 65 °C durante 4 h. Luego de la eliminación del disolvente, el residuo se diluyó en MeOH (2 ml) y se purificó mediante HPLC preparativa eluyendo con agua (0,05% de TFA) y ACN (gradiente 25-30%, 0,035% de TFA). Las fracciones recolectadas se evaporaron a sequedad para dar el compuesto del título. 1H RMN (500 MHz, DMSO-d6) δ ppm 0,84 - 0,93 (m, 6 H), 1,63 - 1,81 (m, 2 H), 2,57 (d, J=4,39 Hz, 3 H), 3,88 (s, 3 H), 4,04 - 4,19 (m, 2 H), 4,36 (s, 2 H), 6,99 (d, J=7,32 Hz, 1 H), 7,61 - 7,76 (m, 1 H), 7,93 (d, J=4,39 Hz, 1 H), 8,30 (s, 1 H), 8,83 (s, 1 H). [M+H] calculado

para C18H23FN6O2, 375; experimental, 375.

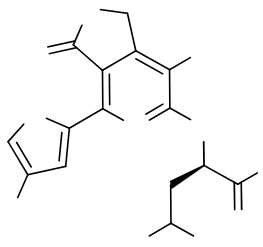
[0812] Ejemplo 108: 6-((1R,2S)-2-Aminociclohexilamino)-7-fluoro-4-(5-metiltiofen-2-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



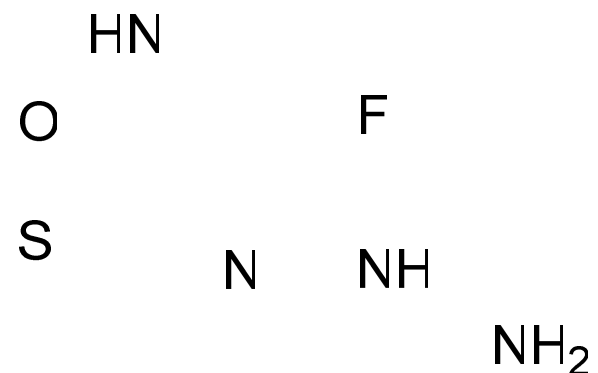
[0813] Se preparó una sal de TFA del compuesto del título de una manera similar al Ejemplo 62 usando 4,4,5,5-tetrametil-2-(5-metiltiofen-2-il)-1,3,2-dioxaborolano en lugar de 1-(difluorometil)-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol. 1H RMN (400 MHz, DMSO-d6) δ ppm 1,31 - 2,01 (m, 8 H), 2,46 (d, J=0,51 Hz, 3 H), 3,80 (br s, 1 H), 4,25 (d, J=4,55 Hz, 1 H), 4,36 - 4,50 (m, 2 H), 6,83 (dd, J=3,79, 1,01 Hz, 1 H), 6,91 (d, J=6,06 Hz, 1 H), 7,73 (br s, 2 H), 8,43 (s, 1 H), 8,82 (d, J=3,54 Hz, 1 H). [M+H] calculado para C18H21FN4OS, 361; experimental, 361.



[0814] Ejemplo 109: (R)-2-(7-Fluoro-4-(4-metiltiofen-2-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida

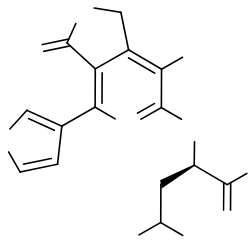


[0815] El compuesto del título se preparó de una manera similar al Ejemplo 70 usando 4,4,5,5-tetrametil-2-(4-metiltiofen-2-il)-1,3,2-dioxaborolano en lugar de 1-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol. 1H RMN (400 MHz, DMSO-d6) δ ppm 0,82 - 0,95 (m, 6 H), 1,20 - 1,32 (m, 2 H), 2,23 (s, 3 H), 4,38 (s, 2 H), 4,59 - 4,72 (m, 2 H), 6,94 - 6,99 (m, 1 H), 7,02 - 7,08 (m, 1 H), 7,15 - 7,23 (m, 1 H), 7,27 - 7,34 (m, 1 H), 8,35 (s, 1 H), 8,78 (d, J=1,26 Hz, 1 H). [M+H] calculado para C18H21FN4O2S, 377;

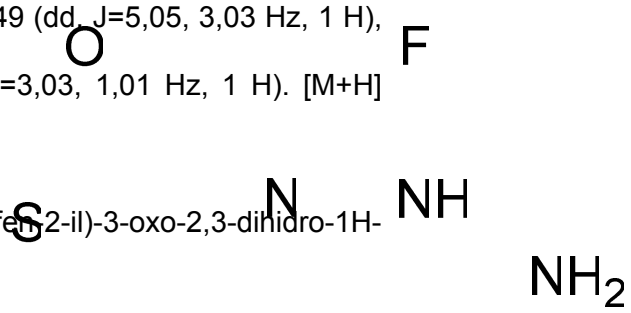


experimental, 377.

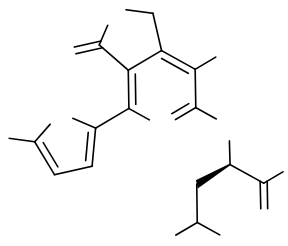
[0816] Ejemplo 110: (R)-2-(7-Fluoro-3-oxo-4-(tiofen-3-il)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida



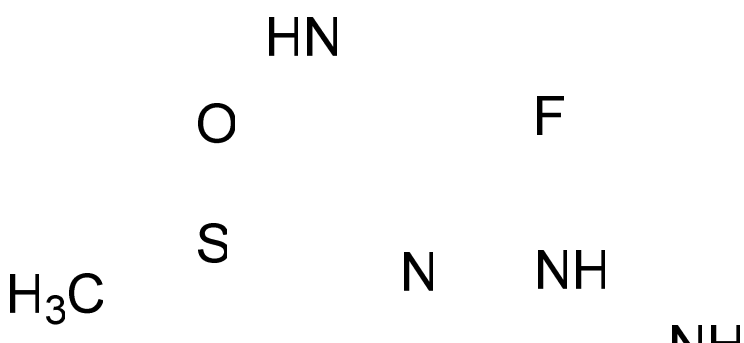
[0817] El compuesto del título se preparó de una manera similar al Ejemplo 70 usando 4,4,5,5-tetrametil-2-(tiofen-3-il)-1,3,2-dioxaborolano en lugar de 1-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol. 1H RMN (400 MHz, DMSO-d6) δ ppm 0,75 - 1,00 (m, 6 H), 1,50 - 1,63 (m, 1 H), 1,69 - 1,83 (m, 2 H), 4,39 (s, 2 H), 4,52 - 4,61 (m, 1 H), 6,93 (br s, 1 H), 7,01 (d, J=7,58 Hz, 1 H), 7,38 (br s, 1 H), 7,49 (dd, J=5,05, 3,03 Hz, 1 H), 8,04 (dd, J=5,05, 1,26 Hz, 1 H), 8,36 (s, 1 H), 8,94 (dd, J=3,03, 1,01 Hz, 1 H). [M+H] calculado para C17H19FN4O2S, 363; experimental, 363.



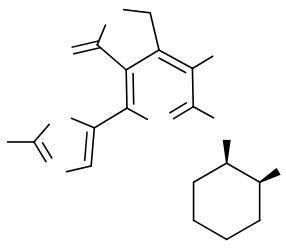
[0818] Ejemplo 111: (R)-2-(7-Fluoro-4-(5-metiltiofen-2-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida



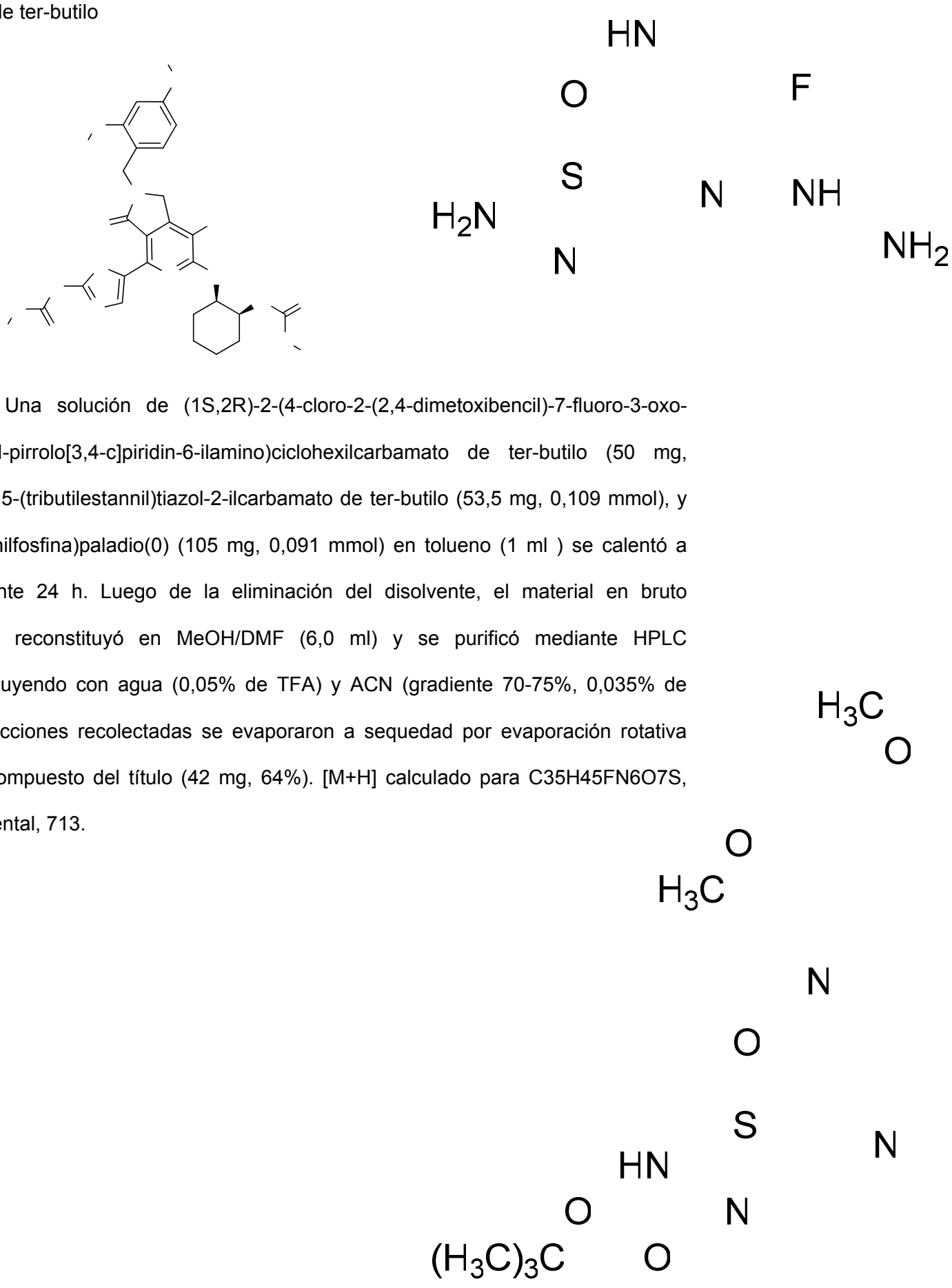
[0819] El compuesto del título se preparó de una manera similar al Ejemplo 70 usando 4,4,5,5-tetrametil-2-(5-metiltiofen-2-il)-1,3,2-dioxaborolano en lugar de 1-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol. 1H RMN (400 MHz, DMSO-d6) δ ppm 0,71 - 0,96 (m, 6 H), 1,52 - 1,85 (m, 3 H), 2,45 (s, 3 H), 4,38 (s, 2 H), 4,56 - 4,74 (m, 1 H), 6,80 (dd, J=3,66, 1,14 Hz, 1 H), 6,93 - 7,10 (m, 2 H), 7,30 (br s, 1 H), 8,32 (s, 1 H), 8,78 (d, J=3,79 Hz, 1 H). [M+H] calculado para C18H21FN4O2S, 377; experimental, 377.



[0820] Ejemplo 112: 6-((1R,2S)-2-Aminociclohexilamino)-4-(2-aminotiazol-5-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona



[0821] A. (5-(6-(((1R,2S)-2-((ter-butoxicarbonil)amino)ciclohexil)amino)-2-(2,4-dimetoxibencil)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-4-il)-1,3-tiazol-2-il)carbamato de ter-butilo

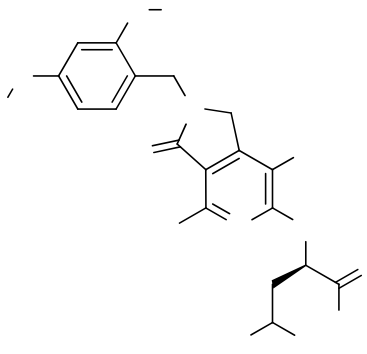


[0822] Una solución de (1S,2R)-2-(4-cloro-2-(2,4-dimetoxibencil)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo (50 mg, 0,091 mmol), 5-(tributilestannil)tiazol-2-ilcarbamato de ter-butilo (53,5 mg, 0,109 mmol), y tetraquis(trifenilfosfina)paladio(0) (105 mg, 0,091 mmol) en tolueno (1 ml) se calentó a 102 °C durante 24 h. Luego de la eliminación del disolvente, el material en bruto resultante se reconstituyó en MeOH/DMF (6,0 ml) y se purificó mediante HPLC preparativa eluyendo con agua (0,05% de TFA) y ACN (gradiente 70-75%, 0,035% de TFA). Las fracciones recolectadas se evaporaron a sequedad por evaporación rotativa para dar el compuesto del título (42 mg, 64%). [M+H] calculado para C35H45FN6O7S, 713; experimental, 713.

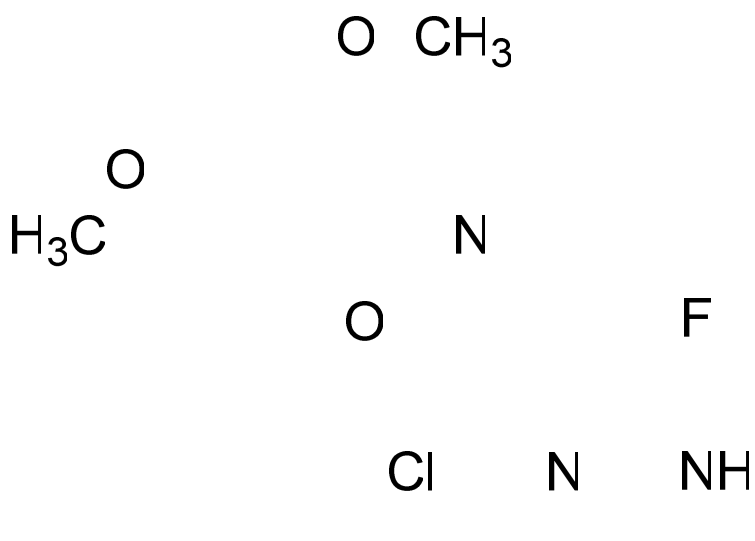
[0823] B. 6-((1R,2S)-2-Aminociclohexilamino)-4-(2-aminotiazol-5-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona

[0824] Una solución de (5-(6-(((1R,2S)-2-((ter-butoxicarbonil)amino)ciclohexil)amino)-2-(2,4-dimetoxibencil)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-4-il)-1,3-tiazol-2-il)carbamato de ter-butilo (41,5 mg, 0,058 mmol) en TFA (5 ml) se calentó a 65 °C durante 3 h. Luego de la eliminación del disolvente, el material en bruto resultante se reconstituyó en MeOH/DMF (6,0 ml) y se purificó mediante HPLC preparativa eluyendo con agua (0,05% de TFA) y ACN (gradiente 10-20%, 0,035% de TFA). Las fracciones recolectadas se evaporaron a sequedad por evaporación rotativa para dar el compuesto del título como un sal de TFA (6,7 mg, 32%). 1H RMN (400 MHz, DMSO-d6) δ ppm 1,12 - 2,11 (m, 9 H), 3,73 (br s, 2 H), 4,19 (d, J=3,79 Hz, 1 H), 4,41 (d, J=3,03 Hz, 2 H), 6,95 (d, J=3,03 Hz, 1 H), 7,77 (br s, 2 H), 8,44 (s, 1 H), 8,93 (s, 1 H). [M+H] calculado para C16H19FN6OS, 363; experimental, 363.

[0825] Preparación 50. (R)-2-(4-Cloro-2-(2,4-dimetoxibencil)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida

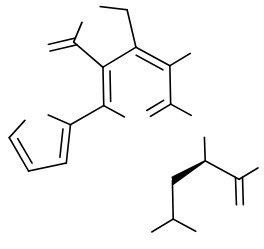


[0826] Una mezcla de 4,6-dicloro-2-(2,4-dimetoxibencil)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona (7 g, 18,86 mmol), N-isopropil-N-metil-2-amina (14,64 ml, 94 mmol), y N-isopropil-N-metil-2-amina (14,64 ml, 94 mmol) en ACN (100 ml) se agitó a 100 °C durante 3 días. Una UPLC mostró que alrededor del 10% de material de partida se mantuvo. La reacción se detuvo, se eliminó el disolvente, y el producto en bruto se reconstituyó en MeOH/DCM y se dispersó sobre gel de sílice (10 g). El disolvente se

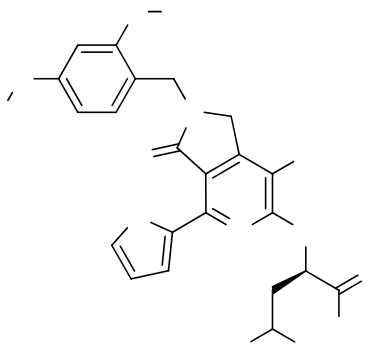


evaporó y el residuo se purificó en una columna de gel de sílice eluyendo con MeOH al 1-3% en DCM durante un período de 45 min. Las fracciones recolectadas se combinaron y se evaporaron a sequedad por evaporación rotativa para dar el compuesto del título (5,3 g, 61%). [M+H] calculado para C22H26ClFN4O4, 465; experimental 465.

