PCT

Industria y Comercio

SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

11-11423

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIRECCIÓN DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-011423- -00000-0000
Fecha: 2011-02-01 18:17:17 Dep: 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 429

SOLICITUD DE PA

INVENCIO

TITULO: DERIVADOS DE PIRAZOLO(3,4) PIRIMIDIM - 4-IL Y SUS USOS PARA TRATAR DIABETES Y OBESIDAD

SOLICITANTE: ASTRAZENECA AB

DIRECCIÓN: S-SE-151 85 Södertälje, Suecia

APODERADO: CARLOS R. OLARTE

BOGOTÁ 01 de Febrero de 2011

P2011/000023

04-03-2011

OLARTEMOURE

OLARTE MOURE & ASOCIADOS

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-011423- -00000-0000
Fecha: 2011-02-01 18:17:17 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTENII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 429

PETITORIO - FORMULARIO Ú
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2011/000023**

SOLICITUD DE:

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

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**	**Nombre:** ASTRAZENECA AB **Dirección:** S-SE-151 85 Södertälje **Nacionalidad o Domicilio:** Suecia **Lugar de Constitución:** Suecia **Teléfono:** _____ **Fax:** _____ **E-mail:** _____	**IDENTIFICACIÓN** **C.C.** [ ] **NIT** [ ] **C.E.** [ ] **Otro** [ ] **Cual** _____ **Número** _____
REPRESENTANTE O APODERADO	**Nombre:** CARLOS R. OLARTE **Dirección:** Diagonal 34 No. 5-28 Bogotá **Teléfono:** 601-7700 **Fax:** 601-7799 **E-mail:** office@olarteraisbeck.com	**IDENTIFICACIÓN** **C.C.** [x] **NIT** [ ] **C.E.** [ ] **Otro** [ ] **Cual** _____ **Número** 79.782.747 **TP** 74.295
INVENTOR (ES) (72)	**Nombre:** VER PAGINA ADJUNTA **Dirección:** VER PAGINA ADJUNTA **Nacionalidad o Domicilio:** VER PAGINA ADJUNTA	

(5) **PCT (86)**

Solicitud Internacional No. PCT/GB2009/050970 Fecha Agosto 03, 2009

Publicación Internacional No. WO 2010/015849 Fecha Febrero 11, 2010

(6) **Título (54)** DERIVADOS DE PIRAZOLO(3,4) PIRIMIDIN - 4-IL Y SUS USOS PARA TRATAR DIABETES Y OBESIDAD

Clasificación Internacional (51) C07D 487/04, A61K 31/519, A61P 3/04, A61P 3/10

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

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Agosto 04, 2008	61/085.919
US	Abril 09, 2009	61/168.048

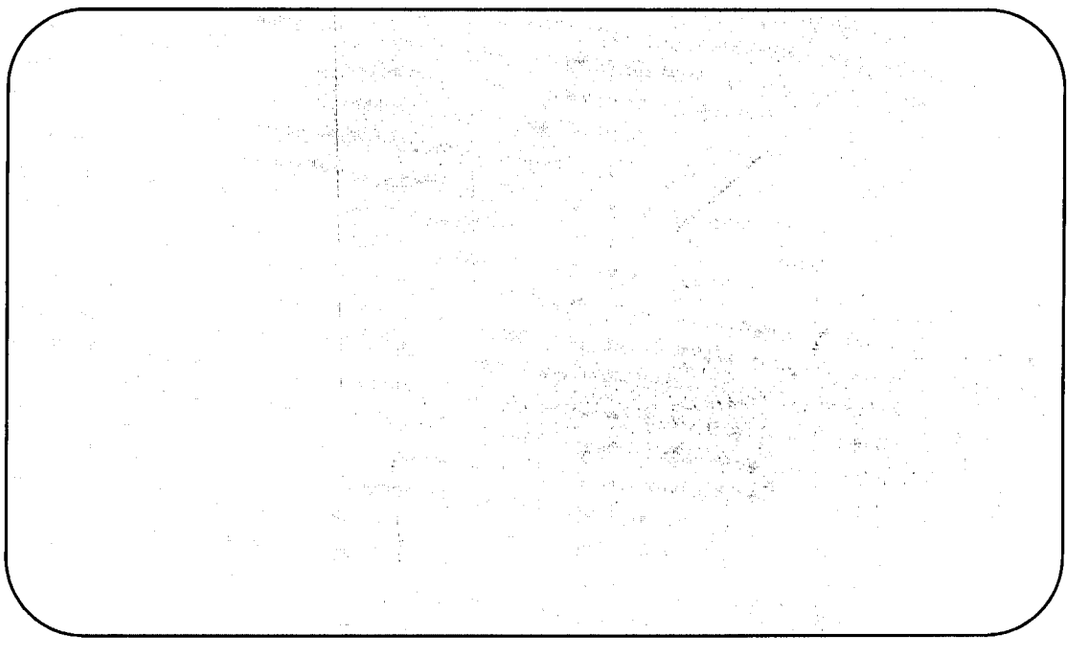
(9) **Comprobante de pago No.** 11- **Fecha** Febrero de 2011

(10) ANEXOS

2

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Adjunto copia simple. Ver Exp. Nº 08-139.814
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(11) FIGURA CARACTERÍSTICA:



(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

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

3

LISTA DE INVENTORES

PCT/GB2009/050970

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Gran Bretaña
Nacionalidad: Británica

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S-431 83 Mölndal
Suecia
Nacionalidad: Sueca

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 009212

Bogotá D.C., Febrero 01 de 2011 - 16:51:59

RECIBIDO DE : OLARTEPAISBECK NI 830.122.870

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	353914470	01/02/2011	4.568.000.00

*** Conceptos Pagados ***

CANT.	REUTISTICO	CONCEPTO	Vr.UNITARIO	Vr.CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCION	571.000.00	571.000.00
				$571.000.00

==========

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

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-011423- -00000-0000
Fecha: 2011-02-01 18:17:17 Dep: 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 376 FASENACIONALI
Act. 411 PRESENTACION Folios: 429

6

Traducción oficial de un documento cuyo original está en inglés

No. 11426

El Ministerio de Relaciones Exteriores en Estocolmo certifica por el presente documento que Mrs. Anna-Karin Östin, de la Oficina de Registro de Compañías de Suecia, Sundsvall, ha expedido y firmado la anterior certificación en su calidad oficial.

En Estocolmo, este día 14 de Agosto de 2007.

(Firmado)

Hay un sello del Ministerio de Relaciones Exteriores de Suecia.

Hay un sello firmado de la Embajada de Sudán en Estocolmo.

Firma de Agneta S...

Y sello de ...

Firma: Mohamed Hussein.

Fecha: 20 de Agosto de 2007.

Sello: "Anne-Maria Bonde - Notario Público de Estocolmo".

Certificación Notarial

Yo, la suscrita Anne-Marie Bonde, Notario Público de la ciudad de Estocolmo, certifico por medio del presente que Anders Burén, debidamente autorizado para firmar en nombre de Astrazeneca AB ha expedido y firmado el anterior documento en original, del cual la presente es una copia auténtica.

Derechos: 340 coronas. Estocolmo, 26 de Octubre de 2007.

Ex oficio:

(Firmado) Sello: "Anne-Marie Bonde – Notario Público de Estocolmo".

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

Apostilla adjunta:

APOSTILLE
(Convention du La Haye du 5 octobre 1961)

1. País:	Suecia
	El presente documento público
2. Ha sido firmado por:	Anne-Marie Bonde
3. Actuando en calidad de:	Notario Público
4. Lleva el sello / estampilla de:	Notario Público de Estocolmo.
	Certificado
5. En:	Estocolmo
6. El:	Día 26 de Octubre de 2007
7. Por:	Björn Sandin, Notario Público
8. Bajo el No.	4071
9. Sello / estampilla:	Björn Sandin, Notario Público de Estocolmo.
10. Firma:	(Firmado)

Certificación:

Certifico que la presente es una traducción verdadera y completa del documento adjunto: "Cert.Min. Rel."

Fecha: 13 de Noviembre de 2007.

Traductor: Jorge Enrique Sierra Reyes.

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

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

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

E-mail: treseser1@yahoo.com. No. 10-054

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

7

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. **Country :** Sweden

   This public document

2. **has been signed by** Anne-Marie Bonde

3. **acting in the capacity of** Notary Public

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

   Notary Public in Stockholm

Certified

5. **at** Stockholm 6. **the** 26.10.2007

7. **by** Björn Sandin

   Notary Public

8. **No** 4071

9. **Seal/stamp:** 10. **Signature:**



OLARTERAISBECK
OLARTE RAISBECK & FRIERI LTDA.

Carlos R. Olart
J. Ian Raisbec
Ana María Frie
Juan Guillermo Mour
Natalia Castr

Zayde Chahí
Simón Salins
Alexander Agudel
Camilo A. Rodrígue
Lina Mosquer
Catalina Barbastefan

Of Couns
Guillermo Chahí
Graciela Mel
Jacqueline Chaparr
Cruz E. de Moncalean

Power of Attorney

The undersigned,

domiciled in

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

Poder

El suscrito,

AstraZeneca AB

domiciliado en

Vastra Malarehamnen 9 S-151 85 Södertälje, Sweden

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

Signature/Firma: Anders Burén
Authorized Signatory

Date/Fecha: 24 OCTOBER 2007

City,Country/Ciudad,País: SÖDERTÄLJE

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

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

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I, the undersigned, Anne-Marie Bonde, Notary Public of the City of Stockholm
hereby certify that
ANDERS BURÉN
duly authorized to sign for
ASTRAZENECA AB
has issued and signed the foregoing document.

Fee 340:- Stockholm 2007-10-26
Crowns Ex officio:

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

Anders Burén
Authorised Signatory

MODEL OF NOTARIAL CERTIFICATION

Notarial Certification

On this date,

The undersigned Notary Public certifies:

1. That

of legal age and domiciled in

signed the foregoing document.

2. That the grantor has executed the foregoing document as DULY AUTHORISED SIGNATORY of ASTRAZENECA AB

3. That ASTRAZENECA AB having its principal place of business located in SODERTALJE, SWEDEN is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.

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

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

1. CERTIFICATE OF INCORPORATION OF ASTRAZENECA AB

2. AUTHORISATION IN FAVOUR OF SIGNATORY

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que

mayor de edad y domiciliado

suscribió el documento que antecede.

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

de

4. Que

con sede principal ubicada en

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

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

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

NOTARY PUBLIC (Signature):
Name and Particulars (e.g. Notary's name, Jurisdiction, Date of Licence Expiration)
SEAL (optional)

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

9

Traducción oficial de un documento cuyo original está en inglés

BOLAGSVERKET

851 81 Sund... Tel. 060-18 40 00 – Fax: 060 129840.
bolagsverket@bolagsverket (ilegible)

Certificado de Existencia

Yo, Anna-Karin Östin, de Bolagsverket, la Oficina de Registro de Compañías de Suecia, certifico por medio del presente documento que

AstraZeneca AB

Registro No. 556011-7482

es una compañía debidamente constituida según las leyes de Suecia, vigente y con existencia corporativa legal hasta donde muestran los registros de esta oficina en la fecha que se indica más adelante.

En testimonio de lo anterior, he puesto mi firma y estampado el sello oficial de Bolagsverket en Sundsvall, este día 8 de Agosto del año 2007.

(Firmado) Anna-Karin Östin.

Hay un sello de Bolagsverket

Bolagsverket, la Oficina de registro de Compañías de Suecia, es el Registrador Oficial de las Compañías Limitadas y otras formas de empresas comerciales en Suecia. Antes de que se expida un Certificado de existencia, los registros radicados en esta oficina se examinan para tener la seguridad de que la compañía en cuestión llena los siguientes requerimientos:

- La compañía tiene una Junta Directiva competente
- La compañía tiene un Auditor titulado calificado.

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

- La compañía ha llenado sus obligaciones con respecto a la radicación correcta de su informe anual.
- La compañía no es el sujeto de acciones legales de división de compañías, terminación o bancarrota.
- La compañía no ha sido disuelta como resultado de una fusión y no ha salido del registro por ninguna otra razón.

El Certificado está firmado por un funcionario autorizado para expedir estos y similares documentos en nombre de Bolagsverket, la Oficina de Registro de Compañías de Suecia.

Sello: "Anne-Marie Bonde -- Notario Público de Estocolmo".

Certificación Notarial

Yo, la suscrita Anne-Marie Bonde, Notario Público de la ciudad de Estocolmo, certifico por medio del presente que Anna-Karin Östin, debidamente autorizada para firmar en nombre de la Oficina de Registro de Compañías de Suecia, ha expedido y firmado el anterior documento en original, del cual la presente es una copia auténtica.

Derechos: 340 coronas. Estocolmo, 26 de Octubre de 2007.

Ex oficio:

(Firmado) Sello: "Anne-Marie Bonde – Notario Público de Estocolmo".

Apostilla adjunta:

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

10

APOSTILLE
(Convention du La Haye du 5 octobre 1961)

1. País:	Suecia
	El presente documento público
2. Ha sido firmado por:	Anne-Marie Bonde
3. Actuando en calidad de:	Notario Público
4. Lleva el sello / estampilla de:	Notario Público de Estocolmo.
	Certificado
5. En:	Estocolmo
6. El:	Día 26 de Octubre de 2007
7. Por:	Björn Sandin, Notario Público
8. Bajo el No.	4070
9. Sello / estampilla:	Björn Sandin, Notario Público de Estocolmo.
10. Firma:	(Firmado)

Certificación:

Certifico que la presente es una traducción verdadera y completa del documento adjunto: "Cert.Bolagsverket"

Fecha: 13 de Noviembre de 2007.

Traductor: Jorge Enrique Sierra Reyes.

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

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

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

E-mail: tresser1@yahoo.com. No. 10-053

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

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country : Sweden

This public document

2. has been signed by Anne-Marie Bonde

3. acting in the capacity of Notary Public

4. bears the seal/stamp of

Notary Public in Stockholm

Certified

5. at Stockholm **6. the** 26.10.2007

7. by Björn Sandin

Notary Public

8. No 4070

9. Seal/stamp: **10. Signature:**

NOTARIUS PUBLICUS STOCKHOLM
BJÖRN SANDIN

Bolagsverket

851 81 Sundsvall
Dockarevägen Badhusparken
Tel: 060-16 40 00 • Fax 060-12 33 40
bolagsverket@bolagsverket.se • bolagsverket.se

Certificate of Good Standing

I, Anna-Karin Östin, of Bolagsverket, the Swedish Companies Registration Office, do hereby certify that

AstraZeneca AB
registration number: **556011-7482**

is a duly incorporated company under the laws of Sweden and is in good standing and has a legal corporate existence as far as the records of this office show as of the date stated below.

In testimony hereof, I have hereunto set my hand and the official seal of Bolagsverket at Sundsvall, this 3rd day of August in the year of two thousand and seven.

Anna-Karin Östin

Bolagsverket, the Swedish Companies Registration Office, is the official register of limited companies and other forms of business enterprise in Sweden. Before a Certificate of Good Standing is issued, the records kept by this office are examined to ensure that the following requirements are fulfilled for the company in question:

- the company has a registered competent board of directors
- the company has a registered qualified auditor
- the company has fulfilled its obligations regarding the correct filing of its annual report
- the company is not the subject of company division, winding up or bankruptcy proceedings
- the company has not been dissolved as the result of a merger and has not been struck off the register for any other reason.

The Certificate is signed by an official authorized to issue these and similar documents on behalf of Bolagsverket, the Swedish Companies Registration Office.

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

12

No. 11426
The Ministry for Foreign Affairs in Stockholm, hereby certifies that
Mrs. Anna-Karin Åström

Swedish Companies Registration Office, Sundsvall

has issued and signed the foregoing attestation in his/her official capacity

For Stockholm this 14th day of August
PAID

Ingela Rosenlund

SIGNATURE OF Ingela Rosenlund
AND STAMP OF : Sw. MFA
SIGNATURE : Mohamed Hussein
DATE : 20-08-07

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BORGE

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 February 2010 (11.02.2010)

PCT

(10) International Publication Number
WO 2010/015849 A3

(51) International Patent Classification:
C07D 487/04 (2006.01) *A61P 3/04* (2006.01)
A61K 31/519 (2006.01) *A61P 3/10* (2006.01)

(21) International Application Number:
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3 August 2009 (03.08.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/085,919 4 August 2008 (04.08.2008) US
61/168,048 9 April 2009 (09.04.2009) US

(71) Applicant *(for all designated States except MG, US)*: **ASTRAZENECA AB** [SE/SE]; S-151 85 Södertälje (SE).

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(54) Title: PYRAZOLO [3,4] PYRIMIDIN-4-YL DERIVATIVES AND THEIR USES TO TREAT DIABETES AND OBESITY

(57) Abstract: A compound of Formula (I) is useful in the treatment or prevention of a disease or medical condition mediated through glucokinase (GLK or GK), leading to a decreased glucose threshold for insulin secretion.

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In one sub-type of diabetes, Maturity-Onset Diabetes of the Young Type 2 (MODY-2), the diabetes is caused by GLK loss of function mutations. Hyperglycaemia in MODY-2 patients results from defective glucose utilisation in both the pancreas and liver. Defective glucose utilisation in the pancreas of MODY-2 patients results in a raised threshold for glucose stimulated insulin secretion. Conversely, rare activating mutations of GLK reduce this threshold resulting in familial hyperinsulinism. In addition to the reduced GLK activity observed in MODY-2 diabetics, hepatic glucokinase activity is also decreased in type 2 diabetics. Importantly, global or liver selective overexpression of GLK prevents or reverses the development of the diabetic phenotype in both dietary and genetic models of the disease. Moreover, acute treatment of type 2 diabetics with fructose improves glucose tolerance through stimulation of hepatic glucose utilisation. This effect is believed to be mediated through a fructose induced increase in cytosolic GLK activity in the hepatocyte by the mechanism described below.

GLK and the K_{ATP} channel are expressed in neurones of the hypothalamus, a region of the brain that is important in the regulation of energy balance and the control of food intake. These neurones have been shown to express orectic and anorectic neuropeptides and have been assumed to be the glucose-sensing neurones within the hypothalamus that are either inhibited or excited by changes in ambient glucose concentrations. The ability of these neurones to sense changes in glucose levels is defective in a variety of genetic and experimentally induced models of obesity. Intracerebroventricular (icv) infusion of glucose analogues, that are competitive inhibitors of glucokinase, stimulate food intake in lean rats. In contrast, icv infusion of glucose suppresses feeding. Thus, small molecule activators of GLK may decrease food intake and weight gain through central effects on GLK. Therefore, GLK activators may be of therapeutic use in treating eating disorders, including obesity, in addition to diabetes. The hypothalamic effects will be additive or synergistic to the effects of the same compounds acting in the liver and/or pancreas in normalising glucose homeostasis, for the treatment of Type 2 diabetes. Thus the GLK system can be described as a potential "Diabesity" target (of benefit in both Diabetes and Obesity).

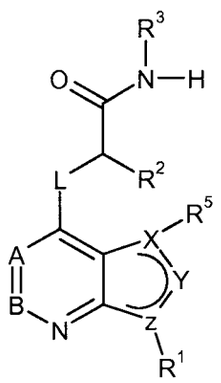
GLK is also expressed in specific entero-endocrine cells where it is believed to control the glucose sensitive secretion of the incretin peptides GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 (Glucagon-Like Peptide-1) from gut K-cells and L-

cells respectively. Therefore, small molecule activators of GLK may have additional beneficial effects on insulin secretion, b-cell function and survival and body weight as a consequence of stimulating GIP and GLP-1 secretion from these entero-endocrine cells.

A group of novel activators of GLK has been found containing a 1H-pyrazolo[3,4-d]pyrimidin-4-yl core. N-(Thiazolyl)-2-[(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thio]acetamide is disclosed in Phosphorus, Sulfur and Silicon, vol 178, 2003, pp1795-1805 which is concerned with antimicrobial activity of related compounds. Similar compounds are also known from commercially available Chemical Libraries.

WO98/35944 discloses that compounds of formula R^1R^2N-C(O)-$C(R^3)(R^4)$-X-R^5 in which R^1-R^5 are each individually selected from a wide range of substituents and X is oxygen or sulfur are useful in treating bulimia and obesity by virtue of their activity at the NPY receptor antagonists. R^5 may be 1*H*- pyrazolo[3,4-d]pyrimidin-4-yl or 4-aminopyrazolo[3,4-d]pyrimidin-6-yl. Specific compounds exemplified are *N*-(4-cyclohexylphenyl)-2-(1*H*-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl) acetamide, *N*-(4-benzoylphenyl)-2-(1*H*-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl) acetamide, 2-(4-amino-1*H*-pyrazolo[3,4-d]pyrimidin-6-ylsulfanyl)- *N*-(4-cyclohexylphenyl) acetamide and 2-(4-amino-1*H*-pyrazolo[3,4-d]pyrimidin-6-ylsulfanyl)- *N*-(4-benzoylphenyl) acetamide.

Thus, according to the first aspect of the invention there is provided a compound of Formula I:



(I)

or a pharmaceutically acceptable salt thereof in which:

A and B are each either N or CR^6, provided that at least one of A and B is CR^6;

X is C or N;

Y is CH or N;

Z is C or N;

wherein X, Y and Z are chosen such that at least two of X, Y and Z are N, the ring containing them is aromatic and any ring nitrogen atom is not quaternised;

R^1 is (1-6C)alkyl, aryl, aryl(1-6C)alkyl or HET-1 wherein the aryl, aryl(1-6C)alkyl and HET-1 are optionally substituted by one, two or three groups independently selected from halo, (1-4C)alkyl, (1-4C)alkoxy, trifluoromethyl, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, cyano, carboxy, (1-6C)alkoxycarbonyl, carbamoyl, *N*-(1-4C)alkylcarbamoyl, *N,N*-di(1-4C)alkylcarbamoyl, aminosulfonyl, (1-6C)alkylaminosulfonyl, di(1-6C)alkylaminosulfonyl, (1-4C)alkanoylamino, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl, di(1-4C)alkylamino(1-4C)alkyl, (1-6C)alkoxycarbonyl(1-4C)alkyl-, (1-6C)alkylsulfonyloxy, (3-6C)cycloalkylsulfonyl, (1-6C)alkylsulfonylamino, azetidinylcarbonyl, pyrrolidinylcarbonyl and HET-3A;

wherein HET-1 is a 5- or 6-membered, C-linked heteroaryl ring, or a fused bicyclic ring system of formula –D-E,

wherein ring D is attached to Z and is 6-membered aryl or heteroaryl ring and ring E is a 5- or 6-membered heteroaryl, heterocyclyl or cycloalkyl ring which is fused to ring D at any available position;

R^2 is (1-6C)alkyl optionally substituted by one or two hydroxy or by one of the following: carboxy, carbamoyl, *N,N*-di(1-4C)alkylcarbamoyl, (1-6C)alkoxycarbonyl, a group $-N(R^7)COR^8$ or a group NR^9R^{10};

or R^2 is a group $-(CHR^4)_n$-P-Q wherein n is 1, 2, 3 or 4;

P is a linker selected from O, SO_2, CONH and NHCO;

Q is selected from (1-6C)alkyl, (3-6C)cycloalkyl and a 4-, 5- or 6-membered heterocyclyl (wherein said heterocyclyl ring contains 1, 2 or 3 heteroatoms independently selected from O, N and S, provided that there are no O-O, S-S or O-S bonds, wherein an available carbon atom in the ring may be oxidised to a carbonyl group, an available sulfur atom in the ring may be oxidised to an SO or SO_2 group and wherein there is optionally a double bond in the ring), and Q is optionally substituted on an available carbon atom by hydroxy or (1-4C)alkoxy;

R^3 is a group HET-2 wherein HET-2 is a 5- or 6-membered C-linked monocyclic heteroaryl ring, containing a nitrogen atom in the 2-position and optionally 1 or 2 further ring heteroatoms independently selected from O, N and S; or HET-2 is an 8-, 9- or 10-membered C-linked bicyclic heteroaryl ring containing a nitrogen atom in the 2-position with up to five further ring heteroatoms independently selected from O, N and S; wherein HET-2 is optionally substituted on an available carbon atom, or on a ring nitrogen atom provided it is not thereby quaternised, with 1 or 2 substituents independently selected from R^{11};

each R^4 is independently selected from hydrogen, hydroxy, methyl and ethyl; provided that when n is >1, then no more than two R^4 groups are hydroxy;

R^5 is H, (1-4C)alkoxy or (1-4C)alkyl;

R^6 is H, (1-4C)alkoxy or (1-4C)alkyl;

R^7 is H or (1-4C)alkyl;

R^8 is (1-4C)alkyl;

R^9 is H or (1-4C)alkyl optionally substituted with hydroxy or methoxy;

R^{10} is H or (1-4C)alkyl;

or $-NR^9R^{10}$ forms an azetidine optionally substituted by hydroxy;

R^{11} is independently selected from halo, (1-4C)alkyl, (1-4C)alkoxy, trifluoromethyl, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, cyano, carboxy, (1-6C)alkoxycarbonyl, carbamoyl, *N*-(1-4C)alkylcarbamoyl, *N,N*-di(1-4C)alkylcarbamoyl, aminosulfonyl, (1-6C)alkylaminosulfonyl, di(1-6C)alkylaminosulfonyl, (1-4C)alkanoylamino, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl (wherein p is 0, 1 or 2), amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl, di(1-4C)alkylamino(1-4C)alkyl, (1-6C)alkoxycarbonyl(1-4C)alkyl-, (1-6C)alkylsulfonyloxy, (3-6C)cycloalkylsulfonyl, (1-6C)alkylsulfonylamino, azetidinylcarbonyl, pyrrolidinylcarbonyl and HET-3;

HET-3 and HET-3A are each independently either a 5- or 6-membered, C-or N- linked unsubstituted heteroaryl ring containing 1, 2 or 3 ring heteroatoms independently selected from O, N and S, or a 4-, 5- or 6-membered, C- or N- linked unsubstituted saturated heterocyclyl ring containing one ring heteroatom selected from O, N and S;

L is S, O or NR^{12}; and

R^{12} is H or (1-4C)alkyl;

but excluding

N-(5-chloro-2-pyridinyl)-2-[(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thio]propanamide;

N-[1-(1-methylethyl)-1H-pyrazol-5-yl]-2-[(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thio]propanamide,

N-(5-(methyl)isoxazol-3-yl)-2-[[1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]thio]butanamide;

N-(5-(methyl)isoxazol-3-yl)-2-[[1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]thio]propanamide;

(2R)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-5-hydroxy-N-(5-methyl-2-pyridyl)pentanamide;

(2R)-N-(5-chloro-2-pyridyl)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-5-hydroxy-pentanamide;

(2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-cyano-2-pyridyl)-3-[(1S)-2-hydroxy-1-methyl-ethoxy]propanamide;

(2R)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-cyano-2-pyridyl)-3-(2-hydroxyethoxy)propanamide;

(2S)-N-(5-cyano-2-pyridyl)-2-[1-(2,5-dimethylphenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-(2-hydroxyethoxy)propanamide;

(2S)-3-(2-hydroxyethoxy)-N-(5-methyl-2-pyridyl)-2-(9-phenylpurin-6-yl)oxy-propanamide;

(2R)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-3-(2-hydroxyethoxy)propanamide;

(2S)-N-(5-chloro-2-pyridyl)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-[(2R)-2-hydroxypropoxy]propanamide;

(2R)-N-(5-chloro-2-pyridyl)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-[(2R)-2-hydroxypropoxy]propanamide;

(2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-cyano-2-pyridyl)-3-(3-hydroxycyclobutoxy)propanamide; and

(2S)-N-(5-chloro-2-pyridyl)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-(3-hydroxycyclobutoxy)propanamide.

In a further aspect of the invention there is provided a compound of the formula (I) or a pharmaceutically acceptable salt thereof wherein:

A and B are each either N or CR^6, provided that at least one of A and B is CR^6;

X is C or N;

Y is CH or N;

Z is C or N;

wherein X, Y and Z are chosen such that at least two of X, Y and Z are N, the ring containing them is aromatic and any ring nitrogen atom is not quaternised;

R^1 is (1-6C)alkyl, aryl, aryl(1-6C)alkyl or HET-1 wherein the aryl, aryl(1-6C)alkyl and HET-1 are optionally substituted by one, two or three groups independently selected from halo, (1-4C)alkyl, (1-4C)alkoxy, trifluoromethyl, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, cyano, carboxy, (1-6C)alkoxycarbonyl, carbamoyl, *N*-(1-4C)alkylcarbamoyl, *N,N*-di(1-4C)alkylcarbamoyl, aminosulfonyl, (1-6C)alkylaminosulfonyl, di(1-6C)alkylaminosulfonyl, (1-4C)alkanoylamino, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl, di(1-4C)alkylamino(1-4C)alkyl, (1-6C)alkoxycarbonyl(1-4C)alkyl-, (1-6C)alkylsulfonyloxy, (3-6C)cycloalkylsulfonyl, (1-6C)alkylsulfonylamino, azetidinylcarbonyl, pyrrolidinylcarbonyl and HET-3A;

wherein HET-1 is a 5- or 6-membered, C-linked heteroaryl ring, or a fused bicyclic ring system of formula –D-E,

wherein ring D is attached to Z and is 6-membered aryl or heteroaryl ring and ring E is a 5- or 6-membered heteroaryl, heterocyclyl or cycloalkyl ring which is fused to ring D at any available position;

R^2 is (1-6C)alkyl optionally substituted by one or two hydroxy or by one of the following: carboxy, carbamoyl, *N,N*-di(1-4C)alkylcarbamoyl, (1-6C)alkoxycarbonyl, a group $-N(R^7)COR^8$ or a group NR^9R^{10};

or R^2 is a group $-(CHR^4)_n$-P-Q wherein n is 1, 2, 3 or 4;

P is a linker selected from O, SO_2, SO_2NH, $NHSO_2$, CONH and NHCO;

Q is selected from (1-6C)alkyl, (3-6C)cycloalkyl and a 4-, 5- or 6-membered heterocyclyl (wherein said heterocyclyl ring contains 1, 2 or 3 heteroatoms independently selected from O, N and S, provided that there are no O-O, S-S or O-S bonds, wherein an available carbon atom in the ring may be oxidised to a carbonyl group, an available sulfur atom in the ring

may be oxidised to an SO or SO_2 group and wherein there is optionally a double bond in the ring), and Q is optionally substituted on an available carbon atom by hydroxy or (1-4C)alkoxy;

R^3 is a group HET-2 wherein HET-2 is a 5- or 6-membered C-linked monocyclic heteroaryl ring, containing a nitrogen atom in the 2-position and optionally 1 or 2 further ring heteroatoms independently selected from O, N and S; or HET-2 is an 8-, 9- or 10-membered C-linked bicyclic heteroaryl ring containing a nitrogen atom in the 2-position with up to five further ring heteroatoms independently selected from O, N and S; wherein HET-2 is optionally substituted on an available carbon atom, or on a ring nitrogen atom provided it is not thereby quaternised, with 1 or 2 substituents independently selected from R^{11};

each R^4 is independently selected from hydrogen, hydroxy, methyl and ethyl; provided that when n is >1, then no more than two R^4 groups are hydroxy;

R^5 is H, (1-4C)alkoxy or (1-4C)alkyl;

R^6 is H, (1-4C)alkoxy or (1-4C)alkyl;

R^7 is H or (1-4C)alkyl;

R^8 is (1-4C)alkyl;

R^9 is H or (1-4C)alkyl;

R^{10} is H or (1-4C)alkyl;

R^{11} is independently selected from halo, (1-4C)alkyl, (1-4C)alkoxy, trifluoromethyl, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, cyano, carboxy, (1-6C)alkoxycarbonyl, carbamoyl, *N*-(1-4C)alkylcarbamoyl, *N,N*-di(1-4C)alkylcarbamoyl, aminosulfonyl, (1-6C)alkylaminosulfonyl, di(1-6C)alkylaminosulfonyl, (1-4C)alkanoylamino, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl (wherein p is 0, 1 or 2), amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl, di(1-4C)alkylamino(1-4C)alkyl, (1-6C)alkoxycarbonyl(1-4C)alkyl-, (1-6C)alkylsulfonyloxy, (3-6C)cycloalkylsulfonyl, (1-6C)alkylsulfonylamino, azetidinylcarbonyl, pyrrolidinylcarbonyl and HET-3;

HET-3 and HET-3A are each independently either a 5- or 6-membered, C-or N- linked unsubstituted heteroaryl ring containing 1, 2 or 3 ring heteroatoms independently selected from O, N and S, or a 4-, 5- or 6-membered, C- or N- linked unsubstituted saturated heterocyclyl ring containing one ring heteroatom selected from O, N and S;

L is S, O or NR^{12}; and

R^{12} is H or (1-4C)alkyl;

but excluding

N-(5-chloro-2-pyridinyl)-2-[(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thio]propanamide;

N-[1-(1-methylethyl)-1H-pyrazol-5-yl]-2-[(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thio]propanamide,

N-(5-(methyl)isoxazol-3-yl)-2-[[1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]thio]butanamide; and

N-(5-(methyl)isoxazol-3-yl)-2-[[1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]thio]propanamide.

The term "aryl" refers to phenyl, naphthyl or a partially saturated bicyclic carbocyclic ring containing between 8 and 12 carbon atoms, preferably between 8 and 10 carbon atoms. Example of partially saturated bicyclic carbocyclic ring include: 1,2,3,4-tetrahydronaphthyl, indanyl, indenyl, 1, 2, 4a,5, 8, 8a-hexahydronaphthyyl or 1,3a-dihydropentalene. Examples of "aryl(1-6C)alkyl" include any of the above examples of "aryl" in conjunction with any of the examples of "(1-6C)alkyl" hereinafter.

Suitable HET-1 groups when HET-1 is a 5- or 6-membered C-linked heteroaryl ring include thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl and triazolyl. More suitably HET-1 groups are pyridyl or pyrazinyl, particularly 2-pyridyl, 4-pyridyl and pyrazinyl. Suitable HET-1 groups when HET-1 is of formula –D-E (as hereinbefore defined) include indanyl, benzodioxolyl, benzimidazolyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, quinolyl, isoquinolyl, benzofurazanyl, indolyl, indazolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, 1,5-naphthyridinyl, 1,6-naphthyridinyl, 1,7-naphthyridinyl, 1,8-naphthyridinyl, pyrrolopyridinyl, pyrrolopyrazinyl, pyrazolopyridinyl and imidazopyridinyl.

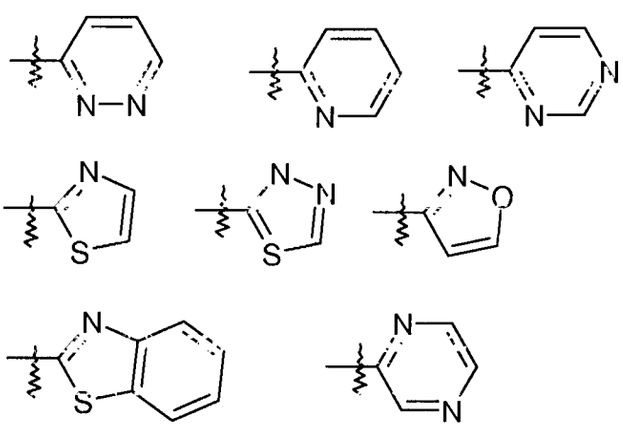
Suitable examples of HET-2 include pyrrolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, thiadiazolyl (1,2,4- and 1,3,4-), oxazolyl, isoxazolyl, triazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, furazanyl, tetrazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, 1,3,5-triazinyl, imidazothiazolyl, benzimidazolyl, benzthiazolyl,

benzisothiazolyl, benzoxazolyl, benzisoxazolyl, quinolyl, isoquinolyl, benzofurazanyl, indolyl, indazolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, 1,5-naphthyridinyl, 1,6-naphthyridinyl, 1,7-naphthyridinyl, 1,8-naphthyridinyl, pyrrolopyridinyl, pyrrolopyrazinyl, pyrazolopyridinyl and imidazopyridinyl.

Suitable examples of HET-3 and HET-3A as heteroaryl rings are furyl, pyrrolyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl and triazolyl. Suitable examples of HET-3 and HET-3A as saturated heterocyclyl rings are oxetane, azetidine, thietane, pyrrolidine, tetrahydrofuran, tetrahydropyran and piperidine.

It will be appreciated that, where definitions of heterocyclyl groups HET-1, HET-2, HET-3 and HET-3A encompass heteroaryl rings which may be substituted on nitrogen, such substitution may not result in charged quaternary nitrogen atoms. It will be appreciated that the definitions of HET-1, HET-2, HET-3 and HET-3A are not intended to include any O-O, O-S or S-S bonds. It will be appreciated that the definitions of HET-1, HET-2, HET-3 and HET-3A are not intended to include unstable structures.

For the avoidance of doubt, reference to the group HET-2 containing a nitrogen in the 2-position, is intended to refer to the 2-position relative to the amide nitrogen atom to which the group is attached. For the avoidance of doubt representative examples are shown below

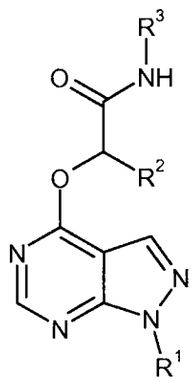


wherein  represents the point of attachment to the amide group.

Examples of the group Q as a 4-, 5-, or 6-membered ring heterocycle as hereinbefore defined include azetidinyl, oxetanyl, pyrrolidinyl, pyrrolidonyl, tetrahydrofuryl,

tetrahydropyranyl, piperidinyl, morpholinyl, piperazinyl and thiomorpholinyl. Particular examples of Q as a heterocycle include azetidinyl and pyrrolidinyl.

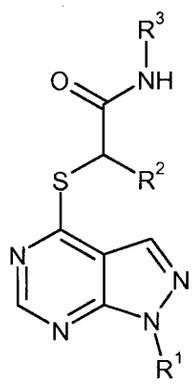
In one aspect of the invention, there is provided a compound of formula (IA) or a pharmaceutically acceptable salt thereof



(IA)

wherein R^1, R^2 and R^3 are as defined for a compound of formula (I) hereinbefore.

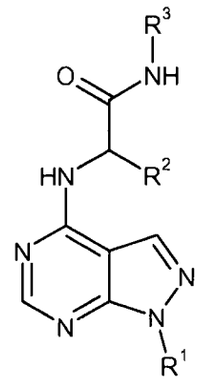
In another aspect of the invention, there is provided a compound of formula (IB) or a pharmaceutically acceptable salt thereof



(IB)

wherein R^1, R^2 and R^3 are as defined for a compound of formula (I) hereinbefore.

In another aspect of the invention, there is provided a compound of formula (IC) or a pharmaceutically acceptable salt thereof



(IC)

wherein R^1, R^2 and R^3 are as defined for a compound of formula (I) hereinbefore.

Reference herein to a compound of formula (I) will be understood to include reference to a compound of formula (IA), (IB) or (IC).

Compounds of Formula (I) may form salts which are within the ambit of the invention. Pharmaceutically-acceptable salts are preferred although other salts may be useful in, for example, isolating or purifying compounds.

In another aspect, the invention relates to compounds of formula (I) as hereinabove defined or to a pharmaceutically-acceptable salt.

In another aspect, the invention relates to compounds of formula (I) as hereinabove defined or to a pro-drug thereof. Suitable examples of pro-drugs of compounds of formula (I) are in-vivo hydrolysable esters of compounds of formula (I). Therefore in another aspect, the invention relates to compounds of formula (I) as hereinabove defined or to an in-vivo hydrolysable ester thereof.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups. However references to individual alkyl groups such as "propyl" are specific for the straight chain version only and references to individual branched-chain alkyl groups such as *t*-butyl are specific for the branched chain version only. For example, "(1-4C)alkyl" includes methyl, ethyl, propyl, isopropyl and *t*-butyl. An analogous convention applies to other generic terms.

Examples of **(1-4C)alkyl** include methyl, ethyl, propyl, isopropyl, butyl and tert-butyl; examples of **(1-6C)alkyl** include (1-4C)alkyl, pentyl and hexyl; examples of **(1-8C)alkyl** include (1-6C)alkyl and heptyl; examples of **(1-4C)alkoxy, (1-6C)alkoxy** and **(1-8C)alkoxy** include methoxy, ethoxy, propoxy, isopropoxy and tertbutoxy; examples of **(1-**

6C)alkoxycarbonyl include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl and tertbutoxycarbonyl; examples of **(1-6C)alkoxycarbonyl(1-4C)alkyl** include methoxycarbonylmethyl, ethoxycarbonylmethyl, propoxycarbonylethyl, isopropoxycarbonylmethyl and tertbutoxycarbonylmethyl; examples of ***N*-(1-4C)alkylcarbamoyl** include methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl and tertbutylcarbamoyl; examples of ***N,N*-di-(1-4C)alkylcarbamoyl** include *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-propylcarbamoyl, *N,N*-di-isopropylcarbamoyl and *N*-methyl-*N*-tertbutylcarbamoyl; examples of **(3-6C)cycloalkyl** include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; examples of **halo** include fluoro, chloro, bromo and iodo; examples of **hydroxy(1-4C)alkyl** include hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-hydroxyisopropyl and 4-hydroxybutyl; examples of **(1-4C)alkoxy(1-4C)alkyl** include methoxymethyl, ethoxymethyl, tert-butoxymethyl, 2-methoxyethyl, 2-ethoxyethyl, methoxypropyl, 2-methoxypropyl and methoxybutyl; examples of **(1-4C)alkylS(O)p(1-4C)alkyl** include methylsulfinylmethyl, ethylsulfinylmethyl, ethylsulfinylethyl, methylsulfinylpropyl, methylsulfinylbutyl, methylsulfonylmethyl, ethylsulfonylmethyl, ethylsulfonylethyl, methylsulfonylpropyl, methylsulfonylbutyl, methylthiomethyl, ethylthiomethyl, ethylthioethyl, methylthiopropyl, and methylthiobutyl; examples of **amino(1-4C)alkyl** include aminomethyl, aminoethyl, 2-aminopropyl, 3-aminopropyl, 1-aminoisopropyl and 4-aminobutyl; examples of **(1-4C)alkylamino(1-4C)alkyl** include (N-methyl)aminomethyl, (N-ethyl)aminomethyl, 1-((N-methyl)amino)ethyl, 2-((N-methyl)amino)ethyl, (N-ethyl)aminoethyl, (N-methyl)aminopropyl, and 4-((N-methyl)amino)butyl; examples of **di(1-4C)alkylamino(1-4C)alkyl** include dimethylaminomethyl, methyl(ethyl)aminomethyl, methyl(ethyl)aminoethyl, (N,N-diethyl)aminoethyl, (N,N-dimethyl)aminopropyl and (N,N-dimethyl)aminobutyl; examples of **(1-4C)alkylamino** include methylamino, ethylamino, propylamino, isopropylamino, butylamino and tert-butylamino; examples of **di(1-4C)alkylamino** include dimethylamino, methyl(ethyl)amino, diethylamino, dipropylamino, di-isopropylamino and dibutylamino; examples of **(1-4C)alkylaminosulfonyl** include methylaminosulfonyl, ethylaminosulfonyl, propylaminosulfonyl, isopropylaminosulfonyl, butylaminosulfonyl and tert-butylaminosulfonyl; examples of **di(1-4C)alkylaminosulfonyl** include dimethylaminosulfonyl, methyl(ethyl)aminosulfonyl, diethylaminosulfonyl,

dipropylaminosulfonyl, di-isopropylaminosulfonyl and dibutylaminosulfonyl; examples of **(1-4C)alkanoylamino** include methanoylamino, ethanoylamino, propanoylamino, isopropanoylamino, butanoylamino and tert-butanoylamino; examples of **–C(O)(1-4C)alkyl** include methylcarbonyl, ethylcarbonyl, propylcarbonyl and tert-butyl carbonyl; examples of **(1-4C)alkylthio** and **(1-6C)alkylthio** include methylthio, ethylthio, isopropylthio and tert-butylthio; examples of **(1-4C)alkylsulfinyl** and **(1-6C)alkylsulfinyl** include methylsulfinyl, ethylsulfinyl, isopropylsulfinyl and tert-butylsulfinyl; examples of **(1-4C)alkylsulfonyl** and **(1-6C)alkylsulfonyl** include methylsulfonyl, ethylsulfonyl, isopropylsulfonyl and tert-butylsulfonyl; example of **(1-6C)alkylsulfonyloxy** include methylsulfonyloxy, ethylsulfonyloxy, isopropylsulfonyloxy and tert-butylsulfonyloxy; examples of **(1-6C)alkylsulfonylamino** include methylsulfonylamino, ethylsulfonylamino, isopropylsulfonylamino and tert-butylsulfonylamino; examples of **(3-6C)cycloalkylsulfonyl** include cyclopropylsulfonyl, cyclobutylsulfonyl, cyclopropylsulfonyl and cyclohexylsulfonyl.

It is to be understood that, insofar as certain of the compounds of Formula (I) defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the property of activating GLK. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. It is also to be understood that certain compounds may exist in tautomeric forms and that the invention also relates to any and all tautomeric forms of the compounds of the invention which activate GLK. It will be understood that compounds described in their pyrimidinol form may also be described as the pyrimidinone tautomer and vice versa. This implies nothing about the actual relative proportions of the two in physical samples.

In particular, it will be understood that the carbon atom to which R^2 is attached is a chiral centre. In one aspect of the invention, this chiral centre has the S-configuration. In another aspect, this chiral centre has the R-configuration.

It is also to be understood that certain compounds of the formula (1) and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated

forms. It is to be understood that the invention encompasses all such solvated forms which activate GLK.

In one embodiment of the invention are provided compounds of formula (I), in an alternative embodiment are provided pharmaceutically-acceptable salts of compounds of formula (I), in a further alternative embodiment are provided in-vivo hydrolysable esters of compounds of formula (I), and in a further alternative embodiment are provided pharmaceutically-acceptable salts of in-vivo hydrolysable esters of compounds of formula (I).

Preferred values of each variable group are as follows. Such values may be used where appropriate with any of the values, definitions, claims, aspects or embodiments defined hereinbefore or hereinafter. In particular, each may be used as an individual limitation on the broadest definition of formula (I) (including formulas (IA), (IB) and (IC)). Further, each of the following values may be used in combination with one or more of the other following values to limit the broadest definition, or any sub-definition, of formula (I).

1) A is N and B is CR^6

2) A is CR^6 and B is N

3) X is C, Y is N and Z is N

4) X is N, Y is CH and Z is N

5) X is N, Y is N and Z is C

6) R^1 is optionally substituted alkyl

7) R^1 is optionally suibstituted aryl

8) R^1 is optionally substituted aryl(1-6C)alkyl

9) R^1 is optionally substituted HET-1

10) R^1 is optionally substituted phenyl or pyridyl (particularly pyrid-2-yl or pyrid-4-yl, more particularly pyrid-2-yl)

11) R^1 is phenyl or pyridyl (particularly pyrid-2-yl), substituted in a 2-position relative to the point of attachment to Z

12) R^1 is phenyl or pyridyl (particularly pyrid-2-yl), substituted in a 2-position relative to the point of attachment to Z

13) R^1 is phenyl or pyridyl (particularly pyrid-2-yl) and R^1 is di-substituted, wherein one substituent is in a 2-position relative to the point of attachment to Z

14) optional subsitituents on R^1 are selected from halo (particularly chloro), (1-4C)alkyl, (1-4C)alkoxy, trifluoromethyl, (1-6C)alkylsulfonyl and cyano

15) R^1 is a fused bicyclic ring system of formula –D-E

16) R^2 is (1-6C)alkyl optionally substituted by one or two hydroxy or R^2 is a group –$(CHR^4)_n$-P-Q

17) R^2 is a group –$(CHR^4)_n$-P-Q

18) R^2 is a group –$(CHR^4)_n$-P-Q; n is 1, 2, 3, or 4 (particularly 1 or 2); one R^4 is optionally hydroxy and the other R^4 groups (where applicable) are hydrogen or methyl; P is an oxygen linker and Q is (1-6C)alkyl, (3-6C)cycloalkyl or a 4-, 5- or 6-membered heterocyclyl, and Q is optionally substituted on an available carbon atom by hydroxy or (1-4C)alkoxy

19) R^2 is a group –$(CHR^4)_n$-P-Q; n is 1, 2, 3, or 4 (particularly 1 or 2); one R^4 is optionally hydroxy and the other R^4 groups (where applicable) are hydrogen or methyl; P is an oxygen linker and Q is (1-6C)alkyl, optionally substituted by hydroxy or (1-4C)alkoxy

20) R^2 is selected from hexyl, butyl, isobutyl, isopropyl, ethyl, methyl, isopropoxymethyl, ethoxymethyl, cyclobutyloxymethyl, methoxymethyl, hydroxyethyl, hydroxypropyl, methylsulfonylethyl, isopropylsulfonylethyl, ethylsulfonylethyl, methylsulfonylaminoethyl, methylsulfonylaminomethyl, cyclopropyloxymethyl, oxetanyloxymethyl, hydroxyethoxymethyl, 1-hydroxyprop-2-yloxymethyl, methoxyethyl, 1-methoxyprop-2yloxymethyl, dimethylaminoethyl, methylcarbonylaminomethyl, carboxyethyl, carbamoylethyl, N-methylcarbamoylethyl, methoxyethoxyethyl, methylcarbonyloxyethyl,

21) R^2 is selected from hexyl, butyl, isobutyl, isopropyl, ethyl, methyl, isopropoxymethyl, ethoxymethyl, cyclobutyloxymethyl, methoxymethyl, hydroxyethyl, hydroxypropyl, methylsulfonylethyl, methylsulfonylaminoethyl, hydroxyethoxymethyl, methoxyethyl, 1-methoxyprop-2yloxymethyl, dimethylaminoethyl, methylcarbonylaminomethyl, carboxyethyl, carbamoylethyl, N-methylcarbamoylethyl, methoxyethoxyethyl, methylcarbonyloxyethyl,

22) R^2 is selected from isopropoxymethyl, ethoxymethyl, cyclobutyloxymethyl, methoxymethyl, hydroxyethyl, hydroxypropyl, cyclopropyloxymethyl, oxetanyloxymethyl, hydroxyethoxymethyl, 1-hydroxyprop-2-yloxymethyl, methoxyethyl, 1-methoxyprop-2yloxymethyl, methoxyethoxyethyl

23) R^2 is selected from isopropoxymethyl, ethoxymethyl, cyclobutyloxymethyl, methoxymethyl, hydroxyethyl, hydroxypropyl, hydroxyethoxymethyl, methoxyethyl, 1-methoxyprop-2yloxymethyl, methoxyethoxyethyl

24) R^3 is selected from optionally substituted pyridyl, thiazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrazolyl, isoxazolyl and thiadiazolyl

25) R^3 is a 6-membered ring

26) R^3 is optionally substituted pyridyl or pyrazinyl

27) R^3 is optionally substituted pyridyl

28) R^3 is pyridyl, substituted at the para position relative to the point of attachment to the CONH group

29) R^3 is 2-pyridyl, substituted at the para position relative to the point of attachment to the CONH group

30) R^{11} is selected from halo, (1-4C)alkyl, (1-6C)alkylsulfonyl, N,N-dialkylcarbamoyl and cyano

31) R^{11} is selected from halo (particularly chloro or fluoro, more particularly chloro) or (1-4C)alkyl (particularly methyl)

32) each R^4 is hydrogen

33) n is >1 and only one R^4 is not hydrogen

34) n is 1, 2 or 3

35) n is 1 or 2

36) R^5 is H

37) R^6 is H

38) R^7 is H

39) R^8 is methyl

40) R^9 is H

41) L is O

42) L is S

43) L is NH

44) R^{10} is H

45) R^{12} is H

46) P is an oxygen linger

47) NR^9R^{10} forms an azetidine ring, optionally substituted with hydroxy, hydroxymethyl or methoxy

48) NR^9R^{10} forms an azetidine ring, optionally substituted with hydroxy or hydroxymethyl

In a further aspect of the invention, there is provided a compound of formula (IA), or a pharmaceutically-acceptable salt thereof wherein

R^1 is phenyl or pyridyl, substituted in the 2-position relative to the point of attachment to Z with a substituent selected from halo (particularly chloro), (1-4C)alkyl, (1-4C)alkoxy, trifluoromethyl, (1-6C)alkylsulfonyl and cyano;

R^2 is (1-6C)alkyl optionally substituted by one or two hydroxy or R^2 is a group $-(CHR^4)_n$-P-Q;

n is 1, 2, 3, or 4 (particularly 1 or 2);

one R^4 is optionally hydroxy and the other R^4 groups (where applicable) are hydrogen or methyl;

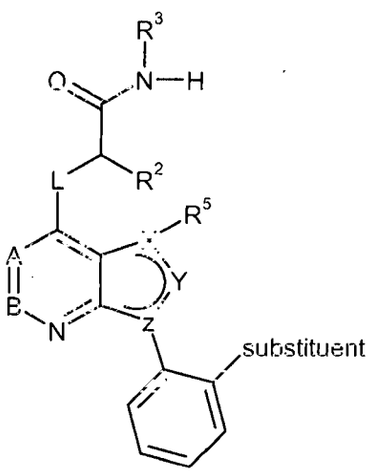
P is an oxygen linker;

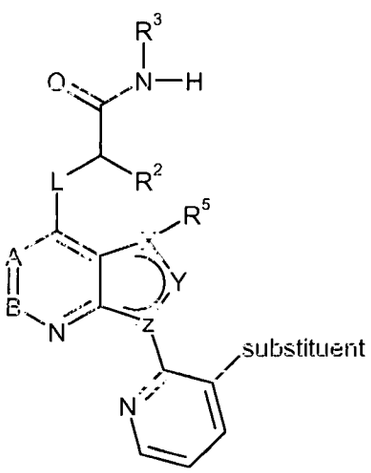
Q is (1-6C)alkyl, (3-6C)cycloalkyl or a 4-, 5- or 6-membered heterocyclyl, and Q is optionally substituted on an available carbon atom by hydroxy or (1-4C)alkoxy;

R^3 is pyridyl, substituted at the para position relative to the point of attachment to the CONH group with a substituent selected from R^{11}; and

R^{11} is selected from halo (particularly fluoro or chloro, more particularly chloro), (1-4C)alkyl, (1-6C)alkylsulfonyl, N,N-dialkylcarbamoyl and cyano.

Reference herein to R^1 being substituted in a 2-position relative to the point of attachment to Z will be understood to refer to the following substitution pattern, illustrated for R^1 is phenyl and pyrid-2-yl:





Further preferred compounds of the invention are each of the Examples, each of which provides a further independent aspect of the invention. In further aspects, the present invention also comprises any two or more compounds of the Examples.

Particular compounds of the invention include any one or more of:

2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-3-methoxy-*N*-(5-methylpyridin-2-yl)propanamide;

(R)-2-{[1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]oxy}-3-methoxy-N-(5-methylpyridin-2-yl)propanamide;

(S)-2-{[1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]oxy}-3-methoxy-N-(5-methylpyridin-2-yl)propanamide;

3-methoxy-2-{[1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)propanamide;

(R)-3-methoxy-2-{[1-(2-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]oxy}-N-(5-methylpyridin-2-yl)propanamide;

(S)-3-methoxy-2-{[1-(2-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]oxy}-N-(5-methylpyridin-2-yl)propanamide;

2-{[1-(2,4-dichlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-3-methoxy-*N*-(5-methylpyridin-2-yl)propanamide;

3-methoxy-2-[(1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)oxy]-*N*-(5-methylpyridin-2-yl)propanamide;

2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)-4-(methylsulfonyl)butanamide;

2-{[1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)-4-(methylsulfonyl)butanamide;

(R)-2-{[1-(2-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]oxy}-N-(5-methylpyridin-2-yl)-4-(methylsulfonyl)butanamide;

(S)-2-{[1-(2-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]oxy}-N-(5-methylpyridin-2-yl)-4-(methylsulfonyl)butanamide;

4-methoxy-2-{[1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)butanamide;

(R)-4-methoxy-2-{[1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]oxy}-N-(5-methylpyridin-2-yl)butanamide;

(S)-4-methoxy-2-{[1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]oxy}-N-(5-methylpyridin-2-yl)butanamide;

4-methoxy-2-{[1-(2-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)butanamide;

(S)-4-methoxy-2-{[1-(2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]oxy}-N-(5-methylpyridin-2-yl)butanamide;

(R)-4-methoxy-2-{[1-(2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]oxy}-N-(5-methylpyridin-2-yl)butanamide;

2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-4-methoxy-*N*-(5-methylpyridin-2-yl)butanamide;

(R)-2-{[1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]oxy}-4-methoxy-N-(5-methylpyridin-2-yl)butanamide;

(S)-2-{[1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]oxy}-4-methoxy-N-(5-methylpyridin-2-yl)butanamide;

4-methoxy-2-{[1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)butanamide;

(R)-4-methoxy-2-{[1-(2-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]oxy}-N-(5-methylpyridin-2-yl)butanamide;

(S)-4-methoxy-2-{[1-(2-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]oxy}-N-(5-methylpyridin-2-yl)butanamide;

2-{[1-(2,4-difluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-4-methoxy-*N*-(5-methylpyridin-2-yl)butanamide;

(R)-2-{[1-(2,4-difluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]oxy}-4-methoxy-N-(5-methylpyridin-2-yl)butanamide;

(S)-2-{[1-(2,4-difluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]oxy}-4-methoxy-N-(5-methylpyridin-2-yl)butanamide;

4-methoxy-*N*-(5-methylpyridin-2-yl)-2-({1-[2-(trifluoromethyl)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl}oxy)butanamide;

(S)-4-methoxy-N-(5-methylpyridin-2-yl)-2-({1-[2-(trifluoromethyl)phenyl]-1H-pyrazolo[3,4-d]pyrimidin-4-yl}oxy)butanamide;

(R)-4-methoxy-N-(5-methylpyridin-2-yl)-2-({1-[2-(trifluoromethyl)phenyl]-1H-pyrazolo[3,4-d]pyrimidin-4-yl}oxy)butanamide;

4-methoxy-2-{[1-(3-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)butanamide;

(R)-4-methoxy-2-{[1-(3-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]oxy}-N-(5-methylpyridin-2-yl)butanamide;

(S)-4-methoxy-2-{[1-(3-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]oxy}-N-(5-methylpyridin-2-yl)butanamide;

4-methoxy-*N*-(5-methylpyridin-2-yl)-2-[(1-pyridin-2-yl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)oxy]butanamide;

4-methoxy-2-{[1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(4-methyl-1,3-thiazol-2-yl)butanamide;

(R)-4-methoxy-2-{[1-(2-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]oxy}-N-(4-methyl-1,3-thiazol-2-yl)butanamide;

(S)-4-methoxy-2-{[1-(2-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]oxy}-N-(4-methyl-1,3-thiazol-2-yl)butanamide;

2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)hexanamide;

2-[(1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)oxy]-*N*-(5-methylpyridin-2-yl)hexanamide

2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyrazin-2-yl)hexanamide;

2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]thio}-*N*-(4-methyl-1,3-thiazol-2-yl)hexanamide;

2-{[1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)butanamide;

(2*R*)-2-{[1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)butanamide;

2-{[1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)propanamide;

(2*S*)-2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-4-(dimethylamino)-*N*-(5-methylpyridin-2-yl)butanamide;

3-acetamido-2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(4-methyl-1,3-thiazol-2-yl)propanamide;

4-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-5-[(5-methylpyridin-2-yl)amino]-5-oxopentanoic acid;

2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N1*-(5-methylpyridin-2-yl)pentanediamide;

2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N5*-methyl-*N1*-(5-methylpyridin-2-yl)pentanediamide;

2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]thio}-4-(2-methoxyethoxy)-*N*-(4-methyl-1,3-thiazol-2-yl)butanamide;

2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]thio}-4-methoxy-*N*-(4-methyl-1,3-thiazol-2-yl)butanamide;

2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]thio}-3-methyl-*N*-(4-methyl-1,3-thiazol-2-yl)pentanamide;

2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]thio}-*N*-isoxazol-3-yl-3-methylpentanamide;

2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]thio}-3-methyl-*N*-(5-methylpyridin-2-yl)pentanamide;

2-[(1-isopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)thio]-4-(2-methoxyethoxy)-*N*-(5-methylpyridin-2-yl)butanamide;

2-[(1-isopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)thio]-4-(2-methoxyethoxy)-*N*-(5-methylpyridin-2-yl)butanamide;

2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]thio}-*N*-(4-methyl-1,3-thiazol-2-yl)hexanamide;

2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]thio}-*N*-isoxazol-3-ylhexanamide;

2-{[1-(2-Chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]thio}-4-(2-methoxyethoxy)- *N*-(4-methyl-1,3-thiazol-2-yl)butanamide;

2-{[1-(2-Chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]thio}-3-methoxy-*N*-(5-methylpyridin-2-yl)propanamide;

2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]thio}-*N*-(4-methyl-1,3-thiazol-2-yl)octanamide;

2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]thio}-*N*-isoxazol-3-yloctanamide;

2-ethoxy-2-{[1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]thio}-*N*-(4-methyl-1,3-thiazol-2-yl)acetamide;

2-ethoxy-*N*-isoxazol-3-yl-2-{[1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]thio}acetamide;

2-[(1-isopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)oxy]-4-methoxy-*N*-(5-methylpyridin-2-yl)butanamide;

(R)-2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]thio}-*N*-(4-methyl-1,3-thiazol-2-yl)hexanamide;

(S)-2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]thio}-*N*-(4-methyl-1,3-thiazol-2-yl)hexanamide;

2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-methyl-*N*-(5-methylpyridin-2-yl)butanamide;

(2S)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-methyl-*N*-(5-methylpyridin-2-yl)butanamide;

(2R)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-methyl-*N*-(5-methylpyridin-2-yl)butanamide;

(2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-methyl-*N*-(5-methylpyridin-2-yl)butanamide;

(2S)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-methoxy-*N*-(5-methylpyridin-2-yl)propanamide;

(2R)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-methoxy-*N*-(5-methylpyridin-2-yl)propanamide;

(2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-methoxy-*N*-(5-methylpyridin-2-yl)propanamide;

(2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-methoxy-*N*-(5-methylpyrazin-2-yl)propanamide;

(2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-isopropoxy-*N*-(5-methylpyridin-2-yl)propanamide;

(2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-isopropoxy-*N*-(5-methylpyrazin-2-yl)propanamide;

(2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-isopropoxy-*N*-(3-methyl-1,2,4-thiadiazol-5-yl)propanamide;

(2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-methyl-*N*-(5-methylpyrazin-2-yl)butanamide;

(2S)-2-(1-(2-chloro-4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-methoxy-*N*-(5-methylpyrazin-2-yl)propanamide;

(2S)-2-(1-(2-chloro-4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-methoxy-*N*-(5-methylpyridin-2-yl)propanamide;

(2S)-2-(1-(2-cyanophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-methoxy-*N*-(5-methylpyridin-2-yl)propanamide;

(2S)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-isopropoxy-*N*-(5-methylpyridin-2-yl)propanamide;

(2R)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-isopropoxy-*N*-(5-methylpyridin-2-yl)propanamide; and/or

(2S)-2-[1-(2-cyanophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-methylpyridin-2-yl)-3-propan-2-yloxypropanamide;

(2S)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(3-methyl-1,2,4-thiadiazol-5-yl)-3-propan-2-yloxypropanamide;

(2S)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-methoxy-N-(3-methyl-1,2,4-thiadiazol-5-yl)propanamide;

(2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-4-methoxy-N-(5-methylpyridin-2-yl)butanamide;

(2S)-2-[1-(3-chloropyridin-2-yl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-ethoxy-N-(5-methylpyridin-2-yl)propanamide;

(2S)-2-[1-(3-chloropyridin-2-yl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-ethoxy-N-(5-methylpyrazin-2-yl)propanamide ;

(2S)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-ethoxy-N-(5-methylpyrazin-2-yl)propanamide;

(2S)-3-isopropoxy-N-(5-methylpyrazin-2-yl)-2-(1-(3-methylpyrazin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide;

(S)-3-methoxy-N-(5-methylpyridin-2-yl)-2-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide;

2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-isopropoxy-N-pyrazin-2-yl-propanamide;

2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-isopropoxy-N-(5-methyl-1,3,4-thiadiazol-2-yl)propanamide;

2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-isopropoxy-N-(5-methylisoxazol-3-yl)propanamide;

2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-isopropoxy-N-(5-methylthiazol-2-yl)propanamide;

2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-3-isopropoxy-propanamide;

2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-cyano-2-pyridyl)-3-isopropoxy-propanamide;

2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-isopropoxy-N-(1,2,4-thiadiazol-5-yl)propanamide;

2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-chloro-2-pyridyl)-3-isopropoxy-propanamide;

2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-isopropoxy-N-(4-methyl-2-pyridyl)propanamide;

2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-isopropoxy-N-(1,3,4-thiadiazol-2-yl)propanamide;

2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-isopropoxy-N-(2-pyridyl)propanamide;

2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-isopropoxy-N-isoxazol-3-yl-propanamide;

2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-isopropoxy-N-pyrimidin-4-yl-propanamide;

(2S)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-isopropoxy-N-(5-methylthiazol-2-yl)propanamide;

(2S)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-3-isopropoxy-propanamide;

(2S)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-cyano-2-pyridyl)-3-isopropoxy-propanamide;

(2S)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-chloro-2-pyridyl)-3-isopropoxy-propanamide;

(2S)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-isopropoxy-N-(2-pyridyl)propanamide;

(2S)-3-isopropoxy-N-(5-methylpyridin-2-yl)-2-(1-(3-methylpyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide;

(2S)-3-isopropoxy-N-(5-methylpyridin-2-yl)-2-(1-(3-(trifluoromethyl)pyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide;

(2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-isopropoxy-N-(6-methylpyridazin-3-yl)propanamide;

(2S)-N-(5-cyanopyridin-2-yl)-3-isopropoxy-2-(1-(3-methylpyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide;

(2S)-N-(5-chloropyridin-2-yl)-3-isopropoxy-2-(1-(3-methylpyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide;

(2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-cyano-2-pyridyl)-3-ethoxy-propanamide;

(2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-ethoxy-N-(5-fluoro-2-pyridyl)propanamide;

(2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-ethoxy-N-(2-pyridyl)propanamide;

(2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-ethoxy-N-pyrimidin-4-yl-propanamide;

(2S)-N-(5-chloro-2-pyridyl)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-ethoxy-propanamide;

(2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(4-cyanothiazol-2-yl)-3-isopropoxy-propanamide;

(2S)-N-(5-chloro-2-pyridyl)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-isopropoxy-propanamide;

(2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-cyano-2-pyridyl)-3-isopropoxy-propanamide;

(2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-isopropoxy-N-(2-pyridyl)propanamide;

(2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-3-isopropoxy-propanamide;

(2S)-N-(5-chloropyridin-2-yl)-3-ethoxy-2-[1-(3-methylpyridin-4-yl)pyrazolo[4,5-e]pyrimidin-4-yl]oxypropanamide;

(2S)-N-(5-chloropyridin-2-yl)-3-ethoxy-2-(1-(3-methylpyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide;

(2S)-3-isopropoxy-N-(5-methylpyridin-2-yl)-2-(1-(2-(methylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide;

(2S)-N-(5-chloropyridin-2-yl)-3-ethoxy-2-(1-(2-(methylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide;

(2R)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-5-hydroxy-N-(5-methyl-2-pyridyl)pentanamide;

(2S)-N-(5-cyano-2-pyridyl)-3-ethoxy-2-[1-[2-(trifluoromethyl)phenyl]pyrazolo[4,5-e]pyrimidin-4-yl]oxy-propanamide;

(2S)-3-ethoxy-N-(5-methylpyrazin-2-yl)-2-[1-[2-(trifluoromethyl)phenyl]pyrazolo[4,5-e]pyrimidin-4-yl]oxy-propanamide;

(2S)-N-(5-chloro-2-pyridyl)-3-ethoxy-2-[1-[3-(trifluoromethyl)-2-pyridyl]pyrazolo[4,5-e]pyrimidin-4-yl]oxy-propanamide;

(2S)-3-isopropoxy-N-(5-methyl-2-pyridyl)-2-[1-(3-methyl-4-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-propanamide;

(2S)-3-(cyclobutoxy)-N-(5-methylpyrazin-2-yl)-2-[1-(3-methyl-4-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-propanamide;

(2S)-3-(cyclobutoxy)-N-(5-methylpyrazin-2-yl)-2-[1-[3-(trifluoromethyl)-2-pyridyl]pyrazolo[4,5-e]pyrimidin-4-yl]oxy-propanamide;

(2S)-2-[1-[5-chloro-3-(trifluoromethyl)-2-pyridyl]pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-(cyclobutoxy)-N-(5-methylpyrazin-2-yl)propanamide;

(2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-ethoxy-N-(5-methylsulfonyl-2-pyridyl)propanamide;

(2S)-3-(cyclobutoxy)-N-(5-methylpyrazin-2-yl)-2-[1-(2-methylsulfonylphenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-propanamide;

(2S)-3-(cyclobutoxy)-N-(5-methylpyrazin-2-yl)-2-[1-(3-methyl-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-propanamide;

(2S)-3-(cyclobutoxy)-N-(5-methylpyrazin-2-yl)-2-(1-phenylpyrazolo[4,5-e]pyrimidin-4-yl)oxy-propanamide;

(2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-4-hydroxy-N-(5-methyl-2-pyridyl)butanamide;

(2S)-3-(cyclobutoxy)-2-[1-(3-methylpyrazin-2-yl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-methyl-2-pyridyl)propanamide;

(2S)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-4-hydroxy-N-(5-methyl-2-pyridyl)butanamide;

(2S)-3-isopropoxy-N-(5-methyl-2-pyridyl)-2-[1-(2-methyl-3-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-propanamide;

6-[[(2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-ethoxy-propanoyl]amino]-N,N-dimethyl-pyridine-3-carboxamide;

(2S)-3-isopropoxy-N-(5-methyl-2-pyridyl)-2-[1-(4-methyl-3-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-propanamide;

(2S)-3-(cyclobutoxy)-N-(5-methylpyrazin-2-yl)-2-[1-(2-methyl-3-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-propanamide;

(2S)-N-(5-chloro-2-pyridyl)-3-ethoxy-2-[1-(2-methyl-3-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-propanamide;

(2S)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-[(1S)-2-methoxy-1-methyl-ethoxy]-N-(5-methylpyrazin-2-yl)propanamide;

(2S)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-[(1S)-2-methoxy-1-methyl-ethoxy]-N-(5-methyl-2-pyridyl)propanamide;

(2S)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-[(1R)-2-methoxy-1-methyl-ethoxy]-N-(5-methyl-2-pyridyl)propanamide;

(2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-[(1R)-2-methoxy-1-methyl-ethoxy]-N-(5-methyl-2-pyridyl)propanamide;

(2R)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-[(1S)-2-methoxy-1-methyl-ethoxy]-N-(5-methylpyrazin-2-yl)propanamide;

(2S)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-(cyclobutoxy)-N-(5-methylpyrazin-2-yl)propanamide;

(2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-(cyclobutoxy)-N-(5-methylpyrazin-2-yl)propanamide;

(2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-(cyclobutoxy)-N-(5-methyl-2-pyridyl)propanamide;

[(3S)-3-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-4-[(5-methyl-2-pyridyl)amino]-4-oxo-butyl] acetate;

(2S)-3-isopropoxy-N-(5-methyl-2-pyridyl)-2-[1-[2-(trifluoromethyl)phenyl]pyrazolo[4,5-e]pyrimidin-4-yl]oxy-propanamide;

(2S)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-methyl-2-pyridyl)-4-methylsulfonyl-butanamide;

(2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-cyano-2-pyridyl)-3-(2-hydroxyethoxy)propanamide;

(2S)-N-(5-chloro-2-pyridyl)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-(2-hydroxyethoxy)propanamide;

(2S)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-4-methanesulfonamido-N-(5-methyl-2-pyridyl)butanamide;

(2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-4-hydroxy-N-(5-methylpyrazin-2-yl)butanamide;

(2S)-N-(5-chloro-2-pyridyl)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-4-hydroxy-butanamide;

(2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-4-hydroxy-N-(2-pyridyl)butanamide;

(2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-4-hydroxy-butanamide;

(2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-cyano-2-pyridyl)-4-hydroxy-butanamide;

(2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-4-hydroxy-N-pyrimidin-4-yl-butanamide; and/or

(2S)-N-(5-chloropyridin-2-yl)-2-[1-(3-chloropyridin-2-yl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-(3-hydroxyazetidin-1-yl)propanamide;

(2S)-2-[1-(3-chloro-2-methylphenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-cyanopyridin-2-yl)-3-(2-hydroxyethoxy)propanamide;

(2S)-2-[1-(3-chloro-2-methylphenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-(2-hydroxyethoxy)-N-(5-methylpyridin-2-yl)propanamide;

(2S)-N-(5-cyanopyridin-2-yl)-2-[1-(3-fluoro-2-methylphenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-(2-hydroxyethoxy)propanamide;

(2S)-2-[1-(3-fluoro-2-methylphenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-(2-hydroxyethoxy)-N-(5-methylpyridin-2-yl)propanamide;

(2S)-N-(5-chloropyridin-2-yl)-2-[1-(3-fluoro-2-methylphenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-(2-hydroxyethoxy)propanamide;

(2S)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-chloropyridin-2-yl)-3-(2-hydroxyethoxy)propanamide;

(2S)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-cyanopyridin-2-yl)-3-(2-hydroxyethoxy)propanamide;

(2S)-2-[1-(3-chloro-2-methylphenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-chloropyridin-2-yl)-3-(2-hydroxyethoxy)propanamide;

(2S)-2-(1-(2-chloro-6-cyanophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-chloropyridin-2-yl)-3-(2-hydroxyethoxy)propanamide;

(2S)-2-(1-(2-chloro-6-cyanophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-((R)-1-hydroxypropan-2-yloxy)-N-(5-methylpyridin-2-yl)propanamide;

(2S)-2-(1-(2-chloro-6-cyanophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-(2-hydroxyethoxy)-N-(5-methylpyridin-2-yl)propanamide;

(2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-isopropoxy-N-(5-(methylsulfonyl)pyridin-2-yl)propanamide;

6-((2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-isopropoxypropanamido)-N,N-dimethylnicotinamide;

(2S)-N-(5-chloropyridin-2-yl)-2-(1-(2,5-dimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-(2-hydroxyethoxy)propanamide;

(2S)-N-(5-chloropyridin-2-yl)-2-(1-(5-fluoro-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-(2-hydroxyethoxy)propanamide;

(S)-2-(1-benzyl-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-(2-hydroxyethoxy)-N-(5-methylpyridin-2-yl)propanamide;

(2S)-N-(5-cyanopyridin-2-yl)-2-(1-(5-fluoro-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-(2-hydroxyethoxy)propanamide;

(2S)-2-(1-(5-cyano-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-cyanopyridin-2-yl)-3-(2-hydroxyethoxy)propanamide;

(2S)-2-(1-(5-cyano-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-(2-hydroxyethoxy)-N-(5-methylpyridin-2-yl)propanamide;

(2S)-N-(5-chloropyridin-2-yl)-2-(1-(5-cyano-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-(2-hydroxyethoxy)propanamide;
(2S)-N-(5-cyanopyridin-2-yl)-2-(1-(2,5-dimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-ethoxypropanamide;
(2S)-N-(5-chloropyridin-2-yl)-3-ethoxy-2-(1-(4-methylpyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide;
(2S)-3-cyclobutoxy-N-(5-methylpyrazin-2-yl)-2-(1-(4-methylpyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide;
(2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-cyanopyridin-2-yl)-3-((R)-1-hydroxypropan-2-yloxy)propanamide;
(2S)-N-(5-chloropyridin-2-yl)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-((R)-1-hydroxypropan-2-yloxy)propanamide;
(2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-fluoropyridin-2-yl)-3-((R)-1-hydroxypropan-2-yloxy)propanamide;
(2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-fluoropyridin-2-yl)-3-((S)-1-hydroxypropan-2-yloxy)propanamide;
(2S)-N-(5-chloropyridin-2-yl)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-((S)-1-hydroxypropan-2-yloxy)propanamide;
(2S)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-(2-hydroxyethoxy)-N-(5-methylpyridin-2-yl)propanamide;
(2S)-2-(3-(2-chlorophenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy)-3-(2-hydroxyethoxy)-N-(5-methylpyridin-2-yl)propanamide;
(2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(3-(2-chlorophenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy)-N-(5-methylpyridin-2-yl)propanamide;
(2S)-2-(3-(2-chlorophenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy)-N-(5-cyanopyridin-2-yl)-3-ethoxypropanamide;
(2S)-N-(5-chloropyridin-2-yl)-3-(2-hydroxyethoxy)-2-(3-o-tolyl-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy)propanamide;
(2S)-3-(2-hydroxyethoxy)-N-(pyridin-2-yl)-2-(1-(2-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide;
(2S)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-((R)-1-hydroxypropan-2-yloxy)-N-(pyridin-2-yl)propanamide;

(2S)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-(2-hydroxyethoxy)-N-(pyridin-2-yl)propanamide;

(2S)-N-(5-chloropyridin-2-yl)-2-(1-(2,3-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-(2-hydroxyethoxy)propanamide;

(2S)-N-(5-cyanopyridin-2-yl)-2-(1-(2,3-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-(2-hydroxyethoxy)propanamide;

(2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-((S)-2-hydroxypropoxy)-N-(5-methylpyridin-2-yl)propanamide;

(2S)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-(3-hydroxyazetidin-1-yl)-N-(5-methylpyridin-2-yl)propanamide;

(2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-(3-hydroxyazetidin-1-yl)-N-(5-methylpyridin-2-yl)propanamide;

(2S)-2-(1-(3-cyano-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-cyanopyridin-2-yl)-3-(2-hydroxyethoxy)propanamide;

(2S)-2-(1-(3-cyano-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-(2-hydroxyethoxy)-N-(5-methylpyridin-2-yl)propanamide;

(2S)-N-(5-chloropyridin-2-yl)-2-(1-(3-cyano-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-(2-hydroxyethoxy)propanamide;

(2S)-N-(5-chloropyridin-2-yl)-3-ethoxy-2-(1-(1-methyl-1H-imidazol-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide;

(2S)-3-isopropoxy-2-(1-(1-methyl-1H-imidazol-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-methylpyridin-2-yl)propanamide;

(2S)-N-(5-chloropyridin-2-yl)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-5-hydroxypentanamide;

(2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-cyanopyridin-2-yl)-5-hydroxypentanamide;

(2S)-N-(5-cyanopyridin-2-yl)-2-(1-(2,3-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-ethoxypropanamide;

(2S)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-3-(3-hydroxyazetidin-1-yl)propanamide;

(2S)-2-[1-(2-chloro-6-cyano-phenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-chloro-2-pyridyl)-3-[(1R)-2-hydroxy-1-methyl-ethoxy]propanamide;

(2S)-2-[1-(2-chloro-6-cyano-phenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-[(1R)-2-hydroxy-1-methyl-ethoxy]-N-(5-methylpyrazin-2-yl)propanamide;

(2S)-2-[1-(2,6-dichlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-3-(2-hydroxyethoxy)propanamide;

(2S)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-(3-hydroxyazetidin-1-yl)-N-(5-methylpyrazin-2-yl)propanamide;

(2S)-2-[1-(2,6-dichlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-(3-hydroxyazetidin-1-yl)-N-(5-methylpyrazin-2-yl)propanamide;

(2S)-3-(azetidin-1-yl)-2-[1-(2-chloro-6-cyano-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-N-(2-pyridyl)propanamide;

(2S)-2-[1-(2-chloro-6-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-3-(3-hydroxyazetidin-1-yl)-N-(2-pyridyl)propanamide;

(2S)-2-[1-(2-chlorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-N-(5-cyano-2-pyridyl)-3-(3-hydroxyazetidin-1-yl)propanamide;

(2S)-2-[1-(2-chloro-6-cyano-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-N-(5-cyano-2-pyridyl)-3-(3-hydroxyazetidin-1-yl)propanamide

(2S)-2-[1-(2-chlorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-3-(3-hydroxyazetidin-1-yl)-N-(2-pyridyl)propanamide;

(2S)-2-[1-(2-chlorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-N-(5-chloro-2-pyridyl)-3-(3-hydroxyazetidin-1-yl)propanamide;

(2S)-3-[(1R)-2-hydroxy-1-methyl-ethoxy]-N-(5-methyl-2-pyridyl)-2-[1-(4-methyl-3-thienyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-propanamide;

(2S)-2-[1-(2-chlorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-3-[3-(hydroxymethyl)azetidin-1-yl]-N-(2-pyridyl)propanamide;

(2S)-2-[1-(2-chloro-6-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-3-(3-hydroxyazetidin-1-yl)propanamide;

(2S)-2-[1-(2,6-dichlorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-3-(3-hydroxyazetidin-1-yl)propanamide;

(2S)-2-[1-(2-chloro-6-cyano-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-3-[(1R)-2-hydroxy-1-methyl-ethoxy]-N-(2-pyridyl)propanamide;

(2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-3-[(1R)-2-hydroxy-1-methyl-ethoxy]-N-(5-methyl-2-pyridyl)propanamide;

(2S)-2-[1-(2,6-dichlorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-3-(3-hydroxyazetidin-1-yl)-N-(2-pyridyl)propanamide;

(2S)-N-(5-cyano-2-pyridyl)-2-[1-(2,6-dichlorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-3-(3-hydroxyazetidin-1-yl)propanamide;

(2S)-N-(5-cyano-2-pyridyl)-2-[1-(2,6-dichlorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-3-(2-hydroxyethoxy)propanamide;

(2S)-N-(5-chloro-2-pyridyl)-2-[1-(2,6-dicyanophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-3-[(1R)-2-hydroxy-1-methyl-ethoxy]propanamide;

(2S)-2-[1-(2-chloro-6-cyano-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-3-(2-hydroxyethoxy)propanamide;

(2S)-2-[1-(2-chloro-6-cyano-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-3-(2-hydroxyethoxy)-N-(2-pyridyl)propanamide;

(2S)-2-[1-(2-chloro-6-cyano-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-3-(3-hydroxyazetidin-1-yl)-N-(5-methylpyrazin-2-yl)propanamide;

(2S)-2-[1-(2-chloro-6-cyano-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-N-(5-chloro-2-pyridyl)-3-(3-hydroxyazetidin-1-yl)propanamide;

(2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-3-(3-hydroxyazetidin-1-yl)-N-(2-pyridyl)propanamide;

(2S)-2-[1-(2-chloro-6-cyano-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-3-(3-hydroxyazetidin-1-yl)propanamide;

(2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-3-(3-hydroxyazetidin-1-yl)propanamide;

(2S)-2-[1-(2-chloro-6-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-3-(2-hydroxyethoxy)propanamide;

(2S)-2-[1-(2-chlorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-3-[(1R)-2-hydroxy-1-methyl-ethoxy]propanamide;

(2S)-2-[1-(2-chloro-6-cyano-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-3-[(1R)-2-hydroxy-1-methyl-ethoxy]propanamide;

(2S)-2-[1-(2-chlorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-3-[(1R)-2-hydroxy-1-methyl-ethoxy]-N-(5-methylpyrazin-2-yl)propanamide;

(2S)-2-[1-(2-chlorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-3-(2-hydroxyethoxy)propanamide;

(2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-3-(3-hydroxyazetidin-1-yl)-N-(5-methylthiazol-2-yl)propanamide;
(2S)-2-[1-(2,6-dichlorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-3-(2-hydroxyethoxy)-N-(2-pyridyl)propanamide;
(2S)-2-[1-(2-chloro-6-cyano-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-N-(5-cyano-2-pyridyl)-3-[(1R)-2-hydroxy-1-methyl-ethoxy]propanamide;
(2S)-2-[1-(2-chlorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-N-(5-cyano-2-pyridyl)-3-[(1R)-2-hydroxy-1-methyl-ethoxy]propanamide;
or a pharmaceutically acceptable salt thereof. The term "any one or more of" means any number of the the above compounds from 1 to 258.

In another aspect the present invention provides a compound selected from one or more (that is any number from 1 to 12) of the following:
(2S)-N-(5-chloropyridin-2-yl)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d] pyrimidin-4-yloxy)-3-(3-hydroxyazetidin-1-yl)propanamide;
(2S)-2-(1-(2-chloro-6-cyanophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-chloropyridin-2-yl)-3-(2-hydroxyethoxy)propanamide;
(2S)-N-(5-chloropyridin-2-yl)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-((R)-1-hydroxypropan-2-yloxy)propanamide;
(2S)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-3-(3-hydroxyazetidin-1-yl)propanamide;
(2S)-2-[1-(2-chloro-6-cyano-phenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-chloro-2-pyridyl)-3-[(1R)-2-hydroxy-1-methyl-ethoxy]propanamide;
(2S)-2-[1-(2-chloro-6-cyano-phenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-[(1R)-2-hydroxy-1-methyl-ethoxy]-N-(5-methylpyrazin-2-yl)propanamide;
(2S)-2-[1-(2,6-dichlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-3-(2-hydroxyethoxy)propanamide;
(2S)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-(3-hydroxyazetidin-1-yl)-N-(5-methylpyrazin-2-yl)propanamide;
(2S)-2-[1-(2,6-dichlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-(3-hydroxyazetidin-1-yl)-N-(5-methylpyrazin-2-yl)propanamide;
(2S)-2-[1-(2-chlorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-N-(5-chloro-2-pyridyl)-3-(3-hydroxyazetidin-1-yl)propanamide;

(2S)-2-[1-(2,6-dichlorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-3-(3-hydroxyazetidin-1-yl)propanamide; and
(2S)-2-[1-(2-chloro-6-cyano-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-3-(3-hydroxyazetidin-1-yl)propanamide;
or a pharmaceutically acceptable salt thereof.

Depending on the computer naming package used certain compounds of the invention are named as pyrazolo[3,4-d]pyrimidin-4-yl compounds and others are named as pyrazolo[4,5-c]pyrimidin-4-yl compounds. It will be understood by those skilled in the art that these terms describe the same heterocyclic ring.

In another aspect the present invention provides a compound of formula I as defined in any of the definitions above but excluding any one of the compounds in either of the lists of compounds immediately above.

The compounds of the invention may be administered in the form of a pro-drug. A pro-drug is a bioprecursor or pharmaceutically acceptable compound being degradable in the body to produce a compound of the invention (such as an ester or amide of a compound of the invention, particularly an in-vivo hydrolysable ester). Various forms of prodrugs are known in the art. For examples of such prodrug derivatives, see:

a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);

b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen;

c) H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);

d) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);

e) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988); and

f) N. Kakeya, *et al.*, Chem Pharm Bull, 32, 692 (1984).

The contents of the above cited documents are incorporated herein by reference.

Examples of pro-drugs are as follows. An in-vivo hydrolysable ester of a compound of the invention containing a carboxy or a hydroxy group is, for example, a pharmaceutically-acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically-acceptable esters for carboxy include C_1 to C_6alkoxymethyl esters for example methoxymethyl, C_1 to C

$_{6}$alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_3 to C_8cycloalkoxycarbonyloxyC_1 to C_6alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters, for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters.

An in-vivo hydrolysable ester of a compound of the invention containing a hydroxy group includes inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and α-acyloxyalkyl ethers and related compounds which as a result of the in-vivo hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of in-vivo hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and N-(dialkylaminoethyl)-N-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl.

A suitable pharmaceutically-acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In one aspect, a suitable acid-addition salt may be one with hydrochloric, sulphuric, methanesulfonic or citric acid. It will be understood that an acid addition salt may be formed with any sufficiently basic group which may for example be in HET-1 or may for example be a substituent R^2. In addition a suitable pharmaceutically-acceptable salt of a benzoxazinone derivative of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

A further feature of the invention is a pharmaceutical composition comprising a compound of Formula (I) as defined above, or a pharmaceutically-acceptable salt thereof, together with a pharmaceutically-acceptable diluent or carrier.

According to another aspect of the invention there is provided a compound of Formula (I) as defined above or a pharmaceutically-acceptable salt thereof for use as a medicament.

According to another aspect of the invention there is provided a compound of Formula (I), or a pharmaceutically-acceptable salt thereof as defined above for use as a medicament for treatment of a disease mediated through GLK, in particular type 2 diabetes.

Further according to the invention there is provided the use of a compound of Formula (I) or a pharmaceutically-acceptable salt thereof in the preparation of a medicament for treatment of a disease mediated through GLK, in particular type 2 diabetes.

The compound is suitably formulated as a pharmaceutical composition for use in this way.

According to another aspect of the present invention there is provided a method of treating GLK mediated diseases, especially diabetes, by administering an effective amount of a compound of Formula (I) or a pharmaceutically-acceptable salt thereof, including the compounds mentioned in the provisos, to a mammal in need of such treatment.

Specific diseases which may be treated by a compound or composition of the invention include: blood glucose lowering in Type 2 Diabetes Mellitus without a serious risk of hypoglycaemia (and potential to treat type 1), dyslipidemia, obesity, insulin resistance, metabolic syndrome X, impaired glucose tolerance.

As discussed above, thus the GLK system can be described as a potential "Diabesity" target (of benefit in both Diabetes and Obesity). Thus, according to another aspect of the invention there is provided the use of a compound of Formula (I) or a pharmaceutically-acceptable salt thereof, in the preparation of a medicament for use in the combined treatment or prevention, particularly treatment, of diabetes and obesity.

According to another aspect of the invention there is provided the use of a compound of Formula (I) or a pharmaceutically-acceptable salt thereof, in the preparation of a medicament for use in the treatment or prevention of obesity.

According to a further aspect of the invention there is provided a method for the combined treatment of obesity and diabetes by administering an effective amount of a compound of Formula (I) or a pharmaceutically-acceptable salt thereof, to a mammal in need of such treatment.

According to another aspect of the invention there is provided a compound of Formula (I) or a pharmaceutically-acceptable salt thereof as defined above for use as a medicament for treatment or prevention, particularly treatment of obesity.

According to a further aspect of the invention there is provided a method for the treatment of obesity by administering an effective amount of a compound of Formula (I) or a pharmaceutically-acceptable salt thereof, to a mammal in need of such treatment.

Compounds of the invention may be particularly suitable for use as pharmaceuticals, for example because of favourable physical and/or pharmacokinetic properties and/or toxicity profile.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing). Dosage forms suitable for oral use are preferred.

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above.

Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent

compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula (I) will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

In using a compound of the Formula (I) for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.5 mg to 75 mg per kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.5 mg to 30 mg per kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.5 mg to 25 mg per kg body weight will be used. Oral administration is however preferred.

The elevation of GLK activity described herein may be applied as a sole therapy or in combination with one or more other substances and/or treatments for the indication being treated. In another aspect the invention provides a pharmaceutical combination comprising a compound of Formula I and another pharmacologically active substance particularly wherein the other pharmacologically active substance is a medicament for the treatment of type 2 diabetes or obesity or a related condition.

Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. Simultaneous treatment may be in a single tablet or in separate tablets. For example in the treatment of diabetes mellitus, chemotherapy may include the following main categories of treatment:

1) Insulin and insulin analogues;
2) Insulin secretagogues including sulphonylureas (for example glibenclamide, glipizide), prandial glucose regulators (for example repaglinide, nateglinide);

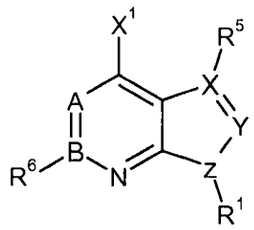
3) Agents that improve incretin action (for example dipeptidyl peptidase IV inhibitors e.g.saxagliptin, sitagliptin, vildagliptin or alogliptin and GLP-1 agonists);
4) Insulin sensitising agents including PPARgamma agonists (for example pioglitazone and rosiglitazone), and agents with combined PPARalpha and gamma activity;
5) Agents that modulate hepatic glucose balance (for example metformin, fructose 1, 6 bisphosphatase inhibitors, glycogen phopsphorylase inhibitors, glycogen synthase kinase inhibitors);
6) Agents designed to reduce the absorption of glucose from the intestine (for example acarbose);
7) Agents that prevent the reabsorption of glucose by the kidney (SGLT inhibitors for example dapagliflozin);
8) Agents designed to treat the complications of prolonged hyperglycaemia (for example aldose reductase inhibitors);
9) Anti-obesity agents (for example sibutramine and orlistat);
10) Anti- dyslipidaemia agents such as, HMG-CoA reductase inhibitors (eg statins); PPARα agonists (fibrates, eg gemfibrozil); bile acid sequestrants (cholestyramine); cholesterol absorption inhibitors (plant stanols, synthetic inhibitors); bile acid absorption inhibitors (IBATi) and nicotinic acid and analogues (niacin and slow release formulations);
11) Antihypertensive agents such as, β blockers (eg atenolol, inderal); ACE inhibitors (eg lisinopril); Calcium antagonists (eg. nifedipine); Angiotensin receptor antagonists (eg candesartan), α antagonists and diuretic agents (eg. furosemide, benzthiazide);
12) Haemostasis modulators such as, antithrombotics, activators of fibrinolysis and antiplatelet agents; thrombin antagonists; factor Xa inhibitors; factor VIIa inhibitors); antiplatelet agents (eg. aspirin, clopidogrel); anticoagulants (heparin and Low molecular weight analogues, hirudin) and warfarin;
13) Agents which antagonise the actions of glucagon; and
14) Anti-inflammatory agents, such as non-steroidal anti-inflammatory drugs (eg. aspirin) and steroidal anti-inflammatory agents (eg. cortisone).

According to another aspect of the present invention there is provided individual compounds produced as end products in the Examples set out below and salts thereof.

A compound of the invention, or a salt thereof, may be prepared by any process known to be applicable to the preparation of such compounds or structurally related compounds. Functional groups may be protected and deprotected using conventional methods. For examples of protecting groups such as amino and carboxylic acid protecting groups (as well as means of formation and eventual deprotection), see T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis", Second Edition, John Wiley & Sons, New York, 1991.

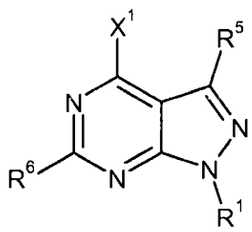
Processes for the synthesis of compounds of Formula (I) are provided as a further feature of the invention. Thus, according to a further aspect of the invention there is provided a process for the preparation of a compound of Formula (I).

Compounds of formula (I) may be prepared by reacting a compound of formula (II)

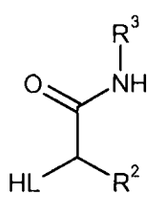


(II)

For example:



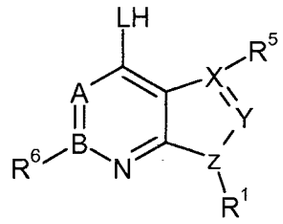
in which R^1, R^2, R^3, R^5 and R^6 are as defined above and X^1 is a leaving group, for example halo, particularly chloro, with a compound of formula (III)



(III)

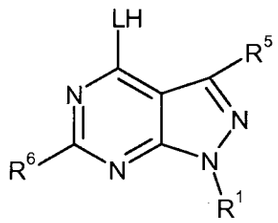
in which R^2, R^3 and L are as defined above in an inert solvent, for example tetrahydrofuran, in the presence of a base, for example lithium bis(trimethylsilyl)amide or sodium hydride, at a temperature in the range of -25°C to 150°C.

Compounds of formula (I) may be also prepared by reacting a compound of formula (IV)

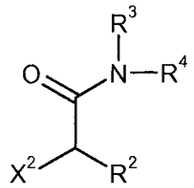


(IV)

For example



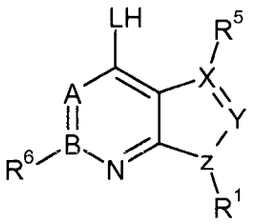
in which R^1, R^5 , R^6 and L are as defined above with a compound of formula (V)



(V)

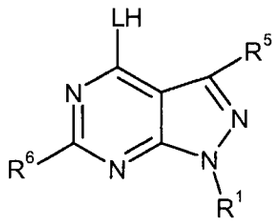
in which R^2, R^3 and L are as defined above and X^2 is a leaving group for example halo particularly chloro, in an inert solvent, for example tetrahydrofuran or dimethylformamide, in the presence of a base, for example potassium carbonate, at a temperature in the range of -25°C to 150°C.

Compounds of formula (I) may be also prepared by reacting a compound of formula (IV)

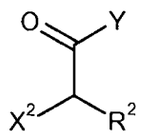


(IV)

for example



in which R^1, R^5 and R^6 are as defined above and L is, for example, S with a compound of formula (V) as defined above wherein the compound of formula (V) is formed in situ by reacting a compound of formula (VI)



(VI)

in which R^2 is as defined above and X^2 is a leaving group, for example halo, particularly bromo, and Y is chloro with a compound of formula (VII)

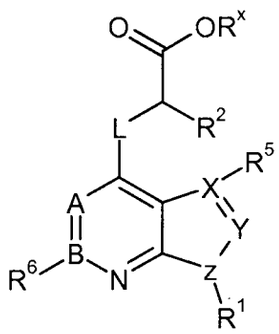
$$H_2NR^3$$

(VII)

in which R^3 is as previously defined in the presence of a base, for example di-*iso*-propylethylamine, in an inert solvent for example dichloromethane at a temperature in the range of -25°C to 150°C.

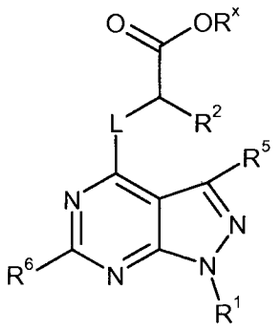
Or where X^2 is hydroxy and Y is alkoxy eg. methoxy in the presence of a Lewis acid such as trimethyl aluminium or isopropylmagnesium bromide.

Compounds of formula (I) may be also prepared by reacting a compound of formula (VIII)



(VIII)

For example



in which R^1, R^5 , R^6 and L are as defined above and R^x is a (1-4C)alkyl with a compound of formula (VII) as defined above in an inert solvent, for example tetrahydrofuran, in the presence of a base, for example sodium hydride, at a temperature in the range of -25°C to 150°C or in the presence of a Lewis acid, for example trimethyl aluminium in a suitable solvent such as toluene.

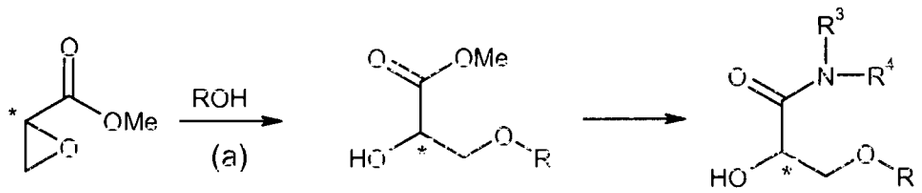
Certain intermediates of formula (II) and (IV) are believed to be novel and comprise an independent aspect of the invention.

When R^2 is (1-6C)alkoxymethyl, compounds of formula (III) may be made as outlined in Scheme 1 below, wherein R is (1-6C)alkyl. The process shown in Scheme 1 comprises a further aspect of the invention.

Ring opening of epoxyesters by alcohols as shown in step a) of Scheme 1 is known in the art, see Synthetic Communications, Vol 33 (2003), pp687-692. The reaction generally requires the use of a Lewis acid catalyst, and specifically magnesium perchlorate ($Mg(ClO_4)_2$) is known in the above reference, used without any added solvent. We have found that this process carries a risk of spontaneous decomposition with rapid gas evolution and/or explosion, which may be reduced both by changing Lewis acid and by

adding solvent to the reaction. In particular, step a) is carried out in the presence of magnesium trifluoromethanesulfonate, suitably in ethyl acetate, toluene or dichloromethane, most particularly in ethyl acetate. This process is exemplified in Intermediate C7a hereinafter.

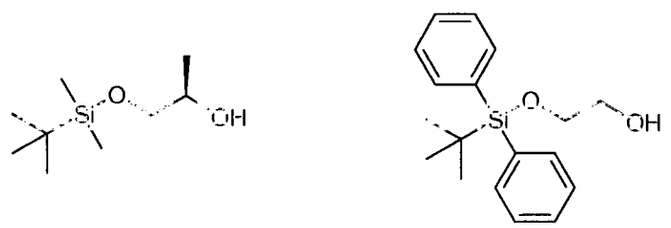
Therefore in a further aspect of the invention there is provided the reaction of methyl oxirane-2-carboxylate (IX) with an alcohol ROH (wherein R is (1-6C)alkyl, (3-6C)cycloalkyl or R^x_3SiO(2-4C)alkyl (wherein each R^x is independently selected from (1-6C)alkyl and phenyl) in the presence of magnesiumtrifluoromethanesulfonate in ethyl acetate, to give a compound of formula (X).



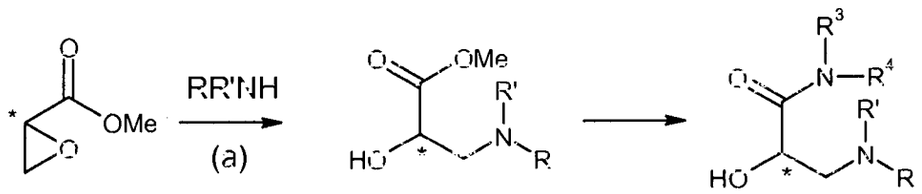
(IX) (X) (III)

Scheme 1

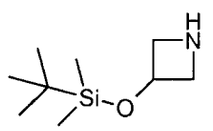
Suitable examples of ROH wherein R is R^x_3SiO(2-4C)alkyl include



In an analogous procedure amines may be used prepare azetidines:



Suitable examples of RR'NH include



In one aspect R is (1-6C)alkyl. In another aspect, R is methyl, ethyl, isopropyl or cyclobutyl.

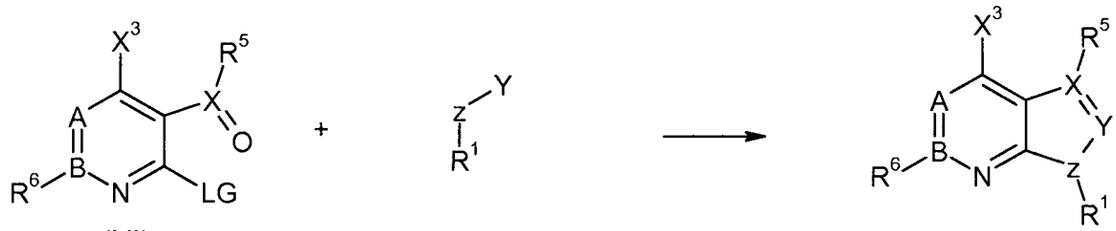
Although compound of formula (IX) is a methyl ester, other alkyl esters may also be used.

It will be appreciated that when the compound of formula (IX) is enantiomerically enriched then the compounds of formula (X) and (III) made therefrom will also be enantiomerically enriched.

The compound of formula (X) may alternatively be reacted with a compound of formula (II) to give a compound of formula (VIII).

Compounds of formula (II) may be made according to the following processes a) to b)

a) by reaction of a compound of formula (XI) wherein X^3 is a leaving group such as halo (for example chloro), or a precursor to the linker group L such as OH, or SH, or a precursor to the leaving group such as OH, SMe, S(p-tolyl) or NH_2; and wherein LG is a leaving group such as chloro, bromo, iodo or trifluoromethanesulfonyl; R^1, R^5, R^6, A, B, X, Y and Z are as previously defined;

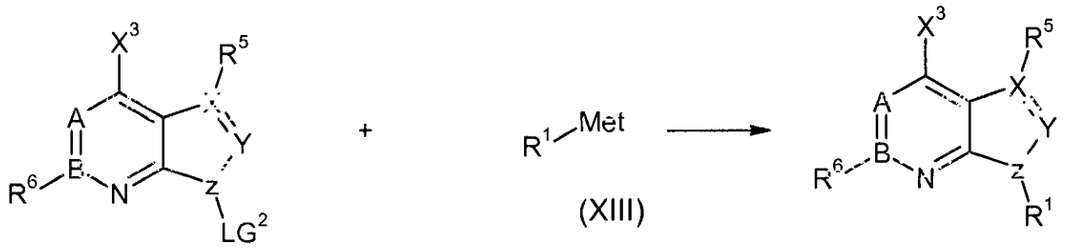


(XI)

Compounds of the formula (XI) may be made by processes known in the art.

It will be appreciated that a compound where X^3 is OH may be transformed into a compound where X^3 is Cl by reaction with a chlorinating agent such as $POCl_3$.

b) By reaction of a compound of formula (XII) with a compound of formula (XIII), wherein R^1, R^5, R^6, A, B, X, X^3, Y and Z are as previously defined; LG^2 is a leaving group such as chloro, bromo, iodo or trifluoromethanesulfonyl when Z=C, and LG^2 is H when Z=N; Met is a group suitable for coupling reactions, such as $-B(OH)_2$ and $-SnBu_3$, mediated by catalysts containing transition metals such as Pd^0 or Cu^I, such as $PdPPh_3$ or CuI.

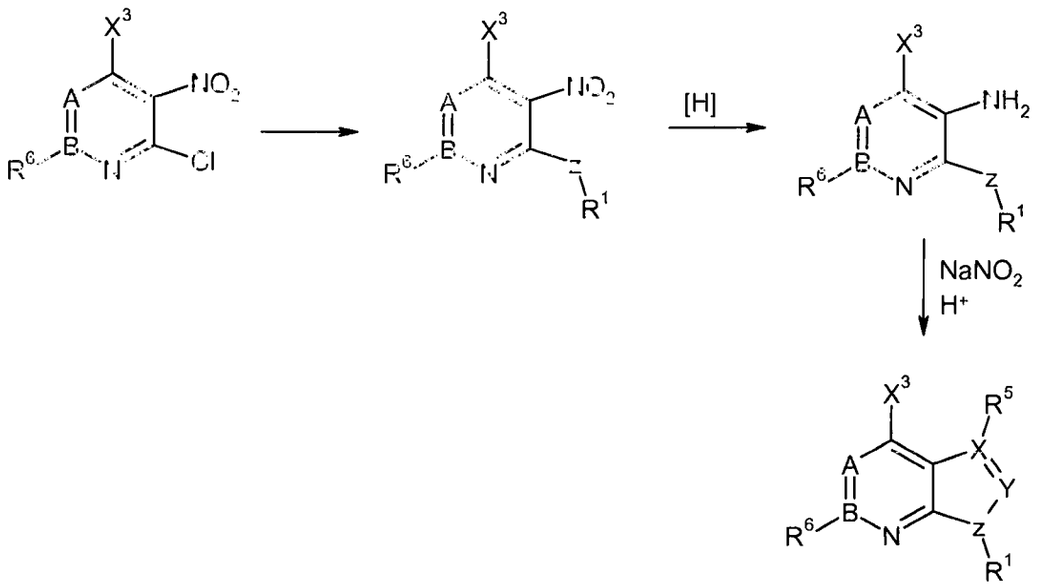


(XII) (XIII)

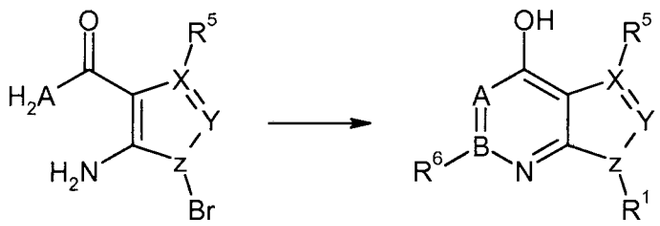
It will be appreciated that the above reaction may alternatively be carried out by the equivalent procedure wherein the Met group is a substitutent on Z and LG^2 is attached to R^1, wherein LG^2 is a leaving group such as chloro, bromo, iodo or trifluoromethanesulfonyl and Met is as previously defined when Z=C but wherein Met is H when Z=N.

It will be understood that compounds such as those of formulae (XI) and (XII) when X^3 is OH may exist in two tautomeric forms, although they are drawn herein in the enol form.

Compounds of the formula (XII) may be made by processes known in the art or by analogy to processes known in the art. For example for X=Y=Z=N the following process may be used:



or for example according to the scheme below, using a reagent such as methyl formate, a mixture of formic acid and sulfuric acid, or trimethylorthoformate when B is C and a reagent such as nitrous acid when B is N.



During the preparation process, it may be advantageous to use a protecting group for a functional group within the molecule. Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower" signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of protecting groups are given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned is of course within the scope of the invention.

A carboxy protecting group may be the residue of an ester-forming aliphatic or araliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 1-20 carbon atoms). Examples of carboxy protecting groups include straight or branched chain (1-12C)alkyl groups (e.g. isopropyl, t-butyl); lower alkoxy lower alkyl groups (e.g. methoxymethyl, ethoxymethyl, isobutoxymethyl; lower aliphatic acyloxy lower alkyl groups, (e.g. acetoxymethyl, propionyloxymethyl, butyryloxymethyl, pivaloyloxymethyl); lower alkoxycarbonyloxy lower alkyl groups (e.g. 1-methoxycarbonyloxyethyl, 1-ethoxycarbonyloxyethyl); aryl lower alkyl groups (e.g. p-methoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (e.g. trimethylsilyl and t-butyldimethylsilyl); tri(lower alkyl)silyl lower alkyl groups (e.g. trimethylsilylethyl); and (2-6C)alkenyl groups (e.g. allyl and vinylethyl).

Methods particularly appropriate for the removal of carboxyl protecting groups include for example acid-, metal- or enzymically-catalysed hydrolysis.

Examples of hydroxy protecting groups include methyl, t-butyl, lower alkenyl groups (e.g. allyl); lower alkanoyl groups (e.g. acetyl); lower alkoxycarbonyl groups (e.g.

t-butoxycarbonyl); lower alkenyloxycarbonyl groups (e.g. allyloxycarbonyl); aryl lower alkoxycarbonyl groups (e.g. benzoyloxycarbonyl, p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl); tri lower alkyl/arylsilyl groups (e.g. trimethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl); tetrahydropyran-2-yl; aryl lower alkyl groups (e.g. benzyl) groups; and triaryl lower alkyl groups (e.g. triphenylmethyl). Examples of amino protecting groups include formyl, aralkyl groups (e.g. benzyl and substituted benzyl, e.g. p-methoxybenzyl, nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-p-anisylmethyl and furylmethyl groups; lower alkoxycarbonyl (e.g. t-butoxycarbonyl); lower alkenyloxycarbonyl (e.g. allyloxycarbonyl); aryl lower alkoxycarbonyl groups (e.g. benzyloxycarbonyl, p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl; trialkylsilyl (e.g. trimethylsilyl and t-butyldimethylsilyl); alkylidene (e.g. methylidene); benzylidene and substituted benzylidene groups.

Methods appropriate for removal of hydroxy and amino protecting groups include, for example, nucleophilic displacement, acid-, base, metal- or enzymically-catalysed hydrolysis, catalytic hydrogenolysis/hydrogenation or photolytically for groups such as o-nitrobenzyloxycarbonyl, or with fluoride ions for silyl groups. For example, methylether protecting groups for hydroxy groups may be removed by trimethylsilyliodide. A tert-butyl ether protecting group for a hydroxy group may be removed by hydrolysis, for example by use of hydrochloric acid in methanol.

Examples of protecting groups for amide groups include aralkoxymethyl (e.g. benzyloxymethyl and substituted benzyloxymethyl); alkoxymethyl (e.g. methoxymethyl and trimethylsilylethoxymethyl); tri alkyl/arylsilyl (e.g. trimethylsilyl, t-butyldimethylsily, t-butyldiphenylsilyl); tri alkyl/arylsilyloxymethyl (e.g. t-butyldimethylsilyloxymethyl, t-butyldiphenylsilyloxymethyl); 4-alkoxyphenyl (e.g. 4-methoxyphenyl); 2,4-di(alkoxy)phenyl (e.g. 2,4-dimethoxyphenyl); 4-alkoxybenzyl (e.g. 4-methoxybenzyl); 2,4-di(alkoxy)benzyl (e.g. 2,4-di(methoxy)benzyl); and alk-1-enyl (e.g. allyl, but-1-enyl and substituted vinyl e.g. 2-phenylvinyl).

Aralkoxymethyl, groups may be introduced onto the amide group by reacting the latter group with the appropriate aralkoxymethyl chloride, and removed by catalytic hydrogenation. Alkoxymethyl, tri alkyl/arylsilyl and tri alkyl/silyloxymethyl groups may be introduced by reacting the amide with the appropriate chloride and removing with acid;

or in the case of the silyl containing groups, fluoride ions. The alkoxyphenyl and alkoxybenzyl groups are conveniently introduced by arylation or alkylation with an appropriate halide and removed by oxidation with ceric ammonium nitrate. Finally alk-1-enyl groups may be introduced by reacting the amide with the appropriate aldehyde and removed with acid.

In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred aspects and embodiments of the compounds of the invention described herein also apply.

The following examples are for illustration purposes and are not intended to limit the scope of this application. Each exemplified compound represents a particular and independent aspect of the invention. In the following non-limiting Examples, unless otherwise stated:

(i) evaporations were carried out by rotary evaporation under reduced pressure and work-up procedures were carried out after removal of residual solids such as drying agents by filtration;

(ii) operations were carried out at room temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon or nitrogen;

(iii) yields are given for illustration only and are not necessarily the maximum attainable;

(iv) the structures of the end-products of the Formula (I) were confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; proton magnetic resonance chemical shift values were measured on the delta scale and peak multiplicities are shown as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; q, quartet; quin, quintet; sextet

(v) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), high-performance liquid chromatography (HPLC), infra-red (IR) or NMR analysis;

(vi) flash chromatography was carried out on silica unless otherwise stated;

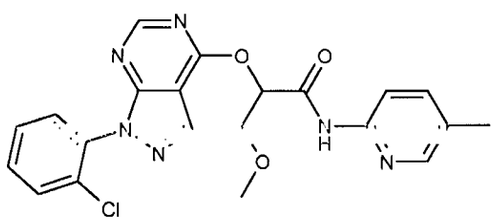
(vii) Enantiomeric excesses (ee's) were determined by HPLC using a chiral stationary phase such as Chiralcel OJ or Chiralpak AD-H and / or by NMR using an appropriate chiral shift reagent such as (1S)-[1,1'-binaphthalene]-2,2'-diol (CAS 18531-99-2) or (1R)-[1,1'-binaphthalene]-2,2'-diol (CAS 18531-94-7).

Abbreviations

ACN	Acetonitrile
n-BuLi	*n*-Butyllithium
m-CPBA	3-Chloroperbenzoic acid
DCM	Dichloromethane
DIPEA	Di-*iso*-propylethylamine
DMAP	4-Di(methylamino)pyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	dimethylsulfoxide
EtOAc	Ethyl acetate
EtOH	Ethanol
FMOC	9-Fluorenylmethyl carbamate
IPA	Isopropyl alcohol
LHMDS	Lithium bis(trimethylsilyl)amide
MeOH	Methanol
TBDMSCl	*tert*-Butyldimethylsilyl chloride
THF	Tetrahydrofuran
ESI	Electrospray ionisation
rt	Room temperature
cat	Catalytic
ee	Enantiomeric excess
HPLC	High performance liquid chromatography
EDCI	1-(3-Dimethylaminopropyl)-2-ethylcarbodiimide hydrochloride

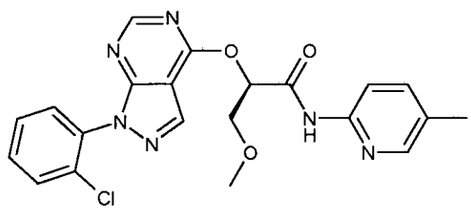
Method 1

Example 1: 2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-3-methoxy-*N*-(5-methylpyridin-2-yl)propanamide

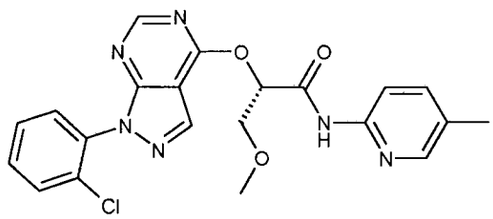


LHMDS (1.40 mL, 1.0 M in THF, 1.40 mmol) was added slowly to a stirred solution of 2-hydroxy-3-methoxy-*N*-(5-methylpyridin-2-yl)propanamide (200 mg, 0.951 mmol) in anhydrous THF (5 mL). The reaction mixture was kept at ambient temperature for 10 minutes, and a solution of 4-chloro-1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (265 mg, 1.00 mmol) in anhydrous THF (3 mL) was added. The reaction mixture was heated at 50°C for 1 ½ hrs (another 3 equivalents of LHMDS were added and the reaction heated for 18 hrs at 50 °C in example 49). Water and EtOAc were added, and the two phases were separated. The organic phase was washed with water, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified with column chromatography (silica gel, eluting with DCM/EtOAc:2/1) to give the title compound as a colourless solid (323 mg), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (br s, 1H), 8.62 (s, 1H), 8.48 (s, 1H), 8.18 (d, 1H), 8.12 (s, 1H), 7.65 (d, 1H), 7.52 (m, 4H), 6.13 (t, 1H), 4.14 (m, 2H), 4.06 (m, 1H), 3.49 (s, 3H), 2.32 (s, 3H), HRMS: calcd for ($M+H^+$) $C_{21}H_{20}{}^{35}ClN_6O_3$: 439.1285. Found: 439.1287.

Example 2: (R)-2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-3-methoxy-*N*-(5-methylpyridin-2-yl)propanamide



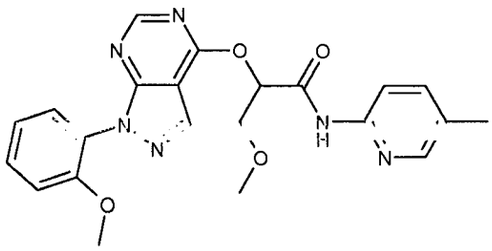
and Example 3: (S)-2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-3-methoxy-*N*-(5-methylpyridin-2-yl)propanamide



The enantiomers of racemic 2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-3-methoxy-*N*-(5-methylpyridin-2-yl)propanamide (100 mg) were separated by preparative HPLC: Column Chiralpak AS (250x20 mm, 5 µm); Mobile phase heptane/IPA:60/40; Flow 15 ml/min; UV 275 nm; Temperature 40°C. This gave (R)-2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-3-methoxy-*N*-(5-methylpyridin-2-yl)propanamide (44.1 mg, >99% ee), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (br s, 1H), 8.59

(s, 1H), 8.44 (s, 1H), 8.15 (d, 1H), 8.10 (s, 1H), 7.62 (m, 1H), 7.51 (m, 4H), 6.10 (t, 1H), 4.07 (m, 2H), 3.46 (s, 3H), 2.29 (s, 3H), and (S)-2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-3-methoxy-*N*-(5-methylpyridin-2-yl)propanamide (45.7 mg, >99% ee), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (br s, 1H), 8.59 (s, 1H), 8.44 (s, 1H), 8.15 (d, 1H), 8.10 (s, 1H), 7.62 (m, 1H), 7.50 (m, 4H), 6.10 (t, 1H), 4.07 (m, 2H), 3.46 (s, 3H), 2.29 (s, 3H).

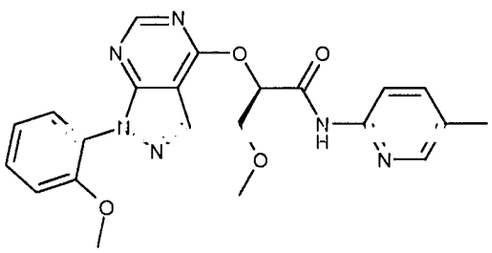
Example 4: 3-methoxy-2-{[1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)propanamide



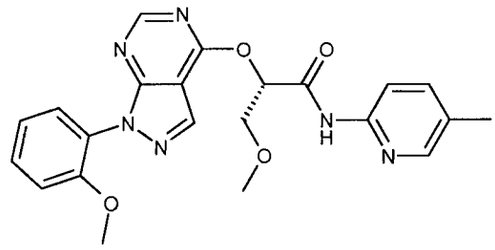
Method 1 from Intermediates A2 and B3

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (br s, 1H), 8.56 (s, 1H), 8.42 (s, 1H), 8.15 (d, 1H), 8.10 (s, 1H), 7.48 (m, 3H), 7.12 (m, 2H), 6.11 (t, 1H), 4.12 (m, 1H), 4.02 (m, 1H), 3.79 (s, 3H), 3.46 (s, 3H), 2.29 (s, 3H), HRMS: calcd for ($M+H^+$) $C_{22}H_{23}N_6O_4$: 435.1780. Found: 435.1773.

Example 5: (R)-3-methoxy-2-{[1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)propanamide

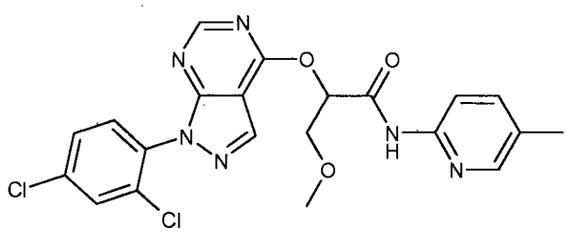


and Example 6: (S)-3-methoxy-2-{[1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)propanamide



The enantiomers of racemic 3-methoxy-2-{[1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)propanamide (100 mg) were separated by preparative HPLC: Column Chiralpak AD (250x20 mm, 5 μm); Mobile phase heptane/IPA:40/60; Flow 15 ml/min; UV 275 nm; Temperature 40°C. This gave (R)-3-methoxy-2-{[1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)propanamide (39.0 mg, >99% ee), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (br s, 1H), 8.56 (s, 1H), 8.41 (s, 1H), 8.15 (d, 1H), 8.09 (d, 1H), 7.48 (m, 3H), 7.12 (m, 2H), 6.10 (dd, 1H), 4.06 (m, 2H), 3.78 (s, 3H), 3.46 (s, 3H), 2.29 (s, 3H), and (S)-3-methoxy-2-{[1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)propanamide (41.1 mg, >99% ee), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (br s, 1H), 8.56 (s, 1H), 8.41 (s, 1H), 8.15 (d, 1H), 8.10 (d, 1H), 7.48 (m, 3H), 7.11 (m, 2H), 6.10 (dd, 1H), 4.06 (m, 2H), 3.78 (s, 3H), 3.46 (s, 3H), 2.29 (s, 3H).

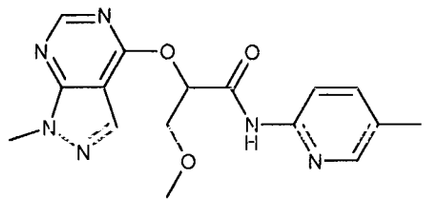
Example 7: 2-{[1-(2,4-Dichlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-3-methoxy-*N*-(5-methylpyridin-2-yl)propanamide



Method 1 from Intermediates A2 and B6

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (br s, 1H), 8.08 (m, 1H), 7.86 (s, 1H), 7.59 (s, 1H), 7.23 (s, 1H), 7.15 (m, 1H), 6.98 (m, 1H), 6.78 (m, 1H), 5.63 (m, 1H), 3.70 (m, 1H), 3.55 (m, 1H), 2.99 (s, 3H), 1.86 (s, 3H), HRMS: calcd for ($M+H^+$) $C_{22}H_{19}{}^{35}Cl_2N_6O_3$: 473.0895. Found: 473.0904.

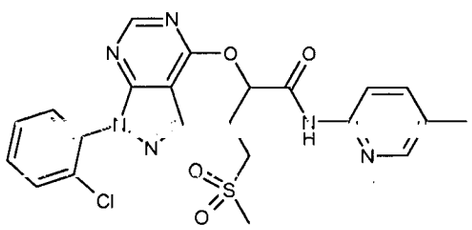
Example 8: 3-methoxy-2-[(1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)oxy]-*N*-(5-methylpyridin-2-yl)propanamide



Method 1 from Intermediates A2 and B11

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (br s, 1H), 8.56 (s, 1H), 8.19 (s, 1H), 8.13 (d, 1H), 8.08 (s, 1H), 7.52 (d, 1H), 6.07 (t, 1H), 4.12 (s, 3H), 4.09 (m, 1H), 4.00 (m, 1H), 3.44 (s, 3H), 2.28 (s, 3H), HRMS: calcd for ($M+H^+$) $C_{16}H_{19}N_6O_3$: 343.1518. Found: 343.1529.

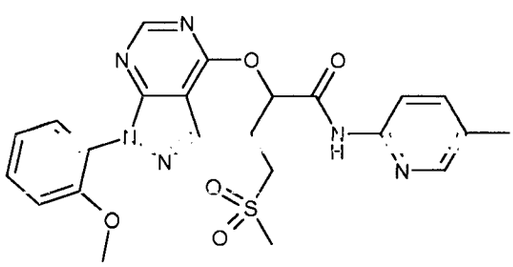
Example 9: 2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)-4-(methylsulfonyl)butanamide



Method 1 from Intermediates A1 and B1

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.01 (br s, 1H), 8.58 (s, 1H), 8.39 (s, 1H), 8.07 (m, 2H), 7.60 (d, 1H), 7.49 (m, 4H), 6.07 (t, 1H), 3.36 (m, 2H), 2.96 (s, 3H), 2.72 (m, 2H), 2.27 (s, 3H), HRMS: calcd for ($M+H^+$) $C_{22}H_{22}{}^{35}ClN_6O_4S$: 501.1111. Found: 501.1070.

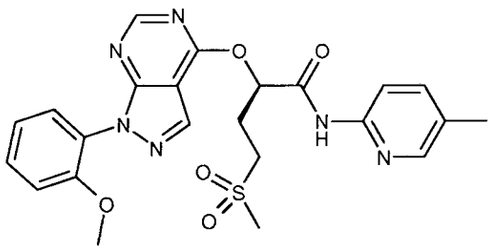
Example 10: 2-{[1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)-4-(methylsulfonyl)butanamide



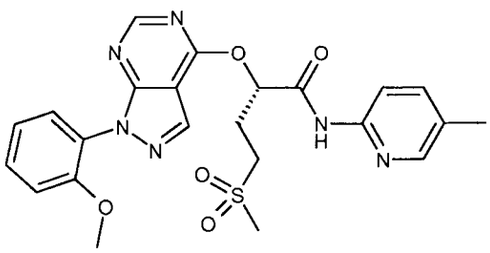
Method 1 from Intermediates A1 and B3

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.00 (br s, 1H), 8.55 (s, 1H), 8.35 (s, 1H), 8.07 (m, 2H), 7.47 (m, 3H), 7.11 (m, 2H), 6.08 (t, 1H), 3.78 (s, 3H), 3.35 (m, 2H), 2.97 (s, 3H), 2.72 (m, 2H), 2.26 (s, 3H), HRMS: calcd for ($M+H^+$) $C_{23}H_{25}N_6O_5S$: 497.1607. Found: 497.1630.

Example 11: (R)-2-{[1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)-4-(methylsulfonyl)butanamide

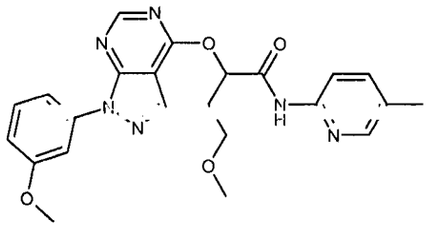


and Example 12: (S)-2-{[1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)-4-(methylsulfonyl)butanamide



The enantiomers of racemic 2-{[1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)-4-(methylsulfonyl)butanamide (48.5 mg) were separated by preparative HPLC: Column Chiralcel OD (250x20 mm, 10 μm); Mobile phase heptane/EtOH:30/70; Flow 20 ml/min; UV 240 nm; Ambient temperature. This gave (R)-2-{[1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)-4-(methylsulfonyl)butanamide (15.0 mg, >99% ee), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (br s, 1H), 8.57 (s, 1H), 8.37 (s, 1H), 8.09 (m, 2H), 7.49 (m, 3H), 7.13 (m, 2H), 6.10 (t, 1H), 3.79 (s, 3H), 3.34 (m, 2H), 2.98 (s, 3H), 2.74 (m, 2H), 2.30 (s, 3H), and (S)-2-{[1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)-4-(methylsulfonyl)butanamide (20.0 mg, >99% ee), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77 (br s, 1H), 8.58 (s, 1H), 8.38 (s, 1H), 8.10 (m, 2H), 7.48 (m, 3H), 7.13 (m, 2H), 6.11 (t, 1H), 3.79 (s, 3H), 3.34 (m, 2H), 2.98 (s, 3H), 2.73 (m, 2H), 2.30 (s, 3H).

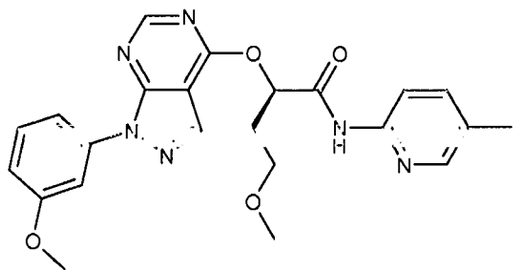
Example 13: 4-methoxy-2-{[1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)butanamide



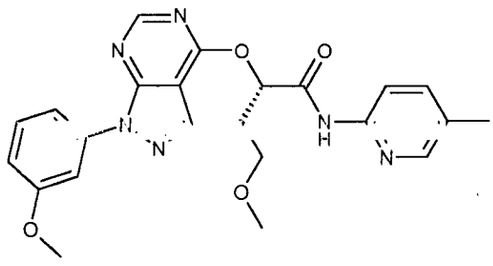
Method 1 from Intermediates A12 and B5

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (br s, 1H), 8.64 (s, 1H), 8.32 (s, 1H), 8.12 (d, 1H), 8.08 (s, 1H), 7.81 (d, 1H), 7.79 (m, 1H), 7.51 (d, 1H), 7.43 (t, 1H), 6.91 (d, 1H), 5.96 (t, 1H), 3.90 (s, 3H), 3.63 (t, 2H), 3.33 (s, 3H), 2.44 (m, 2H), 2.28 (s, 3H), HRMS: calcd for ($M+H^+$) $C_{23}H_{25}N_6O_4$: 449.1937. Found: 449.1936.

Example 14: (R)-4-methoxy-2-{[1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)butanamide



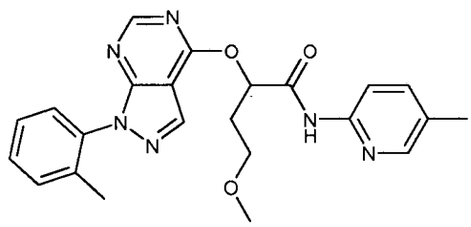
and Example 15: (S)-4-methoxy-2-{[1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)butanamide



The enantiomers of racemic 4-methoxy-2-{[1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)butanamide (140.0 mg) were separated by preparative HPLC: Column Chiralpak IA (250x20 mm, 5 µm); Mobile phase heptane/EtOH:30/70; Flow 12 ml/min; UV 254 nm; Temperature 40°C. This gave (P)-4-methoxy-2-{[1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-

methylpyridin-2-yl)butanamide (63.4 mg, >98% ee), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.90 (br s, 1H), 8.63 (s, 1H), 8.31 (s, 1H), 8.11 (m, 2H), 7.81 (m, 2H), 7.51 (d, 1H), 7.42 (t, 1H), 6.90 (d, 1H), 5.95 (t, 1H), 3.89 (s, 3H), 3.63 (t, 2H), 3.32 (s, 3H), 2.43 (m, 2H), 2.27 (s, 3H), and (S)-4-methoxy-2-{[1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)butanamide (62.7 mg, 99.7% ee), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.92 (br s, 1H), 8.63 (s, 1H), 8.31 (s, 1H), 8.12 (m, 2H), 7.79 (m, 2H), 7.52 (d, 1H), 7.42 (t, 1H), 6.90 (d, 1H), 5.95 (t, 1H), 3.89 (s, 3H), 3.63 (t, 2H), 3.32 (s, 3H), 2.43 (m, 2H), 2.27 (s, 3H).

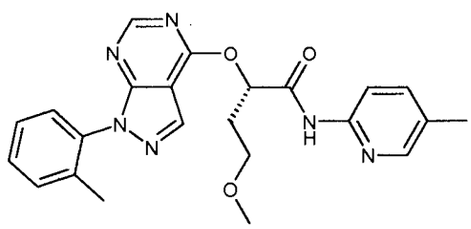
Example 16: 4-methoxy-2-{[1-(2-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)butanamide



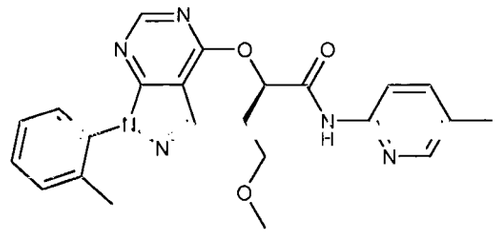
Method 1 from Intermediates A12 and B2

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.90 (br s, 1H), 8.56 (s, 1H), 8.36 (s, 1H), 8.15 (d, 1H), 8.12 (s, 1H), 7.53 (d, 1H), 7.39 (m, 4H), 5.96 (t, 1H), 3.66 (m, 2H), 3.36 (s, 3H), 2.45 (m, 2H), 2.29 (s, 3H), 2.17 (s, 3H), HRMS: calcd for ($M+H^+$) $C_{23}H_{25}N_6O_3$: 433.1988. Found: 433.1984.

Example 17: (S)-4-methoxy-2-{[1-(2-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)butanamide

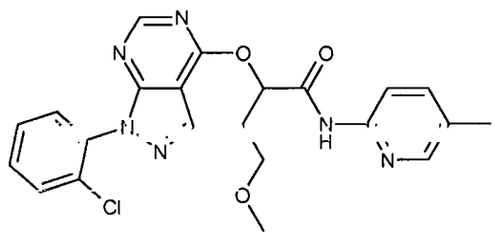


and Example 18: (R)-4-methoxy-2-{[1-(2-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)butanamide



The enantiomers of racemic 4-methoxy-2-{[1-(2-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)butanamide (122.0 mg) were separated by preparative HPLC: Column Chiralcel OD (250x20 mm, 5 µm); Mobile phase MeOH; Flow 15 ml/min; UV 230 nm; Ambient temperature. This gave (S)-4-methoxy-2-{[1-(2-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)butanamide (49.1 mg, >99% ee), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (br s, 1H), 8.57 (s, 1H), 8.36 (s, 1H), 8.12 (m, 2H), 7.53 (d, 1H), 7.39 (m, 4H), 5.96 (t, 1H), 3.65 (t, 2H), 3.34 (s, 3H), 2.46 (m, 2H), 2.29 (s, 3H), 2.16 (s, 3H), and (R)-4-methoxy-2-{[1-(2-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)butanamide (53.5 mg, >99% ee), ^{1}H NMR (300 MHz, CDCl3) δ 8.66 (br s, 1H), 8.56 (s, 1H), 8.35 (s, 1H), 8.13 (d, 1H), 8.09 (d, 1H), 7.52 (dd, 1H), 7.38 (m, 4H), 5.95 (t, 1H), 3.65 (t, 2H), 3.34 (s, 3H), 2.44 (m, 2H), 2.29 (s, 3H), 2.16 (s, 3H).

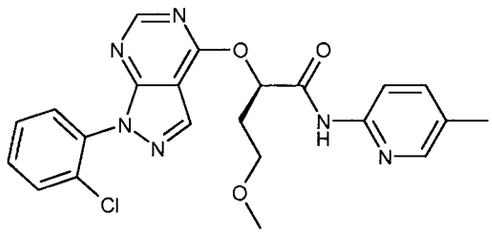
Example 19: 2-{[1-(2-Chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-4-methoxy-*N*-(5-methylpyridin-2-yl)butanamide



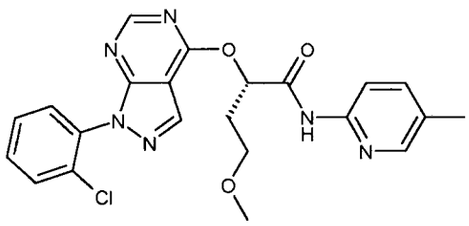
Method 1 from Intermediates A12 and B1

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (br s, 1H), 8.58 (s, 1H), 8.39 (s, 1H), 8.11 (dd, 2H), 7.61 (m, 1H), 7.49 (m, 4H), 5.95 (t, 1H), 3.64 (t, 2H), 3.34 (s, 3H), 2.44 (m, 2H), 2.29 (s, 3H), HRMS: calcd for ($M+H^+$) $C_{22}H_{22}{}^{35}ClN_6O_3$: 453.1442. Found: 453.1452.

Examples 20: (R)-2-{[1-(2-Chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-4-methoxy-*N*-(5-methylpyridin-2-yl)butanamide

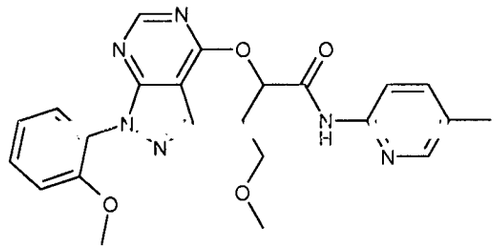


and Example 21: (S)-2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-4-methoxy-*N*-(5-methylpyridin-2-yl)butanamide



The enantiomers of racemic 2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-4-methoxy-*N*-(5-methylpyridin-2-yl)butanamide (200 mg) were separated by preparative HPLC: Column Chiralcel OJ (250x20 mm, 5 μm); Mobile phase heptane/EtOH:30/70; Flow 19 ml/min; UV 285 nm; Temperature 20°C. This gave (R)-2-{[1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]oxy}-4-methoxy-N-(5-methylpyridin-2-yl)butanamide (89 mg , >99% ee), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (br s, 1H), 8.58 (s, 1H), 8.38 (s, 1H), 8.11 (m, 2H), 7.61 (m, 1H), 7.48 (m, 4H), 5.94 (t, 1H), 3.64 (t, 2H), 3.33 (s, 3H), 2.44 (m, 2H), 2.28 (s, 3H), and (S)-2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-4-methoxy-*N*-(5-methylpyridin-2-yl)butanamide (93 mg , >99% ee), ^{1}H NMR (300 MHz, CDCl3) δ 8.67 (br s, 1H), 8.58 (s, 1H), 8.39 (s, 1H), 8.12 (m, 2H), 7.61 (m, 1H), 7.49 (m, 4H), 5.95 (t, 1H), 3.64 (t, 2H), 3.34 (s, 3H), 2.44 (m, 2H), 2.29 (s, 3H).

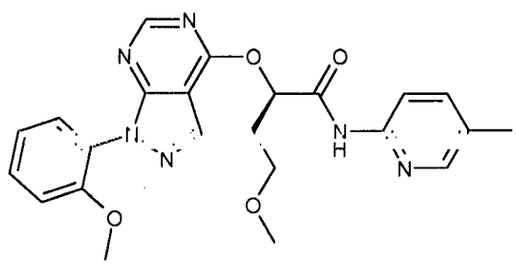
Example 22: 4-Methoxy-2-{[1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)butanamide



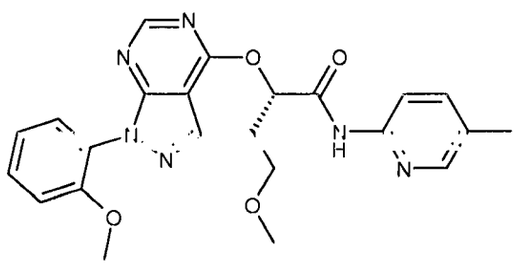
Method 1 from Intermediates A12 and B3

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (br s, 1H), 8.56 (s, 1H), 8.37 (s, 1H), 8.14 (d, 1H), 8.09 (s, 1H), 7.51 (t, 2H), 7.44 (m, 1H), 7.12 (m, 2H), 5.96 (m, 1H), 3.79 (s, 3H), 3.64 (t, 2H), 3.34 (s, 3H), 2.44 (d, 2H), 2.29 (s, 3H), HRMS: calcd for ($M+H^+$) $C_{23}H_{25}N_6O_4$: 449.1937. Found: 449.1951.

Example 23: (R)-4-Methoxy-2-{[1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)butanamide



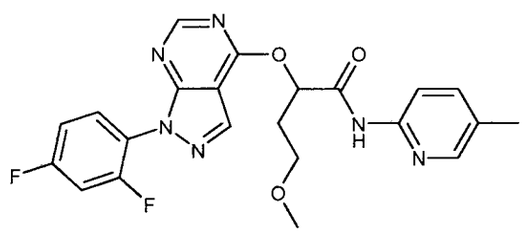
and Example 24: (S)-4-methoxy-2-{[1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)butanamide



The enantiomers of racemic 4-methoxy-2-{[1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)butanamide (100 mg) were separated by preparative HPLC: Column Chiralpak AS (250x20 mm, 5 µm); Mobile phase heptane/IPA:60/40; Flow 13 ml/min; UV 275 nm; Temperature 40°C. This gave (F)-4-methoxy-2-{[1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-

methylpyridin-2-yl)butanamide (54.4 mg, >99% ee), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (br s, 1H), 8.56 (s, 1H), 8.36 (s, 1H), 8.12 (m, 2H), 7.46 (m, 3H), 7.12 (m, 2H), 5.95 (t, 1H), 3.79 (s, 3H), 3.64 (t, 2H), 3.34 (s, 3H), 2.45 (m, 2H), 2.29 (s, 3H), and (S)-4-methoxy-2-{[1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)butanamide (53.7 mg, >99% ee), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (br s, 1H), 8.56 (s, 1H), 8.36 (s, 1H), 8.12 (m, 2H), 7.47 (m, 3H), 7.12 (m, 2H), 5.95 (t, 1H), 3.79 (s, 3H), 3.64 (t, 2H), 3.34 (s, 3H), 2.44 (d, 2H), 2.29 (s, 3H).

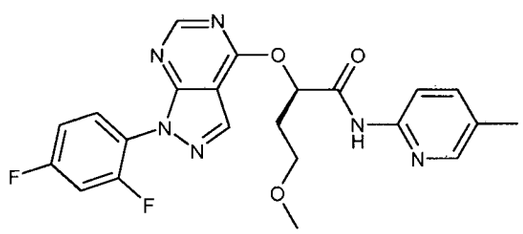
Example 25: 2-{[1-(2,4-Difluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-4-methoxy-*N*-(5-methylpyridin-2-yl)butanamide



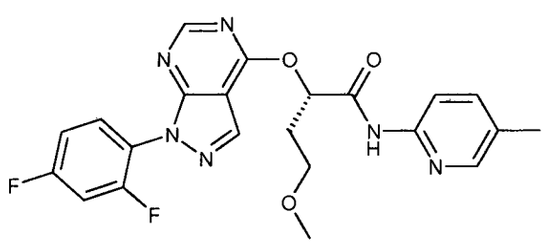
Method 1 from Intermediates A12 and B7

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (br s, 1H), 8.55 (s, 1H), 8.35 (s, 1H), 8.09 (d, 1H), 8.04 (m, 1H), 7.56 (m, 1H), 7.49 (dd, 1H), 7.03 (m, 2H), 5.91 (t, 1H), 3.60 (t, 2H), 3.29 (s, 3H), 2.44(s 3H), 2.40 (m, 2H), HRMS: calcd for ($M+H^+$) $C_{22}H_{21}F_2N_6O_3$: 455.1643. Found: 455.1657.

Example 26: (R)-2-{[1-(2,4-Difluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-4-methoxy-*N*-(5-methylpyridin-2-yl)butanamide

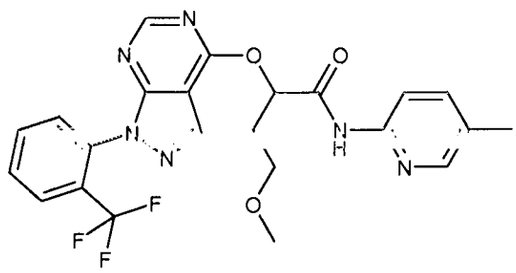


and Example 27: (S)-2-{[1-(2,4-difluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-4-methoxy-*N*-(5-methylpyridin-2-yl)butanamide



The enantiomers of racemic 2-{[1-(2,4-difluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-4-methoxy-*N*-(5-methylpyridin-2-yl)butanamide (160 mg) were separated by preparative HPLC: Column Chiralpal: AS (250x20 mm, 5 µm); Mobile phase heptane/EtOH:75/25; Flow 18 ml/min; UV 230 nm; Temperature 22°C. This gave (*R*)-2-{[1-(2,4-difluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-4-methoxy-*N*-(5-methylpyridin-2-yl)butanamide (37.6 mg, >99% ee), ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (br s, 1H), 8.57 (s, 1H), 8.42 (s, 1H), 8.18 (d, 1H), 8.05 (s, 1H), 7.59 (m, 2H), 7.05 (m, 2H), 5.94 (t, 1H), 3.62 (t, 1H), 3.31 (s, 3H), 2.42 (m, 2H), 2.29 (s, 3H), and (*S*)-2-{[1-(2,4-difluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-4-methoxy-*N*-(5-methylpyridin-2-yl)butanamide (53.7 mg, >99% ee), ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.38 (br s, 1H), 8.56 (s, 1H), 8.44 (s, 1H), 8.22 (d, 1H), 8.04 (s, 1H), 7.59 (m, 2H), 7.05 (m, 2H), 5.94 (t, 1H), 3.62 (t, 1H), 3.31 (s, 3H), 2.42 (m, 2H), 2.30 (s, 3H).

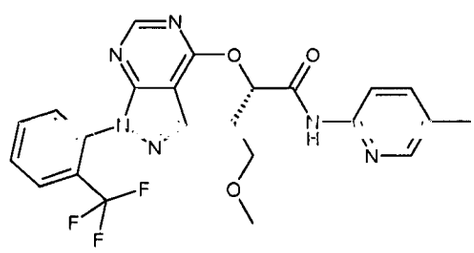
Example 28: 4-Methoxy-*N*-(5-methylpyridin-2-yl)-2-({1-[2-(trifluoromethyl)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl}oxy)butanamide



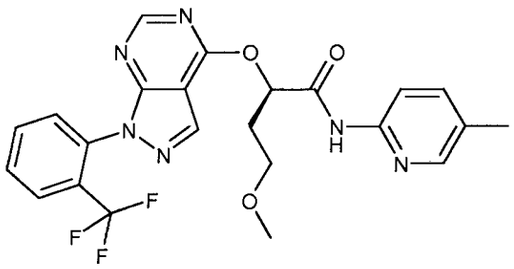
Method 1 from Intermediates A12 and B4

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (br s, 1H), 8.54 (s, 1H), 8.35 (s, 1H), 8.12 (m, 2H), 7.88 (d, 1H), 7.73 (m, 1H), 7.66 (m, 1H), 7.52 (m, 2H), 5.94 (t, 1H), 3.64 (m, 2H), 3.31 (s, 3H), 2.43 (m, 2H), 2.26 (s, 3H), HRMS: calcd for ($M+H^+$) $C_{23}H_{22}F_3N_6O_3$: 487.1705. Found: 487.1708.

Example 29: (S)-4-Methoxy-*N*-(5-methylpyridin-2-yl)-2-({1-[2-(trifluoromethyl)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl}oxy)butanamide

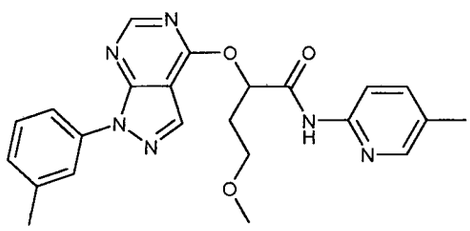


and Example 30: (R)-4-methoxy-*N*-(5-methylpyridin-2-yl)-2-({1-[2-(trifluoromethyl)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl}oxy)butanamide



The enantiomers of racemic 4-methoxy-*N*-(5-methylpyridin-2-yl)-2-({1-[2-(trifluoromethyl)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl}oxy)butanamide (178 mg) were separated by preparative HPLC: Column Chiralpak AD (250x20 mm, 5 μm); Mobile phase heptane/EtOH:30/70; Flow 18 ml/min; UV 254 nm; Temperature 20°C. This gave (S)-4-methoxy-*N*-(5-methylpyridin-2-yl)-2-({1-[2-(trifluoromethyl)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl}oxy)butanamide (61.6 mg, >98% ee) , ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (br s, 1H), 8.58 (s, 1H), 8.39 (s, 1H), 8.14 (m, 2H), 7.92 (d, 1H), 7.78 (t, 1H), 7.71 (t, 1H), 7.55 (t, 2H), 5.98 (m, 1H), 3.67 (t, 2H), 3.36 (s, 3H), 2.47 (m, 2H), 2.31 (s, 3H), and (R)-4-methoxy-*N*-(5-methylpyridin-2-yl)-2-({1-[2-(trifluoromethyl)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl}oxy)butanamide (52.0 mg, >99% ee), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (br s, 1H), 8.58 (s, 1H), 8.39 (s, 1H), 8.14 (m, 2H), 7.92 (d, 1H), 7.78 (t, 1H), 7.71 (t, 1H), 7.55 (t, 2H), 5.98 (t, 1H), 3.67 (t, 2H), 3.36 (s, 3H), 2.47 (m, 2H), 2.31 (s, 3H).

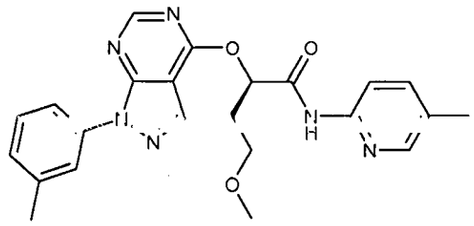
Example 31: 4-Methoxy-2-{[1-(3-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)butanamide



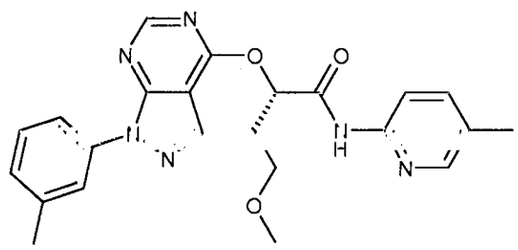
Method 1 from Intermediates A12 and B10

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (br s, 1H), 8.56 (s, 1H), 8.27 (s, 1H), 8.08 (d, 1H), 8.03 (d, 1H), 7.90 (m, 2H), 7.45 (dd, 1H), 7.35 (t, 1H), 7.10 (d, 1H), 5.90 (t, 1H), 3.59 (t, 2H), 3.26 (s, 3H), 2.40 (m, 5H), 2.21 (s, 3H), HRMS: calcd for ($M+H^+$) $C_{23}H_{25}N_6O_3$: 433.1988. Found: 433.2008.

Example 32: (R)-4-Methoxy-2-{[1-(3-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)butanamide

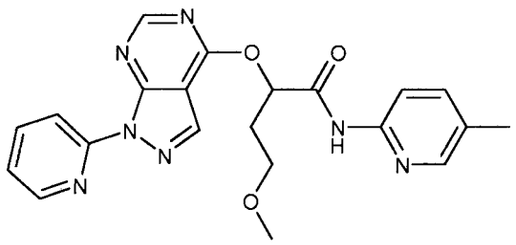


And Example 33: (S)-4-methoxy-2-{[1-(3-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)butanamide



The enantiomers of racemic 4-methoxy-2-{[1-(3-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)butanamide (159 mg) were separated by preparative HPLC: Column Chiralpak IA (250x20 mm, 5 µm); Mobile phase heptane/IPA:30/70; Flow 14 ml/min; UV 265 nm; Temperature 40°C. This gave (R)-4-methoxy-2-{[1-(3-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)butanamide (59 mg, >99% ee), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.64 (br s, 1H), 8.35 (s, 1H), 8.14 (d, 1H), 8.10 (s, 1H), 7.98 (d, 2H), 7.54 (dd, 1H), 7.44 (t, 1H), 7.20 (d, 1H), 5.99 (dd, 1H), 3.65 (t, 2H), 3.35 (s, 3H), 2.49 (d, 3H), 2.48 (s, 2H), 2.31 (s, 3H), and (S)-4-methoxy-2-{[1-(3-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)butanamide(54 mg, >99% ee), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.65 (br s, 1H), 8.35 (s, 1H), 8.14 (d, 1H), 8.10 (s, 1H), 7.98 (d, 2H), 7.54 (m, 1H), 7.44 (t, 1H), 7.20 (d, 1H), 5.99 (dd, 1H), 3.65 (t, 2H), 3.35 (s, 3H), 2.49 (s, 3H), 2.45 (dd, 2H), 2.30 (s, 3H).

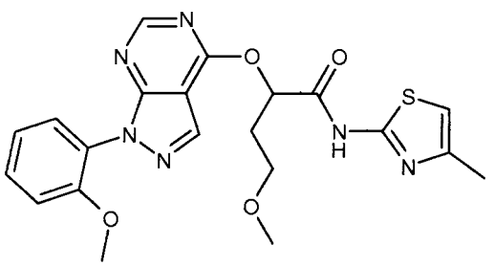
Example 34: 4-Methoxy-*N*-(5-methylpyridin-2-yl)-2-[(1-pyridin-2-yl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)oxy]butanamide



Method 1 from Intermediates A12 and B8

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (br s, 1H), 8.62 (m, 2H), 8.18 (s, 1H), 8.09 (m, 1H), 7.99 (s, 1H), 7.83 (m, 1H), 7.45 (d, 1H), 7.22 (m, 1H), 5.87 (t, 1H), 3.57 (t, 2H), 3.23 (s, 3H), 2.36 (m, 2H), 2.19 (s, 3H), HRMS: calcd for ($M+H^+$) $C_{21}H_{22}N_7O_3$: 420.1784. Found: 420.1797.

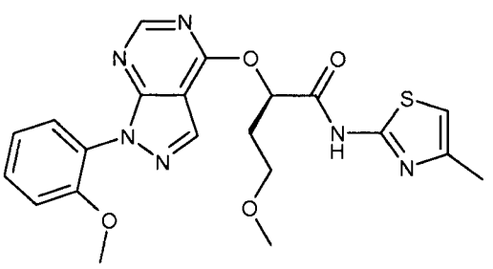
Example 35: 4-Methoxy-2-{[1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(4-methyl-1,3-thiazol-2-yl)butanamide



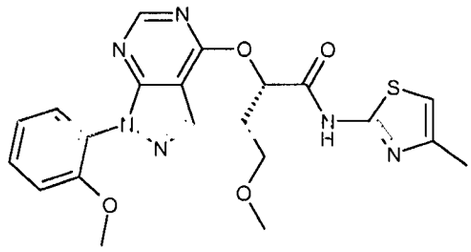
Method 1 from Intermediates A13 and B3

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77 (br s, 1H), 8.52 (s, 1H), 8.34 (s, 1H), 7.46 (m, 2H), 7.11 (m, 2H), 6.52 (s, 1H), 6.01 (t, 1H), 3.77 (d, 3H), 3.62 (m, 2H), 3.32 (d, 3H), 2.42 (m, 2H), 2.31 (s, 3H), HRMS: calcd for ($M+H^+$) $C_{22}H_{23}N_6O_4S$: 455.1501. Found: 455.1490.

Example 36: (R)-4-Methoxy-2-{[1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(4-methyl-1,3-thiazol-2-yl)butanamide

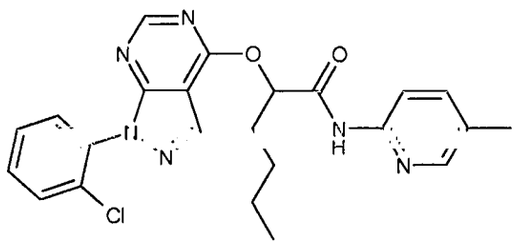


And Example 37: (S)-4-methoxy-2-{[1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(4-methyl-1,3-thiazol-2-yl)butanamide



The enantiomers of racemic 4-methoxy-2-{[1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(4-methyl-1,3-thiazol-2-yl)butanamide (90 mg) were separated by preparative HPLC: Column Chiralpak AD (250x20 mm, 5 µm); Mobile phase heptane/ethanol:50/50; Flow 15 ml/min; UV 270 nm; Temperature 20°C. This gave (R)-4-methoxy-2-{[1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(4-methyl-1,3-thiazol-2-yl)butanamide (24 mg, >99% ee), ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.80 (br s, 1H), 8.58 (s, 1H), 8.35 (s, 1H), 7.51 (m, 1H), 7.46 (m, 1H), 7.14 (m, 2H), 6.57 (d, 1H), 6.06 (t, 1H), 3.81 (s, 3H), 3.65 (t, 2H), 3.34 (s, 3H), 2.46 (m, 2H), 2.35 (d, 3H), and (S)-4-methoxy-2-{[1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(4-methyl-1,3-thiazol-2-yl)butanamide (26.1 mg, >99% ee), ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.87 (br s, 1H), 8.59 (s, 1H), 8.35 (s, 1H), 7.51 (m, 1H), 7.46 (m, 1H), 7.14 (m, 2H), 6.57 (d, 1H), 6.05 (t, 1H), 3.81 (s, 3H), 3.64 (t, 2H), 3.34 (s, 3H), 2.45 (m, 2H), 2.35 (d, 3H).

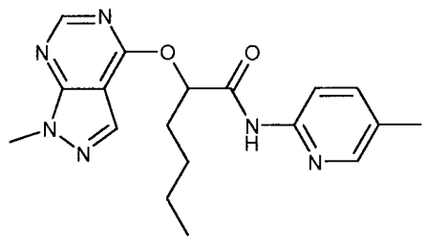
Example 38: 2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)hexanamide



Method 1 from Intermediates A3 and B1

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.47 (br s, 1H), 8.40 (s, 1H), 8.15 (d, 1H), 8.08 (s, 1H), 7.62 (m, 1H), 7.50 (m, 4H), 5.85 (t, 1H), 2.29 (s, 3H), 2.17 (m, 2H), 1.54 (m, 2H), 1.42 (m, 2H), 0.94 (t, 3H), HRMS: calcd for ($M+H^+$) $C_{23}H_{24}{}^{35}ClN_6O_2$: 451.1649. Found: 451.1656.

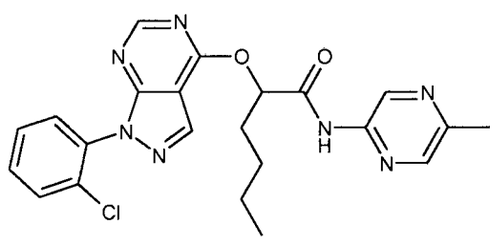
Example 39: 2-[(1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)oxy]-*N*-(5-methylpyridin-2-yl)hexanamide



Method 1 from Intermediates A3 and B11

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (br s, 1H), 8.56 (s, 1H), 8.15 (m, 2H), 8.07 (s, 1H), 7.53 (d, 1H), 5.84 (t, 1H), 4.13 (s, 3H), 2.29 (s, 3H), 2.15 (m, 2H), 1.52 (m, 2H), 1.39 (m, 2H), 0.92 (t, 3H), HRMS: calcd for ($M+H^+$) $C_{18}H_{23}N_6O_2$: 355.1882. Found: 355.1892.

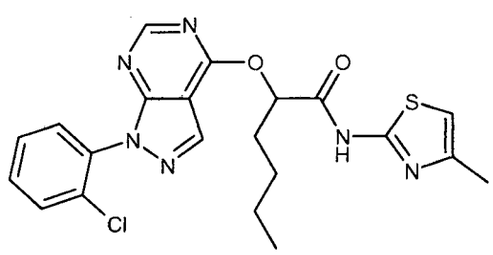
Example 40: 2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyrazin-2-yl)hexanamide



Method 1 from Intermediates A4 and B1

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.46 (s, 1H), 8.59 (s, 1H), 8.48 (br s, 1H), 8.40 (s, 1H), 8.10 (s, 1H), 7.62 (m, 1H), 7.50 (m, 3H), 5.89 (t, 1H), 2.53 (s, 3H), 2.19 (m, 2H), 1.55 (m, 2H), 1.44 (m, 2H), 0.94 (t, 3H), HRMS: calcd for ($M+H^+$) $C_{22}H_{23}{}^{35}ClN_7O_2$: 452.1601. Found: 452.1576.

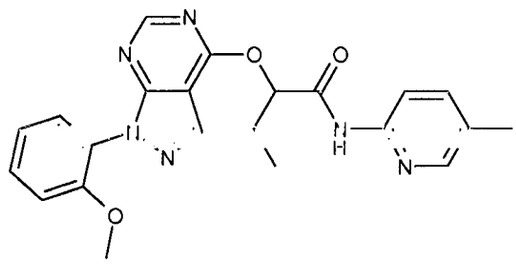
Example 41: 2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]thio}-*N*-(4-methyl-1,3-thiazol-2-yl)hexanamide



Method 1 from Intermediates A5 and B1

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.44 (br s, 1H), 8.58 (s, 1H), 8.38 (s, 1H), 7.62 (m, 1H), 7.51 (m, 3H), 6.56 (s, 1H), 5.95 (t, 1H), 2.33 (s, 3H), 2.17 (m, 2H), 1.53 (m, 2H), 1.41 (m, 2H), 0.93 (t, 3H), HRMS: calcd for (M+H$^+$) $C_{21}H_{22}{}^{35}ClN_6O_2S$: 457.1213. Found: 457.1238.

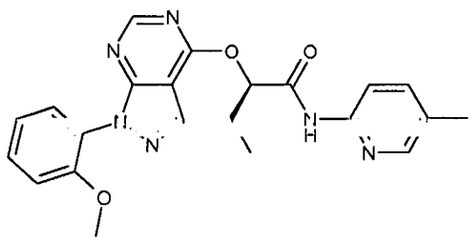
Example 42: 2-{[1-(2-Methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)butanamide



Method 1 from Intermediates A9 and B3

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (br s, 1H), 8.56 (s, 1H), 8.39 (s, 1H), 8.17 (d, 1H), 8.07 (s, 1H), 7.49 (m, 3H), 7.12 (m, 2H), 5.81 (t, 1H), 3.79 (s, 3H), 2.29 (s, 3H), 2.21 (m, 2H), 1.15 (t, 3H), HRMS: calcd for (M+H$^+$) $C_{22}H_{23}N_6O_3$: 419.1831. Found: 419.1810.

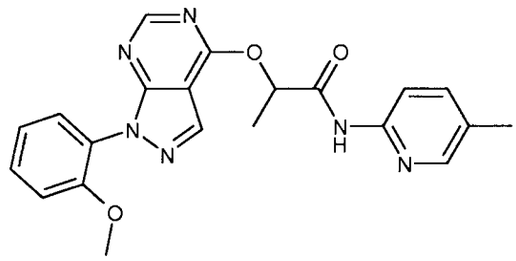
Example 43: (2*R*)-2-{[1-(2-Methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)butanamide



Method 1 from Intermediates A8 and B3

$[\alpha]^{20}{}_D$ −31.8^O (1.0 g/100 ml in ACN), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (br s, 1H), 8.58 (s, 1H), 8.40 (s, 1H), 8.19 (d, 1H), 8.10 (s, 1H), 7.55 (dd, 1H), 7.50 (m, 1H), 7.46 (dd, 1H), 7.13 (m, 2H), 5.83 (m, 1H), 3.81 (s, 3H), 2.31 (s, 3H), 2.22 (m, 2H), 1.13 (m, 3H), HRMS: calcd for (M+H$^+$) $C_{22}H_{23}N_6O_3$: 419.1831. Found: 419.1854.

Example 44: 2-{[1-(2-Methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*-(5-methylpyridin-2-yl)propanamide

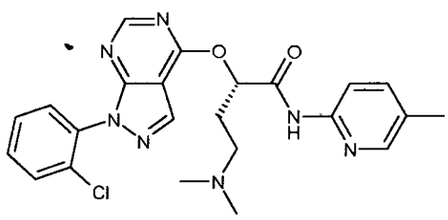


Method 1 from Intermediates A10 and B3

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.88 (br s, 1H), 8.57 (s, 1H), 8.38 (s, 1H), 8.17 (d, 1H), 8.07 (s, 1H), 7.48 (m, 3H), 7.12 (m, 2H), 5.94 (q, 1H), 3.79 (s, 3H), 2.30 (s, 3H), 1.80 (d, 3H), HRMS: calcd for ($M+H^+$) $C_{21}H_{21}N_6O_3$: 405.1675. Found: 405.1676.

There are no examples 45 and 46.

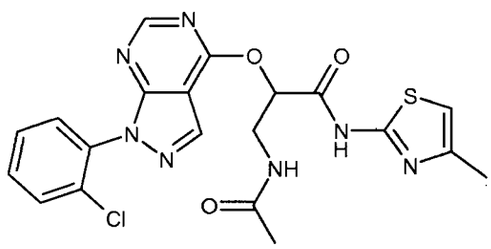
Example 47: (2*S*)-2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-4-(dimethylamino)-*N*-(5-methylpyridin-2-yl)butanamide



Method 1 from Intermediates A11 and B1

$[\alpha]^{20}_D$ +7.3^O (1.0 g/100 ml in ACN), ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.61 (br s, 1H), 8.53 (s, 1H), 8.35 (s, 1H), 8.09 (m, 2H), 7.57 (m, 1H), 7.46 (m, 4H), 5.86 (t, 1H), 2.55 (m, 2H), 2.30 (m, 11H), HRMS: calcd for ($M+H^+$) $C_{23}H_{25}{}^{35}ClN_7O_2$: 466.1758. Found: 466.1763.

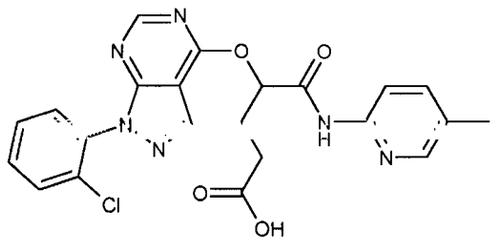
Example 48: 3-Acetamido-2-{[1-(2-chlorophenyl)-1*h*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*n*-(4-methyl-1,3-thiazol-2-yl)propanamide



Method 1 from Intermediates A14 and B1

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.39 (s, 1H), 7.62 (m, 1H), 7.50 (m, 3H), 6.55 (s, 1H), 6.18 (br t, 1H), 6.04 (t, 1H), 4.04 (m, 2H), 2.32 (s, 3H), 2.01 (s, 3H), HRMS: calcd for (M+H$^+$) $C_{20}H_{19}{}^{35}ClN_7O_3S$: 472.0958. Found: 472.0971.

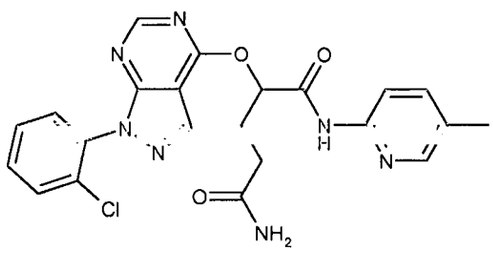
Example 49: 4-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-5-[(5-methylpyridin-2-yl)amino]-5-oxopentanoic acid



Method 1 from Intermediates A15 and B1

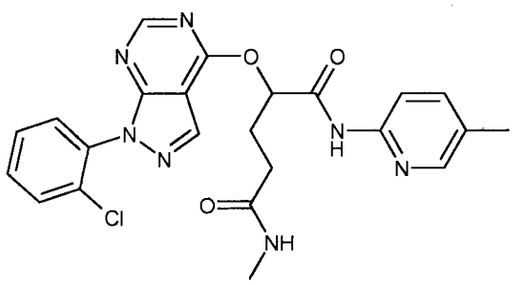
^{1}H NMR (400 MHz, $CDCl_3$) δ 11.44 (br s, 1H), 8.42 (s, 1H), 8.37 (s, 1H), 8.23 (d, 1H), 7.89 (s, 1H), 7.56 (m, 2H), 7.43 (m, 3H), 5.95 (m, 1H), 2.98 (m, 1H), 2.73 (m, 1H), 2.61 (m, 1H), 2.34 (m, 1H), 2.26 (s, 3H), HRMS: calcd for (M+H$^+$) $C_{22}H_{20}{}^{35}ClN_6O_4$: 467.1234. Found: 467.1233.

Example 50: 2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N1*-(5-methylpyridin-2-yl)pentanediamide



A solution of 4-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-5-[(5-methylpyridin-2-yl)amino]-5-oxopentanoic acid (5.0 mg, 0.011 mmol), ammonium chloride (3.0 mg, 0.054 mmol), DIPEA (7.0 mg, 0.054 mmol) and TBTU (7.0 mg, 0.021 mmol) in THF (1 mL) was stirred at ambient temperature for 3 hrs. Water (1 mL) was added and the reaction mixture was purified by preparative HPLC: Mobile phase A: 100% ACN, Mobile phase B: 5% ACN -- 95% 0.1M NH_4OAc in water; Gradient: 0%A to 50% A over 45 min; Flow: 25 ml/min; UV: 235 nm, to give the title compound (3.0 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.18 (br s, 1H), 8.59 (s, 1H), 8.42 (s, 1H), 8.16 (d, 1H), 8.09 (s, 1H), 7.64 (m, 1H), 7.53 (m, 4H), 5.94 (s, 1H), 5.75 (br s, 1H), 5.57 (br s, 1H), 2.58 (m, 4H), 2.32 (s, 3H), HRMS: calcd for (M+H$^+$) $C_{22}H_{21}{}^{35}ClN_7O_3$: 466.1394. Found: 467.1426.

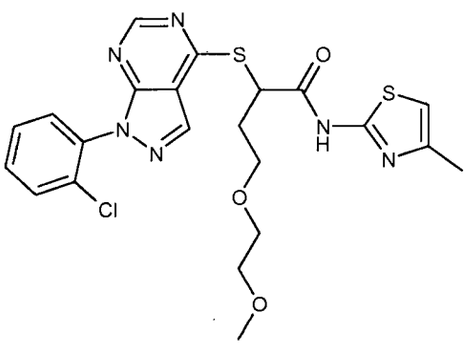
Example 51: 2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-*N*5-methyl-*N1*-(5-methylpyridin-2-yl)pentanediamide



A solution of 4-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]oxy}-5-[(5-methylpyridin-2-yl)amino]-5-oxopentanoic acid (5.0 mg, 0.011 mmol), methylamine (0.021ml (2M in THF), 0.043 mmol) and TBTU (7.0 mg, 0.021 mmol) in THF (1 mL) was stirred at ambient temperature for 5 hrs. Water (1 mL) was added and the reaction mixture was purified by preparative HPLC: Mobile phase A: 100% ACN, Mobile phase B: 5% ACN + 95% 0.1M NH_4OAc in water; Gradient: 0%A to 50% A over 45 min; Flow: 25 ml/min; UV: 235 nm, to give the title compound (3.0 mg). ^1H NMR (500 MHz, $CDCl_3$) δ 8.88 (br s, 1H), 8.57 (s, 1H), 8.39 (s, 1H), 8.11 (m, 2H), 7.62 (m, 1H), 7.51 (m, 4H), 5.91 (m, 1H), 5.63 (br s, 1H), 2.82 (d, 3H), 2.51 (m, 4H), 2.30 (s, 3H), HRMS: calcd for $(M+H^+)$ $C_{23}H_{23}{}^{35}ClN_7O_3$: 480.1551. Found: 480.1503.

Method 2

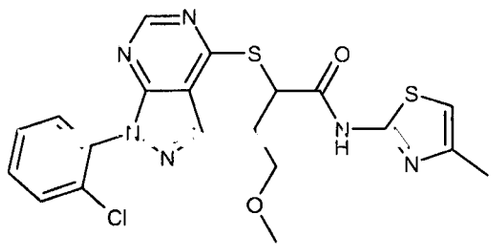
Example 52: 2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]thio}-4-(2-methoxyethoxy)-*N*-(4-methyl-1,3-thiazol-2-yl)butanamide



A solution of 2-bromo-4-(2-methoxyethoxy)-*N*-(4-methyl-1,3-thiazol-2-yl)butanamide (104 mg, 0.308 mmol) in DMF (1 mL) was added to a stirred solution of 1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-thiol (81.0 mg, 0.308 mmol) and K_2CO_3 (51.1 mg, 0.370 mmol) in DMF (2 mL). The reaction mixture was kept at ambient

temperature for 3 hrs (45°C and 17 hrs for example 54, 55 and 56). Water and EtOAc were added, and the two phases were separated. The aqueous phase was extracted with EtOAc. The organic extracts were combined and washed with water, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified with column chromatography (silica gel, eluting with DCM/EtOAc:1/1) to give the title compound as a colourless viscous oil (145 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.06 (br s, 1H), 8.93 (s, 1H), 8.30 (s, 1H), 7.62 (m, 1H), 7.49 (m, 3H), 6.51 (s, 1H), 5.14 (t, 1H), 3.77 (m, 1H), 3.67 (m, 1H), 3.59 (m, 2H), 3.50 (m, 2H), 3.33 (s, 3H), 2.60 (m, 1H), 2.27 (m, 4H), HRMS: calcd for ($M+H^+$) $C_{22}H_{24}{}^{35}ClN_6O_3S_2$: 518.1040. Found: 519.1050.

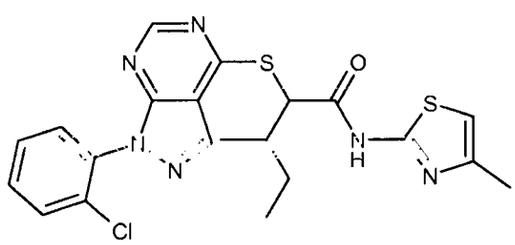
Example 53: 2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]thio}-4-methoxy-*N*-(4-methyl-1,3-thiazol-2-yl)butanamide



Method 2 from Intermediates A18 and B12

^{1}H NMR (500 MHz, $CDCl_3$) δ 11.08 (br s, 1H), 8.95 (s, 1H), 8.30 (s, 1H), 7.62 (d, 1H), 7.49 (m, 3H), 6.51 (s, 1H), 5.09 (t, 1H), 3.66 (m, 1H), 3.57 (m, 1H), 3.34 (s, 3H), 2.59 (m, 1H), 2.30 (s, 3H), 2.22 (m, 1H), HRMS: calcd for ($M+H^+$) $C_{20}H_{20}{}^{35}ClN_6O_2S_2$: 475.0777. Found: 475.0764.

Example 54: 2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]thio}-3-methyl-*N*-(4-methyl-1,3-thiazol-2-yl)pentanamide

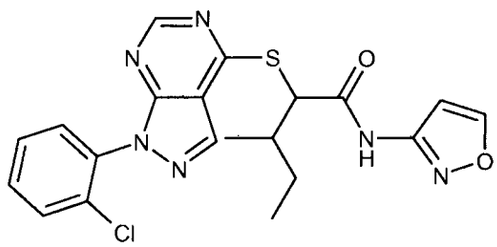


Method 2 from Intermediates A19 and B12

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.48 (br s, 1H), 8.89 (d, 1H), 8.31 (d, 1H), 7.63 (m, 1H), 7.49 (m, 3H), 6.51 (s, 1H), 4.91 (d, 0.56H), 4.81 (d, 0.44H), 2.43 (m, 1H), 2.30 (s, 3H),

1.87 (m, 0.44H), 1.55 (m, 2.56H), 1.21 (m, 3H), 0.99 (t, 3H), HRMS: calcd for ($M+H^+$) $C_{21}H_{22}{}^{35}ClN_6OS_2$: 473.0985. Found: 473.0985.

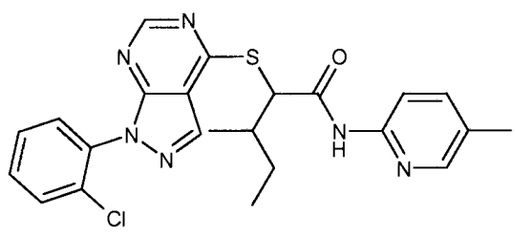
Example 55: 2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]thio}-*N*-isoxazol-3-yl-3-methylpentanamide



Method 2 from Intermediates A21 and B12

^1H NMR (300 MHz, $CDCl_3$) δ 10.06 (br d, 1H), 8.85 (s, 1H), 8.32 (d, 1H), 8.26 (s, 1H), 7.62 (m, 1H), 7.49 (m, 3H), 7.06 (d, 1H), 4.81 (d, 0.57H), 4.73 (d, 0.43H), 2.40 (m, 1H), 1.90 (m, 0.43H), 1.63 (m, 0.57H), 1.47 (m, 1H), 1.22 (m, 3H), 0.99 (m, 3H), HRMS: calcd for ($M+H^+$) $C_{20}H_{20}{}^{35}ClN_6O_2S$: 443.1057. Found: 443.1057.

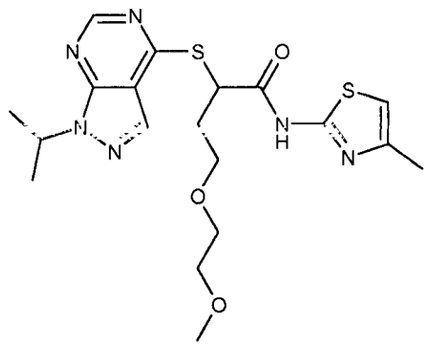
Example 56: 2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]thio}-3-methyl-*N*-(5-methylpyridin-2-yl)pentanamide



Method 2 from Intermediates A20 and B12

^1H NMR (300 MHz, $CDCl_3$) δ 9.33 (br d, 1H), 8.85 (d, 1H), 8.30 (d, 1H), 8.11 (d, 1H), 8.05 (s, 1H), 7.62 (m, 1H), 7.48 (m, 4H), 4.92 (d, 0.69H), 4.82 (d, 0.31H), 2.40 (m, 1H), 2.26 (s, 3H), 1.88 (m, 0.39H), 1.68 (m, 0.61H), 1.48 (m, 1H), 1.22 (m, 3H), 0.99 (m, 3H), HRMS: calcd for ($M+H^+$) $C_{23}H_{24}{}^{35}ClN_6OS$: 467.1420. Found: 467.1420.

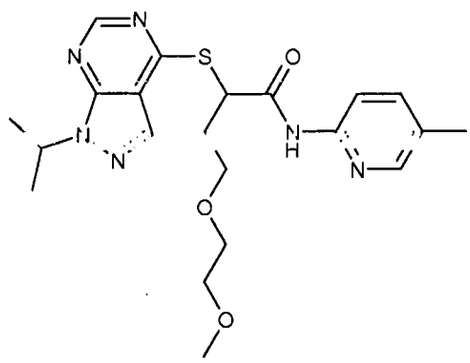
Example 57: 2-[(1-Isopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)thio]-4-(2-methoxyethoxy)-*N*-(4-methyl-1,3-thiazol-2-yl)butanamide



Method 2 from Intermediates A16 and B14

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 7.98 (s, 1H), 6.43 (d, 1H), 5.14 (m, 1H), 5.03 (t, 1H), 3.68 (m, 1H), 3.60 (m, 1H), 3.51 (m, 2H), 3.42 (m, 2H), 3.24 (s, 3H), 2.50 (m, 1H), 2.23 (s, 3H), 1.99 (m, 1H), 1.51 (t, 6H), HRMS: calcd for ($M+H^+$) $C_{19}H_{27}N_6O_3S_2$: 451.1586. Found: 451.1598.

Example 58: 2-[(1-Isopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)thio]-4-(2-methoxyethoxy)-*N*-(5-methylpyridin-2-yl)butanamide

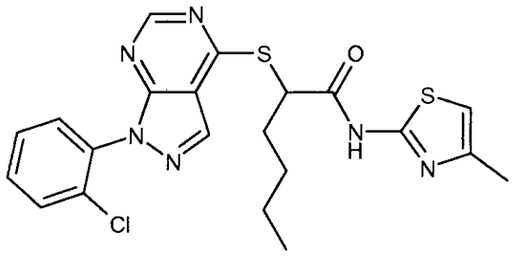


Method 2 from Intermediates A17 and B14

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.01 (br s, 1H), 8.83 (s, 1H), 8.02 (m, 3H), 7.44 (dd, 1H), 5.15 (m, 1H), 5.07 (t, 1H), 3.69 (m, 1H), 3.64 (m, 1H), 3.54 (m, 2H), 3.45 (m, 2H), 3.28 (s, 3H), 2.50 (m, 1H), 2.22 (s, 3H), 2.15 (m, 1H), 1.53 (t, 6H), HRMS: calcd for ($M+H^+$) $C_{21}H_{29}{}^{35}ClN_6O_3S$: 445.2021. Found: 445.2016.

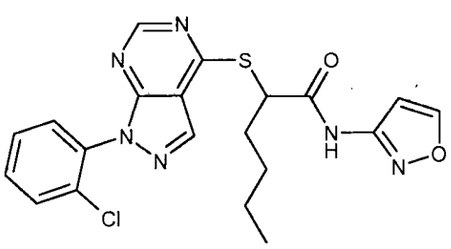
Method 3

Example 59: 2-{[1-(2-chlorophenyl)-1*h*-pyrazolo[3,4-*d*]pyrimidin-4-yl]thio}-*n*-(4-methyl-1,3-thiazol-2-yl)hexanamide



A stirred solution of 2-bromo-hexanoic acid (2.00 g, 10.25 mmol) in thionyl chloride (1.59 g, 13.36 mmol) was refluxed for 30 minutes. The reaction mixture was concentrated in vacuo to remove excess thionyl chloride. The freshly prepared acid chloride (117 mg, 0.548 mmol) was added slowly to a stirred solution of 2-amino-4-methylthiazole (62.1 mg, 0.544 mmol) and DIPEA (67.2 mg, 0.520 mmol) in DCM (2 mL). The reaction mixture was kept at ambient temperature for 25 minutes before it was added to a solution of 1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-thiol (130 mg, 0.495 mmol) and anhydrous potassium carbonate (102.6 mg, 0.742 mmol) in DMF (3 mL). The reaction mixture was kept at ambient temperature for 3 hrs. Water and EtOAc were added and the two phases were separated. The aqueous phase was extracted with EtOAc. The organic extracts were combined and washed three times with water, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified with column chromatography (silica gel, eluting with DCM/EtOAc:5/1) to give the title compound (99 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.92 (s, 1H), 8.95 (s, 1H), 8.29 (s, 1H), 7.63 (m, 1H), 7.50 (m, 3H), 6.51 (s, 1H), 4.80 (t, 1H), 2.30 (m, 4H), 1.97 (m, 1H), 1.57 (m, 2H), 1.42 (m, 2H), 0.94 (t, 3H), HRMS: calcd for $(M+H^+)$ $C_{21}H_{22}{}^{35}ClN_6OS_2$: 473.0985. Found: 473.1027.

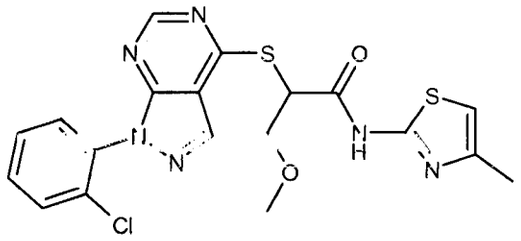
Example 60: 2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]thio}-*N*-isoxazol-3-ylhexanamide



Method 3 from 2-bromo-hexanoic acid, 3-aminoisoxazole and Intermediate B12

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.44 (br s, 1H), 8.89 (s, 1H), 8.30 (s, 1H), 8.26 (d, 1H), 7.63 (m, 1H), 7.50 (m, 3H), 7.05 (d, 1H), 4.73 (t, 1H), 2.26 (m, 1H), 1.93 (m, 1H), 1.55 (m, 2H), 1.42 (m, 2H), 0.95 (t, 3H), HRMS: calcd for ($M+H^+$) $C_{20}H_{20}{}^{35}ClN_6O_2S$: 443.1057. Found: 443.1081.

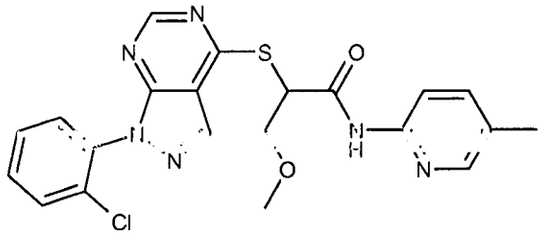
Example 61: 2-{[1-(2-Chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]thio}-4-(2-methoxyethoxy)-*N*--(4-methyl-1,3-thiazol-2-yl) butanamide



Method 3 from 2-chloro-3-methoxy-propionic acid, 2-amino-4-methylthiazole and Intermediate B12.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.31 (s, 1H), 7.63 (m, 1H), 7.50 (m, 3H), 6.53 (s, 1H), 5.24 (t, 1H), 4.05 (d, 2H), 3.50 (s, 3H), 2.31 (s, 3H), HRMS: calcd for ($M+H^+$) $C_{19}H_{18}{}^{35}ClN_6O_2S_2$: 461.0621. Found: 461.0631.

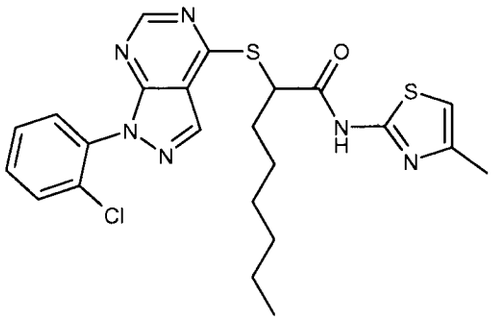
Example 62: 2-{[1-(2-Chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]thio}-3-methoxy-*N*-(5-methylpyridin-2-yl)propanamide



Method 3 from 2-chloro-3-methoxy-propionic acid, 2-amino-5-picoline and Intermediate B12

^{1}H NMR (300 MHz, $_{CDCl3}$) δ 9.54 (br s, 1H), 8.87 (s, 1H), 8.31 (s, 1H), 8.08 (m, 2H), 7.63 (m, 1H), 7.49 (m, 4H), 5.22 (t, 1H), 4.04 (m, 2H), 3.50 (s, 3H), 2.27 (s, 3H), HRMS: calcd for ($M+H^+$) $C_{21}H_{20}{}^{35}ClN_6O_2S$: 455.1057. Found: 455.1085.

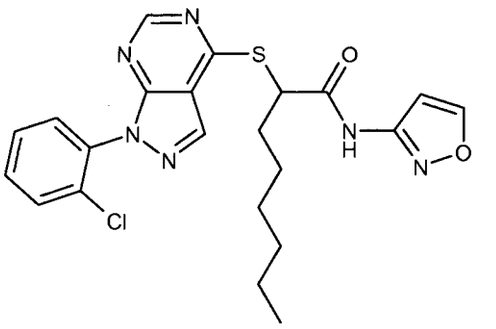
Example 63: 2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]thio}-*N*-(4-methyl-1,3-thiazol-2-yl)octanamide



Method 3 from 2-bromo-octanoic acid, 2-amino-4-methylthiazole and Intermediate B12

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.90 (br s, 1H), 8.94 (s, 1H), 8.29 (s, 1H), 7.63 (m, 1H), 7.50 (m, 3H), 6.51 (s, 1H), 4.80 (t, 1H), 2.30 (m, 4H), 1.95 (m, 1H), 1.59 (m, 2H), 1.32 (m, 6H), 0.88 (t, 3H), HRMS: calcd for ($M+H^+$) $C_{23}H_{26}{}^{35}ClN_6OS_2$: 501.1298. Found: 501.1298.

Example 64: 2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]thio}-*N*-isoxazol-3-yloctanamide



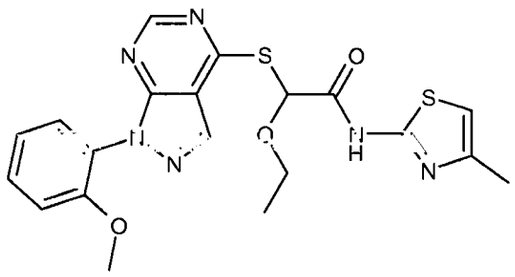
Method 3 from 2-bromo-octanoic acid, 3-aminoisoxazole and Intermediate B12

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.47 (br s, 1H), 8.88 (s, 1H), 8.30 (s, 1H), 8.26 (d, 1H), 7.62 (m, 1H), 7.48 (m, 3H), 7.05 (d, 1H), 4.74 (t, 1H), 2.27 (m, 1H), 1.93 (m, 1H), 1.55 (m, 2H), 1.35 (m, 6H), 0.88 (t, 3H), HRMS: calcd for ($M+H^+$) $C_{22}H_{24}{}^{35}ClN_6O_2S$: 471.1370. Found: 471.1370.

There are no examples 65-70.

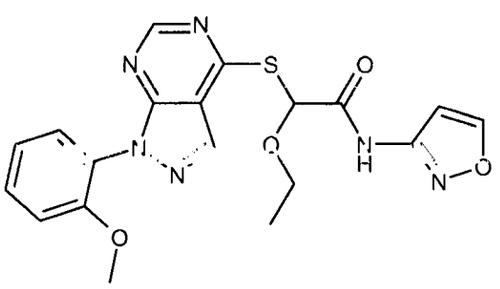
METHOD 4

Example 71: 2-Ethoxy-2-{[1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]thio}-*N*-(4-methyl-1,3-thiazol-2-yl)acetamide



Sodium hydride (95%, 3.7 mg, 0.15 mmol) was added to a stirred solution of 2-amino-4-methylthiazol (17.6 mg, 0.154 mmol) in anhydrous THF (4 mL). The reaction mixture was kept at ambient temperature for 5 minutes before ethyl ethoxy{[1-(2-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]thio}acetate (50 mg, 0.129 mmol) was added. The reaction mixture was stirred at ambient temperature for 1 h. Water and DCM were added and the two phases were separated. The organic phase was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified with column chromatography (silica gel, eluting with a gradient consisting of 40-100% EtOAc in heptane) to give the title compound as a colourless oil (1.1 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.03 (br s, 1H), 8.74 (s, 1H), 8.26 (s, 1H), 7.47 (m, 2H), 7.12 (m, 2H), 6.91 (s, 1H), 6.58 (s, 1H), 4.02 (m, 1H), 3.81 (m, 4H), 2.38 (s, 3H), 1.34 (t, 3H), HRMS: calcd for ($M+H^+$) $C_{20}H_{21}N_6O_3S_2$: 457.1116. Found: 457.1116.

Example 72: 2-Ethoxy-*N*-isoxazol-3-yl-2-{[1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]thio}acetamide



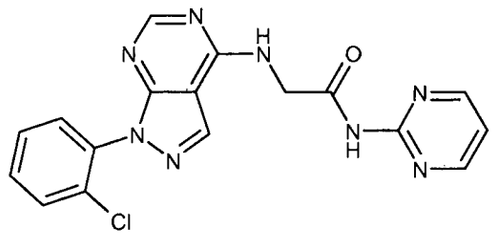
Method 4 from 3-aminoisoxazole and Intermediate A24

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.51 (br s, 1H), 8.75 (s, 1H), 8.33 (s, 1H), 8.27 (s, 1H), 7.47 (m, 2H), 7.13 (t, 3H), 6.82 (s, 1H), 4.03 (m, 1H), 3.82 (m, 5H), 1.35 (t, 3H), HRMS: calcd for ($M+H^+$) $C_{19}H_{19}{}^{35}ClN_6O_4S$: 427.1188. Found: 427.1181.

There is no example 73.

Method 5

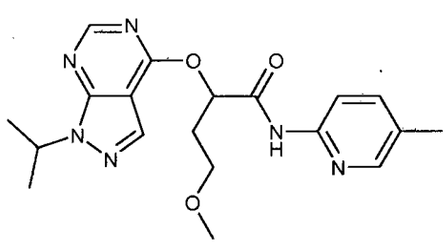
Reference example 74: *N*-2-[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]-*N*-(5-methyl-1,3-thiazol-2-yl)glycinamide



Sodium hydride (95%, 19.08 mg, 0.76 mmol) was added to a stirred solution of 2-aminopyrimidine (62.9 mg, 0.66 mmol) in anhydrous THF (3 mL). The reaction mixture was kept at ambient temperature for 3 hrs before it was added to a solution of methyl *N*-[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]glycinate (200 mg, 0.63 mmol) in anhydrous THF (3 mL). The reaction mixture was stirred at ambient temperature for 1 h. Water and EtOAc were added and the two phases were separated. The aqueous phase was extracted with EtOAc. The organic extracts were combined and concentated in vacuo. The residue was triturated sequentially with DCM, MeOH and EtOAc. The remaining solid was dissolved in hot DMSO and precipitated by the addition of water to give the title compound as a solid (37 mg), ^{1}H NMR (300 MHz, DMSO) δ 10.80 (br s, 1H), 8.87 (br t, 1H), 8.67 (d, 2H), 8.49 (s, 1H), 8.22 (s, 1H), 7.70 (m, 1H), 7.56 (m, 3H), 7.18 (t, 1H), 4.59 (d, 2H), HRMS: calcd for ($M+H^+$) $C_{17}H_{14}{}^{35}ClN_8O$: 381.0979. Found: 381.0980.

There is no example 75.

Example 76: 2-[(1-isopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)oxy]-4-methoxy-*N*-(5-methylpyridin-2-yl)butanamide

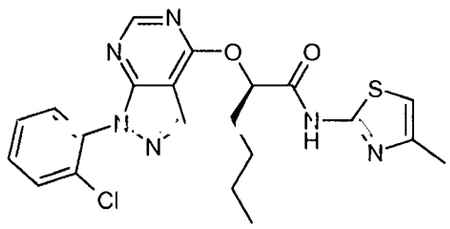


Method 1 from Intermediates A12 and B9

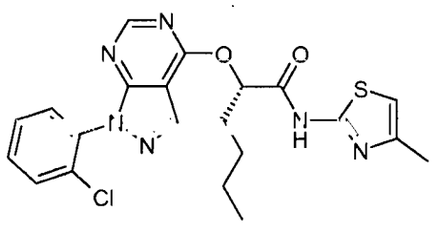
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (br s, 1H), 8.46 (s, 1H), 8.09 (s, 1H), 8.07 (s, 1H), 7.46 (dd, 1H), 5.87 (dd, 1H), 5.13 (m, 1H), 3.56 (t, 2H), 3.25 (s, 3H), 2.35 (m, 2H), 2.22 (s, 3H), 1.52 (dd, 6H), HFMS: calcd for (M^+-H^+) $C_{19}H_{25}N_6O_3$: 385.1988. Found: 385.2007.

There are no examples with Example numbers 77 to 80.

Examples S1: (R)-2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]thio}-*N*-(4-methyl-1,3-thiazol-2-yl)hexanamide



and Example S2: (S)-2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]thio}-*N*-(4-methyl-1,3-thiazol-2-yl)hexanamide

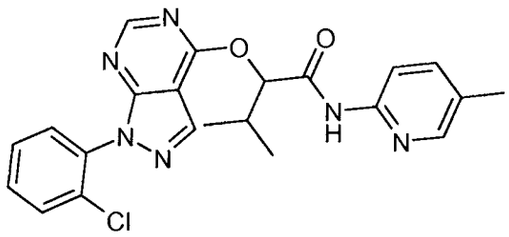


The enantiomers of 2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]thio}-*N*-(4-methyl-1,3-thiazol-2-yl)hexanamide **Example 41** (40 mg) were separated by chiral preparative HPLC: Column Chiralpak AD (250x20 mm, 5 μm), eluting with heptane/ethanol85/5. This gave (R)-2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]thio}-*N*-(4-methyl-1,3-thiazol-2-yl)hexanamide (17 mg, >99% ee).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.44 (br s, 1H), 8.58 (s, 1H), 8.38 (s, 1H), 7.62 (m, 1H), 7.51 (m, 3H), 6.56 (s, 1H), 5.95 (t, 1H), 2.33 (s, 3H), 2.17 (m, 2H), 1.53 (m, 2H), 1.41 (m, 2H), 0.93 (t, 3H)

and (S)-2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]thio}-*N*-(4-methyl-1,3-thiazol-2-yl)hexanamide (17 mg, >99% ee). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.44 (br s, 1H), 8.58 (s, 1H), 8.38 (s, 1H), 7.62 (m, 1H), 7.51 (m, 3H), 6.56 (s, 1H), 5.95 (t, 1H), 2.33 (s, 3H), 2.17 (m, 2H), 1.53 (m, 2H), 1.41 (m, 2H), 0.93 (t, 3H)

Example 83: 2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-methyl-*N*-(5-methylpyridin-2-yl)butanamide



A solution of LHMDS (0.999 mL, 1.00 mmol) in anhydrous THF (15 mL) was added dropwise to a stirred solution of racemic 2-hydroxy-3-methyl-*N*-(5-methylpyridin-2-yl)butanamide **C1** (208 mg, 1.00 mmol) in anhydrous THF (15 mL) over a period of 3 minutes under nitrogen. The resulting suspension was stirred at ambient temperature for 10 minutes, then a solution of 4-chloro-1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine **B1** (265 mg, 1.00 mmol) in anhydrous THF (3 mL) was added dropwise over 1 minute and the resulting mixture heated to 50°C for 3 hours. The mixture was allowed to cool to room temperature then diluted with EtOAc (50 mL), and washed sequentially with water (2 x 25 mL) and saturated brine (25 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The material was purified by flash silica chromatography, elution gradient 30 to 50% EtOAc in DCM. Pure fractions were evaporated to dryness to afford 2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-methyl-N-(5-methylpyridin-2-yl)butanamide (320 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (1H, s), 8.40 (1H, s), 8.38 (1H, s), 8.16 (1H, d), 8.08-8.07 (1H, m), 7.63-7.60 (1H, m), 7.54-7.51 (2H, m), 7.50-7.44 (2H, m), 5.71 (1H, d), 2.59-2.55 (1H, m), 2.28 (3H, s), 1.21 (3H, d), 1.15 (3H, d), m/z (ESI+) (M+H)+ = 437; HPLC t_R = 2.56 min.

The following examples (**84-96**) were prepared in an analogous fashion from the appropriate alcohol and chloro-derivative.