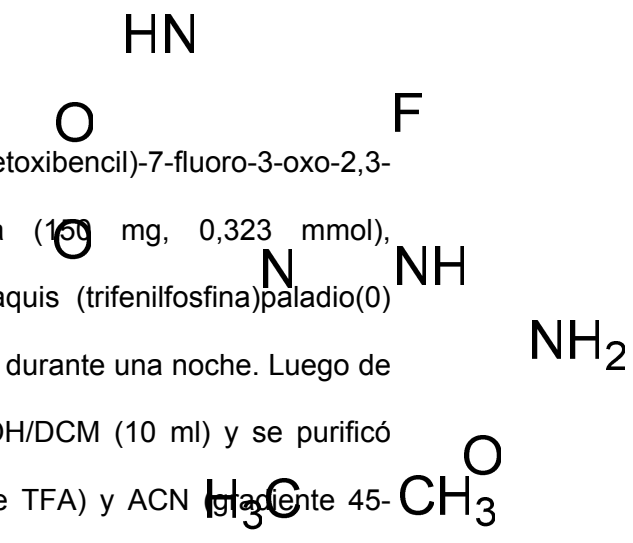
[0827] Ejemplo 113: (R)-2-(7-Fluoro-4-(furan-2-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida

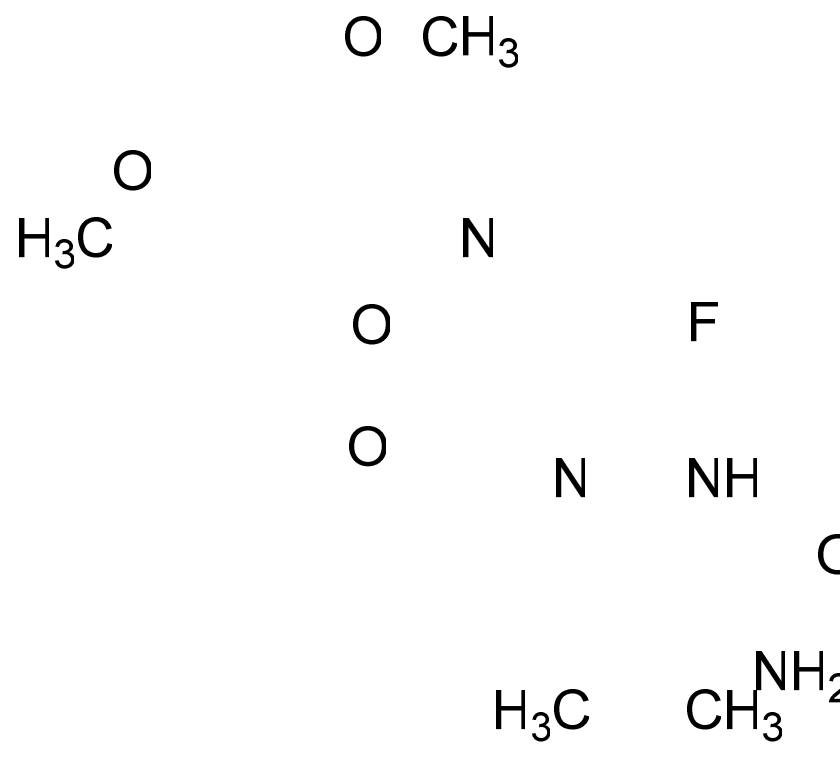


[0828] A. (R)-2-(2-(2,4-Dimetoxibencil)-7-fluoro-4-(furan-2-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida



[0829] Una solución de (R)-2-(4-cloro-2-(2,4-dimetoxibencil)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida (150 mg, 0,323 mmol), tributil(furan-2-il)estannano (138 mg, 0,387 mmol), y tetraquis (trifenilfosfina)paladio(0) (373 mg, 0,323 mmol) en tolueno (1 ml) se calentó a 102 °C durante una noche. Luego de la eliminación del disolvente, el residuo se diluyó en MeOH/DCM (10 ml) y se purificó mediante HPLC preparativa eluyendo con agua (0,05% de TFA) y ACN (gradiente 45-60%, 0,035% de TFA). Las fracciones recolectadas se evaporaron a sequedad por evaporación rotativa para dar el compuesto del título (93,1 mg, 58%). [M+H] calculado



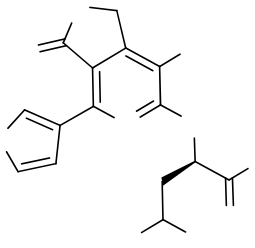


para C26H29FN4O5, 498; experimental 498.

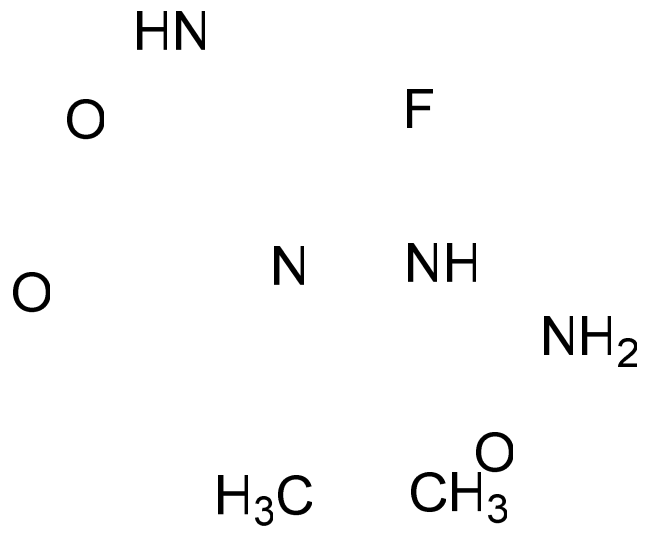
[0830] B. (R)-2-(7-Fluoro-4-(furan-2-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida

[0831] Una solución de (R)-2-(2-(2,4-dimetoxibencil)-7-fluoro-4-(furan-2-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida (93,1 mg, 0,188 mmol) en TFA (5 ml) se calentó a 65 °C durante 3 h. Se eliminó el disolvente y el residuo resultante se diluyó en MeOH/DCM (10 ml) y se purificó mediante HPLC preparativa eluyendo con agua (0,05% de TFA) y ACN (30%, 0,035% de TFA). Las fracciones recolectadas se evaporaron a sequedad por evaporación rotativa para dar el compuesto del título. 1H RMN (400 MHz, DMSO-d6) δ ppm 0,79 - 0,97 (m, 6 H), 1,52 - 1,87 (m, 3 H), 4,38 (s, 2 H), 4,66 - 4,85 (m, 1 H), 6,61 (dd, J=3,54, 1,77 Hz, 1 H), 6,92 - 7,07 (m, 2 H), 7,36 (br s, 1 H), 7,79 (dd, J=1,64, 0,63 Hz, 1 H), 8,04 (dd, J=3,54, 0,51 Hz, 1 H), 8,32 (s, 1 H). [M+H] calculado para C17H19FN4O3, 347; experimental, 347.

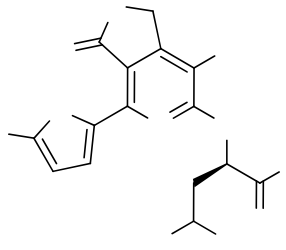
[0832] Ejemplo 114: (R)-2-(7-Fluoro-4-(furan-3-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida



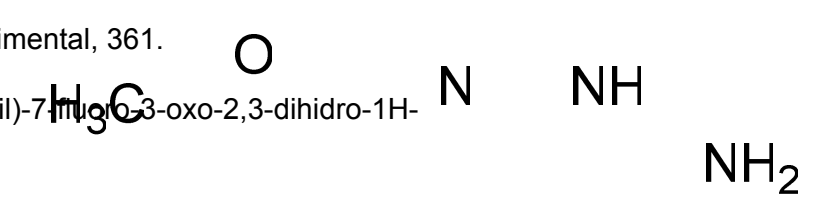
[0833] El compuesto del título se preparó de una manera similar al Ejemplo 70 usando 2-(furan-3-il)-4,4,5,5-tetrametil-1,3,2-dioxaborolano en lugar de 1-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol. 1H RMN (500 MHz, DMSO-d6) δ ppm 0,80 - 0,99 (m, 6 H), 1,21 - 1,33 (m, 1 H), 1,50 - 1,60 (m, 1 H), 1,74 - 1,81 (m, 1 H), 4,38 (s, 2 H), 4,47 - 4,61 (m, 1 H), 6,89 - 6,98 (m, 1 H), 7,03 (d, J=7,81 Hz, 1 H), 7,35 (s, 1 H), 7,42 (s, 1 H), 7,68 (s, 1 H), 8,35 (s, 1 H), 8,98 (s, 1 H). [M+H] calculado para C17H19FN4O3, 347; experimental, 347.



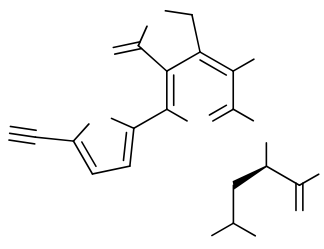
[0834] Ejemplo 115: (R)-2-(7-Fluoro-4-(furan-2-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida



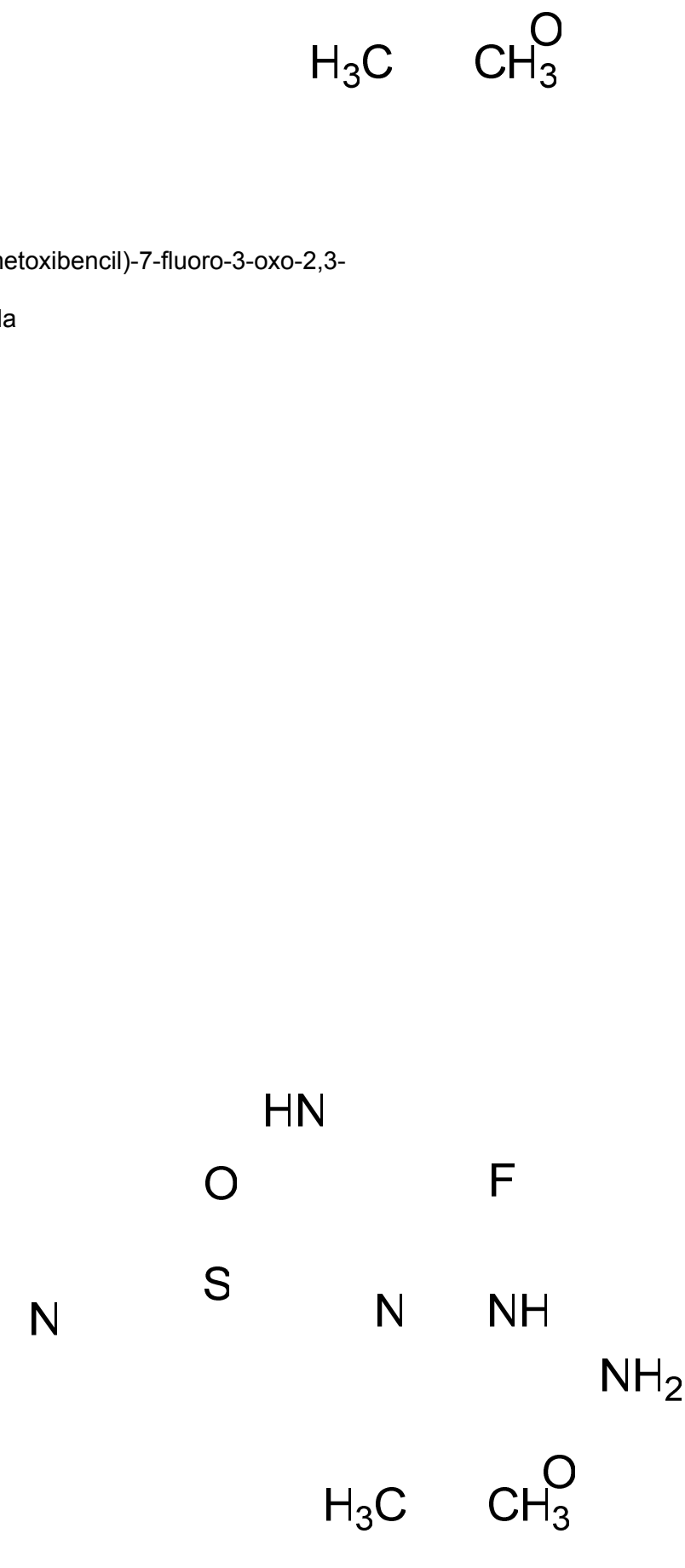
[0835] El compuesto del título se preparó de una manera similar al Ejemplo 113 utilizando tributil(5-metilfurano-2-il)estannano ter-butilo en lugar de tributilo(furan-2-il)estannano. 1H RMN (400 MHz, DMSO-d6) δ ppm 0,84 - 0,97 (m, 6 H), 1,51 - 1,78 (m, 3 H), 2,29 - 2,36 (m, 3 H), 4,36 (s, 2 H), 4,64 - 4,86 (m, 1 H), 6,22 (dd, J=3,28, 1,01 Hz, 1 H), 6,92 (d, J=8,08 Hz, 1 H), 7,01 (br s, 1 H), 7,41 (br s, 1 H), 7,97 (d, J=3,03 Hz, 1 H), 8,26 (s, 1 H). [M+H] calculado para C18H21FN4O3, 361; experimental, 361.

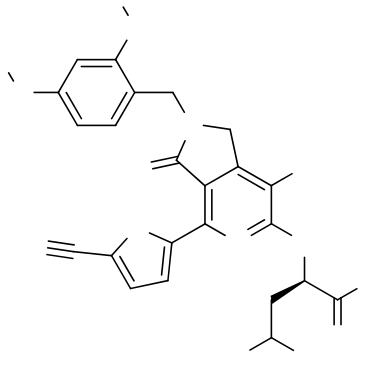


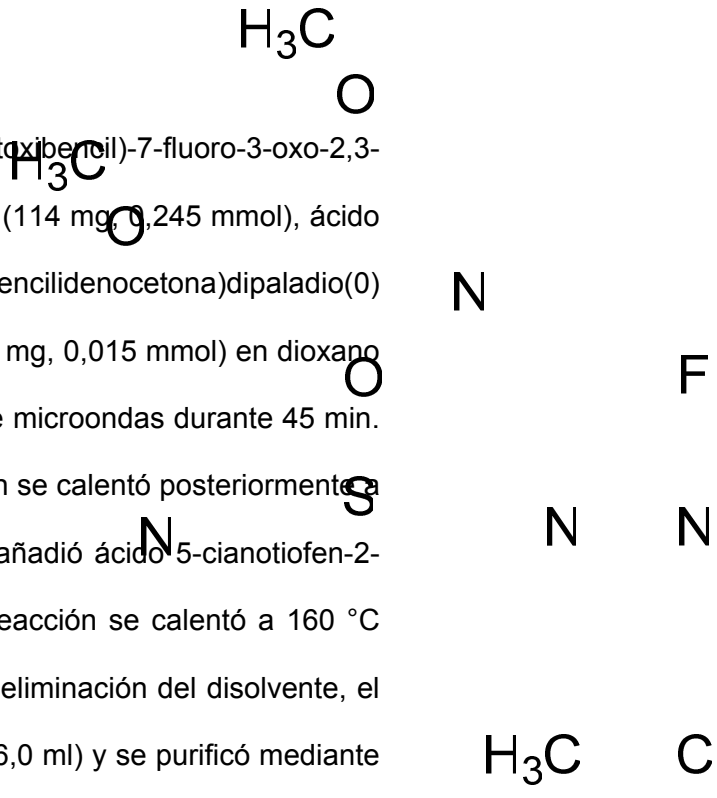
[0836] Ejemplo 116: (R)-2-(4-(5-Cianotiofen-2-il)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida



[0837] A. (R)-2-(4-(5-Cianotiofen-2-il)-2-(2,4-dimetoxibencil)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida







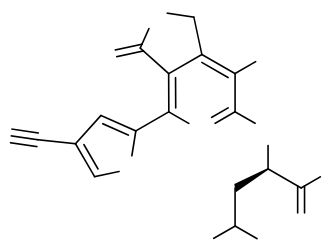
[0838] Una solución de (R)-2-(4-cloro-2-(2,4-dimetoxibencil)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida (114 mg, 0,245 mmol), ácido 5-cianotiofen-2-ilborónico (113 mg, 0,736 mmol), tris(dibencilidenocetona)dipaladio(0) (13,47 mg, 0,015 mmol), y 2-(diciclohexilfosfino)bifenilo (5,16 mg, 0,015 mmol) en dioxano (2 ml) y DMF (0,5 ml) se calentó a 160 °C bajo irradiación de microondas durante 45 min. Una UPLC mostró 50% de conversión. La mezcla de reacción se calentó posteriormente a 160 °C bajo irradiación de microondas durante 45 min. Se añadió ácido 5-cianotiofen-2-ilborónico adicional (113 mg, 0,736 mmol) y la mezcla de reacción se calentó a 160 °C bajo irradiación de microondas durante 60 min. Luego de la eliminación del disolvente, el material en bruto resultante se reconstituyó en MeOH/DMF (6,0 ml) y se purificó mediante HPLC preparativa eluyendo con agua (0,05% de TFA) y ACN (gradiente 40-80 %, 0,035% de TFA). Las fracciones recolectadas se evaporaron a sequedad por evaporación rotativa para dar el compuesto del título. [M+H] calculado para C27H28FN5O4S, 538; experimental, 538.

[0839] B. (R)-2-(4-(5-Cianotiofen-2-il)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida

[0840] Una solución de (R)-2-(4-(5-cianotiofen-2-il)-2-(2,4-dimetoxibencil)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida (68 mg, 0,126 mmol) en TFA (2 ml) se calentó a 65 °C durante 3 h. Luego de la eliminación del disolvente, el material en bruto resultante se reconstituyó en MeOH/DCM (3,0 ml) y se

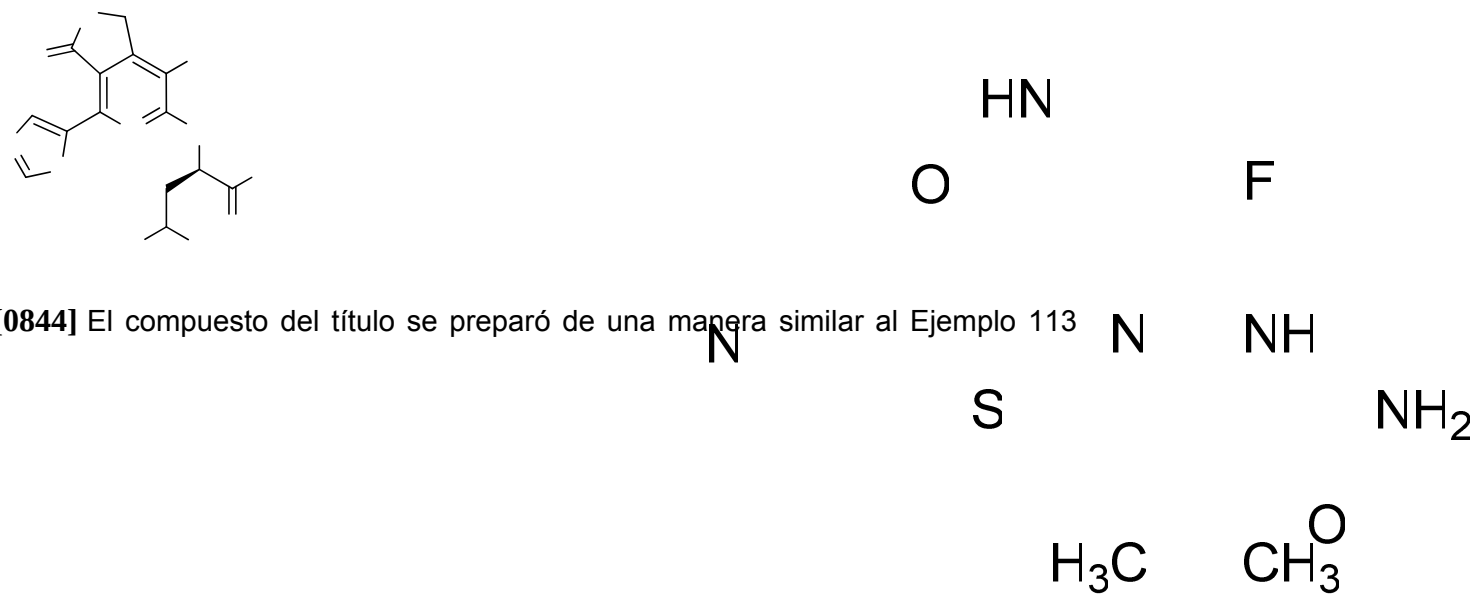
purificó mediante HPLC preparativa eluyendo con agua (0,05% de TFA) y ACN (40%, 0,035% de TFA). Las fracciones recolectadas se combinaron y el disolvente se eliminó a través de evaporación rotatoria para dar el compuesto del título (8,3 mg, 17%). 1H RMN (500 MHz, DMSO-d6) δ ppm 0,86 - 0,96 (m, 6 H), 1,53 - 1,62 (m, 1 H), 1,67 - 1,88 (m, 2 H), 4,45 (s, 2 H), 4,50 - 4,57 (m, 1 H), 6,96 - 7,06 (m, 1 H), 7,32 - 7,54 (m, 2 H), 7,86 - 8,02 (m, 1 H), 8,61 (s, 1 H), 9,00 - 9,15 (m, 1 H). [M+H] calculado para C18H18FN5O2S, 388; experimental, 388.

[0841] Ejemplo 117: (R)-2-(4-(4-Cianotiofen-2-il)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida



[0842] El compuesto del título se preparó de una manera similar al Ejemplo 116 usando ácido 4-cianotiofen-2-ilborónico en lugar de ácido 5-cianotiofen-2-ilborónico. 1H RMN (500 MHz, DMSO-d6) δ ppm 0,80 - 0,96 (m, 6 H), 1,55 - 1,66 (m, 1 H), 1,65 - 1,86 (m, 2 H), 4,44 (s, 2 H), 4,51 - 4,64 (m, 1 H), 6,99 (s, 1 H), 7,04 - 7,20 (m, 1 H), 7,32 (d, J=8,30 Hz, 1 H), 7,37 (s, 1 H), 8,53 - 8,68 (m, 1 H), 9,24 (s, 1 H). [M+H] calculado para C18H18FN5O2S, 388; experimental, 388.

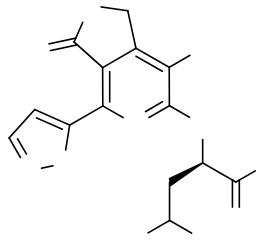
[0843] Ejemplo 118: (R)-2-(7-Fluoro-3-oxo-4-(tiazol-5-il)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida



[0844] El compuesto del título se preparó de una manera similar al Ejemplo 113

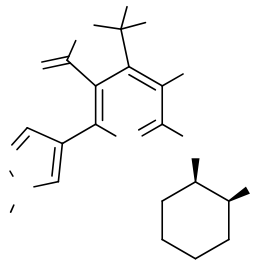
utilizando 5-(tributilestannil)tiazol en lugar de tributil(furan-2-il)estannano. 1H RMN (400 MHz, DMSO-d6) δ ppm 0,77 - 0,98 (m, 6 H), 1,53 - 1,68 (m, 1 H), 1,71 - 1,84 (m, 2 H), 4,42 (s, 2 H), 4,52 - 4,66 (m, 1 H), 6,95 (br s, 1 H), 7,18 (d, J=8,59 Hz, 1 H), 7,34 (br s, 1 H), 8,46 (s, 1 H), 9,11 (s, 1 H), 9,46 (s, 1 H). [M+H] calculado para C16H18FN5O2S, 364; experimental, 364.

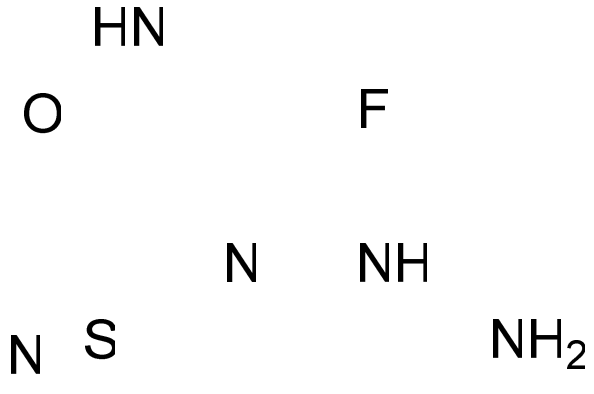
[0845] Ejemplo 119: (R)-2-(7-Fluoro-4-(isotiazol-5-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida



[0846] El compuesto del título se preparó de una manera similar al Ejemplo 116 utilizando 5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)isotiazol en lugar de ácido 5-cianotiofen-2-ilborónico. 1H RMN (500 MHz, DMSO-d6) δ ppm 0,77 - 0,97 (m, 6 H), 1,56 - 1,64 (m, 1 H), 1,67 - 1,86 (m, 2 H), 4,45 (s, 2 H), 4,49 - 4,62 (m, 1 H), 7,00 (s, 1 H), 7,33 (d, J=8,30 Hz, 1 H), 7,44 (s, 1 H), 8,53 - 8,65 (m, 2 H), 8,91 (d, J=1,46 Hz, 1 H). [M+H] calculado para C16H18FN5O2S, 364; experimental, 364.

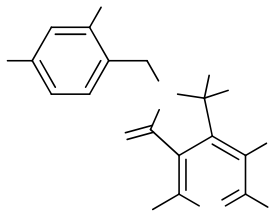
[0847] Ejemplo 120: 6-((1R,2S)-2-Aminociclohexilamino)-7-fluoro-1,1-dimetil-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



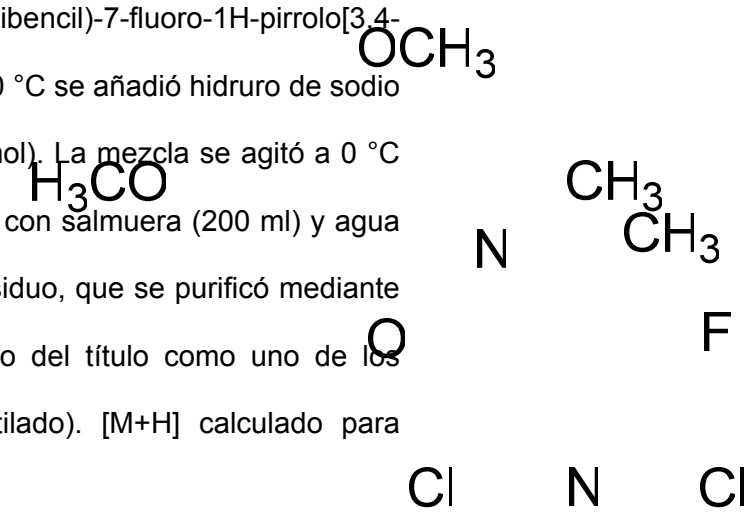


[0848] A. 4,6-Dicloro-2-(2,4-dimetoxibencil)-7-fluoro-1,1-dimetil-1H-pirrolo[3,4-c]piridin-3(2H)-ona

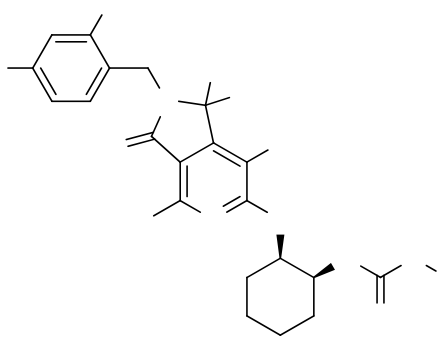




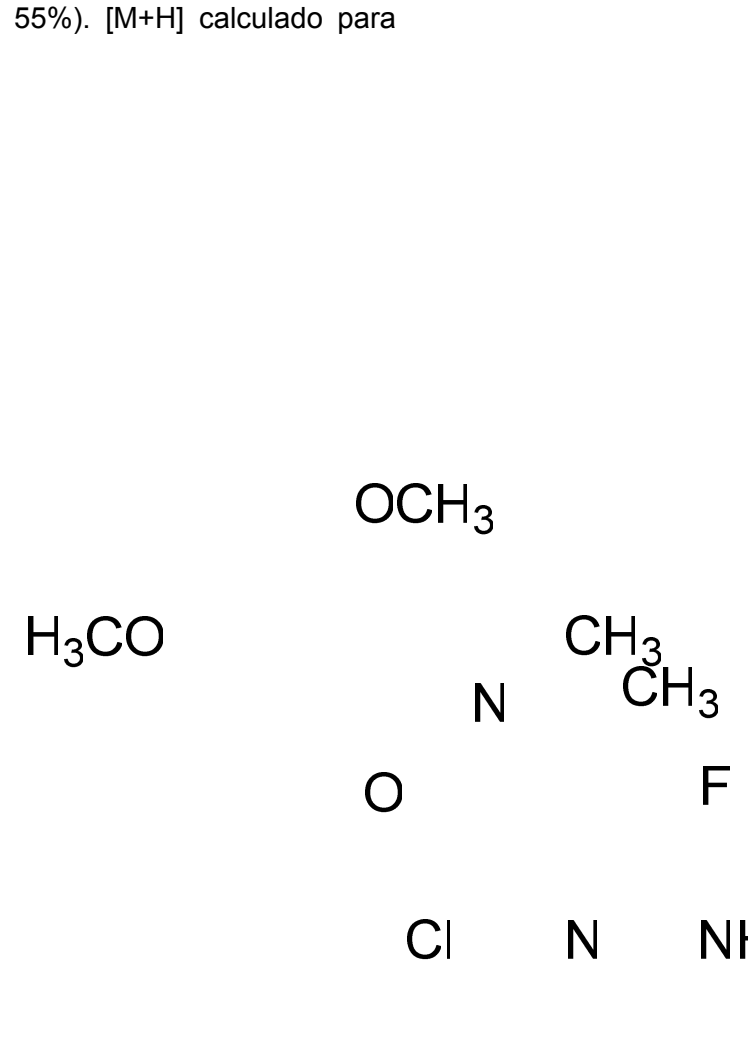
[0849] A una solución de 4,6-dicloro-2-(2,4-dimetoxibencil)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona (500 mg, 1,347 mmol) en DMF (5 ml) a 0 °C se añadió hidruro de sodio (53,9 mg, 1,347 mmol) y yodometano (0,084 ml, 1,347 mmol). La mezcla se agitó a 0 °C durante 1 h, después se diluyó a EtOAc (200 ml) y se lavó con salmuera (200 ml) y agua (200 ml). La fase orgánica se secó y se concentró a un residuo, que se purificó mediante HPLC en fase inversa preparativa para dar el compuesto del título como uno de los productos (50 mg, 9%, se observó producto mono-metilado). [M+H] calculado para C18H17Cl2FN2O3, 400,2; experimental, 399,4.



[0850] B. (1S,2R)-2-(4-cloro-2-(2,4-dimetoxibencil)-7-fluoro-1,1-dimetil-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo

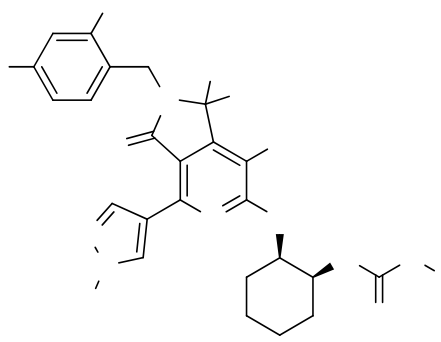


[0851] En un vial de vidrio con tapa hermética, de 10 ml, se disolvió 4,6-dicloro-2-(2,4-dimetoxibencil)-7-fluoro-1,1-dimetil-1H-pirrolo[3,4-c]piridin-3(2H)-ona (50 mg, 0,125 mmol) y (1S,2R)-2-aminociclohexilcarbamato de ter-butilo (53,2 mg, 0,250 mmol) en ACN (2 ml). Se añadió N-etildiisopropilamina (0,033 ml, 0,188 mmol), se cerró herméticamente la tapa, y la mezcla de reacción se calentó a 95 °C durante 72 h. La mezcla de reacción se purificó posteriormente mediante HPLC preparativa y se basificó para dar el compuesto del título como un sólido de color amarillo claro (40 mg, 55%). [M+H] calculado para

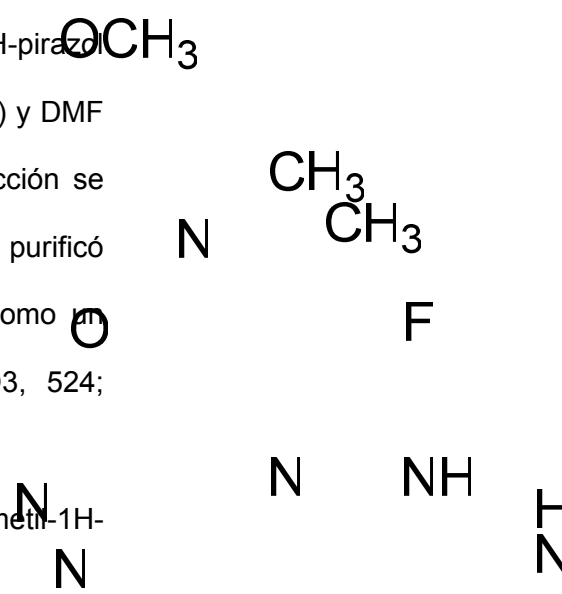


C29H38ClFN4O5, 578,1; experimental, 577,4.

[0852] C. (1S,2R)-2-(2-(2,4-Dimetoxibencil)-7-fluoro-1,1-dimetil-4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo



[0853] En un tubo hermético, se calentó una mezcla de (1S,2R)-2-(4-cloro-2-(2,4-dimetoxibencil)-7-fluoro-1,1-dimetil-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo (30 mg, 0,052 mmol), Na2CO3 acuoso (2 M, 0,065 ml, 0,130 mmol), 1-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (12,98 mg, 0,062 mmol), cloruro de bis(trifenilfosfina)paladio (3,65 mg, 5,20 mmol) y DMF (1 ml) a 160 °C durante 0,5 h en un horno de microondas. La mezcla de reacción se calentó luego a 160 °C durante 4 h adicionales en un horno de microondas y se purificó posteriormente mediante HPLC preparativa para dar el compuesto del título como un sólido de color amarillo (5 mg, 18%). [M+H] calculado para C28H35FN6O3, 524; experimental 524.

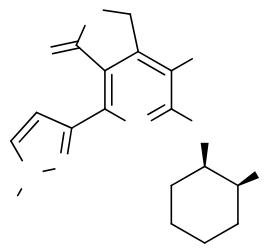


[0854] D. 6-((1R,2S)-2-Aminociclohexilamino)-7-fluoro-1,1-dimetil-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona

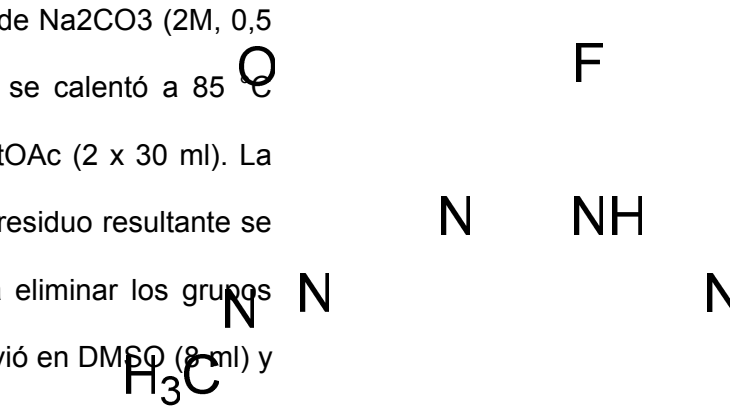
[0855] Una solución de (1S,2R)-2-(2-(2,4-dimetoxibencil)-7-fluoro-1,1-dimetil-4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo (5 mg, 9,57 µmol) en TFA (1 ml) se calentó a 60 °C durante 0,5 h. La mezcla de reacción se purificó posteriormente mediante HPLC preparativa y el producto se liofilizó para dar el compuesto del título como una sal de TFA

(2 mg, 56%). [M+H] calculado para C19H25FN6, 374; experimental, 374.