Example 84: (2S)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-methyl-*N*-(5-methylpyridin-2-yl)butanamide

Example 85: (2R)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-methyl-*N*-(5-methylpyridin-2-yl)butanamide

Example 86: (2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-methyl-*N*-(5-methylpyridin-2-yl)butanamide

Example 87: (2S)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-methoxy-*N*-(5-methylpyridin-2-yl)propanamide

Example 88: (2R)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-methoxy-*N*-(5-methylpyridin-2-yl)propanamide

Example 89: (2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-methoxy-*N*-(5-methylpyridin-2-yl)propanamide

Example 90: (2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-methoxy-*N*-(5-methylpyrazin-2-yl)propanamide

Example 91: (2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-isopropoxy-*N*-(5-methylpyridin-2-yl)propanamide

Example 92: (2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-isopropoxy-*N*-(5-methylpyrazin-2-yl)propanamide

Example 93: (2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-isopropoxy-*N*-(3-methyl-1,2,4-thiadiazol-5-yl)propanamide

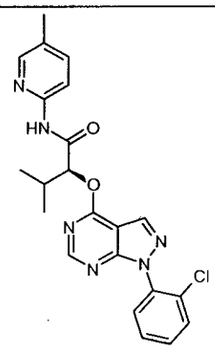
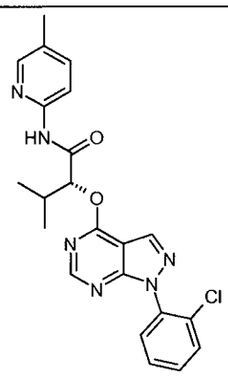
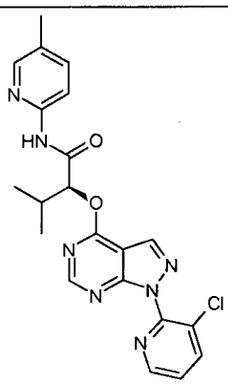
Example 94: (2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-methyl-*N*-(5-methylpyrazin-2-yl)butanamide

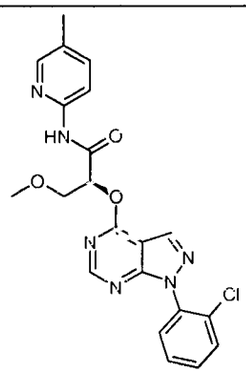
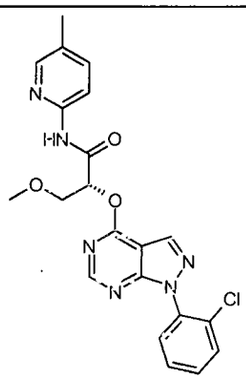
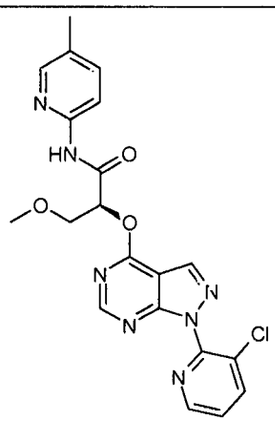
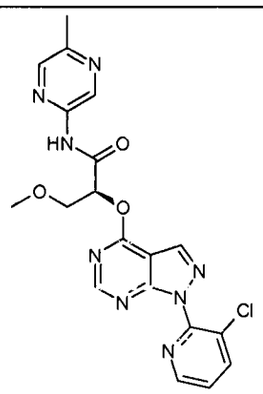
Example 95: (2S)-2-(1-(2-chloro-4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-methoxy-*N*-(5-methylpyrazin-2-yl)propanamide

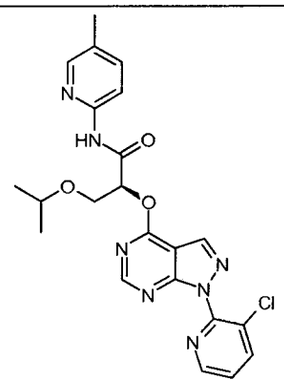
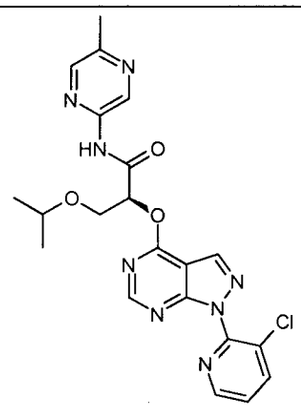
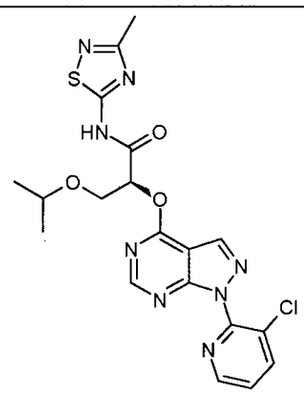
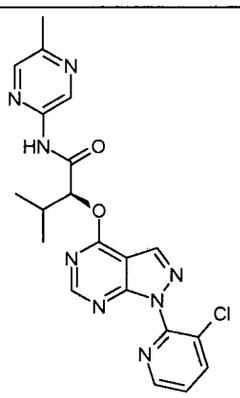
Example 96: (2S)-2-(1-(2-chloro-4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-methoxy-*N*-(5-methylpyridin-2-yl)propanamide

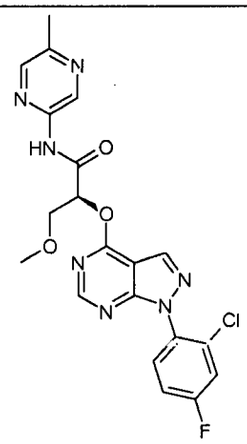
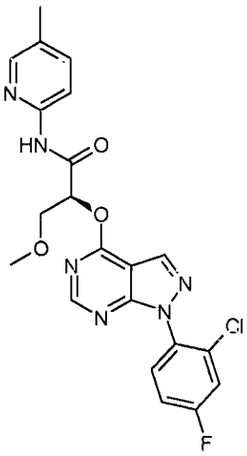
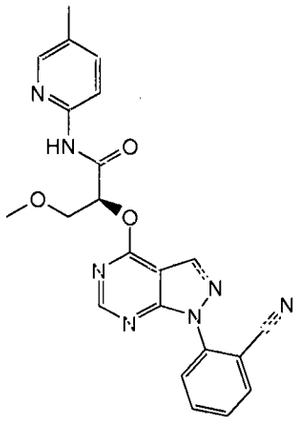
Example 97: (2S)-2-(1-(2-cyanophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-methoxy-*N*-(5-methylpyridin-2-yl)propanamide

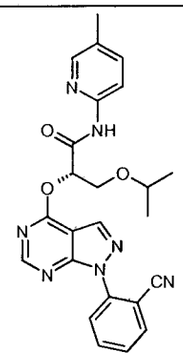
Example 97a: (2S)-2-[1-(2-cyanophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-methylpyridin-2-yl)-3-propan-2-yloxypropanamide

	STRUCTURE	M/Z	^{1}H nmr data (400 MHz)
84		ESI+ (M+H)+ = 437; HPLC t_R = 2.55 min	($CDCl_3$) δ 8.58 (1H, s), 8.40 (1H, s), 8.38 (1H, s), 8.16 (1H, d), 8.08-8.07 (1H, m), 7.63-7.60 (1H, m), 7.54-7.51 (2H, m), 7.50-7.44 (2H, m), 5.71 (1H, d), 2.59-2.55 (1H, m), 2.28 (3H, s), 1.21 (3H, d), 1.15 (3H, d)
85		ESI+ (M+H)+ = 437; HPLC t_R = 2.60 min	($CDCl_3$) δ 8.58 (1H, s), 8.40 (1H, s), 8.38 (1H, s), 8.16 (1H, d), 8.08-8.07 (1H, m), 7.63-7.60 (1H, m), 7.54-7.51 (2H, m), 7.50-7.44 (2H, m), 5.71 (1H, d), 2.59-2.55 (1H, m), 2.28 (3H, s), 1.21 (3H, d), 1.15 (3H, d)
86		ESI+ (M+H)+ = 438; HPLC t_R = 2.11 min	($DMSO-d_6$) δ 10.83 (1H, s), 8.71 (1H, s), 8.69 (1H, dd), 8.55 (1H, s), 8.37 (1H, dd), 8.19 (1H, d), 7.92 (1H, d), 7.76 (1H, dd), 7.60 (1H, dd), 5.57 (1H, d), 2.49-2.40 (1H, m), 2.25 (3H, s), 1.13 (6H, d)

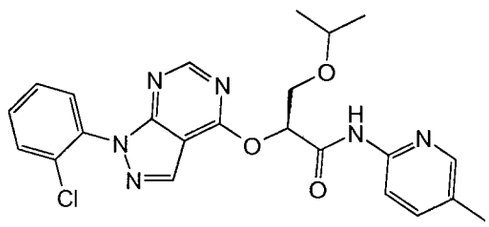
87		ESI+ $(M+H)^+$ = 439; HPLC t_R = 2.21 min	(DMSO-d_6) δ 10.85 (1H, s), 8.62 (1H, s), 8.54 (1H, s), 8.18 (1H, d), 7.88 (1H, d), 7.76 (1H, dd), 7.65-7.56 (4H, m), 5.95-5.94 (1H, m), 4.06-4.01 (1H, m), 3.94-3.90 (1H, m), 3.40 (3H, s), 2.24 (3H, s)
88		ESI+ $(M+H)^+$ = 439; HPLC t_R = 2.20 min	(DMSO-d_6) δ 10.85 (1H,s), 8.62 (1H, s), 8.54 (1H, s), 8.18 (1H, d), 7.88 (1H, d), 7.76 (1H, dd), 7.65-7.56 (4H, m), 5.95-5.94 (1H, m), 4.06-4.01 (1H, m), 3.94-3.90 (1H, m), 3.40 (3H, s), 2.24 (3H, s)
89		ESI+ $(M+H)^+$ = 440; HPLC t_R = 1.77 min	(DMSO-d_6) δ 10.86 (1H, s), 8.67 (1H, s), 8.66 (1H, s), 8.56 (1H, s), 8.33 (1H, dd), 8.17 (1H, d), 7.88 (1H, d), 7.75 (1H, dd), 7.58 (1H, d), 5.95-5.94 (1H, m), 4.07-4.00 (1H, m), 3.94-3.91 (1H, m), 3.40 (3H, s), 2.24 (3H, s)
90		ESI+ $(M+H)^+$ = 441; HPLC t_R = 1.59 min	(DMSO-d_6) δ 11.18 (1H, s), 9.10 (1H, d), 8.68 (1H, s), 8.66 (1H, dd), 8.57 (1H, s), 8.32 (1H, dd), 8.31 (1H, d), 7.74 (1H, dd), 5.99-5.96 (1H, m), 4.10-3.93 (2H, m), 3.41 (3H, s), 2.44 (3H, s)

91		ESI+ (M+H)+ = 468; HPLC t_R = 2.02 min	($CDCl_3$) δ 8.69 (1H, s), 8.63 (1H, s), 8.62 (1H, dd), 8.46 (1H, s), 8.13 (1H, d), 8.10-8.09 (1H, m), 8.00 (1H, dd), 7.52 (1H, dd), 7.47 (1H, dd), 6.02 (1H, t), 4.08 (2H, d), 3.78-3.65 (1H, m), 2.29 (3H, s), 1.18 (6H, m)
92		ESI+ (M+H)+ = 469; HPLC t_R = 1.82 min	($CDCl_3$) δ 1.18 - 1.21 (6H, m), 2.54 (3H, s), 3.70 - 3.76 (1H, m), 4.12 (2H, d), 6.04 (1H, t), 7.46 (1H, dd), 8.00 (1H, dd), 8.12 (1H, d), 8.46 (1H, s), 8.62 (1H, dd), 8.64 (1H, s), 8.71 (1H, s), 9.43 (1H, d)
93		ESI- (M+H)- = 473; HPLC t_R = 2.08 min	($CDCl_3$) δ 1.17 - 1.21 (6H, m), 2.55 (3H, s), 3.65 - 3.76 (1H, m), 4.11 (2H, d), 6.14 (1H, t), 7.48 (1H, dd), 8.02 (1H, dd), 8.44 (1H, s), 8.61 - 8.63 (1H, m), 8.62 (1H, s), 9.96 (1H, s)
94		ESI+ (M+H)+ = 439; HPLC t_R = 1.95 min	($CDCl_3$) δ 1.15 - 1.17 (3H, d), 1.22 (3H, d), 2.53 (3H, s), 2.57 - 2.61 (1H, m), 5.75 (1H, d), 7.46 - 7.49 (1H, m), 8.00 - 8.03 (1H, m), 8.09 (1H, d), 8.37 (1H, s), 8.45 (1H, s), 8.61 - 8.62 (1H, m), 8.63 (1H, s), 9.46 (1H, d)

95		ESI+ $(M+H)^+$ = 458; HPLC t_R = 2.16 min	($CDCl_3$) δ 2.54 (3H, s), 3.48 (3H, s), 4.03 - 4.07 (1H, m), 4.10 - 4.14 (1H, m), 6.12 (1H, t), 7.16 - 7.21 (1H, m), 7.35 - 7.38 (1H, m), 7.50 - 7.54 (1H, m), 8.12 (1H, d), 8.43 (1H, s), 8.59 (1H, s), 8.63 (1H, s), 9.45 (1H, d)
96		ESI+ $(M+H)^+$ = 457; HPLC t_R = 2.27 min	($CDCl_3$) δ 2.29 (3H, s), 3.46 (3H, s), 4.01 - 4.05 (1H, m), 4.09 - 4.13 (1H, m), 6.09 (1H, t), 7.16 - 7.20 (1H, m), 7.35 - 7.38 (1H, m), 7.50 - 7.54 (2H, m), 8.10 (1H, d), 8.14 (1H, d), 8.42 (1H, d), 8.58 (1H, s), 8.73 (1H, s)
97		ESI+ $(M+H)^+$ = 430; HPLC t_R = 1.94 min	(DMSO-d_6) δ 2.24 (3H, s), 3.40 (3H, s), 3.90 - 3.96 (1H, m), 4.01 - 4.09 (1H, m), 5.93 - 5.98 (1H, m), 7.56 - 7.60 (1H, m), 7.71 - 7.77 (1H, m), 7.85 - 7.91 (1H, m), 7.94 - 7.98 (2H, m), 8.12 (1H, d), 8.17 (1H, s), 8.64 (1H, s), 8.64 (1H, s), 10.87 (1H, s),

97a		(ESI+) (M+H)+ = 458; HPLC t_R = 2.29 min.	($CDCl_3$) δ 1.18 (3H, d), 1.20 (3H, d), 2.29 (3H, s), 3.66 - 3.78 (1H, m), 4.09 (2H, d), 6.02 (1H, t), 7.52 (1H, dd), 7.56 (1H, ddd), 7.79 (1H, ddd), 7.89 (1H, dd), 7.92 (1H, dd), 8.09 - 8.11 (1H, m), 8.12 (1H, d), 8.48 (1H, s), 8.63 (1H, s), 8.71 (1H, s)

Example 98: (2S)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-isopropoxy-*N*-(5-methylpyridin-2-yl)propanamide

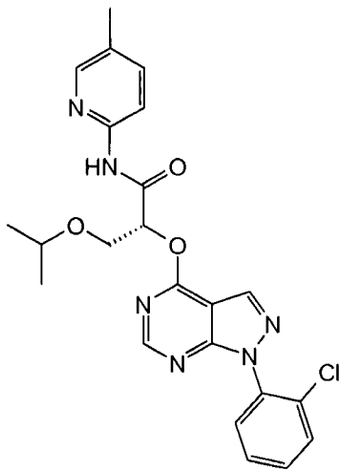


O-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (333 mg, 0.88 mmol) was added to (2S)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-isopropoxypropanoic acid **D2** (300 mg, 0.80 mmol), 5-methylpyridin-2-amine (95 mg, 0.88 mmol) and *N*-ethyldiisopropylamine (0.153 mL, 0.88 mmol) in DCM (15 mL) at room temperature under nitrogen. The resulting solution was stirred at room temperature for 24 hours. The reaction mixture was diluted with DCM (25 mL) and washed with saturated brine (20 mL). The aqueous layer was re-extracted with DCM (30 mL). The combined organics were evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 20 to 50% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford (2S)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-isopropoxy-*N*-(5-methylpyridin-2-yl)propanamide (175 mg, 47.1 %), 10% ee. 143 mg of this material was further purified by chiral preparative HPLC on Chiralcel OJ (50 mm x 20 μm), eluent isohexane/EtOH/MeOH 70/15/15 to afford (2S)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-isopropoxy-*N*-(5-methylpyridin-2-yl)propanamide (56 mg, >99% ee which eluted after the

R enantiomer).

^{1}H NMR (400 MHz, $CDCl_3$) 1.17 - 1.20 (6H, m), 2.29 (3H, s), 3.72 (1H, quin), 4.09 (2H, d), 6.02 (1H, t), 7.44 - 7.55 (4H, m), 7.61 - 7.63 (1H, m), 8.09 - 8.10 (1H, m), 8.13 (1H, d), 8.42 (1H, s), 8.59 (1H, s), 8.69 (1H, s); m/z (ESI)+ $(M+H)^+$ = 467; HPLC t_R = 2.63 min

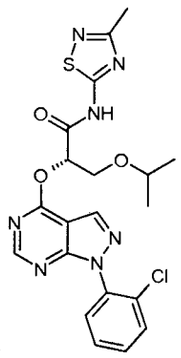
Example 99 : (2R)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-isopropoxy-*N*-(5-methylpyridin-2-yl)propanamide



143 mg of (2S)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-isopropoxy-*N*-(5-methylpyridin-2-yl)propanamide (10%ee) obtained in the preparation of **Example 98** was purified by chiral preparative HPLC on Chiralcel OJ (50 mm x 20 μm), eluent isohexane/EtOH/MeOH 70/15/15 to afford (2R)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-isopropoxy-*N*-(5-methylpyridin-2-yl)propanamide (60 mg, >99% ee which eluted before the S enantiomer).

^{1}H NMR (400 MHz, $CDCl_3$) 1.17 - 1.20 (6H, m), 2.29 (3H, s), 3.72 (1H, quin), 4.09 (2H, d), 6.02 (1H, t), 7.44 - 7.55 (4H, m), 7.61 - 7.63 (1H, m), 8.09 - 8.10 (1H, m), 8.13 (1H, d), 8.42 (1H, s), 8.59 (1H, s), 8.69 (1H, s); m/z (ESI)+ $(M+H)^+$ = 467; HPLC t_R = 2.64 min

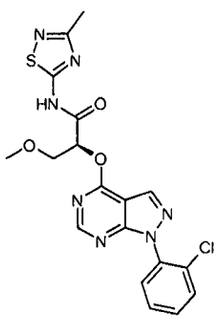
Example 100: (2S)-2-[1-(2-Chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(3-methyl-1,2,4-thiadiazol-5-yl)-3-propan-2-yloxypropanamide



A solution of lithium bis(trimethylsilyl)amide (0.82 mL, 0.82 mmol) was added dropwise to a stirred solution of (S)-2-hydroxy-3-isopropoxy-N-(3-methyl-1,2,4-thiadiazol-5-yl)propanamide (**Intermediate C9**) (200 mg, 0.82 mmol) in anhydrous THF (5 mL) over a period of 3 minutes under nitrogen. The resulting suspension was stirred at ambient temperature for 10 minutes and then a solution of 4-chloro-1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate B1**) in dry THF (1.5 mL) was added dropwise over 1 minute and the reaction heated to 50 °C for 20 hours. The mixture was cooled, diluted with EtOAc (50 mL), washed with water (10 mL) and brine (10 mL). The combined aqueous extracts were acidified with 1M citric acid and extracted with EtOAc (2 × 20 mL), the combined organic extracts were dried ($MgSO_4$) and evaporated. The resulting residue was purified by flash silica chromatography, eluting with an increasing gradient of 60 to 100% EtOAc in isohexane to afford (2S)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(3-methyl-1,2,4-thiadiazol-5-yl)-3-propan-2-yloxypropanamide (300 mg, 78%).

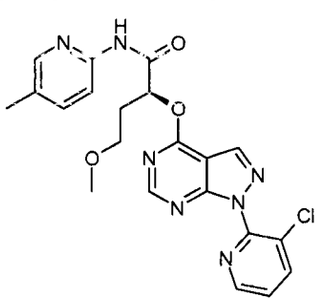
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (3H, d), 1.21 (3H, d), 2.55 (3H, s), 3.68 - 3.76 (1H, m), 4.10 (2H, d), 6.14 (1H, t), 7.45 - 7.57 (3H, m), 7.62 (1H, dd), 8.40 (1H, s), 8.57 (1H, s), 9.98 (1H, s). m/z (ESI-) (M-H)- = 472; HPLC t_R = 2.33 min.

Example 101: (2S)-2-(1-(2-Chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-methoxy-N-(3-methyl-1,2,4-thiadiazol-5-yl)propanamide



A solution of lithium bis(trimethylsilyl)amide (0.947 mL, 0.95 mmol) was added dropwise to a stirred solution of (S)-2-hydroxy-3-methoxy-N-(3-methyl-1,2,4-thiadiazol-5-yl)propanamide (**Intermediate E1**) (187 mg, 0.86 mmol) in anhydrous THF (5 mL) over a period of 3 minutes under nitrogen. The resulting suspension was stirred at ambient temperature for 10 minutes and then a solution of 4-chloro-1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate B1**) (228 mg, 0.86 mmol) in dry THF (1.5 mL) added dropwise over 1 minute and the reaction heated to 50°C for 16 hours. Reaction was cooled, diluted with EtOAc (50 mL), washed with 1M citric acid (25 mL) and brine (25 mL), dried ($MgSO_4$), and evaporated. The residue was purified by flash silica chromatography, elution gradient 0 to 100% EtOAc in isohexane to afford (2S)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-methoxy-N-(3-methyl-1,2,4-thiadiazol-5-yl)propanamide (44 mg, 11%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 (3H, s), 3.41 (3H, s), 4.01 (2H, ddd), 6.13 (1H, t), 7.38 - 7.48 (3H, m), 7.56 (1H, dd), 8.34 (1H, s), 8.51 (1H, s), 9.90 (1H, s). m/z (ESI+) $(M+H)^+$ = 446.08; HPLC t_R = 2.02 min.

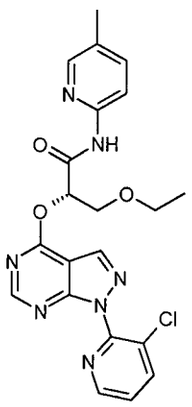
Example 102: (2S)-2-(1-(3-Chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-4-methoxy-N-(5-methylpyridin-2-yl)butanamide



4-Chloro-1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate B15**) (219 mg, 0.82 mmol) was added to sodium methanesulfinate (75 mg, 0.73 mmol) and

sodium hydride (38.0 mg, 0.95 mmol) in THF (5 mL) at 23 °C under nitrogen. The resulting suspension was stirred at ambient temperature for 5 minutes. (S)-2-Hydroxy-4-methoxy-N-(5-methylpyridin-2-yl)butanamide (**Intermediate F1**) (142 mg, 0.63 mmol) was added dropwise and the suspension was stirred at ambient temperature for a further 30 minutes. The mixture was diluted with EtOAc (50 mL), and washed sequentially with water (2 × 25 mL) and saturated brine (25 mL). The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by flash silica chromatography, elution gradient 40 to 100% EtOAc in isohexane to afford (2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-4-methoxy-N-(5-methylpyridin-2-yl)butanamide (250 mg, 87%). 1H NMR (400 MHz, $CDCl_3$) δ 2.29 (3H, s), 2.42 - 2.47 (2H, m), 3.33 (3H, s), 3.64 (2H t), 5.96 - 5.99 (1H, m), 7.45 - 7.48 (1H, m), 7.50 - 7.53 (1H, m), 7.99 - 8.02 (1H, m), 8.08 - 8.09 (1H, m), 8.12 (1H d), 8.43 (1H, s), 8.60 - 8.63 (3H, m); m/z (ESI+) (M+H)+ = 454; HPLC t_R = 1.77 min.

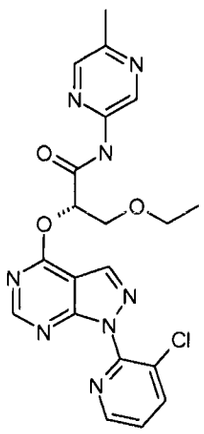
Example 103: (2S)-2-[1-(3-Chloropyridin-2-yl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-ethoxy-N-(5-methylpyridin-2-yl)propanamide



A solution of lithium bis(trimethylsilyl)amide (3.26 mL, 3.26 mmol) was added dropwise to a stirred solution of (S)-3-ethoxy-2-hydroxy-N-(5-methylpyridin-2-yl)propanamide (Intermediate G1) (730 mg, 3.26 mmol) in anhydrous THF (15 mL) over a period of 3 minutes under nitrogen. The resulting suspension was stirred at ambient temperature for 10 minutes and then a solution of 4-chloro-1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediate B15) (866 mg, 3.26 mmol) in dry THF (3 mL) added dropwise over 1 minute and the reaction heated to 50 °C for 3hours. The reaction mixture was diluted with EtOAc (50 mL), and washed sequentially with water (2 × 25 mL) and saturated brine (25 mL). The organic layer was dried ($MgSO_4$) and evaporated. The

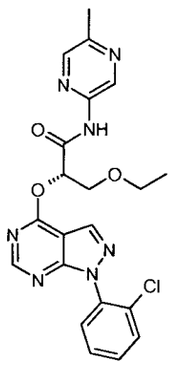
residue was purified by flash silica chromatography eluting with EtOAc to afford (2S)-2-[1-(3-chloropyridin-2-yl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-ethoxy-N-(5-methylpyridin-2-yl)propanamide (930mg, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (3H, t), 2.29 (3H, s), 3.59 - 3.67 (2H, m), 4.06 - 4.17 (2H, m), 6.06 - 6.08 (1H, m), 7.47 (1H, dd), 7.53 (1H, dd), 8.00 (1H, dd), 8.09 - 8.10 (1H, m), 8.13 (1H, d), 8.48 (1H, s), 8.62 (1H, dd), 8.63 (1H, s), 8.65 (1H, s); m/z (ESI+) $(M+H)^+$ = 454.3; HPLC tR = 1.97 min.

Example 104 : (2S)-2-[1-(3-Chloropyridin-2-yl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-ethoxy-N-(5-methylpyrazin-2-yl)propanamide



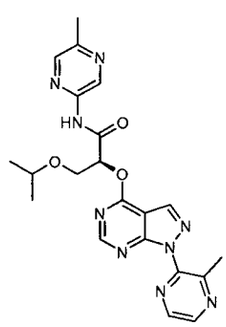
A solution of lithium bis(trimethylsilyl)amide (1.40 mL, 1.40 mmol) was added dropwise to a stirred solution of (S)-3-ethoxy-2-hydroxy-N-(5-methylpyrazin-2-yl)propanamide (**Intermediate H1**) (315 mg, 1.40 mmol) in THF (15 mL) over a period of 3 minutes under nitrogen. The resulting suspension was stirred at ambient temperature for 10 minutes and then a solution of 4-chloro-1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate B15**) (372 mg, 1.40 mmol) in anhydrous THF (3 mL) added dropwise over 1 minute and the reaction heated to 50 °C for 3 hours. The reaction mixture was diluted with EtOAc (50 mL), and washed sequentially with water (2 × 25 mL) and saturated brine (25 mL). The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by flash silica chromatography eluting with EtOAc to afford (2S)-2-[1-(3-chloropyridin-2-yl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-ethoxy-N-(5-methylpyrazin-2-yl)propanamide (330 mg, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (3H, t), 2.54 (3H, s), 3.60 - 3.68 (2H, m), 4.07 - 4.16 (2H, m), 6.09 (1H, t), 7.47 (1H, dd), 8.01 (1H, dd), 8.12 (1H, d), 8.47 (1H, s), 8.62 (1H, dd), 8.64 (1H, s), 8.66 (1H, s), 9.44 (1H, d); m/z (ESI+) $(M+H)^+$ = 455; HPLC t_R = 1.77 min.

Example 105: (2S)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-ethoxy-N-(5-methylpyrazin-2-yl)propanamide



A solution of lithium bis(trimethylsilyl)amide (1.398 mL, 1.40 mmol) was added dropwise to a stirred solution of (S)-3-ethoxy-2-hydroxy-N-(5-methylpyrazin-2-yl)propanamide (**Intermediate H1**) (315 mg, 1.40 mmol) in anhydrous THF (15 mL) over a period of 3 minutes under nitrogen. The resulting suspension was stirred at ambient temperature for 10 minutes and then a solution of 4-chloro-1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate B1**) (371 mg, 1.40 mmol) in dry THF (3 mL) added dropwise over 1 minute and the reaction heated to 50 °C for 3 hours. The reaction mixture was diluted with EtOAc (50 mL), and washed sequentially with water (2 × 25 mL) and saturated brine (25 mL). The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by flash silica chromatography with EtOAc to afford (2S)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-ethoxy-N-(5-methylpyrazin-2-yl)propanamide (460mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (3H, t), 2.54 (3H, s), 3.61 - 3.69 (2H, m), 4.07 - 4.16 (2H, m), 6.09 (1H, t), 7.47 - 7.55 (3H, m), 7.61 - 7.63 (1H, m), 8.12 (1H, d), 8.44 (1H, s), 8.60 (1H, s), 8.68 (1H, s), 9.45 (1H, d); m/z (ESI+) (M+H)+ = 454.3; HPLC t_R = 2.16 min.

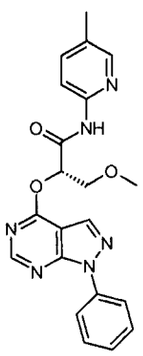
Example 106: (2S)-3-Isopropoxy-N-(5-methylpyrazin-2-yl)-2-(1-(3-methylpyrazin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide



Sodium hydride (22.06 mg, 0.55 mmol) was added to (S)-2-hydroxy-3-isopropoxy-N-(5-methylpyrazin-2-yl)propanamide (**Intermediate C8**) (110 mg, 0.46 mmol) in anhydrous THF (5 mL) at 0 °C under nitrogen. The resulting solution was stirred at 0 °C for 10 minutes and then 4-chloro-1-(3-methylpyrazin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate I4**) (125 mg, 0.51 mmol) in THF (2mL) was added. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour. Further sodium hydride (22.06 mg, 0.55 mmol) was added and the reaction stirred for another hour at room temperature. The reaction mixture was neutralised with 1M citric acid, and then diluted with water (20 mL) and EtOAc (50 mL). The organic layer was separated and the aqueous layer re-extracted with EtOAc (2 × 50 mL). The combined organics were washed with saturated brine (75 mL), dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash silica chromatography, elution gradient 50 to 100% EtOAc in isohexane to afford (2S)-3-isopropoxy-N-(5-methylpyrazin-2-yl)-2-(1-(3-methylpyrazin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide (98 mg, 47.4 %).

^{1}H NMR (400 MHz, $CDCl_3$) 1.20 (6H t), 2.54 (3H, s), 2.61 (3H, s), 3.71 - 3.77 (1H, m), 4.10 (2H d), 6.04 (1H t), 8.12 (1H, s), 8.45 (1H, s), 8.51 - 8.52 (1H, m), 8.64 - 8.66 (2H, m), 8.71 (1H, s), 9.43 (1H, s), m/z (ESI+) $(M+H)^+$ = 450; HPLC t_R = 1.73 min.

Example 107: (S)-3-Methoxy-N-(5-methylpyridin-2-yl)-2-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide

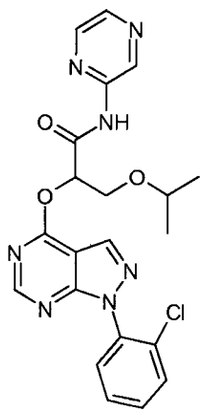


Palladium (10% on Carbon) (25.5 mg, 0.24 mmol) was added to (2S)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-methoxy-N-(5-methylpyridin-2-yl)propanamide (**Example 3**) (105 mg, 0.24 mmol) in methanol (2.5 mL) at ambient temperature under nitrogen. This was then purged with hydrogen and the resulting solution was stirred at ambient temperature for 24 hours. The mixture was filtered through celite and evaporated. The residue was purified by flash silica chromatography eluting with 0 to

100% EtOAc in isohexane to afford (S)-3-methoxy-N-(5-methylpyridin-2-yl)-2-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide (20.0 mg, 20.7 %).

^{1}H NMR (400 MHz, DMSO) δ 2.24 (s, 3H), 3.39 (s, 3H), 3.88 - 4.07 (m, 2H), 5.92 - 5.98 (m, 1H), 7.38 - 7.44 (m, 1H), 7.56 - 7.62 (m, 3H), 7.85 - 7.90 (m, 1H), 8.15 - 8.20 (m, 3H), 8.62 (s, 1H), 8.66 (s, 1H), 10.84 (s, 1H); m/z (ESI+) $(M+H)^+$ = 405.35

Example 108: 2-[1-(2-Chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-isopropoxy-N-pyrazin-2-yl-propanamide



O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (333 mg, 0.88 mmol) was added to (2S)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-isopropoxypropanoic acid (**Intermediate D2**) (300 mg, 0.80 mmol), aminopyrazine (CAS no. 5049-61-6) (84 mg, 0.88 mmol) and N-ethyldiisopropylamine (0.153 mL, 0.88 mmol) in DCM (15 mL) at room temperature under nitrogen. The resulting solution was stirred at room temperature for 24 hours. The reaction mixture was diluted with DCM (10 mL) and water (10 mL) and the organic phase separated using a phase separation cartridge and evaporated. The residue was purified using reverse phase chromatography, eluting with 25-75% acetonitrile in water to give 2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-isopropoxy-N-pyrazin-2-yl-propanamide (142 mg, 39%). ^{1}H NMR (400 MHz, $CDCl_3$) 1.18 - 1.22 (6H, m), 3.70 – 3.78 (1H, m), 4.10 (2H, d), 6.08 (1H, t), 7.40 – 7.50 (2H, m), 7.51 – 7.55 (1H, m), 7.62 – 7.64 (1H, m), 8.24 (1H, s), 8.35 (1H, s), 8.60 (1H, s), 8.80 (1H, s), 9.58 (1H, s); (M+H)+ = 454; HPLC t_R = 2.26.

The following examples were prepared from the appropriate amine using an analogous procedure.

Example 109: 2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-isopropoxy-N-(5-methyl-1,3,4-thiadiazol-2-yl)propanamide

Example 110: 2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-isopropoxy-N-(5-methylisoxazol-3-yl)propanamide

Example 111: 2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-isopropoxy-N-(5-methylthiazol-2-yl)propanamide

Example 112: 2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-3-isopropoxy-propanamide

Example 113: 2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-cyano-2-pyridyl)-3-isopropoxy-propanamide

Example 114: 2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-isopropoxy-N-(1,2,4-thiadiazol-5-yl)propanamide

Example 115: 2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-chloro-2-pyridyl)-3-isopropoxy-propanamide

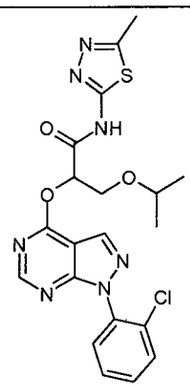
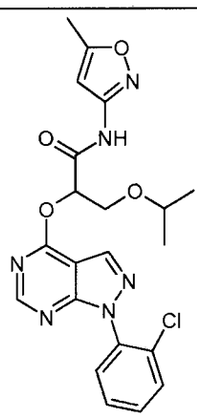
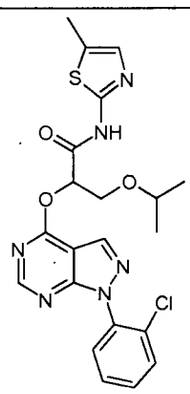
Example 116: 2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-isopropoxy-N-(4-methyl-2-pyridyl)propanamide

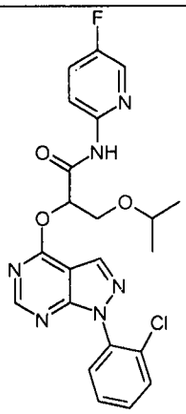
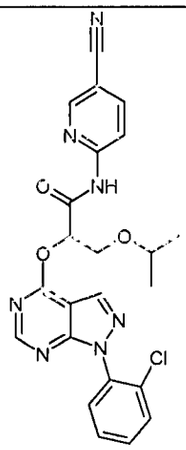
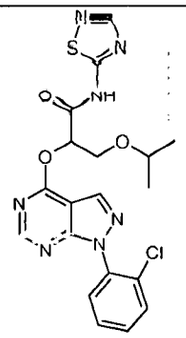
Example 117: 2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-isopropoxy-N-(1,3,4-thiadiazol-2-yl)propanamide

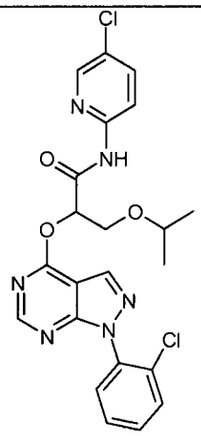
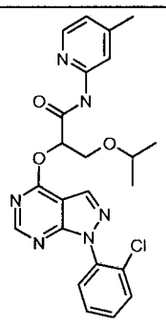
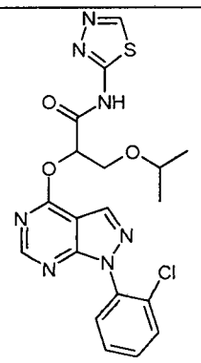
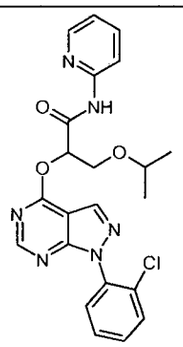
Example 118: 2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-isopropoxy-N-(2-pyridyl)propanamide

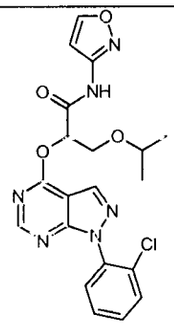
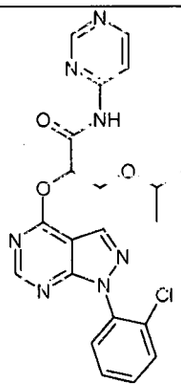
Example 119: 2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-isopropoxy-N-isoxazol-3-yl-propanamide

Example 120: 2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-isopropoxy-N-pyrimidin-4-yl-propanamide

Example no.	Structure	M/Z	^{1}H nmr data (400 MHz, $CDCl_3$)
109		MH- = 472 t_R= 1.47min.	1.18 - 1.22 (6H, m), 3.38 (3H, s), 3.70 – 3.76 (1H, m), 4.10 (2H, d), 6.1 (1H, t), 7.45 – 7.50 (2H, m), 7.50 – 7.55 (1H, m), 7.60 – 7.62 (1H, m), 8.40 (1H, s), 8.60 (1H, s)
110		(M+H)+ = 457 t_R = 2.52 min.	1.18 - 1.22 (6H, m), 2.40 (3H, s), 3.70 – 3.76 (1H, m), 4.08 (2H, d), 6.0 (1H, t), 7.45 – 7.50 (2H, m), 7.50 – 7.55 (1H, m), 7.60 – 7.62 (1H, m), 8.40 (1H, s), 8.60 (1H, s), 8.78 (1H, m).
111		MH- = 471 t_R = 2.32 min	1.18 - 1.22 (6H, m), 2.40 (3H, s), 3.65 – 3.74 (1H, m), 4.10 (2H, d), 6.1 (1H, t), 7.10 (1H, s), 7.45 – 7.50 (2H, m), 7.50 – 7.55 (1H, m), 7.60 – 7.62 (1H, m), 8.40 (1H, s), 8.60 (1H, s).

112		$(M+H)^+$ = 471 t_R = 2.68 min	1.18 - 1.22 (6H, m), 3.70 – 3.76 (1H, m), 4.10 (2H, d), 6.0 (1H, t), 7.45 – 7.55 (3H, m), 7.61 – 7.63 (1H, m), 8.1 (1H, m), 8.24 (1H, m), 8.42 (1H, s), 8.58 (1H, s), 8.8 (1H, s).
113		MH- = 476 t_R = 2.66	1.18 - 1.22 (6H, m), 3.70 – 3.78 (1H, m), 4.10 (2H, d), 6.0 (1H, t), 7.45 – 7.55 (2H, m), 7.60 – 7.63 (1H, m), 7.94 – 7.98 (1H, m), 8.38 (1H, d), 8.40 (1H, s), 8.56 – 8.58 (2H, m), 9.10 (1H, s).
114		MH- = 458 t_R = 1.31min	1.18 - 1.22 (6H, m), 3.68 – 3.76 (1H, m), 4.10 (2H, d), 6.15 (1H, t), 7.45 – 7.50 (2H, m), 7.50 – 7.55 (1H, m), 7.60 – 7.62 (1H, m), 8.37 (2H, m), 8.60 (1H, s), 10.44 (1H, s)

115		(M+H)+ = 488 t_R = 2.92 min	1.18 - 1.22 (6H, m), 3.70 – 3.76 (1H, m), 4.10 (2H, d), 6.0 (1H, t), 7.41 – 7.50 (2H, m), 7.55 (1H, m) 7.61 (1H, m), 7.6 – 7.70 (1H, d), 8.2 (2H, d), 8.40 (1H, s), 8.60 (1H, s), 8.70 (1H, s)
116		MH- = 465 t_R = 2.66 min	1.18 - 1.22 (6H, m), 2.35 (3H, s), 3.70 – 3.76 (1H, m), 4.10 (2H, d), 6.0 (1H, t), 6.80 (1H, d), 7.45 – 7.55 (3H, m), 7.61 – 7.63 (1H, m), 8.1 (1H, s), 8.14 (1H, d), 8.42 (1H, s), 8.60 (1H, s), 8.70 (1H, s)
117		MH- = 458 t_R = 1.23 min	1.18 - 1.22 (6H, m), 3.68 – 3.76 (1H, m), 4.10 (2H, d), 6.15 (1H, t), 7.45 – 7.50 (3H, m), 7.60 (1H, m), 8.40 (1H, s), 8.58 (1H, s), 8.85 (1H, s)
118		(M+H)+ = 453 t_R = 2.53 min	1.19 - 1.25 (6H, m), 3.70 – 3.75 (1H, m), 4.10 (2H, d), 6.0 (1H, t), 7.0 – 7.1 (1H, m) 7.45 – 7.55 (2H, m), 7.56 – 7.59 (1H, m), 7.64 – 7.68 (1H, m), 7.70 – 7.72 (1H, m), 8.20 – 8.40(2H, m), 8.40 (1H, s), 8.60 (1H, s), 8.75 (1H, s)

119		$(M+H)^+$ = 443 t_R = 2.36 min	1.18 - 1.22 (6H, m), 3.68 – 3.76 (1H, m), 4.10 (2H, d), 6.17 (1H, t),7.10 (1H, s) 7.45 – 7.50 (3H, m), 7.60 (1H, m), 8.30 (1H, s), 8.40 (1H, s), 8.58 (1H, s), 8.85 (1H, s)
120		$(M+H)^+$ = 454 t_R = 1.58 min	1.19 - 1.25 (6H, m), 3.70 – 3.77 (1H, m), 4.10 (2H, d), 5.98 (1H, t), 7.0 – 7.1 (1H, m) 7.45 – 7.55 (2H, m), 7.56 – 7.59 (1H, m), 7.64 – 7.68 (1H, m), 7.70 – 7.72 (1H, m), 8.19 (2H, d), 8.41 (1H, s), 8.60 (1H, s).

The examples below were prepared from the examples above by chiral chromatography using either Chiralcel OJ or Chiralcel AD as a chiral stationary phase and eluting with an appropriate mixture of isohexane, ethanol, methanol and triethylamine.

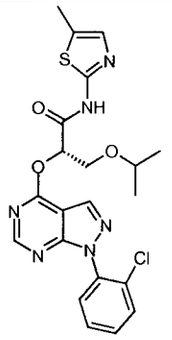
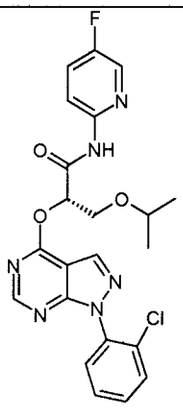
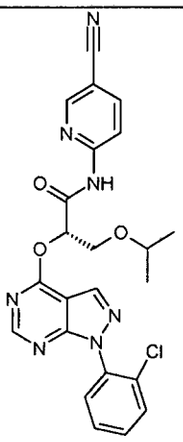
Example 111a: (2S)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-isopropoxy-N-(5-methylthiazol-2-yl)propanamide

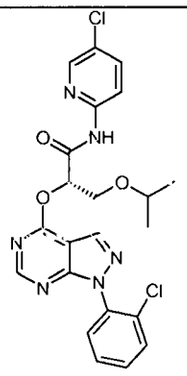
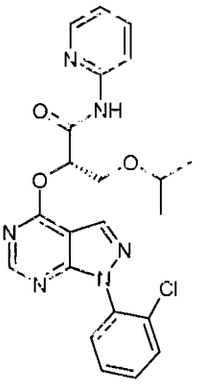
Example 112a: (2S)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-3-isopropoxy-propanamide

Example 113a: (2S)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-cyano-2-pyridyl)-3-isopropoxy-propanamide

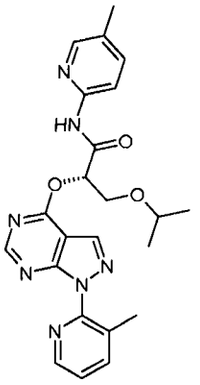
Example 115a: (2S)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-chloro-2-pyridyl)-3-isopropoxy-propanamide

Example 118a; (2S)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-isopropoxy-N-(2-pyridyl)propanamide

Example no.	Structure	M/Z	^{1}H nmr data (400 MHz, $CDCl_3$)
111a		MH- = 471 t_R = 2.32 min	1.17 - 1.20 (6H, m), 2.40 (3H, s), 3.70 -3.76 (1H, m), 4.10 (2H, d), 6.1 (1H, t), 7.10 (1H, s), 7.45 – 7.50 (2H, m), 7.50 – 7.55 (1H, m), 7.60 – 7.62 (1H, m), 8.37 (1H, s), 8.57 (1H, s).
112a		(M+H)+ = 471 t_R = 2.68 min	1.18 - 1.22 (6H, m), 3.70 – 3.76 (1H, m), 4.10 (2H, d), 6.0 (1H, t), 7.45 – 7.55 (3H, m), 7.61 – 7.63 (1H, m), 8.1 (1H, m), 8.24 (1H, m), 8.42 (1H, s), 8.58 (1H, s), 8.8 (1H, s).
113a		MH- = 476 t_R = 2.66 min	1.19 - 1.25 (6H, m), 3.70 – 3.75 (1H, m), 4.10 (2H, d), 6.0 (1H, t), 7.45 – 7.55 (2H, m), 7.60 – 7.63 (1H, m), 7.94 – 7.97 (1H, m), 8.38 (1H, d), 8.40 (1H, s), 8.56 – 8.58 (2H, m), 9.10 (1H, s).

115a		$(M+H)^+$ = 488 t_R = 2.92 min	1.11 - 1.15 (6H, m), 3.60 – 3.65 (1H, m), 4.0 (2H, d), 5.94 (1H, t), 7.41 – 7.50 (3H, m), 7.54 (1H m) 7.56 (1H, d), 7.6 – 7.62 (1H, m), 8.17 (1H, s), 8.30 (1H, s), 8.50 (1H, s), 8.74 (1H, s).
118a		$(M+H)^+$ = 453 t_R = 2.53 min	1.17 - 1.20 (6H, m), 3.70 – 3.76 (1H, m), 4.10 (2H, d), 6.02 (1H, t), 7.0 – 7.1 (1H, m) 7.45 – 7.49 (2H, m), 7.54 – 7.57 (1H, m), 7.64 – 7.68 (1H, m), 7.70 – 7.73 (1H, m), 8.20 – 8.40(2H, m), 8.40 (1H, s), 8.60 (1H, s), 8.70 (1H, s).

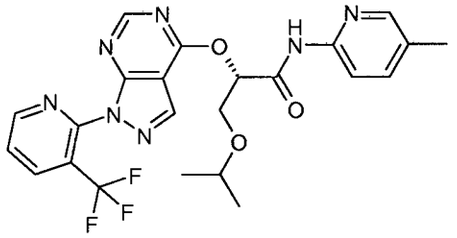
Example 125: (2S)-3-Isopropoxy-N-(5-methylpyridin-2-yl)-2-(1-(3-methylpyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide



A 2M solution of trimethylaluminium in hexane (0.404 mL, 0.81 mmol) was added to 5-methylpyridin-2-amine (84 mg, 0.77 mmol) in toluene (22 mL) at 5 °C under nitrogen. The resulting solution was stirred at 5°C for 20 minutes. (2S)-Methyl 3-isopropoxy-2-(1-(3-methylpyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanoate (300 mg, 0.70 mmol) (**Intermediate J5**) in toluene (6 mL) was added dropwise at 5 °C. After the addition was complete, the solution was allowed to warm to ambient temperature and was then

heated to reflux for 16 hours. The solution was allowed to cool to ambient temperature. The reaction mixture was concentrated, diluted with EtOAc (100 mL) and washed sequentially with 1M citric acid (50 mL), then saturated brine (50 mL). The organic layer was separated, dried ($MgSO_4$) and evaporated. The residue was purified by flash silica chromatography, eluting with EtOAc to afford (2S)-3-isopropoxy-N-(5-methylpyridin-2-yl)-2-(1-(3-methylpyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide (160 mg, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 - 1.12 (6H, m), 2.23 (3H, s), 2.26 (3H, s), 3.62 - 3.68 (1H, m), 4.00 - 4.09 (2H, m), 5.97 (1H, t), 7.30 - 7.33 (1H, m), 7.56 - 7.59 (1H, d), 7.70 - 7.73 (1H, d), 8.01 - 8.01 (1H, s), 8.21 (1H, d), 8.44 (1H, s), 8.46 (1H, m), 8.53 (1H, s), 9.5 (1H, broad s); m/z (ESI+) (M+H)+ = 448; HPLC t_R = 1.98 min.

Example 126: (2S)-3-Isopropoxy-N-(5-methylpyridin-2-yl)-2-(1-(3-(trifluoromethyl)pyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide



(2S)-2-(1-(5-Chloro-3-(trifluoromethyl)pyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-isopropoxy-N-(5-methylpyridin-2-yl)propanamide (**Intermediate K6**) (1 g, 0.73 mmol), and 10% Palladium on Carbon (100 mg, 0.09 mmol) in MeOH (25 mL) were stirred under an atmosphere of hydrogen for 16 hours. The reaction mixture was filtered through celite. 10% Palladium on Carbon (100 mg, 0.09 mmol) added and stirred under an atmosphere of hydrogen for a further 16 hours. The reaction mixture was filtered through celite and evaporated. The residue was purified by flash silica chromatography, elution gradient 1 to 5% MeOH in DCM to afford (2S)-3-isopropoxy-N-(5-methylpyridin-2-yl)-2-(1-(3-(trifluoromethyl)pyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide (0.173 g, 47 %). ^{1}H NMR (400 MHz, DMSO) δ 1.08 - 1.14 (6H, m), 2.24 (3H, s), 3.73 - 3.79 (1H, m), 3.96 - 4.05 (2H, m), 5.90 (1H, s), 7.57 - 7.60 (1H, m), 7.86 - 7.90 (1H, m), 7.94 - 7.98 (1H, m), 8.17 (1H, s), 8.55 (1H, s), 8.58 - 8.61 (1H, m), 8.65 (1H, s), 8.97 - 9.00 (1H, m), 10.82 (1H, s). m/z (ESI+) (M+H)+ = 502; HPLC t_R = 2.30 min.

The following Examples were prepared using a method analogous to that described for

Example 125 using the appropriate ester and arylamine.

Example 127: (2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-isopropoxy-N-(6-methylpyridazin-3-yl)propanamide

Example 127a: (2S)-N-(5-cyanopyridin-2-yl)-3-isopropoxy-2-(1-(3-methylpyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide

Example 127b: (2S)-N-(5-chloropyridin-2-yl)-3-isopropoxy-2-(1-(3-methylpyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide

Example 127c: (2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-cyano-2-pyridyl)-3-ethoxy-propanamide

Example 127d: (2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-ethoxy-N-(5-fluoro-2-pyridyl)propanamide

Example 127e: (2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-ethoxy-N-(2-pyridyl)propanamide

Example 127f: (2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-ethoxy-N-pyrimidin-4-yl-propanamide

Example 127g: (2S)-N-(5-chloro-2-pyridyl)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-ethoxy-propanamide

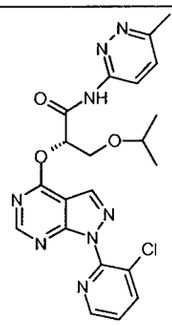
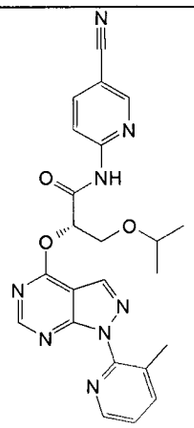
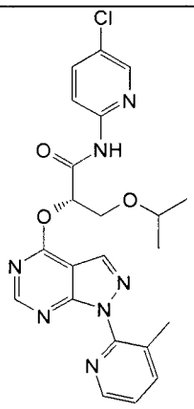
Example 127h: (2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(4-cyanothiazol-2-yl)-3-isopropoxy-propanamide

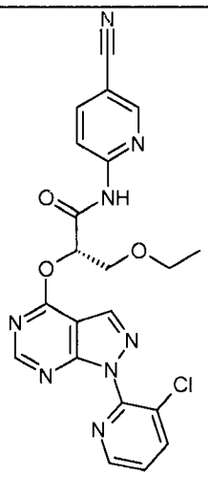
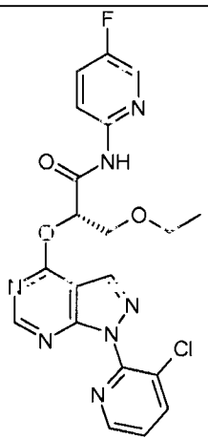
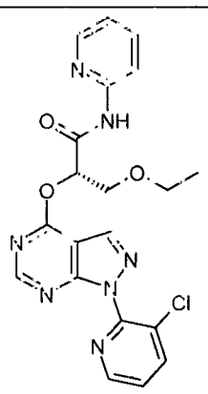
Example 127i: (2S)-N-(5-chloro-2-pyridyl)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-isopropoxy-propanamide

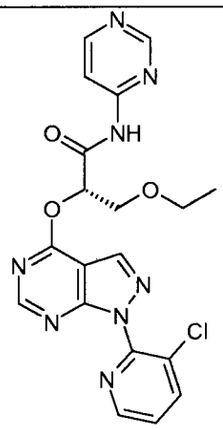
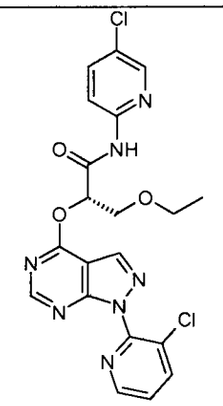
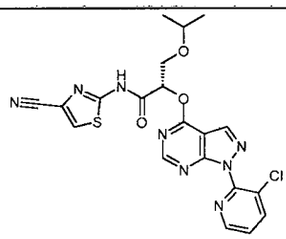
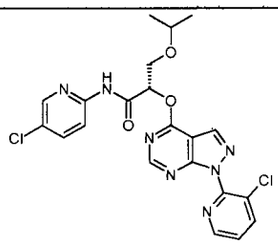
Example 127j: (2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-cyano-2-pyridyl)-3-isopropoxy-propanamide

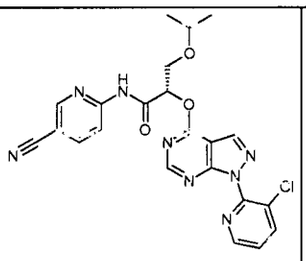
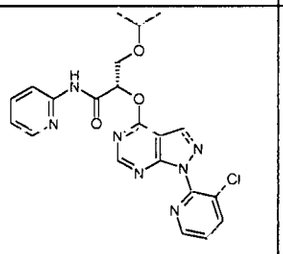
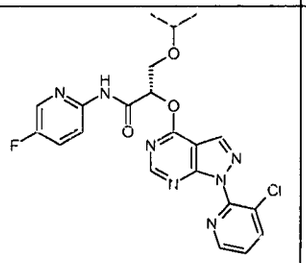
Example 127k: (2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-isopropoxy-N-(2-pyridyl)propanamide

Example 127l: (2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-3-isopropoxy-propanamide

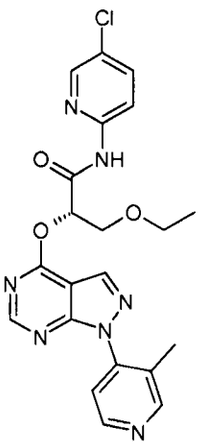
Example no.	Structure	m/z	^{1}H NMR data (400MHz)
127		(M+H)+ = 470 t_R = 1.78 min	($CDCl_3$) 1.18 - 1.22 (6H, m), 2.03 (3H,s) 3.70 – 3.78 (1H, m), 4.10 (2H, d), 6.08 (1H, t), 7.30 (1H, d), 7.46 – 7.50 (1H, m), 8.0 (1H, d), 8.40 (1H, d), 8.60 (2H, m), 9.30 (1H, s).
127a		(M+H)+ = 459; t_R = 2.15 min. ee 89%	(DMSO-d_6) 1.10 - 1.13 (6H, m), 2.11 (3H, s), 3.73 - 3.80 (1H, m), 3.99 - 4.08 (2H, m), 5.91 (1H, q), 7.56 - 7.59 (1H, m), 7.98 - 8.00 (1H, m), 8.13 (1H, d), 8.23 - 8.26 (1H, m), 8.50 (1H, t), 8.48 - 8.55 (1H, m), 8.60 (1H, s), 8.82 (1H, q), 11.50 (1H, s)
127b		(M+H)+ = 468; t_R = 2.24 min. ee 89%	(DMSO-d_6) 1.11 - 1.13 (6H, m), 2.11 (3H, s), 3.73 - 3.79 (1H, m), 3.97 - 4.06 (2H, m), 5.90 (1H, q), 7.56 - 7.59 (1H, m), 7.88 - 7.90 (1H, m), 7.98 - 8.03 (2H, m), 8.40 - 8.41 (1H, m), 8.49 (1H, q), 8.53 (1H, s), 8.59 (1H, s), 11.13 (1H, s).

127c		$(M+H)^+$ = 465.33; t_R = 2.08 min	(DMSO-d_6) 1.14 (3H, t), 3.59 - 3.69 (2H, m), 3.98 - 4.01 (1H, m), 4.06 - 4.10 (1H, m), 5.95 (1H, q), 7.72 - 7.78 (2H, m), 8.02 - 8.05 (1H, m), 8.34 - 8.36 (2H, m), 8.58 (1H, s), 8.68 (2H, t), 11.10 (1H, s)
127d		$(M+H)^+$ = 458.33; t_R = 2.09 min.	(DMSO-d_6) 1.14 (3H, t), 3.59 - 3.69 (2H, m), 4.00 - 4.03 (1H, m), 4.08 - 4.12 (1H, m), 5.97 (1H, q), 7.75 - 7.78 (1H, m), 8.14 (1H, d), 8.24 - 8.27 (1H, m), 8.34 - 8.36 (1H, m), 8.58 (1H, s), 8.68 (2H, d), 8.84 (1H, q), 11.55 (1H, s)
127e		$(M+H)^+$ = 440.63; t_R = 1.87 min.	(DMSO-d_6) 1.15 (3H, t), 3.60 - 3.69 (2H, m), 3.98 - 4.02 (1H, m), 4.06 - 4.11 (1H, m), 5.96 - 5.97 (1H, m), 7.12 - 7.15 (1H, m), 7.75 - 7.78 (2H, m), 7.99 (1H, d), 8.34 - 8.37 (2H, m), 8.58 (1H, s), 8.69 (2H, q), 10.97 (1H, s)

127f		(M+H)+ = 441.32; t_R = 1.65 min.	(DMSO-d_6) 1.14 (3H, t), 3.57 - 3.7 (2H, m), 4.00 - 4.03 (1H, m), 4.08 - 4.12 (1H, m), 5.96 (1H, q), 7.75 - 7.78 (1H, m), 7.98 - 8.00 (1H, m), 8.34 - 8.36 (1H, m), 8.58 (1H, s), 8.66 - 8.68 (1H, m), 8.67 - 8.69 (2H, m), 8.94 (1H, d), 11.46 (1H, s)
127g		(M+H)+ = 474.28; t_R = 2.32 min.	(DMSO-d_6) 1.13 (3H, t), 3.56 - 3.69 (2H, m), 3.96 - 4.00 (1H, m), 4.05 - 4.09 (1H, m), 5.94 (1H, q), 7.73 - 7.77 (1H, m), 7.87 - 7.90 (1H, m), 8.02 (1H, d), 8.32 - 8.35 (1H, m), 8.39 - 8.42 (1H, m), 8.56 (1H, s), 8.66 - 8.68 (2H, m), 11.17 (1H, s)
127h		(M+H)+ = 485; t_R = 2.24 min	($CDCl_3$) 1.20 - 1.24 (6H, m), 3.70 - 3.77 (1H, m), 4.10 (2H, d), 6.10 (1H, t), 7.47 - 7.50 (1H, m), 7.67 (1H, s), 8.01 - 8.03 (1H, m), 8.45 (1H, s), 8.61 - 8.63 (2H, m).
127i		(M+H)+ = 489; t_R = 2.38 min	(DMSO-d_6) 1.11 – 1.14 (6H, m), 3.7 – 3.8(1H, m), 3.9 – 4.0 (2H, m), 5.9 – 5.93 (1H, m), 7.75 – 7.78 (1H, m), 7.9 – 7.92 (1H,m), 8.03 (1H,d), 8.33 – 8.36 (1H, m), 8.40 – 8.41 (1H, m), 8.56 (1H,m), 8.66 – 8.69 (2H, m), 11.1 (1H, s)

127j		MH- = 479; t_R = 1.83 min	(DMSO-d_6) 1.13 (6H, t), 3.75 - 3.81 (1H, m), 4.01 - 4.10 (2H, m), 5.92 - 5.94 (1H, m), 7.75 - 7.78 (1H, m), 8.13 - 8.16 (1H, m), 8.24 - 8.27 (1H, m), 8.34 - 8.36 (1H, m), 8.57 (1H, s), 8.67 - 8.69 (2H, m), 8.84 (1H, q), 11.52 (1H, s)
127k		(M+H)+ = 454; t_R = 1.91 min	(DMSO-d_6) 1.11 – 1.15 (6H, m), 3.75 – 3.81(1H, m), 3.99 – 4.08 (2H, m), 5.92 – 5.93 (1H, m), 7.11 – 7.15 (1H, m), 7.75 – 7.80 (2H, m), 8.03 (1H, d), 8.33 – 8.36 (2H, m), 8.57 (1H, m), 8.66 – 8.69 (2H, m), 11.1 (1H, s)
127l		(M+H)+ = 471; t_R = 2.14 min	(DMSO-d_6) 1.12 – 1.14 (6H, m), 3.75 – 3.8(1H, m), 3.99 – 4.08 (2H, m), 5.9 – 5.92 (1H, m), 7.11 – 7.18 (2H, m), 8.0 – 8.15 (1H, d), 8.33 – 8.36 (2H, m), 8.57 (1H, m), 8.66 – 8.69 (2H, m), 11.1 (1H, s)

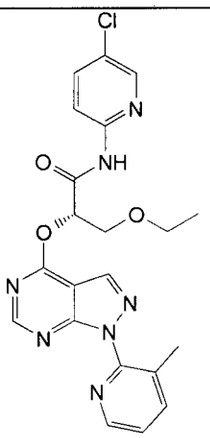
Example 128: (2S)-N-(5-Chloropyridin-2-yl)-3-ethoxy-2-[1-(3-methylpyridin-4-yl)pyrazolo[4,5-e]pyrimidin-4-yl]oxypropanamide



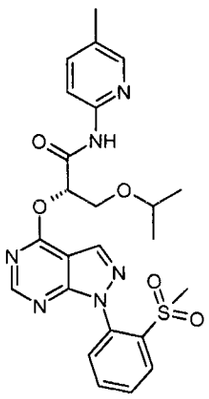
60% Sodium hydride in mineral oil (48.8mg, 1.22 mmol) was added in one portion to (S)-N-(5-chloropyridin-2-yl)-3-ethoxy-2-hydroxypropanamide (**Intermediate H3**) (199 mg, 0.81 mmol) in anhydrous THF (5 mL) cooled to 0 °C under nitrogen. The resulting suspension was stirred at 0 °C for 10 minutes and then 4-chloro-1-(3-methylpyridin-4-yl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate M1**) (200 mg, 0.81 mmol) added portionwise over 1 minute. The mixture was stirred at 0 °C for 15 mins, allowed to warm slowly to ambient temperature and stirred for 2 hours. 1M citric acid (2 mL) was added and the mixture extracted with ethyl acetate (2 × 20 mL). The organic extracts were washed with water (15 mL) and brine (15 mL), dried ($MgSO_4$) and evaporated. The residue was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in EtOAc to afford (2S)-N-(5-chloropyridin-2-yl)-3-ethoxy-2-[1-(3-methylpyridin-4-yl)pyrazolo[4,5-e]pyrimidin-4-yl]oxypropanamide (370 mg, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (3H, t), 2.34 (3H, s), 3.61 - 3.69 (2H, m), 4.06 - 4.14 (2H, m), 6.05 (1H, t), 7.49 (1H, d), 7.68 (1H, dd), 8.22 (1H, dd), 8.23 - 8.25 (1H, m), 8.44 (1H, s), 8.61 (1H, s), 8.63 (1H, dd), 8.69 (1H, s), 8.76 (1H, s) ; m/z (ESI+) (M+H)+ = 454; HPLC t_R = 1.93 min.

The following Examples were prepared using a method analogous to that described for Example 128 using the alcohol and chloro derivative.

Example 128a: (2S)-N-(5-chloropyridin-2-yl)-3-ethoxy-2-(1-(3-methylpyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide

Example no.	Structure	m/z	^{1}H NMR data
128a		(M+H)+ = 454; t_R = 2.08 min. ee 99%	400 MHz, DMSO-d_6 1.11 - 1.15 (3H, m), 2.11 (3H, s), 3.56 - 3.69 (2H, m), 3.96 - 4.06 (2H, m), 5.93 (1H, m), 7.56 - 7.59 (1H, m), 7.88 - 7.90 (1H, m), 7.98 - 8.00 (1H, m), 8.01 - 8.03 (1H, m), 8.40 - 8.41 (1H, m), 8.48 - 8.53 (2H, m), 8.61 (1H, t), 11.16 (1H, s)

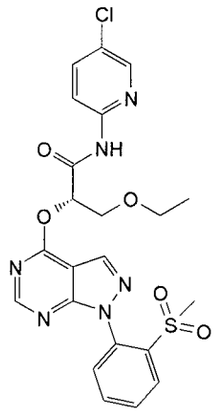
Example 129: (2S)-3-isopropoxy-N-(5-methylpyridin-2-yl)-2-(1-(2-(methylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide



Phosphorus oxychloride (1.864 ml, 20.00 mmol) was added to 1-(2-(methylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol (**Intermediate N1**) (0.290 g, 1 mmol), at ambient temperature. The resulting mixture was stirred at 100 °C for 4 hours. The solution was allowed to cool to ambient temperature. The reaction mixture was evaporated. The residue was dissolved in DCM (30 mL). MP-Carbonate was added and the mixture stirred for 30 minutes then evaporated. The residue was dissolved in THF (5 mL). Sodium hydride (55.9 mg, 1.40 mmol) was added to (S)-2-hydroxy-3-isopropoxy-N-(5-methylpyridin-2-yl)propanamide (**Intermediate C7**) (238 mg, 1.00 mmol) in anhydrous THF (10 mL) at 0°C under nitrogen. The resulting solution was stirred at 0°C for 15 minutes and then the THF solution prepared above was added. The reaction mixture was allowed to warm to ambient temperature and was stirred for 16 hours. The reaction mixture was concentrated, diluted with water (10 mL) and EtOAc (50 mL). The organic layer was separated and the aqueous layer re-extracted with EtOAc (25 mL). The combined organics were washed with saturated brine (25 mL), dried ($MgSO_4$) and evaporated. The residue was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5µ silica, 50 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 0.1% formic acid) and MeCN as eluent to afford (2S)-3-isopropoxy-N-(5-methylpyridin-2-yl)-2-(1-(2-(methylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide (242 mg, 47.5 %, 81% ee). ^{1}H NMR (400 MHz, DMSO-d6) δ 1.12 (6H, dd), 2.24 (3H, s), 3.38 (3H, s), 3.72 - 3.80 (1H, m), 3.96 - 4.05 (2H, m), 5.87 - 5.91 (1H, m), 7.58 (1H, dd), 7.77 (1H, dd), 7.86 - 7.92 (2H, m), 7.94 - 7.99 (1H,

m), 8.16 - 8.21 (2H, m), 8.53 (1H, s), 8.60 (1H, s), 10.82 (1H, s); m/z (ESI+) (M+H)+ = 511; HPLC t_R = 2.07 min.

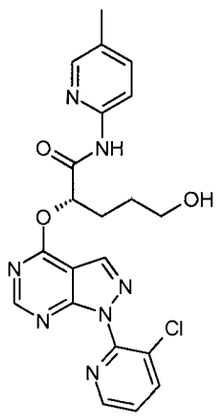
Example 130: (2S)-N-(5-chloropyridin-2-yl)-3-ethoxy-2-(1-(2-(methylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide



Prepared in an analogous fashion to **Example 129** from (**Intermediate H3**).

^{1}H NMR (400 MHz, DMSO) δ 1.13 (3H, t), 3.34 (3H, s), 3.58 - 3.68 (2H, m), 3.95 - 4.09 (2H, m), 5.91 - 5.95 (1H, m), 7.76 (1H, dd), 7.87 - 8.05 (4H, m), 8.19 (1H, dd), 8.40 (1H, d), 8.53 (1H, s), 8.53 (1H, s), 11.18 (1H, s); m/z (ESI+) (M+H)+ = 517; HPLC t_R = 2.41 min; ee 98%.

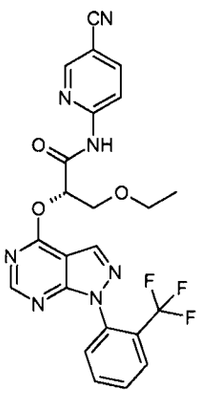
Example 131: (2S)-2-[1-(3-chloropyridin-2-yl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-5-hydroxy-N-(5-methylpyridin-2-yl)pentanamide



A solution of tetrabutylammonium fluoride 2M in THF (0.449 mL, 0.45 mmol) was added in one portion to a stirred solution of (2S)-5-(tert-butyldimethylsilyloxy)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-methylpyridin-2-yl)pentanamide (**Intermediate O1**) (170 mg, 0.30 mmol) in THF (5 mL). The resulting

solution was stirred at ambient temperature for 4 hours, evaporated and the residue dissolved in ethyl acetate (30 mL). This was washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated. The residue was purified by flash silica chromatography, eluting with 0 to 10% MeOH in ethyl acetate to afford the product (100mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61 - 1.68 (1H, m), 1.84 - 1.88 (2H, m), 2.23 - 2.36 (2H, m), 2.30 (3H, s), 3.72 - 3.82 (2H, m), 5.94 - 5.98 (1H, m), 7.46 (1H, dd), 7.54 (1H, dd), 8.01 (1H, dd), 8.08 - 8.10 (1H, m), 8.12 - 8.15 (1H, m), 8.45 (1H, s), 8.61-8.62 (2H, m), 8.63 (1H, s); m/z (ESI+) $(M+H)^+$ = 454; HPLC t_R= 1.51 min.

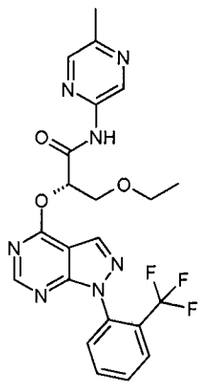
Example 132: (2S)-N-(5-cyanopyridin-2-yl)-3-ethoxy-2-[1-[2-(trifluoromethyl)phenyl]pyrazolo[4,5-e]pyrimidin-4-yl]oxypropanamide



60% Sodium hydride (60.0 mg, 1.50 mmol) was added in one portion to (S)-N-(5-cyanopyridin-2-yl)-3-ethoxy-2-hydroxypropanamide (**Intermediate H4**) (235 mg, 1.00 mmol) in anhydrous THF (5 mL) and the mixture was cooled to 0°C under nitrogen. The resulting suspension was stirred at 0°C for 10 minutes and 4-chloro-1-(2-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate P1**) (298.6 mg, 1.00 mmol) as suspension in dry THF (4 mL) was added dropwise over 1 minute. The mixture was stirred at 0°C for 15 mins, allowed to warm slowly to ambient temperature and stirred for 2 hours. 1M Citric acid (4 mL) was added and the mixture extracted with ethyl acetate (2 × 25 mL). The combined organic extracts were washed with water (25 mL) and brine (25 mL), dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 20 to 100% ethyl acetate in isohexane to give the product (430 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (3H, t), 3.62 - 3.70 (2H, m), 4.08 - 4.14 (2H, m), 6.04 (1H, t), 7.53 - 7.55 (1H, m), 7.68 - 7.77 (2H, m), 7.91 (1H, dd), 7.97 (1H, dd), 8.39 (1H, dd), 8.41 (1H, s), 8.56 (1H, s), 8.57 - 8.59 (1H, m), 9.02 (1H, s);

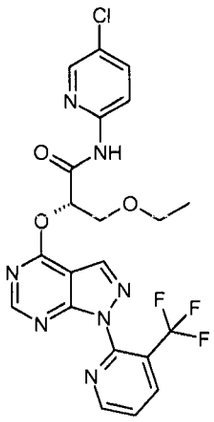
m/z (ESI-) $(M-H)^-$ = 496; HPLC tR= 2.55 min.

Example 133: (2S)-3-ethoxy-N-(5-methylpyrazin-2-yl)-2-[1-[2-(trifluoromethyl)phenyl]pyrazolo[4,5-e]pyrimidin-4-yl]oxypropanamide



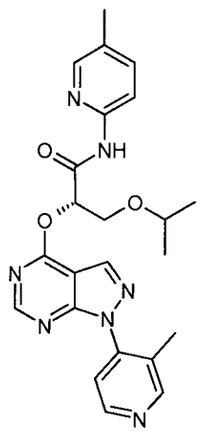
60% Sodium hydride (60.0 mg, 1.50 mmol) was added in one portion to (S)-3-ethoxy-2-hydroxy-N-(5-methylpyrazin-2-yl)propanamide (**Intermediate H1**) (225 mg, 1.00 mmol) in anhydrous THF (5 mL) and the mixture was cooled to 0°C under nitrogen. The resulting suspension was stirred at 0°C for 10 minutes and then 4-chloro-1-(2-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate P1**) (298.6 mg, 1.00 mmol) as suspension in dry THF (4 mL) added dropwise over 1 minute. The mixture was stirred at 0°C for 15 mins, allowed to warm to ambient temperature and stirred for 2 hours. 1M Citric acid (2 mL) was added and the mixture extracted with ethyl acetate (2 × 20 mL). The organic extracts were washed with water (15 mL) and brine (15 mL), dried ($MgSO_4$) and evaporated. The residue was purified by flash silica chromatography, eluting with 60 to 100% ethyl acetate in isohexane to give the product (440 mg, 88%). ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (3H, t), 2.54 (3H, s), 3.61 - 3.69 (2H, m), 4.08 - 4.16 (2H, m), 6.08 (1H, t), 7.52 - 7.57 (1H, m), 7.65 - 7.72 (1H, m), 7.74 - 7.76 (1H, m), 7.90 (1H, dd), 8.12 (1H, d), 8.41 (1H, s), 8.57 (1H, s), 8.68 (1H, s), 9.45 (1H, d) ; m/z (ESI+) $(M+H)^+$ = 488; HPLC tR= 2.27 min.

Example 134: (2S)-N-(5-chloropyridin-2-yl)-3-ethoxy-2-[1-[3-(trifluoromethyl)pyridin-2-yl]pyrazolo[4,5-e]pyrimidin-4-yl]oxypropanamide



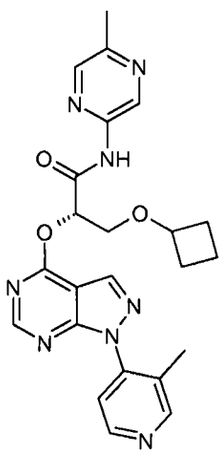
A solution of trimethylaluminium (2M in hexane) (0.322 mL, 0.64 mmol) was added dropwise to a stirred solution of 5-chloropyridin-2-amine (CAS no. 1072-98-6) (79 mg, 0.62 mmol) in toluene (5 mL) at 0°C, over a period of 1 minute under nitrogen. The resulting solution was stirred at 0°C for 20 minutes. A solution of (2S)-methyl 3-ethoxy-2-(1-(3-(trifluoromethyl)pyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanoate (**Intermediate Q1**) (230 mg, 0.56 mmol) in toluene (5 mL) was added dropwise over a period of 2 minutes. The resulting solution was stirred at 0°C for 10 minutes, allowed to warm to ambient temperature and then heated at 60°C for 20 hours. The resulting mixture was allowed to cool and 1M citric acid (10 mL) added with vigorous stirring. Ethyl acetate (35 mL) and water (10 mL) were added and the organic phase was separated, washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated. The residue was purified by flash silica chromatography, eluting with 50 to 100% ethyl acetate in isohexane and then chiral preparative HPLC to give the product (90 mg, 31%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (3H, t), 3.60 - 3.68 (2H, m), 4.06 - 4.15 (2H, m), 6.05 (1H, t), 7.64 - 7.70 (2H, m), 8.22 - 8.25 (2H, m), 8.29 (1H, dd), 8.43 (1H, s), 8.62 (1H, s), 8.84 (1H, s), 8.89 (1H, dd); m/z (ESI+) $(M+H)^+$ = 508: HPLC tR= 2.35 min.

Example 135: (2S)-N-(5-methylpyridin-2-yl)-2-[1-(3-methylpyridin-4-yl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-propan-2-yloxypropanamide



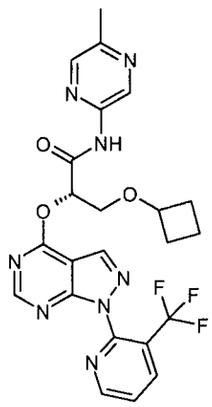
60% Sodium hydride in mineral oil (48.8mg, 1.22 mmol) was added in one portion to (S)-2-hydroxy-3-isopropoxy-N-(5-methylpyridin-2-yl)propanamide (**Intermediate C7**) (194 mg, 0.81 mmol) in anhydrous THF (5 mL) cooled to 0°C under nitrogen. The resulting suspension was stirred at 0°C for 10 minutes and then 4-chloro-1-(3-methylpyridin-4-yl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate M1**) (200 mg, 0.81 mmol) as suspension in dry THF (4 mL) added dropwise over 1 minute. The mixture was stirred at 0°C for 15 mins, allowed to warm slowly to ambient temperature and stirred for 2 hours. 1M Citric acid (2 mL) was added and the mixture extracted with ethyl acetate (2 × 20 mL). The combined organic extracts were washed with water (15 mL) and brine (15 mL), dried ($MgSO_4$) and evaporated. The residue was purified by flash silica chromatography with ethyl acetate to give the product (300mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (3H, d), 1.19 (3H, d), 2.29 (3H, s), 2.34 (3H, s), 3.69 - 3.76 (1H, m), 4.09 (2H, d), 6.01 (1H, t), 7.51 (1H, d), 7.53 (1H, dd), 8.09 - 8.10 (1H, m), 8.13 (1H, d), 8.43 (1H, s), 8.60 (1H, s), 8.62 (1H, dd), 8.67 (1H, s), 8.68 (1H, s); m/z (ESI+) (M+H)+ = 448; HPLC t_R = 1.78 min.

Example 136: (2S)-3-cyclobutyloxy-N-(5-methylpyrazin-2-yl)-2-[1-(3-methylpyridin-4-yl)pyrazolo[4,5-e]pyrimidin-4-yl]oxypropanamide



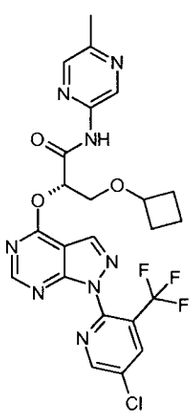
60% Sodium hydride in mineral oil (48.8mg, 1.22 mmol) was added in one portion to (S)-3-cyclobutoxy-2-hydroxy-N-(5-methylpyrazin-2-yl)propanamide (**Intermediate R1**) (205 mg, 0.81 mmol) in anhydrous THF (5 mL) cooled to 0°C under nitrogen. The resulting suspension was stirred at 0°C for 10 minutes and then 4-chloro-1-(3-methylpyridin-4-yl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate M1**) (200 mg, 0.81 mmol) as suspension in dry THF (4 mL) added dropwise over 1 minute. The mixture was stirred at 0°C for 15 mins, allowed to warm slowly to ambient temperature and stirred for 2 hours. 1M Citric acid (2 mL) was added and the mixture extracted with ethyl acetate (2 × 20 mL). The combined organic extracts were washed with water (15 mL) and brine (15 mL), dried ($MgSO_4$) and evaporated. The residue was purified by flash silica chromatography, eluting with 0 to 10% MeOH in ethyl acetate to give the product (360 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 - 1.57 (1H, m), 1.67 - 1.76 (1H, m), 1.88 - 2.00 (2H, m), 2.19 - 2.27 (2H, m), 2.35 (3H, s), 2.54 (3H, s), 3.97 - 4.10 (3H, m), 6.05 (1H, t), 7.49 (1H, d), 8.12 (1H, d), 8.44 (1H, s), 8.61 (1H, s), 8.62 - 8.65 (2H, m), 8.69 (1H, s), 9.44 (1H, d); m/z (ESI+) $(M+H)^+$ = 461; HPLC t_R = 1.67 min.

Example 137: (2S)-3-cyclobutyloxy-N-(5-methylpyrazin-2-yl)-2-[1-[3-(trifluoromethyl)pyridin-2-yl]pyrazolo[4,5-e]pyrimidin-4-yl]oxypropanamide



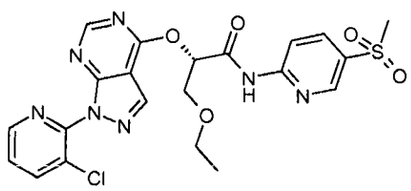
10% Palladium on carbon (200 mg, 1.88 mmol) and (2S)-2-(1-(5-chloro-3-(trifluoromethyl)pyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-cyclobutoxy-N-(5-methylpyrazin-2-yl)propanamide (**Example 138**) (501 mg, 0.91 mmol) in ethanol was stirred under an atmosphere of hydrogen at ambient temperature for 20 hours. The mixture was filtered and fresh catalyst (200 mg) added and the mixture stirred under hydrogen atmosphere for 8 hours. The mixture was filtered, triethylamine (1 mL) added, and the mixture evaporated. The residue was purified by flash silica chromatography eluting with ethyl acetate to give the product (150 mg, 32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 - 1.60 (1H, m), 1.64 - 1.71 (1H, m), 1.92 - 1.97 (2H, m), 2.18 - 2.23 (2H, m), 2.54 (3H, s), 3.98 - 4.07 (3H, m), 6.05 (1H, t), 7.65 - 7.68 (1H, m), 8.12 (1H, d), 8.29 (1H, dd), 8.44 (1H, s), 8.62 - 8.67 (1H, m), 8.65 (1H, s), 8.89 (1H, dd), 9.45 (1H, d); m/z (ESI+) $(M+H)^+$ = 515; HPLC t_R = 2.25 min.

Example 138: (2S)-2-[1-[5-chloro-3-(trifluoromethyl)pyridin-2-yl]pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-cyclobutyloxy-N-(5-methylpyrazin-2-yl)propanamide



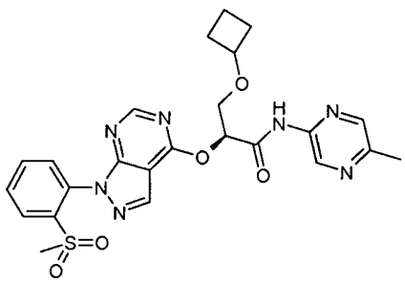
60% Sodium hydride in mineral oil (60mg, 1.50 mmol) was added in one portion to (S)-3-cyclobutoxy-2-hydroxy-N-(5-methylpyrazin-2-yl)propanamide (**Intermediate R1**) (251 mg, 1.00 mmol) in anhydrous THF (5 mL) at 0°C under nitrogen. The resulting suspension was stirred at 0°C for 10 minutes and then 4-chloro-1-(5-chloro-3-(trifluoromethyl)pyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate K3**) (334 mg, 1.00 mmol) as suspension in dry THF (2.5 mL) added dropwise over 1 minute. The mixture was stirred at 0°C for 15 mins, allowed to warm to ambient temperature and stirred for 6 hours. 1M Citric acid (10 mL) was added and the mixture extracted with ethyl acetate (2 × 25 mL). The combined organic extracts were washed with water (25 mL) and brine (25 mL), dried ($MgSO_4$) and evaporated. The residue was purified by flash silica chromatography, eluting with 50 to 100% ethyl acetate in isohexane to give the product (550mg, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 - 1.54 (1H, m), 1.66 - 1.74 (1H, m), 1.89 - 2.01 (2H, m), 2.18 - 2.25 (2H, m), 2.54 (3H, s), 3.98 - 4.08 (3H, m), 6.04 (1H, t), 8.12 (1H, d), 8.25 (1H, d), 8.43 (1H, s), 8.62 (1H, s), 8.63-8.65 (1H, m), 8.82 (1H, d), 9.44 (1H, d); m/z (ESI+) $(M+H)^+$ = 549; HPLC t_R = 2.56 min.

Example 139: (2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-ethoxy-N-(5-(methylsulfonyl)pyridin-2-yl)propanamide



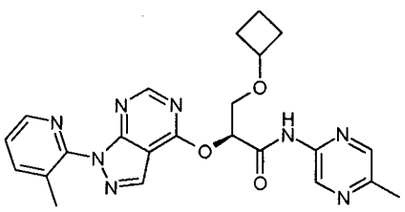
A solution of 3-chloroperoxybenzoic acid (85 mg, 0.38 mmol) in DCM (10 mL) was added dropwise to a stirred solution of (2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-ethoxy-N-(5-(methylthio)pyridin-2-yl)propanamide (**Intermediate S1**) (92 mg, 0.19 mmol), in DCM (10 mL), at 22°C, over a period of 10 minutes. The resulting solution was stirred at 22°C for 3 hours. The reaction mixture was diluted with DCM (20 mL) washed with 2M NaOH (20 mL), dried ($MgSO_4$) and evaporated. The residue was purified by flash silica chromatography, eluting with 10 to 100% ethyl acetate in isohexane to afford the product (80 mg). ^{1}H NMR (400 MHz, DMSO) δ 1.13 (3H, t), 3.26 (3H, s), 3.56 - 3.70 (2H, m), 3.99 - 4.05 (2H, m), 5.96 (1H, q), 7.74 - 7.77 (1H, m), 8.18 - 8.21 (1H, m), 8.26 - 8.29 (1H, m), 8.32 - 8.35 (1H, m), 8.56 (1H, s), 8.66 - 8.68 (2H, m), 8.83 - 8.84 (1H, m), 11.59 (1H, s); m/z (ES+) $(M+H)^+$ = 518; HPLC t_R = 1.88 min.

Example 140: (2S)-3-cyclobutoxy-N-(5-methylpyrazin-2-yl)-2-(1-(2-(methylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide



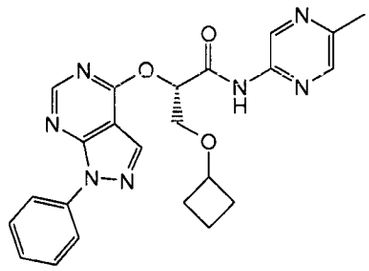
Prepared in an analogous fashion to **Example 129** from **Intermediate N1** and (S)-3-cyclobutoxy-2-hydroxy-N-(5-methylpyrazin-2-yl)propanamide (**Intermediate R1**). ^{1}H NMR (400 MHz, DMSO) δ 1.42 - 1.50 (1H, m), 1.62 (1H, q), 1.80 - 1.92 (2H, m), 2.16 - 2.23 (2H, m), 2.45 (3H, s), 3.38 (3H, s), 3.90 - 3.93 (1H, m), 3.99 (1H, q), 4.08 - 4.15 (1H, m), 5.92 (1H, q), 7.76 - 7.78 (1H, m), 7.88 - 7.92 (1H, m), 7.95 - 7.99 (1H, m), 8.18 - 8.21 (1H, m), 8.32 (1H, d), 8.53 (1H, s), 8.63 (1H, s), 9.11 (1H, s), 11.19 (1H, s); m/z (ESI+) $(M+H)^+ = 524$; HPLC $t_R = 1.97$ min.

Example 141: (2S)-3-cyclobutoxy-N-(5-methylpyrazin-2-yl)-2-(1-(3-methylpyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide



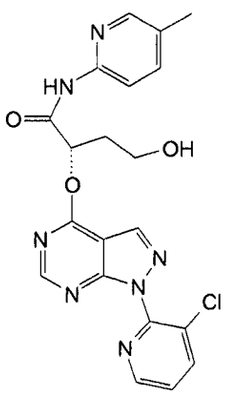
Prepared in an analogous fashion to **Example 106** from **Intermediate J4** and (S)-3-cyclobutoxy-2-hydroxy-N-(5-methylpyrazin-2-yl)propanamide (**Intermediate R1**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 - 1.46 (1H, m), 1.58 - 1.68 (1H, m), 1.82 - 1.94 (2H, m), 2.10 - 2.19 (2H, m), 2.23 (3H, s), 2.47 (3H, s), 3.90 - 4.01 (3H, m), 5.98 (1H, t), 7.31 - 7.34 (1H, m), 7.73 (1H, d), 8.05 (1H, s), 8.36 (1H, s), 8.47 (1H, d), 8.55 (1H, s), 8.59 (1H, s), 9.38 (1H, s); m/z (ESI+) $(M+H)^+ = 461$; HPLC tR = 1.92 min.

Example 142: (S)-3-cyclobutoxy-N-(5-methylpyrazin-2-yl)-2-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide



(2S)-2-(1-(2-Chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-cyclobutoxy-N-(5-methylpyrazin-2-yl)propanamide (**Example 156**) (102 mg, 0.21 mmol) and 10 % palladium on carbon (25 mg, 0.02 mmol) in ethanol (20 mL) were stirred under an atmosphere of hydrogen for 16 hours. The suspension was filtered through celite. 10% Palladium on carbon (25 mg, 0.02 mmol) was added and the resulting suspension was stirred under an atmosphere of hydrogen for 24 hours. The reaction mixture was filtered through celite and evaporated. The residue was purified by flash silica chromatography, eluting with 0 to 50% ethyl acetate in isohexane to afford the product (16.0 mg, 16.9%). ^{1}H NMR (400 MHz, DMSO) δ 1.39 - 1.51 (1H, m), 1.56 - 1.66 (1H, m), 1.78 - 1.90 (2H, m), 2.13 - 2.23 (2H, m), 2.44 (3H, s), 3.89 - 4.14 (3H, m), 5.89 - 5.94 (1H, m), 7.41 (1H, t), 7.59 (2H, t), 8.17 (1H, s), 8.17 (1H, s), 8.32 (1H, s), 8.63 (1H, s), 8.66 (1H, s), 9.09 (1H, s), 11.17 (1H, s); m/z (ESI+) $(M+H)^+$ = 446; HPLC tR = 2.70 min.

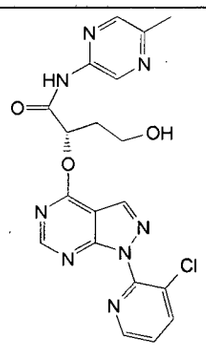
Example 143: (2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-4-hydroxy-N-(5-methyl-2-pyridyl)butanamide

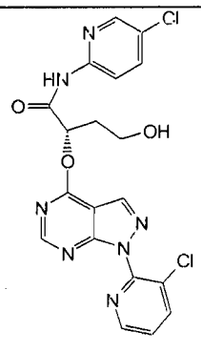
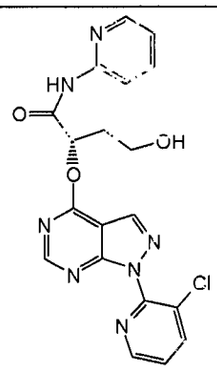
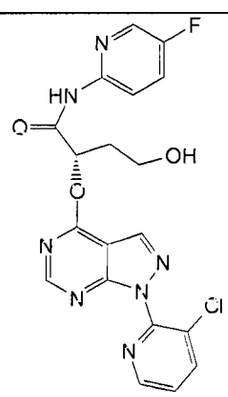


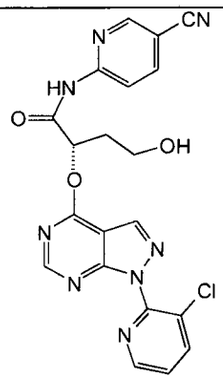
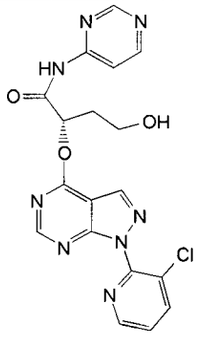
Trimethylaluminium (0.347 mL, 0.69 mmol) was added to 5-methylpyridin-2-amine (71.7 mg, 0.66 mmol) in toluene (8 mL) cooled to 0°C under nitrogen. The resulting solution was

stirred at 0°C for 20 minutes. (3S)-3-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)dihydrofuran-2(3H)-one (**Intermediate T1**) (200 mg, 0.60 mmol) in toluene (2 mL) and the reaction was allowed to warm to room temperature and stirred for 1 hour. The reaction was then heated at 50°C for 2 hours. The reaction mixture was allowed to cool and was neutralised with citric acid (1M, aq.) and then diluted with water (50 mL) and ethyl acetate (50 mL). The organic layer was separated and the aqueous layer re-extracted with ethyl acetate (50 mL). The combined organics were dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, eluting with 0 to 10% MeOH in DCM to afford the product (185 mg, 69.8 %). ^{1}H NMR (400 MHz, $CDCl_3$) 2.30 (3H, s), 2.33 - 2.40 (1H, m), 2.44 - 2.52 (1H, m), 2.55 (1H, s), 3.83 - 3.92 (2H, m), 6.07 - 6.10 (1H, m), 7.46 - 7.49 (1H, m), 7.52 - 7.55 (1H, m), 8.00 - 8.02 (1H, m), 8.09 - 8.10 (1H, m), 8.13 (1H, d), 8.47 (1H, s), 8.61 - 8.62 (1H, m), 8.64 (1H, s), 8.68 (1H, s); m/z (ESI+) $(M+H)^+$ = 440; HPLC t_R = 1.68 min.

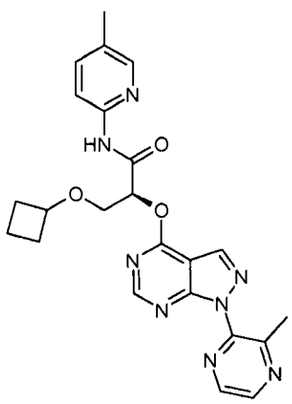
The following examples were prepared using an analogous procedure using **Intermediate T1** and the appropriate amine:

No.	STRUCTURE	NAME	M/Z	**^{1}H NMR data** (400 MHz, $CDCl_3$)
143a		(2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-4-hydroxy-N-(5-methylpyrazin-2-yl)butanamide	ESI+ $(M+H)^+$ =441; HPLC t_R = 1.39 min	δ 2.35 - 2.52 (2H, m), 2.54 (3H, s), 3.85 - 3.98 (2H, m), 6.10 - 6.13 (1H, m), 7.46 - 7.50 (1H, m), 8.00 - 8.03 (1H, m), 8.11 (1H, d), 8.45 (1H, s), 8.60 - 8.63 (1H, m), 8.64 (1H, s), 8.77 (1H, s), 9.43 (1H, d)

143b		(2S)-N-(5-chloro-2-pyridyl)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-4-hydroxy-butanamide	ESI+ (M+H)+ =460; HPLC t_R = 1.82 min	δ 2.33 - 2.52 (3H, m), 3.83 - 3.97 (2H, m), 6.07 - 6.10 (1H, m), 7.46 - 7.50 (1H, m), 7.67 - 7.70 (1H, m), 8.00 - 8.03 (1H, m), 8.22 - 8.23 (1H, m), 8.23 (1H, d), 8.46 (1H, s), 8.61 - 8.63 (1H, m), 8.64 (1H, s), 8.81 (1H, s)
143c		(2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-4-hydroxy-N-(2-pyridyl)butanamide	(ESI+) (M+H)+ = 426; HPLC t_R = 1.40 min	δ 2.33 - 2.53 (3H, m), 3.84 - 3.94 (2H, m), 6.08 - 6.11 (1H, m), 7.06 - 7.09 (1H, m), 7.46 - 7.49 (1H, m), 7.70 - 7.75 (1H, m), 8.00 - 8.02 (1H, m), 8.24 (1H, d), 8.28 - 8.30 (1H, m), 8.47 (1H, s), 8.59 - 8.63 (1H, m), 8.65 (1H, s), 8.76 (1H, s)
143d		(2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-4-hydroxy-butanamide	(ESI+) (M+H)+ = 444; HPLC t_R = 1.62 min	δ 2.33 - 2.41 (1H, m), 2.44 - 2.52 (2H, m), 3.83 - 3.98 (2H, m), 6.07 - 6.11 (1H, m), 7.43 - 7.50 (2H, m), 8.00 - 8.03 (1H, m), 8.14 (1H, s), 8.25 - 8.28 (1H, m),

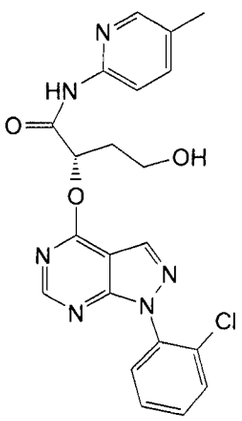
				8.46 (1H, s), 8.59 - 8.63 (1H, m), 8.64 (1H, s), 8.80 (1H, s)
143e		(2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-cyano-2-pyridyl)-4-hydroxy-butanamide	(ESI+) (M-H)- = 449; HPLC t_R = 1.63 min	δ 2.27 (1H, t), 2.35 - 2.52 (2H, m), 3.85 - 3.99 (2H, m), 6.07 - 6.10 (1H, m), 7.47 - 7.50 (1H, m), 7.95 - 7.98 (1H, m), 8.01 - 8.03 (1H, m), 8.37 - 8.40 (1H, m), 8.46 (1H, s), 8.56 - 8.57 (1H, m), 8.61 - 8.63 (1H, m), 8.64 (1H, s), 9.06 (1H, s)
143f		(2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-4-hydroxy-N-pyrimidin-4-yl-butanamide	(ESI+) (M-H)- = 425; HPLC t_R = 1.37 min	δ 2.31 (1H, s), 2.35 - 2.52 (2H, m), 3.86 - 3.97 (2H, m), 6.05 - 6.09 (1H, m), 7.44 - 7.50 (1H, m), 8.00 - 8.03 (1H, m), 8.19 - 8.20 (1H, m), 8.46 (1H, s), 8.59 - 8.67 (3H, m), 8.89 (1H, d), 8.94 (1H, s)

Example 144: (2S)-3-(cyclobutoxy)-2-[1-(3-methylpyrazin-2-yl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-methyl-2-pyridyl)propanamide



Prepared using an analogous procedure to that described for Example 106 using 4-Chloro-1-(3-methylpyrazin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediate I4) with (S)-3-cyclobutoxy-2-hydroxy-N-(5-methylpyridin-2-yl)propanamide (Intermediate U1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 - 1.55 (1H, m), 1.64 - 1.73 (1H, m), 1.89 - 2.00 (2H, m), 2.17 - 2.24 (2H, m), 2.30 (3H, s), 2.61 (3H, s), 3.97 - 4.08 (3H, m), 6.02 - 6.05 (1H, m), 7.51 - 7.54 (1H, m), 8.09 - 8.10 (1H, m), 8.13 (1H, d), 8.47 (1H, s), 8.51 - 8.52 (1H, m), 8.64 (1H, s), 8.65 (2H, d); m/z (ESI+) $(M+H)^+$ = 461; HPLC t_R = 2.05 min.

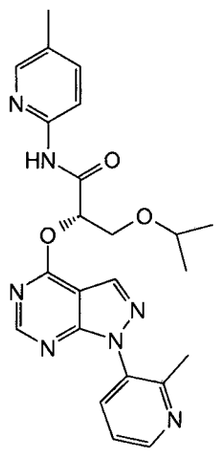
Example 145: (2S)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-4-hydroxy-N-(5-methyl-2-pyridyl)butanamide



Prepared using an analogous procedure to that described for **Example 143** using (3S)-3-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)dihydrofuran-2(3H)-one (**Intermediate T2**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (3H, s), 2.32 - 2.40 (1H, m), 2.44 - 2.52 (1H, m), 2.73 (1H, s), 3.83 - 3.97 (2H, m), 6.07 - 6.10 (1H, m), 7.44 - 7.63 (5H, m),

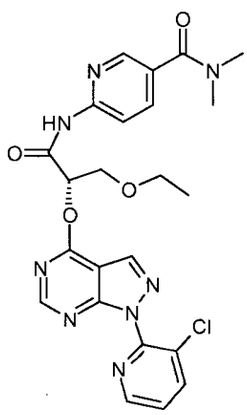
8.09 - 8.10 (1H, m), 8.13 (1H, d), 8.43 (1H, s), 8.59 (1H, s), 8.76 (1H, s); m/z (ESI+) (M+H)+ = 439; HPLC t_R = 1.81 min

Example 146: (2S)-3-isopropoxy-N-(5-methyl-2-pyridyl)-2-[1-(2-methyl-3-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-propanamide



Prepared using an analogous procedure to that described for **Example 106** using **Intermediate C7** and **Intermediate V5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (6H, t), 2.30 (3H, s), 2.45 (3H, s), 3.70 - 3.76 (1H, m), 4.09 - 4.10 (2H, m), 6.01 (1H, t), 7.33 - 7.37 (1H, m), 7.52 - 7.55 (1H, m), 7.75 - 7.77 (1H, m), 8.10 - 8.15 (2H, m), 8.44 (1H, s), 8.58 (1H, s), 8.66 - 8.67 (1H, m), 8.70 (1H, s); m/z (ESI+) (M+H)+ = 448; HPLC t_R = 1.83 min.

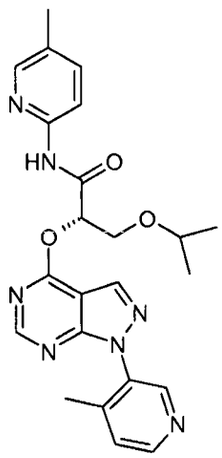
Example 147: 6-[[(2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-ethoxy-propanoyl]amino]-N,N-dimethyl-pyridine-3-carboxamide



Prepared using an analogous procedure to that described for **Example 125** using **Intermediate W1** and **Intermediate L2**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 - 1.28 (3H, m), 3.04 (3H, s), 3.09 (3H, s), 3.58 - 3.70 (2H, m), 4.07 - 4.15 (2H, m), 6.06 (1H, t), 7.46 - 7.49 (1H, m), 7.79 - 7.82 (1H, m), 8.00 - 8.02 (1H, m), 8.27 - 8.30 (1H, m), 8.39 - 8.40

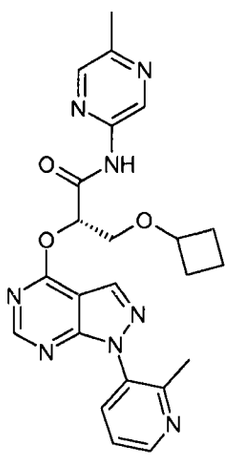
(1H, m), 8.48 (1H, s), 8.61 - 8.62 (1H, m), 8.63 (1H, s), 8.86 (1H, s); m/z (ESI+) $(M+H)^+$ = 511; HPLC tR= 1.72 min.

Example 148: (2S)-3-isopropoxy-N-(5-methyl-2-pyridyl)-2-[1-(4-methyl-3-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-propanamide



Prepared using a procedure analogous to that described for **Example 106** using **Intermediate C7** and **Intermediate X5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (6H, t), 2.25 (3H, s), 2.29 (3H, s), 3.70 - 3.76 (1H, m), 4.09 (2H, d), 6.02 (1H, t), 7.35 (1H, d), 7.51 - 7.54 (1H, m), 8.09 - 8.10 (1H, m), 8.13 (1H, d), 8.44 (1H, s), 8.57 (1H, s), 8.60 (1H, d), 8.65 (1H, s), 8.71 (1H, s); m/z (ES+) $(M+H)^+$ = 448.5; HPLC tR= 1.93 min.

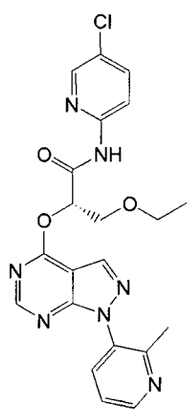
Example 149: (2S)-3-cyclobutoxy-N-(5-methylpyrazin-2-yl)-2-(1-(2-methylpyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide



Sodium hydride (19.54 mg, 0.49 mmol) was added to (S)-3-cyclobutoxy-2-hydroxy-N-(5-methylpyrazin-2-yl)propanamide (**Intermediate R1**) (102 mg, 0.41 mmol) in anhydrous THF (5 mL) at 0 °C under nitrogen. The resulting solution was stirred at 0°C for 10

minutes and then 4-chloro-1-(2-methylpyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate V5**) (100 mg, 0.41 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour. The reaction mixture was neutralised with 1M citric acid and the majority of the THF removed in vacuo. The reaction mixture was diluted with water (20 mL) and ethyl acetate (50 mL). The organic layer was separated and the aqueous layer re-extracted with ethyl acetate (2 × 50 mL). The combined organics were washed with saturated brine (25 mL), dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 0 to 5% MeOH in DCM to afford the product (78 mg, 41.6 %). ^{1}H NMR (400 MHz, DMSO) δ 1.23 - 1.36 (m, 1H), 1.38 - 1.51 (m, 1H), 1.60 - 1.75 (m, 2H), 1.96 - 2.07 (m, 2H), 2.13 (s, 3H), 2.27 (s, 3H), 3.71 - 3.87 (m, 2H), 3.89 - 3.98 (m, 1H), 5.71 - 5.78 (m, 1H), 7.28 - 7.34 (m, 1H), 7.75 (d, 1H), 8.15 (s, 1H), 8.39 (s, 1H), 8.45 - 8.51 (m, 2H), 8.93 (s, 1H), 11.01 (s, 1H); m/z (ESI+) (M+H)+ = 461.48; HPLC tR= 1.75 min

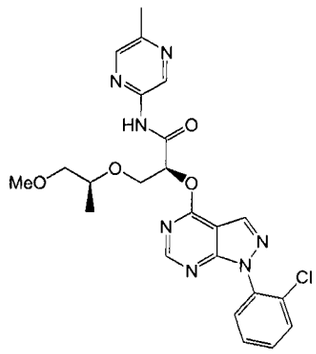
Example 150: (2S)-N-(5-chloropyridin-2-yl)-3-ethoxy-2-(1-(2-methylpyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide



Sodium hydride (21.49 mg, 0.54 mmol) was added to (S)-N-(5-chloropyridin-2-yl)-3-ethoxy-2-hydroxypropanamide (110 mg, 0.45 mmol) in anhydrous THF (5 mL) at 0°C under nitrogen. The resulting solution was stirred at 0°C for 10 minutes and then 4-chloro-1-(2-methylpyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidine (110 mg, 0.45 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour. The reaction mixture was neutralised with 1M citric acid and the majority of the THF removed in vacuo. The reaction mixture was diluted with water (20 mL) and ethyl acetate (50 mL). The organic layer was separated and the aqueous layer re-extracted with ethyl acetate (2 × 20 mL). The combined organics were washed with saturated brine (10 mL), dried

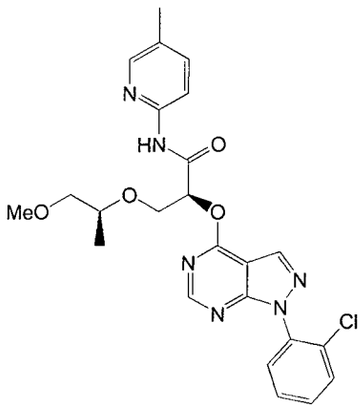
($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 0 to 5% MeOH in DCM to afford the product (24.0 mg, 11.8%). ^{1}H NMR (400 MHz, $CDCl_3$) δ1.23 (t, 3H), 2.45 (s, 3H), 3.59 - 3.72 (m, 2H), 4.05 - 4.16 (m, 2H), 6.06 (t, 1H), 7.31 - 7.38 (m, 1H), 7.66 - 7.71 (m, 1H), 7.73 - 7.78 (m, 1H), 8.21 - 8.27 (m, 2H), 8.42 (s, 1H), 8.57 (s, 1H), 8.64 - 8.69 (m, 1H), 8.89 (s, 1H). m/z (ESI+) (M+H)+ = 454.31; HPLC tR= 1.83 min

Example 151: (2S)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-((S)-1-methoxypropan-2-yloxy)-N-(5-methylpyrazin-2-yl)propanamide



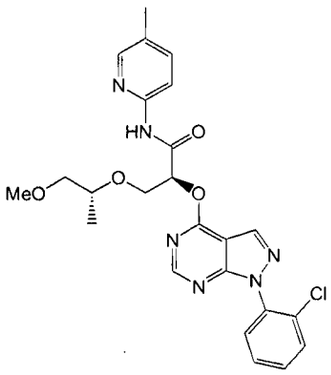
Sodium hydride (23.17 mg, 0.58 mmol) was added in one portion to a stirred solution of (S)-2-hydroxy-3-((S)-1-methoxypropan-2-yloxy)-N-(5-methylpyrazin-2-yl)propanamide (**Intermediate Y3**) (78 mg, 0.29 mmol) in anhydrous THF (5 mL) at 0°C. The resulting mixture was stirred for 10 minutes and then a solution of 4-chloro-1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate B1**) (115 mg, 0.43 mmol) in dry THF (2 mL) added dropwise over 1 minute and the reaction was allowed to warm up to ambient temperature and stirred for 1 hour. The reaction mixture was diluted with ethyl acetate (20 mL), and washed sequentially with water (10 mL) and saturated brine (5 mL). The organic layer was dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 0-100% ethyl acetate in isohexane to afford the product (115 mg, 80 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, 3H), 2.53 (s, 3H), 3.35 - 3.50 (m, 5H), 3.79 - 3.88 (m, 1H), 4.08 - 4.16 (m, 1H), 4.21 - 4.28 (m, 1H), 5.94 - 5.99 (m, 1H), 7.43 - 7.55 (m, 3H), 7.60 - 7.63 (m, 1H), 8.12 - 8.13 (m, 1H), 8.40 (s, 1H), 8.58 (s, 1H), 9.18 (s, 1H), 9.42 (d, 1H). m/z (ESI+) (M+H)+ = 498.36; HPLC t_R = 2.25 min.

Example 152: (2S)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-((S)-1-methoxypropan-2-yloxy)-N-(5-methylpyridin-2-yl)propanamide



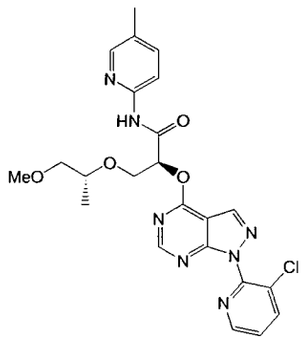
Sodium hydride (21.24 mg, 0.53 mmol) was added to (S)-2-hydroxy-3-((S)-1-methoxypropan-2-yloxy)-N-(5-methylpyridin-2-yl)propanamide (**Intermediate Y5**) (95 mg, 0.35 mmol) in anhydrous THF (5 mL) at 0°C under nitrogen. The resulting solution was stirred at 0°C for 10 minutes and then 4-chloro-1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate B1**) (122 mg, 0.46 mmol) in dry THF (2 mL) was added. The reaction was allowed to warm up to room temperature and stirred for 1 hour. The reaction mixture was diluted with ethyl acetate (20 mL), and washed sequentially with water (10 mL) and saturated brine (5 mL). The organic layer was dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 0-100% ethyl acetate in isohexane to afford the product (160 mg, 91 %). ^{1}H NMR (400 MHz, DMSO) δ 1.09 (d, 3H), 2.24 (s, 3H), 3.23 (s, 3H), 3.26 - 3.38 (m, 2H), 3.77 - 3.86 (m, 1H), 4.00 - 4.16 (m, 2H), 5.85 - 5.91 (m, 1H), 7.55 - 7.70 (m, 4H), 7.73 - 7.78 (m, 1H), 7.88 (d, 1H), 8.16 - 8.19 (m, 1H), 8.54 (s, 1H), 8.59 (s, 1H), 10.79 (s, 1H). m/z (ESI+) $(M+H)^+$ = 497.20; HPLC t_R = 2.36 min.

Example 153: (2S)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-((R)-1-methoxypropan-2-yloxy)-N-(5-methylpyridin-2-yl)propanamide



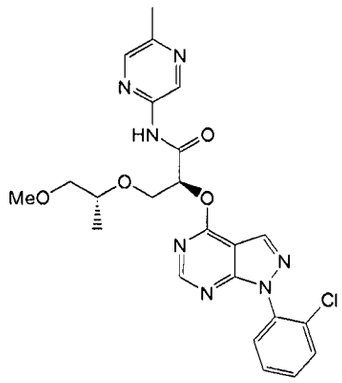
Trimethylaluminium (2M in hexane) (0.489 mL, 0.98 mmol) was added to 5-methylpyridin-2-amine (101 mg, 0.94 mmol) in toluene (3 mL) cooled to 0°C under nitrogen. The resulting solution was stirred at 0°C for 20 minutes. (2S)-Methyl 2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d] pyrimidin-4-yloxy)-3-((R)-1-methoxypropan-2-yloxy) propanoate (**Intermediate Y7**) (358 mg, 0.85 mmol) in toluene (5 mL) was added and the reaction was allowed to warm up to room temperature and then heated at reflux for 4 hours. The reaction mixture was neutralised with 1M citric acid and then diluted with sodium potassium tartrate solution (20%, aq) (20 ml) and ethyl acetate (20 mL) before stirring vigorously for 2 hours. The phases were separated and the organic layer was dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 0 to 100% ethyl acetate in isohexane to afford the product (167 mg, 39.5 %). ^{1}H NMR (400 MHz, DMSO) δ 1.08 (d, 3H), 2.24 (s, 3H), 3.21 (s, 3H), 3.22 - 3.38 (m, 2H), 3.75 - 3.85 (m, 1H), 3.98 - 4.15 (m, 2H), 5.85 - 5.93 (m, 1H), 7.55 - 7.70 (m, 4H), 7.73 - 7.78 (m, 1H), 7.88 (d, 1H), 8.15 - 8.19 (m, 1H), 8.53 (s, 1H), 8.59 (s, 1H), 10.82 (s, 1H). m/z (ESI+) $(M+H)^+$ = 497.37; HPLC t_R = 2.37 min.

Example 154: (2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-((R)-1-methoxypropan-2-yloxy)-N-(5-methylpyridin-2-yl)propanamide



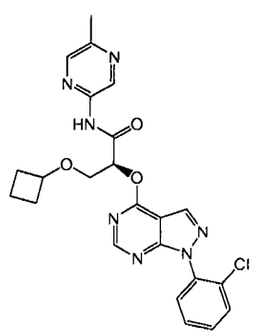
Trimethylaluminium (0.334 mL, 0.67 mmol) was added to 5-methylpyridin-2-amine (69.1 mg, 0.64 mmol) in toluene (8 mL) cooled to 0°C under nitrogen. The resulting solution was stirred at 0°C for 20 minutes. (2S)-Methyl 2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-((R)-1-methoxypropan-2-yloxy)propanoate (**Intermediate Y8**) (245 mg, 0.58 mmol) in toluene (2 mL) was added and the reaction was allowed to warm to room temperature and then heated at reflux for 24 hours. The reaction mixture was allowed to cool and neutralised with citric acid (1M, aq) and then diluted with water (50 mL) and ethyl acetate (50 mL). The organic layer was separated and the aqueous layer re-extracted with ethyl acetate (50 mL). The combined organics were dried ($MgSO_4$), filtered and evaporated. The crude product was purified by preparative HPLC (Phenomenex Gemini C18 110A (axia) column, 5μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 0.1% formic acid) and MeCN as eluents to afford the product (137 mg, 47.4 %). ^{1}H NMR (400 MHz, DMSO) δ 1.10 (d, 3H), 2.26 (s, 3H), 3.23 - 3.42 (m, 5H), 3.76 - 3.85 (m, 1H), 4.10 - 4.16 (m, 2H), 5.95 - 6.00 (m, 1H), 7.55 - 7.60 (m, 1H), 7.68 - 7.73 (m, 1H), 7.86 (d, 1H), 8.14 - 8.18 (m, 1H), 8.24 - 8.29 (m, 1H), 8.54 (s, 2H), 8.62 - 8.67 (m, 1H), 10.21 (s, 1H) m/z (ESI+) (M+H)+ = 498.16; HPLC t_R = 1.84 min.

Example 155: (2S)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-((R)-1-methoxypropan-2-yloxy)-N-(5-methylpyrazin-2-yl)propanamide



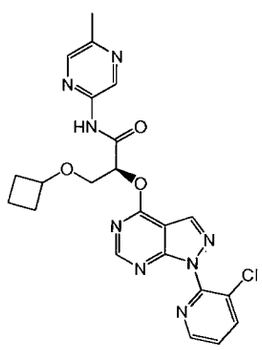
Sodium hydride (14.26 mg, 0.36 mmol) was added to (S)-2-hydroxy-3-((R)-1-methoxypropan-2-yloxy)-N-(5-methylpyrazin-2-yl)propanamide (**Intermediate Y12**) (64 mg, 0.24 mmol) in anhydrous THF (5 mL) at 0°C under nitrogen. The resulting mixture was stirred for 10 minutes at 0°C and 4-chloro-1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine (86 mg, 0.32 mmol) was added and the reaction was allowed to warm up to room temperature and stirred for 1 hour. The reaction mixture was diluted with ethyl acetate (20 mL), and washed sequentially with water (10 mL) and saturated brine (5 mL). The organic layer was dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 0-100% ethyl acetate in isohexane to afford the product (75 mg, 63.4 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ1.16 (d, 3H), 2.52 (s, 3H), 3.33 - 3.48 (m, 5H), 3.80 - 3.89 (m, 1H), 4.16 - 4.27 (m, 2H), 6.01 (t, 1H), 7.45 - 7.55 (m, 3H), 7.60 - 7.64 (m, 1H), 8.11 - 8.12 (m, 1H), 8.41 (s, 1H), 8.59 (s, 1H), 8.94 (s, 1H), 9.42 (d, 1H). m/z (ESI+) (M+H)+ = 498.36; HPLC t_R = 2.19 min.

Example 156: (2S)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-cyclobutoxy-N-(5-methylpyrazin-2-yl)propanamide



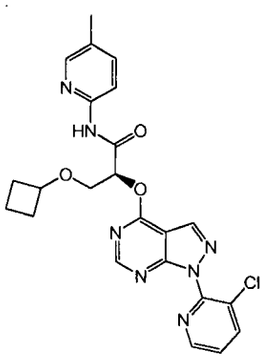
Sodium hydride (44.4 mg, 1.11 mmol) was added to (S)-3-cyclobutoxy-2-hydroxy-N-(5-methylpyrazin-2-yl)propanamide (**Intermediate R1**) (186 mg, 0.74 mmol) in anhydrous THF (5 mL) at 0°C under nitrogen. The resulting mixture was stirred for 10 minutes at 0°C and 4-chloro-1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate B1**) (255 mg, 0.96 mmol) was added and the reaction was allowed to warm up to room temperature and stirred for 30 minutes. The reaction mixture was diluted with ethyl acetate (20 mL), and washed sequentially with water (10 mL) and saturated brine (5 mL). The organic layer was dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 0-100% ethyl acetate in isohexane to afford the product (262 mg, 73.8%). ^{1}H NMR (400 MHz, DMSO) δ 1.39 - 1.52 (m, 1H), 1.56 - 1.67 (m, 1H), 1.77 - 1.91 (m, 2H), 2.13 - 2.24 (m, 2H), 2.44 (s, 3H), 3.88 - 4.02 (m, 2H), 4.06 - 4.15 (m, 1H), 5.89 - 5.94 (m, 1H), 7.56 - 7.70 (m, 3H), 7.73 - 7.78 (m, 1H), 8.31 - 8.33 (m, 1H), 8.54 (s, 1H), 8.63 (s, 1H), 9.10 (s, 1H), 11.17 (s, 1H). m/z (ESI+) (M+H)+ = 480.33; HPLC t_R = 2.45 min.

Example 157: (2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-cyclobutoxy-N-(5-methylpyrazin-2-yl)propanamide



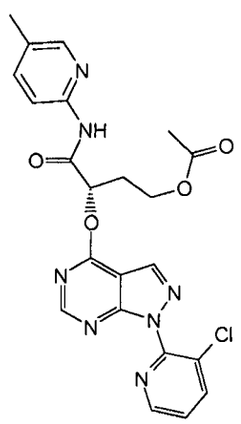
Prepared using an analogous procedure to that described for Example 156 using **Intermediate R1** and **Intermediate B15**. ^{1}H NMR (400 MHz, DMSO) δ 1.40 - 1.52 (m, 1H), 1.56 - 1.67 (m, 1H), 1.78 - 1.92 (m, 2H), 2.14 - 2.23 (m, 2H), 2.45 (s, 3H), 3.89 - 4.01 (m, 2H), 4.06 - 4.15 (m, 1H), 5.89 - 5.95 (m, 1H), 7.73 - 7.78 (m, 1H), 8.31 - 8.33 (m, 1H), 8.35 (d, 1H), 8.56 (s, 1H), 8.65 - 8.69 (m, 2H), 9.09 (s, 1H), 11.18 (s, 1H). m/z (ESI+) (M+H)+ = 481.30; HPLC t_R = 2.06 min.

Example 158: (2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-cyclobutoxy-N-(5-methylpyridin-2-yl)propanamide



Prepared using an analogous procedure to that described for Example 156 using **Intermediate R6** and **Intermediate B15**. ^{1}H NMR (400 MHz, DMSO) δ 1.41 - 1.52 (m, 1H), 1.56 - 1.67 (m, 1H), 1.78 - 1.91 (m, 2H), 2.13 - 2.23 (m, 2H), 2.24 (s, 3H), 3.86 - 3.99 (m, 2H), 4.06 - 4.15 (m, 1H), 5.86 - 5.92 (m, 1H), 7.56 - 7.61 (m, 1H), 7.73 - 7.77 (m, 1H), 7.84 - 7.90 (m, 1H), 8.16 - 8.19 (m, 1H), 8.32 - 8.35 (m, 1H), 8.56 (s, 1H), 8.65 - 8.69 (m, 2H), 10.86 (s, 1H). m/z (ESI+) $(M+H)^+$ = 480.35; HPLC t_R = 2.27 min.

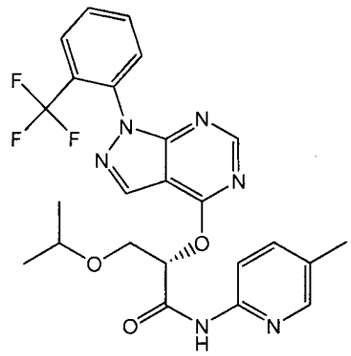
Example 159: [(3S)-3-[1-(3-chloropyridin-2-yl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-4-[(5-methylpyridin-2-yl)amino]-4-oxobutyl] acetate



Acetic anhydride (0.035 mL, 0.38 mmol) was added to (2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-4-hydroxy-N-(5-methylpyridin-2-yl)butanamide (**Example 143**) (150 mg, 0.34 mmol), N,N-Diisopropylethylamine (0.089 mL, 0.51 mmol) and 4-dimethylaminopyridine (4.17 mg, 0.03 mmol) in DCM (2 mL) at 0°C over a period of 5 minutes under nitrogen. The resulting solution was stirred at 0°C for 25 minutes. The volatiles were removed under reduced pressure and the crude product was purified by flash

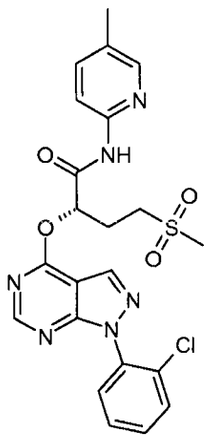
silica chromatography, eluting with 0 to 100% ethyl acetate in isohexane to afford the product (75 mg, 45.6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.95 (3H, s), 2.29 (3H, s), 2.54 (2H, q), 4.31 - 4.39 (2H, m), 6.00 (1H, t), 7.45 - 7.49 (1H, m), 7.53 (1H, d), 8.00 - 8.02 (1H, m), 8.10 - 8.14 (2H, m), 8.43 (1H, s), 8.61 (1H, q), 8.64 (1H, s), 8.80 (1H, s); m/z (ES+) (M+H)+ = 482; HPLC tR= 2.04 min.

Example 160: (2S)-3-isopropoxy-N-(5-methylpyridin-2-yl)-2-(1-(2-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide



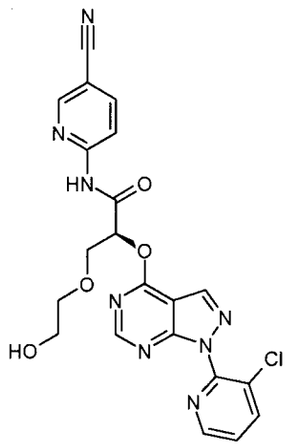
Sodium hydride (10.78 mg, 0.27 mmol) was added to (S)-2-hydroxy-3-isopropoxy-N-(5-methylpyridin-2-yl)propanamide (**Intermediate C7**) (53.5 mg, 0.22 mmol) in anhydrous THF (50 mL) at 0 °C under nitrogen. The resulting solution was stirred at 0°C for 10 minutes and then 4-phenoxy-1-(2-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate Z1**) (80 mg, 0.22 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour. The reaction mixture was neutralised with 1M citric acid and the majority of the THF removed in vacuo. The reaction mixture was diluted with water (20 mL) and ethyl acetate (50 mL). The organic layer was separated and the aqueous layer re-extracted with ethyl acetate (2 × 100 mL). The combined organics were washed with saturated brine (75 mL), dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 50 to 100% ethyl acetate in isohexane. The residue was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents to afford the product (60.0 mg, 53.4%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 - 1.20 (6H, m), 2.30 (3H, s), 3.69 - 3.75 (1H, m), 4.09 (2H, d), 6.01 (1H, t), 7.52 - 7.56 (2H, m), 7.69 (1H, t), 7.76 (1H, t), 7.91 (1H, d), 8.10 - 8.15 (2H, m), 8.42 (1H, s), 8.56 (1H, s), 8.72 (1H, s); m/z (ES+) (M+H)+ = 501; HPLC tR= 2.70 min.

Example 161: - (2S)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-methylpyridin-2-yl)-4-(methylsulfonyl)butanamide



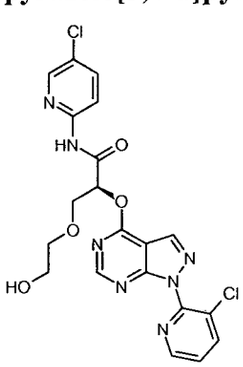
Trimethylaluminium (0.135 mL, 0.27 mmol) was added to 2-amino-5-methylpyridine (28.0 mg, 0.26 mmol) in toluene (5 mL) cooled to 0 °C under nitrogen. (2S)-methyl 2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-4-(methylsulfonyl)butanoate (**Intermediate AA1**) (100 mg, 0.24 mmol) was added and the reaction was heated to 100 °C for 3 hours in the microwave reactor and then allowed to cool. The reaction mixture was neutralised with citric acid (1M, aq) and then diluted with water (30 mL) and ethyl acetate (50 mL). The aqueous layer was washed with ethyl acetate. The combined organics were dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 30 to 50% ethyl acetate in isohexane to afford the product (90 mg, 76%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (3H, s), 2.71 - 2.77 (2H, m), 2.98 (3H, s), 3.32 - 3.38 (2H, m), 6.12 (1H, t), 7.45 - 7.56 (4H, m), 7.62 - 7.64 (1H, m), 8.09 - 8.11 (2H, m), 8.41 (1H, s), 8.61 (1H, s), 8.69 (1H, s); m/z (ES+) $(M+H)^+$ = 501; HPLC tR= 2.05 min.

Example 162: (2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-cyanopyridin-2-yl)-3-(2-hydroxyethoxy)propanamide



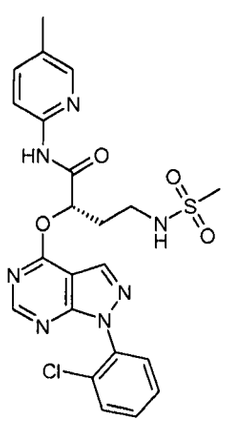
Tetrabutylammonium fluoride (1M in THF) (0.139 mL, 0.14 mmol) was added to (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-cyanopyridin-2-yl)propanamide (**Intermediate AB1**) (100 mg, 0.14 mmol) in THF (2 mL) under nitrogen. The resulting mixture was stirred at ambient temperature for 1 hour. The reaction mixture was quenched with saturated NH_4Cl (1 mL), diluted with DCM (10ml) and poured onto a phase separator. The organic layer was collected and evaporated. The residue was purified by flash silica chromatography, eluting with 0 to 100% ethyl acetate in isohexane to afford the product (38.0 mg, 56.8%). ^1H NMR (300 MHz, $CDCl_3$) δ 2.36 (1H, s), 3.70 - 3.86 (4H, m), 4.16 - 4.27 (2H, m), 6.07 (1H, t), 7.45 - 7.52 (1H, m), 7.93 - 8.05 (2H, m), 8.32 - 8.38 (1H, m), 8.46 (1H, s), 8.55 - 8.58 (1H, m), 8.60 - 8.65 (2H, m), 9.28 (1H, s). m/z (ES+) (M+H)+ = 481.31; HPLC tR= 1.63 min.

Example 163: (2S)-N-(5-chloropyridin-2-yl)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-(2-hydroxyethoxy)propanamide



Tetrabutylammonium fluoride (1M in THF) (0.790 mL, 0.79 mmol) was added to (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-N-(5-chloropyridin-2-yl)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide (**Intermediate AB4**) (576 mg, 0.79 mmol) in THF (2 mL) under nitrogen. The resulting mixture was stirred at ambient temperature for 1 hour. The reaction mixture was quenched with saturated NH_4Cl (1 mL), diluted with DCM (10ml) and poured onto a phase separator. The organic layer was collected and evaporated. The residue was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5µ silica, 50 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. The resulting product decomposed to an extent during evaporation and so was re-purified by flash silica chromatography, eluting with 0 to 10% MeOH in ethyl acetate to afford the product (82 mg, 21%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49 - 2.56 (1H, m), 3.69 - 3.85 (4H, m), 4.14 - 4.25 (2H, m), 6.08 (1H, t), 7.45 - 7.50 (1H, m), 7.67 - 7.72 (1H, m), 7.98 - 8.04 (1H, m), 8.15 - 8.28 (2H, m), 8.47 (1H, s), 8.58 - 8.65 (2H, m), 8.99 (1H, s); m/z (ES+) $(M+H)^+$ = 490.35; HPLC tR= 1.82 min.

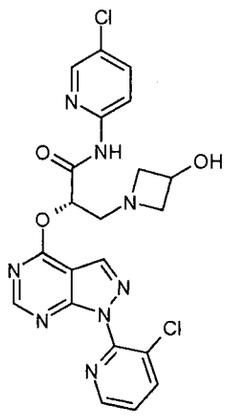
Example 164: (2S)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-methylpyridin-2-yl)-4-(methylsulfonamido)butanamide



Trimethylaluminium (2M in hexane) (0.164 mL, 0.33 mmol) was added to 5-methylpyridin-2-amine (33.8 mg, 0.31 mmol) in toluene (5 mL) cooled to 0°C under nitrogen. The resulting solution was stirred at 0°C for 20 minutes. (3S)-3-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-1-(methylsulfonyl)pyrrolidin-2-one (**Intermediate AC1**) (116 mg, 0.28 mmol) in toluene (1 mL) was added and the reaction was allowed to warm to room temperature and stirred for 1 hour. The reaction was then heated to reflux for 2.5 hours. The reaction mixture was allowed to cool and concentrated

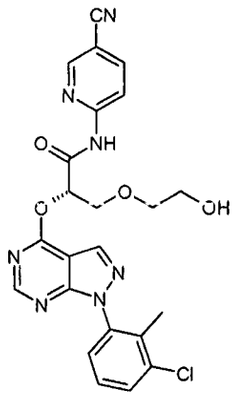
in vacuo. The residue was neutralised with citric acid and sodium potassium tartrate solution (sat.) and stirred vigorously for 45 mins. The mixture was separated and the aqueous re-extracted with ethyl acetate, the organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 50 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 0.1% formic acid) and MeCN as eluents to afford the product (52.0 mg, 35.4%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (3H, s), 2.37 - 2.55 (2H, m), 2.98 (3H, s), 3.35 - 3.55 (2H, m), 4.95 - 5.10 (1H, m), 6.04 (1H, t), 7.44 - 7.58 (4H, m), 7.60 - 7.65 (1H, m), 8.07 - 8.15 (2H, m), 8.44 (1H, s), 8.61 (1H, s), 8.69 (1H, s); m/z (ES+) (M+H)+ = 516.28; HPLC tR= 1.84 min.

Example 165: (2S)-N-(5-chloropyridin-2-yl)-2-[1-(3-chloropyridin-2-yl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-(3-hydroxyazetidin-1-yl)propanamide



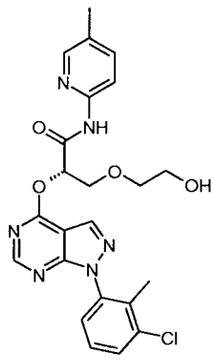
Tetrabutylammonium fluoride (1M in THF) (5.96 mL, 5.96 mmol) was added to (2S)-3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-N-(5-chloropyridin-2-yl)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide (**Intermediate AD1**) (3.67 g, 5.96 mmol) in THF (75 mL) under nitrogen. The resulting mixture was stirred at ambient temperature for 20 hours, saturated ammonium chloride (50 mL) added, diluted with DCM (100 mL) and poured onto a phase separator. The organic layer was evaporated and the crude product was purified by flash silica chromatography, eluting with 0 to 10% MeOH in EtOAc to afford the product (1.7g, 57%). ^{1}H NMR (400 MHz, DMSO) δ 2.95 - 3.10 (3H, m), 3.10 - 3.15 (1H, m), 3.60 - 3.70 (2H, m), 4.14 - 4.21 (1H, m), 5.26 (1H, d), 5.73 - 5.75 (1H, m), 7.74 (1H, dd), 7.88 (1H, dd), 8.01 - 8.07 (1H, m), 8.33 (1H, dd), 8.39 - 8.40 (1H, m), 8.55 (1H, s), 8.66 (1H, s), 8.68 (1H, dd), 11.13 (1H, s); m/z (ESI+) $(M+H)^+$ = 501; HPLC t_R = 1.27 min.

Example 166: (2S)-2-[1-(3-chloro-2-methylphenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-cyanopyridin-2-yl)-3-(2-hydroxyethoxy)propanamide



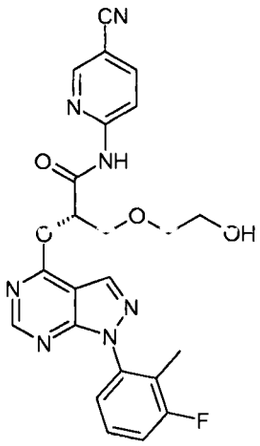
A solution of tetrabutylammonium fluoride (1M in THF) (1.557 mL, 1.56 mmol) was added dropwise to a stirred solution of (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(3-chloro-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-cyanopyridin-2-yl)propanamide (**Intermediate AE1**) (950 mg, 1.30 mmol) in THF (15 mL) over a period of 1 minute and the resulting solution was stirred at ambient temperature for 3 hours. Saturated ammonium chloride (20 mL) was added to the reaction mixture which was then diluted with EtOAc (25 mL) and washed sequentially with water (25 mL) and saturated brine (25 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated in vacuo. The crude product was purified by flash silica chromatography, elution gradient 60 to 100% EtOAc in isohexane and fractions were evaporated to dryness to afford the product as a white foam containing ~10-15% of the opposite enantiomer. Chiral HPLC followed by reverse phase HPLC (acetonitrile/water with 0.1% formic acid modifier gave (350mg, 54%) as a colourless amorphous foam. ^{1}H NMR (400 MHz, DMSO) δ 2.06 (3H, s), 3.51 - 3.57 (2H, m), 3.58 - 3.68 (2H, m), 4.03 - 4.07 (1H, m), 4.11 - 4.15 (1H, m), 4.55 - 4.67 (1H, m), 5.91 - 5.98 (1H, m), 7.42 - 7.47 (2H, m), 7.64 - 7.69 (1H, m), 8.13 (1H, dd), 8.25 (1H, dd), 8.54 (1H, s), 8.62 (1H, s), 8.82 (1H, dd), 11.53 (1H, s); m/z (ESI-) (M-H)- = 492; HPLC t_R = 2.25 min.

Example 167: (2S)-2-[1-(3-chloro-2-methylphenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-(2-hydroxyethoxy)-N-(5-methylpyridin-2-yl)propanamide



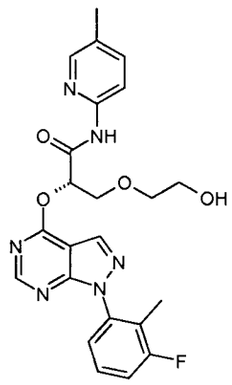
A solution of tetrabutylammonium fluoride (1M in THF) (0.832 mL, 0.83 mmol) was added dropwise to a stirred solution of (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(3-chloro-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-methylpyridin-2-yl)propanamide (**Intermediate AE3**)(500 mg, 0.69 mmol) in THF (15 mL) over a period of 1 minute and the resulting solution stirred at ambient temperature for 3 hours. Saturated ammonium chloride (20 mL) was added to the reaction mixture which was then diluted with EtOAc (25 mL) and washed sequentially with water (25 mL) and saturated brine (25 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated in vacuo. The crude product was purified by flash silica chromatography, elution gradient 60 to 100% EtOAc in isohexane. This was further purified by chiral HPLC to give the product (76mg, 52%). ^1H NMR (400 MHz, DMSO) δ 2.06 (3H, s), 2.24 (3H, s), 3.53 - 3.58 (2H, m), 3.58 - 3.68 (2H, m), 4.00 - 4.05 (1H, m), 4.08 - 4.13 (1H, m), 4.61 (1H, t), 5.93 - 6.01 (1H, m), 7.45 - 7.02 (2H, m), 7.57 - 7.60 (1H, m), 7.66 - 7.69 (1H, m), 7.88 - 7.95 (1H, m), 8.17 - 8.18 (1H, m), 8.54 (1H, s), 8.62 (1H, s), 10.86 (1H, s); m/z (ESI+) $(M+H)^+$ = 483; HPLC t_R = 2.14 min.

Example 168: (2S)-N-(5-cyanopyridin-2-yl)-2-[1-(3-fluoro-2-methylphenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-(2-hydroxyethoxy)propanamide



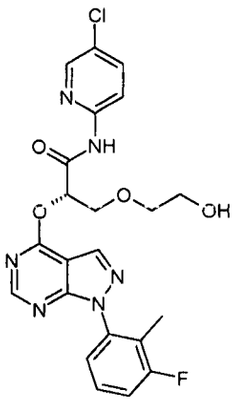
A solution of tetrabutylammonium fluoride (1M in THF, 1.504 mL, 1.50 mmol) was added dropwise to a stirred solution of (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-N-(5-cyanopyridin-2-yl)-2-(1-(3-fluoro-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide (**Intermediate AF1**) (520 mg, 0.73 mmol) in THF (15 mL) over a period of 1 minuteand the resulting solution stirred at ambient temperature for 3 hours. Saturated ammonium chloride (20 mL) was added to the reaction mixture which was then diluted with EtOAc (25 mL), and washed sequentially with water (25 mL) and saturated brine (25 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated in vacuo. The crude product was purified by flash silica chromatography, elution gradient 60 to 100% EtOAc in isohexane and then by chiral HPLC to afford the product (250mg, 72%). ^{1}H NMR (400 MHz, DMSO) δ 1.99 (3H, d), 3.50 - 3.55 (2H, m), 3.58 - 3.67 (2H, m), 4.03 - 4.07 (1H, m), 4.11 - 4.15 (1H, m), 4.52 - 4.65 (1H, m), 5.92 - 5.98 (1H, m), 7.31 - 7.34 (1H, m), 7.40 - 7.50 (2H, m), 8.12 - 8.14 (1H, m), 8.22 - 8.25 (1H, m), 8.55 (1H, s), 8.62 (1H, s), 8.81 - 8.85 (1H, m), 11.5 (1H, s); m/z (ESI-) (M-H)- = 476; HPLC t_R = 2.10 min.

Example 169: (2S)-2-[1-(3-fluoro-2-methylphenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-(2-hydroxyethoxy)-N-(5-methylpyridin-2-yl)propanamide



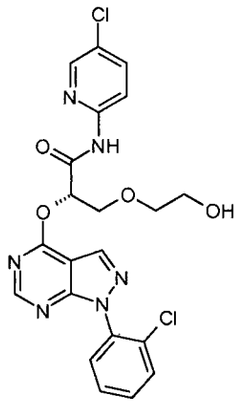
A solution of tetrabutylammonium fluoride (1M in THF) (1.504 mL, 1.50 mmol) was added dropwise to a stirred solution of (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(3-fluoro-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-methylpyridin-2-yl)propanamide (**Intermediate AF2**) (430 mg, 0.61 mmol) in THF (15 mL) over a period of 1 minute and the resulting solution stirred at ambient temperature for 3 hours. Saturated ammonium chloride (20 mL) was added to the reaction mixture which was then diluted with EtOAc (25 mL), and washed sequentially with water (25 mL) and saturated brine (25 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product which was purified by flash silica chromatography, elution gradient 60 to 100% EtOAc in isohexane then by chiral HPLC to afford the product (160mg, 56%). 1H NMR (400 MHz, DMSO) δ 1.99 (3H, d), 2.24 (3H, s), 3.50 - 3.56 (2H, m), 3.58 - 3.68 (2H, m), 4.00 - 4.05 (1H, m), 4.08 - 4.13 (1H, m), 4.61 (1H, t), 5.91 - 5.96 (1H, m), 7.30 - 7.33 (1H, m), 7.40 - 7.51 (2H, m), 7.57 - 7.60 (1H, m), 7.85 - 7.88 (1H, m), 8.17 - 8.18 (1H, m), 8.54 (1H, s), 8.61 (1H, s), 10.85 (1H, s); m/z (ESI+) $(M+H)^+ = 467$; HPLC $t_R = 1.98$ min.

Example 170: (2S)-N-(5-chloropyridin-2-yl)-2-[1-(3-fluoro-2-methylphenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-(2-hydroxyethoxy)propanamide



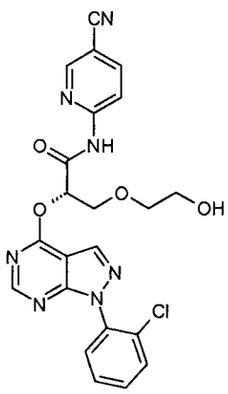
A solution of tetrabutylammonium fluoride (1M in THF) (1.504 mL, 1.50 mmol) was added dropwise to a stirred solution of (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-N-(5-chloropyridin-2-yl)-2-(1-(3-fluoro-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide (**Intermediate AF3**) (600 mg, 0.83 mmol) in THF (15 mL) over a period of 1 minute and the resulting solution stirred at ambient temperature for 3 hours. Saturated ammonium chloride (20 mL) was added to the reaction mixture which was then diluted with EtOAc (25 mL), and washed sequentially with water (25 mL) and saturated brine (25 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated in vacuo. The crude product was purified by flash silica chromatography, elution gradient 60 to 100% EtOAc in isohexane then by chiral HPLC to afford the product (252mg, 62%). ^1H NMR (400 MHz, DMSO) δ 2.07 (3H, s), 3.53 - 3.62 (2H, m), 3.65 - 3.72 (2H, m), 4.06 - 4.22 (2H, m), 4.61 - 4.71 (1H, m), 5.96 - 6.05 (1H, m), 7.36 - 7.42 (1H, m), 7.44 - 7.55 (2H, m), 7.92 - 7.96 (1H, m), 8.08 (1H, d), 8.45 (1H, dd), 8.60 (1H, s), 8.71 (1H, s), 11.18 (1H, s); m/z (ESI-) (M-H)- = 485; HPLC t_R = 2.29 min.

Example 171: (2S)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-chloropyridin-2-yl)-3-(2-hydroxyethoxy)propanamide



Prepared from (2S)-3-[2-(tert-butyl-dimethylsilyl)oxyethoxy]-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-chloropyridin-2-yl)propanamide (Intermediate AG1) (980mg, 1.35mmol) according to the method for Example 167. ^{1}H NMR (400 MHz, DMSO) δ 3.54 - 3.64 (2H, m), 3.65 - 3.78 (2H, m), 4.05 - 4.24 (2H, m), 4.62 - 4.71 (1H, m), 5.96 - 6.04 (1H, m), 7.60 - 7.78 (3H, m), 7.76 (1H, dd), 7.88 (1H, dd), 8.06 (1H, d), 8.45 (1H, dd), 8.60 (1H, s), 8.68 (1H, s), 11.18 (1H, s); m/z (ESI-) (M-H)- = 487; HPLC t_R = 2.17 min.

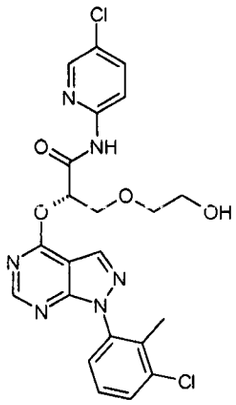
Example 172: (2S)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-cyanopyridin-2-yl)-3-(2-hydroxyethoxy)propanamide



Prepared according to the method for **Example 171** from (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-cyanopyridin-2-yl)propanamide (**Intermediate AG3**). ^{1}H NMR (400 MHz, DMSO) δ 3.52 - 3.61 (2H, m), 3.56 - 3.64 (2H, m), 3.65 - 3.76 (2H, m), 4.04 - 4.25 (2H, m), 4.61 - 4.75 (1H, m), 5.96 - 6.04 (1H, m), 7.57 - 7.78 (3H, m), 7.80 - 7.84 (1H, dd), 8.18

(1H, d), 8.30 (1H, dd), 8.60 (1H, s), 8.70 (1H, s), 8.87 - 8.91 (1H, m), 11.53 (1H, s); m/z (ESI-) (M-H)- = 478; HPLC t_R = 1.99 min.

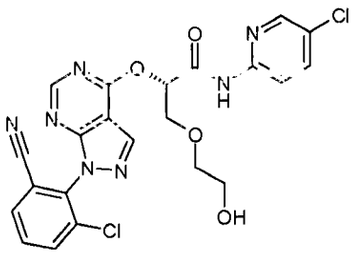
Example 173: (2S)-2-[1-(3-chloro-2-methylphenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-chloropyridin-2-yl)-3-(2-hydroxyethoxy)propanamide



Prepared according to the method for **Example 166** from (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(3-chloro-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-chloropyridin-2-yl)propanamide (**Intermediate AE4**).

1H NMR (400 MHz, $CDCl_3$) δ 2.09 (3H, s), 3.67 - 3.74 (4H, m), 4.08 - 4.18 (2H, m), 6.02 (1H, t), 7.22 - 7.29 (2H, m), 7.47 - 7.49 (1H, m), 7.63 (1H, dd), 8.12 - 8.16 (1H, m), 8.14 - 8.17 (1H, m), 8.34 (1H, s), 8.51 (1H, s), 8.95 (1H, s) (OH signal not observed); m/z (ESI+) $(M+H)^+$ = 503; HPLC t_R = 2.49 min.

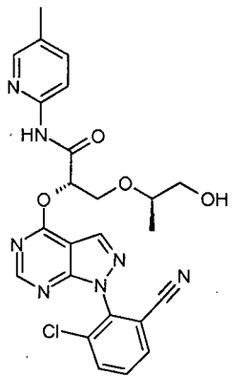
Example 174: (2S)-2-(1-(2-chloro-6-cyanophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-chloropyridin-2-yl)-3-(2-hydroxyethoxy)propanamide



Tetrabutylammonium fluoride (1M in THF) (0.611 mL, 0.61 mmol) was added to (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(2-chloro-6-cyanophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-chloropyridin-2-yl)propanamide (**Intermediate AH1**) in THF (5 mL) under nitrogen. The resulting mixture was stirred at ambient temperature for 1 hour. The reaction mixture was quenched with saturated NH_4Cl (2 mL), diluted with DCM (25 mL) and poured through a phase separator. The organic phase was reduced to give a

gum. This was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 50 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 0.1% formic acid) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford (2S)-2-(1-(2-chloro-6-cyanophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-chloropyridin-2-yl)-3-(2-hydroxyethoxy)propanamide (194 mg, 61.7 %, 84% ee). ^{1}H NMR (400 MHz, DMSO) δ 3.53 (2H, m), 3.70 - 3.58 (2H, m), 4.05 (1H, m), 4.13 (1H, m), 4.62 (1H, t), 5.95 (1H, s), 7.92 - 7.86 (2H, m), 8.06 - 8.00 (1H, m), 8.17 (1H, m), 8.19 (1H, m), 8.42 - 8.38 (1H, m), 8.61 (1H, s), 8.79 (1H, d), 11.21 (1H, s). m/z (ES+) $(M+H)^+$ = 514; HPLC t_R = 2.10 min.

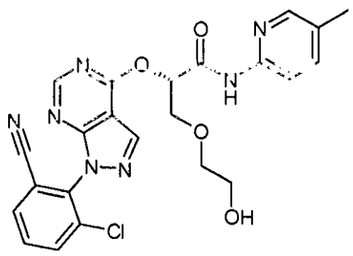
Example 175: (2S)-2-(1-(2-chloro-6-cyanophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-((R)-1-hydroxypropan-2-yloxy)-N-(5-methylpyridin-2-yl)propanamide



1M tetrabutylammonium fluoride in THF (0.503 mL, 0.50 mmol) was added to (2S)-2-(1-(2-chloro-6-cyanophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-methylpyridin-2-yl)-3-((R)-1-(triisopropylsilyloxy)propan-2-yloxy)propanamide (**Intermediate AH8**) (334 mg, 0.50 mmol) in THF (10 mL) under nitrogen. The resulting mixture was stirred at ambient temperature for 1 hour. The reaction mixture was quenched with saturated NH_4Cl (2 mL), diluted with DCM (25 mL) and poured onto a phase separator. The organic phase was reduced and the residue was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 50 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 0.1% formic acid) and MeCN as eluents to afford the product (129 mg, 50.5 %). ^{1}H NMR (400 MHz, $CDCl_3$) d 1.21 - 1.14 (3H, m), 2.30 (3H, s), 3.62 (2H, m), 3.78 (1H, m), 4.14 - 4.03 (1H, m), 4.28 (1H, dd), 6.10 - 6.03 (1H, m), 7.54 (1H, dd), 7.62 (1H, t), 7.79 (1H, m), 7.86 (1H, m), 8.07 (2H, d), 8.51 (1H, d), 8.62 (1H, d),

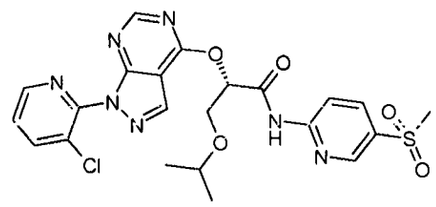
9.28 - 9.18 (1H, m), OH not observed. m/z (ES+) $(M+H)^+$ = 508; HPLC t_R = 1.92 min. ee90%

Example 176: (2S)-2-(1-(2-chloro-6-cyanophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-(2-hydroxyethoxy)-N-(5-methylpyridin-2-yl)propanamide



Tetrabutylammonium fluoride (1M in THF) (0.203 mL, 0.20 mmol) was added to (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(2-chloro-6-cyanophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-methylpyridin-2-yl)propanamide (**Intermediate AH9**) (149 mg, 0.20 mmol) in THF (5 mL) under nitrogen. The resulting mixture was stirred at ambient temperature for 1 hour. The reaction mixture was quenched with saturated NH_4Cl (2 mL), diluted with DCM (25 mL) and poured onto a phase separator. The organic phase was reduced to give a gum. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 50 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 0.1% formic acid) and MeCN as eluents to afford the product (45.0 mg, 44.8 %, 58% ee). ^{1}H NMR (400 MHz, $CDCl_3$) d 2.23 (3H, s), 3.77 - 3.62 (4H, m), 4.20 - 4.04 (2H, m), 6.01 (1H, m), 7.51 - 7.46 (1H, m), 7.55 (1H, t), 7.72 (1H, dd), 7.84 - 7.76 (1H, m), 8.03 (2H, d), 8.46 (1H, d), 8.55 (1H, d), 9.19 - 8.96 (1H, m) OH not observed. m/z (ES+) $(M+H)^+$ = 494; HPLC t_R = 1.82 min.

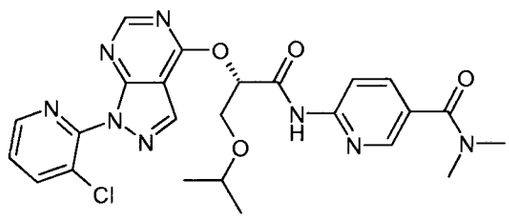
Example 177: (2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-isopropoxy-N-(5-(methylsulfonyl)pyridin-2-yl)propanamide



A solution of 3-chloroperoxybenzoic acid (284 mg, 1.27 mmol) in DCM (10 mL) was added dropwise to a stirred solution of (2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-isopropoxy-N-(5-(methylthio)pyridin-2-yl)propanamide

(**Intermediate AI3**) (317 mg, 0.63 mmol), in DCM (10 mL) at 22°C, over a period of 10 minutes. The resulting solution was stirred at 22 °C for 2 hours. The reaction mixture was diluted with DCM (20 mL), washed with 2M NaOH (20 mL), brine (20 mL), dried ($MgSO_4$) and reduced *in vacuo*. The residue was purified by flash silica chromatography, elution gradient 50 to 100% EtOAc in isohexane to afford the product (273 mg, 81 %) ^1H NMR (400 MHz, DMSO) d 1.14 - 1.10 (6H, m), 3.27 (3H, s), 3.77 (1H, m), 4.10 - 3.99 (2H, m), 5.92 (1H, m), 7.75 (1H, dd), 8.20 (1H, d), 8.28 (1H, dd), 8.34 (1H, dd), 8.56 (1H, s), 8.69 - 8.65 (2H, m), 8.85 - 8.82 (1H, s), 11.56 (1H, s). m/z (ES+) $(M+H)^+ = 532$; HPLC $t_R = 2.03$ min. ee 98%

Example 178: 6-((2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-isopropoxypropanamido)-N,N-dimethylnicotinamide

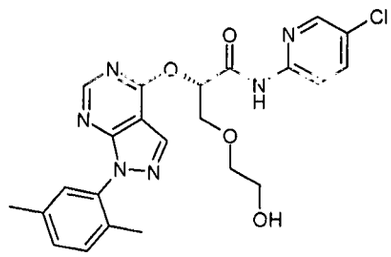


Trimethylaluminium (2M in hexane, 0.376 mL, 0.75 mmol) was added to 6-amino-N,N-dimethylnicotinamide (CAS no. 827588-33-0) (108 mg, 0.65 mmol) in toluene (20 mL) at 0°C under Nitrogen. The resulting solution was stirred at 0°C for 20 minutes. (2S)-Methyl 2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-isopropoxypropanoate (**Intermediate L1**) (256 mg, 0.65 mmol) in toluene (6 mL) was added dropwise at this temperature. After the addition was complete, the solution was allowed to warm to ambient temperature and was then heated to reflux for 16 hours. Allowed to cool to ambient temperature. The reaction mixture was concentrated and diluted with EtOAc (100 mL) and washed with saturated brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. 2M Trimethylaluminium in hexane (0.376 mL, 0.75 mmol) was added to 6-amino-N,N-dimethylnicotinamide (108 mg, 0.65 mmol) in toluene (20 mL) at 0°C under Nitrogen. The resulting solution was stirred at 0°C for 20 minutes. The residue from the above evaporation was dissolved in toluene (6 mL) and added dropwise. After the addition was complete, the solution was allowed to warm to ambient temperature and was then heated to reflux for 16 hours. Allowed to cool to ambient temperature. The reaction mixture was concentrated and diluted with EtOAc (100

mL) and washed with saturated brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product.

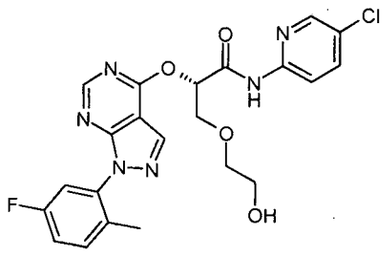
This was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5µ silica, 50 mm diameter, 150 mm length) column, using decreasingly polar mixtures of water (containing 0.5% NH3) and MeCN as eluents to afford the product (30.0 mg, 8.75 %). ^{1}H NMR (400 MHz, DMSO) δ 1.13 (6H, dd), 2.50, 2.97 (6H, s), 3.78 (1H, m), 4.04 (2H, m), 5.93 (1H, s), 7.76 (1H, dd), 7.86 (1H, dd), 8.03 (1H, d), 8.34 (1H, dd), 8.43 (1H, m), 8.57 (1H, s), 8.64 – 8.70 (2H, m), 11.16 (1H, s). m/z (ES+) $(M+H)^+$ = 500; HPLC t_R = 2.41 min.

Example 179: (2S)-N-(5-chloropyridin-2-yl)-2-(1-(2,5-dimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-(2-hydroxyethoxy)propanamide



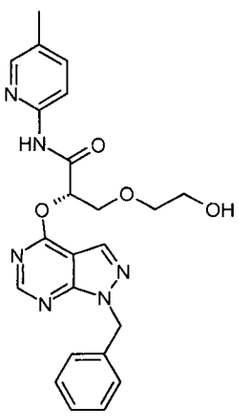
Tetrabutylammonium fluoride (1M in THF) (0.455 mL, 0.45 mmol) was added to (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-N-(5-chloropyridin-2-yl)-2-(1-(2,5-dimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide (**Intermediate AJ1**) (328 mg, 0.45 mmol) in THF (5 mL) under nitrogen. The resulting mixture was stirred at ambient temperature for 1 hour. The reaction mixture was quenched with saturated NH_4Cl (2 mL), diluted with DCM (25 mL) and poured onto a phase separator. The organic layer was loaded onto a silica column and purified by flash silica chromatography, elution gradient 50 to 100% EtOAc in isohexane. This was further purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5µ silica, 50 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 0.1% formic acid) and MeCN as eluents to afford the product (93 mg, 42.4 %). ^{1}H NMR (400 MHz, DMSO) δ 2.00 (3H, s), 2.33 (3H, s), 3.53 (2H, m), 3.57 - 3.68 (2H, m), 4.03 (1H, m), 4.11 (1H, m), 4.66 (1H, t), 5.92 (1H, m), 7.23 (1H, s), 7.28 (1H, d), 7.34 (1H, d), 7.90 (1H, dd), 8.02 (1H, d), 8.41 (1H, d), 8.52 (1H, s), 8.57 (1H, s), 11.23 (1H, s). m/z (ES+) $(M+H)^+$ = 481; HPLC t_R = 2.35 min.

Example 180: (2S)-N-(5-chloropyridin-2-yl)-2-(1-(5-fluoro-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-(2-hydroxyethoxy)propanamide



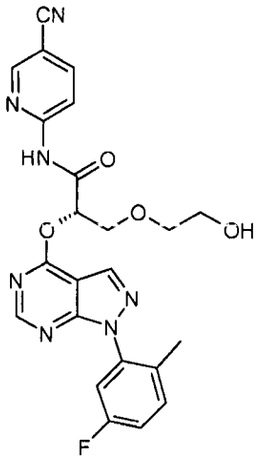
Tetrabutylammonium fluoride (1M in THF) (0.538 mL, 0.54 mmol) was added to (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-N-(5-chloropyridin-2-yl)-2-(1-(5-fluoro-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide (**Intermediate AK5**) (390 mg, 0.54 mmol) in THF (5 mL) under nitrogen. The resulting mixture was stirred at ambient temperature for 1 hour. The reaction mixture was quenched with saturated NH_4Cl (2 mL), diluted with DCM (25 mL) and poured onto a phase separator. The organic phase was evaporated to give the crude product. This was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 50 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 0.1% formic acid) and MeCN as eluents to afford the product (136 mg, 51.9 %, 75% ee). ^{1}H NMR (400 MHz, DMSO) δ 1.88 (3H, s), 3.35 (2H, m), 3.43 (2H, m), 3.84 (1H, dd), 3.92 (1H, dd), 4.47 (1H, t), 5.74 (1H, m), 7.19 (2H, m), 7.36 - 7.29 (1H, m), 7.71 (1H, dd), 7.83 (1H, d), 8.23 (1H, d), 8.37 (1H, s), 8.43 (1H, s), 11.05 (1H, s). m/z (ES+) $(M+H)^+$ = 487; HPLC t_R = 2.28 min.

Example 181: (S)-2-(1-benzyl-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-(2-hydroxyethoxy)-N-(5-methylpyridin-2-yl)propanamide



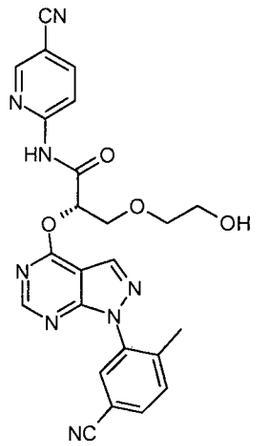
A solution of tetrabutylammonium fluoride (1M inTHF) (0.896 mL, 0.90 mmol) was added to a stirred solution of (S)-2-(1-benzyl-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-N-(5-methylpyridin-2-yl)propanamide (**Intermediate AL1**) (342 mg, 0.50 mmol) in tetrahydrofuran (20 mL). The resulting solution was stirred at ambient temperature for 30 minutes. The reaction mixture was quenched with saturated NH_4Cl (10 mL), and diluted with water (20 mL) and EtOAc (70 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (70 mL), The combined organics were dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 80 to 100% EtOAc in isohexane to afford the product (170 mg, 76 %). ^{1}H NMR (400 MHz, $CDCl_3$) 2.28 (3H, s), 2.91 (1H, s), 3.68 - 3.74 (4H, m), 4.09 - 4.20 (2H, m), 5.65 (2H, s), 6.05 (1H, t), 7.25 - 7.36 (5H, m), 7.50 - 7.53 (1H, m), 8.05 - 8.07 (2H, m), 8.21 (1H, s), 8.57 (1H, s), 8.88 (1H, s); m/z (ES+) $(M+H)^+$ = 449; HPLC t_R = 1.90 min.

Example 182: (2S)-N-(5-cyanopyridin-2-yl)-2-(1-(5-fluoro-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-(2-hydroxyethoxy)propanamide



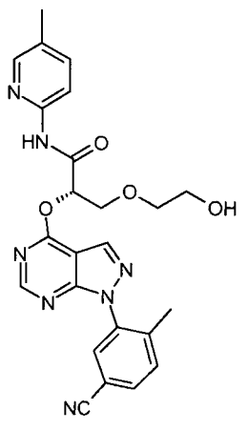
Prepared in an analogous fashion to **Example 181** from **Intermediate AK6**. 1H NMR (400 MHz, $CDCl_3$) 2.14 (3H, s), 2.42 (1H, t), 3.73 - 3.83 (4H, m), 4.17 - 4.25 (2H, m), 6.07 (1H, t), 7.13 - 7.18 (2H, m), 7.35 - 7.38 (1H, m), 7.96 - 7.98 (1H, m), 8.35 - 8.38 (1H, m), 8.40 (1H, s), 8.57 (1H, q), 8.58 (1H, s), 9.32 (1H, s); m/z (ES+) $(M+H)^+$ = 478; HPLC t_R = 2.10 min.

Example 183: (2S)-2-(1-(5-cyano-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-cyanopyridin-2-yl)-3-(2-hydroxyethoxy)propanamide



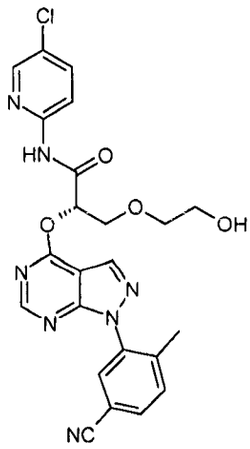
Prepared in an analogous fashion to **Example 181** using **Intermediate AM1**. ^{1}H NMR (400 MHz, $CDCl_3$) 2.30 (3H, s), 3.74 - 3.84 (4H, m), 4.17 - 4.25 (2H, m), 6.07 (1H, t), 7.53 (1H, d), 7.69 - 7.72 (1H, m), 7.74 (1H, s), 7.96 - 7.99 (1H, m), 8.35 - 8.37 (1H, m), 8.43 (1H, s), 8.57 (1H, q), 8.59 (1H, s), 9.33 (1H, s) (no OH observed); m/z (ES+) $(M+H)^+$ = 485; HPLC t_R = 1.90 min.

Example 184: (2S)-2-(1-(5-cyano-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-(2-hydroxyethoxy)-N-(5-methylpyridin-2-yl)propanamide



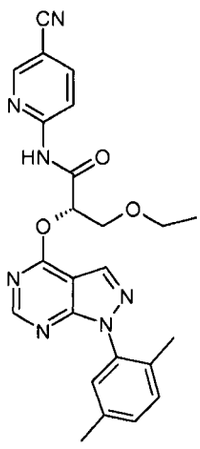
Prepared in an analogous fashion to **Example 181** using **Intermediate AM6**. ^{1}H NMR (400 MHz, $CDCl_3$) 2.29 (3H, s), 2.30 (3H, s), 3.74 - 3.81 (4H, m), 4.17 - 4.25 (2H, m), 6.09 (1H, t), 7.52 - 7.56 (2H, m), 7.69 - 7.75 (2H, m), 8.06 - 8.10 (2H, m), 8.44 (1H, s), 8.59 (1H, s), 8.95 (1H, s); m/z (ES+) $(M+H)^+$ = 474; HPLC t_R = 1.79 min.

Example 185: (2S)-N-(5-chloropyridin-2-yl)-2-(1-(5-cyano-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-(2-hydroxyethoxy)propanamide



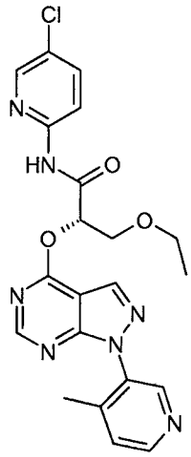
Prepared in an analogous fashion to **Example 181** using **Intermediate AM8**. ^{1}H NMR (400 MHz, $CDCl_3$) 2.30 (3H, s), 3.74 - 3.81 (4H, m), 4.18 - 4.22 (2H, m), 6.08 (1H, t), 7.53 (1H, d), 7.69 - 7.75 (3H, m), 8.19 - 8.21 (1H, m), 8.23 - 8.24 (1H, m), 8.43 (1H, s), 8.59 (1H, s), 9.06 (1H, s) (no OH observed); m/z (ES+) $(M+H)^+$ = 494; HPLC t_R = 2.09 min.

Example 186: (2S)-N-(5-cyanopyridin-2-yl)-2-(1-(2,5-dimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-ethoxypropanamide



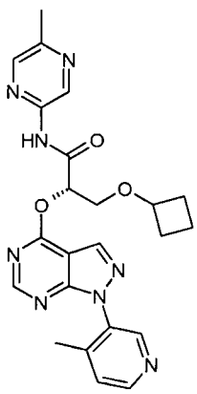
Prepared in an analogous fashion to **Intermediate 181** using **Intermediate H4** and **Intermediate AJ3**. ^{1}H NMR (400 MHz, $CDCl_3$) 1.24 (3H, t), 2.09 (3H, s), 2.38 (3H, s), 3.62 - 3.70 (2H, m), 4.07 - 4.15 (2H, m), 6.03 - 6.05 (1H, m), 7.19 - 7.29 (3H, m), 7.94 - 7.97 (1H, m), 8.39 (1H, s), 8.38 - 8.40 (1H, m), 8.56 (1H, s), 8.57 (1H, q), 9.03 (1H, s); m/z (ES+) (M-H)- = 456; HPLC t_R = 2.57 min.

Example 187: (2S)-N-(5-chloropyridin-2-yl)-3-ethoxy-2-(1-(4-methylpyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide



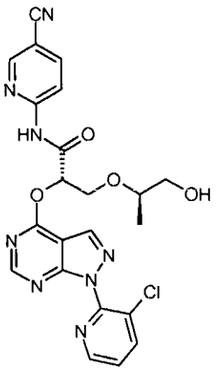
Prepared in an analogous fashion to **Intermediate 181** from **Intermediate X5** and **Intermediate H3**. ^{1}H NMR (400 MHz, $CDCl_3$) 1.21 - 1.26 (3H, m), 2.26 (3H, s), 3.61 - 3.69 (2H, m), 4.06 - 4.15 (2H, m), 6.06 (1H, t), 7.35 (1H, d), 7.67 - 7.70 (1H, m), 8.24 (2H, dd), 8.44 (1H, s), 8.58 (1H, s), 8.60 (1H, d), 8.65 (1H, s), 8.78 (1H, s); m/z (ES+) $(M+H)^+$ = 454; HPLC t_R = 2.07 min.

Example 188: (2S)-3-cyclobutoxy-N-(5-methylpyrazin-2-yl)-2-(1-(4-methylpyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide



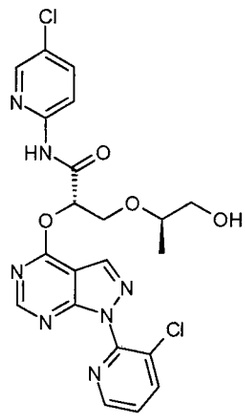
Prepared in an analogous fashion to **Intermediate 1** from **Intermediate X5** and **Intermediate R1**. ^{1}H NMR (400 MHz, $CDCl_3$) 1.48 - 1.55 (1H, m), 1.69 - 1.75 (1H, m), 1.91 - 2.00 (2H, m), 2.19 - 2.27 (5H, m), 2.54 (3H, s), 3.98 - 4.08 (3H, m), 6.05 (1H, t), 7.36 (1H, d), 8.12 - 8.13 (1H, m), 8.45 (1H, s), 8.58 (1H, s), 8.60 (1H, d), 8.65 (1H, s), 8.68 (1H, s), 9.45 (1H, d); m/z (ES+) $(M+H)^+$ = 461; HPLC t_R = 1.82 min.

Example 189: (2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-cyanopyridin-2-yl)-3-((R)-1-hydroxypropan-2-yloxy)propanamide



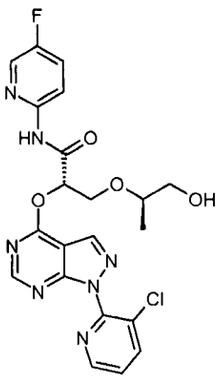
Tetrabutylammonium fluoride (1M in THF) (0.973 mL, 0.97 mmol) was added to (2S)-3-((R)-1-(tert-butyldimethylsilyloxy)propan-2-yloxy)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-cyanopyridin-2-yl)propanamide (**Intermediate AN3**) (395 mg, 0.65 mmol) in THF (10 mL) under nitrogen. The resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was quenched with saturated NH_4Cl (10 mL), extracted with Et_2O (3 × 15 mL), the combined organic layers were back washed with water (10 mL), dried ($MgSO_4$), and evaporated to afford crude product. The crude product was purified by preparative chiral-HPLC on a Merck 50mm 20µm Chiralpak column, eluting isocratically with 30% EtOH in isohexane (modified with Et_3N) as eluent to afford the product (95 mg, 29.6 %). ^1H NMR (400 MHz, $CDCl_3$) δ1.17 (d, 3H), 2.71 - 2.78 (m, 1H), 3.56 - 3.72 (m, 2H), 3.78 - 3.87 (m, 1H), 4.09 - 4.16 (m, 1H), 4.26 - 4.32 (m, 1H), 6.01 - 6.05 (m, 1H), 7.46 - 7.50 (m, 1H), 7.94 - 7.98 (m, 1H), 7.99 - 8.04 (m, 1H), 8.32 - 8.36 (m, 1H), 8.45 (s, 1H), 8.54 - 8.56 (m, 1H), 8.60 - 8.63 (m, 1H), 8.64 (s, 1H), 9.51 (s, 1H); m/z (ESI+) $(M+H)^+$ = 495.42; HPLC t_R = 1.75 min

Example 190: (2S)-N-(5-chloropyridin-2-yl)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-((R)-1-hydroxypropan-2-yloxy)propanamide



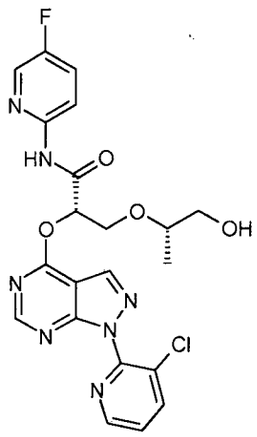
Tetrabutylammonium fluoride (1M in THF) (0.892 mL, 0.89 mmol) was added to (2S)-3-((R)-1-(tert-butyldimethylsilyloxy)propan-2-yloxy)-N-(5-chloropyridin-2-yl)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide (**Intermediate AN4**) (460 mg, 0.74 mmol) in THF (5 mL) under nitrogen. The resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was quenched with saturated NH4Cl (10 mL), extracted with EtOAc (3 × 15 mL), the combined organic layers were back washed with water (10 mL), dried ($MgSO_4$), and evaporated to afford crude product. The crude product was purified by flash silica chromatography, eluting with 0 to 90% EtOAc in isohexane to afford the product (256 mg, 68.3 %). ^{1}H NMR (400 MHz, DMSO) δ1.07 (d, 3H), 3.26 - 3.37 (m, 1H), 3.38 - 3.47 (m, 1H), 3.61 - 3.71 (m, 1H), 4.07 - 4.18 (m, 2H), 4.57 (t, 1H), 5.87 - 5.93 (m, 1H), 7.74 - 7.79 (m, 1H), 7.88 - 7.93 (m, 1H), 8.00 - 8.06 (m, 1H), 8.32 - 8.37 (m, 1H), 8.41 (d, 1H), 8.57 (s, 1H), 8.66 (s, 1H), 8.67 - 8.70 (m, 1H), 11.15 (s, 1H)m/z (ESI+) $(M+H)^+$ = 504.37; HPLC t_R = 1.96 min

Example 191: (2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-fluoropyridin-2-yl)-3-((R)-1-hydroxypropan-2-yloxy)propanamide



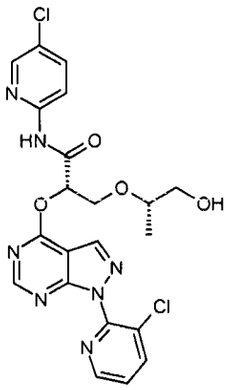
Tetrabutylammonium fluoride (1M in THF) (604 µl, 0.60 mmol) was added to (2S)-3-((R)-1-(tert-butyldimethylsilyloxy)propan-2-yloxy)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-fluoropyridin-2-yl)propanamide (**Intermediate AN5**) (303 mg, 0.50 mmol) in THF (5 mL) under nitrogen. The resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was quenched with saturated NH_4Cl (10 mL), extracted with Et_2O (3 × 15 mL), the combined organic layers were back washed with water (10 mL), dried ($MgSO_4$) and evaporated to afford crude product. The crude product was purified by preparative chiral-HPLC on a Merck 50mm 20µm Chiralpak AS column, eluting isocratically with 30% EtOH in isohexane (modified with Et_3N) as eluent to afford the product (112 mg, 45.6 %). ^1H NMR (400 MHz, $CDCl_3$) δ1.17 (d, 3H), 2.99 - 3.05 (m, 1H), 3.54 - 3.61 (m, 1H), 3.62 - 3.70 (m, 1H), 3.75 - 3.84 (m, 1H), 4.07 - 4.13 (m, 1H), 4.25 - 4.31 (m, 1H), 6.04 - 6.09 (m, 1H), 7.43 - 7.50 (m, 2H), 7.99 - 8.03 (m, 1H), 8.13 (d, 1H), 8.18 - 8.23 (m, 1H), 8.45 (s, 1H), 8.61 - 8.63 (m, 1H), 8.64 (s, 1H), 9.17 (s, 1H); m/z (ESI+) $(M+H)^+$ = 488.42; HPLC t_R = 1.74 min

Example 192: (2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-fluoropyridin-2-yl)-3-((S)-1-hydroxypropan-2-yloxy)propanamide



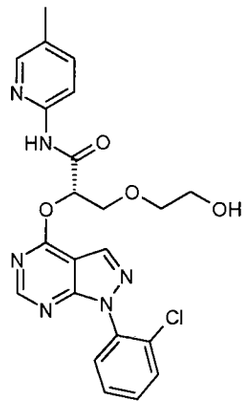
HCl (4M in Dioxane) (0.530 mL, 2.12 mmol) was added to (2S)-3-((S)-1-(tert-butyldimethylsilyloxy)propan-2-yloxy)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-fluoropyridin-2-yl)propanamide (**Intermediate AO3**) (638 mg, 1.06 mmol) in THF (5 mL) at room temperature. The resulting solution was stirred for 20 minutes. The reaction mixture was evaporated and the residue partitioned between EtOAc (25 mL) and sat $NaHCO_3$ (10 mL). The organic layer was dried ($MgSO_4$) and evaporated. The crude product was purified by preparative chiral-HPLC on a Merck 50mm 20μm Chiralpak AS column, eluting isocratically with 30% EtOH in isohexane (modified with Et3N) as eluent to afford the product (397 mg, 77 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ1.16 (d, 3H), 2.73 (s, 1H), 3.51 - 3.68 (m, 2H), 3.69 - 3.78 (m, 1H), 4.12 - 4.28 (m, 2H), 6.06 (t, 1H), 7.42 - 7.50 (m, 2H), 7.99 - 8.03 (m, 1H), 8.13 (d, 1H), 8.21 - 8.26 (m, 1H), 8.47 (s, 1H), 8.60 - 8.65 (m, 2H), 9.09 (s, 1H); m/z (ESI+) $(M+H)^+$ = 488.42; HPLC t_R = 1.75 min

Example 193: (2S)-N-(5-chloropyridin-2-yl)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-((S)-1-hydroxypropan-2-yloxy)propanamide



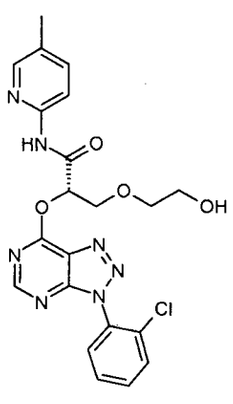
HCl (4M in Dioxane) (0.606 mL, 2.42 mmol) was added to (2S)-3-((S)-1-(tert-butyldimethylsilyloxy)propan-2-yloxy)-N-(5-chloropyridin-2-yl)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide (**Intermediate AO4**) (300 mg, 0.48 mmol) in THF (5 mL) and water (0.5 mL) at room temperature. The resulting solution was stirred at room temperature for 10 minutes. The reaction mixture was evaporated and the residue partitioned between EtOAc (25 mL) and sat $NaHCO_3$ (10 mL). The organic layer was dried ($MgSO_4$) and evaporated. The crude product was purified by preparative chiral-HPLC on a Merck 50mm 20µm Chiralpak AS column, eluting isocratically with 30% EtOH in isohexane (modified with Et3N) as eluent. The fractions containing the desired compound were evaporated to dryness to afford the product (173 mg, 70.7 %). ^1H NMR (400 MHz, $CDCl_3$) δ 1.17 (d, 3H), 2.64 (s, 1H), 3.51 - 3.67 (m, 2H), 3.69 - 3.79 (m, 1H), 4.11 - 4.28 (m, 2H), 6.05 (t, 1H), 7.45 - 7.50 (m, 1H), 7.66 - 7.71 (m, 1H), 7.99 - 8.04 (m, 1H), 8.18 - 8.25 (m, 2H), 8.47 (s, 1H), 8.60 - 8.65 (m, 2H), 9.10 (s, 1H)
m/z (ESI+) $(M+H)^+$ = 504.40; HPLC t_R = 1.96 min

Example 194: (2S)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-(2-hydroxyethoxy)-N-(5-methylpyridin-2-yl)propanamide



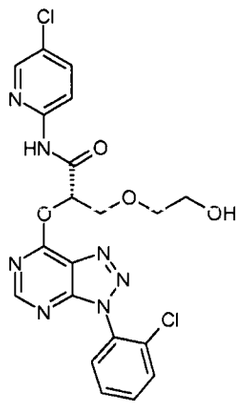
Tetrabutylammonium fluoride (1M in THF) (0.271 mL, 0.27 mmol) was added to (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-methylpyridin-2-yl)propanamide (**Intermediate AG4**) (96 mg, 0.14 mmol) in THF (5 mL) under nitrogen. The resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was quenched with saturated NH_4Cl (10 mL), extracted with Et_2O (3 x 15 mL), the combined organic layers were back washed with water (10 mL), dried ($MgSO_4$), and evaporated to afford crude product. The crude product was purified by flash silica chromatography, eluting with 0 to 10% MeOH in DCM to afford the product (50.0 mg, 79 %). ^1H NMR (400 MHz, $CDCl_3$) δ2.28 (s, 3H), 3.32 (s, 1H), 3.70 - 3.81 (m, 4H), 4.13 - 4.26 (m, 2H), 6.08 (t, 1H), 7.43 - 7.55 (m, 4H), 7.59 - 7.63 (m, 1H), 8.05 - 8.10 (m, 2H), 8.44 (s, 1H), 8.59 (s, 1H), 9.11 (s, 1H); m/z (ESI+) $(M+H)^+$ = 469.45; HPLC t_R = 1.86 min

Example 195: (2S)-2-(3-(2-chlorophenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy)-3-(2-hydroxyethoxy)-N-(5-methylpyridin-2-yl)propanamide



Hydrochloric acid (10%, 2 mL) was added to (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(3-(2-chlorophenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy)-N-(5-methylpyridin-2-yl)propanamide (**Intermediate AP3**) (335 mg, 0.47 mmol) in methanol (30.0 mL) at 0 °C. The resulting solution was stirred at 0 °C for 10 minutes and allowed to warm to room temperature and stirred for 1 hour. The reaction mixture was quenched with saturated NH_4Cl (25 mL) and most of the MeOH was removed by evaporation. The aqueous residue was extracted with EtOAc (3 x 25 mL), the organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 50 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 0.1% formic acid) and MeCN as eluents to afford the product (67.0 mg, 30.1 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ2.31 (s, 3H), 3.73 - 3.85 (m, 4H), 4.20 - 4.35 (m, 2H), 6.06 (t, 1H), 7.49 - 7.63 (m, 4H), 7.68 (d, 1H), 8.05 (s, 1H), 8.09 - 8.22 (m, 2H), 8.68 (s, 1H), OH not observed; m/z (ESI+) $(M+H)^+$ = 470.41; HPLC t_R = 1.80 min

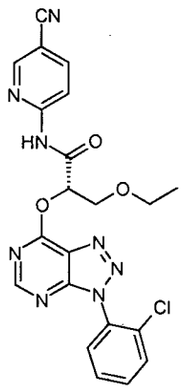
Example 196: (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(3-(2-chlorophenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy)-N-(5-methylpyridin-2-yl)propanamide



Hydrochloric acid (10%, 1 mL) was added dropwise to (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(3-(2-chlorophenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy)-N-(5-chloropyridin-2-yl)propanamide (**Intermediate AP4**) (180 mg, 0.25 mmol) in methanol (20.00 mL) at room temperature. The resulting solution was stirred for 4 hours. Most of the methanol was evaporated and the remaining aq. soln was diluted with saturated NH_4Cl and extracted with EtOAc (2 x 30 mL). The organic layers were combined, dried ($MgSO_4$) and evaporated to give crude product. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 50 mm

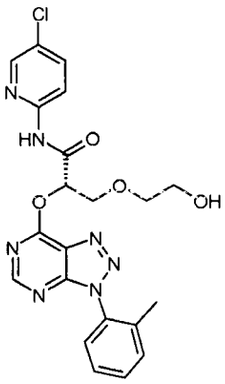
diameter, 150 mm length), using decreasingly polar mixtures of water (containing 0.1% formic acid) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford (2S)-2-(3-(2-chlorophenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy)-N-(5-chloropyridin-2-yl)-3-(2-hydroxyethoxy)propanamide (38.0 mg, 31.4 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ3.72 - 3.83 (m, 4H), 4.19 - 4.32 (m, 2H), 6.15 (t, 1H), 7.50 - 7.63 (m, 3H), 7.66 - 7.72 (m, 2H), 8.15 - 8.27 (m, 2H), 8.72 (s, 1H), 9.16 (s, 1H) OH not observed; m/z (ESI+) $(M+H)^+$ = 490.16; HPLC t_R = 2.15 min

Example 197: (2S)-2-(3-(2-chlorophenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy)-N-(5-cyanopyridin-2-yl)-3-ethoxypropanamide



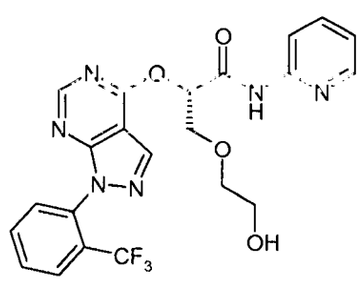
Sodium hydride (82 mg, 2.05 mmol) was added to (S)-N-(5-cyanopyridin-2-yl)-3-ethoxy-2-hydroxypropanamide (**Intermediate H4**) (177 mg, 0.75 mmol) in anhydrous THF (5 mL) at 0 °C under nitrogen. The resulting solution was stirred at 0 °C for 10 minutes and then 7-chloro-3-(2-chlorophenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidine (**Intermediate AP2**) (200 mg, 0.75 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour. The reaction mixture was neutralised with 1M citric acid and the majority of the THF removed in vacuo. The reaction mixture was diluted with water (20 mL) and EtOAc (50 mL). The organic layer was separated and the aqueous layer re-extracted with EtOAc (2 × 50 mL). The combined organics were washed with saturated brine (25 mL), dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 0 to 60% EtOAc in isohexane to afford the product (136 mg, 38.9 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ1.24 (t, 3H), 3.61 - 3.74 (m, 2H), 4.13 - 4.21 (m, 2H), 6.13 (t, 1H), 7.51 - 7.62 (m, 3H), 7.67 - 7.71 (m, 1H), 7.93 - 7.98 (m, 1H), 8.36 - 8.40 (m, 1H), 8.57 - 8.59 (m, 1H), 8.71 (s, 1H), 9.19 (s, 1H); m/z (ESI+) $(M+H)^+$ = 463.23; HPLC t_R = 2.43 min

Example 198: (2S)-N-(5-chloropyridin-2-yl)-3-(2-hydroxyethoxy)-2-(3-o-tolyl-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy)propanamide



Hydrochloric acid (10%, 1 mL) was added dropwise to (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-N-(5-chloropyridin-2-yl)-2-(3-o-tolyl-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy)propanamide (**Intermediate AP7**) (250 mg, 0.35 mmol) in methanol (20.00 mL) at room temperature. The resulting solution was stirred for 4 hours. Most of the methanol was evaporated and the remaining aq. soln was diluted with saturated NH_4Cl and extracted with EtOAc (2 × 30 mL). The organic layers were combined, dried ($MgSO_4$) and evaporated to give crude product. The crude product was purified by flash silica chromatography, eluting with 0 to 100% EtOAc in isohexane to afford the product (81 mg, 48.8 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ2.20 (s, 3H), 2.60 - 2.66 (m, 1H), 3.73 - 3.83 (m, 4H), 4.20 - 4.32 (m, 2H), 6.15 (t, 1H), 7.41 - 7.54 (m, 4H), 8.17 - 8.21 (m, 1H), 8.23 - 8.25 (m, 1H), 8.70 (s, 1H), 9.20 (s, 1H), OH not observed; m/z (ESI+) $(M+H)^+$ = 470.43; HPLC t_R = 2.25 min

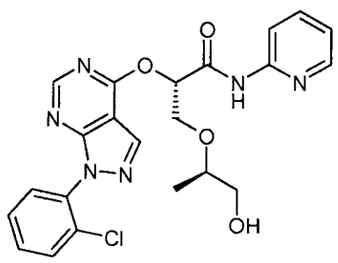
Example 199: (2S)-3-(2-hydroxyethoxy)-N-(pyridin-2-yl)-2-(1-(2-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide



A solution of tetrabutylammonium fluoride (1M in THF) (1.275 mL, 1.28 mmol) wasadded in one portion to a stirred solution of (2S)-3-(2-(tert-

butyldiphenylsilyloxy)ethoxy)-N-(pyridin-2-yl)-2-(1-(2-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide (0.927 g, 1.28 mmol) (Intermediate AQ1) in tetrahydrofuran (15 mL). The resulting solution was stirred at ambient temperature for 30 minutes. The reaction mixture was quenched with saturated NH4Cl (10 mL), and diluted with water (20 mL) and EtOAc (50 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (50 mL), The combined organics were dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 80 to 100% EtOAc in isohexane to afford the product (0.226 g, 36.3 %). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 2.90 (1H, s), 3.75 - 3.80 (4H, m), 4.16 - 4.25 (2H, m), 6.09 (1H, t), 7.06 - 7.10 (1H, m), 7.53 - 7.92 (5H, m), 8.18 - 8.20 (1H, m), 8.28 - 8.30 (1H, m), 8.41 (1H, s), 8.57 (1H, s), 9.01 (1H, s); m/z (ES+) $(M+H)^+$ = 489.31; HPLC t_R = 1.74 min.

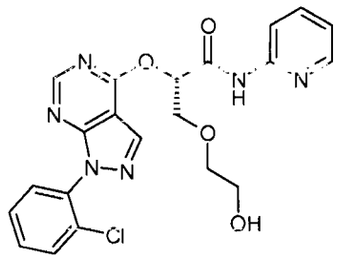
Example 200: (2S)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-((R)-1-hydroxypropan-2-yloxy)-N-(pyridin-2-yl)propanamide



A solution of tetrabutylammonium fluoride (1M in THF) (0.526 mL, 0.53 mmol) was added in one portion to a stirred solution of (2S)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(pyridin-2-yl)-3-((R)-1-(triisopropylsilyloxy)propan-2-yloxy)propanamide (0.329 g, 0.53 mmol) (**Intermediate AQ3**) in tetrahydrofuran (15 mL). The resulting solution was stirred at ambient temperature for 30 minutes. The reaction mixture was quenched with saturated NH_4Cl (10 mL), and diluted with water (20 mL) and EtOAc (50 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (50 mL), The combined organics were dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 80 to 100% EtOAc in isohexane to afford the product (0.247 g, 100 %). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 1.16 - 1.19 (3H, m), 3.45 - 3.85 (4H,m), 4.1 - 4.31 (2H, m), 6.06 - 6.09 (1H, m), 7.05 - 7.09 (1H, m), 7.46 - 7.63 (4H, m), 7.73 - 7.75 (1H, m), 8.17 (1H, d), 8.26 - 8.28 (1H, m), 8.43 (1H, d), 8.60 (1H, s), 9.23 (1H, s); m/z (ES+) $(M+H)^+$ =

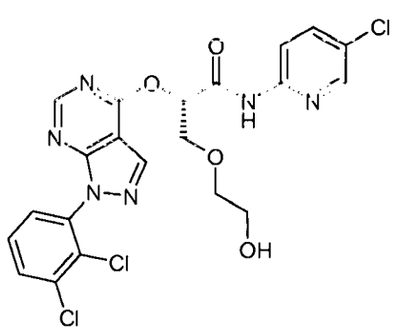
469.24; HPLC t_R = 1.91 min.

Example 201: (2S)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-(2-hydroxyethoxy)-N-(pyridin-2-yl)propanamide



A solution of tetrabutylammonium fluoride (1M inTHF) (0.984 mL, 0.98 mmol) was added in one portion to a stirred solution of (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(pyridin-2-yl)propanamide (**Intermediate AQ5**) (0.682 g, 0.98 mmol) in tetrahydrofuran (15 mL). The resulting solution was stirred at ambient temperature for 30 minutes. The reaction mixture was quenched with saturated NH_4Cl (10 mL), and diluted with water (20 mL) and EtOAc (50 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (50 mL), The combined organics were dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 80 to 100% EtOAc in isohexane to afford the product (0.335 g, 74.9 %). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 2.91 (1H, s), 3.74 - 3.79 (4H, m), 4.15 - 4.25 (2H, m), 6.10 (1H, t), 7.06 - 7.10 (1H, m), 7.45 - 7.63 (4H, m), 7.71 - 7.75 (1H, m), 8.19 (1H, d), 8.27 - 8.29 (1H, m), 8.44 (1H, s), 8.60 (1H, s), 9.01 (1H, s); m/z (ES+) $(M+H)^+$ = 455; HPLC t_R = 1.76 min.

Example 202: (2S)-N-(5-chloropyridin-2-yl)-2-(1-(2,3-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-(2-hydroxyethoxy)propanamide

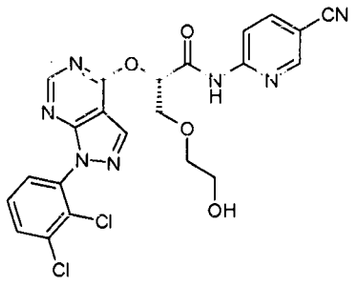


Trimethylaluminium (2M in toluene) (0.638 mL, 1.28 mmol) was added to 5-

chloropyridin-2-amine (164 mg, 1.28 mmol) in toluene (2 mL) under nitrogen. The resulting solution was stirred at room temperature for 15 minutes. (2S)-Methyl 3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(2,3-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanoate (**Intermediate AR1**) (425 mg, 0.64 mmol) in toluene (8 mL) was added sealed into a 20 mL microwave tube. The reaction was heated to 120 °C for 4 hours in the microwave reactor and cooled to RT. The reaction mixture was allowed to cool and concentrated in vacuo. The residue was neutralised with citric acid (1M, aq) and then diluted with water (30 mL) and extracted with EtOAc (2 x 50 mL). The combined organics were dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% EtOAc in isohexane to afford (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-N-(5-chloropyridin-2-yl)-2-(1-(2,3-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide (460 mg, 95 %). m/z (ES+) $(M+H)^+$ = 763; HPLC t_R = 3.94 min.

A solution of tetrabutylammonium fluoride (1M in THF) (0.661 mL, 0.66 mmol) was added dropwise to a stirred solution of (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-N-(5-chloropyridin-2-yl)-2-(1-(2,3-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide (420 mg, 0.55 mmol) in THF (15 mL) over a period of 1 minute. The resulting solution was stirred at ambient temperature for 3 hours. Saturated ammonium chloride (20 mL) was added to the reaction mixture which was then diluted with EtOAc (25 mL), and washed sequentially with water (25 mL) and saturated brine (25 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 50 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 0.1% formic acid) and MeCN as eluents. Fractions containing the desired compound were concentrated to remove most of the MeCN and then EtOAc was added. The organic phase was washed sequentially with saturated $NaHCO_3$ and water the organic layer was evaporated to dryness to afford the product (120 mg, 41.6 %). ^1H NMR (400 MHz, $CDCl_3$) δ 3.75 (4H, m), 4.16 (1H, dd), 4.22 (1H, dd), 6.06 (1H, t), 7.42 (2H, m), 7.66 (2H, m), 8.20 (2H, m), 8.43 (1H, d), 8.58 (1H, s), 9.17 (1H, s); m/z (ES+) $(M+H)^+$ = 525; HPLC t_R = 2.32 min.

Example 203: (2S)-N-(5-cyanopyridin-2-yl)-2-(1-(2,3-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-(2-hydroxyethoxy)propanamide



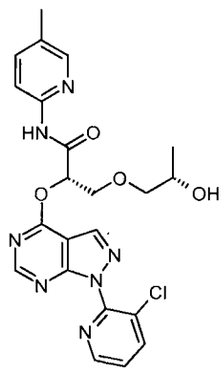
Trimethylaluminium (2M in toluene) (0.638 mL, 1.28 mmol) was added to 6-aminonicotinonitrile (152 mg, 1.28 mmol) in toluene (2 mL) under nitrogen. The resulting solution was stirred at room temperature for 15 minutes. (2S)-methyl 3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(2,3-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanoate (**Intermediate AR1**) (425 mg, 0.64 mmol) in toluene (8 mL) was added sealed into a 20 mL microwave tube. The reaction was heated to 120 °C for 4 hours in the microwave reactor and cooled to R.T. The reaction mixture was allowed to cool and concentrated in vacuo. The residue was neutralised with citric acid (1M, aq) and then diluted with water (30 mL) and extracted with EtOAc (2 x 50 mL). The combined organics were dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% EtOAc in isohexane to afford (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-N-(5-cyanopyridin-2-yl)-2-(1-(2,3-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide (450 mg, 94 %).

m/z (ES+) $(M+H)^+$ = 752; HPLC t_R = 3.74 min.

A solution of tetrabutylammonium fluoride (1M in THF) (0.701 mL, 0.70 mmol) was added dropwise to a stirred solution of (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-N-(5-cyanopyridin-2-yl)-2-(1-(2,3-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide (440 mg, 0.58 mmol) in THF (15 mL) over a period of 1 minute. The resulting solution was stirred at ambient temperature for 3 hours. Saturated ammonium chloride (20 mL) was added to the reaction mixture which was then diluted with EtOAc (25 mL), and washed sequentially with water (25 mL) and saturated brine (25 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by preparative

HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 50 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 0.1% formic acid) and MeCN as eluents. Fractions containing the desired compound were concentrated to remove most of the MeCN and then EtOAc was added. The organic phase was washed sequentially with saturated $NaHCO_3$ and water the organic layer was evaporated to dryness to afford the product (240 mg, 80 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (1H, s), 3.81 – 3.62 (4H, m), 4.14 (2H, m), 6.00 (1H, t), 7.44 – 7.28 (2H, m), 7.60 (1H, dd), 7.90 (1H, dd), 8.29 (1H, dd), 8.36 (1H, s), 8.49 (1H, dd), 8.52 (1H, s), 9.26 (1H, s); m/z (ES+) $(M+H)^+$ = 514; HPLC t_R = 2.13 min.

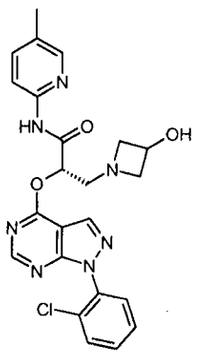
Example 204: (2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-((S)-2-hydroxypropoxy)-N-(5-methylpyridin-2-yl)propanamide



Tetrabutylammonium fluoride (1M in THF) (1.342 mL, 1.34 mmol) was added to (2S)-3-((S)-2-(tert-butyldimethylsilyloxy)propoxy)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-methylpyridin-2-yl)propanamide (**Intermediate AS1**) (803 mg, 1.34 mmol) in THF (6 mL) under nitrogen. The resulting mixture was stirred at ambient temperature for 16 hours. A further portion of Tetrabutylammonium fluoride (1M in THF) (1.342 mL, 1.34 mmol) was added and stirring continued for a further 5 hours.The reaction mixture was quenched with saturated NH4Cl, diluted with DCM and poured onto a phase separator. The organic layer was evaporated to a gum. The crude product was purified by flash silica chromatography, elution gradient 0 to 100% EtOAc in isohexane. 336mg of material was isolated but was found to contain co-running imps. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 50 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 0.1% formic acid) and MeCN as eluents. The relevent fractions were

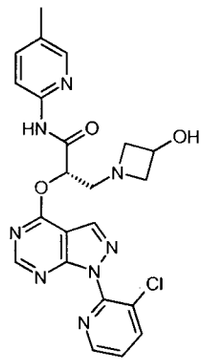
concentrated to remove the acetonitrile, then the remaining aqueous was basified with sat bicarb and extracted into ethylacetate x2. The organics were washed with brine, dried ($MgSO_4$) and concentrated to give (2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-((S)-2-hydroxypropoxy)-N-(5-methylpyridin-2-yl)propanamide (193 mg, 29.7 %, 77% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (3H, d), 2.29 (3H, s), 2.98 (1H, s), 3.37 - 3.44 (1H, m), 3.60 - 3.65 (1H, m), 3.97 - 4.05 (1H, m), 4.10 - 4.26 (2H, m), 6.09 (1H, t), 7.44 - 7.50 (1H, m), 7.51 - 7.57 (1H, m), 7.99 - 8.03 (1H, m), 8.05 - 8.12 (2H, m), 8.47 (1H, s), 8.60 - 8.63 (1H, m), 8.64 (1H, s), 8.86 (1H, s); m/z (ES+) $(M+H)^+$ = 484.46; HPLC t_R = 1.62 min.

Example 205: (2S)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-(3-hydroxyazetidin-1-yl)-N-(5-methylpyridin-2-yl)propanamide



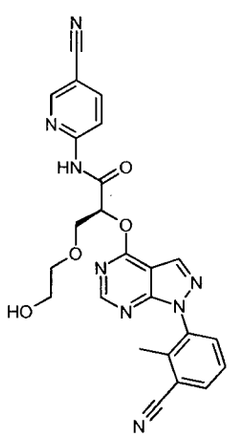
Tetrabutylammonium fluoride (1M in THF) (1.515 mL, 1.51 mmol) was added to (2S)-3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-methylpyridin-2-yl)propanamide (**Intermediate AD7**) (0.9 g, 1.51 mmol) in THF (10 mL) under nitrogen. The resulting mixture was stirred at ambient temperature for 2.5 hours. The reaction mixture was quenched with saturated NH_4Cl, diluted with DCM and poured onto a phase separator. The organic layer was evaporated to a gum. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in EtOAc to afford the product (0.313 g, 43.1 %, 98% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (3H, s), 2.50 - 2.78 (1H, m), 3.15 - 3.31 (4H, m), 3.79 - 3.89 (2H, m), 4.47 - 4.55 (1H, m), 5.91 (1H, t), 7.42 - 7.56 (4H, m), 7.59 - 7.65 (1H, m), 8.08 - 8.14 (2H, m), 8.37 (1H, s), 8.59 (1H, s), 9.53 (1H, s); m/z (ES+) $(M+H)^+$ = 480.41; HPLC t_R = 1.19 min.

Example 206: (2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-(3-hydroxyazetidin-1-yl)-N-(5-methylpyridin-2-yl)propanamide



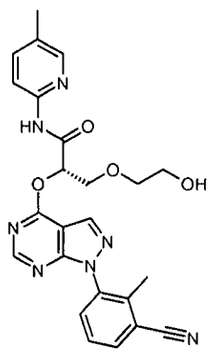
Tetrabutylammonium fluoride (1M in THF) (0.328 mL, 0.33 mmol) was added to (2S)-3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-methylpyridin-2-yl)propanamide (**Intermediate AD9**) (195 mg, 0.33 mmol) in THF (2 mL) under nitrogen. The resulting mixture was stirred at ambient temperature for 6 hours. The reaction mixture was quenched with saturated NH4Cl, diluted with DCM and poured onto a phase separator. The organic layer was evaporated to a gum. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in EtOAc to afford the product (38.0 mg, 24.12 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 - 1.29 (1H, m), 2.29 (3H, s), 3.16 - 3.32 (4H, m), 3.76 - 3.87 (2H, m), 4.46 - 4.53 (1H, m), 5.91 (1H, t), 7.44 - 7.49 (1H, m), 7.50 - 7.55 (1H, m), 7.97 - 8.03 (1H, m), 8.07 - 8.15 (2H, m), 8.42 (1H, s), 8.59 - 8.65 (2H, m), 9.58 (1H, s) m/z (ES+) $(M+H)^+$ = 481.51; HPLC t_R = 1.14 min.

Example 207: (2S)-2-(1-(3-cyano-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-cyanopyridin-2-yl)-3-(2-hydroxyethoxy)propanamide



Tetrabutylammonium fluoride (1M in THF) (0.346 mL, 0.35 mmol) was added to (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(3-cyano-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-cyanopyridin-2-yl)propanamide (**Intermediate AT1**) (250 mg, 0.35 mmol) in THF (2 mL) under nitrogen. The resulting mixture was stirred at ambient temperature for 90 minutes. The reaction mixture was quenched with saturated NH4Cl, diluted with DCM and poured onto a phase separator. The organic layer was evaporated to a gum. The crude product was purified by flash silica chromatography, elution gradient 50 to 100% EtOAc in isohexane to afford the product (69.0 mg, 41.2 %, 92% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 - 2.44 (4H, m), 3.73 - 3.86 (4H, m), 4.15 - 4.26 (2H, m), 6.07 (1H, t), 7.49 (1H, t), 7.63 - 7.68 (1H, m), 7.77 - 7.82 (1H, m), 7.94 - 8.00 (1H, m), 8.34 - 8.38 (1H, m), 8.43 (1H, s), 8.55 - 8.60 (2H, m), 9.34 (1H, s); m/z (ES-) (M-H)- = 483.52; HPLC t_R = 1.95 min.