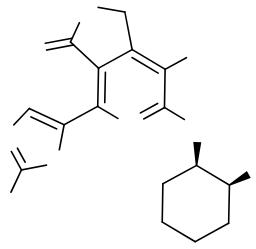
[0856] Ejemplo 121: ((1R,2S)-2-Aminociclohexilamino)-7-fluoro-4-(1-metil-1H-pirazol-3-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



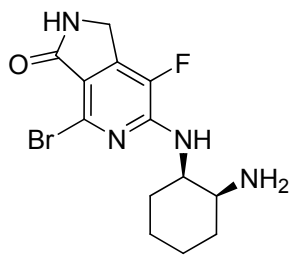
[0857] En un vial de vidrio con tapa hermética, de 30 ml, se disolvieron (1S,2R)-2-(4-cloro-2-(2,4-dimetoxibencil)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo (350 mg, 0,637 mmol), 1-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (172 mg, 0,829 mmol) y PdCl2(PPh3)2 (44,7 mg, 0,064 mmol) en dioxano (5 ml). Se añadió una solución acuosa de Na2CO3 (2M, 0,5 ml) y la tapa fue cerrada herméticamente. La mezcla de reacción se calentó a 85 °C durante 4 h, después se diluyó con agua (5 ml), y se extrajo con EtOAc (2 x 30 ml). La fase orgánica se secó sobre Na2SO4 y se evaporó el disolvente. El residuo resultante se trató con TFA (4 ml) y se calentó a 80 °C durante 1,5 horas para eliminar los grupos protectores. A continuación, se evaporó el TFA y el producto se disolvió en DMSO (8 ml) y se purificó por HPLC preparativa. Las fracciones puras se combinaron, se concentraron y se liofilizaron para dar una sal de TFA del compuesto del título como un sólido de color blanco (52,3 mg, 24%). 1H RMN (400 MHz, DMSO-d6) δ ppm 1,40 - 1,95 (m, 8 H), 3,64 (br s, 1 H), 3,92 (s, 2 H), 4,28 - 4,49 (m, 3 H), 6,76 (d, J=5,31 Hz, 1 H), 7,42 (d, J=2,27 Hz, 1 H), 7,72 (d, J=2,27 Hz, 1 H), 7,98 (br s, 3 H), 8,39 (s, 1 H). [M+H] calculado para C17H21FN6O, 345; experimental, 345.

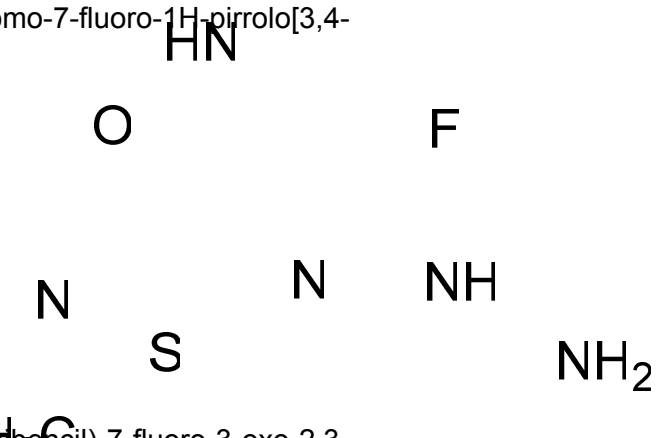


[0858] Ejemplo 122: 6-((1R,2S)-2-Aminociclohexilamino)-7-fluoro-4-(2-metiltiazol-5-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



[0859] A. 6-((1R,2S)-2-Aminociclohexilamino)-4-bromo-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona





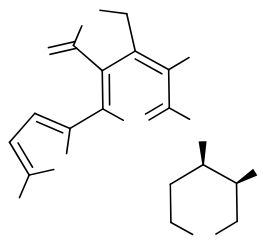
[0860] Una mezcla de (1S,2R)-2-(4-cloro-2-(2,4-dimetoxibencil)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo (200 mg, 0,364 mmol) y ácido bromhídrico en HOAc (10 ml) se agitó a 90 °C durante 6 h. La mezcla se concentró a presión reducida, y el material en bruto resultante se reconstituyó en MeOH (1,0 ml) y se purificó mediante HPLC preparativa eluyendo con agua (0,05% de TFA) y ACN (gradiente 15-30%, 0,035% de TFA). Las fracciones recolectadas se combinaron y el ACN se eliminó mediante evaporación rotatoria. La solución acuosa resultante se neutralizó con solución acuosa saturada de NaHCO3, se lavó con EtOAc (2 x 200 ml), se secó sobre Na2SO4, y se filtró. La fase orgánica se evaporó a sequedad por evaporación rotativa para dar el compuesto del título (38 mg, 30%). [M+H] calculado para C13H16BrFN4O, 343; experimental, 343.

[0861] B. 6-((1R,2S)-2-Aminociclohexilamino)-7-fluoro-4-(2-metiltiazol-5-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona

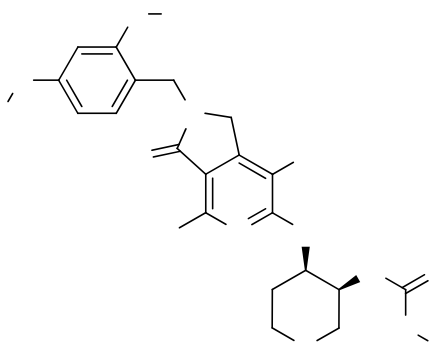
[0862] Una solución de 6-((1R,2S)-2-aminociclohexilamino)-4-bromo-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona (38 mg, 0,111 mmol), ácido 2-metiltiazol-5-carboxílico (15,85 mg, 0,111 mmol), acetato de plata(I) (18,48 mg, 0,111 mmol), y cloruro de cobre(II)

(14,89 mg, 0,111 mmol) en tolueno (1,8 ml) y DMA (0,2 ml) se calentó a 135 °C durante una noche. La mezcla de reacción se filtró a través de una almohadilla de Celite y el disolvente se eliminó al vacío. El material en bruto resultante se reconstituyó en MeOH/DMF (10,0 ml) y se purificó mediante HPLC preparativa eluyendo con agua (0,05% de TFA) y ACN (gradiente 50-90 %, 0,035% de TFA). Las fracciones recolectadas se combinaron y el disolvente se evaporó a sequedad por evaporación rotativa para dar el compuesto del título como una sal de TFA (2,3 mg, 6%). 1H RMN (500 MHz, CDCl3) δ ppm 1,37 - 1,85 (m, 8 H) 2,93 (s, 2 H) 2,97 - 3,08 (m, 3 H) 4,22 - 4,42 (m, 2 H) 6,52 (s, 1 H) 7,53 (d, J=4,39 Hz, 1 H) 7,72 (br s, 1 H) 8,08 (br s, 1 H) 8,27 (s, 1 H) [M+H] calculado para C17H20FN5OS, 362; experimental, 362.

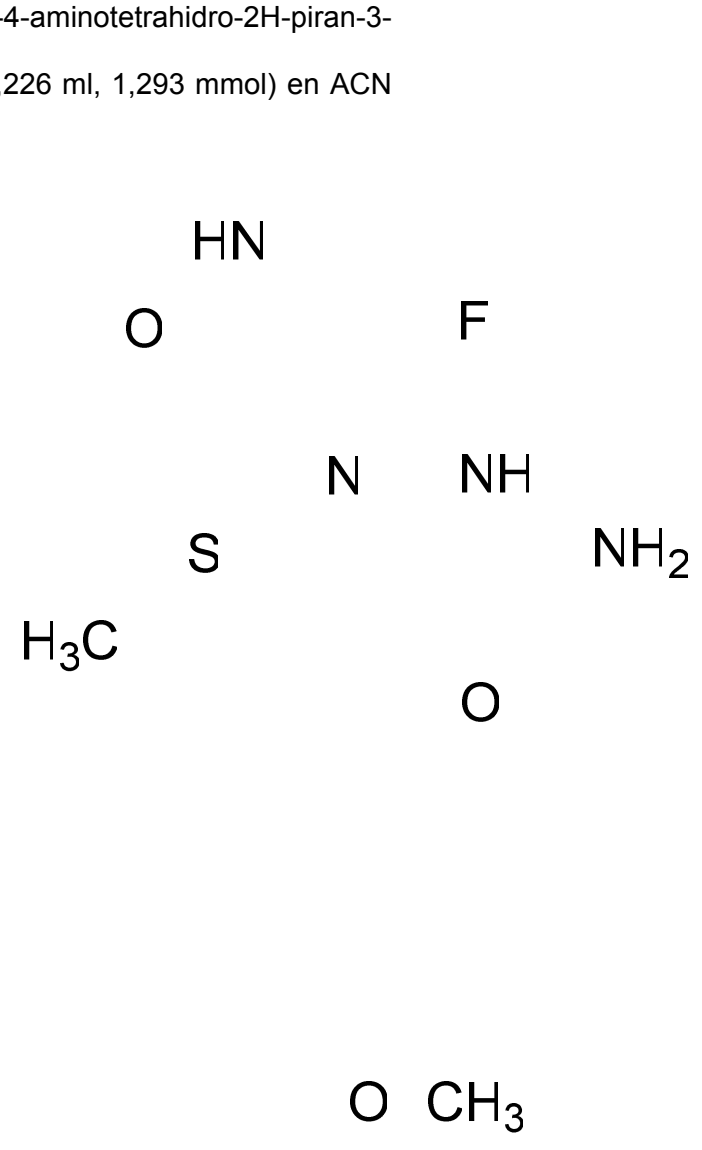
[0863] Ejemplo 123: 6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(5-metiltiofen-2-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



[0864] A. (3R,4R)-4-(4-Cloro-2-(2,4-dimetoxibencil)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)tetrahidro-2H-piran-3-ilcarbamato de ter-butilo

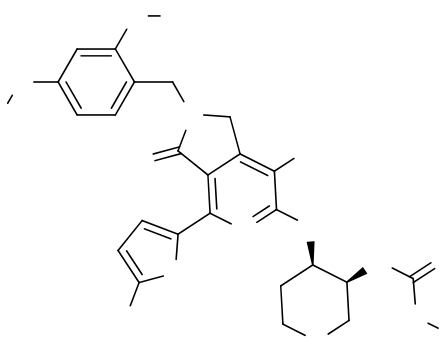


[0865] Una mezcla de 4,6-dicloro-2-(2,4-dimetoxibencil)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona (320 mg, 0,862 mmol), (3R,4R)-4-aminotetrahidro-2H-piran-3-ilcarbamato de ter-butilo (280 mg, 1,293 mmol) y DIPEA (0,226 ml, 1,293 mmol) en ACN

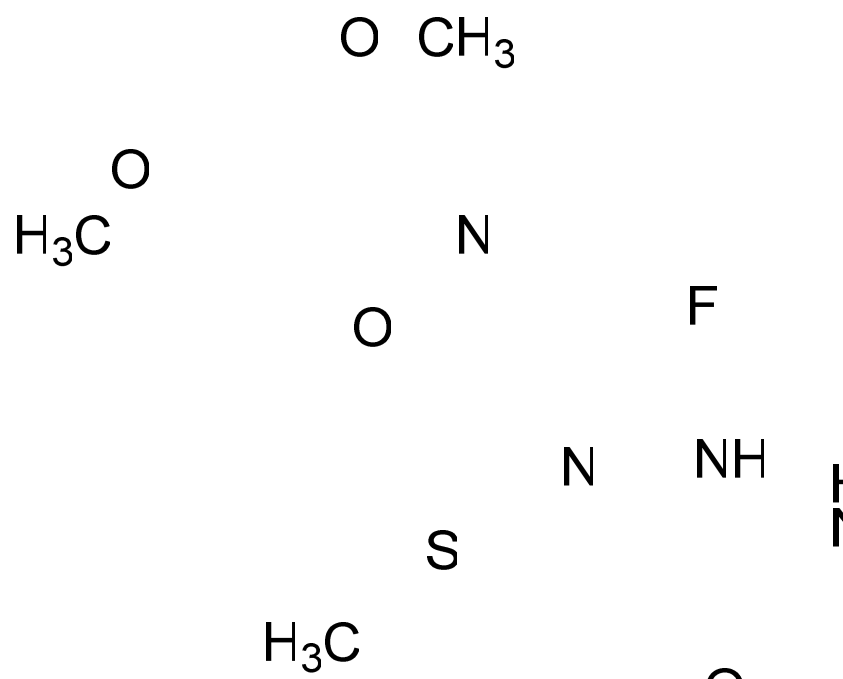


(5 ml) se agitó a 85 °C durante una noche. Una UPLC indicó la presencia de material de partida, por lo que la mezcla se agitó a 85 °C durante una noche. Una UPLC mostró aproximadamente 50% de conversión. La agitación adicional a 85 °C durante 3 días y a 100 °C durante una noche no aumentó apreciablemente la conversión, por lo que se detuvo la reacción y se eliminó el disolvente. El material en bruto resultante se reconstituyó en MeOH/DMF (10 ml) y se purificó mediante HPLC preparativa eluyendo con agua (0,05% de TFA) y ACN (50%, 0,035% de TFA). Las fracciones recolectadas se combinaron y el ACN se eliminó mediante evaporación rotatoria. La solución acuosa resultante se neutralizó con solución acuosa saturada de NaHCO3, se lavó con EtOAc (2 x 200 ml), se secó sobre Na2SO4, y se filtró. La fase orgánica se evaporó a sequedad por evaporación rotativa para dar el compuesto del título (51 mg, 11%). [M+H] calculado para C26H32ClFN4O6, 552; experimental, 552.

[0866] B. (3R,4R)-4-(2-(2,4-dimetoxibencil)-7-fluoro-4-(5-metiltiofen-2-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)tetrahidro-2H-piran-3-ilcarbamato de ter-butilo



[0867] Una solución de (3R,4R)-4-(4-cloro-2-(2,4-dimetoxibencil)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)tetrahidro-2H-piran-3-ilcarbamato de ter-butilo (51 mg, 0,093 mmol), 4,4,5,5-tetrametil-2-(5-metiltiofen-2-il)-1,3,2-dioxaborolano (104 mg, 0,463 mmol), y cloruro de bis(trifenilfosfina)paladio (65,0 mg, 0,093 mmol) en dioxano (1 ml) y Na2CO3 acuoso saturado (1 ml) se calentó a 140 °C durante 40 min. Después de filtrar los sólidos, el disolvente se eliminó del filtrado. El residuo resultante se disolvió en MeOH y DCM (10 ml) y se purificó mediante HPLC preparativa eluyendo con agua (0,05%

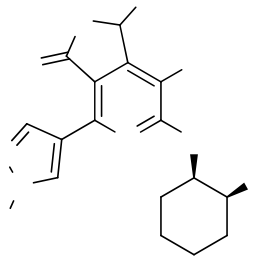


de TFA) y ACN (80%, 0,035% de TFA). Las fracciones recolectadas se combinaron y el disolvente se evaporó a sequedad por evaporación rotativa para dar el compuesto del título (31 mg, 55%). [M+H] calculado paraC31H37FN4O6S, 613; experimental, 613.

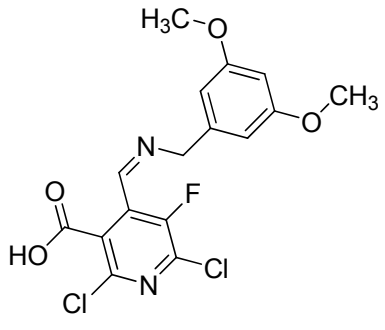
[0868] C. 6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(5-metiltiofen-2-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona

[0869] Una solución de (3R,4R)-4-(2-(2,4-dimetoxibencil)-7-fluoro-4-(5-metiltiofen-2-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)tetrahidro-2H-piran-3-ilcarbamato de ter-butilo (31 mg, 0,051 mmol) en TFA (10 ml) se calentó a 80 °C durante 1 h. Después se eliminó el disolvente, el residuo se disolvió en MeOH y DCM (8 ml) y se purificó mediante HPLC preparativa eluyendo con agua (0,05% de TFA) y ACN (15-30 gradiente%, 0,035% de TFA). Las fracciones recolectadas se combinaron y el disolvente se evaporó a sequedad por evaporación rotativa para dar el compuesto del título como una sal de TFA (13,5 mg, 74%). 1H RMN (500 MHz, DMSO-d6) δ ppm 1,78 (d, J=13,18 Hz, 1 H), 2,03 - 2,18 (m, 1 H), 2,46 (s, 3 H), 3,17 (d, J=4,88 Hz, 1 H), 3,55 - 3,65 (m, 1 H), 3,75 (d, J=13,18 Hz, 1 H), 3,85 (br s, 1 H), 3,96 - 4,06 (m, 2 H), 4,41 (d, J=7,81 Hz, 2 H), 6,84 (d, J=2,44 Hz, 1 H), 7,22 (d, J=4,88 Hz, 1 H), 7,92 (br s, 2 H), 8,47 (s, 1 H), 8,83 (d, J=3,42 Hz, 1 H). [M+H] calculado para C17H19FN4O2S, 363; experimental, 363.

[0870] Ejemplo 124: 6-((1R,2S)-2-Aminociclohexilamino)-7-fluoro-1-metil-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona

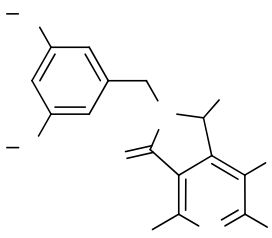


[0871] A. Ácido 2,6-dicloro-4-((3,5-dimetoxibencilimino)metil)-5-fluoronicotínico

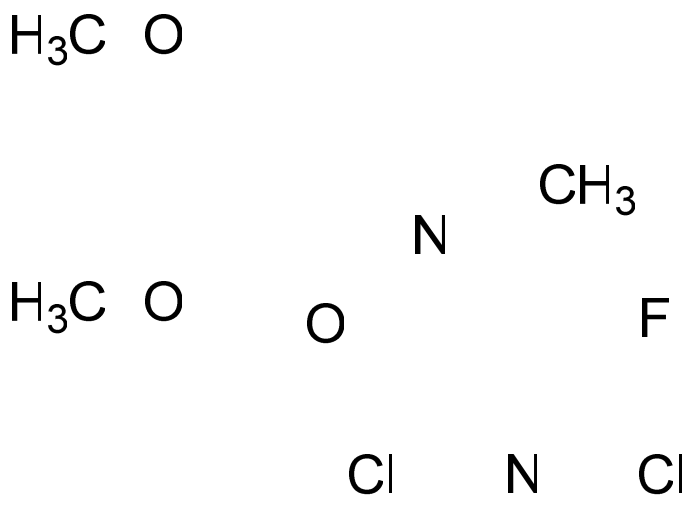


[0872] A. A una solución de (2,4-dimetoxifenil)metanamina (4,4 g, 26,6 mmol) en MeOH (50 ml) se añadió 4,6-dicloro-7-fluoro-1-hidroxifuro[3,4-c]piridin -3(1H)-ona (6,0 g, 25,3 mmol). La mezcla se agitó durante 0,5 h, se filtró y se lavó con éter de petróleo para dar el compuesto del título como un sólido de color blanco (5,8 g, 60%). 1H-RMN (CDCl3, 400 MHz) δ 3,75 (s, 3 H), 3,79 (s, 3 H), 3,93 (s, 2 H), 6,30 (s, 1 H), 6,40-6,42 (m, 2 H), 7,12 (d, J=8,4 Hz, 1 H).

[0873] B. 4,6-Dicloro-2-(3,5-dimetoxibencil)-7-fluoro-1-metil-1H-pirrolo[3,4-c]piridin-3(2H)-ona



[0874] A una mezcla de ácido 2,6-dicloro-4-((3,5-dimetoxibencilimino)metil)-5-fluoronicotínico (5,8 g, 25,3 mmol) en THF (120 ml) se añadió metil-litio (60,0 ml, 126,6 mmol) gota a gota a -78 º C. Después de completarse la adición, la mezcla se agitó durante 2 h. La mezcla de reacción se acidificó con HCl 1 N a pH 7 y el THF se eliminó a presión reducida. La mezcla se extrajo con EtOAc, se lavó con salmuera, se secó sobre Na2SO4 anhidro, y se purificó por cromatografía en gel de sílice eluyendo con PE-EtOAc (5:1) para dar el compuesto del título como un sólido de color blanco (0,93 g, 16%). 1H-RMN (CDCl3, 400 MHz) δ 1,58 (d, J=6,8 Hz, 3 H), 3,79 (s, 3 H), 3,84 (s, 3 H), 4,35 (d, J=14,4 Hz, 1 H), 4,52 (q, J=6,8 Hz, 1 H), 5,07 (d, J=14,4 Hz, 1 H), 6,43-6,45 (m, 2 H), 7,28

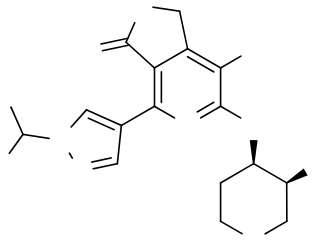


(d, J=9,2 Hz, 1 H). [M+H] calculado para C17H15Cl2FN2O3, 386; experimental, 385.

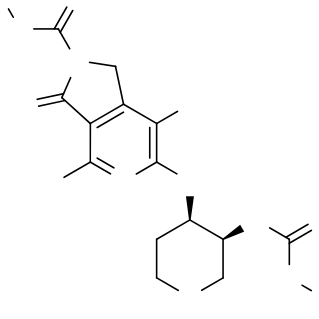
[0875] C. 6-((1R,2S)-2-Aminociclohexilamino)-7-fluoro-1-metil-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona

[0876] Una mezcla de 6-((1R,2S)-2-aminociclohexilamino)-2-(2,4-dimetoxibencil)-7-fluoro-1-metil-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona (20 mg, 0,039 mmol) y TFA (1 ml) se calentó a 60 °C durante 2 h. Luego de la reacción, la mezcla se purificó mediante HPLC preparativa eluyendo con agua (0,05% de TFA) y ACN (gradiente 15-25 %, 0,035% de TFA) para dar el compuesto del título como una sal de TFA (10 mg, 71%). 1H RMN (500 MHz, DMSO-d6) δ ppm 1,41 (d, J=6,59 Hz, 3 H), 1,46 (d, J=7,02 Hz, 2 H), 1,60-1,84 (m, 5 H), 3,68 (br s, 1 H), 3,89 (s, 2 H), 4,44 (br s, 1 H), 4,71 (q, J=6,65 Hz, 1 H), 6,52 (br s, 1 H), 6,73 (d, J=6,53 Hz, 1 H), 7,72 (br s, 2 H), 8,24 - 8,32 (m, 1 H), 8,46 (s, 1 H), 8,82 (s, 1 H). [M+H] calculado para C18H23FN6O, 359; experimental, 359.

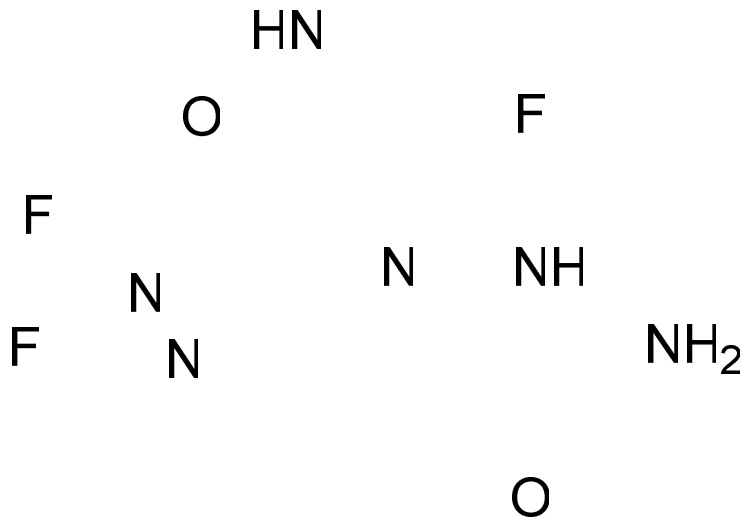
[0877] Ejemplo 125: 6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-4-(1-(difluorometil)-1H-pirazol-4-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona



[0878] A. 6-((3R,4R)-3-(ter-butoxicarbonilamino)tetrahidro-2H-piran-4-ilamino)-4-cloro-7-fluoro-3-oxo-1H-pirrolo[3,4-c]piridin-2(3H)-carboxilato de ter-butilo

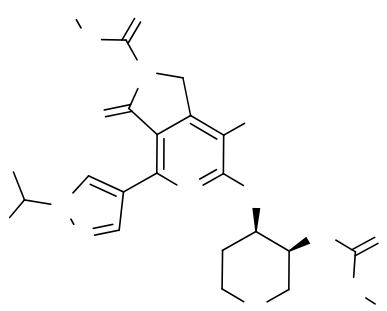


[0879] Una mezcla de 4,6-dicloro-7-fluoro-3-oxo-1H-pirrolo[3,4-c]piridin-2(3H)-

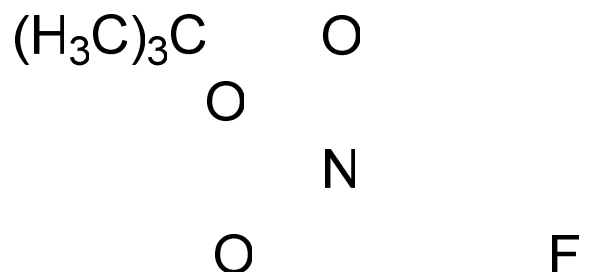


carboxilato de ter-butilo (1,42 g, 4,43 mmol), (3R,4R)-4-aminotetrahidro-2H-piran-3-ilcarbamato de ter-butilo (1,15 g, 5,52 mmol), diisopropiletilamina (3,87 ml, 22,16 mmol) en DMSO (10 ml) y 2-propanol (40 ml) se calentó a 100 °C en un baño de aceite durante 20 h. La solución se concentró luego y el aceite resultante se disolvió en agua (50 ml) y se calentó en un baño de aceite a 50 °C durante 1 h, después se dejó enfriar a temperatura ambiente. La solución se calentó posteriormente a 50 °C durante 15 min, se dejó enfriar a temperatura ambiente, se calentó nuevamente a 50 °C durante 15 min, y se dejó enfriar a temperatura ambiente. El precipitado resultante se filtró y se enjuagó con agua para dar el compuesto del título como un sólido de color blanco-rosáceo pálido (1,90 g, 86%, mezcla 4:1 con regioisómero) que se usó en la etapa siguiente sin purificación adicional. 1H RMN (400 MHz, DMSO-d6) δ ppm 1,36 (s, 9 H), 1,50 (s, 3 H), 1,59-1,61 (m, 1 H), 1,97-1,99 (m, 1 H), 1,97-1,99 (m, 1 H), 3,46-3,49 (m, 2 H), 3,80-3,83 (m, 3 H), 4,31-4,33 (m, 1 H), 4,73 (s, 1 H), 6,59 (d, J=7,30 Hz, 1 H), 7,43 (d, J=7,30 Hz, 1 H). [M+H] calculado para C22H30ClFN4O6, 501; experimental, 501.

[0880] B. 6-((3R,4R)-3-(ter-butoxicarbonilamino)tetrahidro-2H-piran-4-ilamino)-4-(1-(difluorometil)-1H-pirazol-4-il)-7-fluoro-3-oxo-1H-pirrolo[3,4-c]piridin-2(3H)-carboxilato de ter-butilo



[0881] Una mezcla de 6-((3R,4R)-3-(ter-butoxicarbonilamino)tetrahidro-2H-piran-4-ilamino)-4-cloro-7-fluoro-3-oxo-1H-pirrolo[3,4-c]piridin-2(3H)-carboxilato de ter-butilo (500 mg, 0,998 mmol), ácido 1-(difluorometil)-1H-pirazol-4-ilborónico (808 mg, 4,99 mmol), cloruro de bis(trifenilfosfina)paladio (70,1 mg, 0,100 mmol) en dioxano (15 ml) y carbonato

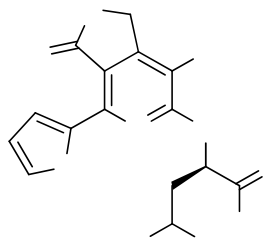


de sodio saturado 2M (2 ml) se calentó a 100 °C en un horno de microondas durante 30 min. La solución se concentró y se purificó por HPLC preparatoria eluyendo con agua (10 mM de NH4HCO3) y ACN/agua (80/20 v/v, gradiente 15-30%, 10 mM de NH4HCO3) para dar el compuesto del título como un sólido de color blanco (132 mg, 23%). 1H RMN (400 MHz, DMSO-d6) δ ppm 1,35 (s, 9 H), 1,52 (s, 9 H), 1,55-1,56 (m, 1 H), 2,46-2,47 (m, 1 H), 3,57-3,59 (m, 2 H), 3,81-3,84 (m, 3 H), 4,61-4,62 (m, 1 H), 4,78 (s, 2 H), 6,61 (d, J=6,35 Hz, 1 H), 7,15 (d, J=6,83 Hz, 1 H), 7,97 (s, 1 H), 8,54 (s, 1 H), 9,24 (s, 1 H). [M+H] calculado para C26H33F3N6O6, 583; experimental, 583.

[0882] C. 6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-4-(1-(difluorometil)-1H-pirazol-4-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona

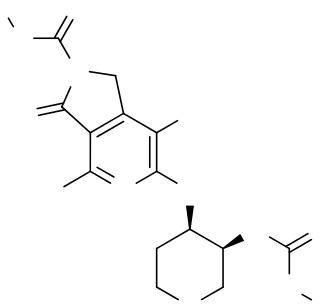
[0883] Se disolvió 6-((3R,4R)-3-(ter-butoxicarbonilamino)tetrahidro-2H-piran-4-ilamino)-4-(1-(difluorometil)-1H-pirazol-4-il)-7-fluoro-3-oxo-1H-pirrolo[3,4-c]piridin-2(3H)-carboxilato de ter-butilo (126 mg, 0,998 mmol) en 2-propanol (5 ml) y la solución se calentó a 75 °C con un bloque de calentamiento. Luego se añadió HCl 2M (2,5 ml), se bajó la temperatura a 65 °C, y la mezcla de reacción se agitó durante 3 h. La solución se concentró y se purificó por HPLC preparatoria eluyendo con agua (10 mM de NH4HCO3) y ACN/agua (80/20 v/v, gradiente 10-50%, 10 mM de NH4HCO3) para dar el compuesto del título como un sólido de color blanco (79 mg, 96%). 1H RMN (400 MHz, DMSO-d6) δ ppm 1,75-1,77 (m, 1 H), 2,09-2,12 (m, 1 H), 3,60-3,63 (m, 1 H), 3,76-3,77 (m, 1 H), 3,88-3,98 (m, 3 H), 4,44 (d, J=6,35 Hz, 2 H), 4,54-4,55 (m, 1 H), 7,17 (d, J=5,86 Hz, 1 H), 7,89 (br s, 1 H), 8,54 (s, 1 H), 8,58 (s, 1 H), 9,43 (s, 1 H). [M+H] calculado para C16H17F3N6O2, 383; experimental, 383.

[0884] Ejemplo 126: (R)-2-(7-Fluoro-3-oxo-4-(tiofen-2-il)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida



[0885] El compuesto del título se preparó de una manera similar al Ejemplo 113 utilizando tributil(tiofen-2-il)estannano en lugar de tributil(furan-2-il)estannano. 1H RMN (500 MHz, DMSO-d6) δ ppm 0,80 - 0,99 (m, 6 H), 1,51 - 1,84 (m, 3 H), 4,40 (s, 2 H), 4,59 - 4,76 (m, 1 H), 6,99 (br s, 1 H), 7,06 - 7,17 (m, 2 H), 7,34 (br s, 1 H), 7,61 (d, J=4,88 Hz, 1 H), 8,40 (s, 1 H), 8,93 - 9,05 (m, 1 H). [M+H] calculado para C17H19FN4O2S, 363; experimental, 363.

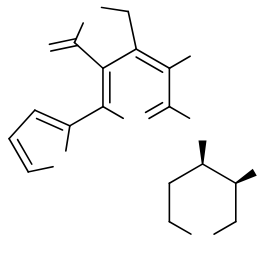
[0886] Preparación 51: 6-((3R,4R)-3-(ter-butoxicarbonilamino)tetrahidro-2H-piran-4-ilamino)-4-cloro-7-fluoro-3-oxo-1H-pirrolo[3,4-c]piridin-2(3H)-carboxilato de ter-butilo



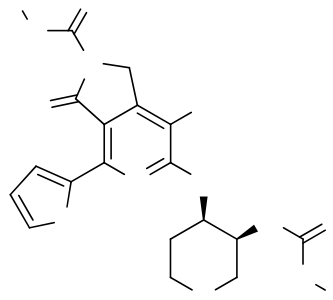
[0887] Una mezcla de 4,6-dicloro-7-fluoro-3-oxo-1H-pirrolo[3,4-c]piridin-2(3H)-carboxilato de ter-butilo (1,24 g, 3,85 mmol), (3R, 4R)-4-aminotetrahidro-2H-piran-3-ilcarbamato de ter-butilo (1,00 g, 4,62 mmol), diisopropiletilamina (3,36 ml, 19,27 mmol) en DMSO (10 ml) y 2-propanol (40 ml) se calentó a 100 °C en un baño de aceite durante 20 h. La reacción se repitió en la misma escala y ambas soluciones de reacción se combinaron y se concentraron. La mezcla se purificó a través de gel de sílice cromatografía ultrarrápida eluyendo con acetato de etilo y hexano (gradiente de EtOAc 10-50%) para dar el compuesto del título como un sólido de color blanco-rosáceo pálido (510 mg, 13%). 1H RMN (400 MHz, DMSO-d6) δ ppm 1,36 (s, 9 H), 1,50 (s, 3 H), 1,59-

1,61 (m, 1 H), 1,97-1,99 (m, 1 H), 1,97-1,99 (m, 1 H), 3,46-3,49 (m, 2 H), 3,80-3,83 (m, 3 H), 4,31-4,33 (m, 1 H), 4,73 (s, 1 H), 6,59 (d, J=7,30 Hz, 1 H), 7,43 (d, J=7,30 Hz, 1 H). [M+H] calculado para C22H30ClFN4O6, 501; experimental, 501.

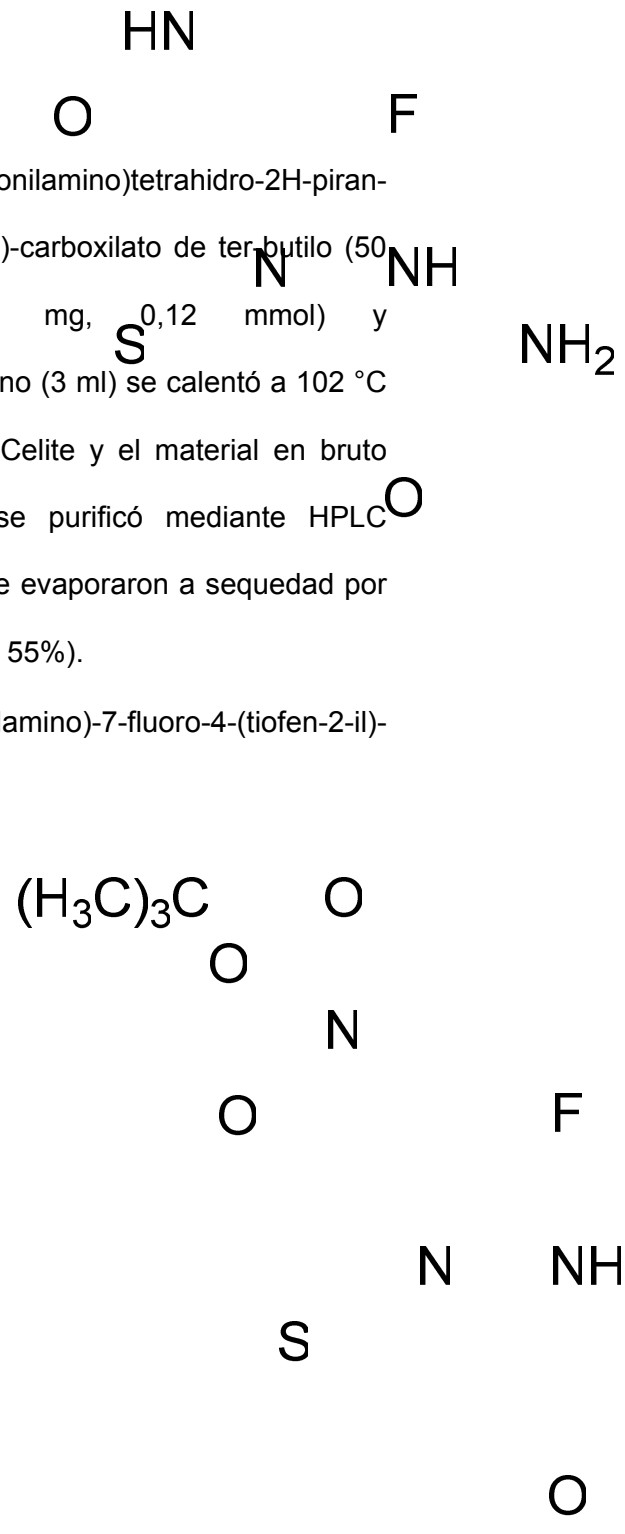
[0888] Ejemplo 127: 6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(tiofen-2-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



[0889] A. 6-((3R,4R)-3-(ter-Butoxicarbonilamino)tetrahidro-2H-piran-4-ilamino)-7-fluoro-3-oxo-4-(tiofen-2-il)-1H-pirrolo[3,4-c]piridin-2(3H)-carboxilato de ter-butilo



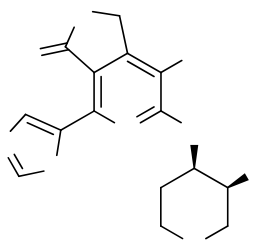
[0890] Una solución de 6-((3R,4R)-3-(ter-butoxicarbonilamino)tetrahidro-2H-piran-4-ilamino)-4-cloro-7-fluoro-3-oxo-1H-pirrolo[3,4-c]piridin-2(3H)-carboxilato de ter-butilo (50 mg, 0,1 mmol), tributil(tiofen-2-il)estannano (44,7 mg, 0,12 mmol) y tetrakis(trifenilfosfina)paladio(0) (115 mg, 0,1 mmol) en tolueno (3 ml) se calentó a 102 °C durante 24 h. El sólido se filtró a través de un lecho de Celite y el material en bruto resultante se reconstituyó en MeOH/DCM (20 ml) y se purificó mediante HPLC preparativa. Las fracciones recolectadas se combinaron y se evaporaron a sequedad por evaporación rotativa para dar el compuesto del título (30 mg, 55%).