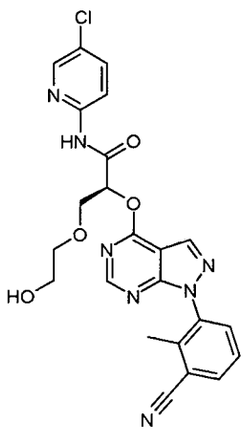
Example 208: (2S)-2-(1-(3-cyano-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-(2-hydroxyethoxy)-N-(5-methylpyridin-2-yl)propanamide



Tetrabutylammonium fluoride (1M in THF) (0.440 mL, 0.44 mmol) was added to (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(3-cyano-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-methylpyridin-2-yl)propanamide (**Intermediate AT6**) (313 mg, 0.44 mmol) in THF (2 mL) under nitrogen. The resulting mixture was stirred at ambient temperature for 2 hours. The reaction mixture was quenched with saturated NH_4Cl, diluted with DCM and poured onto a phase separator. The organic layer was evaporated to a gum. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% methanol in ethyl acetate to afford the product (59.0 mg, 28.3 %, 84% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (3H, s), 2.40 (3H, s), 3.02 (1H, s), 3.72 - 3.83 (4H, m), 4.13 - 4.26 (2H, m), 6.09 (1H, t), 7.45 - 7.57 (2H, m), 7.63 - 7.68 (1H, m), 7.76 -

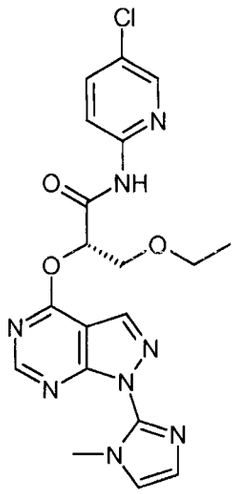
7.81 (1H, m), 8.03 - 8.12 (2H, m), 8.43 (1H, s), 8.58 (1H, s), 8.95 (1H, s); m/z (ES+) $(M+H)^+$ = 474.49; HPLC t_R = 1.83 min.

Example 209: (2S)-N-(5-chloropyridin-2-yl)-2-(1-(3-cyano-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-(2-hydroxyethoxy)propanamide



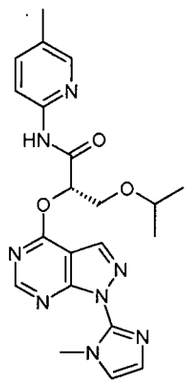
Tetrabutylammonium fluoride (1M in THF) (1.174 mL, 1.17 mmol) was added to (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-N-(5-chloropyridin-2-yl)-2-(1-(3-cyano-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide (**Intermediate AT7**) (860 mg, 1.17 mmol) in THF (2 mL) under nitrogen. The resulting mixture was stirred at ambient temperature for 2 hours. The reaction mixture was quenched with saturated NH4Cl (1 mL), diluted with DCM (10 mL) and poured onto a phase separator. The organic layer was evaporated to a gum. The crude product was purified by flash silica chromatography, elution gradient 0 to 100% EtOAc in isohexane to afford the product (284 mg, 49.0 %, 91% ee). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.40 (3H, s), 2.55 - 2.65 (1H, m), 3.70 - 3.86 (4H, m), 4.14 - 4.27 (2H, m), 6.08 (1H, t), 7.49 (1H, t), 7.63 - 7.73 (2H, m), 7.76 - 7.82 (1H, m), 8.15 - 8.25 (2H, m), 8.44 (1H, s), 8.59 (1H, s), 9.03 (1H, s); m/z (ES+) $(M+H)^+$ = 494.45; HPLC t_R = 2.13 min.

Example 210: (2S)-N-(5-chloropyridin-2-yl)-3-ethoxy-2-(1-(1-methyl-1H-imidazol-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide



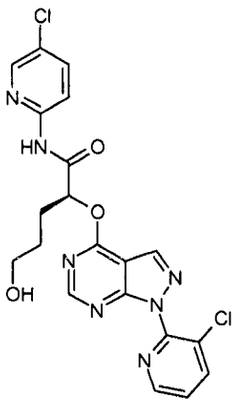
Sodium hydride (60% in oil) (29.2 mg, 0.73 mmol) was added to (S)-N-(5-chloropyridin-2-yl)-3-ethoxy-2-hydroxypropanamide (**Intermediate H3**) (149 mg, 0.61 mmol) in anhydrous THF (5 mL) at 0 °C under nitrogen. The resulting solution was stirred at 0 °C for 10 minutes and then 1-(1-methyl-1H-imidazol-2-yl)-4-phenoxy-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate AV1**) (196 mg, 0.67 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 4 hours. The reaction mixture was quenched with 1M citric (2 mL), extracted with EtOAc, the organic layer was washed with water x2 and brine, dried ($MgSO_4$), filtered and evaporated to afford orange oil. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 50 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 1% NH_3) and MeCN as eluents to afford the product (111 mg, 41.2 %, 95% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (3H, t), 3.56 - 3.72 (5H, m), 4.03 - 4.15 (2H, m), 6.05 (1H, t), 7.02 (1H, d), 7.17 (1H, d), 7.65 - 7.71 (1H, m), 8.19 - 8.26 (2H, m), 8.43 (1H, s), 8.65 (1H, s), 8.78 (1H, s); m/z (ES+) $(M+H)^+$ = 443.40; HPLC t_R = 1.92 min.

Example 211: (2S)-3-isopropoxy-2-(1-(1-methyl-1H-imidazol-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-methylpyridin-2-yl)propanamide



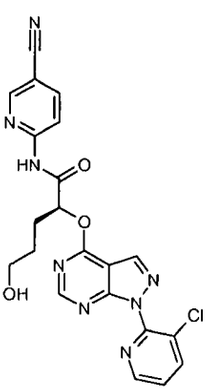
Sodium hydride (60% in oil) (28.8 mg, 0.72 mmol) was added to (S)-2-hydroxy-3-isopropoxy-N-(5-methylpyridin-2-yl)propanamide (**Intermediate C7**) (143 mg, 0.60 mmol) in anhydrous THF (5 mL) at 0 °C under nitrogen. The resulting solution was stirred at 0 °C for 10 minutes and then 1-(1-methyl-1H-imidazol-2-yl)-4-phenoxy-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate AV1**) (193 mg, 0.66 mmol) in THF (1 mL) was added. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours. The reaction mixture was quenched with 1M citric (2 mL), extracted with EtOAc, the organic layer was washed with water x2 and brine, dried ($MgSO_4$), filtered and evaporated to afford orange oil. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5µ silica, 50 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 1% NH_3) and MeCN as eluents to afford the product (90 mg, 34.4 %, 100% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (6H, t), 2.29 (3H, s), 3.65 (3H, s), 3.67 - 3.76 (1H, m), 4.08 (2H, d), 6.01 (1H, t), 7.01 (1H, d), 7.17 (1H, d), 7.49 - 7.55 (1H, m), 8.06 - 8.14 (2H, m), 8.42 (1H, s), 8.65 (1H, s), 8.68 (1H, s); m/z (ES+) $(M+H)^+$ = 437.51; HPLC t_R = 1.89 min.

Example 212: (2S)-N-(5-chloropyridin-2-yl)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-5-hydroxypentanamide



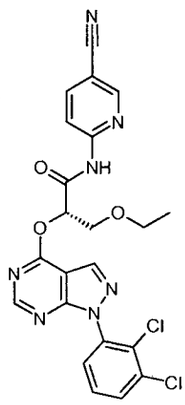
Tetrabutylammonium fluoride (1M in THF) (1.177 mL, 1.18 mmol) was added to (2S)-5-(tert-butyldimethylsilyloxy)-N-(5-chloropyridin-2-yl)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)pentanamide (**Intermediate AW1**) (693 mg, 1.18 mmol) in THF (5 mL) under nitrogen. The resulting mixture was stirred at ambient temperature for 1 hour. The reaction mixture was quenched with saturated NH4Cl (2 mL), diluted with DCM (25 mL) and poured onto a phase separator. The organic layer was loaded onto a silica column and purified by flash silica chromatography, elution gradient 50 to 100% EtOAc in isohexane to afford the product (171 mg, 30.6 %, 95% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 (1H, t), 1.81 - 1.91 (2H, m), 2.21 - 2.39 (2H, m), 3.73 - 3.86 (2H, m), 5.95 (1H, t), 7.44 - 7.50 (1H, m), 7.64 - 7.72 (1H, m), 7.98 - 8.04 (1H, m), 8.20 - 8.27 (2H, m), 8.44 (1H, s), 8.59 - 8.65 (2H, m), 8.72 (1H, s); m/z (ES+) $(M+H)^+$ = 474.36; HPLC t_R = 1.89 min.

Example 213: (2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-cyanopyridin-2-yl)-5-hydroxypentanamide



Tetrabutylammonium fluoride (1M in THF) (1.376 mL, 1.38 mmol) was added to (2S)-5-(tert-butyldimethylsilyloxy)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-cyanopyridin-2-yl)pentanamide (**Intermediate AW2**) (797 mg, 1.38 mmol) in THF (5 mL) under nitrogen. The resulting mixture was stirred at ambient temperature for 1 hour. The reaction mixture was quenched with saturated NH4Cl (2 mL), diluted with DCM (25 mL) and poured onto a phase separator. The organic layer was loaded onto a silica column and purified by flash silica chromatography, elution gradient 50 to 100% EtOAc in isohexane to afford the product (166 mg, 25.9 %, 100% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61 (1H, t), 1.81 - 1.92 (2H, m), 2.22 - 2.40 (2H, m), 3.76 - 3.88 (2H, m), 5.95 (1H, t), 7.45 - 7.50 (1H, m), 7.93 - 7.98 (1H, m), 7.99 - 8.04 (1H, m), 8.35 - 8.41 (1H, m), 8.44 (1H, s), 8.53 - 8.57 (1H, m), 8.60 - 8.64 (2H, m), 9.03 (1H, s); m/z (ES-) (M-H)- = 463.37; HPLC t_R = 1.68 min.

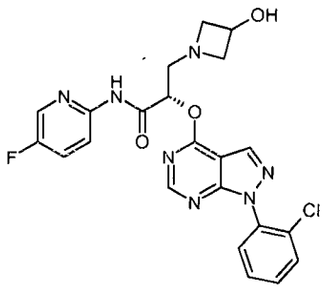
Example 214: (2S)-N-(5-cyanopyridin-2-yl)-2-(1-(2,3-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-ethoxypropanamide



Sodium hydride (60% in oil) (80 mg, 2.00 mmol) was added to (S)-N-(5-cyanopyridin-2-yl)-3-ethoxy-2-hydroxypropanamide (**Intermediate H4**) (314 mg, 1.34 mmol) inTHF (10 mL) at 0°C under nitrogen. The resulting mixture was stirred at 0 °C for 10 minutes. 4-chloro-1-(2,3-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate AR4**) (400 mg, 1.34 mmol) in THF (2 mL) was then added dropwise.and stirred at 0°C for a further 10mins. The reaction was then allowed to warm to r.t. and stirred for 3 1/2 hours. The reaction mixture was quenched with 1M citric acid, extracted with EtOAc and washed with water x2. The organic layer was dried ($MgSO_4$), filtered and evaporated to afford yellow gum (835mg). The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 50 mm diameter, 150 mm length), using decreasingly polar

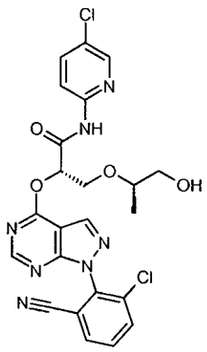
mixtures of water (containing 0.1% formic acid) and MeCN as eluents to afford the product (285 mg, 42.8 %, 96% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (3H, t), 3.58 - 3.74 (2H, m), 4.04 - 4.17 (2H, m), 6.04 (1H, t), 7.37 - 7.48 (2H, m), 7.64 - 7.69 (1H, m), 7.93 - 7.99 (1H, m), 8.36 - 8.41 (1H, m), 8.43 (1H, s), 8.56 - 8.58 (1H, m), 8.58 (1H, s), 9.02 (1H, s); m/z (ES-) (M-H)- = 496.33; HPLC t_R = 2.70 min.

Example 215: (2S)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-3-(3-hydroxyazetidin-1-yl)propanamide



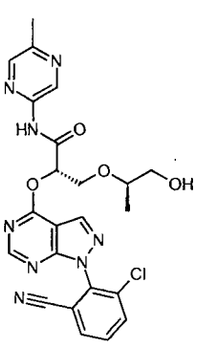
A solution of tetrabutylammonium fluoride (1M inTHF) (7.14 mL, 7.14 mmol) was added in one portion to a stirred solution of (2S)-3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-fluoropyridin-2-yl)propanamide (**Intermediate AX1**) (4.27 g, 7.14 mmol) in tetrahydrofuran (100 mL). The resulting solution was stirred at ambient temperature for 30 minutes. The reaction mixture was quenched with saturated NH_4Cl (30 mL), concentrated to approximately 50 mL and then diluted with water (50 mL) and EtOAc (100 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (100 mL). The combined organics were dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in EtOAc to afford the product (2.54 g, 73.6 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (1H, s), 3.15 - 3.21 (3H, m), 3.27 - 3.31 (1H, m), 3.84 - 3.91 (2H, m), 4.50 - 4.57 (1H, m), 5.90 - 5.93 (1H, m), 7.41 - 7.54 (4H, m), 7.61 - 7.63 (1H, m), 8.14 (1H, d), 8.23 - 8.26 (1H, m), 8.37 (1H, s), 8.59 (1H, s), 9.74 (1H, s); m/z (ES^+) $(M+H)^+$ = 484.17; HPLC t_R= 1.65 min.

Example 216: (2S)-2-[1-(2-chloro-6-cyano-phenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-chloro-2-pyridyl)-3-[(1R)-2-hydroxy-1-methyl-ethoxy]propanamide



A solution of tetrabutylammonium fluoride (1M inTHF) (0.891 mL, 0.89 mmol) was added in one portion to a stirred solution of (2S)-2-(1-(2-chloro-6-cyanophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-chloropyridin-2-yl)-3-((R)-1-(triisopropylsilyloxy)propan-2-yloxy)propanamide (**Intermediate AY1**) (610 mg, 0.89 mmol) in tetrahydrofuran (15 mL). The resulting solution was stirred at ambient temperature for 30 minutes. The reaction mixture was quenched with saturated NH_4Cl (10 mL), and diluted with water (20 mL) and EtOAc (70 mL).The organic layer was separated and the aqueous layer extracted with EtOAc (70 mL), The combined organics were dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 50 to 80% EtOAc in isohexane to afford the product (281 mg, 59.7 %). ^{1}H NMR (400 MHz, DMSO) δ 1.07 (3H, d), 3.33 (1H, q), 3.40 - 3.46 (1H, m), 3.61 - 3.69 (1H, m), 4.09 - 4.16 (2H, m), 4.57 (1H, t), 5.90 (1H, s), 7.87 - 7.91 (2H, m), 8.01 - 8.05 (1H, m), 8.16 - 8.19 (2H, m), 8.40 - 8.41 (1H, m), 8.61 (1H, s), 8.78 (1H, t), 11.17 (1H, d); m/z (ES^-) $(M-H)^-$ = 526; HPLC t_R= 2.94 min.

Example 217: (2S)-2-[1-(2-chloro-6-cyano-phenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-[(1R)-2-hydroxy-1-methyl-ethoxy]-N-(5-methylpyrazin-2-yl)propanamide



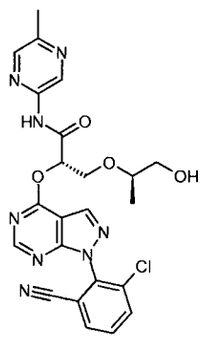
A solution of tetrabutylammonium fluoride (1M inTHF) (0.887 mL, 0.89 mmol) was added in one portion to a stirred solution of (2S)-2-(1-(2-chloro-6-cyanophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-methylpyrazin-2-yl)-3-((R)-1-(triisopropylsilyloxy)propan-2-yloxy)propanamide (**Intermediate AZ1**) (0.59 g, 0.89 mmol) in tetrahydrofuran (15 mL). The resulting solution was stirred at ambient temperature for 30 minutes. The reaction mixture was quenched with saturated NH_4Cl (10 mL), and diluted with water (20 mL) and EtOAc (70 mL).The organic layer was separated and the aqueous layer extracted with EtOAc (70 mL), The combined organics were dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 50 to 80% EtOAc in isohexane to afford the product (0.367 g, 81 %). ^{1}H NMR (400 MHz, CDCl3) δ 1.14 - 1.20 (3H, m), 2.54 (3H, s), 2.70 - 2.84 (1H, m), 3.54-3.72 (2H, m), 3.77 - 3.83 (1H, m), 4.09 - 4.16 (1H, m), 4.28 - 4.32 (1H, m), 6.08 - 6.11 (1H, m), 7.63 (1H, t), 7.78 - 7.81 (1H, m), 7.85 - 7.88 (1H, m), 8.12 (1H, s), 8.50 - 8.53 (1H, m), 8.62 (1H, d), 9.04 - 9.12 (1H, m), 9.41 (1H, s); m/z (ES^+) $(M+H)^+$ = 509.06; HPLC t_R= 2.41 min.

(2S)-2-(1-(2-chloro-6-cyanophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-((R)-1-hydroxypropan-2-yloxy)-N-(5-methylpyrazin-2-yl)propanamide (220 mg, 0.43 mmol) was taken up into Et_2O (20 mL) and warmed to boiling under reflux. The material dissolved and then began to crystallise. The mixture was allowed to cool and stood at ambient temperature for 1 hour. The solid was filtered off to give (2S)-2-(1-(2-chloro-6-cyanophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-((R)-1-hydroxypropan-2-yloxy)-N-(5-methylpyrazin-2-yl)propanamide (200 mg) which was shown to be crystalline by x-ray powder diffraction.

Angle 2-Theta (2θ)	Intensity %
4.234	100.0
20.902	95.6
14.456	95.2
17.730	77.8
13.278	69.4
11.065	63.2

21.237	61.5
19.725	59.4
26.458	59.2
8.463	54.9
26.192	54.8

Example 217: (2S)-2-[1-(2-chloro-6-cyano-phenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-[(1R)-2-hydroxy-1-methyl-ethoxy]-N-(5-methylpyrazin-2-yl)propanamide Alternative method.

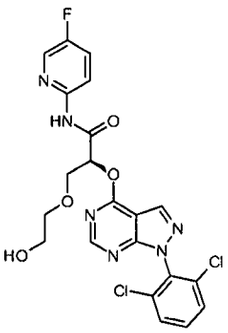


1M TBAF in THF (5.11 mL, 5.11 mmol) was added to (2S)-2-(1-(2-chloro-6-cyanophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-methylpyrazin-2-yl)-3-((R)-1-(triisopropylsilyloxy)propan-2-yloxy)propanamide (**Intermediate AZ1**) (3.4 g, 5.11 mmol) and acetic acid (0.307 g, 5.11 mmol) in THF (35 mL). The resulting solution was stirred at 22 °C for 20 hours. It was quenched with NH_4Cl solution (sat., 25 mL) and diluted with EtOAc (50 mL). The organic phase was washed with saturated sodium bicarbonate (25 mL), water (20 mL), brine (20 mL), dried ($MgSO_4$) and evaporated.

The crude product was purified by flash silica chromatography, eluting with EtOAc to afford the product (2.23g, 85%). This was crystallised from EtOAc (10 mL) and iso-hexane (6 mL) to give the desired product as a white crystalline powder (1.9g, 73%) confirmed to be of the same crystalline form as that described previously.

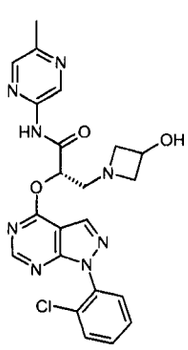
1H NMR (400 MHz, DMSO-d_6) δ 1.06 - 1.07 (3H, m), 2.44 (3H, s), 3.25 - 3.47 (2H, m), 3.62 - 3.67 (1H, m), 4.09 - 4.16 (2H, m), 4.53 - 4.61 (1H, m), 5.90 - 5.96 (1H, m), 7.89 (1H, dd), 8.16 - 8.20 (2H, m), 8.31 - 8.32 (1H, m), 8.62 (1H, s), 8.76 - 8.78 (1H, m), 9.10 - 9.12 (1H, m), 11.17 (1H, s); m/z (ES^-) $(M-H)^-$ = 507; HPLC t_R= 2.44 min.

Example 218: (2S)-2-[1-(2,6-dichlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-3-(2-hydroxyethoxy)propanamide



Tetrabutylammonium fluoride (1M in THF) (0.838 mL, 0.84 mmol) was added dropwise to (S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(2,6-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-fluoropyridin-2-yl)propanamide (**Intermediate BA1**) (0.625 g, 0.84 mmol) in THF (10.34 mL) at ambient temperature under nitrogen. The resulting solution was stirred at ambient temperature for 1 hour. The reaction mixture was quenched with saturated NH_4Cl (10 mL), and diluted with water (20 mL) and EtOAc (70 mL).The organic layer was separated and the aqueous layer extracted with EtOAc (70 mL). The combined organics were dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 25 to 100% EtOAc in isohexane to afford the product (0.307 g, 72.1 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60 (1H, t), 3.71 - 3.81 (4H, m), 4.16 - 4.25 (2H, m), 6.10 (1H, t), 7.43 - 7.49 (2H, m), 7.53 - 7.55 (2H, m), 8.14 (1H, d), 8.22 - 8.25 (1H, m), 8.48 (1H, s), 8.60 (1H, s), 9.00 (1H, s); m/z (ES^+) $(M+H)^+$ = 507.31; HPLC t_R= 2.67 min.

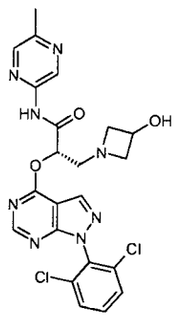
Example 219: (2S)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-(3-hydroxyazetidin-1-yl)-N-(5-methylpyrazin-2-yl)propanamide



Tetrabutylammonium fluoride (1M in THF) (0.87 mL, 0.87 mmol) was added to (2S)-3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-

d]pyrimidin-4-yloxy)-N-(5-methylpyrazin-2-yl)propanamide (**Intermediate BB1**) (520 mg, 0.87 mmol) in tetrahydrofuran (25 mL) under nitrogen. The resulting mixture was stirred at ambient temperature for 2 hours. Further tetrabutylammonium fluoride (1M in THF) (1.7 mL, 1.7 mmol) added and the mixture stirred overnight. The reaction mixture was quenched with saturated ammonium chloride solution (20 mL), diluted with ethyl acetate (50 mL) and stirred for 10 minutes. The organic layer was separated, washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, eluting with 0 to 10% methanol in ethyl acetate, to afford the product (130 mg). ^{1}H NMR (400 MHz, DMSO-d6) δ 2.50 (3H, m), 2.98 - 3.09 (3H, m), 3.15 - 3.21 (1H, m), 3.67 - 3.77 (2H, m), 4.19 - 4.29 (1H, m), 5.31 (1H, d), 5.77 - 5.84 (1H, m), 7.60 - 7.76 (3H, m), 7.80 - 7.82 (1H, m), 8.35 - 8.37 (1H, m), 8.57 (1H, s), 8.64 (1H, s), 9.11 - 9.12 (1H, m), 11.17 (1H, s); m/z (ESI^+) $(M+H)^+ = 481$; HPLC t_R= 1.52 min.

Example 220: (2S)-2-[1-(2,6-dichlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-(3-hydroxyazetidin-1-yl)-N-(5-methylpyrazin-2-yl)propanamide



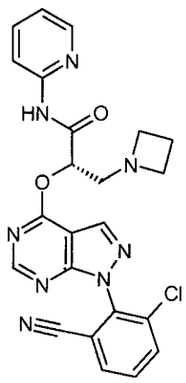
A solution of tetrabutylammonium fluoride (1M inTHF) (0.61 mL, 0.61 mmol) was added in one portion to a stirred solution of (S)-3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-(1-(2,6-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-methylpyrazin-2-yl)propanamide (**Intermediate BB3**) (385 mg, 0.61 mmol) in tetrahydrofuran (15 mL). The resulting solution was stirred at ambient temperature for 30 minutes. The reaction mixture was quenched with saturated ammonium chloride solution (10 mL), and diluted with water (20 mL) and ethyl acetate (70 mL).The organic layer was separated and the aqueous layer extracted with ethyl acetate (70 mL). The combined organics were dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, eluting with 0 to 10% methanol in ethyl acetate, to afford the product (197 mg, 62.5%, 99.4%ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.54 (3H, s), 3.19 - 3.24 (3H,

m), 3.30 - 3.35 (1H, m), 3.88 - 3.93 (2H, m), 4.53 - 4.58 (1H, m), 5.93 - 5.96 (1H, m), 7.43 - 7.47 (1H, m), 7.52 - 7.55 (2H, m), 8.13 (1H, d), 8.41 (1H, s), 8.59 (1H, s), 9.42 (1H, d), 9.81 (1H, s); m/z (ES^+) $(M+H)^+$ = 515; HPLC t_R= 1.58 min.

Amorphous (S)-2-(1-(2,6-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-(3-hydroxyazetidin-1-yl)-N-(5-methylpyrazin-2-yl)propanamide (1700 mg) was heated in refluxing t-butyl methyl ether (800 mL) for 30 minutes. The suspension was filtered, and the filtrate then reduced to a volume of approximately 100 mL. This solution was stirred overnight allowing the temperature to return to ambient. A solid was filtered off and was then dried under vacuum at 60°C for 4 days to give crystalline (S)-2-(1-(2,6-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-(3-hydroxyazetidin-1-yl)-N-(5-methylpyrazin-2-yl)propanamide (1121 mg).

Angle 2-Theta (2θ)	**Intensity %**
12.297	100.0
15.433	88.2
12.175	78.8
19.607	77.2
22.653	77.0
19.955	72.9
27.095	72.7
27.141	72.1
15.766	70.8
16.021	67.8

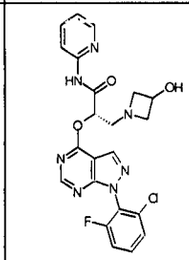
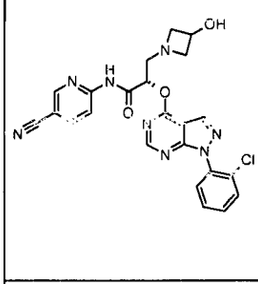
Example 221: (2S)-3-(azetidin-1-yl)-2-[1-(2-chloro-6-cyano-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-N-(2-pyridyl)propanamide

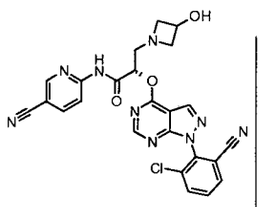
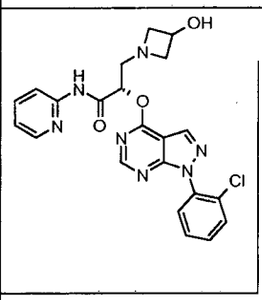
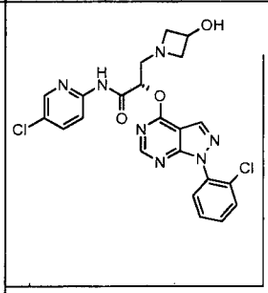


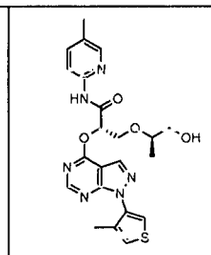
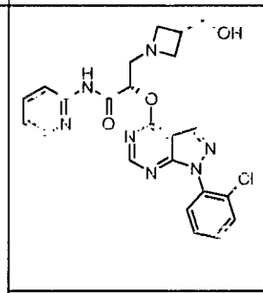
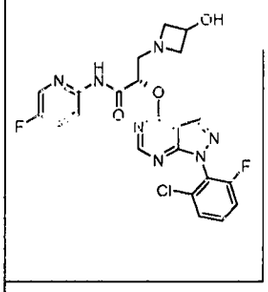
Sodium hydride (116 mg, 2.90 mmol) was added to (S)-3-(azetidin-1-yl)-2-hydroxy-N-(pyridin-2-yl)propanamide (**Intermediate BC1**) (232 mg, 1.05 mmol) in anhydrous THF (50 mL) at 0 °C under nitrogen. The resulting solution was stirred at 0 °C for 10 minutes and then a solution of 3-chloro-2-(4-chloro-1H-pyrazolo[3,4-d]pyrimidin-1-yl)benzonitrile (**Intermediate AH6**) (280 mg, 0.97 mmol) in anhydrous THF (20 mL) was added dropwise over 1 minute. The mixture was stirred at 0°C for 10 minutes and then allowed to warm to ambient temperature for 2 hours. It was then cooled to 0°C, 20% Rochelle salt (20 mL) added and the mixture stirred for 10 minutes. It was extracted with EtOAc (50 mL), the organic phase was washed with water (10 mL) and brine (20 mL), dried ($MgSO_4$), filtered and evaporated. The residue was triturated with EtOAc (10 mL), filtered and the filtrates evaporated. The residue was purified by flash silica chromatography, elution gradient 0 to 20% MeOH in EtOAc and further purified by preparative HPLC (Phenomenex Luna C18 100A column, 5µ silica, 21 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 1% formic acid) and MeCN as eluents to afford the product (100 mg, 22%).

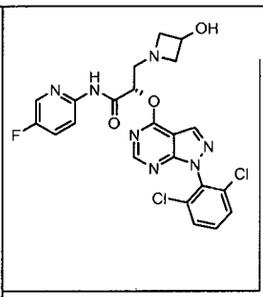
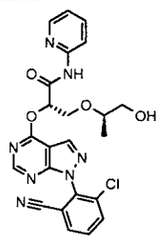
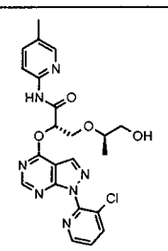
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 - 2.25 (2H, m), 3.08 - 3.17 (1H, m), 3.20 - 3.29 (1H, m), 3.40 - 3.52 (4H, m), 5.84 - 5.91 (1H, m), 7.02 - 7.08 (1H, m), 7.57 - 7.64 (1H, m), 7.65 - 7.71 (1H, m), 7.77 - 7.80 (1H, m), 7.82 - 7.87 (1H, m), 8.21 - 8.25 (1H, m), 8.31 - 8.32 (1H, m), 8.44 - 8.47 (1H, d), 8.58 - 8.61 (1H, d), 9.8 (0.4H, s), 10.08 (0.6H, s) (Mixture of rotamers); m/z (ESI^+) $(M+H)^+$ = 475; HPLC t_R= 1.16 min.

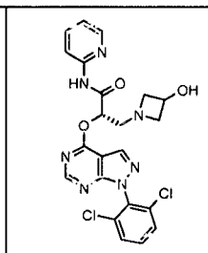
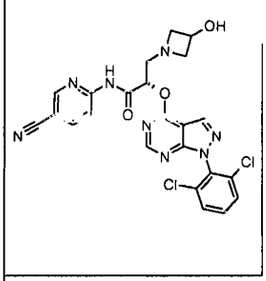
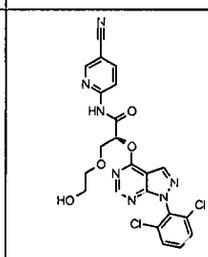
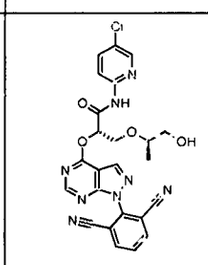
The following examples were prepared using a procedure analogous to that described for **Example 218** using the appropriate intermediate.

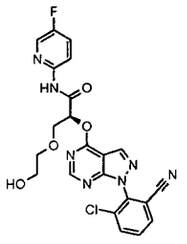
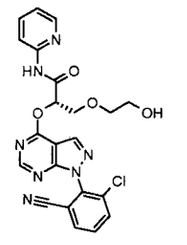
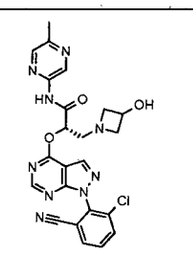
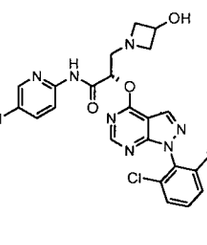
Example number	Structure	^{1}H NMR (400 MHz) δ	LCMS	Intermediate reference
222		(DMSO-d6) 3.00 - 3.13 (3H, m), 3.14 - 3.23 (1H, m), 3.67 - 3.76 (2H, m), 4.18 - 4.27 (1H, m), 5.30 (1H, d), 5.77 - 5.84 (1H, m), 7.72 - 7.20 (1H, m), 7.60 - 7.68 (1H, m), 7.69 - 7.71 (1H, m), 7.76 - 7.85 (2H, m), 8.00 - 8.08 (1H, m), 8.35 - 8.40 (1H, m), 8.60 (1H, s), 8.71 (1H, s), 10.95 (1H, d)	m/z (ES+) (M+H)+ = 484; HPLC tR= 1.17 min.	BD1
223		($CDCl_3$) 2.14 (1H, s, broad), 3.16 - 3.27 (1H, m), 3.20 - 3.24 (2H, m), 3.30 - 3.35 (1H, m), 3.90 - 3.94 (2H, m), 4.55 - 4.61 (1H, m), 5.89 - 5.92 (1H, m), 7.45 - 7.51 (2H, m), 7.52 - 7.55 (1H, m), 7.61 - 7.63 (1H, m), 7.92 - 7.95 (1H, m), 8.33 - 8.35 (1H, m), 8.36 (1H, s), 8.56 - 8.58 (1H, m), 8.59 (1H, s), 10.41 (1H, s)	m/z (ES+) (M+H)+ = 491; HPLC tR= 1.27 min.	BD2

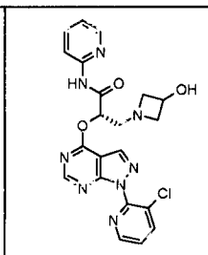
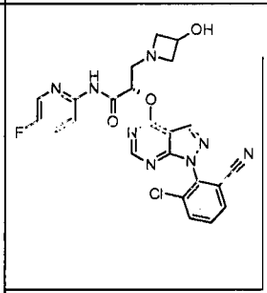
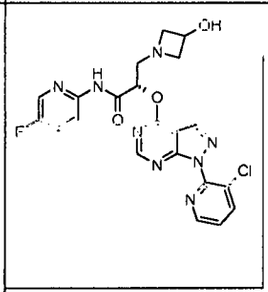
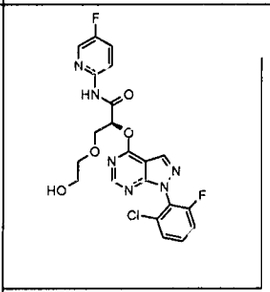
224		($CDCl_3$) 2.10 (1H, s. broad), 3.17 - 3.26 (3H, m), 3.27 - 3.38 (1H, m), 3.91 - 3.96 (2H, m), 4.58 - 4.65 (1H, m), 5.85 - 5.93 (1H, m), 7.60 - 7.65 (1H, m), 7.78 - 7.81 (1H, m), 7.85 - 7.88 (1H, m), 7.92 - 7.96 (1H, m), 8.33 - 8.36 (1H, m), 8.44 - 8.46 (1H, m), 8.57 - 8.62 (2H, m), 10.30 (0.5H, s), 10.60 (0.5H, s).	m/z (ES+) (M+H)+ = 516; HPLC tR= 1.23 min.	BD3
225		(DMSO-d6) 2.98 - 3.12 (3H, m), 3.14 - 3.19 (1H, m), 3.66 - 3.74 (2H, m), 4.18 - 4.27 (1H, m), 5.31 (1H, d), 5.76 - 5.83 (1H, m), 7.15 - 7.19 (1H, m), 7.60 - 7.75 (3H, m), 7.76 - 7.82 (2H, m), 8.06 (1H, d), 8.37 - 8.40 (1H, m), 8.53 (1H, s), 8.58 (1H, s), 10.90 (1H, s)	m/z (ES+) (M+H)+ = 466; HPLC tR= 1.22 min.	BD4
226		(DMSO-d6) 2.96 - 3.05 (3H, m), 3.10 - 3.15 (1H, m), 3.60 - 3.66 (2H, m), 4.14 - 4.20 (1H, m), 5.22 - 5.27 (1H, m), 5.72 - 5.75 (1H, m), 7.56 - 7.70 (3H, m), 7.74 (1H, dd), 7.88 (1H, dd), 8.02 (1H, d), 8.39 - 8.41 (1H, m), 8.52 (1H, s), 8.58 (1H, s), 11.12 (1H, s)	m/z (ES+) (M+H)+ = 500; HPLC tR= 1.44 min.	BD5

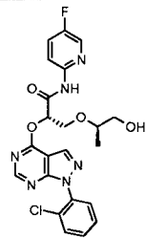
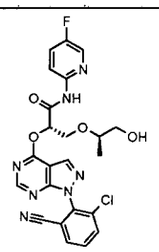
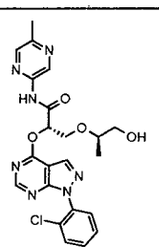
227		(DMSO-d6) 1.06 (3H, d), 2.10 (3H, d), 2.24 (3H, s), 3.30 - 3.40 (1H, m), 3.41 - 3.46 (1H, m), 3.61 - 3.68 (1H, m), 4.03 - 4.11 (2H, m), 4.55 (1H, t), 5.88 - 5.98 (1H, m), 7.40 - 7.43 (1H, m), 7.62 (1H, dd), 7.86 (1H, d), 7.92 - 7.97 (1H, m), 8.19 - 9.02 (1H, m), 8.60 (1H, s), 8.62 (1H, s), 10.85 (1H, s)	m/z (ES+) (M+H)+ = 469; HPLC tR= 2.00 min.	BD6
228		($CDCl_3$) 2.39 (1H, s), 2.68 - 2.71 (1H, m), 3.15 - 3.27 (2H, m), 3.37 - 3.40 (2H, m), 3.54 - 3.59 (2H, m), 3.83 - 3.85 (2H, m), 5.88 - 5.91 (1H, m), 7.03 - 7.06 (1H, m), 7.46 - 7.50 (2H, m), 7.52 - 7.55 (1H, m), 7.61 - 7.63 (1H, m), 7.67 - 7.72 (1H, m), 8.19 (1H, d, 8.4 Hz), 8.29 - 8.31 (1H, m), 8.36 (1H, s), 8.58 (1H, s), 10.20 (1H, s)	m/z (ES+) (M+H)+ = 480; HPLC tR= 1.63 min.	BD7
229		($CDCl_3$) 2.26 (1H, s), 3.15 - 3.22 (3H, m), 3.26 - 3.32 (1H, m), 3.85 - 3.91 (2H, m), 4.53 - 4.55 (1H, m), 5.89 - 5.93 (1H, m), 7.22 - 7.27 (1H, m), 7.41 - 7.52 (3H, m), 8.14 - 8.15 (1H, m), 8.22 - 8.27 (1H, m), 8.41 (1H, s), 8.59 (1H, s), 9.74 (1H, d)	m/z (ES+) (M+H)+ = 502; HPLC tR= 1.72 min.	BD8

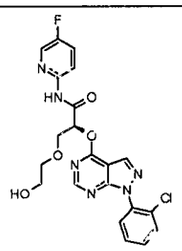
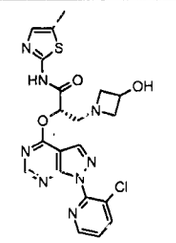
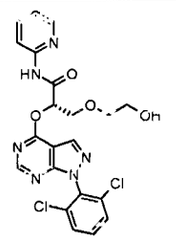
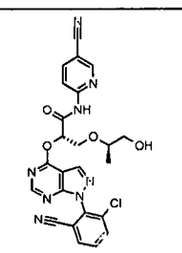
230		($CDCl_3$) 3.16 - 3.22 (3H, m), 3.27 - 3.32 (1H, m), 3.86 - 3.92 (2H, m), 4.54 (1H, s), 5.90 - 5.93 (1H, m), 7.41 - 7.47 (2H, m), 7.52 - 7.55 (2H, m), 8.15 (1H, d), 8.23 - 8.27 (1H, m), 8.41 (1H, s), 8.59 (1H, s), 9.74 (1H, s)	m/z (ES+) (M+H)+ = 518; HPLC tR= 1.78 min.	BD9
231		(DMSO-d6) 1.07 (3H, d), 3.34 (1H, q), 3.40 - 3.46 (1H, m), 3.64 - 3.68 (1H, m), 4.08 - 4.17 (2H, m), 4.55 - 4.58 (1H, m), 5.91 (1H, s), 7.11 - 7.14 (1H, m), 7.74 - 7.79 (1H, m), 7.89 (1H, t), 7.99 (1H, t), 8.13 - 8.19 (2H, m), 8.33 - 8.35 (1H, m), 8.61 (1H, d), 8.78 (1H, t), 10.96 (1H, d)	m/z (ES+) (M+H)+ = 494; HPLC tR= 2.51 min.	BD10
232		($CDCl_3$) 1.15 - 1.17 (3H, m), 2.29 (3H, s), 3.50 - 3.69 (3H, m), 3.75 - 3.80 (1H, m), 4.07 - 4.11 (1H, m), 4.26 - 4.29 (1H, m), 6.05 - 6.08 (1H, m), 7.45 - 7.48 (1H, m), 7.52 - 7.55 (1H, m), 7.97 - 8.10 (3H, m), 8.45 (1H, s), 8.60 - 8.62 (1H, m), 8.64 (1H, s), 9.15 (1H, s)	m/z (ES+) (M+H)+ = 484; HPLC tR= 2.43 min.	BD11

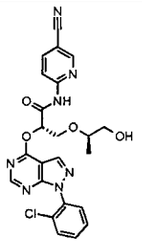
233		($CDCl_3$) 3.18 - 3.32 (4H, m), 3.83 - 3.90 (2H, m), 4.50 - 4.56 (1H, m), 5.90 - 5.93 (1H, m), 7.04 - 7.08 (1H, m), 7.43 - 7.47 (1H, m), 7.52 - 7.55 (2H, m), 7.69 - 7.73 (1H, m), 8.22 - 8.24 (1H, m), 8.28 - 8.30 (1H, m), 8.42 (1H, s), 8.59 (1H, s), 9.66 (1H, s)	m/z (ES+) $(M+H)^+$ = 500; HPLC tR= 1.29 min.	BD12
234		($CDCl_3$) 3.17 - 3.25 (3H, m), 3.31 - 3.36 (1H, m), 3.90 - 3.95 (2H, m), 4.56 - 4.62 (1H, m), 5.88 - 5.91 (1H, m), 7.44 - 7.55 (3H, m), 7.93 - 7.95 (1H, m), 8.34 - 8.36 (1H, m), 8.41 (1H, s), 8.57 - 8.59 (2H, m), 10.44 (1H, s)	m/z (ES+) $(M+H)^+$ = 525; HPLC tR= 1.38 min.	BD13
235		($CDCl_3$) 3.73 - 3.83 (4H, m), 4.17 - 4.25 (2H, m), 6.07 (1H, t), 7.44 - 7.48 (1H, m), 7.52 - 7.56 (2H, m), 7.96 - 7.99 (1H, m), 8.36 - 8.39 (1H, m), 8.48 (1H, s), 8.57 (1H, q), 8.59 (1H, s), 9.32 (1H, s)	m/z (ES+) $(M+H)^+$ = 514; HPLC tR= 2.04min.	BD14
236		($CDCl_3$) d1.17 (d, 3H), 3.55 - 3.71 (m, 2H), 3.76 - 3.85 (m, 1H), 4.07 - 4.14 (m, 2H), 4.25 - 4.31 (m, 1H), 6.04 - 6.08 (m, 1H), 7.66 - 7.72 (m, 1H), 7.78 (t, 1H), 8.10 (d, 2H), 8.17 (d, 1H), 8.24 (d, 1H), 8.56 (s, 1H), 8.67 (s, 1H), 9.25 (s, 1H)	m/z (ES+), $(M+H)^+$ = 519.31; HPLC tR = 2.74 min	BD15

237		(DMSO-d6) d3.50 - 3.56 (m, 2H), 3.58 - 3.70 (m, 2H), 3.99 - 4.16 (m, 2H), 4.61 (t, 1H), 5.91 - 5.97 (m, 1H), 7.68 - 7.77 (m, 1H), 7.89 (t, 1H), 8.00 - 8.07 (m, 1H), 8.15 - 8.21 (m, 2H), 8.34 - 8.37 (m, 1H), 8.61 (s, 1H), 8.79 (d, 1H), 11.12 (s, 1H)	m/z (ES+), (M+H)+ = 498.36; HPLC tR = 1.88 min	BD16
238		(DMSO-d6) d3.50 - 3.57 (m, 2H), 3.58 - 3.70 (m, 2H), 4.01 - 4.17 (m, 2H), 4.62 (t, 1H), 5.93 - 5.98 (m, 1H), 7.10 - 7.16 (m, 1H), 7.73 - 7.80 (m, 1H), 7.89 (t, 1H), 7.96 - 8.02 (m, 1H), 8.15 - 8.21 (m, 2H), 8.33 - 8.37 (m, 1H), 8.61 (s, 1H), 8.80 (d, 1H), 11.00 (s, 1H)	m/z (ES+), (M+H)+ = 480.29; HPLC tR = 1.66 min	BD17
239		($CDCl_3$) d9.93 (1H, s),9.58 (0H, s),9.34 (1H, s),8.54 (1H, d),8.39 (1H, d),8.06 (1H, s),7.80 (1H, d),7.72 (1H, d),7.56 (1H, t),5.87 (1H, q),4.45 - 4.52 (1H, m),3.84 (2H, t),3.25 (2H, q),3.08 - 3.19 (2H, m),2.47 (3H, s)	m/z (ES+), (M+H)+ = 506; HPLC tR = 1.17 min.	BD18
240		($CDCl_3$) d3.08 - 3.17 (2H, m),3.20 - 3.26 (1H, m),3.41 (1H, q),3.77 - 3.87 (2H, m),4.47 (1H, q),5.80 - 5.86 (1H, m),7.52 - 7.62 (2H, m),7.70 - 7.81 (4H, m),8.12 - 8.19 (2H, m),8.39 (1H, d),8.54 (1H, d),9.68 (0H, s),9.90 (1H, s)	m/z (ES+), (M+H)+ = 525; 5min Acid, HPLC tR = 1.39 min	BD19

241		($CDCl_3$) 3.15 - 3.31 (4H, m), 3.83 - 3.90 (2H, m), 4.52 (1H, t), 5.91 - 5.94 (1H, m), 7.04 - 7.07 (1H, m), 7.45 - 7.48 (1H, m), 7.68 - 7.72 (1H, m), 8.00 - 8.02 (1H, m), 8.21 (1H, d), 8.28 - 8.30 (1H, m), 8.41 (1H, s), 8.61 - 8.63 (2H, m), 9.54 (1H, s)	m/z (ES+) $(M+H)^+$ = 467.04; HPLC tR= 1.4 min.	BD20
242		($CDCl_3$) 3.17 - 3.33 (4H, m), 3.87 - 3.93 (2H, m), 4.55 (1H, q), 5.90 - 5.93 (1H, m), 7.41 - 7.46 (1H, m), 7.62 (1H, t), 7.78 - 7.81 (1H, m), 7.85 - 7.88 (1H, m), 8.15 (1H, d), 8.23 - 8.26 (1H, m), 8.46 (1H, d), 8.61 (1H, d), 9.64 - 9.87 (1H, m)	m/z (ES+) $(M+H)^+$ = 509.13; HPLC tR= 1.59 min.	BD21
243		($CDCl_3$) 3.14 - 3.22 (3H, m), 3.27 - 3.32 (1H, m), 3.89 (2H, q), 4.54 (1H, t), 5.91 - 5.94 (1H, m), 7.41 - 7.52 (2H, m), 8.00 - 8.02 (1H, m), 8.14 (1H, d), 8.22 - 8.25 (1H, m), 8.41 (1H, s), 8.61 - 8.63 (1H, m), 8.63 (1H, s), 9.67 (1H, s)	m/z (ES+) $(M+H)^+$ = 485; HPLC tR= 1.44 min.	BD22
244		($CDCl_3$) , 2.55 (1H, d), 3.71 - 3.79 (4H, m), 4.15 - 4.25 (2H, m), 6.09 (1H, t), 7.22 - 7.27 (1H, m), 7.40 - 7.52 (3H, m), 8.14 (1H, t), 8.21 - 8.25 (1H, m), 8.48 (1H, s), 8.60 (1H, s), 8.98 (1H, d)	m/z (ES+) $(M+H)^+$ = 491.09; HPLC tR= 2.68 min.	BD23

245		($CDCl_3$) 1.17 (3H, d), 3.05 (1H, d), 3.55 - 3.61 (1H, m), 3.64 - 3.69 (1H, m), 3.76 - 3.83 (1H, m), 4.08 - 4.12 (1H, m), 4.26 - 4.30 (1H, m), 6.06 - 6.08 (1H, m), 7.44 - 7.55 (4H, m), 7.61 - 7.63 (1H, m), 8.13 (1H, d), 8.20 - 8.23 (1H, m), 8.42 (1H, s), 8.60 (1H, s), 9.18 (1H, s)	m/z (ES+) (M+H)+ = 487.09; HPLC tR= 2.8 min.	BD24
246		(DMSO-d6) 1.07 (3H, d), 3.33 (1H, q), 3.40 - 3.46 (1H, m), 3.63 - 3.69 (1H, m), 4.09 - 4.16 (2H, m), 4.57 (1H, t), 5.89 (1H, s), 7.69 - 7.76 (1H, m), 7.89 (1H, t), 8.02 (1H, d), 8.17 - 8.19 (2H, m), 8.35 (1H, d), 8.61 (1H, s), 8.77 (1H, t), 11.09 (1H, d)	m/z (ES+) (M+H)+ = 512.14; HPLC tR= 2.7 min.	BD25
247		($CDCl_3$) 1.17 (3H, d), 2.54 (3H, s), 2.76 - 2.79 (1H, m), 3.54 - 3.60 (1H, m), 3.64 - 3.69 (1H, m), 3.76 - 3.82 (1H, m), 4.09 - 4.15 (1H, m), 4.28 - 4.32 (1H, m), 6.09 (1H, d), 7.45 - 7.52 (2H, m), 7.44 - 7.55 (1H, m), 7.62 - 7.63 (1H d, m), 8.11 (1H, d), 8.42 (1H, s), 8.61 (1H, s), 9.05 (1H, s), 9.40 - 9.42 (1H, m)	m/z (ES+) (M+H)+ = 484; HPLC tR= 2.52 min.	BD26

248		($CDCl_3$) 2.59 (1H, d), 3.73 - 3.79 (4H, m), 4.15 - 4.25 (2H, m), 6.10 (1H, t), 7.44 - 7.55 (4H, m), 7.61 - 7.64 (1H, m), 8.14 (1H, d), 8.22 - 8.25 (1H, m), 8.44 (1H, s), 8.60 (1H, s), 9.00 (1H, s)	m/z (ES+) (M+H)+ = 473.44; HPLC tR= 1.97 min.	BD27
249		($CDCl_3$) 1.66 - 1.74 (1H, m), 2.40 (3H, s), 3.12 - 3.44 (4H, m), 3.86 - 3.95 (2H, m), 4.52 - 4.61 (1H, m), 5.97 - 6.03 (1H, m), 7.10 (1H, s), 7.43 - 7.49 (1H, m), 7.98 - 8.03 (1H, m), 8.37 (1H, s), 8.58 - 8.64 (2H, m), 10.74 - 11.53 (1H, m)	m/z (ES-) (M-H)- = 485.31; HPLC tR= 1.55 min.	BD28
250		($CDCl_3$) 2.92 (1H, s), 3.73 - 3.80 (4H, m), 4.16 - 4.26 (2H, m), 6.10 (1H, t), 7.06 - 7.09 (1H, m), 7.43 - 7.47 (1H, m), 7.52 - 7.54 (2H, m), 7.71 - 7.75 (1H, m), 8.20 (1H, d), 8.27 - 8.29 (1H, m), 8.48 (1H, s), 8.60 (1H, s), 9.02 (1H, s)	m/z (ES+) (M+H)+ = 489.31; HPLC tR= 2.53 min.	BD29
251		(DMSO-d6) 1.05 - 1.09 (3H, m), 3.25-3.36 (1H, m), 3.40 - 3.46 (1H, m), 3.61 - 3.68 (1H, m), 4.10 - 4.18 (2H, m), 4.58 (1H, t), 5.91 - 5.93 (1H, m), 7.89 (1H, t), 8.12 - 8.19 (3H, m), 8.22 - 8.26 (1H, m), 8.61 (1H, s), 8.77-8.79 (1H, m), 8.82 - 8.83 (1H, m), 11.53 (1H, s)	m/z (ES-) (M-H)- = 517.37; HPLC tR= 2.53 min.	BD30

252		(DMSO-d6) 1.06 - 1.09 (3H, m), 3.33 (1H, t), 3.40 - 3.45 (1H, m), 3.61 - 3.69 (1H, m), 4.09 - 4.17 (2H, m), 4.57 (1H, t), 5.89 - 5.92 (1H, m), 7.56 - 7.69 (3H, m), 7.74 - 7.77 (1H, m), 8.12 - 8.14 (1H, m), 8.23 - 8.26 (1H, m), 8.54 (1H, s), 8.61 (1H, d), 8.82 (1H, m), 11.51 (1H, s)	m/z (ES-) (M-H)- = 492.40; HPLC tR= 2.62 min.	BD31

Example 222: (2S)-2-[1-(2-chloro-6-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-3-(3-hydroxyazetidin-1-yl)-N-(2-pyridyl)propanamide

Example 223: (2S)-2-[1-(2-chlorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-N-(5-cyano-2-pyridyl)-3-(3-hydroxyazetidin-1-yl)propanamide

Example 224: (2S)-2-[1-(2-chloro-6-cyano-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-N-(5-cyano-2-pyridyl)-3-(3-hydroxyazetidin-1-yl)propanamide

Example 225: (2S)-2-[1-(2-chlorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-3-(3-hydroxyazetidin-1-yl)-N-(2-pyridyl)propanamide

Example 226: (2S)-2-[1-(2-chlorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-N-(5-chloro-2-pyridyl)-3-(3-hydroxyazetidin-1-yl)propanamide

Example 227: (2S)-3-[(1R)-2-hydroxy-1-methyl-ethoxy]-N-(5-methyl-2-pyridyl)-2-[1-(4-methyl-3-thienyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-propanamide

Example 228: (2S)-2-[1-(2-chlorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-3-[3-(hydroxymethyl)azetidin-1-yl]-N-(2-pyridyl)propanamide

Example 229: (2S)-2-[1-(2-chloro-6-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-3-(3-hydroxyazetidin-1-yl)propanamide

Example 230: (2S)-2-[1-(2,6-dichlorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-3-(3-hydroxyazetidin-1-yl)propanamide

Example 231: (2S)-2-[1-(2-chloro-6-cyano-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-3-[(1R)-2-hydroxy-1-methyl-ethoxy]-N-(2-pyridyl)propanamide

Example 232: (2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-3-[(1R)-2-hydroxy-1-methyl-ethoxy]-N-(5-methyl-2-pyridyl)propanamide

Example 233: (2S)-2-[1-(2,6-dichlorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-3-(3-hydroxyazetidin-1-yl)-N-(2-pyridyl)propanamide

Example 234: (2S)-N-(5-cyano-2-pyridyl)-2-[1-(2,6-dichlorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-3-(3-hydroxyazetidin-1-yl)propanamide

Example 235: (2S)-N-(5-cyano-2-pyridyl)-2-[1-(2,6-dichlorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-3-(2-hydroxyethoxy)propanamide

Example 236: (2S)-N-(5-chloro-2-pyridyl)-2-[1-(2,6-dicyanophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-3-[(1R)-2-hydroxy-1-methyl-ethoxy]propanamide

Example 237: (2S)-2-[1-(2-chloro-6-cyano-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-3-(2-hydroxyethoxy)propanamide

Example 238: (2S)-2-[1-(2-chloro-6-cyano-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-3-(2-hydroxyethoxy)-N-(2-pyridyl)propanamide

Example 239: (2S)-2-[1-(2-chloro-6-cyano-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-3-(3-hydroxyazetidin-1-yl)-N-(5-methylpyrazin-2-yl)propanamide

Example 240: (2S)-2-[1-(2-chloro-6-cyano-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-N-(5-chloro-2-pyridyl)-3-(3-hydroxyazetidin-1-yl)propanamide

Example 241: (2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-3-(3-hydroxyazetidin-1-yl)-N-(2-pyridyl)propanamide

Example 242: (2S)-2-[1-(2-chloro-6-cyano-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-3-(3-hydroxyazetidin-1-yl)propanamide

Example 243: (2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-3-(3-hydroxyazetidin-1-yl)propanamide

Example 244: (2S)-2-[1-(2-chloro-6-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-3-(2-hydroxyethoxy)propanamide

Example 245: (2S)-2-[1-(2-chlorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-3-[(1R)-2-hydroxy-1-methyl-ethoxy]propanamide

Example 246: (2S)-2-[1-(2-chloro-6-cyano-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-3-[(1R)-2-hydroxy-1-methyl-ethoxy]propanamide

Example 247: (2S)-2-[1-(2-chlorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-3-[(1R)-2-hydroxy-1-methyl-ethoxy]-N-(5-methylpyrazin-2-yl)propanamide

Example 248: (2S)-2-[1-(2-chlorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-3-(2-hydroxyethoxy)propanamide

Example 249: (2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-3-(3-hydroxyazetidin-1-yl)-N-(5-methylthiazol-2-yl)propanamide

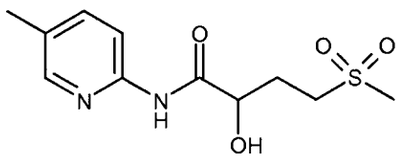
Example 250: (2S)-2-[1-(2,6-dichlorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-3-(2-hydroxyethoxy)-N-(2-pyridyl)propanamide

Example 251: (2S)-2-[1-(2-chloro-6-cyano-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-N-(5-cyano-2-pyridyl)-3-[(1R)-2-hydroxy-1-methyl-ethoxy]propanamide

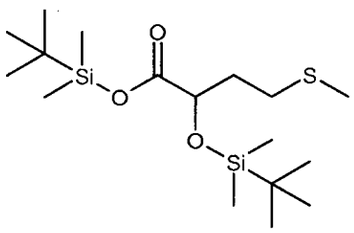
Example 252: (2S)-2-[1-(2-chlorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-N-(5-cyano-2-pyridyl)-3-[(1R)-2-hydroxy-1-methyl-ethoxy]propanamide

PREPARATION OF INTERMEDIATES

Intermediate A1: 2-hydroxy-*N*-(5-methylpyridin-2-yl)-4-(methylsulfonyl)butanamide

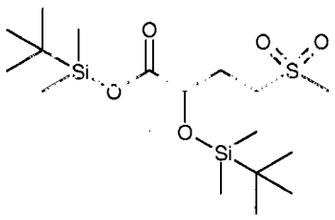


Step 1: *tert*-butyl(dimethyl)silyl 2-{[*tert*-butyl(dimethyl)silyl]oxy}-4-(methylthio)butanoate



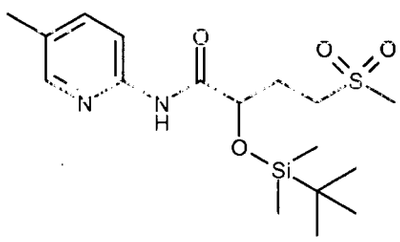
Imidazole (21.76 g, 320 mmol) and TBDMSCl (24.08 g, 151 mmol) was added to a stirred solution of 2-hydroxy-4-(methylthio)butyric acid (6.10 g, 40.6 mmol) in DMF (100 mL). The reaction mixture was kept at ambient temperature for 18 hrs. Water and EtOAc were added, and the two phases were separated. The aqueous phase was extracted with EtOAc. The organic extracts were combined and washed three times with water, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified with column chromatography (silica gel, eluting with a gradient consisting of 0-100% EtOAc in DCM) to give the title compound as a colourless oil (10.20 g), ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.29 (t, 1H), 2.59 (m, 2H), 2.09 (s, 3H), 1.98 (m, 2H), 0.94 (s, 9H), 0.91 (s, 9H), 0.28 (d, 6H), 0.08 (d, 6H).

Step 2: *tert*-butyl(dimethyl)silyl 2-{[*tert*-butyl(dimethyl)silyl]oxy}-4-(methylsulfonyl)butanoate



m-CPBA (77%, 5.70 g, 25.4 mmol) in DCM (10 mL) was added in portions to a stirred solution of *tert*-butyl(dimethyl)silyl 2-{[*tert*-butyl(dimethyl)silyl]oxy}-4-(methylthio)butanoate (Step 1) (5.00 g, 13.2 mmol) in DCM (15 mL). The reaction mixture was kept at ambient temperature for 1 ½ hrs. Water was added and the two phases were separated. The organic phase was washed two times with sodium pyrosulfite (5% in water), dried over $MgSO_4$ and concentrated in vacuo. The residue was purified with column chromatography (silica gel, eluting with a gradient consisting of 0-100% EtOAc in DCM) to give the title compound (2.12 g), ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.33 (t, 1H), 3.18 (m, 1H), 3.04 (m, 1H), 2.91 (s, 3H), 2.26 (m, 2H), 0.94 (s, 9H), 0.91 (s, 9H), 0.29 (d, 6H), 0.10 (m, 6H).

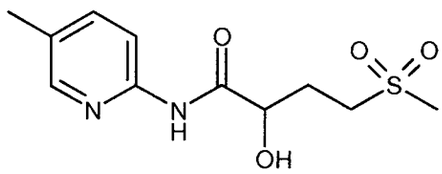
Step 3: 2-{[*tert*-butyl(dimethyl)silyl]oxy}-*N*-(5-methylpyridin-2-yl)-4-(methylsulfonyl)butanamide



Oxalyl chloride (0.74 g, 5.84 mmol) in DCM (2 mL) was added slowly to a stirred solution of *tert*-butyl(dimethyl)silyl 2-{[*tert*-butyl(dimethyl)silyl]oxy}-4-(methylsulfonyl)butanoate (Step 2) (2.00 g, 4.87 mmol) in DCM (8 mL) and DMF (three drops). After 1h at ambient temperature, gas evolution had subsided and the reaction mixture was concentrated in vacuo to remove excess oxalyl chloride. The residue was dissolved in DCM (8 mL) and pyridine (0.50 g, 6.33 mmol) and 2-amino-5-picoline (0.58 g, 5.36 mmol) were added. The reaction mixture was kept at ambient temperature for 1 h. Water was added and the two phases were separated. The aqueous phase was extracted with DCM. The organic extracts were combined and washed with water, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified with column chromatography (silica gel, eluting with

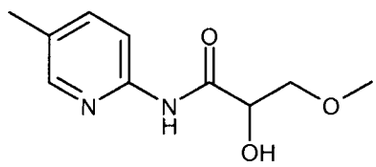
DCM/EtOAc:10/1) to give the title compound as a colourless oil (1.23 g), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.92 (br s, 1H), 8.13 (d, 1H), 8.08 (d, 1H), 7.53 (dd, 1H), 4.44 (t, 1H), 3.19 (m, 1H), 3.05 (m, 1H), 2.90 (s, 3H), 2.44 (m, 1H), 2.28 (m, 4H), 0.97 (s, 9H), 0.19 (d, 6H).

Step 4: 2-hydroxy-*N*-(5-methylpyridin-2-yl)-4-(methylsulfonyl)butanamide

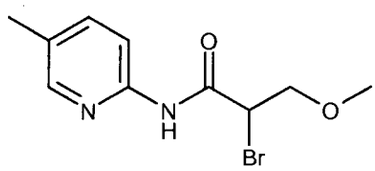


Tetrabutylammoniumfluoride trihydrate (1.43 g, 4.54 mmol) was added to a stirred solution of 2-{[*tert*-butyl(dimethyl)silyl]oxy}-*N*-(5-methylpyridin-2-yl)-4-(methylsulfonyl)butanamide (Step 3) (1.17 g, 3.03 mmol) in THF (10 mL). The reaction mixture was kept at ambient temperature for 30 minutes. Water and EtOAc were added and the two phases were separated. The aqueous phase was extracted with EtOAc. The organic extracts were combined and washed with water, dried over $MgSO_4$ and concentrated in vacuo. The residue was recrystallised from EtOAc to give the title compound as colourless solid (0.57 g), ^{1}H NMR (500 MHz, DMSO) δ 8.14 (d, 1H), 7.99 (d, 1H), 7.62 (dd, 1H), 4.23 (m, 1H), 3.17 (m, 2H), 2.96 (s, 3H), 2.24 (s, 3H), 2.16 (m, 1H), 1.98 (m, 1H).

Intermediate A2: 2-hydroxy-3-methoxy-*N*-(5-methylpyridin-2-yl)propanamide



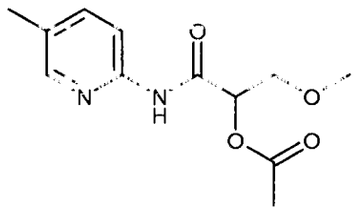
Step 1: 2-bromo-3-methoxy-*N*-(5-methylpyridin-2-yl)propanamide



Bromine (3.38g, 21.13 mmol) was added to a stirred solution of 3-methoxypropionic acid (2.00 g, 19.21 mmol) in thionyl chloride (11.4 g, 96.0 mmol). The reaction mixture was heated at 60°C for 3 hrs before it was concentrated in vacuo to remove excess reagents. The residue was dissolved in DCM (10 mL) and a solution of DIPEA (2.73 g, 21.13 mmol) and 2-amino-5-picoline (2.28 g, 21.13 mmol) in DCM (10 mL) was added slowly at 0°C.

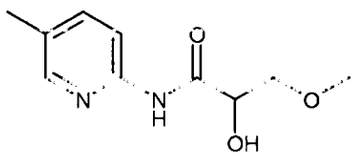
The reaction mixture was stirred at ambient temperature for 45 minutes. Water was added and the two phases were separated. The aqueous phase was extracted with DCM. The organic extracts were combined and washed with water, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified with column chromatography (silica gel, eluting with DCM/EtOAc:5/1) to give the title compound (2.30 g), ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.09 (br s, 1H), 8.10 (m, 2H), 7.55 (dd, 1H), 4.49 (t, 1H), 3.93 (d, 2H), 3.46 (s, 3H), 2.31 (s, 3H).

Step 2: 1-(methoxymethyl)-2-[(5-methylpyridin-2-yl)amino]-2-oxoethyl acetate



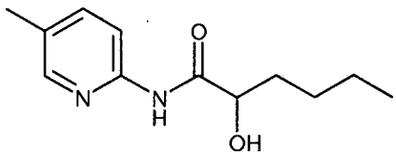
Potassium acetate (2.01 g, 20.50 mmol) was added to a stirred solution of 2-bromo-3-methoxy-*N*-(5-methylpyridin-2-yl)propanamide (Step 1) (1.40 g, 5.13 mmol) in ACN (20 mL). The reaction mixture was refluxed for 5 hrs. The reaction mixture was filtered and concentrated in vacuo. The residue was purified with column chromatography (silica gel, eluting with DCM/EtOAc:2/1) to give the title compound as a colourless solid (1.15 g), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (br s, 1H), 8.11 (m, 2H), 7.52 (dd, 1H), 5.44 (dd, 1H), 3.89 (dd, 1H), 3.78 (dd, 1H), 3.39 (s, 3H), 2.30 (s, 3H), 2.25 (s, 3H).

Step 3: 2-hydroxy-3-methoxy-*N*-(5-methylpyridin-2-yl)propanamide

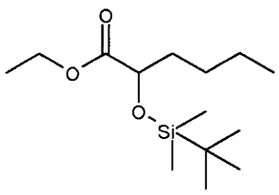


Anhydrous potassium carbonate (50 mg, 0.36 mmol) was added to a stirred solution of 1-(methoxymethyl)-2-[(5-methylpyridin-2-yl)amino]-2-oxoethyl acetate (Step 2) (1.10 g, 4.36 mmol) in MeOH (10 mL). The reaction mixture was kept at ambient temperature for 1 h before it was concentrated in vacuo. The residue was purified with column chromatography (silica gel, eluting with EtOAc) to give the title compound as a colourless solid (0.81 g), ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.39 (br s, 1H), 8.14 (d, 1H), 8.09 (d, 1H), 7.53 (dd, 1H), 4.92 (br s, 1H), 4.41 (dd, 1H), 3.75 (m, 2H), 3.42 (s, 3H), 2.30 (s, 3H).

Intermediate A3: 2-hydroxy-*N*-(5-methylpyridin-2-yl)hexanamide

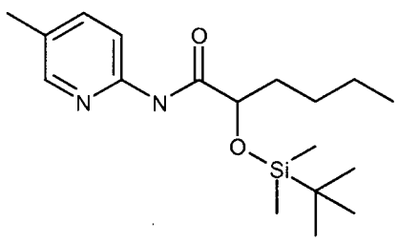


Step 1: ethyl 2-{[*tert*-butyl(dimethyl)silyl]oxy}hexanoate



Imidazole (4.10 g, 60.22 mmol) and TBDMSCl (3.60 g, 23.89 mmol) was added to a stirred solution of 2-hydroxy-hexanoic acid ethyl ester (3.20 g, 19.97 mmol) in DMF (25 mL). The reaction mixture was kept at ambient temperature for 18 hrs. Water and diethyl ether were added and the two phases were separated. The aqueous phase was extracted with diethyl ether. The organic extracts were combined and washed sequentially with 0.5 M HCl and water, dried over $MgSO_4$ and concentrated in vacuo to give the title product (5.30 g), ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.18 (m, 3H), 1.69 (m, 2H), 1.35 (m, 4H), 1.28 (t, 3H), 0.91 (m, 12H), 0.07 (d, 6H).

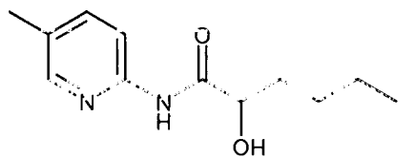
Step 2: 2-{[*tert*-butyl(dimethyl)silyl]oxy}-*N*-(5-methylpyridin-2-yl)hexanamide



n-BuLi (2.25 mL, 1.6 M in hexanes, 3.60 mmol) was added slowly to a stirred solution of 2-amino-5-picoline (390 mg, 3.60 mmol) in anhydrous THF (6 mL). The reaction mixture was kept at ambient temperature for 10 minutes before it was added to a solution of ethyl 2-{[*tert*-butyl(dimethyl)silyl]oxy}hexanoate (Step 1) (820 mg, 3.00 mmol) in anhydrous THF (4 mL). The reaction mixture was stirred at ambient temperature for 1 h. Water and EtOAc were added and the two phases were separated. The organic phase was washed with water, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified with column chromatography (silica gel, eluting with a gradient consisting of 0-100% EtOAc in

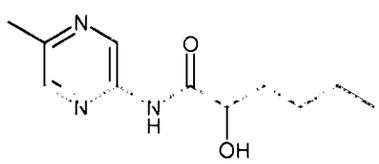
heptane) to give the title compound as a colourless oil (223 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.87 (br s, 1H), 8.13 (m, 2H), 7.51 (dd, 1H), 4.25 (t, 1H), 2.29 (s, 3H), 1.79 (m, 2H), 1.35 (m, 4H), 0.98 (s, 8H), 0.89 (t, 3H), 0.14 (d, 6H).

Step 3: 2-hydroxy-*N*-(5-methylpyridin-2-yl)hexanamide



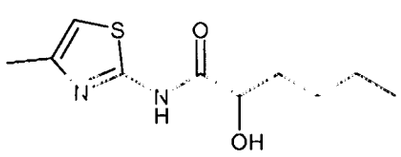
Tetrabutylammoniumfluoride trihydrate (302 mg, 0.96 mmol) was added to a stirred solution of 2-{[*tert*-butyl(dimethyl)silyl]oxy}-*N*-(5-methylpyridin-2-yl)hexanamide (Step 2) (215 mg, 0.64 mmol) in THF (5 mL). The reaction mixture was kept at ambient temperature for 1 h. Water and EtOAc were added and the two phases were separated. The organic phase was washed with water, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified with column chromatography (silica gel, eluting with DCM/EtOAc:2/1) to give the title compound as a colourless solid (135 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.46 (br s, 1H), 8.20 (d, 1H), 8.04 (d, 1H), 7.55 (dd, 1H), 5.47 (br s, 1H), 4.29 (m, 1H), 2.31 (s, 3H), 1.98 (m, 1H), 1.76 (m, 1H), 1.52 (m, 2H), 1.38 (m, 2H), 0.92 (t, 3H).

Intermediate A4: 2-hydroxy-*N*-(5-methylpyrazin-2-yl)hexanamide



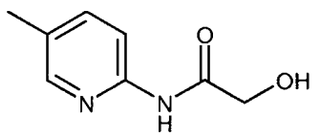
The title compound was prepared in a manner similar to that described for Intermediate A3, starting from ethyl 2-{[*tert*-butyl(dimethyl)silyl]oxy}hexanoate and 2-amino-5-methylpyrazine, ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.46 (s, 1H), 8.98 (br s, 1H), 8.12 (s, 1H), 4.32 (m, 1H), 2.98 (d, 1H), 2.54 (s, 3H), 1.96 (m, 1H), 1.78 (m, 1H), 1.44 (m, 4H), 0.93 (t, 3H).

Intermediate A5: 2-hydroxy-*N*-(4-methyl-1,3-thiazol-2-yl)hexanamide



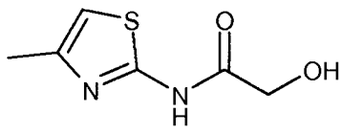
The title compound was prepared in a manner similar to that described for Intermediate A3, starting from ethyl 2-{[*tert*-butyl(dimethyl)silyl]oxy}hexanoate and 2-amino-4-methylthiazole, ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.30 (br s, 1H), 6.54 (s, 1H), 5.12 (br s, 1H), 4.41 (m, 1H), 2.35 (s, 3H), 2.00 (m, 1H), 1.76 (m, 1H), 1.48 (m, 2H), 1.39 (m, 2H), 0.92 (t, 3H).

Intermediate A6: 2-hydroxy-*N*-(5-methylpyridin-2-yl)acetamide



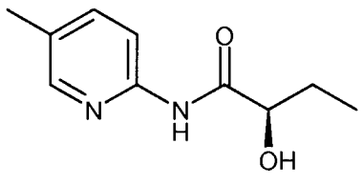
The title compound was prepared in a manner similar to that described for Intermediate A3, starting from methyl glycolate and 2-amino-5-picoline, ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.24 (br s, 1H), 8.19 (d, 1H), 8.07 (d, 1H), 7.57 (dd, 1H), 5.59 (br s, 1H), 4.26 (s, 2H), 2.31 (s, 3H).

Intermediate A7: 2-hydroxy-*N*-(4-methyl-1,3-thiazol-2-yl)acetamide

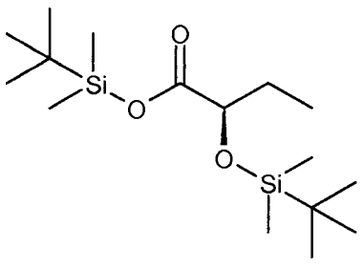


The title compound was prepared in a manner similar to that described for Intermediate A3, starting from methyl glycolate and 2-amino-4-methylthiazole, ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.11 (br s, 1H), 6.55 (s, 1H), 5.58 (br s, 1H), 4.36 (s, 2H), 2.34 (s, 3H).

Intermediate A8: **(2*R*)-2-Hydroxy-*N*-(5-methylpyridin-2-yl)butanamide**

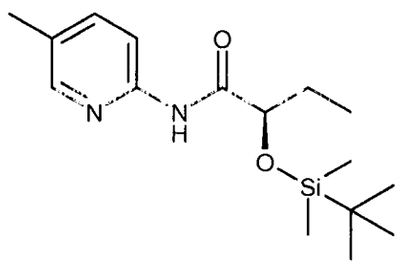


Step 1: *tert*-Butyl(dimethyl)silyl (2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}butanoate



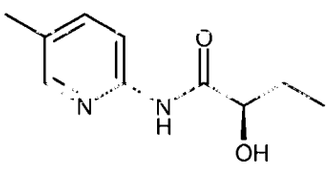
Imidazole (2.61g, 38.43 mmol) and TBDMSCl (3.62g, 24.02 mmol) was added to a stirred solution of (*R*)-2-hydroxy-butyric acid (1.0 g, 9.61 mmol) in DMF (20 mL). The reaction was stirred at ambient temperature for 18 hrs. Water and EtOAc were added and the two phases were separated. The aqueous phase was extracted with EtOAc. The organic extracts were combined and washed three times with water, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified with column chromatography (silica gel, eluting with heptane/EtOAc:5/2) to give the title compound as a colorless oil (2.77 g), ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.09 (dd, 1H), 1.72 (m, 2H), 0.93 (m, 21H), 0.27 (d, 6H), 0.07 (d, 6H).

Step 2: (2*R*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-*N*-(5-methylpyridin-2-yl)butanamide



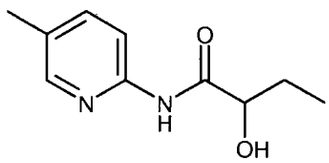
Oxalyl chloride (1.32 g, 10.43 mmol was added slowly to a stirred solution of *tert*-butyl(dimethyl)silyl (2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}butanoate (Step 1) (2.77 g, 8.69 mmol) in DCM (10 mL) and DMF (three drops). After 1h at ambient temperature, gas evolution had subsided and the reaction mixture was concentrated in vacuo to remove excess oxalyl chloride. The residue was dissolved in DCM (10 mL) and pyridine (0.89 g, 11.30 mmol) and 2-amino-5-picoline (1.03 g, 9.56 mmol) were added. The reaction mixture was kept at ambient temperature for 2 hrs. Water was added and the two phases were separated. The aqueous phase was extracted with DCM. The organic extracts were combined and washed with water, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified with column chromatography (silica gel, eluting with heptane/EtOAc:5/2) to give the title compound as a colourless oil (2.0 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.91 (br s, 1H), 8.15 (d, 2H), 7.53 (m, 1H), 4.26 (t, 1H), 2.31 (s, 3H), 1.85 (m, 2H), 0.96 (m, 12H), 0.17 (m, 6H).

Step 3: (2*R*)-2-Hydroxy-*N*-(5-methylpyridin-2-yl)butanamide



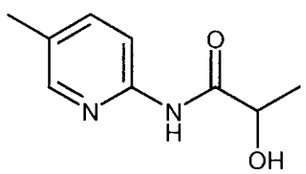
Tetrabutylammoniumfluoride trihydrate (3.21 g, 10.19 mmol) was added to a stirred solution of (2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-*N*-(5-methylpyridin-2-yl)butanamide (Step 2) (2.00g, 6.79 mmol) in THF (20 mL). The reaction mixture was kept at ambient temperature for 2 hrs. Water and EtOAc were added and the two phases were separated. The aqueous phase was extracted with EtOAc. The organic extracts were combined and washed with water, dried over $MgSO_4$ and concentrated in vacuo. The residue was recrystallised from diethyl ether to give the title compound as colourless crystals (1.14 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.35 (br s, 1H), 8.21 (d, 1H), 8.08 (s, 1H), 7.57 (d, 1H), 5.03 (br s, 1H), 4.25 (m, 1H), 2.32 (s, 3H), 2.01 (m, 1H), 1.82 (m, 1H), 1.10 (t, 3H).

Intermediate A9: **2-Hydroxy-*N*-(5-methylpyridin-2-yl)butanamide**



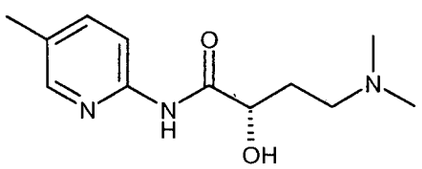
The title compound was prepared in a manner similar to that described for Intermediate A8, starting from 2-hydroxy-butyric acid and 2-amino-5-picoline, ^{1}H NMR (300 MHz, CD_3OD) δ 8.10 (d, 1H), 8.05 (d, 1H), 7.63 (dd, 1H), 4.10 (dd, 1H), 2.30 (s, 3H), 1.87 (m, 1H), 1.71 (m, 1H), 1.00 (t, 3H).

Intermediate A10: **2-Hydroxy-*N*-(5-methylpyridin-2-yl)propanamide**

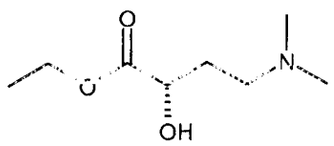


The title compound was prepared in a manner similare to that described for Intermediate A8, starting from 2-hydroxy-propionic acid and 2-amino-5-picoline, ^{1}H NMR (300 MHz, CD_3OD) δ 8.11 (d, 1H), 8.05 (d, 1H), 7.64 (dd, 1H), 4.26 (q, 1H), 2.30 (s, 3H), 1.43 (d, 3H).

Intermediate A11: **(2*S*)-4-(dimethylamino)-2-hydroxy-*N*-(5-methylpyridin-2-yl)butanamide**

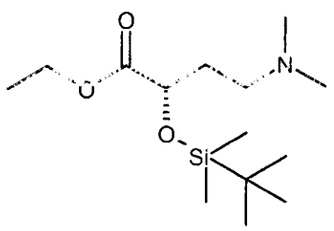


Step 1: ethyl (2*S*)-4-(dimethylamino)-2-hydroxybutanoate



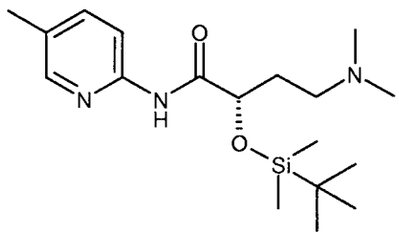
Formic acid (7.0 mL) and formaldehyde (6 mL, 36% in water) was added to (*S*)-4-amino-2-hydroxybutyric acid (2.00 g, 16.79 mmol). The reaction mixture was refluxed under stirring for 6 hrs when gas evolution had subsided. The reaction mixture was cooled to ambient temperature and concentrated HCl (2 mL) was added. The reaction mixture was concentrated in vacuo and EtOH was added. The solution was refluxed for 5 minutes before it again was concentrated in vacuo. The residue was treated with EtOAc and sodium bicarbonate (5% in water). The two phases were separated and the organic phase was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified with column chromatography (silica gel, eluting with a gradient consisting of 0-100% EtOAc in DCM) to give the title compound as a colourless oil (1.81 g), ^{1}H NMR (300 MHz, DMSO) δ 4.08 (m, 2H), 3.10 (m, 5H), 2.70 (s, 6H), 2.06 (m, 1H), 1.92 (m, 1H), 1.20 (t, 1H).

Step 2: ethyl (2*S*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-4-(dimethylamino)butanoate



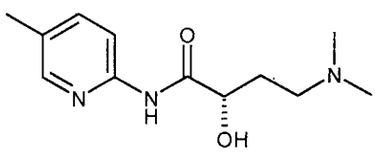
Imidazole (1.98 g, 29.10 mmol) and TBDMSCl (2.34 g, 15.52 mmol) was added to a stirred solution of ethyl (2*S*)-4-(dimethylamino)-2-hydroxybutanoate (Step 1) (3.20 g, 19.97 mmol) in DMF (25 mL). The reaction mixture was kept at ambient temperature for 18 hrs. Water and EtOAc were added and the two phases were separated. The aqueous phase was extracted with EtOAc. The organic extracts were combined and washed three times with water, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified with column chromatography (silica gel, eluting with heptane/EtOAc:2/1) to give the title compound as a colourless oil (2.73 g), ^{1}H NMR (300 MHz, DMSO) δ 4.28 (m, 1H), 4.18 (m, 2H), 2.44 (m, 1H), 2.30 (m, 1H), 2.22 (s, 6H), 1.87 (m, 2H), 1.28 (t, 3H), 0.90 (s, 9 H), 0.08 (d, 6H).

Step 3: (2*S*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-4-(dimethylamino)-*N*-(5-methylpyridin-2-yl)butanamide



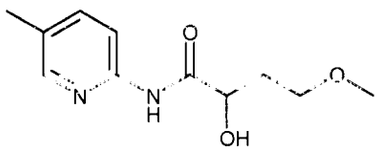
n-BuLi (3.40 mL, 1.6 M in hexanes, 5.44 mmol) was added slowly to a stirred solution of 2-amino-5-picoline (616 mg, 5.70 mmol) in anhydrous THF (8 mL). The reaction mixture was kept at ambient temperature for 10 minutes before a solution of ethyl (2*S*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-4-(dimethylamino)butanoate (Step 2) (1.50 g, 5.18 mmol) in anhydrous THF (2 mL) was added. The reaction mixture was stirred at ambient temperature for 1 h. Water and EtOAc were added and the two phases were separated. The aqueous phase was extracted with EtOAc. The organic extracts were combined and washed with water, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified with column chromatography (silica gel, eluting with EtOAc) to give the title compound (320 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.89 (br s, 1H), 8.12 (m, 2H), 7.51 (dd, 1H), 4.32 (t, 1H), 2.47 (m, 1H), 2.31 (m, 4H), 2.21 (s, 6H), 1.97 (m, 2H), 0.98 (s, 9H), 0.15 (d, 6H).

Step 4: (2*S*)-4-(dimethylamino)-2-hydroxy-*N*-(5-methylpyridin-2-yl)butanamide



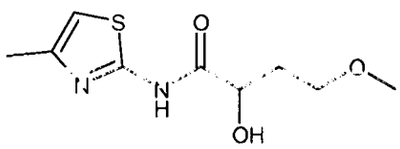
Tetrabutylammoniumfluoride trihydrate (417 mg, 1.32 mmol) was added to a stirred solution of (2*S*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-4-(dimethylamino)-*N*-(5-methylpyridin-2-yl)butanamide (Step 3) (310 mg, 0.88 mmol) in THF (5 mL). The reaction mixture was kept at ambient temperature for 30 minutes. Water and EtOAc were added and the two phases were separated. The organic phase was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified with column chromatography (silica gel, eluting with EtOAc/MeOH:10/1) to give the title compound as a solid (110 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.44 (br s, 1H), 8.15 (d, 1H), 8.12 (d, 1H), 7.51 (dd, 1H), 4.39 (dd, 1H), 2.63 (m, 2H), 2.28 (m, 9H), 2.09 (m, 1H), 1.92 (m, 1H).

Intermediate A12: 2-hydroxy-4-methoxy-*N*-(5-methylpyridin-2-yl)butanamide



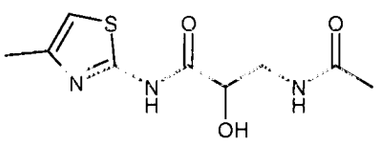
The title compound was prepared in a manner similar to that described for Intermediate A16 and Intermediate A2 (Step 2 - Step 3) starting from diethyl malonate, 2-bromoethyl methyl ether and 2-amino-5-picoline, ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.24 (br s, 1H), 8.14 (m, 2H), 7.52 (dd, 1H), 4.48 (br s, 1H), 4.39 (m, 1H), 3.69 (m, 2H), 3.39 (s, 3H), 2.25 (m, 4H), 2.09 (m, 1H).

Intermediate A13: 2-Hydroxy-4-methoxy-*N*-(4-methyl-1,3-thiazol-2-yl)butanamide

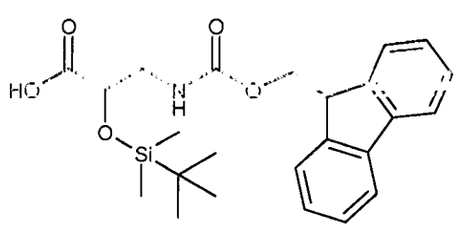


The title compound was prepared in a manner similar to that described for Intermediate A16 and Intermediate A2 (Step 2 - Step 3) starting from diethyl malonate, 2-bromoethyl methyl ether and 2-amino-4-methylthiazol, ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.07 (br s, 1H), 6.53 (d, 1H), 4.68 (br s, 1H), 4.48 (dd, 1H), 3.68 (m, 2H), 3.37 (s, 3H), 2.33 (s, 3H), 2.20 (m, 1H), 2.14 (m, 1H).

Intermediate A14: 3-acetamido-2-hydroxy-*N*-(4-methyl-1,3-thiazol-2-yl)propanamide



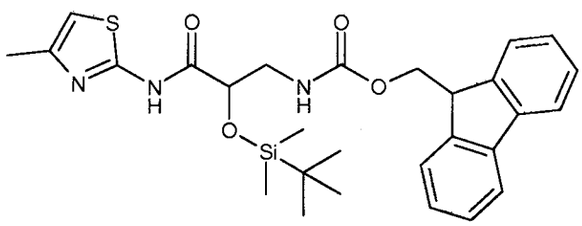
Step 1: 2-(*tert*-Butyl-dimethyl-silanyloxy)-3-(9*H*-fluoren-9-ylmethoxycarbonylamino)-propionic acid



TBDMSCl (1.01 g, 6.72 mmol), DMAP (0.19 g, 1.52 mmol) and pyridine (0.97 g, 12.2 mmol) were added to a stirred solution of FMOC-isoserine (1.00 g, 3.05 mmol) in DMF (20 mL). The reaction mixture was heated at 50°C for 18 hrs. Water (10 mL) was added

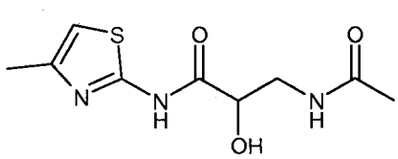
and the reaction mixture was concentated in vacuo. DCM and HCl (0.5 M) were added and the two phases were separated. The aqueous phase was extracted two times with DCM. The organic extracts were combined concentrated in vacuo. The residue was purified with column chromatography (silica gel, eluting with a gradient consisting of 20-100% EtOAc in heptane) to give the title compound (1.3 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, 2H), 7.59 (m, 2H), 7.40 (t, 2H), 7.30 (m, 2H), 5.14 (br s, 1H), 4.29 (m, 4H), 3.53 (m, 2H), 0.91 (s, 9H), 0.10 (s, 6H).

Step 2: 9*H*-fluoren-9-ylmethyl (2-{[*tert*-butyl(dimethyl)silyl]oxy}-3-[(4-methyl-1,3-thiazol-2-yl)amino]-3-oxopropyl)carbamate



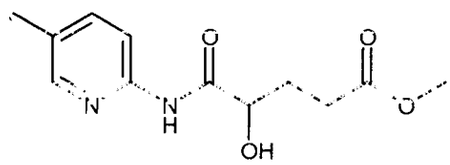
Oxalyl chloride (1.12 g, 8.83 mmol) in DCM (5 mL) was added slowly to a stirred solution of 2-(*tert*-butyl-dimethyl-silanyloxy)-3-(9*H*-fluoren-9-ylmethoxycarbonylamino)-propionic acid (Step 1) (1.30 g, 2.94 mmol) in DCM (25 ml) and DMF (50 µl) at 0°C. After 3 hrs at ambient temperature, gas evolution had subsided and the reaction mixture was concentrated in vacuo. THF (20 mL) and DIPEA (0.57g, 4.4 mmol) were added, followed by the addition of 2-amino-4-methylthiazole (0.403 g, 3.53 mmol) in DCM (5 mL). The reaction mixture was kept at ambient temperature for 3 hrs. Water (0.5 mL) was added and the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluting with a gradient consisting of 0-40% EtOAc in heptane) to give the title compound as a colorless oil (0.10 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.60 (br s, 1H), 7.75 (d, 2H), 7.57 (d, 2H), 7.39 (t, 2H), 7.30 (t, 2H), 6.56 (s, 1H), 5.19 (br s, 1H), 4.41 (t, 1H), 4.37 (d, 2H), 4.21 (t, 1H), 3.66 (m, 1H), 3.49 (m, 1H), 2.35 (s, 3H), 0.98 (s, 9H), 0.20 (s, 6H).

Step 3: 3-acetamido-2-hydroxy-*N*-(4-methyl-1,3-thiazol-2-yl)propanamide

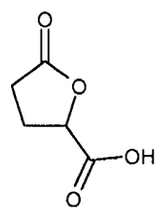


Tetrabutylammoniumfluoride (0.28 mL, 1M in THF, 0.28 mmol) was added to a stirred solution of 9*H*-fluoren-9-ylmethyl (2-{[*tert*-butyl(dimethyl)silyl]oxy}-3-[(4-methyl-1,3-thiazol-2-yl)amino]-3-oxopropyl)carbamate (Step 2) (0.10 g, 0.186 mmol) in THF (5 mL). The reaction mixture was kept at ambient temperature for 3 hrs before DIPEA (0.036g, 0.28 mmol) and acetyl chloride (0.018g, 0.22 mmol) were added. The reaction mixture was stirred for another 3 hrs at ambient temperature and water (1 mL) was added and the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluting with a gradient consisting of 0-20% MeOH in DCM) to give the title compound as a colorless oil (0.04 g). ^{1}H NMR (500 MHz, CD_3OD) δ 6.71 (s, 1H), 4.38 (dd, 1H), 3.64 (dd, 1H), 3.48 (dd, 1H), 2.33 (s, 3H), 1.96 (s, 3H).

Intermediate A15: **methyl 4-hydroxy-5-[(5-methylpyridin-2-yl)amino]-5-oxopentanoate**

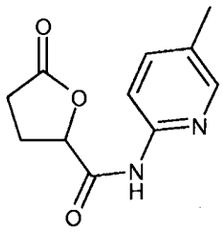


Step 1: 5-oxotetrahydrofuran-2-carboxylic acid



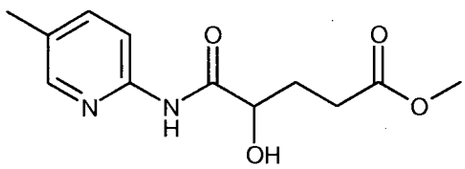
Amberlite(R) IR-120 (3.0 g, washed with 4 x 20 ml THF) was added to a stirred suspension of α-hydroxyglutaric acid zinc salt (0.40g, 1.90 mmol) in THF (15 mL). The reaction mixture was kept at ambient temperature for 16 hrs. The reaction mixture was filtered and the resin was washed three times with THF. The combined extracts was concentrated in vacuo and the residue was purified by column chromatography (silica gel, eluting with a gradient consisting of 5-50% MeOH in DCM) to give the title compound as a colorless oil (0.215 g). ^{1}H NMR (500 MHz, D_2O) δ 5.00 (t, 1H), 2.53 (m, 3H), 2.20 (m, 1H).

Step 2: 5-Oxo-tetrahydro-furan-2-carboxylic acid (5-methyl-pyridin-2-yl)-amide



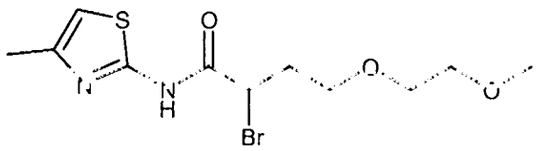
Oxalyl chloride (0.252 g, 1.63 mmol) in DCM (5 mL) was added slowly to a stirred solution of 5-oxotetrahydrofuran-2-carboxylic acid (Step 1) (0.215 g, 1.65 mmol) in DCM (10 ml) and DMF (50 µl) at 0°C. After 3 hrs at ambient temperature, gas evolution had subsided. DIPEA (0.64, 4.95 mmol) was added followed by the addition of 2-amino-5-picoline (0.357 g, 3.3 mmol) in DCM (5 mL). The reaction mixture was kept at ambient temperature for 3 hrs. Water (0.5 mL) was added and the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluting with a gradient consisting of 0-40% MeOH in DCM) to give the title compound as a colorless oil (0.138 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (br s, 1H), 8.13 (d, 1H), 8.08 (d, 1H), 7.54 (dd, 1H), 4.99 (t, 1H), 2.71 (m, 1H), 2.63 (m, 2H), 2.48 (m, 1H), 2.31 (s, 3H).

Step 3: methyl 4-hydroxy-5-[(5-methylpyridin-2-yl)amino]-5-oxopentanoate

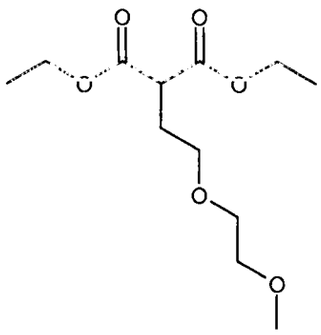


Amberlyst 15 (2.0g, washed with 4 x 20 ml of MeOH) was added to a stirred solution of 5-oxo-tetrahydro-furan-2-carboxylic acid (5-methyl-pyridin-2-yl)-amide (Step 2) (0.138g, 0.63 mmol) in MeOH (10 mL). The reaction mixture was kept at ambient temperature for 16 hrs. HCl (1 M, 5 mL) was added and the reaction mixture was stirred for another hour at ambient temperature. The reaction mixture was filtered and the resin was washed two times with MeOH (10 mL) and HCl (1 M, 2 mL). The combined extracts was concentrated in vacuo and the residue was purified by column chromatography (silica gel, eluting with a gradient consisting of 0-40% MeOH in DCM) to give the title compound as a colorless oil (0.02 g). ^{1}H NMR (500 MHz, THF) δ 9.24 (br s, 1H), 8.16 (d, 1H), 8.09 (s, 1H), 7.53 (d, 1H), 5.34 (d, 1H), 4.17 (m, 1H), 3.62 (s, 3H), 2.47 (m, 2H), 2.28 (s, 3H), 2.17 (m, 1H), 1.95 (m, 1H).

Intermediate A16: 2-bromo-4-(2-methoxyethoxy)-*N*-(4-methyl-1,3-thiazol-2-yl)butanamide

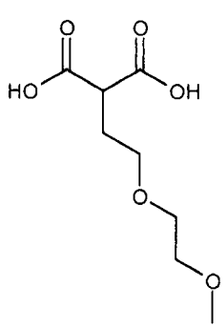


Step 1: diethyl [2-(2-methoxyethoxy)ethyl]malonate



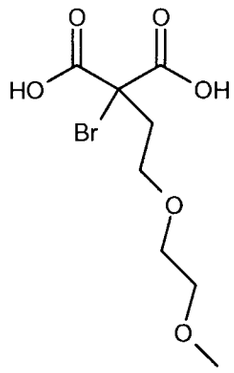
Sodium (0.72 g, 31.31 mmol) was added in portions to EtOH (99.5%, 35 mL) under stirring. When all sodium had dissolved, diethyl malonate (4.80 g, 29.97 mmol) was added slowly during 5 minutes and the reaction mixture was stirred for another 15 minutes. 1-Bromo-2-(2-methoxyethoxy)-ethane (5.50 g, 30.05 mmol) was added and the reaction mixture was refluxed for 2 hrs. Any solids were filtered off and the clear solution was concentrated in vacuo. The residue was taken up in water and diethyl ether and the two phases were separated. The organic phase was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified with column chromatography (silica gel, eluting with EtOAc/MeOH:20/1) to give the title compound as a colourless oil (3.80 g), ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.19 (q, 4H), 3.54 (m, 7H), 3.38 (s, 3H), 2.19 (m, 2H), 1.27 (t, 6H).

Step 2: [2-(2-methoxyethoxy)ethyl]malonic acid



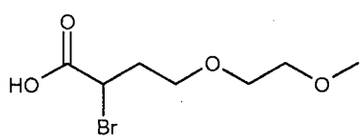
Sodium hydroxide (2.00 g, 50.00 mmol) in water (15 mL) was added to a stirred solution of diethyl [2-(2-methoxyethoxy)ethyl]malonate (Step 1) (2.35 g, 8.96 mmol). The reaction was kept at ambient temperature for 10 minutes before MeOH was removed in vacuo. The resulting solution was acidified to pH=1 by the addition of HCl (5 M). Diethyl ether was added and the two phases were separated. The aqueous phase was extracted three times with diethyl ether. The organic extracts were combined, dried over $MgSO_4$ and concentrated in vacuo to give the title compound as a colourless oil (1.81 g), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (br s, 2H), 3.58 (m, 7H), 3.40 (s, 3H), 2.23 (m, 2H).

Step 3: bromo[2-(2-methoxyethoxy)ethyl]malonic acid



HBr (4.1 M in acetic acid, two drops) and bromine (1.44 g, 9.01 mmol) was added to a stirred solution of [2-(2-methoxyethoxy)ethyl]malonic acid (Step 2) (1.75 g, 8.49 mmol) in diethyl ether. The reaction mixture was kept at ambient temperature for 20 minutes when most of the bromine colour had disappeared. Sodium pyrosulfite (5% in water) was added and the two phases were separated. The aqueous phase was extracted with diethyl ether two times. The organic extracts were combined and washed with water. The organic phase was dried over $MgSO_4$ and concentrated in vacuo to give the title product as a colourless solid (1.91 g), ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (br s, 2H), 3.75 (t, 2H), 3.62 (m, 4H), 3.42 (s, 3H), 2.70 (t, 2H).

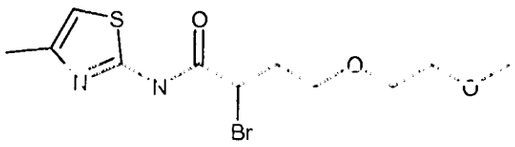
Step 4: 2-bromo-4-(2-methoxyethoxy)butanoic acid



Bromo[2-(2-methoxyethoxy)ethyl]malonic acid (Step 3) (1.15 g, 4.04 mmol) was heated at 150°C under stirring. The heating was discontinued after 10 minutes when gas evolution

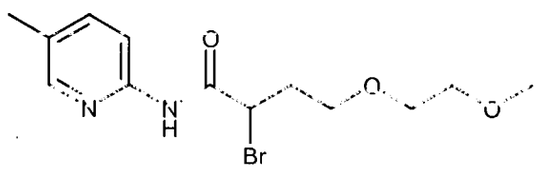
had ceased. This gave the title compound as a yellowish oil (941 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (br s, 1H), 4.56 (dd, 1H), 3.60 (m, 6H), 3.40 (s, 3H), 2.42 (m, 1H), 2.20 (m, 1H).

Step 5: 2-bromo-4-(2-methoxyethoxy)-*N*-(4-methyl-1,3-thiazol-2-yl)butanamide



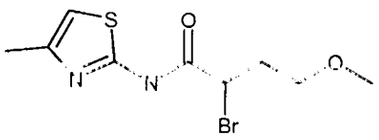
A stirred solution of 2-bromo-4-(2-methoxyethoxy)butanoic acid (Step 4) (200 mg, 0.83 mmol) in thionyl chloride (4 mL) was refluxed for 30 minutes. The reaction mixture was concentrated in vacuo to remove excess thionyl chloride. The residue was dissolved in DCM (2 mL) and was added slowly to a stirred solution of 2-amino-4-methylthiazole (99.5 mg, 0.871 mmol) and DIPEA (117.9 mg, 0.913 mmol) in DCM (4 mL). The reaction mixture was kept at ambient temperature for 1 h before water was added and the two phases were separated. The organic phase was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified with column chromatography (silica gel, eluting with EtOAc/MeOH:1/1) to give the title compound as an oil (105 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.57 (d, 1H), 4.72 (dd, 1H), 3.66 (m, 2H), 3.60 (m, 2H), 3.51 (m, 2H), 3.36 (s, 3H), 2.50 (m, 1H), 2.31 (m, 4H).

Intermediate A17: 2-bromo-4-(2-methoxyethoxy)-*N*-(5-methylpyridin-2-yl)butanamide



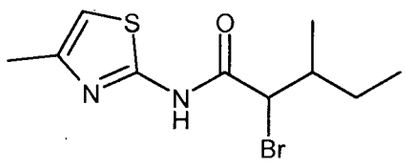
The title compound was prepared in a manner similar to that described for Intermediate A16 (Step 5) starting from 2-bromo-4-(2-methoxyethoxy)butanoic acid and 2-amino-5-picoline.

Intermediate A18: 2-bromo-4-methoxy-*N*-(4-methyl-1,3-thiazol-2-yl)butanamide



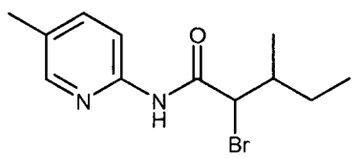
The title compound was prepared in a manner similar to that described for Intermediate A16 starting from diethyl malonate and 2-bromoethyl methyl ether, ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.35 (br s, 1H), 6.61 (d, 1H), 4.66 (dd, 1H), 3.57 (t, 2H), 3.34 (s, 3H), 2.49 (m, 1H), 2.40 (d, 3H), 2.28 (m, 1H).

Intermediate A19: 2-bromo-3-methyl-*N*-(4-methyl-1,3-thiazol-2-yl)pentanamide



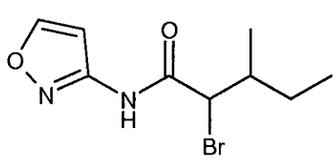
The title compound was prepared in a manner similar to that described for Intermediate A16 (Step 5) starting from 2-methyl-3-methylpentanoic acid and 2-amino-4-methylthiazol, (Diastereomers) ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (br s, 1H), 6.58 (d, 1H), 4.62 (d, 0.37H), 4.45 (d, 0.63H), 2.37 (d, 3H), 2.19 (m, 1H), 1.59 (m, 0.74H), 1.41 (m, 1.26H), 1.07 (d, 1.89H), 0.95 (m, 4.11H).

Intermediate A20: 2-bromo-3-methyl-*N*-(5-methylpyridin-2-yl)pentanamide



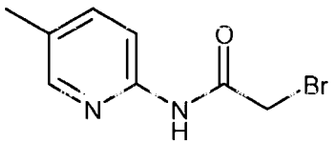
The title compound was prepared in a manner similar to that described for Intermediate A16 (Step 5) starting from 2-methyl-3-methylpentanoic acid and 2-amino-5-picoline, (Diastereomers) ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83 (br s, 0.35H), 8.70 (br s, 0.65H), 8.13 (s, 1H), 8.08 (d, 1H), 7.54 (d, 1H), 4.53 (d, 0.35H), 4.35 (d, 0.65H), 2.31 (s, 3H), 2.20 (m, 1H), 1.66 (m, 1H), 1.37 (m, 1H), 1.08 (d, 1.95H), 1.01 (d, 1.05H), 0.94 (m, 3H).

Intermediate A21: 2-bromo-*N*-isoxazol-3-yl-3-methylpentanamide



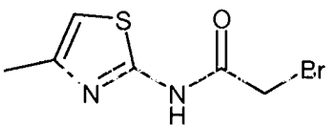
The title compound was prepared in a manner similar to that described for Intermediate A16 (Step 5) starting from 2-methyl-3-methylpentanoic acid and 3-aminoisoxazol, (Diastereomers) ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.57 (br s, 0.62H), 9.47 (br s, 0.38H), 8.33 (d, 1H), 7.10 (dd, 1H), 4.53 (d, 0.38H), 4.37 (d, 0.62H), 2.19 (m, 1H), 1.70 (m, 0.62H), 1.43 (m, 1.38H), 1.08 (d, 1.86H), 1.04 (d, 1.14H), 0.95 (m, 3H).

Intermediate A22: 2-bromo-*N*-(5-methylpyridin-2-yl)acetamide



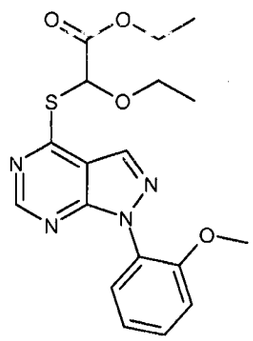
The title compound was prepared in a manner similar to that described for Intermediate A16 (Step 5) starting from bromoacetyl bromide and 2-amino-5-picoline.

Intermediate A23: 2-Bromo-*N*-(4-methyl-1,3-thiazol-2-yl)acetamide



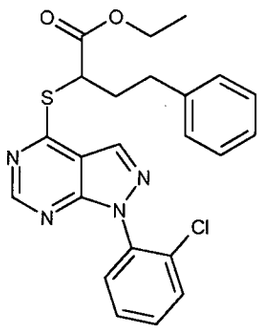
The title compound was prepared in a manner similar to that described for Intermediate A16 (Step 5) starting from bromoacetyl bromide and 2-amino-4-methylthiazole.

Intermediate A24: ethyl ethoxy{[1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]thio}acetate



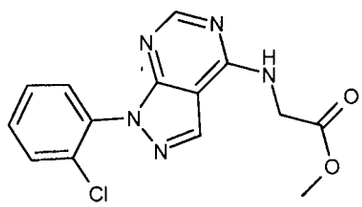
The title compound was prepared in a manner similar to that described for Example 54 starting from 2-chloro-2-ethoxyacetic acid ethyl ester and Intermediate B13, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.26 (s, 1H), 7.46 (m, 2H), 7.13 (m, 2H), 6.88 (s, 1H), 4.32 (m, 2H), 3.90 (m, 1H), 3.78 (m, 4H), 1.31 (m, 6H).

Intermediate A25: ethyl 2-{[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]thio}-4-phenylbutanoate

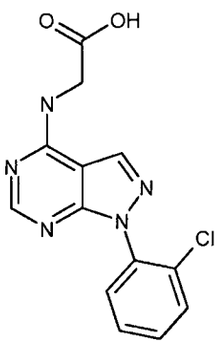


The title compound was prepared in a manner similar to that described for Example 54 starting from ethyl 2-bromo-4-phenylbutanoate and Intermediate B12, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.29 (s, 1H), 7.62 (m, 1H), 7.50 (m, 3H), 7.27 (m, 5H), 4.99 (t, 1H), 4.24 (m, 2H), 2.86 (m, 2H), 2.39 (m, 2H), 1.30 (t, 3H).

Intermediate A26: methyl *N*-[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]glycinate



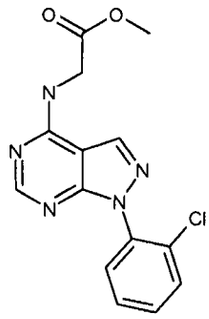
Step 1: *N*-[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]glycine



4-chloro-1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (1.3 g, 4.90 mmol) was added to a stirred solution of glycine (0.72 g, 9.59 mmol) and anhydrous sodium carbonate (0.58 g, 5.48 mmol) in water (10mL). The reaction was refluxed for 2 hrs. The reaction mixture was acidified by the addition of formic acid. The precipitate was filtered, washed with

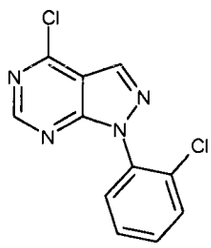
water and dried in vacuo to give the title compound as a colourless solid (1.23 g), ^{1}H NMR (300 MHz, CD_3OD) δ 8.32 (s, 1H), 8.24 (s, 1H), 7.66 (m, 1H), 7.54 (m, 3H), 4.34 (s, 2H).

Step 2: methyl *N*-[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]glycinate



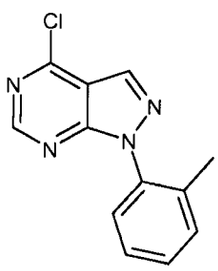
Trimethylsilyldiazomethane (2 M in diethyl ether) was added slowly to a stirred solution of *N*-[1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]glycine (Step 1) (0.80 g, 2.63 mmol) in DCM (4 mL) and MeOH (1 mL) until a yellow colour persisted. A few drops of acetic acid was added after 1 minute followed by the addition of DCM and water. The two phases were separated and the organic phase was concentrated in vacuo to give the title compound (795 mg), ^{1}H NMR (300 MHz, CD3OD) δ 8.32 (s, 1H), 8.24 (s, 1H), 7.66 (m, 1H), 7.54 (m, 3H), 4.39 (s, 2H), 3.77 (s, 3H).

Intermediate B1: 4-chloro-1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine



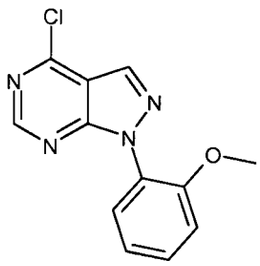
The title compound was prepared using the methods described in *Journal of Organic Chemistry* **1956**, *21*, 1240-1256 and WO2004/009602A1, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.40 (s, 1H), 7.63 (m, 1H), 7.51 (m, 3H).

Intermediate B2: 4-chloro-1-(2-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine



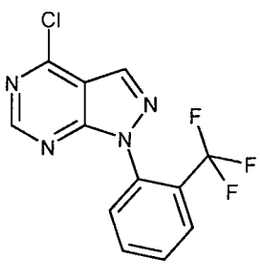
The title compound was prepared using the methods described in *Journal of Organic Chemistry* **1956**, *21*, 1240-1256 and WO2004/009602A1, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.40 (s, 1H), 7.45 (m, 4H), 2.17 (s, 3H).

Intermediate B3: 4-chloro-1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine



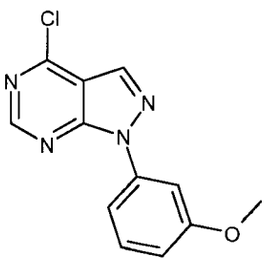
The title compound was prepared using the methods described in *Journal of Organic Chemistry* **1956**, *21*, 1240-1256 and WO2004/009602A1, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.36 (s, 1H), 7.49 (m, 2H), 7.14 (m, 2H), 3.77 (s, 3H).

Intermediate B4: 4-Chloro-1-[2-(trifluoromethyl)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidine



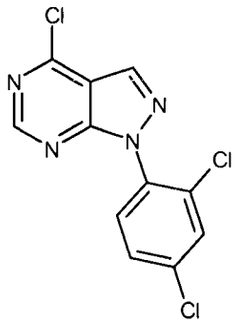
The title compound was prepared using the methods described in *Journal of Organic Chemistry* **1956**, *21*, 1240-1256 and WO2004/009602A1.

Intermediate B5: 4-chloro-1-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine



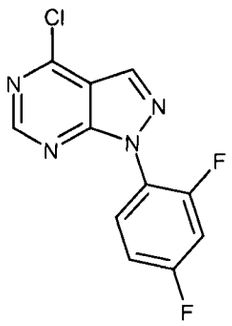
The title compound was prepared using the methods described in *Journal of Organic Chemistry* **1956**, *21*, 1240-1256 and WO2004/009602A1, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.33 (s, 1H), 7.82 (m, 2H), 7.45 (t, 1H), 6.94 (m, 1H), 3.89 (s, 3H).

Intermediate B6: 4-Chloro-1-(2,4-dichlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine



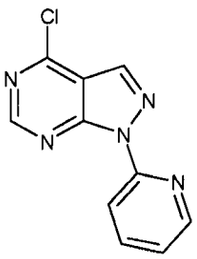
The title compound was prepared using the methods described in *Journal of Organic Chemistry* **1956**, *21*, 1240-1256 and WO2004/009602A1.

Intermediate B7: 4-Chloro-1-(2,4-difluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine



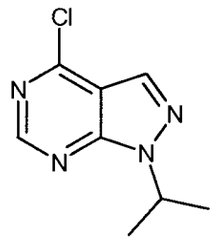
The title compound was prepared using the methods described in *Journal of Organic Chemistry* **1956**, *21*, 1240-1256 and WO2004/009602A1, ^{1}H NMR (400 MHz, DMSO) δ 8.90 (s, 1H), 8.78 (s, 1H), 7.80 (m, 1H), 7.64 (m, 1H), 7.35 (m, 1H).

Intermediate B8: 4-Chloro-1-pyridin-2-yl-1*H*-pyrazolo[3,4-*d*]pyrimidine



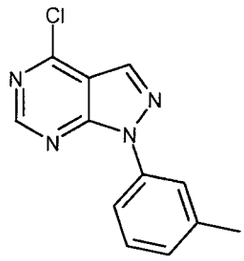
The title compound was prepared using the methods described in *Journal of Organic Chemistry* **1956**, *21*, 1240-1256 and WO2004/009602A1, ^{1}H NMR (400 MHz, DMSO) δ 8.95 (s, 1H), 8.73 (s, 1H), 8.62 (d, 1H), 8.05 (m, 2H), 7.50 (m, 1H).

Intermediate B9: 4-Chloro-1-isopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidine



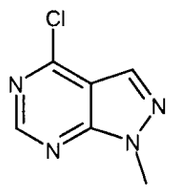
The title compound was prepared using the methods described in *Journal of Organic Chemistry* **1956**, *21*, 1240-1256 and WO2004/009602A1, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.05 (s, 1H), 5.12 (q, 1H), 1.50 (d, 6H).

Intermediate B10: 4-Chloro-1-(3-methylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine



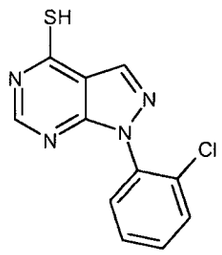
The title compound is commercially available.

Intermediate B11: 4-Chloro-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine



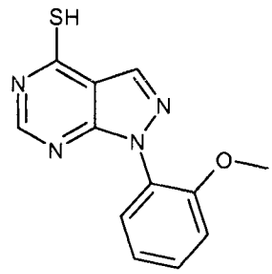
The title compound is commercially available.

Intermediate B12: 1-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-thiol



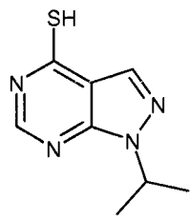
The title compound was prepared using the method described in *Journal of Organic Chemistry* **1956**, *21*, 1240-1256 and WO2004/009602A1, ^{1}H NMR (300 MHz, DMSO) δ 13.82 (br s, 1H), 8.46 (s, 1H), 8.19 (s, 1H), 7.74 (m, 1H), 7.61 (m, 3H).

Intermediate B13: 1-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-thiol



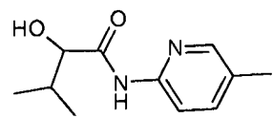
The title compound was prepared using the method described in *Journal of Organic Chemistry* **1956**, *21*, 1240-1256 and WO2004/009602A1, ^{1}H NMR (300 MHz, CDCl3) δ 12.68 (br s, 1H), 8.46 (s, 1H), 7.89 (s, 1H), 7.44 (m, 2H), 7.08 (m, 2H), 3.77 (s, 3H).

Intermediate B14: 1-isopropyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidine-4-thiol



The title compound was prepared using the method described in *Journal of Organic Chemistry* **1956**, *21*, 1240-1256 and WO2004/009602A1.

Intermediate C1: 2-hydroxy-3-methyl-*N*-(5-methylpyridin-2-yl)butanamide

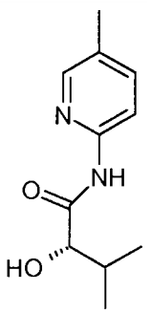
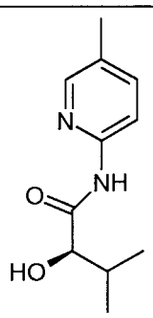


5-Methylpyridin-2-amine (CAS 1603-41-4) (2.014 g, 18.6 mmol) was added in one portion to 2-hydroxy-3-methylbutanoic acid (CAS 4026-18-0) (2.0 g, 16.9 mmol), 2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (7.08 g, 18.6 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (5.80 mL, 33.9 mmol) in DCM (40 mL). The resulting suspension was stirred at ambient temperature for 70 hours. The reaction mixture was concentrated, diluted with EtOAc (150 mL) and washed sequentially with water (150 mL) and saturated brine (75 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 20 to 50% EtOAc in isohexane to afford 2-hydroxy-3-methyl-*N*-(5-methylpyridin-2-yl)butanamide (500 mg).

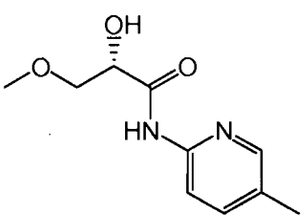
1H NMR (400 MHz, DMSO-d_6) δ 0.87 (3H, d), 0.97 (3H, d), 2.06 - 2.16 (1H, m), 2.29

(3H, s), 3.94-3.98 (1H, m), 5.87 (1H, d), 7.65 (1H, dd), 8.05 (1H, d), 8.16 (1H, d), 9.50 (1H, s), m/z (ESI+) (M+H)+ = 209; HPLC t_R = 1.11 min.

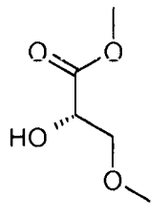
Intermediates C2 and **C3** were prepared in an analogous fashion from enantiopure starting materials (CAS 17407-55-5 and 17407-56-6).

C2		(S)-2-hydroxy-3-methyl-*N*-(5-methylpyridin-2-yl)butanamide	ESI+ (M+H)+ = 209; HPLC t_R = 1.13 min	^{1}H NMR (400 MHz, DMSO-d_6) δ 0.87 (3H, d), 0.97 (3H, d), 2.06 - 2.16 (1H, m), 2.29 (3H, s), 3.94-3.98 (1H, m), 5.87 (1H, d), 7.65 (1H, dd), 8.05 (1H, d), 8.16 (1H, d), 9.50 (1H, s)
C3		(R)-2-hydroxy-3-methyl-*N*-(5-methylpyridin-2-yl)butanamide	ESI+ (M+H)+ = 209; HPLC t_R = 1.12 min	^{1}H NMR (400 MHz, DMSO-d_6) δ 0.82 (3H, d), 0.95 (3H, d), 2.02 - 2.10 (1H, m), 2.24 (3H, s), 3.89 - 3.91 (1H, m), 5.80 (1H, d), 7.61 (1H, dd), 8.00 (1H, d), 8.13 (1H, d), 9.45 (1H, s)

Intermediate C4: (S)-2-hydroxy-3-methoxy-*N*-(5-methylpyridin-2-yl)propanamide

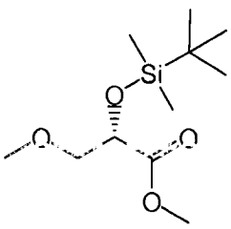


Step 1: Synthesis of C4a: (S)-methyl 2-hydroxy-3-methoxypropanoate



Magnesium perchlorate (0.820 g, 3.67 mmol) was added in one portion to (S)-methyl oxirane-2-carboxylate (CAS 2868-37-3) (1.5 g, 14.7 mmol) and methanol (0.714 mL, 17.6 mmol) cooled to 10 °C. The resulting suspension was stirred at 10 °C for 10 minutes and then warmed to 45 °C for 20 hours. The crude reaction mixture was purified by flash silica chromatography, elution gradient 20 to 50% Et_2O in DCM to afford (S)-methyl 2-hydroxy-3-methoxypropanoate (1.4 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.01 (1H, d), 3.40 (3H, s), 3.65 - 3.72 (2H, m), 3.81 (3H, s), 4.29 - 4.33 (1H, m)

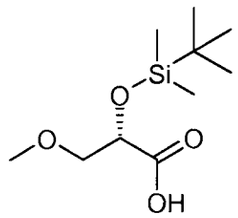
Step 2: Synthesis of C4b: (S)-methyl 2-(tert-butyldimethylsilyloxy)-3-methoxypropanoate



A solution of tert-butylchlorodimethylsilane (661 mg, 4.38 mmol) in DMF (2.5 mL) was added dropwise to a stirred solution of (S)-methyl 2-hydroxy-3-methoxypropanoate **C4a** (490 mg, 3.65 mmol) and 1H-imidazole (497 mg, 7.31 mmol) in DMF (5 mL) at 20°C, over a period of 2 minutes. The resulting solution was stirred at ambient temperature for 3 hours. The reaction mixture was concentrated, diluted with EtOAc (50 mL) and washed sequentially with water (4 x 15 mL) and saturated brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. Purification by flash silica chromatography, elution gradient 20 to 50% EtOAc in isohexane afforded (S)-methyl 2-(tert-butyldimethylsilyloxy)-3-methoxypropanoate (750 mg).

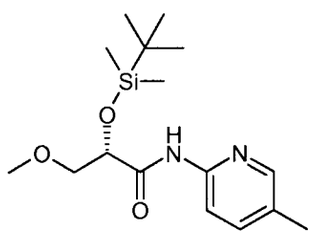
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.11 (3H, s), 0.13 (3H, s), 0.94 (9H, s), 3.40 (3H, s), 3.56 - 3.64 (2H, m), 3.76 (3H, s), 4.37 - 4.41 (1H, m)

Step 3: Synthesis of C4c: (S)-2-(tert-butyldimethylsilyloxy)-3-methoxypropanoic acid



Lithium iodide (535 mg, 3.99 mmol) was added in one portion to (S)-methyl 2-(tert-butyldimethylsilyloxy)-3-methoxypropanoate **C4b** (248 mg, 1.00 mmol) in EtOAc (5 mL). The resulting suspension was protected from light and stirred at reflux (75 °C) for 24 hours. The reaction mixture was diluted with EtOAc (10 mL) and washed sequentially with water (5 mL), 1M sodium metabisulphite (5 mL) and saturated brine (5 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product, an approximate 3:1 mixture of (S)-2-(tert-butyldimethylsilyloxy)-3-methoxypropanoic acid and (S)-methyl 2-(tert-butyldimethylsilyloxy)-3-methoxypropanoate. The material was carried through to the next step without purification.

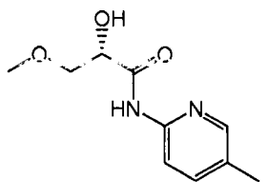
Step 4: Synthesis of C4d: (S)-2-(tert-butyldimethylsilyloxy)-3-methoxy-*N*-(5-methylpyridin-2-yl)propanamide



A solution of 1-chloro-*N*,*N*,2-trimethylprop-1-en-1-amine (1.55 mL, 11.7 mmol) in DCM (5 mL) was added dropwise to a stirred solution of (S)-2-(tert-butyldimethylsilyloxy)-3-methoxypropanoic acid **C4c** (2.5g, 10.7 mmol) in DCM (15 mL) under nitrogen. The resulting solution was stirred at ambient temperature for 30 minutes. *N*-Ethyl-*N*-isopropylpropan-2-amine (2.74 mL, 16.0 mmol) was added in one portion followed by 5-methylpyridin-2-amine (CAS 1603-41-4) (1.27g, 11.73 mmol) in DCM (5 mL) dropwise. The resulting solution was stirred at ambient temperature for 1 hour. 1M Citric acid (10 mL) was added and the mixture extracted with EtOAc (20 mL). The organic phase was washed with water (5 mL) and brine (5 mL), dried over $MgSO_4$, filtered and evaporated to provide the crude product. Purification by flash silica chromatography, elution gradient 20

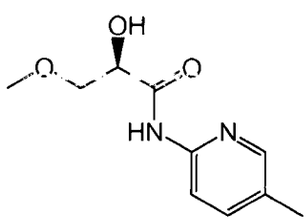
to 100% EtOAc in isohexane furnished (S)-2-(tert-butyldimethylsilyloxy)-3-methoxy-*N*-(5-methylpyridin-2-yl)propanamide (1.4 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.2 (6H, s), 1.01 (9H, s), 2.32 (3H, s), 3.41 (3H, s), 3.66 - 3.75 (2H, m), 4.40 - 4.42 (1H, m), 7.52 (1H, d), 7.14 - 7.16 (2H, m), 9.04 (1H, s), m/z (ESI+) $(M+H)^+$ = 326; HPLC t_R = 2.75 min.

Step 5: Synthesis of C4: (S)-2-hydroxy-3-methoxy-*N*-(5-methylpyridin-2-yl)propanamide

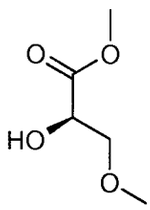


A solution of tetrabutylammonium fluoride (1M in THF) (8.63 mL, 8.63 mmol) was added in one portion to a stirred solution of (S)-2-(tert-butyldimethylsilyloxy)-3-methoxy-*N*-(5-methylpyridin-2-yl)propanamide **C4d** (1.4 g, 4.31 mmol) in THF (20 mL). The resulting solution was stirred at ambient temperature for 4 hours. The reaction mixture was concentrated, diluted with EtOAc (50 mL) and washed sequentially with water (20 mL) and saturated brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product as an oil. Trituration with 1:1 isohexane : EtOAc afforded (S)-2-hydroxy-3-methoxy-*N*-(5-methylpyridin-2-yl)propanamide (340 mg). The residue was purified by flash silica chromatography with EtOAc to afford a second batch of (S)-2-hydroxy-3-methoxy-*N*-(5-methylpyridin-2-yl)propanamide (220 mg).
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (3H, s), 3.44 (3H, s), 3.73 - 3.80 (2H, m), 4.38 - 4.42 (1H, m), 4.63 (1H, d), 7.54 (1H, dd), 8.10 - 8.11 (1H, d), 8.14 (1H, d), 9.33 (1H, s), m/z (ESI+) $(M+H)^+$ = 211; HPLC t_R = 0.77 min.

Intermediate C5: (R)-2-hydroxy-3-methoxy-*N*-(5-methylpyridin-2-yl)propanamide

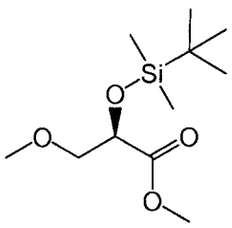


Step 1: Synthesis of C5a: (R)-methyl 2-hydroxy-3-methoxypropanoate



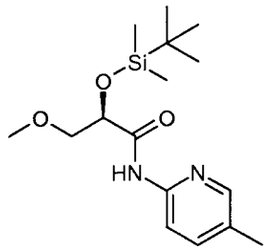
C5a was prepared in an analogous fashion to intermediate **C4a** from (R)-methyl oxirane-2-carboxylate (CAS 111058-32-3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.01 (1H, d), 3.40 (3H, s), 3.65 - 3.72 (2H, m), 3.81 (3H, s), 4.29 - 4.33 (1H, m)

Step 2: Synthesis of C5b: (R)-methyl 2-(tert-butyldimethylsilyloxy)-3-methoxypropanoate



C5b was prepared in an analogous fashion to intermediate **C4b** from (R)-methyl 2-hydroxy-3-methoxypropanoate **C5a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.11 (3H, s), 0.13 (3H, s), 0.94 (9H, s), 3.40 (3H, s), 3.56 - 3.64 (2H, m), 3.76 (3H, s), 4.37 - 4.41 (1H, m)

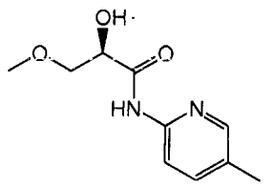
Step 3: Synthesis of C5c: (R)-2-(tert-butyldimethylsilyloxy)-3-methoxy-*N*-(5-methylpyridin-2-yl)propanamide



A solution of n-butyllithium (2.5M in hexanes) (2.04 mL, 3.26 mmol) was added dropwise to a stirred solution of 5-methylpyridin-2-amine (CAS 1603-41-4) (353 mg, 3.26 mmol) in THF (10 mL) cooled to 10 °C under nitrogen. The resulting solution was stirred at ambient temperature for 10 minutes and then added to a solution of (R)-methyl 2-(tert-butyldimethylsilyloxy)-3-methoxypropanoate **C5b** (810 mg, 3.26 mmol) in THF (10 mL) at 10°C. The resulting solution was stirred at ambient temperature for 1 hour. The reaction mixture was diluted with EtOAc (75 mL) and washed sequentially with saturated ammonium chloride (50 mL), water (25 mL) and saturated brine (25 mL). The organic

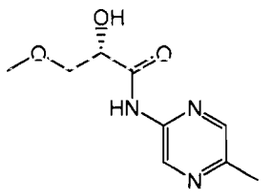
layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. Purification by flash silica chromatography, elution gradient 20 to 50% EtOAc in isohexane provided (R)-2-(tert-butyldimethylsilyloxy)-3-methoxy-*N*-(5-methylpyridin-2-yl)propanamide (300 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.15 (3H, s), 0.16 (3H, s), 0.88 (9H, s), 2.12 (3H, s), 3.46 (3H, s), 3.61 – 3.65 (2H, m), 4.35 – 4.42 (1H, m), 7.47 (1H, d), 8.19 (1H, d), 8.20 (1H, s), 8.97 (1H, s), m/z (ESI+) $(M+H)^+$ = 325; HPLC t_R = 3.08 min.

Step 4: Synthesis of C5:(R)-2-hydroxy-3-methoxy-*N*-(5-methylpyridin-2-yl)propanamide

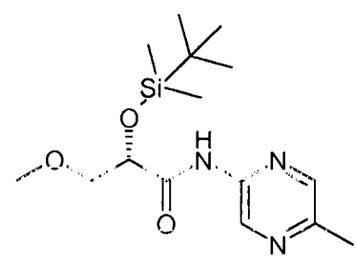


C5 was prepared in an analogous fashion to **C4 (step 5)** from (R)-2-(tert-butyldimethylsilyloxy)-3-methoxy-*N*-(5-methylpyridin-2-yl)propanamide **C5c**.
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (3H, s), 3.44 (3H, s), 3.73 – 3.78 (2H, m), 4.36-4.44 (1H, m), 4.46-4.50 (1H, m), 7.54 (1H, dd), 8.10 (1H, d), 8.14 (1H, d), 9.30 (1H, s), m/z (ESI+) $(M+H)^+$ = 211; HPLC t_R = 0.74 min.

Intermediate C6: (S)-2-hydroxy-3-methoxy-*N*-(5-methylpyrazin-2-yl)propanamide



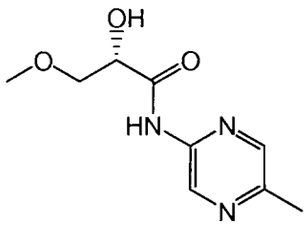
Step 1:Synthesis of C6a: (S)-2-(tert-butyldimethylsilyloxy)-3-methoxy-*N*-(5-methylpyrazin-2-yl)propanamide



C6a was prepared in an analogous fashion to **C4d** from (S)-2-(tert-butyldimethylsilyloxy)-3-methoxypropanoic acid **C4c** and 5-methylpyrazine-2-amine (CAS 5521-58-4).

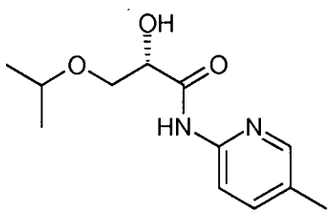
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.18 (3H, s), 0.19 (3H, s), 1.01 (9H, s), 2.54 (3H, s), 3.39 (3H, s), 3.70 (2H, d), 4.41 (1H, t), 8.14 (1H, d), 9.01 (1H, s), 9.42 (1H, d), m/z (ESI+) (M+H)+ = 326; HPLC t_R = 2.67 min.

Step 2: Synthesis of C6: (S)-2-hydroxy-3-methoxy-*N*-(5-methylpyrazin-2-yl)propanamide

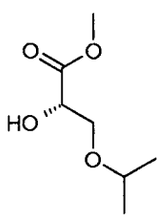


C6 was prepared in an analogous fashion to intermediate **C4 (step 5)** from (S)-2-(tert-butyldimethylsilyloxy)-3-methoxy-*N*-(5-methylpyrazin-2-yl)propanamide **C6a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.55 (3H, s), 3.45 (3H, s), 3.74 – 3.82 (2H, m), 3.85 (1H, s), 4.41 (1H, t), 8.14 (1H, d), 9.18 (1H, s), 9.45 (1H, d), m/z (ESI+) (M+H)+ = 212; HPLC t_R = 0.78 min.

Intermediate C7: (S)-2-hydroxy-3-isopropoxy-*N*-(5-methylpyridin-2-yl)propanamide



Step 1: Synthesis of C7a(S)-methyl 2-hydroxy-3-isopropoxypropanoate

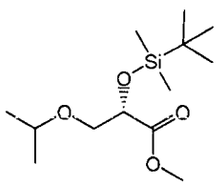


Magnesium perchlorate (2.73 g, 12.24 mmol) was added in one portion to (S)-methyl oxirane-2-carboxylate (CAS 2868-37-3) (5.0 g, 48.98 mmol) and propan-2-ol (4.69 mL, 61.22 mmol) at 10 °C. The resulting suspension was stirred at 10 °C for 10 minutes and then allowed to warm to ambient temperature for 30 minutes during which most of the solids dissolve. Heated to 100 °C for 30 minutes in a microwave reactor. The material was used without purification in the next step.

Alternatively C7a may be prepared as follows.

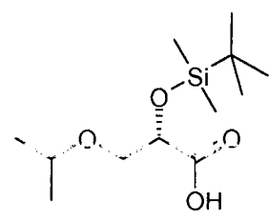
(S)-Methyl oxirane-2-carboxylate (2.04 g, 19.98 mmol), magnesium trifluoromethanesulfonate (1.611 g, 5.00 mmol) and propan-2-ol (1.84 mL, 24.0 mmol) in ethyl acetate (10 mL) were heated at reflux for 90 hours. The mixture was diluted with EtOAc (20 mL), filtered and evaporated. The residue was purified by flash silica chromatography, elution gradient 20 to 50% EtOAc in isohexane to afford (S)-methyl 2-hydroxy-3-isopropoxypropanoate (2.45 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (3H, d), 1.16 (3H, d), 3.00 (1H, d), 3.58 - 3.64 (1H, m), 3.68 - 3.74 (2H, m), 3.69 - 3.73 (1H, m), 3.80 (3H, s), 4.28 - 4.31 (1H, m)

Step 2: Synthesis of C7b: (S)-methyl 2-(tert-butyldimethylsilyloxy)-3-isopropoxypropanoate



C7b was prepared in an analogous fashion to **C4b** from crude (S)-methyl 2-hydroxy-3-isopropoxypropanoate **C7a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.10 (3H, s), 0.11 (3H, s), 0.90 (9H, d), 1.14 (6H, d), 3.50 – 3.7 (3H, m), 3.73 (3H, s), 4.33 – 4.36 (1H, m)

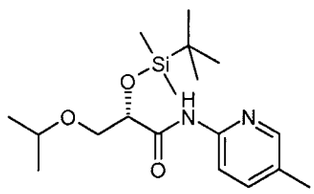
Step 3: Synthesis of C7c: (S)-2-(tert-butyldimethylsilyloxy)-3-isopropoxypropanoic acid



C7c was prepared in an analogous fashion to **C4c** from (S)-methyl 2-(tert-butyldimethylsilyloxy)-3-isopropoxypropanoate **C7b**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.16 (3H, s), 0.17 (3H, s), 0.93 (9H, m), 1.14 (3H, d), 1.16 (3H, d), 3.58 - 3.74 (3H, m), 4.35 - 4.38 (1H, m), 9.31 (1H, s)

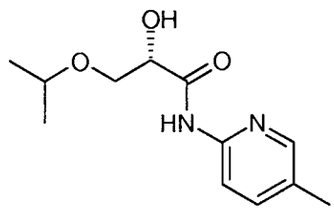
Step 4: Synthesis of C7d: (S)-2-(tert-butyldimethylsilyloxy)-3-isopropoxy-*N*-(5-methylpyridin-2-yl)propanamide



C7d was prepared in an analogous fashion to **C4d** from (S)-2-(tert-butyldimethylsilyloxy)-3-isopropoxypropanoic acid **C7c** and 5-methylpyridin-2-amine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.16 (3H, s), 0.17 (3H, s), 1.01 (9H, s), 1.12 (3H, d), 1.13 (3H, d), 2.29 (3H, s), 3.56 - 3.62 (2H, m), 3.71 - 3.78 (1H, m), 4.40 (1H, dd), 7.47 - 7.51 (1H, m), 8.10 - 8.17 (2H, m), 9.01 (1H, s)

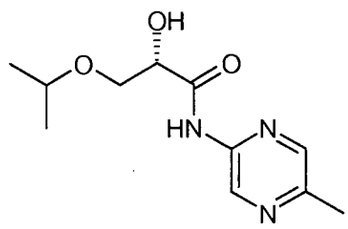
Step 5: Synthesis of C7: (S)-2-hydroxy-3-isopropoxy-*N*-(5-methylpyridin-2-yl)propanamide



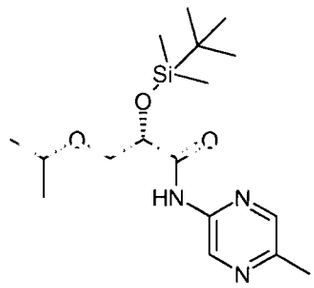
C7 was prepared in an analogous fashion to **C4 (step 5)** from (S)-2-(tert-butyldimethylsilyloxy)-3-isopropoxy-*N*-(5-methylpyridin-2-yl)propanamide **C7d**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (3H, d), 1.21 (3H, d), 2.30 (3H, s), 3.64 - 3.72 (2H, m), 3.76 (2H, d), 4.29 - 4.33 (1H, m), 7.52 (1H, dd), 8.09 - 8.14 (2H, m), 9.18 (1H, s), m/z (ESI+) (M+H)+ = 211; HPLC t_R = 0.77 min.

Intermediate C8: (S)-2-hydroxy-3-isopropoxy-N-(5-methylpyrazin-2-yl)propanamide

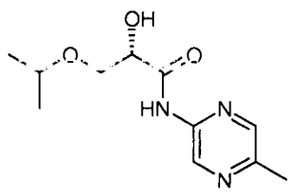


Step 1: Synthesis of C8a: (S)-2-(tert-butyldimethylsilyloxy)-3-isopropoxy-*N*-(5-methylpyrazin-2-yl)propanamide



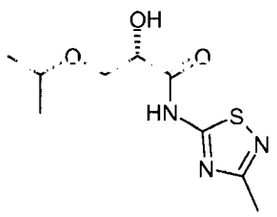
C8a was prepared in an analogous fashion to **C4d** from (S)-2-(tert-butyldimethylsilyloxy)-3-isopropoxypropanoic acid **C7c** and 5-methylpyrazin-2-amine. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.20 (3H, s), 0.21 (3H, s), 1.0 (9H, s), 1.14 (3H, d), 1.17 (3H, d), 2.54 (3H, s), 3.61 - 3.65 (2H, m), 3.77 - 3.80 (1H, m), 4.40 (1H, dd), 8.14 (1H, d), 9.01 (1H, s), 9.43 (1H, d)

Step 2: Synthesis of C8: (S)-2-hydroxy-3-isopropoxy-*N*-(5-methylpyrazin-2-yl)propanamide

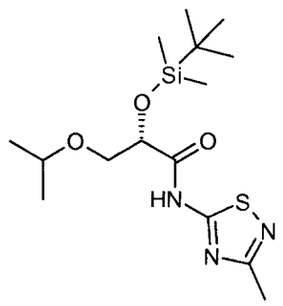


C8 was prepared in an analogous fashion to **C4 (step 5)** from (S)-2-(tert-butyldimethylsilyloxy)-3-isopropoxy-*N*-(5-methylpyrazin-2-yl)propanamide **C8a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (3H, m), 1.21 (3H, d), 2.54 (3H, s), 3.42 (1H, d), 3.67 - 3.82 (3H, m), 4.31 - 4.35 (1H, m), 8.14 (1H, d), 9.14 (1H, s), 9.42 (1H, d)

Intermediate C9: (S)-2-hydroxy-3-isopropoxy-*N*-(3-methyl-1,2,4-thiadiazol-5-yl)propanamide



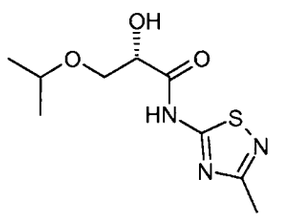
Step 1: Synthesis of C9a: (S)-2-(tert-butyldimethylsilyloxy)-3-isopropoxy-*N*-(3-methyl-1,2,4-thiadiazol-5-yl)propanamide



C9a was prepared in an analogous fashion to **C4d** from (S)-2-(tert-butyldimethylsilyloxy)-3-isopropoxypropanoic acid **C7c** and 3-methyl-1,2,4-thiadiazol-5-amine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.17 (3H, s), 0.19 (3H, s), 0.96 (9H, s), 1.08 (3H, d), 1.13 (3H, d), 2.39 (3H, s), 3.42- 3.66 (2H, m), 3.69 - 3.74 (1H, m), 4.50 - 4.53 (1H, m), 10.00 (1H, s)

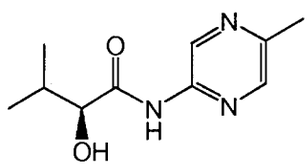
Step 2: Synthesis of C9: (S)-2-hydroxy-3-isopropoxy-*N*-(3-methyl-1,2,4-thiadiazol-5-yl)propanamide



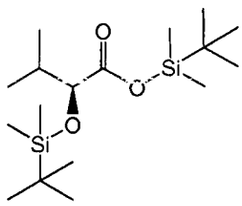
C9 was prepared in an analogous fashion to **C4 (step 5)** from (S)-2-(tert-butyldimethylsilyloxy)-3-isopropoxy-*N*-(3-methyl-1,2,4-thiadiazol-5-yl)propanamide **C9a**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.1 (3H, m), 1.20 (3H, d), 2.55 (3H, s), 3.63 - 3.72 (1H, m), 3.75 (1H, broad s), 3.76 - 3.83 (2H, m), 4.47 - 4.50 (1H, m), 10.20 (1H, broad s)

Intermediate C10: (S)-2-hydroxy-3-methyl-*N*-(5-methylpyrazin-2-yl)butanamide

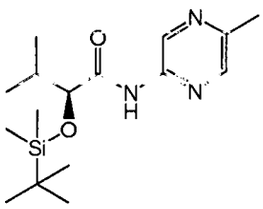


Step 1: Synthesis of C10a: (S)-tert-butyldimethylsilyl 2-(tert-butyldimethylsilyloxy)-3-methylbutanoate



tert-Butyldimethylsilyl chloride (18.77 g, 124.54 mmol) was added to (S)-(+)-2-Hydroxy-3-methylbutyric acid (CAS 17407-55-5) (6.13 g, 51.9 mmol) and 1H-imidazole (16.96 g, 249 mmol) in DMF (259 mL) at 23°C under nitrogen. The resulting solution was stirred at ambient for 60 hours. The reaction mixture was diluted with EtOAc (1400 mL) and the organic phase was washed sequentially with saturated aqueous citric acid (3 x 500 mL), saturated aqueous sodium hydrogen carbonate (3 x 500 mL) and saturated brine (3 x 500 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to provide (S)-tert-butyldimethylsilyl 2-(tert-butyldimethylsilyloxy)-3-methylbutanoate (18.0 g, 100 %). This material was used without further purification.

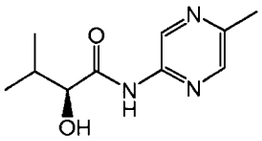
Step 2: Synthesis of C10b: (S)-2-(tert-butyldimethylsilyloxy)-3-methyl-N-(5-methylpyrazin-2-yl)butanamide



DMF (cat.) was added to a stirred solution of (S)-tert-butyldimethylsilyl 2-(tert-butyldimethylsilyloxy)-3-methylbutanoate **C10a** (17.99 g, 51.90 mmol) and oxalyl chloride (5.89 mL, 67.47 mmol) in DCM (259 mL) at 23°C under nitrogen. The resulting solution was stirred at ambient temperature for 2 hours. The reaction mixture was concentrated under reduced pressure and azeotroped with toluene (50 mL). The resulting oil was dissolved in DCM (250 mL) and 5-methylpyrazin-2-amine (6.23 g, 57.1 mmol) added. The resulting solution was stirred for 4 hours at ambient temperature. The reaction mixture was washed sequentially with water (150 mL) and saturated $NaHCO_3$ (150 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. Purification by flash silica chromatography, elution gradient 0 to 70% EtOAc in isohexane afforded (S)-2-(tert-butyldimethylsilyloxy)-3-methyl-*N*-(5-methylpyrazin-2-yl)butanamide

C10b (2.53 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.11 (3H, s), 0.15 (3H, s), 0.95 (3H, d), 1.00 (9H, s), 1.02 (3H, d), 2.15 - 2.18 (1H, m), 2.54 (3H, s), 4.10 (1H, d), 8.13 (1H, d), 8.76 (1H, s), 9.45 (1H, d), m/z (ESI+) (M+H)+ = 324; HPLC tR = 3.25 min.

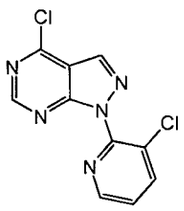
Step 3: Synthesis of C10: (S)-2-hydroxy-3-methyl-*N*-(5-methylpyrazin-2-yl)butanamide



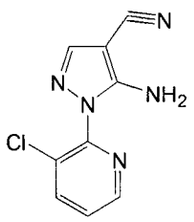
C10 was prepared in an analogous fashion to **C4 (step 5)** from (S)-2-(tert-butyldimethylsilyloxy)-3-methyl-*N*-(5-methylpyrazin-2-yl)butanamide **C10b**.

^{1}H NMR (400 MHz, DMSO-d_6) δ 0.88 (3H, d), 0.98 (3H, d), 2.05 - 2.16 (1H, m), 2.50 (3H, s), 3.99 (1H, dd), 5.84 (1H, d), 8.34 (1H, s), 9.26 (1H, d), 9.89 (1H, s), m/z (ESI+) (M+H)+ = 210; HPLC t_R = 1.24 min.

Intermediate B15: 4-chloro-1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine

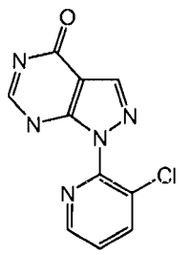


Step 1: Synthesis of B15a: 5-amino-1-(3-chloropyridin-2-yl)-1H-pyrazole-4-carbonitrile



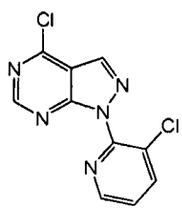
3-Chloro-2-hydrazinylpyridine (CAS 22841-92-5) (19.1 g, 133.03 mmol) was suspended in MeOH (200 mL) under nitrogen at -5°C. 2-(ethoxymethylene)malononitrile (CAS 123-06-8) (16.25 g, 133.03 mmol) was added portionwise and the resulting mixture stirred at ~0 °C for 2 hours. The reaction mixture was heated to reflux for 2 hours then cooled and evaporated to provide 5-amino-1-(3-chloropyridin-2-yl)-1H-pyrazole-4-carbonitrile (29.2g). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.87 (2H, s), 7.61 (1H, dd), 7.79 (1H, s), 8.21 (1H, dd), 8.55 (1H, dd), m/z (ESI+) (M+H)+ = 220; HPLC tR = 1.17 min.

Step 2: Synthesis of B15b: 1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4(7H)-one



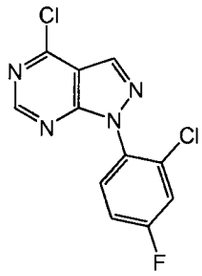
Concentrated sulphuric acid (10.87 mL, 203.92 mmol) was added to a stirred solution of 5-amino-1-(3-chloropyridin-2-yl)-1H-pyrazole-4-carbonitrile **B15a** (29.2 g, 132.95 mmol) in formic acid (200 mL). The resulting solution was stirred at 100 °C for 3 hours. The reaction mixture was cooled and evaporated to approx. half volume. Water (250 mL) was added and the resulting mixture was stirred for 1 hour. A precipitate formed which was collected by filtration and washed with water (3 x 50 mL) then dried *in vacuo* at 50 °C to provide 1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4(7H)-one (30.5 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.72 (1H, dd), 8.10 (1H, s), 8.30 (1H, dd), 8.37 (1H, s), 8.64 (1H, dd), 12.43 (1H, s), m/z (ESI+) $(M+H)^+$ = 248; HPLC t_R = 0.99 min.

Step 3: Synthesis of B15: 4-chloro-1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine

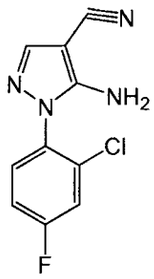


Phosphoryl trichloride (235 mL, 2455.17 mmol) was added to 1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol **B15b** (30.4 g, 122.76 mmol). The resulting solution was stirred at 100 °C for 4 hours. The mixture was concentrated *in vacuo* and to the residue was added an ice/water mixture. The resulting mixture was stirred for 1 hour during which time a solid precipitated. The solid was collected by filtration and washed with water (3 x 75 mL). The crude product was dissolved in EtOAc (500 mL) and dried over $MgSO_4$, filtered and evaporated to afford 4-chloro-1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (28.7 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (1H, dd), 8.37 (1H, dd), 8.69 (1H, dd), 8.83 (1H, s), 8.92 (1H, s), m/z (ESI+) $(M+H)^+$ = 266; HPLC t_R = 1.72 min.

Intermediate B16: 4-chloro-1-(2-chloro-4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidine



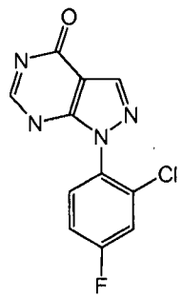
Step 1: Synthesis of B16a: 5-amino-1-(2-chloro-4-fluorophenyl)-1H-pyrazole-4-carbonitrile



2-Chloro-4-fluorophenyl hydrazine hydrochloride (CAS 497959-29-2) (25.0g, 126.9mmol) was partitioned between DCM (250 mL) and 2M NaOH (100 mL). The organic phase was separated and washed sequentially with water (2 x 150 mL) and brine (150 mL), dried over $MgSO_4$ and evaporated to give the free base. This oil was dissolved in MeOH (200 mL) under nitrogen at -5°C and 2-(ethoxymethylene)malononitrile (15.5 g, 127 mmol) was added portionwise. The resulting mixture was stirred at 0°C for 2 hours then at reflux for a further 2 hours. After cooling, the mixture was evaporated to provide 5-amino-1-(2-chloro-4-fluorophenyl)-1H-pyrazole-4-carbonitrile (28.9 g).

^{1}H NMR (400 MHz, DMSO-d_6) δ 6.68 (2H, s), 7.37 (1H, ddd), 7.58 (1H, dd), 7.69 (1H, dd), 7.75 (1H, s), m/z (ESI+) (M+H)+ = 237; HPLC t_R = 1.62 min.

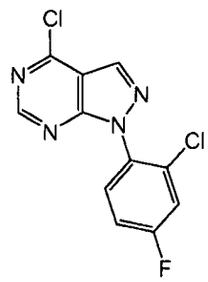
Step 2: Synthesis of B16b: 1-(2-chloro-4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4(7H)-one



B16b (sulphate salt) was prepared in an analogous fashion to **B15b** from 5-amino-1-(2-chloro-4-fluorophenyl)-1H-pyrazole-4-carbonitrile **B15a**.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.44 (1H, ddd), 7.72 (1H, dd), 7.77 (1H, dd), 8.08 (1H, s), 8.33 (1H, s), 12.38 (1H, s), m/z (ESI-) (M-H)- = 263; HPLC t_R = 1.44 min.

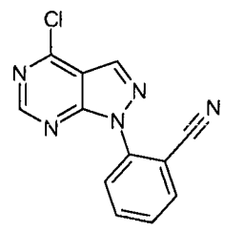
Step 3: Synthesis of B16: 4-chloro-1-(2-chloro-4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidine



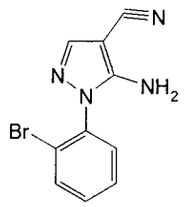
B16 was prepared in an analogous fashion to **B15 (step 3)** from 1-(2-chloro-4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4(7H)-one **B16b**.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.48 - 7.53 (1H, m), 7.79 - 7.83 (2H, m), 8.79 (1H, s), 8.89 (1H, s), m/z (ESI+) (M+H)+ = 283; HPLC t_R = 2.39 min.

Intermediate B17: 2-(4-chloro-1H-pyrazolo[3,4-d]pyrimidin-1-yl)benzonitrile

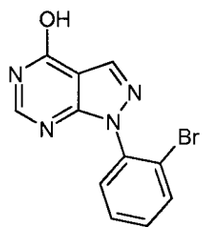


Step 1: Synthesis of B17a: 5-amino-1-(2-bromophenyl)-1H-pyrazole-4-carbonitrile



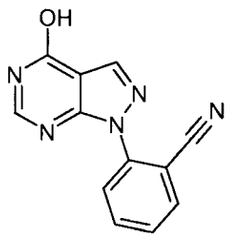
B17a was prepared in an analogous fashion to **B16a** from (2-bromophenyl) hydrazine hydrochloride (CAS 50709-33-6). m/z (ESI+) $(M+H)^+ = 265$; HPLC $t_R = 1.52$ min.

Step 2: Synthesis of B17b:1-(2-bromophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol



B17b (sulphate salt) was prepared in an analogous fashion to **B15b** from **B16a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.51 - 7.55 (1H, m), 7.56 - 7.61 (2H, m), 7.86 - 7.88 (1H, m), 8.04 - 8.08 (1H, m), 8.30 - 8.33 (1H, m), 12.35 (1H, s), m/z (ESI+) $(M+H)^+ =$ 293; HPLC $t_R = 1.34$ min.

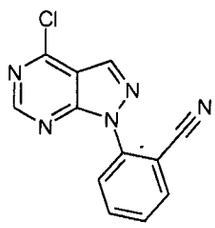
Step 3: Synthesis of B17c: 2-(4-hydroxy-1H-pyrazolo[3,4-d]pyrimidin-1-yl)benzonitrile



1-(2-bromophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol **B17b** (1.456 g, 5 mmol) and zinc cyanide (0.528 g, 4.50 mmol) were dissolved in DMF (15 mL) and sealed into a microwave tube. The tube was evacuated and back flushed with nitrogen several times. 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (0.289 g, 0.50 mmol) and tris(dibenzylideneacetone) dipalladium(0) (0.229 g, 0.25 mmol) were added. The reaction was heated to 160 °C for 10 minutes in the microwave reactor and cooled to RT. This was repeated on exactly the same scale. The two reaction mixtures were combined and diluted with EtOAc (200 mL) and water (30 mL). The biphasic mixture was filtered, and the

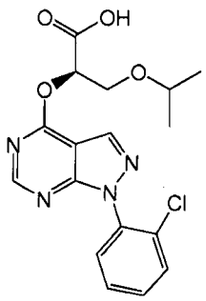
organic phase separated and washed with brine (20 mL) then dried over $MgSO_4$, filtered and evaporated. The residue was purified by hot filtration, then crystallization from MeOH, providing 2-(4-hydroxy-1H-pyrazolo[3,4-d]pyrimidin-1-yl)benzonitrile (1.225 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70 - 7.75 (1H, m), 7.86 - 7.88 (1H, m), 7.91 - 7.95 (1H, m), 8.08 - 8.10 (1H, m), 8.17 (1H, s), 8.43 (1H, s), 12.49 (1H, s), m/z (ESI+) $(M+H)^+$ = 238; HPLC t_R = 1.15 min.

Step 4: Synthesis of B17: 2-(4-chloro-1H-pyrazolo[3,4-d]pyrimidin-1-yl)benzonitrile

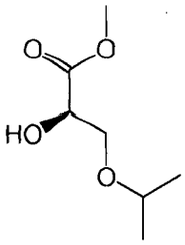


B17 was prepared in an analogous fashion to **B15** from **B17c**. The final material was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM to afford **B17** as a solid (0.495g). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74 - 7.81 (1H, m), 7.96 - 8.02 (2H, m), 8.14 - 8.17 (1H, m), 8.89 (1H, s), 8.98 (1H, s), m/z (ESI+) $(M+H)^+$ = 256; HPLC t_R = 1.97 min.

Intermediate D1: (2R)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-isopropoxypropanoic acid



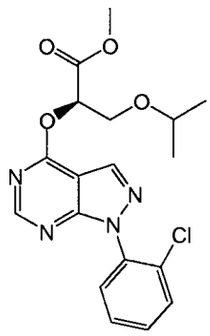
Step 1: Synthesis of D1a: (R)-methyl 2-hydroxy-3-isopropoxypropanoate



D1a was prepared in an analogous fashion to **C4a** from (R)-methyl oxirane-2-carboxylate (CAS 111058-32-3) and isopropanol. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 - 1.16 (6H, m),

3.04 - 3.06 (1H, m), 3.58 - 3.64 (1H, m), 3.68 - 3.75 (2H, m), 3.80 (3H, s), 4.29 - 4.32 (1H, m)

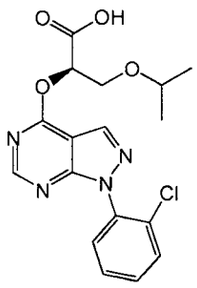
Step 2: Synthesis of D1b: (2R)-methyl 2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-isopropoxypropanoate



(R)-methyl 2-hydroxy-3-isopropoxypropanoate **D1a** (500 mg, 3.08 mmol), 4-chloro-1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine **B1** (817 mg, 3.08 mmol) and potassium carbonate (0.186 mL, 3.08 mmol) were suspended in acetonitrile (15 mL). The reaction was heated to 130 °C for 4 hours in the microwave reactor and cooled to ambient temperature. The reaction mixture was evaporated to dryness and the resulting residue was dissolved in EtOAc (25 mL), and washed sequentially with saturated NH_4Cl (50 mL) and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. Purification by flash silica chromatography, elution gradient 20 to 50% EtOAc in isohexane afforded (2R)-methyl 2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-isopropoxypropanoate **D1b** (965 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 - 1.26 (6H, m), 3.71 - 3.79 (1H, m), 3.80 (3H, s), 4.01 - 4.06 (2H, m), 5.79 - 5.81 (1H, m), 7.44 - 7.54 (3H, m), 7.61 - 7.63 (1H, m), 8.38 (1H, s), 8.54 (1H, s), m/z (ESI+) $(M+H)^+$ = 391; HPLC t_R = 2.51 min.

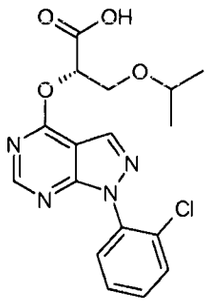
Step 3: Synthesis of D1: (2R)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-isopropoxypropanoic acid



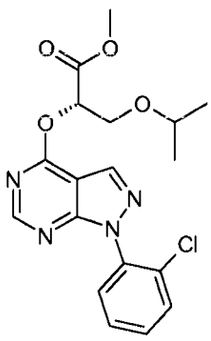
Sodium hydroxide (0.755 mL, 1.51 mmol) was added to a solution of (2R)-methyl 2-(1-(2-

chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-isopropoxypropanoate **D1b** (472 mg, 1.21 mmol) in THF (7 mL) and water (3.5 mL) at ambient temperature. The reaction mixture was stirred for 1 hour. The reaction mixture was diluted with EtOAc (50 mL) and acidified to pH 4 with 2M HCl. The organic layer was separated and the aqueous layer extracted with EtOAc (2 x 50 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated to afford **D1** (325 mg, 70% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 - 1.25 (6H, m), 3.73 - 3.81 (1H, m), 4.05 - 4.08 (2H, m), 5.82 - 5.84 (1H, m), 7.42 - 7.54 (3H, m), 7.58 - 7.61 (1H, m), 8.38 (1H, s), 8.57 (1H, s), m/z (ESI+) $(M+H)^+$ = 377; HPLC t_R = 2.15 min.

Intermediate D2: (2S)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-isopropoxypropanoic acid



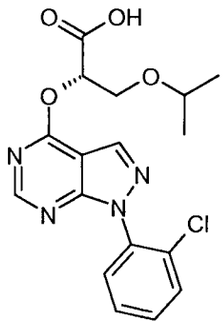
Step 1: Synthesis of D2a: (2S)-methyl 2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-isopropoxypropanoate



D2a was prepared in an analogous fashion to **D1b** from (S)-methyl 2-hydroxy-3-isopropoxypropanoate **C7a** and **B1**.

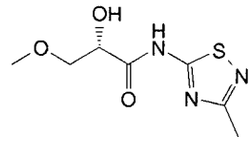
^{1}H NMR δ_H(400 MHz, $CDCl_3$) 1.20 - 1.26 (6H, m), 3.71 - 3.75 (1H, m), 3.80 (3H, s), 4.01 - 4.08 (2H, m), 5.79 - 5.82 (1H, m), 7.43 - 7.50 (2H, m), 7.51 - 7.54 (1H, m), 7.60 (1H t, *J*= 1.6 Hz), 8.37 (1H, s), 8.54 (1H, s), m/z (ESI+) $(M+H)^+$ = 391; HPLC t_R = 2.42 min

Step 2: Synthesis of D2: (2S)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-isopropoxypropanoic acid



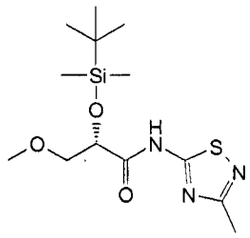
D2 was prepared in an analogous fashion to **D1** from (2S)-methyl 2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-isopropoxypropanoate **D2a**. 60% ee. δ_H(400 MHz, $CDCl_3$) 1.22 - 1.26 (6H, m), 3.75 - 3.81 (1H, m), 4.04 - 4.10 (2H, m), 5.83 - 5.86 (1H, m), 7.43 - 7.54 (3H, m), 7.59 - 7.62 (1H, m), 8.38 (1H, s), 8.57 (1H, s), m/z (ESI+) (M+H)+ = 377; HPLC t_R = 2.12 min.

Intermediate E1: (S)-2-hydroxy-3-methoxy-N-(3-methyl-1,2,4-thiadiazol-5-yl)propanamide



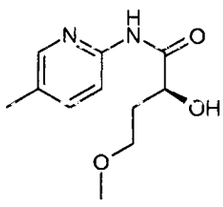
A solution of tetrabutylammonium fluoride (1M inTHF) (2.353 mL, 2.35 mmol) was added in one portion to a stirred solution of (S)-2-(tert-butyldimethylsilyloxy)-3-methoxy-N-(3-methyl-1,2,4-thiadiazol-5-yl)propanamide (**Intermediate E2**) (390 mg, 1.18 mmol) in tetrahydrofuran (10 mL). The resulting solution was stirred at ambient temperature for 4 hours. The reaction mixture was diluted with EtOAc (20 mL), and washed sequentially with water (10 mL) and saturated brine (10 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash silica chromatography, elution gradient 0 to 100% EtOAc in isohexane to afford (S)-2-hydroxy-3-methoxy-N-(3-methyl-1,2,4-thiadiazol-5-yl)propanamide (192 mg, 75 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49 (3H, s), 3.37 (3H, s), 3.60 (1H, d), 3.72 (2H, d), 4.46 (1H, q), 10.20 (1H, s); m/z (ESI+) (M+H)+ = 218.30; HPLC t_R = 0.89 min.

Intermediate E2: (S)-2-(tert-butyldimethylsilyloxy)-3-methoxy-N-(3-methyl-1,2,4-thiadiazol-5-yl)propanamide



A solution of 1-chloro-N,N,2-trimethylprop-1-en-1-amine (1.521 mL, 11.50 mmol) in DCM (2 mL) was added dropwise to a stirred solution of (S)-2-(tert-butyldimethylsilyloxy)-3-methoxypropanoic acid (**Intermediate C4c**)(2.45 g, 10.45 mmol) in DCM (10 mL) over a period of 1 minute under nitrogen. The resulting pale yellow solution was stirred at ambient temperature for 30 minutes. Anhydrous pyridine (1.262 mL, 15.68 mmol) was added in one portion (solution turns deeper yellow) followed by 3-methyl-1,2,4-thiadiazol-5-amine (CAS no. 17467-35-5) (1.204 g, 10.45 mmol) in DCM (3 mL) dropwise over a period of 1 minute. The resulting solution was stirred at ambient temperature for 1 hour. 1M citric acid (50 mL) added and extracted with EtOAc (50 mL). Organic phase washed with water (25 mL) and brine (25 mL), dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash silica chromatography, elution gradient 0 to 30% EtOAc in isohexane to afford (S)-2-(tert-butyldimethylsilyloxy)-3-methoxy-N-(3-methyl-1,2,4-thiadiazol-5-yl)propanamide (390 mg, 11%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.11 (6H, dd), 0.89 (9H, s), 2.49 (3H, s), 3.30 (3H, s), 3.61 (2H, t), 4.46 (1H, dd), 9.75 - 9.90 (1H, s); m/z (ESI+) $(M+H)^+$ = 332.30; HPLC t_R = 2.77 min.

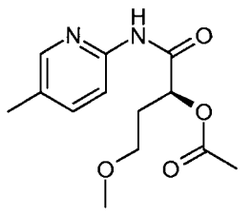
Intermediate F1: (S)-2-Hydroxy-4-methoxy-N-(5-methylpyridin-2-yl)butanamide



Aqueous potassium carbonate 1M (5.257 mL, 5.26 mmol) was added to a solution of (S)-4-methoxy-1-(5-methylpyridin-2-ylamino)-1-oxobutan-2-yl acetate (**Intermediate F2**) (170 mg, 0.64 mmol) in MeOH (0.3 mL) at 0 °C and the mixture was stirred at room temperature for 2 h. The reaction mixture was neutralized with aqueous $KHSO_4$ (1.0 M,

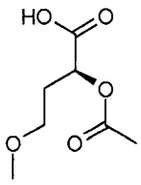
0.29 mL). The reaction mixture was concentrated and the residue was purified by flash silica chromatography, elution gradient 0 to 100% EtOAc in isohexane to afford (S)-2-hydroxy-4-methoxy-N-(5-methylpyridin-2-yl)butanamide (142 mg, 99 %).
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.02 - 2.11 (1H, m), 2.23 - 2.26 (1H, m), 2.30 (3H, s), 3.38 (3H, s), 3.64 - 3.75 (2H, m), 4.38 - 4.41 (1H, m), 4.64 - 4.78 (1H, m), 7.51 - 7.53 (1H, m), 8.13 (2H, t), 9.30 (1H, s); m/z (ESI+) $(M+H)^+$ = 225; HPLC t_R = 0.86 min.

Intermediate F2: (S)-4-methoxy-1-(5-methylpyridin-2-ylamino)-1-oxobutan-2-yl acetate



5-Methylpyridin-2-amine (CAS no. 1603-41-4) (460 mg, 4.26 mmol) was added to (S)-2-acetoxy-4-methoxybutanoic acid (**Intermediate F3**) (500 mg, 2.84 mmol), in THF (8 mL) under nitrogen. The resulting suspension was stirred at 23 °C for 30 minutes. 4-(4,6-Dimethoxy[1.3.5]triazin-2-yl)-4-methylmorpholinium chloride hydrate (CAS no. 3945-69-5) (1.18 g, 4.26 mmol) was added and the suspension stirred for 40 hrs. The reaction mixture was concentrated and purified by flash silica chromatography, elution gradient 0 to 50% EtOAc in isohexane to afford (S)-4-methoxy-1-(5-methylpyridin-2-ylamino)-1-oxobutan-2-yl acetate (410 mg, 54 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.13 - 2.28 (5H, m), 2.30 (3H, s), 3.31 (3H, s), 3.48 - 3.53 (2H, m), 5.37 - 5.40 (1H, m), 7.50 - 7.53 (1H, m), 8.09 - 8.11 (2H, m), 8.52 (1H, s); m/z (ESI+) $(M+H)^+$ = 267; HPLC t_R = 1.22 min.

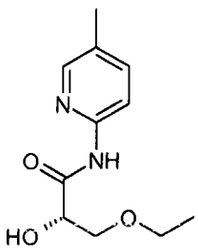
Intermediate F3: (S)-2-Acetoxy-4-methoxybutanoic acid



Sodium nitrate (4.93 g, 57.98 mmol) was added portionwise to (S)-2-amino-4-methoxybutanoic acid (CAS no. 3311-01-1) (3.86 g, 29.0 mmol) in acetic acid (88 mL) at room temperature (with intermittent cooling with an ice bath to keep the temperature near to room temperature). Once the addition was complete, the mixture was left to stir at room temperature for 24 h. The solvent was then removed *in vacuo*, the residue was dissolved in

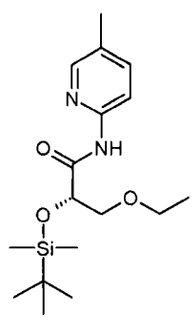
ether (250 mL), and the ethereal solution was washed with water (3 × 100 mL). The organic layer was extracted with saturated $NaHCO_3$ solution (3 × 100 mL). The aqueous extracts were then acidified with 2N HCl and extracted with ether (3 x 100 mL). The combined organic layers were dried ($MgSO_4$) and reduced *in vacuo* to give crude (S)-2-acetoxy-4-methoxybutanoic acid (0.600 g, 11.8 %) which was used without further purification.

Intermediate G1: (2S)-3-Ethoxy-2-hydroxy-N-(5-methylpyridin-2-yl)propanamide



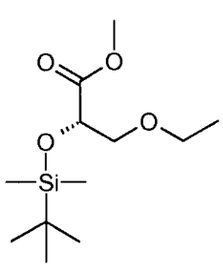
A solution of tetrabutylammonium fluoride (1M in THF) (3.25 mL, 3.25 mmol) was added in one portion to a stirred solution of (S)-2-(tert-butyldimethylsilyloxy)-3-ethoxy-N-(5-methylpyridin-2-yl)propanamide (**Intermediate G2**) (1.1 g, 3.25 mmol) in tetrahydrofuran (25 mL). The resulting solution was stirred at ambient temperature for 4 hours. The reaction mixture was concentrated and diluted with EtOAc (50 mL) washed sequentially with water (20 mL) and saturated brine (20 mL). The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by flash silica chromatography, elution gradient 50 to 100% EtOAc in isohexane to afford (2S)-3-ethoxy-2-hydroxy-N-(5-methylpyridin-2-yl)propanamide (730mg, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (3H, t), 2.30 (3H, s), 3.60 (2H, q), 3.76 - 3.79 (2H, m), 3.87 (1H, s), 4.33-4.38 (1H, m), 7.52 (1H, dd), 8.11 - 8.13 (2H, m), 9.20 (1H, s); m/z (ESI+) $(M+H)^+$ = 225; HPLC t_R = 0.96 min.

Intermediate G2: (2S)-2-(tert-butyl-dimethylsilyl)oxy-3-ethoxy-N-(5-methylpyridin-2-yl)propanamide



A solution of trimethylaluminium (2M in hexane, 2.75 mL, 5.49 mmol) was added dropwise to a stirred solution of 5-methylpyridin-2-amine (0.594 g, 5.49 mmol) in toluene (10 mL) cooled to 0°C, over a period of 5 minutes under nitrogen. The resulting solution was stirred for 15 minutes. A solution of (S)-methyl 2-(tert-butyldimethylsilyloxy)-3-ethoxypropanoate (**Intermediate G3**) (1.31 g, 4.99 mmol) in toluene (5 mL) was added dropwise over a period of 2 minutes. The resulting solution was allowed to warm to ambient temperature and then heated to reflux for 7 hours then allowed to cool to room temperature and 1M citric acid (20 mL) added, diluted with water (25 mL) and the mixture extracted with ethyl acetate (25 mL). The aqueous was re-extracted with ethyl acetate (25 mL), the organic phases combined, washed with water (5 mL) and brine (20 mL), dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash silica chromatography, elution gradient 10 to 100% EtOAc in isohexane to give (2S)-2-(tert-butyl-dimethylsilyl)oxy-3-ethoxy-N-(5-methylpyridin-2-yl)propanamide (1.1 g, 65%). ^1H NMR (400 MHz, $CDCl_3$) δ 0.18 (3H, s), 2.00 (3H, s), 0.99 (9H, s), 1.18 (3H, t), 2.30 (3H, s), 3.51 - 3.61 (2H, m), 3.63 - 3.67 (1H, m), 3.78 - 3.81 (1H, m), 4.41 - 4.43 (1H, m), 7.51 (1H, dd), 8.13 - 8.18 (2H, m), 9.03 (1H, s); m/z (ESI+) $(M+H)^+$ = 339; HPLC t_R = 3.31 min.

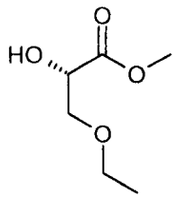
Intermediate G3: Methyl (2S)-2-(tert-butyl-dimethylsilyl)oxy-3-ethoxypropanoate



A solution of tert-butylchlorodimethylsilane (17.71g, 117.52mmol) in dry DMF (50 mL) was added dropwise to a stirred solution of (S)-methyl 2-hydroxy-3-ethoxypropanoate (14.51g, 97.94 mmol) and 1H-imidazole (13.33g, 195.87 mmol) in dry DMF (70 mL) at 20°C, over a period of 2 minutes. The resulting solution was stirred at ambient temperature for 20 hours. The reaction mixture was concentrated and diluted with EtOAc (500 mL), washed sequentially with water (4 × 100 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by flash silica chromatography, elution gradient 20 to 50% EtOAc in isohexane to afford methyl (2S)-2-

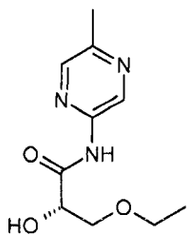
(tert-butyl-dimethylsilyl)oxy-3-ethoxypropanoate (14.8g, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.10 (6H, d), 0.93 (9H, s), 1.19 (3H, t), 3.50 - 3.65 (3H, m), 3.57 - 3.73 (1H, m), 3.75 (3H, s), 4.37 - 4.40 (1H, m), 7.18 (2H, d).

Intermediate G4: Methyl (2S)-3-ethoxy-2-hydroxypropanoate



Magnesium trifluoromethanesulphonate (11.85 g, 36.73 mmol) was added in one portion to (S)-methyl oxirane-2-carboxylate (15.0 g, 146.93 mmol) and ethanol (10.29 ml, 176.32 mmol) cooled to 10°C. The resulting suspension was stirred at 10 °C for 20 minutes, allowed to warm to ambient temperature and then warmed to 50°C for 30 hours. The mixture was allowed to cool and diluted with 9:1 DCM:ether (75 mL), filtered through Celite and washed through with 9:1 DCM:ether (3 × 50 mL) and evaporated.
The residue was purified by flash silica chromatography, elution gradient 10 to 50% Et_2O in DCM to give methyl (2S)-3-ethoxy-2-hydroxypropanoate (11.6 g, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (3H, t), 3.00 (1H, d), 3.47 - 3.58 (2H, m), 3.72 (2H, d), 3.81 (3H, s), 4.23 - 4.34 (1H, m).

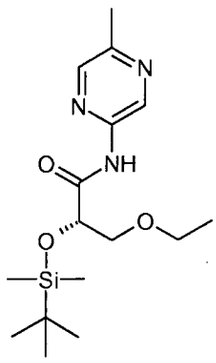
Intermediate H1: (2S)-3-ethoxy-2-hydroxy-N-(5-methylpyrazin-2-yl)propanamide



A solution of tetrabutylammonium fluoride (1M in THF) (4.27 mL, 4.27 mmol) was added in one portion to a stirred solution of (S)-2-(tert-butyldimethylsilyloxy)-3-ethoxy-N-(5-methylpyrazin-2-yl)propanamide (**Intermediate H2**) (1.45 g, 4.27 mmol) in tetrahydrofuran (25 mL). The resulting solution was stirred at ambient temperature for 4 hours. The reaction mixture was concentrated and diluted with EtOAc (50 mL) washed sequentially with water (20 mL) and saturated brine (20 mL). The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by flash silica chromatography eluting with 50% to 100% EtOAc in isohexane to afford (2S)-3-ethoxy-2-hydroxy-N-(5-

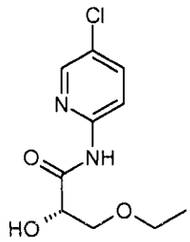
methylpyrazin-2-yl)propanamide (700mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (3H, t), 2.54 (3H, s), 3.49 (1H, d), 3.61 (2H, q), 3.75 - 3.83 (2H, m), 4.35 - 4.39 (1H, m), 8.14 (1H, d), 9.13 (1H, s), 9.43 (1H, d); m/z (ESI+) (M+H)+ = 226; HPLC t_R = 1.00 min.

Intermediate H2: (2S)-2-(tert-butyl-dimethylsilyl)oxy-3-ethoxy-N-(5-methylpyrazin-2-yl)propanamide



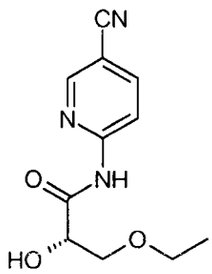
A solution of trimethylaluminium (2M in hexane, 5.51 mL, 11.02 mmol) was added dropwise to a stirred solution of 5-methylpyrazin-2-amine (CAS no. 5521-58-4) (1.20 g, 11.0 mmol) in toluene (20 mL) cooled to 0 °C, over a period of 5 minutes under nitrogen. The resulting solution was stirred for 15 minutes. A solution of (S)-methyl 2-(tert-butyldimethylsilyloxy)-3-ethoxypropanoate (**Intermediate G3**) (2.63 g, 10.0 mmol) in toluene (5 mL) was added dropwise over a period of 2 minutes. The resulting solution was allowed to warm to ambient temperature and then heated to reflux for 3 hours. 20% Sodium potassium tartrate solution (50 mL) then water (25 mL) were added and the mixture extracted with ethyl acetate (25 mL). The aqueous was re-extracted with ethyl acetate (25 mL). The organic phases were combined, washed with water (5 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated The residue was purified by flash silica chromatography, elution gradient 20 to 100% EtOAc in isohexane to give (2S)-2-(tert-butyl-dimethylsilyl)oxy-3-ethoxy-N-(5-methylpyrazin-2-yl)propanamide (1.45g, 42%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.18 (3H, s), 0.20 (3H, s), 0.98 (9H, s), 1.20 (3H, t), 2.54 (3H, s), 3.50 - 3.59 (2H, m), 3.65 - 3.69 (1H, m), 3.77 - 3.80 (1H, m), 4.42 - 4.44 (1H, m), 8.14 (1H, d), 9.01 (1H, s), 9.44 (1H, d); m/z (ESI+) (M+H)+ = 340; HPLC t_R = 3.04 min.

Intermediate H3: (S)-N-(5-chloropyridin-2-yl)-3-ethoxy-2-hydroxypropanamide



Prepared using analogous procedures to those described for **G1** and **G2**, using 5-chloropyridine-2-amine (CAS no. 1072-98-6) and **Intermediate G3**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (3H t), 3.57 - 3.64 (3H, m), 3.74 - 3.81 (2H, m), 4.34 - 4.36 (1H, m), 7.66 - 7.69 (1H, m), 8.21 - 8.23 (1H, m), 9.27 (1H, s); m/z (ESI+) $(M+H)^+$ =245; HPLC t_R = 1.63 min.

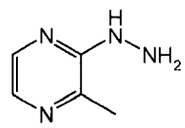
Intermediate H4: (S)-N-(5-cyanopyridin-2-yl)-3-ethoxy-2-hydroxypropanamide



Prepared using a procedure analogous to that described for **G1** and **G2**, using **Intermediate G3** and 2-amino-5-cyanopyridine.

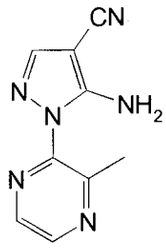
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (3H, t), 3.38 (1H, d), 3.61 (2H, q), 3.73 - 3.84 (2H, m), 4.37 (1H, q), 7.92 - 7.98 (1H, m), 8.35 - 8.40 (1H, m), 8.56 - 8.61 (1H, m), 9.44 (1H, s); m/z (ES+) $(M+H)^+$ = 236.35; HPLC tR= 1.28 min.

Intermediate I1: 2-Hydrazinyl-3-methylpyrazine



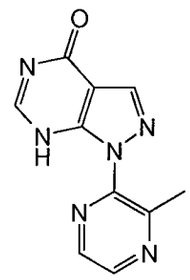
Hydrazine hydrate (9.66 mL, 311.14 mmol) was added to 2-chloro-3-methylpyrazine (CAS no. 95-58-9) (8 g, 62.23 mmol) in ethanol (25 mL). The resulting solution was stirred at 90°C for 16 hours. The resulting solution was evaporated to dryness and the crude product was purified by crystallisation from toluene (125 mL) to afford 2-hydrazinyl-3-methylpyrazine (6.2 g, 80%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.24 (3H, s), 7.61 (1H, d), 7.87 (1H, d).

Intermediate I2: 5-Amino-1-(3-methylpyrazin-2-yl)-1H-pyrazole-4-carbonitrile



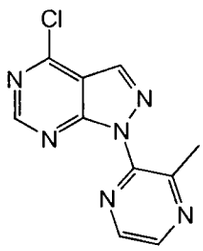
Prepared in an analogous fashion to **B15a** from 2-hydrazinyl-3-methylpyrazine (**Intermediate I1**). ^{1}H NMR (400 MHz, DMSO-d_6) 2.45 (3H, s), 7.84 (1H, s), 8.48 - 8.49 (1H, m), 8.66 (1H, d), m/z (ESI+) (M+H)+ = 201 ; HPLC t_R = 1.04 min.

Intermediate I3: 1-(3-methylpyrazin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4(7H)-one



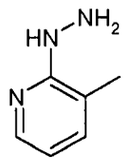
Prepared in an analogous fashion to **B15b** from 5-amino-1-(3-methylpyrazin-2-yl)-1H-pyrazole-4-carbonitrile (**Intermediate I2**). ^{1}H NMR (400 MHz, DMSO-d_6) 2.40 (3H, s), 8.12 - 8.13 (1H, m), 8.41 (1H, s), 8.62 (1H, d), 8.80 (1H, d), 12.45 (1H, s); m/z (ESI+) (M+H)+ = 229; HPLC t_R = 0.85 min.

Intermediate I4 : 4-Chloro-1-(3-methylpyrazin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine



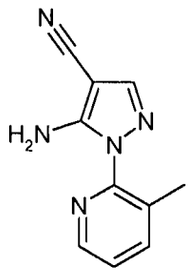
Prepared in an analogous fashion to **Intermediate B15** from 1-(3-methylpyrazin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4(7H)-one (**Intermediate I3**). ^{1}H NMR (400 MHz, DMSO-d_6) 2.43 (3H, s), 8.64 - 8.65 (1H, m), 8.84 (2H, t), 8.93 (1H, s); m/z (ESI+) (M+H)+ = 247 ; HPLC t_R = 1.38min.

Intermediate J1: 2-Hydrazinyl-3-methylpyridine



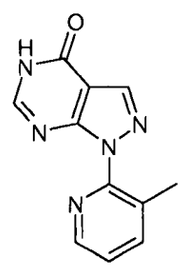
2-Bromo-3-methylpyridine (5.16 g, 30.00 mmol) and hydrazine hydrate (10.92 mL, 224.97 mmol) were mixed. The reaction was heated to 110 °C for 20 hours with stirring. The mixture was cooled to ambient temperature during which a white solid precipitated. This was then collected filtation, washed with ether (3 × 10 mL), slurried in DCM (50 mL), stirred for 10 minutes and then passed through a phase separation cartridge to remove water. The organic liquors were evaporated and dried under high vacuum to give 2-hydrazinyl-3-methylpyridine (2.5 g, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.08 (3H, s), 4.02 (2H, s), 5.50 (1H, s), 6.64 (1H, dd), 7.20 - 7.30 (1H, m), 8.08 (1H, dd). MP=119°C (Lit 122°C).

Intermediate J2: 5-Amino-1-(3-methylpyridin-2-yl)-1H-pyrazole-4-carbonitrile



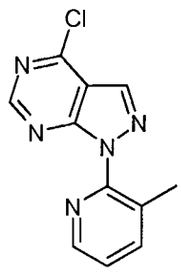
Prepared in an analogous fashion to **B15a** from 2-hydrazinyl-3-methylpyridine (**Intermediate J1**). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.23 (3H, s), 6.82 (2H, s), 7.42 - 7.45 (1H, m), 7.78 (1H, s), 7.88 - 7.90 (1H, m), 8.38 - 8.39 (1H, m). m/z (ESI+) $(M+H)^+$ = 200; HPLC t_R = 1.14 min.

Intermediate J3: 1-(3-methylpyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4(7H)-one



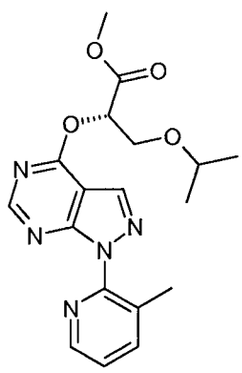
Prepared in an analogous fashion to **B15b** from 5-amino-1-(3-methylpyridin-2-yl)-1H-pyrazole-4-carbonitrile (**Intermediate J2**). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.08 (3H, s), 7.53 - 7.56 (1H, m), 7.94 - 7.97 (1H, d), 8.05 (1H, s), 8.31 (1H, s), 8.46 - 8.47 (1H, m), 12.34 (1H, s). m/z (ESI+) (M+H)+ = 228; HPLC t_R = 0.92 min.

Intermediate J4: 4-Chloro-1-(3-methylpyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine



Prepared in an analogous fashion to **B15** from 1-(3-methylpyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4(7H)-one (**Intermediate J3**). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.12 (3H, s), 7.59 - 7.62 (1H, m), 8.00 - 8.03 (1H, m), 8.50 - 8.52 (1H, m), 8.76 (1H, s), 8.88 (1H, s). m/z (ESI+) (M+H)+ = 246; HPLC t_R = 1.51 min.

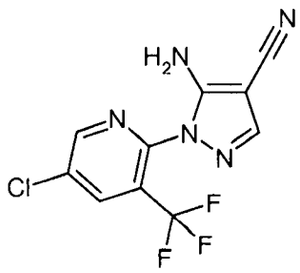
Intermediate J5: (2S)-Methyl 3-isopropoxy-2-(1-(3-methylpyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanoate



60% Sodium hydride (0.720 g, 18.00 mmol) was added to a solution of (S)-methyl 2-hydroxy-3-isopropoxypropanoate (2.353 g, 12.00 mmol) in anhydrous THF (100 mL) at 5°C, under nitrogen. The resulting suspension was stirred at 5°C for 10 minutes and then a solution of 4-chloro-1-(3-methylpyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate J4**) (2.95 g, 12 mmol) in dry THF (50 mL) was added dropwise maintaining a temperature below 5°C. The reaction mixture was stirred at 5°C for 10 mins and then allowed to warm to room temperature. The reaction was stirred at room temperature for 1 hour. The reaction mixture was neutralised with HCl (1M, aq). The

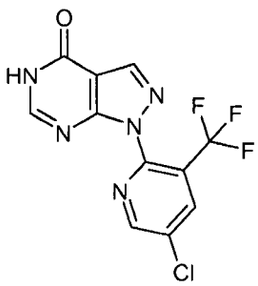
majority of the THF was evaporated *in vacuo* and then EtOAc (75 mL) and water (50 mL) were added. The organic layer was separated and the aqueous layer re-extracted with EtOAc (2 x 50 mL). The combined organics were washed with saturated brine (50 mL),dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash silica chromatography (120 g), elution gradient 30 to 80% EtOAc in isohexane to afford (2S)-methyl 3-isopropoxy-2-(1-(3-methylpyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanoate (3.53 g, 79%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.11 - 1.14 (6H, m), 2.11 (3H, s), 3.68 - 3.74 (4H, m), 3.95 - 4.03 (2H, m), 5.79 - 5.81 (1H, m), 7.56 - 7.59 (1H, dd), 7.98 - 8.00 (1H, d), 8.49 (1H, m), 8.57 (2H, d). m/z (ESI+) $(M+H)^+$ = 372; HPLC t_R = 1.99 min.

Intermediate K1: 5-Amino-1-(5-chloro-3-(trifluoromethyl)pyridin-2-yl)-1H-pyrazole-4-carbonitrile



Prepared in an analogous fashion to **B15a** from 5-chloro-2-hydrazinyl-3-(trifluoromethyl)pyridine (CAS no. 129015-69-6). ^{1}H NMR (400 MHz, DMSO) δ 6.87 (2H, s), 7.69 (1H, s), 8.58 (1H, d), 8.83 (1H, d).

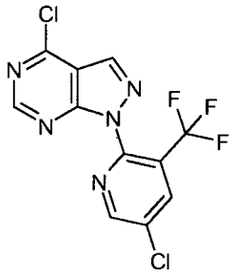
Intermediate K2: 1-(5-Chloro-3-(trifluoromethyl)pyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol



Prepared in an analogous fashion to **B15b** from 5-amino-1-(5-chloro-3-(trifluoromethyl)pyridin-2-yl)-1H-pyrazole-4-carbonitrile (**Intermediate K1**).

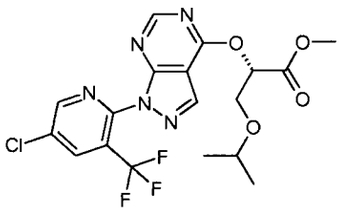
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (1H, s), 8.39 (1H, s), 8.80 (1H, d), 9.05 (1H, d), 12.49 (1H, s). m/z (ESI+) (M+H)+ = 316; HPLC t_R = 1.48 min.

Intermediate K3: 4-Chloro-1-(5-chloro-3-(trifluoromethyl)pyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine



Prepared in an analogous fashion to **B15** from 1-(5-chloro-3-(trifluoromethyl)pyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol (**Intermediate K2**). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.88 - 8.88 (1H, m), 8.95 (1H, s), 9.10 (1H, d), 9.48 (1H, s). m/z (ESI+) (M+H)+ = 334; HPLC t_R = 2.32 min. (93%)

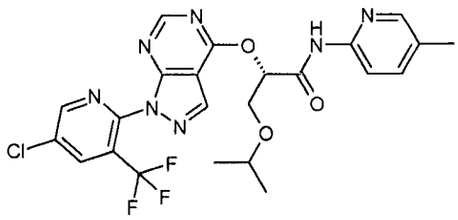
Intermediate K4: (2S)-methyl 2-(1-(5-chloro-3-(trifluoromethyl)pyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-isopropoxypropanoate



Pepared in an analogous fashion to **J5** from 4-chloro-1-(5-chloro-3-(trifluoromethyl)pyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate K3**).

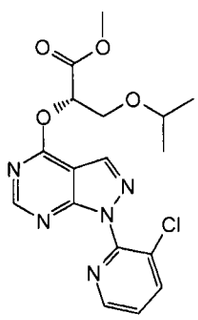
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.10 - 1.14 (6H, m), 3.67 - 3.74 (4H, m), 3.96 - 4.01 (2H, m), 5.80 - 5.82 (1H, m), 8.60 (1H, s), 8.67 (1H, s), 8.83 (1H, d), 9.09 (1H, d). m/z (ESI+) (M+H)+ = 460; HPLC t_R = 2.65 min.

Intermediate K6: (2S)-2-(1-(5-Chloro-3-(trifluoromethyl)pyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-isopropoxy-N-(5-methylpyridin-2-yl)propanamide



Prepared in an analogous fashion to **Example 125** from (2S)-methyl 2-(1-(5-chloro-3-(trifluoromethyl)pyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-isopropoxypropanoate (**Intermediate K4**). ^{1}H NMR (400 MHz, DMSO) δ 1.10 - 1.12 (6H, m), 2.24 (3H, s), 3.72 - 3.78 (1H, m), 3.95 - 4.07 (2H, m), 5.89 (1H, s), 7.58 (1H, d), 7.87 (1H, d), 8.17 (1H, s), 8.57 (1H, s), 8.68 (1H, s), 8.83 (1H, d), 9.08 (1H, d), 10.81 (1H, s); m/z (ESI+) $(M+H)^+$ = 536; HPLC t_R = 2.72 min.

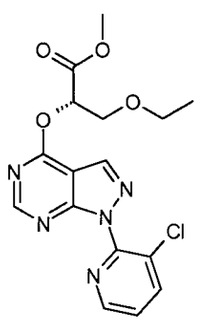
Intermediate L1: (2S)-Methyl 2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-isopropoxypropanoate



Sodium hydride (1.84 g, 45.9 mmol) was added to a stirred solution of (S)-methyl 2-hydroxy-3-isopropoxypropanoate (**Intermediate C7a**) (6.0 g, 30.6 mmol) in anhydrous THF (200 mL) at 0 °C, under nitrogen. The resulting suspension was stirred at 0 °C for 10 minutes and then a solution of 4-chloro-1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate B15**) (8.14 g, 30.59 mmol) in dry THF (50 mL) was added dropwise, maintaining the temperature below 5°C. The reaction mixture was stirred at 0°C for 10 minutes. Then allowed to warm to ambient temperature and stirred for 1 hour. The reaction mixture was neutralised with 1M HCl. The majority of the THF was evaporated *in vacuo* and then EtOAc (100 mL) was added. The organic layer was separated and the aqueous layer re-extracted with EtOAc (2 × 100 mL). The combined organics were washed

with saturated brine (75 mL), dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, elution gradient 20 to 70% EtOAc in isohexane to afford (2S)-methyl 2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-isopropoxypropanoate (7.76 g, 64.8 %), ee 53%. A sample of this (1.48 g) was purified by preparative chiral-HPLC on a 50mm 20um chiralcel OJ column, eluting with 30% isopropanol in isohexane (modified with 0.1%TEA), to give (2S)-methyl 2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-isopropoxypropanoate (1.03 g, 99% ee). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.10 - 1.14 (6H, m), 3.68-3.75 (4H, m), 3.98 - 4.00 (2H, m), 5.80 - 5.82 (1H, m), 7.74 - 7.77 (1H, m), 8.33 - 8.35 (1H, d), 8.59 (1H, s), 8.64 (1H, s), 8.67 - 8.68 (1H, m); m/z (ESI+) (M+H)+ = 392; HPLC t_R = 2.13 min.

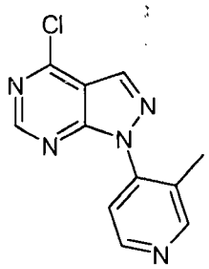
Intermediate L2 : Methyl (2S)-2-[1-(3-chloropyridin-2-yl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-ethoxypropanoate



60% sodium hydride in mineral oil (0.96 g, 24.1 mmol) was added portionwise to (S)-methyl 3-ethoxy-2-hydroxypropanoate (**Intermediate G4**) (2.97 g, 20.1 mmol) in tetrahydrofuran (50 mL) cooled to 0 °C over a period of 1 minute under nitrogen. The resulting solution was stirred at 0 °C for 10 minutes. A solution of 4-chloro-1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate B15**) (5.87 g, 22.1 mmol) in tetrahydrofuran (50 mL) was added dropwise over a period of 2 minutes. The resulting mixture was allowed to warm to ambient temperature and stirred for 2 hour. The reaction was cooled to ~10 °C, 1M citric acid (20 mL) added and the mixture was extracted with EtOAc (2 × 50 mL). The organic extracts were washed with water (25 mL) and saturated brine (25 mL), dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash silica chromatography, elution gradient 50 to 100% EtOAc in isohexane to give the methyl (2S)-2-[1-(3-chloropyridin-2-yl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-ethoxypropanoate (5.7 g, 70% ee). This was further purified by chiral HPLC on Chiralcel

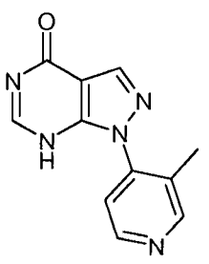
OJ eluting with isohexane / isopropanol / triethylamine (70:30:0.1) at 60 mL / min. to give the enantiomerically pure product (3.8g, 50%) as a colourless gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (3H, t), 3.60 - 3.73 (2H, m), 3.79 (3H, s), 4.00 - 4.11 (2H, m), 5.85 (1H, dd), 7.45 (1H, dd), 8.00 (1H, dd), 8.42 (1H, s), 8.58 (1H, s), 8.61 (1H, dd), m/z (ESI+) $(M+H)^+$ = 378; HPLC tR= 1.84 min.

Intermediate M1: 4-Chloro-1-(3-methylpyridin-4-yl)pyrazolo[5,4-d]pyrimidine



Phosphoryl trichloride (7.59 mL, 79.2 mmol) was added to 1-(3-methylpyridin-4-yl)-7H-pyrazolo[4,5-e]pyrimidin-4-one (**Intermediate M2**) (900 mg, 3.96 mmol) and the resulting suspension was stirred at 100 °C for 24 hours during which a solution formed. This was evaporated, triturated with ether (3 × 10 mL) and dried in vacuo. The resulting solid was suspended in DCM (50 mL) and stirred with 10 g of polymer supported carbonate for 2 hours. The mixture was filtered and evaporated to afford 4-chloro-1-(3-methylpyridin-4-yl)pyrazolo[5,4-d]pyrimidine (700 mg, 72%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.25 (3H, s), 7.62 (1H, d), 8.64 (1H, d), 8.74 (1H, s), 8.83 (1H, s), 8.94 (1H, s); m/z (ESI+) $(M+H)^+$ = 246; HPLC t_R = 1.22 min.

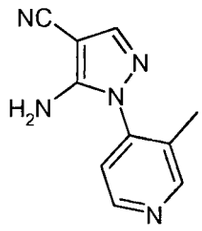
Intermediate M2: 1-(3-Methylpyridin-4-yl)-7H-pyrazolo[4,5-e]pyrimidin-4-one



Concentrated sulphuric acid (0.241 mL, 4.52 mmol) was added to a stirred solution of 5-amino-1-(3-methylpyridin-4-yl)-1H-pyrazole-4-carbonitrile (**Intermediate M3**) (900 mg, 4.52 mmol) in formic acid (10 mL) and the resulting solution stirred at 100 °C for 3 hours. The mixture was cooled and evaporated to ~half volume, water (10 mL) added and stirred. The mixture was adjusted to pH 3-4 with 2M NaOH and stirred for 1 hour. The solid that

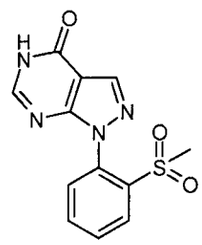
formed was collected by filtration, washed with water (2 × 7.5 mL), acetonitrile (10 mL) and diethyl ether (2 × 10 mL) and dried to afford 1-(3-methylpyridin-4-yl)-7H-pyrazolo[4,5-e]pyrimidin-4-one (750mg, 71%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.22 (3H, s), 7.51 (1H, d), 8.13 (1H, s), 8.38 (1H, s), 8.59 (1H, d), 8.68 (1H, s), 12.48 (1H, s), m/z (ESI+) (M+H)+ = 228; HPLC t_R = 0.73 min.

Intermediate M3: 5-Amino-1-(3-methylpyridin-4-yl)pyrazole-4-carbonitrile



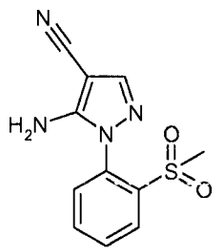
4-Hydrazinyl-3-methylpyridine (CAS no. 114913-51-8) (700 mg, 5.68 mmol) was suspended in MeOH (30 mL) under nitrogen at -5°C. 2-(ethoxymethylene)malononitrile (694 mg, 5.68 mmol) was added portionwise over 2 mins and the mixture stirred at ~0°C for 0.5 hours then heated at reflux for 2 hours. The mixture was allowed to cool and was then evaporated under reduced pressure to afford the crude 5-amino-1-(3-methylpyridin-4-yl)pyrazole-4-carbonitrile which was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.09 (3H, m), 7.07 (1H, d), 7.87 (2H, m), 7.98 (1H, d), 10.22 (1H, s).

Intermediate N1: 1-(2-(methylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one



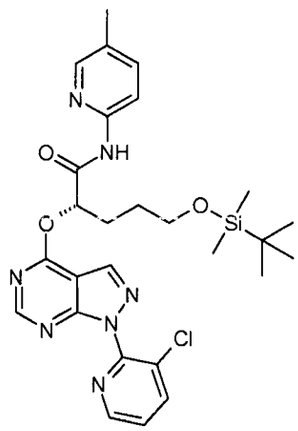
Prepared in an analogous fashion to **B15b** from **N2**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.36 (3H , s), 7.69 - 7.71 (1H, m), 7.85 - 7.89 (1H, m), 7.92 - 7.96 (1H, m), 8.06 - 8.07 (1H, m), 8.15 - 8.17 (1H, m), 8.33 (1H, s), 12.36 (1H, s). m/z (ESI+) (M+H)+ = 291; HPLC t_R = 0.96 min.

Intermediate N2: 5-Amino-1-(2-(methylsulfonyl)phenyl)-1H-pyrazole-4-carbonitrile



Prepared in an analogous fashion to **B15a** from (2-methanesulfonyl)phenylhydrazine (CAS no. 704-42-7). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.26 (3H, s), 6.62 (2H, s), 7.53 - 7.55 (1H, m), 7.79 (1H, s), 7.79 - 7.83 (1H, m), 7.86 - 7.90 (1H, m), 8.09 - 8.12 (1H, m). m/z (ESI+) $(M+H)^+$ = 263; HPLC t_R = 1.11 min.

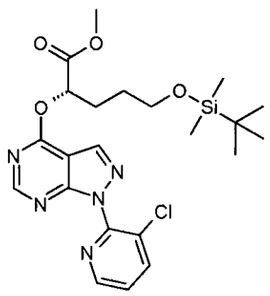
Intermediate O1: (2S)-5-(tert-butyl-dimethylsilyl)oxy-2-[1-(3-chloropyridin-2-yl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-methylpyridin-2-yl)pentanamide



A solution of trimethylaluminium (2M in hexane) (0.491 mL, 0.98 mmol) was added dropwise to a stirred solution of 5-methylpyridin-2-amine (92 mg, 0.85 mmol) in toluene (5 mL) cooled to 0°C, over a period of 1 minute under nitrogen. The resulting solution was stirred at 0°C for 20 minutes. A solution of (2S)-methyl 5-(tert-butyldimethylsilyloxy)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)pentanoate (**Intermediate O2**) (420 mg, 0.85 mmol) in toluene (5 mL) was added dropwise over a period of 2 minutes. The resulting solution was stirred at 0°C for 10 minutes allowed to warm to ambient temperature and then heated at 60°C for 20 hours. The mixture was cooled and 1M citric acid (10 mL) added with vigorous stirring. The mixture was diluted with ethyl acetate (35 mL), washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 50

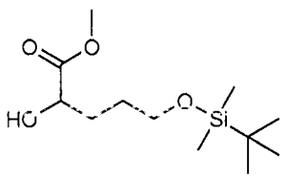
to 100% ethyl acetate in isohexane to give the product (180mg, 37%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (3H, s), 0.05 (3H, s), 0.89 (9H, s), 1.78 - 1.81 (2H, m), 2.20 - 2.30 (2H, m), 2.29 (3H, s), 3.71 (2H, t), 5.90 - 5.93 (1H, m), 7.45 (1H, dd), 7.51 (1H, dd), 7.99 (1H, dd), 8.07 - 8.08 (1H, m), 8.14 (1H, d), 8.42 (1H, s), 8.53 (1H, s), 8.60 (1H, dd), 8.62 (1H, s); m/z (ESI+) (M+H)+ = 568; HPLC tR= 3.33 min.

Intermediate O2: Methyl (2S)-5-(tert-butyl-dimethylsilyl)oxy-2-[1-(3-chloropyridin-2-yl)pyrazolo[4,5-e]pyrimidin-4-yl]oxypentanoate



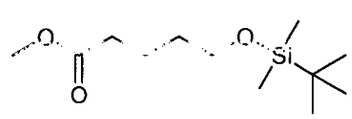
60% Sodium hydride in mineral oil (0.256 g, 6.40 mmol) was added portionwise to methyl 5-(tert-butyldimethylsilyloxy)-2-hydroxypentanoate (**Intermediate O3**) (1.4 g, 5.34 mmol) in tetrahydrofuran (7 mL) cooled to 0°C over a period of 1 minute under nitrogen. The resulting solution was stirred at 0 °C for 10 minutes. A solution of 4-chloro-1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (1.562 g, 5.87 mmol) in tetrahydrofuran (7 mL) was added dropwise over a period of 2 minutes, the mixture was allowed to warm to ambient temperature and stirred for 2 hours. The mixture was cooled to 10°C, 1M citric acid (20 mL) was added and extracted with ethyl acetate (2 × 50 mL). Organic extracts washed with water (25 mL) and saturated brine (25 mL), dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 30 to 100% ethyl acetate in isohexane to give the racemic product. This was purified by chiral HPLC to afford the product (850 mg, 32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (6H, s), 0.90 (9H, s), 1.80 - 1.90 (2H, m), 2.16 - 2.24 (2H, m), 3.72 (2H, t), 3.77 (3H, s), 5.62 (1H, t), 7.47 (1H, dd), 7.99 (1H, dd), 8.36 (1H, s), 8.57 (1H, s), 8.59 (1H, dd); m/z (ESI+) (M+H)+ = 492; HPLC tR= 3.32 min.

Intermediate O3: Methyl 5-(tert-butyl-dimethylsilyl)oxy-2-hydroxypentanoate



A solution of 1.6M butyllithium (6.42 mL, 10.27 mmol) was added dropwise to a stirred solution of diisopropylamine (1.583 mL, 11.20 mmol) in THF (20 mL) cooled to -78°C, over a period of 2 minutes under nitrogen. The resulting solution was stirred at -78°C for 10 minutes and a solution of methyl 5-(tert-butyldimethylsilyloxy)pentanoate (**Intermediate O4**) (2.3 g, 9.33 mmol) in THF (10 mL) was added dropwise over a period of 5 minutes. The resulting solution was stirred at -78°C for 10 minutes and then warmed to ambient temperature. The enolate solution was added dropwise over a period of 10 minutes to iodine (2.65 g, 10.45 mmol) in THF (20 mL) at -78°C under nitrogen, stirred for 10 minutes and allowed to warm to ambient temperature. The mixture was re-cooled to -78°C, poured into 1M citric acid (50 mL) and extracted with ether (2 × 75 mL). The organic extracts were washed with 1M sodium metabisulfite (50 mL), water and brine, dried ($MgSO_4$) and evaporated. The residue was dissolved in 1:1 diethyl ether acetonitrile (60 mL), (2,2,2-trifluoroacetoxy)silver (2.350 g, 10.64 mmol) and silver(I) oxide (3.46 g, 14.93 mmol) were added and the mixture was stirred for 20 hours at room temperature. The mixture was filtered, evaporated. The residue was purified by flash silica chromatography, eluting with 30 to 60% ethyl acetate in isohexane to afford the product (1.4 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.90 (9H, s), 1.56 - 1.80 (3H, m), 1.83 - 1.95 (1H, m), 3.22 (1H, d), 3.66 (2H, t), 3.78 (3H, s), 4.23 - 4.30 (1H, m).

Intermediate O4: methyl 5-(tert-butyl-dimethylsilyl)oxypentanoate

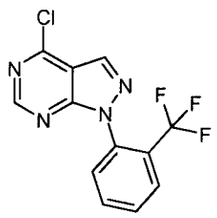


A solution of tert-butylchlorodimethylsilane (27.1 g, 179.79 mmol) in DCM (50 mL) was added dropwise to a stirred solution of methyl 5-hydroxypentanoate (CAS no. 14273-92-8, Huckstep, M.; Taylor, E. J. K.; Caton, M. P. L. Synthesis 1982, 10, 881) (19.8 g, 149.82 mmol) and 1H-imidazole (15.30 g, 224.73 mmol) in DCM (200 mL) at 5°C, over a period of 10 minutes under nitrogen. The resulting suspension was stirred at ambient temperature

for 6 hours. The reaction mixture was diluted with DCM (250 mL), and washed sequentially with water (2 × 200 mL) and saturated brine (200 mL). The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by flash silica chromatography, eluting with 10 to 50% ethyl acetate in isohexane to afford the product (19.3 g, 52%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (6H, s), 0.90 (9H, s), 1.50 - 1.59 (2H, m), 1.65 - 1.72 (2H, m), 2.35 (2H, t), 3.62 (2H, t), 3.65 (3H, s).

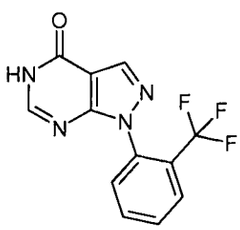
Intermediate P1: 4-Chloro-1-[2-(trifluoromethyl)phenyl]pyrazolo[5,4-d]pyrimidine



Phosphoryl trichloride (34.2 ml, 356.88 mmol) was added to 1-(2-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol (**Intermediate P2**) (5.0 g, 17.84 mmol). The resulting solution was stirred at 100°C for 4 hours.

The mixture was evaporated and the residue added to ice (~200g) with vigorous stirring. The mixture was stirred for 30 mins and the solid was collected by filtration washed with water (3 × 50 mL) and dried by suction. The solid was dissolved in ethyl acetate (250 mL), dried ($MgSO_4$) and evaporated to give the product (4.5g, 85%). ^{1}H NMR (400 MHz, DMSO) δ 7.75 - 7.80 (1H, m), 7.88 - 7.91 (1H, m), 7.95 - 7.98 (1H, m), 8.05 - 8.07 (1H, m), 8.79 (1H, s), 8.88 (1H, s); m/z (ESI+) (M+H)+ = 299; HPLC tR= 2.39 min.

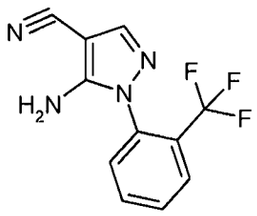
Intermediate P2: 1-[2-(trifluoromethyl)phenyl]-5H-pyrazolo[4,5-e]pyrimidin-4-one



Concentrated sulfuric acid (5.43 mL, 101.96 mmol) in was added to a stirred solution of 5-amino-1-(2-(trifluoromethyl)phenyl)-1H-pyrazole-4-carbonitrile (**Intermediate P3**) (14.3 g, 56.70 mmol) in formic acid (100 mL). The resulting solution was stirred at 100 °C for 4 hours. The mixture was evaporated to approximately half its original volume and water (75 mL) was added. The mixture was stirred for 1 hour, and the solid was collected by

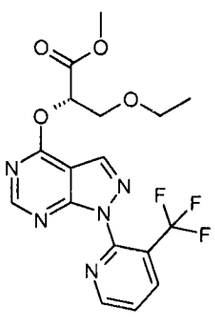
filtration, washed with water (3 × 30mL) and dried in vacuo at 50°C to give the product (10.2g, 64%). ^{1}H NMR (400 MHz, DMSO) δ 7.67 (1H, d), 7.85 - 7.92 (1H, m), 7.93 - 7.97 (1H, m), 7.98 - 8.01 (1H, m), 8.05 (1H, s), 8.32 (1H, s), 12.37 (1H, s); m/z (ESI+) (M+H)+ = 281; HPLC tR= 1.45 min.

Intermediate P3: 5-amino-1-[2-(trifluoromethyl)phenyl]pyrazole-4-carbonitrile



(2-(Trifluoromethyl)phenyl)hydrazine (CAS no. 365-34-4) (10.0 g, 56.77 mmol) was dissolved in MeOH (150 mL) under nitrogen at 0°C. 2-(ethoxymethylene)malononitrile (6.93 g, 56.77 mmol) added portionwise over 2 mins and the mixture stirred at ~0°C for 0.5 hours. The reaction was heated at reflux for 2 hours. Further methanol (15 mL) was added to aid mobility. The mixture was allowed to cool and was evaporated to give the product (14.3 g, 100%) which was used without further purification. ^{1}H NMR (400 MHz, DMSO) δ 6.63 (2H, s), 7.53 (1H, d), 7.73 (1H, s), 7.74 - 7.77 (1H, m), 7.82 - 7.86 (1H, m), 7.91 - 7.94 (1H, m); m/z (ESI+) (M+H)+ = 253; HPLC tR= 1.60 min.

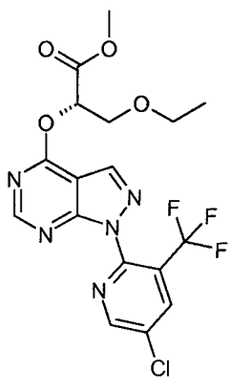
Intermediate Q1 : Methyl (2S)-3-ethoxy-2-[1-[3-(trifluoromethyl)pyridin-2-yl]pyrazolo[4,5-e]pyrimidin-4-yl]oxypropanoate



(2S)-Methyl 2-(1-(5-chloro-3-(trifluoromethyl)pyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-ethoxypropanoate (**Intermediate Q2**) (800 mg, 1.79 mmol) and 10% palladium on carbon (200 mg) in MeOH (30 mL) was stirred under an atmosphere of hydrogen for 24 hours. The mixture was filtered, 10% palladium on carbon (200 mg) and ammonium formate (1.0 g) were added and the mixture was heated to reflux for 2 hours. The mixture was allowed to cool and was filtered and evaporated. The residue was purified by flash

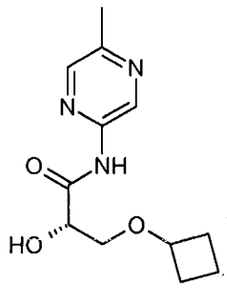
silica chromatography, eluting with 50 to 100% ethyl acetate in isohexane to afford the product (400mg, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (3H, t), 3.62 - 3.73 (2H, m), 3.79 (3H, s), 4.00 - 4.11 (2H, m), 5.84 (1H, dd), 7.63 - 7.66 (1H, m), 8.27 - 8.29 (1H, m), 8.38 (1H, s), 8.58 (1H, s), 8.88 - 8.89 (1H, m); m/z (ESI+) (M+H)+ = 412; HPLC tR= 2.13 min.

Intermediate Q2: Methyl (2S)-2-[1-[5-chloro-3-(trifluoromethyl)pyridin-2-yl]pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-ethoxypropanoate



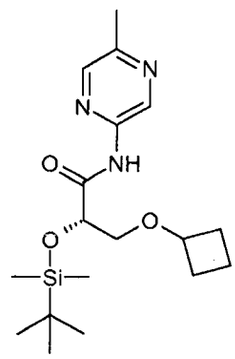
60% Sodium hydride in mineral oil (0.316 g, 7.90 mmol) was added portionwise to (S)-methyl 3-ethoxy-2-hydroxypropanoate (**Intermediate G4**) (0.976 g, 6.59 mmol) in tetrahydrofuran (50 mL) cooled to 5°C over a period of 1 minute under nitrogen. The resulting solution was stirred at 0 °C for 10 minutes. A solution of 4-chloro-1-(5-chloro-3-(trifluoromethyl)pyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate K3**) (1.1 g, 3.29 mmol) was added portionwise over a period of 1 minute. The resulting mixture was allowed to warm to ambient temperature and stirred for 2 hours. The mixture was cooled to 10°C, quenched with 1M citric acid (20 mL) and extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were washed with water (25 mL) and saturated brine (25 mL), dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 20 to 50% ethyl acetate in isohexane to give the product (1.1 g, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (3H, t), 3.72 (2H, d), 3.81 (3H, s), 3.99 - 4.13 (2H, m), 5.84 (1H, dd), 8.22 - 8.24 (1H, m), 8.38 (1H, s), 8.57 (1H, s), 8.81 - 8.82 (1H, m); m/z (ESI+) (M+H)+ = 446; HPLC tR= 2.52 min.

Intermediate R1: (2S)-3-cyclobutyloxy-2-hydroxy-N-(5-methylpyrazin-2-yl)propanamide



A solution of tetrabutylammonium fluoride (1M inTHF) (7.39 mL, 7.39 mmol) was added in one portion to a stirred solution of (S)-2-(tert-butyldimethylsilyloxy)-3-cyclobutoxy-N-(5-methylpyrazin-2-yl)propanamide (**Intermediate R2**) (2.7 g, 7.39 mmol) in tetrahydrofuran (25 mL) and the resulting solution was stirred at ambient temperature for 4 hours. The reaction mixture was concentrated under vacuum, diluted with ethyl acetate (50 mL) and washed sequentially with water (20 mL) and saturated brine (20 mL). The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by flash silica chromatography, eluting with ethyl acetate to afford the product (1.5g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 - 1.56 (1H, m), 1.70 - 1.76 (1H, m), 1.90 - 2.00 (2H, m), 2.19 - 2.26 (2H, m), 2.54 (3H, s), 3.61(1H, d), 3.67 - 3.73 (2H, m), 3.97 - 4.05 (1H, m), 4.35 - 4.38 (1H, m), 8.14 (1H, d), 9.15 (1H, s), 9.43 (1H, d); m/z (ESI+) $(M+H)^+$ = 252; HPLC t_R = 1.31 min.

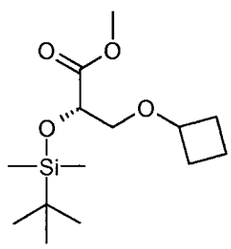
Intermediate R2: (2S)-2-(tert-butyl-dimethylsilyl)oxy-3-cyclobutyloxy-N-(5-methylpyrazin-2-yl)propanamide



A solution of trimethylaluminium (2M in hexane) (11.44 mL, 22.88 mmol) was added dropwise to a stirred solution of 5-methylpyrazin-2-amine (CAS no. 5521-58-4) (2.497 g, 22.88 mmol) in toluene (50 mL) cooled to 0°C, over a period of 5 minutes under nitrogen.

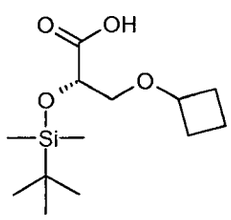
The resulting solution was stirred at 0°C for 15 minutes. A solution of (S)-methyl 2-(tert-butyldimethylsilyloxy)-3-cyclobutoxypropanoate (**Intermediate R3**) (6.0 g, 20.80 mmol) in toluene (10 mL) was added dropwise over a period of 2 minutes. The resulting solution was allowed to warm to ambient temperature and then heated to reflux for 2 hours. The mixture was allowed to cool, 20% sodium potassium tartrate (50 mL) and water (25 mL) were added and the mixture extracted with ethyl acetate (25 mL). The aqueous was re-extracted with ethyl acetate (25 mL). The organic phases were combined, washed with water (5 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 20 to 100% ethyl acetate in isohexane to give the product (2.7 g, 36%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.19 (3H, s), 2.00 (3H, s), 0.99 (9H, s), 1.48 - 1.51 (1H, m), 1.67 - 1.70 (1H, m), 1.91 - 1.94 (2H, m), 2.16 - 2.21 (2H, m), 2.54 (3H, s), 3.55 (1H, dd), 3.69 (1H, dd), 3.93 - 3.97 (1H, m), 4.39 - 4.41 (1H, m), 8.14 (1H, d), 9.00 (1H, s), 9.43 (1H, d); m/z (ESI+) (M+H)+ = 366; HPLC t_R = 3.28 min.

Intermediate R3: (S)-methyl 2-(tert-butyldimethylsilyloxy)-3-cyclobutoxypropanoate



Prepared using a procedure analogous to that described for **Intermediate C7a** using cyclobutanol. ^{1}H NMR (400 MHz, DMSO) δ 0.00 (d, 6H), 0.81 (s, 9H), 1.31 - 1.44 (m, 1H), 1.50 - 1.60 (m, 1H), 1.65 - 1.79 (m, 2H), 2.01 - 2.11 (m, 2H), 3.35 - 3.45 (m, 2H), 3.59 (s, 3H), 3.83 - 3.92 (m, 1H), 4.27 - 4.32 (m, 1H); m/z (EI+) M-C4H9 = 231.1069; GC tR= 10.95 min.

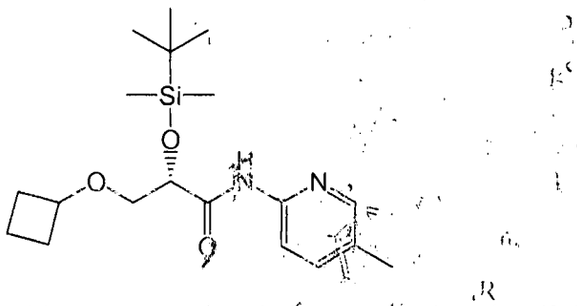
Intermediate R4: (S)-2-(tert-butyldimethylsilyloxy)-3-cyclobutoxypropanoic acid



Lithium iodide (1.986 g, 14.84 mmol) was added to (S)-methyl 2-(tert-butyldimethylsilyloxy)-3-cyclobutoxypropanoate (**Intermediate R3**) (1.07 g, 3.71 mmol)

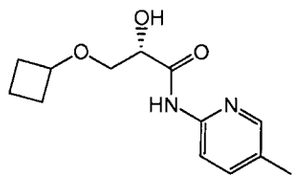
in ethyl acetate (15 mL). The resulting suspension was protected from light and stirred at reflux (75 °C) for 6 hours. The reaction mixture was diluted with ethyl acetate (75 mL) washed sequentially with 1M sodium metabisulphite (25 mL), water (25 mL) and saturated brine (25 mL). The organic layer was dried ($MgSO_4$) and evaporated to afford the crude product (0.920 g, 90%) that was used without further purification. ^{1}H NMR (400 MHz, DMSO) δ 0.09 (d, 6H), 0.91 (s, 9H), 1.40 - 1.54 (m, 1H), 1.59 - 1.71 (m, 1H), 1.75 - 1.90 (m, 2H), 2.10 - 2.22 (m, 2H), 3.40 - 3.57 (m, 2H), 3.90 - 4.02 (m, 1H), 4.25 - 4.31 (m, 1H), 12.55 (s, 1H); m/z (EI+) M+ = 274; GC tR= 11.09 min.

Intermediate R5: (S)-2-(tert-butyldimethylsilyloxy)-3-cyclobutoxy-N-(5-methylpyridin-2-yl)propanamide



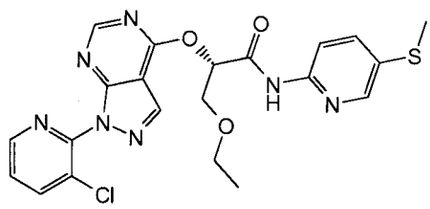
1-Chloro-N,N,2-trimethylprop-1-en-1-amine (0.133 mL, 1.00 mmol) was added to a stirred solution of (S)-2-(tert-butyldimethylsilyloxy)-3-cyclobutoxypropanoic acid (**Intermediate R4**) (250 mg, 0.91 mmol) in DCM (5 mL) at room temperature under nitrogen. The resulting solution was stirred at room temperature for 30 minutes. Pyridine (0.147 mL, 1.82 mmol) was added followed by a solution of 5-methylpyridin-2-amine (108 mg, 1.00 mmol) in DCM (5 mL) and the resulting solution was stirred at ambient temperature for 1 hour. 1M citric acid (10 mL) and DCM (50 mL) were added and the phases were separated. The organic phase washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, eluting with 0 to 30% ethyl acetate in isohexane to afford the product (195 mg, 58.7 %). ^{1}H NMR (400 MHz, DMSO) δ 0.01 (d, 6H), 0.80 (s, 9H), 1.24 - 1.37 (m, 1H), 1.43 - 1.53 (m, 1H), 1.59 - 1.72 (m, 2H), 1.94 - 2.06 (m, 2H), 2.13 (s, 3H), 3.33 - 3.44 (m, 2H), 3.77 - 3.87 (m, 1H), 4.29 - 4.34 (m, 1H), 7.49 - 7.54 (m, 1H), 7.86 (d, 1H), 8.02 - 8.06 (m, 1H), 9.25 (s, 1H); m/z (ESI+) (M+H)+ = 365.47; HPLC tR= 3.60 min.

Intermediate R6: (S)-3-cyclobutoxy-2-hydroxy-N-(5-methylpyridin-2-yl)propanamide



A solution of tetrabutylammonium fluoride (1M inTHF) (0.439 mL, 0.44 mmol) was added to a stirred solution of (S)-2-(tert-butyldimethylsilyloxy)-3-cyclobutoxy-N-(5-methylpyridin-2-yl)propanamide (**Intermediate R5**) (80 mg, 0.22 mmol) in tetrahydrofuran (5 mL). The resulting solution was stirred at room temperature for 4 hours. The reaction mixture was concentrated and diluted with ethyl acetate (20 mL) and washed sequentially with water (5 mL) and saturated brine (5 mL). The organic layer was dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 0 to 60% ethyl acetate in isohexane to afford the product (46.0 mg, 84%). ^{1}H NMR (400 MHz, DMSO) δ 1.34 - 1.49 (m, 1H), 1.52 - 1.64 (m, 1H), 1.71 - 1.85 (m, 2H), 2.05 - 2.16 (m, 2H), 2.24 (s, 3H), 3.46 - 3.56 (m, 2H), 3.87 - 3.97 (m, 1H), 4.17 - 4.24 (m, 1H), 6.02 (d, 1H), 7.59 - 7.66 (m, 1H), 7.98 (d, 1H), 8.12 - 8.17 (m, 1H), 9.48 (s, 1H) m/z (ESI+) (M+H)+ = 251.33; HPLC tR= 1.31 min.

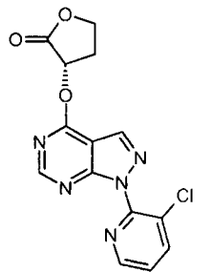
Intermediate S1: (2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-ethoxy-N-(5-(methylthio)pyridin-2-yl)propanamide



2M Trimethylaluminium in hexane (0.457 mL, 0.91 mmol) was added to 5-(methylthio)pyridin-2-amine (CAS no. 77618-99-6) (0.111 g, 0.79 mmol) in toluene (22 mL) at 0°C under nitrogen. The resulting solution was stirred at 0°C for 20 minutes. (2S)-methyl 2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-ethoxypropanoate (**Intermediate L2**) (0.300 g, 0.79 mmol) in toluene (6 mL) was added dropwise at this temperature. After the addition was complete, the solution was allowed to warm to ambient temperature and was then heated at reflux for 16 hours. The mixture was

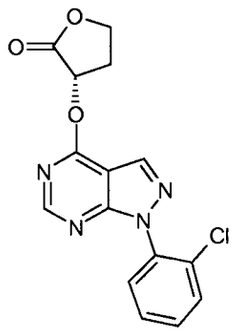
allowed to cool to ambient temperature and left standing for 2 days. The reaction mixture was concentrated, diluted with ethyl acetate (100 mL) then washed with saturated brine (50 mL). The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by flash silica chromatography, , eluting with 0 to 3% MeOH in DCM to afford the product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (3H, t), 2.41 (3H, s), 3.52 - 3.61 (2H, m), 3.99 - 4.07 (2H, m), 5.99 (1H, t), 7.38 - 7.42 (1H, m), 7.57 - 7.60 (1H, m), 7.93 - 7.95 (1H, m), 8.11 - 8.15 (2H, m), 8.40 (1H, s), 8.54 - 8.56 (2H, m), 8.64 (1H, s); m/z (ES+) $(M+H)^+$ = 486; HPLC tR= 2.26 min.

Intermediate T1: (3S)-3-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)dihydrofuran-2(3H)-one



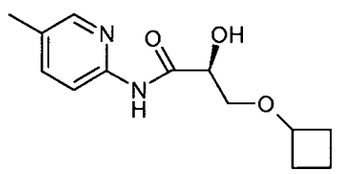
60% Sodium hydride in mineral oil (0.470 g, 11.75 mmol) was added to (S)-3-hydroxydihydrofuran-2(3H)-one (0.764 mL, 9.80 mmol) in anhydrous THF (30 mL) at 0°C under nitrogen. The resulting solution was stirred at 0°C for 10 minutes and then 4-chloro-1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (CAS no. 52079-23-9) (2.87 g, 10.77 mmol) was added portionwise maintaining the temperature below 5°C. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour. The reaction mixture was neutralised with 1M citric acid and the majority of the THF removed in vacuo. The reaction mixture diluted with water (20 mL) and ethyl acetate (50 mL). The organic layer was separated and the aqueous layer re-extracted with ethyl acetate (2 × 100 mL). The combined organics were washed with saturated brine (75 mL), water (75 mL) dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash silica chromatography, eluting with 50 to 100% ethyl acetate in isohexane to afford the product (1.970 g, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) 2.52 - 2.62 (1H, m), 2.92 - 3.00 (1H, m), 4.41 - 4.47 (1H, m), 4.59 - 4.64 (1H, m), 6.11 - 6.16 (1H, m), 7.46 - 7.49 (1H, m), 8.00 - 8.02 (1H, m), 8.37 (1H, s), 8.61 - 8.63 (1H, m), 8.64 (1H, s); m/z (ESI+) $(M+H)^+$ = 332; HPLC t_R = 1.51 min.

Intermediate T2: (3S)-3-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)dihydrofuran-2(3H)-one



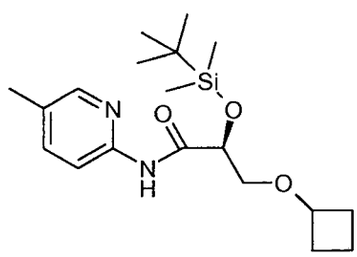
Prepared using an analogous procedure to that described for **Intermediate T1** using **Intermediate B1** ^{1}H NMR (400 MHz, $CDCl_3$) 2.53 - 2.63 (1H, m), 2.92 - 2.99 (1H, m), 4.41 - 4.47 (1H, m), 4.59 - 4.65 (1H, m), 6.12 - 6.16 (1H, m), 7.44 - 7.55 (3H, m), 7.60 - 7.63 (1H, m), 8.33 (1H, s), 8.60 (1H, s); m/z (ESI+) (M+H)+ = 331; HPLC t_R = 1.98 min.

Intermediate U1: (S)-3-cyclobutoxy-2-hydroxy-N-(5-methylpyridin-2-yl)propanamide



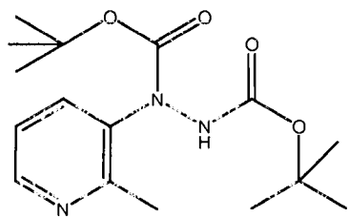
Prepared in an analogous fashion to **Intermediate H1** from (S)-2-(tert-butyldimethylsilyloxy)-3-cyclobutoxy-N-(5-methylpyridin-2-yl)propanamide (**Intermediate U2**) ^{1}H NMR (400 MHz, $CDCl_3$) 1.45 - 1.60 (1H, m), 1.64 - 1.74 (1H, m), 1.90 - 2.04 (2H, m), 2.17 - 2.26 (2H, m), 2.30 (3H, s), 3.63 - 3.74 (2H, m), 3.97 - 4.04 (1H, m), 4.11 - 4.17 (1H, m), 4.34 - 4.36 (1H, m), 7.51 - 7.54 (1H, m), 8.07 - 8.13 (2H, m), 9.26 (1H, s); m/z (ESI+) (M+H)+ =251; HPLC t_R = 1.30 min.

Intermediate U2: (S)-2-(tert-butyldimethylsilyloxy)-3-cyclobutoxy-N-(5-methylpyridin-2-yl)propanamide



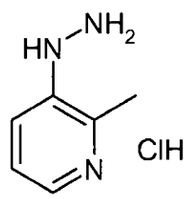
Prepared in an analogous fashion to **Intermediate E2** from (S)-2-(tert-butyldimethylsilyloxy)-3-cyclobutoxypropanoic acid (**Intermediate R4**). ^{1}H NMR (400 MHz, $CDCl_3$) 0.19 (6H, d), 0.99 (9H, s), 1.46 - 1.52 (1H, m), 1.67 - 1.70 (1H, m), 1.89 - 1.94 (2H, m), 2.16 - 2.20 (2H, m), 2.30 (3H, s), 3.49 - 3.54 (1H, m), 3.67 - 3.70 (1H, m), 3.93 - 3.97 (1H, m), 4.36 - 4.38 (1H, m), 7.49 - 7.52 (1H, m), 8.10 - 8.14 (2H, m), 9.01 (1H, s); m/z (ESI+) $(M+H)^+$ = 365; HPLC t_R = 3.57min.

Intermediate V1: di-tert-butyl 1-(2-methylpyridin-3-yl)hydrazine-1,2-dicarboxylate



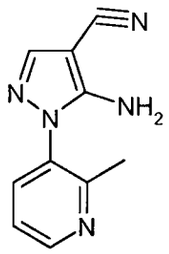
Prepared using a procedure analogous to that described for **Intermediate X1** using 3-bromo-2-methylpyridine (CAS no. 38749-79-0). ^{1}H NMR (400 MHz, DMSO) δ 1.07 - 1.32 (m, 18H), 3.09 (s, 3H), 7.01 - 7.12 (m, 1H), 7.41 - 7.50 (m, 1H), 8.12 - 8.18 (m, 1H), 9.39 - 9.62 (m, 1H); m/z (ESI+) $(M+H)^+$ = 324.39; HPLC t_R= 1.57 min.

Intermediate V2: 3-hydrazinyl-2-methylpyridine hydrochloride



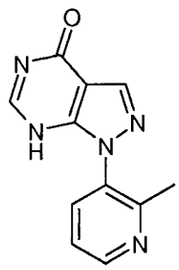
Hydrogen chloride in dioxane (5.67 mL, 22.67 mmol) was added to a solution of di-tert-butyl 1-(2-methylpyridin-3-yl)hydrazine-1,2-dicarboxylate (**Intermediate V1**) (733 mg, 2.27 mmol) in IPA (10 mL). The reaction mixture was heated at reflux for 20 mins. The reaction mixture was allowed to cool and then diluted with diethyl ether (30 mL). The resultant precipitate was collected by filtration and dried in vacuo to afford 3-hydrazinyl-2-methylpyridine hydrochloride (362 mg, 100 %). ^{1}H NMR (400 MHz, DMSO) δ 2.66 (3H, s), 7.80 - 7.83 (1H, m), 7.95 - 7.97 (1H, m), 8.23 - 8.25 (1H, m), 9.15 (1H, s), 11.30 (1H, s); no ion in LCMS (1NH missing).

Intermediate V3: 5-amino-1-(2-methylpyridin-3-yl)-1H-pyrazole-4-carbonitrile



MP-carbonate (2.64 mmol/g) (2.6 g, 6.80 mmol) was added to 3-hydrazinyl-2-methylpyridine hydrochloride (**Intermediate V2**) (362 mg, 2.27 mmol) in DCM (10 mL). The reaction mixture was stirred at room temperature for 6 hours. The reaction mixture was filtered and evaporated. 2-(Ethoxymethylene)malononitrile (277 mg, 2.27 mmol) was added to suspension of the above solid in MeOH (6 mL) under nitrogen cooled to -5°C. The reaction mixture was stirred at 0°C for 30 mins and then allowed to warm to room temperature and heated at reflux under nitrogen for 2 hours. The reaction mixture was allowed to cool and evaporated to dryness to afford the product (210 mg, 46.5%) which was used without further purification. ^{1}H NMR (400 MHz, DMSO) δ 2.23 (3H, s), 6.65 (2H, s), 7.39 - 7.43 (1H, m), 7.74 (1H d), 7.79 (1H, s), 8.58 - 8.60 (1H, m); m/z (ESI+) (M+H)+ = 200; HPLC t_R = 1.21 min.

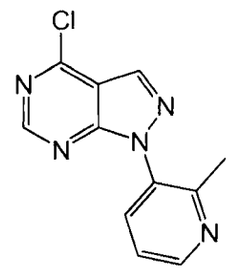
Intermediate V4: 1-(2-methylpyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4(7H)-one



Concentrated sulfuric acid (0.258 mL, 4.85 mmol) was added to a stirred solution of 5-amino-1-(2-methylpyridin-3-yl)-1H-pyrazole-4-carbonitrile (**Intermediate V3**) (878 mg, 4.41 mmol) in formic acid (5 mL). The resulting solution was stirred at 100°C for 1 hour. The reaction was allowed to cool to room temperature and evaporated to approximately half volume and water (25 mL) added. The reaction mixture was adjusted to pH 4 with 2M NaOH. The resultant precipate was collected by filtration, washing well with water, and then dried in vacuo to afford 1-(2-methylpyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-

4(7H)-one (525 mg, 52%). ^{1}H NMR (400 MHz, DMSO) δ 2.28 (3H, s), 7.44 - 7.47 (1H, m), 7.85 - 7.87 (1H, m), 8.09 (1H, s), 8.35 (1H, s), 8.61 - 8.63 (1H, m), 12.3 (1H, s); m/z (ESI+) (M+H)+ = 228; HPLC t_R = 0.65 min.

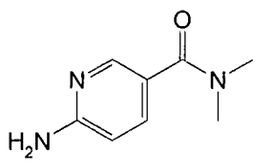
Intermediate V5: 4-chloro-1-(2-methylpyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidine



Prepared using a procedure analogous to that described for **Intermediate X5** using **Intermediate V4**.

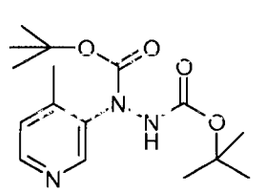
^{1}H NMR (400 MHz, DMSO) δ 2.32 (s, 3H), 7.51 - 7.56 (m, 1H), 7.96 - 8.00 (m, 1H), 8.67 - 8.70 (m, 1H), 8.81 (s, 1H), 8.91 (s, 1H). m/z (ESI+) (M+H)+ = 246.29; HPLC tR= 1.29 min

Intermediate W1: 6-amino-N,N-dimethylnicotinamide



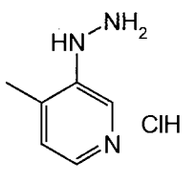
N-Ethyl-N-isopropylpropan-2-amine (12.61 mL, 72.40 mmol) was added to 6-aminonicotinic acid (CAS no. 3167-49-5) (5 g, 36.20 mmol), dimethylamine (2M in THF) (21.72 mL, 43.44 mmol) and EDCI (9.02 g, 47.06 mmol) in THF (150 mL) under nitrogen. The resulting suspension was stirred at r.t. for 18 hours. The reaction mixture was dry loaded onto silica and purified by flash silica chromatography, eluting with 0 to 10% MeOH in ethyl acetate to the product (4.50 g, 75%). ^{1}H NMR (400 MHz, DMSO) δ 2.95 (6H, s), 6.28 (2H, s), 6.38 - 6.44 (1H, m), 7.42 - 7.47 (1H, m), 7.99 - 8.04 (1H, m)

Intermediate X1: di-tert-butyl 1-(4-methylpyridin-3-yl)hydrazine-1,2-dicarboxylate



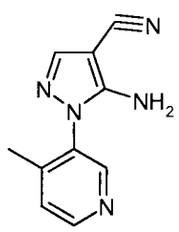
Isopropylmagnesium chloride. lithium chloride complex (0.96 M) (23.62 mL, 22.67 mmol) was added to 3-bromo-4-methylpyridine (CAS no. 3430-22-6) (3 g, 17.44 mmol) in THF (60 mL) cooled to 0 °C under nitrogen. The resulting solution was warmed to room temperature and stirred for 3 hours. The reaction temperature was cooled to 0°C and di-tert-butyl azodicaboxylate (6.02 g, 26.16 mmol) in THF (10 ml) was added dropwise maintaining the temperature below 10°C. The reaction was warmed to room temperature and stirred for 1.5 hours. The reaction mixture was quenched with saturated NH_4Cl (50 mL) and extracted with ethyl acetate (3 × 75 mL). The organic layer was dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 0 to 90% ethyl acetate in isohexane to afford the product (4.50 g, 80%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 - 1.49 (18H, m), 2.34 (3H, s), 6.90 (1H, s), 7.13 (1H, d), 8.36 (1H, d), 8.60 (1H, s); m/z (ESI+) (M+H)+ = 324; HPLC tR= 2.15 min.

Intermediate X2: 3-hydrazinyl-4-methylpyridine hydrochloride



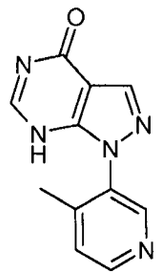
Prepared using a procedure analogous to that described for **Intermediate V2** using **Intermediate X1**.^{1}H NMR (400 MHz, DMSO) δ 2.44 (3H, s), 7.79 - 7.80 (1H, m), 8.38 (2H, d), 9.07 (1H, s), 11.4 (2H, s)

Intermediate X3: 5-amino-1-(4-methylpyridin-3-yl)-1H-pyrazole-4-carbonitrile



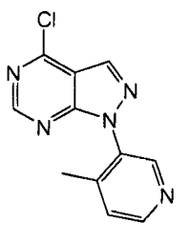
Prepared using a procedure analogous to that described for **Intermediate V3** using **Intermediate X2**. ^{1}H NMR (400 MHz, DMSO) δ 2.09 (3H, s), 6.68 (2H, s), 7.50 (1H, d), 7.80 (1H, s), 8.44 - 8.48 (1H, m), 8.57 (1H, d); m/z (ESI+) (M+H)+ = 200; HPLC tR= 1.47 min.

Intermediate X4: 1-(4-methylpyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4(7H)-one



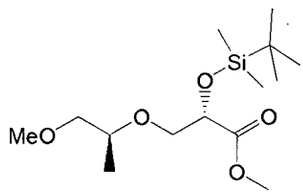
Prepared using a procedure analogous to that described for **Intermediate V4** using **Intermediate X3**. ^{1}H NMR (400 MHz, DMSO) δ 2.15 (3H, s), 7.51 (1H, d), 8.09 (1H, s), 8.37 (1H, s), 8.57 - 8.59 (2H, m), 12.5 (1H, s); m/z (ESI+) $(M+H)^+$ = 228; HPLC t_R = 1.36 min.

Intermediate X5: 4-chloro-1-(4-methylpyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidine



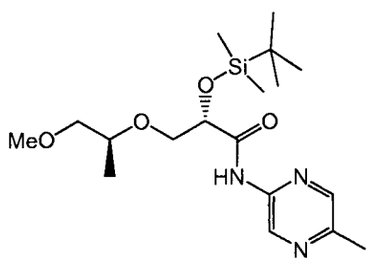
Phosphorus oxychloride (5.10 ml, 54.75 mmol) was added to 1-(4-methylpyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol (0.622 g, 2.74 mmol). The resulting solution was stirred at 100 °C for 2 hours. The reaction mixture was evaporated. Toluene was added to the residue and the reaction mixture was concentrated. This was repeated to remove excess $POCl_3$. The residue was dissolved in DMF (15 mL) and MP carbonate was added (~ 3g) and allowed to stir overnight. The DMF was evaporated in vacuo to afford crude product which was used without further purification. ^{1}H NMR (400 MHz, DMSO) δ 2.1 (3H, s), 7.60 (1H, d), 8.65 (1H, d), 8.68 (1H, s), 8.82 (1H, s), 8.91 (1H, s); m/z (ES+) $(M+H)^+$ = 246; HPLC tR= 1.69 min.

Intermediate Y1: (S)-methyl 2-(tert-butyldimethylsilyloxy)-3-((S)-1-methoxypropan-2-yloxy)propanoate



Magnesium perchlorate (2.79 g, 12.49 mmol) was added in one portion to (S)-methyl oxirane-2-carboxylate (CAS no. 118712-39-3) (5.1 g, 49.96 mmol) and (S)-1-methoxypropan-2-ol (CAS no. 26550-55-0) (4.50 g, 49.96 mmol) at ambient temperature. The resulting suspension was stirred at 50°C for 16 hours. The reaction mixture was diluted with DMF (50 mL) before adding 1H-imidazole (6.80 g, 99.92 mmol) and tert-butylchlorodimethylsilane (9.04 g, 59.95 mmol). The resulting solution was stirred at 40°C for 5 hours. The reaction mixture was evaporated to dryness and re-dissolved in ethyl acetate (125 mL), and washed sequentially with water (50 mL) and saturated brine (25 mL). The organic layer was dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 0 to 50% ethyl acetate in isohexane to afford the product (4.52 g, 30%). ^{1}H NMR (400 MHz, DMSO) δ 0.00 (d, 6H), 0.82 (s, 9H), 0.98 (d, 3H), 3.13 - 3.28 (m, 5H), 3.50 - 3.64 (m, 6H), 4.26 - 4.32 (m, 1H); m/z (ESI+) (M+H)+ = 307.19; HPLC t_R = 10.82 min.

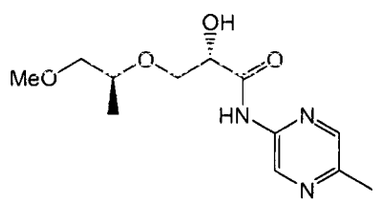
Intermediate Y2: (S)-2-(tert-butyldimethylsilyloxy)-3-((S)-1-methoxypropan-2-yloxy)-N-(5-methylpyrazin-2-yl)propanamide



Trimethylaluminium (2M in hexane) (1.126 mL, 2.25 mmol) was added dropwise to 5-methylpyrazin-2-amine (214 mg, 1.96 mmol) in toluene (5 mL) cooled to 0°C under nitrogen. The resulting solution was stirred for 20 minutes. A solution of (S)-methyl 2-(tert-butyldimethylsilyloxy)-3-((S)-1-methoxypropan-2-yloxy) propanoate (**Intermediate**

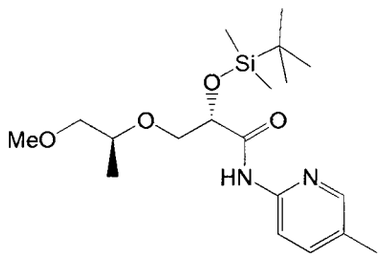
Y1) (600 mg, 1.96 mmol) in toluene (2 mL) was added to the reaction mixture and the resulting solution was stirred at reflux for 5 hours. The reaction was allowed to cool to RT before adding ethyl acetate (30 mL) and 20% sodium potassium tartrate solution (30 mL), which was stirred vigorously for 16 hours. The phases were separated and the organic layer was washed with sat. brine (15 mL), dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 0 to 60% ethyl acetate in isohexane to afford the product (230 mg, 31%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.17 (d, 6H), 0.98 (s, 9H), 1.16 (d, 3H), 2.53 (s, 3H), 3.25 - 3.32 (m, 4H), 3.35 - 3.42 (m, 1H), 3.60 - 3.68 (m, 1H), 3.74 - 3.80 (m, 1H), 3.82 - 3.87 (m, 1H), 4.35 - 4.40 (m, 1H), 8.12 - 8.13 (m, 1H), 8.98 (s, 1H), 9.42 (d, 1H); m/z (ESI+) $(M+H)^+$ = 384.23; HPLC t_R = 10.70 min.

Intermediate Y3: (S)-2-hydroxy-3-((S)-1-methoxypropan-2-yloxy)-N-(5-methylpyrazin-2-yl)propanamide



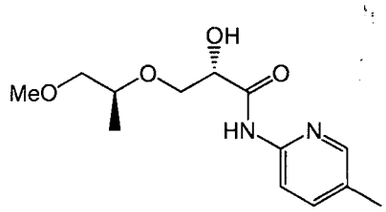
Tetrabutylammonium fluoride (1M in THF) (1199 µl, 1.20 mmol) was added to (S)-2-(tert-butyldimethylsilyloxy)-3-((S)-1-methoxypropan-2-yloxy)-N-(5-methylpyrazin-2-yl)propanamide (**Intermediate Y2**) (230 mg, 0.60 mmol) in THF (3.0 mL) at 20°C. The resulting solution was stirred at room temperature for 3 hours. The reaction mixture was concentrated and diluted with ethyl acetate (50 mL), and washed sequentially with water (25 mL) and saturated brine (10 mL). The organic layer was dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 100% ethyl acetate to afford the product (80 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (d, 3H), 2.53 (s, 3H), 3.34 - 3.45 (m, 5H), 3.66 - 3.81 (m, 2H), 3.97 - 4.03 (m, 1H), 4.30 (d, 1H), 4.34 - 4.39 (m, 1H), 8.13 (d, 1H), 9.30 (s, 1H), 9.41 (d, 1H); m/z (ESI+) $(M+H)^+$ = 270.29; HPLC t_R = 0.95 min.

Intermediate Y4: (S)-2-(tert-butyldimethylsilyloxy)-3-((S)-1-methoxypropan-2-yloxy)-N-(5-methylpyridin-2-yl)propanamide



Trimethylaluminium (2M in hexane) (0.938 mL, 1.88 mmol) was added dropwise to 5-methylpyridin-2-amine (194 mg, 1.79 mmol) in toluene (5 mL) cooled to 0°C under nitrogen. The resulting solution was stirred for 20 minutes. A solution of (S)-methyl 2-(tert-butyldimethylsilyloxy)-3-((S)-1-methoxypropan-2-yloxy) propanoate (**Intermediate Y1**) (500 mg, 1.63 mmol) in toluene (2 mL) was added to the reaction mixture and the resulting solution was stirred at reflux for 5 hours. The reaction was allowed to cool to room temperature before adding ethyl acetate (30 mL) and 20% sodium potassium tartrate solution (30 mL), which was stirred vigourously for 16 hours. The phases were separated and the organic layer was washed with sat. brine (15 mL), dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 0 to 60% ethyl acetate in isohexane to afford the product (388 mg, 62%). ^1H NMR (400 MHz, DMSO) δ 0.01 (d, 6H), 0.81 (s, 9H), 0.93 (d, 3H), 2.13 (s, 3H), 3.06 - 3.21 (m, 5H), 3.44 - 3.53 (m, 1H), 3.57 (d, 2H), 4.29 (t, 1H), 7.49 - 7.55 (m, 1H), 7.87 (d, 1H), 8.01 - 8.05 (m, 1H), 9.25 (s, 1H); m/z (ESI+) (M+H)+ = 383.24; HPLC t_R = 11.31 min.

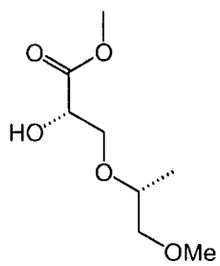
Intermediate Y5: (S)-2-hydroxy-3-((S)-1-methoxypropan-2-yloxy)-N-(5-methylpyridin-2-yl)propanamide



Tetrabutylammonium fluoride (1M in THF) (2028 µl, 2.03 mmol) was added to (S)-2-(tert-butyldimethylsilyloxy)-3-((S)-1-methoxypropan-2-yloxy)-N-(5-methylpyridin-2-yl)propanamide (**Intermediate Y4**) (388 mg, 1.01 mmol) in THF (5 mL) at 20°C. The

resulting solution was stirred at room temperature for 3 hours. The reaction mixture was concentrated, diluted with ethyl acetate (50 mL), and washed sequentially with water (25 mL) and saturated brine (10 mL). The organic layer was dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 0 to 10% MeOH in DCM to afford the product (200 mg, 74 %). ^{1}H NMR (400 MHz, DMSO) δ 1.04 (d, 3H), 2.24 (s, 3H), 3.17 - 3.23 (m, 4H), 3.25 - 3.31 (m, 1H), 3.55 - 3.73 (m, 3H), 4.16 - 4.23 (m, 1H), 5.94 (d, 1H), 7.59 - 7.65 (m, 1H), 7.98 (d, 1H), 8.12 - 8.16 (m, 1H), 9.48 (s, 1H); m/z (ESI+) $(M+H)^+$ = 269.31; HPLC t_R = 1.11 min.

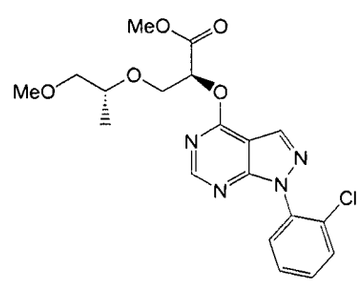
Intermediate Y6: (S)-methyl 2-hydroxy-3-((R)-1-methoxypropan-2-yloxy)propanoate



Magnesium perchlorate (2.73 g, 12.24 mmol) was added in one portion to (S)-methyl oxirane-2-carboxylate (CAS no. 118712-39-3) (5 g, 48.98 mmol) and (R)-1-methoxypropan-2-ol (CAS no. 4984-22-9) (4.41 g, 48.98 mmol) at room temperature. The resulting suspension was stirred at 50°C for 16 hours. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with water (20 mL), dried ($MgSO_4$) and evaporated. This was not isolated and used crude in next step.

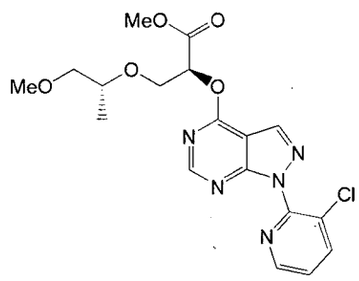
^{1}H NMR (400 MHz, $CDCl_3$) δ1.11 (d, 3H), 3.31 - 3.40 (m, 5H), 3.64 - 3.72 (m, 1H), 3.75 - 3.80 (m, 4H), 3.89 - 3.95 (m, 1H), 4.27 - 4.30 (m, 1H), OH not observed.

Intermediate Y7: (2S)-methyl 2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-((R)-1-methoxypropan-2-yloxy)propanoate



Sodium hydride (94 mg, 2.34 mmol) was added to (S)-methyl 2-hydroxy-3-((R)-1-methoxypropan-2-yloxy)propanoate (**Intermediate Y6**) (300 mg, 1.56 mmol) in anhydrous THF (5 mL) at 0°C under nitrogen. The resulting solution was stirred at 0°C for 10 minutes and then 4-chloro-1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate B1**) (538 mg, 2.03 mmol) was added. The reaction mixture was allowed to warm up to room temperature and stirred for 30 minutes. The reaction mixture was neutralized with 1M citric acid, diluted with ethyl acetate (20 mL), and washed sequentially with water (10 mL) and saturated brine (5 mL). The organic layer was dried (MgSO4) and evaporated. The crude product was purified by flash silica chromatography, eluting with 0-100% ethyl acetate in isohexane to afford the product (358 mg, 54.5 %). ^{1}H NMR (400 MHz, DMSO) δ 1.07 (d, 3H), 3.23 - 3.40 (m, 5H), 3.68 - 3.77 (m, 4H), 4.05 - 4.10 (m, 2H), 5.81 (t, 1H), 7.56 - 7.71 (m, 3H), 7.73 - 7.79 (m, 1H), 8.57 (s, 1H), 8.58 (s, 1H); m/z (ESI+) (M+H)+ = 421.17; HPLC t_R = 1.86 min.

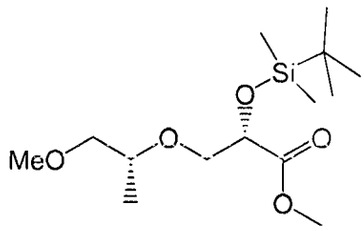
Intermediate Y8: (2S)-methyl 2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-((R)-1-methoxypropan-2-yloxy)propanoate



Sodium hydride (62.4 mg, 1.56 mmol) was to (S)-methyl 2-hydroxy-3-((R)-1-methoxypropan-2-yloxy)propanoate (**Intermediate Y6**) (200 mg, 1.04 mmol) in anhydrous THF (5 mL) at 0°C under nitrogen. The resulting mixture was stirred for 10 minutes at 0°C and then 4-chloro-1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate B15**) (360 mg, 1.35 mmol) was added and the reaction was allowed to warm up to room temperature and stirred for 1 hour. The reaction mixture was diluted with ethyl acetate (20 mL), and washed sequentially with water (10 mL) and saturated brine (5 mL). The organic layer was dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 0-100% ethyl acetate in isohexane to afford the product (245 mg, 55.8 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (d, 3H), 3.33 -

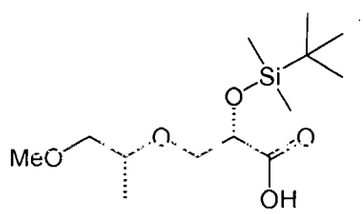
3.48 (m, 5H), 3.74 - 3.82 (m, 4H), 4.13 - 4.18 (m, 2H), 5.81 - 5.86 (m, 1H), 7.43 - 7.48 (m, 1H), 7.98 - 8.02 (m, 1H), 8.39 - 8.41 (m, 1H), 8.58 (s, 1H), 8.60 - 8.63 (m, 1H); m/z (ESI+) $(M+H)^+$ = 422.36; HPLC t_R = 1.93 min.

Intermediate Y9: (S)-methyl 2-(tert-butyldimethylsilyloxy)-3-((R)-1-methoxypropan-2-yloxy)propanoate



tert-Butylchlorodimethylsilane (7.09 g, 47.01 mmol) was added to (S)-methyl 2-hydroxy-3-((R)-1-methoxypropan-2-yloxy)propanoate (**Intermediate Y6**) (7.53 g, 39.18 mmol) and 1H-imidazole (5.33 g, 78.35 mmol) in DMF (50 mL) at room temperature under nitrogen. The resulting solution was stirred at 40°C for 5 hours. The reaction mixture was evaporated to dryness and re-dissolved in ethyl acetate (125 mL), and washed sequentially with water (50 mL) and saturated brine (25 mL). The organic layer was dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 0 to 50% ethyl acetate in isohexane to afford the product (2.58 g, 21.5%). ^{1}H NMR (400 MHz, DMSO) δ -0.01 (d, 6H), 0.81 (s, 9H), 0.97 (d, 3H), 3.13 - 3.29 (m, 5H), 3.49 - 3.64 (m, 6H), 4.26 - 4.31 (m, 1H); m/z (ESI+) $M-C_4H_9$ = 249; GC t_R = 10.92 min.

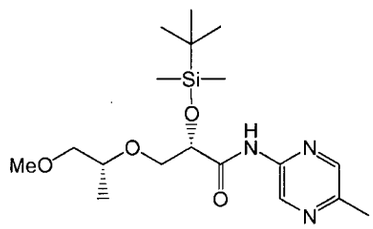
Intermediate Y10: (S)-2-(tert-butyldimethylsilyloxy)-3-((R)-2-methoxypropoxy)propanoic acid



Lithium iodide (4.51 g, 33.67 mmol) was added to (S)-methyl 2-(tert-butyldimethylsilyloxy)-3-((R)-2-methoxypropoxy) propanoate (**Intermediate Y9**) (2.58 g, 8.42 mmol) in ethyl acetate (15 mL). The resulting suspension was protected from light and stirred at reflux (75 °C) for 6 hours. The reaction mixture was diluted with ethyl acetate (75 mL) washed sequentially with 1M sodium metabisulphite (25 mL), water (25

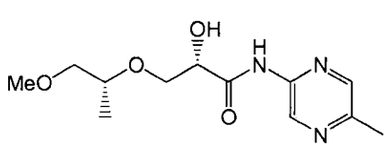
mL) and saturated brine (25 mL). The organic layer was dried ($MgSO_4$) and evaporated to afford crude product (1.166 g, 47.4 %) that was used without further purification.

Intermediate Y11: (S)-2-(tert-butyldimethylsilyloxy)-3-((R)-1-methoxypropan-2-yloxy)-N-(5-methylpyrazin-2-yl)propanamide



1-Chloro-N,N,2-trimethylprop-1-en-1-amine (0.170 mL, 1.28 mmol) was added to a stirred solution of (S)-2-(tert-butyldimethylsilyloxy)-3-((R)-1-methoxypropan-2-yloxy)propanoic acid (**Intermediate Y10**) (250 mg, 0.85 mmol) in DCM (5 mL) at room temperature under nitrogen. The resulting solution was stirred at room temperature for 30 minutes. A solution of 5-methylpyrazin-2-amine (140 mg, 1.28 mmol) in DCM (5 mL) was added to the reaction mixture and the resulting solution was stirred at room temperature for 16 hours. The reaction mixture was quenched with water (20 mL), extracted with DCM (2 × 25 mL), the combined organic layers were dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 0 to 90% ethyl acetate in isohexane to afford the product (170 mg, 51.8 %). ^{1}H NMR (400 MHz, DMSO) δ 0.01 (d, 6H), 0.80 (s, 9H), 0.91 (d, 3H), 2.35 (s, 3H), 3.09 - 3.23 (m, 5H), 3.47 - 3.63 (m, 3H), 4.35 - 4.40 (m, 1H), 8.20 (s, 1H), 9.09 (s, 1H), 9.63 (s, 1H); m/z (ESI+) (M+H)+ = 384.43; HPLC t_R = 2.99 min.

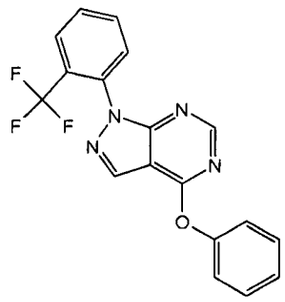
Intermediate Y12: (S)-2-hydroxy-3-((R)-2-methoxypropoxy)-N-(5-methylpyrazin-2-yl)propanamide



Tetrabutylammonium fluoride (881 µl, 0.88 mmol) was added to (S)-2-(tert-butyldimethylsilyloxy)-3-((R)-2-methoxypropoxy)-N-(5-methylpyrazin-2-yl)propanamide (**Intermediate Y11**) (169 mg, 0.44 mmol) in THF (2203 µl) at room temperature under

nitrogen. The resulting solution was stirred at room temperature for 3 hours. The reaction mixture was quenched with water (5 mL), extracted with ethyl acetate (3 × 10 mL), the organic layer was back washed with water (5 mL), dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 0 to 100% ethyl acetate in isohexane to afford the product (64.0 mg, 53.9 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (d, 3H), 2.53 (s, 3H), 3.33 - 3.43 (m, 5H), 3.68 - 3.82 (m, 2H), 4.04 - 4.11 (m, 1H), 4.33 (t, 1H), 4.53 (s, 1H), 8.12 - 8.15 (m, 1H), 9.19 (s, 1H), 9.43 (d, 1H); m/z (ESI+) $(M+H)^+$ = 270.24; HPLC t_R = 1.04 min.

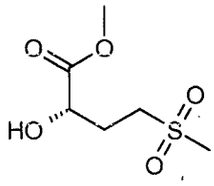
Intermediate Z1: 4-phenoxy-1-(2-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidine



(2-(trifluoromethyl)phenyl)hydrazine (CAS no. 365-34-4) (102 mg, 0.58 mmol) was added to 4,6-diphenoxypyrimidine-5-carbaldehyde (**Intermediate Z2**) (169 mg, 0.58 mmol) in THF (2 mL) the resulting solution was stirred at room temperature for 5 minutes. 2-tert-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine on polystyrene (526 mg, 1.16 mmol) was added and sealed into a microwave tube. The reaction was heated to 150°C for 10 hours in a microwave reactor and cooled to RT. The reaction mixture was filtered and evaporated to drynesss. The crude product was purified by flash silica chromatography, eluting with 10 to 80% ethyl acetate in isohexane to afford the product (88 mg, 42.7 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 - 7.33 (2H, m), 7.34 - 7.39 (1H, m), 7.49 - 7.58 (3H, m), 7.67 - 7.71 (1H, m), 7.74 - 7.78 (1H, m), 7.90 - 7.92 (1H, m), 8.08 (1H, s), 8.56 (1H, s); m/z (ES+) $(M+H)^+$ = 357; HPLC tR= 2.66 min.

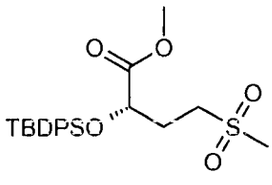
with saturated brine (75 mL), dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 50 to 100% ethyl acetate in isohexane to afford the product (160 mg, 61.6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60 - 2.75 (2H, m), 3.01 (3H, s), 3.25 - 3.38 (2H, m), 3.82 (3H, s), 5.79 - 5.82 (1H, m), 7.44 - 7.54 (3H, m), 7.61 - 7.63 (1H, m), 8.34 (1H, s), 8.54 (1H, s); m/z (ES+) $(M+H)^+$ = 425; HPLC tR= 2.01 min.

Intermediate AA2: (S)-methyl 2-hydroxy-4-(methylsulfonyl)butanoate



Tetrabutylammonium fluoride (1M in THF) (2071 µl, 2.07 mmol) was added to (S)-methyl 2-(tert-butyldiphenylsilyloxy)-4-(methylsulfonyl)butanoate (**Intermediate AA3**) (450 mg, 1.04 mmol) in THF (3106 µl) under nitrogen. The resulting mixture was stirred at ambient temperature for 2 hours. The reaction mixture was quenched with saturated NH_4Cl (10 mL), extracted with Et_2O (3 × 15 mL). The combined organic layers were back washed with water (10 mL), dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 0 to 100% ethyl acetate in isohexane to afford the product (120 mg, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.10 - 2.20 (1H, m), 2.38 - 2.46 (1H, m), 2.94 (4H, m), 3.10 - 3.24 (2H, m), 3.84 (3H, s), 4.34 (1H, q), 7.26 (3H, s).

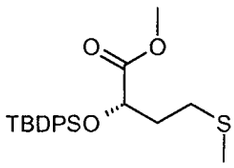
Intermediate AA3: (S)-methyl 2-(tert-butyldiphenylsilyloxy)-4-(methylsulfonyl)butanoate



3-Chloroperoxybenzoic acid (753 mg, 3.05 mmol) was added in one portion to (S)-methyl 2-(tert-butyldiphenylsilyloxy)-4-(methylthio)butanoate (**Intermediate AA4**) (410 mg, 1.02 mmol) in dichloromethane (20 mL) at 25 °C. The resulting suspension was stirred at 25 °C for 2 hours. The reaction mixture was quenched with saturated NaHCO3 (50 mL), washed with water (1 × 50 mL), the organic layer was dried ($MgSO_4$) and evaporated to afford the product (420 mg, 95%) which was used without further purification. ^{1}H NMR (400 MHz,

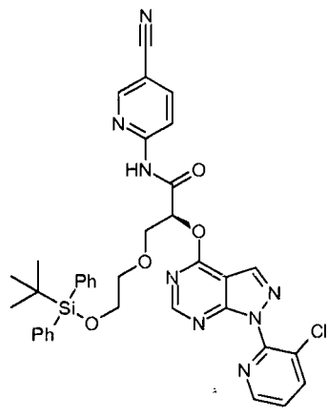
$CDCl_3$) δ 1.10 (9H, s), 2.18 - 2.24 (2H, m), 2.83 (3H, s), 3.00 - 3.04 (1H, m), 3.12 - 3.18 (1H, m), 3.52 (3H, s), 4.38 (1H, t), 7.35 - 7.47 (6H, m), 7.61 - 7.65 (4H, m); m/z (ES+) (M+NH4)+ = 452; HPLC tR= 3.0 min.

Intermediate AA4: (S)-methyl 2-(tert-butyldiphenylsilyloxy)-4-(methylthio)butanoate



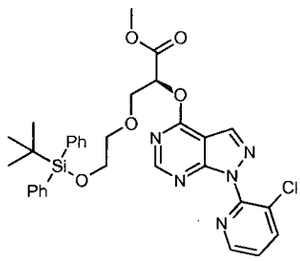
Sodium thiomethoxide (0.187 g, 2.67 mmol) was added to (S)-3-(tert-butyldiphenylsilyloxy)dihydrofuran-2(3H)-one (CAS no. 220351-82-6: Klar, U.; Schwede, W.; Skuballa, W.; Buchmann, B.; Schirner, M. Ger. Offen. 1999 DE 19735575 A1) (0.826 g, 2.43 mmol) in DMF (2 mL) at 0°C . The resulting solution was stirred at room temperature for 16 hours. The reaction mixture was neutralised with 2M HCl and diluted with ethyl acetate. The organic layer was extracted with water (3 × 100 mL), the organic layer was dried ($MgSO_4$) and evaporated to afford (S)-2-(tert-butyldiphenylsilyloxy)-4-(methylthio)butanoic acid (0.160 g, 16.98 %) which was used without further purification. A solution of trimethylsilyldiazomethane (2M solution in ether, 0.412 ml, 0.82 mmol) was added dropwise to a stirred solution of methyl alcohol (0.167 ml, 4.12 mmol) and (S)-2-(tert-butyldiphenylsilyloxy)-4-(methylthio)butanoic acid (0.160 g, 0.41 mmol) in toluene (0.174 ml) over a period of 2 minutes. The resulting solution was stirred at ambient temperature for 2 hours. The reaction mixture was quenched with acetic acid (0.071 ml, 1.24 mmol) and stirred at ambient temperature for 10 minutes. The reaction mixture was evaporated. The residue was purified by flash silica chromatography, eluting with 0 to 50% ethyl acetate in isohexane to afford the product (0.120 g, 72.4%). ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (9H, s), 1.94 - 2.05 (5H, m), 2.48 - 2.60 (2H, m), 3.47 (3H, s), 4.33 - 4.36 (1H, m), 7.34 - 7.45 (6H, m), 7.62 - 7.67 (4H, m); m/z (ES+) (M-Ph)- = 325; HPLC tR= 3.63 min

Intermediate AB1: (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-cyanopyridin-2-yl)propanamide



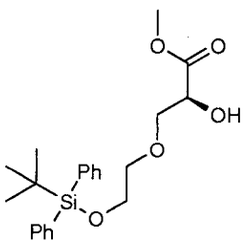
Trimethylaluminium (2M in hexane) (0.455 mL, 0.91 mmol) was added to 6-aminonicotinonitrile (104 mg, 0.87 mmol) in toluene (10 mL) cooled to 0°C under nitrogen. The resulting solution was stirred at 0°C for 20 minutes. (2S)-methyl 3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanoate (**Intermediate AB2**) (500 mg, 0.79 mmol) in toluene (2 mL) was added and the reaction was allowed to warm to room temperature. The temperature was increased to 60°C and stirred for 4 hours, then heated at reflux for 24 hours. The reaction mixture was concentrated in vacuo and neutralised with citric acid (1M, aq) and then diluted with water (10ml) and DCM (10 mL). The mixture was poured onto a phase separator and the organic layer was evaporated in vacuo. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5µ silica, 50 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 0.1% formic acid) and MeCN as eluents. Fractions containing the desired compound were neutralised with MP-carbonate and evaporated to dryness to afford the product (100 mg, 17.6%).
m/z (ES+) $(M+H)^+$ = 719.51; HPLC tR= 3.58 min.

Intermediate AB2: (2S)-methyl 3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanoate



60% Sodium hydride in mineral oil (1.013 g, 25.34 mmol) was added to (S)-methyl 3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-hydroxypropanoate (**Intermediate AB3**) (8.5 g, 21.12 mmol) in tetrahydrofuran (150 mL) cooled to 0°C under nitrogen. The resulting solution was stirred at 0°C for 10 minutes. A solution of 4-chloro-1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (6.18 g, 23.23 mmol) in tetrahydrofuran (20 mL) was added dropwise over a period of 5 minutes. The resulting mixture was allowed to warm to ambient temperature and stirred for 2 hours. The reaction mixture was quenched with 1M citric acid and extracted with ethyl acetate. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 0 to 100% ethyl acetate in isohexane to afford the product (7.15 g, 53.6%). ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (9H, s), 3.68 - 3.79 (5H, m), 3.85 (2H, t), 4.08 - 4.23 (2H, m), 5.84 - 5.89 (1H, m), 7.33 - 7.48 (7H, m), 7.65 - 7.73 (4H, m), 7.97 - 8.03 (1H, m), 8.34 (1H, s), 8.58 (1H, s), 8.59 - 8.63 (1H, m); m/z (ESI+) (M+H)+ = 632; HPLC tR = 3.68 min.

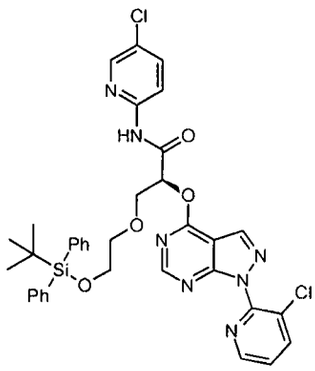
Intermediate AB3: (S)-methyl 3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-hydroxypropanoate



Magnesium trifluoromethanesulfonate (3.95 g, 12.24 mmol) was added in one portion to (S)-methyl oxirane-2-carboxylate (5 g, 48.98 mmol) and 2-(tert-butyldiphenylsilyloxy)ethanol (14.72 g, 48.98 mmol) at 10°C. The resulting suspension was stirred at 10°C for 10 minutes and then warmed to 45°C and stirred for 3 days. The

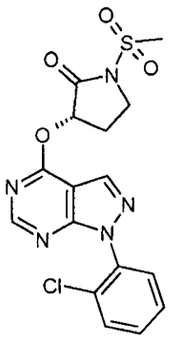
crude product was purified by flash silica chromatography, eluting with 0 to 30% ethyl acetate in isohexane to afford the product (8.50 g, 43.1 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (9H, s), 3.10 (1H, d), 3.62 (2H, t), 3.74 - 3.87 (7H, m), 4.26 - 4.34 (1H, m), 7.35 - 7.46 (6H, m), 7.63 - 7.71 (4H, m); m/z (ESI+) $(M+Na)^+$ = 425.37; HPLC tR = 3.15 min.

Intermediate AB4: (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-N-(5-chloropyridin-2-yl)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide



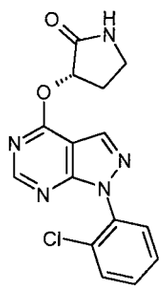
Trimethylaluminium (2M in hexane) (0.455 mL, 0.91 mmol) was added to 5-chloropyridin-2-amine (112 mg, 0.87 mmol) in toluene (10 mL) cooled to 0°C under nitrogen. The resulting solution was stirred at 0°C for 20 minutes. (2S)-methyl 3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanoate (**Intermediate AB2**) (500 mg, 0.79 mmol) in toluene (2 mL) was added and the reaction was heated to reflux for 24 hours. The reaction mixture was concentrated in vacuo and neutralised with citric acid (1M, aq) and then diluted with water (10ml) and DCM (10 mL). The mixture was poured onto a phase separator and the organic layer collected and evaporated. The crude material was used without purification.

Intermediate AC1: (3S)-3-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-1-(methylsulfonyl)pyrrolidin-2-one



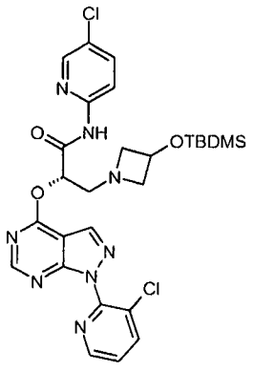
Butyllithium (1.6M in hexane, 1.668 mL, 2.67 mmol) was added dropwise to (3S)-3-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)pyrrolidin-2-one (**Intermediate AC2**) (800 mg, 2.43 mmol) in THF (15 mL) cooled to -78°C under nitrogen. The resulting solution was allowed to warm to r.t., then recooled to -78°C. methanesulfonyl chloride (0.207 mL, 2.67 mmol) was added dropwise and the resulting solution was stirred at r.t. for 2 hours. The reaction mixture was quenched with water (20 mL) and extracted with ethyl acetate (2 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated (995 mg). The crude product was purified by flash silica chromatography, eluting with 50 to 100% ethyl acetate in isohexane to afford the product (368 mg, 37.2%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 - 2.47 (1H, m), 2.83 - 2.92 (1H, m), 3.37 (3H, s), 3.85 - 3.94 (1H, m), 4.06 - 4.16 (1H, m), 6.13 (1H, t), 7.44 - 7.56 (3H, m), 7.59 - 7.66 (1H, m), 8.32 (1H, s), 8.57 (1H, s); m/z (ES+) (M+H)+ = 408.29; HPLC tR= 2.10 min.

Intermediate AC2: (3S)-3-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)pyrrolidin-2-one



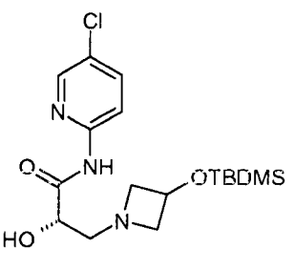
Sodium hydride (60% in oil) (0.435 g, 10.88 mmol) was added to (S)-3-hydroxypyrrolidin-2-one (CAS no. 34368-52-0) (1 g, 9.89 mmol) in THF (50 mL) at 0°C under nitrogen. The resulting suspension was stirred at 0 °C for 10 minutes. A solution of 4-chloro-1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate B15**) (4.01 g, 15.13 mmol) in DMF (25 mL) was added and the resulting mixture was stirred at r.t. for 16 hours. The reaction mixture was quenched with water (20 mL) and extracted with ethyl acetate (2 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated (3.8 g). The crude product was purified by flash silica chromatography, eluting with 0-50% MeOH in ethyl acetate to afford the product (0.810 g, 24.8%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 - 2.42 (1H, m), 2.81 - 2.91 (1H, m), 3.45 - 3.64 (2H, m), 6.05 (1H, t), 6.44 (1H, s), 7.42 - 7.51 (2H, m), 7.51 - 7.56 (1H, m), 7.57 - 7.66 (1H, m), 8.33 (1H, s), 8.60 (1H, s); m/z (ES+) (M+H)+ = 330.27; HPLC tR= 1.61 min.

Intermediate AD1: (2S)-3-[3-(tert-butyl-dimethylsilyl)oxyazetidin-1-yl]-N-(5-chloropyridin-2-yl)-2-[1-(3-chloropyridin-2-yl)pyrazolo[4,5-e]pyrimidin-4-yl]oxypropanamide



Sodium hydride (0.715 g, 17.88 mmol) was added to (S)-3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-N-(5-chloropyridin-2-yl)-2-hydroxypropanamide (**Intermediate AD2**) (2.3 g, 5.96 mmol) in anhydrous THF (25 mL) at 0 °C under nitrogen. The resulting solution was stirred at 0 °C for 10 minutes and then 4-chloro-1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate B15**) (2.265 g, 5.96 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 3 hours. The reaction mixture was neutralised with 1M citric acid and diluted with water (25 mL) and EtOAc (50 mL). The organic layer was separated and washed with saturated brine (25 mL), dried ($MgSO_4$) and evaporated to give the product (3.67g, 100%) which was used for the next stage without purification. m/z (ESI+) $(M+H)^+$ = 615; HPLC t_R = 2.43 min.

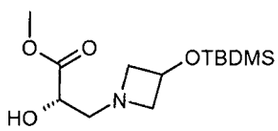
Intermediate AD2: (2S)-3-[3-(tert-butyl-dimethylsilyl)oxyazetidin-1-yl]-N-(5-chloropyridin-2-yl)-2-hydroxypropanamide



Trimethylaluminium (5.75 mL, 11.50 mmol) was added to 5-chloropyridin-2-amine (1.285 g, 10.00 mmol) in toluene (50 mL) cooled to 0 °C under nitrogen. The resulting solution was stirred at 0°C for 10 minutes, (S)-methyl 3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-hydroxypropanoate (**Intermediate AD3**) (2.894 g, 10.00 mmol) in toluene (20 mL)

was added, the reaction allowed to warm to room temperature and then heated at 80°C for 4 hours. The reaction mixture was cooled, concentrated in vacuo and the residue neutralised with 1M citric acid (30 mL), diluted with water (25 mL) and extracted with EtOAc (2 x 30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to afford crude product which was purified by flash silica chromatography with EtOAc as eluent to afford the product (2.5g, 65%). 1H NMR (400 MHz, DMSO) δ 0.01 (6H, s), 0.84 (9H, m), 2.65 - 2.70 (2H, m), 2.76 - 2.83 (2H, m), 3.56 - 3.59 (2H, m), 4.07 - 4.10 (1H, m), 4.28 - 4.34 (1H, m), 5.78 (1H, s), 7.92 (1H, dd), 8.12 (1H, dd), 8.36 - 8.37 (1H, m), 9.87 (1H, s); m/z (ESI+) $(M+H)^+ = 386$; HPLC $t_R = 1.64$ min.

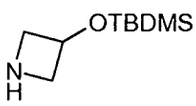
Intermediate AD3: Methyl (2S)-3-[3-(tert-butyl-dimethylsilyl)oxyazetidin-1-yl]-2-hydroxypropanoate



3-(tert-butyldimethylsilyloxy)azetidine (**Intermediate AD4**) (11.0 g, 58.71 mmol) and (S)-methyl oxirane-2-carboxylate (5.99 g, 58.71 mmol) were dissolved in butyronitrile (75 mL) and heated to 100 °C for 90 minutes. Reaction turns from colourless to yellow during the period of heating. The resulting mixture was cooled and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in EtOAc to afford the product (9.6g, 56%). 1H NMR (400 MHz, $CDCl_3$) δ 0.04 (6H, s), 0.85 (9H, s), 2.71 - 2.79 (2H, m), 2.87 - 2.95 (2H, m), 3.58 - 3.68 (2H, m), 3.75 (3H, s), 4.10 - 4.12 (1H, m), 4.35 - 4.39 (1H, t) (OH signal not observed).

The procedure may also be carried out in an analogous manner using azetidin-3-yloxy-tert-butyl-dimethylsilane and diphenylmethane (1:1) (**Intermediate AD5**).

Intermediate AD4: Azetidin-3-yloxy-tert-butyl-dimethylsilane



A solution of tert-butylchlorodimethylsilane (12.01 g, 79.69 mmol) in DCM (20 mL) was added dropwise to a stirred solution of azetidin-3-ol hydrochloride (CAS no. 18621-18-6) (8.73 g, 79.69 mmol) and anhydrous N-ethyl-N-isopropylpropan-2-amine (34.1 mL, 199.22 mmol) in DCM (20 mL) cooled to 10°C, over a period of 2 minutes under nitrogen. The resulting solution was stirred at ambient temperature for 20 hours. The reaction

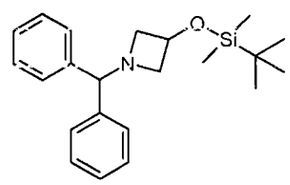
mixture was concentrated, diluted with EtOAc (75 mL), and washed sequentially with saturated $NaHCO_3$ (25 mL), water (20 mL), and saturated brine (20 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford the product (11.1 g, 74%). 1H NMR (400 MHz, $CDCl_3$) δ 0.04 (6H, s), 0.87 (9H, m), 2.80 (1H, s), 3.57 - 3.61 (2H, m), 3.67 - 3.71 (2H, m), 4.57 - 4.64 (1H, m).

Intermediate AD5: Azetidin-3-yloxy-tert-butyl-dimethylsilane and diphenylmethane (1:1)



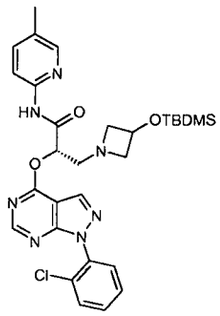
1-benzhydryl-3-(tert-butyldimethylsilyloxy)azetidine (**Intermediate AD6**) (3.12 g, 8.82 mmol) and palladium on carbon (0.3 g, 0.28 mmol) in methanol (60 mL) were stirred under an atmosphere of hydrogen at ambient temperature for 18 hours. The reaction mixture was filtered and concentrated to a colourless liquid, 3-(tert-butyldimethylsilyloxy)azetidine compound with diphenylmethane (1:1) (3.02 g, 96 %). This was used without further purification. 1H NMR (400 MHz, $CDCl_3$) δ 0.00 (6H, s), 0.84 (9H, s), 3.52 - 3.58 (2H, m), 3.61 - 3.67 (2H, m), 3.95 (2H, s), 4.55 - 4.63 (1H, m), 7.12 - 7.27 (10H, m), 7.64 (1H, s).

Intermediate AD6: (1-Benzhydrylazetidin-3-yl)oxy-tert-butyl-dimethylsilane



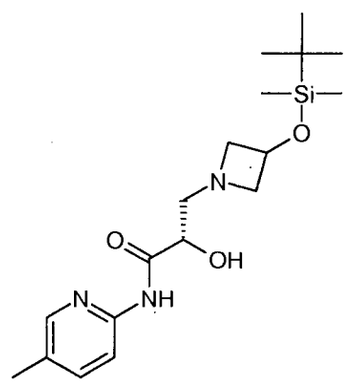
tert-Butyldimethylsilyl chloride (1.524 g, 10.11 mmol) was added to 1-benzhydrylazetidin-3-ol (CAS no. 18621-17-5) (2.2 g, 9.19 mmol) and imidazole (1.565 g, 22.98 mmol) in DCM (46.0 mL) at r.t. under nitrogen. The resulting solution was stirred at r.t. for 3 hours. The reaction mixture was quenched with water, poured onto a phase separator and evaporated to afford the product (3.66 g, 113 %). 1H NMR (400 MHz, $CDCl_3$) δ 0.00 (6H, s), 0.85 (9H, s), 2.81 (2H, s), 3.52 (2H, s), 4.35 (1H, s), 4.40 - 4.49 (1H, m), 7.08 - 7.43 (10H, m); m/z (ES+) $(M+H)^+$ = 354.55; HPLC t_R = 2.04 min.

Intermediate AD7: (2S)-3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-methylpyridin-2-yl)propanamide



Sodium hydride (132 mg, 3.30 mmol) was added to (S)-3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-hydroxy-N-(5-methylpyridin-2-yl)propanamide (**Intermediate AD8**) (482 mg, 1.32 mmol) in anhydrous THF (5 mL) at 0 °C under nitrogen. The resulting solution was stirred at 0 °C for 10 minutes and then 4-chloro-1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate B1**) (385 mg, 1.45 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 3 hours. The reaction mixture was neutralised with 1M citric acid and diluted with water and EtOAc. The organic layer was separated and washed with saturated brine, dried ($MgSO_4$) and evaporated to afford the product (908 mg) which was used without further purification. m/z (ES+) $(M+H)^+$ = 594.52; HPLC t_R = 1.87 min.

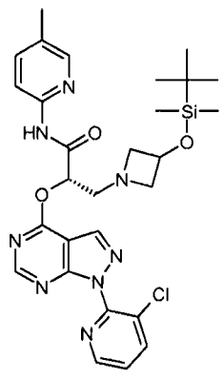
Intermediate AD8: (S)-3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-hydroxy-N-(5-methylpyridin-2-yl)propanamide



Trimethylaluminium (2M in toluene) (0.993 mL, 1.99 mmol) was added to 5-methylpyridin-2-amine (205 mg, 1.90 mmol) in toluene (10 mL) cooled to 0 °C under nitrogen. The resulting solution was stirred at 0°C for 10 minutes. (S)-methyl 3-(3-(tert-

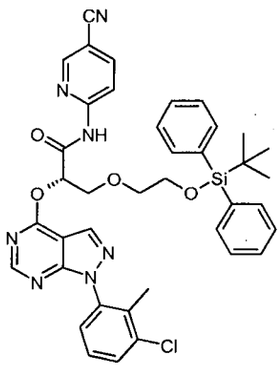
butyldimethylsilyloxy)azetidin-1-yl)-2-hydroxypropanoate (**Intermediate AD3**) (500 mg, 1.73 mmol) in toluene (4 mL) was added and the reaction was allowed to warm to room temperature and then heated at 80°C for 4 hours. The reaction mixture was concentrated in vacuo. The residue was neutralised with citric acid (1M, aq) and then diluted with water and extracted with EtOAc. The combined organics were dried ($MgSO_4$) and evaporated to afford the product (482 mg, 76 %). 1H NMR (400 MHz, $CDCl_3$) δ 0.05 (6H, s), 0.88 (9H, s), 2.30 (3H, s), 3.15 - 3.23 (1H, m), 3.37 - 3.51 (3H, m), 4.15 - 4.30 (2H, m), 4.32 - 4.39 (1H, m), 4.58 - 4.66 (1H, m), 7.48 - 7.53 (1H, m), 8.04 (1H, d), 8.12 - 8.15 (1H, m), 9.46 (1H, s); m/z (ES+) $(M+H)^+$ = 366.53; HPLC t_R = 1.50 min.

Intermediate AD9: (2S)-3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-methylpyridin-2-yl)propanamide



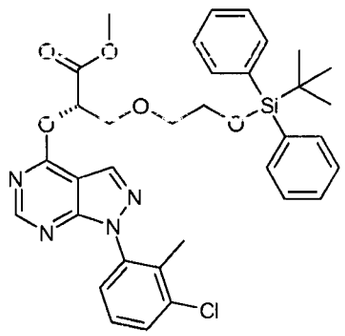
Sodium hydride (15.76 mg, 0.39 mmol) was added to (S)-3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-hydroxy-N-(5-methylpyridin-2-yl)propanamide (**Intermediate AD8**) (120 mg, 0.33 mmol) in anhydrous THF (5 mL) at 0 °C under nitrogen. The resulting solution was stirred at 0 °C for 10 minutes and then 4-chloro-1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate B15**) (96 mg, 0.36 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 5 hours. A further portion of Sodium hydride (15.76 mg, 0.39 mmol) was added and stirring continued for 1 hour more. The reaction mixture was neutralised with 1M citric acid and diluted with water and EtOAc. The organic layer was separated and washed with saturated brine, dried ($MgSO_4$) and evaporated to afford the product (195 mg). m/z (ES+) $(M+H)^+$ = 595.61; HPLC t_R = 1.83 min.

Intermediate AE1: (2S)-3-[2-(tert-butyl-diphenylsilyl)oxyethoxy]-2-[1-(3-chloro-2-methylphenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-cyanopyridin-2-yl)propanamide



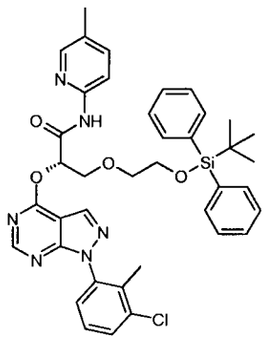
A solution of 2M Trimethyl aluminium in toluene (1.790 mL, 3.58 mmol) in toluene (15 mL) was added dropwise to a stirred suspension of 6-aminonicotinonitrile (0.426 g, 3.58 mmol) in toluene (15 mL) cooled to 0°C, over a period of 2 minutes under nitrogen and the resulting suspension stirred for 20 minutes at 0°C. A solution of (2S)-methyl 3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(3-chloro-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanoate (**Intermediate AE2**) (1.05 g, 1.63 mmol) in toluene (10 mL) was added dropwise over 2 minutes, the mixture allowed to warm to ambient temperature and then heated to 60°C for 20hrs. Cooled to ~5°C and a 10% solution of Rochelle's salt (25 mL) added followed by ethyl acetate (30 mL) and stirred at ambient temperature for 30 minutes. The organic phase was separated, washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and evaporated to a yellow gum. The crude product was purified by flash silica chromatography, elution gradient 20 to 50% EtOAc in isohexane to afford the product (1.1g, 92%). ^{1}H NMR (400 MHz, DMSO) δ 0.89 (9H, s), 2.03 (3H, s), 3.71 - 3.78 (4H, m), 4.05 - 4.10 (1H, m), 4.14 - 4.19 (1H, m), 6.00 - 6.02 (1H, m), 7.34 - 7.45 (8H, m), 7.59 - 7.61 (4H, m), 7.67 - 7.69 (1H, m), 8.11 - 8.14 (1H, m), 8.20 - 8.23 (1H, m), 8.51 (1H, s), 8.84 (1H, s), 8.80 - 8.82 (1H, m), 11.55 (1H, s); m/z (ESI+) $(M+H)^+$ = 732; HPLC t_R = 3.48 min.

Intermediate AE2: (2S)-Methyl 3-[2-(tert-butyl-diphenylsilyl)oxyethoxy]-2-[1-(3-chloro-2-methylphenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxypropanoate



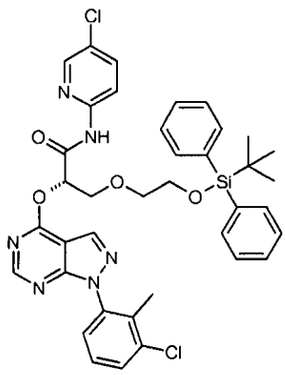
Sodium hydride (60% in mineral oil) (0.191 g, 4.77 mmol) was added in one portion to (S)-methyl 3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-hydroxypropanoate (**Intermediate AB3**) (1.6 g, 3.97 mmol) in THF (15 mL) cooled to 0°C under nitrogen. Slow gas evolution. The resulting suspension was stirred at 0 °C for 10 minutes. A solution of 4-chloro-1-(3-chloro-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate AE5**) (1.109 g, 3.97 mmol) in THF (10 mL) was added dropwise over 2 minutes. The resulting suspension was stirred at 0 °C for 10 minutes, allowed to warm to ambient temperature and stirred for 72 hours to give an orange solution. Cooled to ~5°C, 1M citric acid (30 mL) added, the mixture stirred for 10 minutes, diluted with EtOAc (50 mL), the organic phase separated and washed sequentially with water (25 mL) and saturated brine (25 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated in vacuo. The crude product was purified by flash silica chromatography, elution gradient 20 to 50% EtOAc in isohexane to afford the product (2.1g, 82%). ^{1}H NMR (400 MHz, DMSO) δ 0.95 (9H, s), 2.03 (3H, s), 3.68 (3H, s), 3.67 - 3.74 (2H, m), 3.78 - 3.82 (2H, m), 4.04 - 4.07 (1H, m), 4.11 - 4.15 (1H, m), 5.87 - 5.91 (1H, m), 7.37 - 7.45 (8H, m), 7.61 - 7.65 (4H, m), 7.67 - 7.69 (1H, m), 8.48 (1H, s), 8.57 (1H, s); m/z (ESI+) $(M+H)^+$ = 645; HPLC t_R = 3.65 min.

Intermediate AE3: (2S)-3-[2-(tert-butyl-dimethylsilyl)oxyethoxy]-2-[1-(3-chloro-2-methylphenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-methylpyridin-2-yl)propanamide



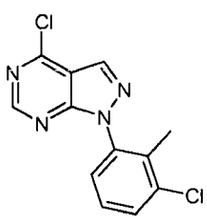
A solution of 2M trimethyl aluminium in toluene (1.790 mL, 3.58 mmol) in toluene (15 mL) was added dropwise to a stirred suspension of 5-methylpyridin-2-amine (0.387 g, 3.58 mmol) in toluene (15 mL) cooled to 0°C, over a period of 2 minutes under nitrogen and the resulting suspension was stirred at 0°C for 20 minutes. A solution of (2S)-methyl 3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(3-chloro-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanoate (**Intermediate AE2**) (1.05 g, 1.63 mmol) in toluene (10 mL) was added dropwise over 2 minutes, the mixture allowed to warm to ambient temperature and then heated to 60°C for 20hrs. The reaction was cooled to ~5°C and a 10% solution of Rochelles salt (25 mL) added followed by ethyl acetate (30 mL). The organic phase was separated, washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and evaporated. . The crude product was purified by flash silica chromatography, elution gradient 20 to 50% EtOAc in iso-hexane to afford the product (1.1g, 94%). ^{1}H NMR (400 MHz, DMSO) δ 0.89 (9H, s), 2.03 (3H, s), 2.24 (3H, s), 3.70 - 3.79 (4H, m), 4.03 - 4.07 (1H, m), 4.12 - 4.16 (1H, m), 5.99 - 6.00 (1H, m), 7.33 - 7.47 (8H, m), 7.55 - 7.62 (5H, m), 7.67 - 7.69 (1H, m), 7.86 - 7.89 (1H, m), 8.17 - 8.18 (1H, m), 8.50 (1H, s), 8.53 (1H, s), 10.87 (1H, s); m/z (ESI+) $(M+H)^+$ = 721; HPLC t_R = 3.63 min.

Intermediate AE4: (2S)-3-[2-(tert-butyl-diphenylsilyl)oxyethoxy]-2-[1-(3-chloro-2-methylphenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-chloropyridin-2-yl)propanamide



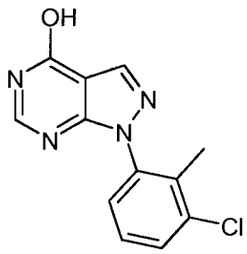
Sodium hydride (60% in mineral oil) (88 mg, 2.20 mmol) was added in one portion to (S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-N-(5-chloropyridin-2-yl)-2-hydroxypropanamide (**Intermediate AU3**) (499 mg, 1.00 mmol) in THF (25 mL) cooled to 0°C under nitrogen. Slow gas evolution and the resulting suspension was stirred at 0 °C for 10 minutes. 4-chloro-1-(3-chloro-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate AE5**) (279.1 mg, 1.00 mmol) was added in one portion, stirred at 0 °C for 10 minutes, allowed to warm to ambient temperature and stirred for 20 hours. Cooled to ~5°C, 1M citric acid (30 mL) added and the the mixture stirred for 10 minutes. The mixture was diluted with EtOAc (50 mL), the organic phase separated and washed sequentially with water (25 mL) and saturated brine (25 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product which was purified by flash silica chromatography, elution gradient 20 to 50% EtOAc in isohexane to afford the product (550mg, 74%). ^{1}H NMR (400 MHz, DMSO) δ 0.89 (9H, s), 2.03 (3H, s), 3.70 - 3.79 (4H, m), 4.02 - 4.18(2H, m), 5.98 - 6.03 (1H, d), 7.32 - 7.47 (8H, m), 7.59 - 7.62 (4H, m), 7.67 - 7.69 (1H, m), 7.86 - 7.88 (1H, m), 8.00 - 8.03 (1H, m), 8.39 (1H, dd), 8.51 (1H, s), 8.54 (1H, s), 11.19 (1H, s); m/z (ESI+) $(M+H)^+$ = 741/743/745 (Cl_2 pattern); HPLC t_R = 3.83 min.

Intermediate AE5: 4-Chloro-1-(3-chloro-2-methylphenyl)pyrazolo[5,4-d]pyrimidine



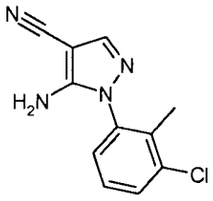
Phosphoryl trichloride (16.09 mL, 172.63 mmol) was added in one portion to 1-(3-chloro-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol (**Intermediate AE6**) (3.0 g, 11.51 mmol) and the resulting suspension was heated to 100 °C to give a solution and stirred for 4 hours. Evaporated, the residue poured into ice/water and stirred for 30 minutes. The solids were filtered, washed with water (4 × 20 mL), dissolved in ethyl acetate (100 mL), dried ($MgSO_4$), filtered and evaporated to afford the product (2.8 g) which was used withour further purification. ^{1}H NMR (400 MHz, DMSO) δ 2.06 (3H, s), 7.41 - 7.54 (2H, m), 7.71 - 7.73 (1H, m), 8.79 (1H, s), 8.89 (1H, s); m/z (ESI+) $(M+H)^+$ = 279; HPLC t_R = 2.59 min.

Intermediate AE6: 1-(3-chloro-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol



Concentrated sulfuric acid (1.595 mL, 29.93 mmol) was added to a stirred solution of 5-amino-1-(3-chloro-2-methylphenyl)-1H-pyrazole-4-carbonitrile (**Intermediate AE7**) (6.33 g, 27.21 mmol) in formic acid (40 mL). The resulting solution was stirred at 100 °C for 24 hours. The reaction was allowed to cool to room temperature and evaporated to ~half volume, water (100 mL) added and stirred for 1 hour. The formed ppt was filtered off, washed well with water and dried overnight in a vacuum over P_2O_5 to afford the product (5.82 g, 82 %). ^{1}H NMR (400 MHz, DMSO) δ 2.04 (3H, s), 7.37 - 7.46 (2H, m), 7.64 - 7.68 (1H, m), 8.06 (1H, d), 8.33 (1H, s), 12.35 (1H, s); m/z (ES-) (M-H)- = 259.24; HPLC t_R = 1.68 min.

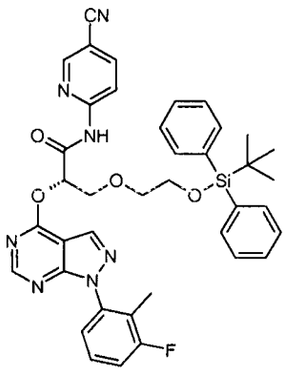
Intermediate AE7: 5-amino-1-(3-chloro-2-methylphenyl)-1H-pyrazole-4-carbonitrile



(3-Chloro-2-methylphenyl)hydrazine hydrochloride (CAS no. 65208-12-0) (9 g, 46.61 mmol) was partitioned between EtOAc (100 mL) and NaOH (2M, aq) (60 mL). The

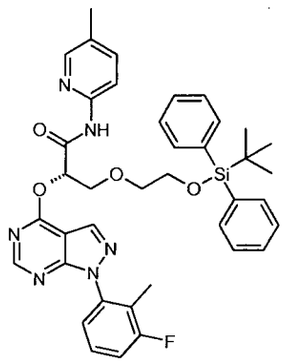
organic layer separated and washed with water (50 mL), brine (50 mL), dried ($MgSO_4$), filtered and concentrated. The resultant oil was suspended in MeOH (100 mL) under nitrogen at -5°C. 2-(Ethoxymethylene)malononitrile (5.69 g, 46.61 mmol) was added portionwise over 5 mins and the mixture stirred at ~0°C for 30 mins. The reaction mixture was allowed to warm to room temperature and then heated at reflux under nitrogen for 2 hours. The reaction mixture was allowed to cool and evaporated to dryness. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% EtOAc in isohexane to afford the product(6.33 g, 58.4 %). ^{1}H NMR (400 MHz, DMSO) δ 2.02 (3H, s), 6.57 (2H, s), 7.25 - 7.32 (1H, m), 7.37 (1H, t), 7.58 - 7.64 (1H, m), 7.77 (1H, s); m/z (ES+) $(M+H)^+$ = 233.28; HPLC t_R = 1.89 min.

Intermediate AF1: (2S)-3-[2-(tert-butyl-dimethylsilyl)oxyethoxy]-N-(5-cyanopyridin-2-yl)-2-[1-(3-fluoro-2-methylphenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxypropanamide



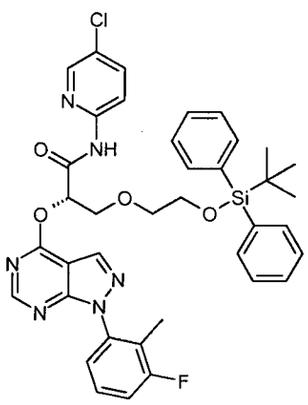
Prepared using a procedure analogous to that described for Intermediate AE1 using (2S)-methyl 3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(3-fluoro-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanoate (**Intermediate AF4**) and 6-aminonicotinonitrile. ^{1}H NMR (400 MHz, DMSO) d 0.89 (9H, s), 1.96 (3H, d), 3.83 - 3.69 (4H, m), 4.12 - 4.04 (1H, m), 4.17 (1H, dd), 6.02 (1H, m), 7.51 - 7.27 (9H, m), 7.60 (4H, m), 8.13 (1H, d), 8.22 (1H, dd), 8.51 (1H, s), 8.55 (1H, s), 8.81 (1H, d), 11.56 (1H, s). m/z (ES+) $(M+H)^+$ = 716; HPLC t_R = 3.29 min.

Intermediate AF2: (2S)-3-[2-(tert-butyl-dimethylsilyl)oxyethoxy]-2-[1-(3-fluoro-2-methylphenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-methylpyridin-2-yl)propanamide



Prepared using a procedure analogous to that described for Intermediate AE1 using (2S)-methyl 3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(3-fluoro-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanoate (**Intermediate AF4**) and 5-methylpyridin-2-amine. ^{1}H NMR (400 MHz, DMSO) d 0.88 (9H, s), 1.96 (3H, d), 2.24 (3H, s), 3.75 (4H, m), 4.08 - 4.02 (1H, m), 4.14 (1H, m), 5.99 (1H, m), 7.50 - 7.29 (9H, m), 7.63 - 7.54 (5H, m), 7.89 (1H, d), 8.17 (1H, s), 8.51 (1H, s), 8.55 (1H, s), 10.94 (1H, s).
m/z (ES+) $(M+H)^+$ = 705; HPLC t_R = 3.42 min.

Intermediate AF3: (2S)-3-[2-(tert-butyl-dimethylsilyl)oxyethoxy]-N-(5-chloropyridin-2-yl)-2-[1-(3-fluoro-2-methylphenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxypropanamide

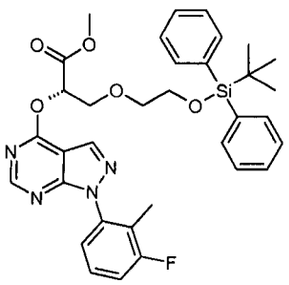


Prepared using a procedure analogous to that described for Intermediate AE1 using (2S)-methyl 3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(3-fluoro-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanoate (**Intermediate AF4**) and 5-chloropyridin-2-amine. ^{1}H NMR (400 MHz, DMSO) d 0.87 (9H, s), 1.96 (3H, d), 3.75 (4H,m), 4.10 - 4.02

(1H, m), 4.15 (1H, m), 6.00 (1H, m), 7.38 (9 H, m), 7.63 - 7.57 (4H, m), 7.88 (1H, dd), 8.03 (1H, d), 8.40 (1H, d), 8.52 (1H, s), 8.56 (1H, s), 11.25 (1H, s).

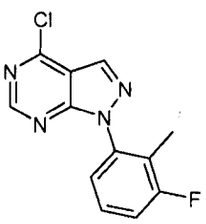
m/z (ES+) $(M+H)^+$ = 725; HPLC t_R = 3.63 min.

Intermediate AF4: (2S)-methyl 3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(3-fluoro-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanoate



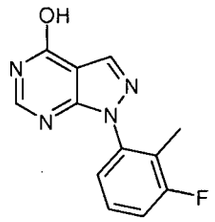
Prepared using a procedure analogous to that described for Intermediate AE2 using (S)-methyl 3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-hydroxypropanoate (**Intermediate AB3**) and 4-chloro-1-(3-fluoro-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate AF5**). ^{1}H NMR (400 MHz, DMSO) d 0.94 (9H, s), 1.96 (3H, d), 3.81 - 3.63 (7H, m), 4.09 - 4.02 (1H, m), 4.13 (1H, m), 5.89 (1H, m), 7.50 - 7.30 (9H, m), 7.63 (4H, m), 8.49 (1H, s), 8.59 (1H, s). m/z (ES+) $(M+H)^+$ = 629; HPLC t_R = 3.43 min.

Intermediate AF5: 4-chloro-1-(3-fluoro-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine



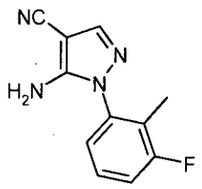
Prepared using a procedure analogous to that described for **Intermediate AE5** using 1-(3-fluoro-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol (**Intermediate AF6**). ^{1}H NMR (400 MHz, DMSO) d 1.99 (3H, d), 7.37 (1H, d), 7.45 (2H, m), 8.77 (1H, s), 8.89 (1H, s). m/z (ES+) $(M+H)^+$ = 263; HPLC t_R = 2.38 min.

Intermediate AF6: 1-(3-fluoro-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol



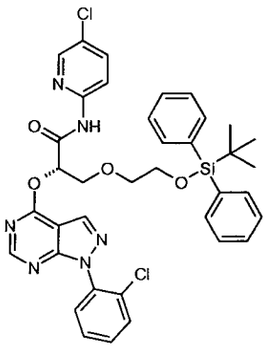
Prepared using a procedure analogous to that described for **Intermediate AE6** using 5-amino-1-(3-fluoro-2-methylphenyl)-1H-pyrazole-4-carbonitrile (**Intermediate AF7**) ^{1}H NMR (400 MHz, DMSO) d 1.97 (3H, d), 7.28 (1H, d), 7.48 - 7.35 (2H, m), 8.07 (1H, d), 8.33 (1H, s), 12.34 (1H, s); m/z (ES+) $(M+H)^+$ = 245; HPLC t_R = 1.43 min.

Intermediate AF7: 5-amino-1-(3-fluoro-2-methylphenyl)-1H-pyrazole-4-carbonitrile



Prepared using a procedure analogous to that described for **Intermediate AE7** using (3-fluoro-2-methylphenyl)hydrazine hydrochloride. ^{1}H NMR (400 MHz, DMSO) d 1.94 (3H, d), 6.56 (2H, s), 7.15 (1H, d), 7.42 - 7.30 (2H, m), 7.76 (1H, s); m/z (ES+) $(M+H)^+$ = 217; HPLC t_R = 1.63 min.

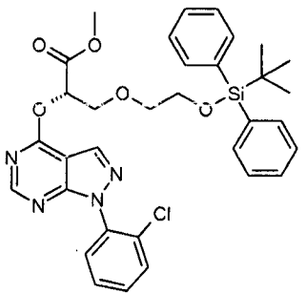
Intermediate AG1: (2S)-3-[2-(tert-butyl-dimethylsilyl)oxyethoxy]-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-chloropyridin-2-yl)propanamide



Prepared from (2S)-methyl 3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanoate (**Intermediate AG2**) (950mg, 1.51 mmol) according to the method for **Intermediate AE3** using 5-

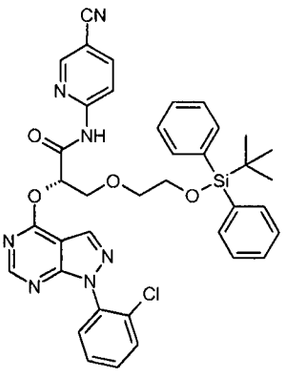
chloropyridin-2-amine. ^{1}H NMR (400 MHz, DMSO) δ 0.88 (9H, s), 3.71 - 3.84 (4H, m), 4.02 - 4.07 (1H, m), 4.13 - 4.18 (1H, m), 5.97 - 5.99 (1H, m), 7.34 - 7.43 (6H, m), 7.56 - 7.67 (7H, m), 7.74 - 7.77 (1H, m), 7.86 - 7.89 (1H, m), 8.00 - 8.03 (1H, m), 8.40 - 8.41 (1H, m), 8.52 (1H, s), 8.57 (1H, s), 11.25 (1H, s); m/z (ESI+) $(M+H)^+$ = 727; HPLC t_R = 3.49 min.

Intermediate AG2: Methyl (2S)-3-[2-(tert-butyl-diphenylsilyl)oxyethoxy]-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxypropanoate



Prepared according to the method for **Intermediate AE2** from (S)-methyl 3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-hydroxypropanoate (Intermediate AB3) and 4-chloro-1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate B1**). ^{1}H NMR (400 MHz, DMSO) δ 0.94 (9H, s), 3.56 - 3.75 (4H, m), 3.68 (3H, s), 3.90 - 4.09 (2H, m), 5.80 - 5.85 (1H, m), 7.29 - 7.43 (6H, m), 7.50 - 7.67 (7H, m), 7.67 - 7.74 (1H, m), 8.43 (1H, s), 8.52 (1H, s); m/z (ESI+) $(M+H)^+$ = 631; HPLC t_R = 3.38 min.

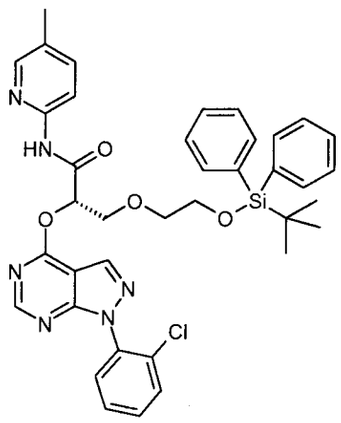
Intermediate AG3: (2S)-3-[2-(tert-butyl-diphenylsilyl)oxyethoxy]-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-cyanopyridin-2-yl)propanamide



Prepared according to the method for (**Intermediate AE1**) from (2S)-methyl 3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-

yloxy)propanoate (**Intermediate AG2**). ^{1}H NMR (400 MHz, DMSO) δ 0.91 (9H, s), 3.68 - 3.80 (4H, m), 4.09 - 4.19 (2H, m), 5.98 - 6.04 (1H, m), 7.34 - 7.48 (6H, m), 7.56 - 7.68 (7H, m), 7.74 - 7.77 (1H, m), 8.11 - 8.15 (1H, m), 8.21 - 8.24 (1H, m), 8.52 (1H, s), 8.54 (1H, s), 8.82 - 8.83 (1H, m), 11.60 (1H, s); m/z (ESI+) $(M+H)^+$ = 718; HPLC t_R = 3.13 min.

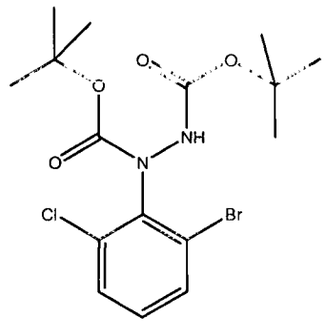
Intermediate AG4: (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-methylpyridin-2-yl)propanamide



Sodium hydride (14.21 mg, 0.36 mmol) was added to (S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-hydroxy-N-(5-methylpyridin-2-yl)propanamide (**Intermediate AU2**) (85 mg, 0.18 mmol) in anhydrous THF (5 mL) at 0 °C under nitrogen. The resulting solution was stirred at 0 °C for 10 minutes and then 4-chloro-1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine (47.1 mg, 0.18 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour. The reaction mixture was neutralised with 1M citric acid and the majority of the THF removed in vacuo. The reaction mixture was diluted with water (20 mL) and EtOAc (50 mL). The organic layer was separated and the aqueous layer re-extracted with EtOAc (2 × 20 mL). The combined organics were washed with saturated brine (10 mL), dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 0 to 20% EtOAc in isohexane to give (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-methylpyridin-2-yl)propanamide (126 mg, 100 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ0.99 (s, 9H), 2.29 (s, 3H), 3.67 - 3.73 (m, 2H), 3.77 - 3.84 (m, 2H), 4.13 - 4.25 (m, 2H), 6.07 (t, 1H), 7.29 - 7.54 (m,

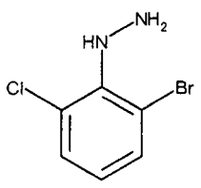
10H), 7.59 - 7.69 (m, 5H), 8.06 - 8.16 (m, 2H), 8.38 (s, 1H), 8.58 (s, 1H), 8.66 (s, 1H); m/z (ES+), $(M+H)^+$ = 707.62; HPLC t_R = 3.81 min

Intermediate AH1: di-tert-butyl 1-(2-bromo-6-chlorophenyl)hydrazine-1,2-dicarboxylate



To a stirred solution of 2.5 M Butyllithium in hexanes (13.79 mL, 34.47 mmol) at -20°C was added dropwise 2,2,6,6-tetramethylpiperidine (5.82 mL, 34.47 mmol) in THF (30 mL). This was stirred for 30 minutes. This solution was cooled down to -78°C, and a solution of 1-bromo-3-chlorobenzene (6 g, 31.34 mmol) in THF (20 mL) was added dropwise so as to mantain the temperature at <-70°C. After 2 hours (Z)-di-tert-butyl diazene-1,2-dicarboxylate (10.82 g, 47.01 mmol) in THF (30 mL) added dropwise at -78°C. Stirred at this temperature for 2 hours, then allowed to warm to room temperature overnight. Water (150 mL) added. The mixture was extracted with EtOAc (2 × 300 mL). The extracts were combined, washed with brine (100 mL), dried ($MgSO_4$) and reduced go give a residue which was purified by flash silica chromatography, elution gradient 0-10% EtOAc in hexane. Fractions containing suspected product were combined, and reduced to give di-tert-butyl 1-(2-bromo-6-chlorophenyl)hydrazine-1,2-dicarboxylate (9.59 g, 72.5 %). ^{1}H NMR (400 MHz, DMSO) δ 1.30-1.50 (18H, s), 7.28 (1H, m), 7.55 (1H, dd), 7.67 (1H, dd), 9.18 (1H, s). m/z (ES+) $(M+Na)^+$ = 443; HPLC t_R = 10.76 min.

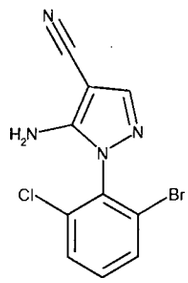
Intermediate AH2: (2-bromo-6-chlorophenyl)hydrazine hydrochloride



4M Hydrogen chloride in dioxane (28.2 mL, 112.64 mmol) was added to di-tert-butyl 1-(2-bromo-6-chlorophenyl)hydrazine-1,2-dicarboxylate (**Intermediate AH1**) (9.5 g, 22.53

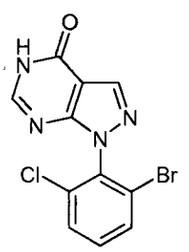
mmol) in iPrOH (30 mL) at ambient temperature. The resulting solution was heated to 60 °C and stirred for 20 minutes. The reaction mixture was allowed to cool to ambient temperature. A solid was filtered off, and dried under vacuum to afford the product (4.71 g). ^{1}H NMR (400 MHz, DMSO) d 6.97 (1H, s), 7.06 (1H, t), 7.41 (1H, dd), 7.52 (1H, dd), 9.83 (3H, s). m/z M^+ = 220; GC-MS tR= 10.419 min.

Intermediate AH3: 5-amino-1-(2-bromo-6-chlorophenyl)-1H-pyrazole-4-carbonitrile



(2-Bromo-6-chlorophenyl)hydrazine hydrochloride (**Intermediate AH2**) (4.71 g, 18.26 mmol) was partitioned between DCM (300 mL) and 2M NaOH (20 mL). Allowed to Stir for 1 hour. The two phases were separated. The organic phase was reduced under vacuum to give the free base. This was dissolved in MeOH (60 mL), and stirred in a cooling bath at 0°C. (Ethoxymethylene)malononitrile (2.230 g, 18.26 mmol) added portionwise. The reaction mixture was then allowed to warm to ambient temperature and stirred for 1 hour. The mixture was then heated to reflux and stirred for 16 hours. Allowed to cool to ambient temperature. The reaction mixture was concentrated to give a solid, which was triturated under MeOH. A solid was filtered off. This was dried to afford the product (4.59 g, 85 %). ^{1}H NMR (400 MHz, DMSO) δ 6.79 (2H, s), 7.54 - 7.47 (1H, m), 7.70 (1H, dd), 7.79 (1H, s), 7.81 (1H, d). m/z (ES+) $(M+H)^+$ = 299; HPLC t_R = 1.70 min.

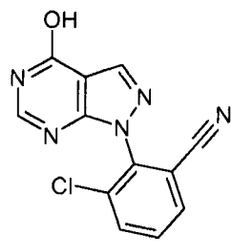
Intermediate AH4: 1-(2-bromo-6-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one



Concentrated sulfuric acid (0.905 mL, 16.97 mmol) was added to a stirred solution of 5-amino-1-(2-bromo-6-chlorophenyl)-1H-pyrazole-4-carbonitrile (**Intermediate AH3**) (4.59

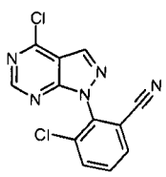
g, 15.43 mmol) in formic acid (30 mL). The resulting solution was heated to 100 °C and stirred for 4 hours. The reaction mixture was allowed to cool to ambient temperature. The reaction mixture was evaporated to dryness. The residue was triturated under water. A solid was filtered off. This was dried under vacuum to afford the product (3.71 g, 73.8 %). ^{1}H NMR (400 MHz, DMSO) δ 7.58 (1H, t), 7.80 - 7.76 (1H, m), 7.88 (1H, dd), 8.08 (1H, d), 8.40 (1H, s), 12.44 (1H, s). m/z (ES+) $(M+H)^+$ = 327; HPLC t_R = 1.48 min.

Intermediate AH5: 3-chloro-2-(4-hydroxy-1H-pyrazolo[3,4-d]pyrimidin-1-yl)benzonitrile



1-(2-bromo-6-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (**Intermediate AH4**)(1012 mg, 3.11 mmol) and zinc cyanide (329 mg, 2.80 mmol) were dissolved in DMF (15 mL). Sealed into a microwave tube. The tube was purged with nitrogen. 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (180 mg, 0.31 mmol) and tris(dibenzylideneacetone)dipalladium(0) (142 mg, 0.16 mmol) added. The reaction was heated to 160 °C for 15 minutes in the microwave reactor, then allowed to cool to ambient temperature. The DMF was removed by evaporation. The crude product was absorbed onto silica and then purified by flash silica chromatography, elution gradient 0 to 10% MeOH in DCM to afford the product (769 mg, 91 %). ^{1}H NMR (400 MHz, DMSO) δ 7.89 - 7.83 (1H, t), 8.14 (1H, s), 8.15 (2H, d), 8.49 (1H, s), 12.56 (1H, s); m/z (ES+) $(M+H)^+$ = 272; HPLC t_R = 1.29 min.

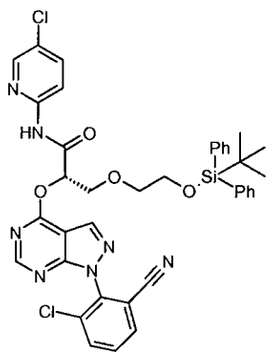
Intermediate AH6: 3-Chloro-2-(4-chloro-1H-pyrazolo[3,4-d]pyrimidin-1-yl)benzonitrile



Phosphorus oxychloride (7.93 mL, 85.03 mmol) was added to 3-chloro-2-(4-hydroxy-1H-pyrazolo[3,4-d]pyrimidin-1-yl)benzonitrile (**Intermediate AH5**) (1.155 g, 4.25 mmol).

The resulting mixture was heated to 100 °C and stirred for 4 hours. The reaction mixture was allowed to cool to ambient temperature. The reaction mixture was evaporated to near dryness. Poured onto ice/water with stirring. A solid precipitate was collected by filtration. This was dried overnight under vacuum to afford the product (0.928 g, 75 %). ^{1}H NMR (400 MHz, DMSO) δ 8.02 - 7.96 (1H, t), 8.26 (1H, d), 8.28 (1H, s), 9.05 (2H, d). m/z M^+ = 289; GCMS tR= 13.82 min.

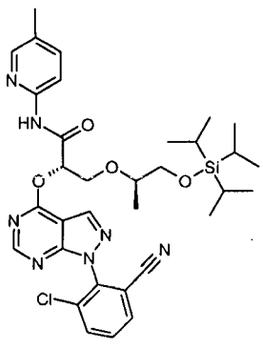
Intermediate AH7: (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(2-chloro-6-cyanophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-chloropyridin-2-yl)propanamide



60% Sodium hydride (95 mg, 2.38 mmol) was added to (S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-N-(5-chloropyridin-2-yl)-2-hydroxypropanamide (**Intermediate AU3**) (540 mg, 1.08 mmol) in anhydrous THF (15 mL), at 0°C, under nitrogen. The resulting solution was stirred at 0°C for 10 minutes. 3-chloro-2-(4-chloro-1H-pyrazolo[3,4-d]pyrimidin-1-yl)benzonitrile (**Intermediate AH6**) (314 mg, 1.08 mmol) was added. The reaction mixture was allowed to warm to room temperature and was then stirred for 2 hours. The reaction mixture was neutralised with 1M citric acid and then diluted with water (50 mL) and EtOAc (100 mL). The organic layer was separated and the aqueous layer re-extracted with EtOAc (2 × 100 mL). The combined organics were washed with saturated brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash silica chromatography, elution gradient 30 to 50% EtOAc in isohexane. Fractions were evaporated to dryness to afford (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(2-chloro-6-cyanophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-chloropyridin-2-yl)propanamide (466 mg, 57.2 %). ^{1}H NMR (400 MHz, DMSO) δ 0.89 (9H, d), 3.83 - 3.66 (4H, m), 4.11 - 4.04 (1H, m), 4.20 - 4.12 (1H, m), 6.00 (1H, s), 7.44 - 7.31 (6H, m), 7.60 (4H, m), 7.87 (2H, m), 8.03 (1H, t), 8.22 -

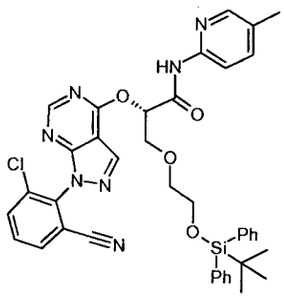
8.13 (2H, m), 8.39 (1H, d), 8.62 (1H, d), 8.68 (1H, d), 11.23 (1H, s). m/z (ES+) $(M+H)^+$ = 752; HPLC t_R = 3.89 min.

Intermediate AH8: (2S)-2-(1-(2-chloro-6-cyanophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-methylpyridin-2-yl)-3-((R)-1-(triisopropylsilyloxy)propan-2-yloxy)propanamide



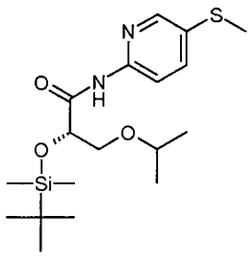
Sodium hydride (64.3 mg, 1.61 mmol) was added to (S)-2-hydroxy-N-(5-methylpyridin-2-yl)-3-((R)-1-(triisopropylsilyloxy)propan-2-yloxy)propanamide (**Intermediate AU4**) (300 mg, 0.73 mmol) in anhydrous THF (10 mL) at 0°C under nitrogen. The resulting solution was stirred at 0°C for 10 minutes and then 3-chloro-2-(4-chloro-1H-pyrazolo[3,4-d]pyrimidin-1-yl)benzonitrile (**Intermediate AH6**) (212 mg, 0.73 mmol) added. The reaction mixture was allowed to warm to ambient temperature and stirred for 2 hours. The reaction mixture was neutralised with 1M citric acid and then diluted with water (50 mL) and EtOAc (100 mL). The organic layer was separated and the aqueous layer re-extracted with EtOAc (2 x 100 mL). The combined organics were washed with saturated brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash silica chromatography, elution gradient 20 to 40% EtOAc in isohexane to afford the product (334 mg, 68.8 %). ^{1}H NMR (400 MHz, DMSO) δ 0.98 - 0.86 (21H, m), 1.09 (3H, d), 2.24 (3H, s), 3.58 - 3.47 (1H, m), 3.64 (1H,m), 3.81 - 3.71 (1H, m), 4.10 (2H,m), 5.92 (1H, s), 7.58 (1H, d), 7.89 (2H, t), 8.18 (3H, m), 8.59 (1H, s), 8.72 (1H, s), 10.88 (1H, s). m/z (ES+) $(M+H)^+$ = 664; HPLC t_R = 3.99 min.

Intermediate AH9: (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(2-chloro-6-cyanophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-methylpyridin-2-yl)propanamide



Prepared using a procedure analogous to that described with **Intermediate AH7** using (S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-N-(5-methylpyridin-2-yl)-2-hydroxypropanamide (**Intermediate AU2**) and 3-chloro-2-(4-chloro-1H-pyrazolo[3,4-d]pyrimidin-1-yl)benzonitrile (**Intermediate AH6**). m/z (ES+) $(M+H)^+$ = 732; HPLC t_R = 3.76 min

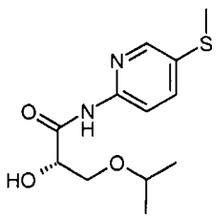
Intermediate AI1: (S)-2-(tert-butyldimethylsilyloxy)-3-isopropoxy-N-(5-(methylthio)pyridin-2-yl)propanamide



Trimethylaluminium (2M in toluene) (10.40 mL, 20.80 mmol) was added to 5-(methylthio)pyridin-2-amine (CAS no. 77618-99-6) (2.54 g, 18.09 mmol) in toluene (100 mL) cooled to 0°C under nitrogen. The resulting solution was stirred at 0°C for 20 minutes. (S)-methyl 2-(tert-butyldimethylsilyloxy)-3-isopropoxypropanoate (**Intermediate C7b**) (5 g, 18.09 mmol) was added and the reaction was allowed to warm to room temperature. The reaction was allowed to stir at room temperature for 1 hour. The temperature was increased to 60°C and stirred for a further 24 hours. The reaction mixture was neutralised with citric acid (1M, aq) and then diluted with water and EtOAc (200 mL). The organic layer was separated and the aqueous layer re-extracted with EtOAc (100 mL). The combined organics were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% Et2O in isohexane to afford the product (3.95 g, 56.8 %). ^{1}H NMR (400 MHz, DMSO) δ 0.10 - 0.13 (6H, d),

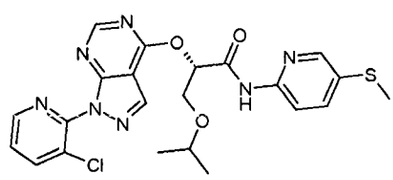
0.90 - 0.92 (9H, m); 1.04 - 1.07 (6H, m), 2.40 (3H +DMSO, s), 3.54 - 3.63 (3H, m), 4.42 - 4.44 (1H, m), 7.77 - 7.80 (1H, dd), 8.03 - 8.06 (1H, d), 8.26 (1H, d), 9.49 (1H, s); m/z (ES+) $(M+H)^+ = 385$; HPLC $t_R = 3.66$ min.

Intermediate AI2: (S)-2-hydroxy-3-isopropoxy-N-(5-(methylthio)pyridin-2-yl)propanamide



A solution of tetrabutylammonium fluoride (1M inTHF) (10.04 mL, 10.04 mmol) was added in one portion to a stirred solution of (S)-2-(tert-butyldimethylsilyloxy)-3-isopropoxy-N-(5-(methylthio)pyridin-2-yl)propanamide (**Intermediate AI1**) in tetrahydrofuran (50 mL). The resulting solution was stirred at ambient temperature for 30 minutes. The majority of the THF was evaporated *in vacuo*. The residue was diluted with EtOAc (100 mL), washed sequentially with water (25 mL) and saturated brine (25 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 30 to 50% EtOAc in isohexane to afford the product (2.38 g, 88 %). 1H NMR (400 MHz, DMSO) δ 1.03 - 1.07 (6H, m), 3.28 (3H, s), 3.53 - 3.64 (3H, m), 4.19 - 4.22 (1H, m), 5.95 (1H, d), 7.77 - 7.80 (1H, d), 8.04 - 8.06 (1H, d), 8.24 - 8.25 (1H, s), 9.60 (1H, s); m/z (ES+) $(M+H)^+ = 271$; HPLC $t_R = 1.74$ min.

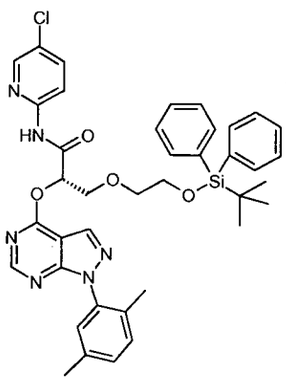
Intermediate AI3: (2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-isopropoxy-N-(5-(methylthio)pyridin-2-yl)propanamide



60% Sodium hydride (111 mg, 2.77 mmol) was added to a solution of (S)-2-hydroxy-3-isopropoxy-N-(5-(methylthio)pyridin-2-yl)propanamide (**Intermediate AI2**) (500 mg, 1.85 mmol) in anhydrous THF (30 mL) at 0°C under nitrogen. The resulting suspension was stirred at 0°C for 10 minutes and then a solution of 4-chloro-1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate B15**) (492 mg, 1.85 mmol) in dry THF (10

mL) added dropwise, maintaining the temperature below 5°C. The reaction mixture was stirred at 0°C for 10 minutes and then allowed to warm to room temperature. The reaction was stirred at room temperature for 1 hour. The reaction mixture was neutralised with HCl (1M, aq). The majority of the THF was evaporated *in vacuo* and then EtOAc (100 mL) was added. The organic layer was separated and the aqueous layer re-extracted with EtOAc (2 x 100 mL). The combined organics were washed with saturated brine (75 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash silica chromatography (330 g), elution gradient 20 to 70% EtOAc in isohexane to afford the product (609 mg, 65.9 %). ^{1}H NMR (400 MHz, DMSO) δ 1.12 (6H, dd), 3.28 (3H, s), 3.76 (1H, dt), 4.07 - 3.96 (2H, m), 5.90 (1H, s), 7.78 - 7.72 (2H, m), 7.95 (1H, d), 8.27 (1H, dd), 8.33 (1H, dd), 8.56 (1H, s), 8.65 (1H, s), 8.67 (1H, dd), 10.97 (1H, s). m/z (ES+) $(M+H)^+$ = 500; HPLC t_R = 2.43 min.

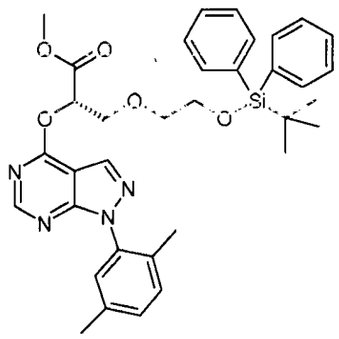
Intermediate AJ1: (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-N-(5-chloropyridin-2-yl)-2-(1-(2,5-dimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide



Trimethylaluminium (2M in toluene) (0.692 mL, 1.38 mmol) was added dropwise to a stirred solution of 5-chloropyridin-2-amine (163 mg, 1.27 mmol) in toluene (15 mL), under nitrogen at 0°C. The resulting solution was allowed to stir at this temperature for a further 20 minutes. (2S)-Methyl 3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(2,5-dimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanoate (**Intermediate AJ2**) (721 mg, 1.15 mmol) in toluene (6 mL) was added slowly to the mixture at 0°C. The reaction mixture was then heated to 100°C and was stirred for 5 hours using the microwave. The reaction mixture was allowed to cool to ambient temperature, then was evaporated to afford a crude product. The crude product was purified by flash silica chromatography. Fractions were evaporated to dryness to afford a crude product (428 mg).

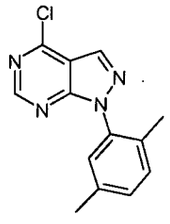
Trimethylaluminium (2M in toluene) (0.258 mL, 0.52 mmol) was added dropwise to a stirred solution of 5-chloropyridin-2-amine (66.3 mg, 0.52 mmol) in toluene (6 mL), under nitrogen at 0°C. The resulting solution was allowed to stir at this temperature for a further 20 minutes. The crude product in toluene (6 mL) was added slowly to the mixture at 0°C. The reaction mixture was then heated to 100°C and was stirred for 5 hours using the microwave. The reaction mixture was allowed to cool to ambient temperature, then was evaporated to afford a crude product. This was purified by flash silica chromatography, elution gradient 0 to 30% EtOAc in isohexane to afford the product (328 mg). m/z (ES+) $(M+H)^+ = 721$; HPLC $t_R = 3.76$ min.

Intermediate AJ2: (2S)-methyl 3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(2,5-dimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanoate



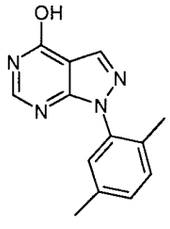
60% sodium hydride (0.187 g, 4.67 mmol) was added to (S)-methyl 3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-hydroxypropanoate (**Intermediate AB3**) (1.568 g, 3.90 mmol) in anhydrous THF (20 mL) at 0 °C under nitrogen. The resulting solution was stirred at 0 °C for 10 minutes and then 4-chloro-1-(2,5-dimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate AJ3**)(1.008 g, 3.90 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour. The reaction mixture was neutralised with 1M citric acid and the majority of the THF removed *in vacuo*. The residue was diluted with water (20 mL) and EtOAc (100 mL). The organic layer was separated and the aqueous layer re-extracted with EtOAc (100 mL). The combined organics were washed with saturated brine (75 mL), dried ($MgSO_4$) and evaporated to give the crude product. This was purified by flash silica chromatography, elution gradient 0 to 20% EtOAc in isohexane to afford the product (1.400 g, 57.5 %). m/z (ES+) $(M+H)^+ = 625$; HPLC $t_R =$ 3.53 min.

Intermediate AJ3: 4-Chloro-1-(2,5-dimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidine



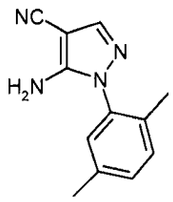
Phosphorus oxychloride (7.76 mL, 83.24 mmol) was added to 1-(2,5-dimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol (1 g, 4.16 mmol). The resulting solution was stirred at 100 °C for 2 hours. LCMS showed reaction was complete. The reaction mixture was evaporated. Ice/water and then EtOAc were added. The organic layer was separated and the aqueous layer re-extracted with EtOAc. The combined organics were washed with water, dried (MgSO4) and concentrated to give crude product (1.077 g, 100 %) which was used without purification. ^{1}H NMR (400 MHz, DMSO) δ 2.00 (3H, s), 2.35 (3H, s), 7.26 - 7.37 (3H, m), 8.72 (1H, s), 8.86 (1H, s); m/z (ES+) $(M+H)^+$ = 259; HPLC t_R = 2.48 min.

Intermediate AJ4: 1-(2,5-dimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol



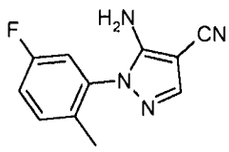
Concentrated sulfuric acid (3.06 mL, 57.37 mmol) was added to a stirred solution of 5-amino-1-(2,5-dimethylphenyl)-1H-pyrazole-4-carbonitrile (**Intermediate AJ5**) (11.07 g, 52.16 mmol) in formic acid (70 mL). The resulting solution was stirred at 100 °C for 24 hours. The reaction was allowed to cool to room temperature and evaporated to ~half volume, water (100 mL) added and stirred for 1 hour. The formed ppt was filtered off, washed well with water and dried overnight in a vacuum over P_2O_5 to afford the product (8.71 g, 69.5 %) which was used without purification. ^{1}H NMR (400 MHz, DMSO) δ 2.00 (3H, s), 2.33 (3H, s), 3.43 (2H, s), 7.18 (1H, s), 7.24 - 7.31 (2H, m), 8.04 (1H, d), 8.28 (1H, s), 12.27 (1H, s); m/z (ES+) $(M+H)^+$ = 241; HPLC t_R = 1.6 min.

Intermediate AJ5: 5-amino-1-(2,5-dimethylphenyl)-1H-pyrazole-4-carbonitrile



2,5-Dimethylphenylhydrazine hydrochloride (CAS no. 56737-78-1) (10 g, 57.92 mmol) was partitioned between EtOAc (100 mL) and NaOH (2M, aq) (60 mL). The organic layer separated and washed with water (50 mL), brine (50 mL), dried (MgSO4), filtered and concentrated to afford free base of the starting material. The resultant oil was suspended in MeOH (100 mL) under nitrogen at -5°C. 2-(ethoxymethylene)malononitrile (7.07 g, 57.92 mmol) added portionwise over 5 mins and the mixture stirred at ~0°C for 30 mins. The reaction mixture was allowed to warm to room temperature and then heated at reflux under nitrogen for 2 hours. The reaction mixture was allowed to cool and evaporated to dryness to afford the product (11.07 g, 90 %) which was used without purification. ^{1}H NMR (400 MHz, DMSO) δ 1.98 (3H, s), 2.31 (3H, s), 6.39 (2H, s), 7.07 (1H, s), 7.21 - 7.28 (2H, m), 7.72 (1H, s); m/z (ES+) $(M+H)^+$ = 213; HPLC t_R = 1.79 min.

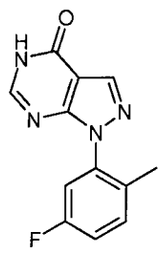
Intermediate AK1: 5-amino-1-(5-fluoro-2-methylphenyl)-1H-pyrazole-4-carbonitrile



(Ethoxymethylene)malononitrile (CAS no. 123-06-8) (3.18 g, 26.04 mmol) was added portionwise to the stirred solution of (5-fluoro-2-methylphenyl)hydrazine hydrochloride (CAS no. 325-50-8) (4.6 g, 26.04 mmol) and N,N-diisopropylethylamine (5.90 mL, 33.86 mmol) in MeOH (50 mL), under nitrogen at 5°C. The resulting solution was allowed to stir for a further 30 minutes at this temperature. The reaction mixture was then heated to reflux and was stirred for 3 hours. The reaction mixture was allowed to cool to ambient temperature. The reaction mixture was evaporated to dryness, redissolved in EtOAc (200 mL), washed with water (50 mL), and saturated brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. This was purified by flash silica chromatography, elution gradient 0 to 50% EtOAc in isohexane to afford the product (1.076 g, 19.11 %). ^{1}H NMR (400 MHz, DMSO) δ 2.00 (3H, s), 6.56 (2H, s), 7.20 (1H,

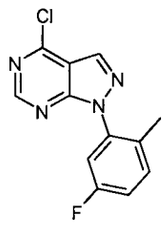
dd), 7.29 (1H, td), 7.43 (1H, t), 7.75 (1H, s); m/z (ES+) $(M+H)^+$ = 217; HPLC t_R = 1.61 min.

Intermediate AK2: 1-(5-fluoro-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one



Sulfuric acid (0.353 mL, 6.61 mmol) was added to a stirred solution of 5-amino-1-(5-fluoro-2-methylphenyl)-1H-pyrazole-4-carbonitrile (**Intermediate AK1**) (1.3 g, 6.01 mmol) in formic acid (10 mL), under nitrogen at 5°C. The reaction mixture was then heated to 100°C and was stirred for 16 hours. The reaction mixture was allowed to cool to ambient temperature, then was evaporated to half volume. A percipitate was filtered off. This solid was washed with water, then dried under vacuum to afford the product (0.713 g, 48.6 %). ^{1}H NMR (400 MHz, DMSO) δ 2.05 (3H, s), 7.30 - 7.36 (2H, m), 7.45 - 7.51 (1H, m), 8.08 (1H, s), 8.32 (1H, s), 12.33 (1H, s). m/z (ES+) $(M+H)^+$ = 245; HPLC t_R = 1.43 min.

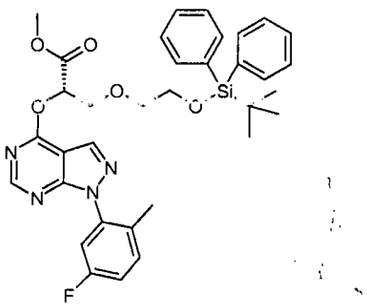
Intermediate AK3: 4-chloro-1-(5-fluoro-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine



Phosphorus oxychloride (5442 µl, 58.39 mmol) was added to 1-(5-fluoro-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (**Intermediate AK2**) (713 mg, 2.92 mmol), at ambient temperature. The resulting mixture was heated to 100 °C and stirred for 4 hours. The mixture was allowed to cool to ambient temperature. The reaction mixture was evaporated to near dryness. Dissolved into toluene, evaporated, dissolved, in toluene and evaporated to dryness again. The solid was dried under vacuum to give crude product. This was partitioned between EtOAc (70 mL), and water (25 mL). The organic phase was dried

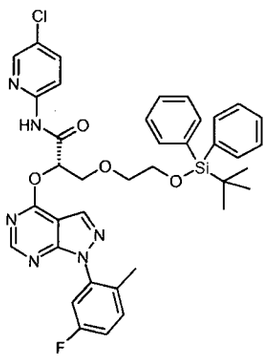
($MgSO_4$), evaporated, then dried under vacuum to afford the product (732 mg, 95 %). ^1H NMR (400 MHz, DMSO) δ 2.13 (3H, s), 7.52 - 7.42 (2H, m), 7.64 - 7.58 (1H, m), 8.83 (1H, s), 8.96 (1H, s); m/z (ES+) $(M+H)^+ = 263$; HPLC $t_R = 2.39$ min.

Intermediate AK4: (2S)-methyl 3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(5-fluoro-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanoate



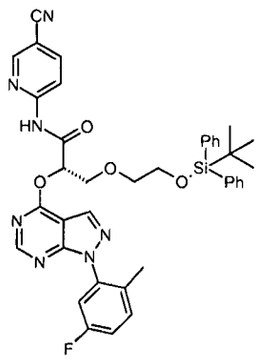
60% Sodium hydride (156 mg, 3.89 mmol) was added to (S)-methyl 3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-hydroxypropanoate (**Intermediate AB3**) (1119 mg, 2.78 mmol) in anhydrous THF (15 mL) at 0 °C under nitrogen. The resulting solution was stirred at 0 °C for 10 minutes and then 4-chloro-1-(5-fluoro-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate AK3**) (730 mg, 2.78 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour. The reaction mixture was neutralised with 1M citric acid and the majority of the THF removed *in vacuo*. The residue was diluted with water (20 mL) and EtOAc (100 mL). The organic layer was separated and the aqueous layer re-extracted with EtOAc (100 mL). The combined organics were washed with saturated brine (75 mL), dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica (120 g) chromatography, elution gradient 0 to 20% EtOAc in isohexane to afford the product (932 mg, 53.3 %). ^1H NMR (400 MHz, DMSO) δ 0.94 (9H, s), 2.03 (3H, s), 3.80 - 3.65 (7H, m), 4.16 - 4.03 (2H, m), 5.89 (1H, dd), 7.46 - 7.33 (8H, m), 7.54 - 7.48 (1H, m), 7.65 - 7.61 (4H, m), 8.48 (1H, s), 8.59 (1H, s); m/z (ES+) $(M+H)^+ = 629$; HPLC $t_R = 3.41$ min.

Intermediate AK5: (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-N-(5-chloropyridin-2-yl)-2-(1-(5-fluoro-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide



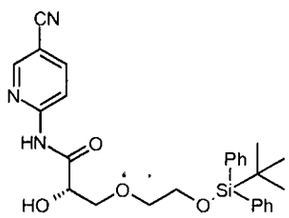
Trimethylaluminium (2M in toluene) (0.556 mL, 1.11 mmol) was added dropwise to a stirred solution of 5-chloropyridin-2-amine (143 mg, 1.11 mmol) in toluene (10 mL), under nitrogen at 0°C. The resulting solution was allowed to stir at this temperature for a further 20 minutes. (2S)-methyl 3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(5-fluoro-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanoate (**Intermediate AK4**) (466 mg, 0.74 mmol) in toluene (5 mL) was added slowly to the mixture at 0°C. The reaction mixture was then heated to 100°C and was stirred for 6 hours using the microwave. The reaction mixture was allowed to cool to ambient temperature, then evaporated to afford a gum. This was dissolved in EtOAc (75 mL), and washed sequentially with Rochelle's solution (20 mL), and water (20 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 30% EtOAc in isohexane to afford the product (390 mg, 72.6 %). ^{1}H NMR (400 MHz, DMSO) δ 0.88 (9H, s), 2.03 (3H, s), 3.82 - 3.67 (4H, m), 4.05 (1H, m), 4.15 (1H, m), 6.00 (1H, m), 7.45 - 7.31 (8H, m), 7.50 (1H, t), 7.60 (4H, m), 7.87 (1H, dd), 8.02 (1H, d), 8.40 (1H, d), 8.51 (1H, s), 8.56 (1H, s), 11.25 (1H, s); m/z (ES+) $(M+H)^+$ = 725; HPLC t_R = 3.63 min.

Intermediate AK6: (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-N-(5-cyanopyridin-2-yl)-2-(1-(5-fluoro-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide



Prepared in an analogous fashion to **Intermediate AL1** using **Intermediate AK3** and **Intermediate AK7**. ^{1}H NMR (400 MHz, $CDCl_3$) 0.99 (9H, s), 2.13 (3H, s), 3.70 - 3.73 (2H, m), 3.84 (2H, t), 4.19 - 4.21 (2H, m), 6.04 (1H, t), 7.13 - 7.17 (2H, m), 7.32 - 7.42 (7H, m), 7.63 - 7.66 (4H, m), 7.91 - 7.94 (1H, m), 8.35 (1H, s), 8.36 - 8.38 (1H, m), 8.51 (1H, q), 8.57 (1H, s), 9.02 (1H, s); m/z (ES+) $(M+H)^+$ = 716.5; HPLC t_R = 3.69 min.

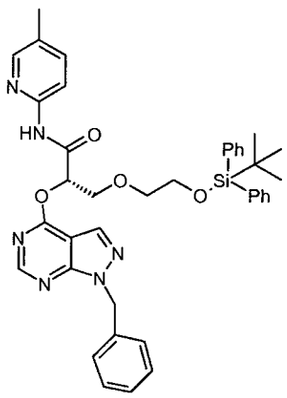
Intermediate AK7: (S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-N-(5-cyanopyridin-2-yl)-2-hydroxypropanamide



Trimethylaluminium (2M in toluene) (0.621 mL, 1.24 mmol) was added to a solution of 6-aminonicotinonitrile (148 mg, 1.24 mmol) in toluene (10 mL) at 0°C under nitrogen. The reaction mixture was stirred at 0°C for 20 mins and then (S)-methyl 3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-hydroxypropanoate (**Intermediate AB3**) (250 mg, 0.62 mmol) was added. The reaction mixture was allowed to warm to room temperature and then heated at reflux under nitogen for 4 hours. The reaction mixture was allowed to cool to room temperature and the concentrated in vacuo. The residue was neutralised with citric acid (1M, aq) and then diluted with water and DCM (50 mL). The organic layer was separated and the aqueous layer re-extracted with DCM (30 mL). The combined organics were dried ($MgSO_4$), filtered and evaporated in vacuo.The crude product was purified by flash silica chromatography, elution gradient 20 to 50% EtOAc in isohexane to afford the

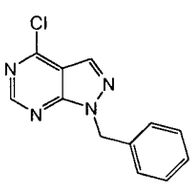
product (202 mg, 66.4 %). ^{1}H NMR (400 MHz, $CDCl_3$) 1.04 (9H, s), 3.65 - 3.67 (2H, m), 3.81 - 3.91 (4H, m), 4.36 (1H, t), 7.35 - 7.45 (6H, m), 7.65 - 7.67 (4H, m), 7.92 - 7.95 (1H, m), 8.36 - 8.39 (1H, m), 8.54 - 8.56 (1H m), 9.43 (1H, s); m/z (ES+) $(M+H)^+$ = 490; HPLC t_R = 3.08 min.

Intermediate AL1: (S)-2-(1-benzyl-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-N-(5-methylpyridin-2-yl)propanamide



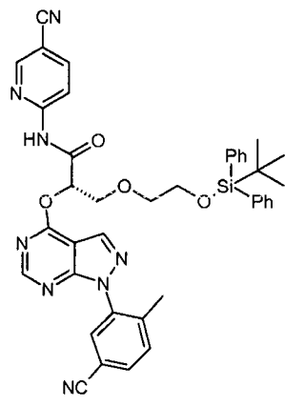
Sodium hydride (90 mg, 2.25 mmol) was added to (S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-hydroxy-N-(5-methylpyridin-2-yl)propanamide (538 mg, 1.12 mmol) **(Intermediate AU2)** in anhydrous THF (20 mL) at 0°C under nitrogen. The resulting solution was stirred at 0°C for 10 minutes and then 1-benzyl-4-chloro-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate AL2**) (250 mg, 1.02 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was neutralised with 1M citric acid, diluted with water (20 mL) and EtOAc (50 mL). The organic layer was separated and the aqueous layer re-extracted with EtOAc (2 x 50 mL). The combined organics were washed with saturated brine (75 mL),dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by flash silica chromatography, elution gradient 30 to 50% EtOAc in isohexane to afford the product (540 mg, 77 %). m/z (ES+) $(M+H)^+$ = 687; HPLC t_R = 3.89 min.

Intermediate AL2: 1-benzyl-4-chloro-1H-pyrazolo[3,4-d]pyrimidine



Triethylamine (1.181 mL, 8.48 mmol) was added to 4,6-dichloropyrimidine-5-carbaldehyde (CAS no. 5305-40-8) (500 mg, 2.83 mmol) and benzylhydrazine dihydrochloride (CAS no. 20570-96-1) (551 mg, 2.83 mmol) in THF (15 mL) at room temperature under nitrogen. The resulting suspension was stirred at room temperature for 10 minutes and then heated at 65°C for 50 mins. Silica was added to the reaction mixture and concentrated in vacuo. The crude product was purified by flash silica chromatography, elution gradient 20 to 50% EtOAc in isohexane to afford the product (500 mg, 72.3 %). ^{1}H NMR (400 MHz, $CDCl_3$) 5.67 (2H, s), 7.28 - 7.38 (5H, m), 8.16 (1H, s), 8.79 (1H, s); m/z (ES+) $(M+H)^+ = 245$; HPLC $t_R = 2.29$ min.

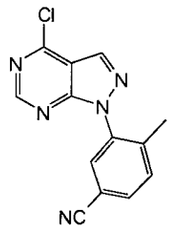
Intermediate AM1: (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(5-cyano-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-cyanopyridin-2-yl)propanamide



Prepared in an analogous fashion to **Intermediate AL1** using **Intermediate AM2** and **Intermediate AK7**.

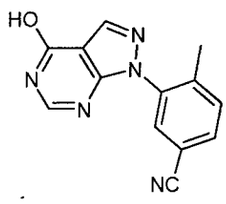
1H NMR (400 MHz, $CDCl_3$) 1.00 (9H, s), 2.28 (3H, s), 3.70 - 3.74 (2H, m), 3.84 (2H, t), 4.12 4.20 - 4.21 (2H, m), 6.04 (1H, t), 7.32 - 7.43 (6H, m), 7.52 - 7.54 (1H, m), 7.63 - 7.73 (6H, m), 7.91 - 7.94 (1H, m), 8.35 - 8.38 (2H, m), 8.51 (1H, q), 8.57 (1H, s), 9.02 (1H, s); m/z (ES+) $(M+H)^+ = 723.5$; HPLC $t_R = 3.57$ min.

Intermediate AM2: 3-(4-chloro-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-4-methylbenzonitrile



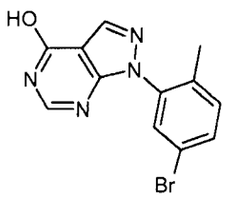
Phosphorus oxychloride (8.90 mL, 95.52 mmol) was added to 3-(4-hydroxy-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-4-methylbenzonitrile (**Intermediate AM3**) (1.2 g, 4.78 mmol). The resulting solution was stirred at 100 °C for 4 hours. The reaction mixture was evaporated and then azetroped with toluene to remove any residual $POCl_3$. Ice/water was added and the formed precipitate was filtered washing well with water and dried overnight in vacuo over P_2O_5 to afford 3-(4-chloro-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-4-methylbenzonitrile (1.16g, 90%). ^{1}H NMR (400 MHz, DMSO) 2.21 (3H, s), 7.73 (1H, d), 7.97 - 8.00 (1H, m), 8.06 (1H, d), 8.81 (1H, s), 8.91 (1H, s); HPLC t_R = 2.05 min.

Intermediate AM3: 3-(4-hydroxy-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-4-methylbenzonitrile



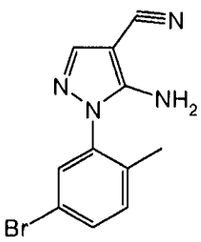
1-(5-Bromo-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol (**Intermediate AM4**) (1.38 g, 4.52 mmol), and zinc cyanide (0.478 g, 4.07 mmol) were dissolved in DMF (15 mL) and sealed into a microwave tube. The reaction mixture was evacuated and back flushed with nitrogen several times. 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (0.262 g, 0.45 mmol) and tris(dibenzylideneacetone)dipalladium(0) (0.207 g, 0.23 mmol) were added. The reaction was heated to 160 °C for 10 minutes in the microwave reactor and cooled to RT. The reaction mixture was diluted with EtOAc (100 mL) and water (50 mL) and then filtered. Solid was taken up in hot methanol, filtered and dried under vacuum to afford the product (0.99g , 89 %) which was used without further purification. ^{1}H NMR (400 MHz, DMSO) 2.19 (3H, s), 7.67 (1H, d), 7.92 - 7.96 (2H, m), 8.10 (1H, s), 8.35 (1H, s), 12.38 (1H, s); m/z (ES-) (M-H)- = 250; HPLC t_R = 1.23 min.

Intermediate AM4: 1-(5-bromo-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4(7H)-one



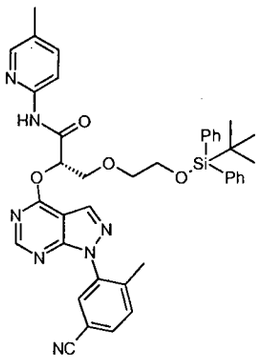
Concentrated sulfuric acid (1.160 mL, 21.76 mmol) was added to a stirred solution of 5-amino-1-(5-bromo-2-methylphenyl)-1H-pyrazole-4-carbonitrile (**Intermediate AM5**) (5.481 g, 19.78 mmol) in formic acid (35 mL). The resulting solution was stirred at 100 °C for 24 hours. The reaction was allowed to cool to room temperature and evaporated to approximately half the volume, water (50 mL) added and stirred for 1 hour. The formed precipitate was filtered off, washed well with water and dried overnight under vacuum over P_2O_5 to afford the product (4.47 g, 74.0 %). ^{1}H NMR (400 MHz, DMSO)2.05 (3H, s), 7.40 - 7.42 (1H, m), 7.63 - 7.67 (2H, m), 8.08 - 8.09 (1H, m), 8.32 (1H, s), 12.34 (1H, s); m/z (ES-) (M-H)- = 305, 303; HPLC t_R = 1.62 min.

Intermediate AM5: 5-amino-1-(5-bromo-2-methylphenyl)-1H-pyrazole-4-carbonitrile



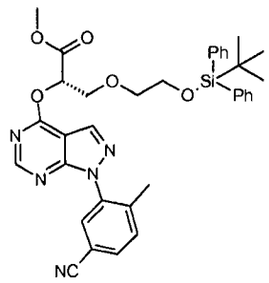
(5-Bromo-2-methylphenyl)hydrazine hydrochloride (CAS no. 214915-80-7) (5 g, 21.05 mmol) was partitioned between EtOAc (50 mL) and NaOH (2M, aq) (30 mL). The organic layer separated and washed with water (50 mL), brine (50 mL), dried ($MgSO_4$), filtered and concentrated to afford free base of the starting material. The resultant oil was suspended in MeOH (50 mL) under nitrogen at -5°C. 2-(ethoxymethylene)malononitrile (2.57 g, 21.05 mmol) added portionwise over 5 mins and the mixture stirred at ~0°C for 30 mins. The reaction mixture was allowed to warm to room temperature and then heated at reflux under nitrogen for 2 hours. The reaction mixture was allowed to cool and evaporated to dryness to afford the product (5.48 g, 94 %). ^{1}H NMR (400 MHz, DMSO) 1.99 (3H, s), 6.59 (2H, s), 7.36 (1H, d), 7.49 (1H, d), 7.60 - 7.63 (1H, m), 7.76 (1H, s); m/z (ES+) $(M+H)^+$ = 277+279; HPLC t_R = 2.01 min.

Intermediate AM6: (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(5-cyano-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-methylpyridin-2-yl)propanamide



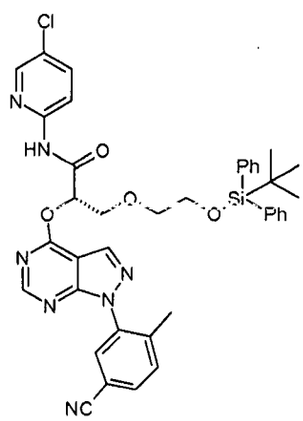
Trimethylaluminium (2M in toluene) (0.472 mL, 0.94 mmol) was added to a solution of 5-methylpyridin-2-amine (102 mg, 0.94 mmol) in toluene (10 mL) at 0°C under nitrogen in a microwave vial. The reaction mixture was stirred at 0°C for 20 mins and then (2S)-methyl 3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(5-cyano-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanoate (**Intermediate AM7**) (300 mg, 0.47 mmol) was added. The reaction mixture was allowed to warm to room temperature and then heated in the microwave at 120°C for 2 hours.The reaction mixture was allowed to cool to room temperature and the concentrated in vacuo. The residue was neutralised with citric acid (1M, aq) and then diluted with water and DCM (50 mL). The organic layer was separated and the aqueous layer re-extracted with DCM (30 mL). The combined organics were dried ($MgSO_4$), filtered and evaporated in vacuo.The crude product was purified by flash silica chromatography, elution gradient 20 to 50% Et2O in isohexane to afford the product (125 mg, 37.2 %). ^{1}H NMR (400 MHz, $CDCl_3$) 0.99 (9H, s), 2.27 (3H, s), 2.29 (3H, s), 3.69 - 3.72 (2H, m), 3.81 (2H, t), 4.16 - 4.24 (2H, m), 6.07 - 6.09 (1H, m), 7.16 - 7.41 (6H, m), 7.51 (1H, s), 7.53 (1H, s), 7.63 - 7.65 (4H, m), 7.68 - 7.72 (2H, m), 8.08 - 8.08 (1H, m), 8.14 (1H, d), 8.37 (1H, s), 8.57 (1H, s), 8.67 (1H, s); m/z (ES+) $(M+H)^+$ = 712.6; HPLC t_R = 3.65 min.

Intermediate AM7: (2S)-methyl 3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(5-cyano-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanoate



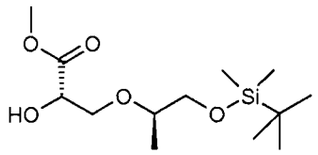
Sodium hydride (108 mg, 2.69 mmol) was added to (S)-methyl 3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-hydroxypropanoate (795 mg, 1.97 mmol) (**Intermediate AB3**) in anhydrous THF (20 mL) at 0°C under nitrogen. The resulting solution was stirred at 0°C for 10 minutes and then 3-(4-chloro-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-4-methylbenzonitrile (**Intermediate AM2**) (484 mg, 1.79 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour. The reaction mixture was neutralised with 1M citric acid and the reaction mixture diluted with water (10 mL) and EtOAc (30 mL). The organic layer was separated and the aqueous layer re-extracted with EtOAc (2 × 30 mL). The combined organics were washed with saturated brine (75 mL),dried ($MgSO_4$), filtered and concentrated in vacuo.The crude product was purified by flash silica chromatography, elution gradient 30 to 50% Et_2O in isohexane to afford the product (300 mg, 26.3 %). m/z (ES+) $(M+H)^+$ = 636.5; HPLC t_R = 3.65 min.

Intermediate AM8: (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-N-(5-chloropyridin-2-yl)-2-(1-(5-cyano-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide



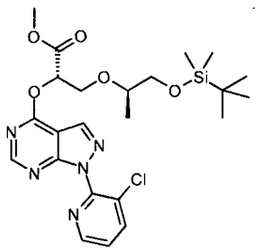
Prepared in an analogous fashion to **Intermediate AM6** using 5-chloropyridyl-2-amine. m/z (ES+) $(M+H)^+$ = 732.5; HPLC t_R = 3.77 min.

Intermediate AN1: (S)-Methyl 3-((R)-1-(tert-butyldimethylsilyloxy)propan-2-yloxy)-2-hydroxypropanoate



Magnesium trifluoromethanesulfonate (1.165 g, 3.61 mmol) was added in one portion to (S)-methyl oxirane-2-carboxylate (1.475 g, 14.45 mmol) and (R)-1-(tert-butyldimethylsilyloxy)propan-2-ol (CAS no. 136918-07-5) (2.75 g, 14.45 mmol) cooled to 10°C. The resulting suspension was stirred at 10°C for 10 minutes and then warmed to 45°C and stirred for 2 days. The crude product was purified by flash silica chromatography, eluting with 0 to 30% EtOAc in isohexane to afford the product (1.680 g, 39.8 %). ^{1}H NMR (400 MHz, DMSO) δ0.00 (s, 6H), 0.83 (s, 9H), 0.98 (d, 3H), 3.35 - 3.45 (m, 2H), 3.47 - 3.65 (m, 3H), 3.66 (s, 3H), 4.09 - 4.15 (m, 1H), 5.37 (d, 1H).

Intermediate AN2: (2S)-methyl 3-((R)-1-(tert-butyldimethylsilyloxy)propan-2-yloxy)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanoate

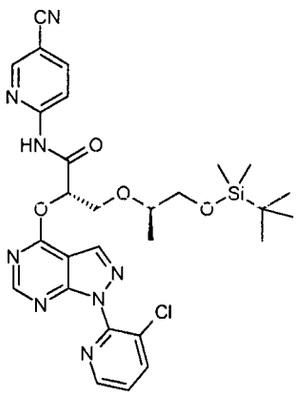


Sodium hydride (0.164 g, 4.10 mmol) was added to (S)-methyl 3-((R)-1-(tert-butyldimethylsilyloxy)propan-2-yloxy)-2-hydroxypropanoate (**Intermediate AN1**) (1 g, 3.42 mmol) in anhydrous THF (20 mL) at 0 °C under nitrogen. The resulting solution was stirred at 0 °C for 10 minutes and then 4-chloro-1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate B15**) (0.910 g, 3.42 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour. The reaction mixture was neutralised with 1M citric acid and the majority of the THF removed in vacuo. The reaction mixture was diluted with water (20 mL) and EtOAc (50 mL). The organic layer was separated and the aqueous layer re-extracted with EtOAc (2 × 50 mL). The combined

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organics were washed with saturated brine (25 mL), dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 40 to 70% EtOAc in isohexane to afford the product (0.911 g, 51.0%). ^{1}H NMR (400 MHz, DMSO) δ0.00 (d, 6H), 0.81 (s, 9H), 1.04 (d, 3H), 3.47 - 3.62 (m, 3H), 3.68 (s, 3H), 4.08 (d, 2H), 5.81 (t, 1H), 7.71 - 7.77 (m, 1H), 8.29 - 8.34 (m, 1H), 8.54 - 8.58 (m, 2H), 8.64 - 8.67 (m, 1H); m/z (ES+), $(M+H)^+$ = 522.50; HPLC t_R = 3.38 min

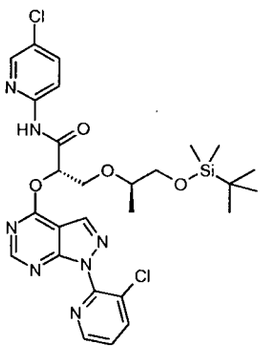
Intermediate AN3: (2S)-3-((R)-1-(tert-butyldimethylsilyloxy)propan-2-yloxy)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-cyanopyridin-2-yl)propanamide



Trimethylaluminium (2M in hexanes) (1.839 mL, 3.68 mmol) was added to 6-aminonicotinonitrile (CAS no. 4214-73-7) (411 mg, 3.45 mmol) in DCM (8 mL) cooled to 0 °C under nitrogen. The resulting solution was stirred at 0°C for 20 minutes. (2S)-methyl 3-((R)-1-(tert-butyldimethylsilyloxy)propan-2-yloxy)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanoate (**Intermediate AN2**) (600 mg, 1.15 mmol) in toluene (8 mL) was added and the reaction was allowed to warm to room temperature and then heated to 100°C for 5 hours in the microwave reactor. The reaction was allowed to cool to room temperature before adding EtOAc (50 mL) and 20% sodium potassium tartrate solution (30 mL), which was stirred vigorously for 16 hours. The phases were separated and the organic layer was washed with sat. brine (15 mL), dried ($MgSO_4$) and evaporated. The crude product was purified by flash alumina chromatography, eluting with 0 to 50% EtOAc in isohexane to afford the product (395 mg, 56.4 %). ^{1}H NMR (400 MHz, DMSO) δ-0.01 (d, 6H), 0.80 (s, 9H), 1.08 (d, 3H), 3.47 - 3.62 (m, 2H), 3.67 - 3.77 (m, 1H), 4.09 - 4.21 (m, 2H), 5.92 - 5.97 (m, 1H), 7.75 - 7.80 (m, 1H), 8.13 - 8.17 (m, 1H), 8.22 -

8.29 (m, 1H), 8.34 - 8.37 (m, 1H), 8.58 (s, 1H), 8.63 (s, 1H), 8.67 - 8.71 (m, 1H), 8.83 - 8.85 (m, 1H), 11.55 (s, 1H); m/z (ES+), $(M+H)^+$ = 607.47; HPLC t_R = 3.27 min

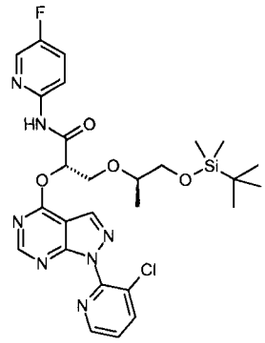
Intermediate AN4: (2S)-3-((R)-1-(tert-butyldimethylsilyloxy)propan-2-yloxy)-N-(5-chloropyridin-2-yl)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide



Trimethylaluminium (2M in Hexanes) (0.551 mL, 1.10 mmol) was added to 5-chloropyridin-2-amine (135 mg, 1.05 mmol) in toluene (5 mL) cooled to 0 °C under nitrogen. The resulting solution was stirred at 0°C for 20 minutes. (2S)-methyl 3-((R)-1-(tert-butyldimethylsilyloxy)propan-2-yloxy)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanoate (**Intermediate AN2**) (500 mg, 0.96 mmol) in toluene (5 mL) was added and the reaction was allowed to warm to room temperature and then heated to 100°C for 5 hours in the microwave reactor. The reaction was allowed to cool to room temperature before adding EtOAc (50 mL) and 20% sodium potassium tartrate solution (30 mL), which was stirred vigorously for 16 hours. The phases were separated and the organic layer was washed with sat. brine (15 mL), dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 30 to 50% EtOAc in isohexane afford the product (460 mg, 78 %). ^{1}H NMR (400 MHz, DMSO) δ-0.01 (d, 6H), 0.80 (s, 9H), 1.08 (d, 3H), 3.47 - 3.63 (m, 2H), 3.67 - 3.76 (m, 1H), 4.07 - 4.19 (m, 2H), 5.89 - 5.96 (m, 1H), 7.75 - 7.80 (m, 1H), 7.89 - 7.94 (m, 1H), 8.02 - 8.07 (m, 1H), 8.33 - 8.37 (m, 1H), 8.41 - 8.43 (m, 1H), 8.58 (s, 1H), 8.63 (s, 1H), 8.67 - 8.72 (m, 1H), 11.18 (s, 1H); m/z (ES+), $(M+H)^+$ = 618.44; HPLC t_R = 3.53 min

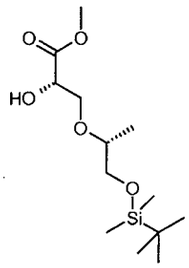
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Intermediate AN5: (2S)-3-((R)-1-(tert-butyldimethylsilyloxy)propan-2-yloxy)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-fluoropyridin-2-yl)propanamide



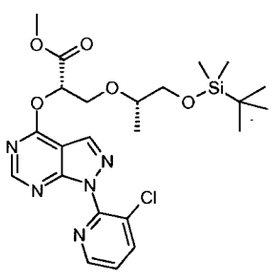
Trimethylaluminium (2M in hexane)(0.474 mL, 0.95 mmol) was added to 5-fluoropyridin-2-amine (102 mg, 0.91 mmol) in toluene (7 mL) cooled to 0 °C under nitrogen. The resulting solution was stirred at 0°C for 20 minutes. (2S)-Methyl 3-((R)-1-(tert-butyldimethylsilyloxy)propan-2-yloxy)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanoate (**Intermediate AN2**) (430 mg, 0.82 mmol) in toluene (7 mL) was added and the reaction was allowed to warm to room temperature and then heated to 100°C for 5 hours in the microwave reactor. The reaction was allowed to cool to room temperature before adding EtOAc (30 mL) and 20% sodium potassium tartrate solution (30 mL), which was stirred vigorously for 16 hours. The phases were separated and the organic layer was washed with sat. brine (15 mL), dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 30 to 50% EtOAc in isohexane to give (2S)-3-((R)-1-(tert-butyldimethylsilyloxy)propan-2-yloxy)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-fluoropyridin-2-yl)propanamide (303 mg, 61.1 %). ^{1}H NMR (400 MHz, DMSO) δ-0.01 (d, 6H), 0.80 (s, 9H), 1.09 (d, 3H), 3.46 - 3.63 (m, 2H), 3.67 - 3.77 (m, 1H), 4.07 - 4.20 (m, 2H), 5.90 - 5.95 (m, 1H), 7.71 - 7.80 (m, 2H), 8.02 - 8.08 (m, 1H), 8.33 - 8.39 (m, 2H), 8.58 (s, 1H), 8.63 (s, 1H), 8.67 - 8.71 (m, 1H), 11.09 (s, 1H); m/z (ES+), $(M+H)^+$ = 602.48; HPLC t_R = 3.33 min

Intermediate AO1: (S)-Methyl 3-((S)-1-(tert-butyldimethylsilyloxy)propan-2-yloxy)-2-hydroxypropanoate



Magnesium trifluoromethanesulfonate (0.974 g, 3.02 mmol) was added in one portion to (S)-methyl oxirane-2-carboxylate (1.234 g, 12.08 mmol) and (S)-1-(tert-butyldimethylsilyloxy)propan-2-ol (CAS no. 113534-13-7) (2.30 g, 12.08 mmol) in EtOAc (5 mL) cooled to 10°C. The resulting suspension was stirred at 10°C for 10 minutes and then warmed to 45°C and stirred for 2 days. The crude product was purified by flash silica chromatography, eluting with 0 to 30% EtOAc in isohexane to afford the product (1.336 g, 37.8 %). ^{1}H NMR (400 MHz, DMSO) δ0.00 (s, 6H), 0.83 (s, 9H), 0.98 (d, 3H), 3.34 - 3.53 (m, 3H), 3.55 - 3.64 (m, 5H), 4.11 (q, 1H), 5.39 (d, 1H)

Intermediate AO2: (2S)-methyl 3-((S)-1-(tert-butyldimethylsilyloxy)propan-2-yloxy)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanoate

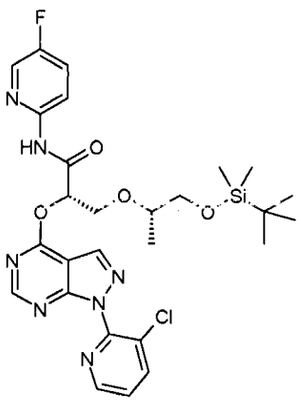


Sodium hydride (0.219 g, 5.48 mmol) was added to (S)-methyl 3-((S)-1-(tert-butyldimethylsilyloxy)propan-2-yloxy)-2-hydroxypropanoate (**Intermediate AO1**) (1.336 g, 4.57 mmol) in anhydrous THF (30 mL) at 0 °C under nitrogen. The resulting solution was stirred at 0 °C for 10 minutes and then 4-chloro-1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (1.216 g, 4.57 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour. The reaction mixture was neutralised with 1M citric acid and the majority of the THF removed in vacuo. The reaction mixture was diluted with water (20 mL) and EtOAc (50 mL). The organic layer was separated and the aqueous layer re-extracted with EtOAc (2 × 50 mL). The combined

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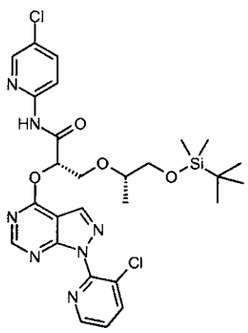
organics were washed with saturated brine (25 mL), dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 30 to 60% EtOAc in isohexane to give (2S)-methyl 3-((S)-1-(tert-butyldimethylsilyloxy)propan-2-yloxy)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanoate (1.658g, 69.5%). m/z (ES+), $(M+H)^+$ = 522.50; HPLC t_R = 3.35 min

Intermediate AO3: (2S)-3-((S)-1-(tert-butyldimethylsilyloxy)propan-2-yloxy)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-fluoropyridin-2-yl)propanamide



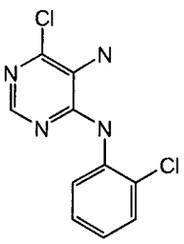
Trimethylaluminium (2M in hexanes)(0.608 mL, 1.22 mmol) was added to 5-fluoropyridin-2-amine (130 mg, 1.16 mmol) in toluene (8 mL) cooled to 0 °C under nitrogen. The resulting solution was stirred at 0°C for 20 minutes. (2S)-methyl 3-((S)-1-(tert-butyldimethylsilyloxy)propan-2-yloxy)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanoate (**Intermediate AO2**) (552 mg, 1.06 mmol) in toluene (8 mL) was added and the reaction was heated to 100°C for 5 hours in the microwave reactor. The reaction was allowed to cool to room temperature before adding EtOAc (30 mL) and 20% sodium potassium tartrate solution (30 mL), which was stirred vigorously for 16 hours. The phases were separated and the organic layer was washed with sat. brine (15 mL), dried ($MgSO_4$) and evaporated to afford the product (638 mg, 100 %) which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (d, 6H), 0.87 (s, 9H), 1.17 (d, 3H), 3.51 - 3.58 (m, 1H), 3.60 - 3.69 (m, 2H), 4.18 - 4.22 (m, 2H), 6.00 (t, 1H), 7.40 - 7.49 (m, 2H), 7.98 - 8.03 (m, 1H), 8.13 (d, 1H), 8.22 - 8.28 (m, 1H), 8.44 (s, 1H), 8.60 - 8.64 (m, 2H), 8.94 (s, 1H); m/z (ES+), $(M+H)^+$ = 602.55; HPLC t_R = 3.35 min

Intermediate AO4: (2S)-3-((S)-1-(tert-butyldimethylsilyloxy)propan-2-yloxy)-N-(5-chloropyridin-2-yl)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide



Trimethylaluminium (2M in hexanes)(0.551 mL, 1.10 mmol) was added to 5-chloropyridin-2-amine (135 mg, 1.05 mmol) in toluene (8 mL) cooled to 0 °C under nitrogen. The resulting solution was stirred at 0°C for 20 minutes. (2S)-methyl 3-((S)-1-(tert-butyldimethylsilyloxy)propan-2-yloxy)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanoate (**Intermediate AO2**) (500 mg, 0.96 mmol) in toluene (8 mL) was added and the reaction was heated to 100°C for 5 hours in the microwave reactor. The reaction was allowed to cool to room temperature before adding EtOAc (30 mL) and 20% sodium potassium tartrate solution (30 mL), which was stirred vigorously for 16 hours. The phases were separated and the organic layer was washed with sat. brine (15 mL), dried ($MgSO_4$) and evaporated to give crude product (300 mg) that was used without further purification. m/z (ES+), $(M+H)^+ = 618.44$; HPLC t_R = 23.55 min

Intermediate AP1: 6-chloro-N4-(2-chlorophenyl)pyrimidine-4,5-diamine

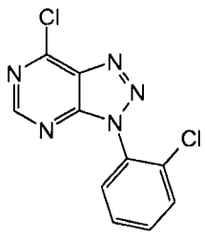


4,6-Dichloropyrimidin-5-amine (CAS no. 5413-85-4) (2 g, 12.20 mmol) and 2-chloroaniline (CAS no. 95-51-2) (1.556 g, 12.20 mmol) were dissolved in ethylene glycol (12 mL) and sealed into a microwave tube. The reaction was heated to 100°C for 1 hour in the microwave reactor and cooled to room temperature. The reaction mixture was quenched with water (50 mL), extracted with EtOAc (3 × 50 mL), the organic layer was

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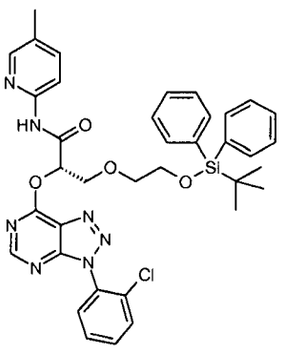
dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, eluting with 0 to 60% EtOAc in isohexane to afford the product (2.65 g, 85 %). ^1H NMR (400 MHz, DMSO) δ5.38 (s, 2H), 7.19 - 7.25 (m, 1H), 7.32 - 7.38 (m, 1H), 7.49 - 7.54 (m, 1H), 7.57 - 7.62 (m, 1H), 7.73 (s, 1H), 8.38 (s, 1H); m/z (ES+), $(M+H)^+$ = 255.25; HPLC t_R = 1.82 min.

Intermediate AP2: 7-chloro-3-(2-chlorophenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidine



Sodium nitrite (0.298 g, 4.31 mmol) was added to 6-chloro-N4-(2-chlorophenyl)pyrimidine-4,5-diamine (**Intermediate AP1**) (1 g, 3.92 mmol) in acetic acid (50%Aq, 25 mL) and DCM (25 mL) at room temperature. The resulting solution was stirred at room temperature for 15 minutes. The reaction mixture was separated and the organic phase was washed with water (10 mL), dried ($MgSO_4$) and evaporated to give crude product (0.600 g) that was used without further purification. ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 - 7.65 (m, 3H), 7.68 - 7.73 (m, 1H), 8.97 (s, 1H); m/z (ES+), $(M+H)^+$ = 266.21; HPLC t_R = 2.33 min

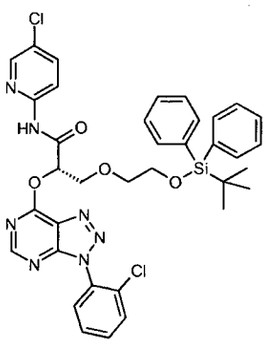
Intermediate AP3: (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(3-(2-chlorophenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy)-N-(5-chloropyridin-2-yl)propanamide



Sodium hydride (50.1 mg, 1.25 mmol) was added to (S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-hydroxy-N-(5-methylpyridin-2-yl)propanamide (**Intermediate AU2**) (250 mg, 0.52 mmol) in anhydrous THF (5 mL) at 0 °C under

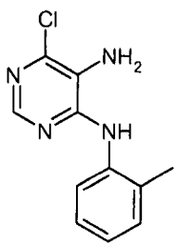
nitrogen. The resulting solution was stirred at 0 °C for 10 minutes and then 7-chloro-3-(2-chlorophenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidine (**Intermediate AP2**) (278 mg, 1.04 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour. The reaction mixture was neutralised with 1M citric acid and the majority of the THF removed in vacuo. The reaction mixture was diluted with water (20 mL) and EtOAc (50 mL). The organic layer was separated and the aqueous layer re-extracted with EtOAc (2 × 50 mL). The combined organics were washed with saturated brine (15 mL), dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 0 to 50% EtOAc in isohexane to give (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(3-(2-chlorophenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy)-N-(5-methylpyridin-2-yl)propanamide (335 mg, 91 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ0.97 (s, 9H), 2.28 (s, 3H), 3.67 - 3.84 (m, 4H), 4.26 (d, 2H), 6.15 (t, 1H), 7.30 - 7.41 (m, 5H), 7.48 - 7.71 (m, 10H), 8.06 - 8.14 (m, 2H), 8.68 (s, 1H), 8.76 (s, 1H); m/z (ES+), $(M+H)^+$ = 708.65; HPLC t_R = 3.84 min

Intermediate AP4: (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(3-(2-chlorophenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy)-N-(5-chloropyridin-2-yl)propanamide



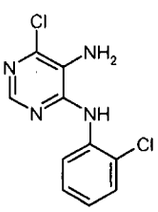
Sodium hydride (38.5 mg, 0.96 mmol) was added to (S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-N-(5-chloropyridin-2-yl)-2-hydroxypropanamide (**Intermediate AU3**) (200 mg, 0.40 mmol) in anhydrous THF (5 mL) at 0 °C under nitrogen. The resulting solution was stirred at 0 °C for 10 minutes and then 7-chloro-3-(2-chlorophenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidine (**Intermediate AP2**) (107 mg, 0.40 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour. The reaction mixture was neutralised with 1M citric acid and the majority of the THF removed in vacuo. The reaction mixture was diluted with water (20

mL) and EtOAc (50 mL). The organic layer was separated and the aqueous layer re-extracted with EtOAc (2 × 50 mL). The combined organics were washed with saturated brine (25 mL), dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 0 to 50% EtOAc in isohexane to give (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(3-(2-chlorophenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy)-N-(5-chloropyridin-2-yl)propanamide (290 mg, 99 %). m/z (ES+), $(M+H)^+$ = 728.38 : HPLC t_R = 3.91 min**Intermediate AP5: 6-chloro-N4-o-tolylpyrimidine-4,5-diamine**



4,6-dichloropyrimidin-5-amine (2 g, 12.20 mmol) and o-toluidine (1.309 mL, 12.20 mmol) were dissolved in ethylene glycol (10 mL) and sealed into a microwave tube. The reaction was heated to 100°C for 1 hour in the microwave reactor and cooled to room temperature. The reaction mixture was quenched with water (20 mL), extracted with EtOAc (3 x 20 mL), the organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, eluting with 0 to 50% EtOAc in isohexane to afford the product (2.300 g, 80 %). ^{1}H NMR (400 MHz, DMSO) δ2.15 (s, 3H), 5.28 (s, 2H), 7.08 - 7.33 (m, 4H), 7.68 (s, 1H), 8.18 (s, 1H); m/z (ES+), $(M+H)^+$ = 235.34; HPLC t_R = 1.54 min.

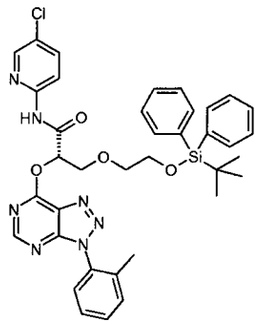
Intermediate AP6: 7-chloro-3-o-tolyl-3H-[1,2,3]triazolo[4,5-d]pyrimidine



Sodium nitrite (0.323 g, 4.69 mmol) was added to 6-chloro-N4-o-tolylpyrimidine-4,5-diamine (**Intermediate AP5**)(1 g, 4.26 mmol) in acetic acid (50%Aq) (25 mL)and DCM (25 mL) at room temperature. The resulting solution was stirred at room temperature for 15 minutes. The reaction mixture was separated and the organic phase was washed with

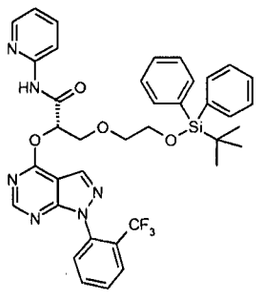
water (10 mL), dried ($MgSO_4$) and evaporated to give crude 7-chloro-3-o-tolyl-3H-[1,2,3]triazolo[4,5-d]pyrimidine (0.980 g, 94 %) that was used without further purification. ^1H NMR (400 MHz, $CDCl_3$) δ2.19 (s, 3H), 7.42 - 7.57 (m, 4H), 8.95 (s, 1H) m/z (ES+), $(M+H)^+$ = 246.29; HPLC t_R = 2.28 min

Intermediate AP7: (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-N-(5-chloropyridin-2-yl)-2-(3-o-tolyl-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy)propanamide



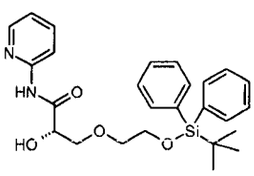
Sodium hydride (57.7 mg, 1.44 mmol) was added to (S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-N-(5-chloropyridin-2-yl)-2-hydroxypropanamide (**Intermediate AU3**) (300 mg, 0.60 mmol) in anhydrous THF (7 ml) at 0 °C under nitrogen. The resulting solution was stirred at 0 °C for 10 minutes and then 7-chloro-3-o-tolyl-3H-[1,2,3]triazolo[4,5-d]pyrimidine (148 mg, 0.60 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour. The reaction mixture was neutralised with 1M citric acid and the majority of the THF removed in vacuo. The reaction mixture was diluted with water (20 mL) and EtOAc (50 mL). The organic layer was separated and the aqueous layer re-extracted with EtOAc (2 x 50 mL). The combined organics were washed with saturated brine (15 mL), dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 0 to 50% EtOAc in isohexane to give (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-N-(5-chloropyridin-2-yl)-2-(3-o-tolyl-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yloxy)propanamide (410 mg, 100 %). ^1H NMR (400 MHz, $CDCl_3$) δ0.97 (s, 9H), 2.19 (s, 3H), 3.67 - 3.85 (m, 4H), 4.26 (d, 2H), 6.14 (t, 1H), 7.31 - 7.54 (m, 10H), 7.60 - 7.68 (m, 5H), 8.18 - 8.23 (m, 2H), 8.66 (s, 1H), 8.91 (s, 1H); m/z (ES+), $(M+H)^+$ = 708.61; HPLC t_R = 4.02 min

Intermediate AQ1: (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-N-(pyridin-2-yl)-2-(1-(2-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide



Sodium hydride (117 mg, 2.93 mmol) was added to (S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-hydroxy-N-(pyridin-2-yl)propanamide (618mg, 1.33 mmol) (Intermediate AQ2) in anhydrous THF (20 mL) at 0 °C under nitrogen. The resulting solution was stirred at 0 °C for 10 minutes and then 4-chloro-1- (2-(trifluoromethyl) phenyl)-1H-pyrazolo[3,4-d] pyrimidine (514 mg, 1.46 mmol) (Intermediate B4) was added. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour. The reaction mixture was neutralised with 1M citric acid and the majority of the THF removed in vacuo. The reaction mixture was diluted with water (20 mL) and EtOAc (50 mL). The organic layer was separated and the aqueous layer re-extracted with EtOAc (2 x 100 mL). The combined organics were washed with saturated brine (75 mL), dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 50 to 100% EtOAc in isohexane to afford the product (919 mg, 95 %). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 0.99 (9H, t), 3.70 - 3.72 (2H, m), 3.82 (2H, t), 4.16 - 4.25 (2H, m), 6.05 - 6.07 (1H, m), 7.04 - 7.07 (1H, m), 7.31 - 7.75 (14H, m), 7.89 - 7.92 (1H, m), 8.24 - 8.28 (2H, m), 8.36 (1H, s), 8.55 (1H, s), 8.73 (1H, s); m/z (ES+) $(M+H)^+$ = 279.1; HPLC Rt= 3.71 min.

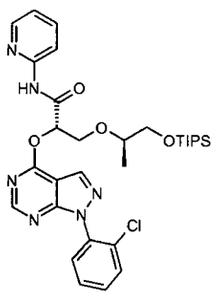
Intermediate AQ2: (S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-hydroxy-N-(pyridin-2-yl)propanamide



Trimethylaluminium (3.73 mL, 7.45 mmol) was added to pyridin-2-amine (0.701 g, 7.45 mmol) in toluene (6 ml) cooled to 0 °C under nitrogen. The resulting solution was stirred at

0°C for 20 minutes. (S)-methyl 3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-hydroxypropanoate (1.5 g, 3.73 mmol) (**Intermediate AB3**) in toluene (6 ml) was added and the reaction was allowed to warm to room temperature and then heated to 110 for 5 hours in a microwave. The reaction mixture was allowed to cool and concentrated in vacuo. The residue was neutralised with citric acid (1M, aq) and then diluted with water (25mL) and extracted with EtOAc (2 x 50 mL). The combined organics were washed with brine (20ml), then dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, eluting with 30 to 50% EtOAc in isohexane to afford the product (1.085 g, 62.7 %). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 1.05 (9H, t), 3.60 - 3.66 (2H, m), 3.67 (1H, d), 3.82-3.84 (2H d, *m*), 3.80 - 3.85 (2H, m), 4.33 - 4.35 (1H, m), 7.03 - 7.06 (1H, m), 7.35 - 7.68 (10H, m), 7.70 (1H, d), 8.22 (1H, d), 8.29 - 8.30 (1H, m),9.15 (1H,s); m/z (ES+) $(M+H)^+$ = 465.42; HPLC t_R = 3.13 min.

Intermediate AQ3: (2S)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(pyridin-2-yl)-3-((R)-1-(triisopropylsilyloxy)propan-2-yloxy)propanamide

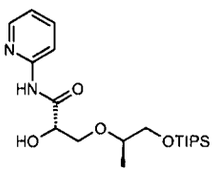


Sodium hydride (78 mg, 1.95 mmol) was added to (S)-2-hydroxy-N-(pyridin-2-yl)-3-((R)-1-(triisopropylsilyloxy)propan-2-yloxy)propanamide (**Intermediate AQ4**) (387 mg, 0.98 mmol) in anhydrous THF (20 mL). The resulting solution was stirred at 0 °C for 10 minutes and then 4-chloro-1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate B1**) (250 mg, 0.89 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour. The reaction mixture was neutralised with 1M citric acid and the majority of the THF removed in vacuo. The reaction mixture was diluted with water (20 mL) and EtOAc (50 mL). The organic layer was separated and the aqueous layer re-extracted with EtOAc (2 x 100 mL). The combined organics were washed with saturated brine (75 mL), dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 50 to 100% EtOAc in isohexane to afford the product (329 mg, 59.4 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 - 1.15 (24H,

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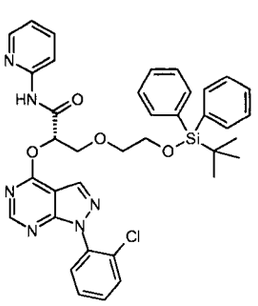
m), 3.55 - 3.78 (3H, m), 4.19 - 4.35 (2H, m), 6.03 (1H, t), 7.05 (1H, t) 7.40 - 7.65 (4H, m), 7.7 (1H, t), 8.2- 8.3 (2H, m), 8.43 (1H, s), 8.58 (1H, s), 8.75 (1H, s); m/z (ES+) M+ = 625.44; HPLC t_R = 4.02 min.

Intermediate AQ4: (S)-2-hydroxy-N-(pyridin-2-yl)-3-((R)-1-(triisopropylsilyloxy)propan-2-yloxy)propanamide



Trimethylaluminium (2M in toluene) (2.99 ml, 5.98 mmol) was added to pyridin-2-amine (0.563 g, 5.98 mmol) in toluene (20.18 ml) cooled to 0 °C under nitrogen. The resulting solution was stirred at 0°C for 20 minutes. (S)-methyl 2-hydroxy-3-((R)-1-(triisopropylsilyloxy)propan-2-yloxy)propanoate (1 g, 2.99 mmol) (**Intermediate AN1**) in toluene (6.73 mL) was added and the reaction was allowed to warm to room temperature and then heated at reflux for 5 hours. The reaction mixture was allowed to cool and concentrated in vacuo. The residue was neutralised with citric acid (1M, aq) and then diluted with water (25mL) and extracted with EtOAc (2 × 50 mL). The combined organics were washed with brine (20ml), then dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 30 to 50% EtOAc in isohexane to afford the product (0.657 g, 55.4 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 - 1.17 (24H, m), 3.61 - 3.69 (3H, m), 3.82 - 3.86 (1H, m), 4.00 - 4.04 (1H, m), 4.13 (1H, d), 4.32 (1H, q), 7.02 - 7.06 (1H, m), 7.67 - 7.72 (1H, m), 8.23 (1H, d), 8.29 - 8.31 (1H, m), 9.20 (1H, s); m/z (ES+) $(M+H)^+$ = 397.44; HPLC t_R = 3.36 min.

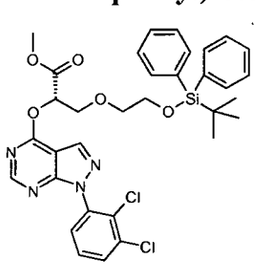
Intermediate AQ5: (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(pyridin-2-yl)propanamide



Sodium hydride (91 mg, 2.27 mmol) was added to (S)-3-(2-(tert-

butyldiphenylsilyloxy)ethoxy)-2-hydroxy-N-(pyridin-2-yl)propanamide (**Intermediate AQ4**) (480 mg, 1.03 mmol) (intermediate 3) in anhydrous THF (20 mL) at 0 °C under nitrogen. The resulting solution was stirred at 0 °C for 10 minutes and then 4-chloro-1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate B1**) (320 mg, 1.14 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour. The reaction mixture was neutralised with 1M citric acid and the majority of the THF removed in vacuo. The reaction mixture was diluted with water (20 mL) and EtOAc (50 mL). The organic layer was separated and the aqueous layer re-extracted with EtOAc (2 x 100 mL). The combined organics were washed with saturated brine (75 mL), dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 50 to 100% EtOAc in isohexane to afford the product (682 mg, 95 %). ^1H NMR: (400 MHz, $CDCl_3$) δ 0.98 - 1.00 (9H, m), 3.69 - 3.72 (2H, m), 3.81 (2H, t), 4.16 - 4.25 (2H, m), 6.06 - 6.09 (1H, m), 7.04 - 7.07 (1H, m), 7.31 - 7.66 (14H, m), 7.68 - 7.73 (1H, m), 8.24 - 8.28 (2H, m), 8.38 (1H, s), 8.58 (1H, s), 8.75 (1H, s); m/z (ES+) M+ = 693.61; HPLC t_R = 3.79 min.

Intermediate AR1: (2S)-Methyl 3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(2,3-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanoate

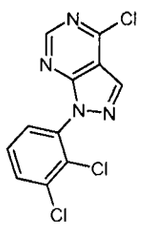


Sodium hydride (0.167 g, 4.17 mmol) was added to (S)-methyl 3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-hydroxypropanoate (**Intermediate AB3**) (1.4 g, 3.48 mmol) in anhydrous THF (25 ml) at 0 °C under nitrogen. The resulting solution was stirred at 0 °C for 10 minutes and then 4-chloro-1-(2,3-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate AR2**) (1.432 g, 3.83 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour. The reaction mixture was neutralised with 1M citric acid and the majority of the THF removed in vacuo. The reaction mixture was diluted with water (20 mL) and EtOAc (50 mL). The organic layer was separated and the aqueous layer re-extracted with EtOAc (2 x 100 mL). The combined organics were washed with saturated brine (75 mL), dried ($MgSO_4$) and evaporated. The

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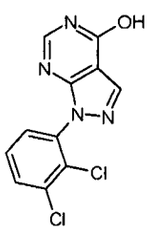
crude product was purified by flash silica chromatography, eluting with 50 to 100% EtOAc in isohexane. Fractions containing the product were evaporated to dryness to afford crude product which unfortunately was contaminated with starting alcohol and Methyl glycidate. The crude product was repurified by flash silica chromatography, elution gradient 0 to 30% EtOAc in toluene to afford the product (0.860 g, 37.1 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (9H, s), 3.80 – 3.69 (5H, m), 3.85 (2H, t), 4.15 – 4.08 (1H, m), 4.20 (1H, dd), 5.87 (1H, dd), 7.48 – 7.33 (8H, m), 7.75 – 7.60 (5H, m), 8.32 (1H, s), 8.54 (1H, s). m/z (ES+) $(M+H)^+$ = 667; HPLC t_R = 3.8 min.

Intermediate AR2: 4-chloro-1-(2,3-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine



Phosphorus oxychloride (26.5 ml, 284.60 mmol) was added to 1-(2,3-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol (**Intermediate AR3**) (4 g, 14.23 mmol), at ambient temperature. The resulting mixture was stirred at 100 °C for 4 hours. Allowed to cool to Ambient temperature. The reaction mixture was evaporated to near dryness, dissolved in toluene, evaporated, re-dissolved in toluene and evaporated to dryness again. The solid was triturated with EtOH. A solid was filtered off and dried under vacuum to give the product (2.450 g, 57.5 %). ^{1}H NMR (400 MHz, DMSO) δ 7.65 (1H, m), 7.73 - 7.75 (1H, dd), 7.94 - 7.97 (1H, dd), 8.83 (1H, s), 8.91 (1H, s); m/z (ES+) $(M+H)^+$ = 518; HPLC t_R = 1.89 min.

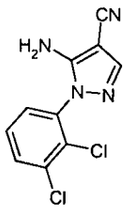
Intermediate AR3: 1-(2,3-Dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol



Concentrated sulfuric acid (1.666 mL, 31.25 mmol) in was added to a stirred solution of 5-amino-1-(2,3-dichlorophenyl)-1H-pyrazole-4-carbonitrile (**Intermediate AR4**) (7.19 g, 28.41 mmol) in formic acid (40 mL). The resulting solution was stirred at 100 °C for 16 hours. Allowed to cool to ambient temperature. The reaction mixture was evaporated to dryness. The residue was triturated under water. A solid was filtered off and dried under

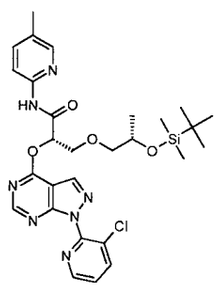
vacuum to give the product (6.64 g, 83 %). ^{1}H NMR (400 MHz, DMSO) δ 7.57 - 7.61 (1H, m), 7.63 - 7.66 (1H, m), 7.88 - 7.91 (1H, dd), 8.09 (1H, d), 8.36 (1H, s), 12.40 (1H, s); m/z (ES+) $(M+H)^+$ = 281; HPLC t_R = 1.61 min.

Intermediate AR4: 5-amino-1-(2,3-dichlorophenyl)-1H-pyrazole-4-carbonitrile



(2,3-Dichlorophenyl)hydrazine hydrochloride (CAS no. 21938-47-6) (6.06 g, 28.4 mmol) was partitioned between EtOAc and 2M NaOH. Separared. The organic solution was dried ($MgSO_4$), filtered and reduced to give the free base. 2-(Ethoxymethylene)malononitrile (3.47 g, 28.39 mmol) was added portionwise to a stirred solution of (2,3-dichlorophenyl)hydrazine in MeOH (50 mL), under nitrogen at 5°C. The resulting solution was allowed to stir for a further 1 hour. The reaction mixture was then heated to reflux and was stirred for 3 hours. The reaction mixture was allowed to cool to ambient temperature, then was evaporated to afford the product (7.19 g, 100 %) which was used without further purification. ^{1}H NMR (400 MHz, DMSO) δ 6.75 (2H, s), 7.48 - 7.53 (2H, m), 7.77 (1H, s), 7.79 - 7.84 (1H, m).

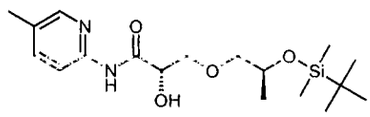
Intermediate AS1: (2S)-3-((S)-2-(tert-butyldimethylsilyloxy)propoxy)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-methylpyridin-2-yl)propanamide



Sodium hydride (134 mg, 3.36 mmol) was added to (S)-3-((S)-2-(tert-butyldimethylsilyloxy)propoxy)-2-hydroxy-N-(5-methylpyridin-2-yl)propanamide (**Intermediate AS2**) (495 mg, 1.34 mmol) in anhydrous THF (5 mL) at 0 °C under nitrogen. The resulting solution was stirred at 0 °C for 10 minutes and then 4-chloro-1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate B15**) (393 mg, 1.48

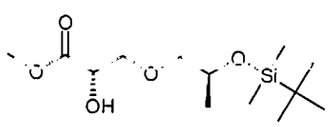
mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours. The reaction mixture was neutralised with 1M citric acid and diluted with water and EtOAc. The organic layer was separated and washed with saturated brine, dried ($MgSO_4$) and evaporated to give (2S)-3-((S)-2-(tert-butyldimethylsilyloxy)propoxy)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-methylpyridin-2-yl)propanamide (843 mg, 105 %). m/z (ES+) $(M+H)^+$ = 598.58; HPLC t_R = 3.36 min.