[0891] B. 6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(tiofen-2-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona

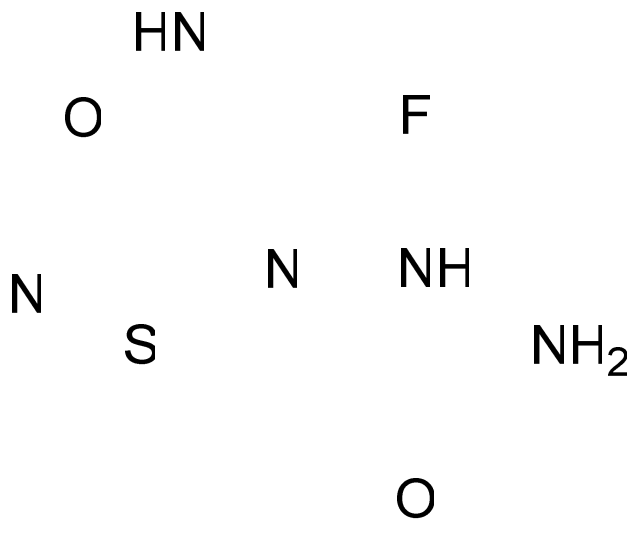
[0892] Una solución de 6-((3R,4R)-3-(ter-butoxicarbonilamino)tetrahidro-2H-piran-4-ilamino)-7-fluoro-3-oxo-4-(tiofen-2-il)-1H-pirrolo[3,4-c]piridin-2(3H)-carboxilato de ter-butilo (30 mg, 0,055 mmol) en TFA/DCM (1:1, 10 ml) se agitó a temperatura ambiente durante 2 h. Se eliminó el disolvente y el material en bruto resultante se reconstituyó en MeOH/DCM (20 ml) y se purificó mediante HPLC preparativa. Las fracciones recolectadas se combinaron y se evaporaron a sequedad por evaporación rotativa para dar el compuesto del título (16 mg, 85%). 1H RMN (500 MHz, DMSO-d6) δ ppm 1,79 (d, J=9,76 Hz, 1 H), 2,12 (qd, J=12,94, 5,13 Hz, 1 H), 3,56 - 3,68 (m, 1 H), 3,75 (d, J=11,72 Hz, 1 H), 3,89 (br s, 1 H), 4,02 (d, J=11,72 Hz, 2 H), 4,28 - 4,37 (m, 1 H), 4,38 - 4,49 (m, 2 H), 7,10 - 7,20 (m, 1 H), 7,28 (d, J=4,88 Hz, 1 H), 7,59 - 7,70 (m, 1 H), 7,93 (br s, 2 H), 8,52 (s, 1 H), 9,02 (dd, J=3,91, 0,98 Hz, 1 H). [M+H] calculado para C16H17FN4O2S, 349; experimental, 349.

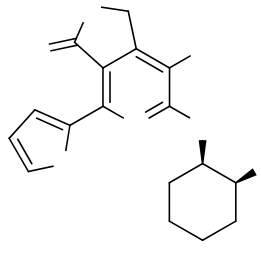
[0893] Ejemplo 128: 6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(tiazol-5-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



[0894] Se preparó una sal de TFA del compuesto del título de una manera similar al Ejemplo 127 utilizando 5-(tributilestannil)tiazol en lugar de tributil(tiofen-2-il)estannano. 1H RMN (500 MHz, DMSO-d6) δ ppm 1,78 (dd, J=13,67, 4,39 Hz, 1 H), 2,04 - 2,20 (m, 1 H), 3,53 - 3,66 (m, 1 H), 3,69 - 3,85 (m, 2 H), 4,01 (d, J=11,72 Hz, 2 H), 4,25 - 4,38 (m, 1 H), 4,41 - 4,55 (m, 2 H), 7,38 (s, 1 H), 7,94 (br s, 2 H), 8,62 (s, 1 H), 9,15 (s, 1 H), 9,52 (s, 1 H). [M+H] calculado para C15H16FN5O2S, 350; experimental, 350.

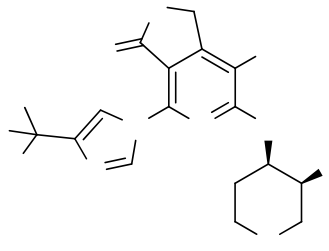
[0895] Ejemplo 129: 6-((1R,2S)-2-Aminociclohexilamino)-7-fluoro-4-(tiofen-2-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



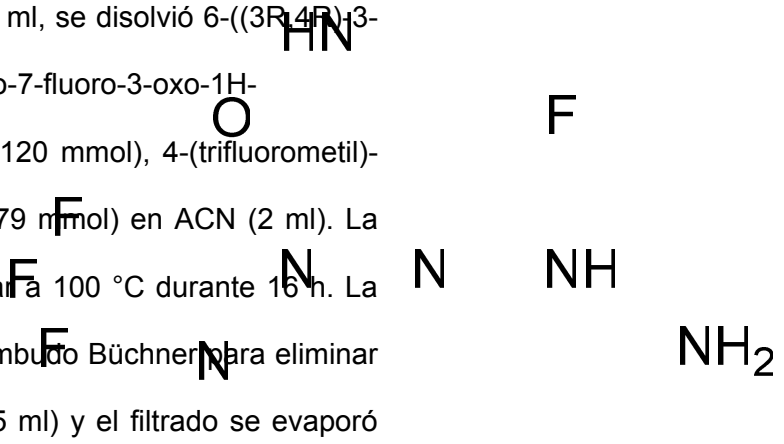


[0896] En un vial de vidrio con tapa hermética, de 30 ml, se disolvieron (1S,2R)-2-(4-cloro-2-(2,4-dimetoxibencil)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo (300 mg, 0,546 mmol), 4,4,5,5-tetrametil-2-(tiofen-2-il)-1,3,2-dioxaborolano (172 mg, 0,820 mmol), y trans-dicloro bis-(trifenilfosfina)paladio II (38,4 mg, 0,055 mmol) en dioxano (5 ml). Se añadió una solución acuosa de Na2CO3 2N (0,5 ml), la tapa fue cerrada herméticamente y la mezcla se dejó reaccionar a 85 °C durante 3 h. La mezcla de reacción se diluyó posteriormente con agua (5 ml) y se extrajo en EtOAc (2 x 30 ml). La capa orgánica se secó sobre sulfato de sodio y se evaporó. El residuo resultante se trató con TFA (4 ml) y se calentó a 80 °C durante 1 hora para eliminar los grupos protectores. A continuación, se evaporó el TFA a partir de la mezcla de reacción. El producto se reconstituyó en DMSO (8 ml) y se purificó a continuación mediante HPLC preparativa eluyendo con agua (0,05% de TFA) y ACN (gradiente 15-45 %, 0,035% de TFA). Las fracciones puras se combinaron y se evaporaron a un volumen mínimo. Se añadió NaHCO3 acuoso saturado (10 ml) y la mezcla se extrajo con AcOEt (3 x 25 ml). Las capas orgánicas se combinaron, se secaron sobre sulfato de sodio, y se evaporaron para dar el compuesto del título como un sólido de color amarillo pálido (83 mg, 44%). 1H RMN (400 MHz, DMSO-d6) δ ppm 1,16 - 1,80 (m, 8 H), 3,18 (br s, 1 H), 3,86 - 4,11 (m, 1 H), 4,39 (s, 2 H), 6,60 (d, J=6,57 Hz, 1 H), 7,13 (dd, J=5,05, 3,79 Hz, 1 H), 7,60 (dd, J=5,18, 1,14 Hz, 1 H), 8,39 (s, 1 H), 9,00 (dd, J=3,79, 1,01 Hz, 1 H). [M+H] calculado para C17H19FN4OS, 347; experimental, 347.

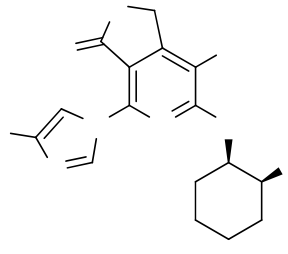
[0897] Ejemplo 130: 6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(4-(trifluorometil)-1H-imidazol-1-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



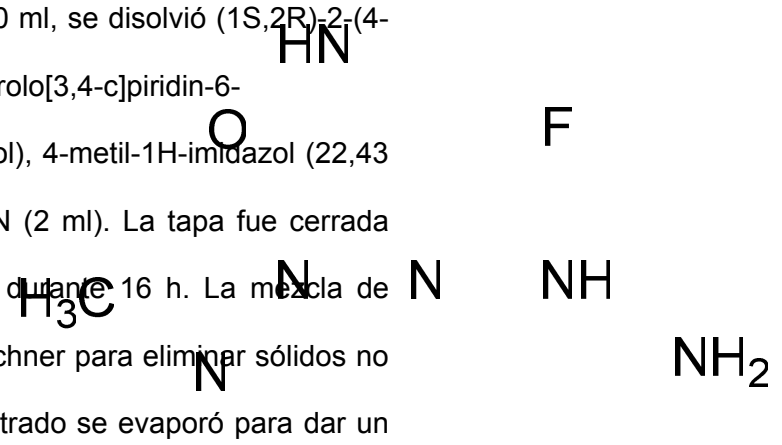
[0898] En un vial de vidrio con tapa hermética, de 10 ml, se disolvió 6-((3R,4R)-3-(ter-butoxicarbonilamino)tetrahidro-2H-piran-4-ilamino)-4-cloro-7-fluoro-3-oxo-1H-pirrolo[3,4-c]piridin-2(3H)-carboxilato de ter-butilo (60 mg, 0,120 mmol), 4-(trifluorometil)-1H-imidazol (48,9 mg, 0,359 mmol) y K2CO3 (66,2 mg, 0,479 mmol) en ACN (2 ml). La tapa se cerró herméticamente y la mezcla se hizo reaccionar a 100 °C durante 16 h. La mezcla de reacción se filtró posteriormente a través de un embudo Büchner para eliminar K2CO3 no disueltos. Los sólidos se lavaron con ACN (2 x 5 ml) y el filtrado se evaporó para dar un residuo, que se trató con TFA (2 ml) a temperatura ambiente durante 20 minutos para eliminar los grupos protectores. A continuación, se evaporó el TFA a partir de la mezcla de reacción. El producto se reconstituyó en DMSO (5 ml) y se purificó luego por HPLC preparativa eluyendo con agua (0,05% de TFA) y ACN (gradiente 15-45 %, 0,035% de TFA). Las fracciones puras se combinaron, se evaporaron a un volumen mínimo, y se liofilizaron para dar una sal de TFA del compuesto del título como un sólido de color marrón (4,2 mg, 8,8%). ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 1,67 (m, 1 H), 2,05 (td, J=12,88, 7,33 Hz, 1 H), 3,30 - 3,90 (m, 4 H), 3,78 - 3,99 (m, 2 H), 4,44 (s, 2 H), 6,49 (br s, 2 H), 7,54 (d, J=5,56 Hz, 1 H), 7,85 (br s, 2 H), 8,67 - 8,80 (m, 2 H). [M+H] calculado para C16H16F4N6O2, 401; experimental, 401.



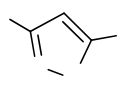
[0899] Ejemplo 131: 6-((1R,2S)-2-Aminociclohexilamino)-7-fluoro-4-(4-metil-1H-imidazol-1-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



[0900] En un vial de vidrio con tapa hermética, de 10 ml, se disolvió (1S,2R)-2-(4-cloro-2-(2,4-dimetoxibencil)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ter-butilo (50 mg, 0,091 mmol), 4-metil-1H-imidazol (22,43 mg, 0,273 mmol) y K2CO3 (50,3 mg, 0,364 mmol) en ACN (2 ml). La tapa fue cerrada herméticamente y la mezcla se hizo reaccionar a 100 °C durante 16 h. La mezcla de reacción se filtró posteriormente a través de un embudo Büchner para eliminar sólidos no disueltos. Los sólidos se lavaron con ACN (2 x 5 ml) y el filtrado se evaporó para dar un residuo, que se trató con TFA (4 ml) y se calentó a 80 °C durante 1 hora para eliminar los grupos protectores. A continuación, se evaporó el TFA a partir de la mezcla de reacción. El residuo resultante se reconstituyó en DMSO (5 ml) y se purificó mediante HPLC preparativa eluyendo con agua (0,05% de TFA) y ACN (gradiente 15-65 %, 0,035% de TFA). Las fracciones puras se combinaron, se evaporaron a un volumen mínimo, y se liofilizaron para dar una sal de TFA del compuesto del título como un sólido de color blanco (7,2 mg, 23%). 1H RMN (400 MHz, DMSO-d6) δ ppm 1,20-1,65 (m,, 8 H), 3,65 - 3,79 (m, 5 H), 4,15 (s, 2 H), 6,40 (d, 1 H), 6,51 (d, 1 H), 6,73 (m, 1 H), 6,97 (d, 1 H), 7,26 (d, 1 H), 8,68 (br s, 1 H). [M+H] calculado para C17H21FN6O, 345; experimental, 345.



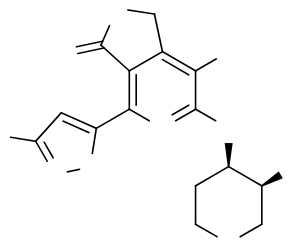
[0901] Preparación 52: 3-Metil-5-(tributilestannil)isotiazol



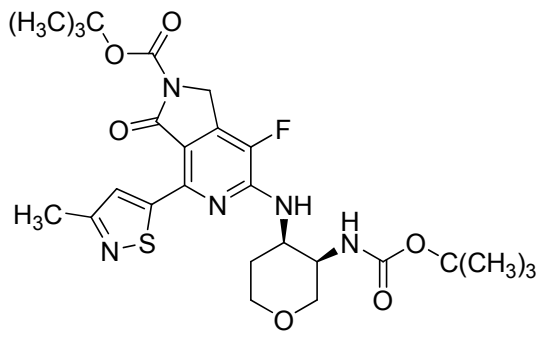
[0902] A una solución fría (-78 °C) de 3-metilisotiazol (100 mg, 1,0 mmol) en THF anhidro (2,0 ml) se añadió n-butil-litio (0,693 ml, 1,1 mmol) gota a gota. Después de agitar durante 60 min a -78 °C, se añadió una solución de tributilclorostannano (0,326 ml, 1,210 mmol) en THF anhidro (0,5 ml) a la mezcla de reacción. La mezcla de reacción se agitó

durante 30 min a -78 °C y luego se dejó calentar a temperatura ambiente durante un período de 2 a 3 h. Se añadió NaHCO3 acuoso saturado y la fase acuosa se extrajo con AcOEt (3 x 50 ml). La fase orgánica combinada se secó sobre Na2SO4 anhidro, se filtró y se evaporó a vacío. El residuo se purificó por cromatografía en columna de gel de sílice (9:1 hexano/acetato de etilo, columna Flash 60) para dar el compuesto del título. 1H RMN (500 MHz, CDCl3) δ ppm 0,86 - 0,94 (m, 9 H), 1,05 - 1,21 (m, 6 H), 1,26 - 1,38 (m, 6 H), 1,44 - 1,65 (m, 6 H), 2,56 (s, 3 H), 6,97 - 7,04 (m, 1 H)

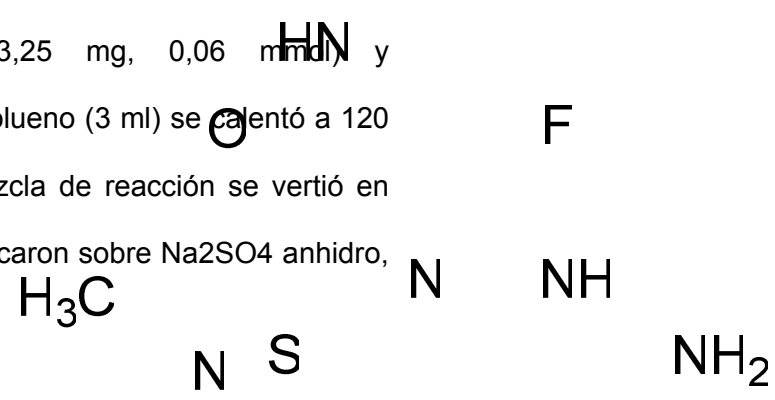
[0903] Ejemplo 132: 6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(3-metilisotiazol-5-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



[0904] A. 6-((3R,4R)-3-(ter-butoxicarbonilamino)tetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(3-metilisotiazol-5-il)-3-oxo-1H-pirrolo[3,4-c]piridin-2(3H)-carboxilato de ter-butilo



[0905] Una solución de 6-((3R,4R)-3-(ter-butoxicarbonilamino)tetrahidro-2H-piran-4-ilamino)-4-cloro-7-fluoro-3-oxo-1H-pirrolo[3,4-c]piridin-2(3H)-carboxilato de ter-butilo (10 mg, 0,02 mmol), 3-metil-5-(tributilestannil)isotiazol (23,25 mg, 0,06 mmol) y tetrakis(trifenilfosfina)paladio(0) (23,07 mg, 0,02 mmol) en tolueno (3 ml) se calentó a 120 °C durante 45 min bajo irradiación de microondas. La mezcla de reacción se vertió en agua y se extrajo con EtOAc. Los extractos orgánicos se secaron sobre Na2SO4 anhidro,

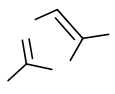


se filtraron y se evaporaron al vacío. Después de la eliminación del disolvente, el material en bruto resultante se reconstituyó en DMF y se purificó mediante HPLC preparativa eluyendo con agua (0,05% de TFA) y ACN (gradiente 55-80 %, 0,035% de TFA). Las fracciones recolectadas se combinaron y el ACN se eliminó mediante evaporación rotatoria. La solución resultante se neutralizó con NaHCO3 acuoso saturado acuoso y se lavó con EtOAc (2 x 50 ml), se secó sobre Na2SO4 anhidro, se filtró, y la fase orgánica se destiló hasta sequedad mediante evaporación rotatoria para dar el compuesto del título. [M+H] calculado para C26H34FN5O6S, 564; experimental, 564.