Intermediate AS2: (S)-3-((S)-2-(tert-Butyldimethylsilyloxy)propoxy)-2-hydroxy-N-(5-methylpyridin-2-yl)propanamide



Trimethylaluminium (1.966 mL, 3.93 mmol) was added slowly to 5-methylpyridin-2-amine (0.407 g, 3.76 mmol) in toluene (20 mL) cooled to 0 °C under nitrogen. The resulting solution was stirred at 0°C for 10 minutes. (S)-methyl 3-((S)-2-(tert-butyldimethylsilyloxy)propoxy)-2-hydroxypropanoate (**Intermediate AS3**) (1 g, 3.42 mmol) in toluene (4 mL) was added and the reaction was allowed to warm to room temperature and then heated at reflux for 4 hours (a further 5ml toluene was added to aid stirring). The reaction mixture was concentrated in vacuo. The residue was neutralised with citric acid (1M, aq) and then diluted with water and extracted with EtOAc. The combined organics were dried ($MgSO_4$) and evaporated to afford the product (0.994 g) which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07 (6H, d), 0.88 (9H, s), 1.15 (3H, d), 2.30 (3H, s), 2.79 - 3.11 (1H, m), 3.39 - 3.51 (2H, m), 3.80 - 3.91 (2H, m), 3.94 - 4.03 (1H, m), 4.31 - 4.36 (1H, m), 7.49 - 7.56 (1H, m), 8.09 - 8.16 (2H, m), 9.20 (1H, s); m/z (ES+) $(M+H)^+$ = 369.52; HPLC t_R = 2.73 min.

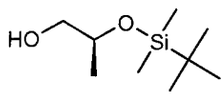
Intermediate AS3: (S)-Methyl 3-((S)-2-(tert-butyldimethylsilyloxy)propoxy)-2-hydroxypropanoate



Magnesium trifluoromethanesulfonate (1.779 g, 5.52 mmol) was added in one portion to (S)-2-(tert-butyldimethylsilyloxy)propan-1-ol (**Intermediate AS4**) (4.2 g, 22.06 mmol) and (S)-methyl oxirane-2-carboxylate (2.252 g, 22.06 mmol) in EtOAc (25 mL). The resulting suspension was stirred at 80 °C for 24 hours. A further 1.5g of the oxirane was

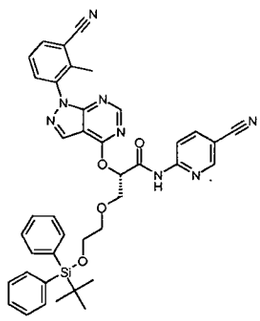
added and the reaction stirred for 4 days. The reaction mixture was diluted with EtOAc, filtered through celite and evaporated to dryness. The crude product was purified by flash silica chromatography, elution gradient 0 to 30% EtOAc in isohexane to afford the product (2.70 g, 41.8 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (6H, d), 0.82 (9H, s), 1.06 (3H, d), 3.04 (1H, d), 3.25 - 3.39 (2H, m), 3.65 - 3.78 (5H, m), 3.83 - 3.92 (1H, m), 4.19 - 4.27 (1H, m)

Intermediate AS4: (S)-2-(tert-butyldimethylsilyloxy)propan-1-ol



Diisobutylaluminum hydride (1M in DCM) (41.4 mL, 41.42 mmol) was added dropwise to a stirred solution of (S)-ethyl 2-(tert-butyldimethylsilyloxy)propanoate (CAS no. 106513-42-2) (5 mL, 18.83 mmol) in diethyl ether (25 mL) at -78°C under nitrogen. The resulting mixture was stirred at r.t. for 2 hours. The reaction mixture was carefully quenched with 20% Rochelle's solution (>100 ml) and at -78°C and allowed to warm to r.t.. After 2 hours of vigourous stirring the mixture was extracted with Et2O x2, the organic layer was dried ($MgSO_4$), filtered and evaporated to afford colourless liquid, (S)-2-(tert-butyldimethylsilyloxy)propan-1-ol (3.50 g, 98 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (6H, s), 0.81 (9H, s), 1.03 (3H, d), 1.71 - 1.90 (1H, m), 3.24 - 3.33 (1H, m), 3.35 - 3.44 (1H, m), 3.78 - 3.87 (1H, m).

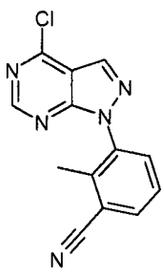
Intermediate AT1: (2S)-3-(2-(tert-Butyldiphenylsilyloxy)ethoxy)-2-(1-(3-cyano-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-cyanopyridin-2-yl)propanamide



Sodium hydride (60% in oil) (87 mg, 2.17 mmol) was added to (S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-N-(5-cyanopyridin-2-yl)-2-hydroxypropanamide (**Intermediate AU1**) (484 mg, 0.99 mmol) in anhydrous THF (25 ml) at 0 °C under

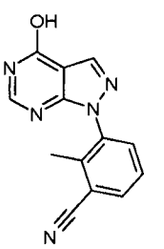
nitrogen. The resulting solution was stirred at 0 °C for 10 minutes and then 3-(4-chloro-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2-methylbenzonitrile (**Intermediate AT2**) (267 mg, 0.99 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 4 hours. The reaction mixture was neutralised with 1M citric acid and diluted with water and EtOAc. The organic layer was separated and the aqueous layer re-extracted with EtOAc. The combined organics were washed with saturated brine, dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 0 to 50% EtOAc in isohexane to afford the product (251 mg, 35.1 %). m/z (ES+) $(M+H)^+$ = 723.67; HPLC t_R = 3.75 min.

Intermediate AT2: 3-(4-chloro-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2-methylbenzonitrile



Phosphoryl trichloride (9.92 ml, 103.49 mmol) was added to 3-(4-hydroxy-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2-methylbenzonitrile (**Intermediate AT3**) (1.3 g, 5.17 mmol). The resulting solution was stirred at 100 °C for 2 hours. The reaction mixture was evaporated (azeotroping with toluene x3) giving a brown oil which was triturated with ice/water to give afford the product (1.200 g) which was used without further purification. ^{1}H NMR (400 MHz, DMSO) δ 2.28 (3H, s), 7.65 (1H, t), 7.86 (1H, d), 8.06 (1H, d), 8.81 (1H, s), 8.90 (1H, s)

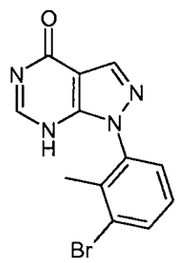
Intermediate AT3: 3-(4-hydroxy-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2-methylbenzonitrile



1-(3-bromo-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol (**Intermediate AT4**) (2 g, 6.55 mmol) and Zinc cyanide (0.693 g, 5.90 mmol) were dissolved in DMF (30 mL)and

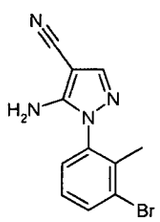
sealed into a microwave tube. The tube was purged with nitrogen. 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (0.379 g, 0.66 mmol) and tris(dibenzylideneacetone)dipalladium(0) (0.300 g, 0.33 mmol) added. The reaction was heated to 160 °C for 10 minutes in the microwave reactor and cooled to RT. The reaction mixture was filtered and the solid washed with DMF (until the filtrate was colourless) to afford the product (1.340 g, 81 %) which was used without further purification. ^{1}H NMR (400 MHz, DMSO) δ 2.19 (3H, s), 7.54 (1H, t), 7.71 (1H, d), 7.94 (1H, d), 8.02 (1H, s), 8.30 (1H, s), 12.32 (1H, s)

Intermediate AT4: 1-(3-bromo-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4(7H)-one



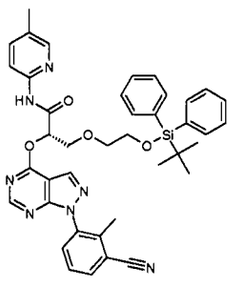
Concentrated sulfuric acid (2.67 mL, 50.01 mmol) was added to a stirred solution of 5-amino-1-(3-bromo-2-methylphenyl)-1H-pyrazole-4-carbonitrile (**Intermediate AT5**) (12.6 g, 45.47 mmol) in formic acid (80 mL). The resulting solution was stirred at 100 °C for 18 hours. The reaction was allowed to cool to room temperature and evaporated to ~half volume, water (100 mL) added and stirred for 2 hours. The formed ppt was filtered off, washed well with water and dried overnight in a vacuum over P_2O_5. The resulting solid was then slurried in DCM (100 mL), filtered and dried to afford the product (9.30 g, 67.0 %) which was used without further purification. ^{1}H NMR (400 MHz, DMSO) δ 2.06 (3H, s), 7.34 (1H, t), 7.43 (1H, d), 7.82 (1H, d), 8.06 (1H, d), 8.33 (1H, s), 12.34 (1H, s); m/z (ES-) (M-H)- = 303.26, 305.21; HPLC t_R = 1.72 min.

Intermediate AT5: 5-amino-1-(3-bromo-2-methylphenyl)-1H-pyrazole-4-carbonitrile



(3-Bromo-2-methylphenyl)hydrazine (CAS no. 459817-67-5) (10 g, 49.74 mmol) was suspended in MeOH (100 mL) under nitrogen at 0°C. 2-(Ethoxymethylene)malononitrile (6.07 g, 49.74 mmol) added portionwise over 5 mins and the mixture stirred at ~0°C for 2 hours. The reaction mixture was allowed to warm to room temperature and then heated at reflux under nitrogen for 2 hours. No reaction. The starting material was NMR'ed and found to be a salt, so N-ethyl-N-isopropylpropan-2-amine (17.33 mL, 99.47 mmol) was added and stirred for a further 16 hours. The reaction mixture was evaporated to dryness and redissolved in EtOAc, and washed sequentially with water x2 and saturated brine. The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product, 5-amino-1-(3-bromo-2-methylphenyl)-1H-pyrazole-4-carbonitrile (12.60 g, 91 %). m/z (ES+) $(M+H)^+$ = 279.25; HPLC t_R = 1.95 min.

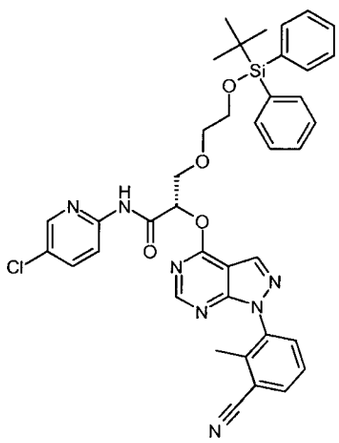
Intermediate AT6: (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(3-cyano-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-methylpyridin-2-yl)propanamide



Sodium hydride (60% in oil) (92 mg, 2.30 mmol) was added to (S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-hydroxy-N-(5-methylpyridin-2-yl)propanamide (**Intermediate AU2**) (500 mg, 1.04 mmol) in anhydrous THF (25 ml) at 0 °C under nitrogen. The resulting solution was stirred at 0 °C for 10 minutes and then 3-(4-chloro-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2-methylbenzonitrile (**Intermediate AT2**) (282 mg, 1.04 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 4 hours. The reaction mixture was neutralised with 1M citric acid and diluted with water and EtOAc. The organic layer was separated and the aqueous layer re-extracted with EtOAc. The combined organics were washed with saturated brine, dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 0 to 50% EtOAc in isohexane. No separation was achieved. The column was repeated with a 0-10% MeOH/DCM gradient. Still no separation! Mixed fractions were evaporated to

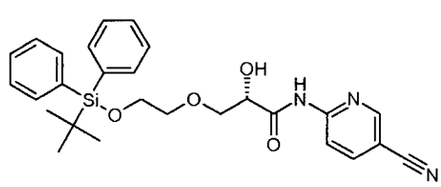
dryness to afford (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(3-cyano-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-methylpyridin-2-yl)propanamide (313 mg, 42.1 %). m/z (ES+) $(M+H)^+$ = 712.63; HPLC t_R = 3.85 min.

Intermediate AT7: (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-N-(5-chloropyridin-2-yl)-2-(1-(3-cyano-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide



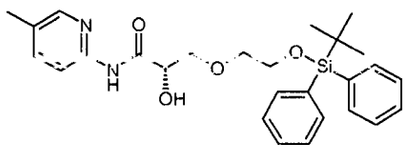
Trimethylaluminium (2M in toluene) (1.850 mL, 3.70 mmol) was added to 5-chloropyridin-2-amine (260 mg, 2.02 mmol) in toluene (8 mL) cooled to 0 °C under nitrogen. The resulting solution was stirred at 0°C for 15 minutes. (S)-3-(2-(tert-Butyldiphenylsilyloxy)ethoxy)-N-(5-chloropyridin-2-yl)-2-hydroxypropanamide (**Intermediate AU3**) in toluene (2 mL) was added and the reaction was allowed to warm to room temperature and then heated at reflux for 18 hours. The reaction mixture was allowed to cool and concentrated in vacuo. The residue was neutralised with citric acid (1M, aq) and then diluted with water and extracted with EtOAc ×2. The combined organics were washed with brine, dried ($MgSO_4$) and evaporated to afford the product (860 mg) which was used without further purification. m/z (ES+) $(M+H)^+$ = 732.66; HPLC t_R = 3.89 min.

Intermediate AU1: (S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-N-(5-cyanopyridin-2-yl)-2-hydroxypropanamide



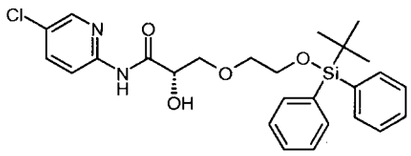
Trimethylaluminium (2M in toluene) (6.21 mL, 12.42 mmol) was added to 6-aminonicotinonitrile (1.480 g, 12.42 mmol) in toluene (80 mL) at 0°C under nitrogen. The resulting solution was stirred at 0°C for 15 minutes. (S)-Methyl 3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-hydroxypropanoate (**Intermediate AB3**) (2.5 g, 6.21 mmol) in toluene (20 mL) was added. The reaction was heated to 110 °C for 2 hours and cooled to RT. The reaction mixture was concentrated. The residue was neutralised with citric acid (1M, aq) and then diluted with water and extracted with EtOAc. The combined organics were dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, elution gradient 20 to 50% EtOAc in isohexane to afford the product (1.780 g, 58.5 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (9H, s), 3.65 - 3.69 (3H, m), 3.81 - 3.91 (4H, m), 4.35 (1H, q), 7.35 - 7.45 (6H, m), 7.65 - 7.67 (4H, m), 7.92 - 7.95 (1H, m), 8.36 - 8.38 (1H, m), 8.55 - 8.56 (1H, m), 9.40 (1H, s); m/z (ES+) $(M+H)^+$ = 490; HPLC t_R = 3.07 min.

Intermediate AU2: (S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-hydroxy-N-(5-methylpyridin-2-yl)propanamide



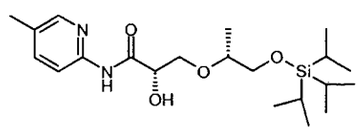
Trimethylaluminium (2M in toluene) (4.97 mL, 9.94 mmol) was added carefully to 5-methylpyridin-2-amine (1.075 g, 9.94 mmol) in toluene (20 mL) at 0°C under nitrogen. The resulting solution was stirred at 0°C for 15 minutes. (S)-methyl 3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-hydroxypropanoate (**Intermediate AB3**) (2 g, 4.97 mmol) in toluene (4 mL) was added. The reaction was heated to 120 °C for 1 hour in the microwave reactor and cooled to RT. The reaction mixture was concentrated. The residue was neutralised with citric acid (1M, aq) and then diluted with water and extracted with EtOAc. The combined organics were dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% EtOAc in isohexane to afford the product (1.800 g, 76 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (9H, s), 2.29 (3H, s), 3.65 (2H, t), 3.76 - 3.90 (5H, m), 4.31 - 4.37 (1H, m), 7.34 - 7.45 (6H, m), 7.48 - 7.54 (1H, m), 7.64 - 7.71 (4H, m), 8.07 - 8.13 (2H, m), 9.13 (1H, s); m/z (ES+) $(M+H)^+$ = 479.60; HPLC t_R = 3.16 min.

Intermediate AU3: (S)-3-(2-(tert-Butyldiphenylsilyloxy)ethoxy)-N-(5-chloropyridin-2-yl)-2-hydroxypropanamide



Trimethylaluminium (2M in toluene) (4.97 mL, 9.94 mmol) was added carefully to 5-chloropyridin-2-amine (1.277 g, 9.94 mmol) in toluene (10 mL) at 0°C under nitrogen. The resulting solution was stirred at 0°C for 15 minutes. (S)-Methyl 3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-hydroxypropanoate (**Intermediate AB3**) (2 g, 4.97 mmol) in toluene (2 mL) was added. The reaction was heated to 120 °C for 2 hours in the microwave reactor. The reaction mixture was allowed to cool. The residue was neutralised with citric acid (1M, aq) and then diluted with water and extracted with EtOAc. The combined organics were dried (MgSO4) and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% EtOAc in isohexane to afford the product (1.52 g, 61.3 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (9H, s), 3.63 - 3.68 (3H, m), 3.79 - 3.83 (2H, m), 3.85 (2H, d), 4.33 (1H, q), 7.34 - 7.46 (6H, m), 7.63 - 7.69 (5H, m), 8.18 - 8.25 (2H, m), 9.19 (1H, s); m/z (ES+) $(M+H)^+$ = 499.55; HPLC t_R = 3.43 min.

Intermediate AU4: (S)-2-hydroxy-N-(5-methylpyridin-2-yl)-3-((R)-1-(triisopropylsilyloxy)propan-2-yloxy)propanamide

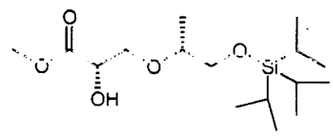


Trimethylaluminium (2M in toluene) (8.97 ml, 17.94 mmol) was added to 5-methylpyridin-2-amine (1.940 g, 17.94 mmol) in toluene (70 ml) cooled to 0 °C under nitrogen. The resulting solution was stirred at 0°C for 20 minutes. (S)-methyl 2-hydroxy-3-((R)-1-(triisopropylsilyloxy)propan-2-yloxy)propanoate (**Intermediate AU5**) (3.0 g, 8.97 mmol) in toluene (20 ml) was added and the reaction was allowed to warm to room temperature and then heated at reflux for 5 hours. The reaction mixture was allowed to cool and concentrated in vacuo. The residue was neutralised with citric acid (1M, aq) and then diluted with water (50 mL) and extracted with EtOAc (2 × 100 mL). The combined organics were dried ($MgSO_4$) filtered and evaporated. The crude product was purified by flash silica chromatography, eluting with 30 to 50% EtOAc in isohexane to afford the

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product (2.40 g, 65.2 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 - 1.15 (24H, m), 2.29 (3H, s), 3.60 - 3.68 (3H, m), 3.82 - 3.86 (1H, m), 3.98 - 4.02 (1H, m), 4.14 - 4.15 (1H, m), 4.30 - 4.34 (1H, m), 7.49 - 7.52 (1H, m), 8.11 - 8.13 (2H, m), 9.14 (1H, s); m/z (ES+) $(M+H)^+$ = 411.44; HPLC t_R= 3.46 min.

Intermediate AU5: (S)-methyl 2-hydroxy-3-((R)-1-(triisopropylsilyloxy)propan-2-yloxy)propanoate

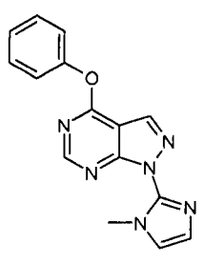


Prepared using a procedure analogous to that described for **Intermediate AN1** using (R)-1-(triisopropylsilyloxy)propan-2-ol (CAS no. 871657-72-6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 - 1.16 (24H, m), 3.39 (1H, d), 3.54 - 3.59 (2H, m), 3.67 - 3.72 (1H, m), 3.78 (3H, s), 3.80 - 3.91 (2H, m), 4.27 - 4.31 (1H, m).

Intermediate AU5: (R)-methyl 2-hydroxy-3-((S)-1-(triisopropylsilyloxy)propan-2-yloxy)propanoate Alternative Procedure

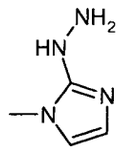
Magnesium trifluoromethanesulfonate (1.263 g, 3.92 mmol) was added to a mixture of (S)-1-(triisopropylsilyloxy)propan-2-ol (4.55 g, 19.59 mmol) and (R)-methyl oxirane-2-carboxylate (2 g, 19.59 mmol) in ethyl acetate (40 mL). The resulting suspension was heated to 80°C for 72 hours. Further (R)-methyl oxirane-2-carboxylate (2 g, 19.59 mmol) was added and the mixture stirred at 80°C for 48 hrs. Further (R)-methyl oxirane-2-carboxylate (2 g, 19.59 mmol) was added and the mixture stirred for 24hrs. The mixture was allowed to cool, filtered through a bed of silica (~10g), washed through with EtOAc and evaporated. The crude product was purified by flash silica chromatography, elution gradient 10 to 50% EtOAc in isohexane, to afford the product (2.7g, 41%).

Intermediate AV1: 1-(1-methyl-1H-imidazol-2-yl)-4-phenoxy-1H-pyrazolo[3,4-d]pyrimidine



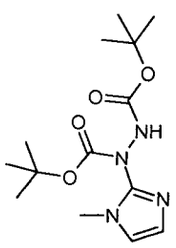
2-Hydrazinyl-1-methyl-1H-imidazole hydrochloride (**Intermediate AV2**) (305 mg, 2.05 mmol) was added to 4,6-diphenoxypyrimidine-5-carbaldehyde (**Intermediate Z2**) (600 mg, 2.05 mmol) in THF (15 mL) the resulting solution was stirred at room temperature for 5 minutes. 2-tert-Butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine on polystyrene (2.8 g, 6.2 mmol) was added and sealed into a microwave tube. The reaction was heated to 120 °C for 10 hours in the microwave reactor and cooled to RT. The reaction mixture was filtered and evaporated to drynesss. The crude product was purified by flash silica chromatography eluting with 0 to 5% MeOH in DCM to afford the product (190 mg, 32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.59 (3H, s), 6.95 (1H, d), 7.11 (1H, d), 7.24 - 7.20 (2H, m), 7.32 - 7.26 (1H, m), 7.44 (2H, m), 8.03 (1H, s), 8.59 (1H, s); m/z (ES^+) $(M+H)^+$ = 293; HPLC t_R= 1.65 min.

Intermediate AV2: 2-Hydrazinyl-1-methyl-1H-imidazole hydrochloride



4 M Hydrogen chloride in dioxane (50 mL, 200.00 mmol) was added to di-tert-butyl 1-(1-methyl-1H-imidazol-2-yl)hydrazine-1,2-dicarboxylate (**Intermediate AV3**) (5.9 g, 18.89 mmol) in ethyl acetate (50 mL) at 22°C. The resulting solution was stirred at 22 °C for 20 hours. The reaction mixture was evaporated to dryness to afford the product (2.80 g) which was used without purification. 1H NMR (400 MHz, DMSO) δ 3.38 (3H, s), 6.90 (1H, d), 6.96 (1H, d).

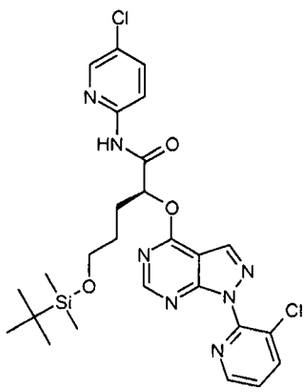
Intermediate AV3: di-tert-Butyl 1-(1-methyl-1H-imidazol-2-yl)hydrazine-1,2-dicarboxylate



n-Butyllithium (1.6M in hexane, 20.76 mL, 33.22 mmol) was added dropwise to 1-methyl-1H-imidazole (CAS no. 616-47-7) (3 g, 36.54 mmol), in THF (10 mL) cooled to –70 °C over a period of 10 minutes under nitrogen. The resulting solution was stirred at –70 °C for 10 minutes. di-tert-Butyl diazene-1,2-dicarboxylate (CAS no. 870-50-8) (7.65 g, 33.22

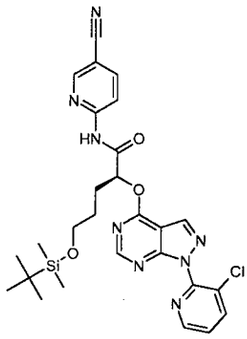
mmol) in THF (6 ml) added dropwise over 10 minutes, not allowing the solution to rise above -65°C. After the addition was complete the solution was allowed to warm to ambient temperature overnight. Water (20 mL) added at RT. The THF was removed under vacuum. Extracted with EtOAc (2 × 40mL). The organic extracts were combined, washed with brine (15 mL), dried over MgSO4 and reduced to give crude product. The crude product was purified by flash silica chromatography eluting with 20 to 100% EtOAc in isohexane to afford the product (6.17 g, 59.5%). m/z (ESI+) $(M+H)^+$ = 313; HPLC t_R = 1.36 min.

Intermediate AW1: (2S)-5-(tert-butyldimethylsilyloxy)-N-(5-chloropyridin-2-yl)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)pentanamide



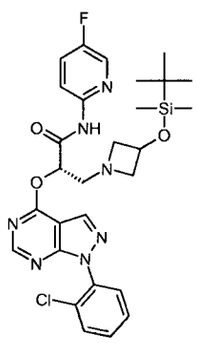
A solution of trimethylaluminium (2M in toluene) (0.795 mL, 1.59 mmol) was added dropwise to a stirred solution of 5-chloropyridin-2-amine (178 mg, 1.38 mmol) in toluene (5 mL) cooled to 0°C under nitrogen. The resulting solution was stirred at 0°C for 15 minutes. A solution of (2S)-methyl 5-(tert-butyldimethylsilyloxy)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)pentanoate (**Intermediate O2**) (680 mg, 1.38 mmol) in toluene (5 mL) was added dropwise. The resulting solution was stirred at 0°C for 10 minutes allowed to warm to ambient temperature and then heated at reflux for 18 hours. The reaction mixture was allowed to cool to r.t. and concentrated. The residue was diluted with ethyl acetate and treated with 1M citric acid (2ml). The layers were separated and the organics were washed with water and brine, dried ($MgSO_4$) and concentrated to a yellow foam, (2S)-5-(tert-butyldimethylsilyloxy)-N-(5-chloropyridin-2-yl)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)pentanamide (693 mg, 85 %). m/z (ES+) $(M+H)^+$ = 588.46; HPLC t_R = 3.54 min.

Intermediate AW2: (2S)-5-(tert-butyldimethylsilyloxy)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-cyanopyridin-2-yl)pentanamide



A solution of trimethylaluminium (2M in toluene) (0.795 mL, 1.59 mmol) was added dropwise to a stirred solution of 6-aminonicotinonitrile (165 mg, 1.38 mmol) in toluene (5 mL) cooled to 0°C, over a period of 1 minute under nitrogen. The resulting solution was stirred at 0°C for 20 minutes. A solution of (2S)-methyl 5-(tert-butyldimethylsilyloxy)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)pentanoate (**Intermediate O2**) (680 mg, 1.38 mmol) in toluene (5 mL) was added dropwise. The resulting solution was stirred at 0°C for 10 minutes allowed to warm to ambient temperature and then heated at reflux for 18 hours. The reaction mixture was allowed to cool to r.t. and concentrated. The residue was diluted with ethyl acetate and treated with 1M citric acid (2ml). The layers were separated and the organics were washed with water and brine, dried ($MgSO_4$) and evaporated to afford the product (797 mg) which was used without further purification. m/z (ES-) (M-H)- = 577.45; HPLC t_R = 3.29 min.

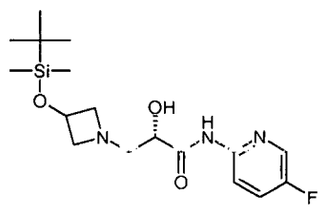
Intermediate AX1: (2S)-3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-fluoropyridin-2-yl)propanamide



Sodium hydride (60% dispersion in mineral oil) (0.682 g, 17.05 mmol) was added to (S)-3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-N-(5-fluoropyridin-2-yl)-2-hydroxypropanamide (**Intermediate AX2**) (3.0 g, 8.12 mmol) in anhydrous THF (80 mL)

at 0 °C under nitrogen. The resulting solution was stirred at 0°C for 10 minutes and then 4-chloro-1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate B1**) (2.63 g, 8.93 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 3 hours. The reaction mixture was neutralised with 1M citric acid and then diluted with water (50 mL) and EtOAc (100 mL). The organic layer was separated and the aqueous layer re-extracted with EtOAc (100 mL). The combined organics were washed with saturated brine (75 mL),dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by flash silica chromatography, elution gradient 30 to 70% EtOAc in isohexane to afford the product (4.29 g, 88 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (6H, s), 0.88 (9H, s), 3.06 - 3.10 (2H, m), 3.15 - 3.19 (1H, m), 3.27 - 3.31 (1H, m), 3.87 - 3.90 (2H, m), 4.41 - 4.48 (1H, m), 5.89 - 5.92 (1H, m), 7.40 - 7.55 (4H, m), 7.61 - 7.63 (1H, m), 8.15 (1H, d), 8.22 - 8.26 (1H, m), 8.36 (1H, s), 8.59 (1H, s), 9.82 (1H, s); m/z (ES^+) $(M+H)^+$ = 598; HPLC t_R= 2.82 min.

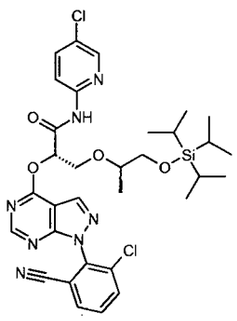
Intermediate AX2: (S)-3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-N-(5-fluoropyridin-2-yl)-2-hydroxypropanamide



Trimethylaluminium (2M solution in toluene) (15.89 mL, 31.79 mmol) was added to 5-fluoropyridin-2-amine (3.10 g, 27.64 mmol) in toluene (80 mL) cooled to 0 °C under nitrogen over a period of 10 minutes. The resulting solution was stirred at 0°C for 10 minutes. (S)-methyl 3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-hydroxypropanoate (**Intermediate AD3**) (8 g, 27.64 mmol) in toluene (20 mL) was added over 10 minutes and the reaction was allowed to warm to room temperature and then heated at 90°C for 2 hours. The reaction mixture was cooled and poured into a 20% solution of Rochelle's salt (50 mL), diluted with ethyl acetate (200 mL) and stirred for 2 hours. The organic phase was separated, washed with water and brine, dried ($MgSO_4$) filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 80 to 100% EtOAc in isohexane to afford the product (5.28 g, 51.7 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.028 (3H, s), 0.033 (3H, s), 0.87 (9H, s), 2.90 (2H, d), 3.02 - 3.08 (2H, m), 3.68 - 3.74

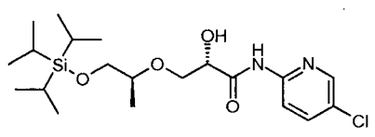
(2H, m), 4.00 (1H, t), 4.41 - 4.48 (1H, m), 7.41 - 7.45 (1H, m), 8.15 (1H, d), 8.21 - 8.24 (1H, m), 9.85 (1H, s); m/z (ES^+) $(M+H)^+$ = 370; HPLC t_R= 1.97 min.

Intermediate AY1: (2S)-2-(1-(2-chloro-6-cyanophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-chloropyridin-2-yl)-3-((R)-1-(triisopropylsilyloxy)propan-2-yloxy)propanamide



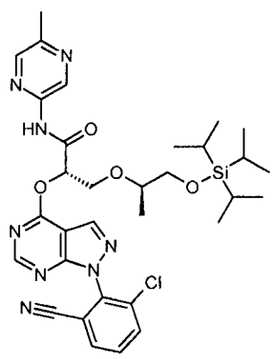
Sodium hydride (60% dispersion in mineral oil) (93 mg, 2.32 mmol) was added to (S)-N-(5-chloropyridin-2-yl)-2-hydroxy-3-((R)-1-(triisopropylsilyloxy)propan-2-yloxy)propanamide (**Intermediate AY2**) (500 mg, 1.16 mmol) in anhydrous THF (25 mL) at 0°C under nitrogen. The resulting solution was stirred at 0°C for 10 minutes and then 3-chloro-2-(4-chloro-1H-pyrazolo[3,4-d]pyrimidin-1-yl)benzonitrile (**Intermediate AH6**) (370 mg, 1.28 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was adjusted to pH 7 by addition of 1M citric acid and then diluted with water (20 mL) and EtOAc (50 mL). The organic layer was separated and the aqueous layer re-extracted with EtOAc (2 × 50 mL). The combined organics were washed with saturated brine (75 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by flash silica chromatography, elution gradient 50 to 100% EtOAc in isohexane to afford the product (626 mg, 79 %). ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 - 1.09 (21H, m), 1.13 - 1.17 (3H, m), 3.60 - 3.77 (3H, m), 4.20 - 4.33 (2H, m), 5.99 - 6.03 (1H, m), 7.60 - 7.70 (2H, m), 7.78 - 7.81 (1H, m), 7.85 - 7.87 (1H, m), 8.22 - 8.25 (2H, m), 8.50 (1H, d), 8.60 (1H, d), 8.82 (1H, s); m/z (ES^-) $(M-H)^-$ = 682; HPLC t_R= 4.04 min.

Intermediate AY2: (S)-N-(5-chloropyridin-2-yl)-2-hydroxy-3-((R)-1-(triisopropylsilyloxy)propan-2-yloxy)propanamide



Trimethylaluminium (2M solution in toluene) (2.99 mL, 5.98 mmol) was added to a solution of 5-chloropyridin-2-amine (0.769 g, 5.98 mmol) in toluene (20 mL) at 0°C under nitrogen. The reaction mixture was stirred at 0 °C for 20 mins and then (S)-methyl 2-hydroxy-3-((R)-1-(triisopropylsilyloxy)propan-2-yloxy)propanoate (**Intermediate AU5**) (1 g, 2.99 mmol) was added. The reaction mixture was allowed to warm to room temperature and then heated at reflux under nitogen for 4 hours. The reaction mixture was allowed to cool to room temperature and the concentrated in vacuo. The residue was neutralised with citric acid (1M, aq.) and then diluted with water and DCM (50 mL). The organic layer was separated and the aqueous layer re-extracted with DCM (30 mL). The combined organics were dried ($MgSO_4$), filtered and evaporated in vacuo.The crude product was purified by flash silica chromatography, elution gradient 20 to 50% EtOAc in isohexane to afford the product (0.935 g, 72.6 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 - 1.13 (24H, m), 3.62 - 3.67 (3H, m), 3.81 - 3.84 (1H, m), 4.02 - 4.06 (1H, m), 4.20 (1H, d), 4.31 (1H, q), 7.65 - 7.67 (1H, m), 8.22 - 8.25 (2H, m), 9.23 (1H, s); m/z (ES^-) $(M-H)^-$ = 429; HPLC t_R= 3.81 min.

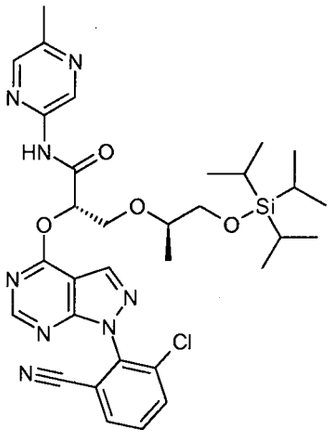
Intermediate AZ1: (2S)-2-(1-(2-chloro-6-cyanophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-methylpyrazin-2-yl)-3-((R)-1-(triisopropylsilyloxy)propan-2-yloxy)propanamide



Sodium hydride (60% dispersion in mineral oil) (0.116 g, 2.89 mmol) was added to (S)-2-hydroxy-N-(5-methylpyrazin-2-yl)-3-((R)-1-(triisopropylsilyloxy)propan-2-yloxy)propanamide (**Intermediate AZ2**) (0.595 g, 1.45 mmol) in anhydrous THF (20 mL) at 0 °C under nitrogen. The resulting solution was stirred at 0 °C for 10 minutes and then 3-chloro-2-(4-chloro-1H-pyrazolo[3,4-d]pyrimidin-1-yl)benzonitrile (**Intermediate AH6**) (0.438 g, 1.31 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour. The reaction mixture was adjusted to pH 7 by addition

of 1M citric acid and the majority of the THF removed in vacuo. The reaction mixture was diluted with water (20 mL) and EtOAc (50 mL). The organic layer was separated and the aqueous layer re-extracted with EtOAc (2 × 100 mL). The combined organics were washed with saturated brine (75 mL), dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 50 to 100% EtOAc in isohexane to afford the product (0.590 g, 67.5 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 - 1.08 (21H, m), 1.12 - 1.17 (3H, m), 2.54 (3H, s), 3.59 - 3.78 (3H, m), 4.21 - 4.26 (1H, m), 4.29 - 4.36 (1H, m), 6.02 - 6.06 (1H, m), 7.60 - 7.65 (1H, m), 7.78 - 7.81 (1H, m), 7.85 - 7.87 (1H, m), 8.11 - 8.13 (1H, m), 8.50 (1H, d), 8.61 (1H, d), 8.71 (1H, d), 9.44 (1H, t); m/z (ES^+) M^+ = 665.26; HPLC t_R= 4.02 min.

Intermediate AZ1: (2S)-2-[1-(2-chloro-6-cyanophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-methylpyrazin-2-yl)-3-[(2R)-1-tri(propan-2-yl)silyloxypropan-2-yl]oxypropanamide. Alternative preparation.

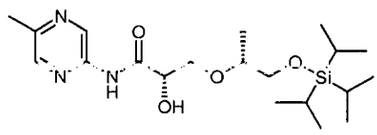


Tris(dibenzylideneacetone)dipalladium(0) (0.261 g, 0.29 mmol) was added in one portion to a de-gassed mixture of (2S)-2-(1-(2-bromo-6-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-methylpyrazin-2-yl)-3-((R)-1-(triisopropylsilyloxy)propan-2-yloxy)propanamide (**Intermediate BO1**) (4.1 g, 5.70 mmol), zinc cyanide (0.335 g, 2.85 mmol) and 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (0.330 g, 0.57 mmol) in N-methylpyrrolidone (41 mL) at 20°C under nitrogen. The resulting suspension was degassed under vaccum with inlet of nitrogen four times and then heated to 110 °C (internal temperature) for 1 hour. The mixture was cooled, poured into water (100 mL) and extracted with ethyl acetate (2 × 50 mL). The organic layers were combined and washed with water (4 × 50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and evaporated.

The crude product was purified by flash silica chromatography, elution gradient 30 to 100% EtOAc in isohexane to afford the product (3.0 g, 79%).

1H NMR (400.13 MHz, DMSO-d_6) δ 0.90 - 1.08 (21H, m), 1.09 - 1.11 (3H, m), 2.45 (3H, s), 3.53 - 3.58 (1H, m), 3.60 - 3.66 (1H, m), 3.75 - 3.78 (1H, m), 4.10 - 4.15 (2H, m), 5.94 - 5.99 (1H, m), 7.87 - 7.91 (1H, m), 8.16 - 8.19 (2H, m), 8.31 - 8.33 (1H, m), 8.60 - 8.61 (1H, m), 8.73 (1H, s), 9.10 - 9.12 (1H, d), 11.20 (1H, s); m/z (ES^-) $(M-H)^-$ = 663; HPLC t_R= 3.79 min.

Intermediate AZ2: (S)-2-hydroxy-N-(5-methylpyrazin-2-yl)-3-((R)-1-(triisopropylsilyloxy)propan-2-yloxy)propanamide



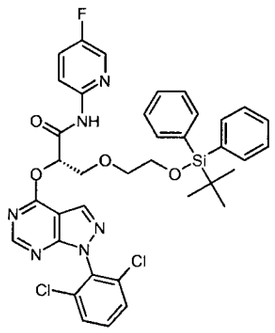
Trimethylaluminium (2M solution in toluene) (5.98 mL, 11.96 mmol) was added to 5-methylpyrazin-2-amine (1.305 g, 11.96 mmol) in toluene (20 mL) cooled to 0 °C under nitrogen. The resulting solution was stirred at 0°C for 20 minutes. (R)-methyl 2-hydroxy-3-((S)-1-(triisopropylsilyloxy)propan-2-yloxy)propanoate (**Intermediate AU5**) (2 g, 5.98 mmol) in toluene (6 mL) was added and the reaction was allowed to warm to room temperature and then refluxed for 6 hours. The reaction mixture was allowed to cool and concentrated in vacuo. The residue was neutralised with citric acid (1M, aq.) and then diluted with water (25 mL) and extracted with EtOAc (2 × 50 mL). The combined organics were washed with brine (20mL), then dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 30 to 50% EtOAc in isohexane to afford the product (1.390 g, 56.5 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 - 1.17 (24H, m), 2.54 (3H, s), 3.62 - 3.67 (3H, m), 3.81 - 3.85 (1H, m), 4.05 - 4.09 (1H, m), 4.22 (1H, d), 4.34 (1H, q), 8.13 (1H, d), 9.12 (1H, s), 9.44 (1H, d); m/z (ES^+) $(M+H)^+$ = 412.34; HPLC t_R= 3.82 min.

Intermediate AZ2: (S)-2-hydroxy-N-(5-methylpyrazin-2-yl)-3-((R)-1-(triisopropylsilyloxy)propan-2-yloxy)propanamide. Alternative preparation.

Trimethylaluminium (2M solution in toluene) (72.5 mL, 145 mmol) was added to 5-methylpyrazin-2-amine (13.64 g, 125.0 mmol) in toluene (520 mL) cooled to 0 °C under nitrogen. The resulting solution was stirred at 0°C for 20 minutes. (R)-methyl 2-hydroxy-3-((S)-1-(triisopropylsilyloxy)propan-2-yloxy)propanoate (**Intermediate AU5**) (33.5 g,

100.0 mmol) in toluene (130 mL) was added and the reaction was allowed to warm to room temperature and then stirred at 72°C for 2.5 hours. The reaction mixture was allowed to cool then poured into a stirred mixture of ethyl acetate (500 mL) and aqueous solution of Rochelle salt (20% w/v, 500 mL). The mixture was stirred for 15 minutes then the organics separated and washed with water (500 mL) followed by brine (500 mL), then dried ($MgSO_4$), filtered and concentrated. The residues were dissolved in iso-hexane (300 mL) and stood for 15 minutes at 20°C before cooling to 5°C over 30 minutes. The solid formed was isolated by filtration, washed with iso-hexane cooled to 5°C (200 mL) and dried at 40°C under high vacuum to afford the product (26.7 g, 64%). The filtrates were combined and concentrated to 100 mL total volume and the mixture stood for 16 hours. The solid formed was isolated by filtration, washed with iso-hexane cooled to 5°C (100 mL), dried at 40°C under high vacuum and combined with the initial batch to afford the product (30.1 g, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 - 1.17 (24H, m), 2.54 (3H, s), 3.62 - 3.67 (3H, m), 3.81 - 3.85 (1H, m), 4.05 - 4.09 (1H, m), 4.22 (1H, d), 4.34 (1H, q), 8.13 (1H, d), 9.12 (1H, s), 9.44 (1H, d); m/z (ES^+) $(M+H)^+$ = 412.34; HPLC t_R= 3.82 min.

Intermediate BA1: (S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(2,6-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-fluoropyridin-2-yl)propanamide

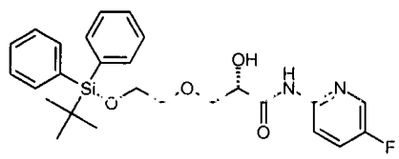


Sodium hydride (60% dispersion in mineral oil) (83 mg, 2.07 mmol) was added to (S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-N-(5-fluoropyridin-2-yl)-2-hydroxypropanamide (**Intermediate BA2**) (500 mg, 1.04 mmol) in anhydrous THF (20 mL) at 0°C under nitrogen. The resulting solution was stirred at 0 °C for 10 minutes and then 4-chloro-1-(2,6-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate BA3**) (310 mg, 1.04 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was adjusted to pH 7 by addition of 1M citric acid

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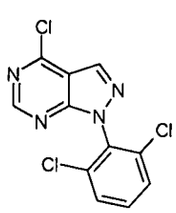
and the reaction mixture diluted with water (20 mL) and EtOAc (50 mL). The organic layer was separated and the aqueous layer re-extracted with EtOAc (2 × 50 mL). The combined organics were washed with saturated brine (75 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by flash silica chromatography, elution gradient 25 to 100% EtOAc in isohexane to afford the product (637 mg, 82 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (9H, t), 3.69 - 3.72 (2H, m), 3.82 (2H, t), 4.16 - 4.24 (2H, m), 6.06 (1H, t), 7.31 - 7.47 (8H, m), 7.52 - 7.55 (2H, m), 7.63 - 7.66 (4H, m), 8.12 (1H, d), 8.26 - 8.29 (1H, m), 8.42 (1H, s), 8.58 (1H, s), 8.79 (1H, s).

Intermediate BA2: (S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-N-(5-fluoropyridin-2-yl)-2-hydroxypropanamide



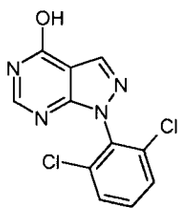
Trimethylaluminium (2M solution in toluene) (2.86 mL, 5.71 mmol) was added to 5-fluoropyridin-2-amine in toluene (8 mL) cooled to 0 °C under nitrogen. The resulting solution was stirred at 0°C for 20 minutes. (S)-Methyl 3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-hydroxypropanoate (**Intermediate AB3**) in toluene (8 mL) was added and the reaction was allowed to warm to room temperature and then heated at reflux for 24 hours. The reaction mixture was allowed to cool and concentrated in vacuo. The residue was neutralised with citric acid (1M, aq.) and then diluted with water (30 mL) and extracted with EtOAc (2 × 50 mL). The combined organics were dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 30 to 50% EtOAc in isohexane to afford the product (1.32 g, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 9H), 3.60 - 3.68 (m, 3H), 3.79 - 3.83 (m, 2H), 3.86 (d, 2H), 4.31 - 4.35 (m, 1H), 7.34 - 7.46 (m, 7H), 7.64 - 7.69 (m, 4H), 8.14 (d, 1H), 8.22 - 8.28 (m, 1H), 9.18 (s, 1H); m/z (ES^+), $(M+H)^+$ = 483.63; HPLC t_R = 3.08 min.

Intermediate BA3: 4-chloro-1-(2,6-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine



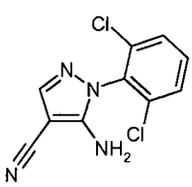
Phosphorus oxychloride (7.96 mL, 85.38 mmol) was added to 1-(2,6-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol (**Intermediate BA4**) (1.2 g, 4.27 mmol). The resulting solution was stirred at 100 °C for 20 hours. LCMS showed reaction was complete. The reaction mixture was evaporated. Ice/water and then EtOAc were added. The organic layer was separated and the aqueous layer re-extracted with EtOAc. The combined organics were washed with water, dried ($MgSO_4$) and concentrated to give the product (1.110 g, 87 %) which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 - 7.58 (3H, m), 8.45 (1H, s), 8.82 (1H, s); m/z (ES^+) $(M+H)^+$ = 299; HPLC t_R= 2.77 min.

Intermediate BA4: 1-(2,6-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol



Concentrated sulfuric acid (1.297 mL, 24.34 mmol) was added to a stirred solution of 5-amino-1-(2,6-dichlorophenyl)-1H-pyrazole-4-carbonitrile (**Intermediate BA5**) (5.6 g, 22.13 mmol) in formic acid (35 mL). The resulting solution was stirred at 100 °C for 24 hours. The reaction was allowed to cool to room temperature and evaporated to ~half volume, water (100 mL) added and stirred for 1 hour. The formed precipitate was filtered off, washed well with water and dried overnight in a vacuum over P_2O_5 to afford the product (4.07 g, 65.4 %) which was used without further purification. ^{1}H NMR (400 MHz, DMSO) δ 7.65 - 7.69 (1H, m), 7.75 - 7.78 (2H, m), 8.09 (1H, d), 8.41 (1H, s), 12.44 (1H, s); m/z (ES^-) $(M-H)^-$ = 279; HPLC t_R= 1.41 min.

Intermediate BA5: 5-amino-1-(2,6-dichlorophenyl)-1H-pyrazole-4-carbonitrile

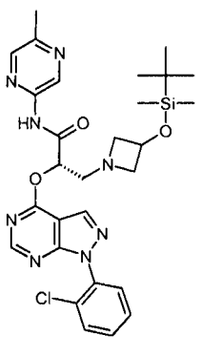


(2,6-Dichlorophenyl)hydrazine hydrochloride (5 g, 23.42 mmol) was partitioned between EtOAc (100 mL) and NaOH (2M, aq) (40 mL). The organic layer separated and washed with water (50 mL), brine (50 mL), dried ($MgSO_4$), filtered and concentrated. The resultant oil was suspended in methanol (50 mL) under nitrogen at -5°C. 2-(Ethoxymethylene)malononitrile (2.86 g, 23.42 mmol) added portionwise over 5 mins and

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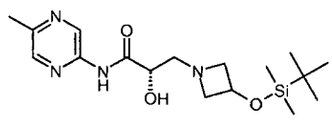
the mixture stirred at 0°C for 30 mins. The reaction mixture was allowed to warm to room temperature and then heated at reflux under nitrogen for 2 hours. The reaction mixture was allowed to cool and evaporated to dryness to afford the product (5.60 g, 94 %) which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.47 (2H, s), 7.43 - 7.47 (1H, m), 7.51 - 7.53 (2H, m), 7.73 (1H, s); m/z (ES^+) $(M+H)^+$ = 253; HPLC t_R= 1.62 min.

Intermediate BB1: (2S)-3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-methylpyrazin-2-yl)propanamide



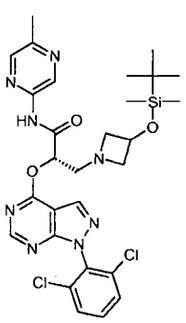
Sodium hydride (87 mg, 2.18 mmol) was added to (S)-3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-hydroxy-N-(5-methylpyrazin-2-yl)propanamide (**Intermediate BB2**) (400 mg, 1.09 mmol) in anhydrous tetrahydrofuran (15 mL) at 0°C under nitrogen. The resulting solution was stirred at 0°C for 10 minutes and then 4-chloro-1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine (318 mg, 1.20 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours. The reaction mixture was adjusted to pH 7 by addition of 1M citric acid and then diluted with water (30 mL) and ethyl acetate (50 mL). The organic layer was separated and the aqueous layer re-extracted with ethyl acetate (50 mL). The combined organics were washed with saturated brine (75 mL), dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, eluting with 40 to 100% ethyl acetate in isohexane followed by 0-20% methanol in ethyl acetate to afford the product (532 mg, 82 %). 1H NMR (400 MHz, $CDCl_3$) δ 0.00 (6H, s), 0.83 (9H, s), 2.45 (3H, s), 3.61 - 3.90 (4H, m), 4.47 - 4.60 (2H, m), 4.69 (1H, m), 6.22 (1H, m), 7.36 - 7.48 (3H, m), 7.51 - 7.57 (1H, m), 8.03 (1H, s), 8.38 (1H, s), 8.50 (1H, s), 9.27 (1H, s), 10.31 (1H, s); m/z (ES^+) $(M+H)^+$ = 595; HPLC t_R= 2.63 min.

Intermediate BB2: (S)-3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-hydroxy-N-(5-methylpyrazin-2-yl)propanamide



Trimethylaluminum (6.22 mL, 12.44 mmol) was added to 5-methylpyrazin-2-amine (1.357 g, 12.44 mmol) in anhydrous toluene (20 mL) cooled to 0 °C under nitrogen. The resulting solution was stirred at 0°C for 10 minutes. (S)-methyl 3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-hydroxypropanoate (**Intermediate AD3**) (2 g, 6.91 mmol) in anhydrous toluene (10 mL) was added and the resulting solution was allowed to warm to room temperature and then heated at 80°C overnight. The reaction was allowed to cool to room temperature and a solution of Rochelle salt in water (20%, 75ml) was added. The mixture diluted with water (25 mL) and ethyl acetate (75 mL) and allowed to stir for 2 hours. The organic layer was separated and the aqueous was extracted with ethyl acetate (75 mL). The combined organics were washed with brine (75 mL), dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, eluting with 20 to 50% ethyl acetate in isohexane. This was further purified by flash silica chromatography, eluting with 0 to 10% methanol in dichloromethane, to afford the product (1.50 g, 59.2 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (3H, d), 0.04 (3H, s), 0.87 (9H, q), 2.54 (3H, s), 2.93 (2H, d), 3.09 (2H, q), 3.71 - 3.77 (2H, m), 4.04 (1H, t), 4.46 (1H, t), 8.13 (1H, d), 9.39 (1H, d), 9.81 (1H, s); m/z (ES^+) $(M+H)^+ = 367.34$; HPLC t_R= 1.76 min.

Intermediate BB3: (S)-3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-(1-(2,6-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-methylpyrazin-2-yl)propanamide

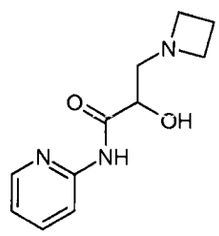


Sodium hydride (87 mg, 2.18 mmol) was added to (S)-3-(3-(tert-

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butyldimethylsilyloxy)azetidin-1-yl)-2-hydroxy-N-(5-methylpyrazin-2-yl)propanamide (**Intermediate BB2**) (400 mg, 1.09 mmol) in anhydrous tetrahydrofuran (15 mL) at 0°C under nitrogen. The resulting solution was stirred at 0°C for 10 minutes and then 4-chloro-1-(2,6-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate BA3**) (360 mg, 1.20 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours. The reaction mixture was neutralised with 1M citric acid and then diluted with water (30 mL) and ethyl acetate (50 mL). The organic layer was separated and the aqueous layer re-extracted with ethyl acetate (50 mL). The combined organics were washed with saturated brine (75 mL), dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, eluting with 40 to 80% ethyl acetate in isohexane, to afford the product (395 mg, 57.5 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (6H, s), 0.88 (9H, s), 2.54 (3H, s), 3.09 - 3.13 (2H, m), 3.16 - 3.21 (1H, m), 3.29 - 3.34 (1H, m), 3.87 - 3.92 (2H, m), 4.51 (1H, qn), 5.92 - 5.95 (1H, m), 7.43 - 7.47 (1H, m), 7.52 - 7.55 (2H, m), 8.14 (1H, d), 8.41 (1H, s), 8.59 (1H, s), 9.42 (1H, d), 9.96 (1H, s); m/z (ES$^+$) $(M+H)^+$ = 631; HPLC t_R= 2.94 min.

Intermediate BC1: (S)-3-(azetidin-1-yl)-2-hydroxy-N-(pyridin-2-yl)propanamide

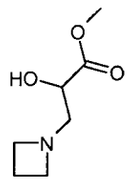


Trimethylaluminium (8.31 mL, 16.62 mmol) was added to pyridin-2-amine (1.360 g, 14.45 mmol) in toluene (30 mL) cooled to 0 °C under nitrogen. The resulting solution was stirred at 0°C for 10 minutes. (S)-Methyl 3-(azetidin-1-yl)-2-hydroxypropanoate (**Intermediate BC2**) (2.3 g, 14.45 mmol) in toluene (10 mL) and THF (5 mL) was added and the resulting solution was allowed to warm to room temperature and then heated at 60°C for 8 hours. The reaction cooled and 20% Rochelle salt (50 mL) added followed by EtOAc (50 mL) and the mixture stirred at ambient temperature overnight. The organic phase separated and the aqueous phase re-extracted with EtOAc (2 × 50 mL). The organic phases were combined, dried ($MgSO_4$) and evaporated to afford the product (2.7g) which was used without further purification.

1H NMR (400 MHz, $CDCl_3$) δ 2.10 - 2.17 (2H, m), 2.86 (2H, d), 3.36 (4H, t), 4.00 (1H, t),

7.02 - 7.06 (1H, m), 7.67 - 7.72 (1H, m), 8.19 - 8.23 (1H, m), 8.29 - 8.32 (1H, m), 9.91 (1H, s)

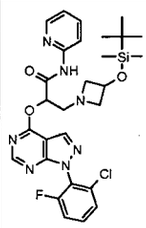
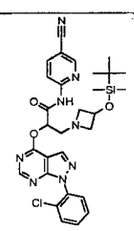
Intermediate BC2: (S)-methyl 3-(azetidin-1-yl)-2-hydroxypropanoate

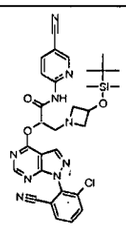
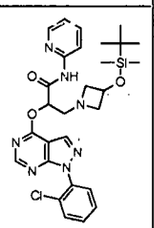
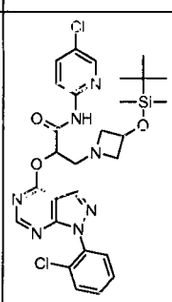


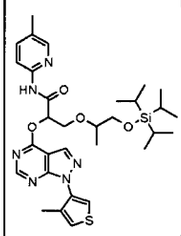
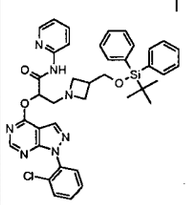
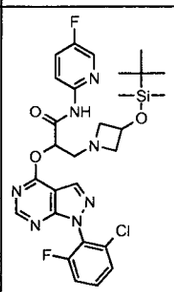
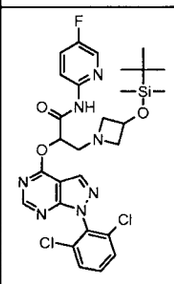
(S)-Methyl oxirane-2-carboxylate (1475 mg, 14.45 mmol) in acetonitrile (2 mL)was added to azetidine (825 mg, 14.45 mmol) in acetonitrile (8 mL). The reaction was heated to 100 °C for 60 minutes in the microwave reactor and cooled to room temperature. The mixture was evaporated to afford the crude product (2.3 g) which was used without further purification.

1H NMR (400 MHz, $CDCl_3$) δ 2.04 - 2.14 (2H, m), 2.71 - 2.81 (2H, m), 3.27 (4H, t), 3.77 (3H, s), 4.11 - 4.13 (1H, m)

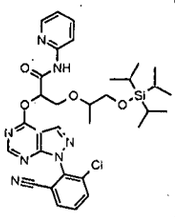
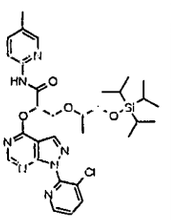
The following intermediates were prepared using a procedure analogous to that described for **Intermediate BB1** using the appropriate intermediates.

Intermediate number	**Structure**	**1H NMR (400 MHz) δ**	**LCMS**	**Intermediate refs.**
BD1		(DMSO-d6) 0.02 (6H, s), 0.84 (9H, q), 3.02 - 3.25 (4H, s), 3.70 - 3.79 (2H, m), 4.35 - 4.42 (1H, m), 5.75 - 5.79 (1H, m), 7.11 - 7.14 (1H, m), 7.54 - 7.60 (1H, m), 7.65 - 7.67 (1H, m), 7.71 - 7.78 (2H, m), 7.94 - 7.99 (1H, m), 8.33 - 8.35 (1H, m), 8.56 (1H, d), 8.67 (1H, d), 10.94 (1H, d)	m/z (ES+) (M+H)+ = 598; HPLC tR= 3.19 min.	BI1, BH1
BD2			m/z (ES+) (M+H)+ = 605; HPLC tR= 1.95 min.	BE1, B1

BD3			m/z (ES+) (M+H)+ = 630; HPLC tR= 1.89 min.	BE1, AH6
BD4			m/z (ES+) (M+H)+ = 580; HPLC tR= 2.46 min.	BE2, B1
BD5		(DMSO-d6) 0.03 (6H, s), 0.85 (9H, s), 2.90 - 2.95 (1H, m), 3.00 - 3.06 (1H, m), 3.10 - 3.16 (1H, m), 3.62 - 3.69 (2H, m), 4.30 - 4.39 (1H, m), 5.71 - 5.77 (1H, d), 7.54 - 7.65 (3H, m), 7.74 - 7.77 (1H, m), 7.87 - 7.90 (1H, m), 7.99 - 8.03 (1H, d), 8.39 - 8.40 (1H, m), 8.52 (1H, s), 8.58 (1H, s), 11.12 (1H, s)	m/z (ES+) (M+H)+ = 614; HPLC tR= 2.91 min.	AD2, B1

BD6		(DMSO-d6) 0.91 - 1.04 (18H, m), 1.08 (3H, d), 2.09 (3H, d), 2.24 (3H, s), 3.50 - 3.54 (1H, m), 3.62 - 3.66 (1H, m), 3.68 - 3.74 (1H, m), 4.06 - 4.14 (2H, m), 5.87 - 5.94 (1H, m), 7.40 - 7.41 (1H, m), 7.57 - 7.60 (1H, m), 7.82 (1H, d), 7.86 - 7.89 (1H, m), 8.17 - 8.17 (1H, m), 8.50 (1H, s), 8.55 (1H, s), 10.82 (1H, s)	m/z (ES+) (M+H)+ = 625; HPLC tR= 3.77 min.	AU4, BF1
BD7			m/z (ES+) (M+H)+ = 718; HPLC tR= 3.17 min.	BG1, B1
BD8		($CDCl_3$) 0.04 (6H, s), 0.88 (9H, s), 3.06 - 3.10 (2H, m), 3.15 - 3.20 (1H, m), 3.26 - 3.32 (1H, m), 3.86 - 3.91 (2H, m), 4.49 - 4.52 (1H, m), 5.89 - 5.92 (1H, m), 7.22 - 7.27 (1H, m), 7.40 - 7.44 (2H, m), 7.44 - 7.52 (1H, m), 8.15 - 8.16 (1H, m), 8.22 - 8.26 (1H, m), 8.41 (1H, d), 8.59 (1H, s), 9.83 (1H, d)	m/z (ES+) (M+H)+ = 616; HPLC tR= 3.02 min.	AX2, BH1
BD9		($CDCl_3$) 0.05 (6H, s), 0.89 (9H, s), 3.07 - 3.11 (2H, m), 3.17 - 3.21 (1H, m), 3.28 - 3.33 (1H, m), 3.89 - 3.92 (2H, m), 4.52 (1H, qn), 5.90 - 5.93 (1H, m), 7.42 - 7.48 (2H, m), 7.53 - 7.56 (2H, m), 8.17 (1H, d), 8.24 - 8.28 (1H, m), 8.42 (1H, s), 8.59 (1H, s), 9.85 (1H, s)	m/z (ES+) (M+H)+ = 632; HPLC tR= 3.05 min.	AX2, BA3

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BD10		(DMSO-d6) 0.91 - 1.01 (21H, m), 1.10 (3H, d), 3.52 - 3.57 (1H, m), 3.62 - 3.68 (1H, m), 3.75 - 3.78 (1H, m), 4.11 - 4.14 (2H, m), 5.94 (1H, s), 7.11 - 7.14 (1H, m), 7.74 - 7.79 (1H, m), 7.87 - 7.91 (1H, m), 7.99 (1H, t), 8.16 - 8.19 (2H, m), 8.33 - 8.36 (1H, m), 8.60 (1H, s), 8.73 (1H, s), 10.99 (1H, s)	m/z (ES+) (M+H)+ = 650; HPLC tR= 4.07 min.	AQ4, AH6
BD11		($CDCl_3$) 1.00 - 1.04 (21H, m), 1.13 (3H, d), 2.29 (3H, s), 3.56 - 3.74 (3H, m), 4.20 - 4.31 (2H, m), 6.00 - 6.03 (1H, m), 7.45 - 7.48 (1H, m), 7.51 - 7.53 (1H, m), 7.99 - 8.02 (1H, m), 8.08 - 8.09 (1H, m), 8.13 (1H, d), 8.46 (1H, s), 8.61 - 8.62 (2H, m), 8.65 (1H, s)	m/z (ES+) (M+H)+ = 640; HPLC tR= 3.90 min.	AU2, B15

Intermediate BD1 (2S)-3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-(1-(2-chloro-6-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(pyridin-2-yl)propanamide

Intermediate BD2 (2S)-3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-cyanopyridin-2-yl)propanamide

Intermediate BD3 (2S)-3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-(1-(2-chloro-6-cyanophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-cyanopyridin-2-yl)propanamide

Intermediate BD4 (2S)-3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(pyridin-2-yl)propanamide

Intermediate BD5 (2S)-3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-chloropyridin-2-yl)propanamide

Intermediate BD6 (2S)-N-(5-methylpyridin-2-yl)-2-(1-(4-methylthiophen-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-((R)-1-(triisopropylsilyloxy)propan-2-yloxy)propanamide

Intermediate BD7 (2S)-3-(3-((tert-butyldiphenylsilyloxy)methyl)azetidin-1-yl)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(pyridin-2-yl)propanamide

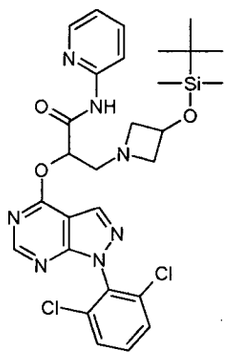
Intermediate BD8 (2S)-3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-(1-(2-chloro-6-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-fluoropyridin-2-yl)propanamide

Intermediate BD9 (S)-3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-(1-(2,6-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-fluoropyridin-2-yl)propanamide

Intermediate BD10 (2S)-2-(1-(2-chloro-6-cyanophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(pyridin-2-yl)-3-((R)-1-(triisopropylsilyloxy)propan-2-yloxy)propanamide

Intermediate BD11 (2S)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-methylpyridin-2-yl)-3-((R)-1-(triisopropylsilyloxy)propan-2-yloxy)propanamide

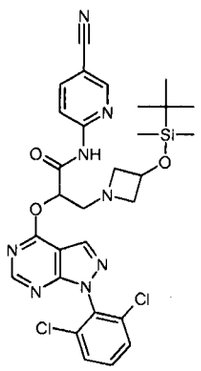
Intermediate BD12: (S)-3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-(1-(2,6-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(pyridin-2-yl)propanamide



Trimethylaluminium (0.362 mL, 0.72 mmol) was added to a solution of pyridin-2-amine (68.1 mg, 0.72 mmol) in toluene (8 mL) at 0°C under nitrogen. The reaction mixture was stirred at 0°C for 20 mins and then (S)-methyl 3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-(1-(2,6-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanoate (**Intermeidate BJ1**) (200 mg, 0.36 mmol) in toluene (4 mL) was added. The reaction mixture was allowed to warm to room temperature and then heated at reflux under nitogen for 4 hours. The reaction mixture was allowed to cool to room temperature and the

concentrated. The residue was neutralised to pH 7 with citric acid (1M, aq) and then diluted with water and DCM (50 mL). The organic layer was separated and the aqueous layer re-extracted with DCM (30 mL). The combined organics were dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 20 to 50% EtOAc in isohexane to afford the product (151 mg, 67.9 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (6H, s), 0.88 (9H, s), 3.05 - 3.09 (2H, m), 3.17 - 3.31 (2H, m), 3.86 - 3.91 (2H, m), 4.50 (1H, t), 5.89 - 5.92 (1H, m), 7.04 - 7.07 (1H, m), 7.42 - 7.47 (1H, m), 7.52 - 7.55 (2H, m), 7.68 - 7.72 (1H, m), 8.22 - 8.24 (1H, m), 8.29 - 8.31 (1H, m), 8.42 (1H, s), 8.58 (1H, s), 9.63 (1H, s); m/z (ES^+) $(M+H)^+$ = 616; HPLC t_R= 1.95 min.

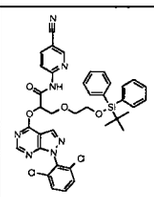
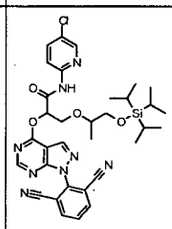
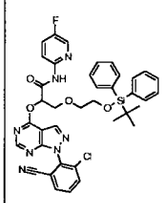
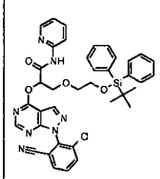
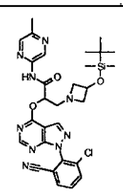
Intermediate BD13: (S)-3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-N-(5-cyanopyridin-2-yl)-2-(1-(2,6-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide

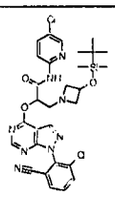
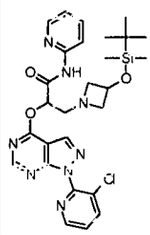
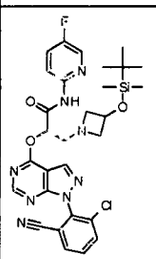
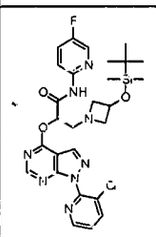


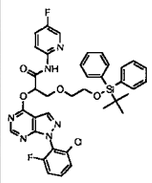
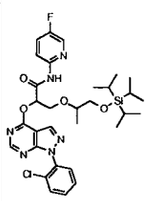
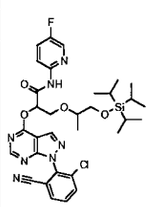
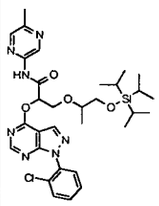
Using a procedure analogous to that described for **Intermediate BD12** using 6-aminonicotinonitrile and (S)-methyl 3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-(1-(2,6-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanoate (**Intermediate BJ1**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.89 (9H, s), 3.11 - 3.19 (3H, m), 3.30 - 3.35 (1H, m), 3.90 - 3.94 (2H, m), 4.54 (1H, t), 5.87 - 5.91 (1H, m), 7.43 - 7.47 (1H, m), 7.52 - 7.55 (2H, m), 7.92 - 7.94 (1H, m), 8.33 - 8.36 (1H, m), 8.40 (1H, s), 8.57 (1H, s), 8.59 (1H, q), 10.57 (1H, s); m/z (ES^+) M^+ = 639; HPLC t_R= 2.02 min.

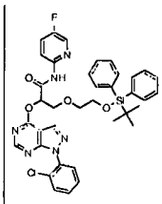
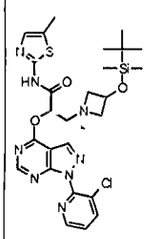
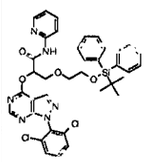
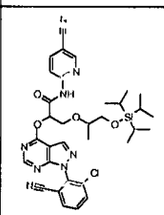
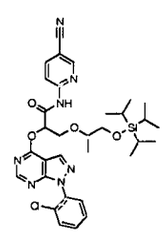
The following intermediates were prepared using a procedure analogous to that described for **Intermediate BB1** using the appropriate intermediates.

Intermediate number	Structure	1H NMR (400 MHz) δ	LCMS	Intermediate refs.
BD14			m/z (ES+) (M+H)+ = 752; HPLC tR= 3.78 min.	AK7, BA3
BD15		($CDCl_3$) 0.95 - 1.09 (m, 21H), 1.15 (d, 3H), 3.58 - 3.79 (m, 3H), 4.18 - 4.25 (m, 1H), 4.27 - 4.34 (m, 1H), 6.01 (t, 1H), 7.65 - 7.70 (m, 1H), 7.78 (t, 1H), 8.10 (d, 2H), 8.20 - 8.25 (m, 2H), 8.56 (s, 1H), 8.66 (s, 1H), 8.78 (s, 1H)		AY2, BK1
BD16		(DMSO-d6) 0.88 (s, 9H), 3.62 - 3.78 (m, 4H), 3.93 - 4.12 (m, 2H), 5.93 - 5.99 (m, 1H), 7.24 - 7.35 (m, 6H), 7.50 - 7.59 (m, 5H), 7.73 - 7.80 (m, 1H), 7.89 - 7.96 (m, 1H), 7.98 - 8.04 (m, 2H), 8.17 - 8.21 (m, 1H), 8.47 - 8.52 (m, 2H), 10.50 (s, 1H)	m/z (ES+), (M+H)+ = 736.55; HPLC tR = 3.66 min	BA1, AH6
BD17		(DMSO-d6) 0.97 (s, 9H), 3.71 - 3.90 (m, 4H), 4.08 - 4.22 (m, 2H), 6.03 - 6.10 (m, 1H), 7.07 - 7.13 (m, 1H), 7.33 - 7.45 (m, 6H), 7.60 - 7.66 (m, 5H), 7.71 - 7.78 (m, 1H), 7.85 (t, 1H), 7.94 - 7.99 (m, 1H), 8.06 - 8.13 (m, 2H), 8.30 - 8.34 (m, 1H), 8.57 - 8.60 (m, 1H), 10.43 (s, 1H)	m/z (ES+), (M+H)+ = 718.58; HPLC tR = 3.59 min	AQ2, AH6
BD18		($CDCl_3$) 0.00 (6H, s),0.81 (9H, s),2.47 (3H, s),2.99 - 3.09 (2H, m),3.11 (2H, d),4.40 - 4.50 (1H, m),3.81 - 3.88 (2H, m),5.83 - 5.88 (1H, m),7.53 - 7.58 (1H, m),7.70 -	m/z (ES+), (M+H)+ = 620; 5min, Acid,	BB2, AH6

		7.74 (1H, m),7.77 - 7.81 (1H, m),8.07 (1H, s),8.33 - 8.41 (1H, m),8.54 (1H, d),9.32 - 9.36 (1H, m),10.08 (1H, s),9.71 (0H, s)	HPLC tR = 1.81 min	
BD19		($CDCl_3$) 0.00 (6H, d), 0.78 - 0.82 (9H, m), 3.06 (2H, q), 3.23 (1H, d), 3.85 (2H, d), 4.43 - 4.46 (1H, m), 5.81 - 5.84 (1H, m), 7.19 (1H, s), 7.54 (1H, d), 7.57 - 7.61 (1H, m), 7.70 - 7.74 (1H, m), 7.77 - 7.80 (1H, m), 8.11 - 8.14 (1H, m), 8.18 - 8.19 (1H, m), 8.38 (1H, d), 8.53 (1H, d), 10.00 (1H, s)	m/z (ES+), (M+H)+ = 639; 5min Acid, HPLC tR = 2.01 min	AD2, AH6
BD20		($CDCl_3$) 0.05 (6H, t), 0.89 (9H, t), 3.05 - 3.10 (2H, m), 3.17 - 3.22 (1H, m), 3.30 (1H, q), 3.86 - 3.91 (2H, m), 4.50 (1H, t), 5.91 - 5.94 (1H, m), 7.04 - 7.08 (1H, m), 7.42 - 7.49 (1H, m), 7.68 - 7.73 (1H, m), 8.00 - 8.03 (1H, m), 8.21 - 8.24 (1H, m), 8.30 - 8.32 (1H, m), 8.42 (1H, s), 8.62 - 8.64 (2H, m), 9.59 (1H, s)	m/z (ES+) M+ = 581.36; HPLC tR= 2.57 min.	BE2, B15
BD21		($CDCl_3$) 0.03 - 0.06 (6H, m), 0.88 - 0.89 (9H, m), 3.07 - 3.33 (4H, m), 3.91 (2H, s), 4.50 - 4.54 (1H, m), 5.89 (1H, d), 7.40 - 7.46 (1H, m), 7.62 (1H, t), 7.77 - 7.81 (1H, m), 7.84 - 7.87 (1H, m), 8.16 (1H, d), 8.22 - 8.26 (1H, m), 8.45 (1H, d), 8.60 (1H, d), 9.74 - 10.00 (1H, m)	m/z (ES+) M+ = 623.20; HPLC tR= 2.81 min.	AX2, AH6
BD22		($CDCl_3$) 0.04 (6H s), 0.88 (9H s), 3.07 - 3.29 (4H, m), 3.89 (2H, s), 4.50 (1H, t), 5.91 (1H, t), 7.40 - 7.52 (2H, m), 8.00 - 8.02 (1H, m), 8.15 (1H, d), 8.22 - 8.25 (1H, m), 8.40 (1H, s), 8.61 - 8.63 (2H, m), 9.79 (1H, s)	m/z (ES+) (M+H)+ = 623.20; HPLC tR= 2.81 min.	AX2, B15

BD23		($CDCl_3$) 0.99 (9H, d), 3.68 - 3.72 (2H, m), 3.81 - 3.84 (2H, m), 4.18 - 4.21 (2H, m), 6.06 (1H, t), 7.22 - 7.27 (1H, m), 7.31 - 7.52 (9H, m), 7.63 - 7.68 (4H, m), 8.11 (1H, t), 8.25 - 8.29 (1H, m), 8.42 (1H, d), 8.58 (1H, d), 8.77 (1H, d)	m/z (ES+) (M+H)+ = 729.22; HPLC tR= 3.76 min.	BA2, BH1
BD24		($CDCl_3$) 0.98 - 1.07 (21H, m), 1.14 (3H, d), 3.59 - 3.67 (1H, m), 3.61 - 3.66 (1H, m), 3.71 - 3.75 (1H, m), 4.20 - 4.24 (1H, m), 4.28 - 4.32 (1H, m), 6.02 (1H, t), 7.42 - 7.45 (1H, m), 7.46 - 7.49 (2H, m), 7.52 - 7.55 (1H, m), 7.61 - 7.63 (1H, m), 8.13 (1H, d), 8.26 - 8.29 (1H, m), 8.42 (1H, s), 8.58 (1H, s), 8.79 (1H, s)	m/z (ES+) M+ = 643.39; HPLC tR= 3.96 min.	BL1, B1
BD25		($CDCl_3$) 0.98 - 1.07 (21H, m), 1.13 - 1.17 (3H, m), 3.59 - 3.77 (3H, m), 4.21 - 4.33 (2H, m), 6.00 - 6.04 (1H, m), 7.43 - 7.47 (1H, m), 7.60 - 7.65 (1H, m), 7.78 - 7.81 (1H, m), 7.85 - 7.87 (1H, m), 8.14 (1H, t), 8.25 - 8.29 (1H, m), 8.51 (1H, d), 8.60 (1H, d), 8.80 (1H, s)		BL1, AH6
BD26		($CDCl_3$) 0.98 - 1.08 (21H, m), 1.15 (3H, d), 2.04 (3H, s), 2.54 (3H, s), 3.59 - 3.68 (2H, m), 3.71 - 3.75 (1H, m), 4.21 - 4.33 (2H, m), 6.04 (1H, t), 7.46 - 7.50 (2H, m), 7.51 - 7.55 (1H, m), 7.61 - 7.63 (1H, m), 8.11 (1H, d), 8.41 (1H, s), 8.59 (1H, s), 8.70 (1H, s), 9.44 (1H, d)	m/z (ES+) = 641.87; HPLC tR= 4.08 min.	AZ2, B1

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BD27		($CDCl_3$) 0.99 (9H, s), 3.69 - 3.72 (2H, m), 3.81 - 3.86 (2H, m), 4.16 - 4.24 (2H, m), 6.07 (1H, t), 7.31 - 7.68 (15H, m), 8.11 (1H, s), 8.25 - 8.28 (1H, m), 8.37 (1H, s), 8.58 (1H, s), 8.77 (1H, s)	m/z (ES+) $(M+H)^+$ = 711.41; HPLC tR= 3.79 min.	BA2, B1
BD28		($CDCl_3$) 0.05 (6H, s), 0.88 (9H, s), 2.38 - 2.41 (3H, m), 3.05 - 3.16 (3H, m), 3.29 - 3.36 (1H, m), 3.90 - 3.96 (2H, m), 4.50 - 4.58 (1H, m), 5.96 - 6.01 (1H, m), 7.08 - 7.12 (1H, m), 7.44 - 7.49 (1H, m), 7.98 - 8.02 (1H, m), 8.37 (1H, s), 8.60 - 8.64 (2H, m), 11.11 - 11.47 (1H, m)	m/z (ES+) $(M+H)^+$ = 601.39; HPLC tR= 2.61 min.	BM1, B15
BD29		($CDCl_3$) 0.99 (9H, t), 3.69 - 3.72 (2H, m), 3.82 (2H, t), 4.16 - 4.25 (2H, m), 6.06 - 6.08 (1H, m), 7.04 - 7.07 (1H, m), 7.31 - 7.46 (7H, m), 7.51 - 7.54 (2H, m), 7.63 - 7.73 (5H, m), 8.26 - 8.29 (1H, m), 8.43 (1H, s), 8.58 (1H, s), 8.76 (1H, s)	m/z (ES+) $(M+H)^+$ = 727.48; HPLC tR= 3.98 min.	AQ2, BA3
BD30		(DMSO-d6) 0.88 - 1.01 (21H, m), 1.09 (3H, d), 3.52 - 3.56 (1H, m), 3.65 (1H, q), 3.73 - 3.77 (1H, m), 4.10 - 4.16 (2H, m), 5.93 - 5.95 (1H, m), 7.87 - 7.91 (1H, m), 8.12 - 8.19 (3H, m), 8.23 - 8.27 (1H, m), 8.60 (1H, s), 8.73 (1H, d), 8.82 - 8.83 (1H, m), 11.57 (1H, s)	m/z (ES+) $(M+H)^+$ = 673.49 & 675.57; HPLC tR= 4 min.	BN1, AH6
BD31		($CDCl_3$) 0.98 - 1.08 (21H, m), 1.15 (3H, t), 3.61 - 3.76 (3H, m), 4.20 - 4.24 (1H, m), 4.30 - 4.34 (1H, m), 6.00 (1H, t), 7.46 - 7.54 (3H, m), 7.61 - 7.64 (1H, m), 7.94 - 7.97 (1H, m), 8.37 - 8.41 (2H, m), 8.56 - 8.58 (2H, m), 9.05 (1H, s)	m/z (ES+) $(M+H)^+$ = 648.54 & 650.50; HPLC tR= 4.08 min.	BN1, B1

Intermediate BD14 (S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-N-(5-cyanopyridin-2-yl)-2-(1-(2,6-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanamide

Intermediate BD15 (S)-N-(5-chloropyridin-2-yl)-2-(1-(2,6-dicyanophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-((R)-1-(triisopropylsilyloxy)propan-2-yloxy)propanamide

Intermediate BD16 (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(2-chloro-6-cyanophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-fluoropyridin-2-yl)propanamide

Intermediate BD17 (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(2-chloro-6-cyanophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(pyridin-2-yl)propanamide

Intermediate BD18 (2S)-3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-(1-(2-chloro-6-cyanophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-methylpyrazin-2-yl)propanamide

Intermediate BD19 (2S)-3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-(1-(2-chloro-6-cyanophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-chloropyridin-2-yl)propanamide

Intermediate BD20 (2S)-3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(pyridin-2-yl)propanamide

Intermediate BD21 (2S)-3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-(1-(2-chloro-6-cyanophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-fluoropyridin-2-yl)propanamide

Intermediate BD22 (2S)-3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-fluoropyridin-2-yl)propanamide

Intermediate BD23 (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(2-chloro-6-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-fluoropyridin-2-yl)propanamide

Intermediate BD24 (2S)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-fluoropyridin-2-yl)-3-((R)-1-(triisopropylsilyloxy)propan-2-yloxy)propanamide

Intermediate BD25 (2S)-2-(1-(2-chloro-6-cyanophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-fluoropyridin-2-yl)-3-((R)-1-(triisopropylsilyloxy)propan-2-yloxy)propanamide

Intermediate BD26 (2S)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-methylpyrazin-2-yl)-3-((R)-1-(triisopropylsilyloxy)propan-2-yloxy)propanamide

Intermediate BD27 (2S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-fluoropyridin-2-yl)propanamide

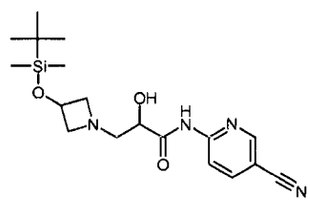
Intermediate BD28 (2S)-3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-methylthiazol-2-yl)propanamide

Intermediate BD29 (S)-3-(2-(tert-butyldiphenylsilyloxy)ethoxy)-2-(1-(2,6-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(pyridin-2-yl)propanamide

Intermediate BD30 (2S)-2-(1-(2-chloro-6-cyanophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-cyanopyridin-2-yl)-3-((R)-1-(triisopropylsilyloxy)propan-2-yloxy)propanamide

Intermediate BD31 (2S)-2-(1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-cyanopyridin-2-yl)-3-((R)-1-(triisopropylsilyloxy)propan-2-yloxy)propanamide

Intermediate BE1: (S)-3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-N-(5-cyanopyridin-2-yl)-2-hydroxypropanamide

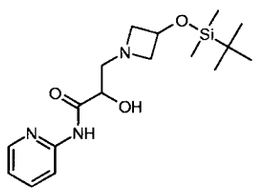


Trimethylaluminium (7.95 mL, 15.89 mmol) was added to 6-aminonicotinonitrile (1.646 g, 13.82 mmol) in toluene (50 mL) cooled to 0 °C under nitrogen. The resulting solution was stirred at 0°C for 10 minutes. (S)-Methyl 3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-hydroxypropanoate (**Intermediate AD3**) (4.0 g, 13.82 mmol) in toluene (20 mL) was added and the resulting solution was allowed to warm to room temperature and then heated at 60°C for 3 hours. The mixture was cooled to ~10°C and quenched by the addition of 20% Rochelle salt solution. It was then diluted with EtOAc (50 mL) and stirred for 2 hours. The organic phase was separated, washed with water and brine, dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash chromatography on silica with EtOAc as eluent to afford the product containing some 6-aminonicotinonitrile (4.1 g). This was used without further purification.

^{1}H NMR (400 MHz, DMSO-d6) δ 0.02 (6H, s), 0.83 (9H, s), 2.69 - 2.71 (2H, m), 2.76 -

2.82 (2H, m), 3.56 - 3.61 (2H, m), 4.12 - 4.14 (1H, m), 4.30 - 4.38 (1H, m), 5.85 (1H, s, broad), 8.20 - 8.32 (3H, m), 10.30 (1H, s, broad); m/z (ES^+) $(M+H)^+$ = 377; HPLC t_R= 1.43 min.

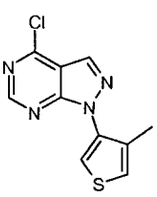
Intermediate BE2: (S)-3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-hydroxy-N-(pyridin-2-yl)propanamide



Trimethylaluminium (2.384 mL, 4.77 mmol) was added to pyridin-2-amine (0.390 g, 4.15 mmol) in toluene (30 mL) cooled to 0 °C under nitrogen. The resulting solution was stirred at 0°C for 10 minutes. (S)-methyl 3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-hydroxypropanoate (**Intermediate AD3**) (1.2 g, 4.15 mmol) in toluene (10 mL) was added and the reaction was allowed to warm to room temperature and then heated at 80°C for 4 hours. The reaction mixture was cooled, 20% Rochelle salt in water (75 mL) added and stirred for 2 hours. The mixture was extracted with ethyl acetate (2×5 mL) and the combined organic extracts washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in EtOAc to afford the product (1.25g).

^{1}H NMR (400 MHz, DMSO-d6) δ 0.03 (6H, s), 0.83 (9H, m), 2.65 - 2.74 (2H, m), 2.78 - 2.88 (2H, m), 3.56 - 3.60 (2H, m), 4.07 - 4.12 (1H, m), 4.27 - 4.36 (1H, m), 5.77 - 5.83 (1H, m), 7.11 - 7.14 (1H, m), 7.78 - 7.82 (1H, m), 8.05 - 8.10 (1H, m), 8.30 - 8.32 (1H, m), 9.65 (1H, s) m/z (ES^+) $(M+H)^+$ = 352; HPLC t_R= 1.25 min.

Intermediate BF1: 4-chloro-1-(4-methylthiophen-3-yl)-1H-pyrazolo[3,4-d]pyrimidine

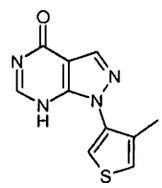


Phosphoryl trichloride (4.2 mL, 45 mmol) was added in one portion to 1-(4-methylthiophen-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol (**Intermediate BF2**) (700 mg, 3.01 mmol). The resulting suspension was heated to 100 °C to give a solution and stirred for 2 hours. The mixture was evaporated and ice added to the residue and stirred for 30

minutes. It was then filtered and the solids washed with water (3 × 10 mL). The crude product was dissolved in ethyl acetate (40 mL), dried with $MgSO_4$, filtered and evaporated to give the product (700 mg, 93%).

^{1}H NMR (400 MHz, DMSO-d6) δ 2.09 (3H, d), 7.43 - 7.45 (1H, m), 7.89 (1H, d), 8.72 (1H, s), 8.90 (1H, s); m/z (ES^+) $(M+H)^+$ = 251; HPLC t_R= 2.26 min.

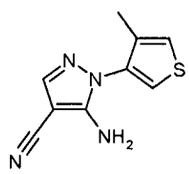
Intermediate BF2: 1-(4-methylthiophen-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4(7H)-one



Concentrated sulfuric acid (0.237 mL, 4.46 mmol) was added to a stirred solution of 5-amino-1-(4-methylthiophen-3-yl)-1H-pyrazole-4-carbonitrile (**Intermediate BF3**) (910 mg, 4.46 mmol) in formic acid (15 mL). The resulting solution was stirred at 100 °C for 20 hours. It was then cooled and evaporated to ~half volume. Water (10 mL) was added and stirred for 1 hour. It was then filtered, washed with water (3 × 5mL) and dried under high vacuum at 45°C to afford the product (700 mg, 67%) which was used without further purification.

^{1}H NMR (400 MHz, DMSO-d6) δ 2.07 (3H, d), 7.36 - 7.38 (1H, m), 7.77 (1H, d), 8.09 (1H, s), 8.28 (1H, s), 12.31 (1H, s); m/z (ES^+) $(M+H)^+$ = 233; HPLC t_R= 1.29 min.

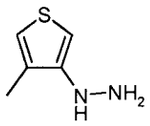
Intermediate BF3: 5-amino-1-(4-methylthiophen-3-yl)-1H-pyrazole-4-carbonitrile



(4-Methylthiophen-3-yl)hydrazine (**Intermediate BF4**) (910 mg, 7.10 mmol) was suspended in MeOH (30 mL) under nitrogen, 2-(ethoxymethylene)malononitrile (867 mg, 7.10 mmol) added in one portion and the mixture stirred at ambient temperature for 1 hour then heated at reflux for 2 hours. The mixture was cooled, evaporated and dried under high vacuum. The crude product was purified by flash silica chromatography, elution gradient 30 to 100% EtOAc in isohexane to afford the product (780 mg, 54%).

^{1}H NMR (400 MHz, DMSO-d6) δ 1.97 (3H, s), 6.51 (2H, s), 7.34 - 7.35 (1H, m), 7.69 - 7.72 (1H, m), 7.73 (1H, s); m/z (ES^+) $(M+H)^+$ = 205; HPLC t_R= 1.40 min.

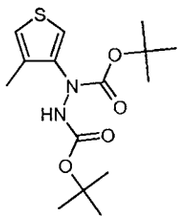
Intermediate BF4: (4-methylthiophen-3-yl)hydrazine



A solution of 4M HCl in dioxane (43.4 mL, 173.55 mmol) was added dropwise to a stirred solution of di-tert-butyl 1-(4-methylthiophen-3-yl)hydrazine-1,2-dicarboxylate (**Intermediate BF5**) (5.7 g, 17.36 mmol) in isopropanol (50 mL) over a period of 1 minute. The resulting solution was stirred at reflux for 2 hours. The mixture was evaporated, co-evaporated with 1,4-dioxane (3×50 mL) and dried under high vacuum. The residue was suspended in DCM and washed with 1M NaOH. The organic phase was washed with water, dried by passing through a phase separating membrane and evaporated to afford the product (910mg) which was used without further purification.

^{1}H NMR (400 MHz, DMSO-d6) δ 1.96 (3H, s), 3.85 (2H, s), 6.14 (1H, s), 6.17 (1H, d), 6.91 - 6.92 (1H, m).

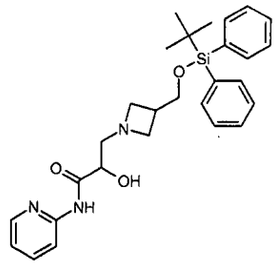
Intermediate BF5: di-tert-butyl 1-(4-methylthiophen-3-yl)hydrazine-1,2-dicarboxylate



Isopropylmagnesium chloride – lithium chloride complex (0.96M) (40.5 mL, 38.91 mmol) was added to 3-bromo-4-methylthiophene (CAS no. 30318-99-1) (5.3 g, 29.93 mmol) in THF (60 mL) cooled to 0°C under nitrogen. The resulting solution was warmed to room temperature and stirred for 3 hours. The reaction temperature was cooled to 0°C and di-tert-butyl azodicarboxylate (10.34 g, 44.90 mmol) in THF (30 mL) was added dropwise maintaining the temperature below 10 °C. The reaction was warmed to room temperature and stirred for 20 hours. The reaction mixture was cooled to ~10 °C, saturated NH_4Cl (150 mL) added, and extracted with EtOAc (3 × 75 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash silica chromatography, elution gradient 20 to 50% Et2O in isohexane to give the product (7.0 g).

^{1}H NMR (400 MHz, DMSO-d6) δ 1.37 - 1.40 (18H, m), 2.08 (3H, s), 7.06 (1H, d), 7.26 (1H, d), 8.68 (1H, s)

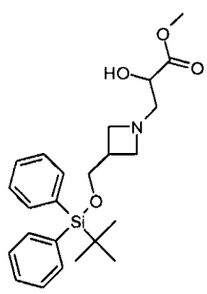
Intermediate BG1: (S)-3-(3-((tert-butyldiphenylsilyloxy)methyl)azetidin-1-yl)-2-hydroxy-N-(pyridin-2-yl)propanamide



Trimethylaluminium (1.344 mL, 2.69 mmol) was added to pyridin-2-amine (220 mg, 2.34 mmol) in toluene (20 mL) cooled to 0 °C under nitrogen over a period of 10 minutes. The resulting solution was stirred at 0°C for 10 minutes. (S)-Methyl 3-(3-((tert-butyldiphenylsilyloxy)methyl)azetidin-1-yl)-2-hydroxypropanoate (**Intermediate BG2**) (1.43 g, 2.34 mmol) in toluene (5 mL) was added over 10 minutes and the reaction was allowed to warm to room temperature and then heated at 110°C for 2 hours. The reaction mixture was cooled and poured into a 20% solution of Rochelle salt (30 mL), diluted with ethyl acetate (80 mL) and stirred for 1 hour. The organic phase was separated, washed with water and brine, dried over $MgSO_4$ filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 100% (10% MeOH in DCM) in DCM to afford the product (681 mg, 59.5 %).

m/z (ES^+) $(M+H)^+$ = 491; HPLC t_R= 2.67 min.

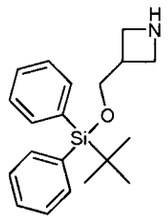
Intermediate BG2: (S)-methyl 3-(3-((tert-butyldiphenylsilyloxy)methyl)azetidin-1-yl)-2-hydroxypropanoate



3-((tert-Butyldiphenylsilyloxy)methyl)azetidine (**Intermediate BG3**) (7.461 g, 22.92 mmol) and (S)-methyl oxirane-2-carboxylate (2.340 g, 22.92 mmol) were dissolved in acetonitrile (50 mL) and heated to 85 °C for 90 minutes. The resulting mixture was cooled and evaporated to dryness. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM to afford the product (9.6 g, 56%).

^{1}H(400 MHz, $CDCl_3$) δ 1.05 (9H s), 2.69 (1H, t), 2.73 - 2.82 (2H, m), 3.08 (2H, q), 3.38 (2H, q), 3.70 - 3.78 (5H, m), 4.09 - 4.12 (1H, m), 7.36 - 7.45 (6H, m), 7.62 - 7.66 (4H, m); m/z (ES^+) $(M+H)^+$ = 428.41; HPLC t_R= 2.43 min.

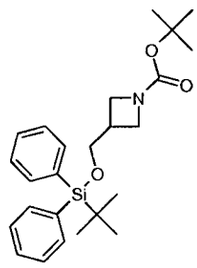
Intermediate BG3: 3-((tert-butyldiphenylsilyloxy)methyl)azetidine



2,2,2-Trifluoroacetic acid (42.9 mL, 556.53 mmol) was added to tert-butyl 3-((tert-butyldiphenylsilyloxy)methyl)azetidine-1-carboxylate (**Intermediate BG4**) (9.87 g, 23.19 mmol) in anhydrous DCM (50 mL) at 0 °C then allowed to stirred at room temperature for 1 hour. The solution was concentrated and made basic using sodium hydroxide (250 mL, 2M) was added.the suspension was extracted with DCM and dried with Na_2SO_4 to afford the product (7.46 g, 99 %)

^{1}H(400 MHz, $CDCl_3$) δ 1.03 - 1.07 (9H, m), 2.87 - 2.95 (1H, m), 3.47 - 3.51 (2H, m), 3.60 (2H, t), 3.77 (2H, d), 7.35 - 7.45 (6H, m), 7.62 - 7.73 (4H, m); m/z (ES^+) $(M+H)^+$ = 326.22; HPLC t_R= 2.45 min.

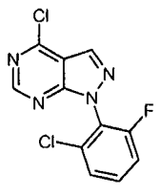
Intermediate BG4: tert-butyl 3-((tert-butyldiphenylsilyloxy)methyl)azetidine-1-carboxylate



A solution of tert-butylchlorodiphenylsilane (5.56 mL, 21.36 mmol) in DCM (20 mL) was added dropwise to a stirred solution of tert-butyl 3-(hydroxymethyl)azetidine-1-carboxylate (CAS no. 142253-56-3) (4.0 g, 21 mmol) and anhydrous N-ethyl-N-isopropylpropan-2-amine (9.1 mL, 53 mmol) in DCM (45 mL) cooled to 10°C, over a period of 2 minutes under nitrogen. The resulting solution was stirred at ambient temperature for 3 hours 4-dimethylaminopyridine (100 mg) was added and the reaction was left overnight. The reaction mixture was concentrated and diluted with EtOAc (75

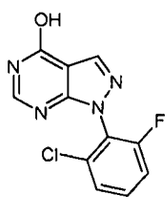
mL), and washed sequentially with saturated $NaHCO_3$ (25 mL), water (20 mL) and saturated brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford the crude product (9.87 g) which was used without further purification. ^1H(400 MHz, $CDCl_3$) δ 1.06 (9H, q), 1.44 (9H, d), 2.68 (1H, s), 3.72 - 3.75 (4H, m), 3.92 (2H, t), 7.36 - 7.45 (6H, m), 7.63 - 7.73 (4H, m); HPLC t_R= 3.75 min.

Intermediate BH1: 4-chloro-1-(2-chloro-6-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidine



Phosphorus oxychloride (17.54 mL, 188.18 mmol) was added to 1-(2-chloro-6-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol (**Intermediate BH2**) (2.49 g, 9.41 mmol). The resulting solution was stirred at 100 °C for 1 hour. The reaction mixture was evaporated. Ice/water (100 mL) and then EtOAc (100 mL) were added. The organic layer was separated and the aqueous layer re-extracted with EtOAc (100 mL) . The combined organics were washed with water (100 mL), dried ($MgSO_4$) and concentrated to give the crude product (2.48 g) which was used without further purification. ^1H(400 MHz, DMSO-d6) δ 7.60 - 7.65 (1H, m), 7.67 - 7.70 (1H, m), 7.75 - 7.81 (1H, m), 8.89 (1H, s), 8.92 - 8.95 (1H, m).

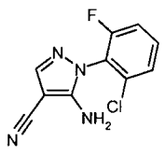
Intermediate BH2: 1-(2-chloro-6-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol



Concentrated sulfuric acid (0.867 mL, 16.27 mmol) was added to a stirred solution of 5-amino-1-(2-chloro-6-fluorophenyl)-1H-pyrazole-4-carbonitrile (**Intermediate BH3**) (3.5 g, 14.79 mmol) in formic acid (25 mL). The resulting solution was stirred at 100 °C for 24 hours. The reaction was allowed to cool to room temperature and evaporated to approximately half volume, water (100 mL) added and stirred for 1 hour. The formed precipitate was filtered off, washed well with water and dried overnight in a vacuum over P_2O_5 to afford the product (2.51 g, 64.1 %) which was used without further purification.

^{1}H(400 MHz, DMSO-d6) δ 7.53 - 7.58 (1H, m), 7.61 - 7.64 (1H, m), 7.68 - 7.74 (1H, m), 8.09 - 8.10 (1H, m), 8.41 (1H, s), 12.46 (1H, s); m/z (ES^+) $(M+H)^+$ = 265; HPLC t_R= 1.79 min.

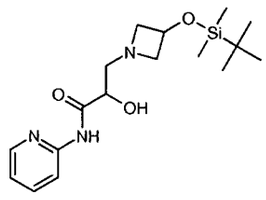
Intermediate BH3: 5-amino-1-(2-chloro-6-fluorophenyl)-1H-pyrazole-4-carbonitrile



(2-Chloro-6-fluorophenyl)hydrazine hydrochloride (CAS no. 529512-79-6) (5 g, 25.38 mmol) was partitioned between EtOAc (100 mL) and NaOH (2M, aq) (40 mL). The organic layer separated and washed with water (50 mL), brine (50 mL), dried ($MgSO_4$), filtered and concentrated. The resultant oil was suspended in MeOH (50 mL) under nitrogen at -5°C. 2-(Ethoxymethylene)malononitrile (3.10 g, 25.38 mmol) added portionwise over 5 mins and the mixture stirred at ~0°C for 30 mins. The reaction mixture was allowed to warm to room temperature and then heated at reflux under nitrogen for 2 hours. The reaction mixture was allowed to cool and evaporated to dryness to afford the product (3.52 g) which was used without further purification.

^{1}H(400 MHz, $CDCl_3$) δ 4.51 (2H, s), 7.21 - 7.26 (1H, m), 7.39 - 7.42 (1H, m), 7.47 - 7.53 (1H, m), 7.72 (1H, s); m/z (ES^+) $(M+H)^+$ = 237; HPLC t_R= 1.54 min.

Intermediate BI1: (S)-3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-hydroxy-N-(pyridin-2-yl)propanamide

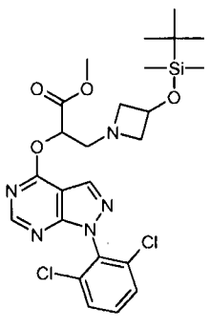


Trimethylaluminium (7.60 mL, 15.20 mmol) was added to pyridin-2-amine (1.431 g, 15.20 mmol) in anhydrous toluene (30 mL) cooled to 0 °C under nitrogen. The resulting solution was stirred at 0°C for 10 minutes. (S)-Methyl 3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-hydroxypropanoate (**Intermediate AD3**) (2.2 g, 7.60 mmol) in anhydrous toluene (10 mL) was added and the resulting solution was allowed to warm to room temperature and then heated at 80°C for 4 hours. The mixture was cooled to room temperature, neutralised with Rochelle salt in water (20%, 75 mL), diluted with water (50 mL) and

extracted with EtOAc (2 × 50 mL). The organic phase was separated, washed with brine, dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 20 to 50% EtOAc in isohexane to give impure product. This was shown to contain the starting amine so was re-purified by flash silica chromatography, elution gradient 0 to 10% MeOH in DCM to afford the product (1.928 g, 72.2%).

^{1}H(400 MHz, $CDCl_3$) δ 0.02 - 0.04 (6H, m), 0.87 (9H s), 2.90 - 2.92 (2H, m), 3.05 (2H, q), 3.69 - 3.77 (2H, m), 4.02 (1H, t), 4.41 - 4.48 (1H, m), 7.03 - 7.06 (1H, m), 7.67 - 7.72 (1H, m), 8.19 - 8.21 (1H, m), 8.30 - 8.32 (1H, m), 9.78 (1H, s); m/z (ES^+) $(M+H)^+$ = 353.12; HPLC t_R= 1.93 min.

Intermediate BJ1: (S)-methyl 3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-(1-(2,6-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)propanoate

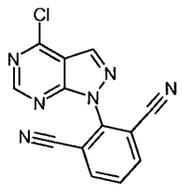


Sodium hydride (60% dispersion in mineral oil) (127 mg, 3.17 mmol) was added to (S)-methyl 3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-hydroxypropanoate (**Intermediate AD3**) (765 mg, 2.64 mmol) in anhydrous THF (30 mL) at 0°C under nitrogen. The resulting solution was stirred at 0°C for 10 minutes and then 4-chloro-1-(2,6-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate BA3**) (871 mg, 2.91 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was neutralised with 1M citric acid and the reaction mixture diluted with water (20 mL) and EtOAc (50 mL). The organic layer was separated and the aqueous layer re-extracted with EtOAc (2 × 50 mL). The combined organics were washed with saturated brine (75 mL),dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by flash silica chromatography, elution gradient 50 to 100% EtOAc in isohexane to afford the product (445 mg, 30.5 %).

^{1}H(400 MHz, $CDCl_3$) δ 0.05 (6H, s), 0.89 (9H, s), 3.03 - 3.11 (3H, m), 3.18 - 3.23 (1H, m),

3.77 - 3.79 (1H, m), 3.80 (3H, s), 3.86 (1H, d), 4.46 (1H, t), 5.66 (1H, q), 7.45 (1H, t), 7.51 - 7.55 (2H, m), 8.37 (1H, s), 8.53 (1H, s); m/z (ES^+) $(M+H)^+$ = 554.8; HPLC t_R= 1.95 min.

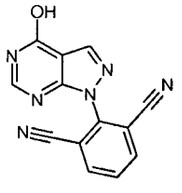
Intermediate BK1: 2-(4-chloro-1H-pyrazolo[3,4-d]pyrimidin-1-yl)isophthalonitrile



Phosphoryl trichloride (6842 µl, 71.40 mmol) was added to 2-(4-hydroxy-1H-pyrazolo[3,4-d]pyrimidin-1-yl)isophthalonitrile (**Intermediate BK2**) (1872 mg, 7.14 mmol). The resulting solution was stirred at 100 °C for 4 hours. The reaction mixture was evaporated and ice/water added to the residue. After stirring for 1 hour a precipitate formed that was filtered off and washed with water (3 × 5 mL) to give a yellow solid. This was dried under high vacuum for 20 hours to give the product (879 mg, 43.9 %) which was used without further purification.

^{1}H NMR (400 MHz, DMSO) δ 8.01 (t, 1H), 8.49 (d, 2H), 9.01 (d, 2H); m/z (ES^-), $(M-H)^-$ = 279.15; HPLC t_R = 2.17 min.

Intermediate BK2: 2-(4-hydroxy-1H-pyrazolo[3,4-d]pyrimidin-1-yl)isophthalonitrile

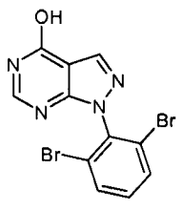


1-(2,6-dibromophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol (**Intermediate BK3**) (686 mg, 1.85 mmol) and zinc cyanide (392 mg, 3.34 mmol) were dissolved in DMF (9270 µl) and sealed into a microwave tube. The tube was purged with nitrogen. 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (215 mg, 0.37 mmol) and tris(dibenzylideneacetone)dipalladium(0) (170 mg, 0.19 mmol) were added. The reaction was heated to 150 °C for 5 minutes in the microwave reactor and cooled to room temperature. The solvent was evaporated. The crude product was absorbed onto celite and purified by flash silica chromatography, elution gradient 0 to 10% MeOH in DCM to afford the product (420 mg, 86 %).

^{1}H NMR (400 MHz, DMSO) δ 8.02 (t, 1H), 8.23 (s, 1H), 8.49 (d, 2H), 8.58 (s, 1H), 12.67

(s, 1H); m/z (ES^-) $(M-H)^-$ = 261.13; HPLC t_R = 1.42 min.

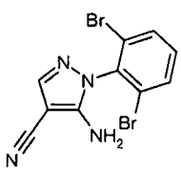
Intermediate BK3: 1-(2,6-dibromophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol



Conc. sulfuric acid (1.323 mL, 24.83 mmol) was added to a stirred solution of 5-amino-1-(2,6-dibromophenyl)-1H-pyrazole-4-carbonitrile (**Intermediate BK4**) (5.66 g, 16.55 mmol) in formic acid (50 mL). The resulting solution was stirred at 100 °C for 3 hours. The reaction mixture was cooled and evaporated to approximately half volume, water (20 mL) added and stirred for 1 hour. The resulting precipitate was filtered, washed with water (3 × 10 mL) and dried in vacuo at 50 °C to give the product (3.60 g, 58.8 %) which was used without further purification.

^{1}H NMR (400 MHz, DMSO) δ 7.49 (t, 1H), 7.90 (d, 2H), 8.07 - 8.10 (m, 1H), 8.39 (s, 1H), 12.43 (s, 1H); m/z (ES^+), $(M+H)^+$ = 371.07; HPLC t_R = 1.92 min.

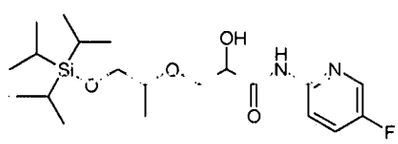
Intermediate BK4: 5-amino-1-(2,6-dibromophenyl)-1H-pyrazole-4-carbonitrile



2-(Ethoxymethylene)malononitrile (197 mg, 1.62 mmol) was added portionwise to a stirred solution of (2,6-dibromophenyl)hydrazine (CAS no. 14763-29-2) (430 mg, 1.62 mmol) in MeOH (8085 µl), under nitrogen at 5°C. The resulting solution was allowed to stir for a further 1 hour. The reaction mixture was then heated to reflux and was stirred for 3 hours. The reaction mixture was allowed to cool to ambient temperature, then was evaporated to afford crude product which was used without further purification.

m/z (ES^+), $(M+H)^+$ = 343.06; HPLC t_R = 1.91 min.

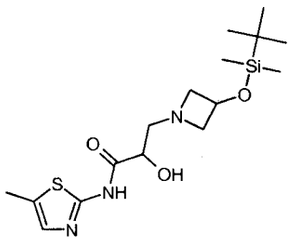
Intermediate BL1: (S)-N-(5-fluoropyridin-2-yl)-2-hydroxy-3-((S)-1-(triisopropylsilyloxy)propan-2-yloxy)propanamide



Trimethylaluminium (5.98 mL, 11.96 mmol) was added to 5-fluoropyridin-2-amine (1.340 g, 11.96 mmol) in toluene (20 mL) cooled to 0 °C under nitrogen. The resulting solution was stirred at 0°C for 20 minutes. (S)-Methyl 2-hydroxy-3-((R)-1-(triisopropylsilyloxy)propan-2-yloxy)propanoate (**Intermediate AU5**) (2 g, 5.98 mmol) in toluene (6 mL) was added and the reaction was allowed to warm to room temperature and then refluxed for 6 hours. The reaction mixture was allowed to cool and concentrated in vacuo. The residue was neutralised with citric acid (1M, aq) and then diluted with water (25mL) and extracted with EtOAc (2 × 50 mL). The combined organics were washed with brine (20 mL), then dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 30 to 50% EtOAc in isohexane to afford the product (1.863 g, 75 %).

^{1}H(400 MHz, $CDCl_3$) δ 1.03 - 1.17 (24H, m), 3.61 - 3.68 (3H, m), 3.81 - 3.85 (1H, m), 4.02 - 4.06 (1H, m), 4.16 (1H, d), 4.31 (1H, t), 7.40 - 7.45 (1H, m), 8.14 (1H, d), 8.25 - 8.28 (1H, m), 9.22 (1H, s); m/z (ES^+) $(M+H)^+$ = 415.31; HPLC t_R= 3.9 min.

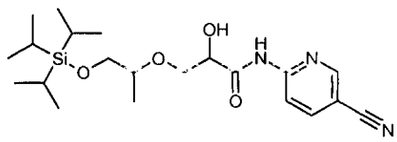
Intermediate BM1: (S)-3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-hydroxy-N-(5-methylthiazol-2-yl)propanamide



Trimethylaluminium (1M in heptane) (3.97 mL, 3.97 mmol) was added to 5-methylthiazol-2-amine (0.434 g, 3.80 mmol) in DCM (40 mL) cooled to 0 °C under nitrogen. The resulting solution was stirred at 0°C for 10 minutes. (S)-Methyl 3-(3-(tert-butyldimethylsilyloxy)azetidin-1-yl)-2-hydroxypropanoate (**Intermediate AD3**) (1 g, 3.45 mmol) in DCM (10 mL) was added and the reaction was allowed to warm to room temperature and then heated at reflux for 2 hours, then left to cool to room temperature overnight. Rochelle solution (20%; 50mL) was added and the resulting mixture was stirred vigorously for 90 mins. The mixture was diluted with DCM (50 mL) and the layers separated. The organics were dried ($MgSO_4$) and evaporated (733mg). The residue was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in EtOAc to afford the product (0.300 g, 23.37 %).

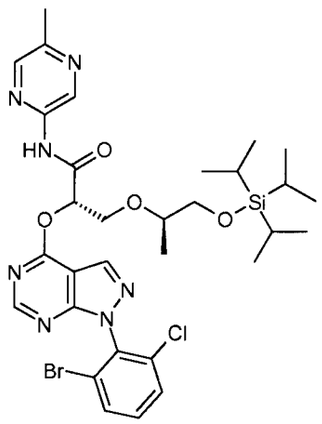
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (6H, s), 0.87 (9H, s), 2.40 (3H, s), 2.90 (2H, d), 2.99 - 3.10 (2H, m), 3.66 - 3.79 (2H, m), 4.04 (1H, t), 4.41 - 4.50 (1H, m), 7.08 - 7.10 (1H, m); m/z (ES^+) $(M+H)^+$ = 372.39; HPLC t_R= 2.13 min.

Intermediate BN1: (S)-N-(5-cyanopyridin-2-yl)-2-hydroxy-3-((R)-1-(triisopropylsilyloxy)propan-2-yloxy)propanamide



Trimethylaluminium (5.98 mL, 11.96 mmol) was added to 6-aminonicotinonitrile (1.424 g, 11.96 mmol) in toluene (20 mL) cooled to 0 °C under nitrogen. The resulting solution was stirred at 0°C for 20 minutes. (S)-Methyl 2-hydroxy-3-((R)-1-(triisopropylsilyloxy)propan-2-yloxy)propanoate (**Intermediate AU5**) (2 g, 5.98 mmol) in toluene (6 mL) was added and the reaction was allowed to warm to room temperature and then refluxed for 6 hours. The reaction mixture was allowed to cool and concentrated in vacuo. The residue was neutralised with citric acid (1M, aq) and then diluted with water (25mL) and extracted with EtOAc (2 × 50 mL). The combined organics were washed with brine (20 mL), then dried ($MgSO_4$) and evaporated. The crude product was purified by flash silica chromatography, eluting with 30 to 50% EtOAc in isohexane to afford the product (1.760 g, 69.8 %). ^{1}H(400 MHz, $CDCl_3$) δ 1.05 - 1.18 (27H, m), 1.25 (2H, q), 1.53 (11H, s), 2.04 (1H, s), 2.26 (1H, d), 3.63 - 3.67 (3H, m), 3.81 - 3.84 (1H, m), 4.08 - 4.15 (1H, m), 4.32 (2H, d), 7.92 - 7.95 (1H, m), 8.38 - 8.40 (1H, m), 8.58 (1H, q), 9.45 (1H, s); m/z (ES^+) $(M+H)^+$ = 422.26; HPLC t_R= 3.85 min.

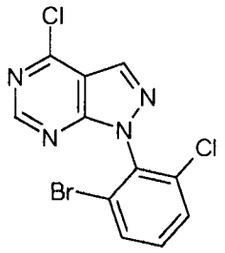
Intermediate BO1: (2S)-2-[1-(2-bromo-6-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-methylpyrazin-2-yl)-3-[(2R)-1-tri(propan-2-yl)silyloxypropan-2-yl]oxypropanamide



Sodium hydride (0.875 g, 21.87 mmol) was added to (S)-2-hydroxy-N-(5-methylpyrazin-2-yl)-3-((R)-1-(triisopropylsilyloxy)propan-2-yloxy)propanamide (**Intermediate AZ2**) (3.0 g, 7.29 mmol) in anhydrous THF (35 mL) at 0 °C under nitrogen. The resulting solution was stirred at 0 °C for 10 minutes and then a solution of 1-(2-bromo-6-chlorophenyl)-4-chloro-1H-pyrazolo[3,4-d]pyrimidine (**Intermediate BO2**) (2.507 g, 7.29 mmol) in anhydrous THF (20 mL) was added dropwise over 1 minute. The mixture was stirred at 0°C for 10minutes and then allowed to warm to ambient temperature for 6 hours.
It was then cooled to ~0°C, the mixture poured into ice cold 1M citric acid and diluted with EtOAc (50 mL). It was stirred vigarously for 10 minutes. The organic phase was separated, washed with water and brine, dried over $MgSO_4$, filtered and evaporated.

The crude product was purified by flash silica chromatography, elution gradient 20 to 50% EtOAc in isohexane to afford the product (4.90 g, 93 %).
1H NMR (400.13 MHz, DMSO-d_6) δ 0.88 - 1.03 (21H, m), 1.09 - 1.11 (3H, m), 2.44 (3H, s), 3.52 - 3.57 (1H, m), 3.63 - 3.67 (1H, m), 3.73 - 3.78 (1H, m), 4.09 - 4.18 (2H, m), 5.92 - 5.98 (1H, m), 7.60 - 7.64 (1H, m), 7.80 - 7.83 (1H, m), 7.91 - 7.93 (1H, m), 8.30 - 8.31 (1H, m), 8.53 - 8.54 (1H, m), 8.63 (1H, s), 9.11 (1H, s), 11.19 (1H, s); m/z (ES^-) $(M-H)^-$ = 718; HPLC t_R= 3.95 min.

Intermediate BO2: 1-(2-bromo-6-chlorophenyl)-4-chloropyrazolo[4,5-e]pyrimidine



Phosphoryl trichloride (30.4 ml, 326.37 mmol) was added in one portion to 1-(2-bromo-6-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol (**Intermediate AH4**) (4.25 g, 13.05 mmol) and the resulting suspension was stirred at 100 °C for 2 hours.

It was then cooled and evaporated. The residue was dissolved in toluene (60 mL), poured onto ice, diluted with ethyl acetate (40 mL) and stirred for 1 hour. The organic phase was separated, washed with water (4 × 25 mL) and brine (25 mL), dried over $MgSO_4$, filtered and evaporated to a pale yellow oil that crystallised on standing to afford the product (4.3g, 95%) which was used without further purification.

1H NMR (400.13 MHz, DMSO-d_6) δ 7.66 (1H, dd), 7.84 (1H, dd), 7.94 (1H, dd), 8.89 (1H, s), 8.93 (1H, s); m/z (ES^+) $(M+H)^+$ = 345; HPLC t_R= 2.90 min.

BIOLOGICAL

Tests:

The biological effects of the compounds of formula (I) may be tested in the following way:

(1) Enzymatic activity

Enzymatic activity of recombinant human pancreatic GLK may be measured by incubating GLK, ATP and glucose. The rate of product formation may be determined by coupling the assay to a G-6-P dehydrogenase, NADP/NADPH system and measuring the linear increase with time of optical density at 340nm as described in Brocklehurst et al (Diabetes 2004, **53**, 535-541).

Compounds of the invention generally activate glucokinase with an EC_{50} of less than about 100μM with the exception of Examples 2, 5, 8, 11, 14, 23, 32, 36 and 76.

Examples of the invention have been found to have the following mean EC_{50}s (μM):

Ex. No.	EC50 / uM	Ex. No.	EC50 / uM	Ex. No.	EC50 / uM	Ex. No.	EC50 / uM	Ex. No.	EC50 / uM
1	0.62	56	3.1	112a	0.22	149	0.66	204	1.3
2	>93	57	30	113	0.3	150	1	205	0.24
3	0.17	58	1.95	113a	0.3	151	1.7	206	0.57
4	3.4	59	0.65	114	2.1	152	0.49	207	5
5	>100	60	1.7	115	0.11	153	0.28	208	2.8
6	0.68	61	1.7	115a	0.098	154	1.2	209	1.5
7	3.7	62	12	116	2.3	155	0.76	210	1.2
8	91	63	>4.5	117	6.8	156	0.087	211	1.1
9	0.52	64	10	118	0.15	157	0.14	212	0.49
10	2.7	65	>91	118a	0.12	158	0.15	213	1.1
11	>52	66	>91	119	1.2	159	0.85	214	0.32
12	2.4	67	2.4	120	0.54	160	0.28	215	0.2285
13	1.4	68	>8.4	125	0.31	161	0.61	216	0.1634
14	>82	69	0.52	126	0.57	162	1.5	217	0.4415
15	2.7	70	15	127	6	163	0.58	218	0.2147
16	0.29	71	1.6	127a	1.1	164	0.93	219	0.28
17	0.064	72	2.9	127b	0.84	165	0.37	220	0.22
18	32	73	>18	127c	0.67	166	2.9	221	0.31
19	0.095	74	>100	127d	0.67	167	1.1	222	0.14
20	9.3	75	>100	127e	0.55	168	3.9	223	0.31
21	0.032	76	>36	127f	1.1	169	1.7	224	0.51
22	0.19	81	4.7	127g	0.3	170	1.5	225	0.22
23	>100	82	0.1	127h	6.4	171	0.33	226	0.13
24	0.12	83	0.87	127i	0.36	172	0.81	227	0.32
25	1.2	84	0.47	127j	0.58	173	0.92	228	0.46
26	35	85	9.5	127k	0.56	174	0.23	229	0.11
27	1	86	1.5	127l	0.5	175	0.27	230	0.11
28	0.11	87	0.32	128	0.92	176	0.38	231	0.26

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29	0.058	88	5.1	128a	0.62	177	1.5	232	0.54
30	4.8	89	1.5	129	1.3	178	4.3	233	0.21
31	0.35	90	5.4	130	1.1	179	0.62	234	0.21
32	>80	91	0.16	131	0.41	180	0.94	235	0.4
33	>1.7	92	0.42	132	0.47	181	3.3	236	0.74
34	1.9	93	3.3	133	1.1	182	3	237	0.47
35	2.1	94	9.2	134	0.44	183	7.7	238	0.42
36	>82	95	39	135	5.9	184	1.5	239	0.49
37	1.3	96	1.3	136	2.1	185	3.7	240	0.45
38	0.02	97	1.2	137	0.35	186	1.8	241	0.35
39	11	97a	0.46	138	0.81	187	1.7	242	0.22
40	0.14	98	0.11	139	1.4	188	1.1	243	0.57
41	0.12	99	9.3	140	1.2	189	0.6	244	0.33
42	0.41	100	1	141	0.34	190	0.37	245	0.47
43	4.2	101	5	142	2.4	191	0.84	246	0.22
44	3.4	102	0.13	143	0.18	192	0.36	247	0.59
45	1.4	103	0.28	143a	2.6	193	3.3	248	0.64
46	1.6	104	1.2	143b	0.26	194	0.58	249	0.59
47	1	105	0.51	143c	0.61	195	2	250	0.23
48	11	106	6.9	143d	0.59	196	1.7	251	0.35
49	34	107	3.6	143e	0.53	197	0.6	252	0.45
50	0.59	108	1.3	143f	0.98	198	2.2		
51	4.4	109	3.2	144	0.51	199	1.1		
52	2.9	110	1	145	0.23	200	0.44		
53	0.78	111	0.33	146	0.96	201	0.65		
54	4	111a	0.21	147	7.8	202	0.34		
55	>20	112	0.26	148	0.93	203	0.83		

The following compounds were also found to have a mean EC_{50} of more than about 100μM:

2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]sulfanyl-N-(5-methyl-2-pyridyl)octanamide;

2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]sulfanyl-4-(2-methoxyethoxy)-N-(5-methyl-2-pyridyl)butanamide;

2-(1-methylpyrazolo[4,5-e]pyrimidin-4-yl)oxy-N-(5-methyl-2-pyridyl)-4-methylsulfonyl-butanamide;

(R)-4-methoxy-N-(5-methyl-2-pyridyl)-2-[1-(2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-butanamide;

(R)-2-[1-(2-methoxyphenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-methyl-2-pyridyl)propanamide;

2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-isopropoxy-N-(5-methyl-1,3,4-oxadiazol-2-yl)propanamide;

2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(4-cyano-2-pyridyl)-3-isopropoxy-propanamide;

2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-isopropoxy-N-pyrimidin-2-yl-propanamide;

(2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-isopropoxy-N-(3-methyl-2-pyridyl)propanamide;

(2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-isopropoxy-N-(4-methoxy-2-pyridyl)propanamide;

(2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(1,5-dimethyl-1,2,4-triazol-3-yl)-3-isopropoxy-propanamide.

Production of recombinant GLK:

Human GLK was obtained by PCR from human pancreatic mRNA respectively, using established techniques described in Sambrook J, Fritsch EF & Maniatis T, 1989. PCR primers were designed according to the GLK cDNA sequences shown in Tanizawa et al 1991 and Bonthron, D.T. *et al* 1994 (later corrected in Warner, J.P. 1995).

Cloning in Bluescript II vectors

GLK was cloned in E. coli using pBluescript II, (Short et al 1998) a recombinant cloning vector system similar to that employed by Yanisch-Perron C *et al* (1985), comprising a colEI-based replicon bearing a polylinker DNA fragment containing multiple unique

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restriction sites, flanked by bacteriophage T3 and T7 promoter sequences; a filamentous phage origin of replication and an ampicillin drug resistance marker gene.

Transformations

E. Coli transformations were generally carried out by electroporation. 400 mL cultures of strains DH5a or BL21(DE3) were grown in L-broth to an OD 600 of 0.5 and harvested by centrifugation at 2,000g. The cells were washed twice in ice-cold deionised water, resuspended in 1mL 10% glycerol and stored in aliquots at -70^{0}C. Ligation mixes were desalted using Millipore V series™ membranes (0.0025mm) pore size). 40mL of cells were incubated with 1mL of ligation mix or plasmid DNA on ice for 10 minutes in 0.2cm electroporation cuvettes, and then pulsed using a Gene Pulser™ apparatus (BioRad) at 0.5kVcm^{-1}, 250mF. Transformants were selected on L-agar supplemented with tetracyline at 10mg/mL or ampicillin at 100mg/mL.

Expression

GLK was expressed from the vector pTB375NBSE in E.coli BL21 cells,, producing a recombinant protein containing a 6-His tag immediately adjacent to the N-terminal methionine. Alternatively, another suitable vector is pET21(+)DNA, Novagen, Cat number 697703. The 6-His tag was used to allow purification of the recombinant protein on a column packed with nickel-nitrilotriacetic acid agarose purchased from Qiagen (cat no 30250).

(2) Oral Glucose Tolerance Test (OGTT) or Glucose profile

Oral glucose tolerance tests were done on conscious Zucker obese fa/fa rats (age 12-13 weeks or older). The animals were fasted for 2 hours before use for experiments. A test compound or a vehicle was given orally 120 minutes before oral administration of a glucose solution at a dose of 2 g/kg body weight. Blood glucose levels were measured using a Accucheck glucometer from tail bled samples taken at different time points before and after administration of glucose (time course of 60 minutes). A time curve of the blood glucose levels was generated and the area-under-the-curve (AUC) for 120 minutes was calculated (the time of glucose administration being time zero). Percent reduction in glucose excursion was determined using the AUC in the vehicle-control group as zero percent reduction.

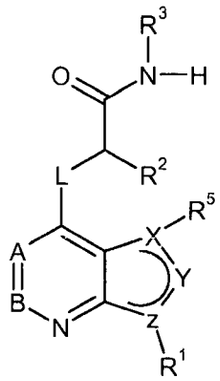
For Glucose profile a test compound or vehicle was given 60 minutes before conscious Zucker obese fa/fa rats (age 12-13 weeks or older) entered a dark cycle (12-hours). Blood

glucose mevels were measured using a Accucheck glucometer from tail bled samples taken at different time points during the 12-hour dark cycle. A time curve of the blood glucose levels was generated and the area-under-the-curve (AUC) for 12-hours was calculated (the beginning of the dark cycle being time zero). Percent reduction in glucose excursion was determined using the AUC in the vehicle-control group as zero percent reduction.

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Claims:

1. A compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof in which:

A and B are each either N or CR^6, provided that at least one of A and B is CR^6;

X is C or N;

Y is CH or N;

Z is C or N;

wherein X, Y and Z are chosen such that at least two of X, Y and Z are N, the ring containing them is aromatic and any ring nitrogen atom is not quaternised;

R^1 is (1-6C)alkyl, aryl, aryl(1-6C)alkyl or HET-1 wherein the aryl, aryl(1-6C)alkyl and HET-1 are optionally substituted by one, two or three groups independently selected from halo, (1-4C)alkyl, (1-4C)alkoxy, trifluoromethyl, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, cyano, carboxy, (1-6C)alkoxycarbonyl, carbamoyl, *N*-(1-4C)alkylcarbamoyl, *N,N*-di(1-4C)alkylcarbamoyl, aminosulfonyl, (1-6C)alkylaminosulfonyl, di(1-6C)alkylaminosulfonyl, (1-4C)alkanoylamino, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl, di(1-4C)alkylamino(1-4C)alkyl, (1-6C)alkoxycarbonyl(1-4C)alkyl-, (1-6C)alkylsulfonyloxy, (3-6C)cycloalkylsulfonyl, (1-6C)alkylsulfonylamino, azetidinylcarbonyl, pyrrolidinylcarbonyl and HET-3A;

wherein HET-1 is a 5- or 6-membered, C-linked heteroaryl ring, or a fused bicyclic ring system of formula –D-E,

wherein ring D is attached to Z and is 6-membered aryl or heteroaryl ring and ring E is a 5- or 6-membered heteroaryl, heterocyclyl or cycloalkyl ring which is fused to ring D at any available position;

R^2 is (1-6C)alkyl optionally substituted by one or two hydroxy or by one of the following: carboxy, carbamoyl, *N,N*-di(1-4C)alkylcarbamoyl, (1-6C)alkoxycarbonyl, a group $-N(R^7)COR^8$ or a group NR^9R^{10};

or R^2 is a group $-(CHR^4)_n$-P-Q wherein n is 1, 2, 3 or 4;

P is a linker selected from O, SO_2, CONH and NHCO;

Q is selected from (1-6C)alkyl, (3-6C)cycloalkyl and a 4-, 5- or 6-membered heterocyclyl (wherein said heterocyclyl ring contains 1, 2 or 3 heteroatoms independently selected from O, N and S, provided that there are no O-O, S-S or O-S bonds, wherein an available carbon atom in the ring may be oxidised to a carbonyl group, an available sulfur atom in the ring may be oxidised to an SO or SO_2 group and wherein there is optionally a double bond in the ring), and Q is optionally substituted on an available carbon atom by hydroxy or (1-4C)alkoxy;

R^3 is a group HET-2 wherein HET-2 is a 5- or 6-membered C-linked monocyclic heteroaryl ring, containing a nitrogen atom in the 2-position and optionally 1 or 2 further ring heteroatoms independently selected from O, N and S; or HET-2 is an 8-, 9- or 10-membered C-linked bicyclic heteroaryl ring containing a nitrogen atom in the 2-position with up to five further ring heteroatoms independently selected from O, N and S;

wherein HET-2 is optionally substituted on an available carbon atom, or on a ring nitrogen atom provided it is not thereby quaternised, with 1 or 2 substituents independently selected from R^{11};

each R^4 is independently selected from hydrogen, hydroxy, methyl and ethyl; provided that when n is >1, then no more than two R^4 groups are hydroxy;

R^5 is H, (1-4C)alkoxy or (1-4C)alkyl;

R^6 is H, (1-4C)alkoxy or (1-4C)alkyl;

R^7 is H or (1-4C)alkyl;

R^8 is (1-4C)alkyl;

R^9 is H or (1-4C)alkyl optionally substituted with hydroxy or methoxy;

R^{10} is H or (1-4C)alkyl;

or $-NR^9R^{10}$ forms an azetidine optionally substituted by hydroxy;

R^{11} is independently selected from halo, (1-4C)alkyl, (1-4C)alkoxy, trifluoromethyl, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, cyano, carboxy, (1-6C)alkoxycarbonyl, carbamoyl, *N*-(1-4C)alkylcarbamoyl, *N,N*-di(1-4C)alkylcarbamoyl, aminosulfonyl, (1-6C)alkylaminosulfonyl, di(1-6C)alkylaminosulfonyl, (1-4C)alkanoylamino, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl (wherein p is 0, 1 or 2), amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl, di(1-4C)alkylamino(1-4C)alkyl, (1-6C)alkoxycarbonyl(1-4C)alkyl-, (1-6C)alkylsulfonyloxy, (3-6C)cycloalkylsulfonyl, (1-6C)alkylsulfonylamino, azetidinylcarbonyl, pyrrolidinylcarbonyl and HET-3;

HET-3 and HET-3A are each independently either a 5- or 6-membered, C-or N- linked unsubstituted heteroaryl ring containing 1, 2 or 3 ring heteroatoms independently selected from O, N and S, or a 4-, 5- or 6-membered, C- or N- linked unsubstituted saturated heterocyclyl ring containing one ring heteroatom selected from O, N and S;

L is S, O or NR^{12}; and

R^{12} is H or (1-4C)alkyl;

but excluding

N-(5-chloro-2-pyridinyl)-2-[(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thio]propanamide;

N-[1-(1-methylethyl)-1H-pyrazol-5-yl]-2-[(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thio]propanamide,

N-(5-(methyl)isoxazol-3-yl)-2-[[1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]thio]butanamide;

N-(5-(methyl)isoxazol-3-yl)-2-[[1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]thio]propanamide;

(2R)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-5-hydroxy-N-(5-methyl-2-pyridyl)pentanamide;

(2R)-N-(5-chloro-2-pyridyl)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-5-hydroxy-pentanamide;

(2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-cyano-2-pyridyl)-3-[(1S)-2-hydroxy-1-methyl-ethoxy]propanamide;

(2R)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-cyano-2-pyridyl)-3-(2-hydroxyethoxy)propanamide;

(2S)-N-(5-cyano-2-pyridyl)-2-[1-(2,5-dimethylphenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-(2-hydroxyethoxy)propanamide;

(2S)-3-(2-hydroxyethoxy)-N-(5-methyl-2-pyridyl)-2-(9-phenylpurin-6-yl)oxy-propanamide;

(2R)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-3-(2-hydroxyethoxy)propanamide;

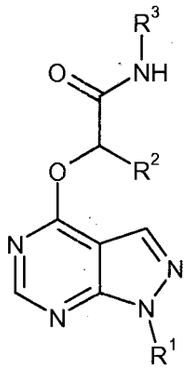
(2S)-N-(5-chloro-2-pyridyl)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-[(2R)-2-hydroxypropoxy]propanamide;

(2R)-N-(5-chloro-2-pyridyl)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-[(2R)-2-hydroxypropoxy]propanamide;

(2S)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-cyano-2-pyridyl)-3-(3-hydroxycyclobutoxy)propanamide; and

(2S)-N-(5-chloro-2-pyridyl)-2-[1-(3-chloro-2-pyridyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-(3-hydroxycyclobutoxy)propanamide.

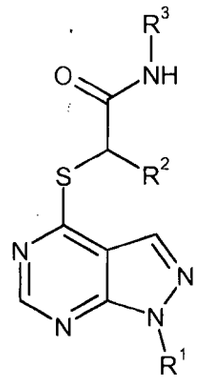
2. A compound of formula (I) as claimed in claim 1, or a pharmaceutically acceptable salt thereof, which is a compound of formula (IA):



(IA)

in which R^1, R^2, and R^3 are as defined in claim 1.

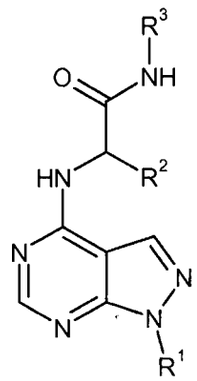
3. A compound of formula (I) as claimed in claim 1, or a pharmaceutically acceptable salt thereof, which is a compound of formula (IB)



(IB)

in which R^1, R^2, and R^3 are as defined in claim 1.

4. A compound of formula (I) as claimed in claim 1, or a pharmaceutically acceptable salt thereof, which is a compound of formula (IC).



(IC)

in which R^1, R^2, and R^3 are as defined in claim 1.

5. A compound of formula (I) as claimed in claim 1 or claim 2, or a pharmaceutically acceptable salt thereof, wherein

R^1 is HET-1 optionally substituted by one or two substituents independently selected from halo (particularly chloro), (1-4C)alkyl, (1-4C)alkoxy, trifluoromethyl, (1-6C)alkylsulfonyl and cyano.

6. A compound of formula (I) as claimed in claim 1, claim 2 or claim 5, or a pharmaceutically acceptable salt thereof, wherein

R^2 is (1-6C)alkyl optionally substituted by one or two hydroxy or R^2 is a group $-(CHR^4)_n$-P-Q;

n is 1, 2, 3, or 4;

one R^4 is optionally hydroxy and the other R^4 groups (where applicable) are hydrogen or methyl;

P is an oxygen linker;

Q is (1-6C)alkyl, (3-6C)cycloalkyl or a 4-, 5- or 6-membered heterocyclyl, and Q is optionally substituted on an available carbon atom by hydroxy or (1-4C)alkoxy.

7. A compound of formula (I) as claimed in claim 1, claim 2, claim 5, or claim 6, or a pharmaceutically acceptable salt thereof, wherein

R^3 is pyridyl, substituted at the para position relative to the point of attachment to the CONH group with a substituent selected from halo, (1-4C)alkyl, (1-6C)alkylsulfonyl, N,N-dialkylcarbamoyl and cyano.

8. A compound of the formula (I) as claimed in Claim 1 or a pharmaceutically acceptable salt thereof , which is a compound of the examples herein, or a pharmaceutically acceptable salt thereof.

9. A compound of the formula (I) as claimed in Claim 1 selected from one or more of the following:

(2S)-N-(5-chloropyridin-2-yl)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d] pyrimidin-4-yloxy)-3-(3-hydroxyazetidin-1-yl)propanamide;

(2S)-2-(1-(2-chloro-6-cyanophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-N-(5-chloropyridin-2-yl)-3-(2-hydroxyethoxy)propanamide;

(2S)-N-(5-chloropyridin-2-yl)-2-(1-(3-chloropyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)-3-((R)-1-hydroxypropan-2-yloxy)propanamide;

(2S)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-3-(3-hydroxyazetidin-1-yl)propanamide;

(2S)-2-[1-(2-chloro-6-cyano-phenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-chloro-2-pyridyl)-
3-[(1R)-2-hydroxy-1-methyl-ethoxy]propanamide;
(2S)-2-[1-(2-chloro-6-cyano-phenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-
3-[(1R)-2-hydroxy-1-methyl-ethoxy]-N-(5-methylpyrazin-2-yl)propanamide;
(2S)-2-[1-(2,6-dichlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-3-(2-hydroxyethoxy)propanamide;
(2S)-2-[1-(2-chlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-(3-hydroxyazetidin-1-yl)-N-(5-methylpyrazin-2-yl)propanamide;
(2S)-2-[1-(2,6-dichlorophenyl)pyrazolo[4,5-e]pyrimidin-4-yl]oxy-3-(3-hydroxyazetidin-1-yl)-N-(5-methylpyrazin-2-yl)propanamide;
(2S)-2-[1-(2-chlorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-N-(5-chloro-2-pyridyl)-3-(3-hydroxyazetidin-1-yl)propanamide;
(2S)-2-[1-(2,6-dichlorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-3-(3-hydroxyazetidin-1-yl)propanamide; and
(2S)-2-[1-(2-chloro-6-cyano-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]oxy-N-(5-fluoro-2-pyridyl)-3-(3-hydroxyazetidin-1-yl)propanamide;
or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition comprising a compound according to any one of Claims 1 to 9, or a pharmaceutically-acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

11. A compound according to any one of Claims 1 to 9 or a pharmaceutically-acceptable salt thereof for use as a medicament.

12. The use of a compound according to any one of Claims 1 to 9, or a pharmaceutically-acceptable salt thereof for the preparation of a medicament for treatment of type 2 diabetes.

13. A method of treating GLK mediated diseases by administering an effective amount of a compound of Formula (I) as claimed in any one of Claims 1 to 9 or a pharmaceutically-acceptable salt thereof, to a mammal in need of such treatment.

14. The method of Claim 13 wherein the GLK mediated disease is type 2 diabetes.

15. A compound according to any one of Claims 1 to 9 or a pharmaceutically-acceptable salt thereof for use as a medicament for the treatment of a disease mediated through GLK.

16. A compound according to claim 15 wherein the disease mediated through GLK is type-2 diabetes.

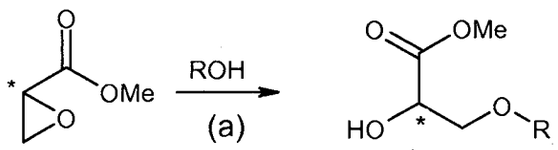
17. A process for the preparation of a compound of Formula (I) as described herein.

18. A pharmaceutical combination comprising a compound as claimed in any one of claims 1 to 9 and another pharmacologically active substance.

19. A pharmaceutical combination as claimed in claim 18 wherein the other pharmacologically active substance is a medicament for the treatment of type 2 diabetes.

20. A compound according to claim 15 wherein the disease mediated through GLK is obesity.

21. The reaction of methyl oxirane-2-carboxylate (IX) with an alcohol ROH (wherein R is (1-6C)alkyl, (3-6C)cycloalkyl or R^x_3SiO(2-4C)alkyl (wherein each R^x is independently selected from (1-6C)alkyl and phenyl) in the presence of magnesiumtrifluoromethanesulfonate in ethyl acetate, to give a compound of formula (X).



(IX) (X)

AGENTES TERAPÉUTICOS 414

La presente invención se refiere a un grupo de 2-{[1-sustituido-1*H*-pirazolo[3,4-*d*]pirimidin-4-il](tio,oxi o amino)-*N*-(heteroaril)alcanamidas que son útiles en el tratamiento o prevención de una enfermedad o afección médica mediada por glucoquinasa (GLK o GK). Se sabe que los activadores de GK (GKA) activan la GK en las células β-pancreáticas, lo que conduce a una reducción del umbral de glucosa para la secreción de insulina. Adicionalmente, los GKA activan la GK hepática, estimulando así la captación de glucosa hepática y suprimiendo la salida de glucosa hepática. El efecto farmacológico neto de los GKA es el de reducir los niveles de glucosa en sangre. Por lo tanto, dichos compuestos pueden ser útiles en el tratamiento de la diabetes tipo 2 y la obesidad. La invención también se refiere a composiciones farmacéuticas que comprenden dichos compuestos y a métodos de tratamiento de enfermedades mediadas por GLK que utilizan dichos compuestos.

La biología de la glucoquinasa y los mecanismos mediante los cuales los GKA podrían proporcionar posibles beneficios terapéuticos para la Diabetes tipo 2 se han descrito ampliamente en la bibliografía (ver por ejemplo Matschinsky FM et al. (2006) Diabetes 55: 1-12, Leighton B, Atkinson A, Coghlan MP (2005) Biochemical SocietyTransactions 33: 371-374 y "Glucokinase and Glycemic Disease: From Basics to Novel Therapeutics." Frontiers in Diabetes vol 16, eds. Matschinsky FM and Magnuson MA, Karger (Basel) 2005). En las células β pancreáticas y células parenquimales hepáticas el principal transportador de glucosa en la membrana plasmática es GLUT2. En concentraciones de glucosa fisiológicas la tasa a la que el GLUT2 transporta glucosa a través de la membrana no es una tasa que limite la tasa total de captación de glucosa en estas células. La tasa de la captación de glucosa se ve limitada por la tasa de fosforilación de glucosa para convertirse en glucosa-6-fosfato (G-6-P), que es catalizada por la glucoquinasa (GLK). La GLK tiene una alta Km (6-10mM) para la glucosa y no se inhibe por las concentraciones fisiológicas de G-6-P. La expresión de la GLK se limita a unos pocos tipos de tejidos y células, entre las que se destacan las células β pancreáticas y las células hepáticas (hepatocitos). En estas células, la actividad de la GLK limita la tasa de la utilización de glucosa y, por lo tanto, regula la cantidad de secreción de insulina inducida por glucosa y la síntesis de glucógeno hepático. Estos procesos son fundamentales en el

mantenimiento de la homeostasis de la glucosa en todo el cuerpo y ambos son disfuncionales en la diabetes.

En un subtipo de diabetes, la diabetes de la madurez de comienzo juvenil tipo 2 (MODY-2), la diabetes es causada por la pérdida de mutaciones funcionales de la GLK. La hiperglucemia en pacientes con MODY-2 resulta de una utilización de la glucosa defectuosa tanto en el páncreas como en el hígado. La utilización de la glucosa defectuosa en el páncreas de pacientes con MODY-2 resulta en un umbral más elevado de secreción de insulina estimulada por glucosa. A la inversa, infrecuentes mutaciones activadoras de GLK reducen este umbral, lo que resulta en hiperinsulinismo familiar. Además de la actividad de la GLK reducida observada en diabéticos con MODY-2, la actividad de la glucoquinasa hepática se ve también reducida en diabéticos tipo 2 . Cabe destacar que la sobreexpresión selectiva hepática o global de la GLK previene o revierte el desarrollo del fenotipo diabético tanto en modelos de dieta como genéticos de la enfermedad. Más aun, el tratamiento agudo de diabéticos tipo 2 con fructosa mejora la tolerancia a la glucosa a través de la estimulación de la utilización de la glucosa hepática. Se cree que este efecto es mediado por un aumento en la actividad citosólica de la GLK inducido por fructosa en el hepatocito mediante el mecanismo descrito más abajo.

La GLK y el canal de K_{ATP} se expresan en neuronas del hipotálamo, una región del cerebro que es importante en la regulación del equilibrio energético y el control de la ingesta de alimentos. Se ha demostrado que estas neuronas expresan neuropéptidos orexigénicos y anorexigénicos y se ha asumido que son las neuronas sensoras de glucosa en el hipotálamo las que son inhibidas o excitadas por cambios en las concentraciones ambientales de glucosa. La capacidad de estas neuronas de detectar cambios en los niveles de glucosa es defectuosa en una variedad de modelos genéticos e inducidos experimentalmente de la obesidad. La infusión intracerebroventricular (icv) de análogos de glucosa, que son inhibidores competitivos de glucoquinasa, estimula la ingesta de alimentos en ratas flacas. Por el contrario, la infusión icv de glucosa suprime la alimentación. Por lo tanto, los activadores de GLK de molécula pequeña pueden reducir la ingesta de alimentos y el aumento de peso mediante efectos centrales en la GLK. Por lo tanto, los activadores de GLK pueden ser terapéuticamente útiles en el tratamiento de trastornos alimenticios, incluida la obesidad, además de la diabetes. Los efectos hipotalámicos serán adicionales o sinergéticos con respecto a los efectos de los mismos

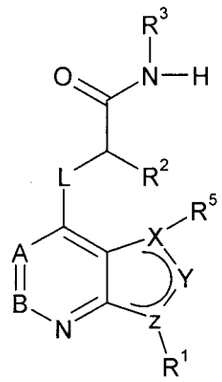
compuestos que actúan en el hígado y/o páncreas para la normalización de la homeostasis de la glucosa en el tratamiento de la diabetes tipo 2. De esta manera, el sistema GLK puede describirse como un posible objetivo de la "diabesidad" (beneficioso tanto para la diabetes como para la obesidad).

La GLK también se expresa en células enteroendócrinas en donde se cree que controla la secreción sensible a la glucosa de los péptidos de incretina GIP (polipéptido insulinotrópico dependiente de glucosa) y GLP-1 (péptido similar a glucagón 1) de células K y células L del intestino, respectivamente. Por lo tanto, los activadores de molécula pequeña de GLK pueden presentar efectos beneficiosos adicionales sobre la secreción de insulina, la función y supervivencia de las células β y el peso corporal como consecuencia de la estimulación de la secreción de los GIP y GLP-1 de estas células enteroendócrinas.

Se ha encontrado que un grupo de activadores de GLK novedosos tiene un núcleo de 1H-pirazolo[3,4-d]pirimidin-4-ilo. En Phosphorus, Sulphur and Silicon, vol 178, 2003, pp1795-1805 se describe la N-(tiazolil)-2-[(1-fenil-1H-pirazolo[3,4-d]pirimidin-4-il)tio]acetamida que está relacionada con la actividad antimicrobiana de compuestos relacionados. También se conocen compuestos similares a partir de Bibliotecas Químicas comercialmente disponibles.

El documento WO98/35944 revela que compuestos de fórmula R^1R^2N-C(O)-$C(R^3)(R^4)$-X-R^5 en la que R^1-R^5 se seleccionan cada uno individualmente de una amplia gama de sustituyentes y X es oxígeno o azufre son útiles en el tratamiento de bulimia y obesidad en virtud de su actividad en los antagonistas del receptor NPY. R^5 puede ser 1*H*-pirazolo[3,4-d]pirimidin-4-ilo o 4-aminopirazolo[3,4-d]pirimidin-6-ilo. Compuestos específicos ejemplificados son *N*-(4-ciclohexilfenil)-2-(1*H*-pirazolo[3,4-d]pirimidin-4-ilsulfanil) acetamida, *N*-(4-benzoilfenil)-2-(1*H*-pirazolo[3,4-d]pirimidin-4-ilsulfanil) acetamida, 2-(4-amino-1*H*-pirazolo[3,4-d]pirimidin-6-ilsulfanil)- *N*-(4-ciclohexilfenil) acetamida y 2-(4-amino-1*H*-pirazolo[3,4-d]pirimidin-6-ilsulfanil)- *N*-(4-benzoilfenil) acetamida.

Por lo tanto, de acuerdo con el primer aspecto de la invención se proporciona un compuesto de fórmula I:



(I)

o una sal farmacéuticamente aceptable del mismo en donde:

A y B son cada uno N o CR^6, siempre que al menos uno de A y B sea CR^6;

X es C o N;

Y es CH o N;

Z es C o N;

en donde X, Y y Z se seleccionan de forma tal que al menos dos de X, Y y Z son N, el anillo que los contiene es aromático y ningún átomo de nitrógeno del anillo está cuaternizado;

R^1 es alquilo(1-6C), arilo, arilalquilo(1-6C) o HET-1 en donde el arilo, arilalquilo(1-6C) y HET-1 están opcionalmente sustituidos por uno, dos o tres grupos que se seleccionan independientemente de halo, alquilo(1-4C), alcoxi(1-4C), trifluorometilo, alquil(1-6C)tio, alquil(1-6C)sulfinilo, alquil(1-6C)sulfonilo, ciano, carboxi, alcoxi(1-6C)carbonilo, carbamoilo, *N*-alquil(1-4C)carbamoilo, *N,N*-dialquil(1-4C)carbamoilo, aminosulfonilo, alquil(1-6C)aminosulfonilo, dialquil(1-6C)aminosulfonilo, alcanoil(1-4C)amino, hidroxialquilo(1-4C), alcoxi(1-4C)alquilo(1-4C), alquil(1-4C)S(O)palquilo(1-4C), aminoalquilo(1-4C), alquil(1-4C)aminoalquilo(1-4C), dialquil(1-4C)aminoalquilo(1-4C), alcoxi(1-6C)carbonilalquilo(1-4C)-, alquil(1-6C)sulfoniloxi, cicloalquil(3-6C)sulfonilo, alquil(1-6C)sulfonilamino, azetidinilcarbonilo, pirrolidinilcarbonilo y HET-3A;

en donde HET-1 es un anillo heteroarilo unido a C de 5 ó 6 miembros, o un sistema de anillos bicíclico fusionado de fórmula –D-E,

en donde el anillo D está unido a Z y es un anillo arilo o heteroarilo de 6 miembros y un anillo E es un anillo heteroarilo, heterociclilo o cicloalquilo de 5 ó 6 miembros que está fusionado al anillo D en cualquier posición disponible;

R^2 es alquilo(1-6C) opcionalmente sustituido por uno o dos hidroxi o por uno de los siguientes: carboxi, carbamoilo, *N,N*-dialquil(1-4C)carbamoilo, alcoxi(1-6C)carbonilo, un grupo $-N(R^7)COR^8$ o un grupo NR^9R^{10};

o R^2 es un grupo $-(CHR^4)_n$-P-Q en donde n es 1, 2, 3 ó 4;

P es un enlazante que se selecciona de O, SO_2, CONH y NHCO;

Q se selecciona de alquilo(1-6C), cicloalquilo(3-6C) y un heterociclilo de 4, 5 ó 6 miembros (en donde dicho anillo heterociclilo contiene 1, 2 ó 3 heteroátomos que se seleccionan independientemente de O, N y S, siempre que no haya enlaces O-O, S-S ni O-S, en donde un átomo de carbono disponible en el anillo puede oxidarse para convertirse en un grupo carbonilo, un átomo de azufre disponible en el anillo puede oxidarse para convertirse en un grupo SO o SO_2 y en donde opcionalmente hay un enlace doble en el anillo) y Q está opcionalmente sustituido en un átomo de carbono disponible por hidroxi o alcoxi(1-4C);

R^3 es un grupo HET-2 en donde HET-2 es un anillo heteroarilo monocíclico unido a C de 5 ó 6 miembros, que contiene un átomo de nitrógeno en la posición 2 y opcionalmente 1 ó 2 heteroátomos del anillo adicionales que se seleccionan independientemente de O, N y S; o HET-2 es un anillo heteroarilo bicíclico unido a C de 8, 9 ó 10 miembros que contiene un átomo de nitrógeno en la posición 2 con hasta cinco heteroátomos del anillo adicionales que se seleccionan independientemente de O, N y S;

en donde HET-2 está opcionalmente sustituido en un átomo de carbono disponible, o en un átomo de nitrógeno del anillo siempre que no quede de este modo cuaternizado, con 1 ó 2 sustituyentes que se seleccionan independientemente de R^{11};

cada R^4 se selecciona independientemente de hidrógeno, hidroxi, metilo y etilo; siempre que cuando n es >1, entonces no más de dos grupos R^4 son hidroxi;

R^5 es H, alcoxi(1-4C) o alquilo(1-4C);

R^6 es H, alcoxi(1-4C) o alquilo(1-4C);

R^7 es H o alquilo(1-4C);

R^8 es alquilo(1-4C);

R^9 es H o alquilo(1-4C) opcionalmente sustituido por hidroxi o metoxi;

R^{10} es H o alquilo(1-4C);

o $-NR^9R^{10}$ forma una azetidina opcionalmente sustituida por hidroxi;

R^{11} se selecciona independientemente de halo, alquilo(1-4C), alcoxi(1-4C), trifluorometilo,

alquil(1-6C)tio, alquil(1-6C)sulfinilo, alquil(1-6C)sulfonilo, ciano, carboxi, alcoxi(1-6C)carbonilo, carbamoilo, *N*-alquil(1-4C)carbamoilo, *N,N*-dialquil(1-4C)carbamoilo, aminosulfonilo, alquil(1-6C)aminosulfonilo, dialquil(1-6C)aminosulfonilo, alcanoil(1-4C)amino, hidroxialquilo(1-4C), alcoxi(1-4C)alquilo(1-4C), alquil(1-4C)S(O)palquilo(1-4C) (en donde p es 0, 1 ó 2), aminoalquilo(1-4C), alquil(1-4C)aminoalquilo(1-4C), dialquil(1-4C)aminoalquilo(1-4C), alcoxi(1-6C)carbonilalquilo(1-4C)-, alquil(1-6C)sulfoniloxi, cicloalquil(3-6C)sulfonilo, alquil(1-6C)sulfonilamino, azetidinilcarbonilo, pirrolidinilcarbonilo y HET-3;

HET-3 y HET-3A son cada uno independientemente un anillo heteroarilo insustituido unido a C o N de 5 ó 6 miembros que contiene 1, 2 ó 3 heteroátomos del anillo que se seleccionan independientemente de O, N y S, o un anillo heterociclilo saturado insustituido unido a C o N de 4, 5 ó 6 miembros que contiene un heteroátomo del anillo que se selecciona de O, N y S;

L es S, O o NR^{12}; y

R^{12} es H o alquilo(1-4C);

pero excluyendo

N-(5-cloro-2-piridinil)-2-[(1-fenil-1H-pirazolo[3,4-d]pirimidin-4-il)tio]propanamida;

N-[1-(1-metiletil)-1H-pirazol-5-il]-2-[(1-fenil-1H-pirazolo[3,4-d]pirimidin-4-il)tio]propanamida,

N-(5-(metil)isoxazol-3-il)-2-[[1-(4-fluorofenil)-1H-pirazolo[3,4-d]pirimidin-4-il]tio]butanamida;

N-(5-(metil)isoxazol-3-il)-2-[[1-(4-fluorofenil)-1H-pirazolo[3,4-d]pirimidin-4-il]tio]propanamida;

(2R)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-5-hidroxi-N-(5-metil-2-piridil)pentanamida;

(2R)-N-(5-cloro-2-piridil)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-5-hidroxi-pentanamida;

(2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-ciano-2-piridil)-3-[(1S)-2-hidroxi-1-metil-etoxi]propanamida;

(2R)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-ciano-2-piridil)-3-(2-hidroxietoxi)propanamida;

(2S)-N-(5-ciano-2-piridil)-2-[1-(2,5-dimetilfenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-(2-

hidroxietoxi)propanamida;
(2S)-3-(2-hidroxietoxi)-N-(5-metil-2-piridil)-2-(9-fenilpurin-6-il)oxi-propanamida;
(2R)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-3-(2-hidroxietoxi)propanamida;
(2S)-N-(5-cloro-2-piridil)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-[(2R)-2-hidroxipropoxi]propanamida;
(2R)-N-(5-cloro-2-piridil)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-[(2R)-2-hidroxipropoxi]propanamida;
(2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-ciano-2-piridil)-3-(3-hidroxiciclobutoxi)propanamida; y
(2S)-N-(5-cloro-2-piridil)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-(3-hidroxiciclobutoxi)propanamida.

En un aspecto adicional de la invención se proporciona un compuesto de la fórmula (I) o una sal farmacéuticamente aceptable del mismo en donde:
A y B son cada uno N o CR^6, siempre que al menos uno de A y B sea CR^6;
X es C o N;
Y es CH o N;
Z es C o N;
en donde X, Y y Z se seleccionan de forma tal que al menos dos de X, Y y Z son N, el anillo que los contiene es aromático y ningún átomo de nitrógeno del anillo está cuaternizado;
R^1 es alquilo(1-6C), arilo, arilalquilo(1-6C) o HET-1 en donde el arilo, arilalquilo(1-6C) y HET-1 están opcionalmente sustituidos por uno, dos o tres grupos que se seleccionan independientemente de halo, alquilo(1-4C), alcoxi(1-4C), trifluorometilo, alquil(1-6C)tio, alquil(1-6C)sulfinilo, alquil(1-6C)sulfonilo, ciano, carboxi, alcoxi(1-6C)carbonilo, carbamoilo, *N*-alquil(1-4C)carbamoilo, *N,N*-dialquil(1-4C)carbamoilo, aminosulfonilo, alquil(1-6C)aminosulfonilo, dialquil(1-6C)aminosulfonilo, alcanoil(1-4C)amino, hidroxialquilo(1-4C), alcoxi(1-4C)alquilo(1-4C), alquil(1-4C)S(O)palquilo(1-4C), aminoalquilo(1-4C), alquil(1-4C)aminoalquilo(1-4C), dialquil(1-4C)aminoalquilo(1-4C), alcoxi(1-6C)carbonilalquilo(1-4C)-, alquil(1-6C)sulfoniloxi, cicloalquil(3-6C)sulfonilo, alquil(1-6C)sulfonilamino, azetidinilcarbonilo, pirrolidinilcarbonilo y HET-3A;
en donde HET-1 es un anillo heteroarilo unido a C de 5 ó 6 miembros, o un sistema de

anillos bicíclico fusionado de fórmula –D-E,

en donde el anillo D está unido a Z y es un anillo arilo o heteroarilo de 6 miembros y un anillo E es un anillo heteroarilo, heterociclilo o cicloalquilo de 5 ó 6 miembros que está fusionado al anillo D en cualquier posición disponible;

R^2 es alquilo(1-6C) opcionalmente sustituido por uno o dos hidroxi o por uno de los siguientes: carboxi, carbamoilo, *N,N*-dialquil(1-4C)carbamoilo, alcoxi(1-6C)carbonilo, un grupo $-N(R^7)COR^8$ o un grupo NR^9R^{10};

o R^2 es un grupo $-(CHR^4)_n$-P-Q en donde n es 1, 2, 3 ó 4;

P es un enlazante que se selecciona de O, SO_2, SO_2NH, $NHSO_2$, CONH y NHCO;

Q se selecciona de alquilo(1-6C), cicloalquilo(3-6C) y un heterociclilo de 4, 5 ó 6 miembros (en donde dicho anillo heterociclilo contiene 1, 2 ó 3 heteroátomos que se seleccionan independientemente de O, N y S, siempre que no haya enlaces O-O, S-S ni O-S, en donde un átomo de carbono disponible en el anillo puede oxidarse para convertirse en un grupo carbonilo, un átomo de azufre disponible en el anillo puede oxidarse para convertirse en un grupo SO o SO_2 y en donde opcionalmente hay un enlace doble en el anillo) y Q está opcionalmente sustituido en un átomo de carbono disponible por hidroxi o alcoxi(1-4C);

R^3 es un grupo HET-2 en donde HET-2 es un anillo heteroarilo monocíclico unido a C de 5 ó 6 miembros, que contiene un átomo de nitrógeno en la posición 2 y opcionalmente 1 ó 2 heteroátomos del anillo adicionales que se seleccionan independientemente de O, N y S;

o HET-2 es un anillo heteroarilo bicíclico unido a C de 8, 9 ó 10 miembros que contiene un átomo de nitrógeno en la posición 2 con hasta cinco heteroátomos del anillo adicionales que se seleccionan independientemente de O, N y S;

en donde HET-2 está opcionalmente sustituido en un átomo de carbono disponible, o en un átomo de nitrógeno del anillo siempre que no quede de este modo cuaternizado, con 1 ó 2 sustituyentes que se seleccionan independientemente de R^{11};

cada R^4 se selecciona independientemente de hidrógeno, hidroxi, metilo y etilo; siempre que cuando n es >1, entonces no más de dos grupos R^4 son hidroxi;

R^5 es H, alcoxi(1-4C) o alquilo(1-4C);

R^6 es H, alcoxi(1-4C) o alquilo(1-4C);

R^7 es H o alquilo(1-4C);

R^8 es alquilo(1-4C);

R^9 es H o alquilo(1-4C);

R^{10} es H o alquilo(1-4C);

R^{11} se selecciona independientemente de halo, alquilo(1-4C), alcoxi(1-4C), trifluorometilo, alquil(1-6C)tio, alquil(1-6C)sulfinilo, alquil(1-6C)sulfonilo, ciano, carboxi, alcoxi(1-6C)carbonilo, carbamoilo, *N*-alquil(1-4C)carbamoilo, *N,N*-dialquil(1-4C)carbamoilo, aminosulfonilo, alquil(1-6C)aminosulfonilo, dialquil(1-6C)aminosulfonilo, alcanoil(1-4C)amino, hidroxialquilo(1-4C), alcoxi(1-4C)alquilo(1-4C), alquil(1-4C)S(O)palquilo(1-4C) (en donde p es 0, 1 ó 2), aminoalquilo(1-4C), alquil(1-4C)aminoalquilo(1-4C), dialquil(1-4C)aminoalquilo(1-4C), alcoxi(1-6C)carbonilalquilo(1-4C)-, alquil(1-6C)sulfoniloxi, cicloalquil(3-6C)sulfonilo, alquil(1-6C)sulfonilamino, azetidinilcarbonilo, pirrolidinilcarbonilo y HET-3;

HET-3 y HET-3A son cada uno independientemente un anillo heteroarilo insustituido unido a C o N de 5 ó 6 miembros que contiene 1, 2 ó 3 heteroátomos del anillo que se seleccionan independientemente de O, N y S, o un anillo heterociclilo saturado insustituido unido a C o N de 4, 5 ó 6 miembros que contiene un heteroátomo del anillo que se selecciona de O, N y S;

L es S, O o NR^{12}; y

R^{12} es H o alquilo(1-4C);

pero excluyendo

N-(5-cloro-2-piridinil)-2-[(1-fenil-1H-pirazolo[3,4-d]pirimidin-4-il)tio]propanamida;

N-[1-(1-metiletil)-1H-pirazol-5-il]-2-[(1-fenil-1H-pirazolo[3,4-d]pirimidin-4-il)tio]propanamida,

N-(5-(metil)isoxazol-3-il)-2-[[1-(4-fluorofenil)-1H-pirazolo[3,4-d]pirimidin-4-il]tio]butanamida; y

N-(5-(metil)isoxazol-3-il)-2-[[1-(4-fluorofenil)-1H-pirazolo[3,4-d]pirimidin-4-il]tio]propanamida.

El término "arilo" se refiere a fenilo, naftilo o un anillo carbocíclico bicíclico parcialmente saturado que contiene entre 8 y 12 átomos de carbono, preferiblemente entre 8 y 10 átomos de carbono. Ejemplos de anillo carbocíclico bicíclico parcialmente saturado incluyen: 1,2,3,4-tetrahidronaftilo, indanilo, indenilo, 1, 2, 4a,5, 8, 8a-hexahidronaftiilo o 1,3a-dihidropentaleno. Ejemplos de "arilalquilo(1-6C)" incluyen cualquiera de los ejemplos precedentes de "arilo" junto con cualquiera de los ejemplos

de "alquilo(1-6C)" que se describen más adelante en la presente.

Grupos HET-1 adecuados cuando HET-1 es un anillo heteroarilo unido a C de 5 ó 6 miembros incluyen tiazolilo, isotiazolilo, tiadiazolilo, piridilo, pirazinilo, piridazinilo, pirazolilo, imidazolilo, pirimidinilo, oxazolilo, isoxazolilo, oxadiazolilo y triazolilo. Más adecuadamente grupos HET-1 son piridilo o pirazinilo, particularmente 2-piridilo, 4-piridilo y pirazinilo.

Grupos HET-1 adecuados cuando HET-1 es de fórmula –D-E (como se define anteriormente en la presente) incluyen indanilo, benzodioxolilo, benzimidazolilo, benztiazolilo, benzisotiazolilo, benzoxazolilo, benzisoxazolilo, quinolilo, isoquinolilo, benzofurazanilo, indolilo, indazolilo, cinnolinilo, quinazolinilo, quinoxalinilo, ftalazinilo, 1,5-naftiridinilo, 1,6-naftiridinilo, 1,7-naftiridinilo, 1,8-naftiridinilo, pirrolopiridinilo, pirrolopirazinilo, pirazolopiridinilo e imidazopiridinilo.

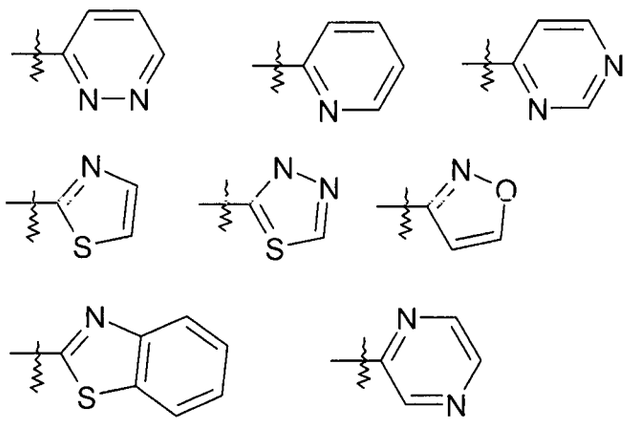
Ejemplos adecuados de HET-2 incluyen pirrolilo, tiazolilo, isotiazolilo, pirazolilo, imidazolilo, tiadiazolilo (1,2,4- y 1,3,4-), oxazolilo, isoxazolilo, triazolilo, 1,3,4-oxadiazolilo, 1,2,4-oxadiazolilo, furazanilo, tetrazolilo, piridilo, pirazinilo, piridazinilo, pirimidinilo, 1,3,5-triazinilo, imidazotiazolilo, benzimidazolilo, benztiazolilo, benzisotiazolilo, benzoxazolilo, benzisoxazolilo, quinolilo, isoquinolilo, benzofurazanilo, indolilo, indazolilo, cinnolinilo, quinazolinilo, quinoxalinilo, ftalazinilo, 1,5-naftiridinilo, 1,6-naftiridinilo, 1,7-naftiridinilo, 1,8-naftiridinilo, pirrolopiridinilo, pirrolopirazinilo, pirazolopiridinilo e imidazopiridinilo.

Ejemplos adecuados de HET-3 y HET-3A como anillos heteroarilo son furilo, pirrolilo, tienilo, tiazolilo, isotiazolilo, tiadiazolilo, piridilo, pirazinilo, piridazinilo, pirazolilo, imidazolilo, pirimidinilo, oxazolilo, isoxazolilo y triazolilo. Ejemplos adecuados de HET-3 y HET-3A como anillos heterociclilo saturados son oxetano, azetidina, tietano, pirrolidina, tetrahidrofurano, tetrahidropirano y piperidina.

Se apreciará que, cuando las definiciones de grupos heterociclilo HET-1, HET-2, HET-3 y HET-3A abarcan anillos heteroarilo que pueden sustituirse en nitrógeno, dicha sustitución puede no resultar en átomos de nitrógeno cuaternarios cargados. Se apreciará que las definiciones de HET-1, HET-2, HET-3 y HET-3A no pretenden incluir todos los enlaces O-O, O-S o S-S. Se apreciará que las definiciones de HET-1, HET-2, HET-3 y HET-3A no pretenden incluir estructuras inestables.

Para evitar dudas, la referencia al grupo HET-2 que contiene un nitrógeno en la

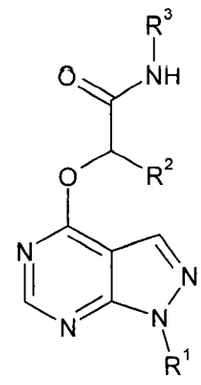
posición 2 se refiere a la posición 2 con relación al átomo de nitrógeno de la amida a la que se encuentra unido el grupo. Con el fin de evitar dudas, a continuación se muestran ejemplos representativos



en donde  representa el punto de unión al grupo amida.

Ejemplos del grupo Q como un heterociclo del anillo de 4, 5 ó 6 miembros como se define anteriormente en la presente incluyen azetidinilo, oxetanilo, pirrolidinilo, pirrolidonilo, tetrahidrofurilo, tetrahidropiranilo, piperidinilo, morfolinilo, piperazinilo y tiomorfolinilo. Ejemplos particulares de Q como un heterociclo incluyen azetidinilo y pirrolidinilo.

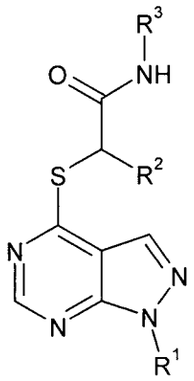
En un aspecto de la invención, se proporciona un compuesto de fórmula (IA) o una sal farmacéuticamente aceptable del mismo



(IA)

en donde R^1, R^2 y R^3 son tal como se definen para un compuesto de fórmula (I) precedente.

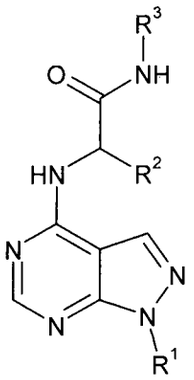
En otro aspecto de la invención, se proporciona un compuesto de fórmula (IB) o una sal farmacéuticamente aceptable del mismo



(IB)

en donde R^1, R^2 y R^3 son tal como se definen para un compuesto de fórmula (I) precedente.

En otro aspecto de la invención, se proporciona un compuesto de fórmula (IC) o una sal farmacéuticamente aceptable del mismo



(IC)

en donde R^1, R^2 y R^3 son tal como se definen para un compuesto de fórmula (I) precedente.

En la presente se entenderá que toda referencia a un compuesto de fórmula (I) también incluye un compuesto de fórmula (IA), (IB) o (IC).

Los compuestos de Fórmula (I) pueden formar sales que se encuentran dentro del ámbito de la invención. Se prefieren las sales farmacéuticamente aceptable aunque otras sales pueden ser útiles, por ejemplo, para aislar o purificar compuestos.

En otro aspecto, la invención se refiere a compuestos de fórmula (I) tal como se definen anteriormente en la presente o a una sal farmacéuticamente aceptable.

En otro aspecto, la invención se refiere a compuestos de fórmula (I) tal como se definen anteriormente en la presente o a un profármaco de los mismos. Ejemplos adecuados de profármacos de compuestos de fórmula (I) son ésteres hidrolizables *in vivo* de compuestos de fórmula (I). Por lo tanto en otro aspecto, la invención se refiere a

compuestos de fórmula (I) tal como se definen anteriormente en la presente o a un éster hidrolizable *in vivo* de los mismos.

En esta memoria descriptiva el término genérico "alquilo" incluye grupos alquilo de cadena recta y de cadena ramificada. Sin embargo referencias a grupos alquilo individuales tal como "propilo" son específicas para la versión de cadena recta solamente y referencias a grupos alquilo individuales de cadena ramificada tales como *t*-butilo son específicas para la versión de cadena ramificada solamente. Por ejemplo, "alquilo(1-4C)" incluye metilo, etilo, propilo, isopropilo y *t*-butilo. Una convención análoga se aplica a otros términos genéricos.

Ejemplos de **alquilo(1-4C)** incluyen metilo, etilo, propilo, isopropilo, butilo y terc-butilo; ejemplos de **alquilo(1-6C)** incluyen alquilo(1-4C), pentilo y hexilo; ejemplos de **alquilo(1-8C)** incluyen alquilo(1-6C) y heptilo; ejemplos de **alcoxi(1-4C), alcoxi(1-6C) y alcoxi(1-8C)** incluyen metoxi, etoxi, propoxi, isopropoxi y terc-butoxi; ejemplos de **alcoxi(1-6C)carbonilo** incluyen metoxicarbonilo, etoxicarbonilo, propoxicarbonilo, isopropoxicarbonilo y terc-butoxicarbonilo; ejemplos de **alcoxi(1-6C)carbonilalquilo(1-4C)** incluyen metoxicarbonilmetilo, etoxicarbonilmetilo, propoxicarboniletilo, isopropoxicarbonilmetil y terc-butoxicarbonilmetilo; ejemplos de ***N*-alquil(1-4C)carbamoilo** incluyen metilcarbamoilo, etilcarbamoilo, propilcarbamoilo, isopropilcarbamoilo y terc-butilcarbamoilo; ejemplos de ***N,N*-di-alquil(1-4C)carbamoilo** incluyen *N,N*-dimetilcarbamoilo, *N,N*-dietilcarbamoilo, *N*-metil-*N*-propilcarbamoilo, *N,N*-di-isopropilcarbamoilo y *N*-metil-*N*-terc-butilcarbamoilo; ejemplos de **cicloalquilo(3-6C)** incluyen ciclopropilo, ciclobutilo, ciclopentilo y ciclohexilo; ejemplos de **halo** incluyen fluoro, cloro, bromo y yodo; ejemplos de **hidroxialquilo(1-4C)** incluyen hidroximetilo, 1-hidroxietilo, 2-hidroxietilo, 2-hidroxipropilo, 3-hidroxipropilo, 1-hidroxiisopropilo y 4-hidroxibutilo; ejemplos de **alcoxi(1-4C)alquilo(1-4C)** incluyen metoximetilo, etoximetilo, terc-butoximetilo, 2-metoxietilo, 2-etoxietilo, metoxipropilo, 2-metoxipropilo y metoxibutilo; ejemplos de **alquil(1-4C)S(O)palquilo(1-4C)** incluyen metilsulfinilmetilo, etilsulfinilmetilo, etilsulfiniletilo, metilsulfinilpropilo, metilsulfinilbutilo, metilsulfonilmetilo, etilsulfonilmetilo, etilsulfoniletilo, metilsulfonilpropilo, metilsulfonilbutilo, metiltiometilo, etiltiometilo, etiltioetilo, metiltiopropilo y metiltiobutilo; ejemplos de **aminoalquilo(1-4C)** incluyen aminometilo, aminoetilo, 2-aminopropilo, 3-aminopropilo, 1-aminoisopropilo y 4-aminobutilo; ejemplos de **alquil(1-**

4C)aminoalquilo(1-4C) incluyen (N-metil)aminometilo, (N-etil)aminometilo, 1-((N-metil)amino)etilo, 2-((N-metil)amino)etilo, (N-etil)aminoetilo, (N-metil)aminopropilo y 4-((N-metil)amino)butilo; ejemplos de **dialquil(1-4C)aminoalquilo(1-4C)** incluyen dimetilaminometilo, metil(etil)aminometilo, metil(etil)aminoetilo, (N,N-dietil)aminoetilo, (N,N-dimetil)aminopropilo y (N,N-dimetil)aminobutilo; ejemplos de **alquil(1-4C)amino** incluyen metilamino, etilamino, propilamino, isopropilamino, butilamino y terc-butilamino; ejemplos de **dialquil(1-4C)amino** incluyen dimetilamino, metil(etil)amino, dietilamino, dipropilamino, di-isopropilamino y dibutilamino; ejemplos de **alquil(1-4C)aminosulfonilo** incluyen metilaminosulfonilo, etilaminosulfonilo, propilaminosulfonilo, isopropilaminosulfonilo, butilaminosulfonilo y terc-butilaminosulfonilo; ejemplos de **dialquil(1-4C)aminosulfonilo** incluyen dimetilaminosulfonilo, metil(etil)aminosulfonilo, dietilaminosulfonilo, dipropilaminosulfonilo, di-isopropilaminosulfonilo y dibutilaminosulfonilo; ejemplos de **alcanoil(1-4C)amino** incluyen metanoilamino, etanoilamino, propanoilamino, isopropanoilamino, butanoilamino y terc-butanoilamino; ejemplos de **–C(O)alquilo(1-4C)** incluyen metilcarbonilo, etilcarbonilo, propilcarbonilo y terc-butil carbonilo; ejemplos de **alquil(1-4C)tio** y **alquil(1-6C)tio** incluyen metiltio, etiltio, isopropiltio y terc-butiltio; ejemplos de **alquil(1-4C)sulfinilo** y **alquil(1-6C)sulfinilo** incluyen metilsulfinilo, etilsulfinilo, isopropilsulfinilo y terc-butilsulfinilo; ejemplos de **alquil(1-4C)sulfonilo y alquil(1-6C)sulfonilo** incluyen metilsulfonilo, etilsulfonilo, isopropilsulfonilo y terc-butilsulfonilo; ejemplos de **alquil(1-6C)sulfoniloxi** incluyen metilsulfoniloxi, etilsulfoniloxi, isopropilsulfoniloxi y terc-butilsulfoniloxi; ejemplos de **alquil(1-6C)sulfonilamino** incluyen metilsulfonilamino, etilsulfonilamino, isopropilsulfonilamino y terc-butilsulfonilamino; ejemplos de **cicloalquil(3-6C)sulfonilo** incluyen ciclopropilsulfonilo, ciclobutilsulfonilo, ciclopropilsulfonilo y ciclohexilsulfonilo.

Deberá entenderse que, en la medida en que ciertos compuestos de fórmula (I) definidos anteriormente pueden existir en formas racémicas u ópticamente activas en virtud de uno o más átomos de carbono asimétricos, la invención incluye en su definición cualquier forma racémica u ópticamente activa que presente la propiedad de estimular la GLK. La síntesis de formas ópticamente activas puede llevarse a cabo mediante técnicas convencionales de la química orgánica bien conocidas en la técnica, por ejemplo mediante síntesis a partir de materiales de partida ópticamente activos o mediante resolución de una

forma racémica. También deberá entenderse que ciertos compuestos pueden existir en formas tautoméricas y que la invención también se refiere a todas las formas tautoméricas de los compuestos de la invención que activan la GLK. Se comprenderá que los compuestos descritos en su forma pirimidinol también pueden describirse como el tautómero pirimidinona y viceversa. Esto no supone nada acerca de las proporciones relativas reales de ambos en muestras físicas.

En particular, se comprenderá que el átomo de carbono al que está unido R^2 es un centro quiral. En un aspecto de la invención, este centro quiral tiene la configuración S. En otro aspecto, este centro quiral tiene la configuración R.

También deberá entenderse que ciertos compuestos de la fórmula (I) y sales de los mismos pueden existir en formas solvatadas así como en formas no solvatadas tales como, por ejemplo, formas hidratadas. Deberá entenderse que la invención abarca todas las formas solvatadas que activan la GLK.

En una realización de la invención se proporcionan compuestos de fórmula (I), en una realización alternativa se proporcionan sales de compuestos de fórmula (I), en una realización alternativa se proporcionan sales farmacéuticamente aceptables de compuestos de fórmula (I), en realización alternativa adicional se proporcionan ésteres hidrolizables *in vivo* de compuestos de fórmula (I) y en una realización alternativa adicional se proporcionan sales farmacéuticamente aceptables de ésteres hidrolizables *in vivo* de compuestos de fórmula (I).

Valores preferidos de cada grupo variable son como se describe a continuación. Dichos valores pueden utilizarse donde sea apropiado con cualquiera de los valores, definiciones, reivindicaciones, aspectos o realizaciones definidas anteriormente o más adelante en la presente. En particular, cada uno puede utilizarse como una limitación individual dentro de la más amplia definición de la fórmula (I) (incluyendo fórmulas (IA), (IB) y (IC)). Asimismo, cada uno de los siguientes valores puede utilizarse en combinación con uno o más de los siguientes valores para limitar la más amplia definición o cualquier sub-definición de la fórmula (I).

1) A es N y B es CR^6

2) A es CR^6 y B es N

3) X es C y es N y Z es N

4) X es N Y es CH y Z es N

5) X es N y es N y Z es C

6) R^1 es alquilo opcionalmente sustituido

7) R^1 es arilo opcionalmente sustituido

8) R^1 es arilalquilo(1-6C) opcionalmente sustituido

9) R^1 es HET-1 opcionalmente sustituido

10) R^1 es fenilo o piridilo opcionalmente sustituido (particularmente pirid-2-ilo o pirid-4-ilo, más particularmente pirid-2-ilo)

11) R^1 es fenilo o piridilo (particularmente pirid-2-ilo), sustituido en una posición 2 con relación al punto de unión a Z

12) R^1 es fenilo o piridilo (particularmente pirid-2-ilo), sustituido en una posición 2 con relación al punto de unión a Z

13) R^1 es fenilo o piridilo (particularmente pirid-2-ilo) y R^1 es di-sustituido, en donde un sustituyente está en una posición 2 con relación al punto de unión a Z

14) sustituyentes opcionales en R^1 se seleccionan de halo (particularmente cloro), alquilo(1-4C), alcoxi(1-4C), trifluorometilo, alquil(1-6C)sulfonilo y ciano

15) R^1 es un sistema de anillos bicíclico fusionado de fórmula –D-E

16) R^2 es alquilo(1-6C) opcionalmente sustituido por uno o dos hidroxi o R^2 es un grupo $-(CHR^4)_n$-P-Q

17) R^2 es un grupo $-(CHR^4)_n$-P-Q

18) R^2 es un grupo $-(CHR^4)_n$-P-Q; n es 1, 2, 3 ó 4 (particularmente 1 ó 2); un R^4 es opcionalmente hidroxi y los otros grupos R^4 (donde corresponda) son hidrógeno o metilo; P es un enlazante de oxígeno y Q es alquilo(1-6C), cicloalquilo(3-6C) o un heterociclilo de 4, 5 ó 6 miembros y Q está opcionalmente sustituido en un átomo de carbono disponible por hidroxi o alcoxi(1-4C)

19) R^2 es un grupo $-(CHR^4)_n$-P-Q; n es 1, 2, 3 ó 4 (particularmente 1 ó 2); un R^4 es opcionalmente hidroxi y los otros grupos R^4 (donde corresponda) son hidrógeno o metilo; P es un enlazante de oxígeno y Q es alquilo(1-6C), opcionalmente sustituido por hidroxi o alcoxi(1-4C)

20) R^2 se selecciona de hexilo, butilo, isobutilo, isopropilo, etilo, metilo, isopropoximetilo, etoximetilo, ciclobutiloximetilo, metoximetilo, hidroxietilo, hidroxipropilo, metilsulfoniletilo, isopropilsulfoniletilo, etilsulfoniletilo, metilsulfonilaminoetilo, metilsulfonilaminometilo, ciclopropiloximetilo, oxetaniloximetilo, hidroxietoximetilo, 1-

hidroxiprop-2-iloximetilo, metoxietilo, 1-metoxiprop-2-iloximetilo, dimetilaminoetilo, metilcarbonilaminometilo, carboxietilo, carbamoiletilo, N-metilcarbamoiletilo, metoxietoxietilo, metilcarboniloxietilo,

21) R^2 se selecciona de hexilo, butilo, isobutilo, isopropilo, etilo, metilo, isopropoximetilo, etoximetilo, ciclobutiloximetilo, metoximetilo, hidroxietilo, hidroxipropilo, metilsulfoniletilo, metilsulfonilaminoetilo, hidroxietoximetilo, metoxietilo, 1-metoxiprop-2-iloximetilo, dimetilaminoetilo, metilcarbonilaminometilo, carboxietilo, carbamoiletilo, N-metilcarbamoiletilo, metoxietoxietilo, metilcarboniloxietilo,

22) R^2 se selecciona de isopropoximetilo, etoximetilo, ciclobutiloximetilo, metoximetilo, hidroxietilo, hidroxipropilo, ciclopropiloximetilo, oxetaniloximetilo, hidroxietoximetilo, 1-hidroxiprop-2-iloximetilo, metoxietilo, 1-metoxiprop-2-iloximetilo, metoxietoxietil

23) R^2 se selecciona de isopropoximetilo, etoximetilo, ciclobutiloximetilo, metoximetilo, hidroxietilo, hidroxipropilo, hidroxietoximetilo, metoxietilo, 1-metoxiprop-2-iloximetilo, metoxietoxietilo

24) R^3 se selecciona de piridilo, tiazolilo, pirimidinilo, pirazinilo, piridazinilo, pirazolilo, isoxazolilo y tiadiazolilo opcionalmente sustituido

25) R^3 es un anillo de 6 miembros

26) R^3 es piridilo o pirazinilo opcionalmente sustituido

27) R^3 es piridilo opcionalmente sustituido

28) R^3 es piridilo, sustituido en la posición para con relación al punto de unión al grupo CONH

29) R^3 es 2-piridilo, sustituido en la pocición para con relación al punto de unión al grupo CONH

30) R^{11} se selecciona de halo, alquilo(1-4C), alquil(1-6C)sulfonilo, N,N-dialquilcarbamoilo y ciano

31) R^{11} se selecciona de halo (particularmente cloro o fluoro, más particularmente cloro) o alquilo(1-4C) (particularmente metilo)

32) cada R^4 es hidrógeno

33) n es >1 y solamente un R^4 no es hidrógeno

34) n es 1, 2 ó 3

35) n es 1 ó 2

36) R^5 es H

37) R^6 es H

38) R^7 es H

39) R^8 es metilo

40) R^9 es H

41) L es O

42) L es S

43) L es NH

44) R^{10} es H

45) R^{12} es H

46) P es un enlazante de oxígeno

47) NR^9R^{10} forma un anillo azetidina, opcionalmente sustituido por hidroxi, hidroximetilo o metoxi

48) NR^9R^{10} forma un anillo azetidina, opcionalmente sustituido por hidroxi o hidroximetilo.

En un aspecto adicional de la invención, se proporciona un compuesto de fórmula (IA), o una sal farmacéuticamente aceptable del mismo en donde

R^1 es fenilo o piridilo, sustituido en la posición 2 con relación al punto de unión a Z con un sustituyente que se selecciona de halo (particularmente cloro), alquilo(1-4C), alcoxi(1-4C), trifluorometilo, alquil(1-6C)sulfonilo y ciano;

R^2 es alquilo(1-6C) opcionalmente sustituido por uno o dos hidroxi o R^2 es un grupo $-(CHR^4)_n$-P-Q;

n es 1, 2, 3 ó 4 (particularmente 1 ó 2);

un R^4 es opcionalmente hidroxi y los otros grupos R^4 (donde corresponda) son hidrógeno o metilo;

P es un enlazante de oxígeno;

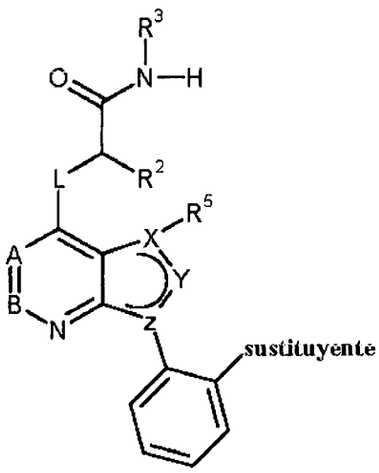
Q es alquilo(1-6C), cicloalquilo(3-6C) o un heterociclilo de 4, 5 ó 6 miembros y Q está opcionalmente sustituido en un átomo de carbono disponible por hidroxi o alcoxi(1-4C);

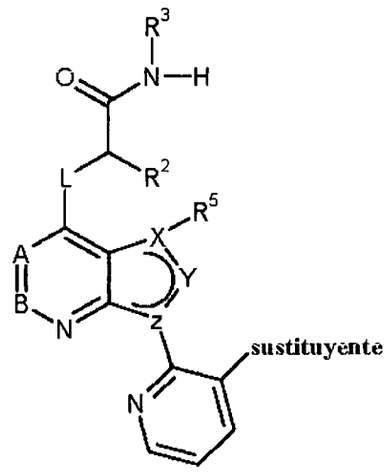
R^3 es piridilo, sustituido en la posición para con relación al punto de unión al grupo CONH con un sustituyente que se selecciona de R^{11}; y

R^{11} se selecciona de halo (particularmente fluoro o cloro, más particularmente cloro), alquilo(1-4C), alquil(1-6C)sulfonilo, N,N-dialquilcarbamoilo y ciano.

En la presente se entenderá que toda referencia a R^1 sustituido en una posición 2

con relación al punto de unión a Z se refiere al siguiente patrón de sustitución, ilustrado para R^1 es fenilo y pirid-2-ilo:





Los compuestos preferidos adicionales de la invención son cada uno de los Ejemplos, cada uno de los cuales proporciona un aspecto independiente adicional de la invención. En aspectos adicionales, la presente invención también comprende dos o más compuestos de los Ejemplos.

Los compuestos particulares de la invención incluyen uno o más de:

2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-3-metoxi-*N*-(5-metilpiridin-2-il)propanamida;

(R)-2-{[1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-il]oxi}-3-metoxi-N-(5-metilpiridin-2-il)propanamida;

(S)-2-{[1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-il]oxi}-3-metoxi-N-(5-metilpiridin-2-il)propanamida;

3-metoxi-2-{[1-(2-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)propanamida;

(R)-3-metoxi-2-{[1-(2-metoxifenil)-1H-pirazolo[3,4-d]pirimidin-4-il]oxi}-N-(5-metilpiridin-2-il)propanamida;

(S)-3-metoxi-2-{[1-(2-metoxifenil)-1H-pirazolo[3,4-d]pirimidin-4-il]oxi}-N-(5-metilpiridin-2-il)propanamida;

2-{[1-(2,4-diclorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-3-metoxi-*N*-(5-metilpiridin-2-il)propanamida;

3-metoxi-2-[(1-metil-1*H*-pirazolo[3,4-*d*]pirimidin-4-il)oxi]-*N*-(5-metilpiridin-2-il)propanamida;

2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)-4-(metilsulfonil)butanamida;

2-{[1-(2-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)-4-(metilsulfonil)butanamida;

(R)-2-{[1-(2-metoxifenil)-1H-pirazolo[3,4-d]pirimidin-4-il]oxi}-N-(5-metilpiridin-2-il)-4-(metilsulfonil)butanamida;

(S)-2-{[1-(2-metoxifenil)-1H-pirazolo[3,4-d]pirimidin-4-il]oxi}-N-(5-metilpiridin-2-il)-4-(metilsulfonil)butanamida;

4-metoxi-2-{[1-(3-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)butanamida;

(R)-4-metoxi-2-{[1-(3-metoxifenil)-1H-pirazolo[3,4-d]pirimidin-4-il]oxi}-N-(5-metilpiridin-2-il)butanamida;

(S)-4-metoxi-2-{[1-(3-metoxifenil)-1H-pirazolo[3,4-d]pirimidin-4-il]oxi}-N-(5-metilpiridin-2-il)butanamida;

4-metoxi-2-{[1-(2-metilfenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)butanamida;

(S)-4-metoxi-2-{[1-(2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-il]oxi}-N-(5-metilpiridin-2-il)butanamida;

(R)-4-metoxi-2-{[1-(2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-il]oxi}-N-(5-metilpiridin-2-il)butanamida;

2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-4-metoxi-*N*-(5-metilpiridin-2-il)butanamida;

(R)-2-{[1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-il]oxi}-4-metoxi-N-(5-metilpiridin-2-il)butanamida;

(S)-2-{[1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-il]oxi}-4-metoxi-N-(5-metilpiridin-2-il)butanamida;

4-metoxi-2-{[1-(2-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)butanamida;

(R)-4-metoxi-2-{[1-(2-metoxifenil)-1H-pirazolo[3,4-d]pirimidin-4-il]oxi}-N-(5-metilpiridin-2-il)butanamida;

(S)-4-metoxi-2-{[1-(2-metoxifenil)-1H-pirazolo[3,4-d]pirimidin-4-il]oxi}-N-(5-metilpiridin-2-il)butanamida;

2-{[1-(2,4-difluorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-4-metoxi-*N*-(5-metilpiridin-2-il)butanamida;

(R)-2-{[1-(2,4-difluorofenil)-1H-pirazolo[3,4-d]pirimidin-4-il]oxi}-4-metoxi-N-(5-metilpiridin-2-il)butanamida;

(S)-2-{[1-(2,4-difluorofenil)-1H-pirazolo[3,4-d]pirimidin-4-il]oxi}-4-metoxi-N-(5-metilpiridin-2-il)butanamida;

4-metoxi-*N*-(5-metilpiridin-2-il)-2-({1-[2-(trifluorometil)fenil]-1*H*-pirazolo[3,4-*d*]pirimidin-4-il}oxi)butanamida;

(S)-4-metoxi-N-(5-metilpiridin-2-il)-2-({1-[2-(trifluorometil)fenil]-1H-pirazolo[3,4-d]pirimidin-4-il}oxi)butanamida;

(R)-4-metoxi-N-(5-metilpiridin-2-il)-2-({1-[2-(trifluorometil)fenil]-1H-pirazolo[3,4-d]pirimidin-4-il}oxi)butanamida;

4-metoxi-2-{[1-(3-metilfenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)butanamida;

(R)-4-metoxi-2-{[1-(3-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-il]oxi}-N-(5-metilpiridin-2-il)butanamida;

(S)-4-metoxi-2-{[1-(3-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-il]oxi}-N-(5-metilpiridin-2-il)butanamida;

4-metoxi-*N*-(5-metilpiridin-2-il)-2-[(1-piridin-2-il-1*H*-pirazolo[3,4-*d*]pirimidin-4-il)oxi]butanamida;

4-metoxi-2-{[1-(2-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(4-metil-1,3-tiazol-2-il)butanamida;

(R)-4-metoxi-2-{[1-(2-metoxifenil)-1H-pirazolo[3,4-d]pirimidin-4-il]oxi}-N-(4-metil-1,3-tiazol-2-il)butanamida;

(S)-4-metoxi-2-{[1-(2-metoxifenil)-1H-pirazolo[3,4-d]pirimidin-4-il]oxi}-N-(4-metil-1,3-tiazol-2-il)butanamida;

2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)hexanamida;

2-[(1-metil-1*H*-pirazolo[3,4-*d*]pirimidin-4-il)oxi]-*N*-(5-metilpiridin-2-il)hexanamida

2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpirazin-2-

il)hexanamida;
2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]tio}-*N*-(4-metil-1,3-tiazol-2-il)hexanamida;
2-{[1-(2-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)butanamida;
(2*R*)-2-{[1-(2-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)butanamida;
2-{[1-(2-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)propanamida;
(2*S*)-2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-4-(dimetilamino)-*N*-(5-metilpiridin-2-il)butanamida;
3-acetamido-2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(4-metil-1,3-tiazol-2-il)propanamida;
4-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-5-[(5-metilpiridin-2-il)amino]-5-oxopentanoico ácido;
2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N1*-(5-metilpiridin-2-il)pentanodiamida;
2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N5*-metil-*N1*-(5-metilpiridin-2-il)pentanodiamida;
2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]tio}-4-(2-metoxietoxi)-*N*-(4-metil-1,3-tiazol-2-il)butanamida;
2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]tio}-4-metoxi-*N*-(4-metil-1,3-tiazol-2-il)butanamida;
2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]tio}-3-metil-*N*-(4-metil-1,3-tiazol-2-il)pentanamida;
2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]tio}-*N*-isoxazol-3-il-3-metilpentanamida;
2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]tio}-3-metil-*N*-(5-metilpiridin-2-il)pentanamida;
2-[(1-isopropil-1*H*-pirazolo[3,4-*d*]pirimidin-4-il)tio]-4-(2-metoxietoxi)-*N*-(5-metilpiridin-2-il)butanamida;
2-[(1-isopropil-1*H*-pirazolo[3,4-*d*]pirimidin-4-il)tio]-4-(2-metoxietoxi)-*N*-(5-metilpiridin-

2-il)butanamida;

2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]tio}-*N*-(4-metil-1,3-tiazol-2-il)hexanamida;

2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]tio}-*N*-isoxazol-3-ilhexanamida;

2-{[1-(2-Clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]tio}-4-(2-metoxietoxi)- *N*-(4-metil-1,3-tiazol-2-il)butanamida;

2-{[1-(2-Clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]tio}-3-metoxi-*N*-(5-metilpiridin-2-il)propanamida;

2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]tio}-*N*-(4-metil-1,3-tiazol-2-il)octanamida;

2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]tio}-*N*-isoxazol-3-iloctanamida;

2-etoxi-2-{[1-(2-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]tio}-*N*-(4-metil-1,3-tiazol-2-il)acetamida;

2-etoxi-*N*-isoxazol-3-il-2-{[1-(2-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]tio}acetamida;

2-[(1-isopropil-1*H*-pirazolo[3,4-*d*]pirimidin-4-il)oxi]-4-metoxi-*N*-(5-metilpiridin-2-il)butanamida;

(R)-2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]tio}-*N*-(4-metil-1,3-tiazol-2-il)hexanamida;

(S)-2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]tio}-*N*-(4-metil-1,3-tiazol-2-il)hexanamida;

2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-metil-*N*-(5-metilpiridin-2-il)butanamida;

(2S)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-metil-*N*-(5-metilpiridin-2-il)butanamida;

(2R)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-metil-*N*-(5-metilpiridin-2-il)butanamida;

(2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-metil-*N*-(5-metilpiridin-2-il)butanamida;

(2S)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-metoxi-*N*-(5-metilpiridin-2-il)propanamida;

(2R)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-metoxi-*N*-(5-metilpiridin-

2-il)propanamida;
(2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-metoxi-*N*-(5-metilpiridin-2-il)propanamida;
(2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-metoxi-*N*-(5-metilpirazin-2-il)propanamida;
(2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-isopropoxi-*N*-(5-metilpiridin-2-il)propanamida;
(2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-isopropoxi-*N*-(5-metilpirazin-2-il)propanamida;
(2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-isopropoxi-*N*-(3-metil-1,2,4-tiadiazol-5-il)propanamida;
(2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-metil-*N*-(5-metilpirazin-2-il)butanamida;
(2S)-2-(1-(2-cloro-4-fluorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-metoxi-*N*-(5-metilpirazin-2-il)propanamida;
(2S)-2-(1-(2-cloro-4-fluorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-metoxi-*N*-(5-metilpiridin-2-il)propanamida;
(2S)-2-(1-(2-cianofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-metoxi-*N*-(5-metilpiridin-2-il)propanamida;
(2S)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-isopropoxi-*N*-(5-metilpiridin-2-il)propanamida;
(2R)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-isopropoxi-*N*-(5-metilpiridin-2-il)propanamida; y/o
(2S)-2-[1-(2-cianofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-metilpiridin-2-il)-3-propan-2-iloxipropanamida;
(2S)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(3-metil-1,2,4-tiadiazol-5-il)-3-propan-2-iloxipropanamida;
(2S)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-metoxi-N-(3-metil-1,2,4-tiadiazol-5-il)propanamida;
(2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-4-metoxi-N-(5-metilpiridin-2-il)butanamida;
(2S)-2-[1-(3-cloropiridin-2-il)pirazolo[4,5-e]pirimidin-4-il]oxi-3-etoxi-N-(5-metilpiridin-

2-il)propanamida;
(2S)-2-[1-(3-cloropiridin-2-il)pirazolo[4,5-e]pirimidin-4-il]oxi-3-etoxi-N-(5-metilpirazin-2-il)propanamida ;
(2S)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-etoxi-N-(5-metilpirazin-2-il)propanamida;
(2S)-3-isopropoxi-N-(5-metilpirazin-2-il)-2-(1-(3-metilpirazin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida;
(S)-3-metoxi-N-(5-metilpiridin-2-il)-2-(1-fenil-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida;
2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-isopropoxi-N-pirazin-2-il-propanamida;
2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-isopropoxi-N-(5-metil-1,3,4-tiadiazol-2-il)propanamida;
2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-isopropoxi-N-(5-metilisoxazol-3-il)propanamida;
2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-isopropoxi-N-(5-metiltiazol-2-il)propanamida;
2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-3-isopropoxi-propanamida;
2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-ciano-2-piridil)-3-isopropoxi-propanamida;
2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-isopropoxi-N-(1,2,4-tiadiazol-5-il)propanamida;
2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-cloro-2-piridil)-3-isopropoxi-propanamida;
2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-isopropoxi-N-(4-metil-2-piridil)propanamida;
2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-isopropoxi-N-(1,3,4-tiadiazol-2-il)propanamida;
2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-isopropoxi-N-(2-piridil)propanamida;
2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-isopropoxi-N-isoxazol-3-il-

propanamida;
2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-isopropoxi-N-pirimidin-4-il-propanamida;
(2S)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-isopropoxi-N-(5-metiltiazol-2-il)propanamida;
(2S)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-3-isopropoxi-propanamida;
(2S)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-ciano-2-piridil)-3-isopropoxi-propanamida;
(2S)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-cloro-2-piridil)-3-isopropoxi-propanamida;
(2S)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-isopropoxi-N-(2-piridil)propanamida;
(2S)-3-isopropoxi-N-(5-metilpiridin-2-il)-2-(1-(3-metilpiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida;
(2S)-3-isopropoxi-N-(5-metilpiridin-2-il)-2-(1-(3-(trifluorometil)piridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida;
(2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-isopropoxi-N-(6-metilpiridazin-3-il)propanamida;
(2S)-N-(5-cianopiridin-2-il)-3-isopropoxi-2-(1-(3-metilpiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida;
(2S)-N-(5-cloropiridin-2-il)-3-isopropoxi-2-(1-(3-metilpiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida;
(2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-ciano-2-piridil)-3-etoxi-propanamida;
(2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-etoxi-N-(5-fluoro-2-piridil)propanamida;
(2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-etoxi-N-(2-piridil)propanamida;
(2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-etoxi-N-pirimidin-4-il-propanamida;
(2S)-N-(5-cloro-2-piridil)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-etoxi-

propanamida;
(2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(4-cianotiazol-2-il)-3-isopropoxi-propanamida;
(2S)-N-(5-cloro-2-piridil)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-isopropoxi-propanamida;
(2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-ciano-2-piridil)-3-isopropoxi-propanamida;
(2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-isopropoxi-N-(2-piridil)propanamida;
(2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-3-isopropoxi-propanamida;
(2S)-N-(5-cloropiridin-2-il)-3-etoxi-2-[1-(3-metilpiridin-4-il)pirazolo[4,5-e]pirimidin-4-il]oxipropanamida;
(2S)-N-(5-cloropiridin-2-il)-3-etoxi-2-(1-(3-metilpiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida;
(2S)-3-isopropoxi-N-(5-metilpiridin-2-il)-2-(1-(2-(metilsulfonil)fenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida;
(2S)-N-(5-cloropiridin-2-il)-3-etoxi-2-(1-(2-(metilsulfonil)fenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida;
(2R)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-5-hidroxi-N-(5-metil-2-piridil)pentanamida;
(2S)-N-(5-ciano-2-piridil)-3-etoxi-2-[1-[2-(trifluorometil)fenil]pirazolo[4,5-e]pirimidin-4-il]oxi-propanamida;
(2S)-3-etoxi-N-(5-metilpirazin-2-il)-2-[1-[2-(trifluorometil)fenil]pirazolo[4,5-e]pirimidin-4-il]oxi-propanamida;
(2S)-N-(5-cloro-2-piridil)-3-etoxi-2-[1-[3-(trifluorometil)-2-piridil]pirazolo[4,5-e]pirimidin-4-il]oxi-propanamida;
(2S)-3-isopropoxi-N-(5-metil-2-piridil)-2-[1-(3-metil-4-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-propanamida;
(2S)-3-(ciclobutoxi)-N-(5-metilpirazin-2-il)-2-[1-(3-metil-4-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-propanamida;
(2S)-3-(ciclobutoxi)-N-(5-metilpirazin-2-il)-2-[1-[3-(trifluorometil)-2-piridil]pirazolo[4,5-

e]pirimidin-4-il]oxi-propanamida;
(2S)-2-[1-[5-cloro-3-(trifluorometil)-2-piridil]pirazolo[4,5-e]pirimidin-4-il]oxi-3-(ciclobutoxi)-N-(5-metilpirazin-2-il)propanamida;
(2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-etoxi-N-(5-metilsulfonil-2-piridil)propanamida;
(2S)-3-(ciclobutoxi)-N-(5-metilpirazin-2-il)-2-[1-(2-metilsulfonilfenil)pirazolo[4,5-e]pirimidin-4-il]oxi-propanamida;
(2S)-3-(ciclobutoxi)-N-(5-metilpirazin-2-il)-2-[1-(3-metil-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-propanamida;
(2S)-3-(ciclobutoxi)-N-(5-metilpirazin-2-il)-2-(1-fenilpirazolo[4,5-e]pirimidin-4-il)oxi-propanamida;
(2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-4-hidroxi-N-(5-metil-2-piridil)butanamida;
(2S)-3-(ciclobutoxi)-2-[1-(3-metilpirazin-2-il)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-metil-2-piridil)propanamida;
(2S)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-4-hidroxi-N-(5-metil-2-piridil)butanamida;
(2S)-3-isopropoxi-N-(5-metil-2-piridil)-2-[1-(2-metil-3-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-propanamida;
6-[[(2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-etoxi-propanoil]amino]-N,N-dimetil-piridina-3-carboxamida;
(2S)-3-isopropoxi-N-(5-metil-2-piridil)-2-[1-(4-metil-3-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-propanamida;
(2S)-3-(ciclobutoxi)-N-(5-metilpirazin-2-il)-2-[1-(2-metil-3-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-propanamida;
(2S)-N-(5-cloro-2-piridil)-3-etoxi-2-[1-(2-metil-3-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-propanamida;
(2S)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-[(1S)-2-metoxi-1-metil-etoxi]-N-(5-metilpirazin-2-il)propanamida;
(2S)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-[(1S)-2-metoxi-1-metil-etoxi]-N-(5-metil-2-piridil)propanamida;
(2S)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-[(1R)-2-metoxi-1-metil-etoxi]-

N-(5-metil-2-piridil)propanamida;

(2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-[(1R)-2-metoxi-1-metil-etoxi]-N-(5-metil-2-piridil)propanamida;

(2R)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-[(1S)-2-metoxi-1-metil-etoxi]-N-(5-metilpirazin-2-il)propanamida;

(2S)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-(ciclobutoxi)-N-(5-metilpirazin-2-il)propanamida;

(2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-(ciclobutoxi)-N-(5-metilpirazin-2-il)propanamida;

(2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-(ciclobutoxi)-N-(5-metil-2-piridil)propanamida;

[(3S)-3-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-4-[(5-metil-2-piridil)amino]-4-oxo-butil] acetato;

(2S)-3-isopropoxi-N-(5-metil-2-piridil)-2-[1-[2-(trifluorometil)fenil]pirazolo[4,5-e]pirimidin-4-il]oxi-propanamida;

(2S)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-metil-2-piridil)-4-metilsulfonil-butanamida;

(2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-ciano-2-piridil)-3-(2-hidroxietoxi)propanamida;

(2S)-N-(5-cloro-2-piridil)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-(2-hidroxietoxi)propanamida;

(2S)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-4-metanosulfonamido-N-(5-metil-2-piridil)butanamida;

(2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-4-hidroxi-N-(5-metilpirazin-2-il)butanamida;

(2S)-N-(5-cloro-2-piridil)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-4-hidroxi-butanamida;

(2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-4-hidroxi-N-(2-piridil)butanamida;

(2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-4-hidroxi-butanamida;

(2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-ciano-2-piridil)-4-

hidroxi-butanamida;
(2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-4-hidroxi-N-pirimidin-4-il-butanamida; y/o
(2S)-N-(5-cloropiridin-2-il)-2-[1-(3-cloropiridin-2-il)pirazolo[4,5-e]pirimidin-4-il]oxi-3-(3-hidroxiazetidin-1-il)propanamida;
(2S)-2-[1-(3-cloro-2-metilfenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-cianopiridin-2-il)-3-(2-hidroxietoxi)propanamida;
(2S)-2-[1-(3-cloro-2-metilfenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-(2-hidroxietoxi)-N-(5-metilpiridin-2-il)propanamida;
(2S)-N-(5-cianopiridin-2-il)-2-[1-(3-fluoro-2-metilfenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-(2-hidroxietoxi)propanamida;
(2S)-2-[1-(3-fluoro-2-metilfenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-(2-hidroxietoxi)-N-(5-metilpiridin-2-il)propanamida;
(2S)-N-(5-cloropiridin-2-il)-2-[1-(3-fluoro-2-metilfenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-(2-hidroxietoxi)propanamida;
(2S)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-cloropiridin-2-il)-3-(2-hidroxietoxi)propanamida;
(2S)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-cianopiridin-2-il)-3-(2-hidroxietoxi)propanamida;
(2S)-2-[1-(3-cloro-2-metilfenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-cloropiridin-2-il)-3-(2-hidroxietoxi)propanamida;
(2S)-2-(1-(2-cloro-6-cianofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-cloropiridin-2-il)-3-(2-hidroxietoxi)propanamida;
(2S)-2-(1-(2-cloro-6-cianofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-((R)-1-hidroxipropan-2-iloxi)-N-(5-metilpiridin-2-il)propanamida;
(2S)-2-(1-(2-cloro-6-cianofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-(2-hidroxietoxi)-N-(5-metilpiridin-2-il)propanamida;
(2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-isopropoxi-N-(5-(metilsulfonil)piridin-2-il)propanamida;
6-((2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-isopropoxipropanamido)-N,N-dimetilnicotinamida;
(2S)-N-(5-cloropiridin-2-il)-2-(1-(2,5-dimetilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-

(2-hidroxietoxi)propanamida;
(2S)-N-(5-cloropiridin-2-il)-2-(1-(5-fluoro-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-(2-hidroxietoxi)propanamida;
(S)-2-(1-bencil-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-(2-hidroxietoxi)-N-(5-metilpiridin-2-il)propanamida;
(2S)-N-(5-cianopiridin-2-il)-2-(1-(5-fluoro-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-(2-hidroxietoxi)propanamida;
(2S)-2-(1-(5-ciano-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-cianopiridin-2-il)-3-(2-hidroxietoxi)propanamida;
(2S)-2-(1-(5-ciano-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-(2-hidroxietoxi)-N-(5-metilpiridin-2-il)propanamida;
(2S)-N-(5-cloropiridin-2-il)-2-(1-(5-ciano-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-(2-hidroxietoxi)propanamida;
(2S)-N-(5-cianopiridin-2-il)-2-(1-(2,5-dimetilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-etoxipropanamida;
(2S)-N-(5-cloropiridin-2-il)-3-etoxi-2-(1-(4-metilpiridin-3-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida;
(2S)-3-ciclobutoxi-N-(5-metilpirazin-2-il)-2-(1-(4-metilpiridin-3-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida;
(2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-cianopiridin-2-il)-3-((R)-1-hidroxipropan-2-iloxi)propanamida;
(2S)-N-(5-cloropiridin-2-il)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-((R)-1-hidroxipropan-2-iloxi)propanamida;
(2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-fluoropiridin-2-il)-3-((R)-1-hidroxipropan-2-iloxi)propanamida;
(2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-fluoropiridin-2-il)-3-((S)-1-hidroxipropan-2-iloxi)propanamida;
(2S)-N-(5-cloropiridin-2-il)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-((S)-1-hidroxipropan-2-iloxi)propanamida;
(2S)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-(2-hidroxietoxi)-N-(5-metilpiridin-2-il)propanamida;
(2S)-2-(3-(2-clorofenil)-3H-[1,2,3]triazolo[4,5-d]pirimidin-7-iloxi)-3-(2-hidroxietoxi)-N-

(5-metilpiridin-2-il)propanamida;
(2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-(3-(2-clorofenil)-3H-[1,2,3]triazolo[4,5-d]pirimidin-7-iloxi)-N-(5-metilpiridin-2-il)propanamida;
(2S)-2-(3-(2-clorofenil)-3H-[1,2,3]triazolo[4,5-d]pirimidin-7-iloxi)-N-(5-cianopiridin-2-il)-3-etoxipropanamida;
(2S)-N-(5-cloropiridin-2-il)-3-(2-hidroxietoxi)-2-(3-o-tolil-3H-[1,2,3]triazolo[4,5-d]pirimidin-7-iloxi)propanamida;
(2S)-3-(2-hidroxietoxi)-N-(piridin-2-il)-2-(1-(2-(trifluorometil)fenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida;
(2S)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-((R)-1-hidroxipropan-2-iloxi)-N-(piridin-2-il)propanamida;
(2S)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-(2-hidroxietoxi)-N-(piridin-2-il)propanamida;
(2S)-N-(5-cloropiridin-2-il)-2-(1-(2,3-diclorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-(2-hidroxietoxi)propanamida;
(2S)-N-(5-cianopiridin-2-il)-2-(1-(2,3-diclorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-(2-hidroxietoxi)propanamida;
(2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-((S)-2-hidroxipropoxi)-N-(5-metilpiridin-2-il)propanamida;
(2S)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-(3-hidroxiazetidin-1-il)-N-(5-metilpiridin-2-il)propanamida;
(2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-(3-hidroxiazetidin-1-il)-N-(5-metilpiridin-2-il)propanamida;
(2S)-2-(1-(3-ciano-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-cianopiridin-2-il)-3-(2-hidroxietoxi)propanamida;
(2S)-2-(1-(3-ciano-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-(2-hidroxietoxi)-N-(5-metilpiridin-2-il)propanamida;
(2S)-N-(5-cloropiridin-2-il)-2-(1-(3-ciano-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-(2-hidroxietoxi)propanamida;
(2S)-N-(5-cloropiridin-2-il)-3-etoxi-2-(1-(1-metil-1H-imidazol-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida;
(2S)-3-isopropoxi-2-(1-(1-metil-1H-imidazol-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-

(5-metilpiridin-2-il)propanamida;
(2S)-N-(5-cloropiridin-2-il)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-5-hidroxipentanamida;
(2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-cianopiridin-2-il)-5-hidroxipentanamida;
(2S)-N-(5-cianopiridin-2-il)-2-(1-(2,3-diclorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-etoxipropanamida;
(2S)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-3-(3-hidroxiazetidin-1-il)propanamida;
(2S)-2-[1-(2-cloro-6-ciano-fenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-cloro-2-piridil)-3-[(1R)-2-hidroxi-1-metil-etoxi]propanamida;
(2S)-2-[1-(2-cloro-6-ciano-fenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-[(1R)-2-hidroxi-1-metil-etoxi]-N-(5-metilpirazin-2-il)propanamida;
(2S)-2-[1-(2,6-diclorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-3-(2-hidroxietoxi)propanamida;
(2S)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-(3-hidroxiazetidin-1-il)-N-(5-metilpirazin-2-il)propanamida;
(2S)-2-[1-(2,6-diclorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-(3-hidroxiazetidin-1-il)-N-(5-metilpirazin-2-il)propanamida;
(2S)-3-(azetidin-1-il)-2-[1-(2-cloro-6-ciano-fenil)pirazolo[3,4-d]pirimidin-4-il]oxi-N-(2-piridil)propanamida;
(2S)-2-[1-(2-cloro-6-fluoro-fenil)pirazolo[3,4-d]pirimidin-4-il]oxi-3-(3-hidroxiazetidin-1-il)-N-(2-piridil)propanamida;
(2S)-2-[1-(2-clorofenil)pirazolo[3,4-d]pirimidin-4-il]oxi-N-(5-ciano-2-piridil)-3-(3-hidroxiazetidin-1-il)propanamida;
(2S)-2-[1-(2-cloro-6-ciano-fenil)pirazolo[3,4-d]pirimidin-4-il]oxi-N-(5-ciano-2-piridil)-3-(3-hidroxiazetidin-1-il)propanamida
(2S)-2-[1-(2-clorofenil)pirazolo[3,4-d]pirimidin-4-il]oxi-3-(3-hidroxiazetidin-1-il)-N-(2-piridil)propanamida;
(2S)-2-[1-(2-clorofenil)pirazolo[3,4-d]pirimidin-4-il]oxi-N-(5-cloro-2-piridil)-3-(3-hidroxiazetidin-1-il)propanamida;
(2S)-3-[(1R)-2-hidroxi-1-metil-etoxi]-N-(5-metil-2-piridil)-2-[1-(4-metil-3-

tienil)pirazolo[3,4-d]pirimidin-4-il]oxi-propanamida;
(2S)-2-[1-(2-clorofenil)pirazolo[3,4-d]pirimidin-4-il]oxi-3-[3-(hidroximetil)azetidin-1-il]-N-(2-piridil)propanamida;
(2S)-2-[1-(2-cloro-6-fluoro-fenil)pirazolo[3,4-d]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-3-(3-hidroxiazetidin-1-il)propanamida;
(2S)-2-[1-(2,6-diclorofenil)pirazolo[3,4-d]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-3-(3-hidroxiazetidin-1-il)propanamida;
(2S)-2-[1-(2-cloro-6-ciano-fenil)pirazolo[3,4-d]pirimidin-4-il]oxi-3-[(1R)-2-hidroxi-1-metil-etoxi]-N-(2-piridil)propanamida;
(2S)-2-[1-(3-cloro-2-piridil)pirazolo[3,4-d]pirimidin-4-il]oxi-3-[(1R)-2-hidroxi-1-metil-etoxi]-N-(5-metil-2-piridil)propanamida;
(2S)-2-[1-(2,6-diclorofenil)pirazolo[3,4-d]pirimidin-4-il]oxi-3-(3-hidroxiazetidin-1-il)-N-(2-piridil)propanamida;
(2S)-N-(5-ciano-2-piridil)-2-[1-(2,6-diclorofenil)pirazolo[3,4-d]pirimidin-4-il]oxi-3-(3-hidroxiazetidin-1-il)propanamida;
(2S)-N-(5-ciano-2-piridil)-2-[1-(2,6-diclorofenil)pirazolo[3,4-d]pirimidin-4-il]oxi-3-(2-hidroxietoxi)propanamida;
(2S)-N-(5-cloro-2-piridil)-2-[1-(2,6-dicianofenil)pirazolo[3,4-d]pirimidin-4-il]oxi-3-[(1R)-2-hidroxi-1-metil-etoxi]propanamida;
(2S)-2-[1-(2-cloro-6-ciano-fenil)pirazolo[3,4-d]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-3-(2-hidroxietoxi)propanamida;
(2S)-2-[1-(2-cloro-6-ciano-fenil)pirazolo[3,4-d]pirimidin-4-il]oxi-3-(2-hidroxietoxi)-N-(2-piridil)propanamida;
(2S)-2-[1-(2-cloro-6-ciano-fenil)pirazolo[3,4-d]pirimidin-4-il]oxi-3-(3-hidroxiazetidin-1-il)-N-(5-metilpirazin-2-il)propanamida;
(2S)-2-[1-(2-cloro-6-ciano-fenil)pirazolo[3,4-d]pirimidin-4-il]oxi-N-(5-cloro-2-piridil)-3-(3-hidroxiazetidin-1-il)propanamida;
(2S)-2-[1-(3-cloro-2-piridil)pirazolo[3,4-d]pirimidin-4-il]oxi-3-(3-hidroxiazetidin-1-il)-N-(2-piridil)propanamida;
(2S)-2-[1-(2-cloro-6-ciano-fenil)pirazolo[3,4-d]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-3-(3-hidroxiazetidin-1-il)propanamida;
(2S)-2-[1-(3-cloro-2-piridil)pirazolo[3,4-d]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-3-(3-

hidroxiazetidin-1-il)propanamida;
(2S)-2-[1-(2-cloro-6-fluoro-fenil)pirazolo[3,4-d]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-3-(2-hidroxietoxi)propanamida;
(2S)-2-[1-(2-clorofenil)pirazolo[3,4-d]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-3-[(1R)-2-hidroxi-1-metil-etoxi]propanamida;
(2S)-2-[1-(2-cloro-6-ciano-fenil)pirazolo[3,4-d]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-3-[(1R)-2-hidroxi-1-metil-etoxi]propanamida;
(2S)-2-[1-(2-clorofenil)pirazolo[3,4-d]pirimidin-4-il]oxi-3-[(1R)-2-hidroxi-1-metil-etoxi]-N-(5-metilpirazin-2-il)propanamida;
(2S)-2-[1-(2-clorofenil)pirazolo[3,4-d]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-3-(2-hidroxietoxi)propanamida;
(2S)-2-[1-(3-cloro-2-piridil)pirazolo[3,4-d]pirimidin-4-il]oxi-3-(3-hidroxiazetidin-1-il)-N-(5-metiltiazol-2-il)propanamida;
(2S)-2-[1-(2,6-diclorofenil)pirazolo[3,4-d]pirimidin-4-il]oxi-3-(2-hidroxietoxi)-N-(2-piridil)propanamida;
(2S)-2-[1-(2-cloro-6-ciano-fenil)pirazolo[3,4-d]pirimidin-4-il]oxi-N-(5-ciano-2-piridil)-3-[(1R)-2-hidroxi-1-metil-etoxi]propanamida;
(2S)-2-[1-(2-clorofenil)pirazolo[3,4-d]pirimidin-4-il]oxi-N-(5-ciano-2-piridil)-3-[(1R)-2-hidroxi-1-metil-etoxi]propanamida;
o una sal farmacéuticamente aceptable de los mismos. El término "uno cualquiera o más de" significa cualquier número de los compuestos precedentes de 1 a 258.

En otro aspecto la presente invención proporciona un compuesto que se selecciona de uno o más (esto es cualquier número de 1 a 12) de los siguientes:
(2S)-N-(5-cloropiridin-2-il)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]-pirimidin-4-iloxi)-3---(3-hidroxiazetidin-1-il)propanamida;
(2S)-2-(1-(2-cloro-6-cianofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-cloropiridin-2-il)-3-(2-hidroxietoxi)propanamida;
(2S)-N-(5-cloropiridin-2-il)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-((R)-1-hidroxipropan-2-iloxi)propanamida;
(2S)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-3-(3-hidroxiazetidin-1-il)propanamida;
(2S)-2-[1-(2-cloro-6-ciano-fenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-cloro-2-piridil)-3-

[(1R)-2-hidroxi-1-metil-etoxi]propanamida;
(2S)-2-[1-(2-cloro-6-ciano-fenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-[(1R)-2-hidroxi-1-metil-etoxi]-N-(5-metilpirazin-2-il)propanamida;
(2S)-2-[1-(2,6-diclorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-3-(2-hidroxietoxi)propanamida;
(2S)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-(3-hidroxiazetidin-1-il)-N-(5-metilpirazin-2-il)propanamida;
(2S)-2-[1-(2,6-diclorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-(3-hidroxiazetidin-1-il)-N-(5-metilpirazin-2-il)propanamida;
(2S)-2-[1-(2-clorofenil)pirazolo[3,4-d]pirimidin-4-il]oxi-N-(5-cloro-2-piridil)-3-(3-hidroxiazetidin-1-il)propanamida;
(2S)-2-[1-(2,6-diclorofenil)pirazolo[3,4-d]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-3-(3-hidroxiazetidin-1-il)propanamida; y
(2S)-2-[1-(2-cloro-6-ciano-fenil)pirazolo[3,4-d]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-3-(3-hidroxiazetidin-1-il)propanamida;
o una sal farmacéuticamente aceptable de los mismos.

Dependiendo del paquete informático utilizado para los nombres ciertos compuestos de la invención se denominan compuestos pirazolo[3,4-d]pirimidin-4-ilo y otros se denominan compuestos pirazolo[4,5-e]pirimidin-4-ilo. Los expertos en la técnica entenderán que dichos términos describen el mismo anillo heterocíclico.

En otro aspecto la presente invención proporciona un compuesto de fórmula I tal como se define en cualquiera de las definiciones anteriores pero excluyendo cualquiera de los compuestos en cualquiera de las listas de compuestos inmediatamente precedentes.

Los compuestos de la invención pueden administrarse en forma de un profármaco. Un profármaco es un bioprecursor o un compuesto farmacéuticamente aceptable que puede degradarse en el cuerpo para producir un compuesto de la invención (tal como un éster o amida de un compuesto de la invención, particularmente un éster hidrolizable *in vivo*). En la técnica se conocen varias formas de profármacos. Para ver ejemplos de dichos derivados de profármacos, véase:

a) Design of Prodrugs, editado por H. Bundgaard, (Elsevier, 1985) y Methods in Enzymology, Vol. 42, p. 309-396, editado por K. Widder, et al. (Academic Press, 1985);

b) A Textbook of Drug Design and Development, editado por Krogsgaard-Larsen;

c) H. Bundgaard, Capítulo 5 "Design and Application of Prodrugs", de H. Bundgaard p. 113-191 (1991);

d) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);

e) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988); y

f) N. Kakeya, *et al.*, Chem Pharm Bull, 32, 692 (1984).

Los contenidos de los documentos citados anteriormente se incorporan a la presente a modo de referencia. A continuación se describen ejemplos de profármacos. Un éster hidrolizable *in vivo* de un compuesto de la invención que contiene un grupo hidroxi o carboxi es, por ejemplo, un éster farmacéuticamente aceptable que se hidroliza en el cuerpo humano o animal para producir el alcohol o ácido original. Ésteres farmacéuticamente aceptables adecuados para carboxi incluyen ésteres metílicos de alcoxi C_1 a C_6 por ejemplo metoximetilo, ésteres metílicos de alcanoiloxi C_1 a C_6 por ejemplo ésteres de pivaloiloximetilo, ftalidilo, ésteres de cicloalcoxicarboniloxi C_3 a C_8alquilo C_1 a C_6 por ejemplo 1-ciclohexilcarboniloxietilo; ésteres 1,3-dioxolen-2-onilmetílicos, por ejemplo 5-metil-1,3-dioxolen-2-onilmetilo; y ésteres de alcoxicarboniloxietilo C_{1-6}.

Un éster hidrolizable *in vivo* de un compuesto de la invención que contiene un grupo hidroxi incluye ésteres inorgánicos tales como ésteres de fosfato (incluidos ésteres cíclicos fosforamídicos) y éteres de α-aciloxialquilo y compuestos relacionados que como resultado de la hidrólisis *in vivo* del éster se desintegran para proporcionar el/los grupos hidroxi base. Ejemplos de éteres de α-aciloxialquilo incluyen acetoximetoxi y 2,2-dimetilpropioniloxi-metoxi. Una selección de ésteres hidrolizables *in vivo* que forman grupos para hidroxi incluyen alcanoilo, benzoilo, fenilacetilo y benzoilo y fenilacetilo sustituidos, alcoxicarbonilo (para proporcionar ésteres de alquilcarbonato), dialquilcarbamoilo y N(dialquilaminoetil)-*N*-alquilcarbamoilo (para proporcionar carbamatos), dialquilaminoacetilo y carboxiacetilo.

Una sal farmacéuticamente aceptable adecuada de un compuesto de la invención es, por ejemplo, una sal de adición de ácido de un compuesto de la invención que es suficientemente básica, por ejemplo, una sal de adición de ácido con, por ejemplo, un ácido orgánico o inorgánico, por ejemplo ácido clorhídrico, bromhídrico, sulfúrico, fosfórico, trifluoroacético, cítrico o maleico. En un aspecto, una sal de adición de ácido adecuada puede ser una sal con ácido clorhídrico, sulfúrico, metanosulfónico o cítrico. Se comprenderá que una sal de adición de ácido puede formarse con cualquier grupo que sea

lo suficientemente básico que puede estar, por ejemplo, en HET-1 o puede ser, por ejemplo, un sustituyente de R^2. Adicionalmente, una sal farmacéuticamente aceptable adecuada de un derivado de benzoxazinona de la invención que es suficientemente ácida es una sal de metal alcalino, por ejemplo una sal de sodio o potasio, una sal de metal alcalinotérreo, por ejemplo una sal de calcio o magnesio, una sal de amonio o una sal con una base orgánica que proporciona un catión fisiológicamente aceptable, por ejemplo una sal con metilamina, dimetilamina, trimetilamina, piperidina, morfolina o tris-(2-hidroxietil)amina.

Una característica adicional de la invención es una composición farmacéutica que comprende un compuesto de fórmula (I) tal como se define anteriormente, o una sal farmacéuticamente aceptable del mismo, junto con un diluyente o portador farmacéuticamente aceptable.

De acuerdo con otro aspecto de la invención se proporciona un compuesto de fórmula (I) tal como se define anteriormente, o una sal farmacéuticamente aceptable del mismo para su uso como un medicamento.

De acuerdo con otro aspecto de la invención se proporciona un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, tal como se define anteriormente, para su uso como un medicamento para el tratamiento de una enfermedad mediada por GLK, en particular diabetes tipo 2.

De acuerdo con otro aspecto de la invención se proporciona un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, en la preparación de un medicamento para el tratamiento de una enfermedad mediada por GLK, en particular diabetes tipo 2.

El compuesto se formula de forma adecuada como una composición farmacéutica para su uso en este sentido.

De acuerdo con otro aspecto de la presente invención se proporciona un método de tratamiento de enfermedades mediadas por GLK, especialmente diabetes, mediante la administración de una cantidad efectiva de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, incluidos los compuestos mencionados en las condiciones, a un mamífero que necesita dicho tratamiento.

Las enfermedades específicas que pueden tratarse con un compuesto o composición de la invención incluyen: reducción de glucosa en sangre en Diabetes mellitus tipo 2 sin

riesgo serio de hipoglicemia (y potencial para tratar el tipo 1), diclipidemia, obesidad, resistencia a la insulina, síndrome metabólico X y tolerancia a la glucosa alterada.

De esta manera, tal como se plantea anteriormente, el sistema GLK puede describirse como un objetivo potencial de la "Diabesidad" (en beneficio tanto de la Diabetes como de la Obesidad). Por lo tanto, de acuerdo con otro aspecto de la invención se proporciona el uso de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, en la preparación de un medicamento para su uso en el tratamiento o prevención combinados, en particular el tratamiento, de la diabetes y la obesidad.

De acuerdo con otro aspecto de la invención se proporciona el uso de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, en la preparación de un medicamento para su uso en el tratamiento o prevención de la obesidad.

De acuerdo con un aspecto adicional de la invención se proporciona un método para el tratamiento combinado de la obesidad y diabetes mediante la administración de una cantidad efectiva de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, a un mamífero que necesita dicho tratamiento.

De acuerdo con otro aspecto de la invención se proporciona un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo tal como se define anteriormente para su uso como un medicamento para el tratamiento o prevención, particularmente el tratamiento, de la obesidad.

De acuerdo con un aspecto adicional de la invención se proporciona un método para el tratamiento de la obesidad mediante la administración de una cantidad efectiva de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, a un mamífero que necesita dicho tratamiento.

Los compuestos de la invención pueden ser particularmente adecuados para su uso como productos farmacéuticos, por ejemplo, debido a las propiedades físicas y/o farmacocinéticas ventajosas y/o el perfil de toxicidad favorable.

Las composiciones de la invención pueden presentarse en formas adecuadas para uso oral (por ejemplo, como comprimidos, grageas, cápsulas duras o blandas, suspensiones acuosas u oleosas, emulsiones, gránulos o polvos dispersables, jarabes o elixires), para uso tópico (por ejemplo, como cremas, ungüentos, geles o soluciones o suspensiones acuosas u oleosas), para administración mediante inhalación (por ejemplo, como un polvo dividido finamente o un aerosol líquido), para administración mediante insuflación (por ejemplo,

como un polvo dividido finamente) o para administración parenteral (por ejemplo, como una solución oleosa u acuosa estéril para dosificación intravenosa, subcutánea, intramuscular o dosificación intramuscular o como un supositorio para dosificación rectal). Se prefieren formas de dosificación adecuadas para uso oral.

Las composiciones de la invención pueden obtenerse mediante procedimientos convencionales utilizando excipientes farmacéuticos convencionales bien conocidos en la técnica. De esta manera, las composiciones para uso oral pueden contener, por ejemplo, uno o más agentes colorantes, edulcorantes, saborizantes y/o conservantes.

Los excipientes adecuados farmacéuticamente aceptables para la formulación en comprimidos incluyen, por ejemplo, diluyentes inertes tales como lactosa, carbonato de sodio, fosfato de calcio o carbonato de calcio, agentes granulantes y desintegrantes tales como almidón de maíz o ácido algénico; agentes aglutinantes tales como almidón; agentes lubricantes tales como estearato de magnesio, ácido esteárico o talco; agentes conservantes tales como p-hidroxibenzoato de etilo o propilo, y antioxidantes, tales como ácido ascórbico. Las formulaciones en comprimidos pueden estar sin recubrir o recubiertas ya sea para modificar su desintegración y la subsiguiente absorción del ingrediente activo dentro del tracto gastrointestinal, o para mejorar su estabilidad y/o apariencia, según el caso, utilizando agentes de revestimiento convencionales y procedimientos bien conocidos en la técnica.

Las composiciones para uso oral pueden presentarse en forma de cápsulas de gelatina duras en las cuales el ingrediente activo se mezcla con un diluyente sólido inerte, por ejemplo, carbonato de calcio, fosfato de calcio o caolina, o como cápsulas de gelatina blandas en las cuales el ingrediente activo se mezcla con agua o un aceite tal como aceite de maní, parafina líquida o aceite de oliva.

Las suspensiones acuosas generalmente contienen el ingrediente activo en forma de polvo dividido finamente junto con uno o más agentes de suspensión, tales como carboximetilcelulosa de sodio, metilcelulosa, hidroxipropilmetilcelulosa, alginato de sodio, polivinilpirrolidona, goma tragacanto y goma acacia; agentes dispersantes o humectantes tales como lecitina o productos para condensación de un óxido de alquileno con ácidos grasos (por ejemplo, estearato de polioxietileno), o productos para condensación de óxido de etileno con alcoholes alifáticos de cadena larga, por ejemplo, heptadecaetilenooxicetanol, o productos para condensación de óxido de etileno con ésteres

parciales derivados de ácidos grasos y un hexitol tales como monooleato de sorbitol polioxietilenado, o productos para condensación de óxido de etileno con alcoholes alifáticos de cadena larga, por ejemplo, heptadecaetilenooxicetanol, o productos para condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y un hexitol tales como monooleato de sorbitol polioxietilenado, o productos para condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y anhídridos de hexitol, por ejemplo, monooleato de sorbitán polietilenado. Las suspensiones acuosas también pueden contener uno o más conservantes (tales como p-hidroxibenzoato de etilo o propilo), antioxidantes (tales como ácido ascórbico), agentes colorantes, agentes saborizantes y/o agentes edulcorantes (tales como sacarosa, sacarina o aspartamo).

Las suspensiones oleosas pueden formularse mediante suspensión del ingrediente activo en un aceite vegetal (tal como aceite de maní, aceite de oliva, aceite de sésamo o aceite de coco) o en un aceite mineral (tal como parafina líquida). Las suspensiones oleosas también pueden contener un agente espesante tal como cera de abeja, parafina dura o alcohol cetílico. Los agentes edulcorantes, tales como los descritos anteriormente, y los agentes saborizantes pueden agregarse para proporcionar una preparación oral agradable. Dichas composiciones pueden conservarse mediante la adición de un antioxidante tal como ácido ascórbico.

Los polvos y gránulos dispersables adecuados para la preparación de una suspensión acuosa mediante la adición de agua generalmente contienen el ingrediente activo junto con un agente dispersante o humectante, un agente de suspensión y uno o más conservantes. Los agentes humectantes o dispersantes y agentes de suspensión adecuados se ejemplifican a través de los mencionados anteriormente. También pueden estar presentes excipientes tales como agentes edulcorantes, saborizantes y colorantes.

Las composiciones farmacéuticas de la invención también pueden presentarse en forma de emulsiones de aceite en agua. La fase oleosa puede ser un aceite vegetal, tal como aceite de oliva o aceite de maní, o un aceite mineral, tal como, por ejemplo, parafina líquida o una mezcla de cualquiera de los mismos. Los agentes emulsificantes adecuados pueden ser, por ejemplo, gomas naturales tales como goma acacia o goma tragacanto, fosfatidas naturales tales como soja, lecitina, ésteres o ésteres parciales derivados de ácidos grasos y anhídridos de hexitol (por ejemplo, monooleato de sorbitán) y productos para condensación de dichos ésteres parciales con óxido de etileno tales como monooleato de

sorbitán polioxietilenado. Las emulsiones también pueden contener agentes edulcorantes, saborizantes y conservantes.

Los jarabes y elixires pueden formularse con agentes edulcorantes tales como glicerol, propilenglicol, sorbitol, aspartamo o sacarosa, y también pueden contener un agente emoliente, conservante, saborizante y/o colorante.

Las composiciones farmacéuticas también pueden presentarse en forma de una suspensión acuosa u oleosa inyectable estéril que puede formularse de acuerdo con procedimientos conocidos utilizando uno o más de los agentes dispersantes o humectantes y los agentes de suspensión apropiados que se han mencionado anteriormente. Una preparación inyectable estéril también puede ser una solución o suspensión inyectable estéril en un disolvente o diluyente no tóxico parenteralmente aceptable, por ejemplo, una solución en 1,3-butanodiol.

Las composiciones para administración mediante inhalación pueden presentarse en forma de un aerosol presurizado convencional adaptado para dispersar el ingrediente activo como un aerosol que contiene gotas líquidas o sólidas finamente divididas. Pueden utilizarse propelentes en aerosol convencionales tales como hidrocarburos fluorados volátiles o hidrocarburos y el dispositivo de aerosol se adapta convenientemente para dispersar una cantidad medida de ingrediente activo.

Por información adicional, el lector puede remitirse al Capítulo 25.2 en el Volumen 5 de Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

La cantidad de ingrediente activo que se combina con uno o más excipientes para producir una forma de dosificación única variará necesariamente según el huésped tratado y la vía de administración particular. Por ejemplo, una formulación para la administración oral en humanos contendrá generalmente, por ejemplo, entre 0,5 mg a 2 g de agente activo combinado con una cantidad apropiada y conveniente de excipientes, la cual puede variar de aproximadamente 5 a aproximadamente 98 por ciento en peso de la composición total. Las formas de dosificación unitarias generalmente contendrán entre aproximadamente 1 mg y aproximadamente 500 mg de un ingrediente activo. Para obtener mayor información acerca de las vías de administración y los regímenes de dosificación, ver el Capítulo 25.3, Volumen 5, de Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

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El tamaño de la dosis con fines terapéuticos o profilácticos de un compuesto de Fórmula I naturalmente variará de acuerdo con la naturaleza y gravedad de las afecciones, la edad y el sexo del animal o paciente y la vía de administración de acuerdo con principios bien conocidos en la medicina.

Cuando se utiliza un compuesto de la fórmula (I) con fines terapéuticos o profilácticos generalmente se administrará en una dosis diaria entre, por ejemplo, 0,5 mg y 75 mg por kilo de peso corporal, el cual podrá administrarse en dosis divididas si es necesario. En general se administrarán dosis más bajas cuando se emplee una vía parenteral. Así, por ejemplo, para la administración intravenosa se utilizará generalmente una dosis entre por ejemplo, 0,5 mg y 30 mg por kilo de peso corporal. En forma similar, para la administración por inhalación, se utilizará una dosis entre, por ejemplo, 0,5 mg y 25 mg por kilo de peso corporal. Sin embargo, se prefiere la administración oral.

El aumento de la actividad de la GLK descrito en la presente puede aplicarse como única terapia o en combinación con una o más sustancias y/o tratamientos para la indicación que se está tratando. En otro aspecto la invención proporciona una combinación farmacéutica que comprende un compuesto de fórmula I y otra sustancia farmacológicamente activa particularmente cuando la otra sustancia farmacológicamente activa es un medicamento para el tratamiento de la diabetes tipo 2 u obesidad o una afección relacionada.

Tal tratamiento conjunto puede alcanzarse mediante la administración simultánea, secuencial o separada de los componentes individuales del tratamiento. El tratamiento simultáneo puede proporcionarse en un comprimido o en comprimidos separados. Por ejemplo en el tratamiento de la diabetes mellitus, la quimioterapia puede incluir las siguientes categorías principales de tratamiento:

1) Insulina y análogos de la insulina;
2) Secretagogos de insulina, incluyendo sulfonilureas (por ejemplo glibenclamida, glipizida), reguladores de la glucosa prandial (por ejemplo repaglinida, nateglinida);
3) Agentes que mejoran la acción de la incretina (por ejemplo inhibidores de dipeptidil peptidasa IV, por ejemplo, saxagliptina, citagliptina, vildagliptina o alogliptina y agonistas de GLP-1);
4) Agentes sensibilizantes a la insulina, incluidos los agonistas de PPARgamma (por

ejemplo pioglitazona y rosiglitazona) y agentes con actividad de PPARalfa y gamma combinada;

5) Agentes que modulan el equilibrio de la glucosa hepática (por ejemplo metformina, inhibidores de fructosa-1,6-bisfosfatasa, inhibidores de glucógeno fosforilasa, inhibidores de glucógeno sintasa quinasa);

6) Agentes diseñados para reducir la absorción de glucosa del intestino (por ejemplo acarbosa);

7) Agentes que previenen la reabsorción de la glucosa por parte del riñón (inhibidores de SGLT por ejemplo dapagliflozina);

8) Agentes diseñados para tratar las complicaciones de la hiperglicemia prolongada (por ejemplo, inhibidores de aldosa reductasa);

9) Agentes anti-obesidad (por ejemplo sibutramina y orlistat);

10) Agentes anti-dislipidemia tales como, inhibidores de la HMG-CoA reductasa (por ej. estatinas); agonistas de PPARα (fibratos, por ej. gemfibrozil); secuestrantes del ácido biliar (colestiramina); inhibidores de la absorción de colesterol (estanoles vegetales, inhibidores sintéticos); inhibidores de la absorción del ácido biliar ileal (IBATi) y ácido nicotínico y análogos (niacina y formulaciones de liberación lenta);

11) Agentes antihipertensivos tales como β bloqueadores (por ej. atenolol, inderal); inhibidores de ACE (por ej. lisinopril); antagonistas de calcio (por ej. nifedipina); antagonistas del receptor de angiotensina (por ej. candesartán), α antagonistas y agentes diuréticos (por ej. furosemida, benztiazida);

12) Moduladores de la hemostasis, tales como anti-trombóticos, activadores de la fibrinólisis y agentes antiplaquetarios; antagonistas de la trombina; inhibidores del factor Xa; inhibidores del factor VIIa; agentes antiplaquetarios (por ej. aspirina, clopidogrel); anticoagulantes (heparina y análogos de bajo peso molecular, hirudina) y warfarina;

13) Agentes que antagonizan las acciones del glucagón; y

14) Agentes anti-inflamatorios, tales como fármacos anti-inflamatorios no esteroideos (por ej. aspirina) y agentes anti-inflamatorios esteroideos (por ej. cortisona).

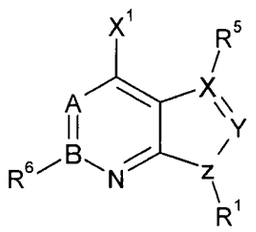
De acuerdo con otro aspecto de la presente invención se proporcionan compuestos

individuales producidos como productos finales en los Ejemplos descritos más adelante y sales de los mismos.

Un compuesto de la invención, o una sal del mismo, puede prepararse mediante cualquier proceso conocido para aplicar a la preparación de dichos compuestos o compuestos estructuralmente relacionados. Los grupos funcionales pueden protegerse o desprotegerse utilizando métodos convencionales. Por ejemplos de grupos protectores tales como grupos protectores de amino y ácido carboxílico (así como medios de formación y eventual desprotección), ver T.W. Greene y P.G.M. Wuts, "Protective Groups in Organic Synthesis", Segunda Edición, John Wiley & Sons, Nueva York, 1991.

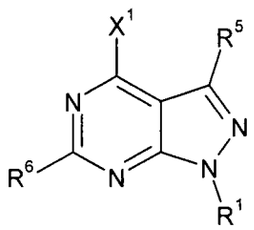
Los procesos para la síntesis de compuestos de fórmula (I) se proporcionan como una característica adicional de la invención. Por lo tanto, de acuerdo con un aspecto adicional de la invención se proporciona un proceso para la preparación de un compuesto de fórmula (I).

Los compuestos de fórmula (I) pueden prepararse haciendo reaccionar un compuesto de fórmula (II)

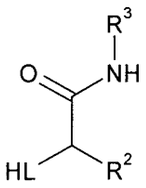


(II)

Por ejemplo:



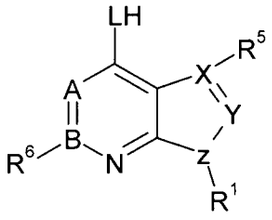
en donde R^1, R^2, R^3, R^5 y R^6 son tal como se definen anteriormente y X^1 es un grupo saliente, por ejemplo halo, particularmente cloro, con un compuesto de fórmula (III)



(III)

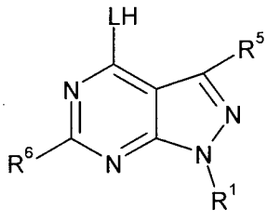
en donde R^2, R^3 y l son tal como se definen anteriormente en un disolvente inerte, por ejemplo tetrahidrofurano, en presencia de una base, por ejemplo bis(trimetilsilil)amida de litio o hidruro de sodio, a una temperatura en el rango de -25°C a 150°C.

Los compuestos de fórmula (I) también pueden prepararse haciendo reaccionar un compuesto de fórmula (IV)

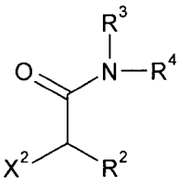


(IV)

Por ejemplo



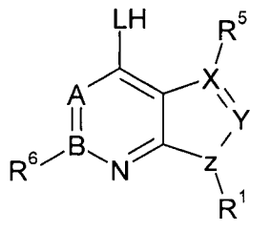
en donde R^1, R^5, R^6 y l son tal como se definen anteriormente con un compuesto de fórmula (V)



(V)

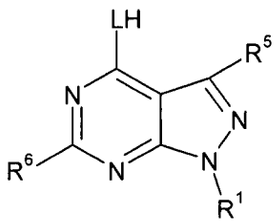
en donde R^2, R^3 y l son tal como se definen anteriormente y X^2 es un grupo saliente por ejemplo halo particularmente cloro, en un disolvente inerte, por ejemplo tetrahidrofurano o dimetilformamida, en presencia de una base, por ejemplo carbonato de potasio, a una temperatura en el rango de -25°C a 150°C.

Los compuestos de fórmula (I) también pueden prepararse haciendo reaccionar un compuesto de fórmula (IV)

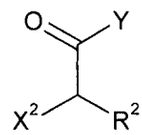


(IV)

por ejemplo



en donde R^1, R^5 y R^6 son tal como se definen anteriormente y l es, por ejemplo, S con un compuesto de fórmula (V) tal como se define anteriormente en donde el compuesto de fórmula (V) se forma in situ haciendo reaccionar un compuesto de fórmula (VI)



(VI)

en donde R^2 es tal como se define anteriormente y X^2 es un grupo saliente, por ejemplo halo, particularmente bromo e Y es cloro con un compuesto de fórmula (VII)

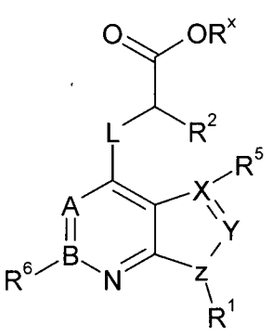
$$H_2NR^3$$

(VII)

en donde R^3 es como se define previamente en presencia de una base, por ejemplo di-*iso*-propiletilamina, en un disolvente inerte por ejemplo diclorometano a una temperatura en el rango de -25°C a 150°C.

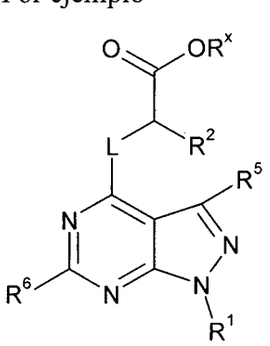
O en donde X^2 es hidroxi e Y es alcoxi por ejemplo metoxi en presencia de un ácido de Lewis tal como trimetilaluminio o bromuro de isopropilmagnesio.

Los compuestos de fórmula (I) también pueden prepararse haciendo reaccionar un compuesto de fórmula (VIII)



(VIII)

Por ejemplo



en donde R^1, R^5, R^6 y l son tal como se definen anteriormente y R^x es un alquilo(1-4C) con un compuesto de fórmula (VII) tal como se define anteriormente en un disolvente inerte, por ejemplo tetrahidrofurano, en presencia de una base, por ejemplo hidruro de sodio, a una temperatura en el rango de -25°C a 150°C o en presencia de un ácido de Lewis, por ejemplo trimetilaluminio en un disolvente adecuado tal como tolueno.

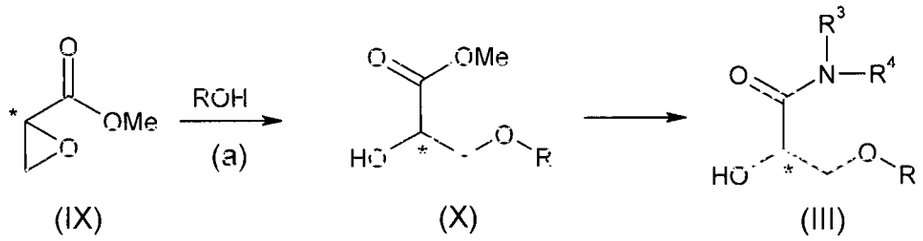
Se cree que ciertos productos intermedios de fórmula (II) y (IV) son novedosos y comprenden un aspecto independiente de la invención.

Cuando R^2 es alcoxi(1-6C)metilo, los compuestos de fórmula (III) pueden prepararse como se ilustra en el Esquema 1 más adelante, en donde R es alquilo(1-6C). El proceso que se muestra en el Esquema 1 comprende un aspecto adicional de la invención.

La apertura de anillos de epoxiésteres por parte de alcoholes como se muestra en la etapa a) del Esquema 1 se conoce en la técnica, ver Synthetic Communications, Vol 33 (2003), pp687-692. La reacción generalmente requiere el uso de un catalizador de ácido de Lewis y en la referencia precedente específicamente se conoce el perclorato de magnesio ($Mg(ClO_4)_2$), utilizado sin ningún disolvente agregado. Hemos encontrado que este proceso conlleva un riesgo de descomposición espontánea con rápido desprendimiento de

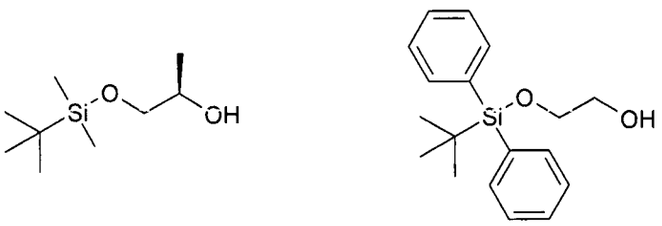
gas y/o explosión, que puede reducirse cambiando el ácido de Lewis y agregando disolvente a la reacción. En particular, la etapa a) se lleva a cabo en presencia de trifluorometanosulfonato de magnesio, adecuadamente en acetato de etilo, tolueno o diclorometano, más particularmente en acetato de etilo. Este proceso se ejemplifica en el Producto Intermedio C7a más adelante en la presente.

Por lo tanto en un aspecto adicional de la invención se proporciona la reacción de oxirano-2-carboxilato de metilo (IX) con un alcohol ROH (en donde R es alquilo(1-6C), cicloalquilo(3-6C) o R^x_3SiOalquilo(2-4C) (en donde cada R^x se selecciona independientemente de alquilo(1-6C) y fenilo) en presencia de trifluorometanosulfonato de magnesio en acetato de etilo, para proporcionar un compuesto de fórmula (X).

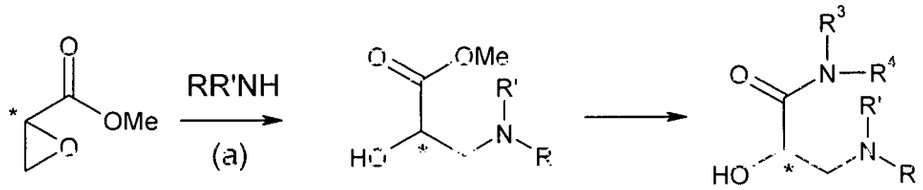


Esquema 1

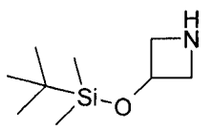
Ejemplos adecuados de ROH en donde R es R^x_3SiOalquilo(2-4C) incluyen



En un procedimiento análogo pueden utilizarse aminas para preparar azetidinas:



Ejemplos adecuados de RR'NH incluyen



En un aspecto R es alquilo(1-6C). En otro aspecto, R es metilo, etilo, isopropilo o ciclobutilo.

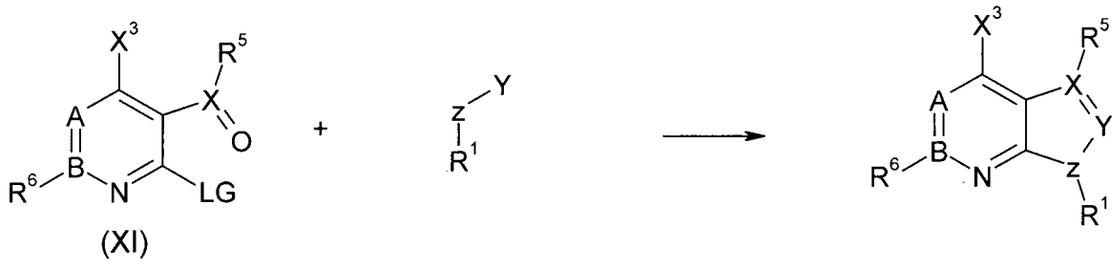
Aunque el compuesto de fórmula (IX) es un éster metílico, también pueden utilizarse otros ésteres de alquilo.

Se apreciará que cuando el compuesto de fórmula (IX) está enriquecido enantioméricamente entonces los compuestos de fórmula (X) y (III) obtenidos a partir del mismos también estarán enriquecidos enantioméricamente.

El compuesto de fórmula (X) alternativamente puede hacerse reaccionar con un compuesto de fórmula (II) para proporcionar un compuesto de fórmula (VIII).

Los compuestos de fórmula (II) pueden prepararse de acuerdo con los siguientes procesos a) a b)

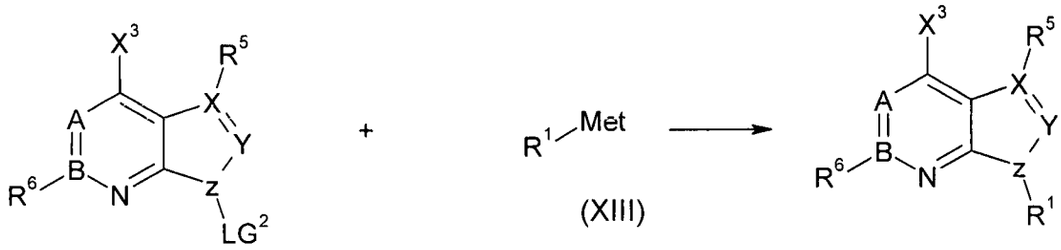
a) mediante reacción de un compuesto de fórmula (XI) en donde X^3 es un grupo saliente tal como halo (por ejemplo cloro), o un precursor para el grupo enlazante L tal como OH, o SH, o un precursor para el grupo saliente tal como OH, SMe, S(p-tolilo) o NH_2; y en donde LG es un grupo saliente tal como cloro, bromo, yodo o trifluorometanosulfonilo; R^1, R^5, R^6, A, B, X, Y y Z son como se definen previamente;



(XI)

Los compuestos de la fórmula (XI) pueden prepararse mediante procesos conocidos en la técnica. Se apreciará que un compuesto en donde X^3 es OH puede transformarse en un compuesto en donde X^3 es Cl mediante reacción con un agente de cloración tal como $POCl_3$.

b) Mediante reacción de un compuesto de fórmula (XII) con un compuesto de fórmula (XIII), en donde R^1, R^5, R^6, A, B, X, X^3, Y y Z son como se definen previamente; LG^2 es un grupo saliente tal como cloro, bromo, yodo o trifluorometanosulfonilo cuando Z=C y lG^2 es H cuando Z=N; Met es un grupo adecuado para reacciones de acoplamiento, tales como $-B(OH)_2$ y $-SnBu_3$, mediadas por catalizadores que contienen metales de transición tales como Pd^0 o Cu^I, tales como $PdPPh_3$ o CuI.



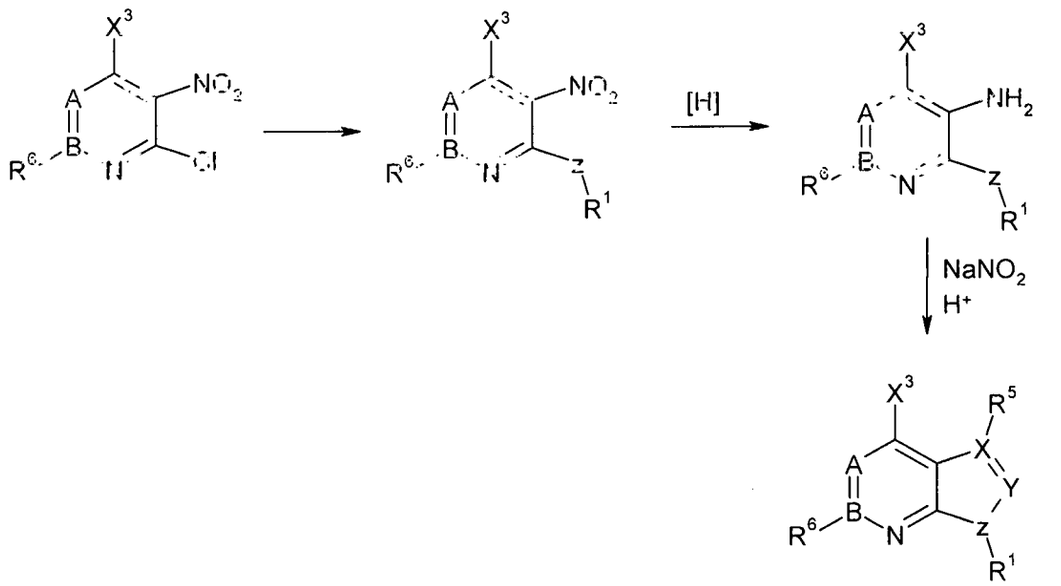
(XII)

(XIII)

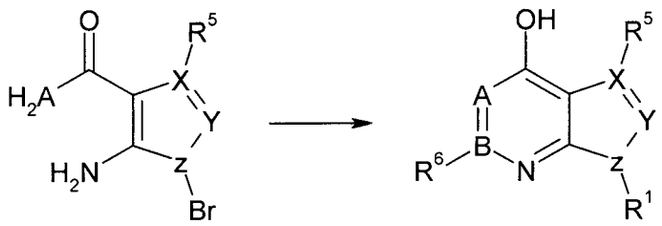
Se apreciará que la reacción precedente alternativamente puede llevarse a cabo mediante el procedimiento equivalente en donde el grupo Met es un sustituyente en Z y LG^2 está unido a R^1, en donde LG^2 es un grupo saliente tal como cloro, bromo, yodo o trifluorometanosulfonilo y Met es como se define previamente cuando Z=C pero en donde Met es H cuando Z=N.

Se comprenderá que compuestos tales como los de las fórmulas (XI) y (XII) cuando X^3 es OH pueden existir en dos formas tautoméricas, aunque se ilustran aquí en la forma enol.

Los compuestos de la fórmula (XII) pueden prepararse mediante procesos conocidos en la técnica o mediante analogía con procesos conocidos en la técnica. Por ejemplo para X=Y=Z=N puede utilizarse el siguiente proceso:



o por ejemplo de acuerdo con el esquema a continuación, utilizando un reactivo tal como formiato de metilo, una mezcla de ácido fórmico y ácido sulfúrico, o trimetilortoformiato cuando B es C y un reactivo tal como ácido nitroso cuando B es N.



Durante el proceso de preparación, puede resultar ventajoso utilizar un grupo protector para un grupo funcional dentro de la molécula. Los grupos protectores pueden eliminarse mediante cualquier método conveniente según se describe en la bibliografía o que el químico capacitado sepa que es adecuado para la eliminación del grupo protector en cuestión. Dichos métodos se seleccionan de forma tal que provoquen la eliminación del grupo protector con un mínimo de alteración de los demás grupos de la molécula.

A continuación se proporcionan ejemplos específicos de grupos protectores, en los que "inferior", como en, por ejemplo, alquilo inferior, significa que el grupo al cual se aplica preferiblemente tiene de 1 a 4 átomos de carbono. Se comprenderá que estos ejemplos no son taxativos. De la misma manera, en donde se proporcionan ejemplos específicos de métodos para la eliminación de los grupos protectores, los mismos tampoco son taxativos. Evidentemente, el uso de grupos protectores y métodos de desprotección que no se mencionan específicamente también se encuentran dentro del alcance de la invención.

Un grupo protector carboxi puede ser el residuo de un alcohol alifático o aralifático formador de ésteres o de un silanol formador de ésteres (conteniendo dicho alcohol o silanol preferiblemente 1 - 20 átomos de carbonos). Ejemplos de grupos protectores carboxi incluyen grupos alquilo(C1-12) de cadena lineal o ramificada (por ejemplo isopropilo y t-butilo); grupos alcoxi inferior - alquilo inferior (por ejemplo metoximetilo, etoximetilo e isobutoximetilo); grupos aciloxi alifático inferior - alquilo inferior (por ejemplo acetoximetilo, propioniloximetilo, butiriloximetilo y pivaloiloximetilo); grupos alcoxicarboniloxi inferior - alquilo inferior (por ejemplo 1-metoxicarboniloxietilo y 1-etoxicarboniloxietilo); grupos arilo - alquilo inferior (por ejemplo bencilo, p-metoxibencilo, o-nitrobencilo, p-nitrobencilo, benzhidrilo y ftalidilo); grupos tri(alquilo inferior)sililo (por ejemplo trimetilsililo y t-butildimetilsililo); grupos tri(alquilo inferior)sililo-alquilo inferior (por ejemplo trimetilsililetilo); y grupos alquenilo(C2-6) (por ejemplo alilo y viniletilo).

Entre los métodos particularmente apropiados para la eliminación de los grupos protectores carboxilo se incluyen, por ejemplo, la hidrólisis catalizada por ácido, base, metal o enzimas.

Ejemplos de grupos protectores hidroxi incluyen metilo, t-butilo, grupos alquenilo inferior (por ejemplo alilo); grupos alcanoílo inferior (por ejemplo acetilo); grupos alcoxicarbonilo inferior (por ejemplo t-butoxicarbonilo); grupos alqueniloxicarbonilo inferior (por ejemplo aliloxicarbonilo); grupos arilo-alqueniloxicarbonilo inferior (por ejemplo benciloxicarbonilo, p-metoxibenciloxicarbonilo, o-nitrobenciloxicarbonilo y p-nitrobenciloxicarbonilo); grupos tri alquil/arilsililo inferior (por ejemplo trimetilsililo, t-butildimetilsililo y t-butildifenilsililo); tetrahidropiran-2-ilo; grupos arilo - alquilo inferior (por ejemplo bencilo) y grupos triarilo - alquilo inferior (por ejemplo, trifenilmetilo). Ejemplos de grupos protectores amino incluyen formilo, grupos aralquilo (por ejemplo bencilo y bencilo sustituido, por ejemplo p-metoxibencilo, nitrobencilo y 2,4-dimetoxibencilo y trifenilmetilo); grupos di-p-anisilmetilo y furilmetilo; alcoxicarbonilo inferior (por ejemplo t-butoxicarbonilo); alqueniloxicarbonilo inferior (por ejemplo aliloxicarbonilo); grupos arilo-alcoxicarbonilo inferior (por ejemplo benciloxicarbonilo, p-metoxibenciloxicarbonilo, o-nitrobenciloxicarbonilo y p-nitrobenciloxicarbonilo); trialquilsililo (por ejemplo trimetilsililo y t-butildimetilsililo); alquilideno (por ejemplo metilideno) y grupos bencilideno y bencilideno sustituido.

Los métodos apropiados para eliminar los grupos hidroxi y amino protectores incluyen, por ejemplo, hidrogenación, desplazamiento nucleofílico, hidrólisis catalizada enzimáticamente por ácido, base, metal o enzimas, hidrogenólisis catalítica / hidrogenación o fotolíticamente para grupos tales como o-nitrobenciloxicarbonilo, o con iones de fluoruro para grupos sililo. Por ejemplo, grupos protectores metiléter para grupos hidroxi pueden eliminarse mediante trimetilsililyoduro. Un grupo protector éter de terc-butilo para un grupo hidroxi puede eliminarse mediante hidrólisis, por ejemplo utilizando ácido clorhídrico en metanol.

Ejemplos de grupos protectores para grupos amida incluyen aralcoximetilo (por ejemplo benciloximetilo y benciloximetilo sustituido); alcoximetilo (por ejemplo metoximetilo y trimetilsililetoximetilo); tri alquil/arilsililo (por ejemplo trimetilsililo, t-butildimetilsililo, t-butildifenilsililo); tri alquil/arilsililoximetilo (por ejemplo t-butildimetilsililoximetilo, t-butildifenilsililoximetilo); 4-alcoxifenilo (por ejemplo 4-

metoxifenilo); 2,4-di(alcoxi)fenilo (por ejemplo 2,4-dimetoxifenilo); 4-alcoxibencilo (por ejemplo 4-metoxibencilo); 2,4-di(alcoxi)bencilo (por ejemplo 2,4-di(metoxi)bencilo); y alqu-1-enilo (por ejemplo alilo, but-1-enilo y vinilo sustituido por ejemplo 2-fenilvinilo).

Los grupos aralcoximetilo pueden introducirse en el grupo amida haciendo reaccionar éste último grupo con el cloruro de aralcoximetilo apropiado y retirarse mediante hidrogenación catalítica. Los grupos alcoximetilo, tri alquil/arilsililo y tri alquil/sililoximetilo pueden introducirse haciendo reaccionar la amida con el cloruro apropiado y retirarse con ácido; o en el caso de los grupos que contienen sililo, iones de fluoruro. Los grupos alcoxifenilo y alcoxibencilo pueden introducirse de forma conveniente mediante arilación o alquilación con un haluro apropiado y retirarse mediante oxidación con nitrato de amonio cérico. Finalmente los grupos alqu-1-enilo pueden introducirse haciendo reaccionar la amida con el aldehído apropiado y retirarse con ácido.

En las otras características de composición farmacéutica, proceso, método, uso y fabricación de medicamento precedentes también se aplican los aspectos y las realizaciones alternativos y preferidos de los compuestos de la invención descritos en la presente.

Los siguientes ejemplos se describen solamente a efectos ilustrativos y no pretenden limitar el alcance de esta solicitud. Cada compuesto ejemplificado representa un aspecto particular e independiente de la invención. En los siguientes Ejemplos no taxativos, a menos que se indique de otra forma:

(i) las evaporaciones se llevaron a cabo por evaporación rotativa al vacío y los procedimientos de elaboración se llevaron a cabo luego de la eliminación de los sólidos residuales, tales como agentes de secado, mediante filtración;

(ii) las operaciones se llevaron a cabo a temperatura ambiente, es decir, en el rango 18-25°C y bajo una atmósfera de gas inerte tal como argón o nitrógeno;

(iii) los rendimientos se proporcionan solamente a modo ilustrativo y no necesariamente representan el máximo obtenible;

(iv) las estructuras de los productos finales de la fórmula (I) se confirmaron mediante resonancia magnética nuclear (generalmente de protones) (NMR) y técnicas de espectros de masa; los desplazamientos químicos de resonancia magnética de protones se midieron en escala delta y las multiplicidades de picos se muestran de la siguiente manera: s, singulete; d, doblete; t, triplete; m, multiplete; br, ancho; q, cuartete; quin, quintete;

sexteto;

(v) en general, los productos intermedios no se caracterizaron totalmente y la pureza se evaluó mediante cromatografía de capa fina (TLC), cromatografía líquida de alto rendimiento (HPLC), análisis por NMR o infrarrojo;

(vi) la cromatografía instantánea se llevó a cabo en sílice a menos que se indique de otra forma;

(vii) Los excesos enantioméricos (ee) se determinaron mediante HPLC utilizando una fase estacionaria quiral tal como Chiralcel OJ o Chiralpak AD-H y / o mediante NMR utilizando un reactivo de desplazamiento quiral apropiado tal como (1S)-[1,1'-binaftaleno]-2,2'-diol (CAS 18531-99-2) o (1R)-[1,1'-binaftaleno]-2,2'-diol (CAS 18531-94-7).

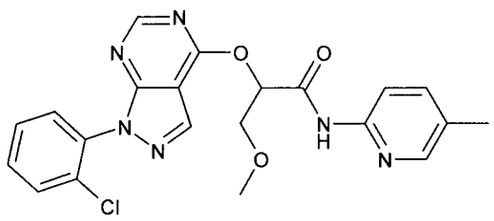
Abreviaturas

ACN	Acetonitrilo
n-BuLi	*n*-Butillitio
m-CPBA	Ácido 3-cloroperbenzoico
DCM	Diclorometano
DIPEA	Di-*iso*-propiletilamina
DMAP	4-Di(metilamino)piridina
DMF	*N*,*N*-Dimetilformamida
DMSO	dimetilsulfóxido
EtOAc	Acetato de etilo
EtOH	Etanol
FMOC	9-Fluorenilmetil carbamato
IPA	Alcohol isopropílico
LHMDS	Litio bis(trimetilsilil)amida
MeOH	Metanol
TBDMSCl	Cloruro de *terc*-butildimetilsililo
THF	Tetrahidrofurano
ESI	Ionización por electropulverización
TA	Temperatura ambiente
cat	Catalíltico
ee	Exceso enantiomérico

HPLC	Cromatografía líquida de alto rendimiento
EDCI	1-(3-Dimetilaminopropil)-2-etilcarbodiimida clorhidrato

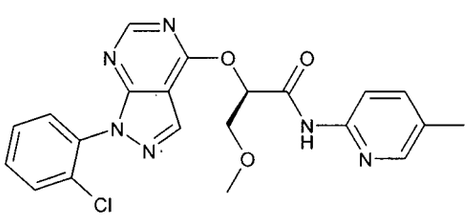
Método 1

Ejemplo 1: 2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-3-metoxi-*N*-(5-metilpiridin-2-il)propanamida



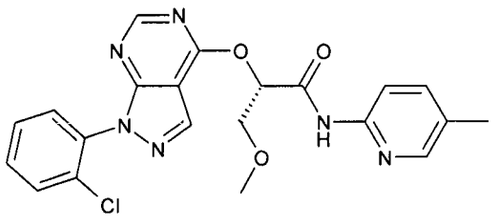
Se agregó lentamente LHMDS (1,40 mL, 1,0 M en THF, 1,40 mmol) a una solución agitada de 2-hidroxi-3-metoxi-*N*-(5-metilpiridin-2-il)propanamida (200 mg, 0,951 mmol) en THF anhidro (5 mL). La mezcla de reacción se mantuvo a temperatura ambiente durante 10 minutos y se agregó una solución de 4-cloro-1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidina (265 mg, 1,00 mmol) en THF anhidro (3 mL). La mezcla de reacción se calentó a 50°C durante 1 ½ hrs (se agregaron otros 3 equivalentes de LHMDS y la reacción se calentó durante 18 hrs a 50 °C en el ejemplo 49). Se agregaron agua y EtOAc y las dos fases se separaron. La fase orgánica se lavó con agua, se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se purificó con cromatografía en columna (gel de sílice, eluyendo con DCM/EtOAc:2/1) para proporcionar el compuesto del título como un sólido incoloro (323 mg), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8,67 (br s, 1H), 8,62 (s, 1H), 8,48 (s, 1H), 8,18 (d, 1H), 8,12 (s, 1H), 7,65 (d, 1H), 7,52 (m, 4H), 6,13 (t, 1H), 4,14 (m, 2H), 4,06 (m, 1H), 3,49 (s, 3H), 2,32 (s, 3H), HRMS: calculado para ($M+H^+$) $C_{21}H_{20}{}^{35}ClN_6O_3$: 439,1285. Encontrado: 439,1287.

Ejemplo 2: (R)-2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-3-metoxi-*N*-(5-metilpiridin-2-il)propanamida



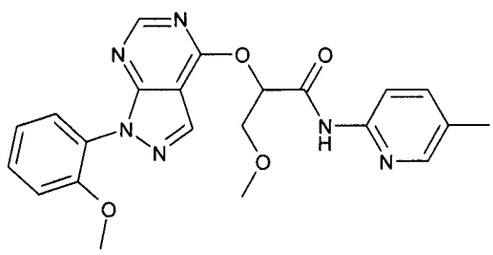
y Ejemplo 3: (S)-2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-3-metoxi-*N*-

(5-metilpiridin-2-il)propanamida



Los enantiómeros de 2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-3-metoxi-*N*-(5-metilpiridin-2-il)propanamida racémica (100 mg) se separaron mediante HPLC preparativa: Columna Chiralpak AS (250x20 mm, 5 µm); Face móvil heptano/IPA:60/40; Flujo 15 ml/min; UV 275 nm; Temperatura 40°C. Esto proporcionó (R)-2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-3-metoxi-*N*-(5-metilpiridin-2-il)propanamida (44,1 mg, >99% ee), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8,70 (br s, 1H), 8,59 (s, 1H), 8,44 (s, 1H), 8,15 (d, 1H), 8,10 (s, 1H), 7,62 (m, 1H), 7,51 (m, 4H), 6,10 (t, 1H), 4,07 (m, 2H), 3,46 (s, 3H), 2,29 (s, 3H) y (S)-2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-3-metoxi-*N*-(5-metilpiridin-2-il)propanamida (45,7 mg, >99% ee), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8,69 (br s, 1H), 8,59 (s, 1H), 8,44 (s, 1H), 8,15 (d, 1H), 8,10 (s, 1H), 7,62 (m, 1H), 7,50 (m, 4H), 6,10 (t, 1H), 4,07 (m, 2H), 3,46 (s, 3H), 2,29 (s, 3H).

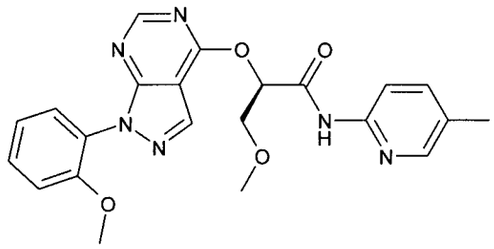
Ejemplo 4: 3-metoxi-2-{[1-(2-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)propanamida



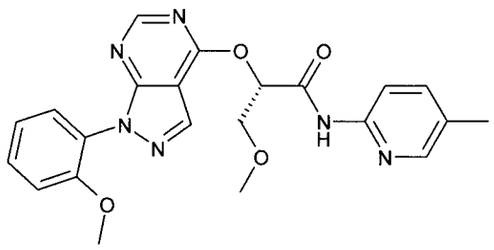
Método 1 a partir de los Productos Intermedios A2 y B3

^{1}H NMR (300 MHz, $CDCl_3$) δ 8,67 (br s, 1H), 8,56 (s, 1H), 8,42 (s, 1H), 8,15 (d, 1H), 8,10 (s, 1H), 7,48 (m, 3H), 7,12 (m, 2H), 6,11 (t, 1H), 4,12 (m, 1H), 4,02 (m, 1H), 3,79 (s, 3H), 3,46 (s, 3H), 2,29 (s, 3H), HRMS: calculado para (M^--H^+) $C_{22}H_{23}N_6O_4$: 435,1780. Encontrado: 435,1773.

Ejemplo 5: (R)-3-metoxi-2-{[1-(2-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)propanamida

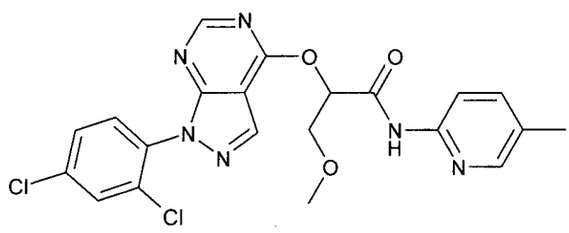


y Ejemplo 6: (S)-3-metoxi-2-{[1-(2-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)propanamida



Los enantiómeros de 3-metoxi-2-{[1-(2-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)propanamida racémica (100 mg) se separaron mediante HPLC preparativa: Columna Chiralpak AD (250x20 mm, 5 µm); Fase móvil heptano/IPA:40/60; Flujo 15 ml/min; UV 275 nm; Temperatura 40°C. Esto proporcionó (R)-3-metoxi-2-{[1-(2-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)propanamida (39,0 mg, >99% ee), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8,69 (br s, 1H), 8,56 (s, 1H), 8,41 (s, 1H), 8,15 (d, 1H), 8,09 (d, 1H), 7,48 (m, 3H), 7,12 (m, 2H), 6,10 (dd, 1H), 4,06 (m, 2H), 3,78 (s, 3H), 3,46 (s, 3H), 2,29 (s, 3H) y (S)-3-metoxi-2-{[1-(2-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)propanamida (41,1 mg, >99% ee), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8,69 (br s, 1H), 8,56 (s, 1H), 8,41 (s, 1H), 8,15 (d, 1H), 8,10 (d, 1H), 7,48 (m, 3H), 7,11 (m, 2H), 6,10 (dd, 1H), 4,06 (m, 2H), 3,78 (s, 3H), 3,46 (s, 3H), 2,29 (s, 3H).

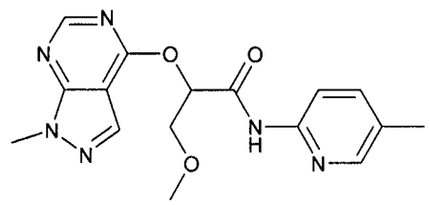
Ejemplo 7: 2-{[1-(2,4-Diclorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-3-metoxi-*N*-(5-metilpiridin-2-il)propanamida



Método 1 a partir de los Productos Intermedios A2 y B6

^{1}H NMR (400 MHz, $CDCl_3$) δ 9,37 (br s, 1H), 8,08 (m, 1H), 7,86 (s, 1H), 7,59 (s, 1H), 7,23 (s, 1H), 7,15 (m, 1H), 6,98 (m, 1H), 6,78 (m, 1H), 5,63 (m, 1H), 3,70 (m, 1H), 3,55 (m, 1H), 2,99 (s, 3H), 1,86 (s, 3H), HRMS: calculado para ($M+H^+$) $C_{22}H_{19}{}^{35}Cl_2N_6O_3$: 473,0895. Encontrado: 473,0904.

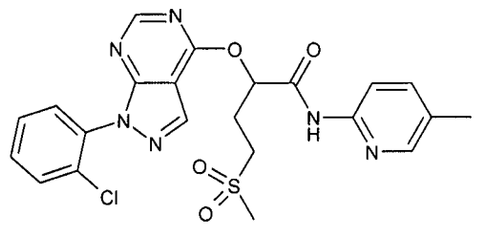
Ejemplo 8: 3-metoxi-2-[(1-metil-1*H*-pirazolo[3,4-*d*]pirimidin-4-il)oxi]-*N*-(5-metilpiridin-2-il)propanamida



Método 1 a partir de los Productos Intermedios A2 y B11

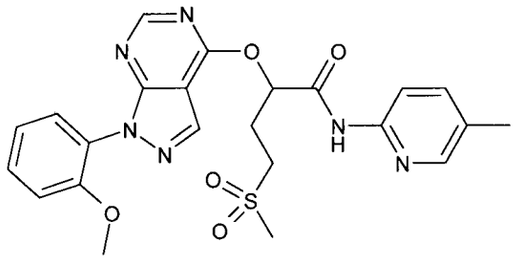
^{1}H NMR (500 MHz, $CDCl_3$) δ 8,65 (br s, 1H), 8,56 (s, 1H), 8,19 (s, 1H), 8,13 (d, 1H), 8,08 (s, 1H), 7,52 (d, 1H), 6,07 (t, 1H), 4,12 (s, 3H), 4,09 (m, 1H), 4,00 (m, 1H), 3,44 (s, 3H), 2,28 (s, 3H), HRMS: calculado para ($M+H^+$) $C_{16}H_{19}N_6O_3$: 343,1518. Encontrado: 343,1529.

Ejemplo 9: 2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)-4-(metilsulfonil)butanamida



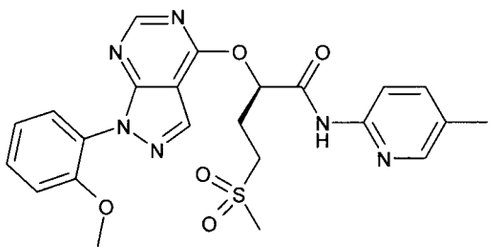
Método 1 a partir de los Productos Intermedios A1 y B1 ^{1}H NMR (500 MHz, $CDCl_3$) δ 9,01 (br s, 1H), 8,58 (s, 1H), 8,39 (s, 1H), 8,07 (m, 2H), 7,60 (d, 1H), 7,49 (m, 4H), 6,07 (t, 1H), 3,36 (m, 2H), 2,96 (s, 3H), 2,72 (m, 2H), 2,27 (s, 3H), HRMS: calculado para ($M+H^+$) $C_{22}H_{22}{}^{35}ClN_6O_4S$: 501,1111. Encontrado: 501,1070.

Ejemplo 10: 2-{[1-(2-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)-4-(metilsulfonil)butanamida

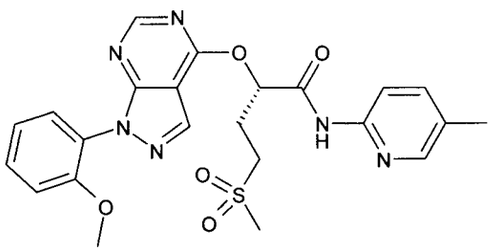


Método 1 a partir de los Productos Intermedios A1 y B3 ^{1}H NMR (300 MHz, $CDCl_3$) δ 9,00 (br s, 1H), 8,55 (s, 1H), 8,35 (s, 1H), 8,07 (m, 2H), 7,47 (m, 3H), 7,11 (m, 2H), 6,08 (t, 1H), 3,78 (s, 3H), 3,35 (m, 2H), 2,97 (s, 3H), 2,72 (m, 2H), 2,26 (s, 3H), HRMS: calculado para ($M+H^+$) $C_{23}H_{25}N_6O_5S$: 497,1607. Encontrado: 497,1630.

Ejemplo 11: (R)-2-{[1-(2-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)-4-(metilsulfonil)butanamida



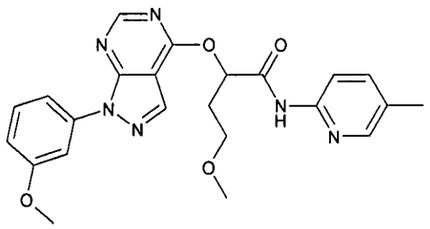
y Ejemplo 12: (S)-2-{[1-(2-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)-4-(metilsulfonil)butanamida



Los enantiómeros de 2-{[1-(2-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)-4-(metilsulfonil)butanamida racémica (48,5 mg) se separaron mediante HPLC preparativa: Columna Chiralcel OD (250x20 mm, 10 µm); Fase móvil heptano/EtOH:30/70; Flujo 20 ml/min; UV 240 nm; Temperatura ambiente. Esto proporcionó (R)-2-{[1-(2-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)-4-(metilsulfonil)butanamida (15,0 mg, >99% ee), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8,79 (br s, 1H), 8,57 (s, 1H), 8,37 (s, 1H), 8,09 (m, 2H), 7,49 (m, 3H), 7,13 (m, 2H), 6,10 (t, 1H), 3,79 (s, 3H), 3,34 (m, 2H), 2,98 (s, 3H), 2,74 (m, 2H), 2,30 (s, 3H) y (S)-

2-{[1-(2-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)-4-(metilsulfonil)butanamida (20,0 mg, >99% ee), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8,77 (br s, 1H), 8,58 (s, 1H), 8,38 (s, 1H), 8,10 (m, 2H), 7,48 (m, 3H), 7,13 (m, 2H), 6,11 (t, 1H), 3,79 (s, 3H), 3,34 (m, 2H), 2,98 (s, 3H), 2,73 (m, 2H), 2,30 (s, 3H).

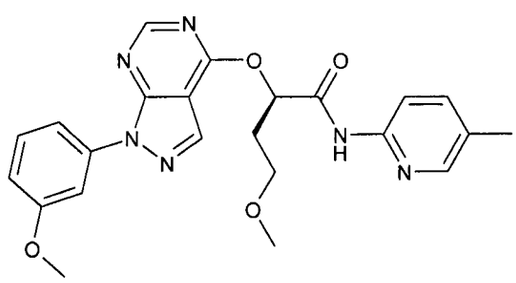
Ejemplo 13: 4-metoxi-2-{[1-(3-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)butanamida



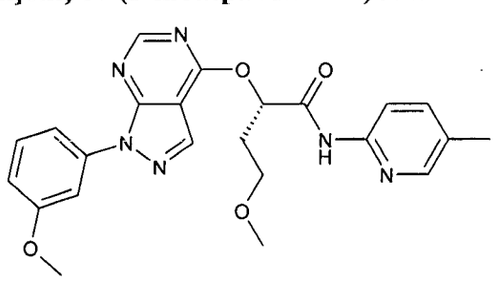
Método 1 a partir de los Productos Intermedios A12 y B5

^{1}H NMR (500 MHz, $CDCl_3$) δ 8,72 (br s, 1H), 8,64 (s, 1H), 8,32 (s, 1H), 8,12 (d, 1H), 8,08 (s, 1H), 7,81 (d, 1H), 7,79 (m, 1H), 7,51 (d, 1H), 7,43 (t, 1H), 6,91 (d, 1H), 5,96 (t, 1H), 3,90 (s, 3H), 3,63 (t, 2H), 3,33 (s, 3H), 2,44 (m, 2H), 2,28 (s, 3H), HRMS: calculado para ($M+H^+$) $C_{23}H_{25}N_6O_4$: 449,1937. Encontrado: 449,1936.

Ejemplo 14: (R)-4-metoxi-2-{[1-(3-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)butanamida



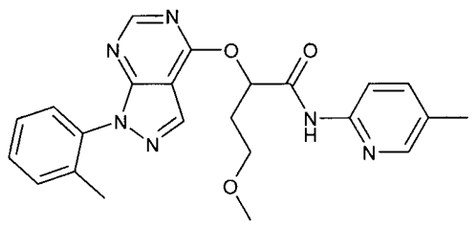
y Ejemplo 15: (S)-4-metoxi-2-{[1-(3-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)butanamida



Los enantiómeros de 4-metoxi-2-{[1-(3-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-

il]oxi}-*N*-(5-metilpiridin-2-il)butanamida racémica (140,0 mg) se separaron mediante HPLC preparativa: Columna Chiralpak IA (250x20 mm, 5 µm); Fase móvil heptano/EtOH:30/70; Flujo 12 ml/min; UV 254 nm; Temperatura 40°C. Esto proporcionó (R)-4-metoxi-2-{[1-(3-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)butanamida (63,4 mg, >98% ee), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8,90 (br s, 1H), 8,63 (s, 1H), 8,31 (s, 1H), 8,11 (m, 2H), 7,81 (m, 2H), 7,51 (d, 1H), 7,42 (t, 1H), 6,90 (d, 1H), 5,95 (t, 1H), 3,89 (s, 3H), 3,63 (t, 2H), 3,32 (s, 3H), 2,43 (m, 2H), 2,27 (s, 3H) y (S)-4-metoxi-2-{[1-(3-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)butanamida (62,7 mg, 99,7% ee), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8,92 (br s, 1H), 8,63 (s, 1H), 8,31 (s, 1H), 8,12 (m, 2H), 7,79 (m, 2H), 7,52 (d, 1H), 7,42 (t, 1H), 6,90 (d, 1H), 5,95 (t, 1H), 3,89 (s, 3H), 3,63 (t, 2H), 3,32 (s, 3H), 2,43 (m, 2H), 2,27 (s, 3H).

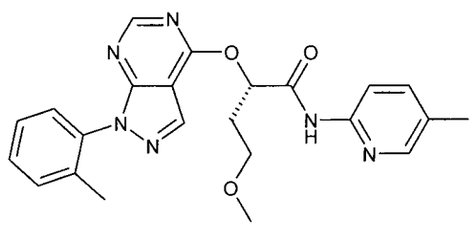
Ejemplo 16: 4-metoxi-2-{[1-(2-metilfenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)butanamida



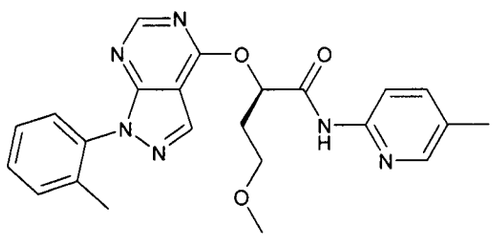
Método 1 a partir de los Productos Intermedios A12 y B2

^{1}H NMR (500 MHz, $CDCl_3$) δ 8,90 (br s, 1H), 8,56 (s, 1H), 8,36 (s, 1H), 8,15 (d, 1H), 8,12 (s, 1H), 7,53 (d, 1H), 7,39 (m, 4H), 5,96 (t, 1H), 3,66 (m, 2H), 3,36 (s, 3H), 2,45 (m, 2H), 2,29 (s, 3H), 2,17 (s, 3H), HRMS: calculado para ($M+H^+$) $C_{23}H_{25}N_6O_3$: 433,1988. Encontrado: 433,1984.

Ejemplo 17: (S)-4-metoxi-2-{[1-(2-metilfenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)butanamida

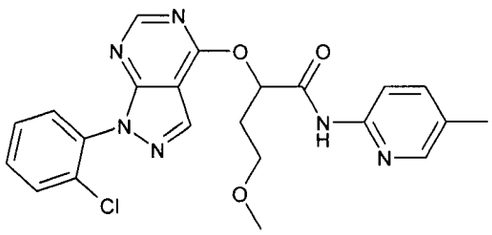


y Ejemplo 18: (R)-4-metoxi-2-{[1-(2-metilfenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)butanamida



Los enantiómeros de 4-metoxi-2-{[1-(2-metilfenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)butanamida racémica (122,0 mg) se separaron mediante HPLC preparativa: Columna Chiralcel OD (250x20 mm, 5 µm); Fase móvil MeOH; Flujo 15 ml/min; UV 230 nm; Temperatura ambiente. Esto proporcionó (S)-4-metoxi-2-{[1-(2-metilfenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)butanamida (49,1 mg, >99% ee), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8,67 (br s, 1H), 8,57 (s, 1H), 8,36 (s, 1H), 8,12 (m, 2H), 7,53 (d, 1H), 7,39 (m, 4H), 5,96 (t, 1H), 3,65 (t, 2H), 3,34 (s, 3H), 2,46 (m, 2H), 2,29 (s, 3H), 2,16 (s, 3H) y (R)-4-metoxi-2-{[1-(2-metilfenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)butanamida (53,5 mg, >99% ee), ^{1}H NMR (300 MHz, CDCl3) δ 8,66 (br s, 1H), 8,56 (s, 1H), 8,35 (s, 1H), 8,13 (d, 1H), 8,09 (d, 1H), 7,52 (dd, 1H), 7,38 (m, 4H), 5,95 (t, 1H), 3,65 (t, 2H), 3,34 (s, 3H), 2,44 (m, 2H), 2,29 (s, 3H), 2,16 (s, 3H).

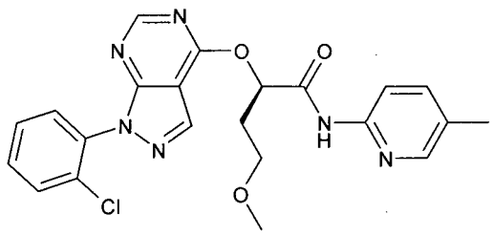
Ejemplo 19: 2-{[1-(2-Clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-4-metoxi-*N*-(5-metilpiridin-2-il)butanamida



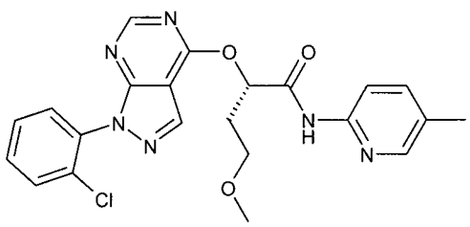
Método 1 a partir de los Productos Intermedios A12 y B1

^{1}H NMR (300 MHz, $CDCl_3$) δ 8,70 (br s, 1H), 8,58 (s, 1H), 8,39 (s, 1H), 8,11 (dd, 2H), 7,61 (m, 1H), 7,49 (m, 4H), 5,95 (t, 1H), 3,64 (t, 2H), 3,34 (s, 3H), 2,44 (m, 2H), 2,29 (s, 3H), HRMS: calculado para ($M+H^+$) $C_{22}H_{22}{}^{35}ClN_6O_3$: 453,1442. Encontrado: 453,1452.

Ejemplos 20: (R)-2-{[1-(2-Clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-4-metoxi-*N*-(5-metilpiridin-2-il)butanamida

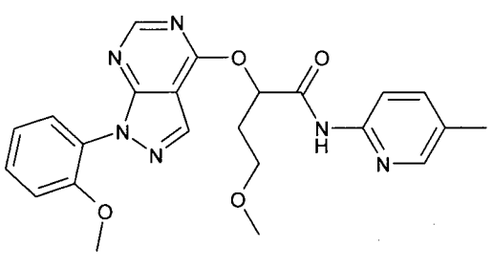


y Ejemplo 21: (S)-2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-4-metoxi-*N*-(5-metilpiridin-2-il)butanamida



Los enantiómeros de 2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-4-metoxi-*N*-(5-metilpiridin-2-il)butanamida racémica (200 mg) se separaron mediante HPLC preparativa: Columna Chiralcel OJ (250x20 mm, 5 μm); Fase móvil heptano/EtOH:30/70; Flujo 19 ml/min; UV 285 nm; Temperatura 20ºC. Esto proporcionó (R)-2-{[1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-il]oxi}-4-metoxi-N-(5-metilpiridin-2-il)butanamida (89 mg, >99% ee), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8,76 (br s, 1H), 8,58 (s, 1H), 8,38 (s, 1H), 8,11 (m, 2H), 7,61 (m, 1H), 7,48 (m, 4H), 5,94 (t, 1H), 3,64 (t, 2H), 3,33 (s, 3H), 2,44 (m, 2H), 2,28 (s, 3H) y (S)-2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-4-metoxi-*N*-(5-metilpiridin-2-il)butanamida (93 mg, >99% ee), ^{1}H NMR (300 MHz, CDCl3) δ 8,67 (br s, 1H), 8,58 (s, 1H), 8,39 (s, 1H), 8,12 (m, 2H), 7,61 (m, 1H), 7,49 (m, 4H), 5,95 (t, 1H), 3,64 (t, 2H), 3,34 (s, 3H), 2,44 (m, 2H), 2,29 (s, 3H).

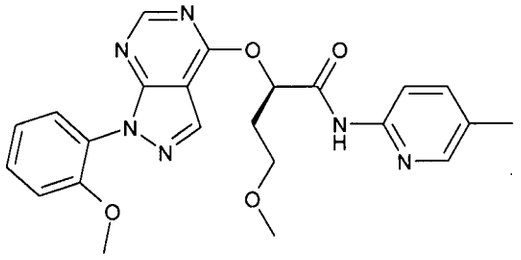
Ejemplo 22: 4-Metoxi-2-{[1-(2-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)butanamida



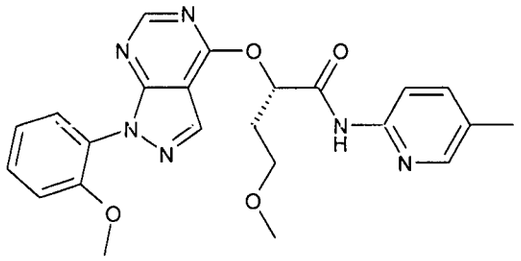
Método 1 a partir de los Productos Intermedios A12 y B3

^{1}H NMR (300 MHz, $CDCl_3$) δ 8,67 (br s, 1H), 8,56 (s, 1H), 8,37 (s, 1H), 8,14 (d, 1H), 8,09 (s, 1H), 7,51 (t, 2H), 7,44 (m, 1H), 7,12 (m, 2H), 5,96 (m, 1H), 3,79 (s, 3H), 3,64 (t, 2H), 3,34 (s, 3H), 2,44 (d, 2H), 2,29 (s, 3H), HPMS: calculado para ($M+H^+$) $C_{22}H_{25}N_6O_4$: 449,1937. Encontrado: 449,1951.

Ejemplo 23: (R)-4-Metoxi-2-{[1-(2-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)butanamida



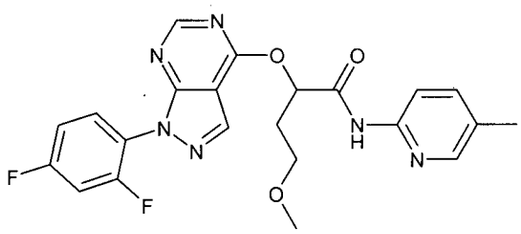
y Ejemplo 24: (S)-4-metoxi-2-{[1-(2-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)butanamida



Los enantiómeros de 4-metoxi-2-{[1-(2-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)butanamida racémica (100 mg) se separaron mediante HPLC preparativa: Columna Chiralpal: AS (250x20 mm, 5 µm); Fase móvil heptano/IPA:60/40; Flujo 13 ml/min; UV 275 nm; Temperatura 40°C. Esto proporcionó (R)-4-metoxi-2-{[1-(2-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)butanamida (54,4 mg, >99% ee), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8,66 (br s, 1H), 8,56 (s, 1H), 8,36 (s, 1H), 8,12 (m, 2H), 7,46 (m, 3H), 7,12 (m, 2H), 5,95 (t, 1H), 3,79 (s, 3H), 3,64 (t, 2H), 3,34 (s, 3H), 2,45 (m, 2H), 2,29 (s, 3H) y (S)-4-metoxi-2-{[1-(2-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)butanamida (53,7 mg, >99% ee), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8,65 (br s, 1H), 8,56 (s, 1H), 8,36 (s, 1H), 8,12 (m, 2H), 7,47 (m, 3H), 7,12 (m, 2H), 5,95 (t, 1H), 3,79 (s, 3H), 3,64 (t, 2H), 3,34 (s, 3H), 2,44 (d, 2H), 2,29 (s, 3H).

Ejemplo 25: 2-{[1-(2,4-Difluorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-4-metoxi-

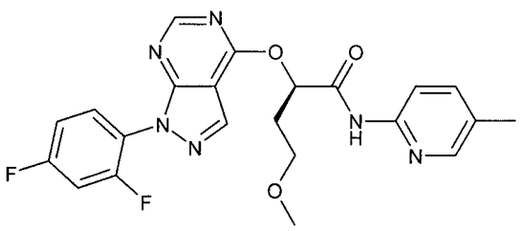
***N*-(5-metilpiridin-2-il)butanamida**



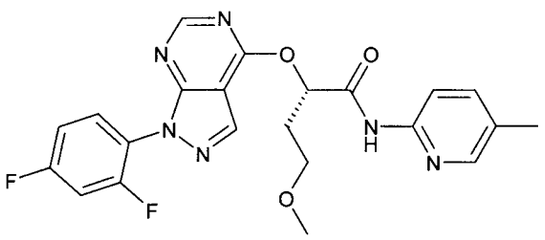
Método 1 a partir de los Productos Intermedios A12 y B7

^{1}H NMR (400 MHz, $CDCl_3$) δ 9,01 (br s, 1H), 8,55 (s, 1H), 8,35 (s, 1H), 8,09 (d, 1H), 8,04 (m, 1H), 7,56 (m, 1H), 7,49 (dd, 1H), 7,03 (m, 2H), 5,91 (t, 1H), 3,60 (t, 2H), 3,29 (s, 3H), 2,44(s 3H), 2,40 (m, 2H), HRMS: calculado para ($M+H^+$) $C_{22}H_{21}F_2N_6O_3$: 455,1643. Encontrado: 455,1657.

Ejemplo 26: (R)-2-{[1-(2,4-Difluorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-4-metoxi-*N*-(5-metilpiridin-2-il)butanamida



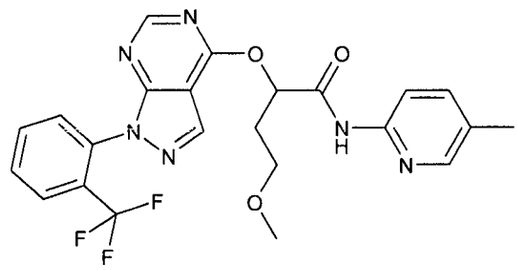
y Ejemplo 27: (S)-2-{[1-(2,4-difluorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-4-metoxi-*N*-(5-metilpiridin-2-il)butanamida



Los enantiómeros de 2-{[1-(2,4-difluorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-4-metoxi-*N*-(5-metilpiridin-2-il)butanamida racémica (160 mg) se separaron mediante HPLC preparativa: Columna Chiralpak AS (250x20 mm, 5 µm); Fase móvil heptano/EtOH:75/25; Flujo 18 ml/min; UV 230 nm; Temperatura 22°C. Esto proporcionó (R)-2-{[1-(2,4-difluorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-4-metoxi-*N*-(5-metilpiridin-2-il)butanamida (37,6 mg, >99% ee), ^{1}H NMR (400 MHz, $CDCl_3$) δ 9,17 (br s, 1H), 8,57 (s, 1H), 8,42 (s, 1H), 8,18 (d, 1H), 8,05 (s, 1H), 7,59 (m, 2H), 7,05 (m, 2H), 5,94 (t, 1H), 3,62 (t, 1H), 3,31 (s, 3H), 2,42 (m, 2H), 2,29 (s, 3H) y (S)-2-{[1-(2,4-difluorofenil)-1*H*-

pirazolo[3,4-*d*]pirimidin-4-il]oxi}-4-metoxi-*N*-(5-metilpiridin-2-il)butanamida (53,7 mg, >99% ee), ^{1}H NMR (400 MHz, $CDCl_3$) δ 9,38 (br s, 1H), 8,56 (s, 1H), 8,44 (s, 1H), 8,22 (d, 1H), 8,04 (s, 1H), 7,59 (m, 2H), 7,05 (m, 2H), 5,94 (t, 1H), 3,62 (t, 1H), 3,31 (s, 3H), 2,42 (m, 2H), 2,30 (s, 3H).

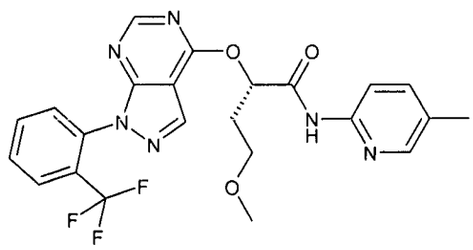
Ejemplo 28: 4-Metoxi-*N*-(5-metilpiridin-2-il)-2-({1-[2-(trifluorometil)fenil]-1*H*-pirazolo[3,4-*d*]pirimidin-4-il}oxi)butanamida



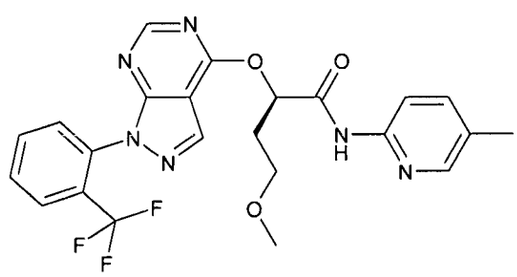
Método 1 a partir de los Productos Intermedios A12 y B4

^{1}H NMR (400 MHz, $CDCl_3$) δ 9,20 (br s, 1H), 8,54 (s, 1H), 8,35 (s, 1H), 8,12 (m, 2H), 7,88 (d, 1H), 7,73 (m, 1H), 7,66 (m, 1H), 7,52 (m, 2H), 5,94 (t, 1H), 3,64 (m, 2H), 3,31 (s, 3H), 2,43 (m, 2H), 2,26 (s, 3H), HRMS: calculado para ($M+H^+$) $C_{23}H_{22}F_3N_6O_3$: 487,1705. Encontrado: 487,1708.

Ejemplo 29: (S)-4-Metoxi-*N*-(5-metilpiridin-2-il)-2-({1-[2-(trifluorometil)fenil]-1*H*-pirazolo[3,4-*d*]pirimidin-4-il}oxi)butanamida



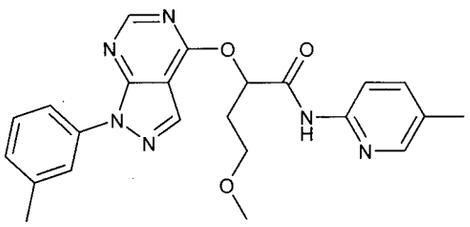
y Ejemplo 30: (R)-4-metoxi-*N*-(5-metilpiridin-2-il)-2-({1-[2-(trifluorometil)fenil]-1*H*-pirazolo[3,4-*d*]pirimidin-4-il}oxi)butanamida



Los enantiómeros de 4-metoxi-*N*-(5-metilpiridin-2-il)-2-({1-[2-(trifluorometil)fenil]-1*H*-

pirazolo[3,4-*d*]pirimidin-4-il}oxi)butanamida racémica (178 mg) se separaron mediante HPLC preparativa: Columna Chiralpak AD (250x20 mm, 5 µm); Fase móvil heptano/EtOH:30/70; Flujo 18 ml/min; UV 254 nm; Temperatura 20°C. Esto proporcionó (S)-4-metoxi-*N*-(5-metilpiridin-2-il)-2-({1-[2-(trifluorometil)fenil]-1*H*-pirazolo[3,4-*d*]pirimidin-4-il}oxi)butanamida (61,6 mg, >98% ee), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8,65 (br s, 1H), 8,58 (s, 1H), 8,39 (s, 1H), 8,14 (m, 2H), 7,92 (d, 1H), 7,78 (t, 1H), 7,71 (t, 1H), 7,55 (t, 2H), 5,98 (m, 1H), 3,67 (t, 2H), 3,36 (s, 3H), 2,47 (m, 2H), 2,31 (s, 3H) y (R)-4-metoxi-*N*-(5-metilpiridin-2-il)-2-({1-[2-(trifluorometil)fenil]-1*H*-pirazolo[3,4-*d*]pirimidin-4-il}oxi)butanamida (52,0 mg, >99% ee), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8,66 (br s, 1H), 8,58 (s, 1H), 8,39 (s, 1H), 8,14 (m, 2H), 7,92 (d, 1H), 7,78 (t, 1H), 7,71 (t, 1H), 7,55 (t, 2H), 5,98 (t, 1H), 3,67 (t, 2H), 3,36 (s, 3H), 2,47 (m, 2H), 2,31 (s, 3H).

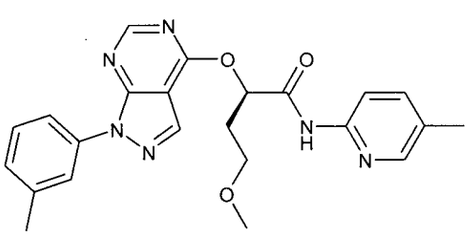
Ejemplo 31: 4-Metoxi-2-{[1-(3-metilfenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)butanamida



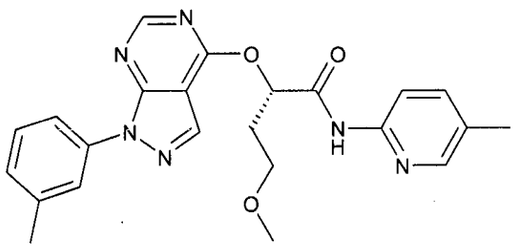
Método 1 a partir de los Productos Intermedios A12 y B10

^{1}H NMR (400 MHz, $CDCl_3$) δ 9,19 (br s, 1H), 8,56 (s, 1H), 8,27 (s, 1H), 8,08 (d, 1H), 8,03 (d, 1H), 7,90 (m, 2H), 7,45 (dd, 1H), 7,35 (t, 1H), 7,10 (d, 1H), 5,90 (t, 1H), 3,59 (t, 2H), 3,26 (s, 3H), 2,40 (m, 5H), 2,21 (s, 3H), HRMS: calculado para ($M+H^+$) $C_{23}H_{25}N_6O_3$: 433,1988. Encontrado: 433,2008.

Ejemplo 32: (R)-4-Metoxi-2-{[1-(3-metilfenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)butanamida

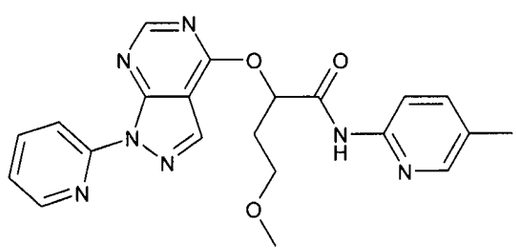


Y Ejemplo 33: (S)-4-metoxi-2-{[1-(3-metilfenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)butanamida



Los enantiómeros de 4-metoxi-2-{[1-(3-metilfenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)butanamida racémica (159 mg) se separaron mediante HPLC preparativa: Columna Chiralpal: IA (250x20 mm, 5 µm); Fase móvil heptano/IPA:30/70; Flujo 14 ml/min; UV 265 nm; Temperatura 40°C. Esto proporcionó (R)-4-metoxi-2-{[1-(3-metilfenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)butanamida (59 mg, >99% ee), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8,66 (s, 1H), 8,64 (br s, 1H), 8,35 (s, 1H), 8,14 (d, 1H), 8,10 (s, 1H), 7,98 (d, 2H), 7,54 (dd, 1H), 7,44 (t, 1H), 7,20 (d, 1H), 5,99 (dd, 1H), 3,65 (t, 2H), 3,35 (s, 3H), 2,49 (d, 3H), 2,48 (s, 2H), 2,31 (s, 3H) y (S)-4-metoxi-2-{[1-(3-metilfenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)butanamida(54 mg, >99% ee), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8,66 (s, 1H), 8,65 (br s, 1H), 8,35 (s, 1H), 8,14 (d, 1H), 8,10 (s, 1H), 7,98 (d, 2H), 7,54 (m, 1H), 7,44 (t, 1H), 7,20 (d, 1H), 5,99 (dd, 1H), 3,65 (t, 2H), 3,35 (s, 3H), 2,49 (s, 3H), 2,45 (dd, 2H), 2,30 (s, 3H).

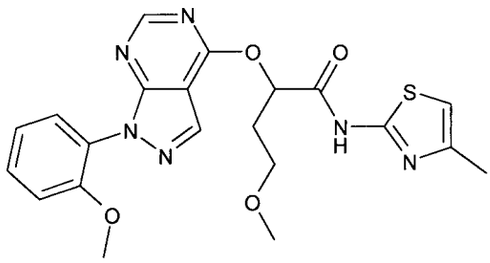
Ejemplo 34: 4-Metoxi-*N*-(5-metilpiridin-2-il)-2-[(1-piridin-2-il-1*H*-pirazolo[3,4-*d*]pirimidin-4-il)oxi]butanamida



Método 1 a partir de los Productos Intermedios A12 y B8

^{1}H NMR (400 MHz, $CDCl_3$) δ 9,34 (br s, 1H), 8,62 (m, 2H), 8,18 (s, 1H), 8,09 (m, 1H), 7,99 (s, 1H), 7,83 (m, 1H), 7,45 (d, 1H), 7,22 (m, 1H), 5,87 (t, 1H), 3,57 (t, 2H), 3,23 (s, 3H), 2,36 (m, 2H), 2,19 (s, 3H), HRMS: calculado para ($M+H^+$) $C_{21}H_{22}N_7O_3$: 420,1784. Encontrado: 420,1797.

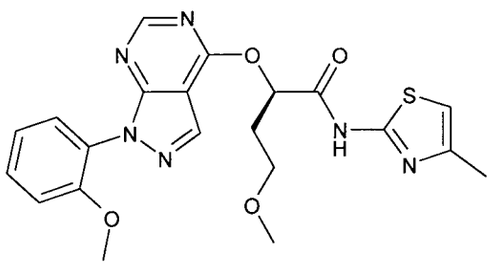
Ejemplo 35: 4-Metoxi-2-{[1-(2-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(4-metil-1,3-tiazol-2-il)butanamida



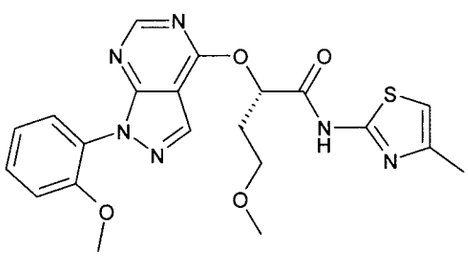
Método 1 a partir de los Productos Intermedios A13 y B3

^{1}H NMR (300 MHz, $CDCl_3$) δ 8,77 (br s, 1H), 8,52 (s, 1H), 8,34 (s, 1H), 7,46 (m, 2H), 7,11 (m, 2H), 6,52 (s, 1H), 6,01 (t, 1H), 3,77 (d, 3H), 3,62 (m, 2H), 3,32 (d, 3H), 2,42 (m, 2H), 2,31 (s, 3H), HRMS: calculado para ($M+H^+$) $C_{22}H_{23}N_6O_4S$: 455,1501. Encontrado: 455,1490.

Ejemplo 36: (R)-4-Metoxi-2-{[1-(2-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(4-metil-1,3-tiazol-2-il)butanamida



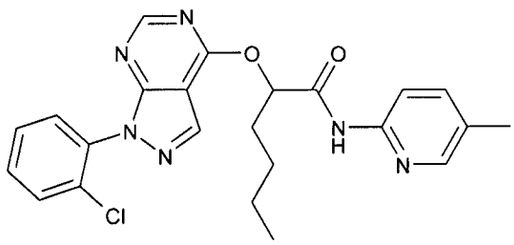
Y Ejemplo 37: (S)-4-metoxi-2-{[1-(2-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(4-metil-1,3-tiazol-2-il)butanamida



Los enantiómeros de 4-metoxi-2-{[1-(2-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(4-metil-1,3-tiazol-2-il)butanamida racémica (90 mg) se separaron mediante HPLC preparativa: Columna Chiralpak AD (250x20 mm, 5 µm); Fase móvil heptano/etanol:50/50; Flujo 15 ml/min; UV 270 nm; Temperatura 20°C. Esto proporcionó (R)-4-metoxi-2-{[1-(2-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(4-metil-1,3-tiazol-2-il)butanamida (24 mg, >99% ee), ^{1}H NMR (500 MHz, $CDCl_3$) δ 9,80 (br s, 1H), 8,58 (s, 1H), 8,35 (s, 1H), 7,51 (m, 1H), 7,46 (m, 1H), 7,14 (m, 2H), 6,57 (d, 1H), 6,06 (t,

1H), 3,81 (s, 3H), 3,65 (t, 2H), 3,34 (s, 3H), 2,46 (m, 2H), 2,35 (d, 3H) y (S)-4-metoxi-2-{[1-(2-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(4-metil-1,3-tiazol-2-il)butanamida (26,1 mg, >99% ee), ^{1}H NMR (500 MHz, $CDCl_3$) δ 9,87 (br s, 1H), 8,59 (s, 1H), 8,35 (s, 1H), 7,51 (m, 1H), 7,46 (m, 1H), 7,14 (m, 2H), 6,57 (d, 1H), 6,05 (t, 1H), 3,81 (s, 3H), 3,64 (t, 2H), 3,34 (s, 3H), 2,45 (m, 2H), 2,35 (d, 3H).

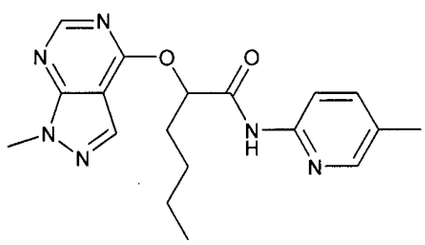
Ejemplo 38: 2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)hexanamida



Método 1 a partir de los Productos Intermedios A3 y B1

^{1}H NMR (300 MHz, $CDCl_3$) δ 8,59 (s, 1H), 8,47 (br s, 1H), 8,40 (s, 1H), 8,15 (d, 1H), 8,08 (s, 1H), 7,62 (m, 1H), 7,50 (m, 4H), 5,85 (t, 1H), 2,29 (s, 3H), 2,17 (m, 2H), 1,54 (m, 2H), 1,42 (m, 2H), 0,94 (t, 3H), HRMS: calculado para (M+H$^+$) $C_{23}H_{24}{}^{35}ClN_6O_2$: 451,1649. Encontrado: 451,1656.

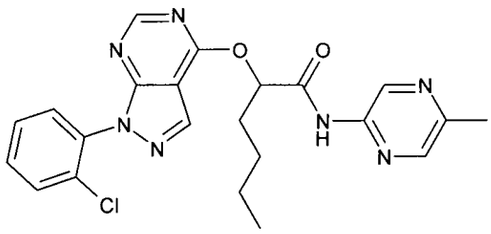
Ejemplo 39: 2-[(1-metil-1*H*-pirazolo[3,4-*d*]pirimidin-4-il)oxi]-*N*-(5-metilpiridin-2-il)hexanamida



Método 1 a partir de los Productos Intermedios A3 y B11

^{1}H NMR (500 MHz, $CDCl_3$) δ 8,60 (br s, 1H), 8,56 (s, 1H), 8,15 (m, 2H), 8,07 (s, 1H), 7,53 (d, 1H), 5,84 (t, 1H), 4,13 (s, 3H), 2,29 (s, 3H), 2,15 (m, 2H), 1,52 (m, 2H), 1,39 (m, 2H), 0,92 (t, 3H), HRMS: calculado para (M+H$^+$) $C_{18}H_{23}N_6O_2$: 355,1882. Encontrado: 355,1892.

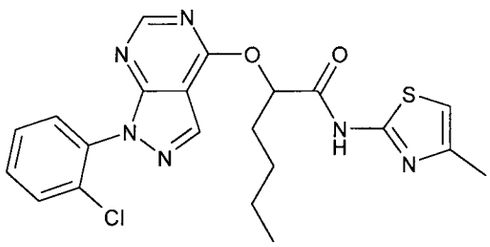
Ejemplo 40: 2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpirazin-2-il)hexanamida



Método 1 a partir de los Productos Intermedios A4 y B1

^{1}H NMR (300 MHz, $CDCl_3$) δ 9,46 (s, 1H), 8,59 (s, 1H), 8,48 (br s, 1H), 8,40 (s, 1H), 8,10 (s, 1H), 7,62 (m, 1H), 7,50 (m, 3H), 5,89 (t, 1H), 2,53 (s, 3H), 2,19 (m, 2H), 1,55 (m, 2H), 1,44 (m, 2H), 0,94 (t, 3H), HRMS: calculado para ($M+H^+$) $C_{22}H_{23}{}^{35}ClN_7O_2$: 452,1601. Encontrado: 452,1576.

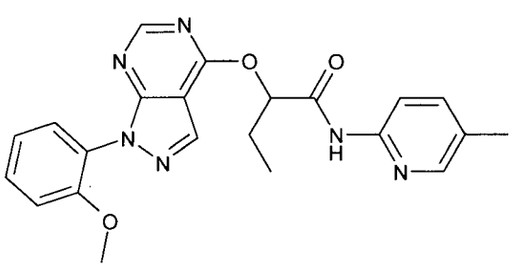
Ejemplo 41: 2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]tio}-*N*-(4-metil-1,3-tiazol-2-il)hexanamida



Método 1 a partir de los Productos Intermedios A5 y B1

^{1}H NMR (300 MHz, $CDCl_3$) δ 9,44 (br s, 1H), 8,58 (s, 1H), 8,38 (s, 1H), 7,62 (m, 1H), 7,51 (m, 3H), 6,56 (s, 1H), 5,95 (t, 1H), 2,33 (s, 3H), 2,17 (m, 2H), 1,53 (m, 2H), 1,41 (m, 2H), 0,93 (t, 3H), HRMS: calculado para ($M+H^+$) $C_{21}H_{22}{}^{35}ClN_6O_2S$: 457,1213. Encontrado: 457,1238.

Ejemplo 42: 2-{[1-(2-Metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)butanamida

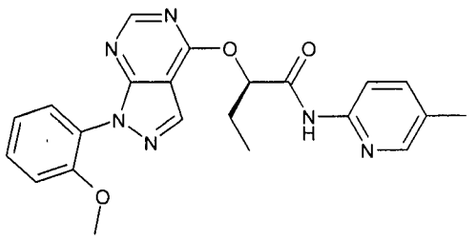


Método 1 a partir de los Productos Intermedios A9 y B3

^{1}H NMR (300 MHz, $CDCl_3$) δ 8,72 (br s, 1H), 8,56 (s, 1H), 8,39 (s, 1H), 8,17 (d, 1H), 8,07 (s, 1H), 7,49 (m, 3H), 7,12 (m, 2H), 5,81 (t, 1H), 3,79 (s, 3H), 2,29 (s, 3H), 2,21 (m,

2H), 1,15 (t, 3H), HRMS: calculado para (M+H$^+$) $C_{22}H_{23}N_6O_3$: 419,1831. Encontrado: 419,1810.

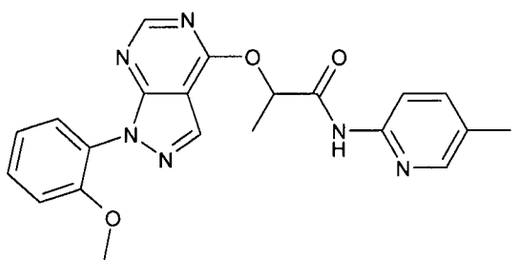
Ejemplo 43: (2*R*)-2-{[1-(2-Metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)butanamida



Método 1 a partir de los Productos Intermedios A8 y B3

$[\alpha]^{20}_D$ –31,8° (1,0 g/100 ml en ACN), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8,70 (br s, 1H), 8,58 (s, 1H), 8,40 (s, 1H), 8,19 (d, 1H), 8,10 (s, 1H), 7,55 (dd, 1H), 7,50 (m, 1H), 7,46 (dd, 1H), 7,13 (m, 2H), 5,83 (m, 1H), 3,81 (s, 3H), 2,31 (s, 3H), 2,22 (m, 2H), 1,13 (m, 3H), HRMS: calculado para (M+H$^+$) $C_{22}H_{23}N_6O_3$: 419,1831. Encontrado: 419,1854.

Ejemplo 44: 2-{[1-(2-Metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N*-(5-metilpiridin-2-il)propanamida

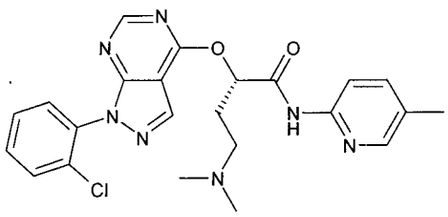


Método 1 a partir de los Productos Intermedios A10 y B3

^{1}H NMR (300 MHz, $CDCl_3$) δ 8,88 (br s, 1H), 8,57 (s, 1H), 8,38 (s, 1H), 8,17 (d, 1H), 8,07 (s, 1H), 7,48 (m, 3H), 7,12 (m, 2H), 5,94 (q, 1H), 3,79 (s, 3H), 2,30 (s, 3H), 1,80 (d, 3H), HRMS: calculado para (M+H$^+$) $C_{21}H_{21}N_6O_3$: 405,1675. Encontrado: 405,1676.

No hay ejemplos 45 y 46.

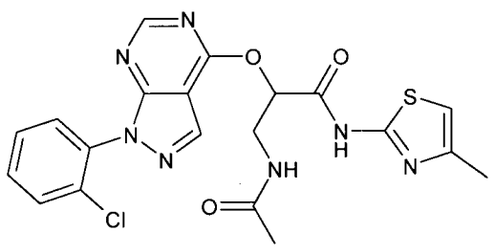
Ejemplo 47: (2*S*)-2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-4-(dimetilamino)-*N*-(5-metilpiridin-2-il)butanamida



Método 1 a partir de los Productos Intermedios A11 y B1

$[\alpha]^{20}_{D}$ +7,3^{O} (1,0 g/100 ml en ACN), ^{1}H NMR (300 MHz, $CDCl_3$) δ 9,61 (br s, 1H), 8,53 (s, 1H), 8,35 (s, 1H), 8,09 (m, 2H), 7,57 (m, 1H), 7,46 (m, 4H), 5,86 (t, 1H), 2,55 (m, 2H), 2,30 (m, 11H), HRMS: calculado para ($M+H^+$) $C_{23}H_{25}{}^{35}ClN_7O_2$: 466,1758. Encontrado: 466,1763.

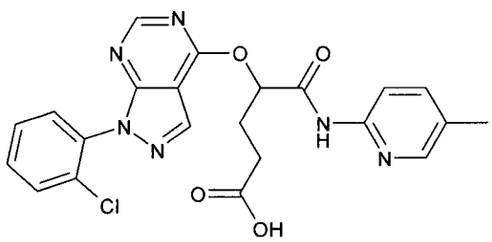
Ejemplo 48: 3-Acetamido-2-{[1-(2-clorofenil)-1*h*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*n*-(4-metil-1,3-tiazol-2-il)propanamida



Método 1 a partir de los Productos Intermedios A14 y B1

^{1}H NMR (500 MHz, $CDCl_3$) δ 8,59 (s, 1H), 8,39 (s, 1H), 7,62 (m, 1H), 7,50 (m, 3H), 6,55 (s, 1H), 6,18 (br t, 1H), 6,04 (t, 1H), 4,04 (m, 2H), 2,32 (s, 3H), 2,01 (s, 3H), HRMS: calculado para ($M+H^+$) $C_{20}H_{19}{}^{35}ClN_7O_3S$: 472,0958. Encontrado: 472,0971.

Ejemplo 49: Ácido 4-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-5-[(5-metilpiridin-2-il)amino]-5-oxopentanoico

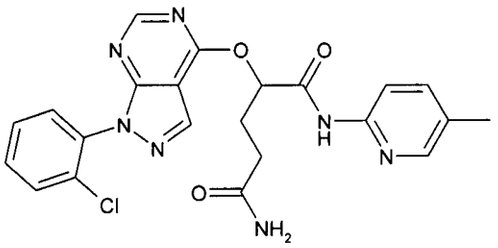


Método 1 a partir de los Productos Intermedios A15 y B1

^{1}H NMR (400 MHz, $CDCl_3$) δ 11,44 (br s, 1H), 8,42 (s, 1H), 8,37 (s, 1H), 8,23 (d, 1H), 7,89 (s, 1H), 7,56 (m, 2H), 7,43 (m, 3H), 5,95 (m, 1H), 2,98 (m, 1H), 2,73 (m, 1H), 2,61 (m, 1H), 2,34 (m, 1H), 2,26 (s, 3H), HRMS: calculado para ($M+H^+$) $C_{22}H_{20}{}^{35}ClN_6O_4$:

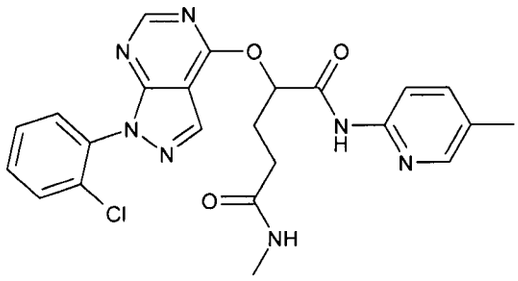
467,1234. Encontrado: 467,1233.

Ejemplo 50: 2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N1*-(5-metilpiridin-2-il)pentanodiamida



Una solución de ácido 4-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-5-[(5-metilpiridin-2-il)amino]-5-oxopentanoico (5,0 mg, 0,011 mmol), cloruro de amonio (3,0 mg, 0,054 mmol), DIPEA (7,0 mg, 0,054 mmol) y TBTU (7,0 mg, 0,021 mmol) en THF (1 mL) se agitó a temperatura ambiente durante 3 hrs. Se agregó agua (1 mL) y la mezcla de reacción se purificó mediante HPLC preparativa: Fase móvil A: 100% ACN, Fase móvil B: 5% ACN :- 95% NH_4OAc 0,1M en agua; Gradiente: 0%A a 50% A durante 45 min; Flujo: 25 ml/min; UV: 235 nm, para proporcionar el compuesto del título (3,0 mg). ^1H NMR (500 MHz, $CDCl_3$) δ 9,18 (br s, 1H), 8,59 (s, 1H), 8,42 (s, 1H), 8,16 (d, 1H), 8,09 (s, 1H), 7,64 (m, 1H), 7,53 (m, 4H), 5,94 (s, 1H), 5,75 (br s, 1H), 5,57 (br s, 1H), 2,58 (m, 4H), 2,32 (s, 3H), HRMS: calculado para ($M+H^+$) $C_{22}H_{21}{}^{35}ClN_7O_3$: 466,1394. Encontrado: 467,1426.

Ejemplo 51: 2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-*N5*-metil-*N1*-(5-metilpiridin-2-il)pentanodiamida

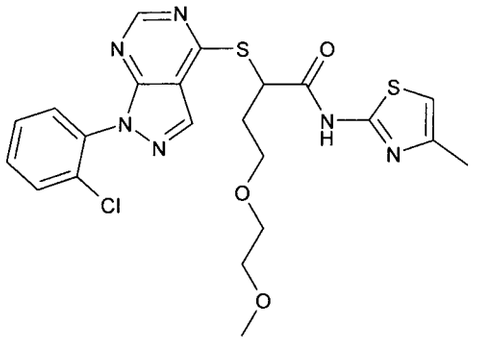


Una solución de ácido 4-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]oxi}-5-[(5-metilpiridin-2-il)amino]-5-oxopentanoico (5,0 mg, 0,011 mmol), metilamina (0,021ml (2M en THF), 0,043 mmol) y TBTU (7,0 mg, 0,021 mmol) en THF (1 mL) se agitó a temperatura ambiente durante 5 hrs. Se agregó agua (1 mL) y la mezcla de reacción se purificó mediante HPLC preparativa: Fase móvil A: 100% ACN, Fase móvil B: 5% ACN :- 95% NH_4OAc 0,1M en agua; Gradiente: 0%A a 50% A durante 45 min; Flujo: 25

ml/min; UV: 235 nm, para proporcionar el compuesto del título (3,0 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8,88 (br s, 1H), 8,57 (s, 1H), 8,39 (s, 1H), 8,11 (m, 2H), 7,62 (m, 1H), 7,51 (m, 4H), 5,91 (m, 1H), 5,63 (br s, 1H), 2,82 (d, 3H), 2,51 (m, 4H), 2,30 (s, 3H), HRMS: calculado para ($M+H^+$) $C_{23}H_{23}{}^{35}ClN_7O_3$: 480,1551. Encontrado: 480,1503.

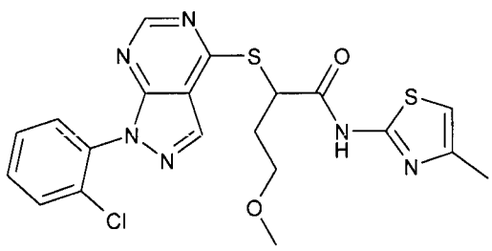
Método 2

Ejemplo 52: 2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]tio}-4-(2-metoxietoxi)-*N*-(4-metil-1,3-tiazol-2-il)butanamida



Una solución de 2-bromo-4-(2-metoxietoxi)-*N*-(4-metil-1,3-tiazol-2-il)butanamida (104 mg, 0,308 mmol) en DMF (1 mL) se agregó a una solución agitada de 1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidina-4-tiol (81,0 mg, 0,308 mmol) y K_2CO_3 (51,1 mg, 0,370 mmol) en DMF (2 mL). La mezcla de reacción se mantuvo a temperatura ambiente durante 3 hrs (45°C y 17 hrs para los ejemplos 54, 55 y 56). Se agregaron agua y EtOAc y las dos fases se separaron. La fase acuosa se extrajo con EtOAc. Los extractos orgánicos se combinaron y se lavaron con agua, se secaron sobre $MgSO_4$ y se concentraron al vacío. El residuo se purificó con cromatografía en columna (gel de sílice, eluyendo con DCM/EtOAc:1/1) para proporcionar el compuesto del título como un aceite viscoso incoloro (145 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ 11,06 (br s, 1H), 8,93 (s, 1H), 8,30 (s, 1H), 7,62 (m, 1H), 7,49 (m, 3H), 6,51 (s, 1H), 5,14 (t, 1H), 3,77 (m, 1H), 3,67 (m, 1H), 3,59 (m, 2H), 3,50 (m, 2H), 3,33 (s, 3H), 2,60 (m, 1H), 2,27 (m, 4H), HRMS: calculado para ($M+H^+$) $C_{22}H_{24}{}^{35}ClN_6O_3S_2$: 518,1040. Encontrado: 519,1050.

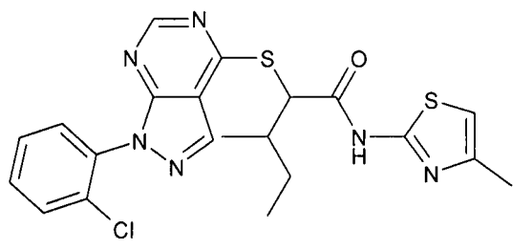
Ejemplo 53: 2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]tio}-4-metoxi-*N*-(4-metil-1,3-tiazol-2-il)butanamida



Método 2 a partir de los Productos Intermedios A18 y B12

^{1}H NMR (500 MHz, $CDCl_3$) δ 11,08 (br s, 1H), 8,95 (s, 1H), 8,30 (s, 1H), 7,62 (d, 1H), 7,49 (m, 3H), 6,51 (s, 1H), 5,09 (t, 1H), 3,66 (m, 1H), 3,57 (m, 1H), 3,34 (s, 3H), 2,59 (m, 1H), 2,30 (s, 3H), 2,22 (m, 1H), HRMS: calculado para ($M+H^+$) $C_{20}H_{20}{}^{35}ClN_6O_2S_2$: 475,0777. Encontrado: 475,0764.

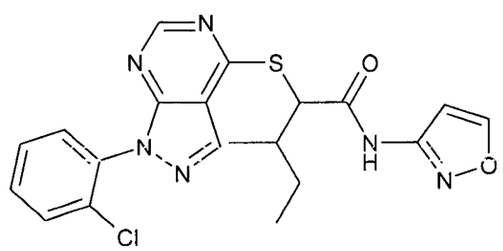
Ejemplo 54: 2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]tio}-3-metil-*N*-(4-metil-1,3-tiazol-2-il)pentanamida



Método 2 a partir de los Productos Intermedios A19 y B12

^{1}H NMR (300 MHz, $CDCl_3$) δ 10,48 (br s, 1H), 8,89 (d, 1H), 8,31 (d, 1H), 7,63 (m, 1H), 7,49 (m, 3H), 6,51 (s, 1H), 4,91 (d, 0,56H), 4,81 (d, 0,44H), 2,43 (m, 1H), 2,30 (s, 3H), 1,87 (m, 0,44H), 1,55 (m, 2,56H), 1,21 (m, 3H), 0,99 (t, 3H), HRMS: calculado para ($M+H^+$) $C_{21}H_{22}{}^{35}ClN_6OS_2$: 473,0985. Encontrado: 473,0985.

Ejemplo 55: 2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]tio}-*N*-isoxazol-3-il-3-metilpentanamida

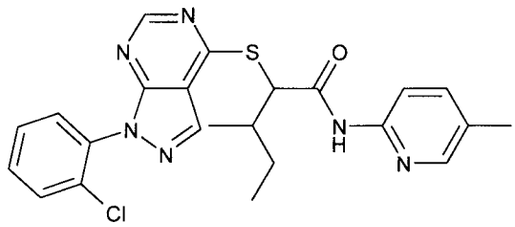


Método 2 a partir de los Productos Intermedios A21 y B12

^{1}H NMR (300 MHz, $CDCl_3$) δ 10,06 (br d, 1H), 8,85 (s, 1H), 8,32 (d, 1H), 8,26 (s, 1H), 7,62 (m, 1H), 7,49 (m, 3H), 7,06 (d, 1H), 4,81 (d, 0,57H), 4,73 (d, 0,43H), 2,40 (m, 1H),

1,90 (m, 0,43H), 1,63 (m, 0,57H), 1,47 (m, 1H), 1,22 (m, 3H), 0,99 (m, 3H), HRMS: calculado para (M+H$^+$) $C_{20}H_{20}{}^{35}ClN_6O_2S$: 443,1057. Encontrado: 443,1057.

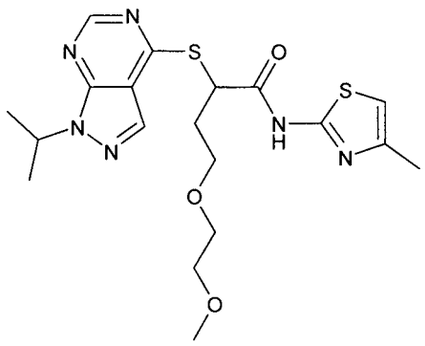
Ejemplo 56: 2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]tio}-3-metil-*N*-(5-metilpiridin-2-il)pentanamida



Método 2 a partir de los Productos Intermedios A20 y B12

^{1}H NMR (300 MHz, $CDCl_3$) δ 9,33 (br d, 1H), 8,85 (d, 1H), 8,30 (d, 1H), 8,11 (d, 1H), 8,05 (s, 1H), 7,62 (m, 1H), 7,48 (m, 4H), 4,92 (d, 0,69H), 4,82 (d, 0,31H), 2,40 (m, 1H), 2,26 (s, 3H), 1,88 (m, 0,39H), 1,68 (m, 0,61H), 1,48 (m, 1H), 1,22 (m, 3H), 0,99 (m, 3H), HRMS: calculado para (M+H$^+$) $C_{23}H_{24}{}^{35}ClN_6OS$: 467,1420. Encontrado: 467,1420.

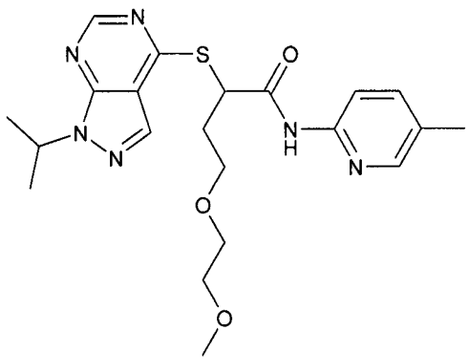
Ejemplo 57: 2-[(1-Isopropil-1*H*-pirazolo[3,4-*d*]pirimidin-4-il)tio]-4-(2-metoxietoxi)-*N*-(4-metil-1,3-tiazol-2-il)butanamida



Método 2 a partir de los Productos Intermedios A16 y B14

^{1}H NMR (400 MHz, $CDCl_3$) δ 8,82 (s, 1H), 7,98 (s, 1H), 6,43 (d, 1H), 5,14 (m, 1H), 5,03 (t, 1H), 3,68 (m, 1H), 3,60 (m, 1H), 3,51 (m, 2H), 3,42 (m, 2H), 3,24 (s, 3H), 2,50 (m, 1H), 2,23 (s, 3H), 1,99 (m, 1H), 1,51 (t, 6H), HRMS: calculado para (M+H$^+$) $C_{19}H_{27}N_6O_3S_2$: 451,1586. Encontrado: 451,1598.

Ejemplo 58: 2-[(1-Isopropil-1*H*-pirazolo[3,4-*d*]pirimidin-4-il)tio]-4-(2-metoxietoxi)-*N*-(5-metilpiridin-2-il)butanamida

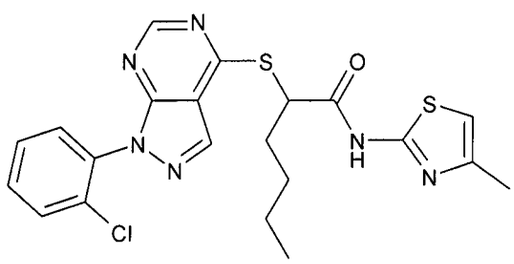


Método 2 a partir de los Productos Intermedios A17 y B14

^{1}H NMR (400 MHz, $CDCl_3$) δ 10,01 (br s, 1H), 8,83 (s, 1H), 8,02 (m, 3H), 7,44 (dd, 1H), 5,15 (m, 1H), 5,07 (t, 1H), 3,69 (m, 1H), 3,64 (m, 1H), 3,54 (m, 2H), 3,45 (m, 2H), 3,28 (s, 3H), 2,50 (m, 1H), 2,22 (s, 3H), 2,15 (m, 1H), 1,53 (t, 6H), HRMS: calculado para ($M+H^+$) $C_{21}H_{29}{}^{35}ClN_6O_3S$: 445,2021. Encontrado: 445,2016.

Método 3

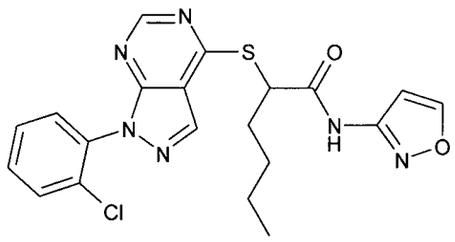
Ejemplo 59: 2-{[1-(2-clorofenil)-1*h*-pirazolo[3,4-*d*]pirimidin-4-il]tio}-*n*-(4-metil-1,3-tiazol-2-il)hexanamida



Una solución agitada de ácido 2-bromo-hexanoico (2,00 g, 10,25 mmol) en cloruro de tionilo (1,59 g, 13,36 mmol) se sometió a reflujo durante 30 minutos. La mezcla de reacción se concentró al vacío para eliminar el exceso de cloruro de tionilo. El cloruro de ácido recientemente preparado (117 mg, 0,548 mmol) se agregó lentamente a una solución agitada de 2-amino-4-metiltiazol (62,1 mg, 0,544 mmol) y DIPEA (67,2 mg, 0,520 mmol) en DCM (2 mL). La mezcla de reacción se mantuvo a temperatura ambiente durante 25 minutos antes de que la misma se agregara a una solución de 1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidina-4-tiol (130 mg, 0,495 mmol) y carbonato de potasio anhidro (102,6 mg, 0,742 mmol) en DMF (3 mL). La mezcla de reacción se mantuvo a temperatura ambiente durante 3 hrs. Se agregaron agua y EtOAc y las dos fases se separaron. La fase acuosa se extrajo con EtOAc. Los extractos orgánicos se combinaron y se lavaron tres

veces con agua, se secaron sobre $MgSO_4$ y se concentraron al vacío. El residuo se purificó con cromatografía en columna (gel de sílice, eluyendo con DCM/EtOAc:5/1) para proporcionar el compuesto del título (99 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ 10,92 (s, 1H), 8,95 (s, 1H), 8,29 (s, 1H), 7,63 (m, 1H), 7,50 (m, 3H), 6,51 (s, 1H), 4,80 (t, 1H), 2,30 (m, 4H), 1,97 (m, 1H), 1,57 (m, 2H), 1,42 (m, 2H), 0,94 (t, 3H), HRMS: calculado para ($M+H^+$) $C_{21}H_{22}{}^{35}ClN_6OS_2$: 473,0985. Encontrado: 473,1027.

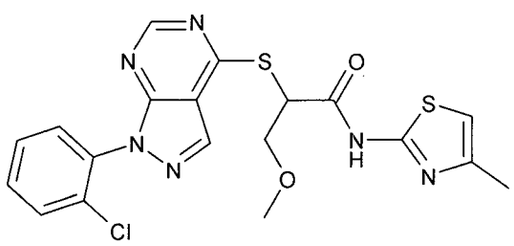
Ejemplo 60: 2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]tio}-*N*-isoxazol-3-ilhexanamida



Método 3 a partir de ácido 2-bromo-hexanoico, 3-aminoisoxazol y el Producto Intermedio B12

^{1}H NMR (300 MHz, $CDCl_3$) δ 10,44 (br s, 1H), 8,89 (s, 1H), 8,30 (s, 1H), 8,26 (d, 1H), 7,63 (m, 1H), 7,50 (m, 3H), 7,05 (d, 1H), 4,73 (t, 1H), 2,26 (m, 1H), 1,93 (m, 1H), 1,55 (m, 2H), 1,42 (m, 2H), 0,95 (t, 3H), HRMS: calculado para ($M+H^+$) $C_{20}H_{20}{}^{35}ClN_6O_2S$: 443,1057. Encontrado: 443,1081.

Ejemplo 61: 2-{[1-(2-Clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]tio}-4-(2-metoxietoxi)-*N*--(4-metil-1,3-tiazol-2-il) butanamida

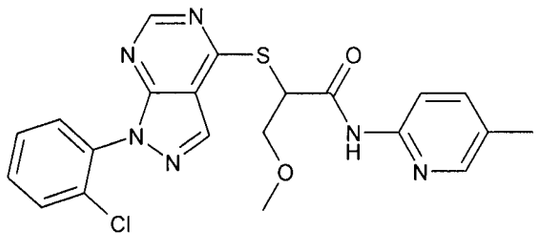


Método 3 a partir de ácido 2-cloro-3-metoxi-propiónico, 2-amino-4-metiltiazol y el Producto Intermedio B12

^{1}H NMR (300 MHz, $CDCl_3$) δ 8,87 (s, 1H), 8,31 (s, 1H), 7,63 (m, 1H), 7,50 (m, 3H), 6,53 (s, 1H), 5,24 (t, 1H), 4,05 (d, 2H), 3,50 (s, 3H), 2,31 (s, 3H), HRMS: calculado para ($M+H^+$) $C_{19}H_{18}{}^{35}ClN_6O_2S_2$: 461,0621. Encontrado: 461,0631.

Ejemplo 62: 2-{[1-(2-Clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]tio}-3-metoxi-*N*-(5-

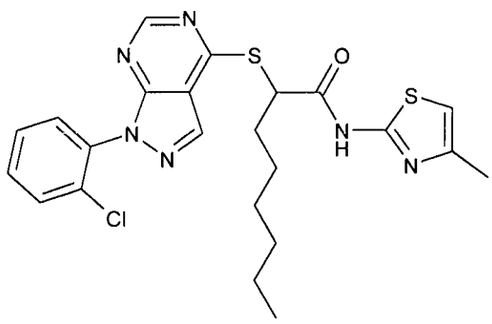
metilpiridin-2-il)propanamida



Método 3 a partir de ácido 2-cloro-3-metoxi-propiónico, 2-amino-5-picolina y el Producto Intermedio B12

^{1}H NMR (300 MHz, $CDCl_3$) δ 9,54 (br s, 1H), 8,87 (s, 1H), 8,31 (s, 1H), 8,08 (m, 2H), 7,63 (m, 1H), 7,49 (m, 4H), 5,22 (t, 1H), 4,04 (m, 2H), 3,50 (s, 3H), 2,27 (s, 3H), HRMS: calculado para ($M+H^+$) $C_{21}H_{20}{}^{35}ClN_6O_2S$: 455,1057. Encontrado: 455,1085.

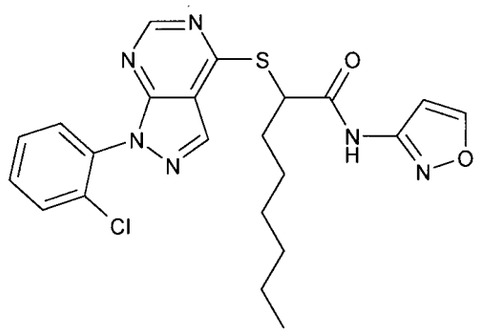
Ejemplo 63: 2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]tio}-*N*-(4-metil-1,3-tiazol-2-il)octanamida



Método 3 a partir de ácido 2-bromo-octanoico, 2-amino-4-metiltiazol y el Producto Intermedio B12

^{1}H NMR (300 MHz, $CDCl_3$) δ 10,90 (br s, 1H), 8,94 (s, 1H), 8,29 (s, 1H), 7,63 (m, 1H), 7,50 (m, 3H), 6,51 (s, 1H), 4,80 (t, 1H), 2,30 (m, 4H), 1,95 (m, 1H), 1,59 (m, 2H), 1,32 (m, 6H), 0,88 (t, 3H), HRMS: calculado para ($M+H^+$) $C_{23}H_{26}{}^{35}ClN_6OS_2$: 501,1298. Encontrado: 501,1298.

Ejemplo 64: 2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]tio}-*N*-isoxazol-3-iloctanamida



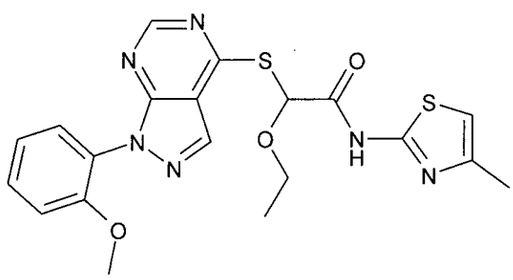
Método 3 a partir de ácido 2-bromo-octanoico, 3-aminoisoxazol y el Producto Intermedio B12

^{1}H NMR (300 MHz, $CDCl_3$) δ 10,47 (br s, 1H), 8,88 (s, 1H), 8,30 (s, 1H), 8,26 (d, 1H), 7,62 (m, 1H), 7,48 (m, 3H), 7,05 (d, 1H), 4,74 (t, 1H), 2,27 (m, 1H), 1,93 (m, 1H), 1,55 (m, 2H), 1,35 (m, 6H), 0,88 (t, 3H), HRMS: calculado para ($M+H^+$) $C_{22}H_{24}{}^{35}ClN_6O_2S$: 471,1370. Encontrado: 471,1370.

No hay ejemplos 65-70.

MÉTODO 4

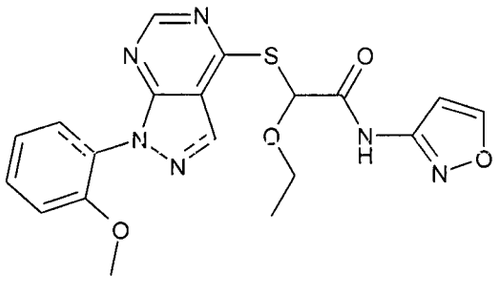
Ejemplo 71: 2-Etoxi-2-{[1-(2-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]tio}-*N*-(4-metil-1,3-tiazol-2-il)acetamida



Se agregó hidruro de sodio (95%, 3,7 mg, 0,15 mmol) a una solución agitada de 2-amino-4-metiltiazol (17,6 mg, 0,154 mmol) en THF anhidro (4 mL). La mezcla de reacción se mantuvo a temperatura ambiente durante 5 minutos antes de agregarse etoxi{[1-(2-metoxifenil)-1H-pirazolo[3,4-d]pirimidin-4-il]tio}acetato de etilo (50 mg, 0,129 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1 h. Se agregaron agua y DCM y las dos fases se separaron. La fase orgánica se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se purificó con cromatografía en columna (gel de sílice, eluyendo con un gradiente que consiste en 40-100% EtOAc en heptano) para proporcionar el compuesto del título como un aceite incoloro (1,1 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ 10,03 (br s, 1H), 8,74 (s, 1H), 8,26 (s, 1H), 7,47 (m, 2H), 7,12 (m, 2H), 6,91 (s, 1H), 6,58 (s, 1H), 4,02 (m,

1H), 3,81 (m, 4H), 2,38 (s, 3H), 1,34 (t, 3H), HRMS: calculado para (M+H$^+$) $C_{20}H_{21}N_6O_3S_2$: 457,1116. Encontrado: 457,1116.

Ejemplo 72: 2-Etoxi-*N*-isoxazol-3-il-2-{[1-(2-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]tio}acetamida



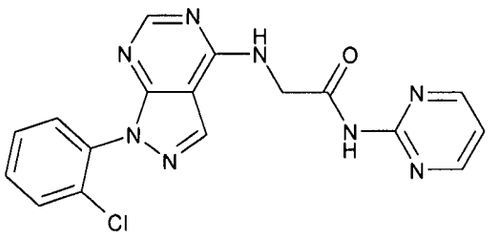
Método 4 a partir de 3-aminoisoxazol y el Producto Intermedio A24

^{1}H NMR (300 MHz, $CDCl_3$) δ 9,51 (br s, 1H), 8,75 (s, 1H), 8,33 (s, 1H), 8,27 (s, 1H), 7,47 (m, 2H), 7,13 (t, 3H), 6,82 (s, 1H), 4,03 (m, 1H), 3,82 (m, 5H), 1,35 (t, 3H), HRMS: calculado para (M+H$^+$) $C_{19}H_{19}{}^{35}ClN_6O_4S$: 427,1188. Encontrado: 427,1181.

No hay ejemplo 73.

Método 5

Ejemplo de referencia 74: *N*-2-[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]-*N*-(5-metil-1,3-tiazol-2-il)glicinamida

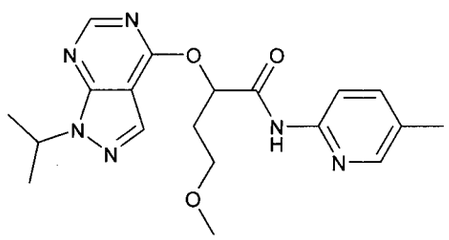


Se agregó hidruro de sodio (95%, 19,08 mg, 0,76 mmol) a una solución agitada de 2-aminopirimidina (62,9 mg, 0,66 mmol) en THF anhidro (3 mL). La mezcla de reacción se mantuvo a temperatura ambiente durante 3 hrs antes de que la misma se agregara a una solución de *N*-[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]glicinato de metilo (200 mg, 0,63 mmol) en THF anhidro (3 mL). La mezcla de reacción se agitó a temperatura ambiente durante 1 h. Se agregaron agua y EtOAc y las dos fases se separaron. La fase acuosa se extrajo con EtOAc. Los extractos orgánicos se combinaron y se concentraron al vacío. El residuo se trituró secuencialmente con DCM, MeOH y EtOAc. El sólido remanente se disolvió en DMSO caliente y se precipitó mediante la adición de agua para

proporcionar el compuesto del título como un sólido (37 mg), ^{1}H NMR (300 MHz, DMSO) δ 10,80 (br s, 1H), 8,87 (br t, 1H), 8,67 (d, 2H), 8,49 (s, 1H), 8,22 (s, 1H), 7,70 (m, 1H), 7,56 (m, 3H), 7,18 (t, 1H), 4,59 (d, 2H), HRMS: calculado para (M+H$^+$) $C_{17}H_{14}{}^{35}ClN_8O$: 381,0979. Encontrado: 381,0980.

No hay ejemplo 75.

Ejemplo 76: 2-[(1-isopropil-1*H*-pirazolo[3,4-*d*]pirimidin-4-il)oxi]-4-metoxi-*N*-(5-metilpiridin-2-il)butanamida

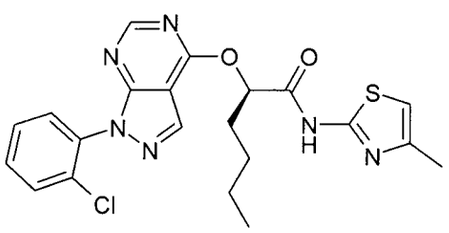


Método 1 a partir de los Productos Intermedios A12 y B9

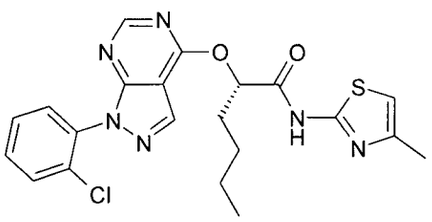
^{1}H NMR (400 MHz, $CDCl_3$) δ 8,92 (br s, 1H), 8,46 (s, 1H), 8,09 (s, 1H), 8,07 (s, 1H), 7,46 (dd, 1H), 5,87 (dd, 1H), 5,13 (m, 1H), 3,56 (t, 2H), 3,25 (s, 3H), 2,35 (m, 2H), 2,22 (s, 3H), 1,52 (dd, 6H), HRMS: calculado para (M+H$^+$) $C_{19}H_{25}N_6O_3$: 385,1988. Encontrado: 385,2007.

No hay ejemplos con números de Ejemplos 77 a 80.

Ejemplos 81: (R)-2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]tio}-*N*-(4-metil-1,3-tiazol-2-il)hexanamida



y Ejemplo 82: (S)-2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]tio}-*N*-(4-metil-1,3-tiazol-2-il)hexanamida



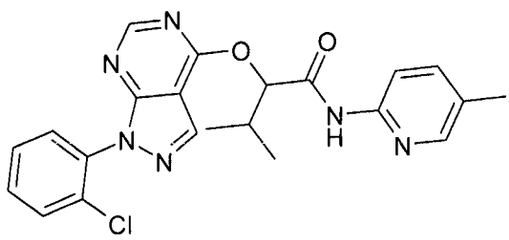
Los enantiómeros de 2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]tio}-*N*-(4-metil-

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1,3-tiazol-2-il)hexanamida **Ejemplo 41** (40 mg) se separaron mediante HPLC preparativa quiral: Columna Chiralpak AD (250x20 mm, 5 µm), eluyendo con heptano/etanol 85/5. Esto proporcionó (R)-2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]tio}-*N*-(4-metil-1,3-tiazol-2-il)hexanamida (17 mg, >99% ee). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9,44 (br s, 1H), 8,58 (s, 1H), 8,38 (s, 1H), 7,62 (m, 1H), 7,51 (m, 3H), 6,56 (s, 1H), 5,95 (t, 1H), 2,33 (s, 3H), 2,17 (m, 2H), 1,53 (m, 2H), 1,41 (m, 2H), 0,93 (t, 3H)

y (S)-2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]tio}-*N*-(4-metil-1,3-tiazol-2-il)hexanamida (17 mg, >99% ee). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9,44 (br s, 1H), 8,58 (s, 1H), 8,38 (s, 1H), 7,62 (m, 1H), 7,51 (m, 3H), 6,56 (s, 1H), 5,95 (t, 1H), 2,33 (s, 3H), 2,17 (m, 2H), 1,53 (m, 2H), 1,41 (m, 2H), 0,93 (t, 3H)

Ejemplo 83: 2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-metil-*N*-(5-metilpiridin-2-il)butanamida



Una solución de LHMDS (0,999 mL, 1,00 mmol) en THF anhidro (15 mL) se agregó gota a gota a una solución agitada de 2-hidroxi-3-metil-*N*-(5-metilpiridin-2-il)butanamida racémica **C1** (208 mg, 1,00 mmol) en THF anhidro (15 mL) durante un período de 3 minutos bajo nitrógeno. La suspensión resultante se agitó a temperatura ambiente durante 10 minutos, luego se agregó gota a gota una solución de 4-cloro-1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidina **B1** (265 mg, 1,00 mmol) en THF anhidro (3 mL) durante 1 minuto y la mezcla resultante se calentó hasta alcanzar 50°C durante 3 horas. La mezcla se dejó enfriar hasta alcanzar la temperatura ambiente y luego se diluyó con EtOAc (50 mL) y se lavó secuencialmente con agua (2 x 25 mL) y salmuera saturada (25 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar el producto bruto. El material se purificó mediante cromatografía instantánea en sílice, gradiente de elución 30 a 50% EtOAc en DCM. Las fracciones puras se evaporaron hasta secarse para proporcionar 2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-metil-N-(5-

metilpiridin-2-il)butanamida (320 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8,58 (1H, s), 8,40 (1H, s), 8,38 (1H, s), 8,16 (1H, d), 8,08-8,07 (1H, m), 7,63-7,60 (1H, m), 7,54-7,51 (2H, m), 7,50-7,44 (2H, m), 5,71 (1H, d), 2,59-2,55 (1H, m), 2,28 (3H, s), 1,21 (3H, d), 1,15 (3H, d), m/z (ESI+) (M+H)+ = 437; HPLC t_R = 2,56 min.

Los siguientes Ejemplos (**84-96**) se prepararon en una forma análoga a partir del derivado de cloro y alcohol apropiado.

Ejemplo 84: (2S)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-metil-*N*-(5-metilpiridin-2-il)butanamida

Ejemplo 85: (2R)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-metil-*N*-(5-metilpiridin-2-il)butanamida

Ejemplo 86: (2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-metil-*N*-(5-metilpiridin-2-il)butanamida

Ejemplo 87: (2S)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-metoxi-*N*-(5-metilpiridin-2-il)propanamida

Ejemplo 88: (2R)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-metoxi-*N*-(5-metilpiridin-2-il)propanamida

Ejemplo 89: (2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-metoxi-*N*-(5-metilpiridin-2-il)propanamida

Ejemplo 90: (2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-metoxi-*N*-(5-metilpirazin-2-il)propanamida

Ejemplo 91: (2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-isopropoxi-*N*-(5-metilpiridin-2-il)propanamida

Ejemplo 92: (2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-isopropoxi-*N*-(5-metilpirazin-2-il)propanamida

Ejemplo 93: (2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-isopropoxi-*N*-(3-metil-1,2,4-tiadiazol-5-il)propanamida

Ejemplo 94: (2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-metil-*N*-(5-metilpirazin-2-il)butanamida

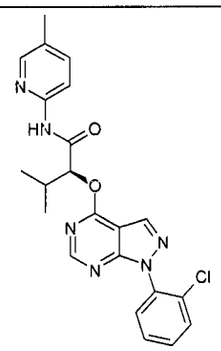
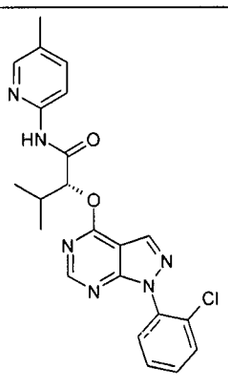
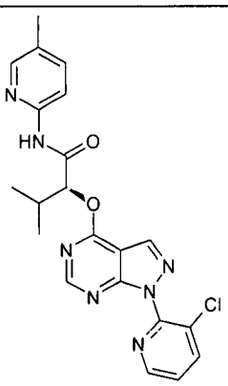
Ejemplo 95: (2S)-2-(1-(2-cloro-4-fluorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-metoxi-*N*-(5-metilpirazin-2-il)propanamida

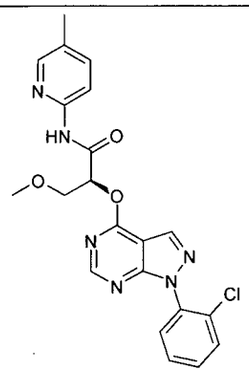
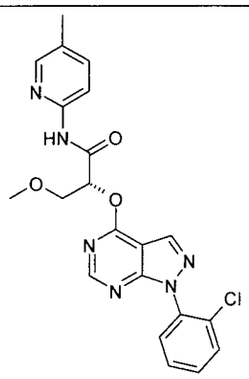
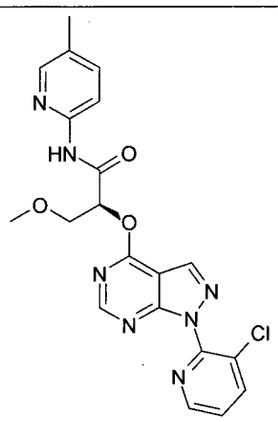
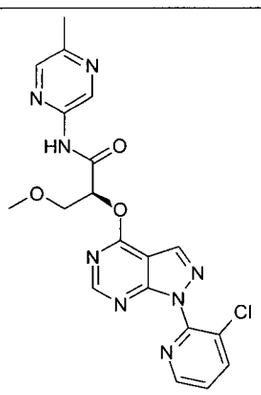
Ejemplo 96: (2S)-2-(1-(2-cloro-4-fluorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-metoxi-*N*-(5-metilpiridin-2-il)propanamida

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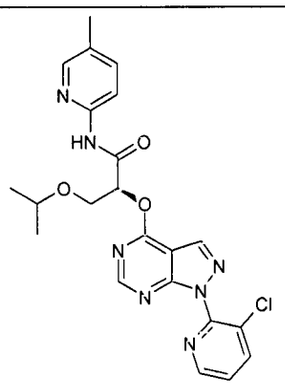
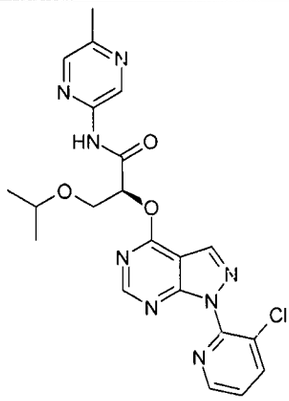
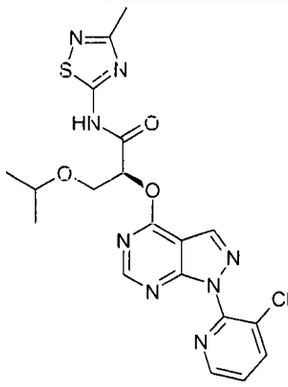
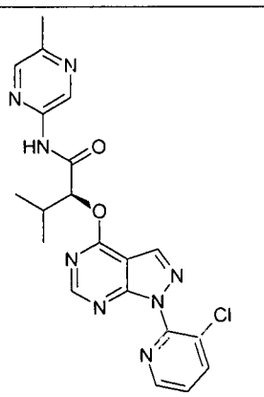
Ejemplo 97: (2S)-2-(1-(2-cianofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-metoxi-*N*-(5-metilpiridin-2-il)propanamida

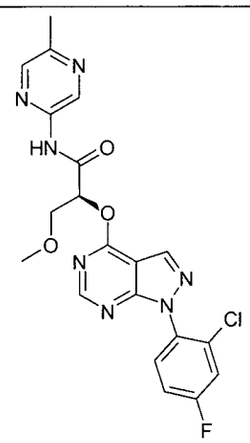
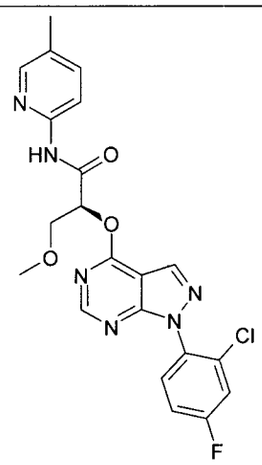
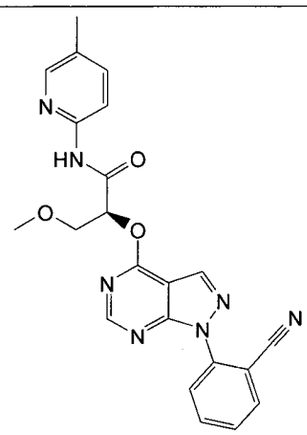
Ejemplo 97a: (2S)-2-[1-(2-cianofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-metilpiridin-2-il)-3-propan-2-iloxipropanamida

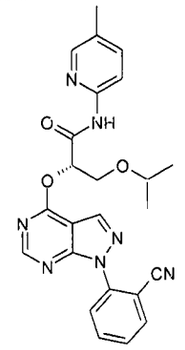
	ESTRUCTURA	M/Z	Datos ^{1}H NMR (400 MHz)
84		ESI+ (M+H)+ = 437; HPLC t_R = 2,55 min	($CDCl_3$) δ 8,58 (1H, s), 8,40 (1H, s), 8,38 (1H, s), 8,16 (1H, d), 8,08-8,07 (1H, m), 7,63-7,60 (1H, m), 7,54-7,51 (2H, m), 7,50-7,44 (2H, m), 5,71 (1H, d), 2,59-2,55 (1H, m), 2,28 (3H, s), 1,21 (3H, d), 1,15 (3H, d)
85		ESI+ (M+H)+ = 437; HPLC t_R = 2,60 min	($CDCl_3$) δ 8,58 (1H, s), 8,40 (1H, s), 8,38 (1H, s), 8,16 (1H, d), 8,08-8,07 (1H, m), 7,63-7,60 (1H, m), 7,54-7,51 (2H, m), 7,50-7,44 (2H, m), 5,71 (1H, d), 2,59-2,55 (1H, m), 2,28 (3H, s), 1,21 (3H, d), 1,15 (3H, d)
86		ESI+ (M+H)+ = 438; HPLC t_R = 2,11 min	(DMSO-d_6) δ 10,83 (1H, s), 8,71 (1H, s), 8,69 (1H, dd), 8,55 (1H, s), 8,37 (1H, dd), 8,19 (1H, d), 7,92 (1H, d), 7,76 (1H, dd), 7,60 (1H, dd), 5,57 (1H, d), 2,49-2,40 (1H, m), 2,25 (3H, s), 1,13 (6H, d)

87		ESI+ (M+H)+ = 439; HPLC t_R = 2,21 min	(DMSO-d_6) δ 10,85 (1H, s), 8,62 (1H, s), 8,54 (1H, s), 8,18 (1H, d), 7,88 (1H, d), 7,76 (1H, dd), 7,65-7,56 (4H, m), 5,95-5,94 (1H, m), 4,06-4,01 (1H, m), 3,94-3,90 (1H, m), 3,40 (3H, s), 2,24 (3H, s)
88		ESI+ (M+H)+ = 439; HPLC t_R = 2,20 min	(DMSO-d_6) δ 10,85 (1H,s), 8,62 (1H, s), 8,54 (1H, s), 8,18 (1H, d), 7,88 (1H, d), 7,76 (1H, dd), 7,65-7,56 (4H, m), 5,95-5,94 (1H, m), 4,06-4,01 (1H, m), 3,94-3,90 (1H, m), 3,40 (3H, s), 2,24 (3H, s)
89		ESI+ (M+H)+ = 440; HPLC t_R = 1,77 min	(DMSO-d_6) δ 10,86 (1H, s), 8,67 (1H, s), 8,66 (1H, s), 8,56 (1H, s), 8,33 (1H, dd), 8,17 (1H, d), 7,88 (1H, d), 7,75 (1H, dd), 7,58 (1H, d), 5,95-5,94 (1H, m), 4,07-4,00 (1H, m), 3,94-3,91 (1H, m), 3,40 (3H, s), 2,24 (3H, s)
90		ESI+ (M+H)+ = 441; HPLC t_R = 1,59 min	(DMSO-d_6) δ 11,18 (1H, s), 9,10 (1H, d), 8,68 (1H, s), 8,66 (1H, dd), 8,57 (1H, s), 8,32 (1H, dd), 8,31 (1H, d), 7,74 (1H, dd), 5,99-5,96 (1H, m), 4,10-3,93 (2H, m), 3,41 (3H, s), 2,44 (3H, s)

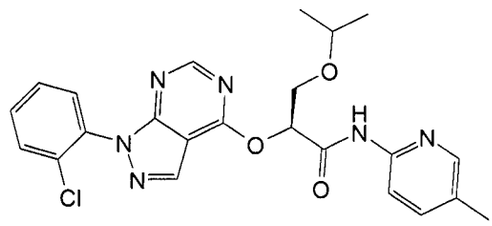
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91		ESI+ (M+H)+ = 468; HPLC t_R = 2,02 min	($CDCl_3$) δ 8,69 (1H, s), 8,63 (1H, s), 8,62 (1H, dd), 8,46 (1H, s), 8,13 (1H, d), 8,10-8,09 (1H, m), 8,00 (1H, dd), 7,52 (1H, dd), 7,47 (1H, dd), 6,02 (1H, t), 4,08 (2H, d), 3,78-3,65 (1H, m), 2,29 (3H, s), 1,18 (6H, m)
92		ESI+ (M+H)+ = 469; HPLC t_R = 1,82 min	($CDCl_3$) δ 1,18 - 1,21 (6H, m), 2,54 (3H, s), 3,70 - 3,76 (1H, m), 4,12 (2H, d), 6,04 (1H, t), 7,46 (1H, dd), 8,00 (1H, dd), 8,12 (1H, d), 8,46 (1H, s), 8,62 (1H, dd), 8,64 (1H, s), 8,71 (1H, s), 9,43 (1H, d)
93		ESI- (M+H)- = 473; HPLC t_R = 2,08 min	($CDCl_3$) δ 1,17 - 1,21 (6H, m), 2,55 (3H, s), 3,65 - 3,76 (1H, m), 4,11 (2H, d), 6,14 (1H, t), 7,48 (1H, dd), 8,02 (1H, dd), 8,44 (1H, s), 8,61 - 8,63 (1H, m), 8,62 (1H, s), 9,96 (1H, s)
94		ESI+ (M+H)+ = 439; HPLC t_R = 1,95 min	($CDCl_3$) δ 1,15 - 1,17 (3H, d), 1,22 (3H, d), 2,53 (3H, s), 2,57 - 2,61 (1H, m), 5,75 (1H, d), 7,46 - 7,49 (1H, m), 8,00 - 8,03 (1H, m), 8,09 (1H, d), 8,37 (1H, s), 8,45 (1H, s), 8,61 - 8,62 (1H, m), 8,63 (1H, s), 9,46 (1H, d)

95		ESI+ (M+H)+ = 458; HPLC t_R = 2,16 min	($CDCl_3$) δ 2,54 (3H, s), 3,48 (3H, s), 4,03 - 4,07 (1H, m), 4,10 - 4,14 (1H, m), 6,12 (1H, t), 7,16 - 7,21 (1H, m), 7,35 - 7,38 (1H, m), 7,50 - 7,54 (1H, m), 8,12 (1H, d), 8,43 (1H, s), 8,59 (1H, s), 8,63 (1H, s), 9,45 (1H, d)
96		ESI+ (M+H)+ = 457; HPLC t_R = 2,27 min	($CDCl_3$) δ 2,29 (3H, s), 3,46 (3H, s), 4,01 - 4,05 (1H, m), 4,09 - 4,13 (1H, m), 6,09 (1H, t), 7,16 - 7,20 (1H, m), 7,35 - 7,38 (1H, m), 7,50 - 7,54 (2H, m), 8,10 (1H, d), 8,14 (1H, d), 8,42 (1H, d), 8,58 (1H, s), 8,73 (1H, s)
97		ESI+ $(M+H)^+$ = 430; HPLC t_R = 1,94 min	($DMSO-d_6$) δ 2,24 (3H, s), 3,40 (3H, s), 3,90 - 3,96 (1H, m), 4,01 - 4,09 (1H, m), 5,93 - 5,98 (1H, m), 7,56 - 7,60 (1H, m), 7,71 - 7,77 (1H, m), 7,85 - 7,91 (1H, m), 7,94 - 7,98 (2H, m), 8,12 (1H, d), 8,17 (1H, s), 8,64 (1H, s), 8,64 (1H, s), 10,87 (1H, s),

97a		(ESI+) (M+H)+ = 458; HPLC t_R = 2,29 min.	($CDCl_3$) δ 1,18 (3H, d), 1,20 (3H, d), 2,29 (3H, s), 3,66 - 3,78 (1H, m), 4,09 (2H, d), 6,02 (1H, t), 7,52 (1H, dd), 7,56 (1H, ddd), 7,79 (1H, ddd), 7,89 (1H, dd), 7,92 (1H, dd), 8,09 - 8,11 (1H, m), 8,12 (1H, d), 8,48 (1H, s), 8,63 (1H, s), 8,71 (1H, s)

Ejemplo 98: (2S)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-isopropoxi-*N*-(5-metilpiridin-2-il)propanamida

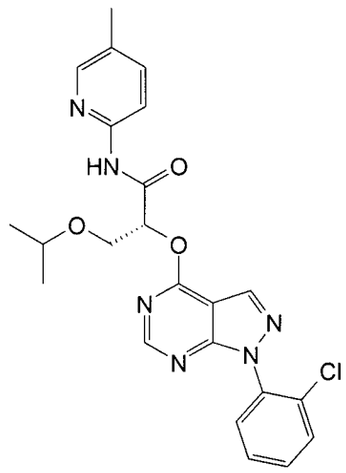


Se agregó hexafluorofosfato de O-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (333 mg, 0,88 mmol) a ácido (2S)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-isopropoxipropanoico **D2** (300 mg, 0,80 mmol), 5-metilpiridin-2-amina (95 mg, 0,88 mmol) y *N*-etildiisopropilamina (0,153 mL, 0,88 mmol) en DCM (15 mL) a temperatura ambiente bajo nitrógeno. La solución resultante se agitó a temperatura ambiente durante 24 horas. La mezcla de reacción se diluyó con DCM (25 mL) y se lavó con salmuera saturada (20 mL). La capa acuosa se extrajo nuevamente con DCM (30 mL). Los elementos orgánicos combinados se evaporaron para proporcionar el producto bruto. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 20 a 50% EtOAc en isohexano. Las fracciones puras se evaporaron hasta secarse para proporcionar (2S)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-isopropoxi-*N*-(5-metilpiridin-2-il)propanamida (175 mg, 47,1 %), 10% ee. Adicionalmente se purificaron 143 mg de este material mediante HPLC preparativa quiral en Chiralcel OJ (50 mm x 20 µm), eluyente isohexano/EtOH/MeOH 70/15/15 para proporcionar (2S)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-isopropoxi-*N*-(5-metilpiridin-2-

il)propanamida (56 mg, >99% ee que eluyó después del enantiómero R).

^{1}H NMR (400 MHz, $CDCl_3$) 1,17 - 1,20 (6H, m), 2,29 (3H, s), 3,72 (1H, quin), 4,09 (2H, d), 6,02 (1H, t), 7,44 - 7,55 (4H, m), 7,61 - 7,63 (1H, m), 8,09 - 8,10 (1H, m), 8,13 (1H, d), 8,42 (1H, s), 8,59 (1H, s), 8,69 (1H, s); m/z (ESI)+ (M+H)+ = 467; HPLC t_R = 2,63 min

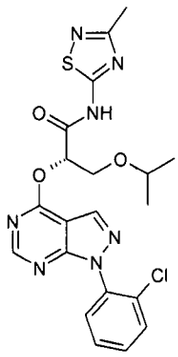
Ejemplo 99 : (2R)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-isopropoxi-*N*-(5-metilpiridin-2-il)propanamida



Se purificaron 143 mg de (2S)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-isopropoxi-*N*-(5-metilpiridin-2-il)propanamida (10%ee) obtenidos en la preparación del **Ejemplo 98** mediante HPLC preparativa quiral en Chiralcel OJ (50 mm x 20 μm), eluyente isohexano/EtOH/MeOH 70/15/15 para proporcionar (2R)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-isopropoxi-*N*-(5-metilpiridin-2-il)propanamida (60 mg, >99% ee que eluyó antes del enantiómero S).

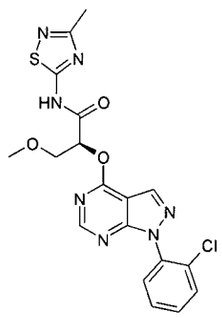
^{1}H NMR (400 MHz, $CDCl_3$) 1,17 - 1,20 (6H, m), 2,29 (3H, s), 3,72 (1H, quin), 4,09 (2H, d), 6,02 (1H, t), 7,44 - 7,55 (4H, m), 7,61 - 7,63 (1H, m), 8,09 - 8,10 (1H, m), 8,13 (1H, d), 8,42 (1H, s), 8,59 (1H, s), 8,69 (1H, s); m/z (ESI)+ (M+H)+ = 467; HPLC t_R = 2,64 min

Ejemplo 100: (2S)-2-[1-(2-Clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(3-metil-1,2,4-tiadiazol-5-il)-3-propan-2-iloxipropanamida



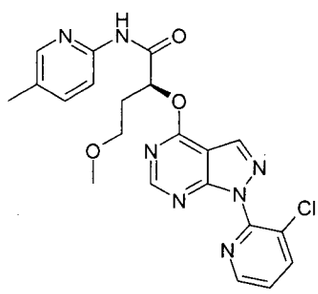
Una solución de bis(trimetilsilil)amida de litio (0,82 mL, 0,82 mmol) se agregó gota a gota a una solución agitada de (S)-2-hidroxi-3-isopropoxi-N-(3-metil-1,2,4-tiadiazol-5-il)propanamida (**Producto Intermedio C9**) (200 mg, 0,82 mmol) en THF anhidro (5 mL) durante un período de 3 minutos bajo nitrógeno. La suspensión resultante se agitó a temperatura ambiente durante 10 minutos y luego se agregó gota a gota una solución de 4-cloro-1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio B1**) en THF seco (1,5 mL) durante 1 minuto y la reacción se calentó hasta alcanzar 50°C durante 20 horas. La mezcla se enfrió, se diluyó con EtOAc (50 mL), se lavó con agua (10 mL) y salmuera (10 mL). Los extractos acuosos combinados se acidificaron con ácido cítrico 1M y se extrajeron con EtOAc (2 × 20 mL), los extractos orgánicos combinados se secaron ($MgSO_4$) y se evaporaron. El residuo resultante se purificó mediante cromatografía instantánea en sílice, eluyendo con un gradiente creciente de 60 a 100% EtOAc en isohexano para proporcionar (2S)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(3-metil-1,2,4-tiadiazol-5-il)-3-propan-2-iloxipropanamida (300 mg, 78%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 1,18 (3H, d), 1,21 (3H, d), 2,55 (3H, s), 3,68 - 3,76 (1H, m), 4,10 (2H, d), 6,14 (1H, t), 7,45 - 7,57 (3H, m), 7,62 (1H, dd), 8,40 (1H, s), 8,57 (1H, s), 9,98 (1H, s). m/z (ESI-) (M-H)- = 472; HPLC t_R = 2,33 min.

Ejemplo 101: (2S)-2-(1-(2-Clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-metoxi-N-(3-metil-1,2,4-tiadiazol-5-il)propanamida



Una solución de bis(trimetilsilil)amida de litio (0,947 mL, 0,95 mmol) se agregó gota a gota a una solución agitada de (S)-2-hidroxi-3-metoxi-N-(3-metil-1,2,4-tiadiazol-5-il)propanamida (**Producto Intermedio E1**) (187 mg, 0,86 mmol) en THF anhidro (5 mL) durante un período de 3 minutos bajo nitrógeno. La suspensión resultante se agitó a temperatura ambiente durante 10 minutos y luego se agregó gota a gota una solución de 4-cloro-1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio B1**) (228 mg, 0,86 mmol) en THF seco (1,5 mL) durante 1 minuto y la reacción se calentó hasta alcanzar 50°C durante 16 horas. La reacción se enfrió, se diluyó con EtOAc (50 mL), se lavó con ácido cítrico 1M (25 mL) y salmuera (25 mL), se secó ($MgSO_4$) y se evaporó. El residuo se purificó mediante cromatografía instantánea en sílice, gradiente de elución 0 a 100% EtOAc en isohexano para proporcionar (2S)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-metoxi-N-(3-metil-1,2,4-tiadiazol-5-il)propanamida (44 mg, 11%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 2,48 (3H, s), 3,41 (3H, s), 4,01 (2H, ddd), 6,13 (1H, t), 7,38 - 7,48 (3H, m), 7,56 (1H, dd), 8,34 (1H, s), 8,51 (1H, s), 9,90 (1H, s). m/z (ESI+) (M+H)+ = 446,08; HPLC t_R = 2,02 min.

Ejemplo 102: (2S)-2-(1-(3-Cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-4-metoxi-N-(5-metilpiridin-2-il)butanamida

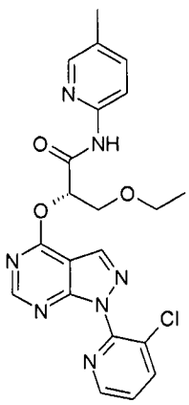


Se agregó 4-cloro-1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio B15**) (219 mg, 0,82 mmol) a metanosulfinato de sodio (75 mg, 0,73 mmol) e hidruro de sodio (38,0 mg, 0,95 mmol) en THF (5 mL) a 23°C bajo nitrógeno. La

suspensión resultante se agitó a temperatura ambiente durante 5 minutos. Se agregó gota a gota (S)-2-hidroxi-4-metoxi-N-(5-metilpiridin-2-il)butanamida (**Producto Intermedio F1**) (142 mg, 0,63 mmol) y la suspensión se agitó a temperatura ambiente durante unos 30 minutos adicionales. La mezcla se diluyó con EtOAc (50 mL) y se lavó secuencialmente con agua (2 × 25 mL) y salmuera saturada (25 mL). La capa orgánica se secó ($MgSO_4$) y se evaporó. El residuo se purificó mediante cromatografía instantánea en sílice, gradiente de elución 40 a 100% EtOAc en isohexano para proporcionar (2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-4-metoxi-N-(5-metilpiridin-2-il)butanamida (250 mg, 87%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2,29 (3H, s), 2,42 - 2,47 (2H, m), 3,33 (3H, s), 3,64 (2H t), 5,96 - 5,99 (1H, m), 7,45 - 7,48 (1H, m), 7,50 - 7,53 (1H, m), 7,99 - 8,02 (1H, m), 8,08 - 8,09 (1H, m), 8,12 (1H d), 8,43 (1H, s), 8,60 - 8,63 (3H, m); m/z (ESI+) $(M+H)^+$ = 454; HPLC t_R = 1,77 min.

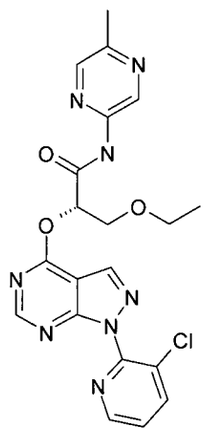
Ejemplo 103: (2S)-2-[1-(3-Cloropiridin-2-il)pirazolo[4,5-e]pirimidin-4-il]oxi-3-etoxi-N-(5-metilpiridin-2-il)propanamida



Una solución de bis(trimetilsilil)amida de litio (3,26 mL, 3,26 mmol) se agregó gota a gota a una solución agitada de (S)-3-etoxi-2-hidroxi-N-(5-metilpiridin-2-il)propanamida (Producto Intermedio G1) (730 mg, 3,26 mmol) en THF anhidro (15 mL) durante un período de 3 minutos bajo nitrógeno. La suspensión resultante se agitó a temperatura ambiente durante 10 minutos y luego se agregó gota a gota una solución de 4-cloro-1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidina (Producto Intermedio B15) (866 mg, 3,26 mmol) en THF seco (3 mL) durante 1 minuto y la reacción se calentó hasta alcanzar 50°C durante 3 horas. La mezcla de reacción se diluyó con EtOAc (50 mL) y se lavó secuencialmente con agua (2 × 25 mL) y salmuera saturada (25 mL). La capa orgánica se

secó ($MgSO_4$) y se evaporó. El residuo se purificó mediante cromatografía instantánea en sílice eluyendo con EtOAc para proporcionar (2S)-2-[1-(3-cloropiridin-2-il)pirazolo[4,5-e]pirimidin-4-il]oxi-3-etoxi-N-(5-metilpiridin-2-il)propanamida (930mg, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,20 (3H, t), 2,29 (3H, s), 3,59 - 3,67 (2H, m), 4,06 - 4,17 (2H, m), 6,06 - 6,08 (1H, m), 7,47 (1H, dd), 7,53 (1H, dd), 8,00 (1H, dd), 8,09 - 8,10 (1H, m), 8,13 (1H, d), 8,48 (1H, s), 8,62 (1H, dd), 8,63 (1H, s), 8,65 (1H, s); m/z (ESI+) (M+H)+ = 454,3; HPLC tR = 1,97 min.

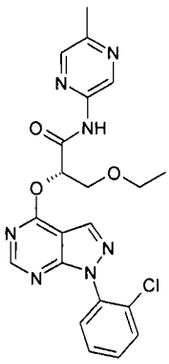
Ejemplo 104 : (2S)-2-[1-(3-Cloropiridin-2-il)pirazolo[4,5-e]pirimidin-4-il]oxi-3-etoxi-N-(5-metilpirazin-2-il)propanamida



Una solución de bis(trimetilsilil)amida de litio (1,40 mL, 1,40 mmol) se agregó gota a gota a una solución agitada de (S)-3-etoxi-2-hidroxi-N-(5-metilpirazin-2-il)propanamida (**Producto Intermedio H1**) (315 mg, 1,40 mmol) en THF (15 mL) durante un período de 3 minutos bajo nitrógeno. La suspensión resultante se agitó a temperatura ambiente durante 10 minutos y luego se agregó gota a gota una solución de 4-cloro-1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio B15**) (372 mg, 1,40 mmol) en THF anhidro (3 mL) durante 1 minuto y la reacción se calentó hasta alcanzar 50°C durante 3 horas. La mezcla de reacción se diluyó con EtOAc (50 mL) y se lavó secuencialmente con agua (2 × 25 mL) y salmuera saturada (25 mL). La capa orgánica se secó ($MgSO_4$) y se evaporó. El residuo se purificó mediante cromatografía instantánea en sílice eluyendo con EtOAc para proporcionar (2S)-2-[1-(3-cloropiridin-2-il)pirazolo[4,5-e]pirimidin-4-il]oxi-3-etoxi-N-(5-metilpirazin-2-il)propanamida (330 mg, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,24 (3H, t), 2,54 (3H, s), 3,60 - 3,68 (2H, m), 4,07 - 4,16 (2H, m), 6,09 (1H, t), 7,47 (1H, dd), 8,01 (1H, dd), 8,12 (1H, d), 8,47 (1H, s), 8,62 (1H, dd), 8,64 (1H, s), 8,66

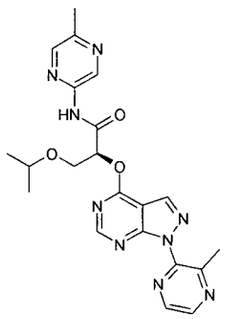
(1H, s), 9,44 (1H, d); m/z (ESI+) (M+H)+ = 455; HPLC t_R = 1,77 min.

Ejemplo 105: (2S)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-etoxi-N-(5-metilpirazin-2-il)propanamida



Una solución de bis(trimetilsilil)amida de litio (1,398 mL, 1,40 mmol) se agregó gota a gota a una solución agitada de (S)-3-etoxi-2-hidroxi-N-(5-metilpirazin-2-il)propanamida (**Producto Intermedio H1**) (315 mg, 1,40 mmol) en THF anhidro (15 mL) durante un período de 3 minutos bajo nitrógeno. La suspensión resultante se agitó a temperatura ambiente durante 10 minutos y luego se agregó gota a gota una solución de 4-cloro-1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio B1**) (371 mg, 1,40 mmol) en THF seco (3 mL) durante 1 minuto y la reacción se calentó hasta alcanzar 50°C durante 3 horas. La mezcla de reacción se diluyó con EtOAc (50 mL) y se lavó secuencialmente con agua (2 × 25 mL) y salmuera saturada (25 mL). La capa orgánica se secó ($MgSO_4$) y se evaporó. El residuo se purificó mediante cromatografía instantánea en sílice con EtOAc para proporcionar (2S)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-etoxi-N-(5-metilpirazin-2-il)propanamida (460mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,23 (3H, t), 2,54 (3H, s), 3,61 - 3,69 (2H, m), 4,07 - 4,16 (2H, m), 6,09 (1H, t), 7,47 - 7,55 (3H, m), 7,61 - 7,63 (1H, m), 8,12 (1H, d), 8,44 (1H, s), 8,60 (1H, s), 8,68 (1H, s), 9,45 (1H, d); m/z (ESI+) (M+H)+ = 454,3; HPLC t_R = 2,16 min.

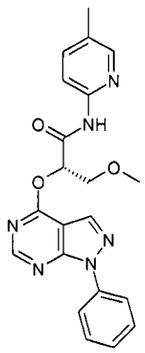
Ejemplo 106: (2S)-3-Isopropoxi-N-(5-metilpirazin-2-il)-2-(1-(3-metilpirazin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida



Se agregó hidruro de sodio (22,06 mg, 0,55 mmol) a (S)-2-hidroxi-3-isopropoxi-N-(5-metilpirazin-2-il)propanamida (**Producto Intermedio C8**) (110 mg, 0,46 mmol) en THF anhidro (5 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos y luego se agregó 4-cloro-1-(3-metilpirazin-2-il)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio I4**) (125 mg, 0,51 mmol) en THF (2mL). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 1 hora. Se agregó más hidruro de sodio (22,06 mg, 0,55 mmol) y la reacción se agitó durante otra hora a temperatura ambiente. La mezcla de reacción se neutralizó con ácido cítrico 1M y luego se diluyó con agua (20 mL) y EtOAc (50 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc (2 × 50 mL). Los elementos orgánicos combinados se lavaron con salmuera saturada (75 mL), se secaron ($MgSO_4$), se filtraron y se evaporaron. El residuo se purificó mediante cromatografía instantánea en sílice, gradiente de elución 50 a 100% EtOAc en isohexano para proporcionar (2S)-3-isopropoxi-N-(5-metilpirazin-2-il)-2-(1-(3-metilpirazin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida (98 mg, 47,4 %).

^{1}H NMR (400 MHz, $CDCl_3$) 1,20 (6H t), 2,54 (3H, s), 2,61 (3H, s), 3,71 - 3,77 (1H, m), 4,10 (2H d), 6,04 (1H t), 8,12 (1H, s), 8,45 (1H, s), 8,51 - 8,52 (1H, m), 8,64 - 8,66 (2H, m), 8,71 (1H, s), 9,43 (1H, s), m/z (ESI+) (M+H)+ = 450; HPLC t_R = 1,73 min.

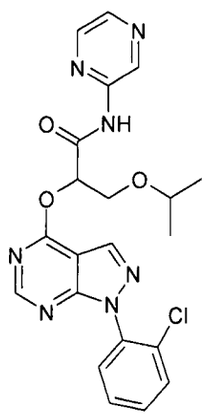
Ejemplo 107: (S)-3-Metoxi-N-(5-metilpiridin-2-il)-2-(1-fenil-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida



Se agregó paladio (10% sobre carbono) (25,5 mg, 0,24 mmol) a (2S)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-metoxi-N-(5-metilpiridin-2-il)propanamida (**Ejemplo 3**) (105 mg, 0,24 mmol) en metanol (2,5 mL) a temperatura ambiente bajo nitrógeno. Esto luego se purgó con hidrógeno y la solución resultante se agitó a temperatura ambiente durante 24 horas. La mezcla se filtró a través de celite y se evaporó. El residuo se purificó mediante cromatografía instantánea en sílice eluyendo con 0 a 100% EtOAc en isohexano para proporcionar (S)-3-metoxi-N-(5-metilpiridin-2-il)-2-(1-fenil-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida (20,0 mg, 20,7 %).

^{1}H NMR (400 MHz, DMSO) δ 2,24 (s, 3H), 3,39 (s, 3H), 3,88 - 4,07 (m, 2H), 5,92 - 5,98 (m, 1H), 7,38 - 7,44 (m, 1H), 7,56 - 7,62 (m, 3H), 7,85 - 7,90 (m, 1H), 8,15 - 8,20 (m, 3H), 8,62 (s, 1H), 8,66 (s, 1H), 10,84 (s, 1H); m/z (ESI+) $(M+H)^+$ = 405,35

Ejemplo 108: 2-[1-(2-Clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-isopropoxi-N-pirazin-2-il-propanamida



Se agregó hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (333 mg, 0,88 mmol) a ácido (2S)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-isopropoxipropanoico (**Producto Intermedio D2**) (300 mg, 0,80 mmol), aminopirazina (CAS no. 5049-61-6) (84 mg, 0,88 mmol) y N-etildiisopropilamina (0,153 mL, 0,88 mmol)

en DCM (15 mL) a temperatura ambiente bajo nitrógeno. La solución resultante se agitó a temperatura ambiente durante 24 horas. La mezcla de reacción se diluyó con DCM (10 mL) y agua (10 mL) y la fase orgánica se separó utilizando un cartucho de separación de fases y se evaporó. El residuo se purificó utilizando cromatografía en fase inversa, eluyendo con 25-75% acetonitrilo en agua para proporcionar 2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-isopropoxi-N-pirazin-2-il-propanamida (142 mg, 39%). ^{1}H NMR (400 MHz, $CDCl_3$) 1,18 - 1,22 (6H, m), 3,70 – 3,78 (1H, m), 4,10 (2H, d), 6,08 (1H, t), 7,40 – 7,50 (2H, m), 7,51 – 7,55 (1H, m), 7,62 – 7,64 (1H, m), 8,24 (1H, s), 8,35 (1H, s), 8,60 (1H, s), 8,80 (1H, s), 9,58 (1H, s); (M+H)+ = 454; HPLC t_R = 2,26.

Los siguientes Ejemplos se prepararon a partir de la amina apropiada utilizando un procedimiento análogo.

Ejemplo 109: 2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-isopropoxi-N-(5-metil-1,3,4-tiadiazol-2-il)propanamida

Ejemplo 110: 2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-isopropoxi-N-(5-metilisoxazol-3-il)propanamida

Ejemplo 111: 2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-isopropoxi-N-(5-metiltiazol-2-il)propanamida

Ejemplo 112: 2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-3-isopropoxi-propanamida

Ejemplo 113: 2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-ciano-2-piridil)-3-isopropoxi-propanamida

Ejemplo 114: 2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-isopropoxi-N-(1,2,4-tiadiazol-5-il)propanamida

Ejemplo 115: 2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-cloro-2-piridil)-3-isopropoxi-propanamida

Ejemplo 116: 2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-isopropoxi-N-(4-metil-2-piridil)propanamida

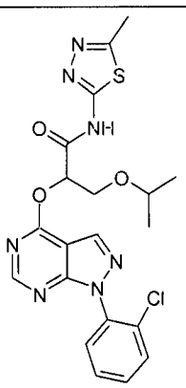
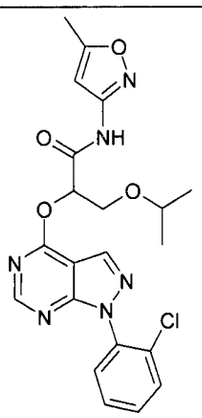
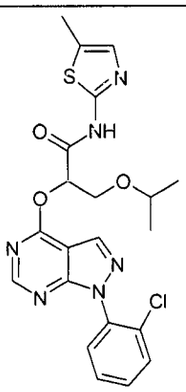
Ejemplo 117: 2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-isopropoxi-N-(1,3,4-tiadiazol-2-il)propanamida

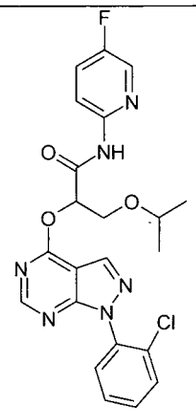
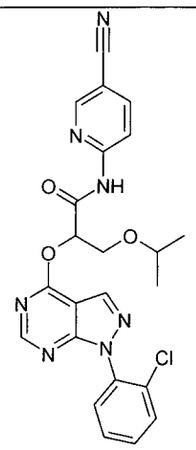
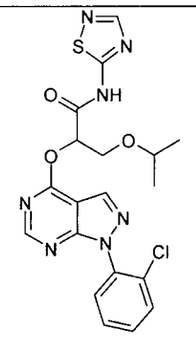
Ejemplo 118: 2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-isopropoxi-N-(2-piridil)propanamida

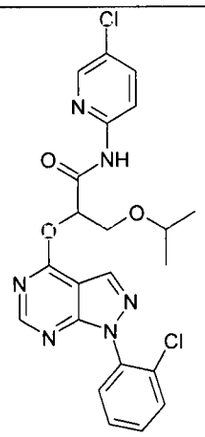
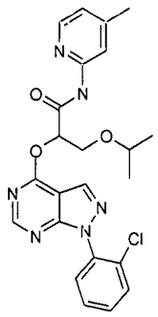
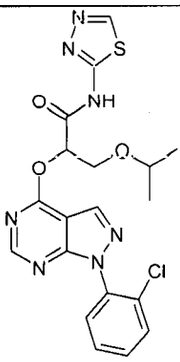
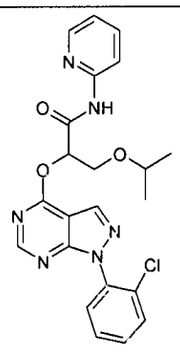
269

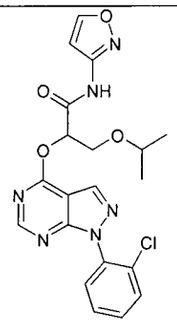
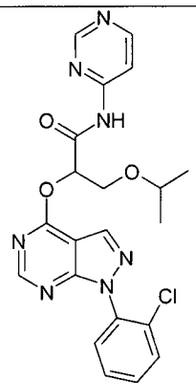
Ejemplo 119: 2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-isopropoxi-N-isoxazol-3-il-propanamida

Ejemplo 120: 2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-isopropoxi-N-pirimidin-4-il-propanamida

Ejemplo no.	**Estructura**	**M/Z**	**Datos de ^{1}H NMR (400 MHz, $CDCl_3$)**
109		MH- = 472 t_R = 1,47min.	1,18 - 1,22 (6H, m), 3,38 (3H, s), 3,70 – 3,76 (1H, m), 4,10 (2H, d), 6,1 (1H, t), 7,45 – 7,50 (2H, m), 7,50 – 7,55 (1H, m), 7,60 – 7,62 (1H, m), 8,40 (1H, s), 8,60 (1H, s)
110		(M+H)+ = 457 t_R = 2,52 min.	1,18 - 1,22 (6H, m), 2,40 (3H, s), 3,70 – 3,76 (1H, m), 4,08 (2H, d), 6,0 (1H, t), 7,45 – 7,50 (2H, m), 7,50 – 7,55 (1H, m), 7,60 – 7,62 (1H, m), 8,40 (1H, s), 8,60 (1H, s), 8,78 (1H, m).
111		MH- = 471 t_R = 2,32 min	1,18 - 1,22 (6H, m), 2,40 (3H, s), 3,65 – 3,74 (1H, m), 4,10 (2H, d), 6,1 (1H, t), 7,10 (1H, s), 7,45 – 7,50 (2H, m), 7,50 – 7,55 (1H, m), 7,60 – 7,62 (1H, m), 8,40 (1H, s), 8,60 (1H, s).