[0906] B. 6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(3-metilisotiazol-5-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona

[0907] A una solución de 6-((3R,4R)-3-(ter-butoxicarbonilamino)tetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(3-metilisotiazol-5-il)-3-oxo-1H-pirrolo[3,4-c]piridin-2(3H)-carboxilato de ter-butilo (5,5 mg, 9,76 µmol) en DCM (2,0 ml) se añadió TFA (2,0 ml, 26,0 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1 h, y se concentró al vacío. El material en bruto resultante se reconstituyó en DMF y se purificó mediante HPLC preparativa eluyendo con agua (0,05% de TFA) y ACN (gradiente 55-80%, 0,035% de TFA). Las fracciones recolectadas se combinaron y el ACN se eliminó mediante evaporación rotatoria. La solución resultante se neutralizó con NaHCO3 acuoso saturado, se lavó con EtOAc (2 x 50 ml), se secó sobre Na2SO4 anhidro, se filtró, y la fase orgánica se destiló hasta sequedad mediante evaporación rotatoria. El residuo se recristalizó en THF/hexano para dar una sal de TFA del compuesto del título. [M+H] calculado para C16H18FN5O2S, 364; experimental, 364.

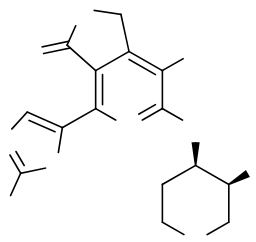
[0908] Preparación 53: 1: 2-Metil-5-(tributilestannil)tiazol



[0909] A una solución fría (-78 °C) de 2-metiltiazol (2,80 g, 28,2 mmol) en THF anhidro (100 ml) se añadió butil-litio (19,41 ml, 31,1 mmol) gota a gota. Después de agitar

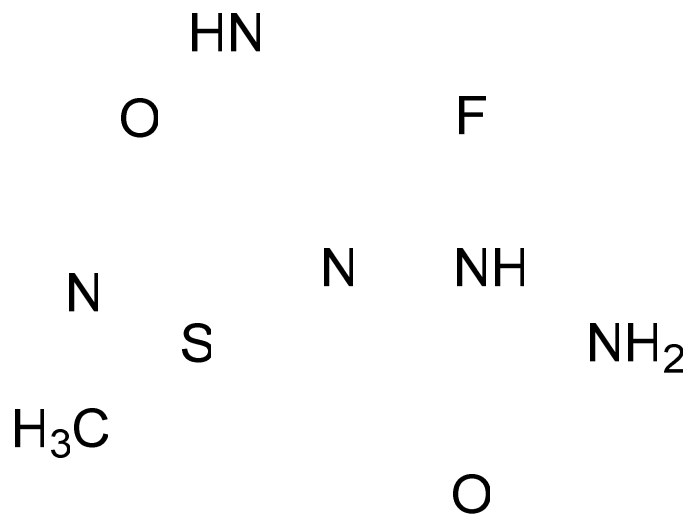
durante 60 min a -78 °C, se añadió una solución de tributilclorostannano (9,14 ml, 33,9 mmol) en THF anhidro a la mezcla de reacción. La mezcla de reacción se agitó durante 30 min a -78 °C y luego se dejó calentar a temperatura ambiente durante un período de 2 a 3 h. Se añadió NaHCO3 acuoso saturado y la fase acuosa se extrajo con éter (3 x 200 ml). La fase orgánica combinada se secó sobre Na2SO4 anhidro, se filtró y se evaporó a vacío. El producto en bruto se purificó en una columna de gel de sílice eluyendo con 10-50% de EtOAc en hexano durante un período de 60 min. Se recolectaron las fracciones y el disolvente se eliminó al vacío para dar el compuesto del título como un aceite de color amarillo (72%). 1H RMN (500 MHz, DMSO-d6) δ ppm 0,71 - 0,92 (m, 9 H), 0,96 - 1,18 (m, 6 H), 1,23 - 1,38 (m, 6 H), 1,40 - 1,64 (m, 6 H), 2,69 (s, 3 H), 7,56 (d, J=12,69 Hz, 1 H).

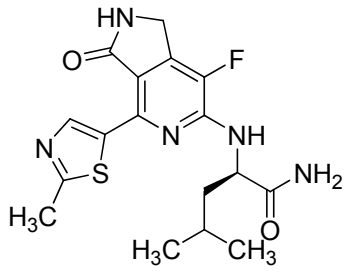
[0910] Ejemplo 133: 6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(2-metiltiazol-5-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona



[0911] Se preparó una sal de TFA del compuesto del título de una manera similar al Ejemplo 132 utilizando 2-metil-5-(tributilestannil)tiazol en lugar de 3-metil-5-(tributilestannil)isotiazol. 1H RMN (500 MHz, DMSO-d6) δ ppm 1,24 (s, 1 H), 1,73 (d, J=12,69 Hz, 1 H), 1,93 - 2,03 (m, 1 H), 2,57 - 2,71 (m, 4 H), 3,38 - 3,44 (m, 1 H), 3,48 - 3,55 (m, 1 H), 3,67 (d, J=11,72 Hz, 1 H), 3,82 - 3,97 (m, 2 H), 4,22 (br s, 1 H), 4,43 (s, 2 H), 7,06 (br s, 1 H), 8,52 (s, 1 H), 9,21 - 9,34 (m, 1 H). [M+H] calculado para C16H18FN5O2S, 364; experimental, 364.

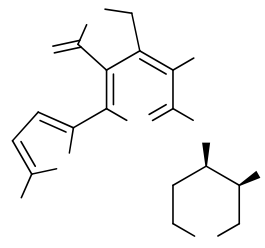
[0912] Ejemplo 134: (R)-2-(7-Fluoro-4-(2-metiltiazol-5-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida





[0913] El compuesto del título se preparó de una manera similar al Ejemplo 113 utilizando 2-metil-5-(tributilestannil)tiazol en lugar de tributil(furan-2-il)estannano. 1H RMN (500 MHz, DMSO-d6) δ ppm 0,74 - 0,98 (m, 6 H), 1,54 - 1,63 (m, 1 H), 1,64 - 1,83 (m, 2 H), 2,61 - 2,68 (m, 3 H), 4,41 (s, 2 H), 4,56 (ddd, J=10,50, 8,30, 4,15 Hz, 1 H), 6,97 (s, 1 H), 7,19 (d, J=7,81 Hz, 1 H), 7,35 (s, 1 H), 8,45 (s, 1 H), 9,22 (s, 1 H). [M+H] calculado para C17H20FN5O2S, 378; experimental, 378.

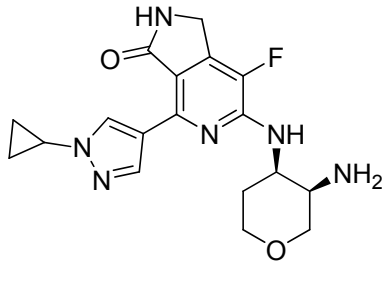
[0914] Ejemplo 135: 6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-4-(5-clorotiofen-2-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona



[0915] A una solución de 6-((3R,4R)-3-aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(tiofen-2-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona (12 mg, 0,034 mmol) en DCM (3 ml) se añadió piridina (8,17 mg, 0,103 mmol) y 1-cloropirrolidin-2,5-diona (4,60 mg, 0,034 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se diluyó posteriormente con MeOH (3 ml) y se purificó mediante HPLC preparativa eluyendo con agua (0,05% de TFA) y ACN (gradiente 45-70%, 0,035% de TFA). Las fracciones recolectadas se combinaron y el disolvente se eliminó por evaporación rotativa. El producto resultante se purificó por segunda vez con un eluyente de gradiente de ACN 15-45% en 0,035% de TFA (aq). Las fracciones recolectadas se combinaron y el disolvente se eliminó por evaporación rotativa para dar una sal de TFA

del compuesto del título (2 mg, 15%). 1H RMN (500 MHz, CD3OD) δ ppm 1,92 (d, J=13,18 Hz, 1 H), 2,14 (dd, J=12,69, 4,88 Hz, 1 H), 3,56 - 3,66 (m, 2 H), 3,65 - 3,78 (m, 1 H), 3,90 (d, J=12,20 Hz, 1 H), 4,04 - 4,19 (m, 3 H), 4,37 - 4,47 (m, 1 H), 6,99 (d, J=3,91 Hz, 1 H), 8,80 (d, J=3,91 Hz, 1 H). [M+H] calculado para C16H16ClFN4O2S, 383; experimental, 383.

[0916] Ejemplo 136: 6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-4-(1-ciclopropil-1H-pirazol-4-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona



[0917] Se cargó un vial de microondas de 2 ml, con 6-((3R,4R)-3-(ter-butoxicarbonilamino)tetrahidro-2H-piran-4-ilamino)-4-cloro-7-fluoro-3-oxo-1H-pirrolo[3,4-c]piridin-2(3H)-carboxilato de ter-butilo (55 mg, 0,11 mmol), 1-ciclopropil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (77 mg, 0,329 mmol), y cloruro de bis(trifenilfosfina)paladio (15,41 mg, 0,022 mmol) y se colocó en un ambiente inerte. Se añadió dioxano (1,1 ml) y la suspensión de color amarillo se desgasificó durante 5 min. A continuación se añadió Na2CO3 (220 µl, 0,439 mmol) a la suspensión, que causó que la suspensión de reacción se torne de color naranja. La mezcla se desgasificó durante 3 minutos más. Se tapó el recipiente y la mezcla de reacción se calentó a 80 °C durante 4 h. La mezcla de reacción se diluyó posteriormente con EtOAc (10 ml) y se lavó con agua (8 ml) seguido por salmuera (8 ml). La fase orgánica se recolectó, se secó sobre Na2SO4, y se concentró a un aceite, que se diluyó con DCM (2 ml) y se trató con HCl (4 M en dioxano, 1 ml). La mezcla se agitó durante 1 hora a temperatura ambiente, y luego se concentró. El residuo se diluyó con MeOH (2 ml) y se purificó mediante HPLC preparativa para dar una sal de TFA del compuesto del título como un sólido de color blanco. 1H RMN

(DMSO-d6) δ ppm 1,75 (t, 1 H), 2,03 - 2,17 (m, 1 H), 3,57 - 3,67 (m, 1 H), 3,78 (br s, 1 H), 3,82 - 3,88 (m, 1 H), 3,93 - 4,02 (m, 2 H), 4,39 (d, J=5,3 Hz, 2 H), 4,45 - 4,54 (m, 1 H), 4,82 (d, J=5,8 Hz, 2H), 5,15 (dd, J=17,2, 1,5 Hz, 1H), 5,22 (dd, J=10,2, 1,4 Hz, 1 H), 6,04 (dddd, J=16,8, 10,6, 5,8, 5,7 Hz, 1 H), 7,09 (d, J=5,3 Hz, 1 H), 7,93 (d, J=4,3 Hz, 3 H), 8,32 (s, 1 H), 8,40 (s, 1 H), 8,85 - 9,03 (m, 1 H). [M+H] calculado para C18H21FN6O2, 373; experimental, 373.

[0918] TABLA 1, a continuación, se enumeran los datos de inhibición de la SYK para muchos de los compuestos que se describen en los ejemplos, donde los valores de pIC50 más grandes representan una mayor potencia. Los compuestos se ensayaron de acuerdo con el ensayo que se describe en la página 63 de la memoria descriptiva.

Tabla 1. Inhibición de SYK (pIC50) para Compuestos de Ejemplo (Ej)

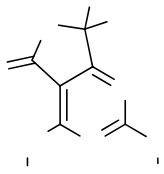
Ej	pIC50	Ej	pIC50	Ej	pIC50	Ej	pIC50	Ej	pIC50	Ej	pIC50	Ej	pIC50
1	8,1	21	6,3	41	5,9	61	7,2	81	8,5	101	7,2	121	5,4
2	6,9	22	5,7	42	6,8	62	8,0	82	9,2	102	8,4	122	6,2
3	7,6	23	8,7	43	5,3	63	8,1	83	6,6	103	6,9	123	8,1
4	7,8	24	7,6	44	6,2	64	8,0	84	7,7	104	8,7	124	7,6
5	6,2	25	9,0	45	6,1	65	8,0	85	8,4	105	9,0	125	8,0
6	6,3	26	7,5	46	5,8	66	6,3	86	5,6	106	8,6	126	8,1
7	6,0	27	7,4	47	8,6	67	7,4	87	7,2	107	6,3	127	8,2
8	8,1	28	8,6	48	6,1	68	7,0	88	8,5	108	8,6	128	7,7
9	5,1	29	8,5	49	<4,7	69	6,8	89	8,4	109	8,5	129	8,4
10	<4,7	30	8,4	50	8,6	70	8,8	90	8,0	110	7,3	130	5,0
11	5,9	31	8,6	51	7,2	71	8,1	91	6,6	111	8,1	131	<4,7
12	5,7	32	5,4	52	7,2	72	7,5	92	7,9	112	8,7	132	8,4
13	8,7	33	7,3	53	5,8	73	8,1	93	8,0	113	6,7	133	7,6

Ej	pIC50	Ej	pIC50	Ej	pIC50	Ej	pIC50	Ej	pIC50	Ej	pIC50	Ej	pIC50
14	6,9	34	6,5	54	6,6	74	8,3	94	8,5	114	6,6	134	
15	6,0	35	7,3	55	7,8	75	9,1	95	5,4	115	6,5	135	
16	5,5	36	7,6	56	5,6	76	9,3	96	6,7	116	8,1	136	7,5
17	7,4	37	6,0	57	7,8	77	7,5	97	6,8	117	7,9		
18	7,1	38	6,2	58	5,8	78	8,4	98	5,7	118	7,9		
19	6,6	39	5,5	59	7,1	79	7,7	99	8,5	119	7,8		
20	6,7	40	6,6	60	7,8	80	5,5	100	6,8	120	6,6		

[0919] Tal como se utiliza en esta memoria descriptiva y las reivindicaciones adjuntas, artículos singulares como “un”, “una”, “el” y “la” pueden referirse a un solo objeto o a una pluralidad de objetos a menos que el contexto indique claramente lo contrario. Así, por ejemplo, la referencia a una composición que contiene “un compuesto” puede incluir un solo compuesto o dos o más compuestos. Se ha de entender que la descripción anterior está destinada a ser ilustrativa y no restrictiva. Numerosas realizaciones serán evidentes para los expertos en la técnica al leer la descripción anterior. Por lo tanto, el alcance de la invención debe ser determinado con referencia a las reivindicaciones adjuntas, e incluye el pleno alcance de equivalentes a los que tales demandas tienen derecho. Las descripciones de todos los artículos y referencias, incluyendo patentes, solicitudes de patentes y publicaciones, se incorporan a la presente memoria por referencia en su totalidad y para todos los propósitos.

REIVINDICACIONES

1. Un compuesto de fórmula 1,



,

o su sal aceptable para uso farmacéutico, donde:

G se selecciona de N y C(R5);

L1 y L2 se seleccionan cada uno de ellos independientemente de NH y un enlace;

R1 y R2 se seleccionan cada uno de ellos independientemente de hidrógeno, halo, alquilo C1-3, y haloalquilo C1-3, o R1 y R2, junto con el átomo al cual están unidos, forman un cicloalquilo C3-6;

R3 se selecciona de alquilo C2-6, cicloalquilo C3-8, heterocicloalquilo C2-5, y heteroarilo C1-9, cada uno opcionalmente sustituido con uno a cinco sustituyentes independientemente seleccionados de halo, oxo, NO2, -CN, R6, y R7;

R4 se selecciona de cicloalquilo C3-8, heterociclilo C2-5, arilo C6-14, y heteroarilo C1-9, cada uno opcionalmente sustituido con uno a cinco sustituyentes independientemente seleccionados de halo, oxo, CN, R6, y R7;

R5 se selecciona de hidrógeno, halo, CN, alquilo C1-4, alquenilo C2-4, alquinilo C2-4, heterociclilo C2-5, heteroarilo C1-5, y R10, donde los restos alquilo, alquenilo, alquinilo están cada uno de ellos opcionalmente sustituidos con uno a cinco sustituyentes seleccionados independientemente de halo, -CN, oxo y R10, y donde el resto heterociclilo tiene 3 a 6 átomos del anillo y el resto heteroarilo tiene 5 o 6 átomos del anillo, y los restos heterociclilo y heteroarilo están cada uno de ellos opcionalmente sustituidos con uno a cuatro sustituyentes seleccionados independientemente de halo, NO2, -CN, alquilo C1-4, alquenilo C2-4, alquinilo C2-4, haloalquilo C1-4, y R10;

cada R6 se selecciona independientemente de OR8, -N(R8)R9, -NR8C(O)R9, -C(O)R8, -C(O)OR8, -C(O)N(R8)R9, -C(O)N(R8)OR9, -C(O)N(R8)S(O)2R9, -N(R8)S(O)2R9, -S(O)nR8, y -S(O)2N(R8)R9;

cada R7 se selecciona independientemente de alquilo C1-6, alquenilo C2-6, alquinilo C2-6, C3-6 cicloalquilo (CH2)m-, C6-14 aril-(CH2)m-, C2-5 heterociclilo (CH2)m-, y C1-9 heteroaril-(CH2)m-, cada uno de ellos opcionalmente sustituido con uno a cinco sustituyentes independientemente seleccionados de halo, oxo, NO2, -CN, alquilo C1-6, haloalquilo C1-6 y R10;

cada R8 y R9 se selecciona independientemente de hidrogeno o de alquilo C1-6, alquenilo C2-6, alquinilo C2-6, C3-6 cicloalquilo (CH2)m-, C6-14 aril-(CH2)m-, C2-5 heterociclilo (CH2)m-, y C1-9 heteroaril-(CH2)m-, cada uno de ellos opcionalmente sustituido con uno a cinco sustituyentes independientemente seleccionados de halo, oxo, NO2, -CN, alquilo C1-6, haloalquilo C1-6 y R10; cada R10 se selecciona independientemente de OR11, -N(R11)R12, -N(R11)C(O)R12, -C(O)R11, -C(O)OR11, -C(O)N(R11)R12, -C(O)N(R11)OR12, -C(O)N(R11)S(O)2R12, -NR11S(O)2R12, -S(O)nR11, y -S(O)2N(R11)R12;

cada R11 y R12 se selecciona independientemente de hidrógeno y alquilo C1-6;

cada n se selecciona independientemente de 0, 1 y 2; y

cada m se selecciona independientemente de 0, 1, 2, 3, y 4;

donde cada uno de los restos heteroarilo antes mencionados tiene uno a cuatro heteroátomos seleccionados independientemente de N, O, y S, y cada uno de los restos heterociclilo antes mencionados está saturado o parcialmente insaturado y tiene uno o dos heteroátomos independientemente seleccionados de N, O y S.

2. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con la reivindicación 1, donde L1 es NH.

3. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con la reivindicación 1, donde L1 es un enlace.

4. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con cualquiera de las reivindicaciones precedentes, donde L2 es NH.

5. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con cualquiera de las reivindicaciones 1 a 3, donde L2 es un enlace.

6. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con cualquiera de las reivindicaciones precedentes, donde G es N.

7. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con cualquiera de las reivindicaciones 1 a 5, donde G es C(R5).

8. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con cualquiera de las reivindicaciones precedentes, donde R1 y R2 son ambos hidrógeno.

9. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con cualquiera de las reivindicaciones precedentes, donde R3 es cicloalquilo C3-8, sustituido opcionalmente con de uno a cinco sustituyentes seleccionados independientemente de halo, oxo, -NO2, -CN, R6, y R7.

10. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con la reivindicación 9, donde R3 es 2-amino-C3-8 cicloalqu-1-ilo, opcionalmente sustituido con uno a cuatro sustituyentes independientemente seleccionados de halo, oxo, -NO2, -CN, R6, y R7.

11. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con la reivindicación 10, donde R3 es 2-amino-ciclohex-1-ilo, opcionalmente sustituido con uno a cuatro sustituyentes independientemente seleccionados de halo, oxo, -NO2, -CN, R6, y R7.

12. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con cualquiera de las reivindicaciones 1 a 8, donde R3 es un alquilo C2-6, opcionalmente sustituido con uno a cinco sustituyentes independientemente seleccionados de halo, oxo, -NO2, -CN, R6, y R7.

13. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con la reivindicación 12, donde R3 es 2-amino-alqu-1-ilo C2-6, opcionalmente sustituido con uno a cuatro sustituyentes independientemente seleccionados de halo, oxo, -NO2, -CN, R6, y R7.

14. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con la reivindicación 13, donde R3 es un 2-aminoetan-1-ilo, opcionalmente sustituido con uno a cuatro sustituyentes independientemente seleccionados de halo, oxo, -NO2, -CN, R6, y R7.

15. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con la reivindicación 14, donde R3 es un 2-amino-2-oxoetan-1-ilo, opcionalmente sustituido con uno a dos sustituyentes independientemente seleccionados de halo, oxo, -NO2, -CN, R6, y R7.

16. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con cualquiera de las reivindicaciones 1 a 8, donde R3 es un heterociclilo C2-5, opcionalmente

sustituido con uno a cinco sustituyentes independientemente seleccionados de halo, oxo, -NO2, -CN, R6, y R7.

17. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con la reivindicación 16, donde R3 es heterociclilo C2-5 sustituido con un amino y opcionalmente sustituido con de uno a cuatro sustituyentes adicionales independientemente seleccionados de halo, oxo, -NO2, -CN, R6, y R7.

18. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con la reivindicación 17, donde R3 es 3-aminotetrahidro-2H-piran-4-ilo, opcionalmente sustituido con uno a cuatro sustituyentes independientemente seleccionados de halo, oxo, -NO2, -CN, R6, y R7.

19. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con cualquiera de las reivindicaciones 1, y 3 a 8, donde R3 es heterociclilo C2-5 o un amino-heterociclilo C2-5 sustituido, cada uno opcionalmente sustituido con uno a cinco o de uno a cuatro sustituyentes respectivamente, independientemente seleccionados de halo, oxo, -NO2, -CN, R6, y R7, donde uno de los heteroátomos del resto heterociclilo se une directamente a L1, y L1 es un enlace.

20. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con cualquiera de las reivindicaciones precedentes, donde R4 se selecciona de arilo C6-14 y heteroarilo C1-9, cada uno opcionalmente sustituido con uno a cinco sustituyentes independientemente seleccionados de halo, oxo, -CN, R6, y R7.

21. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con cualquiera de las reivindicaciones precedentes, donde R4 es fenilo opcionalmente

sustituido con uno a cinco sustituyentes independientemente seleccionados de halo, -CN, R6, y R7.

22. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con cualquiera de las reivindicaciones 1 a 20, donde R4 es un heteroarilo C1-9 opcionalmente sustituido con uno a cinco sustituyentes independientemente seleccionados de halo, oxo, -CN, R6, y R7.

23. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con la reivindicación 22, donde R4 es un heteroarilo C2-4 monocíclico opcionalmente sustituido con uno a cuatro sustituyentes independientemente seleccionados de halo, -CN, R6, y R7.

24. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con la reivindicación 23, donde R4 se selecciona de pirrolilo, furanilo, tiofenilo, pirazolilo, imidazolilo, isoxazolilo, oxazolilo, isotiazolilo, y tiazolilo, cada uno de ellos sustituido opcionalmente con de uno a tres sustituyentes seleccionados independientemente de halo, -CN, R6, y R7.

25. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con la reivindicación 24, donde R4 se selecciona de tiofenilo, pirazolilo, isotiazolilo, y tiazolilo, cada uno de ellos sustituido opcionalmente con de uno a tres sustituyentes seleccionados independientemente de halo, -CN, R6, y R7.

26. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con la reivindicación 25, donde R4 es pirazolilo sustituido opcionalmente con de uno a tres sustituyentes seleccionados independientemente de halo, -CN, R6, y R7.

27. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con la reivindicación 19, donde R4 es pirazol-4-ilo opcionalmente sustituido con uno a tres sustituyentes independientemente seleccionados de halo, -CN, R6, y R7.

28. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con cualquiera de las reivindicaciones 20 a 27, donde R4 está sustituido con metilo, etilo, ciclopropilo o haloalquilo C1-2.

29. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con cualquiera de las reivindicaciones 1 a 5 y 7 a 28, donde R5 es heteroarilo C1-5 , opcionalmente sustituido con uno a cuatro sustituyentes independientemente seleccionados de halo, NO2, -CN, alquilo C1-4, alquenilo C2-4, alquinilo C2-4, haloalquilo C1-4, y R10.

30. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con cualquiera de las reivindicaciones 1 a 5 y 7 a 28, donde R5 se selecciona de hidrógeno y halo.

31. Un compuesto o sal aceptable para uso farmacéutico de acuerdo con la reivindicación 30, donde R5 se selecciona de cloro y flúor.

32. Un compuesto de acuerdo con la reivindicación 1, el cual se selecciona de los siguientes compuestos:

2-((1R,2S)-2-aminociclohexilamino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(3-fluorofenilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(3-clorofenilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

4-(1H-indazol-6-ilamino)-2-((1R,2S)-2-aminociclohexilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(3-trifluorometil)fenilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

cis-2-(2-aminociclohexilamino)-4-(3-(trifluorometil)fenilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-(1-metil-1H-pirazol-4-il)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-(4-etilpiperazin-1-il)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-(ciclohexilamino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

cis-2-(2-hidroxiciclohexilamino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-(3-aminopiperidin-1-il)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

6-((1R,2S)-2-aminociclohexilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(1-metil-1H-pirazol-4-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(1-isobutil-1H-pirazol-4-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-fenil-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(benzo[b]tiofen-3-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(1-etil-1H-pirazol-4-il)-6,7-dihidro-5H-

pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(1-bencil-1H-pirazol-4-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(imidazo[1,2-a]piridin-3-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(1-propil-1H-pirazol-4-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(1-(2-metoxietil)-1H-pirazol-4-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

4-(1H-indazol-6-ilamino)-6-((1R,2S)-2-aminociclohexilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-4-(4-fluoro-3-metilfenilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-7-fluoro-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-aminotetrahidro-2H-piran-4-ilamino)-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-7-cloro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-7-fluoro-4-(pirazolo[1,5-a]piridin-3-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

2-(2-(aminometil)piperidin-1-il)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

6-((1R,2S)-2-aminociclohexilamino)-4-(3-(metilsulfonil)fenilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclopentilamino)-4-(3-(metilsulfonil)fenilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(R)-4-metil-2-(4-(3-(metilsulfonil)fenilamino)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)pentanamida;

(R)-4-metil-2-(4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)pentanamida;

2-((1R,2S)-2-(dimetilamino)ciclohexilamino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-(metilamino)ciclohexilamino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2'-((1R,2S)-2-(aminociclohexilamino)-4'-(m-tolilamino)espiro[ciclopropano-1,7-pirrolo[3,4-d]pirimidin-5'(6'H)-ona;

2-(2-aminoetilamino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-(2-amino-2-metilpropilamino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-(5-oxo-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-2-ilamino)acetamida;

2-((2-aminoetil)(metil)amino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-(pirrolidin-2-ilmetilamino)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-(3-aminopirrolidin-1-il)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(1,5-dimetil-1H-pirazol-4-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(1-propil-1H-indol-2-il)-6,7-dihidro-5H-

pirrolo[3,4-d]pirimidin-5-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(1H-pirazol-5-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

2-(3-aminopropil)-4-(m-tolilamino)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

6-((1R,2S)-2-aminociclohexilamino)-4-(benzofuran-3-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-7-fluoro-4-(imidazo[1,2-a]piridin-3-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-4-(benzo[b]tiofen-3-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1S,2R)-2-aminociclohexilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(R)-6-(2-amino-3-etoxipropilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(R)-6-(2-amino-3-etoxipropilamino)-7-fluoro-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-(2-amino-3,3,3-trifluoropropilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(R)-4-metil-2-(3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)pentanamida;

6-(cis-4-aminotetrahidrofuran-3-ilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-4-(1-etil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-4-(1-etil-1H-pirazol-4-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-4-(1-ciclopropil-1H-pirazol-4-il)-1H-pirrolo[3,4-

c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-4-(1-(difluorometil)-1H-pirazol-4-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-4-(1-ciclopropil-1H-pirazol-4-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

cis-6-(2-aminociclohexilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-(cis-2-amino-4,4-difluorociclopentilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-(cis-2-amino-3,3-difluorociclohexilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-(cis-2-amino-3,3-difluorociclohexilamino)-4-(1-(difluorometil)-1H-pirazol-4-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-(cis-2-amino-3,3-difluorociclohexilamino)-4-(1-ciclopropil-1H-pirazol-4-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(R)-2-(7-fluoro-4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

(R)-2-(4-(1-(difluorometil)-1H-pirazol-4-il)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

(R)-2-(4-(1-ciclopropil-1H-pirazol-4-il)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

(R)-2-(4-(benzofuran-3-il)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

(R)-2-(7-fluoro-3-oxo-4-(pirazolo[1,5-a]piridin-3-il)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

6-((1R,2S)-2-aminociclohexilamino)-7-cloro-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-7-carbonitrilo;

(R)-6-(2-amino-3-metoxipropilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(R)-6-(2-amino-3-metoxipropilamino)-3-oxo-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-7-carbonitrilo;

(R)-6-(2-amino-3-metoxipropilamino)-7-fluoro-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

7-acriloil-6-((1R,2S)-2-aminociclohexilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-7-yodo-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-7-(1H-pirazol-4-il)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-(cis-2-amino-3,3-difluorociclohexilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-7-(1-metil-1H-pirazol-5-il)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-aminotetrahidro-2H-piran-4-ilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-4-aminotetrahidro-2H-piran-3-ilamino)-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

ter-butilo (1S,2R)-2-(3-oxo-7-fenil-4-(m-tolilamino)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)ciclohexilcarbamato de ;

6-((1R,2S)-2-aminociclohexilamino)-7-metil-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-

3(2H)-ona;

6-((3R,4R)-3-aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(m-tolilamino)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-7-metil-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(R)-6-(2-amino-3-metoxipropilamino)-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(pirazolo[1,5-a]piridin-3-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-aminotetrahidro-2H-piran-4-ilamino)-4-(1-(difluorometil)-1H-pirazol-4-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-aminotetrahidro-2H-piran-4-ilamino)-4-(benzofuran-3-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(S)-6-(3-aminopirrolidin-1-il)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(S)-6-(3-aminopiperidin-1-il)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-7-fluoro-4-(1-isopropil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

7-fluoro-4,6-bis(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-aminociclohexilamino)-7-bromo-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

2-((1R,2S)-2-aminociclohexilamino)-4-(1-(4-fluorofenil)-1H-pirazol-4-il)-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-5-ona;

(R)-6-(2-amino-3-metoxipropilamino)-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(tiofen-3-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(4-metiltiofen-2-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-Aminociclohexilamino)-7-fluoro-4-(4-metiltiofen-2-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-Aminociclohexilamino)-7-fluoro-4-(tiofen-3-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(R)-2-(7-Fluoro-4-(1-metil-1H-pirazol-4-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-N,4-dimetilpentanamida;

6-((1R,2S)-2-Aminociclohexilamino)-7-fluoro-4-(5-metiltiofen-2-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(R)-2-(7-Fluoro-4-(4-metiltiofen-2-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

(R)-2-(7-Fluoro-3-oxo-4-(tiofen-3-il)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

(R)-2-(7-Fluoro-4-(5-metiltiofen-2-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

6-((1R,2S)-2-Aminociclohexilamino)-4-(2-aminotiazol-5-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(R)-2-(7-Fluoro-4-(furan-2-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

(R)-2-(7-Fluoro-4-(furan-3-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

(R)-2-(7-Fluoro-4-(furan-2-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

(R)-2-(4-(5-Cianotiofen-2-il)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

(R)-2-(4-(4-Cianotiofen-2-il)-7-fluoro-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

(R)-2-(7-Fluoro-3-oxo-4-(tiazol-5-il)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

(R)-2-(7-Fluoro-4-(isotiazol-5-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

6-((1R,2S)-2-Aminociclohexilamino)-7-fluoro-1,1-dimetil-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

((1R,2S)-2-Aminociclohexilamino)-7-fluoro-4-(1-metil-1H-pirazol-3-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-Aminociclohexilamino)-7-fluoro-4-(2-metiltiazol-5-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(5-metiltiofen-2-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-Aminociclohexilamino)-7-fluoro-1-metil-4-(1-metil-1H-pirazol-4-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(R)-2-(7-Fluoro-3-oxo-4-(tiofen-2-il)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(tiofen-2-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(tiazol-5-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-Aminociclohexilamino)-7-fluoro-4-(tiofen-2-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(4-(trifluorometil)-1H-imidazol-1-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((1R,2S)-2-Aminociclohexilamino)-7-fluoro-4-(4-metil-1H-imidazol-1-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(3-metilisotiazol-5-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-7-fluoro-4-(2-metiltiazol-5-il)-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

(R)-2-(7-Fluoro-4-(2-metiltiazol-5-il)-3-oxo-2,3-dihidro-1H-pirrolo[3,4-c]piridin-6-ilamino)-4-metilpentanamida;

6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-4-(5-clorotiofen-2-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

6-((3R,4R)-3-Aminotetrahidro-2H-piran-4-ilamino)-4-(1-ciclopropil-1H-pirazol-4-il)-7-fluoro-1H-pirrolo[3,4-c]piridin-3(2H)-ona;

un estereoisómero de cualquiera de los compuestos antes mencionados; y

un sal aceptable para uso farmacéutico de cualquiera de los compuestos o estereoisómeros antes mencionados.

33. Una composición farmacéutica que comprende:

un compuesto o sal aceptable para uso farmacéutico según se definió en cualquiera de las reivindicaciones 1 a 32; y

un excipiente aceptable para uso farmacéutico.

34. Un uso de un compuesto o sal aceptable para uso farmacéutico según se definió en cualquiera de las reivindicaciones 1 a 32, como medicamento.

35. Un uso de un compuesto o sal aceptable para uso farmacéutico según se

definió en cualquiera de las reivindicaciones 1 a 32, para la producción de un medicamento para el tratamiento de una enfermedad o afección para la cual se indica un inhibidor de SYK.

36. Un método para tratar una enfermedad o afección en un sujeto para la cual se indica un inhibidor de la SYK, comprendiendo el método la administración al sujeto de una cantidad eficaz de un compuesto o sal aceptable para uso farmacéutico según se define en cualquiera de las reivindicaciones 1 a 32.

37. Un método para el tratamiento de una enfermedad o afección en un sujeto, el método comprende administrar al sujeto una cantidad eficaz de un o sal aceptable para uso farmacéutico según se define en cualquiera de las reivindicaciones 1 a 32, donde la enfermedad o afección se selecciona de riñitis alérgica, asma alérgico, y dermatitis atópica, artritis reumatoide, esclerosis múltiple, lupus eritematoso sistémico, soriasis, púrpura trombocitopénica inmune, enfermedad inflamatoria intestinal, enfermedad pulmonar obstructiva crónica y trombosis.

38. Un método para tratar una enfermedad o afección en un sujeto, el método comprende la administración al sujeto de una cantidad eficaz de un compuesto o sal aceptable para uso farmacéutico según se define en cualquiera de las reivindicaciones 1 a 32, donde la enfermedad o afección se selecciona de una malignidad hematológica y un cáncer epitelial.

39. Un método de acuerdo con la reivindicación 38, donde la malignidad hematológica se selecciona de leucemia mieloide aguda, leucemia linfocítica crónica de las células B, linfoma de las células B, y linfoma de las células T.

40. Un método de acuerdo con la reivindicación 38, donde el cáncer epitelial se selecciona de cáncer de pulmón, cáncer pancreático, y cáncer de colon.

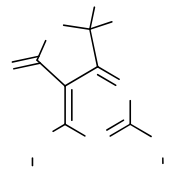
41. Una combinación de una cantidad eficaz de un compuesto o sal aceptable para uso farmacéutico según se define en cualquiera de las reivindicaciones 1 a 32, y al menos un agente farmacológicamente activo adicional.

42. Una combinación de acuerdo con la reivindicación 41, donde el agente farmacológicamente activo adicional es DMARD.

43. Una combinación de acuerdo con la reivindicación 42, donde el DMARD es metotrexato.

RESUMEN

Se divulgan los compuestos de fórmula 1,



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y sus sales aceptables para uso farmacéutico, donde G, L1, L2, R1, R2, R3, y R4 se definen en la memoria descriptiva. La presente divulgación además se refiere a materiales y métodos para preparar los compuestos de fórmula 1, las composiciones farmacéuticas que los contienen, y su uso para tratar trastornos, enfermedades, y afecciones que involucran el sistema inmune y la inflamación, que incluyen artritis reumatoide, malignidades hematológicas, canceres epiteliales (es decir, carcinomas), y otros trastornos, enfermedades, y afecciones para las cuales se indica la inhibición de la SYK.