112		(M+H)+ = 471 t_R = 2,68 min	1,18 - 1,22 (6H, m), 3,70 – 3,76 (1H, m), 4,10 (2H, d), 6,0 (1H, t), 7,45 – 7,55 (3H, m), 7,61 – 7,63 (1H, m), 8,1 (1H, m), 8,24 (1H, m), 8,42 (1H, s), 8,58 (1H, s), 8,8 (1H, s).
113		MH- = 476 t_R = 2,66	1,18 - 1,22 (6H, m), 3,70 – 3,78 (1H, m), 4,10 (2H, d), 6,0 (1H, t), 7,45 – 7,55 (2H, m), 7,60 – 7,63 (1H, m), 7,94 – 7,98 (1H, m), 8,38 (1H, d), 8,40 (1H, s), 8,56 – 8,58 (2H, m), 9,10 (1H, s).
114		MH- = 458 t_R = 1,31min	1,18 - 1,22 (6H, m), 3,68 – 3,76 (1H, m), 4,10 (2H, d), 6,15 (1H, t), 7,45 – 7,50 (2H, m), 7,50 – 7,55 (1H, m), 7,60 – 7,62 (1H, m), 8,37 (2H, m), 8,60 (1H, s), 10,44 (1H, s)

115		(M+H)+ = 488 t_R = 2,92 min	1,18 - 1,22 (6H, m), 3,70 – 3,76 (1H, m), 4,10 (2H, d), 6,0 (1H, t), 7,41 – 7,50 (2H, m), 7,55 (1H, m) 7,61 (1H, m), 7,6 – 7,70 (1H, d), 8,2 (2H, d), 8,40 (1H, s), 8,60 (1H, s), 8,70 (1H, s)
116		MH- = 465 t_R = 2,66 min	1,18 - 1,22 (6H, m), 2,35 (3H, s), 3,70 – 3,76 (1H, m), 4,10 (2H, d), 6,0 (1H, t), 6,80 (1H, d), 7,45 – 7,55 (3H, m), 7,61 – 7,63 (1H, m), 8,1 (1H, s), 8,14 (1H, d), 8,42 (1H, s), 8,60 (1H, s), 8,70 (1H, s)
117		MH- = 458 t_R = 1,23 min	1,18 - 1,22 (6H, m), 3,68 – 3,76 (1H, m), 4,10 (2H, d), 6,15 (1H, t), 7,45 – 7,50 (3H, m), 7,60 (1H, m), 8,40 (1H, s), 8,58 (1H, s), 8,85 (1H, s)
118		(M+H)+ = 453 t_R = 2,53 min	1,19 - 1,25 (6H, m), 3,70 – 3,75 (1H, m), 4,10 (2H, d), 6,0 (1H, t), 7,0 – 7,1 (1H, m) 7,45 – 7,55 (2H, m), 7,56 – 7,59 (1H, m), 7,64 – 7,68 (1H, m), 7,70 – 7,72 (1H, m), 8,20 – 8,40(2H, m), 8,40 (1H, s), 8,60 (1H, s), 8,75 (1H, s)

119		(M+H)+ = 443 t_R = 2,36 min	1,18 - 1,22 (6H, m), 3,68 – 3,76 (1H, m), 4,10 (2H, d), 6,17 (1H, t),7,10 (1H, s) 7,45 – 7,50 (3H, m), 7,60 (1H, m), 8,30 (1H, s), 8,40 (1H, s), 8,58 (1H, s), 8,85 (1H, s)
120		(M+H)+ = 454 t_R = 1,58 min	1,19 - 1,25 (6H, m), 3,70 – 3,77 (1H, m), 4,10 (2H, d), 5,98 (1H, t), 7,0 – 7,1 (1H, m) 7,45 – 7,55 (2H, m), 7,56 – 7,59 (1H, m), 7,64 – 7,68 (1H, m), 7,70 – 7,72 (1H, m), 8,19 (2H, d), 8,41 (1H, s), 8,60 (1H, s).

Los ejemplos que figuran a continuación se prepararon a partir de los ejemplos precedentes mediante cromatografía quiral utilizando Chiralcel OJ o Chiralcel AD como fase estacionaria quiral y eluyendo con una mezcla apropiada de isohexano, etanol, metanol y trietilamina.

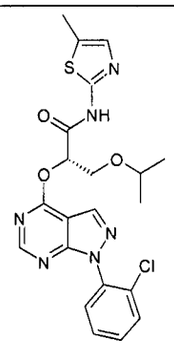
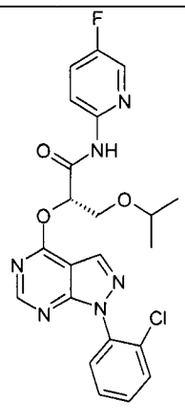
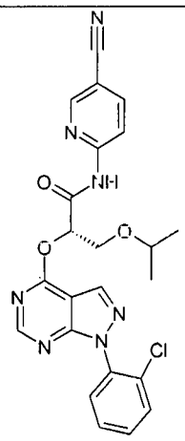
Ejemplo 111a: (2S)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-isopropoxi-N-(5-metiltiazol-2-il)propanamida

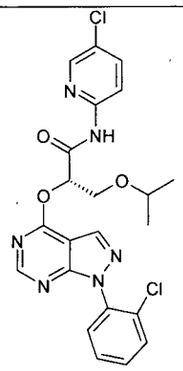
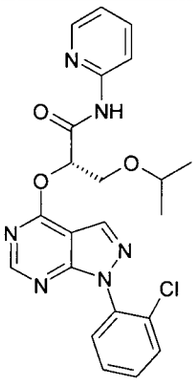
Ejemplo 112a: (2S)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-3-isopropoxi-propanamida

Ejemplo 113a: (2S)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-ciano-2-piridil)-3-isopropoxi-propanamida

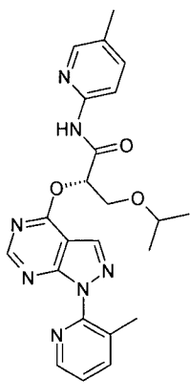
Ejemplo 115a: (2S)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-cloro-2-piridil)-3-isopropoxi-propanamida

Ejemplo 118a; (2S)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-isopropoxi-N-(2-piridil)propanamida

Ejemplo no.	Estructura	M/Z	Datos de ^{1}H NMR (400 MHz, $CDCl_3$)
111a		MH- = 471 t_R = 2,32 min	1,17 - 1,20 (6H, m), 2,40 (3H, s), 3,70 -3,76 (1H, m), 4,10 (2H, d), 6,1 (1H, t), 7,10 (1H, s), 7,45 – 7,50 (2H, m), 7,50 – 7,55 (1H, m), 7,60 – 7,62 (1H, m), 8,37 (1H, s), 8,57 (1H, s).
112a		(M+H)+ = 471 t_R = 2,68 min	1,18 - 1,22 (6H, m), 3,70 – 3,76 (1H, m), 4,10 (2H, d), 6,0 (1H, t), 7,45 – 7,55 (3H, m), 7,61 – 7,63 (1H, m), 8,1 (1H, m), 8,24 (1H, m), 8,42 (1H, s), 8,58 (1H, s), 8,8 (1H, s).
113a		MH- = 476 t_R = 2,66 min	1,19 - 1,25 (6H, m), 3,70 – 3,75 (1H, m), 4,10 (2H, d), 6,0 (1H, t), 7,45 – 7,55 (2H, m), 7,60 – 7,63 (1H, m), 7,94 – 7,97 (1H, m), 8,38 (1H, d), 8,40 (1H, s), 8,56 – 8,58 (2H, m), 9,10 (1H, s).

115a		(M+H)+ = 488 t_R = 2,92 min	1,11 - 1,15 (6H, m), 3,60 – 3,65 (1H, m), 4,0 (2H, d), 5,94 (1H, t), 7,41 – 7,50 (3H, m), 7,54 (1H m) 7,56 (1H, d), 7,6 – 7,62 (1H, m), 8,17 (1H, s), 8,30 (1H, s), 8,50 (1H, s), 8,74 (1H, s).
118a		(M+H)+ = 453 t_R = 2,53 min	1,17 - 1,20 (6H, m), 3,70 – 3,76 (1H, m), 4,10 (2H, d), 6,02 (1H, t), 7,0 – 7,1 (1H, m) 7,45 – 7,49 (2H, m), 7,54 – 7,57 (1H, m), 7,64 – 7,68 (1H, m), 7,70 – 7,73 (1H, m), 8,20 – 8,40(2H, m), 8,40 (1H, s), 8,60 (1H, s), 8,70 (1H, s).

Ejemplo 125: (2S)-3-Isopropoxi-N-(5-metilpiridin-2-il)-2-(1-(3-metilpiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida

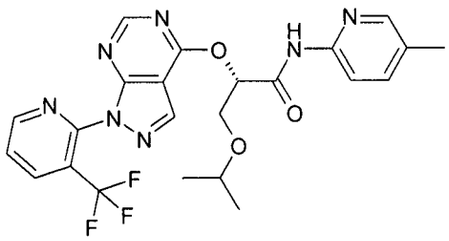


Se agregó una solución 2M de trimetilaluminio en hexano (0,404 mL, 0,81 mmol) a 5-metilpiridin-2-amina (84 mg, 0,77 mmol) en tolueno (22 mL) a 5°C bajo nitrógeno. La solución resultante se agitó a 5°C durante 20 minutos. Se agregó gota a gota (2S)-metil 3-isopropoxi-2-(1-(3-metilpiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanoato (300 mg, 0,70 mmol) (**Producto Intermedio J5**) en tolueno (6 mL) a 5°C. Después de que se completó la adición, la solución se dejó entibiar hasta alcanzar la temperatura ambiente y

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luego se calentó hasta alcanzar reflujo durante 16 horas. La solución se dejó enfriar hasta alcanzar la temperatura ambiente. La mezcla de reacción se concentró, se diluyó con EtOAc (100 mL) y se lavó secuencialmente con ácido cítrico 1M (50 mL) y luego salmuera saturada (50 mL). La capa orgánica se separó, se secó ($MgSO_4$) y se evaporó. El residuo se purificó mediante cromatografía instantánea en sílice, eluyendo con EtOAc para proporcionar (2S)-3-isopropoxi-N-(5-metilpiridin-2-il)-2-(1-(3-metilpiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida (160 mg, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,09 - 1,12 (6H, m), 2,23 (3H, s), 2,26 (3H, s), 3,62 - 3,68 (1H, m), 4,00 - 4,09 (2H, m), 5,97 (1H, t), 7,30 - 7,33 (1H, m), 7,56 - 7,59 (1H, d), 7,70 - 7,73 (1H, d), 8,01 - 8,01 (1H, s), 8,21 (1H, d), 8,44 (1H, s), 8,46 (1H, m), 8,53 (1H, s), 9,5 (1H, ancho s); m/z (ESI+) $(M+H)^+$ = 448; HPLC t_R = 1,98 min.

Ejemplo 126: (2S)-3-Isopropoxi-N-(5-metilpiridin-2-il)-2-(1-(3-(trifluorometil)piridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida



Se agitaron (2S)-2-(1-(5-cloro-3-(trifluorometil)piridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-isopropoxi-N-(5-metilpiridin-2-il)propanamida (**Producto Intermedio K6**) (1 g, 0,73 mmol) y 10% paladio sobre carbono (100 mg, 0,09 mmol) en MeOH (25 mL) bajo una atmósfera de hidrógeno durante 16 horas. La mezcla de reacción se filtró a través de celite. Se agregó 10% paladio sobre carbono (100 mg, 0,09 mmol) y se agitó bajo una atmósfera de hidrógeno durante unas 16 horas adicionales. La mezcla de reacción se filtró a través de celite y se evaporó. El residuo se purificó mediante cromatografía instantánea en sílice, gradiente de elución 1 a 5% MeOH en DCM para proporcionar (2S)-3-isopropoxi-N-(5-metilpiridin-2-il)-2-(1-(3-(trifluorometil)piridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida (0,173 g, 47 %). ^{1}H NMR (400 MHz, DMSO) δ 1,08 - 1,14 (6H, m), 2,24 (3H, s), 3,73 - 3,79 (1H, m), 3,96 - 4,05 (2H, m), 5,90 (1H, s), 7,57 - 7,60 (1H, m), 7,86 - 7,90 (1H, m), 7,94 - 7,98 (1H, m), 8,17 (1H, s), 8,55 (1H, s), 8,58 - 8,61 (1H, m), 8,65 (1H, s), 8,97 - 9,00 (1H, m), 10,82 (1H, s). m/z (ESI+) $(M+H)^+$ = 502; HPLC t_R = 2,30 min.

Los siguientes Ejemplos se prepararon utilizando un método análogo al descrito para el ejemplo 125, utilizando el éster y la arilamina apropiados.

Ejemplo 127: (2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-isopropoxi-N-(6-metilpiridazin-3-il)propanamida

Ejemplo 127a: (2S)-N-(5-cianopiridin-2-il)-3-isopropoxi-2-(1-(3-metilpiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida

Ejemplo 127b: (2S)-N-(5-cloropiridin-2-il)-3-isopropoxi-2-(1-(3-metilpiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida

Ejemplo 127c: (2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-ciano-2-piridil)-3-etoxi-propanamida

Ejemplo 127d: (2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-etoxi-N-(5-fluoro-2-piridil)propanamida

Ejemplo 127e: (2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-etoxi-N-(2-piridil)propanamida

Ejemplo 127f: (2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-etoxi-N-pirimidin-4-il-propanamida

Ejemplo 127g: (2S)-N-(5-cloro-2-piridil)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-etoxi-propanamida

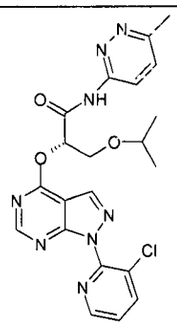
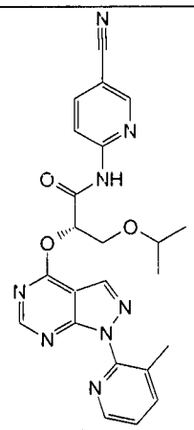
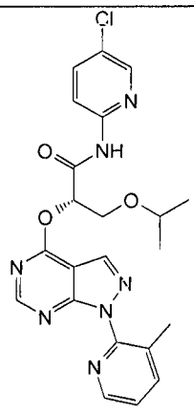
Ejemplo 127h: (2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(4-cianotiazol-2-il)-3-isopropoxi-propanamida

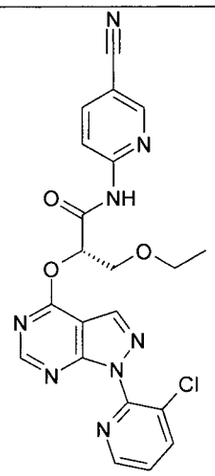
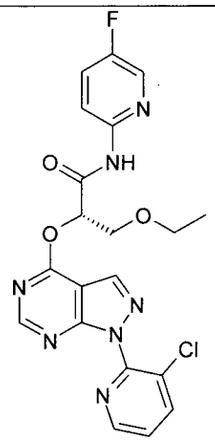
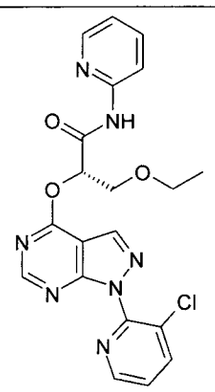
Ejemplo 127i: (2S)-N-(5-cloro-2-piridil)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-isopropoxi-propanamida

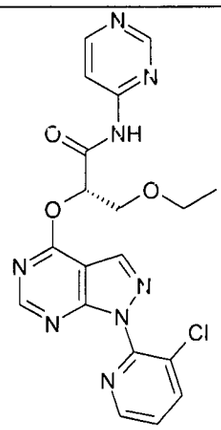
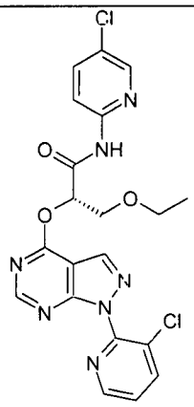
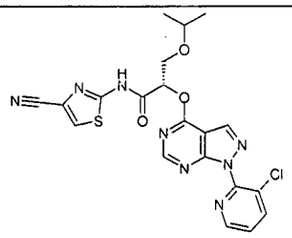
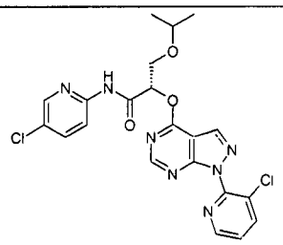
Ejemplo 127j: (2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-ciano-2-piridil)-3-isopropoxi-propanamida

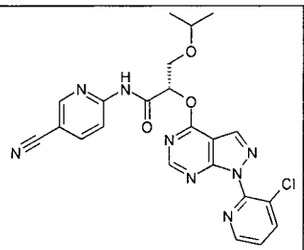
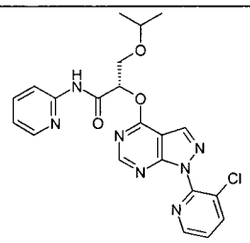
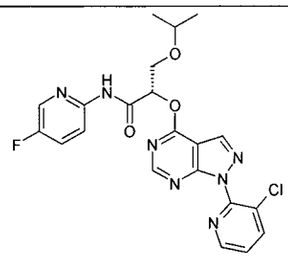
Ejemplo 127k: (2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-isopropoxi-N-(2-piridil)propanamida

Ejemplo 127l: (2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-3-isopropoxi-propanamida

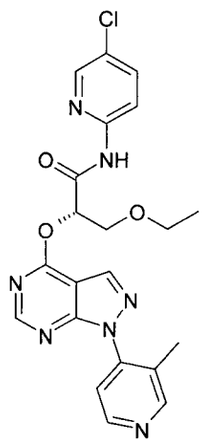
Ejemplo no.	Estructura	m/z	Datos de ^{1}H NMR (400MHz)
127		(M+H)+ = 470 t_R = 1,78 min	($CDCl_3$) 1,18 - 1,22 (6H, m), 2,03 (3H,s) 3,70 – 3,78 (1H, m), 4,10 (2H, d), 6,08 (1H, t), 7,30 (1H, d), 7,46 – 7,50 (1H, m), 8,0 (1H, d), 8,40 (1H, d), 8,60 (2H, m), 9,30 (1H, s).
127a		(M+H)+ = 459; t_R = 2,15 min. ee 89%	(DMSO-d_6) 1,10 - 1,13 (6H, m), 2,11 (3H, s), 3,73 - 3,80 (1H, m), 3,99 - 4,08 (2H, m), 5,91 (1H, q), 7,56 - 7,59 (1H, m), 7,98 - 8,00 (1H, m), 8,13 (1H, d), 8,23 - 8,26 (1H, m), 8,50 (1H, t), 8,48 - 8,55 (1H, m), 8,60 (1H, s), 8,82 (1H, q), 11,50 (1H, s)
127b		(M+H)+ = 468; t_R = 2,24 min. ee 89%	(DMSO-d_6) 1,11 - 1,13 (6H, m), 2,11 (3H, s), 3,73 - 3,79 (1H, m), 3,97 - 4,06 (2H, m), 5,90 (1H, q), 7,56 - 7,59 (1H, m), 7,88 - 7,90 (1H, m), 7,98 - 8,03 (2H, m), 8,40 - 8,41 (1H, m), 8,49 (1H, q), 8,53 (1H, s), 8,59 (1H, s), 11,13 (1H, s).

127c		(M+H)+ = 465,33; t_R = 2,08 min	(DMSO-d_6) 1,14 (3H, t), 3,59 - 3,69 (2H, m), 3,98 - 4,01 (1H, m), 4,06 - 4,10 (1H, m), 5,95 (1H, q), 7,72 - 7,78 (2H, m), 8,02 - 8,05 (1H, m), 8,34 - 8,36 (2H, m), 8,58 (1H, s), 8,68 (2H, t), 11,10 (1H, s)
127d		(M+H)+ = 458,33; t_R = 2,09 min.	(DMSO-d_6) 1,14 (3H, t), 3,59 - 3,69 (2H, m), 4,00 - 4,03 (1H, m), 4,08 - 4,12 (1H, m), 5,97 (1H, q), 7,75 - 7,78 (1H, m), 8,14 (1H, d), 8,24 - 8,27 (1H, m), 8,34 - 8,36 (1H, m), 8,58 (1H, s), 8,68 (2H, d), 8,84 (1H, q), 11,55 (1H, s)
127e		(M+H)+ = 440,63; t_R = 1,87 min.	(DMSO-d_6) 1,15 (3H, t), 3,60 - 3,69 (2H, m), 3,98 - 4,02 (1H, m), 4,06 - 4,11 (1H, m), 5,96 - 5,97 (1H, m), 7,12 - 7,15 (1H, m), 7,75 - 7,78 (2H, m), 7,99 (1H, d), 8,34 - 8,37 (2H, m), 8,58 (1H, s), 8,69 (2H, q), 10,97 (1H, s)

127f		$(M+H)^+$ = 441,32; t_R = 1,65 min.	(DMSO-d_6) 1,14 (3H, t), 3,57 - 3,7 (2H, m), 4,00 - 4,03 (1H, m), 4,08 - 4,12 (1H, m), 5,96 (1H, q), 7,75 - 7,78 (1H, m), 7,98 - 8,00 (1H, m), 8,34 - 8,36 (1H, m), 8,58 (1H, s), 8,66 - 8,68 (1H, m), 8,67 - 8,69 (2H, m), 8,94 (1H, d), 11,46 (1H, s)
127g		$(M+H)^+$ = 474,28; t_R = 2,32 min.	(DMSO-d_6) 1,13 (3H, t), 3,56 - 3,69 (2H, m), 3,96 - 4,00 (1H, m), 4,05 - 4,09 (1H, m), 5,94 (1H, q), 7,73 - 7,77 (1H, m), 7,87 - 7,90 (1H, m), 8,02 (1H, d), 8,32 - 8,35 (1H, m), 8,39 - 8,42 (1H, m), 8,56 (1H, s), 8,66 - 8,68 (2H, m), 11,17 (1H, s)
127h		$(M+H)^+$ = 485; t_R = 2,24 min	($CDCl_3$) 1,20 - 1,24 (6H, m), 3,70 - 3,77 (1H, m), 4,10 (2H, d), 6,10 (1H, t), 7,47 - 7,50 (1H, m), 7,67 (1H, s), 8,01 - 8,03 (1H, m), 8,45 (1H, s), 8,61 - 8,63 (2H, m).
127i		$(M+H)^+$ = 489; t_R = 2,38 min	(DMSO-d_6) 1,11 – 1,14 (6H, m), 3,7 – 3,8(1H, m), 3,9 – 4,0 (2H, m), 5,9 – 5,93 (1H, m), 7,75 – 7,78 (1H, m), 7,9 – 7,92 (1H,m), 8,03 (1H,d), 8,33 – 8,36 (1H, m), 8,40 – 8,41 (1H, m), 8,56 (1H,m), 8,66 – 8,69 (2H, m), 11,1 (1H, s)

127j		MH- = 479; t_R = 1,83 min	(DMSO-d_6) 1,13 (6H, t), 3,75 - 3,81 (1H, m), 4,01 - 4,10 (2H, m), 5,92 - 5,94 (1H, m), 7,75 - 7,78 (1H, m), 8,13 - 8,16 (1H, m), 8,24 - 8,27 (1H, m), 8,34 - 8,36 (1H, m), 8,57 (1H, s), 8,67 - 8,69 (2H, m), 8,84 (1H, q), 11,52 (1H, s)
127k		(M+H)+ = 454; t_R = 1,91 min	(DMSO-d_6) 1,11 – 1,15 (6H, m), 3,75 – 3,81(1H, m), 3,99 – 4,08 (2H, m), 5,92 – 5,93 (1H, m), 7,11 – 7,15 (1H, m), 7,75 – 7,80 (2H, m), 8,03 (1H, d), 8,33 – 8,36 (2H, m), 8,57 (1H, m), 8,66 – 8,69 (2H, m), 11,1 (1H, s)
127l		(M+H)+ = 471; t_R = 2,14 min	(DMSO-d_6) 1,12 – 1,14 (6H, m), 3,75 – 3,8(1H, m), 3,99 – 4,08 (2H, m), 5,9 – 5,92 (1H, m), 7,11 – 7,18 (2H, m), 8,0 – 8,15 (1H, d), 8,33 – 8,36 (2H, m), 8,57 (1H, m), 8,66 – 8,69 (2H, m), 11,1 (1H, s)

Ejemplo 128: (2S)-N-(5-Cloropiridin-2-il)-3-etoxi-2-[1-(3-metilpiridin-4-il)pirazolo[4,5-e]pirimidin-4-il]oxipropanamida

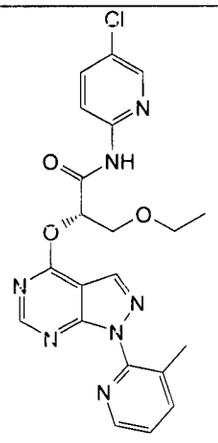


Se agregó hidruro de sodio al 60% en aceite mineral (48,8mg, 1,22 mmol) en una porción a

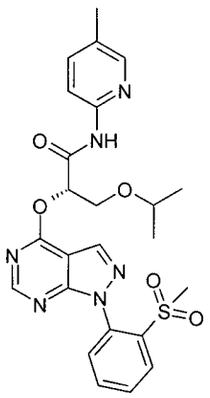
(S)-N-(5-cloropiridin-2-il)-3-etoxi-2-hidroxipropanamida (**Producto Intermedio H3**) (199 mg, 0,81 mmol) en THF anhidro (5 mL) enfriado hasta alcanzar 0°C bajo nitrógeno. La suspensión resultante se agitó a 0°C durante 10 minutos y luego se agregó en porciones 4-cloro-1-(3-metilpiridin-4-il)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio M1**) (200 mg, 0,81 mmol) durante 1 minuto. La mezcla se agitó a 0°C durante 15 mins, se dejó entibiar lentamente hasta alcanzar la temperatura ambiente y se agitó durante 2 horas. Se agregó ácido cítrico 1M (2 mL) y la mezcla se extrajo con acetato de etilo (2 × 20 mL). Los extractos orgánicos se lavaron con agua (15 mL) y salmuera (15 mL), se secaron ($MgSO_4$) y se evaporaron. El residuo se purificó mediante cromatografía instantánea en sílice, gradiente de elución 0 a 10% MeOH en EtOAc para proporcionar (2S)-N-(5-cloropiridin-2-il)-3-etoxi-2-[1-(3-metilpiridin-4-il)pirazolo[4,5-e]pirimidin-4-il]oxipropanamida (370 mg, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,23 (3H, t), 2,34 (3H, s), 3,61 - 3,69 (2H, m), 4,06 - 4,14 (2H, m), 6,05 (1H, t), 7,49 (1H, d), 7,68 (1H, dd), 8,22 (1H, dd), 8,23 - 8,25 (1H, m), 8,44 (1H, s), 8,61 (1H, s), 8,63 (1H, dd), 8,69 (1H, s), 8,76 (1H, s) ; m/z (ESI+) $(M+H)^+$ = 454; HPLC t_R = 1,93 min.

Los siguientes Ejemplos se prepararon utilizando un método análogo al descrito para el ejemplo 128 utilizando el derivado de alcohol y cloro.

Ejemplo 128a. (2S)-N-(5-cloropiridin-2-il)-3-etoxi-2-(1-(3-metilpiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida

Ejemplo no.	**Estructura**	**m/z**	**Datos de ^{1}H NMR**
128a		$(M+H)^+$ = 454; t_R = 2,08 min. ee 99%	400 MHz, DMSO-d_6 1,11 - 1,15 (3H, m), 2,11 (3H, s), 3,56 - 3,69 (2H, m), 3,96 - 4,06 (2H, m), 5,93 (1H, m), 7,56 - 7,59 (1H, m), 7,88 - 7,90 (1H, m), 7,98 - 8,00 (1H, m), 8,01 - 8,03 (1H, m), 8,40 - 8,41 (1H, m), 8,48 - 8,53 (2H, m), 8,61 (1H, t), 11,16 (1H, s)

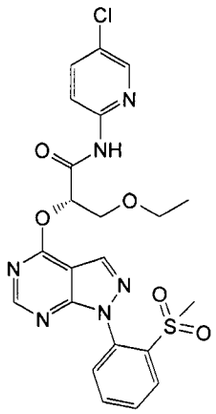
Ejemplo 129: (2S)-3-isopropoxi-N-(5-metilpiridin-2-il)-2-(1-(2-(metilsulfonil)fenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida



Se agregó oxicloruro de fósforo (1,864 ml, 20,00 mmol) a 1-(2-(metilsulfonil)fenil)-1H-pirazolo[3,4-d]pirimidin-4-ol (**Producto Intermedio N1**) (0,290 g, 1 mmol), a temperatura ambiente. La mezcla resultante se agitó a 100°C durante 4 horas. La solución se dejó enfriar hasta alcanzar la temperatura ambiente. La mezcla de reacción se evaporó. El residuo se disolvió en DCM (30 mL). Se agregó MP-carbonato y la mezcla se agitó durante 30 minutos y luego se evaporó. El residuo se disolvió en THF (5 mL). Se agregó hidruro de sodio (55,9 mg, 1,40 mmol) a (S)-2-hidroxi-3-isopropoxi-N-(5-metilpiridin-2-il)propanamida (**Producto Intermedio C7**) (238 mg, 1,00 mmol) en THF anhidro (10 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 15 minutos y luego se agregó la solución de THF preparada anteriormente. La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 16 horas. La mezcla de reacción se concentró, se diluyó con agua (10 mL) y EtOAc (50 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc (25 mL). Los elementos orgánicos combinados se lavaron con salmuera saturada (25 mL), se secaron ($MgSO_4$) y se evaporaron. El residuo se purificó mediante HPLC preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, 50 mm de diámetro, 150 mm de longitud), utilizando mezclas cada vez menos polares de agua (que contenía ácido fórmico al 0,1%) y MeCN como eluyente para proporcionar (2S)-3-isopropoxi-N-(5-metilpiridin-2-il)-2-(1-(2-(metilsulfonil)fenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida (242 mg, 47,5 %, 81% ee). ^{1}H NMR (400 MHz, DMSO-d6) δ 1,12 (6H, dd), 2,24 (3H, s), 3,38 (3H, s), 3,72 - 3,80 (1H, m), 3,96 - 4,05 (2H, m), 5,87 - 5,91 (1H, m), 7,58 (1H, dd), 7,77 (1H, dd), 7,86 -

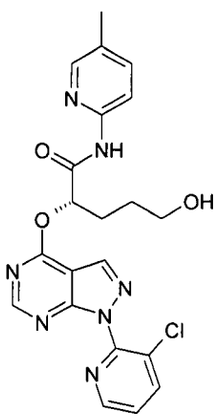
7,92 (2H, m), 7,94 - 7,99 (1H, m), 8,16 - 8,21 (2H, m), 8,53 (1H, s), 8,60 (1H, s), 10,82 (1H, s); m/z (ESI+) $(M+H)^+$ = 511; HPLC t_R = 2,07 min.

Ejemplo 130: (2S)-N-(5-cloropiridin-2-il)-3-etoxi-2-(1-(2-(metilsulfonil)fenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida



Se preparó en una forma análoga al **Ejemplo 129** a partir de (**Producto Intermedio H3**). ^{1}H NMR (400 MHz, DMSO) δ 1,13 (3H, t), 3,34 (3H, s), 3,58 - 3,68 (2H, m), 3,95 - 4,09 (2H, m), 5,91 - 5,95 (1H, m), 7,76 (1H, dd), 7,87 - 8,05 (4H, m), 8,19 (1H, dd), 8,40 (1H, d), 8,53 (1H, s), 8,53 (1H, s), 11,18 (1H, s); m/z (ESI+) $(M+H)^+$ = 517; HPLC t_R = 2,41 min; ee 98%.

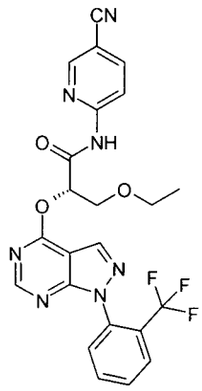
Ejemplo 131: (2S)-2-[1-(3-cloropiridin-2-il)pirazolo[4,5-e]pirimidin-4-il]oxi-5-hidroxi-N-(5-metilpiridin-2-il)pentanamida



Una solución de fluoruro de tetrabutilamonio 2M en THF (0,449 mL, 0,45 mmol) se agregó en una porción a una solución agitada de (2S)-5-(terc-butildimetilsililoxi)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-metilpiridin-2-il)pentanamida (**Producto Intermedio O1**) (170 mg, 0,30 mmol) en THF (5 mL). La solución resultante

se agitó a temperatura ambiente durante 4 horas, se evaporó y el residuo se disolvió en acetato de etilo (30 mL). Esto se lavó con agua (20 mL) y salmuera (20 mL), se secó ($MgSO_4$) y se evaporó. El residuo se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 10% MeOH en acetato de etilo para proporcionar el producto (100mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,61 - 1,68 (1H, m), 1,84 - 1,88 (2H, m), 2,23 - 2,36 (2H, m), 2,30 (3H, s), 3,72 - 3,82 (2H, m), 5,94 - 5,98 (1H, m), 7,46 (1H, dd), 7,54 (1H, dd), 8,01 (1H, dd), 8,08 - 8,10 (1H, m), 8,12 - 8,15 (1H, m), 8,45 (1H, s), 8,61-8,62 (2H, m), 8,63 (1H, s); m/z (ESI+) (M+H)+ = 454; HPLC t_R = 1,51 min.

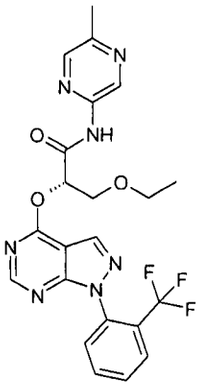
Ejemplo 132: (2S)-N-(5-cianopiridin-2-il)-3-etoxi-2-[1-[2-(trifluorometil)fenil]pirazolo[4,5-e]pirimidin-4-il]oxipropanamida



Se agregó hidruro de sodio al 60% (60,0 mg, 1,50 mmol) en una porción a (S)-N-(5-cianopiridin-2-il)-3-etoxi-2-hidroxipropanamida (**Producto Intermedio H4**) (235 mg, 1,00 mmol) en THF anhidro (5 mL) y la mezcla se enfrió hasta alcanzar 0°C bajo nitrógeno. La suspensión resultante se agitó a 0°C durante 10 minutos y se agregó gota a gota 4-cloro-1-(2-(trifluorometil)fenil)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio P1**) (298,6 mg, 1,00 mmol) como suspensión en THF seco (4 mL) durante 1 minuto. La mezcla se agitó a 0°C durante 15 mins, se dejó entibiar lentamente hasta alcanzar la temperatura ambiente y se agitó durante 2 horas. Se agregó ácido cítrico 1M (4 mL) y la mezcla se extrajo con acetato de etilo (2 × 25 mL). Los extractos orgánicos combinados se lavaron con agua (25 mL) y salmuera (25 mL), se secaron ($MgSO_4$) y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 20 a 100% acetato de etilo en isohexano para proporcionar el producto (430 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,25 (3H, t), 3,62 - 3,70 (2H, m), 4,08 - 4,14 (2H, m), 6,04 (1H, t), 7,53 - 7,55 (1H, m), 7,68 - 7,77 (2H, m), 7,91 (1H, dd), 7,97 (1H, dd), 8,39 (1H, dd), 8,41 (1H, s),

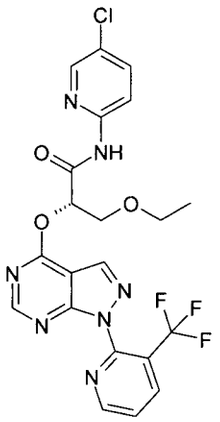
8,56 (1H, s), 8,57 - 8,59 (1H, m), 9,02 (1H, s); m/z (ESI-) $(M-H)^-$ = 496; HPLC tR = 2,55 min.

Ejemplo 133: (2S)-3-etoxi-N-(5-metilpirazin-2-il)-2-[1-[2-(trifluorometil)fenil]pirazolo[4,5-e]pirimidin-4-il]oxipropanamida



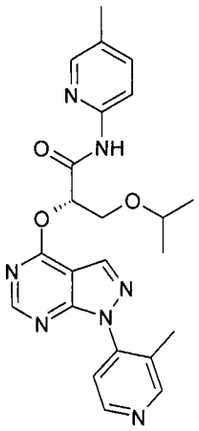
Se agregó hidruro de sodio al 60% (60,0 mg, 1,50 mmol) en una porción a (S)-3-etoxi-2-hidroxi-N-(5-metilpirazin-2-il)propanamida (**Producto Intermedio H1**) (225 mg, 1,00 mmol) en THF anhidro (5 mL) y la mezcla se enfrió hasta alcanzar 0°C bajo nitrógeno. La suspensión resultante se agitó a 0°C durante 10 minutos y luego se agregó gota a gota 4-cloro-1-(2-(trifluorometil)fenil)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio P1**) (298,6 mg, 1,00 mmol) como suspensión en THF seco (4 mL) durante 1 minuto. La mezcla se agitó a 0°C durante 15 mins, se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 2 horas. Se agregó ácido cítrico 1M (2 mL) y la mezcla se extrajo con acetato de etilo (2 × 20 mL). Los extractos orgánicos se lavaron con agua (15 mL) y salmuera (15 mL), se secaron ($MgSO_4$) y se evaporaron. El residuo se purificó mediante cromatografía instantánea en sílice, eluyendo con 60 a 100% acetato de etilo en isohexano para proporcionar el producto (440 mg, 88%). ^1H NMR (400 MHz, $CDCl_3$) δ 1,25 (3H, t), 2,54 (3H, s), 3,61 - 3,69 (2H, m), 4,08 - 4,16 (2H, m), 6,08 (1H, t), 7,52 - 7,57 (1H, m), 7,65 - 7,72 (1H, m), 7,74 - 7,76 (1H, m), 7,90 (1H, dd), 8,12 (1H, d), 8,41 (1H, s), 8,57 (1H, s), 8,68 (1H, s), 9,45 (1H, d) ; m/z (ESI+) $(M+H)^+$ = 488; HPLC tR = 2,27 min.

Ejemplo 134: (2S)-N-(5-cloropiridin-2-il)-3-etoxi-2-[1-[3-(trifluorometil)piridin-2-il]pirazolo[4,5-e]pirimidin-4-il]oxipropanamida



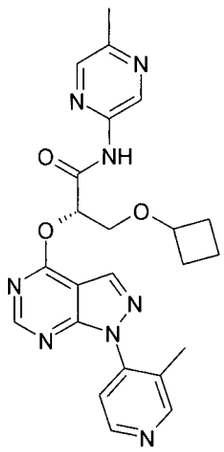
Una solución de trimetilaluminio (2M en hexano) (0,322 mL, 0,64 mmol) se agregó gota a gota a una solución agitada de 5-cloropiridin-2-amina (CAS no. 1072-98-6) (79 mg, 0,62 mmol) en tolueno (5 mL) a 0°C, durante un período de 1 minuto bajo nitrógeno. La solución resultante se agitó a 0°C durante 20 minutos. Una solución de (2S)-metil 3-etoxi-2-(1-(3-(trifluorometil)piridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanoato (**Producto Intermedio Q1**) (230 mg, 0,56 mmol) en tolueno (5 mL) se agregó gota a gota durante un período de 2 minutos. La solución resultante se agitó a 0°C durante 10 minutos, se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó a 60°C durante 20 horas. La mezcla resultante se dejó enfriar y se agregó ácido cítrico 1M (10 mL) con agitación vigorosa. Se agregaron acetato de etilo (35 mL) y agua (10 mL) y la fase orgánica se separó, se lavó con agua (20 mL) y salmuera (20 mL), se secó ($MgSO_4$) y se evaporó. El residuo se purificó mediante cromatografía instantánea en sílice, eluyendo con 50 a 100% acetato de etilo en isohexano y luego HPLC preparativa quiral para proporcionar el producto (90 mg, 31%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,22 (3H, t), 3,60 - 3,68 (2H, m), 4,06 - 4,15 (2H, m), 6,05 (1H, t), 7,64 - 7,70 (2H, m), 8,22 - 8,25 (2H, m), 8,29 (1H, dd), 8,43 (1H, s), 8,62 (1H, s), 8,84 (1H, s), 8,89 (1H, dd); m/z (ESI+) $(M+H)^+$ = 508: HPLC tR = 2,35 min.

Ejemplo 135: (2S)-N-(5-metilpiridin-2-il)-2-[1-(3-metilpiridin-4-il)pirazolo[4,5-e]pirimidin-4-il]oxi-3-propan-2-iloxipropanamida



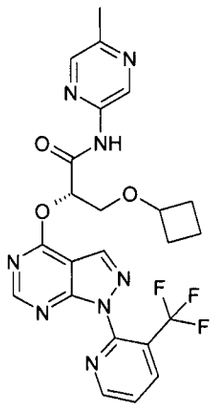
Se agregó hidruro de sodio al 60% en aceite mineral (48,8mg, 1,22 mmol) en una porción a (S)-2-hidroxi-3-isopropoxi-N-(5-metilpiridin-2-il)propanamida (**Producto Intermedio C7**) (194 mg, 0,81 mmol) en THF anhidro (5 mL) enfriado hasta alcanzar 0°C bajo nitrógeno. La suspensión resultante se agitó a 0°C durante 10 minutos y luego se agregó gota a gota 4-cloro-1-(3-metilpiridin-4-il)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio M1)** (200 mg, 0,81 mmol) como suspensión en THF seco (4 mL) durante 1 minuto. La mezcla se agitó a 0°C durante 15 mins, se dejó entibiar lentamente hasta alcanzar la temperatura ambiente y se agitó durante 2 horas. Se agregó ácido cítrico 1M (2 mL) y la mezcla se extrajo con acetato de etilo (2 × 20 mL). Los extractos orgánicos combinados se lavaron con agua (15 mL) y salmuera (15 mL), se secaron ($MgSO_4$) y se evaporaron. El residuo se purificó mediante cromatografía instantánea en sílice con acetato de etilo para proporcionar el producto (300mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,17 (3H, d), 1,19 (3H, d), 2,29 (3H, s), 2,34 (3H, s), 3,69 - 3,76 (1H, m), 4,09 (2H, d), 6,01 (1H, t), 7,51 (1H, d), 7,53 (1H, dd), 8,09 - 8,10 (1H, m), 8,13 (1H, d), 8,43 (1H, s), 8,60 (1H, s), 8,62 (1H, dd), 8,67 (1H, s), 8,68 (1H, s); m/z (ESI+) $(M+H)^+$ = 448; HPLC t_R = 1,78 min.

Ejemplo 136: (2S)-3-ciclobutiloxi-N-(5-metilpirazin-2-il)-2-[1-(3-metilpiridin-4-il)pirazolo[4,5-e]pirimidin-4-il]oxipropanamida



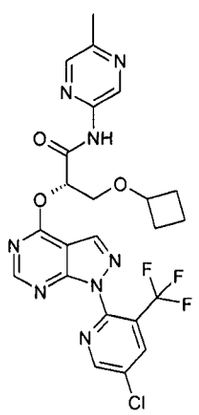
Se agregó hidruro de sodio al 60% en aceite mineral (48,8mg, 1,22 mmol) en una porción a (S)-3-ciclobutoxi-2-hidroxi-N-(5-metilpirazin-2-il)propanamida (**Producto Intermedio R1**) (205 mg, 0,81 mmol) en THF anhidro (5 mL) enfriado hasta alcanzar 0°C bajo nitrógeno. La suspensión resultante se agitó a 0°C durante 10 minutos y luego se agregó gota a gota 4-cloro-1-(3-metilpiridin-4-il)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio M1)** (200 mg, 0,81 mmol) como suspensión en THF seco (4 mL) durante 1 minuto. La mezcla se agitó a 0°C durante 15 mins, se dejó entibiar lentamente hasta alcanzar la temperatura ambiente y se agitó durante 2 horas. Se agregó ácido cítrico 1M (2 mL) y la mezcla se extrajo con acetato de etilo (2 × 20 mL). Los extractos orgánicos combinados se lavaron con agua (15 mL) y salmuera (15 mL), se secaron ($MgSO_4$) y se evaporaron. El residuo se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 10% MeOH en acetato de etilo para proporcionar el producto (360 mg, 96%). ^1H NMR (400 MHz, $CDCl_3$) δ 1,48 - 1,57 (1H, m), 1,67 - 1,76 (1H, m), 1,88 - 2,00 (2H, m), 2,19 - 2,27 (2H, m), 2,35 (3H, s), 2,54 (3H, s), 3,97 - 4,10 (3H, m), 6,05 (1H, t), 7,49 (1H, d), 8,12 (1H, d), 8,44 (1H, s), 8,61 (1H, s), 8,62 - 8,65 (2H, m), 8,69 (1H, s), 9,44 (1H, d); m/z (ESI+) $(M+H)^+$ = 461; HPLC t_R = 1,67 min.

Ejemplo 137: (2S)-3-ciclobutiloxi-N-(5-metilpirazin-2-il)-2-[1-[3-(trifluorometil)piridin-2-il]pirazolo[4,5-e]pirimidin-4-il]oxipropanamida



Se agitó 10% paladio sobre carbono (200 mg, 1,88 mmol) y (2S)-2-(1-(5-cloro-3-(trifluorometil)piridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-ciclobutoxi-N-(5-metilpirazin-2-il)propanamida (**Ejemplo 138**) (501 mg, 0,91 mmol) en etanol bajo una atmósfera de hidrógeno a temperatura ambiente durante 20 horas. La mezcla se filtró y se agregó catalizador nuevo (200 mg) y la mezcla se agitó bajo atmósfera de hidrógeno durante 8 horas. La mezcla se filtró, se agregó trietilamina (1 mL) y la mezcla se evaporó. El residuo se purificó mediante cromatografía instantánea en sílice eluyendo con acetato de etilo para proporcionar el producto (150 mg, 32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,46 - 1,60 (1H, m), 1,64 - 1,71 (1H, m), 1,92 - 1,97 (2H, m), 2,18 - 2,23 (2H, m), 2,54 (3H, s), 3,98 - 4,07 (3H, m), 6,05 (1H, t), 7,65 - 7,68 (1H, m), 8,12 (1H, d), 8,29 (1H, dd), 8,44 (1H, s), 8,62 - 8,67 (1H, m), 8,65 (1H, s), 8,89 (1H, dd), 9,45 (1H, d); m/z (ESI+) $(M+H)^+$ = 515; HPLC t_R = 2,25 min.

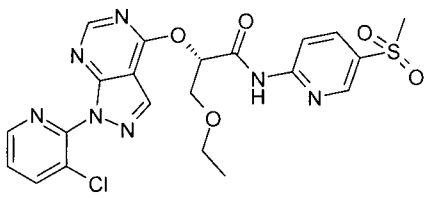
Ejemplo 138: (2S)-2-[1-[5-cloro-3-(trifluorometil)piridin-2-il]pirazolo[4,5-e]pirimidin-4-il]oxi-3-ciclobutiloxi-N-(5-metilpirazin-2-il)propanamida



Se agregó hidruro de sodio al 60% en aceite mineral (60mg, 1,50 mmol) en una porción a (S)-3-ciclobutoxi-2-hidroxi-N-(5-metilpirazin-2-il)propanamida (**Producto Intermedio**

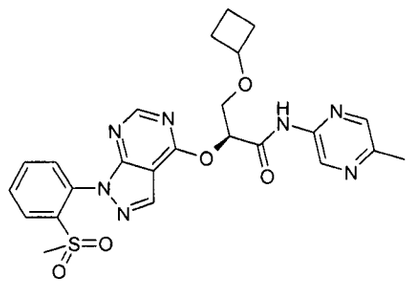
R1) (251 mg, 1,00 mmol) en THF anhidro (5 mL) a 0°C bajo nitrógeno. La suspensión resultante se agitó a 0°C durante 10 minutos y luego se agregó gota a gota 4-cloro-1-(5-cloro-3-(trifluorometil)piridin-2-il)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio K3**) (334 mg, 1,00 mmol) como suspensión en THF seco (2,5 mL) durante 1 minuto. La mezcla se agitó a 0°C durante 15 mins, se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 6 horas. Se agregó ácido cítrico 1M (10 mL) y la mezcla se extrajo con acetato de etilo (2 × 25 mL). Los extractos orgánicos combinados se lavaron con agua (25 mL) y salmuera (25 mL), se secaron ($MgSO_4$) y se evaporaron. El residuo se purificó mediante cromatografía instantánea en sílice, eluyendo con 50 a 100% acetato de etilo en isohexano para proporcionar el producto (550mg, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,46 - 1,54 (1H, m), 1,66 - 1,74 (1H, m), 1,89 - 2,01 (2H, m), 2,18 - 2,25 (2H, m), 2,54 (3H, s), 3,98 - 4,08 (3H, m), 6,04 (1H, t), 8,12 (1H, d), 8,25 (1H, d), 8,43 (1H, s), 8,62 (1H, s), 8,63-8,65 (1H, m), 8,82 (1H, d), 9,44 (1H, d); m/z (ESI+) (M+H)+ = 549; HPLC t_R = 2,56 min.

Ejemplo 139: (2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-etoxi-N-(5-(metilsulfonil)piridin-2-il)propanamida



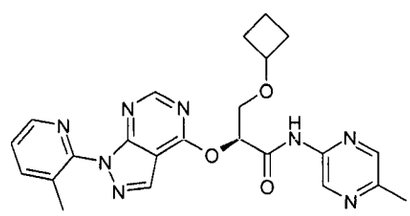
Una solución de ácido 3-cloroperoxibenzoico (85 mg, 0,38 mmol) en DCM (10 mL) se agregó gota a gota a una solución agitada de (2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-etoxi-N-(5-(metiltio)piridin-2-il)propanamida (**Producto Intermedio S1**) (92 mg, 0,19 mmol), en DCM (10 mL), a 22°C, durante un período de 10 minutos. La solución resultante se agitó a 22°C durante 3 horas. La mezcla de reacción se diluyó con DCM (20 mL), se lavó con NaOH 2M (20 mL), se secó ($MgSO_4$) y se evaporó. El residuo se purificó mediante cromatografía instantánea en sílice, eluyendo con 10 a 100% acetato de etilo en isohexano para proporcionar el producto (80 mg). ^{1}H NMR (400 MHz, DMSO) δ 1,13 (3H, t), 3,26 (3H, s), 3,56 - 3,70 (2H, m), 3,99 - 4,05 (2H, m), 5,96 (1H, q), 7,74 - 7,77 (1H, m), 8,18 - 8,21 (1H, m), 8,26 - 8,29 (1H, m), 8,32 - 8,35 (1H, m), 8,56 (1H, s), 8,66 - 8,68 (2H, m), 8,83 - 8,84 (1H, m), 11,59 (1H, s); m/z (ES+) $(M+H)^+$ = 518; HPLC tR = 1,88 min.

Ejemplo 140: (2S)-3-ciclobutoxi-N-(5-metilpirazin-2-il)-2-(1-(2-(metilsulfonil)fenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida



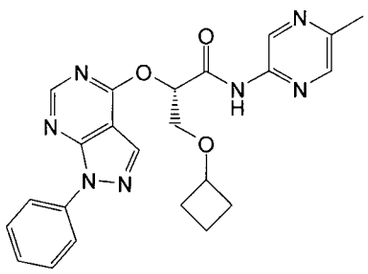
Se preparó en una forma análoga al **Ejemplo 129** a partir del **Producto Intermedio N1** y (S)-3-ciclobutoxi-2-hidroxi-N-(5-metilpirazin-2-il)propanamida (**Producto Intermedio R1**). ^{1}H NMR (400 MHz, DMSO) δ 1,42 - 1,50 (1H, m), 1,62 (1H, q), 1,80 - 1,92 (2H, m), 2,16 - 2,23 (2H, m), 2,45 (3H, s), 3,38 (3H, s), 3,90 - 3,93 (1H, m), 3,99 (1H, q), 4,08 - 4,15 (1H, m), 5,92 (1H, q), 7,76 - 7,78 (1H, m), 7,88 - 7,92 (1H, m), 7,95 - 7,99 (1H, m), 8,18 - 8,21 (1H, m), 8,32 (1H, d), 8,53 (1H, s), 8,63 (1H, s), 9,11 (1H, s), 11,19 (1H, s); m/z (ESI+) $(M+H)^+ = 524$; HPLC t_R = 1,97 min.

Ejemplo 141: (2S)-3-ciclobutoxi-N-(5-metilpirazin-2-il)-2-(1-(3-metilpiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida



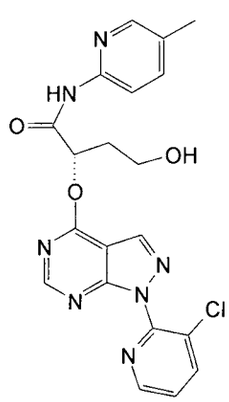
Se preparó en una forma análoga al **Ejemplo 106** a partir del **Producto Intermedio J4** y (S)-3-ciclobutoxi-2-hidroxi-N-(5-metilpirazin-2-il)propanamida (**Producto Intermedio R1**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,39 - 1,46 (1H, m), 1,58 - 1,68 (1H, m), 1,82 - 1,94 (2H, m), 2,10 - 2,19 (2H, m), 2,23 (3H, s), 2,47 (3H, s), 3,90 - 4,01 (3H, m), 5,98 (1H, t), 7,31 - 7,34 (1H, m), 7,73 (1H, d), 8,05 (1H, s), 8,36 (1H, s), 8,47 (1H, d), 8,55 (1H, s), 8,59 (1H, s), 9,38 (1H, s); m/z (ESI+) $(M+H)^+ = 461$; HPLC t_R = 1,92 min.

Ejemplo 142: (S)-3-ciclobutoxi-N-(5-metilpirazin-2-il)-2-(1-fenil-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida



Se agitaron (2S)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-ciclobutoxi-N-(5-metilpirazin-2-il)propanamida (**Ejemplo 156**) (102 mg, 0,21 mmol) y 10 % paladio sobre carbono (25 mg, 0,02 mmol) en etanol (20 mL) bajo una atmósfera de hidrógeno durante 16 horas. La suspensión se filtró a través de celite. Se agregó 10% paladio sobre carbono (25 mg, 0,02 mmol) y la suspensión resultante se agitó bajo una atmósfera de hidrógeno durante 24 horas. La mezcla de reacción se filtró a través de celite y se evaporó. El residuo se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 50% acetato de etilo en isohexano para proporcionar el producto (16,0 mg, 16,9%). ^{1}H NMR (400 MHz, DMSO) δ 1,39 - 1,51 (1H, m), 1,56 - 1,66 (1H, m), 1,78 - 1,90 (2H, m), 2,13 - 2,23 (2H, m), 2,44 (3H, s), 3,89 - 4,14 (3H, m), 5,89 - 5,94 (1H, m), 7,41 (1H, t), 7,59 (2H, t), 8,17 (1H, s), 8,17 (1H, s), 8,32 (1H, s), 8,63 (1H, s), 8,66 (1H, s), 9,09 (1H, s), 11,17 (1H, s); m/z (ESI+) $(M+H)^+$ = 446; HPLC tR = 2,70 min.

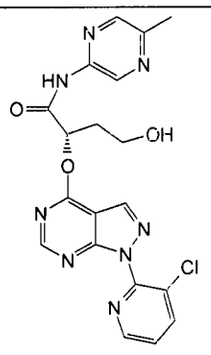
Ejemplo 143: (2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-4-hidroxi-N-(5-metil-2-piridil)butanamida

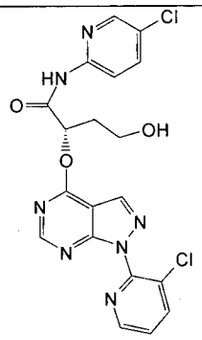
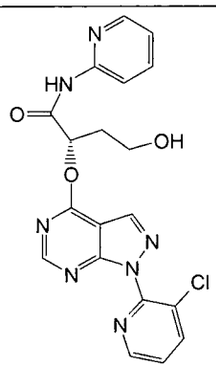
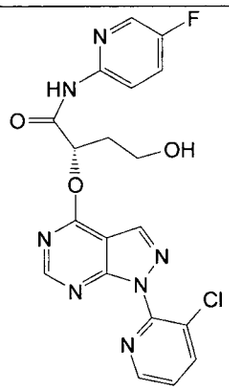


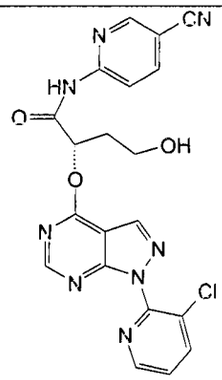
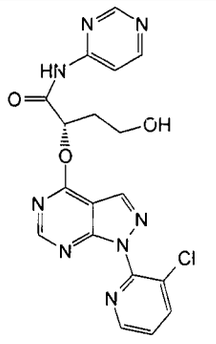
Se agregó trimetilaluminio (0,347 mL, 0,69 mmol) a 5-metilpiridin-2-amina (71,7 mg, 0,66 mmol) en tolueno (8 mL) enfriado hasta alcanzar 0°C bajo nitrógeno. La solución

resultante se agitó a 0°C durante 20 minutos. (3S)-3-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)dihidrofuran-2(3H)-ona (**Producto Intermedio T1**) (200 mg, 0,60 mmol) en tolueno (2 mL) y la reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 1 hora. La reacción luego se calentó a 50°C durante 2 horas. La mezcla de reacción se dejó enfriar y se neutralizó con ácido cítrico (1M, ac.) y luego se diluyó con agua (50 mL) y acetato de etilo (50 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con acetato de etilo (50 mL). Los elementos orgánicos combinados se secaron ($MgSO_4$), se filtraron y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 10% MeOH en DCM para proporcionar el producto (185 mg, 69,8 %). ^{1}H NMR (400 MHz, $CDCl_3$) 2,30 (3H, s), 2,33 - 2,40 (1H, m), 2,44 - 2,52 (1H, m), 2,55 (1H, s), 3,83 - 3,92 (2H, m), 6,07 - 6,10 (1H, m), 7,46 - 7,49 (1H, m), 7,52 - 7,55 (1H, m), 8,00 - 8,02 (1H, m), 8,09 - 8,10 (1H, m), 8,13 (1H, d), 8,47 (1H, s), 8,61 - 8,62 (1H, m), 8,64 (1H, s), 8,68 (1H, s); m/z (ESI+) $(M+H)^+$ = 440; HPLC t_R = 1,68 min.

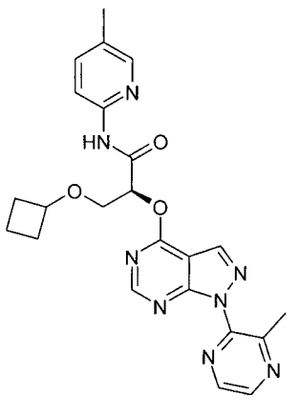
Los siguientes Ejemplos se prepararon utilizando un procedimiento análogo utilizando el **Producto Intermedio T1** y la amina apropiada:

No.	ESTRUCTURA	NOMBRE	M/Z	**Datos de ^{1}H NMR** (400 MHz, $CDCl_3$)
143a		(2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-4-hidroxi-N-(5-metilpirazin-2-il)butanamida	ESI+ $(M+H)^+$ = 441; HPLC t_R = 1,39 min	δ 2,35 - 2,52 (2H, m), 2,54 (3H, s), 3,85 - 3,98 (2H, m), 6,10 - 6,13 (1H, m), 7,46 - 7,50 (1H, m), 8,00 - 8,03 (1H, m), 8,11 (1H, d), 8,45 (1H, s), 8,60 - 8,63 (1H, m), 8,64 (1H, s), 8,77 (1H, s), 9,43 (1H, d)

143b		(2S)-N-(5-cloro-2-piridil)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-4-hidroxi-butanamida	ESI+ (M+H)+ = 460; HPLC t_R = 1,82 min	δ 2,33 - 2,52 (3H, m), 3,83 - 3,97 (2H, m), 6,07 - 6,10 (1H, m), 7,46 - 7,50 (1H, m), 7,67 - 7,70 (1H, m), 8,00 - 8,03 (1H, m), 8,22 - 8,23 (1H, m), 8,23 (1H, d), 8,46 (1H, s), 8,61 - 8,63 (1H, m), 8,64 (1H, s), 8,81 (1H, s)
143c		(2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-4-hidroxi-N-(2-piridil)butanamida	(ESI+) (M+H)+ = 426; HPLC t_R = 1,40 min	δ 2,33 - 2,53 (3H, m), 3,84 - 3,94 (2H, m), 6,08 - 6,11 (1H, m), 7,06 - 7,09 (1H, m), 7,46 - 7,49 (1H, m), 7,70 - 7,75 (1H, m), 8,00 - 8,02 (1H, m), 8,24 (1H, d), 8,28 - 8,30 (1H, m), 8,47 (1H, s), 8,59 - 8,63 (1H, m), 8,65 (1H, s), 8,76 (1H, s)
143d		(2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-4-hidroxi-butanamida	(ESI+) (M+H)+ = 444; HPLC t_R = 1,62 min	δ 2,33 - 2,41 (1H, m), 2,44 - 2,52 (2H, m), 3,83 - 3,98 (2H, m), 6,07 - 6,11 (1H, m), 7,43 - 7,50 (2H, m), 8,00 - 8,03 (1H, m), 8,14 (1H, s), 8,25 - 8,28 (1H, m),

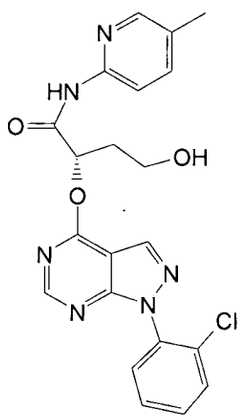
				8,46 (1H, s), 8,59 - 8,63 (1H, m), 8,64 (1H, s), 8,80 (1H, s)
143e		(2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-ciano-2-piridil)-4-hidroxi-butanamida	(ESI+) (M-H)- = 449; HPLC t_R = 1,63 min	δ 2,27 (1H, t), 2,35 - 2,52 (2H, m), 3,85 - 3,99 (2H, m), 6,07 - 6,10 (1H, m), 7,47 - 7,50 (1H, m), 7,95 - 7,98 (1H, m), 8,01 - 8,03 (1H, m), 8,37 - 8,40 (1H, m), 8,46 (1H, s), 8,56 - 8,57 (1H, m), 8,61 - 8,63 (1H, m), 8,64 (1H, s), 9,06 (1H, s)
143f		(2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-4-hidroxi-N-pirimidin-4-il-butanamida	(ESI+) (M-H)- = 425; HPLC t_R = 1,37 min	δ 2,31 (1H, s), 2,35 - 2,52 (2H, m), 3,86 - 3,97 (2H, m), 6,05 - 6,09 (1H, m), 7,44 - 7,50 (1H, m), 8,00 - 8,03 (1H, m), 8,19 - 8,20 (1H, m), 8,46 (1H, s), 8,59 - 8,67 (3H, m), 8,89 (1H, d), 8,94 (1H, s)

Ejemplo 144: (2S)-3-(ciclobutoxi)-2-[1-(3-metilpirazin-2-il)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-metil-2-piridil)propanamida



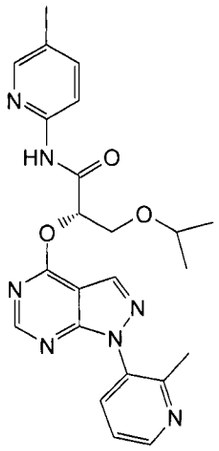
Se preparó utilizando un procedimiento análogo al descrito para el ejemplo 106 utilizando 4-cloro-1-(3-metilpirazin-2-il)-1H-pirazolo[3,4-d]pirimidina (Producto Intermedio I4) con (S)-3-ciclobutoxi-2-hidroxi-N-(5-metilpiridin-2-il)propanamida (Producto Intermedio U1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,43 - 1,55 (1H, m), 1,64 - 1,73 (1H, m), 1,89 - 2,00 (2H, m), 2,17 - 2,24 (2H, m), 2,30 (3H, s), 2,61 (3H, s), 3,97 - 4,08 (3H, m), 6,02 - 6,05 (1H, m), 7,51 - 7,54 (1H, m), 8,09 - 8,10 (1H, m), 8,13 (1H, d), 8,47 (1H, s), 8,51 - 8,52 (1H, m), 8,64 (1H, s), 8,65 (2H, d); m/z (ESI+) (M+H)+ = 461; HPLC t_R = 2,05 min.

Ejemplo 145: (2S)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-4-hidroxi-N-(5-metil-2-piridil)butanamida



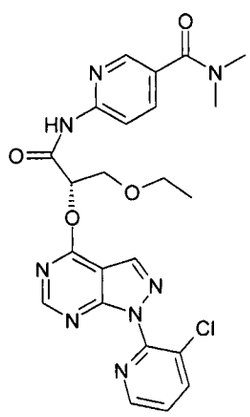
Se preparó utilizando un procedimiento análogo al descrito para el **Ejemplo 143** utilizando (3S)-3-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)dihidrofuran-2(3H)-ona (**Producto Intermedio T2**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2,29 (3H, s), 2,32 - 2,40 (1H, m), 2,44 - 2,52 (1H, m), 2,73 (1H, s), 3,83 - 3,97 (2H, m), 6,07 - 6,10 (1H, m), 7,44 - 7,63 (5H, m), 8,09 - 8,10 (1H, m), 8,13 (1H, d), 8,43 (1H, s), 8,59 (1H, s), 8,76 (1H, s); m/z (ESI+) (M+H)+ = 439; HPLC t_R = 1,81 min

Ejemplo 146: (2S)-3-isopropoxi-N-(5-metil-2-piridil)-2-[1-(2-metil-3-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-propanamida



Se preparó utilizando un procedimiento análogo al descrito para el **Ejemplo 106** utilizando el **Producto Intermedio C7** y el **Producto Intermedio V5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,19 (6H, t), 2,30 (3H, s), 2,45 (3H, s), 3,70 - 3,76 (1H, m), 4,09 - 4,10 (2H, m), 6,01 (1H, t), 7,33 - 7,37 (1H, m), 7,52 - 7,55 (1H, m), 7,75 - 7,77 (1H, m), 8,10 - 8,15 (2H, m), 8,44 (1H, s), 8,58 (1H, s), 8,66 - 8,67 (1H, m), 8,70 (1H, s); m/z (ESI+) $(M+H)^+$ = 448; HPLC t_R = 1,83 min.

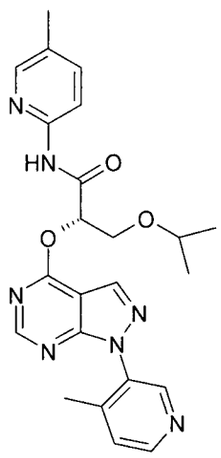
Ejemplo 147: 6-[[(2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-etoxi-propanoil]amino]-N,N-dimetil-piridina-3-carboxamida



Se preparó utilizando un procedimiento análogo al descrito para el **Ejemplo 125** utilizando el **Producto Intermedio W1** y el **Producto Intermedio L2**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,20 - 1,28 (3H, m), 3,04 (3H, s), 3,09 (3H, s), 3,58 - 3,70 (2H, m), 4,07 - 4,15 (2H, m), 6,06 (1H, t), 7,46 - 7,49 (1H, m), 7,79 - 7,82 (1H, m), 8,00 - 8,02 (1H, m), 8,27 - 8,30 (1H, m), 8,39 - 8,40 (1H, m), 8,48 (1H, s), 8,61 - 8,62 (1H, m), 8,63 (1H, s), 8,86 (1H, s); m/z

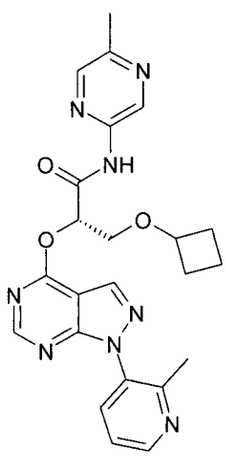
(ESI+) (M+H)+ = 511; HPLC tR = 1,72 min.

Ejemplo 148: (2S)-3-isopropoxi-N-(5-metil-2-piridil)-2-[1-(4-metil-3-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-propanamida



Se preparó utilizando un procedimiento análogo al descrito para el **Ejemplo 106** utilizando el **Producto Intermedio C7** y el **Producto Intermedio X5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,19 (6H, t), 2,25 (3H, s), 2,29 (3H, s), 3,70 - 3,76 (1H, m), 4,09 (2H, d), 6,02 (1H, t), 7,35 (1H, d), 7,51 - 7,54 (1H, m), 8,09 - 8,10 (1H, m), 8,13 (1H, d), 8,44 (1H, s), 8,57 (1H, s), 8,60 (1H, d), 8,65 (1H, s), 8,71 (1H, s); m/z (ES+) (M+H)+ = 448,5; HPLC tR = 1,93 min.

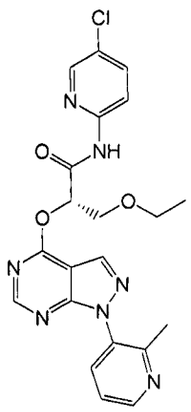
Ejemplo 149: (2S)-3-ciclobutoxi-N-(5-metilpirazin-2-il)-2-(1-(2-metilpiridin-3-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida



Se agregó hidruro de sodio (19,54 mg, 0,49 mmol) a (S)-3-ciclobutoxi-2-hidroxi-N-(5-metilpirazin-2-il)propanamida (**Producto Intermedio R1**) (102 mg, 0,41 mmol) en THF anhidro (5 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos y luego se agregó 4-cloro-1-(2-metilpiridin-3-il)-1H-pirazolo[3,4-d]pirimidina

(**Producto Intermedio V5**) (100 mg, 0,41 mmol). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 1 hora. La mezcla de reacción se neutralizó con ácido cítrico 1M y la mayor parte del THF se eliminó al vacío. La mezcla de reacción se diluyó con agua (20 mL) y acetato de etilo (50 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con acetato de etilo (2 × 50 mL). Los elementos orgánicos combinados se lavaron con salmuera saturada (25 mL), se secaron ($MgSO_4$) y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 5% MeOH en DCM para proporcionar el producto (78 mg, 41,6 %). ^{1}H NMR (400 MHz, DMSO) δ 1,23 - 1,36 (m, 1H), 1,38 - 1,51 (m, 1H), 1,60 - 1,75 (m, 2H), 1,96 - 2,07 (m, 2H), 2,13 (s, 3H), 2,27 (s, 3H), 3,71 - 3,87 (m, 2H), 3,89 - 3,98 (m, 1H), 5,71 - 5,78 (m, 1H), 7,28 - 7,34 (m, 1H), 7,75 (d, 1H), 8,15 (s, 1H), 8,39 (s, 1H), 8,45 - 8,51 (m, 2H), 8,93 (s, 1H), 11,01 (s, 1H); m/z (ESI+) $(M+H)^+$ = 461,48; HPLC tR = 1,75 min

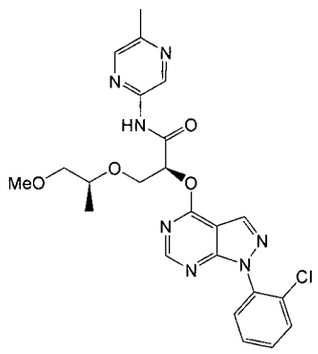
Ejemplo 150: (2S)-N-(5-cloropiridin-2-il)-3-etoxi-2-(1-(2-metilpiridin-3-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida



Se agregó hidruro de sodio (21,49 mg, 0,54 mmol) a (S)-N-(5-cloropiridin-2-il)-3-etoxi-2-hidroxipropanamida (110 mg, 0,45 mmol) en THF anhidro (5 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos y luego se agregó 4-cloro-1-(2-metilpiridin-3-il)-1H-pirazolo[3,4-d]pirimidina (110 mg, 0,45 mmol). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 1 hora. La mezcla de reacción se neutralizó con ácido cítrico 1M y la mayor parte del THF se eliminó al vacío. La mezcla de reacción se diluyó con agua (20 mL) y acetato de etilo (50 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con acetato de etilo (2 × 20 mL). Los elementos orgánicos combinados se lavaron con salmuera saturada

(10 mL), se secaron ($MgSO_4$) y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 5% MeOH en DCM para proporcionar el producto (24,0 mg, 11,8%). ^1H NMR (400 MHz, $CDCl_3$) δ1,23 (t, 3H), 2,45 (s, 3H), 3,59 - 3,72 (m, 2H), 4,05 - 4,16 (m, 2H), 6,06 (t, 1H), 7,31 - 7,38 (m, 1H), 7,66 - 7,71 (m, 1H), 7,73 - 7,78 (m, 1H), 8,21 - 8,27 (m, 2H), 8,42 (s, 1H), 8,57 (s, 1H), 8,64 - 8,69 (m, 1H), 8,89 (s, 1H). m/z (ESI+) (M+H)+ = 454,31; HPLC tR = 1,83 min

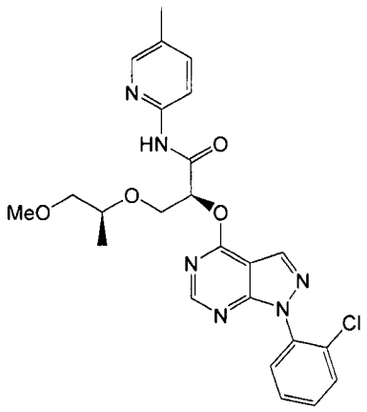
Ejemplo 151: (2S)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-((S)-1-metoxipropan-2-iloxi)-N-(5-metilpirazin-2-il)propanamida



Se agregó hidruro de sodio (23,17 mg, 0,58 mmol) en una porción a una solución agitada de (S)-2-hidroxi-3-((S)-1-metoxipropan-2-iloxi)-N-(5-metilpirazin-2-il)propanamida (**Producto Intermedio Y3**) (78 mg, 0,29 mmol) en THF anhidro (5 mL) a 0°C. La mezcla resultante se agitó durante 10 minutos y luego se agregó gota a gota una solución de 4-cloro-1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio B1**) (115 mg, 0,43 mmol) en THF seco (2 mL) durante 1 minuto y la reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 1 hora. La mezcla de reacción se diluyó con acetato de etilo (20 mL) y se lavó secuencialmente con agua (10 mL) y salmuera saturada (5 mL). La capa orgánica se secó ($MgSO_4$) y se evaporó. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0-100% acetato de etilo en isohexano para proporcionar el producto (115 mg, 80 %). ^1H NMR (400 MHz, $CDCl_3$) δ 1,20 (d, 3H), 2,53 (s, 3H), 3,35 - 3,50 (m, 5H), 3,79 - 3,88 (m, 1H), 4,08 - 4,16 (m, 1H), 4,21 - 4,28 (m, 1H), 5,94 - 5,99 (m, 1H), 7,43 - 7,55 (m, 3H), 7,60 - 7,63 (m, 1H), 8,12 - 8,13 (m, 1H), 8,40 (s, 1H), 8,58 (s, 1H), 9,18 (s, 1H), 9,42 (d, 1H). m/z (ESI+) (M+H)+ = 498,36; HPLC t_R = 2,25 min.

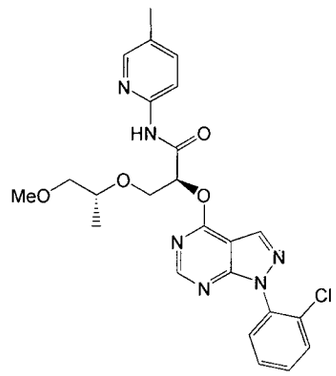
Ejemplo 152: (2S)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-((S)-1-

metoxipropan-2-iloxi)-N-(5-metilpiridin-2-il)propanamida



Se agregó hidruro de sodio (21,24 mg, 0,53 mmol) a (S)-2-hidroxi-3-((S)-1-metoxipropan-2-iloxi)-N-(5-metilpiridin-2-il)propanamida (**Producto Intermedio Y5**) (95 mg, 0,35 mmol) en THF anhidro (5 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos y luego se agregó 4-cloro-1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio B1**) (122 mg, 0,46 mmol) en THF seco (2 mL). La reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 1 hora. La mezcla de reacción se diluyó con acetato de etilo (20 mL) y se lavó secuencialmente con agua (10 mL) y salmuera saturada (5 mL). La capa orgánica se secó ($MgSO_4$) y se evaporó. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0-100% acetato de etilo en isohexano para proporcionar el producto (160 mg, 91 %). ^{1}H NMR (400 MHz, DMSO) δ 1,09 (d, 3H), 2,24 (s, 3H), 3,23 (s, 3H), 3,26 - 3,38 (m, 2H), 3,77 - 3,86 (m, 1H), 4,00 - 4,16 (m, 2H), 5,85 - 5,91 (m, 1H), 7,55 - 7,70 (m, 4H), 7,73 - 7,78 (m, 1H), 7,88 (d, 1H), 8,16 - 8,19 (m, 1H), 8,54 (s, 1H), 8,59 (s, 1H), 10,79 (s, 1H). m/z (ESI+) $(M+H)^+$ = 497,20; HPLC t_R = 2,36 min.

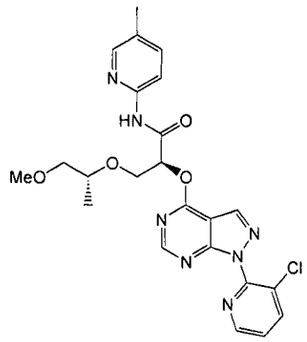
Ejemplo 153: (2S)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-((R)-1-metoxipropan-2-iloxi)-N-(5-metilpiridin-2-il)propanamida



Se agregó trimetilaluminio (2M en hexano) (0,489 mL, 0,98 mmol) a 5-metilpiridin-2-amina (101 mg, 0,94 mmol) en tolueno (3 mL) enfriado hasta alcanzar 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 20 minutos. Se agregó (2S)-metil 2-(1-(2-clorofenil)-1H-pirazolo[3,4-d] pirimidin-4-iloxi)-3-((R)-1-metoxipropan-2-iloxi) propanoato (**Producto Intermedio Y7**) (358 mg, 0,85 mmol) en tolueno (5 mL) y la reacción se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó a reflujo durante 4 horas. La mezcla de reacción se neutralizó con ácido cítrico 1M y luego se diluyó con solución de tartrato de potasio y sodio (20%, ac) (20 ml) y acetato de etilo (20 mL) antes de agitar vigorosamente durante 2 horas. Las fases se separaron y la capa orgánica se secó ($MgSO_4$) y se evaporó. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 100% acetato de etilo en isohexano para proporcionar el producto (167 mg, 39,5 %). ^{1}H NMR (400 MHz, DMSO) δ 1,08 (d, 3H), 2,24 (s, 3H), 3,21 (s, 3H), 3,22 - 3,38 (m, 2H), 3,75 - 3,85 (m, 1H), 3,98 - 4,15 (m, 2H), 5,85 - 5,93 (m, 1H), 7,55 - 7,70 (m, 4H), 7,73 - 7,78 (m, 1H), 7,88 (d, 1H), 8,15 - 8,19 (m, 1H), 8,53 (s, 1H), 8,59 (s, 1H), 10,82 (s, 1H). m/z (ESI+) (M+H)+ = 497,37; HPLC t_R = 2,37 min.

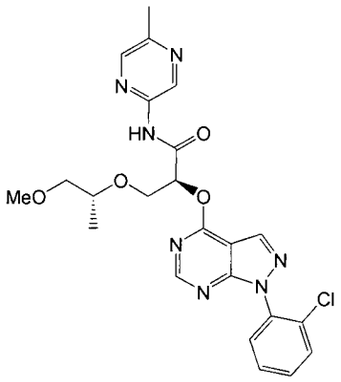
Ejemplo 154: (2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-((R)-1-metoxipropan-2-iloxi)-N-(5-metilpiridin-2-il)propanamida

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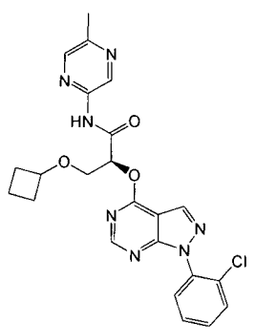
Se agregó trimetilaluminio (0,334 mL, 0,67 mmol) a 5-metilpiridin-2-amina (69,1 mg, 0,64 mmol) en tolueno (8 mL) enfriado hasta alcanzar 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 20 minutos. Se agregó (2S)-metil 2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-((R)-1-metoxipropan-2-iloxi)propanoato (**Producto Intermedio Y8**) (245 mg, 0,58 mmol) en tolueno (2 mL) y la reacción se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó a reflujo durante 24 horas. La mezcla de reacción se dejó enfriar y se neutralizó con ácido cítrico (1M, ac) y luego se diluyó con agua (50 mL) y acetato de etilo (50 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con acetato de etilo (50 mL). Los elementos orgánicos combinados se secaron ($MgSO_4$), se filtraron y se evaporaron. El producto bruto se purificó mediante HPLC preparativa (columna Phenomenex Gemini C18 110A (Axia), 5µ sílice, 19 mm de diámetro, 100 mm de longitud), utilizando mezclas cada vez menos polares de agua (que contenía ácido fórmico al 0,1%) y MeCN como eluyentes para proporcionar el producto (137 mg, 47,4 %). ^{1}H NMR (400 MHz, DMSO) δ 1,10 (d, 3H), 2,26 (s, 3H), 3,23 - 3,42 (m, 5H), 3,76 - 3,85 (m, 1H), 4,10 - 4,16 (m, 2H), 5,95 - 6,00 (m, 1H), 7,55 - 7,60 (m, 1H), 7,68 - 7,73 (m, 1H), 7,86 (d, 1H), 8,14 - 8,18 (m, 1H), 8,24 - 8,29 (m, 1H), 8,54 (s, 2H), 8,62 - 8,67 (m, 1H), 10,21 (s, 1H) m/z (ESI-) $(M+H)^+$ = 498,16; HPLC t_R = 1,84 min.

Ejemplo 155: (2S)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-((R)-1-metoxipropan-2-iloxi)-N-(5-metilpirazin-2-il)propanamida



Se agregó hidruro de sodio (14,26 mg, 0,36 mmol) a (S)-2-hidroxi-3-((R)-1-metoxipropan-2-iloxi)-N-(5-metilpirazin-2-il)propanamida (**Producto Intermedio Y12**) (64 mg, 0,24 mmol) en THF anhidro (5 mL) a 0°C bajo nitrógeno. La mezcla resultante se agitó durante 10 minutos a 0°C y se agregó 4-cloro-1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidina (86 mg, 0,32 mmol) y la reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 1 hora. La mezcla de reacción se diluyó con acetato de etilo (20 mL) y se lavó secuencialmente con agua (10 mL) y salmuera saturada (5 mL). La capa orgánica se secó ($MgSO_4$) y se evaporó. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0-100% acetato de etilo en isohexano para proporcionar el producto (75 mg, 63,4 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ1,16 (d, 3H), 2,52 (s, 3H), 3,33 - 3,48 (m, 5H), 3,80 - 3,89 (m, 1H), 4,16 - 4,27 (m, 2H), 6,01 (t, 1H), 7,45 - 7,55 (m, 3H), 7,60 - 7,64 (m, 1H), 8,11 - 8,12 (m, 1H), 8,41 (s, 1H), 8,59 (s, 1H), 8,94 (s, 1H), 9,42 (d, 1H). m/z (ESI+) (M+H)+ = 498,36; HPLC t_R = 2,19 min.

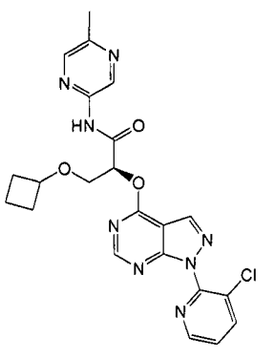
Ejemplo 156: (2S)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-ciclobutoxi-N-(5-metilpirazin-2-il)propanamida



Se agregó hidruro de sodio (44,4 mg, 1,11 mmol) a (S)-3-ciclobutoxi-2-hidroxi-N-(5-

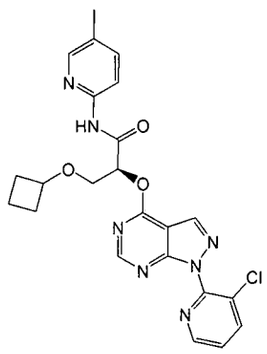
metilpirazin-2-il)propanamida (**Producto Intermedio R1**) (186 mg, 0,74 mmol) en THF anhidro (5 mL) a 0°C bajo nitrógeno. La mezcla resultante se agitó durante 10 minutos a 0°C y se agregó 4-cloro-1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio B1**) (255 mg, 0,96 mmol) y la reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 30 minutos. La mezcla de reacción se diluyó con acetato de etilo (20 mL) y se lavó secuencialmente con agua (10 mL) y salmuera saturada (5 mL). La capa orgánica se secó ($MgSO_4$) y se evaporó. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0-100% acetato de etilo en isohexano para proporcionar el producto (262 mg, 73,8%). ^{1}H NMR (400 MHz, DMSO) δ 1,39 - 1,52 (m, 1H), 1,56 - 1,67 (m, 1H), 1,77 - 1,91 (m, 2H), 2,13 - 2,24 (m, 2H), 2,44 (s, 3H), 3,88 - 4,02 (m, 2H), 4,06 - 4,15 (m, 1H), 5,89 - 5,94 (m, 1H), 7,56 - 7,70 (m, 3H), 7,73 - 7,78 (m, 1H), 8,31 - 8,33 (m, 1H), 8,54 (s, 1H), 8,63 (s, 1H), 9,10 (s, 1H), 11,17 (s, 1H). m/z (ESI+) $(M+H)^+$ = 480,33; HPLC t_R = 2,45 min.

Ejemplo 157: (2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-ciclobutoxi-N-(5-metilpirazin-2-il)propanamida



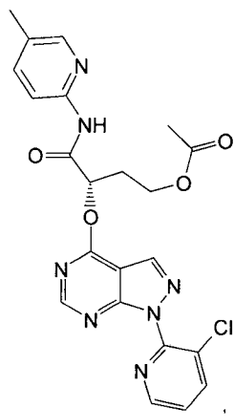
Se preparó utilizando un procedimiento análogo al descrito para el Ejemplo 156 utilizando el **Producto Intermedio R1** y **el Producto Intermedio B15**. ^{1}H NMR (400 MHz, DMSO) δ 1,40 - 1,52 (m, 1H), 1,56 - 1,67 (m, 1H), 1,78 - 1,92 (m, 2H), 2,14 - 2,23 (m, 2H), 2,45 (s, 3H), 3,89 - 4,01 (m, 2H), 4,06 - 4,15 (m, 1H), 5,89 - 5,95 (m, 1H), 7,73 - 7,78 (m, 1H), 8,31 - 8,33 (m, 1H), 8,35 (d, 1H), 8,56 (s, 1H), 8,65 - 8,69 (m, 2H), 9,09 (s, 1H), 11,18 (s, 1H). m/z (ESI+) $(M+H)^+$ = 481,30; HPLC t_R = 2,06 min.

Ejemplo 158: (2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-ciclobutoxi-N-(5-metilpiridin-2-il)propanamida



Se preparó utilizando un procedimiento análogo al descrito para el ejemplo 156 utilizando el **Producto Intermedio R6** y **el Producto Intermedio B15**. ^{1}H NMR (400 MHz, DMSO) δ 1,41 - 1,52 (m, 1H), 1,56 - 1,67 (m, 1H), 1,78 - 1,91 (m, 2H), 2,13 - 2,23 (m, 2H), 2,24 (s, 3H), 3,86 - 3,99 (m, 2H), 4,06 - 4,15 (m, 1H), 5,86 - 5,92 (m, 1H), 7,56 - 7,61 (m, 1H), 7,73 - 7,77 (m, 1H), 7,84 - 7,90 (m, 1H), 8,16 - 8,19 (m, 1H), 8,32 - 8,35 (m, 1H), 8,56 (s, 1H), 8,65 - 8,69 (m, 2H), 10,86 (s, 1H). m/z (ESI+) (M+H)+ = 480,35; HPLC t_R = 2,27 min.

Ejemplo 159: acetato de [(3S)-3-[1-(3-cloropiridin-2-il)pirazolo[4,5-e]pirimidin-4-il]oxi-4-[(5-metilpiridin-2-il)amino]-4-oxobutilo]

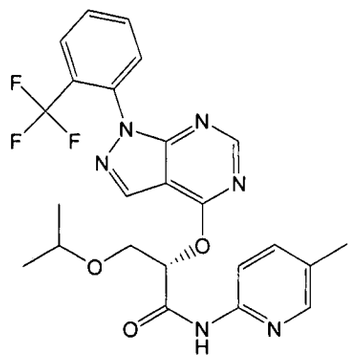


Se agregó anhídrido acético (0,035 mL, 0,38 mmol) a (2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-4-hidroxi-N-(5-metilpiridin-2-il)butanamida (**Ejemplo 143**) (150 mg, 0,34 mmol), N,N-Diisopropiletilamina (0,089 mL, 0,51 mmol) y 4-dimetilaminopiridina (4,17 mg, 0,03 mmol) en DCM (2 mL) a 0°C durante un período de 5 minutos bajo nitrógeno. La solución resultante se agitó a 0°C durante 25 minutos. Los

volátiles se retiraron bajo presión reducida y el producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 100% acetato de etilo en isohexano para proporcionar el producto (75 mg, 45,6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,95 (3H, s), 2,29 (3H, s), 2,54 (2H, q), 4,31 - 4,39 (2H, m), 6,00 (1H, t), 7,45 - 7,49 (1H, m), 7,53 (1H, d), 8,00 - 8,02 (1H, m), 8,10 - 8,14 (2H, m), 8,43 (1H, s), 8,61 (1H, q), 8,64 (1H, s), 8,80 (1H, s);

m/z (ES+) $(M+H)^+$ = 482; HPLC tR = 2,04 min.

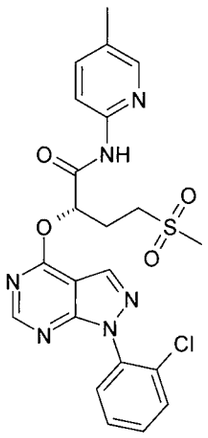
Ejemplo 160: (2S)-3-isopropoxi-N-(5-metilpiridin-2-il)-2-(1-(2-(trifluorometil)fenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida



Se agregó hidruro de sodio (10,78 mg, 0,27 mmol) a (S)-2-hidroxi-3-isopropoxi-N-(5-metilpiridin-2-il)propanamida (**Producto Intermedio C7**) (53,5 mg, 0,22 mmol) en THF anhidro (50 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos y luego se agregó 4-fenoxi-1-(2-(trifluorometil)fenil)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio Z1**) (80 mg, 0,22 mmol). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 1 hora. La mezcla de reacción se neutralizó con ácido cítrico 1M y la mayor parte del THF se eliminó al vacío. La mezcla de reacción se diluyó con agua (20 mL) y acetato de etilo (50 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con acetato de etilo (2 × 100 mL). Los elementos orgánicos combinados se lavaron con salmuera saturada (75 mL), se secaron ($MgSO_4$) y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 50 a 100% acetato de etilo en isohexano. El residuo se purificó mediante HPLC preparativa utilizando mezclas cada vez menos polares de agua (que contenía amoníaco al 1%) y MeCN como eluyentes para proporcionar el producto (60,0 mg, 53,4%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,17 - 1,20 (6H, m), 2,30 (3H, s), 3,69 - 3,75 (1H, m), 4,09 (2H, d), 6,01 (1H, t), 7,52 - 7,56 (2H, m), 7,69 (1H, t), 7,76 (1H, t), 7,91

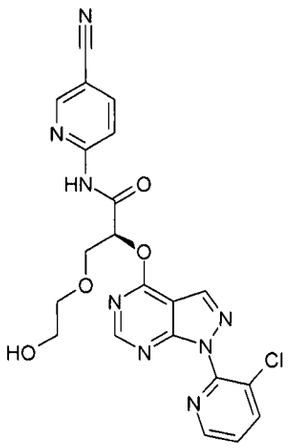
(1H, d), 8,10 - 8,15 (2H, m), 8,42 (1H, s), 8,56 (1H, s), 8,72 (1H, s); m/z (ES+) (M+H)+ = 501; HPLC tR = 2,70 min.

Ejemplo 161: - (2S)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-metilpiridin-2-il)-4-(metilsulfonil)butanamida



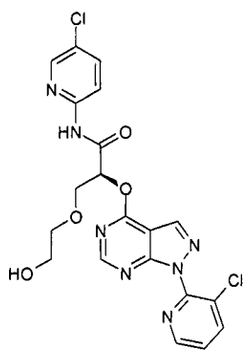
Se agregó trimetilaluminio (0,135 mL, 0,27 mmol) a 2-amino-5-metilpiridina (28,0 mg, 0,26 mmol) en tolueno (5 mL) enfriado hasta alcanzar 0°C bajo nitrógeno. Se agregó (2S)-metil 2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-4-(metilsulfonil)butanoato (**Producto Intermedio AA1**) (100 mg, 0,24 mmol) y la reacción se calentó hasta alcanzar 100°C durante 3 horas en el reactor de microondas y luego se dejó enfriar. La mezcla de reacción se neutralizó con ácido cítrico (1M, ac) y luego se diluyó con agua (30 mL) y acetato de etilo (50 mL). La capa acuosa se lavó con acetato de etilo. Los elementos orgánicos combinados se secaron ($MgSO_4$) y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 30 a 50% acetato de etilo en isohexano para proporcionar el producto (90 mg, 76%) ^1H NMR (400 MHz, $CDCl_3$) δ 2,31 (3H, s), 2,71 - 2,77 (2H, m), 2,98 (3H, s), 3,32 - 3,38 (2H, m), 6,12 (1H, t), 7,45 - 7,56 (4H, m), 7,62 - 7,64 (1H, m), 8,09 - 8,11 (2H, m), 8,41 (1H, s), 8,61 (1H, s), 8,69 (1H, s); m/z (ES+) (M+H)+ = 501; HPLC tR = 2,05 min.

Ejemplo 162: (2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-cianopiridin-2-il)-3-(2-hidroxietoxi)propanamida



Se agregó fluoruro de tetrabutilamonio (1M en THF) (0,139 mL, 0,14 mmol) a (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-cianopiridin-2-il)propanamida (**Producto Intermedio AB1**) (100 mg, 0,14 mmol) en THF (2 mL) bajo nitrógeno. La mezcla resultante se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se aplacó con NH_4Cl saturado (1 mL), se diluyó con DCM (10ml) y se vertió en un separador de fases. La capa orgánica se recogió y se evaporó. El residuo se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 100% acetato de etilo en isohexano para proporcionar el producto (38,0 mg, 56,8%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2,36 (1H, s), 3,70 - 3,86 (4H, m), 4,16 - 4,27 (2H, m), 6,07 (1H, t), 7,45 - 7,52 (1H, m), 7,93 - 8,05 (2H, m), 8,32 - 8,38 (1H, m), 8,46 (1H, s), 8,55 - 8,58 (1H, m), 8,60 - 8,65 (2H, m), 9,28 (1H, s). m/z (ES+) $(M+H)^+$ = 481,31; HPLC tR = 1,63 min.

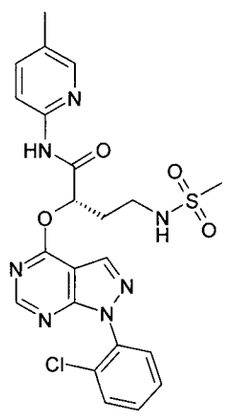
Ejemplo 163: (2S)-N-(5-cloropiridin-2-il)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-(2-hidroxietoxi)propanamida



Se agregó fluoruro de tetrabutilamonio (1M en THF) (0,790 mL, 0,79 mmol) a (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-N-(5-cloropiridin-2-il)-2-(1-(3-cloropiridin-2-il)-1H-

pirazolo[3,4-d]pirimidin-4-iloxi)propanamida (**Producto Intermedio AB4**) (576 mg, 0,79 mmol) en THF (2 mL) bajo nitrógeno. La mezcla resultante se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se aplacó con NH_4Cl saturado (1 mL), se diluyó con DCM (10ml) y se vertió en un separador de fases. La capa orgánica se recogió y se evaporó. El residuo se purificó mediante HPLC preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, 50 mm de diámetro, 150 mm de longitud), utilizando mezclas cada vez menos polares de agua (que contenía NH3 al 1%) y MeCN como eluyentes. El producto resultante se descompuso en cierto grado durante la evaporación y por lo tanto se purificó nuevamente mediante cromatografía instantánea en sílice, eluyendo con 0 a 10% MeOH en acetato de etilo para proporcionar el producto (82 mg, 21%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2,49 - 2,56 (1H, m), 3,69 - 3,85 (4H, m), 4,14 - 4,25 (2H, m), 6,08 (1H, t), 7,45 - 7,50 (1H, m), 7,67 - 7,72 (1H, m), 7,98 - 8,04 (1H, m), 8,15 - 8,28 (2H, m), 8,47 (1H, s), 8,58 - 8,65 (2H, m), 8,99 (1H, s); m/z (ES+) (M+H)+ = 490,35; HPLC tR = 1,82 min.

Ejemplo 164: (2S)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-metilpiridin-2-il)-4-(metilsulfonamido)butanamida

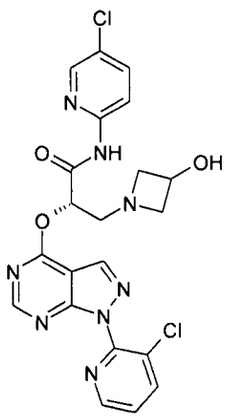


Se agregó trimetilaluminio (2M en hexano) (0,164 mL, 0,33 mmol) a 5-metilpiridin-2-amina (33,8 mg, 0,31 mmol) en tolueno (5 mL) enfriado hasta alcanzar 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 20 minutos. Se agregó (3S)-3-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-1-(metilsulfonil)pirrolidin-2-ona (**Producto Intermedio AC1**) (116 mg, 0,28 mmol) en tolueno (1 mL) y la reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 1 hora. La reacción luego se calentó hasta alcanzar reflujo durante 2,5 horas. La mezcla de reacción se dejó enfriar y se concentró al vacío. El residuo se neutralizó con ácido cítrico y solución de

tartrato de potasio y sodio (sat.) y se agitó vigorosamente durante 45 mins. La mezcla se separó y la fase acuosa se extrajo nuevamente con acetato de etilo, la capa orgánica se secó ($MgSO_4$) y se evaporó. El residuo se purificó mediante HPLC preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, 50 mm de diámetro, 150 mm de longitud), utilizando mezclas cada vez menos polares de agua (que contenía ácido fórmico al 0,1%) y MeCN como eluyentes para proporcionar el producto (52,0 mg, 35,4%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2,30 (3H, s), 2,37 - 2,55 (2H, m), 2,98 (3H, s), 3,35 - 3,55 (2H, m), 4,95 - 5,10 (1H, m), 6,04 (1H, t), 7,44 - 7,58 (4H, m), 7,60 - 7,65 (1H, m), 8,07 - 8,15 (2H, m), 8,44 (1H, s), 8,61 (1H, s), 8,69 (1H, s);

m/z (ES+) $(M+H)^+$ = 516,28; HPLC tR = 1,84 min.

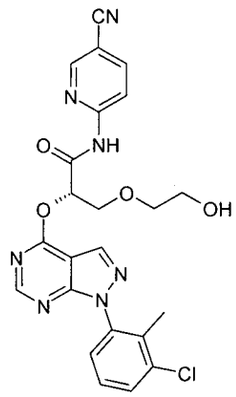
Ejemplo 165: (2S)-N-(5-cloropiridin-2-il)-2-[1-(3-cloropiridin-2-il)pirazolo[4,5-e]pirimidin-4-il]oxi-3-(3-hidroxiazetidin-1-il)propanamida



Se agregó fluoruro de tetrabutilamonio (1M en THF) (5,96 mL, 5,96 mmol) a (2S)-3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-N-(5-cloropiridin-2-il)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida (**Producto Intermedio AD1**) (3,67 g, 5,96 mmol) en THF (75 mL) bajo nitrógeno. La mezcla resultante se agitó a temperatura ambiente durante 20 horas, se agregó cloruro de amonio saturado (50 mL), se diluyó con DCM (100 mL) y se vertió en un separador de fases. La capa orgánica se evaporó y el producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 10% MeOH en EtOAc para proporcionar el producto (1,7g, 57%). ^{1}H NMR (400 MHz, DMSO) δ 2,95 - 3,10 (3H, m), 3,10 - 3,15 (1H, m), 3,60 - 3,70 (2H, m), 4,14 - 4,21 (1H, m), 5,26 (1H, d), 5,73 - 5,75 (1H, m), 7,74 (1H, dd), 7,88 (1H, dd), 8,01 - 8,07 (1H, m), 8,33 (1H, dd), 8,39 - 8,40 (1H, m), 8,55 (1H, s), 8,66 (1H, s), 8,68 (1H, dd), 11,13 (1H, s);

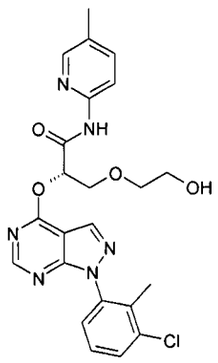
m/z (ESI+) $(M+H)^+$ = 501; HPLC t_R = 1,27 min.

Ejemplo 166: (2S)-2-[1-(3-cloro-2-metilfenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-cianopiridin-2-il)-3-(2-hidroxietoxi)propanamida



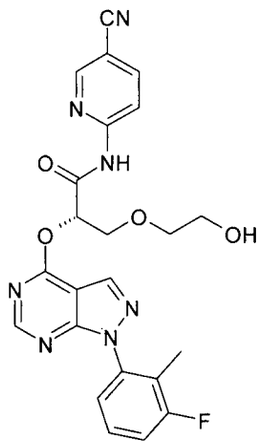
Una solución de fluoruro de tetrabutilamonio (1M en THF) (1,557 mL, 1,56 mmol) se agregó gota a gota a una solución agitada de (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(3-cloro-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-cianopiridin-2-il)propanamida (**Producto Intermedio AE1**) (950 mg, 1,30 mmol) en THF (15 mL) durante un período de 1 minuto y la solución resultante se agitó a temperatura ambiente durante 3 horas. Se agregó cloruro de amonio saturado (20 mL) a la mezcla de reacción que luego se diluyó con EtOAc (25 mL) y se lavó secuencialmente con agua (25 mL) y salmuera saturada (25 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó al vacío. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 60 a 100% EtOAc en isohexano y las fracciones se evaporaron hasta secarse para proporcionar el producto como una espuma blanca que contenía ~10-15% del enantiómero opuesto. La HPLC quiral y luego la HPLC de fase inversa (acetonitrilo/agua con modificador de ácido fórmico al 0,1%) proporcionaron (350mg, 54%) una espuma amorfa. ^{1}H NMR (400 MHz, DMSO) δ 2,06 (3H, s), 3,51 - 3,57 (2H, m), 3,58 - 3,68 (2H, m), 4,03 - 4,07 (1H, m), 4,11 - 4,15 (1H, m), 4,55 - 4,67 (1H, m), 5,91 - 5,98 (1H, m), 7,42 - 7,47 (2H, m), 7,64 - 7,69 (1H, m), 8,13 (1H, dd), 8,25 (1H, dd), 8,54 (1H, s), 8,62 (1H, s), 8,82 (1H, dd), 11,53 (1H, s); m/z (ESI-) (M-H)- = 492; HPLC t_R = 2,25 min.

Ejemplo 167: (2S)-2-[1-(3-cloro-2-metilfenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-(2-hidroxietoxi)-N-(5-metilpiridin-2-il)propanamida



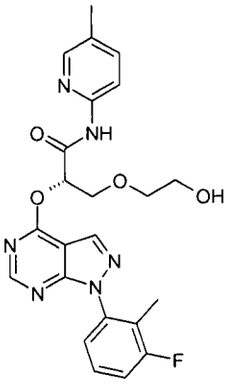
Una solución de fluoruro de tetrabutilamonio (1M en THF) (0,832 mL, 0,83 mmol) se agregó gota a gota a una solución agitada de (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(3-cloro-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-metilpiridin-2-il)propanamida (**Producto Intermedio AE3**) (500 mg, 0,69 mmol) en THF (15 mL) durante un período de 1 minuto y la solución resultante se agitó a temperatura ambiente durante 3 horas. Se agregó cloruro de amonio saturado (20 mL) a la mezcla de reacción que luego se diluyó con EtOAc (25 mL) y se lavó secuencialmente con agua (25 mL) y salmuera saturada (25 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó al vacío. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 60 a 100% EtOAc en isohexano. Esto se purificó adicionalmente mediante HPLC quiral para proporcionar el producto (76mg, 52%). ^{1}H NMR (400 MHz, DMSO) δ 2,06 (3H, s), 2,24 (3H, s), 3,53 - 3,58 (2H, m), 3,58 - 3,68 (2H, m), 4,00 - 4,05 (1H, m), 4,08 - 4,13 (1H, m), 4,61 (1H, t), 5,93 - 6,01 (1H, m), 7,45 - 7,02 (2H, m), 7,57 - 7,60 (1H, m), 7,66 - 7,69 (1H, m), 7,88 - 7,95 (1H, m), 8,17 - 8,18 (1H, m), 8,54 (1H, s), 8,62 (1H, s), 10,86 (1H, s); m/z (ESI+) $(M+H)^+$ = 483; HPLC t_R = 2,14 min.

Ejemplo 168: (2S)-N-(5-cianopiridin-2-il)-2-[1-(3-fluoro-2-metilfenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-(2-hidroxietoxi)propanamida



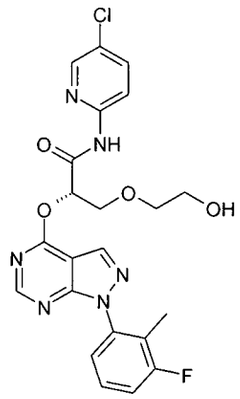
Una solución de fluoruro de tetrabutilamonio (1M en THF, 1,504 mL, 1,50 mmol) se agregó gota a gota a una solución agitada de (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-N-(5-cianopiridin-2-il)-2-(1-(3-fluoro-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida (**Producto Intermedio AF1**) (520 mg, 0,73 mmol) en THF (15 mL) durante un período de 1 minuto y la solución resultante se agitó a temperatura ambiente durante 3 horas. Se agregó cloruro de amonio saturado (20 mL) a la mezcla de reacción que luego se diluyó con EtOAc (25 mL) y se lavó secuencialmente con agua (25 mL) y salmuera saturada (25 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó al vacío. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 60 a 100% EtOAc en isohexano, y luego mediante HPLC quiral para proporcionar el producto (250mg, 72%). ^{1}H NMR (400 MHz, DMSO) δ 1,99 (3H, d), 3,50 - 3,55 (2H, m), 3,58 - 3,67 (2H, m), 4,03 - 4,07 (1H, m), 4,11 - 4,15 (1H, m), 4,52 - 4,65 (1H, m), 5,92 - 5,98 (1H, m), 7,31 - 7,34 (1H, m), 7,40 - 7,50 (2H, m), 8,12 - 8,14 (1H, m), 8,22 - 8,25 (1H, m), 8,55 (1H, s), 8,62 (1H, s), 8,81 - 8,85 (1H, m), 11,5 (1H, s); m/z (ESI-) (M-H)- = 476; HPLC t_R = 2,10 min.

Ejemplo 169: (2S)-2-[1-(3-fluoro-2-metilfenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-(2-hidroxietoxi)-N-(5-metilpiridin-2-il)propanamida



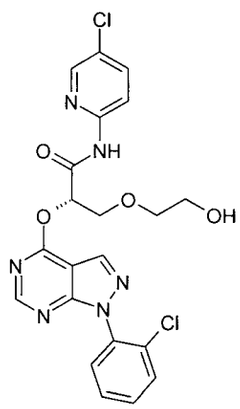
Una solución de fluoruro de tetrabutilamonio (1M en THF) (1,504 mL, 1,50 mmol) se agregó gota a gota a una solución agitada de (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(3-fluoro-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-metilpiridin-2-il)propanamida (**Producto Intermedio AF2**) (430 mg, 0,61 mmol) en THF (15 mL) durante un período de 1 minuto y la solución resultante se agitó a temperatura ambiente durante 3 horas. Se agregó cloruro de amonio saturado (20 mL) a la mezcla de reacción que luego se diluyó con EtOAc (25 mL) y se lavó secuencialmente con agua (25 mL) y salmuera saturada (25 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el producto bruto que se purificó mediante cromatografía instantánea en sílice, gradiente de elución 60 a 100% EtOAc en isohexano, luego mediante HPLC quiral para proporcionar el producto (160mg, 56%). ^{1}H NMR (400 MHz, DMSO) δ 1,99 (3H, d), 2,24 (3H, s), 3,50 - 3,56 (2H, m), 3,58 - 3,68 (2H, m), 4,00 - 4,05 (1H, m), 4,08 - 4,13 (1H, m), 4,61 (1H, t), 5,91 - 5,96 (1H, m), 7,30 - 7,33 (1H, m), 7,40 - 7,51 (2H, m), 7,57 - 7,60 (1H, m), 7,85 - 7,88 (1H, m), 8,17 - 8,18 (1H, m), 8,54 (1H, s), 8,61 (1H, s), 10,85 (1H, s); m/z (ESI+) $(M+H)^+$ = 467; HPLC t_R = 1,98 min.

Ejemplo 170: (2S)-N-(5-cloropiridin-2-il)-2-[1-(3-fluoro-2-metilfenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-(2-hidroxietoxi)propanamida



Una solución de fluoruro de tetrabutilamonio (1M en THF) (1,504 mL, 1,50 mmol) se agregó gota a gota a una solución agitada de (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-N-(5-cloropiridin-2-il)-2-(1-(3-fluoro-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida (**Producto Intermedio AF3**) (600 mg, 0,83 mmol) en THF (15 mL) durante un período de 1 minuto y la solución resultante se agitó a temperatura ambiente durante 3 horas. Se agregó cloruro de amonio saturado (20 mL) a la mezcla de reacción que luego se diluyó con EtOAc (25 mL) y se lavó secuencialmente con agua (25 mL) y salmuera saturada (25 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó al vacío. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 60 a 100% EtOAc en isohexano, luego mediante HPLC quiral para proporcionar el producto (252mg, 62%). ^{1}H NMR (400 MHz, DMSO) δ 2,07 (3H, s), 3,53 - 3,62 (2H, m), 3,65 - 3,72 (2H, m), 4,06 - 4,22 (2H, m), 4,61 - 4,71 (1H, m), 5,96 - 6,05 (1H, m), 7,36 - 7,42 (1H, m), 7,44 - 7,55 (2H, m), 7,92 - 7,96 (1H, m), 8,08 (1H, d), 8,45 (1H, dd), 8,60 (1H, s), 8,71 (1H, s), 11,18 (1H, s); m/z (ESI-) (M-H)- = 485; HPLC t_R = 2,29 min.

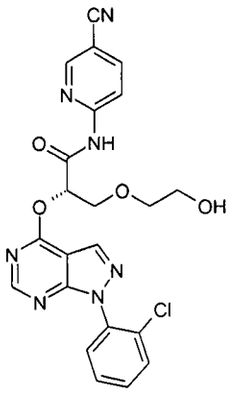
Ejemplo 171: (2S)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-cloropiridin-2-il)-3-(2-hidroxietoxi)propanamida



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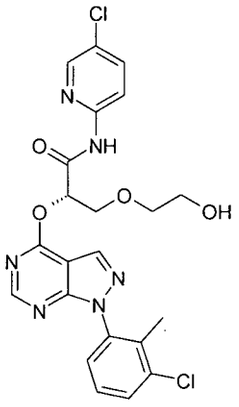
Se preparó a partir de (2S)-3-[2-(terc-butil-dimetilsilil)oxietoxi]-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-cloropiridin-2-il)propanamida (**Producto Intermedio AG1**) (980mg, 1,35mmol) de acuerdo con el procedimiento para el Ejemplo 167. ^{1}H NMR (400 MHz, DMSO) δ 3,54 - 3,64 (2H, m), 3,65 - 3,78 (2H, m), 4,05 - 4,24 (2H, m), 4,62 - 4,71 (1H, m), 5,96 - 6,04 (1H, m), 7,60 - 7,78 (3H, m), 7,76 (1H, dd), 7,88 (1H, dd), 8,06 (1H, d), 8,45 (1H, dd), 8,60 (1H, s), 8,68 (1H, s), 11,18 (1H, s); m/z (ESI-) (M-H)- = 487; HPLC t_R = 2,17 min.

Ejemplo 172: (2S)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-cianopiridin-2-il)-3-(2-hidroxietoxi)propanamida



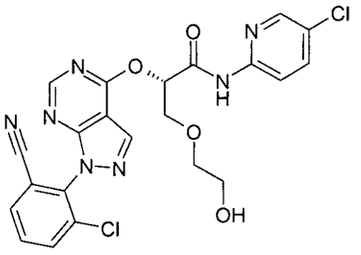
Se preparó de acuerdo con el procedimiento para el **Ejemplo 171** a partir de (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-cianopiridin-2-il)propanamida (**Producto Intermedio AG3**). ^{1}H NMR (400 MHz, DMSO) δ 3,52 - 3,61 (2H, m), 3,56 - 3,64 (2H, m), 3,65 - 3,76 (2H, m), 4,04 - 4,25 (2H, m), 4,61 - 4,75 (1H, m), 5,96 - 6,04 (1H, m), 7,57 - 7,78 (3H, m), 7,80 - 7,84 (1H, dd), 8,18 (1H, d), 8,30 (1H, dd), 8,60 (1H, s), 8,70 (1H, s), 8,87 - 8,91 (1H, m), 11,53 (1H, s); m/z (ESI-) (M-H)- = 478; HPLC t_R = 1,99 min.

Ejemplo 173: (2S)-2-[1-(3-cloro-2-metilfenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-cloropiridin-2-il)-3-(2-hidroxietoxi)propanamida



Se preparó de acuerdo con el procedimiento para el **Ejemplo 166** a partir de (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(3-cloro-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-cloropiridin-2-il)propanamida (**Producto Intermedio AE4**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2,09 (3H, s), 3,67 - 3,74 (4H, m), 4,08 - 4,18 (2H, m), 6,02 (1H, t), 7,22 - 7,29 (2H, m), 7,47 - 7,49 (1H, m), 7,63 (1H, dd), 8,12 - 8,16 (1H, m), 8,14 - 8,17 (1H, m), 8,34 (1H, s), 8,51 (1H, s), 8,95 (1H, s) (no se observó señal de OH); m/z (ESI+) $(M+H)^+$ = 503; HPLC t_R = 2,49 min.

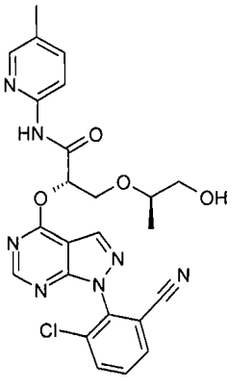
Ejemplo 174: (2S)-2-(1-(2-cloro-6-cianofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-cloropiridin-2-il)-3-(2-hidroxietoxi)propanamida



Se agregó fluoruro de tetrabutilamonio (1M en THF) (0,611 mL, 0,61 mmol) a (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(2-cloro-6-cianofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-cloropiridin-2-il)propanamida (**Producto Intermedio AH1**) en THF (5 mL) bajo nitrógeno. La mezcla resultante se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se aplacó con NH_4Cl saturado (2 mL), se diluyó con DCM (25 mL) y se vertió a través de un separador de fases. La fase orgánica se redujo para proporcionar una goma. Esto se purificó mediante HPLC preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, 50 mm de diámetro, 150 mm de longitud), utilizando mezclas cada vez menos polares de agua (que contenía ácido fórmico al 0,1%) y MeCN como eluyentes. Las fracciones que contenían el compuesto deseado se evaporaron hasta secarse para

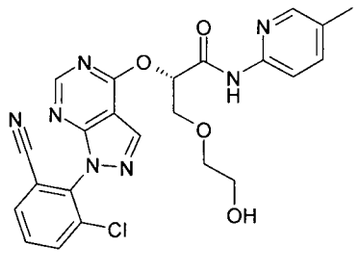
proporcionar (2S)-2-(1-(2-cloro-6-cianofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-cloropiridin-2-il)-3-(2-hidroxietoxi)propanamida (194 mg, 61,7 %, 84% ee). ^{1}H NMR (400 MHz, DMSO) δ 3,53 (2H, m), 3,70 - 3,58 (2H, m), 4,05 (1H, m), 4,13 (1H, m), 4,62 (1H, t), 5,95 (1H, s), 7,92 - 7,86 (2H, m), 8,06 - 8,00 (1H, m), 8,17 (1H, m), 8,19 (1H, m), 8,42 - 8,38 (1H, m), 8,61 (1H, s), 8,79 (1H, d), 11,21 (1H, s). m/z (ES+) $(M+H)^+$ = 514; HPLC t_R = 2,10 min.

Ejemplo 175: (2S)-2-(1-(2-cloro-6-cianofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-((R)-1-hidroxipropan-2-iloxi)-N-(5-metilpiridin-2-il)propanamida



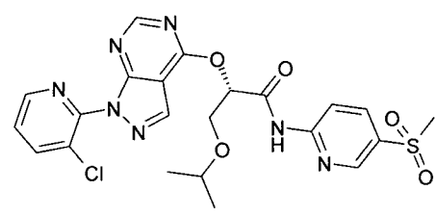
Se agregó fluoruro de tetrabutilamonio 1M en THF (0,503 mL, 0,50 mmol) a (2S)-2-(1-(2-cloro-6-cianofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-metilpiridin-2-il)-3-((R)-1-(triisopropilsililoxi)propan-2-iloxi)propanamida (**Producto Intermedio AHS**) (334 mg, 0,50 mmol) en THF (10 mL) bajo nitrógeno. La mezcla resultante se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se aplacó con NH_4Cl saturado (2 mL), se diluyó con DCM (25 mL) y se vertió en un separador de fases. La fase orgánica se redujo y el residuo se purificó mediante HPLC preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, 50 mm de diámetro, 150 mm de longitud), utilizando mezclas cada vez menos polares de agua (que contenía ácido fórmico al 0,1%) y MeCN como eluyentes para proporcionar el producto (129 mg, 50,5 %). ^{1}H NMR (400 MHz, $CDCl_3$) d 1,21 - 1,14 (3H, m), 2,30 (3H, s), 3,62 (2H, m), 3,78 (1H, m), 4,14 - 4,03 (1H, m), 4,28 (1H, dd), 6,10 - 6,03 (1H, m), 7,54 (1H, dd), 7,62 (1H, t), 7,79 (1H, m), 7,86 (1H, m), 8,07 (2H, d), 8,51 (1H, d), 8,62 (1H, d), 9,28 - 9,18 (1H, m), No se observó OH. m/z (ES+) $(M+H)^+$ = 508; HPLC t_R = 1,92 min. ee 90%

Ejemplo 176: (2S)-2-(1-(2-cloro-6-cianofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-(2-hidroxietoxi)-N-(5-metilpiridin-2-il)propanamida



Se agregó fluoruro de tetrabutilamonio (1M en THF) (0,203 mL, 0,20 mmol) a (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(2-cloro-6-cianofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-metilpiridin-2-il)propanamida (**Producto Intermedio AH9**) (149 mg, 0,20 mmol) en THF (5 mL) bajo nitrógeno. La mezcla resultante se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se aplacó con NH_4Cl saturado (2 mL), se diluyó con DCM (25 mL) y se vertió en un separador de fases. La fase orgánica se redujo para proporcionar una goma. El producto bruto se purificó mediante HPLC preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, 50 mm de diámetro, 150 mm de longitud), utilizando mezclas cada vez menos polares de agua (que contenía ácido fórmico al 0,1%) y MeCN como eluyentes para proporcionar el producto (45,0 mg, 44,8 %, 58% ee). ^{1}H NMR (400 MHz, $CDCl_3$) d 2,23 (3H, s), 3,77 - 3,62 (4H, m), 4,20 - 4,04 (2H, m), 6,01 (1H, m), 7,51 - 7,46 (1H, m), 7,55 (1H, t), 7,72 (1H, dd), 7,84 - 7,76 (1H, m), 8,03 (2H, d), 8,46 (1H, d), 8,55 (1H, d), 9,19 - 8,96 (1H, m) No se observó OH. m/z (ES+) $(M+H)^+ = 494$; HPLC t_R = 1,82 min.

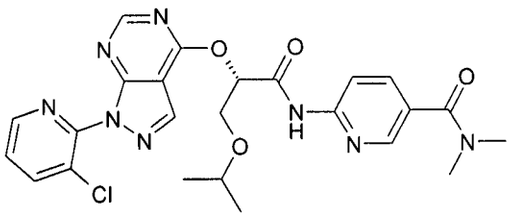
Ejemplo 177: (2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-isopropoxi-N-(5-(metilsulfonil)piridin-2-il)propanamida



Una solución de ácido 3-cloroperoxibenzoico (284 mg, 1,27 mmol) en DCM (10 mL) se agregó gota a gota a una solución agitada de (2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-isopropoxi-N-(5-(metiltio)piridin-2-il)propanamida (**Producto Intermedio AI3**) (317 mg, 0,63 mmol), en DCM (10 mL) a 22°C, durante un período de 10 minutos. La solución resultante se agitó a 22°C durante 2 horas. La mezcla de reacción se diluyó con DCM (20 mL), se lavó con NaOH 2M (20 mL), salmuera (20

mL), se secó ($MgSO_4$) y se redujo al vacío. El residuo se purificó mediante cromatografía instantánea en sílice, gradiente de elución 50 a 100% EtOAc en isohexano para proporcionar el producto (273 mg, 81 %) ^{1}H NMR (400 MHz, DMSO) d 1,14 - 1,10 (6H, m), 3,27 (3H, s), 3,77 (1H, m), 4,10 - 3,99 (2H, m), 5,92 (1H, m), 7,75 (1H, dd), 8,20 (1H, d), 8,28 (1H, dd), 8,34 (1H, dd), 8,56 (1H, s), 8,69 - 8,65 (2H, m), 8,85 - 8,82 (1H, s), 11,56 (1H, s). m/z (ES+) $(M+H)^+$ = 532; HPLC t_R = 2,03 min. ee 98%

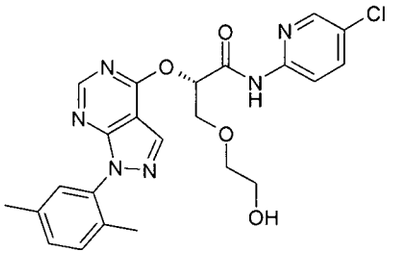
Ejemplo 178: 6-((2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-isopropoxipropanamido)-N,N-dimetilnicotinamida



Se agregó trimetilaluminio (2M en hexano, 0,376 mL, 0,75 mmol) a 6-amino-N,N-dimetilnicotinamida (CAS no. 827588-33-0) (108 mg, 0,65 mmol) en tolueno (20 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 20 minutos. Se agregó gota a gota (2S)-metil 2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-isopropoxipropanoato (**Producto Intermedio L1**) (256 mg, 0,65 mmol) en tolueno (6 mL) a esta temperatura. Después de que se completó la adición, la solución se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó hasta alcanzar reflujo durante 16 horas. Se dejó enfriar hasta alcanzar la temperatura ambiente. La mezcla de reacción se concentró y se diluyó con EtOAc (100 mL) y se lavó con salmuera saturada (50 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó. Se agregó trimetilaluminio 2M en hexano (0,376 mL, 0,75 mmol) a 6-amino-N,N-dimetilnicotinamida (108 mg, 0,65 mmol) en tolueno (20 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 20 minutos. El residuo de la evaporación precedente se disolvió en tolueno (6 mL) y se agregó gota a gota. Después de que se completó la adición, la solución se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó hasta alcanzar reflujo durante 16 horas. Se dejó enfriar hasta alcanzar la temperatura ambiente. La mezcla de reacción se concentró y se diluyó con EtOAc (100 mL) y se lavó con salmuera saturada (50 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el producto bruto. Esto se purificó mediante HPLC preparativa (columna Waters XBridge Prep C18 OBD, 5µ

sílice, 50 mm de diámetro, 150 mm de longitud), utilizando mezclas cada vez menos polares de agua (que contenía NH3 al 0,5%) y MeCN como eluyentes para proporcionar el producto (30,0 mg, 8,75 %). ^{1}H NMR (400 MHz, DMSO) δ 1,13 (6H, dd), 2,50, 2,97 (6H, s), 3,78 (1H, m), 4,04 (2H, m), 5,93 (1H, s), 7,76 (1H, dd), 7,86 (1H, dd), 8,03 (1H, d), 8,34 (1H, dd), 8,43 (1H, m), 8,57 (1H, s), 8,64 – 8,70 (2H, m), 11,16 (1H, s). m/z (ES+) $(M+H)^+$ = 500; HPLC t_R = 2,41 min.

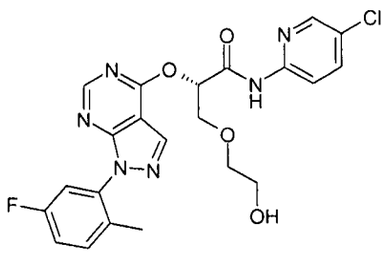
Ejemplo 179: (2S)-N-(5-cloropiridin-2-il)-2-(1-(2,5-dimetilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-(2-hidroxietoxi)propanamida



Se agregó fluoruro de tetrabutilamonio (1M en THF) (0,455 mL, 0,45 mmol) a (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-N-(5-cloropiridin-2-il)-2-(1-(2,5-dimetilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida (**Producto Intermedio AJ1**) (328 mg, 0,45 mmol) en THF (5 mL) bajo nitrógeno. La mezcla resultante se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se aplacó con NH_4Cl saturado (2 mL), se diluyó con DCM (25 mL) y se vertió en un separador de fases. La capa orgánica se cargó en una columna de sílice y se purificó mediante cromatografía instantánea en sílice, gradiente de elución 50 a 100% EtOAc en isohexano. Esto se purificó adicionalmente mediante HPLC preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, 50 mm de diámetro, 150 mm de longitud), utilizando mezclas cada vez menos polares de agua (que contenía ácido fórmico al 0,1%) y MeCN como eluyentes para proporcionar el producto (93 mg, 42,4 %). ^{1}H NMR (400 MHz, DMSO) δ 2,00 (3H, s), 2,33 (3H, s), 3,53 (2H, m), 3,57 - 3,68 (2H, m), 4,03 (1H, m), 4,11 (1H, m), 4,66 (1H, t), 5,92 (1H, m), 7,23 (1H, s), 7,28 (1H, d), 7,34 (1H, d), 7,90 (1H, dd), 8,02 (1H, d), 8,41 (1H, d), 8,52 (1H, s), 8,57 (1H, s), 11,23 (1H, s). m/z (ES+) $(M+H)^+$ = 481; HPLC t_R = 2,35 min.

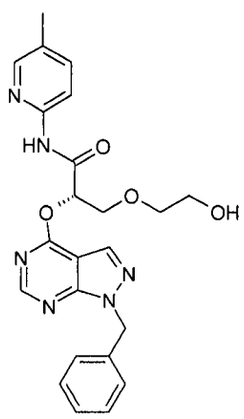
Ejemplo 180: (2S)-N-(5-cloropiridin-2-il)-2-(1-(5-fluoro-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-(2-hidroxietoxi)propanamida

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Se agregó fluoruro de tetrabutilamonio (1M en THF) (0,538 mL, 0,54 mmol) a (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-N-(5-cloropiridin-2-il)-2-(1-(5-fluoro-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida (**Producto Intermedio AK5**) (390 mg, 0,54 mmol) en THF (5 mL) bajo nitrógeno. La mezcla resultante se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se aplacó con NH_4Cl saturado (2 mL), se diluyó con DCM (25 mL) y se vertió en un separador de fases. La fase orgánica se evaporó para proporcionar el producto bruto. Esto se purificó mediante HPLC preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, 50 mm de diámetro, 150 mm de longitud), utilizando mezclas cada vez menos polares de agua (que contenía ácido fórmico al 0,1%) y MeCN como eluyentes para proporcionar el producto (136 mg, 51,9 %, 75% ee). ^{1}H NMR (400 MHz, DMSO) δ 1,88 (3H, s), 3,35 (2H, m), 3,43 (2H, m), 3,84 (1H, dd), 3,92 (1H, dd), 4,47 (1H, t), 5,74 (1H, m), 7,19 (2H, m), 7,36 - 7,29 (1H, m), 7,71 (1H, dd), 7,83 (1H, d), 8,23 (1H, d), 8,37 (1H, s), 8,43 (1H, s), 11,05 (1H, s). m/z (ES+) $(M+H)^+$ = 487; HPLC t_R = 2,28 min.

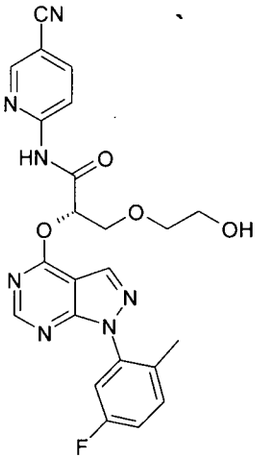
Ejemplo 181: (S)-2-(1-bencil-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-(2-hidroxietoxi)-N-(5-metilpiridin-2-il)propanamida



Una solución de fluoruro de tetrabutilamonio (1M en THF) (0,896 mL, 0,90 mmol) se agregó a una solución agitada de (S)-2-(1-bencil-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-(2-(terc-butildifenilsililoxi)etoxi)-N-(5-metilpiridin-2-il)propanamida (**Producto**

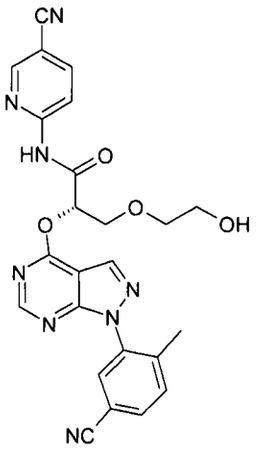
Intermedio AL1) (342 mg, 0,50 mmol) en tetrahidrofurano (20 mL). La solución resultante se agitó a temperatura ambiente durante 30 minutos. La mezcla de reacción se aplacó con NH_4Cl saturado (10 mL) y se diluyó con agua (20 mL) y EtOAc (70 mL). La capa orgánica se separó y la capa acuosa se extrajo con EtOAc (70 mL), los elementos orgánicos combinados se secaron ($MgSO_4$), se filtraron y se evaporaron para proporcionar el producto bruto. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 80 a 100% EtOAc en isohexano para proporcionar el producto (170 mg, 76 %). ^{1}H NMR (400 MHz, $CDCl_3$) 2,28 (3H, s), 2,91 (1H, s), 3,68 - 3,74 (4H, m), 4,09 - 4,20 (2H, m), 5,65 (2H, s), 6,05 (1H, t), 7,25 - 7,36 (5H, m), 7,50 - 7,53 (1H, m), 8,05 - 8,07 (2H, m), 8,21 (1H, s), 8,57 (1H, s), 8,88 (1H, s);
m/z (ES+) $(M+H)^+$ = 449; HPLC t_R = 1,90 min.

Ejemplo 182: (2S)-N-(5-cianopiridin-2-il)-2-(1-(5-fluoro-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-(2-hidroxietoxi)propanamida



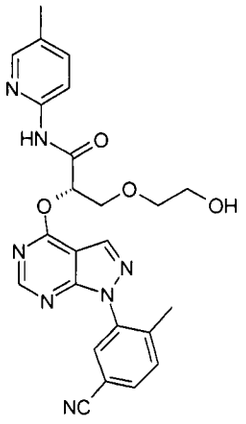
Se preparó en una forma análoga al **Ejemplo 181** a partir del **Producto Intermedio AK6**. ^{1}H NMR (400 MHz, $CDCl_3$) 2,14 (3H, s), 2,42 (1H, t), 3,73 - 3,83 (4H, m), 4,17 - 4,25 (2H, m), 6,07 (1H, t), 7,13 - 7,18 (2H, m), 7,35 - 7,38 (1H, m), 7,96 - 7,98 (1H, m), 8,35 - 8,38 (1H, m), 8,40 (1H, s), 8,57 (1H, q), 8,58 (1H, s), 9,32 (1H, s); m/z (ES+) $(M+H)^+$ = 478; HPLC t_R = 2,10 min.

Ejemplo 183: (2S)-2-(1-(5-ciano-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-cianopiridin-2-il)-3-(2-hidroxietoxi)propanamida



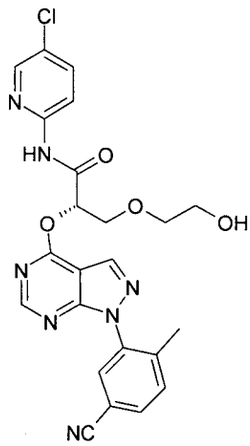
Se preparó en una forma análoga al **Ejemplo 181** utilizando el **Producto Intermedio AM1**. ^{1}H NMR (400 MHz, $CDCl_3$) 2,30 (3H, s), 3,74 - 3,84 (4H, m), 4,17 - 4,25 (2H, m), 6,07 (1H, t), 7,53 (1H, d), 7,69 - 7,72 (1H, m), 7,74 (1H, s), 7,96 - 7,99 (1H, m), 8,35 - 8,37 (1H, m), 8,43 (1H, s), 8,57 (1H, q), 8,59 (1H, s), 9,33 (1H, s) (no se observó OH); m/z (ES+) $(M+H)^+ = 485$; HPLC t_R = 1,90 min.

Ejemplo 184: (2S)-2-(1-(5-ciano-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-(2-hidroxietoxi)-N-(5-metilpiridin-2-il)propanamida



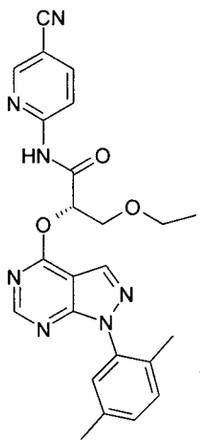
Se preparó en una forma análoga al **Ejemplo 181** utilizando el **Producto Intermedio AM6**. ^{1}H NMR (400 MHz, $CDCl_3$) 2,29 (3H, s), 2,30 (3H, s), 3,74 - 3,81 (4H, m), 4,17 - 4,25 (2H, m), 6,09 (1H, t), 7,52 - 7,56 (2H, m), 7,69 - 7,75 (2H, m), 8,06 - 8,10 (2H, m), 8,44 (1H, s), 8,59 (1H, s), 8,95 (1H, s); m/z (ES+) $(M+H)^+ = 474$; HPLC t_R = 1,79 min.

Ejemplo 185: (2S)-N-(5-cloropiridin-2-il)-2-(1-(5-ciano-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-(2-hidroxietoxi)propanamida



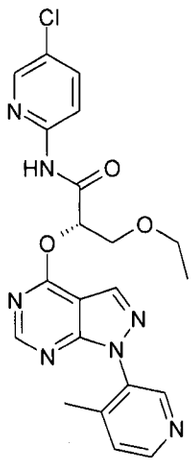
Se preparó en una forma análoga al **Ejemplo 181** utilizando el **Producto Intermedio AM8**. ^{1}H NMR (400 MHz, $CDCl_3$) 2,30 (3H, s), 3,74 - 3,81 (4H, m), 4,18 - 4,22 (2H, m), 6,08 (1H, t), 7,53 (1H, d), 7,69 - 7,75 (3H, m), 8,19 - 8,21 (1H, m), 8,23 - 8,24 (1H, m), 8,43 (1H, s), 8,59 (1H, s), 9,06 (1H, s) (no se observó OH); m/z (ES+) $(M+H)^+$ = 494; HPLC t_R = 2,09 min.

Ejemplo 186: (2S)-N-(5-cianopiridin-2-il)-2-(1-(2,5-dimetilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-etoxipropanamida



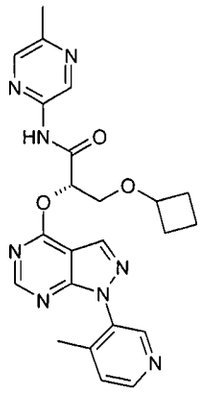
Se preparó en una forma análoga al **Producto Intermedio 181** utilizando el **Producto Intermedio H4** y el **Producto Intermedio AJ3**. ^{1}H NMR (400 MHz, $CDCl_3$) 1,24 (3H, t), 2,09 (3H, s), 2,38 (3H, s), 3,62 - 3,70 (2H, m), 4,07 - 4,15 (2H, m), 6,03 - 6,05 (1H, m), 7,19 - 7,29 (3H, m), 7,94 - 7,97 (1H, m), 8,39 (1H, s), 8,38 - 8,40 (1H, m), 8,56 (1H, s), 8,57 (1H, q), 9,03 (1H, s); m/z (ES+) (M-H)- = 456; HPLC t_R = 2,57 min.

Ejemplo 187: (2S)-N-(5-cloropiridin-2-il)-3-etoxi-2-(1-(4-metilpiridin-3-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida



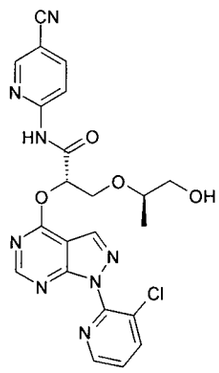
Se preparó en una forma análoga al **Producto Intermedio 181** a partir del **Producto Intermedio X5** y el **Producto Intermedio H3**. ^{1}H NMR (400 MHz, $CDCl_3$) 1,21 - 1,26 (3H, m), 2,26 (3H, s), 3,61 - 3,69 (2H, m), 4,06 - 4,15 (2H, m), 6,06 (1H, t), 7,35 (1H, d), 7,67 - 7,70 (1H, m), 8,24 (2H, dd), 8,44 (1H, s), 8,58 (1H, s), 8,60 (1H, d), 8,65 (1H, s), 8,78 (1H, s); m/z (ES+) $(M+H)^+$ = 454; HPLC t_R = 2,07 min.

Ejemplo 188: (2S)-3-ciclobutoxi-N-(5-metilpirazin-2-il)-2-(1-(4-metilpiridin-3-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida



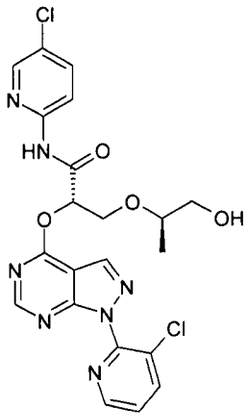
Se preparó en una forma análoga al **Producto Intermedio 1** a partir del **Producto Intermedio X5** y el **Producto Intermedio R1**. ^{1}H NMR (400 MHz, $CDCl_3$) 1,48 - 1,55 (1H, m), 1,69 - 1,75 (1H, m), 1,91 - 2,00 (2H, m), 2,19 - 2,27 (5H, m), 2,54 (3H, s), 3,98 - 4,08 (3H, m), 6,05 (1H, t), 7,36 (1H, d), 8,12 - 8,13 (1H, m), 8,45 (1H, s), 8,58 (1H, s), 8,60 (1H, d), 8,65 (1H, s), 8,68 (1H, s), 9,45 (1H, d); m/z (ES+) $(M+H)^+$ = 461; HPLC t_R = 1,82 min.

Ejemplo 189: (2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-cianopiridin-2-il)-3-((R)-1-hidroxipropan-2-iloxi)propanamida



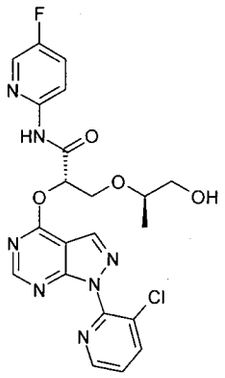
Se agregó fluoruro de tetrabutilamonio (1M en THF) (0,973 mL, 0,97 mmol) a (2S)-3-((R)-1-(terc-butildimetilsililoxi)propan-2-iloxi)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-cianopiridin-2-il)propanamida (**Producto Intermedio AN3**) (395 mg, 0,65 mmol) en THF (10 mL) bajo nitrógeno. La mezcla resultante se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se aplacó con NH_4Cl saturado (10 mL), se extrajo con Et_2O (3 × 15 mL), las capas orgánicas combinadas lavaron a contracorriente con agua (10 mL), se secaron ($MgSO_4$) y se evaporaron para proporcionar el producto bruto. El producto bruto se purificó mediante HPLC quiral preparativa en una columna Merck 50mm 20µm Chiralpak, eluyendo isocráticamente con 30% EtOH en isohexano (modificado con Et_3N) como eluyente para proporcionar el producto (95 mg, 29,6 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ1,17 (d, 3H), 2,71 - 2,78 (m, 1H), 3,56 - 3,72 (m, 2H), 3,78 - 3,87 (m, 1H), 4,09 - 4,16 (m, 1H), 4,26 - 4,32 (m, 1H), 6,01 - 6,05 (m, 1H), 7,46 - 7,50 (m, 1H), 7,94 - 7,98 (m, 1H), 7,99 - 8,04 (m, 1H), 8,32 - 8,36 (m, 1H), 8,45 (s, 1H), 8,54 - 8,56 (m, 1H), 8,60 - 8,63 (m, 1H), 8,64 (s, 1H), 9,51 (s, 1H); m/z (ESI+) $(M+H)^+$ = 495,42; HPLC t_R = 1,75 min

Ejemplo 190: (2S)-N-(5-cloropiridin-2-il)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-((R)-1-hidroxipropan-2-iloxi)propanamida



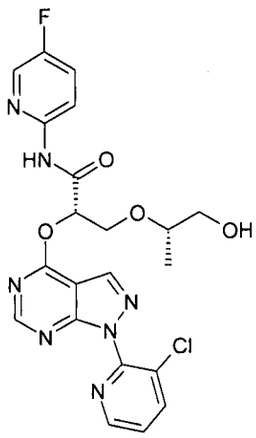
Se agregó fluoruro de tetrabutilamonio (1M en THF) (0,892 mL, 0,89 mmol) a (2S)-3-((R)-1-(terc-butildimetilsililoxi)propan-2-iloxi)-N-(5-cloropiridin-2-il)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida (**Producto Intermedio AN4**) (460 mg, 0,74 mmol) en THF (5 mL) bajo nitrógeno. La mezcla resultante se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se aplacó con NH_4Cl saturado (10 mL), se extrajo con EtOAc (3 × 15 mL), las capas orgánicas combinadas se lavaron a contracorriente con agua (10 mL), se secaron ($MgSO_4$) y se evaporaron para proporcionar el producto bruto. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 90% EtOAc en isohexano para proporcionar el producto (256 mg, 68,3 %). ^{1}H NMR (400 MHz, DMSO) δ1,07 (d, 3H), 3,26 - 3,37 (m, 1H), 3,38 - 3,47 (m, 1H), 3,61 - 3,71 (m, 1H), 4,07 - 4,18 (m, 2H), 4,57 (t, 1H), 5,87 - 5,93 (m, 1H), 7,74 - 7,79 (m, 1H), 7,88 - 7,93 (m, 1H), 8,00 - 8,06 (m, 1H), 8,32 - 8,37 (m, 1H), 8,41 (d, 1H), 8,57 (s, 1H), 8,66 (s, 1H), 8,67 - 8,70 (m, 1H), 11,15 (s, 1H)m/z (ESI+) $(M+H)^+$ = 504,37; HPLC t_R = 1,96 min

Ejemplo 191: (2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-fluoropiridin-2-il)-3-((R)-1-hidroxipropan-2-iloxi)propanamida



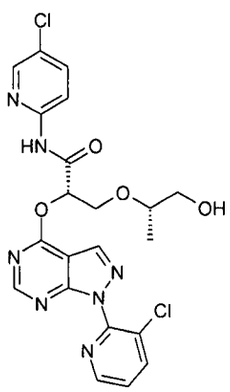
Se agregó fluoruro de tetrabutilamonio (1M en THF) (604 µl, 0,60 mmol) a (2S)-3-((R)-1-(terc-butildimetilsililoxi)propan-2-iloxi)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-fluoropiridin-2-il)propanamida (**Producto Intermedio AN5**) (303 mg, 0,50 mmol) en THF (5 mL) bajo nitrógeno. La mezcla resultante se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se aplacó con NH_4Cl saturado (10 mL), se extrajo con Et_2O (3 × 15 mL), las capas orgánicas combinadas se lavaron a contracorriente con agua (10 mL), se secaron ($MgSO_4$) y se evaporaron para proporcionar el producto bruto. El producto bruto se purificó mediante HPLC quiral preparativa en una columna Merck 50mm 20µm Chiralpak AS, eluyendo isocráticamente con 30% EtOH en isohexano (modificado con Et_3N) como eluyente para proporcionar el producto (112 mg, 45,6 %). ^1H NMR (400 MHz, $CDCl_3$) δ1,17 (d, 3H), 2,99 - 3,05 (m, 1H), 3,54 - 3,61 (m, 1H), 3,62 - 3,70 (m, 1H), 3,75 - 3,84 (m, 1H), 4,07 - 4,13 (m, 1H), 4,25 - 4,31 (m, 1H), 6,04 - 6,09 (m, 1H), 7,43 - 7,50 (m, 2H), 7,99 - 8,03 (m, 1H), 8,13 (d, 1H), 8,18 - 8,23 (m, 1H), 8,45 (s, 1H), 8,61 - 8,63 (m, 1H), 8,64 (s, 1H), 9,17 (s, 1H); m/z (ESI+) $(M+H)^+$ = 488,42; HPLC t_R = 1,74 min

Ejemplo 192: (2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-fluoropiridin-2-il)-3-((S)-1-hidroxipropan-2-iloxi)propanamida



Se agregó HCl (4M en Dioxano) (0,530 mL, 2,12 mmol) a (2S)-3-((S)-1-(terc-butildimetilsililoxi)propan-2-iloxi)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-fluoropiridin-2-il)propanamida (**Producto Intermedio AO3**) (638 mg, 1,06 mmol) en THF (5 mL) a temperatura ambiente. La solución resultante se agitó durante 20 minutos. La mezcla de reacción se evaporó y el residuo se dividió entre EtOAc (25 mL) y $NaHCO_3$ sat (10 mL). La capa orgánica se secó ($MgSO_4$) y se evaporó. El producto bruto se purificó mediante HPLC quiral preparativa en una columna Merck 50mm 20µm Chiralpak AS, eluyendo isocráticamente con 30% EtOH en isohexano (modificado con Et_3N) como eluyente para proporcionar el producto (397 mg, 77 %). ^1H NMR (400 MHz, $CDCl_3$) δ1,16 (d, 3H), 2,73 (s, 1H), 3,51 - 3,68 (m, 2H), 3,69 - 3,78 (m, 1H), 4,12 - 4,28 (m, 2H), 6,06 (t, 1H), 7,42 - 7,50 (m, 2H), 7,99 - 8,03 (m, 1H), 8,13 (d, 1H), 8,21 - 8,26 (m, 1H), 8,47 (s, 1H), 8,60 - 8,65 (m, 2H), 9,09 (s, 1H); m/z (ESI+) $(M+H)^+$ = 488,42; HPLC t_R = 1,75 min

Ejemplo 193: (2S)-N-(5-cloropiridin-2-il)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-((S)-1-hidroxipropan-2-iloxi)propanamida

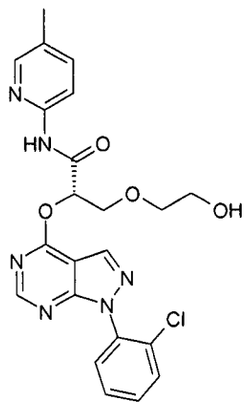


Se agregó HCl (4M en Dioxano) (0,606 mL, 2,42 mmol) a (2S)-3-((S)-1-(terc-

butildimetilsililoxi)propan-2-iloxi)-N-(5-cloropiridin-2-il)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida (**Producto Intermedio AO4**) (300 mg, 0,48 mmol) en THF (5 mL) y agua (0,5 mL) a temperatura ambiente. La solución resultante se agitó a temperatura ambiente durante 10 minutos. La mezcla de reacción se evaporó y el residuo se dividió entre EtOAc (25 mL) y $NaHCO_3$ sat (10 mL). La capa orgánica se secó ($MgSO_4$) y se evaporó. El producto bruto se purificó mediante HPLC quiral preparativa en una columna Merck 50mm 20µm Chiralpak AS, eluyendo isocráticamente con 30% EtOH en isohexano (modificado con Et_3N) como eluyente. Las fracciones que contenían el compuesto deseado se evaporaron hasta secarse para proporcionar el producto (173 mg, 70,7 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,17 (d, 3H), 2,64 (s, 1H), 3,51 - 3,67 (m, 2H), 3,69 - 3,79 (m, 1H), 4,11 - 4,28 (m, 2H), 6,05 (t, 1H), 7,45 - 7,50 (m, 1H), 7,66 - 7,71 (m, 1H), 7,99 - 8,04 (m, 1H), 8,18 - 8,25 (m, 2H), 8,47 (s, 1H), 8,60 - 8,65 (m, 2H), 9,10 (s, 1H)

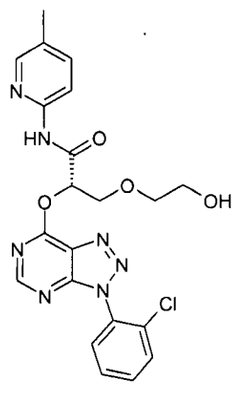
m/z (ESI+) $(M+H)^+$ = 504,40; HPLC t_R = 1,96 min

Ejemplo 194: (2S)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-(2-hidroxietoxi)-N-(5-metilpiridin-2-il)propanamida



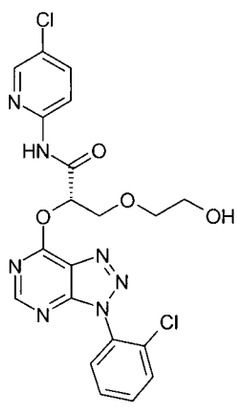
Se agregó fluoruro de tetrabutilamonio (1M en THF) (0,271 mL, 0,27 mmol) a (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-metilpiridin-2-il)propanamida (**Producto Intermedio AG4**) (96 mg, 0,14 mmol) en THF (5 mL) bajo nitrógeno. La mezcla resultante se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se aplacó con NH_4Cl saturado (10 mL), se extrajo con Et_2O (3 x 15 mL), las capas orgánicas combinadas se lavaron a contracorriente con agua (10 mL), se secaron ($MgSO_4$) y se evaporaron para proporcionar el producto bruto. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 10% MeOH en DCM para proporcionar el producto (50,0 mg, 79 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ2,28 (s, 3H), 3,32 (s, 1H), 3,70 - 3,81 (m, 4H), 4,13 - 4,26 (m, 2H), 6,08 (t, 1H), 7,43 - 7,55 (m, 4H), 7,59 - 7,63 (m, 1H), 8,05 - 8,10 (m, 2H), 8,44 (s, 1H), 8,59 (s, 1H), 9,11 (s, 1H); m/z (ESI+) $(M+H)^+$ = 469,45; HPLC t_R = 1,86 min

Ejemplo 195: (2S)-2-(3-(2-clorofenil)-3H-[1,2,3]triazolo[4,5-d]pirimidin-7-iloxi)-3-(2-hidroxietoxi)-N-(5-metilpiridin-2-il)propanamida



Se agregó ácido clorhídrico (10%, 2 mL) a (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-(3-(2-clorofenil)-3H-[1,2,3]triazolo[4,5-d]pirimidin-7-iloxi)-N-(5-metilpiridin-2-il)propanamida (**Producto Intermedio AP3**) (335 mg, 0,47 mmol) en metanol (30,0 mL) a 0°C. La solución resultante se agitó a 0°C durante 10 minutos y se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 1 hora. La mezcla de reacción se aplacó con NH_4Cl saturado (25 mL) y la mayor parte del MeOH se retiró mediante evaporación. El residuo acuoso se extrajo con EtOAc (3 x 25 mL), la capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el producto bruto. El producto bruto se purificó mediante HPLC preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, 50 mm de diámetro, 150 mm de longitud), utilizando mezclas cada vez menos polares de agua (que contenía ácido fórmico al 0,1%) y MeCN como eluyentes para proporcionar el producto (67,0 mg, 30,1 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ2,31 (s, 3H), 3,73 - 3,85 (m, 4H), 4,20 - 4,35 (m, 2H), 6,06 (t, 1H), 7,49 - 7,63 (m, 4H), 7,68 (d, 1H), 8,05 (s, 1H), 8,09 - 8,22 (m, 2H), 8,68 (s, 1H), No se observó OH; m/z (ESI+) $(M+H)^+$ = 470,41; HPLC t_R = 1,80 min

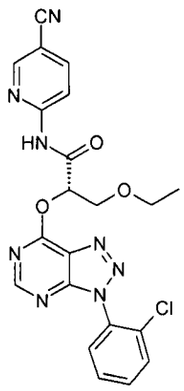
Ejemplo 196: (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-(3-(2-clorofenil)-3H-[1,2,3]triazolo[4,5-d]pirimidin-7-iloxi)-N-(5-metilpiridin-2-il)propanamida



Se agregó gota a gota ácido clorhídrico (10%, 1 mL) a (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-(3-(2-clorofenil)-3H-[1,2,3]triazolo[4,5-d]pirimidin-7-iloxi)-N-(5-cloropiridin-2-il)propanamida (**Producto Intermedio AP4**) (180 mg, 0,25 mmol) en metanol (20,00 mL) a temperatura ambiente. La solución resultante se agitó durante 4 horas. La mayor parte del metanol se evaporó y la solución acuosa restante se diluyó con NH_4Cl saturado y se extrajo con EtOAc (2 x 30 mL). Se combinaron las capas orgánicas, se secaron ($MgSO_4$) y se evaporaron para proporcionar el producto bruto. El producto

bruto se purificó mediante HPLC preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, 50 mm de diámetro, 150 mm de longitud), utilizando mezclas cada vez menos polares de agua (que contenía ácido fórmico al 0,1%) y MeCN como eluyentes. Las fracciones que contenían el compuesto deseado se evaporaron hasta secarse para proporcionar (2S)-2-(3-(2-clorofenil)-3H-[1,2,3]triazolo[4,5-d]pirimidin-7-iloxi)-N-(5-cloropiridin-2-il)-3-(2-hidroxietoxi)propanamida (38,0 mg, 31,4 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ3,72 - 3,83 (m, 4H), 4,19 - 4,32 (m, 2H), 6,15 (t, 1H), 7,50 - 7,63 (m, 3H), 7,66 - 7,72 (m, 2H), 8,15 - 8,27 (m, 2H), 8,72 (s, 1H), 9,16 (s, 1H) No se observó OH; m/z (ESI+) $(M+H)^+$ = 490,16; HPLC t_R = 2,15 min

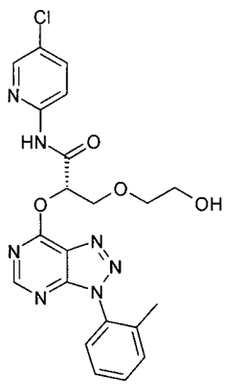
Ejemplo 197: (2S)-2-(3-(2-clorofenil)-3H-[1,2,3]triazolo[4,5-d]pirimidin-7-iloxi)-N-(5-cianopiridin-2-il)-3-etoxipropanamida



Se agregó hidruro de sodio (82 mg, 2,05 mmol) a (S)-N-(5-cianopiridin-2-il)-3-etoxi-2-hidroxipropanamida (**Producto Intermedio H4**) (177 mg, 0,75 mmol) en THF anhidro (5 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos y luego se agregó 7-cloro-3-(2-clorofenil)-3H-[1,2,3]triazolo[4,5-d]pirimidina (**Producto Intermedio AP2**) (200 mg, 0,75 mmol). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 1 hora. La mezcla de reacción se neutralizó con ácido cítrico 1M y la mayor parte del THF se eliminó al vacío. La mezcla de reacción se diluyó con agua (20 mL) y EtOAc (50 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc (2 × 50 mL). Los elementos orgánicos combinados se lavaron con salmuera saturada (25 mL), se secaron ($MgSO_4$) y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 60% EtOAc en isohexano para proporcionar el producto (136 mg, 38,9 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ1,24 (t, 3H), 3,61 - 3,74 (m, 2H), 4,13 - 4,21 (m, 2H),

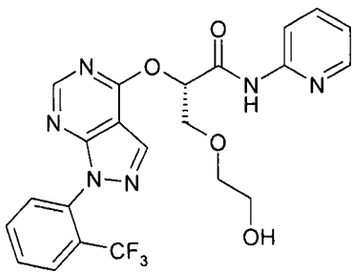
6,13 (t, 1H), 7,51 - 7,62 (m, 3H), 7,67 - 7,71 (m, 1H), 7,93 - 7,98 (m, 1H), 8,36 - 8,40 (m, 1H), 8,57 - 8,59 (m, 1H), 8,71 (s, 1H), 9,19 (s, 1H); m/z (ESI+) $(M+H)^+$ = 463,23; HPLC t_R = 2,43 min

Ejemplo 198: (2S)-N-(5-cloropiridin-2-il)-3-(2-hidroxietoxi)-2-(3-o-tolil-3H-[1,2,3]triazolo[4,5-d]pirimidin-7-iloxi)propanamida



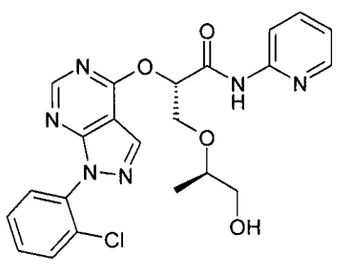
Se agregó gota a gota ácido clorhídrico (10%, 1 mL) a (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-N-(5-cloropiridin-2-il)-2-(3-o-tolil-3H-[1,2,3]triazolo[4,5-d]pirimidin-7-iloxi)propanamida (**Producto Intermedio AP7**) (250 mg, 0,35 mmol) en metanol (20,00 mL) a temperatura ambiente. La solución resultante se agitó durante 4 horas. La mayor parte del metanol se evaporó y la solución acuosa restante se diluyó con NH_4Cl saturado y se extrajo con EtOAc (2 × 30 mL). Se combinaron las capas orgánicas, se secaron ($MgSO_4$) y se evaporaron para proporcionar el producto bruto. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 100% EtOAc en isohexano para proporcionar el producto (81 mg, 48,8 %). ^1H NMR (400 MHz, $CDCl_3$) δ2,20 (s, 3H), 2,60 - 2,66 (m, 1H), 3,73 - 3,83 (m, 4H), 4,20 - 4,32 (m, 2H), 6,15 (t, 1H), 7,41 - 7,54 (m, 4H), 8,17 - 8,21 (m, 1H), 8,23 - 8,25 (m, 1H), 8,70 (s, 1H), 9,20 (s, 1H), No se observó OH; m/z (ESI+) $(M+H)^+$ = 470,43; HPLC t_R = 2,25 min

Ejemplo 199: (2S)-3-(2-hidroxietoxi)-N-(piridin-2-il)-2-(1-(2-(trifluorometil)fenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida



Una solución de fluoruro de tetrabutilamonio (1M en THF) (1,275 mL, 1,28 mmol) se agregó en una porción a una solución agitada de (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-N-(piridin-2-il)-2-(1-(2-(trifluorometil)fenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida (0,927 g, 1,28 mmol) (**Producto Intermedio AQ1**) en tetrahidrofurano (15 mL). La solución resultante se agitó a temperatura ambiente durante 30 minutos. La mezcla de reacción se aplacó con NH_4Cl saturado (10 mL) y se diluyó con agua (20 mL) y EtOAc (50 mL). La capa orgánica se separó y la capa acuosa se extrajo con EtOAc (50 mL), los elementos orgánicos combinados se secaron ($MgSO_4$), se filtraron y se evaporaron para proporcionar el producto bruto. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 80 a 100% EtOAc en isohexano para proporcionar el producto (0,226 g, 36,3 %). ^1H NMR: (400 MHz, $CDCl_3$) δ 2,90 (1H, s), 3,75 - 3,80 (4H, m), 4,16 - 4,25 (2H, m), 6,09 (1H, t), 7,06 - 7,10 (1H, m), 7,53 - 7,92 (5H, m), 8,18 - 8,20 (1H, m), 8,28 - 8,30 (1H, m), 8,41 (1H, s), 8,57 (1H, s), 9,01 (1H, s); m/z (ES+) $(M+H)^+$ = 489,31; HPLC t_R = 1,74 min.

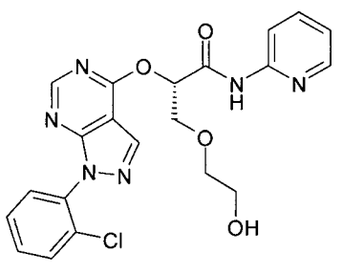
Ejemplo 200: (2S)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-((R)-1-hidroxipropan-2-iloxi)-N-(piridin-2-il)propanamida



Una solución de fluoruro de tetrabutilamonio (1M en THF) (0,526 mL, 0,53 mmol) se agregó en una porción a una solución agitada de (2S)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(piridin-2-il)-3-((R)-1-(triisopropilsililoxi)propan-2-iloxi)propanamida (0,329 g, 0,53 mmol) (**Producto Intermedio AQ3**) en tetrahidrofurano (15 mL). La solución resultante se agitó a temperatura ambiente durante 30 minutos. La

mezcla de reacción se aplacó con NH_4Cl saturado (10 mL) y se diluyó con agua (20 mL) y EtOAc (50 mL). La capa orgánica se separó y la capa acuosa se extrajo con EtOAc (50 mL), los elementos orgánicos combinados se secaron ($MgSO_4$), se filtraron y se evaporaron para proporcionar el producto bruto. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 80 a 100% EtOAc en isohexano, para proporcionar el producto (0,247 g, 100 %). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 1,16 - 1,19 (3H, m), 3,45 - 3,85 (4H,m), 4,1 - 4,31 (2H, m), 6,06 - 6,09 (1H, m), 7,05 - 7,09 (1H, m), 7,46 - 7,63 (4H, m), 7,73 - 7,75 (1H, m), 8,17 (1H, d), 8,26 - 8,28 (1H, m), 8,43 (1H, d), 8,60 (1H, s), 9,23 (1H, s); m/z (ES+) $(M+H)^+$ = 469,24; HPLC t_R = 1,91 min.

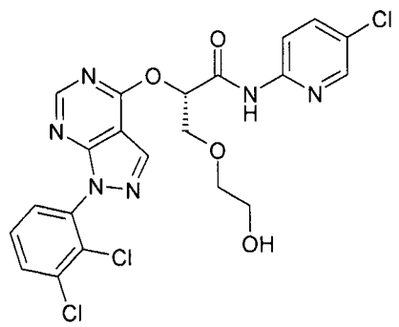
Ejemplo 201: (2S)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-(2-hidroxietoxi)-N-(piridin-2-il)propanamida



Una solución de fluoruro de tetrabutilamonio (1M en THF) (0,984 mL, 0,98 mmol) se agregó en una porción a una solución agitada de (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(piridin-2-il)propanamida (**Producto Intermedio AQ5**) (0,682 g, 0,98 mmol) en tetrahidrofurano (15 mL). La solución resultante se agitó a temperatura ambiente durante 30 minutos. La mezcla de reacción se aplacó con NH_4Cl saturado (10 mL) y se diluyó con agua (20 mL) y EtOAc (50 mL). La capa orgánica se separó y la capa acuosa se extrajo con EtOAc (50 mL), los elementos orgánicos combinados se secaron ($MgSO_4$), se filtraron y se evaporaron para proporcionar el producto bruto. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 80 a 100% EtOAc en isohexano para proporcionar el producto (0,335 g, 74,9 %). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 2,91 (1H, s), 3,74 - 3,79 (4H, m), 4,15 - 4,25 (2H, m), 6,10 (1H, t), 7,06 - 7,10 (1H, m), 7,45 - 7,63 (4H, m), 7,71 - 7,75 (1H, m), 8,19 (1H, d), 8,27 - 8,29 (1H, m), 8,44 (1H, s), 8,60 (1H, s), 9,01 (1H, s); m/z (ES+) $(M+H)^+$ = 455; HPLC t_R = 1,76 min.

Ejemplo 202: (2S)-N-(5-cloropiridin-2-il)-2-(1-(2,3-diclorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-(2-hidroxietoxi)propanamida

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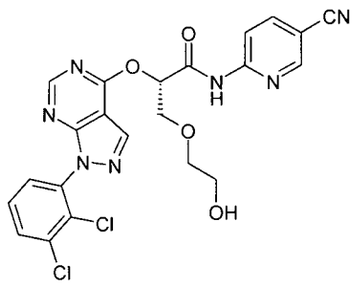


Se agregó trimetilaluminio (2M en tolueno) (0,638 mL, 1,28 mmol) a 5-cloropiridin-2-amina (164 mg, 1,28 mmol) en tolueno (2 mL) bajo nitrógeno. La solución resultante se agitó a temperatura ambiente durante 15 minutos. Se agregó 3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(2,3-diclorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanoato de (2S)-metilo (**Producto Intermedio AR1**) (425 mg, 0,64 mmol) en tolueno (8 mL) sellado en un tubo de microondas de 20 mL. La reacción se calentó hasta alcanzar 120°C durante 4 horas en el reactor de microondas y se enfrió hasta alcanzar la TA. La mezcla de reacción se dejó enfriar y se concentró al vacío. El residuo se neutralizó con ácido cítrico (1M, ac) y luego se diluyó con agua (30 mL) y se extrajo con EtOAc (2 x 50 mL). Los elementos orgánicos combinados se secaron ($MgSO_4$) y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 0 a 50% EtOAc en isohexano para proporcionar (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-N-(5-cloropiridin-2-il)-2-(1-(2,3-diclorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida (460 mg, 95 %). m/z (ES+) $(M+H)^+ = 763$; HPLC t_R = 3,94 min.

Una solución de fluoruro de tetrabutilamonio (1M en THF) (0,661 mL, 0,66 mmol) se agregó gota a gota a una solución agitada de (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-N-(5-cloropiridin-2-il)-2-(1-(2,3-diclorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida (420 mg, 0,55 mmol) en THF (15 mL) durante un período de 1 minuto. La solución resultante se agitó a temperatura ambiente durante 3 horas. Se agregó cloruro de amonio saturado (20 mL) a la mezcla de reacción que luego se diluyó con EtOAc (25 mL) y se lavó secuencialmente con agua (25 mL) y salmuera saturada (25 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el producto bruto. El producto bruto se purificó mediante HPLC preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, 50 mm de diámetro, 150 mm de longitud), utilizando mezclas cada

vez menos polares de agua (que contenía ácido fórmico al 0,1%) y MeCN como eluyentes. Las fracciones que contenían el compuesto deseado se concentraron para eliminar la mayor parte del MeCN y luego se agregó EtOAc. La fase orgánica se lavó secuencialmente con $NaHCO_3$ saturado y agua y la capa orgánica se evaporó hasta secarse para proporcionar el producto (120 mg, 41,6 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3,75 (4H, m), 4,16 (1H, dd), 4,22 (1H, dd), 6,06 (1H, t), 7,42 (2H, m), 7,66 (2H, m), 8,20 (2H, m), 8,43 (1H, d), 8,58 (1H, s), 9,17 (1H, s); m/z (ES+) $(M+H)^+$ = 525; HPLC t_R = 2,32 min.

Ejemplo 203: (2S)-N-(5-cianopiridin-2-il)-2-(1-(2,3-diclorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-(2-hidroxietoxi)propanamida



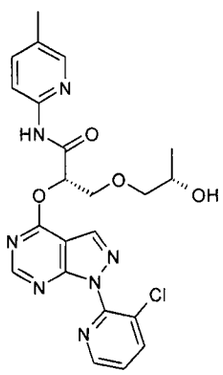
Se agregó trimetilaluminio (2M en tolueno) (0,638 mL, 1,28 mmol) a 6-aminonicotinonitrilo (152 mg, 1,28 mmol) en tolueno (2 mL) bajo nitrógeno. La solución resultante se agitó a temperatura ambiente durante 15 minutos. Se agregó (2S)-metil 3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(2,3-diclorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanoato (**Producto Intermedio AR1**) (425 mg, 0,64 mmol) en tolueno (8 mL) sellado en un tubo de microondas de 20 mL. La reacción se calentó hasta alcanzar 120°C durante 4 horas en el reactor de microondas y se enfrió hasta alcanzar la TA. La mezcla de reacción se dejó enfriar y se concentró al vacío. El residuo se neutralizó con ácido cítrico (1M, ac) y luego se diluyó con agua (30 mL) y se extrajo con EtOAc (2 x 50 mL). Los elementos orgánicos combinados se secaron ($MgSO_4$) y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 0 a 50% EtOAc en isohexano, para proporcionar (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-N-(5-cianopiridin-2-il)-2-(1-(2,3-diclorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida (450 mg, 94 %).

m/z (ES+) $(M+H)^+$ = 752; HPLC t_R = 3,74 min.

Una solución de fluoruro de tetrabutilamonio (1M en THF) (0,701 mL, 0,70 mmol) se

agregó gota a gota a una solución agitada de (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-N-(5-cianopiridin-2-il)-2-(1-(2,3-diclorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida (440 mg, 0,58 mmol) en THF (15 mL) durante un período de 1 minuto. La solución resultante se agitó a temperatura ambiente durante 3 horas. Se agregó cloruro de amonio saturado (20 mL) a la mezcla de reacción que luego se diluyó con EtOAc (25 mL) y se lavó secuencialmente con agua (25 mL) y salmuera saturada (25 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el producto bruto. El producto bruto se purificó mediante HPLC preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, 50 mm de diámetro, 150 mm de longitud), utilizando mezclas cada vez menos polares de agua (que contenía ácido fórmico al 0,1%) y MeCN como eluyentes. Las fracciones que contenían el compuesto deseado se concentraron para eliminar la mayor parte del MeCN y luego se agregó EtOAc. La fase orgánica se lavó secuencialmente con $NaHCO_3$ saturado y agua y la capa orgánica se evaporó hasta secarse para proporcionar el producto (240 mg, 80 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2,37 (1H, s), 3,81 – 3,62 (4H, m), 4,14 (2H, m), 6,00 (1H, t), 7,44 – 7,28 (2H, m), 7,60 (1H, dd), 7,90 (1H, dd), 8,29 (1H, dd), 8,36 (1H, s), 8,49 (1H, dd), 8,52 (1H, s), 9,26 (1H, s); m/z (ES+) $(M+H)^+$ = 514; HPLC t_R = 2,13 min.

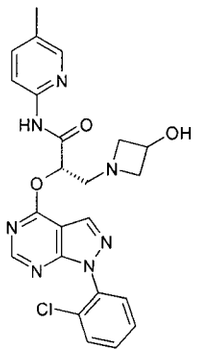
Ejemplo 204: (2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-((S)-2-hidroxipropoxi)-N-(5-metilpiridin-2-il)propanamida



Se agregó fluoruro de tetrabutilamonio (1M en THF) (1,342 mL, 1,34 mmol) a (2S)-3-((S)-2-(terc-butildimetilsililoxi)propoxi)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-metilpiridin-2-il)propanamida (**Producto Intermedio AS1**) (803 mg, 1,34 mmol) en THF (6 mL) bajo nitrógeno. La mezcla resultante se agitó a temperatura ambiente durante 16 horas. Se agregó una porción adicional de fluoruro de tetrabutilamonio (1M en THF) (1,342 mL, 1,34 mmol) y se continuó agitando durante 5

horas adicionales. La mezcla de reacción se aplacó con NH_4Cl saturado, se diluyó con DCM y se vertió en un separador de fases. La capa orgánica se evaporó hasta proporcionar una goma. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 0 a 100% EtOAc en isohexano. Se aislaron 336mg de material pero se encontró que contenían impurezas. El producto bruto se purificó mediante HPLC preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, 50 mm de diámetro, 150 mm de longitud), utilizando mezclas cada vez menos polares de agua (que contenía ácido fórmico al 0,1%) y MeCN como eluyentes. Las fracciones relevantes se concentraron para eliminar el acetonitrilo, luego se basificó el material acuoso restante con bicarbonato saturado y se extrajo y colocó en etilacetato x2. Los elementos orgánicos se lavaron con salmuera, se secaron ($MgSO_4$) y se concentraron para proporcionar (2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-((S)-2-hidroxipropoxi)-N-(5-metilpiridin-2-il)propanamida (193 mg, 29,7 %, 77% ee). ^1H NMR (400 MHz, $CDCl_3$) δ 1,14 (3H, d), 2,29 (3H, s), 2,98 (1H, s), 3,37 - 3,44 (1H, m), 3,60 - 3,65 (1H, m), 3,97 - 4,05 (1H, m), 4,10 - 4,26 (2H, m), 6,09 (1H, t), 7,44 - 7,50 (1H, m), 7,51 - 7,57 (1H, m), 7,99 - 8,03 (1H, m), 8,05 - 8,12 (2H, m), 8,47 (1H, s), 8,60 - 8,63 (1H, m), 8,64 (1H, s), 8,86 (1H, s); m/z (ES+) $(M+H)^+$ = 484,46; HPLC t_R = 1,62 min.

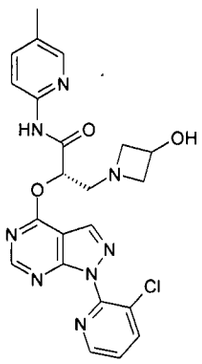
Ejemplo 205: (2S)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-(3-hidroxiazetidin-1-il)-N-(5-metilpiridin-2-il)propanamida



Se agregó fluoruro de tetrabutilamonio (1M en THF) (1,515 mL, 1,51 mmol) a (2S)-3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-metilpiridin-2-il)propanamida (**Producto Intermedio AD7**) (0,9 g, 1,51 mmol) en THF (10 mL) bajo nitrógeno. La mezcla resultante se agitó a temperatura ambiente durante 2,5 horas. La mezcla de reacción se aplacó con NH_4Cl saturado, se diluyó con DCM y se vertió en un separador de fases. La capa orgánica se evaporó hasta proporcionar

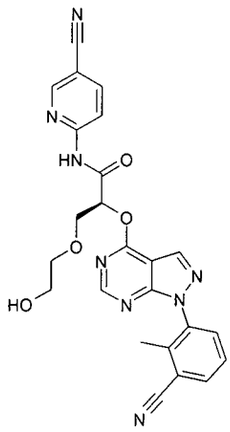
una goma. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 0 a 10% MeOH en EtOAc para proporcionar el producto (0,313 g, 43,1 %, 98% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2,29 (3H, s), 2,50 - 2,78 (1H, m), 3,15 - 3,31 (4H, m), 3,79 - 3,89 (2H, m), 4,47 - 4,55 (1H, m), 5,91 (1H, t), 7,42 - 7,56 (4H, m), 7,59 - 7,65 (1H, m), 8,08 - 8,14 (2H, m), 8,37 (1H, s), 8,59 (1H, s), 9,53 (1H, s); m/z (ES+) $(M+H)^+$ = 480,41; HPLC t_R = 1,19 min.

Ejemplo 206: (2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-(3-hidroxiazetidin-1-il)-N-(5-metilpiridin-2-il)propanamida



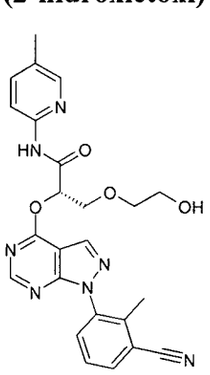
Se agregó fluoruro de tetrabutilamonio (1M en THF) (0,328 mL, 0,33 mmol) a (2S)-3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-metilpiridin-2-il)propanamida (**Producto Intermedio AD9**) (195 mg, 0,33 mmol) en THF (2 mL) bajo nitrógeno. La mezcla resultante se agitó a temperatura ambiente durante 6 horas. La mezcla de reacción se aplacó con NH_4Cl saturado, se diluyó con DCM y se vertió en un separador de fases. La capa orgánica se evaporó hasta proporcionar una goma. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 0 a 10% MeOH en EtOAc para proporcionar el producto (38,0 mg, 24,12 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,23 - 1,29 (1H, m), 2,29 (3H, s), 3,16 - 3,32 (4H, m), 3,76 - 3,87 (2H, m), 4,46 - 4,53 (1H, m), 5,91 (1H, t), 7,44 - 7,49 (1H, m), 7,50 - 7,55 (1H, m), 7,97 - 8,03 (1H, m), 8,07 - 8,15 (2H, m), 8,42 (1H, s), 8,59 - 8,65 (2H, m), 9,58 (1H, s) m/z (ES+) $(M+H)^+$ = 481,51; HPLC t_R = 1,14 min.

Ejemplo 207: (2S)-2-(1-(3-ciano-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-cianopiridin-2-il)-3-(2-hidroxietoxi)propanamida



Se agregó fluoruro de tetrabutilamonio (1M en THF) (0,346 mL, 0,35 mmol) a (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(3-ciano-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-cianopiridin-2-il)propanamida (**Producto Intermedio AT1**) (250 mg, 0,35 mmol) en THF (2 mL) bajo nitrógeno. La mezcla resultante se agitó a temperatura ambiente durante 90 minutos. La mezcla de reacción se aplacó con NH_4Cl saturado, se diluyó con DCM y se vertió en un separador de fases. La capa orgánica se evaporó hasta proporcionar una goma. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 50 a 100% EtOAc en isohexano para proporcionar el producto (69,0 mg, 41,2 %, 92% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2,37 - 2,44 (4H, m), 3,73 - 3,86 (4H, m), 4,15 - 4,26 (2H, m), 6,07 (1H, t), 7,49 (1H, t), 7,63 - 7,68 (1H, m), 7,77 - 7,82 (1H, m), 7,94 - 8,00 (1H, m), 8,34 - 8,38 (1H, m), 8,43 (1H, s), 8,55 - 8,60 (2H, m), 9,34 (1H, s); m/z (ES-) (M-H)- = 483,52; HPLC t_R = 1,95 min.

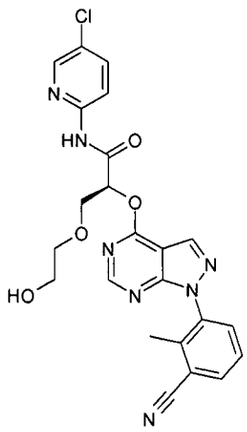
Ejemplo 208: (2S)-2-(1-(3-ciano-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-(2-hidroxietoxi)-N-(5-metilpiridin-2-il)propanamida



Se agregó fluoruro de tetrabutilamonio (1M en THF) (0,440 mL, 0,44 mmol) a (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(3-ciano-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-

iloxi)-N-(5-metilpiridin-2-il)propanamida (**Producto Intermedio AT6**) (313 mg, 0,44 mmol) en THF (2 mL) bajo nitrógeno. La mezcla resultante se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se aplacó con NH_4Cl saturado, se diluyó con DCM y se vertió en un separador de fases. La capa orgánica se evaporó hasta proporcionar una goma. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 0 a 10% metanol en acetato de etilo para proporcionar el producto (59,0 mg, 28,3 %, 84% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2,30 (3H, s), 2,40 (3H, s), 3,02 (1H, s), 3,72 - 3,83 (4H, m), 4,13 - 4,26 (2H, m), 6,09 (1H, t), 7,45 - 7,57 (2H, m), 7,63 - 7,68 (1H, m), 7,76 - 7,81 (1H, m), 8,03 - 8,12 (2H, m), 8,43 (1H, s), 8,58 (1H, s), 8,95 (1H, s); m/z (ES+) $(M+H)^+$ = 474,49; HPLC t_R = 1,83 min.

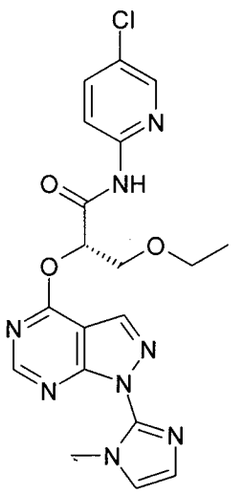
Ejemplo 209: (2S)-N-(5-cloropiridin-2-il)-2-(1-(3-ciano-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-(2-hidroxietoxi)propanamida



Se agregó fluoruro de tetrabutilamonio (1M en THF) (1,174 mL, 1,17 mmol) a (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-N-(5-cloropiridin-2-il)-2-(1-(3-ciano-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida (**Producto Intermedio AT7**) (860 mg, 1,17 mmol) en THF (2 mL) bajo nitrógeno. La mezcla resultante se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se aplacó con NH_4Cl saturado (1 mL), se diluyó con DCM (10 mL) y se vertió en un separador de fases. La capa orgánica se evaporó hasta proporcionar una goma. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 0 a 100% EtOAc en isohexano para proporcionar el producto (284 mg, 49,0 %, 91% ee). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2,40 (3H, s), 2,55 - 2,65 (1H, m), 3,70 - 3,86 (4H, m), 4,14 - 4,27 (2H, m), 6,08 (1H, t), 7,49 (1H, t), 7,63 - 7,73 (2H, m), 7,76 - 7,82 (1H, m), 8,15 - 8,25 (2H, m), 8,44 (1H, s),

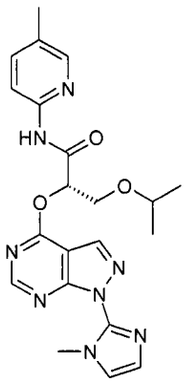
8,59 (1H, s), 9,03 (1H, s); m/z (ES+) $(M+H)^+$ = 494,45; HPLC t_R = 2,13 min.

Ejemplo 210: (2S)-N-(5-cloropiridin-2-il)-3-etoxi-2-(1-(1-metil-1H-imidazol-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida



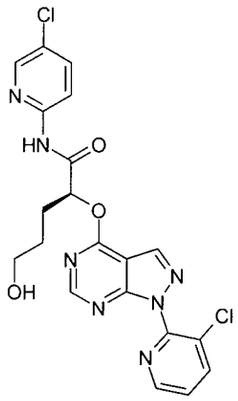
Se agregó hidruro de sodio (60% en aceite) (29,2 mg, 0,73 mmol) a (S)-N-(5-cloropiridin-2-il)-3-etoxi-2-hidroxipropanamida (**Producto Intermedio H3**) (149 mg, 0,61 mmol) en THF anhidro (5 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos y luego se agregó 1-(1-metil-1H-imidazol-2-il)-4-fenoxi-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio AV1**) (196 mg, 0,67 mmol). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 4 horas. La mezcla de reacción se aplacó con cítrico 1M (2 mL), se extrajo con EtOAc, la capa orgánica se lavó con agua x2 y salmuera, se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un aceite naranja. El producto bruto se purificó mediante HPLC preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, 50 mm de diámetro, 150 mm de longitud), utilizando mezclas cada vez menos polares de agua (que contenía NH3 al 1%) y MeCN como eluyentes para proporcionar el producto (111 mg, 41,2 %, 95% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,22 (3H, t), 3,56 - 3,72 (5H, m), 4,03 - 4,15 (2H, m), 6,05 (1H, t), 7,02 (1H, d), 7,17 (1H, d), 7,65 - 7,71 (1H, m), 8,19 - 8,26 (2H, m), 8,43 (1H, s), 8,65 (1H, s), 8,78 (1H, s); m/z (ES+) $(M+H)^+$ = 443,40; HPLC t_R = 1,92 min.

Ejemplo 211: (2S)-3-isopropoxi-2-(1-(1-metil-1H-imidazol-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-metilpiridin-2-il)propanamida



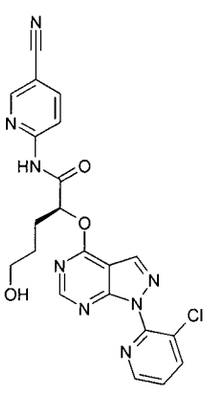
Se agregó hidruro de sodio (60% en aceite) (28,8 mg, 0,72 mmol) a (S)-2-hidroxi-3-isopropoxi-N-(5-metilpiridin-2-il)propanamida (**Producto Intermedio C7**) (143 mg, 0,60 mmol) en THF anhidro (5 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos y luego se agregó 1-(1-metil-1H-imidazol-2-il)-4-fenoxi-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio AV1**) (193 mg, 0,66 mmol) en THF (1 mL). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 2 horas. La mezcla de reacción se aplacó con cítrico 1M (2 mL), se extrajo con EtOAc, la capa orgánica se lavó con agua x2 y salmuera, se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un aceite naranja. El producto bruto se purificó mediante HPLC preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, 50 mm de diámetro, 150 mm de longitud), utilizando mezclas cada vez menos polares de agua (que contenía NH_3 al 1%) y MeCN como eluyentes para proporcionar el producto (90 mg, 34,4 %, 100% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,18 (6H, t), 2,29 (3H, s), 3,65 (3H, s), 3,67 - 3,76 (1H, m), 4,08 (2H, d), 6,01 (1H, t), 7,01 (1H, d), 7,17 (1H, d), 7,49 - 7,55 (1H, m), 8,06 - 8,14 (2H, m), 8,42 (1H, s), 8,65 (1H, s), 8,68 (1H, s); m/z (ES+) $(M+H)^+$ = 437,51; HPLC t_R = 1,89 min.

Ejemplo 212: (2S)-N-(5-cloropiridin-2-il)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-5-hidroxipentanamida



Se agregó fluoruro de tetrabutilamonio (1M en THF) (1,177 mL, 1,18 mmol) a (2S)-5-(terc-butildimetilsililoxi)-N-(5-cloropiridin-2-il)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)pentanamida (**Producto Intermedio AW1**) (693 mg, 1,18 mmol) en THF (5 mL) bajo nitrógeno. La mezcla resultante se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se aplacó con NH_4Cl saturado (2 mL), se diluyó con DCM (25 mL) y se vertió en un separador de fases. La capa orgánica se cargó en una columna de sílice y se purificó mediante cromatografía instantánea en sílice, gradiente de elución 50 a 100% EtOAc en isohexano para proporcionar el producto (171 mg, 30,6 %, 95% ee). ^1H NMR (400 MHz, $CDCl_3$) δ 1,59 (1H, t), 1,81 - 1,91 (2H, m), 2,21 - 2,39 (2H, m), 3,73 - 3,86 (2H, m), 5,95 (1H, t), 7,44 - 7,50 (1H, m), 7,64 - 7,72 (1H, m), 7,98 - 8,04 (1H, m), 8,20 - 8,27 (2H, m), 8,44 (1H, s), 8,59 - 8,65 (2H, m), 8,72 (1H, s); m/z (ES+) $(M+H)^+$ = 474,36; HPLC t_R = 1,89 min.

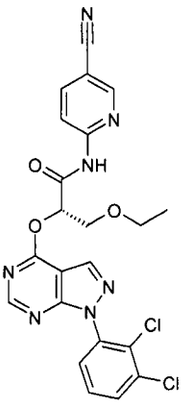
Ejemplo 213: (2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-cianopiridin-2-il)-5-hidroxipentanamida



Se agregó fluoruro de tetrabutilamonio (1M en THF) (1,376 mL, 1,38 mmol) a (2S)-5-(terc-butildimetilsililoxi)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-

(5-cianopiridin-2-il)pentanamida (**Producto Intermedio AW2**) (797 mg, 1,38 mmol) en THF (5 mL) bajo nitrógeno. La mezcla resultante se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se aplacó con NH_4Cl saturado (2 mL), se diluyó con DCM (25 mL) y se vertió en un separador de fases. La capa orgánica se cargó en una columna de sílice y se purificó mediante cromatografía instantánea en sílice, gradiente de elución 50 a 100% EtOAc en isohexano, para proporcionar el producto (166 mg, 25,9 %, 100% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,61 (1H, t), 1,81 - 1,92 (2H, m), 2,22 - 2,40 (2H, m), 3,76 - 3,88 (2H, m), 5,95 (1H, t), 7,45 - 7,50 (1H, m), 7,93 - 7,98 (1H, m), 7,99 - 8,04 (1H, m), 8,35 - 8,41 (1H, m), 8,44 (1H, s), 8,53 - 8,57 (1H, m), 8,60 - 8,64 (2H, m), 9,03 (1H, s); m/z (ES-) (M-H)- = 463,37; HPLC t_R = 1,68 min.

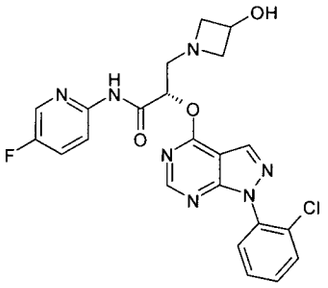
Ejemplo 214: (2S)-N-(5-cianopiridin-2-il)-2-(1-(2,3-diclorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-etoxipropanamida



Se agregó hidruro de sodio (60% en aceite) (80 mg, 2,00 mmol) a (S)-N-(5-cianopiridin-2-il)-3-etoxi-2-hidroxipropanamida (**Producto Intermedio H4**) (314 mg, 1,34 mmol) en THF (10 mL) a 0°C bajo nitrógeno. La mezcla resultante se agitó a 0°C durante 10 minutos. Luego se agregó gota a gota 4-cloro-1-(2,3-diclorofenil)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio AR4**) (400 mg, 1,34 mmol) en THF (2 mL) y se agitó a 0°C durante 10mins adicionales. La reacción luego se dejó entibiar hasta alcanzar la t.a. y se agitó durante 3 1/2 horas. La mezcla de reacción se aplacó con ácido cítrico 1M, se extrajo con EtOAc y se lavó con agua x2. La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar una goma amarilla (835mg). El producto bruto se purificó mediante HPLC preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, 50 mm de diámetro, 150 mm de longitud), utilizando mezclas cada vez menos polares de agua (que contenía ácido fórmico al 0,1%) y MeCN como eluyentes para proporcionar el

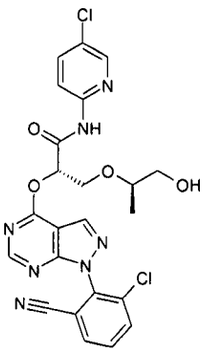
producto (285 mg, 42,8 %, 96% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,24 (3H, t), 3,58 - 3,74 (2H, m), 4,04 - 4,17 (2H, m), 6,04 (1H, t), 7,37 - 7,48 (2H, m), 7,64 - 7,69 (1H, m), 7,93 - 7,99 (1H, m), 8,36 - 8,41 (1H, m), 8,43 (1H, s), 8,56 - 8,58 (1H, m), 8,58 (1H, s), 9,02 (1H, s); m/z (ES-) (M-H)- = 496,33; HPLC t_R = 2,70 min.

Ejemplo 215: (2S)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-3-(3-hidroxiazetidin-1-il)propanamida



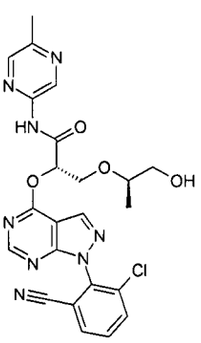
Una solución de fluoruro de tetrabutilamonio (1M en THF) (7,14 mL, 7,14 mmol) se agregó en una porción a una solución agitada de (2S)-3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-fluoropiridin-2-il)propanamida (**Producto Intermedio AX1**) (4,27 g, 7,14 mmol) en tetrahidrofurano (100 mL). La solución resultante se agitó a temperatura ambiente durante 30 minutos. La mezcla de reacción se aplacó con NH_4Cl saturado (30 mL), se concentró hasta proporcionar aproximadamente 50 mL y luego se diluyó con agua (50 mL) y EtOAc (100 mL). La capa orgánica se separó y la capa acuosa se extrajo con EtOAc (100 mL). Los elementos orgánicos combinados se secaron ($MgSO_4$), se filtraron y se evaporaron para proporcionar el producto bruto. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 0 a 10% MeOH en EtOAc para proporcionar el producto (2,54 g, 73,6 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2,35 (1H, s), 3,15 - 3,21 (3H, m), 3,27 - 3,31 (1H, m), 3,84 - 3,91 (2H, m), 4,50 - 4,57 (1H, m), 5,90 - 5,93 (1H, m), 7,41 - 7,54 (4H, m), 7,61 - 7,63 (1H, m), 8,14 (1H, d), 8,23 - 8,26 (1H, m), 8,37 (1H, s), 8,59 (1H, s), 9,74 (1H, s); m/z (ES^+) $(M+H)^+$ = 484,17; HPLC t_R = 1,65 min.

Ejemplo 216: (2S)-2-[1-(2-cloro-6-ciano-fenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-cloro-2-piridil)-3-[(1R)-2-hidroxi-1-metil-etoxi]propanamida



Una solución de fluoruro de tetrabutilamonio (1M en THF) (0,891 mL, 0,89 mmol) se agregó en una porción a una solución agitada de (2S)-2-(1-(2-cloro-6-cianofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-cloropiridin-2-il)-3-((R)-1-(triisopropilsililoxi)propan-2-iloxi)propanamida (**Producto Intermedio AY1**) (610 mg, 0,89 mmol) en tetrahidrofurano (15 mL). La solución resultante se agitó a temperatura ambiente durante 30 minutos. La mezcla de reacción se aplacó con NH_4Cl saturado (10 mL) y se diluyó con agua (20 mL) y EtOAc (70 mL). La capa orgánica se separó y la capa acuosa se extrajo con EtOAc (70 mL), los elementos orgánicos combinados se secaron ($MgSO_4$), se filtraron y se evaporaron para proporcionar el producto bruto. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 50 a 80% EtOAc en isohexano para proporcionar el producto (281 mg, 59,7 %). ^{1}H NMR (400 MHz, DMSO) δ 1,07 (3H, d), 3,33 (1H, q), 3,40 - 3,46 (1H, m), 3,61 - 3,69 (1H, m), 4,09 - 4,16 (2H, m), 4,57 (1H, t), 5,90 (1H, s), 7,87 - 7,91 (2H, m), 8,01 - 8,05 (1H, m), 8,16 - 8,19 (2H, m), 8,40 - 8,41 (1H, m), 8,61 (1H, s), 8,78 (1H, t), 11,17 (1H, d); m/z (ES$^-$) $(M-H)^-$ = 526; HPLC t_R = 2,94 min.

Ejemplo 217: (2S)-2-[1-(2-cloro-6-ciano-fenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-[(1R)-2-hidroxi-1-metil-etoxi]-N-(5-metilpirazin-2-il)propanamida



Una solución de fluoruro de tetrabutilamonio (1M en THF) (0,887 mL, 0,89 mmol) se

agregó en una porción a una solución agitada de (2S)-2-(1-(2-cloro-6-cianofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-metilpirazin-2-il)-3-((R)-1-(triisopropilsililoxi)propan-2-iloxi)propanamida (**Producto Intermedio AZ1**) (0,59 g, 0,89 mmol) en tetrahidrofurano (15 mL). La solución resultante se agitó a temperatura ambiente durante 30 minutos. La mezcla de reacción se aplacó con NH_4Cl saturado (10 mL) y se diluyó con agua (20 mL) y EtOAc (70 mL). La capa orgánica se separó y la capa acuosa se extrajo con EtOAc (70 mL), los elementos orgánicos combinados se secaron ($MgSO_4$), se filtraron y se evaporaron para proporcionar el producto bruto. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 50 a 80% EtOAc en isohexano para proporcionar el producto (0,367 g, 81 %). ^{1}H NMR (400 MHz, CDCl3) δ 1,14 - 1,20 (3H, m), 2,54 (3H, s), 2,70 - 2,84 (1H, m), 3,54-3,72 (2H, m), 3,77 - 3,83 (1H, m), 4,09 - 4,16 (1H, m), 4,28 - 4,32 (1H, m), 6,08 - 6,11 (1H, m), 7,63 (1H, t), 7,78 - 7,81 (1H, m), 7,85 - 7,88 (1H, m), 8,12 (1H, s), 8,50 - 8,53 (1H, m), 8,62 (1H, d), 9,04 - 9,12 (1H, m), 9,41 (1H, s); m/z (ES^+) $(M+H)^+$ = 509,06; HPLC t_R = 2,41 min.

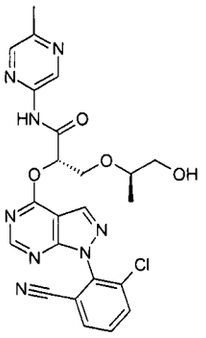
Se recogió (2S)-2-(1-(2-cloro-6-cianofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-((R)-1-hidroxipropan-2-iloxi)-N-(5-metilpirazin-2-il)propanamida (220 mg, 0,43 mmol) y se colocó en Et_2O (20 mL) y se entibió hasta hervir a reflujo. El material se disolvió y luego comenzó a cristalizar. La mezcla se dejó enfriar y se mantuvo a temperatura ambiente durante 1 hora. El sólido se retiró mediante filtración para proporcionar (2S)-2-(1-(2-cloro-6-cianofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-((R)-1-hidroxipropan-2-iloxi)-N-(5-metilpirazin-2-il)propanamida (200 mg), la cual se comprobó que era cristalina mediante difracción de polvo de rayos X.

Ángulo 2-Theta (2θ)	**% de Intensidad**
4,234	100,0
20,902	95,6
14,456	95,2
17,730	77,8
13,278	69,4
11,065	63,2
21,237	61,5

19,725	59,4
26,458	59,2
8,463	54,9
26,192	54,8

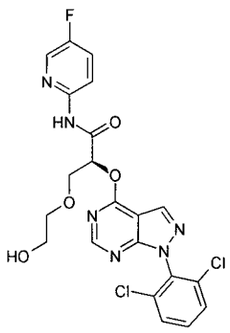
Ejemplo 217: (2S)-2-[1-(2-cloro-6-ciano-fenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-[(1R)-2-hidroxi-1-metil-etoxi]-N-(5-metilpirazin-2-il)propanamida

Método alternativo.



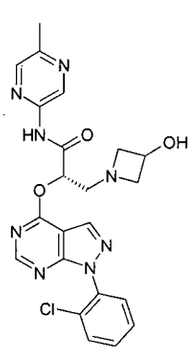
Se agregó TBAF 1M en THF (5,11 mL, 5,11 mmol) a (2S)-2-(1-(2-cloro-6-cianofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-metilpirazin-2-il)-3-((R)-1-(triisopropilsililoxi)propan-2-iloxi)propanamida (**Producto Intermedio AZ1**) (3,4 g, 5,11 mmol) y ácido acético (0,307 g, 5,11 mmol) en THF (35 mL). La solución resultante se agitó a 22°C durante 20 horas. Ésta se aplacó con solución de NH_4Cl (sat., 25 mL) y se diluyó con EtOAc (50 mL). La fase orgánica se lavó con bicarbonato de sodio saturado (25 mL), agua (20 mL), salmuera (20 mL), se secó ($MgSO_4$) y se evaporó. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con EtOAc para proporcionar el producto (2,23g, 85%). Esto se cristalizó a partir de EtOAc (10 mL) e iso-hexano (6 mL) para proporcionar el producto deseado como un polvo cristalino blanco (1,9g, 73%) que se confirmó que era la misma forma cristalina que la descrita previamente. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1,06 - 1,07 (3H, m), 2,44 (3H, s), 3,25 - 3,47 (2H, m), 3,62 - 3,67 (1H, m), 4,09 - 4,16 (2H, m), 4,53 - 4,61 (1H, m), 5,90 - 5,96 (1H, m), 7,89 (1H, dd), 8,16 - 8,20 (2H, m), 8,31 - 8,32 (1H, m), 8,62 (1H, s), 8,76 - 8,78 (1H, m), 9,10 - 9,12 (1H, m), 11,17 (1H, s); m/z (ES$^-$) $(M-H)^-$ = 507; HPLC t_R = 2,44 min.

Ejemplo 218: (2S)-2-[1-(2,6-diclorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-3-(2-hidroxietoxi)propanamida



Se agregó gota a gota fluoruro de tetrabutilamonio (1M en THF) (0,838 mL, 0,84 mmol) a (S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(2,6-diclorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-fluoropiridin-2-il)propanamida (**Producto Intermedio BA1**) (0,625 g, 0,84 mmol) en THF (10,34 mL) a temperatura ambiente bajo nitrógeno. La solución resultante se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se aplacó con NH_4Cl saturado (10 mL) y se diluyó con agua (20 mL) y EtOAc (70 mL). La capa orgánica se separó y la capa acuosa se extrajo con EtOAc (70 mL). Los elementos orgánicos combinados se secaron ($MgSO_4$), se filtraron y se evaporaron para proporcionar el producto bruto. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 25 a 100% EtOAc en isohexano, para proporcionar el producto (0,307 g, 72,1 %). ^1H NMR (400 MHz, $CDCl_3$) δ 2,60 (1H, t), 3,71 - 3,81 (4H, m), 4,16 - 4,25 (2H, m), 6,10 (1H, t), 7,43 - 7,49 (2H, m), 7,53 - 7,55 (2H, m), 8,14 (1H, d), 8,22 - 8,25 (1H, m), 8,48 (1H, s), 8,60 (1H, s), 9,00 (1H, s); m/z (ES^+) $(M+H)^+$ = 507,31; HPLC t_R = 2,67 min.

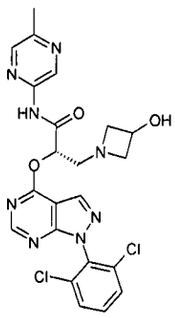
Ejemplo 219: (2S)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-(3-hidroxiazetidin-1-il)-N-(5-metilpirazin-2-il)propanamida



Se agregó fluoruro de tetrabutilamonio (1M en THF) (0,87 mL, 0,87 mmol) a (2S)-3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-metilpirazin-2-il)propanamida (**Producto Intermedio BB1**) (520 mg, 0,87

mmol) en tetrahidrofurano (25 mL) bajo nitrógeno. La mezcla resultante se agitó a temperatura ambiente durante 2 horas. Se agregó fluoruro de tetrabutilamonio adicional (1M en THF) (1,7 mL, 1,7 mmol) y la mezcla se agitó durante toda la noche. La mezcla de reacción se aplacó con solución de cloruro de amonio saturado (20 mL), se diluyó con acetato de etilo (50 mL) y se agitó durante 10 minutos. La capa orgánica se separó, se lavó con agua (50 mL) y salmuera (50 mL), se secó ($MgSO_4$), se filtró y se evaporó. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 10% metanol en acetato de etilo, para proporcionar el producto (130 mg). ^{1}H NMR (400 MHz, DMSO-d6) δ 2,50 (3H, m), 2,98 - 3,09 (3H, m), 3,15 - 3,21 (1H, m), 3,67 - 3,77 (2H, m), 4,19 - 4,29 (1H, m), 5,31 (1H, d), 5,77 - 5,84 (1H, m), 7,60 - 7,76 (3H, m), 7,80 - 7,82 (1H, m), 8,35 - 8,37 (1H, m), 8,57 (1H, s), 8,64 (1H, s), 9,11 - 9,12 (1H, m), 11,17 (1H, s); m/z (ESI$^+$) $(M+H)^+$ = 481; HPLC t_R = 1,52 min.

Ejemplo 220: (2S)-2-[1-(2,6-diclorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-(3-hidroxiazetidin-1-il)-N-(5-metilpirazin-2-il)propanamida



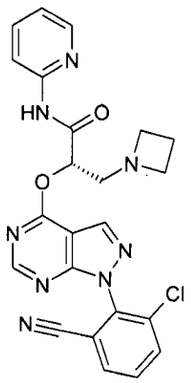
Una solución de fluoruro de tetrabutilamonio (1M en THF) (0,61 mL, 0,61 mmol) se agregó en una porción a una solución agitada de (S)-3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-(1-(2,6-diclorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-metilpirazin-2-il)propanamida (**Producto Intermedio BB3**) (385 mg, 0,61 mmol) en tetrahidrofurano (15 mL). La solución resultante se agitó a temperatura ambiente durante 30 minutos. La mezcla de reacción se aplacó con solución de cloruro de amonio saturado (10 mL) y se diluyó con agua (20 mL) y acetato de etilo (70 mL). La capa orgánica se separó y la capa acuosa se extrajo con acetato de etilo (70 mL). Los elementos orgánicos combinados se secaron ($MgSO_4$), se filtraron y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 10% metanol en acetato de etilo, para proporcionar el producto (197 mg, 62,5%, 99,4%ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2,54 (3H, s), 3,19 - 3,24 (3H, m), 3,30 - 3,35 (1H, m), 3,88 - 3,93 (2H, m), 4,53 - 4,58 (1H, m),

5,93 - 5,96 (1H, m), 7,43 - 7,47 (1H, m), 7,52 - 7,55 (2H, m), 8,13 (1H, d), 8,41 (1H, s), 8,59 (1H, s), 9,42 (1H, d), 9,81 (1H, s); m/z (ES^+) $(M+H)^+ = 515$; HPLC $t_R = 1,58$ min.

Se calentó (S)-2-(1-(2,6-diclorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-(3-hidroxiazetidin-1-il)-N-(5-metilpirazin-2-il)propanamida amorfa (1700 mg) en t-butil metil éter a reflujo (800 mL) durante 30 minutos. La suspensión se filtró y el filtrado luego se redujo hasta un volumen de aproximadamente 100 mL. Esta solución se agitó durante toda la noche, permitiendo que la temperatura volviera a la temperatura ambiente. Se retiró un sólido mediante filtración y luego se secó al vacío a 60°C durante 4 días para proporcionar (S)-2-(1-(2,6-diclorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-(3-hidroxiazetidin-1-il)-N-(5-metilpirazin-2-il)propanamida cristalina (1121 mg).

Ángulo 2-Theta (2θ)	**% de Intensidad**
12,297	100,0
15,433	88,2
12,175	78,8
19,607	77,2
22,653	77,0
19,955	72,9
27,095	72,7
27,141	72,1
15,766	70,8
16,021	67,8

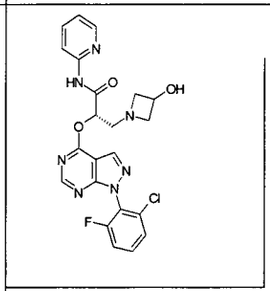
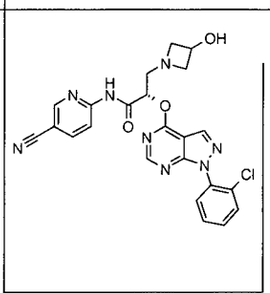
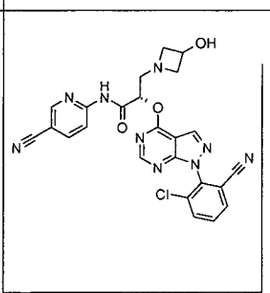
Ejemplo 221: (2S)-3-(azetidin-1-il)-2-[1-(2-cloro-6-ciano-fenil)pirazolo[3,4-d]pirimidin-4-il]oxi-N-(2-piridil)propanamida

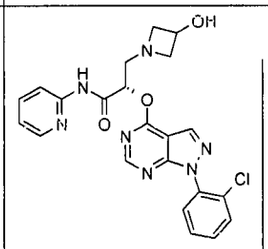
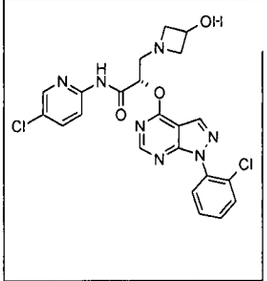
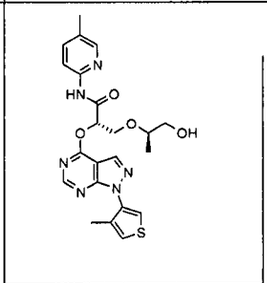


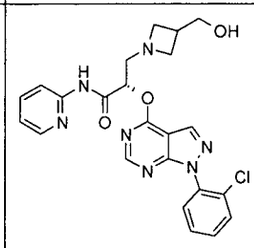
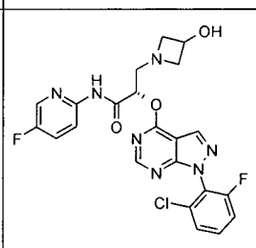
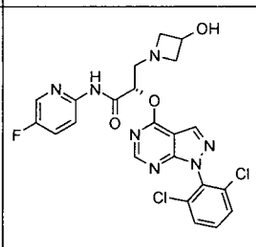
Se agregó hidruro de sodio (116 mg, 2,90 mmol) a (S)-3-(azetidin-1-il)-2-hidroxi-N-(piridin-2-il)propanamida (**Producto Intermedio BC1**) (232 mg, 1,05 mmol) en THF anhidro (50 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos y luego se agregó gota a gota una solución de 3-cloro-2-(4-cloro-1H-pirazolo[3,4-d]pirimidin-1-il)benzonitrilo (**Producto Intermedio AH6**) (280 mg, 0,97 mmol) en THF anhidro (20 mL) durante 1 minuto. La mezcla se agitó a 0°C durante 10 minutos y luego se dejó entibiar hasta alcanzar la temperatura ambiente durante 2 horas. Ésta luego se enfrió hasta alcanzar 0°C, se agregó sal de Rochelle al 20% (20 mL) y la mezcla se agitó durante 10 minutos. Ésta se extrajo con EtOAc (50 mL), la fase orgánica se lavó con agua (10 mL) y salmuera (20 mL), se secó ($MgSO_4$), se filtró y se evaporó. El residuo se trituró con EtOAc (10 mL), se filtró y los filtrados se evaporaron. El residuo se purificó mediante cromatografía instantánea en sílice, gradiente de elución 0 a 20% MeOH en EtOAc, y se purificó adicionalmente mediante HPLC preparativa (columna Phenomenex Luna C18 100A, 5µ sílice, 21 mm de diámetro, 150 mm de longitud), utilizando mezclas cada vez menos polares de agua (que contenía ácido fórmico al 1%) y MeCN como eluyentes para proporcionar el producto (100 mg, 22%).

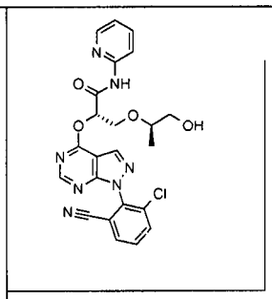
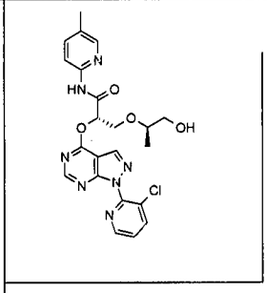
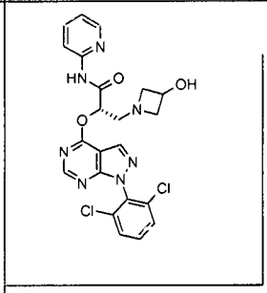
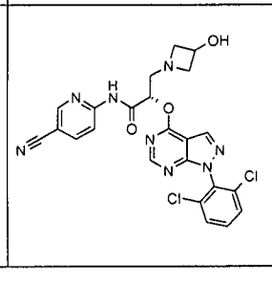
^{1}H NMR (400 MHz, $CDCl_3$) δ 2,17 - 2,25 (2H, m), 3,08 - 3,17 (1H, m), 3,20 - 3,29 (1H, m), 3,40 - 3,52 (4H, m), 5,84 - 5,91 (1H, m), 7,02 - 7,08 (1H, m), 7,57 - 7,64 (1H, m), 7,65 - 7,71 (1H, m), 7,77 - 7,80 (1H, m), 7,82 - 7,87 (1H, m), 8,21 - 8,25 (1H, m), 8,31 - 8,32 (1H, m), 8,44 - 8,47 (1H, d), 8,58 - 8,61 (1H, d), 9,8 (0,4H, s), 10,08 (0,6H, s) (Mezcla de rotámeros); m/z (ESI$^+$) $(M+H)^+$ = 475; HPLC t_R = 1,16 min.

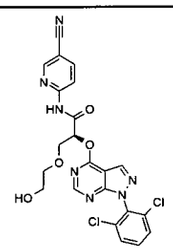
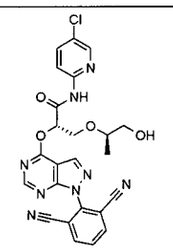
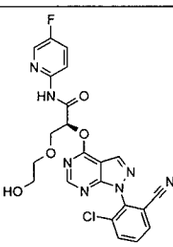
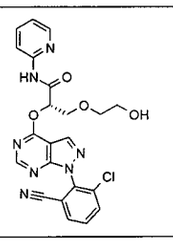
Los siguientes Ejemplos se prepararon utilizando un método análogo al descrito para el ejemplo **218**, utilizando el producto intermedio apropiado.

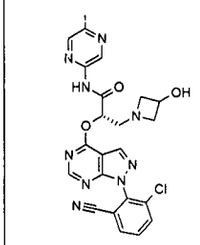
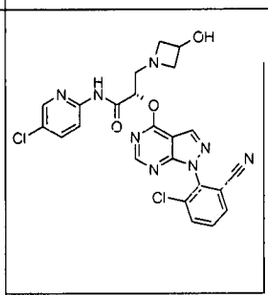
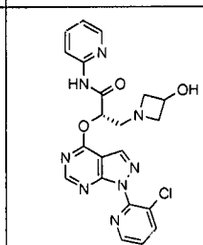
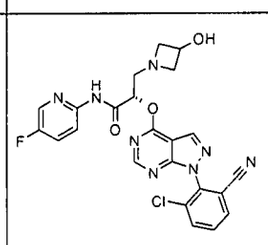
Número de ejemplo	Estructura	^{1}H NMR (400 MHz) δ	LCMS	Referencia al producto intermedio
222		(DMSO-d6) 3,00 - 3,13 (3H, m), 3,14 - 3,23 (1H, m), 3,67 - 3,76 (2H, m), 4,18 - 4,27 (1H, m), 5,30 (1H, d), 5,77 - 5,84 (1H, m), 7,72 - 7,20 (1H, m), 7,60 - 7,68 (1H, m), 7,69 - 7,71 (1H, m), 7,76 - 7,85 (2H, m), 8,00 - 8,08 (1H, m), 8,35 - 8,40 (1H, m), 8,60 (1H, s), 8,71 (1H, s), 10,95 (1H, d)	m/z (ES+) (M+H)+ = 484; HPLC tR = 1,17 min.	BD1
223		($CDCl_3$) 2,14 (1H, s, ancho), 3,16 - 3,27 (1H, m), 3,20 - 3,24 (2H, m), 3,30 - 3,35 (1H, m), 3,90 - 3,94 (2H, m), 4,55 - 4,61 (1H, m), 5,89 - 5,92 (1H, m), 7,45 - 7,51 (2H, m), 7,52 - 7,55 (1H, m), 7,61 - 7,63 (1H, m), 7,92 - 7,95 (1H, m), 8,33 - 8,35 (1H, m), 8,36 (1H, s), 8,56 - 8,58 (1H, m), 8,59 (1H, s), 10,41 (1H, s)	m/z (ES+) (M+H)+ = 491; HPLC tR = 1,27 min.	BD2
224		($CDCl_3$) 2,10 (1H, s. ancho), 3,17 - 3,26 (3H, m), 3,27 - 3,38 (1H, m), 3,91 - 3,96 (2H, m), 4,58 - 4,65 (1H, m), 5,85 - 5,93 (1H, m), 7,60 - 7,65 (1H, m), 7,78 - 7,81 (1H, m), 7,85 - 7,88 (1H, m), 7,92 - 7,96 (1H, m), 8,33 -	m/z (ES+) (M+H)+ = 516; HPLC tR = 1,23 min.	BD3

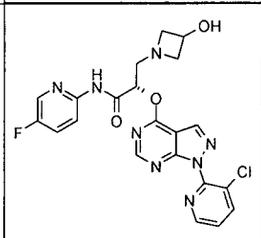
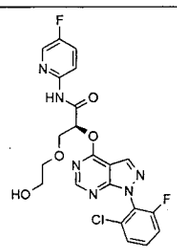
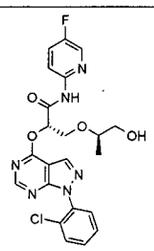
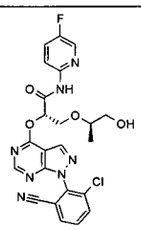
		8,36 (1H, m), 8,44 - 8,46 (1H, m), 8,57 - 8,62 (2H, m), 10,30 (0,5H, s), 10,60 (0,5H, s).		
225		(DMSO-d6) 2,98 - 3,12 (3H, m), 3,14 - 3,19 (1H, m), 3,66 - 3,74 (2H, m), 4,18 - 4,27 (1H, m), 5,31 (1H, d), 5,76 - 5,83 (1H, m), 7,15 - 7,19 (1H, m), 7,60 - 7,75 (3H, m), 7,76 - 7,82 (2H, m), 8,06 (1H, d), 8,37 - 8,40 (1H, m), 8,53 (1H, s), 8,58 (1H, s), 10,90 (1H, s)	m/z (ES+) (M+H)+ = 466; HPLC tR = 1,22 min.	BD4
226		(DMSO-d6) 2,96 - 3,05 (3H, m), 3,10 - 3,15 (1H, m), 3,60 - 3,66 (2H, m), 4,14 - 4,20 (1H, m), 5,22 - 5,27 (1H, m), 5,72 - 5,75 (1H, m), 7,56 - 7,70 (3H, m), 7,74 (1H, dd), 7,88 (1H, dd), 8,02 (1H, d), 8,39 - 8,41 (1H, m), 8,52 (1H, s), 8,58 (1H, s), 11,12 (1H, s)	m/z (ES+) (M+H)+ = 500; HPLC tR = 1,44 min.	BD5
227		(DMSO-d6) 1,06 (3H, d), 2,10 (3H, d), 2,24 (3H, s), 3,30 - 3,40 (1H, m), 3,41 - 3,46 (1H, m), 3,61 - 3,68 (1H, m), 4,03 - 4,11 (2H, m), 4,55 (1H, t), 5,88 - 5,98 (1H, m), 7,40 - 7,43 (1H, m), 7,62 (1H, dd), 7,86 (1H, d), 7,92 - 7,97 (1H, m), 8,19 - 9,02 (1H, m), 8,60 (1H, s), 8,62 (1H, s),	m/z (ES+) (M+H)+ = 469; HPLC tR = 2,00 min.	BD6

		10,85 (1H, s)		
228		($CDCl_3$) 2,39 (1H, s), 2,68 - 2,71 (1H, m), 3,15 - 3,27 (2H, m), 3,37 - 3,40 (2H, m), 3,54 - 3,59 (2H, m), 3,83 - 3,85 (2H, m), 5,88 - 5,91 (1H, m), 7,03 - 7,06 (1H, m), 7,46 - 7,50 (2H, m), 7,52 - 7,55 (1H, m), 7,61 - 7,63 (1H, m), 7,67 - 7,72 (1H, m), 8,19 (1H, d, 8,4 Hz), 8,29 - 8,31 (1H, m), 8,36 (1H, s), 8,58 (1H, s), 10,20 (1H, s)	m/z (ES+) (M+H)+ = 480; HPLC tR = 1,63 min.	BD7
229		($CDCl_3$) 2,26 (1H, s), 3,15 - 3,22 (3H, m), 3,26 - 3,32 (1H, m), 3,85 - 3,91 (2H, m), 4,53 - 4,55 (1H, m), 5,89 - 5,93 (1H, m), 7,22 - 7,27 (1H, m), 7,41 - 7,52 (3H, m), 8,14 - 8,15 (1H, m), 8,22 - 8,27 (1H, m), 8,41 (1H, s), 8,59 (1H, s), 9,74 (1H, d)	m/z (ES+) (M+H)+ = 502; HPLC tR = 1,72 min.	BD8
230		($CDCl_3$) 3,16 - 3,22 (3H, m), 3,27 - 3,32 (1H, m), 3,86 - 3,92 (2H, m), 4,54 (1H, s), 5,90 - 5,93 (1H, m), 7,41 - 7,47 (2H, m), 7,52 - 7,55 (2H, m), 8,15 (1H, d), 8,23 - 8,27 (1H, m), 8,41 (1H, s), 8,59 (1H, s), 9,74 (1H, s)	m/z (ES+) (M+H)+ = 518; HPLC tR = 1,78 min.	BD9

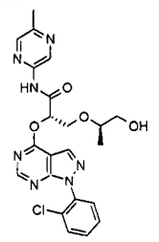
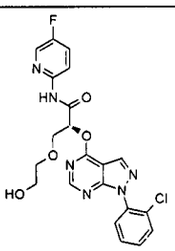
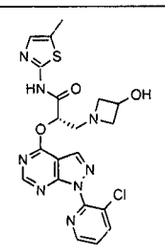
231		(DMSO-d6) 1,07 (3H, d), 3,34 (1H, q), 3,40 - 3,46 (1H, m), 3,64 - 3,68 (1H, m), 4,08 - 4,17 (2H, m), 4,55 - 4,58 (1H, m), 5,91 (1H, s), 7,11 - 7,14 (1H, m), 7,74 - 7,79 (1H, m), 7,89 (1H, t), 7,99 (1H, t), 8,13 - 8,19 (2H, m), 8,33 - 8,35 (1H, m), 8,61 (1H, d), 8,78 (1H, t), 10,96 (1H, d)	m/z (ES+) (M+H)+ = 494; HPLC tR = 2,51 min.	BD10
232		($CDCl_3$) 1,15 - 1,17 (3H, m), 2,29 (3H, s), 3,50 - 3,69 (3H, m), 3,75 - 3,80 (1H, m), 4,07 - 4,11 (1H, m), 4,26 - 4,29 (1H, m), 6,05 - 6,08 (1H, m), 7,45 - 7,48 (1H, m), 7,52 - 7,55 (1H, m), 7,97 - 8,10 (3H, m), 8,45 (1H, s), 8,60 - 8,62 (1H, m), 8,64 (1H, s), 9,15 (1H, s)	m/z (ES+) (M+H)+ = 484; HPLC tR = 2,43 min.	BD11
233		($CDCl_3$) 3,18 - 3,32 (4H, m), 3,83 - 3,90 (2H, m), 4,50 - 4,56 (1H, m), 5,90 - 5,93 (1H, m), 7,04 - 7,08 (1H, m), 7,43 - 7,47 (1H, m), 7,52 - 7,55 (2H, m), 7,69 - 7,73 (1H, m), 8,22 - 8,24 (1H, m), 8,28 - 8,30 (1H, m), 8,42 (1H, s), 8,59 (1H, s), 9,66 (1H, s)	m/z (ES+) (M+H)+ = 500; HPLC tR = 1,29 min.	BD12
234		($CDCl_3$) 3,17 - 3,25 (3H, m), 3,31 - 3,36 (1H, m), 3,90 - 3,95 (2H, m), 4,56 - 4,62 (1H, m), 5,88 - 5,91 (1H, m), 7,44 - 7,55 (3H, m), 7,93 - 7,95 (1H, m),	m/z (ES+) (M+H)+ = 525; HPLC tR = 1,38 min.	BD13

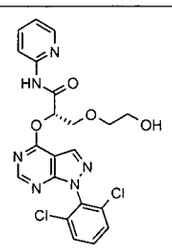
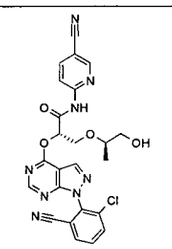
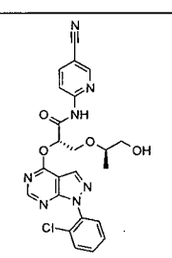
		8,34 - 8,36 (1H, m), 8,41 (1H, s), 8,57 - 8,59 (2H, m), 10,44 (1H, s)		
235		($CDCl_3$) 3,73 - 3,83 (4H, m), 4,17 - 4,25 (2H, m), 6,07 (1H, t), 7,44 - 7,48 (1H, m), 7,52 - 7,56 (2H, m), 7,96 - 7,99 (1H, m), 8,36 - 8,39 (1H, m), 8,48 (1H, s), 8,57 (1H, q), 8,59 (1H, s), 9,32 (1H, s)	m/z (ES+) (M+H)+ = 514; HPLC tR = 2,04min.	BD14
236		($CDCl_3$) d1,17 (d, 3H), 3,55 - 3,71 (m, 2H), 3,76 - 3,85 (m, 1H), 4,07 - 4,14 (m, 2H), 4,25 - 4,31 (m, 1H), 6,04 - 6,08 (m, 1H), 7,66 - 7,72 (m, 1H), 7,78 (t, 1H), 8,10 (d, 2H), 8,17 (d, 1H), 8,24 (d, 1H), 8,56 (s, 1H), 8,67 (s, 1H), 9,25 (s, 1H)	m/z (ES+), (M+H)+ = 519,31; HPLC tR = 2,74 min	BD15
237		(DMSO-d6) d3,50 - 3,56 (m, 2H), 3,58 - 3,70 (m, 2H), 3,99 - 4,16 (m, 2H), 4,61 (t, 1H), 5,91 - 5,97 (m, 1H), 7,68 - 7,77 (m, 1H), 7,89 (t, 1H), 8,00 - 8,07 (m, 1H), 8,15 - 8,21 (m, 2H), 8,34 - 8,37 (m, 1H), 8,61 (s, 1H), 8,79 (d, 1H), 11,12 (s, 1H)	m/z (ES+), (M+H)+ = 498,36; HPLC tR = 1,88 min	BD16
238		(DMSO-d6) d3,50 - 3,57 (m, 2H), 3,58 - 3,70 (m, 2H), 4,01 - 4,17 (m, 2H), 4,62 (t, 1H), 5,93 - 5,98 (m, 1H), 7,10 - 7,16 (m,	m/z (ES+), (M+H)+ = 480,29; HPLC tR =	BD17

		1H), 7,73 - 7,80 (m, 1H), 7,89 (t, 1H), 7,96 - 8,02 (m, 1H), 8,15 - 8,21 (m, 2H), 8,33 - 8,37 (m, 1H), 8,61 (s, 1H), 8,80 (d, 1H), 11,00 (s, 1H)	1,66 min	
239		($CDCl_3$) d9,93 (1H, s),9,58 (0H, s),9,34 (1H, s),8,54 (1H, d),8,39 (1H, d),8,06 (1H, s),7,80 (1H, d),7,72 (1H, d),7,56 (1H, t),5,87 (1H, q),4,45 - 4,52 (1H, m),3,84 (2H, t),3,25 (2H, q),3,08 - 3,19 (2H, m),2,47 (3H, s)	m/z (ES+), (M+H)+ = 506; HPLC tR = 1,17 min.	BD18
240		($CDCl_3$) d3,08 - 3,17 (2H, m),3,20 - 3,26 (1H, m),3,41 (1H, q),3,77 - 3,87 (2H, m),4,47 (1H, q),5,80 - 5,86 (1H, m),7,52 - 7,62 (2H, m),7,70 - 7,81 (4H, m),8,12 - 8,19 (2H, m),8,39 (1H, d),8,54 (1H, d),9,68 (0H, s),9,90 (1H, s)	m/z (ES+), (M+H)+ = 525; 5min Ácido, HPLC tR = 1,39 min	BD19
241		($CDCl_3$) 3,15 - 3,31 (4H, m), 3,83 - 3,90 (2H, m), 4,52 (1H, t), 5,91 - 5,94 (1H, m), 7,04 - 7,07 (1H, m), 7,45 - 7,48 (1H, m), 7,68 - 7,72 (1H, m), 8,00 - 8,02 (1H, m), 8,21 (1H, d), 8,28 - 8,30 (1H, m), 8,41 (1H, s), 8,61 - 8,63 (2H, m), 9,54 (1H, s)	m/z (ES+) (M+H)+ = 467,04; HPLC tR = 1,4 min.	BD20
242		($CDCl_3$) 3,17 - 3,33 (4H, m), 3,87 - 3,93 (2H, m), 4,55 (1H, q), 5,90 - 5,93 (1H, m), 7,41 - 7,46 (1H, m), 7,62 (1H, t), 7,78 - 7,81 (1H, m), 7,85 - 7,88 (1H, m),	m/z (ES+) (M+H)+ = 509,13; HPLC tR = 1,59 min.	BD21

		8,15 (1H, d); 8,23 - 8,26 (1H, m), 8,46 (1H, d), 8,61 (1H, d), 9,64 - 9,87 (1H, m)		
243		($CDCl_3$) 3,14 - 3,22 (3H, m), 3,27 - 3,32 (1H, m), 3,89 (2H, q), 4,54 (1H, t), 5,91 - 5,94 (1H, m), 7,41 - 7,52 (2H, m), 8,00 - 8,02 (1H, m), 8,14 (1H, d), 8,22 - 8,25 (1H, m), 8,41 (1H, s), 8,61 - 8,63 (1H, m), 8,63 (1H, s), 9,67 (1H, s)	m/z (ES+) (M+H)+ = 485; HPLC tR = 1,44 min.	BD22
244		($CDCl_3$), 2,55 (1H, d), 3,71 - 3,79 (4H, m), 4,15 - 4,25 (2H, m), 6,09 (1H, t), 7,22 - 7,27 (1H, m), 7,40 - 7,52 (3H, m), 8,14 (1H, t), 8,21 - 8,25 (1H, m), 8,48 (1H, s), 8,60 (1H, s), 8,98 (1H, d)	m/z (ES+) (M+H)+ = 491,09; HPLC tR = 2,68 min.	BD23
245		($CDCl_3$) 1,17 (3H, d), 3,05 (1H, d), 3,55 - 3,61 (1H, m), 3,64 - 3,69 (1H, m), 3,76 - 3,83 (1H, m), 4,08 - 4,12 (1H, m), 4,26 - 4,30 (1H, m), 6,06 - 6,08 (1H, m), 7,44 - 7,55 (4H, m), 7,61 - 7,63 (1H, m), 8,13 (1H, d), 8,20 - 8,23 (1H, m), 8,42 (1H, s), 8,60 (1H, s), 9,18 (1H, s)	m/z (ES+) (M+H)+ = 487,09; HPLC tR = 2,8 min.	BD24
246		(DMSO-d6) 1,07 (3H, d), 3,33 (1H, q), 3,40 - 3,46 (1H, m), 3,63 - 3,69 (1H, m), 4,09 - 4,16 (2H, m), 4,57 (1H, t), 5,89 (1H, s),	m/z (ES+) (M+H)+ = 512,14; HPLC tR =	BD25

3A

		7,69 - 7,76 (1H, m), 7,89 (1H, t), 8,02 (1H, d), 8,17 - 8,19 (2H, m), 8,35 (1H, d), 8,61 (1H, s), 8,77 (1H, t), 11,09 (1H, d)	2,7 min.	
247		($CDCl_3$) 1,17 (3H, d), 2,54 (3H, s), 2,76 - 2,79 (1H, m), 3,54 - 3,60 (1H, m), 3,64 - 3,69 (1H, m), 3,76 - 3,82 (1H, m), 4,09 - 4,15 (1H, m), 4,28 - 4,32 (1H, m), 6,09 (1H, d), 7,45 - 7,52 (2H, m), 7,44 - 7,55 (1H, m), 7,62 - 7,63 (1H d, m), 8,11 (1H, d), 8,42 (1H, s), 8,61 (1H, s), 9,05 (1H, s), 9,40 - 9,42 (1H, m)	m/z (ES+) (M+H)+ = 484; HPLC tR = 2,52 min.	BD26
248		($CDCl_3$) 2,59 (1H, d), 3,73 - 3,79 (4H, m), 4,15 - 4,25 (2H, m), 6,10 (1H, t), 7,44 - 7,55 (4H, m), 7,61 - 7,64 (1H, m), 8,14 (1H, d), 8,22 - 8,25 (1H, m), 8,44 (1H, s), 8,60 (1H, s), 9,00 (1H, s)	m/z (ES+) (M+H)+ = 473,44; HPLC tR = 1,97 min.	BD27
249		($CDCl_3$) 1,66 - 1,74 (1H, m), 2,40 (3H, s), 3,12 - 3,44 (4H, m), 3,86 - 3,95 (2H, m), 4,52 - 4,61 (1H, m), 5,97 - 6,03 (1H, m), 7,10 (1H, s), 7,43 - 7,49 (1H, m), 7,98 - 8,03 (1H, m), 8,37 (1H, s), 8,58 - 8,64 (2H, m), 10,74 - 11,53 (1H, m)	m/z (ES-) (M-H)- = 485,31; HPLC tR = 1,55 min.	BD28

250		($CDCl_3$) 2,92 (1H, s), 3,73 - 3,80 (4H, m), 4,16 - 4,26 (2H, m), 6,10 (1H, t), 7,06 - 7,09 (1H, m), 7,43 - 7,47 (1H, m), 7,52 - 7,54 (2H, m), 7,71 - 7,75 (1H, m), 8,20 (1H, d), 8,27 - 8,29 (1H, m), 8,48 (1H, s), 8,60 (1H, s), 9,02 (1H, s)	m/z (ES+) (M+H)+ = 489,31; HPLC tR = 2,53 min.	BD29
251		(DMSO-d6) 1,05 - 1,09 (3H, m), 3,25-3,36 (1H, m), 3,40 - 3,46 (1H, m), 3,61 - 3,68 (1H, m), 4,10 - 4,18 (2H, m), 4,58 (1H, t), 5,91 - 5,93 (1H, m), 7,89 (1H, t), 8,12 - 8,19 (3H, m), 8,22 - 8,26 (1H, m), 8,61 (1H, s), 8,77-8,79 (1H, m), 8,82 - 8,83 (1H, m), 11,53 (1H, s)	m/z (ES-) (M-H)- = 517,37; HPLC tR = 2,53 min.	BD30
252		(DMSO-d6) 1,06 - 1,09 (3H, m), 3,33 (1H, t), 3,40 - 3,45 (1H, m), 3,61 - 3,69 (1H, m), 4,09 - 4,17 (2H, m), 4,57 (1H, t), 5,89 - 5,92 (1H, m), 7,56 - 7,69 (3H, m), 7,74 - 7,77 (1H, m), 8,12 - 8,14 (1H, m), 8,23 - 8,26 (1H, m), 8,54 (1H, s), 8,61 (1H, d), 8,82 (1H, m), 11,51 (1H, s)	m/z (ES-) (M-H)- = 492,40; HPLC tR = 2,62 min.	BD31

Ejemplo 222: (2S)-2-[1-(2-cloro-6-fluoro-fenil)pirazolo[3,4-d]pirimidin-4-il]oxi-3-(3-hidroxiazetidin-1-il)-N-(2-piridil)propanamida

Ejemplo 223: (2S)-2-[1-(2-clorofenil)pirazolo[3,4-d]pirimidin-4-il]oxi-N-(5-ciano-2-piridil)-3-(3-hidroxiazetidin-1-il)propanamida

Ejemplo 224: (2S)-2-[1-(2-cloro-6-ciano-fenil)pirazolo[3,4-d]pirimidin-4-il]oxi-N-(5-ciano-2-piridil)-3-(3-hidroxiazetidin-1-il)propanamida

Ejemplo 225: (2S)-2-[1-(2-clorofenil)pirazolo[3,4-d]pirimidin-4-il]oxi-3-(3-hidroxiazetidin-1-il)-N-(2-piridil)propanamida

Ejemplo 226: (2S)-2-[1-(2-clorofenil)pirazolo[3,4-d]pirimidin-4-il]oxi-N-(5-cloro-2-piridil)-3-(3-hidroxiazetidin-1-il)propanamida

Ejemplo 227: (2S)-3-[(1R)-2-hidroxi-1-metil-etoxi]-N-(5-metil-2-piridil)-2-[1-(4-metil-3-tienil)pirazolo[3,4-d]pirimidin-4-il]oxi-propanamida

Ejemplo 228: (2S)-2-[1-(2-clorofenil)pirazolo[3,4-d]pirimidin-4-il]oxi-3-[3-(hidroximetil)azetidin-1-il]-N-(2-piridil)propanamida

Ejemplo 229: (2S)-2-[1-(2-cloro-6-fluoro-fenil)pirazolo[3,4-d]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-3-(3-hidroxiazetidin-1-il)propanamida

Ejemplo 230: (2S)-2-[1-(2,6-diclorofenil)pirazolo[3,4-d]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-3-(3-hidroxiazetidin-1-il)propanamida

Ejemplo 231: (2S)-2-[1-(2-cloro-6-ciano-fenil)pirazolo[3,4-d]pirimidin-4-il]oxi-3-[(1R)-2-hidroxi-1-metil-etoxi]-N-(2-piridil)propanamida

Ejemplo 232: (2S)-2-[1-(3-cloro-2-piridil)pirazolo[3,4-d]pirimidin-4-il]oxi-3-[(1R)-2-hidroxi-1-metil-etoxi]-N-(5-metil-2-piridil)propanamida

Ejemplo 233: (2S)-2-[1-(2,6-diclorofenil)pirazolo[3,4-d]pirimidin-4-il]oxi-3-(3-hidroxiazetidin-1-il)-N-(2-piridil)propanamida

Ejemplo 234: (2S)-N-(5-ciano-2-piridil)-2-[1-(2,6-diclorofenil)pirazolo[3,4-d]pirimidin-4-il]oxi-3-(3-hidroxiazetidin-1-il)propanamida

Ejemplo 235: (2S)-N-(5-ciano-2-piridil)-2-[1-(2,6-diclorofenil)pirazolo[3,4-d]pirimidin-4-il]oxi-3-(2-hidroxietoxi)propanamida

Ejemplo 236: (2S)-N-(5-cloro-2-piridil)-2-[1-(2,6-dicianofenil)pirazolo[3,4-d]pirimidin-4-il]oxi-3-[(1R)-2-hidroxi-1-metil-etoxi]propanamida

Ejemplo 237: (2S)-2-[1-(2-cloro-6-ciano-fenil)pirazolo[3,4-d]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-3-(2-hidroxietoxi)propanamida

Ejemplo 238: (2S)-2-[1-(2-cloro-6-ciano-fenil)pirazolo[3,4-d]pirimidin-4-il]oxi-3-(2-hidroxietoxi)-N-(2-piridil)propanamida

Ejemplo 239: (2S)-2-[1-(2-cloro-6-ciano-fenil)pirazolo[3,4-d]pirimidin-4-il]oxi-3-(3-hidroxiazetidin-1-il)-N-(5-metilpirazin-2-il)propanamida

Ejemplo 240: (2S)-2-[1-(2-cloro-6-ciano-fenil)pirazolo[3,4-d]pirimidin-4-il]oxi-N-(5-cloro-2-piridil)-3-(3-hidroxiazetidin-1-il)propanamida

Ejemplo 241: (2S)-2-[1-(3-cloro-2-piridil)pirazolo[3,4-d]pirimidin-4-il]oxi-3-(3-hidroxiazetidin-1-il)-N-(2-piridil)propanamida

Ejemplo 242: (2S)-2-[1-(2-cloro-6-ciano-fenil)pirazolo[3,4-d]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-3-(3-hidroxiazetidin-1-il)propanamida

Ejemplo 243: (2S)-2-[1-(3-cloro-2-piridil)pirazolo[3,4-d]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-3-(3-hidroxiazetidin-1-il)propanamida

Ejemplo 244: (2S)-2-[1-(2-cloro-6-fluoro-fenil)pirazolo[3,4-d]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-3-(2-hidroxietoxi)propanamida

Ejemplo 245: (2S)-2-[1-(2-clorofenil)pirazolo[3,4-d]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-3-[(1R)-2-hidroxi-1-metil-etoxi]propanamida

Ejemplo 246: (2S)-2-[1-(2-cloro-6-ciano-fenil)pirazolo[3,4-d]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-3-[(1R)-2-hidroxi-1-metil-etoxi]propanamida

Ejemplo 247: (2S)-2-[1-(2-clorofenil)pirazolo[3,4-d]pirimidin-4-il]oxi-3-[(1R)-2-hidroxi-1-metil-etoxi]-N-(5-metilpirazin-2-il)propanamida

Ejemplo 248: (2S)-2-[1-(2-clorofenil)pirazolo[3,4-d]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-3-(2-hidroxietoxi)propanamida

Ejemplo 249: (2S)-2-[1-(3-cloro-2-piridil)pirazolo[3,4-d]pirimidin-4-il]oxi-3-(3-hidroxiazetidin-1-il)-N-(5-metiltiazol-2-il)propanamida

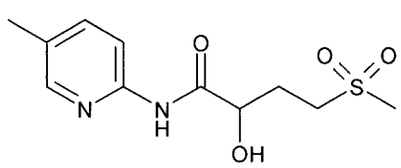
Ejemplo 250: (2S)-2-[1-(2,6-diclorofenil)pirazolo[3,4-d]pirimidin-4-il]oxi-3-(2-hidroxietoxi)-N-(2-piridil)propanamida

Ejemplo 251: (2S)-2-[1-(2-cloro-6-ciano-fenil)pirazolo[3,4-d]pirimidin-4-il]oxi-N-(5-ciano-2-piridil)-3-[(1R)-2-hidroxi-1-metil-etoxi]propanamida

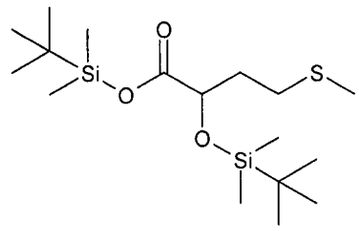
Ejemplo 252: (2S)-2-[1-(2-clorofenil)pirazolo[3,4-d]pirimidin-4-il]oxi-N-(5-ciano-2-piridil)-3-[(1R)-2-hidroxi-1-metil-etoxi]propanamida

PREPARACIÓN DE PRODUCTOS INTERMEDIOS

Producto Intermedio A1: 2-hidroxi-*N*-(5-metilpiridin-2-il)-4-(metilsulfonil)butanamida

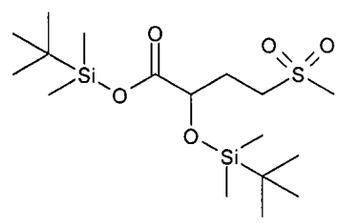


Etapa 1: *terc*-butil(dimetil)silil 2-{[*terc*-butil(dimetil)silil]oxi}-4-(metiltio)butanoato



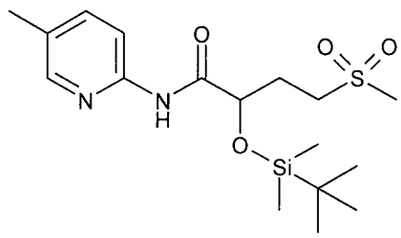
Se agregaron imidazol (21,76 g, 320 mmol) y TBDMSCl (24,08 g, 151 mmol) a una solución agitada de ácido 2-hidroxi-4-(metiltio)butírico (6,10 g, 40,6 mmol) en DMF (100 mL). La mezcla de reacción se mantuvo a temperatura ambiente durante 18 hrs. Se agregaron agua y EtOAc y las dos fases se separaron. La fase acuosa se extrajo con EtOAc. Los extractos orgánicos se combinaron y se lavaron tres veces con agua, se secaron sobre $MgSO_4$ y se concentraron al vacío. El residuo se purificó con cromatografía en columna (gel de sílice, eluyendo con un gradiente que consistía en 0-100% EtOAc en DCM) para proporcionar el compuesto del título como un aceite incoloro (10,20 g), ^{1}H NMR (300 MHz, $CDCl_3$) δ 4,29 (t, 1H), 2,59 (m, 2H), 2,09 (s, 3H), 1,98 (m, 2H), 0,94 (s, 9H), 0,91 (s, 9H), 0,28 (d, 6H), 0,08 (d, 6H).

Etapa 2: *terc*-butil(dimetil)silil 2-{[*terc*-butil(dimetil)silil]oxi}-4-(metilsulfonil)butanoato



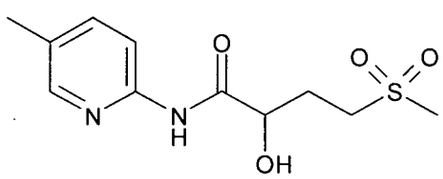
Se agregó en porciones *m*-CPBA (77%, 5,70 g, 25,4 mmol) en DCM (10 mL) a una solución agitada de *terc*-butil(dimetil)silil 2-{[*terc*-butil(dimetil)silil]oxi}-4-(metiltio)butanoato (Etapa 1) (5,00 g, 13,2 mmol) en DCM (15 mL). La mezcla de reacción se mantuvo a temperatura ambiente durante 1 ½ hrs. Se agregó agua y las dos fases se separaron. La fase orgánica se lavó dos veces con pirosulfito de sodio (5% en agua), se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se purificó con cromatografía en columna (gel de sílice, eluyendo con un gradiente que consistía en 0-100% EtOAc en DCM) para proporcionar el compuesto del título (2,12 g), ^{1}H NMR (300 MHz, $CDCl_3$) δ 4,33 (t, 1H), 3,18 (m, 1H), 3,04 (m, 1H), 2,91 (s, 3H), 2,26 (m, 2H), 0,94 (s, 9H), 0,91 (s, 9H), 0,29 (d, 6H), 0,10 (m, 6H).

Etapa 3: 2-{[*terc*-butil(dimetil)silil]oxi}-*N*-(5-metilpiridin-2-il)-4-(metilsulfonil)butanamida



Se agregó lentamente cloruro de oxalilo (0,74 g, 5,84 mmol) en DCM (2 mL) a una solución agitada de *terc*-butil(dimetil)silil 2-{[*terc*-butil(dimetil)silil]oxi}-4-(metilsulfonil)butanoato (Etapa 2) (2,00 g, 4,87 mmol) en DCM (8 mL) y DMF (tres gotas). Después de 1h a temperatura ambiente, el desprendimiento de gas había disminuido y la mezcla de reacción se concentró al vacío para eliminar el exceso de cloruro de oxalilo. El residuo se disolvió en DCM (8 mL) y se agregaron piridina (0,50 g, 6,33 mmol) y 2-amino-5-picolina (0,58 g, 5,36 mmol). La mezcla de reacción se mantuvo a temperatura ambiente durante 1 h. Se agregó agua y las dos fases se separaron. La fase acuosa se extrajo con DCM. Los extractos orgánicos se combinaron y se lavaron con agua, se secaron sobre $MgSO_4$ y se concentraron al vacío. El residuo se purificó con cromatografía en columna (gel de sílice, eluyendo con DCM/EtOAc:10/1) para proporcionar el compuesto del título como un aceite incoloro (1,23 g), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8,92 (br s, 1H), 8,13 (d, 1H), 8,08 (d, 1H), 7,53 (dd, 1H), 4,44 (t, 1H), 3,19 (m, 1H), 3,05 (m, 1H), 2,90 (s, 3H), 2,44 (m, 1H), 2,28 (m, 4H), 0,97 (s, 9H), 0,19 (d, 6H).

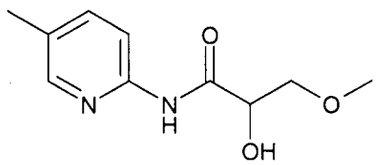
Etapa 4: 2-hidroxi-*N*-(5-metilpiridin-2-il)-4-(metilsulfonil)butanamida



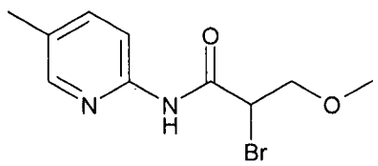
Se agregó trihidrato de tetrabutilamoniofluoruro (1,43 g, 4,54 mmol) a una solución agitada de 2-{[*terc*-butil(dimetil)silil]oxi}-*N*-(5-metilpiridin-2-il)-4-(metilsulfonil)butanamida (Etapa 3) (1,17 g, 3,03 mmol) en THF (10 mL). La mezcla de reacción se mantuvo a temperatura ambiente durante 30 minutos. Se agregaron agua y EtOAc y las dos fases se separaron. La fase acuosa se extrajo con EtOAc. Los extractos orgánicos se combinaron y se lavaron con agua, se secaron sobre $MgSO_4$ y se concentraron

al vacío. El residuo se recristalizó a partir de EtOAc para proporcionar el compuesto del título como un sólido incoloro (0,57 g), ^{1}H NMR (500 MHz, DMSO) δ 8,14 (d, 1H), 7,99 (d, 1H), 7,62 (dd, 1H), 4,23 (m, 1H), 3,17 (m, 2H), 2,96 (s, 3H), 2,24 (s, 3H), 2,16 (m, 1H), 1,98 (m, 1H).

Producto Intermedio A2: 2-hidroxi-3-metoxi-*N*-(5-metilpiridin-2-il)propanamida

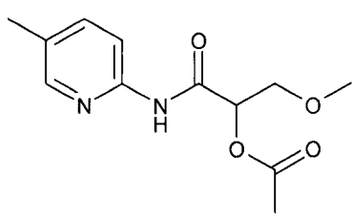


Etapa 1: 2-bromo-3-metoxi-*N*-(5-metilpiridin-2-il)propanamida



Se agregó bromo (3,38g, 21,13 mmol) a una solución agitada de ácido 3-metoxipropiónico (2,00 g, 19,21 mmol) en cloruro de tionilo (11,4 g, 96,0 mmol). La mezcla de reacción se calentó a 60°C durante 3 hrs antes de concentrarse al vacío para eliminar el exceso de reactivos. El residuo se disolvió en DCM (10 mL) y se agregaron lentamente una solución de DIPEA (2,73 g, 21,13 mmol) y 2-amino-5-picolina (2,28 g, 21,13 mmol) en DCM (10 mL) a 0°C. La mezcla de reacción se agitó a temperatura ambiente durante 45 minutos. Se agregó agua y las dos fases se separaron. La fase acuosa se extrajo con DCM. Los extractos orgánicos se combinaron y se lavaron con agua, se secaron sobre $MgSO_4$ y se concentraron al vacío. El residuo se purificó con cromatografía en columna (gel de sílice, eluyendo con DCM/EtOAc:5/1) para proporcionar el compuesto del título (2,30 g), ^{1}H NMR (300 MHz, $CDCl_3$) δ 9,09 (br s, 1H), 8,10 (m, 2H), 7,55 (dd, 1H), 4,49 (t, 1H), 3,93 (d, 2H), 3,46 (s, 3H), 2,31 (s, 3H).

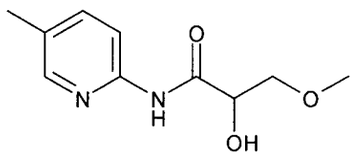
Etapa 2: 1-(metoximetil)-2-[(5-metilpiridin-2-il)amino]-2-oxoetil acetato



Se agregó acetato de potasio (2,01 g, 20,50 mmol) a una solución agitada de 2-bromo-3-

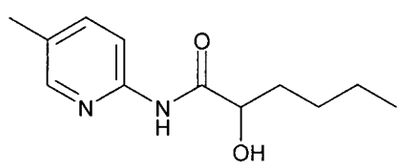
metoxi-*N*-(5-metilpiridin-2-il)propanamida (Etapa 1) (1,40 g, 5,13 mmol) en ACN (20 mL). La mezcla de reacción se sometió a reflujo durante 5 hrs. La mezcla de reacción se filtró y se concentró al vacío. El residuo se purificó con cromatografía en columna (gel de sílice, eluyendo con DCM/EtOAc:2/1) para proporcionar el compuesto del título como un sólido incoloro (1,15 g), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8,57 (br s, 1H), 8,11 (m, 2H), 7,52 (dd, 1H), 5,44 (dd, 1H), 3,89 (dd, 1H), 3,78 (dd, 1H), 3,39 (s, 3H), 2,30 (s, 3H), 2,25 (s, 3H).

Etapa 3: 2-hidroxi-3-metoxi-*N*-(5-metilpiridin-2-il)propanamida

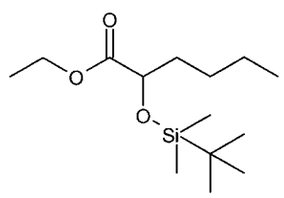


Se agregó carbonato de potasio anhidro (50 mg, 0,36 mmol) a una solución agitada de 1-(metoximetil)-2-[(5-metilpiridin-2-il)amino]-2-oxoetil acetato (Etapa 2) (1,10 g, 4,36 mmol) en MeOH (10 mL). La mezcla de reacción se mantuvo a temperatura ambiente durante 1 h antes de concentrarse al vacío. El residuo se purificó con cromatografía en columna (gel de sílice, eluyendo con EtOAc) para proporcionar el compuesto del título como un sólido incoloro (0,81 g), ^{1}H NMR (300 MHz, $CDCl_3$) δ 9,39 (br s, 1H), 8,14 (d, 1H), 8,09 (d, 1H), 7,53 (dd, 1H), 4,92 (br s, 1H), 4,41 (dd, 1H), 3,75 (m, 2H), 3,42 (s, 3H), 2,30 (s, 3H).

Producto Intermedio A3: 2-hidroxi-*N*-(5-metilpiridin-2-il)hexanamida



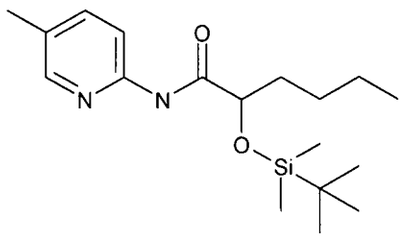
Etapa 1: Etil 2-{[*terc*-butil(dimetil)silil]oxi}hexanoato



Se agregaron imidazol (4,10 g, 60,22 mmol) y TBDMSCl (3,60 g, 23,89 mmol) a una solución agitada de éster etílico de ácido 2-hidroxi-hexanoico (3,20 g, 19,97 mmol) en DMF (25 mL). La mezcla de reacción se mantuvo a temperatura ambiente durante 18 hrs.

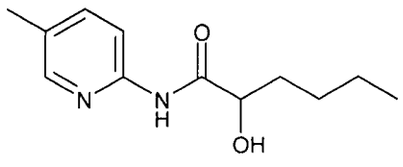
Se agregaron agua y éter dietílico y las dos fases se separaron. La fase acuosa se extrajo con éter dietílico. Los extractos orgánicos se combinaron y se lavaron secuencialmente con HCl 0,5 M y agua, se secaron sobre $MgSO_4$ y se concentraron al vacío para proporcionar el producto del título (5,30 g), ^{1}H NMR (300 MHz, $CDCl_3$) δ 4,18 (m, 3H), 1,69 (m, 2H), 1,35 (m, 4H), 1,28 (t, 3H), 0,91 (m, 12H), 0,07 (d, 6H).

Etapa 2: 2-{[*terc*-butil(dimetil)silil]oxi}-*N*-(5-metilpiridin-2-il)hexanamida



Se agregó lentamente *n*-BuLi (2,25 mL, 1,6 M en hexanos, 3,60 mmol) a una solución agitada de 2-amino-5-picolina (390 mg, 3,60 mmol) en THF anhidro (6 mL). La mezcla de reacción se mantuvo a temperatura ambiente durante 10 minutos antes de que la misma se agregara a una solución de etil 2-{[*terc*-butil(dimetil)silil]oxi}hexanoato (Etapa 1) (820 mg, 3,00 mmol) en THF anhidro (4 mL). La mezcla de reacción se agitó a temperatura ambiente durante 1 h. Se agregaron agua y EtOAc y las dos fases se separaron. La fase orgánica se lavó con agua, se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se purificó con cromatografía en columna (gel de sílice, eluyendo con un gradiente que consistía en 0-100% EtOAc en heptano) para proporcionar el compuesto del título como un aceite incoloro (223 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8,87 (br s, 1H), 8,13 (m, 2H), 7,51 (dd, 1H), 4,25 (t, 1H), 2,29 (s, 3H), 1,79 (m, 2H), 1,35 (m, 4H), 0,98 (s, 8H), 0,89 (t, 3H), 0,14 (d, 6H).

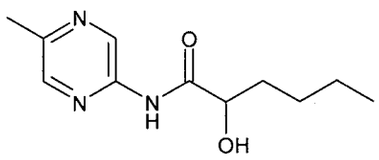
Etapa 3: 2-hidroxi-*N*-(5-metilpiridin-2-il)hexanamida



Se agregó trihidrato de tetrabutilamoniofluoruro (302 mg, 0,96 mmol) a una solución agitada de 2-{[*terc*-butil(dimetil)silil]oxi}-*N*-(5-metilpiridin-2-il)hexanamida (Etapa 2) (215 mg, 0,64 mmol) en THF (5 mL). La mezcla de reacción se mantuvo a temperatura ambiente durante 1 h. Se agregaron agua y EtOAc y las dos fases se separaron. La fase

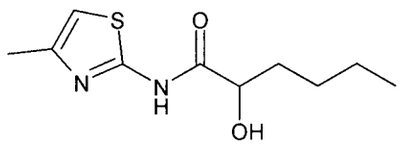
orgánica se lavó con agua, se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se purificó con cromatografía en columna (gel de sílice, eluyendo con DCM/EtOAc:2/1) para proporcionar el compuesto del título como un sólido incoloro (135 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ 9,46 (br s, 1H), 8,20 (d, 1H), 8,04 (d, 1H), 7,55 (dd, 1H), 5,47 (br s, 1H), 4,29 (m, 1H), 2,31 (s, 3H), 1,98 (m, 1H), 1,76 (m, 1H), 1,52 (m, 2H), 1,38 (m, 2H), 0,92 (t, 3H).

Producto Intermedio A4: 2-hidroxi-*N*-(5-metilpirazin-2-il)hexanamida



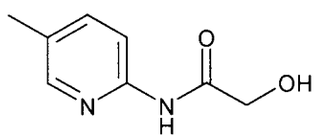
El compuesto del título se preparó en una manera similar a la descrita para el Producto Intermedio A3, comenzando a partir de etil 2-{[*terc*-butil(dimetil)silil]oxi}hexanoato y 2-amino-5-metilpirazina, ^{1}H NMR (300 MHz, $CDCl_3$) δ 9,46 (s, 1H), 8,98 (br s, 1H), 8,12 (s, 1H), 4,32 (m, 1H), 2,98 (d, 1H), 2,54 (s, 3H), 1,96 (m, 1H), 1,78 (m, 1H), 1,44 (m, 4H), 0,93 (t, 3H).

Producto Intermedio A5: 2-hidroxi-*N*-(4-metil-1,3-tiazol-2-il)hexanamida



El compuesto del título se preparó en una manera similar a la descrita para el Producto Intermedio A3, comenzando a partir de etil 2-{[*terc*-butil(dimetil)silil]oxi}hexanoato y 2-amino-4-metiltiazol, ^{1}H NMR (300 MHz, $CDCl_3$) δ 10,30 (br s, 1H), 6,54 (s, 1H), 5,12 (br s, 1H), 4,41 (m, 1H), 2,35 (s, 3H), 2,00 (m, 1H), 1,76 (m, 1H), 1,48 (m, 2H), 1,39 (m, 2H), 0,92 (t, 3H).

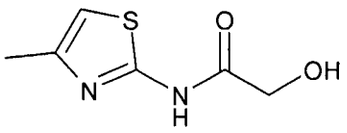
Producto Intermedio A6: 2-hidroxi-*N*-(5-metilpiridin-2-il)acetamida



El compuesto del título se preparó en una manera similar a la descrita para el Producto Intermedio A3, comenzando a partir de metil glicolato y 2-amino-5-picolina, ^{1}H NMR (300 MHz, $CDCl_3$) δ 9,24 (br s, 1H), 8,19 (d, 1H), 8,07 (d, 1H), 7,57 (dd, 1H), 5,59 (br s,

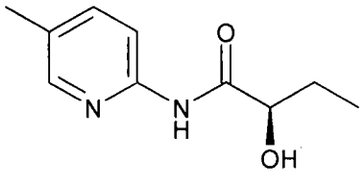
1H), 4,26 (s, 2H), 2,31 (s, 3H).

Producto Intermedio A7: 2-hidroxi-*N*-(4-metil-1,3-tiazol-2-il)acetamida

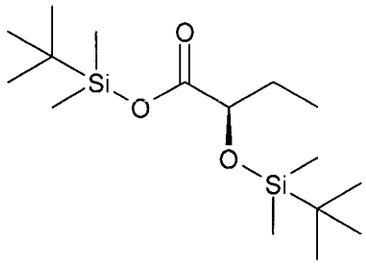


El compuesto del título se preparó en una manera similar a la descrita para el Producto Intermedio A3, comenzando a partir de metil glicolato y 2-amino-4-metiltiazol, ^{1}H NMR (300 MHz, $CDCl_3$) δ 10,11 (br s, 1H), 6,55 (s, 1H), 5,58 (br s, 1H), 4,36 (s, 2H), 2,34 (s, 3H).

Producto Intermedio A8: (2*R*)-2-Hidroxi-*N*-(5-metilpiridin-2-il)butanamida

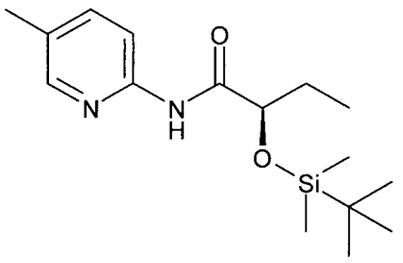


Etapa 1: *terc*-Butil(dimetil)silil (2*R*)-2-{[*terc*-butil(dimetil)silil]oxi}butanoato



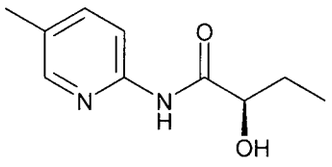
Se agregaron imidazol (2,61g, 38,43 mmol) y TBDMSCl (3,62g, 24,02 mmol) a una solución agitada de ácido (*R*)-2-hidroxi-butírico (1,0 g, 9,61 mmol) en DMF (20 mL). La reacción se agitó a temperatura ambiente durante 18 hrs. Se agregaron agua y EtOAc y las dos fases se separaron. La fase acuosa se extrajo con EtOAc. Los extractos orgánicos se combinaron y se lavaron tres veces con agua, se secaron sobre $MgSO_4$ y se concentraron al vacío. El residuo se purificó con cromatografía en columna (gel de sílice, eluyendo con heptano/EtOAc:5/2) para proporcionar el compuesto del título como un aceite incoloro (2,77 g), ^{1}H NMR (300 MHz, $CDCl_3$) δ 4,09 (dd, 1H), 1,72 (m, 2H), 0,93 (m, 21H), 0,27 (d, 6H), 0,07 (d, 6H).

Etapa 2: (2*R*)-2-{[*terc*-Butil(dimetil)silil]oxi}-*N*-(5-metilpiridin-2-il)butanamida



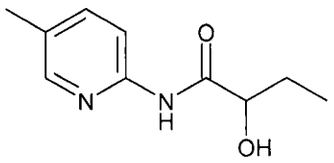
Se agregó lentamente cloruro de oxalilo (1,32 g, 10,43 mmol) a una solución agitada de *terc*-butil(dimetil)silil (2*R*)-2-{[*terc*-butil(dimetil)silil]oxi}butanoato (Etapa 1) (2,77 g, 8,69 mmol) en DCM (10 mL) y DMF (tres gotas). Después de 1h a temperatura ambiente, el desprendimiento de gas había disminuido y la mezcla de reacción se concentró al vacío para eliminar el exceso de cloruro de oxalilo. El residuo se disolvió en DCM (10 mL) y se agregaron piridina (0,89 g, 11,30 mmol) y 2-amino-5-picolina (1,03 g, 9,56 mmol). La mezcla de reacción se mantuvo a temperatura ambiente durante 2 hrs. Se agregó agua y las dos fases se separaron. La fase acuosa se extrajo con DCM. Los extractos orgánicos se combinaron y se lavaron con agua, se secaron sobre $MgSO_4$ y se concentraron al vacío. El residuo se purificó con cromatografía en columna (gel de sílice, eluyendo con heptano/EtOAc:5/2) para proporcionar el compuesto del título como un aceite incoloro (2,0 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8,91 (br s, 1H), 8,15 (d, 2H), 7,53 (m, 1H), 4,26 (t, 1H), 2,31 (s, 3H), 1,85 (m, 2H), 0,96 (m, 12H), 0,17 (m, 6H).

Etapa 3: (2*R*)-2-Hidroxi-*N*-(5-metilpiridin-2-il)butanamida



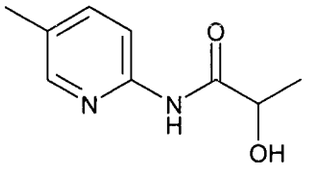
Se agregó trihidrato de tetrabutilamoniofluoruro (3,21 g, 10,19 mmol) a una solución agitada de (2*R*)-2-{[*terc*-butil(dimetil)silil]oxi}-*N*-(5-metilpiridin-2-il)butanamida (Etapa 2) (2,00g, 6,79 mmol) en THF (20 mL). La mezcla de reacción se mantuvo a temperatura ambiente durante 2 hrs. Se agregaron agua y EtOAc y las dos fases se separaron. La fase acuosa se extrajo con EtOAc. Los extractos orgánicos se combinaron y se lavaron con agua, se secaron sobre $MgSO_4$ y se concentraron al vacío. El residuo se recristalizó a partir de éter dietílico para proporcionar el compuesto del título como cristales incoloros (1,14 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9,35 (br s, 1H), 8,21 (d, 1H), 8,08 (s, 1H), 7,57 (d, 1H), 5,03 (br s, 1H), 4,25 (m, 1H), 2,32 (s, 3H), 2,01 (m, 1H), 1,82 (m, 1H), 1,10 (t, 3H).

Producto Intermedio A9: **2-Hidroxi-*N*-(5-metilpiridin-2-il)butanamida**



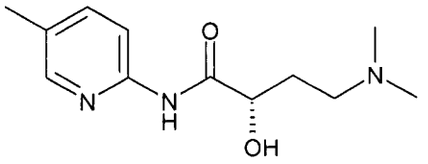
El compuesto del título se preparó en una manera similar a la descrita para el Producto Intermedio A8, comenzando a partir de ácido 2-hidroxi-butírico y 2-amino-5-picolina, ^{1}H NMR (300 MHz, CD_3OD) δ 8,10 (d, 1H), 8,05 (d, 1H), 7,63 (dd, 1H), 4,10 (dd, 1H), 2,30 (s, 3H), 1,87 (m, 1H), 1,71 (m, 1H), 1,00 (t, 3H).

Producto Intermedio A10: **2-Hidroxi-*N*-(5-metilpiridin-2-il)propanamida**

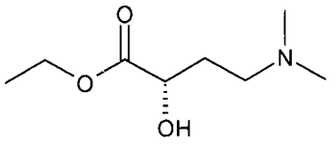


El compuesto del título se preparó en una manera similar a la descrita para el Producto Intermedio A8, comenzando a partir de ácido 2-hidroxi-propiónico y 2-amino-5-picolina, ^{1}H NMR (300 MHz, CD_3OD) δ 8,11 (d, 1H), 8,05 (d, 1H), 7,64 (dd, 1H), 4,26 (q, 1H), 2,30 (s, 3H), 1,43 (d, 3H).

Producto Intermedio A11: **(2*S*)-4-(dimetilamino)-2-hidroxi-*N*-(5-metilpiridin-2-il)butanamida**



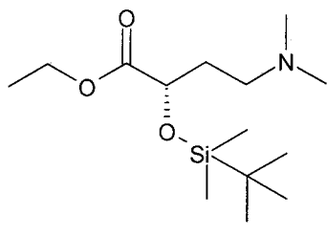
Etapa 1: Etil (2*S*)-4-(dimetilamino)-2-hidroxibutanoato



Se agregaron ácido fórmico (7,0 mL) y formaldehído (6 mL, 36% en agua) a ácido (S)-4-amino-2-hidroxibutírico (2,00 g, 16,79 mmol). La mezcla de reacción se sometió a reflujo bajo agitación durante 6 hrs cuando el desprendimiento de gas había disminuido. La mezcla de reacción se enfrió hasta alcanzar la temperatura ambiente y se agregó HCl concentrado (2mL). La mezcla de reacción se concentró al vacío y se agregó EtOH. La

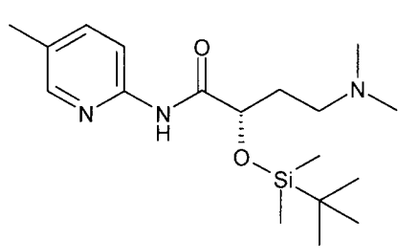
solución se sometió a reflujo durante 5 minutos antes de concentrarse nuevamente al vacío. El residuo se trató con EtOAc y bicarbonato de sodio (5% en agua). Las dos fases se separaron y la fase orgánica se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se purificó con cromatografía en columna (gel de sílice, eluyendo con un gradiente que consistía en 0-100% EtOAc en DCM) para proporcionar el compuesto del título como un aceite incoloro (1,81 g), ^{1}H NMR (300 MHz, DMSO) δ 4,08 (m, 2H), 3,10 (m, 5H), 2,70 (s, 6H), 2,06 (m, 1H), 1,92 (m, 1H), 1,20 (t, 1H).

Etapa 2: Etil (2*S*)-2-{[*terc*-butil(dimetil)silil]oxi}-4-(dimetilamino)butanoato



Se agregaron imidazol (1,98 g, 29,10 mmol) y TBDMSCl (2,34 g, 15,52 mmol) a una solución agitada de etil (2*S*)-4-(dimetilamino)-2-hidroxibutanoato (Etapa 1) (3,20 g, 19,97 mmol) en DMF (25 mL). La mezcla de reacción se mantuvo a temperatura ambiente durante 18 hrs. Se agregaron agua y EtOAc y las dos fases se separaron. La fase acuosa se extrajo con EtOAc. Los extractos orgánicos se combinaron y se lavaron tres veces con agua, se secaron sobre $MgSO_4$ y se concentraron al vacío. El residuo se purificó con cromatografía en columna (gel de sílice, eluyendo con heptano/EtOAc:2/1) para proporcionar el compuesto del título como un aceite incoloro (2,73 g), ^{1}H NMR (300 MHz, DMSO) δ 4,28 (m, 1H), 4,18 (m, 2H), 2,44 (m, 1H), 2,30 (m, 1H), 2,22 (s, 6H), 1,87 (m, 2H), 1,28 (t, 3H), 0,90 (s, 9 H), 0,08 (d, 6H).

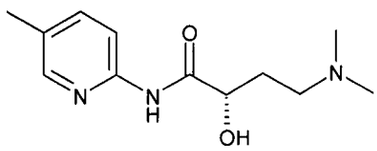
Etapa 3: (2*S*)-2-{[*terc*-butil(dimetil)silil]oxi}-4-(dimetilamino)-*N*-(5-metilpiridin-2-il)butanamida



Se agregó lentamente n-BuLi (3,40 mL, 1,6 M en hexanos, 5,44 mmol) a una solución agitada de 2-amino-5-picolina (616 mg, 5,70 mmol) en THF anhidro (8 mL). La mezcla de

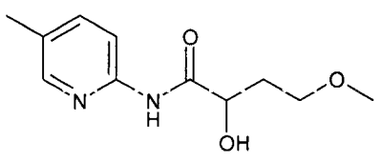
reacción se mantuvo a temperatura ambiente durante 10 minutos antes de agregarse una solución de etil (2*S*)-2-{[*terc*-butil(dimetil)silil]oxi}-4-(dimetilamino)butanoato (Etapa 2) (1,50 g, 5,18 mmol) en THF anhidro (2 mL). La mezcla de reacción se agitó a temperatura ambiente durante 1 h. Se agregaron agua y EtOAc y las dos fases se separaron. La fase acuosa se extrajo con EtOAc. Los extractos orgánicos se combinaron y se lavaron con agua, se secaron sobre $MgSO_4$ y se concentraron al vacío. El residuo se purificó con cromatografía en columna (gel de sílice, eluyendo con EtOAc) para proporcionar el compuesto del título (320 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8,89 (br s, 1H), 8,12 (m, 2H), 7,51 (dd, 1H), 4,32 (t, 1H), 2,47 (m, 1H), 2,31 (m, 4H), 2,21 (s, 6H), 1,97 (m, 2H), 0,98 (s, 9H), 0,15 (d, 6H).

Etapa 4: (2*S*)-4-(dimetilamino)-2-hidroxi-*N*-(5-metilpiridin-2-il)butanamida



Se agregó trihidrato de tetrabutilamoniofluoruro (417 mg, 1,32 mmol) a una solución agitada de (2*S*)-2-{[*terc*-butil(dimetil)silil]oxi}-4-(dimetilamino)-*N*-(5-metilpiridin-2-il)butanamida (Etapa 3) (310 mg, 0,88 mmol) en THF (5 mL). La mezcla de reacción se mantuvo a temperatura ambiente durante 30 minutos. Se agregaron agua y EtOAc y las dos fases se separaron. La fase orgánica se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se purificó con cromatografía en columna (gel de sílice, eluyendo con EtOAc/MeOH:10/1) para proporcionar el compuesto del título como un sólido (110 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ 9,44 (br s, 1H), 8,15 (d, 1H), 8,12 (d, 1H), 7,51 (dd, 1H), 4,39 (dd, 1H), 2,63 (m, 2H), 2,28 (m, 9H), 2,09 (m, 1H), 1,92 (m, 1H).

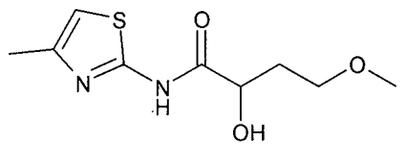
Producto Intermedio A12: 2-hidroxi-4-metoxi-*N*-(5-metilpiridin-2-il)butanamida



El compuesto del título se preparó en una manera similar a la descrita para el Producto Intermedio A16 y el Producto Intermedio A2 (Etapa 2 - Etapa 3) comenzando a partir de malonato de dietilo, éter metílico de 2-bromoetilo y 2-amino-5-picolina, ^{1}H NMR (300 MHz, $CDCl_3$) δ 9,24 (br s, 1H), 8,14 (m, 2H), 7,52 (dd, 1H), 4,48 (br s, 1H), 4,39 (m, 1H),

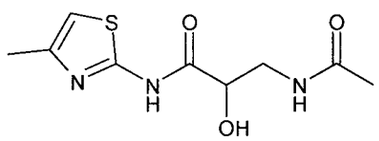
3,69 (m, 2H), 3,39 (s, 3H), 2,25 (m, 4H), 2,09 (m, 1H).

Producto Intermedio A13: **2-Hidroxi-4-metoxi-*N*-(4-metil-1,3-tiazol-2-il)butanamida**

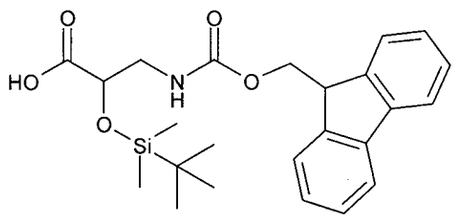


El compuesto del título se preparó en una manera similar a la descrita para el Producto Intermedio A16 y el Producto Intermedio A2 (Etapa 2 - Etapa 3), comenzando a partir de malonato de dietilo, éter metílico de 2-bromoetilo y 2-amino-4-metiltiazol, ^{1}H NMR (300 MHz, $CDCl_3$) δ 10,07 (br s, 1H), 6,53 (d, 1H), 4,68 (br s, 1H), 4,48 (dd, 1H), 3,68 (m, 2H), 3,37 (s, 3H), 2,33 (s, 3H), 2,20 (m, 1H), 2,14 (m, 1H).

Producto Intermedio A14: **3-acetamido-2-hidroxi-*N*-(4-metil-1,3-tiazol-2-il)propanamida**

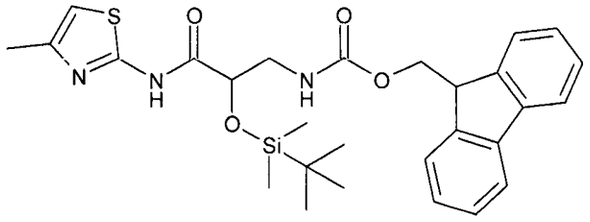


<u>Etapa 1:</u> Ácido 2-(*terc*-butil-dimetil-silaniloxi)-3-(9*H*-fluoren-9-ilmetoxicarbonilamino)-propiónico



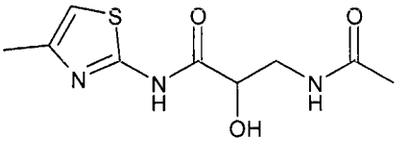
Se agregaron TBDMSCl (1,01 g, 6,72 mmol), DMAP (0,19 g, 1,52 mmol) y piridina (0,97 g, 12,2 mmol) a una solución agitada de FMOC-isoserina (1,00 g, 3,05 mmol) en DMF (20 mL). La mezcla de reacción se calentó a 50°C durante 18 hrs. Se agregó agua (10 mL) y la mezcla de reacción se concentró al vacío. Se agregaron DCM y HCl (0,5 M) y las dos fases se separaron. La fase acuosa se extrajo dos veces con DCM. Los extractos orgánicos se combinaron y concentraron al vacío. El residuo se purificó con cromatografía en columna (gel de sílice, eluyendo con un gradiente que consistía en 20-100% EtOAc en heptano) para proporcionar el compuesto del título (1,3 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7,76 (d, 2H), 7,59 (m, 2H), 7,40 (t, 2H), 7,30 (m, 2H), 5,14 (br s, 1H), 4,29 (m, 4H), 3,53 (m, 2H), 0,91 (s, 9H), 0,10 (s, 6H).

Etapa 2: 9*H*-fluoren-9-ilmetil (2-{[*terc*-butil(dimetil)silil]oxi}-3-[(4-metil-1,3-tiazol-2-il)amino]-3-oxopropil)carbamato



Se agregó lentamente cloruro de oxalilo (1,12 g, 8,83 mmol) en DCM (5 mL) a una solución agitada de ácido 2-(*terc*-butil-dimetil-silaniloxi)-3-(9*H*-fluoren-9-ilmetoxicarbonilamino)-propiónico (Etapa 1) (1,30 g, 2,94 mmol) en DCM (25 ml) y DMF (50 µl) a 0°C. Después de 3 hrs a temperatura ambiente, el desprendimiento de gas había disminuido y la mezcla de reacción se concentró al vacío. Se agregaron THF (20 mL) y DIPEA (0,57g, 4,4 mmol) y luego 2-amino-4-metiltiazol (0,403 g, 3,53 mmol) en DCM (5 mL). La mezcla de reacción se mantuvo a temperatura ambiente durante 3 hrs. Se agregó agua (0,5 mL) y la mezcla de reacción se concentró al vacío. El residuo se purificó mediante cromatografía en columna (gel de sílice, eluyendo con un gradiente que consistía en 0-40% EtOAc en heptano) para proporcionar el compuesto del título como un aceite incoloro (0,10 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9,60 (br s, 1H), 7,75 (d, 2H), 7,57 (d, 2H), 7,39 (t, 2H), 7,30 (t, 2H), 6,56 (s, 1H), 5,19 (br s, 1H), 4,41 (t, 1H), 4,37 (d, 2H), 4,21 (t, 1H), 3,66 (m, 1H), 3,49 (m, 1H), 2,35 (s, 3H), 0,98 (s, 9H), 0,20 (s, 6H).

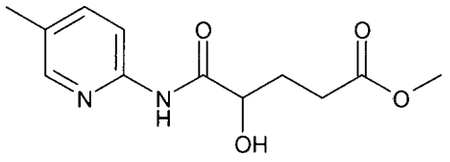
Etapa 3: 3-acetamido-2-hidroxi-*N*-(4-metil-1,3-tiazol-2-il)propanamida



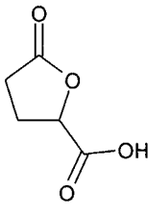
Se agregó tetrabutilamoniofluoruro (0,28 mL, 1M en THF, 0,28 mmol) a una solución agitada de 9*H*-fluoren-9-ilmetil (2-{[*terc*-butil(dimetil)silil]oxi}-3-[(4-metil-1,3-tiazol-2-il)amino]-3-oxopropil)carbamato (Etapa 2) (0,10 g, 0,186 mmol) en THF (5 mL). La mezcla de reacción se mantuvo a temperatura ambiente durante 3 hrs antes de agregarse DIPEA (0,036g, 0,28 mmol) y cloruro de acetilo (0,018g, 0,22 mmol). La mezcla de reacción se agitó durante otras 3 hrs a temperatura ambiente y se agregó agua (1 mL) y la mezcla de reacción se concentró al vacío. El residuo se purificó mediante cromatografía en columna (gel de sílice, eluyendo con un gradiente que consistía en 0-20% MeOH en DCM)

para proporcionar el compuesto del título como un aceite incoloro (0,04 g). ^{1}H NMR (500 MHz, CD_3OD) δ 6,71 (s, 1H), 4,38 (dd, 1H), 3,64 (dd, 1H), 3,48 (dd, 1H), 2,33 (s, 3H), 1,96 (s, 3H).

Producto Intermedio A15: **Metil 4-hidroxi-5-[(5-metilpiridin-2-il)amino]-5-oxopentanoato**

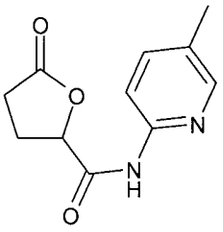


Etapa 1: Ácido 5-oxotetrahidrofuran-2-carboxílico



Se agregó Amberlite(R) IR-120 (3,0 g, se lavó con 4 x 20 ml THF) a una suspensión agitada de sal de zinc de ácido α-hidroxiglutárico (0,40g, 1,90 mmol) en THF (15 mL). La mezcla de reacción se mantuvo a temperatura ambiente durante 16 hrs. La mezcla de reacción se filtró y la resina se lavó tres veces con THF. Los extractos combinados se concentraron al vacío y el residuo se purificó mediante cromatografía en columna (gel de sílice, eluyendo con un gradiente que consistía en 5-50% MeOH en DCM) para proporcionar el compuesto del título como un aceite incoloro (0,215 g). ^{1}H NMR (500 MHz, D_2O) δ 5,00 (t, 1H), 2,53 (m, 3H), 2,20 (m, 1H).

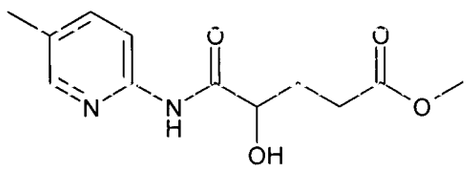
Etapa 2: Ácido 5-oxo-tetrahidro-furan-2-carboxílico (5-metil-piridin-2-il)-amida



Se agregó lentamente cloruro de oxalilo (0,252 g, 1,63 mmol) en DCM (5 mL) a una solución agitada de ácido 5-oxotetrahidrofuran-2-carboxílico (Etapa 1) (0,215 g, 1,65 mmol) en DCM (10 ml) y DMF (50 µl) a 0°C. Después de 3 hrs a temperatura ambiente, el desprendimiento de gas había disminuido. Se agregó DIPEA (0,64, 4,95 mmol) y luego 2-

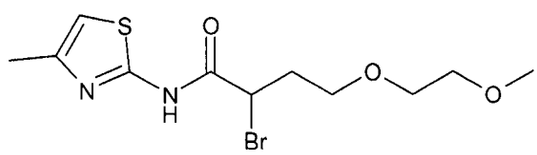
amino-5-picolina (0,357 g, 3,3 mmol) en DCM (5 mL). La mezcla de reacción se mantuvo a temperatura ambiente durante 3 hrs. Se agregó agua (0,5 mL) y la mezcla de reacción se concentró al vacío. El residuo se purificó mediante cromatografía en columna (gel de sílice, eluyendo con un gradiente que consistía en 0-40% MeOH en DCM) para proporcionar el compuesto del título como un aceite incoloro (0,138 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8,74 (br s, 1H), 8,13 (d, 1H), 8,08 (d, 1H), 7,54 (dd, 1H), 4,99 (t, 1H), 2,71 (m, 1H), 2,63 (m, 2H), 2,48 (m, 1H), 2,31 (s, 3H).

Etapa 3: Metil 4-hidroxi-5-[(5-metilpiridin-2-il)amino]-5-oxopentanoato

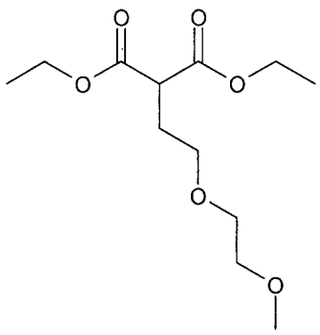


Se agregó Amberlyst 15 (2,0g, lavado con 4 x 20 mL de MeOH) a una solución agitada de (5-metil-piridin-2-il)-amida de ácido 5-oxo-tetrahidro-furan-2-carboxílico (Etapa 2) (0,138g, 0,63 mmol) en MeOH (10 mL). La mezcla de reacción se mantuvo a temperatura ambiente durante 16 hrs. Se agregó HCl (1 M, 5 mL) y la mezcla de reacción se agitó durante otra hora a temperatura ambiente. La mezcla de reacción se filtró y la resina se lavó dos veces con MeOH (10 mL) y HCl (1 M, 2 mL). Los extractos combinados se concentraron al vacío y el residuo se purificó mediante cromatografía en columna (gel de sílice, eluyendo con un gradiente que consistía en 0-40% MeOH en DCM) para proporcionar el compuesto del título como un aceite incoloro (0,02 g). ^{1}H NMR (500 MHz, THF) δ 9,24 (br s, 1H), 8,16 (d, 1H), 8,09 (s, 1H), 7,53 (d, 1H), 5,34 (d, 1H), 4,17 (m, 1H), 3,62 (s, 3H), 2,47 (m, 2H), 2,28 (s, 3H), 2,17 (m, 1H), 1,95 (m, 1H).

Producto Intermedio A16: 2-bromo-4-(2-metoxietoxi)-*N*-(4-metil-1,3-tiazol-2-il)butanamida

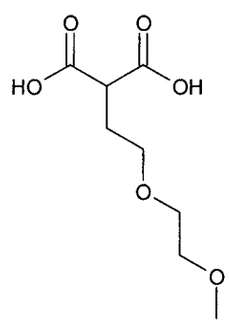


Etapa 1: dietil [2-(2-metoxietoxi)etil]malonato



Se agregó en porciones sodio (0,72 g, 31,31 mmol) a EtOH (99,5%, 35 mL) bajo agitación. Cuando todo el sodio se había disuelto, se agregó malonato de dietilo (4,80 g, 29,97 mmol) lentamente durante 5 minutos y la mezcla de reacción se agitó durante otros 15 minutos. Se agregó 1-bromo-2-(2-metoxietoxi)-etano (5,50 g, 30,05 mmol) y la mezcla de reacción se sometió a reflujo durante 2 hrs. Todos los sólidos se retiraron por filtración y la solución clara se concentró al vacío. El residuo se recogió en agua y éter dietílico y las dos fases se separaron. La fase orgánica se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se purificó con cromatografía en columna (gel de sílice, eluyendo con EtOAc/MeOH:20/1) para proporcionar el compuesto del título como un aceite incoloro (3,80 g), ^{1}H NMR (300 MHz, $CDCl_3$) δ 4,19 (q, 4H), 3,54 (m, 7H), 3,38 (s, 3H), 2,19 (m, 2H), 1,27 (t, 6H).

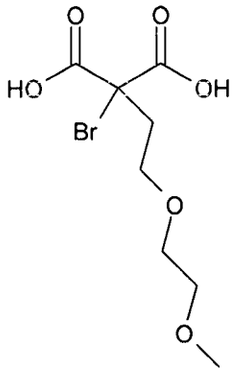
Etapa 2: Ácido [2-(2-metoxietoxi)etil]malónico



Se agregó hidróxido de sodio (2,00 g, 50,00 mmol) en agua (15 mL) a una solución agitada de dietil [2-(2-metoxietoxi)etil]malonato (Etapa 1) (2,35 g, 8,96 mmol). La reacción se mantuvo a temperatura ambiente durante 10 minutos antes de que se retirara MeOH al vacío. La solución resultante se acidificó hasta alcanzar pH = 1 mediante la adición de HCl (5 M). Se agregó éter dietílico y las dos fases se separaron. La fase acuosa se extrajo tres veces con éter dietílico. Los extractos orgánicos se combinaron, se secaron sobre $MgSO_4$ y se concentraron al vacío para proporcionar el compuesto del título como un aceite incoloro (1,81 g), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7,16 (br s, 2H), 3,58 (m, 7H), 3,40 (s, 3H), 2,23

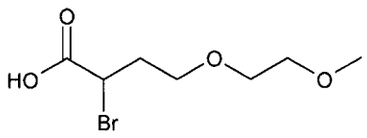
(m, 2H).

Etapa 3: Ácido bromo[2-(2-metoxietoxi)etil]malónico



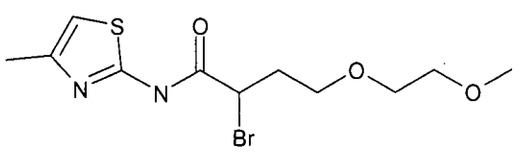
Se agregaron HBr (4,1 M en ácido acético, dos gotas) y bromo (1,44 g, 9,01 mmol) a una solución agitada de ácido [2-(2-metoxietoxi)etil]malónico (Etapa 2) (1,75 g, 8,49 mmol) en éter dietílico. La mezcla de reacción se mantuvo a temperatura ambiente durante 20 minutos una vez desaparecida la mayor parte del color del bromo. Se agregó pirosulfito de sodio (5% en agua) y las dos fases se separaron. La fase acuosa se extrajo con éter dietílico dos veces. Los extractos orgánicos se combinaron y se lavaron con agua. La fase orgánica se secó sobre $MgSO_4$ y se concentró al vacío para proporcionar el producto del título como un sólido incoloro (1,91 g), ^{1}H NMR (300 MHz, $CDCl_3$) δ 6,91 (br s, 2H), 3,75 (t, 2H), 3,62 (m, 4H), 3,42 (s, 3H), 2,70 (t, 2H).

Etapa 4: Ácido 2-bromo-4-(2-metoxietoxi)butanoico



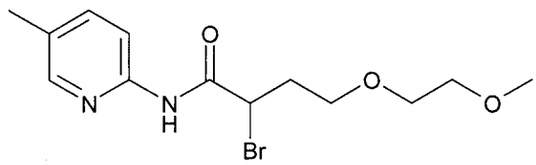
Se calentó ácido bromo[2-(2-metoxietoxi)etil]malónico (Etapa 3) (1,15 g, 4,04 mmol) a 150°C bajo agitación. El calentamiento se interrumpió después de 10 minutos cuando el desprendimiento de gas había cesado. Esto proporcionó el compuesto del título como un aceite amarillento (941 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7,01 (br s, 1H), 4,56 (dd, 1H), 3,60 (m, 6H), 3,40 (s, 3H), 2,42 (m, 1H), 2,20 (m, 1H).

Etapa 5: 2-bromo-4-(2-metoxietoxi)-*N*-(4-metil-1,3-tiazol-2-il)butanamida



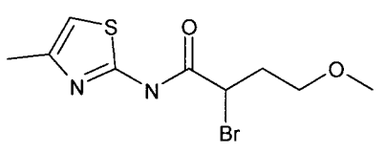
Una solución agitada de ácido 2-bromo-4-(2-metoxietoxi)butanoico (Etapa 4) (200 mg, 0,83 mmol) en cloruro de tionilo (4 mL) se sometió a reflujo durante 30 minutos. La mezcla de reacción se concentró al vacío para eliminar el exceso de cloruro de tionilo. El residuo se disolvió en DCM (2 mL) y se agregó lentamente a una solución agitada de 2-amino-4-metiltiazol (99,5 mg, 0,871 mmol) y DIPEA (117,9 mg, 0,913 mmol) en DCM (4 mL). La mezcla de reacción se mantuvo a temperatura ambiente durante 1 h antes de agregarse agua y las dos fases se separaron. La fase orgánica se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se purificó con cromatografía en columna (gel de sílice, eluyendo con EtOAc/MeOH:1/1) para proporcionar el compuesto del título como un aceite (105 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ 6,57 (d, 1H), 4,72 (dd, 1H), 3,66 (m, 2H), 3,60 (m, 2H), 3,51 (m, 2H), 3,36 (s, 3H), 2,50 (m, 1H), 2,31 (m, 4H).

Producto Intermedio A17: 2-bromo-4-(2-metoxietoxi)-*N*-(5-metilpiridin-2-il)butanamida



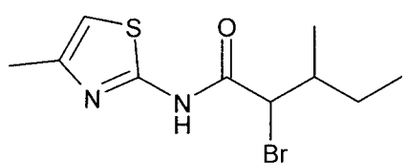
El compuesto del título se preparó en una manera similar a la descrita para el Producto Intermedio A16 (Etapa 5), comenzando a partir de ácido 2-bromo-4-(2-metoxietoxi)butanoico y 2-amino-5-picolina.

Producto Intermedio A18: 2-bromo-4-metoxi-*N*-(4-metil-1,3-tiazol-2-il)butanamida



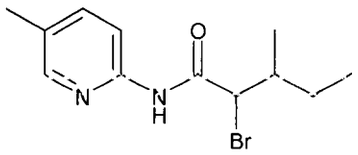
El compuesto del título se preparó en una manera similar a la descrita para el Producto Intermedio A16, comenzando a partir de malonato de dietilo y éter metílico de 2-bromoetilo, ^{1}H NMR (500 MHz, $CDCl_3$) δ 10,35 (br s, 1H), 6,61 (d, 1H), 4,66 (dd, 1H), 3,57 (t, 2H), 3,34 (s, 3H), 2,49 (m, 1H), 2,40 (d, 3H), 2,28 (m, 1H).

Producto Intermedio A19: 2-bromo-3-metil-*N*-(4-metil-1,3-tiazol-2-il)pentanamida



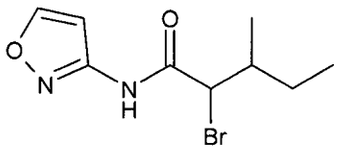
El compuesto del título se preparó en una manera similar a la descrita para el Producto Intermedio A16 (Etapa 5) comenzando a partir de ácido 2-metil-3-metilpentanoico y 2-amino-4-metiltiazol, (Diastereómeros) ^{1}H NMR (300 MHz, $CDCl_3$) δ 9,72 (br s, 1H), 6,58 (d, 1H), 4,62 (d, 0,37H), 4,45 (d, 0,63H), 2,37 (d, 3H), 2,19 (m, 1H), 1,59 (m, 0,74H), 1,41 (m, 1,26H), 1,07 (d, 1,89H), 0,95 (m, 4,11H).

Producto Intermedio A20: 2-bromo-3-metil-*N*-(5-metilpiridin-2-il)pentanamida



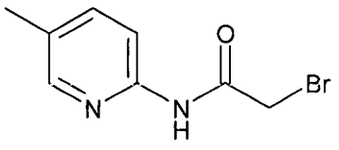
El compuesto del título se preparó en una manera similar a la descrita para el Producto Intermedio A16 (Etapa 5) comenzando a partir de ácido 2-metil-3-metilpentanoico y 2-amino-5-picolina, (Diastereómeros) ^{1}H NMR (300 MHz, $CDCl_3$) δ 8,83 (br s, 0,35H), 8,70 (br s, 0,65H), 8,13 (s, 1H), 8,08 (d, 1H), 7,54 (d, 1H), 4,53 (d, 0,35H), 4,35 (d, 0,65H), 2,31 (s, 3H), 2,20 (m, 1H), 1,66 (m, 1H), 1,37 (m, 1H), 1,08 (d, 1,95H), 1,01 (d, 1,05H), 0,94 (m, 3H).

Producto Intermedio A21: 2-bromo-*N*-isoxazol-3-il-3-metilpentanamida



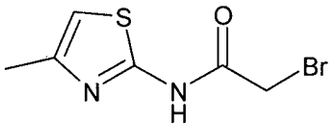
El compuesto del título se preparó en una manera similar a la descrita para el Producto Intermedio A16 (Etapa 5) comenzando a partir de ácido 2-metil-3-metilpentanoico y 3-aminoisoxazol, (Diastereómeros) ^{1}H NMR (300 MHz, $CDCl_3$) δ 9,57 (br s, 0,62H), 9,47 (br s, 0,38H), 8,33 (d, 1H), 7,10 (dd, 1H), 4,53 (d, 0,38H), 4,37 (d, 0,62H), 2,19 (m, 1H), 1,70 (m, 0,62H), 1,43 (m, 1,38H), 1,08 (d, 1,86H), 1,04 (d, 1,14H), 0,95 (m, 3H).

Producto Intermedio A22: 2-bromo-*N*-(5-metilpiridin-2-il)acetamida



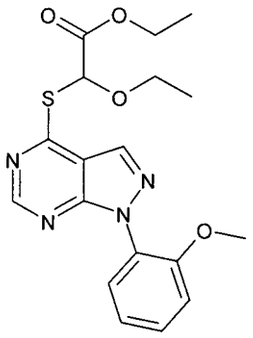
El compuesto del título se preparó en una manera similar a la descrita para el Producto Intermedio A16 (Etapa 5) comenzando a partir de bromuro de bromoacetilo y 2-amino-5-picolina.

Producto Intermedio A23: 2-Bromo-*N*-(4-metil-1,3-tiazol-2-il)acetamida



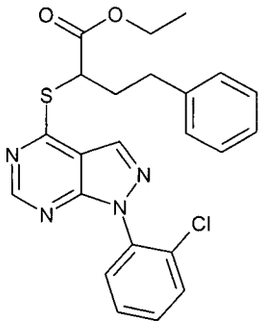
El compuesto del título se preparó en una manera similar a la descrita para el Producto Intermedio A16 (Etapa 5) comenzando a partir de bromuro de bromoacetilo y 2-amino-4-metiltiazol.

Producto Intermedio A24: Etil etoxi{[1-(2-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]tio}acetato



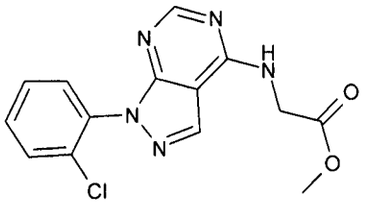
El compuesto del título se preparó en una manera similar a la descrita para el ejemplo 54 comenzando a partir de éter etílico de ácido 2-cloro-2-etoxiacético y el Producto Intermedio B13, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8,76 (s, 1H), 8,26 (s, 1H), 7,46 (m, 2H), 7,13 (m, 2H), 6,88 (s, 1H), 4,32 (m, 2H), 3,90 (m, 1H), 3,78 (m, 4H), 1,31 (m, 6H).

Producto Intermedio A25: Etil 2-{[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]tio}-4-fenilbutanoato

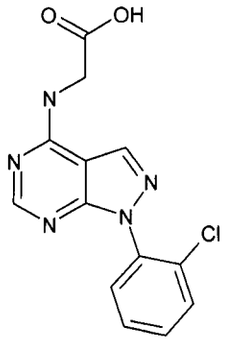


El compuesto del título se preparó en una manera similar a la descrita para el ejemplo 54 comenzando a partir de etil 2-bromo-4-fenilbutanoato y el Producto Intermedio B12, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8,69 (s, 1H), 8,29 (s, 1H), 7,62 (m, 1H), 7,50 (m, 3H), 7,27 (m, 5H), 4,99 (t, 1H), 4,24 (m, 2H), 2,86 (m, 2H), 2,39 (m, 2H), 1,30 (t, 3H).

Producto Intermedio A26: Metil *N*-[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]glicinato

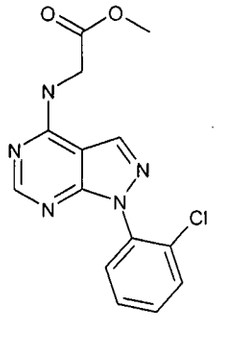


Etapa 1: *N*-[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]glicina



Se agregó 4-cloro-1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidina (1,3 g, 4,90 mmol) a una solución agitada de glicina (0,72 g, 9,59 mmol) y carbonato de sodio anhidro (0,58 g, 5,48 mmol) en agua (10mL). La reacción se sometió a reflujo durante 2 hrs. La mezcla de reacción se acidificó mediante la adición de ácido fórmico. El precipitado se filtró, se lavó con agua y se secó al vacío para proporcionar el compuesto del título como un sólido incoloro (1,23 g), ^{1}H NMR (300 MHz, CD_3OD) δ 8,32 (s, 1H), 8,24 (s, 1H), 7,66 (m, 1H), 7,54 (m, 3H), 4,34 (s, 2H).

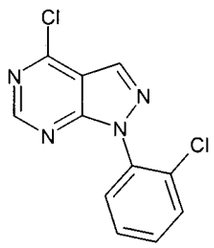
Etapa 2: Metil *N*-[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]glicinato



Se agregó lentamente trimetilsilildiazometano (2 M en éter dietílico) a una solución agitada de *N*-[1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidin-4-il]glicina (Etapa 1) (0,80 g, 2,63 mmol) en DCM (4 mL) y MeOH (1 mL) hasta que persistió un color amarillo. Se

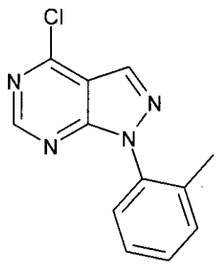
agregaron unas pocas gotas de ácido acético después de 1 minuto y luego se agregaron DCM y agua. Las dos fases se separaron y la fase orgánica se concentró al vacío para proporcionar el compuesto del título (795 mg), ^{1}H NMR (300 MHz, CD3OD) δ 8,32 (s, 1H), 8,24 (s, 1H), 7,66 (m, 1H), 7,54 (m, 3H), 4,39 (s, 2H), 3,77 (s, 3H).

Producto Intermedio B1: 4-cloro-1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidina



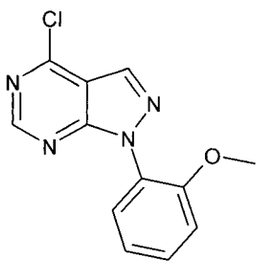
El compuesto del título se preparó utilizando los métodos descritos en *Journal of Organic Chemistry* **1956**, *21*, 1240-1256 y WO2004/009602A1, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8,82 (s, 1H), 8,40 (s, 1H), 7,63 (m, 1H), 7,51 (m, 3H).

Producto Intermedio B2: 4-cloro-1-(2-metilfenil)-1*H*-pirazolo[3,4-*d*]pirimidina



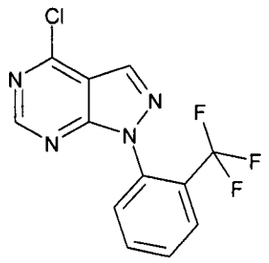
El compuesto del título se preparó utilizando los métodos descritos en *Journal of Organic Chemistry* **1956**, *21*, 1240-1256 y WO2004/009602A1, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8,82 (s, 1H), 8,40 (s, 1H), 7,45 (m, 4H), 2,17 (s, 3H).

Producto Intermedio B3: 4-cloro-1-(2-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidina



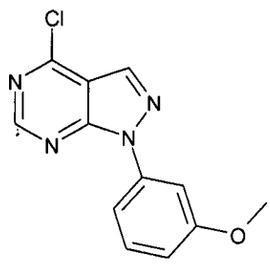
El compuesto del título se preparó utilizando los métodos descritos en *Journal of Organic Chemistry* **1956**, *21*, 1240-1256 y WO2004/009602A1, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8,79 (s, 1H), 8,36 (s, 1H), 7,49 (m, 2H), 7,14 (m, 2H), 3,77 (s, 3H).

Producto Intermedio B4: 4-Cloro-1-[2-(trifluorometil)fenil]-1*H*-pirazolo[3,4-*d*]pirimidina



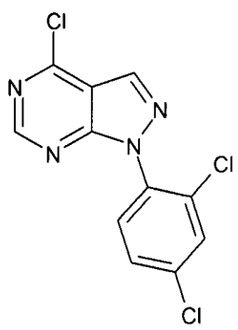
El compuesto del título se preparó utilizando los métodos descritos en *Journal of Organic Chemistry* **1956**, *21*, 1240-1256 y WO2004/009602A1.

Producto Intermedio B5: 4-cloro-1-(3-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidina



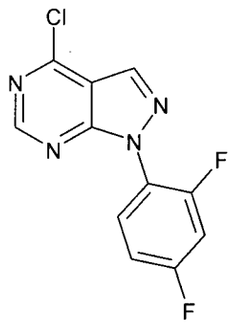
El compuesto del título se preparó utilizando los métodos descritos en *Journal of Organic Chemistry* **1956**, *21*, 1240-1256 y WO2004/009602A1, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8,88 (s, 1H), 8,33 (s, 1H), 7,82 (m, 2H), 7,45 (t, 1H), 6,94 (m, 1H), 3,89 (s, 3H).

Producto Intermedio B6: 4-Cloro-1-(2,4-diclorofenil)-1*H*-pirazolo[3,4-*d*]pirimidina



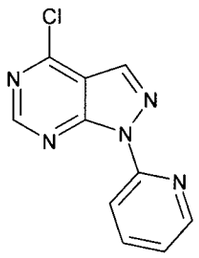
El compuesto del título se preparó utilizando los métodos descritos en *Journal of Organic Chemistry* **1956**, *21*, 1240-1256 y WO2004/009602A1.

Producto Intermedio B7: 4-Cloro-1-(2,4-difluorofenil)-1*H*-pirazolo[3,4-*d*]pirimidina



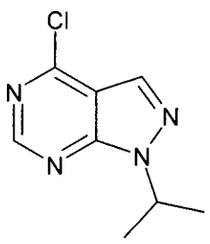
El compuesto del título se preparó utilizando los métodos descritos en *Journal of Organic Chemistry* **1956**, *21*, 1240-1256 y WO2004/009602A1, ^{1}H NMR (400 MHz, DMSO) δ 8,90 (s, 1H), 8,78 (s, 1H), 7,80 (m, 1H), 7,64 (m, 1H), 7,35 (m, 1H).

Producto Intermedio B8: 4-Cloro-1-piridin-2-il-1*H*-pirazolo[3,4-*d*]pirimidina



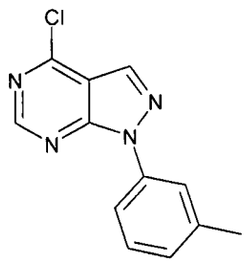
El compuesto del título se preparó utilizando los métodos descritos en *Journal of Organic Chemistry* **1956**, *21*, 1240-1256 y WO2004/009602A1, ^{1}H NMR (400 MHz, DMSO) δ 8,95 (s, 1H), 8,73 (s, 1H), 8,62 (d, 1H), 8,05 (m, 2H), 7,50 (m, 1H).

Producto Intermedio B9: 4-Cloro-1-isopropil-1*H*-pirazolo[3,4-*d*]pirimidina



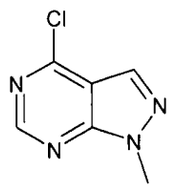
El compuesto del título se preparó utilizando los métodos descritos en *Journal of Organic Chemistry* **1956**, *21*, 1240-1256 y WO2004/009602A1, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8,64 (s, 1H), 8,05 (s, 1H), 5,12 (q, 1H), 1,50 (d, 6H).

Producto Intermedio B10: 4-Cloro-1-(3-metilfenil)-1*H*-pirazolo[3,4-*d*]pirimidina



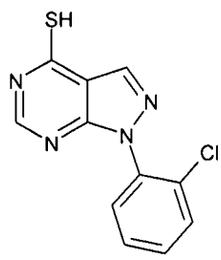
El compuesto del título está comercialmente disponible.

Producto Intermedio B11: 4-Cloro-1-metil-1*H*-pirazolo[3,4-*d*]pirimidina



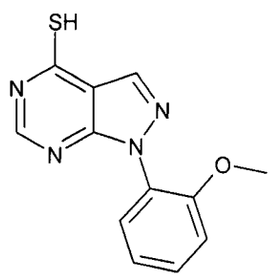
El compuesto del título está comercialmente disponible.

Producto Intermedio B12: 1-(2-clorofenil)-1*H*-pirazolo[3,4-*d*]pirimidina-4-tiol



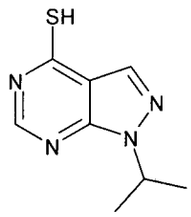
El compuesto del título se preparó utilizando el método descrito en *Journal of Organic Chemistry* **1956**, *21*, 1240-1256 y WO2004/009602A1, ^{1}H NMR (300 MHz, DMSO) δ 13,82 (br s, 1H), 8,46 (s, 1H), 8,19 (s, 1H), 7,74 (m, 1H), 7,61 (m, 3H).

Producto Intermedio B13: 1-(2-metoxifenil)-1*H*-pirazolo[3,4-*d*]pirimidina-4-tiol



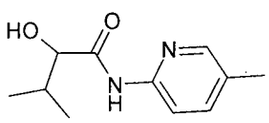
El compuesto del título se preparó utilizando el método descrito en *Journal of Organic Chemistry* **1956**, *21*, 1240-1256 y WO2004/009602A1, ^{1}H NMR (300 MHz, CDCl3) δ 12,68 (br s, 1H), 8,46 (s, 1H), 7,89 (s, 1H), 7,44 (m, 2H), 7,08 (m, 2H), 3,77 (s, 3H).

Producto Intermedio B14: 1-isopropil-1,5-dihidro-4*H*-pirazolo[3,4-*d*]pirimidina-4-tiol



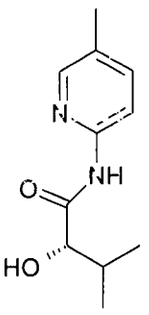
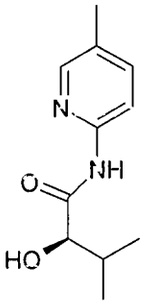
El compuesto del título se preparó utilizando el método descrito en *Journal of Organic Chemistry* **1956**, *21*, 1240-1256 y WO2004/009602A1.

Producto Intermedio C1: 2-hidroxi-3-metil-*N*-(5-metilpiridin-2-il)butanamida

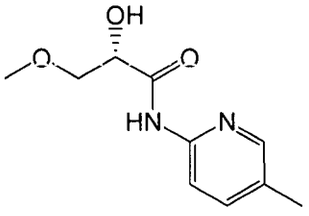


Se agregó 5-metilpiridin-2-amina (CAS 1603-41-4) (2,014 g, 18,6 mmol) en una porción a ácido 2-hidroxi-3-metilbutanoico (CAS 4026-18-0) (2,0 g, 16,9 mmol), hexafluorofosfato de 2-(3H-[1,2,3]triazolo[4,5-b]piridin-3-il)-1,1,3,3-tetrametilisouronio (V) (7,08 g, 18,6 mmol) y *N*-etil-*N*-isopropilpropan-2-amina (5,80 mL, 33,9 mmol) en DCM (40 mL). La suspensión resultante se agitó a temperatura ambiente durante 70 horas. La mezcla de reacción se concentró, se diluyó con EtOAc (150 mL) y se lavó secuencialmente con agua (150 mL) y salmuera saturada (75 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar el producto bruto. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 20 a 50% EtOAc en isohexano para proporcionar 2-hidroxi-3-metil-*N*-(5-metilpiridin-2-il)butanamida (500 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0,87 (3H, d), 0,97 (3H, d), 2,06 - 2,16 (1H, m), 2,29 (3H, s), 3,94-3,98 (1H, m), 5,87 (1H, d), 7,65 (1H, dd), 8,05 (1H, d), 8,16 (1H, d), 9,50 (1H, s), m/z (ESI+) (M+H)+ = 209; HPLC t_R = 1,11 min.

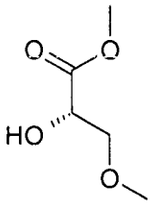
Los **Productos Intermedios C2 y C3** se prepararon en una forma análoga a partir de materiales de partida enantioméricamente puros (CAS 17407-55-5 y 17407-56-6).

C2		(S)-2-hidroxi-3-metil-*N*-(5-metilpiridin-2-il)butanamida	ESI+ (M+H)+ = 209; HPLC t_R = 1,13 min	^{1}H NMR (400 MHz, DMSO-d_6) δ 0,87 (3H, d), 0,97 (3H, d), 2,06 - 2,16 (1H, m), 2,29 (3H, s), 3,94-3,98 (1H, m), 5,87 (1H, d), 7,65 (1H, dd), 8,05 (1H, d), 8,16 (1H, d), 9,50 (1H, s)
C3		(R)-2-hidroxi-3-metil-*N*-(5-metilpiridin-2-il)butanamida	ESI+ (M+H)+ = 209; HPLC t_R = 1,12 min	^{1}H NMR (400 MHz, DMSO-d_6) δ 0,82 (3H, d), 0,95 (3H, d), 2,02 - 2,10 (1H, m), 2,24 (3H, s), 3,89 - 3,91 (1H, m), 5,80 (1H, d), 7,61 (1H, dd), 8,00 (1H, d), 8,13 (1H, d), 9,45 (1H, s)

Producto Intermedio C4: (S)-2-hidroxi-3-metoxi-*N*-(5-metilpiridin-2-il)propanamida



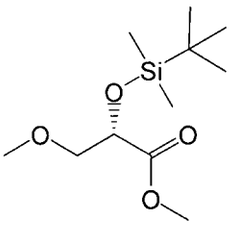
Etapa 1: Síntesis de C4a: (S)-metil 2-hidroxi-3-metoxipropanoato



Se agregó perclorato de magnesio (0,820 g, 3,67 mmol) en una porción a (S)-metil oxirano-2-carboxilato (CAS 2868-37-3) (1,5 g, 14,7 mmol) y metanol (0,714 mL, 17,6 mmol) enfriado hasta alcanzar 10°C. La suspensión resultante se agitó a 10°C durante 10

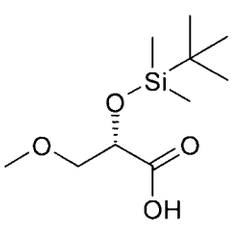
minutos y luego se entibió hasta alcanzar 45°C durante 20 horas. La mezcla de reacción bruta se purificó mediante cromatografía instantánea en sílice, gradiente de elución 20 a 50% Et_2O en DCM, para proporcionar (S)-metil 2-hidroxi-3-metoxipropanoato (1,4 g). ^1H NMR (400 MHz, $CDCl_3$) δ 3,01 (1H, d), 3,40 (3H, s), 3,65 - 3,72 (2H, m), 3,81 (3H, s), 4,29 - 4,33 (1H, m)

Etapa 2: Síntesis de C4b: (S)-metil 2-(terc-butildimetilsililoxi)-3-metoxipropanoato



Una solución de terc-butilclorodimetilsilano (661 mg, 4,38 mmol) en DMF (2,5 mL) se agregó gota a gota a una solución agitada de (S)-metil 2-hidroxi-3-metoxipropanoato **C4a** (490 mg, 3,65 mmol) y 1H-imidazol (497 mg, 7,31 mmol) en DMF (5 mL) a 20°C, durante un período de 2 minutos. La solución resultante se agitó a temperatura ambiente durante 3 horas. La mezcla de reacción se concentró, se diluyó con EtOAc (50 mL) y se lavó secuencialmente con agua (4 x 15 mL) y salmuera saturada (20 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar el producto bruto. La purificación mediante cromatografía instantánea en sílice, gradiente de elución 20 a 50% EtOAc en isohexano, proporcionó (S)-metil 2-(terc-butildimetilsililoxi)-3-metoxipropanoato (750 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 0,11 (3H, s), 0,13 (3H, s), 0,94 (9H, s), 3,40 (3H, s), 3,56 - 3,64 (2H, m), 3,76 (3H, s), 4,37 - 4,41 (1H, m)

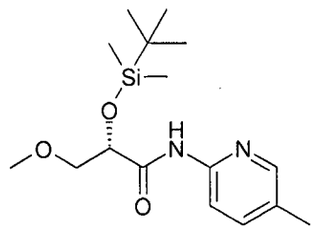
Etapa 3: Síntesis de C4c: ácido (S)-2-(terc-butildimetilsililoxi)-3-metoxipropanoico



Se agregó yoduro de litio (535 mg, 3,99 mmol) en una porción a (S)-metil 2-(terc-butildimetilsililoxi)-3-metoxipropanoato **C4b** (248 mg, 1,00 mmol) en EtOAc (5 mL). La suspensión resultante se protegió de la luz y se agitó a reflujo (75°C) durante 24 horas. La mezcla de reacción se diluyó con EtOAc (10 mL) y se lavó secuencialmente con agua (5 mL), metabisulfito de sodio 1M (5 mL) y salmuera saturada (5 mL). La capa orgánica se

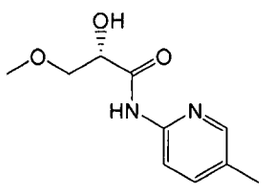
secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar el producto bruto, una mezcla aproximada 3:1 de ácido (S)-2-(terc-butildimetilsililoxi)-3-metoxipropanoico y (S)-metil 2-(terc-butildimetilsililoxi)-3-metoxipropanoato. El material se llevó a la siguiente etapa sin purificación.

Etapa 4: Síntesis de C4d: (S)-2-(terc-butildimetilsililoxi)-3-metoxi-*N*-(5-metilpiridin-2-il)propanamida



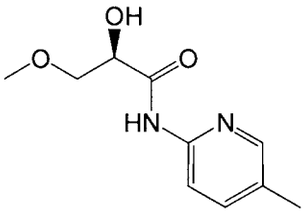
Una solución de 1-cloro-*N*,*N*,2-trimetilprop-1-en-1-amina (1,55 mL, 11,7 mmol) en DCM (5 mL) se agregó gota a gota a una solución agitada de ácido (S)-2-(terc-butildimetilsililoxi)-3-metoxipropanoico **C4c** (2,5g, 10,7 mmol) en DCM (15 mL) bajo nitrógeno. La solución resultante se agitó a temperatura ambiente durante 30 minutos. Se agregó *N*-etil-*N*-isopropilpropan-2-amina (2,74 mL, 16,0 mmol) en una porción y luego 5-metilpiridin-2-amina (CAS 1603-41-4) (1,27g, 11,73 mmol) en DCM (5 mL) gota a gota. La solución resultante se agitó a temperatura ambiente durante 1 hora. Se agregó ácido cítrico 1M (10 mL) y la mezcla se extrajo con EtOAc (20 mL). La fase orgánica se lavó con agua (5 mL) y salmuera (5 mL), se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar el producto bruto. La purificación mediante cromatografía instantánea en sílice, gradiente de elución 20 a 100% EtOAc en isohexano, proporcionó (S)-2-(terc-butildimetilsililoxi)-3-metoxi-*N*-(5-metilpiridin-2-il)propanamida (1,4 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0,2 (6H, s), 1,01 (9H, s), 2,32 (3H, s), 3,41 (3H, s), 3,66 - 3,75 (2H, m), 4,40 - 4,42 (1H, m), 7,52 (1H, d), 7,14 - 7,16 (2H, m), 9,04 (1H, s), m/z (ESI+) $(M+H)^+$ = 326; HPLC t_R = 2,75 min.

Etapa 5: Síntesis de C4: (S)-2-hidroxi-3-metoxi-*N*-(5-metilpiridin-2-il)propanamida

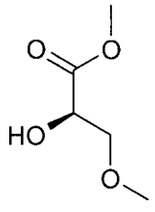


Una solución de fluoruro de tetrabutilamonio (1M en THF) (8,63 mL, 8,63 mmol) se agregó en una porción a una solución agitada de (S)-2-(terc-butildimetilsililoxi)-3-metoxi-*N*-(5-metilpiridin-2-il)propanamida **C4d** (1,4 g, 4,31 mmol) en THF (20 mL). La solución resultante se agitó a temperatura ambiente durante 4 horas. La mezcla de reacción se concentró, se diluyó con EtOAc (50 mL) y se lavó secuencialmente con agua (20 mL) y salmuera saturada (20 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar el producto bruto como un aceite. La trituración con 1:1 isohexano:EtOAc proporcionó (S)-2-hidroxi-3-metoxi-*N*-(5-metilpiridin-2-il)propanamida (340 mg). El residuo se purificó mediante cromatografía instantánea en sílice con EtOAc para proporcionar un segundo lote de (S)-2-hidroxi-3-metoxi-*N*-(5-metilpiridin-2-il)propanamida (220 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2,31 (3H, s), 3,44 (3H, s), 3,73 - 3,80 (2H, m), 4,38 - 4,42 (1H, m), 4,63 (1H, d), 7,54 (1H, dd), 8,10 - 8,11 (1H, d), 8,14 (1H, d), 9,33 (1H, s), m/z (ESI+) (M+H)+ = 211; HPLC t_R = 0,77 min.

Producto Intermedio C5: (R)-2-hidroxi-3-metoxi-*N*-(5-metilpiridin-2-il)propanamida

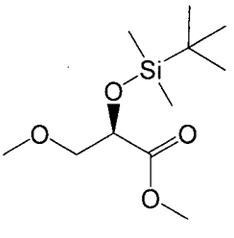


Etapa 1: Síntesis de C5a: (R)-Metil 2-hidroxi-3-metoxipropanoato



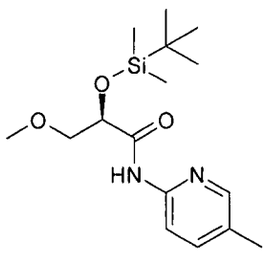
Se preparó **C5a** en una forma análoga al producto intermedio **C4a** a partir de (R)-metil oxirano-2-carboxilato (CAS 111058-32-3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3,01 (1H, d), 3,40 (3H, s), 3,65 - 3,72 (2H, m), 3,81 (3H, s), 4,29 - 4,33 (1H, m)

Etapa 2: Síntesis de C5b: (R)-Metil 2-(terc-butildimetilsililoxi)-3-metoxipropanoato



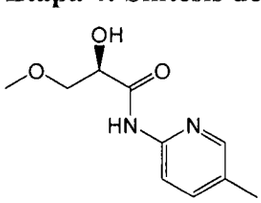
Se preparó **C5b** en una forma análoga al producto intermedio **C4b** a partir de (R)-metil 2-hidroxi-3-metoxipropanoato **C5a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0,11 (3H, s), 0,13 (3H, s), 0,94 (9H, s), 3,40 (3H, s), 3,56 - 3,64 (2H, m), 3,76 (3H, s), 4,37 - 4,41 (1H, m)

Etapa 3: Síntesis de C5c: (R)-2-(terc-butildimetilsililoxi)-3-metoxi-*N*-(5-metilpiridin-2-il)propanamida



Una solución de n-butillitio (2,5M en hexanos) (2,04 mL, 3,26 mmol) se agregó gota a gota a una solución agitada de 5-metilpiridin-2-amina (CAS 1603-41-4) (353 mg, 3,26 mmol) en THF (10 mL) enfriado hasta alcanzar 10°C bajo nitrógeno. La solución resultante se agitó a temperatura ambiente durante 10 minutos y luego se agregó a una solución de (R)-metil 2-(terc-butildimetilsililoxi)-3-metoxipropanoato **C5b** (810 mg, 3,26 mmol) en THF (10 mL) a 10°C. La solución resultante se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se diluyó con EtOAc (75 mL) y se lavó secuencialmente con cloruro de amonio saturado (50 mL), agua (25 mL) y salmuera saturada (25 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar el producto bruto. La purificación mediante cromatografía instantánea en sílice, gradiente de elución 20 a 50% EtOAc en isohexano, proporcionó (R)-2-(terc-butildimetilsililoxi)-3-metoxi-*N*-(5-metilpiridin-2-il)propanamida (300 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0,15 (3H, s), 0,16 (3H, s), 0,88 (9H, s), 2,12 (3H, s), 3,46 (3H, s), 3,61 – 3,65 (2H, m), 4,35 – 4,42 (1H, m), 7,47 (1H, d), 8,19 (1H, d), 8,20 (1H, s), 8,97 (1H, s), m/z (ESI+) $(M+H)^+$ = 325; HPLC t_R = 3,08 min.

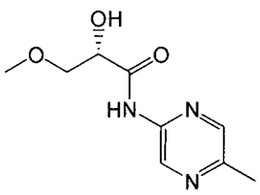
Etapa 4: Síntesis de C5:(R)-2-hidroxi-3-metoxi-*N*-(5-metilpiridin-2-il)propanamida



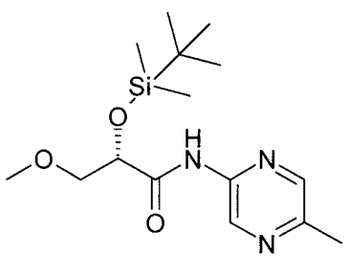
Se preparó **C5** en una forma análoga al **C4 (etapa 5)** a partir de (R)-2-(terc-butildimetilsililoxi)-3-metoxi-*N*-(5-metilpiridin-2-il)propanamida **C5c**. ^{1}H NMR (400

MHz, $CDCl_3$) δ 2,31 (3H, s), 3,44 (3H, s), 3,73 – 3,78 (2H, m), 4,36-4,44 (1H, m), 4,46-4,50 (1H, m), 7,54 (1H, dd), 8,10 (1H, d), 8,14 (1H, d), 9,30 (1H, s), m/z (ESI+) $(M+H)^+$ = 211; HPLC t_R = 0,74 min.

Producto Intermedio C6: (S)-2-hidroxi-3-metoxi-*N*-(5-metilpirazin-2-il)propanamida

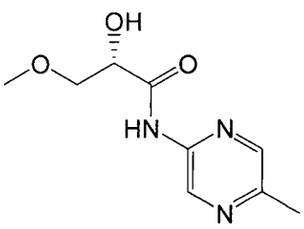


Etapa 1: Síntesis de C6a: (S)-2-(terc-butildimetilsililoxi)-3-metoxi-*N*-(5-metilpirazin-2-il)propanamida



Se preparó **C6a** en una forma análoga al **C4d** a partir de ácido (S)-2-(terc-butildimetilsililoxi)-3-metoxipropanoico **C4c** y 5-metilpirazina-2-amina (CAS 5521-58-4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0,18 (3H, s), 0,19 (3H, s), 1,01 (9H, s), 2,54 (3H, s), 3,39 (3H, s), 3,70 (2H, d), 4,41 (1H, t), 8,14 (1H, d), 9,01 (1H, s), 9,42 (1H, d), m/z (ESI+) $(M+H)^+$ = 326; HPLC t_R = 2,67 min.

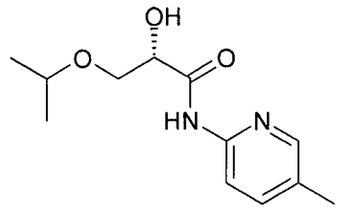
Etapa 2: Síntesis de C6: (S)-2-hidroxi-3-metoxi-*N*-(5-metilpirazin-2-il)propanamida



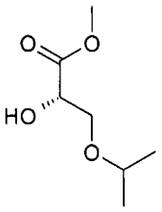
Se preparó **C6** en una forma análoga al producto intermedio **C4 (etapa 5)** a partir de (S)-2-(terc-butildimetilsililoxi)-3-metoxi-*N*-(5-metilpirazin-2-il)propanamida **C6a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2,55 (3H, s), 3,45 (3H, s), 3,74 – 3,82 (2H, m), 3,85 (1H, s), 4,41 (1H, t), 8,14 (1H, d), 9,18 (1H, s), 9,45 (1H, d), m/z (ESI+) $(M+H)^+$ = 212; HPLC t_R = 0,78 min.

Producto Intermedio C7: (S)-2-hidroxi-3-isopropoxi-*N*-(5-metilpiridin-2-

il)propanamida



Etapa 1: Síntesis de C7a: (S)-Metil 2-hidroxi-3-isopropoxipropanoato

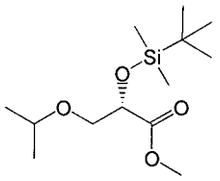


Se agregó perclorato de magnesio (2,73 g, 12,24 mmol) en una porción a (S)-metil oxirano-2-carboxilato (CAS 2868-37-3) (5,0 g, 48,98 mmol) y propan-2-ol (4,69 mL, 61,22 mmol) a 10°C. La suspensión resultante se agitó a 10°C durante 10 minutos y luego se dejó entibiar hasta alcanzar la temperatura ambiente durante 30 minutos, tiempo durante el cual la mayoría de los sólidos se disolvieron. Se calentó hasta alcanzar 100°C durante 30 minutos en un reactor de microondas. El material se utilizó sin purificación en la siguiente etapa.

De forma alternativa, C7a puede prepararse como se describe a continuación.

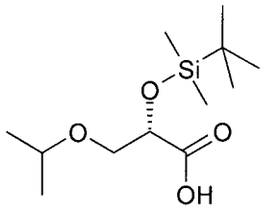
Se calentaron (S)-metil oxirano-2-carboxilato (2,04 g, 19,98 mmol), trifluorometanosulfonato de magnesio (1,611 g, 5,00 mmol) y propan-2-ol (1,84 mL, 24,0 mmol) en acetato de etilo (10 mL) a reflujo durante 90 horas. La mezcla se diluyó con EtOAc (20 mL), se filtró y se evaporó. El residuo se purificó mediante cromatografía instantánea en sílice, gradiente de elución 20 a 50% EtOAc en isohexano para proporcionar (S)-metil 2-hidroxi-3-isopropoxipropanoato (2,45 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,13 (3H, d), 1,16 (3H, d), 3,00 (1H, d), 3,58 - 3,64 (1H, m), 3,68 - 3,74 (2H, m), 3,69 - 3,73 (1H, m), 3,80 (3H, s), 4,28 - 4,31 (1H, m)

Etapa 2: Síntesis de C7b: (S)-metil 2-(terc-butildimetilsililoxi)-3-isopropoxipropanoato



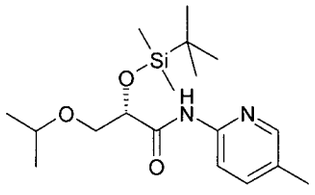
Se preparó **C7b** en una forma análoga al **C4b** a partir de (S)-metil 2-hidroxi-3-isopropoxipropanoato bruto **C7a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0,10 (3H, s), 0,11 (3H, s), 0,90 (9H, d), 1,14 (6H, d), 3,50 – 3,7 (3H, m), 3,73 (3H, s), 4,33 – 4,36 (1H, m)

Etapa 3: Síntesis de C7c: ácido (S)-2-(terc-butildimetilsililoxi)-3-isopropoxipropanoico



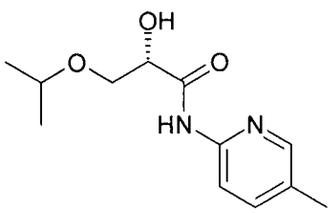
C7c se preparó en una forma análoga al **C4c** a partir de (S)-metil 2-(terc-butildimetilsililoxi)-3-isopropoxipropanoato **C7b**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0,16 (3H, s), 0,17 (3H, s), 0,93 (9H, m), 1,14 (3H, d), 1,16 (3H, d), 3,58 - 3,74 (3H, m), 4,35 - 4,38 (1H, m), 9,31 (1H, s)

Etapa 4: Síntesis de C7d: (S)-2-(terc-butildimetilsililoxi)-3-isopropoxi-*N*-(5-metilpiridin-2-il)propanamida



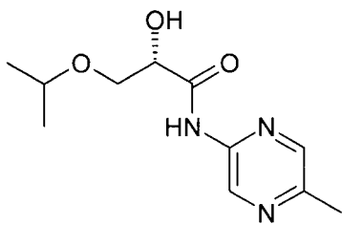
C7d se preparó en una forma análoga al **C4d** a partir de ácido (S)-2-(terc-butildimetilsililoxi)-3-isopropoxipropanoico **C7c** y 5-metilpiridin-2-amina. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0,16 (3H, s), 0,17 (3H, s), 1,01 (9H, s), 1,12 (3H, d), 1,13 (3H, d), 2,29 (3H, s), 3,56 - 3,62 (2H, m), 3,71 - 3,78 (1H, m), 4,40 (1H, dd), 7,47 - 7,51 (1H, m), 8,10 - 8,17 (2H, m), 9,01 (1H, s)

Etapa 5: Síntesis de C7: (S)-2-hidroxi-3-isopropoxi-*N*-(5-metilpiridin-2-il)propanamida

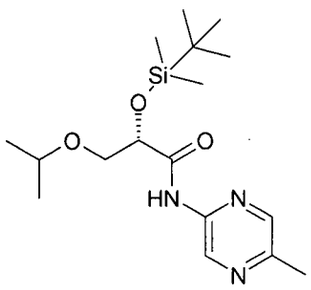


C7 se preparó en una forma análoga al **C4 (etapa 5)** a partir de (S)-2-(terc-butildimetilsililoxi)-3-isopropoxi-*N*-(5-metilpiridin-2-il)propanamida **C7d**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,19 (3H, d), 1,21 (3H, d), 2,30 (3H, s), 3,64 - 3,72 (2H, m), 3,76 (2H, d), 4,29 - 4,33 (1H, m), 7,52 (1H, dd), 8,09 - 8,14 (2H, m), 9,18 (1H, s), m/z (ESI+) $(M+H)^+$ = 211; HPLC t_R = 0,77 min.

Producto Intermedio C8: (S)-2-hidroxi-3-isopropoxi-N-(5-metilpirazin-2-il)propanamida

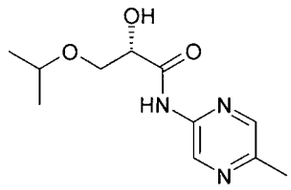


Etapa 1: Síntesis de C8a: (S)-2-(terc-butildimetilsililoxi)-3-isopropoxi-*N*-(5-metilpirazin-2-il)propanamida



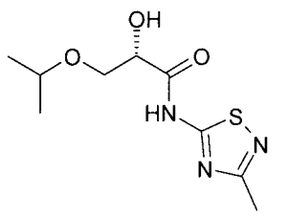
C8a se preparó en una forma análoga al **C4d** a partir de ácido (S)-2-(terc-butildimetilsililoxi)-3-isopropoxipropanoico **C7c** y 5-metilpirazin-2-amina. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0,20 (3H, s), 0,21 (3H, s), 1,0 (9H, s), 1,14 (3H, d), 1,17 (3H, d), 2,54 (3H, s), 3,61 - 3,65 (2H, m), 3,77 - 3,80 (1H, m), 4,40 (1H, dd), 8,14 (1H, d), 9,01 (1H, s), 9,43 (1H, d)

Etapa 2: Síntesis de C8: (S)-2-hidroxi-3-isopropoxi-*N*-(5-metilpirazin-2-il)propanamida

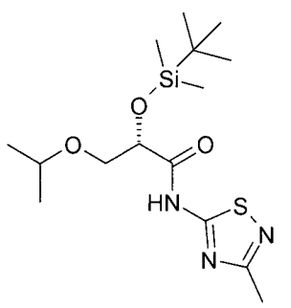


C8 se preparó en una forma análoga al **C4 (etapa 5)** a partir de (S)-2-(terc-butildimetilsililoxi)-3-isopropoxi-*N*-(5-metilpirazin-2-il)propanamida **C8a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,19 (3H, m), 1,21 (3H, d), 2,54 (3H, s), 3,42 (1H, d), 3,67 - 3,82 (3H, m), 4,31 - 4,35 (1H, m), 8,14 (1H, d), 9,14 (1H, s), 9,42 (1H, d)

Producto Intermedio C9: (S)-2-hidroxi-3-isopropoxi-*N*-(3-metil-1,2,4-tiadiazol-5-il)propanamida

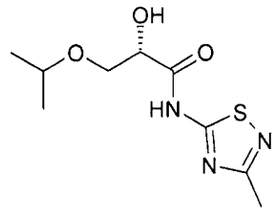


Etapa 1: Síntesis de C9a: (S)-2-(terc-butildimetilsililoxi)-3-isopropoxi-*N*-(3-metil-1,2,4-tiadiazol-5-il)propanamida



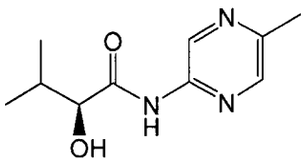
C9a se preparó en una forma análoga al **C4d** a partir de ácido (S)-2-(terc-butildimetilsililoxi)-3-isopropoxipropanoico **C7c** y 3-metil-1,2,4-tiadiazol-5-amina. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0,17 (3H, s), 0,19 (3H, s), 0,96 (9H, s), 1,08 (3H, d), 1,13 (3H, d), 2,39 (3H, s), 3,42- 3,66 (2H, m), 3,69 - 3,74 (1H, m), 4,50 - 4,53 (1H, m), 10,00 (1H, s)

Etapa 2: Síntesis de C9: (S)-2-hidroxi-3-isopropoxi-*N*-(3-metil-1,2,4-tiadiazol-5-il)propanamida

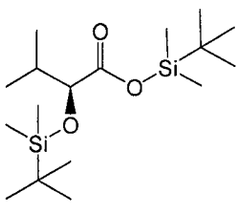


C9 se preparó en una forma análoga al **C4 (etapa 5)** a partir de (S)-2-(terc-butildimetilsililoxi)-3-isopropoxi-*N*-(3-metil-1,2,4-tiadiazol-5-il)propanamida **C9a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,1 (3H, m), 1,20 (3H, d), 2,55 (3H, s), 3,63 - 3,72 (1H, m), 3,75 (1H, ancho s), 3,76 - 3,83 (2H, m), 4,47 - 4,50 (1H, m), 10,20 (1H, ancho s)

Producto Intermedio C10: (S)-2-hidroxi-3-metil-*N*-(5-metilpirazin-2-il)butanamida

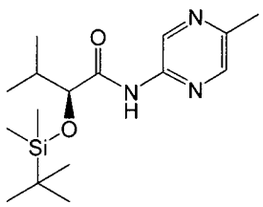


Etapa 1: Síntesis de C10a: (S)-terc-butildimetilsilil 2-(terc-butildimetilsililoxi)-3-metilbutanoato



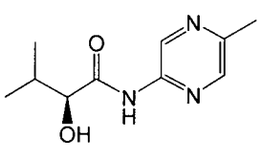
Se agregó cloruro de terc-butildimetilsililo (18,77 g, 124,54 mmol) a ácido (S)-(+)-2-hidroxi-3-metilbutírico (CAS 17407-55-5) (6,13 g, 51,9 mmol) y 1H-imidazol (16,96 g, 249 mmol) en DMF (259 mL) a 23°C bajo nitrógeno. La solución resultante se agitó a temperatura ambiente durante 60 horas. La mezcla de reacción se diluyó con EtOAc (1400 mL) y la fase orgánica se lavó secuencialmente con ácido cítrico saturado acuoso (3 x 500 mL), hidrogenocarbonato de sodio saturado acuoso (3 x 500 mL) y salmuera saturada (3 x 500 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar (S)-terc-butildimetilsilil 2-(terc-butildimetilsililoxi)-3-metilbutanoato (18,0 g, 100 %). Este material se utilizó sin purificación adicional.

Etapa 2: Síntesis de C10b: (S)-2-(terc-butildimetilsililoxi)-3-metil-N-(5-metilpirazin-2-il)butanamida



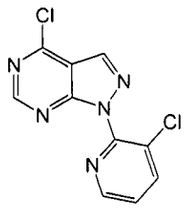
Se agregó DMF (cat.) a una solución agitada de (S)-terc-butildimetilsilil 2-(terc-butildimetilsililoxi)-3-metilbutanoato **C10a** (17,99 g, 51,90 mmol) y cloruro de oxalilo (5,89 mL, 67,47 mmol) en DCM (259 mL) a 23°C bajo nitrógeno. La solución resultante se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se concentró bajo presión reducida y se sometió a azeotropía con tolueno (50 mL). El aceite resultante se disolvió en DCM (250 mL) y se agregó 5-metilpirazin-2-amina (6,23 g, 57,1 mmol). La solución resultante se agitó durante 4 horas a temperatura ambiente. La mezcla de reacción se lavó secuencialmente con agua (150 mL) y $NaHCO_3$ saturado (150 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar el producto bruto. La purificación mediante cromatografía instantánea en sílice, gradiente de elución 0 a 70% EtOAc en isohexano, proporcionó (S)-2-(terc-butildimetilsililoxi)-3-metil-*N*-(5-metilpirazin-2-il)butanamida **C10b** (2,53 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0,11 (3H, s), 0,15 (3H, s), 0,95 (3H, d), 1,00 (9H, s), 1,02 (3H, d), 2,15 - 2,18 (1H, m), 2,54 (3H, s), 4,10 (1H, d), 8,13 (1H, d), 8,76 (1H, s), 9,45 (1H, d), m/z (ESI+) (M+H)+ = 324; HPLC tR = 3,25 min.

Etapa 3: Síntesis de C10: (S)-2-hidroxi-3-metil-*N*-(5-metilpirazin-2-il)butanamida

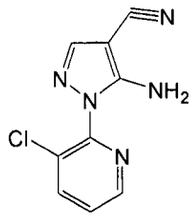


C10 se preparó en una forma análoga al **C4 (etapa 5)** a partir de (S)-2-(terc-butildimetilsililoxi)-3-metil-*N*-(5-metilpirazin-2-il)butanamida **C10b**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0,88 (3H, d), 0,98 (3H, d), 2,05 - 2,16 (1H, m), 2,50 (3H, s), 3,99 (1H, dd), 5,84 (1H, d), 8,34 (1H, s), 9,26 (1H, d), 9,89 (1H, s), m/z (ESI+) (M+H)+ = 210; HPLC t_R = 1,24 min.

Producto Intermedio B15: 4-cloro-1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidina

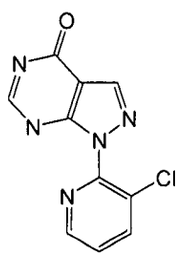


Etapa 1: Síntesis de B15a: 5-amino-1-(3-cloropiridin-2-il)-1H-pirazol-4-carbonitrilo



Se suspendió 3-cloro-2-hidrazinilpiridina (CAS 22841-92-5) (19,1 g, 133,03 mmol) en MeOH (200 mL) bajo nitrógeno a -5°C. Se agregó en porciones 2-(etoximetileno)malononitrilo (CAS 123-06-8) (16,25 g, 133,03 mmol y la mezcla resultante se agitó a ~0°C durante 2 horas. La mezcla de reacción se calentó hasta alcanzar reflujo durante 2 horas, luego se enfrió y se evaporó para proporcionar 5-amino-1-(3-cloropiridin-2-il)-1H-pirazol-4-carbonitrilo (29,2g). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6,87 (2H, s), 7,61 (1H, dd), 7,79 (1H, s), 8,21 (1H, dd), 8,55 (1H, dd), m/z (ESI+) $(M+H)^+$ = 220; HPLC tR = 1,17 min.

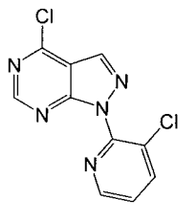
Etapa 2: Síntesis de B15b: 1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4(7H)-ona



Se agregó ácido sulfúrico concentrado (10,87 mL, 203,92 mmol) a una solución agitada de 5-amino-1-(3-cloropiridin-2-il)-1H-pirazol-4-carbonitrilo **B15a** (29,2 g, 132,95 mmol) en ácido fórmico (200 mL). La solución resultante se agitó a 100°C durante 3 horas. La mezcla de reacción se enfrió y se evaporó hasta proporcionar aprox. la mitad del volumen. Se agregó agua (250 mL) y la mezcla resultante se agitó durante 1 hora. Se formó un precipitado que se recogió mediante filtración y se lavó con agua (3 x 50 mL) y luego se secó al vacío a 50°C para proporcionar 1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4(7H)-ona (30,5 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7,72 (1H, dd), 8,10 (1H, s), 8,30

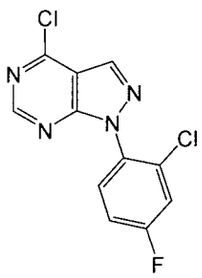
(1H, dd), 8,37 (1H, s), 8,64 (1H, dd), 12,43 (1H, s), m/z (ESI+) (M+H)+ = 248; HPLC t_R = 0,99 min.

Etapa 3: Síntesis de B15: 4-cloro-1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidina

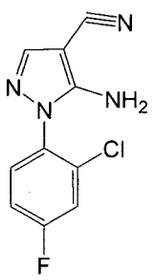


Se agregó tricloruro de fosforilo (235 mL, 2455,17 mmol) a 1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-ol **B15b** (30,4 g, 122,76 mmol). La solución resultante se agitó a 100°C durante 4 horas. La mezcla se concentró al vacío y al residuo se agregó una mezcla de hielo/agua. La mezcla resultante se agitó durante 1 hora, tiempo durante el cual se precipitó un sólido. El sólido se recogió mediante filtración y se lavó con agua (3 x 75 mL). El producto bruto se disolvió en EtOAc (500 mL) y se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar 4-cloro-1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidina (28,7 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7,78 (1H, dd), 8,37 (1H, dd), 8,69 (1H, dd), 8,83 (1H, s), 8,92 (1H, s), m/z (ESI+) (M+H)+ = 266; HPLC t_R = 1,72 min.

Producto Intermedio B16: 4-cloro-1-(2-cloro-4-fluorofenil)-1H-pirazolo[3,4-d]pirimidina



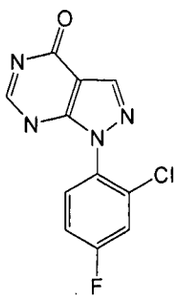
Etapa 1: Síntesis de B16a: 5-amino-1-(2-cloro-4-fluorofenil)-1H-pirazol-4-carbonitrilo



Se dividió 2-cloro-4-fluorofenil hidrazina clorhidrato (CAS 497959-29-2) (25,0g, 126,9mmol) entre DCM (250 mL) y NaOH 2M (100 mL). La fase orgánica se separó y se

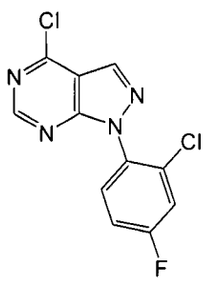
lavó secuencialmente con agua (2 x 150 mL) y salmuera (150 mL), se secó sobre $MgSO_4$ y se evaporó para proporcionar la base libre. Este aceite se disolvió en MeOH (200 mL) bajo nitrógeno a -5°C y se agregó 2-(etoximetileno)malononitrilo (15,5 g, 127 mmol) en porciones. La mezcla resultante se agitó a 0°C durante 2 horas y luego a reflujo durante 2 horas adicionales. Después de enfriarse, la mezcla se evaporó para proporcionar 5-amino-1-(2-cloro-4-fluorofenil)-1H-pirazol-4-carbonitrilo (28,9 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6,68 (2H, s), 7,37 (1H, ddd), 7,58 (1H, dd), 7,69 (1H, dd), 7,75 (1H, s), m/z (ESI+) (M+H)+ = 237; HPLC t_R = 1,62 min.

Etapa 2: Síntesis de B16b: 1-(2-cloro-4-fluorofenil)-1H-pirazolo[3,4-d]pirimidin-4(7H)-ona



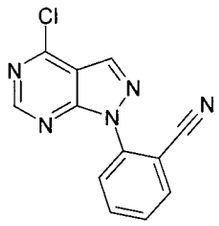
B16b (sal de sulfato) se preparó en una forma análoga al **B15b** a partir de 5-amino-1-(2-cloro-4-fluorofenil)-1H-pirazol-4-carbonitrilo **B15a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7,44 (1H, ddd), 7,72 (1H, dd), 7,77 (1H, dd), 8,08 (1H, s), 8,33 (1H, s), 12,38 (1H, s), m/z (ESI-) (M-H)- = 263; HPLC t_R = 1,44 min.

Etapa 3: Síntesis de B16: 4-cloro-1-(2-cloro-4-fluorofenil)-1H-pirazolo[3,4-d]pirimidina

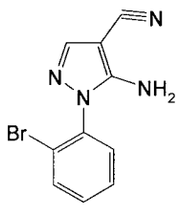


B16 se preparó en una forma análoga al **B15 (etapa 3)** a partir de 1-(2-cloro-4-fluorofenil)-1H-pirazolo[3,4-d]pirimidin-4(7H)-ona **B16b**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7,48 - 7,53 (1H, m), 7,79 - 7,83 (2H, m), 8,79 (1H, s), 8,89 (1H, s), m/z (ESI+) (M+H)+ = 283; HPLC t_R = 2,39 min.

Producto Intermedio B17: 2-(4-cloro-1H-pirazolo[3,4-d]pirimidin-1-il)benzonitrilo

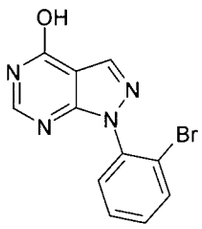


Etapa 1: Síntesis de B17a: 5-amino-1-(2-bromofenil)-1H-pirazol-4-carbonitrilo



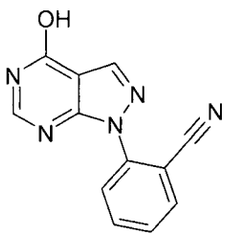
B17a se preparó en una forma análoga al **B16a** a partir de (2-bromofenil) hidrazina clorhidrato (CAS 50709-33-6). m/z (ESI+) $(M+H)^+ = 265$; HPLC $t_R = 1,52$ min.

Etapa 2: Síntesis de B17b:1-(2-bromofenil)-1H-pirazolo[3,4-d]pirimidin-4-ol



B17b (sal de sulfato) se preparó en una forma análoga al **B15b** a partir de **B16a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7,51 - 7,55 (1H, m), 7,56 - 7,61 (2H, m), 7,86 - 7,88 (1H, m), 8,04 - 8,08 (1H, m), 8,30 - 8,33 (1H, m), 12,35 (1H, s), m/z (ESI+) $(M+H)^+ = 293$; HPLC t_R = 1,34 min.

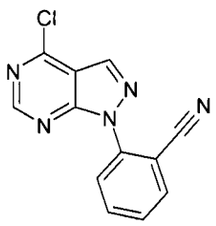
Etapa 3: Síntesis de B17c: 2-(4-hidroxi-1H-pirazolo[3,4-d]pirimidin-1-il)benzonitrilo



Se disolvió 1-(2-bromofenil)-1H-pirazolo[3,4-d]pirimidin-4-ol **B17b** (1,456 g, 5 mmol) y cianuro de zinc (0,528 g, 4,50 mmol) en DMF (15 mL) y se selló en un tubo de microondas. El tubo se vació y lavó con nitrógeno varias veces. Se agregaron 9,9-dimetil-

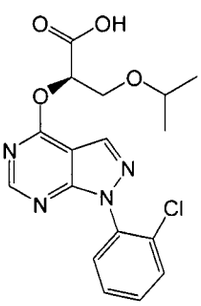
4,5-bis(difenilfosfino)xanteno (0,289 g, 0,50 mmol) y tris(dibencilidenoacetona) dipaladio(0) (0,229 g, 0,25 mmol). La reacción se calentó hasta alcanzar 160°C durante 10 minutos en el reactor de microondas y se enfrió hasta alcanzar la TA. Esto se repitió exactamente en la misma escala. Las dos mezclas de reacción se combinaron y se diluyeron con EtOAc (200 mL) y agua (30 mL). La mezcla bifásica se filtró y la fase orgánica se separó y se lavó con salmuera (20 mL), luego se secó sobre $MgSO_4$, se filtró y se evaporó. El residuo se purificó mediante filtración en caliente y luego mediante cristalización a partir de MeOH, proporcionando 2-(4-hidroxi-1H-pirazolo[3,4-d]pirimidin-1-il)benzonitrilo (1,225 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7,70 - 7,75 (1H, m), 7,86 - 7,88 (1H, m), 7,91 - 7,95 (1H, m), 8,08 - 8,10 (1H, m), 8,17 (1H, s), 8,43 (1H, s), 12,49 (1H, s), m/z (ESI+) $(M+H)^+$ = 238; HPLC t_R = 1,15 min.

Etapa 4: Síntesis de B17: 2-(4-cloro-1H-pirazolo[3,4-d]pirimidin-1-il)benzonitrilo

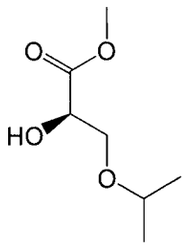


B17 se preparó en una forma análoga al **B15** a partir de **B17c**. El material final se purificó mediante cromatografía instantánea en sílice, gradiente de elución 0 a 5% MeOH en DCM, para proporcionar **B17** como un sólido (0,495g). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7,74 - 7,81 (1H, m), 7,96 - 8,02 (2H, m), 8,14 - 8,17 (1H, m), 8,89 (1H, s), 8,98 (1H, s), m/z (ESI+) $(M+H)^+$ = 256; HPLC t_R = 1,97 min.

Producto Intermedio D1: ácido (2R)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-isopropoxipropanoico

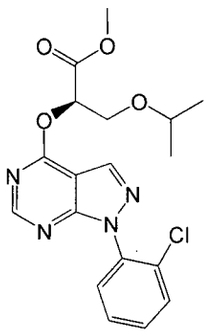


Etapa 1: Síntesis de D1a: (R)-metil 2-hidroxi-3-isopropoxipropanoato



D1a se preparó en una forma análoga al **C4a** a partir de (R)-metil oxirano-2-carboxilato (CAS 111058-32-3) e isopropanol. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,12 - 1,16 (6H, m), 3,04 - 3,06 (1H, m), 3,58 - 3,64 (1H, m), 3,68 - 3,75 (2H, m), 3,80 (3H, s), 4,29 - 4,32 (1H, m)

Etapa 2: Síntesis de D1b: (2R)-metil 2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-isopropoxipropanoato

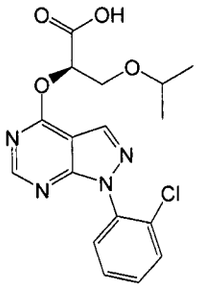


Se suspendieron (R)-metil 2-hidroxi-3-isopropoxipropanoato **D1a** (500 mg, 3,08 mmol), 4-cloro-1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidina **B1** (817 mg, 3,08 mmol) y carbonato de potasio (0,186 mL, 3,08 mmol) en acetonitrilo (15 mL). La reacción se calentó hasta alcanzar 130°C durante 4 horas en el reactor de microondas y se enfrió hasta alcanzar la temperatura ambiente. La mezcla de reacción se evaporó hasta secarse y el residuo resultante se disolvió en EtOAc (25 mL) y se lavó secuencialmente con NH_4Cl saturado (50 mL) y salmuera saturada (50 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar el producto bruto. La purificación mediante cromatografía instantánea en sílice, gradiente de elución 20 a 50% EtOAc en isohexano proporcionó (2R)-metil 2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-isopropoxipropanoato **D1b** (965 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,22 - 1,26 (6H, m), 3,71 - 3,79 (1H, m), 3,80 (3H, s), 4,01 - 4,06 (2H, m), 5,79 - 5,81 (1H, m), 7,44 - 7,54 (3H, m), 7,61 - 7,63 (1H, m), 8,38 (1H, s), 8,54 (1H, s), m/z (ESI+) (M+H)+ = 391; HPLC t_R = 2,51 min.

Etapa 3: Síntesis de D1: ácido (2R)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-

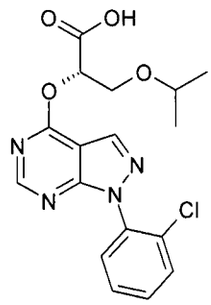
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iloxi)-3-isopropoxipropanoico

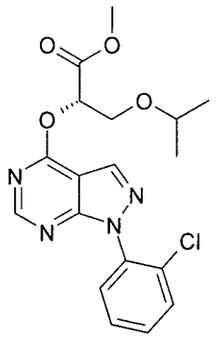


Se agregó hidróxido de sodio (0,755 mL, 1,51 mmol) a una solución de (2P)-metil 2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-isopropoxipropanoato **D1b** (472 mg, 1,21 mmol) en THF (7 mL) y agua (3,5 mL) a temperatura ambiente. La mezcla de reacción se agitó durante 1 hora. La mezcla de reacción se diluyó con EtOAc (50 mL) y se acidificó hasta alcanzar pH 4 con HCl 2M. La capa orgánica se separó y la capa acuosa se extrajo con EtOAc (2 x 50 mL). Los elementos orgánicos combinados se secaron sobre $MgSO_4$, se filtraron y se concentraron para proporcionar **D1** (325 mg, 70% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,21 - 1,25 (6H, m), 3,73 - 3,81 (1H, m), 4,05 - 4,08 (2H, m), 5,82 - 5,84 (1H, m), 7,42 - 7,54 (3H, m), 7,58 - 7,61 (1H, m), 8,38 (1H, s), 8,57 (1H, s), m/z (ESI+) $(M+H)^+$ = 377; HPLC t_R = 2,15 min.

Producto Intermedio D2: ácido (2S)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-isopropoxipropanoico

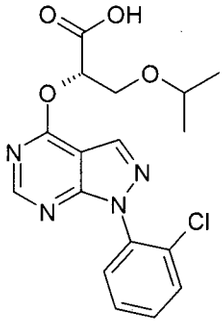


Etapa 1: Síntesis de D2a: (2S)-metil 2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-isopropoxipropanoato



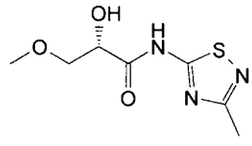
D2a se preparó en una forma análoga al **D1b** a partir de (S)-metil 2-hidroxi-3-isopropoxipropanoato **C7a** y **B1**. ^{1}H NMR δ_H(400 MHz, $CDCl_3$) 1,20 - 1,26 (6H, m), 3,71 - 3,75 (1H, m), 3,80 (3H, s), 4,01 - 4,08 (2H, m), 5,79 - 5,82 (1H, m), 7,43 - 7,50 (2H, m), 7,51 - 7,54 (1H, m), 7,60 (1H t, J = 1,6 Hz), 8,37 (1H, s), 8,54 (1H, s), m/z (ESI+) (M+H)+ = 391; HPLC t_R = 2,42 min

Etapa 2: Síntesis de D2: ácido (2S)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-isopropoxipropanoico



D2 se preparó en una forma análoga al **D1** a partir de (2S)-metil 2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-isopropoxipropanoato **D2a**. 60% ee.
δ_H(400 MHz, $CDCl_3$) 1,22 - 1,26 (6H, m), 3,75 - 3,81 (1H, m), 4,04 - 4,10 (2H, m), 5,83 - 5,86 (1H, m), 7,43 - 7,54 (3H, m), 7,59 - 7,62 (1H, m), 8,38 (1H, s), 8,57 (1H, s), m/z (ESI+) (M+H)+ = 377; HPLC t_R = 2,12 min.

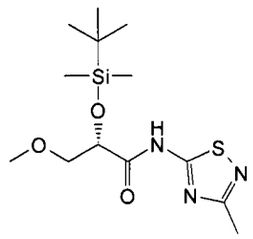
Producto Intermedio E1: (S)-2-hidroxi-3-metoxi-N-(3-metil-1,2,4-tiadiazol-5-il)propanamida



Una solución de fluoruro de tetrabutilamonio (1M en THF) (2,353 mL, 2,35 mmol) se

agregó en una porción a una solución agitada de (S)-2-(terc-butildimetilsililoxi)-3-metoxi-N-(3-metil-1,2,4-tiadiazol-5-il)propanamida (**Producto Intermedio E2**) (390 mg, 1,18 mmol) en tetrahidrofurano (10 mL). La solución resultante se agitó a temperatura ambiente durante 4 horas. La mezcla de reacción se diluyó con EtOAc (20 mL) y se lavó secuencialmente con agua (10 mL) y salmuera saturada (10 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó. El residuo se purificó mediante cromatografía instantánea en sílice, gradiente de elución 0 a 100% EtOAc en isohexano para proporcionar (S)-2-hidroxi-3-metoxi-N-(3-metil-1,2,4-tiadiazol-5-il)propanamida (192 mg, 75 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2,49 (3H, s), 3,37 (3H, s), 3,60 (1H, d), 3,72 (2H, d), 4,46 (1H, q), 10,20 (1H, s); m/z (ESI+) $(M+H)^+$ = 218,30; HPLC t_R = 0,89 min.

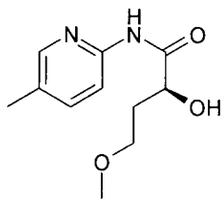
Producto Intermedio E2: (S)-2-(terc-butildimetilsililoxi)-3-metoxi-N-(3-metil-1,2,4-tiadiazol-5-il)propanamida



Una solución de 1-cloro-N,N,2-trimetilprop-1-en-1-amina (1,521 mL, 11,50 mmol) en DCM (2 mL) se agregó gota a gota a una solución agitada de ácido (S)-2-(terc-butildimetilsililoxi)-3-metoxipropanoico (**Producto Intermedio C4c**) (2,45 g, 10,45 mmol) en DCM (10 mL) durante un período de 1 minuto bajo nitrógeno. La solución color amarillo claro resultante se agitó a temperatura ambiente durante 30 minutos. Se agregó piridina anhidra (1,262 mL, 15,68 mmol) en una porción (la solución se volvió de un color amarillo más intenso) y luego 3-metil-1,2,4-tiadiazol-5-amina (CAS no. 17467-35-5) (1,204 g, 10,45 mmol) en DCM (3 mL) gota a gota durante un período de 1 minuto. La solución resultante se agitó a temperatura ambiente durante 1 hora. Se agregó ácido cítrico 1M (50 mL) y se extrajo con EtOAc (50 mL). La fase orgánica se lavó con agua (25 mL) y salmuera (25 mL), se secó ($MgSO_4$), se filtró y se evaporó. El residuo se purificó mediante cromatografía instantánea en sílice, gradiente de elución 0 a 30% EtOAc en isohexano para proporcionar (S)-2-(terc-butildimetilsililoxi)-3-metoxi-N-(3-metil-1,2,4-tiadiazol-5-il)propanamida (390 mg, 11%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0,11 (6H, dd), 0,89 (9H, s), 2,49 (3H, s), 3,30 (3H, s), 3,61 (2H, t), 4,46 (1H, dd), 9,75 - 9,90 (1H, s); m/z (ESI+)

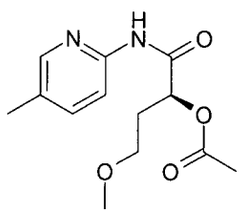
(M+H)+ = 332,30; HPLC t_R = 2,77 min.

Producto Intermedio F1: (S)-2-hidroxi-4-metoxi-N-(5-metilpiridin-2-il)butanamida



Se agregó carbonato de potasio acuoso 1M (5,257 mL, 5,26 mmol) a una solución de (S)-4-metoxi-1-(5-metilpiridin-2-ilamino)-1-oxobutan-2-il acetato (**Producto Intermedio F2**) (170 mg, 0,64 mmol) en MeOH (0,3 mL) a 0°C y la mezcla se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se neutralizó con $KHSO_4$ acuoso (1,0 M, 0,29 mL). La mezcla de reacción se concentró y el residuo se purificó mediante cromatografía instantánea en sílice, gradiente de elución 0 a 100% EtOAc en isohexano, para proporcionar (S)-2-hidroxi-4-metoxi-N-(5-metilpiridin-2-il)butanamida (142 mg, 99 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2,02 - 2,11 (1H, m), 2,23 - 2,26 (1H, m), 2,30 (3H, s), 3,38 (3H, s), 3,64 - 3,75 (2H, m), 4,38 - 4,41 (1H, m), 4,64 - 4,78 (1H, m), 7,51 - 7,53 (1H, m), 8,13 (2H, t), 9,30 (1H, s); m/z (ESI+) (M+H)+ = 225; HPLC t_R = 0,86 min.

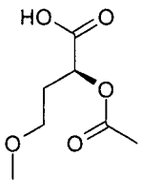
Producto Intermedio F2: (S)-4-metoxi-1-(5-metilpiridin-2-ilamino)-1-oxobutan-2-il acetato



Se agregó 5-metilpiridin-2-amina (CAS no. 1603-41-4) (460 mg, 4,26 mmol) a ácido (S)-2-acetoxi-4-metoxibutanoico (**Producto Intermedio F3**) (500 mg, 2,84 mmol) en THF (8 mL) bajo nitrógeno. La suspensión resultante se agitó a 23°C durante 30 minutos. Se agregó hidrato de cloruro de 4-(4,6-dimetoxi[1,3,5]triazin-2-il)-4-metilmorfolinio (CAS no. 3945-69-5) (1,18 g, 4,26 mmol) y la suspensión se agitó durante 40 hrs. La mezcla de reacción se concentró y se purificó mediante cromatografía instantánea en sílice, gradiente de elución 0 a 50% EtOAc en isohexano para proporcionar (S)-4-metoxi-1-(5-metilpiridin-2-ilamino)-1-oxobutan-2-il acetato (410 mg, 54 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2,13 - 2,28 (5H, m), 2,30 (3H, s), 3,31 (3H, s), 3,48 - 3,53 (2H, m), 5,37 - 5,40 (1H, m), 7,50 -

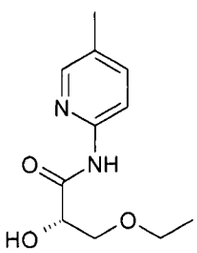
7,53 (1H, m), 8,09 - 8,11 (2H, m), 8,52 (1H, s); m/z (ESI+) $(M+H)^+$ = 267; HPLC t_R = 1,22 min.

Producto Intermedio F3: Ácido (S)-2-acetoxi-4-metoxibutanoico



Se agregó nitrato de sodio (4,93 g, 57,98 mmol) en porciones a ácido (S)-2-amino-4-metoxibutanoico (CAS no. 3311-01-1) (3,86 g, 29,0 mmol) en ácido acético (88 mL) a temperatura ambiente (con enfriamiento intermitente con un baño de hielo para mantener la temperatura cercana a la temperatura ambiente). Una vez que se completó la adición, la mezcla se dejó agitar a temperatura ambiente durante 24 h. El disolvente luego se eliminó al vacío, el residuo se disolvió en éter (250 mL) y la solución etérea se lavó con agua (3 × 100 mL). La capa orgánica se extrajo con solución de $NaHCO_3$ saturada (3 × 100 mL). Los extractos acuosos luego se acidificaron con HCl 2N y se extrajeron con éter (3 × 100 mL). Las capas orgánicas combinadas se secaron ($MgSO_4$) y se redujeron al vacío para proporcionar ácido (S)-2-acetoxi-4-metoxibutanoico bruto (0,600 g, 11,8 %) que se utilizó sin purificación adicional.

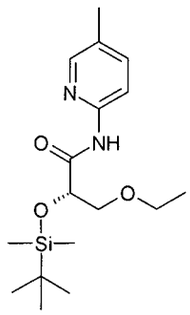
Producto Intermedio G1: (2S)-3-Etoxi-2-hidroxi-N-(5-metilpiridin-2-il)propanamida



Una solución de fluoruro de tetrabutilamonio (1M en THF) (3,25 mL, 3,25 mmol) se agregó en una porción a una solución agitada de (S)-2-(terc-butildimetilsililoxi)-3-etoxi-N-(5-metilpiridin-2-il)propanamida (**Producto Intermedio G2**) (1,1 g, 3,25 mmol) en tetrahidrofurano (25 mL). La solución resultante se agitó a temperatura ambiente durante 4 horas. La mezcla de reacción se concentró y se diluyó con EtOAc (50 mL), se lavó secuencialmente con agua (20 mL) y salmuera saturada (20 mL). La capa orgánica se secó ($MgSO_4$) y se evaporó. El residuo se purificó mediante cromatografía instantánea en sílice, gradiente de elución 50 a 100% EtOAc en isohexano, para proporcionar (2S)-3-etoxi-2-

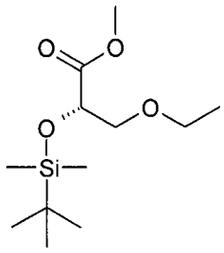
hidroxi-N-(5-metilpiridin-2-il)propanamida (730mg, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,24 (3H, t), 2,30 (3H, s), 3,60 (2H, q), 3,76 - 3,79 (2H, m), 3,87 (1H, s), 4,33-4,38 (1H, m), 7,52 (1H, dd), 8,11 - 8,13 (2H, m), 9,20 (1H, s); m/z (ESI+) (M+H)+ = 225; HPLC t_R = 0,96 min.

Producto Intermedio G2: (2S)-2-(terc-butil-dimetilsilil)oxi-3-etoxi-N-(5-metilpiridin-2-il)propanamida



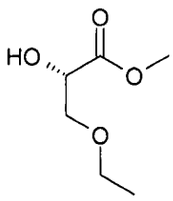
Una solución de trimetilaluminio (2M en hexano, 2,75 mL, 5,49 mmol) se agregó gota a gota a una solución agitada de 5-metilpiridin-2-amina (0,594 g, 5,49 mmol) en tolueno (10 mL) enfriado hasta alcanzar 0°C, durante un período de 5 minutos bajo nitrógeno. La solución resultante se agitó durante 15 minutos. Se agregó una solución de (S)-metil 2-(terc-butildimetilsililoxi)-3-etoxipropanoato (**Producto Intermedio G3**) (1,31 g, 4,99 mmol) en tolueno (5 mL) gota a gota durante un período de 2 minutos. La solución resultante se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó hasta alcanzar reflujo durante 7 horas, luego se dejó enfriar hasta alcanzar la temperatura ambiente y se agregó ácido cítrico 1M (20 mL), se diluyó con agua (25 mL) y la mezcla se extrajo con acetato de etilo (25 mL). La capa acuosa se extrajo nuevamente con acetato de etilo (25 mL), las fases orgánicas se combinaron, se lavaron con agua (5 mL) y salmuera (20 mL), se secaron sobre $MgSO_4$, se filtraron y se evaporaron. El residuo se purificó mediante cromatografía instantánea en sílice, gradiente de elución 10 a 100% EtOAc en isohexano para proporcionar (2S)-2-(terc-butil-dimetilsilil)oxi-3-etoxi-N-(5-metilpiridin-2-il)propanamida (1,1 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0,18 (3H, s), 2,00 (3H, s), 0,99 (9H, s), 1,18 (3H, t), 2,30 (3H, s), 3,51 - 3,61 (2H, m), 3,63 - 3,67 (1H, m), 3,78 - 3,81 (1H, m), 4,41 - 4,43 (1H, m), 7,51 (1H, dd), 8,13 - 8,18 (2H, m), 9,03 (1H, s); m/z (ESI+) (M+H)+ = 339; HPLC t_R = 3,31 min.

Producto Intermedio G3: Metil (2S)-2-(terc-butil-dimetilsilil)oxi-3-etoxipropanoato



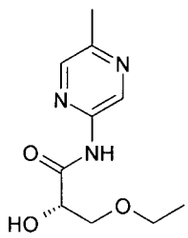
Una solución de terc-butilclorodimetilsilano (17,71g, 117,52mmol) en DMF seco (50 mL) se agregó gota a gota a una solución agitada de (S)-metil 2-hidroxi-3-etoxipropanoato (14,51g, 97,94 mmol) y 1H-imidazol (13,33g, 195,87 mmol) en DMF seco (70 mL) a 20°C, durante un período de 2 minutos. La solución resultante se agitó a temperatura ambiente durante 20 horas. La mezcla de reacción se concentró y se diluyó con EtOAc (500 mL), se lavó secuencialmente con agua (4 × 100 mL) y salmuera saturada (100 mL). La capa orgánica se secó ($MgSO_4$) y se evaporó. El residuo se purificó mediante cromatografía instantánea en sílice, gradiente de elución 20 a 50% EtOAc en isohexano, para proporcionar metil (2S)-2-(terc-butil-dimetilsilil)oxi-3-etoxipropanoato (14,8g, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0,10 (6H, d), 0,93 (9H, s), 1,19 (3H, t), 3,50 - 3,65 (3H, m), 3,57 - 3,73 (1H, m), 3,75 (3H, s), 4,37 - 4,40 (1H, m), 7,18 (2H, d).

Producto Intermedio G4: Metil (2S)-3-etoxi-2-hidroxipropanoato



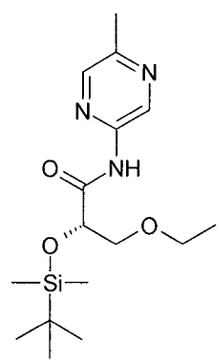
Se agregó trifluorometanosulfonato de magnesio (11,85 g, 36,73 mmol) en una porción a (S)-metil oxirano-2-carboxilato (15,0 g, 146,93 mmol) y etanol (10,29 ml, 176,32 mmol) enfriado hasta alcanzar 10°C. La suspensión resultante se agitó a 10°C durante 20 minutos, se dejó entibiar hasta alcanzar la temperatura ambiente y luego se entibió hasta alcanzar 50°C durante 30 horas. La mezcla se dejó enfriar y se diluyó con 9:1 DCM:éter (75 mL), se filtró a través de Celite y se lavó con 9:1 DCM:éter (3 × 50 mL) y se evaporó. El residuo se purificó mediante cromatografía instantánea en sílice, gradiente de elución 10 a 50% Et_2O en DCM, para proporcionar metil (2S)-3-etoxi-2-hidroxipropanoato (11,6 g, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,19 (3H, t), 3,00 (1H, d), 3,47 - 3,58 (2H, m), 3,72 (2H, d), 3,81 (3H, s), 4,23 - 4,34 (1H, m).

Producto Intermedio H1: (2S)-3-etoxi-2-hidroxi-N-(5-metilpirazin-2-il)propanamida



Una solución de fluoruro de tetrabutilamonio (1M en THF) (4,27 mL, 4,27 mmol) se agregó en una porción a una solución agitada de (S)-2-(terc-butildimetilsililoxi)-3-etoxi-N-(5-metilpirazin-2-il)propanamida (**Producto Intermedio H2**) (1,45 g, 4,27 mmol) en tetrahidrofurano (25 mL). La solución resultante se agitó a temperatura ambiente durante 4 horas. La mezcla de reacción se concentró y se diluyó con EtOAc (50 mL) y se lavó secuencialmente con agua (20 mL) y salmuera saturada (20 mL). La capa orgánica se secó ($MgSO_4$) y se evaporó. El residuo se purificó mediante cromatografía instantánea en sílice eluyendo con 50% a 100% EtOAc en isohexano para proporcionar (2S)-3-etoxi-2-hidroxi-N-(5-metilpirazin-2-il)propanamida (700mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,24 (3H, t), 2,54 (3H, s), 3,49 (1H, d), 3,61 (2H, q), 3,75 - 3,83 (2H, m), 4,35 - 4,39 (1H, m), 8,14 (1H, d), 9,13 (1H, s), 9,43 (1H, d); m/z (ESI+) (M+H)+ = 226; HPLC t_R = 1,00 min.

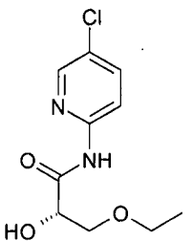
Producto Intermedio H2: (2S)-2-(terc-butil-dimetilsilil)oxi-3-etoxi-N-(5-metilpirazin-2-il)propanamida



Una solución de trimetilaluminio (2M en hexano, 5,51 mL, 11,02 mmol) se agregó gota a gota a una solución agitada de 5-metilpirazin-2-amina (CAS no. 5521-58-4) (1,20 g, 11,0 mmol) en tolueno (20 mL) enfriado hasta alcanzar 0°C, durante un período de 5 minutos bajo nitrógeno. La solución resultante se agitó durante 15 minutos. Una solución de (S)-metil 2-(terc-butildimetilsililoxi)-3-etoxipropanoato (**Producto Intermedio G3**) (2,63 g, 10,0 mmol) en tolueno (5 mL) se agregó gota a gota durante un período de 2 minutos. La

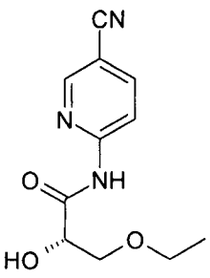
solución resultante se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó hasta alcanzar reflujo durante 3 horas. Se agregaron solución de tartrato de potasio y sodio al 20% (50 mL) y luego agua (25 mL) y la mezcla se extrajo con acetato de etilo (25 mL). La capa acuosa se extrajo nuevamente con acetato de etilo (25 mL). Las fases orgánicas se combinaron, se lavaron con agua (5 mL) y salmuera (20 mL), se secaron ($MgSO_4$) y se evaporaron. El residuo se purificó mediante cromatografía instantánea en sílice, gradiente de elución 20 a 100% EtOAc en isohexano para proporcionar (2S)-2-(terc-butil-dimetilsilil)oxi-3-etoxi-N-(5-metilpirazin-2-il)propanamida (1,45g, 42%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0,18 (3H, s), 0,20 (3H, s), 0,98 (9H, s), 1,20 (3H, t), 2,54 (3H, s), 3,50 - 3,59 (2H, m), 3,65 - 3,69 (1H, m), 3,77 - 3,80 (1H, m), 4,42 - 4,44 (1H, m), 8,14 (1H, d), 9,01 (1H, s), 9,44 (1H, d); m/z (ESI+) $(M+H)^+$ = 340; HPLC t_R = 3,04 min.

Producto Intermedio H3: (S)-N-(5-cloropiridin-2-il)-3-etoxi-2-hidroxipropanamida



Se preparó utilizando procedimientos análogos a los descritos para **G1 y G2,** utilizando 5-cloropiridina-2-amina (CAS no. 1072-98-6) y el **Producto Intermedio G3**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,24 (3H t), 3,57 - 3,64 (3H, m), 3,74 - 3,81 (2H, m), 4,34 - 4,36 (1H, m), 7,66 - 7,69 (1H, m), 8,21 - 8,23 (1H, m), 9,27 (1H, s); m/z (ESI+) $(M+H)^+$ = 245; HPLC t_R = 1,63 min.

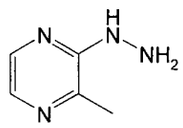
Producto Intermedio H4: (S)-N-(5-cianopiridin-2-il)-3-etoxi-2-hidroxipropanamida



Se preparó utilizando un procedimiento análogo al descrito para **G1** y **G2**, utilizando el **Producto Intermedio G3** y 2-amino-5-cianopiridina. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,24 (3H, t), 3,38 (1H, d), 3,61 (2H, q), 3,73 - 3,84 (2H, m), 4,37 (1H, q), 7,92 - 7,98 (1H, m), 8,35 - 8,40 (1H, m), 8,56 - 8,61 (1H, m), 9,44 (1H, s);

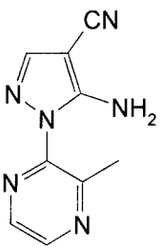
m/z (ES+) (M+H)+ = 236,35; HPLC tR = 1,28 min.

Producto Intermedio I1: 2-Hidrazinil-3-metilpirazina



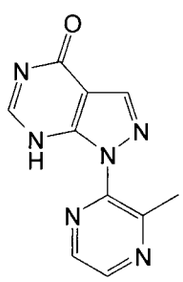
Se agregó hidrato de hidrazina (9,66 mL, 311,14 mmol) a 2-cloro-3-metilpirazina (CAS no. 95-58-9) (8 g, 62,23 mmol) en etanol (25 mL). La solución resultante se agitó a 90°C durante 16 horas. La solución resultante se evaporó hasta secarse y el producto bruto se purificó mediante cristalización a partir de tolueno (125 mL) para proporcionar 2-hidrazinil-3-metilpirazina (6,2 g, 80%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2,24 (3H, s), 7,61 (1H, d), 7,87 (1H, d).

Producto Intermedio I2: 5-Amino-1-(3-metilpirazin-2-il)-1H-pirazol-4-carbonitrilo



Se preparó en una forma análoga al **B15a** a partir de 2-hidrazinil-3-metilpirazina (**Producto Intermedio I1**). ^{1}H NMR (400 MHz, DMSO-d_6) 2,45 (3H, s), 7,84 (1H, s), 8,48 - 8,49 (1H, m), 8,66 (1H, d), m/z (ESI+) (M+H)+ = 201 ; HPLC t_R = 1,04 min.

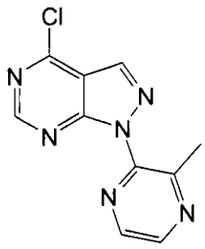
Producto Intermedio I3: 1-(3-metilpirazin-2-il)-1H-pirazolo[3,4-d]pirimidin-4(7H)-ona



Se preparó en una forma análoga al **B15b** a partir de 5-amino-1-(3-metilpirazin-2-il)-1H-pirazol-4-carbonitrilo (**Producto Intermedio I2**). ^{1}H NMR (400 MHz, DMSO-d_6) 2,40 (3H, s), 8,12 - 8,13 (1H, m), 8,41 (1H, s), 8,62 (1H, d), 8,80 (1H, d), 12,45 (1H, s); m/z (ESI+) (M+H)+ = 229; HPLC t_R = 0,85 min.

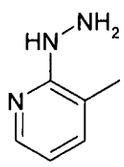
Producto Intermedio I4 : 4-Cloro-1-(3-metilpirazin-2-il)-1H-pirazolo[3,4-

d]pirimidina



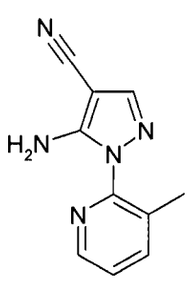
Se preparó en una forma análoga al **Producto Intermedio B15** a partir de 1-(3-metilpirazin-2-il)-1H-pirazolo[3,4-d]pirimidin-4(7H)-ona (**Producto Intermedio I3**). ^{1}H NMR (400 MHz, DMSO-d_6) 2,43 (3H, s), 8,64 - 8,65 (1H, m), 8,84 (2H, t), 8,93 (1H, s); m/z (ESI+) $(M+H)^+$ = 247 ; HPLC t_R = 1,38min.

Producto Intermedio J1: 2-Hidrazinil-3-metilpiridina



Se mezclaron 2-bromo-3-metilpiridina (5,16 g, 30,00 mmol) e hidrato de hidrazina (10,92 mL, 224,97 mmol). La reacción se calentó hasta alcanzar 110°C durante 20 horas con agitación. La mezcla se enfrió hasta alcanzar la temperatura ambiente durante lo cual se precipitó un sólido. Esto luego se recogió por filtración, se lavó con éter (3 × 10 mL), se suspendió en DCM (50 mL), se agitó durante 10 minutos y luego se pasó a través de un cartucho de separación de fases para eliminar agua. Los licores orgánicos se evaporaron y se secaron al alto vacío para proporcionar 2-hidrazinil-3-metilpiridina (2,5 g, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2,08 (3H, s), 4,02 (2H, s), 5,50 (1H, s), 6,64 (1H, dd), 7,20 - 7,30 (1H, m), 8,08 (1H, dd). MP = 119°C (Lit 122°C).

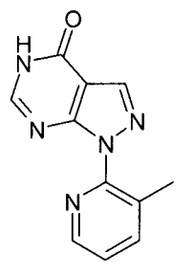
Producto Intermedio J2: 5-Amino-1-(3-metilpiridin-2-il)-1H-pirazol-4-carbonitrilo



Se preparó en una forma análoga al **B15a** a partir de 2-hidrazinil-3-metilpiridina

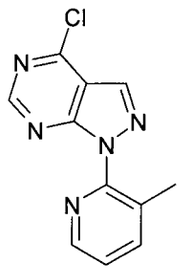
(**Producto Intermedio J1**). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2,23 (3H, s), 6,82 (2H, s), 7,42 - 7,45 (1H, m), 7,78 (1H, s), 7,88 - 7,90 (1H, m), 8,38 - 8,39 (1H, m). m/z (ESI+) (M+H)+ = 200; HPLC t_R = 1,14 min.

Producto Intermedio J3: 1-(3-metilpiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4(7H)-ona



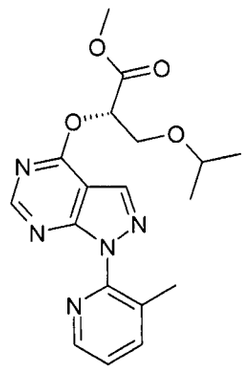
Se preparó en una forma análoga al **B15b** a partir de 5-amino-1-(3-metilpiridin-2-il)-1H-pirazol-4-carbonitrilo (**Producto Intermedio J2**). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2,08 (3H, s), 7,53 - 7,56 (1H, m), 7,94 - 7,97 (1H, d), 8,05 (1H, s), 8,31 (1H, s), 8,46 - 8,47 (1H, m), 12,34 (1H, s). m/z (ESI+) (M+H)+ = 228; HPLC t_R = 0,92 min.

Producto Intermedio J4: 4-Cloro-1-(3-metilpiridin-2-il)-1H-pirazolo[3,4-d]pirimidina



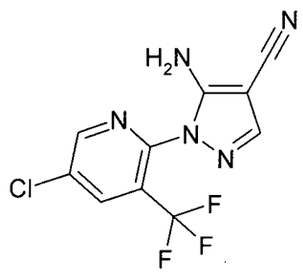
Se preparó en una forma análoga al **B15** a partir de 1-(3-metilpiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4(7H)-ona (**Producto Intermedio J3**). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2,12 (3H, s), 7,59 - 7,62 (1H, m), 8,00 - 8,03 (1H, m), 8,50 - 8,52 (1H, m), 8,76 (1H, s), 8,88 (1H, s). m/z (ESI+) (M+H)+ = 246; HPLC t_R = 1,51 min.

Producto Intermedio J5: (2S)-Metil 3-isopropoxi-2-(1-(3-metilpiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanoato



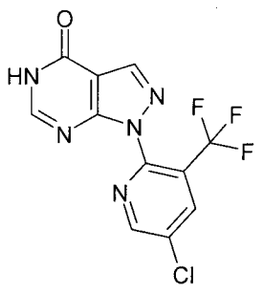
Se agregó hidruro de sodio al 60% (0,720 g, 18,00 mmol) a una solución de (S)-Metil 2-hidroxi-3-isopropoxipropanoato (2,353 g, 12,00 mmol) en THF anhidro (100 mL) a 5°C, bajo nitrógeno. La suspensión resultante se agitó a 5°C durante 10 minutos y luego se agregó una solución de 4-cloro-1-(3-metilpiridin-2-il)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio J4**) (2,95 g, 12 mmol) en THF seco (50 mL) gota a gota, manteniendo una temperatura por debajo de 5°C. La mezcla de reacción se agitó a 5°C durante 10 mins y luego se dejó entibiar hasta alcanzar la temperatura ambiente. La reacción se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se neutralizó con HCl (1M, ac). La mayor parte del THF se evaporó al vacío y luego se agregaron EtOAc (75 mL) y agua (50 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc (2 x 50 mL). Los elementos orgánicos combinados se lavaron con salmuera saturada (50 mL), se secaron ($MgSO_4$), se filtraron y se concentraron al vacío. El producto bruto se purificó mediante cromatografía instantánea en sílice (120 g), gradiente de elución 30 a 80% EtOAc en isohexano para proporcionar (2S)-Metil 3-isopropoxi-2-(1-(3-metilpiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanoato (3,53 g, 79%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1,11 - 1,14 (6H, m), 2,11 (3H, s), 3,68 - 3,74 (4H, m), 3,95 - 4,03 (2H, m), 5,79 - 5,81 (1H, m), 7,56 - 7,59 (1H, dd), 7,98 - 8,00 (1H, d), 8,49 (1H, m), 8,57 (2H, d). m/z (ESI+) $(M+H)^+$ = 372; HPLC t_R = 1,99 min.

Producto Intermedio K1: 5-Amino-1-(5-cloro-3-(trifluorometil)piridin-2-il)-1H-pirazol-4-carbonitrilo



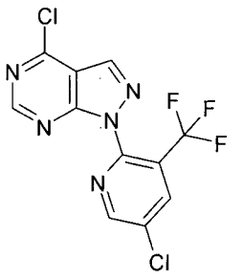
Se preparó en una forma análoga al **B15a** a partir de 5-cloro-2-hidrazinil-3-(trifluorometil)piridina (CAS no. 129015-69-6). ^{1}H NMR (400 MHz, DMSO) δ 6,87 (2H, s), 7,69 (1H, s), 8,58 (1H, d), 8,83 (1H, d).

Producto Intermedio K2: 1-(5-Cloro-3-(trifluorometil)piridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-ol



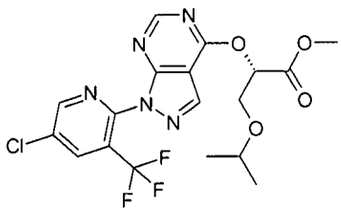
Se preparó en una forma análoga al **B15b** a partir de 5-amino-1-(5-cloro-3-(trifluorometil)piridin-2-il)-1H-pirazol-4-carbonitrilo (**Producto Intermedio K1**). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8,10 (1H, s), 8,39 (1H, s), 8,80 (1H, d), 9,05 (1H, d), 12,49 (1H, s). m/z (ESI+) (M+H)+ = 316; HPLC t_R = 1,48 min.

Producto Intermedio K3: 4-Cloro-1-(5-cloro-3-(trifluorometil)piridin-2-il)-1H-pirazolo[3,4-d]pirimidina



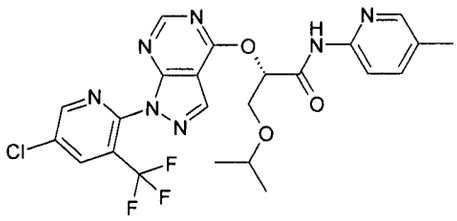
Se preparó en una forma análoga al **B15** a partir de 1-(5-cloro-3-(trifluorometil)piridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-ol (**Producto Intermedio K2**). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8,88 - 8,88 (1H, m), 8,95 (1H, s), 9,10 (1H, d), 9,48 (1H, s). m/z (ESI+) (M+H)+ = 334; HPLC t_R = 2,32 min. (93%)

Producto Intermedio K4: (2S)-Metil 2-(1-(5-cloro-3-(trifluorometil)piridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-isopropoxipropanoato



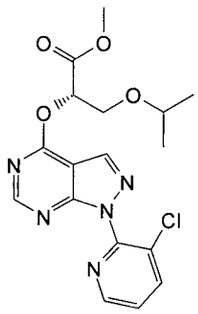
Se preparó en una forma análoga al **J5** a partir de 4-cloro-1-(5-cloro-3-(trifluorometil)piridin-2-il)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio K3**). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1,10 - 1,14 (6H, m), 3,67 - 3,74 (4H, m), 3,96 - 4,01 (2H, m), 5,80 - 5,82 (1H, m), 8,60 (1H, s), 8,67 (1H, s), 8,83 (1H, d), 9,09 (1H, d). m/z (ESI+) (M+H)+ = 460; HPLC t_R = 2,65 min.

Producto Intermedio K6: (2S)-2-(1-(5-Cloro-3-(trifluorometil)piridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-isopropoxi-N-(5-metilpiridin-2-il)propanamida



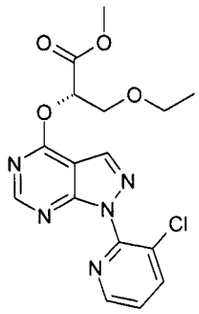
Se preparó en una forma análoga al **Ejemplo 125** a partir de (2S)-metil 2-(1-(5-cloro-3-(trifluorometil)piridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-isopropoxipropanoato (**Producto Intermedio K4**). ^{1}H NMR (400 MHz, DMSO) δ 1,10 - 1,12 (6H, m), 2,24 (3H, s), 3,72 - 3,78 (1H, m), 3,95 - 4,07 (2H, m), 5,89 (1H, s), 7,58 (1H, d), 7,87 (1H, d), 8,17 (1H, s), 8,57 (1H, s), 8,68 (1H, s), 8,83 (1H, d), 9,08 (1H, d), 10,81 (1H, s); m/z (ESI+) (M+H)+ = 536; HPLC t_R = 2,72 min.

Producto Intermedio L1: (2S)-Metil 2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-isopropoxipropanoato



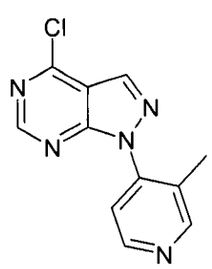
Se agregó hidruro de sodio (1,84 g, 45,9 mmol) a una solución agitada de (S)-metil 2-hidroxi-3-isopropoxipropanoato (**Producto Intermedio C7a**) (6,0 g, 30,6 mmol) en THF anhidro (200 mL) a 0°C, bajo nitrógeno. La suspensión resultante se agitó a 0°C durante 10 minutos y luego se agregó una solución de 4-cloro-1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio B15**) (8,14 g, 30,59 mmol) en THF seco (50 mL) gota a gota, manteniendo la temperatura por debajo de 5°C. La mezcla de reacción se agitó a 0°C durante 10 minutos. Luego se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 1 hora. La mezcla de reacción se neutralizó con HCl 1M. La mayor parte del THF se evaporó al vacío y luego se agregó EtOAc (100 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc (2 × 100 mL). Los elementos orgánicos combinados se lavaron con salmuera saturada (75 mL), se secaron ($MgSO_4$) y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 20 a 70% EtOAc en isohexano para proporcionar (2S)-metil 2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-isopropoxipropanoato (7,76 g, 64,8 %), ee 53%. Una muestra de esto (1,48 g) se purificó mediante HPLC quiral preparativa en una columna Chiralcel OJ, 50mm 20um, eluyendo con 30% isopropanol en isohexano (modificado con TEA al 0,1%), para proporcionar (2S)-metil 2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-isopropoxipropanoato (1,03 g, 99% ee). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1,10 - 1,14 (6H, m), 3,68-3,75 (4H, m), 3,98 - 4,00 (2H, m), 5,80 - 5,82 (1H, m), 7,74 - 7,77 (1H, m), 8,33 - 8,35 (1H, d), 8,59 (1H, s), 8,64 (1H, s), 8,67 - 8,68 (1H, m); m/z (ESI+) (M+H)+ = 392; HPLC t_R = 2,13 min.

Producto Intermedio L2 : Metil (2S)-2-[1-(3-cloropiridin-2-il)pirazolo[4,5-e]pirimidin-4-il]oxi-3-etoxipropanoato



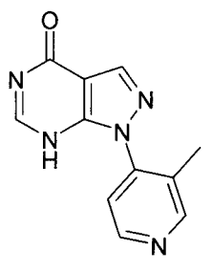
Se agregó hidruro de sodio al 60% en aceite mineral (0,96 g, 24,1 mmol) en porciones a (S)-metil 3-etoxi-2-hidroxipropanoato (**Producto Intermedio G4**) (2,97 g, 20,1 mmol) en tetrahidrofurano (50 mL) enfriado hasta 0°C durante un período de 1 minuto bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos. Una solución de 4-cloro-1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio B15**) (5,87 g, 22,1 mmol) en tetrahidrofurano (50 mL) se agregó gota a gota durante un período de 2 minutos. La mezcla resultante se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 2 horas. La reacción se enfrió hasta alcanzar ~10°C, se agregó ácido cítrico 1M (20 mL) y la mezcla se extrajo con EtOAc (2 × 50 mL). Los extractos orgánicos se lavaron con agua (25 mL) y salmuera saturada (25 mL), se secaron sobre $MgSO_4$, se filtraron y se evaporaron. El residuo se purificó mediante cromatografía instantánea en sílice, gradiente de elución 50 a 100% EtOAc en isohexano para proporcionar el metil (2S)-2-[1-(3-cloropiridin-2-il)pirazolo[4,5-e]pirimidin-4-il]oxi-3-etoxipropanoato (5,7 g, 70% ee). Esto se purificó adicionalmente mediante HPLC quiral en Chiralcel OJ eluyendo con isohexano / isopropanol / trietilamina (70:30:0,1) a 60 mL / min. para proporcionar el producto enantioméricamente puro (3,8g, 50%) como una goma incolora. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,25 (3H, t), 3,60 - 3,73 (2H, m), 3,79 (3H, s), 4,00 - 4,11 (2H, m), 5,85 (1H, dd), 7,45 (1H, dd), 8,00 (1H, dd), 8,42 (1H, s), 8,58 (1H, s), 8,61 (1H, dd), m/z (ESI+) $(M+H)^+$ = 378; HPLC tR = 1,84 min.

Producto Intermedio M1: 4-Cloro-1-(3-metilpiridin-4-il)pirazolo[5,4-d]pirimidina



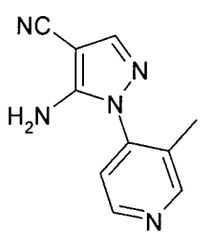
Se agregó tricloruro de fosforilo (7,59 mL, 79,2 mmol) a 1-(3-metilpiridin-4-il)-7H-pirazolo[4,5-e]pirimidin-4-ona (**Producto Intermedio M2**) (900 mg, 3,96 mmol) y la suspensión resultante se agitó a 100°C durante 24 horas, tiempo durante el cual se formó una solución. Esto se evaporó, se trituró con éter (3 × 10 mL) y se secó al vacío. El sólido resultante se suspendió en DCM (50 mL) y se agitó con 10 g de carbonato soportado por polímero durante 2 horas. La mezcla se filtró y se evaporó para proporcionar 4-cloro-1-(3-metilpiridin-4-il)pirazolo[5,4-d]pirimidina (700 mg, 72%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2,25 (3H, s), 7,62 (1H, d), 8,64 (1H, d), 8,74 (1H, s), 8,83 (1H, s), 8,94 (1H, s); m/z (ESI+) (M+H)+ = 246; HPLC t_R = 1,22 min.

Producto Intermedio M2: 1-(3-Metilpiridin-4-il)-7H-pirazolo[4,5-e]pirimidin-4-ona



Se agregó ácido sulfúrico concentrado (0,241 mL, 4,52 mmol) a una solución agitada de 5-amino-1-(3-metilpiridin-4-il)-1H-pirazol-4-carbonitrilo (**Producto Intermedio M3**) (900 mg, 4,52 mmol) en ácido fórmico (10 mL) y la solución resultante se agitó a 100°C durante 3 horas. La mezcla se enfrió y se evaporó hasta proporcionar ~la mitad del volumen, se agregó agua (10 mL) y se agitó. La mezcla se ajustó hasta alcanzar pH 3-4 con NaOH 2M y se agitó durante 1 hora. El sólido que se formó se recogió mediante filtración, se lavó con agua (2 × 7,5 mL), acetonitrilo (10 mL) y éter dietílico (2 × 10 mL) y se secó para proporcionar 1-(3-metilpiridin-4-il)-7H-pirazolo[4,5-e]pirimidin-4-ona (750mg, 71%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2,22 (3H, s), 7,51 (1H, d), 8,13 (1H, s), 8,38 (1H, s), 8,59 (1H, d), 8,68 (1H, s), 12,48 (1H, s), m/z (ESI+) (M+H)+ = 228; HPLC t_R = 0,73 min.

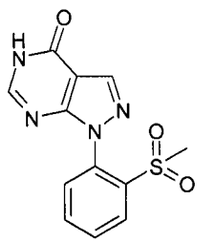
Producto Intermedio M3: 5-Amino-1-(3-metilpiridin-4-il)pirazol-4-carbonitrilo



Se suspendió 4-hidrazinil-3-metilpiridina (CAS no. 114913-51-8) (700 mg, 5,68 mmol) en

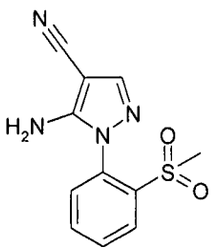
MeOH (30 mL) bajo nitrógeno a -5°C. Se agregó 2-(etoximetileno)malononitrilo (694 mg, 5,68 mmol) en porciones durante 2 min: y la mezcla se agitó a ~0°C durante 0,5 horas, luego se calentó a reflujo durante 2 horas. La mezcla se dejó enfriar y luego se evaporó bajo presión reducida para proporcionar el 5-amino-1-(3-metilpiridin-4-il)pirazol-4-carbonitrilo bruto que se utilizó sin purificación adicional. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2,09 (3H, m), 7,07 (1H, d), 7,87 (2H, m), 7,98 (1H, d), 10,22 (1H, s).

Producto Intermedio N1: 1-(2-(metilsulfonil)fenil)-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona



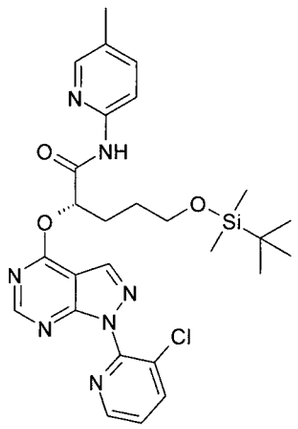
Se preparó en una forma análoga al **B15b** a partir de **N2**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3,36 (3H, s), 7,69 - 7,71 (1H, m), 7,85 - 7,89 (1H, m), 7,92 - 7,96 (1H, m), 8,06 - 8,07 (1H, m), 8,15 - 8,17 (1H, m), 8,33 (1H, s), 12,36 (1H, s). m/z (ESI+) $(M+H)^+$ = 291; HPLC t_R = 0,96 min.

Producto Intermedio N2: 5-Amino-1-(2-(metilsulfonil)fenil)-1H-pirazol-4-carbonitrilo



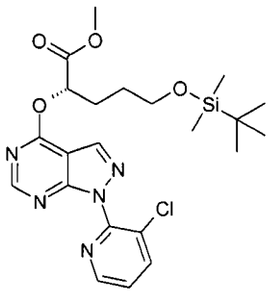
Se preparó en una forma análoga al **B15a** a partir de (2-metanosulfonil)fenilhidrazina (CAS no. 704-42-7). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3,26 (3H, s), 6,62 (2H, s), 7,53 - 7,55 (1H, m), 7,79 (1H, s), 7,79 - 7,83 (1H, m), 7,86 - 7,90 (1H, m), 8,09 - 8,12 (1H, m). m/z (ESI+) $(M+H)^+$ = 263; HPLC t_R = 1,11 min.

Producto Intermedio O1: (2S)-5-(terc-butil-dimetilsilil)oxi-2-[1-(3-cloropiridin-2-il)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-metilpiridin-2-il)pentanamida



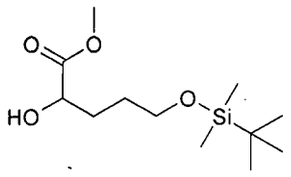
Una solución de trimetilaluminio (2M en hexano) (0,491 mL, 0,98 mmol) se agregó gota a gota a una solución agitada de 5-metilpiridin-2-amina (92 mg, 0,85 mmol) en tolueno (5 mL) enfriado a 0°C, durante un período de 1 minuto bajo nitrógeno. La solución resultante se agitó a 0°C durante 20 minutos. Una solución de (2S)-metil 5-(terc-butildimetilsililoxi)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)pentanoato (**Producto Intermedio O2**) (420 mg, 0,85 mmol) en tolueno (5 mL) se agregó gota a gota durante un período de 2 minutos. La solución resultante se agitó a 0°C durante 10 minutos se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó a 60°C durante 20 horas. La mezcla se enfrió y se agregó ácido cítrico 1M (10 mL) con agitación vigorosa. La mezcla se diluyó con acetato de etilo (35 mL), se lavó con agua (10 mL) y salmuera (10 mL), se secó ($MgSO_4$) y se evaporó. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 50 a 100% acetato de etilo en isohexano para proporcionar el producto (180mg, 37%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0,04 (3H, s), 0,05 (3H, s), 0,89 (9H, s), 1,78 - 1,81 (2H, m), 2,20 - 2,30 (2H, m), 2,29 (3H, s), 3,71 (2H, t), 5,90 - 5,93 (1H, m), 7,45 (1H, dd), 7,51 (1H, dd), 7,99 (1H, dd), 8,07 - 8,08 (1H, m), 8,14 (1H, d), 8,42 (1H, s), 8,53 (1H, s), 8,60 (1H, dd), 8,62 (1H, s);
m/z (ESI+) (M+H)+ = 568; HPLC tR = 3,33 min.

Producto Intermedio O2: Metil (2S)-5-(terc-butil-dimetilsilil)oxi-2-[1-(3-cloropiridin-2-il)pirazolo[4,5-e]pirimidin-4-il]oxipentanoato



Se agregó hidruro de sodio al 60% en aceite mineral (0,256 g, 6,40 mmol) en porciones a metil 5-(terc-butildimetilsililoxi)-2-hidroxipentanoato (**Producto Intermedio O3**) (1,4 g, 5,34 mmol) en tetrahidrofurano (7 mL) enfriado hasta alcanzar 0°C durante un período de 1 minuto bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos. Una solución de 4-cloro-1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidina (1,562 g, 5,87 mmol) en tetrahidrofurano (7 mL) se agregó gota a gota durante un período de 2 minutos, la mezcla se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 2 horas. La mezcla se enfrió hasta alcanzar 10°C, se agregó ácido cítrico 1M (20 mL) y se extrajo con acetato de etilo (2 × 50 mL). Los extractos orgánicos se lavaron con agua (25 mL) y salmuera saturada (25 mL), se secaron ($MgSO_4$) y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 30 a 100% acetato de etilo en isohexano para proporcionar el producto racémico. Esto se purificó mediante HPLC quiral para proporcionar el producto (850 mg, 32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0,08 (6H, s), 0,90 (9H, s), 1,80 - 1,90 (2H, m), 2,16 - 2,24 (2H, m), 3,72 (2H, t), 3,77 (3H, s), 5,62 (1H, t), 7,47 (1H, dd), 7,99 (1H, dd), 8,36 (1H, s), 8,57 (1H, s), 8,59 (1H, dd); m/z (ESI+) $(M+H)^+$ = 492; HPLC tR = 3,32 min.

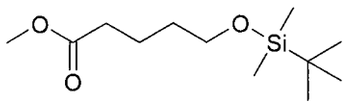
Producto Intermedio O3: Metil 5-(terc-butil-dimetilsilil)oxi-2-hidroxipentanoato



Una solución de butillitio 1,6M (6,42 mL, 10,27 mmol) se agregó gota a gota a una solución agitada de diisopropilamina (1,583 mL, 11,20 mmol) en THF (20 mL) enfriado hasta alcanzar -78°C, durante un período de 2 minutos bajo nitrógeno. La solución resultante se agitó a -78°C durante 10 minutos y se agregó una solución de metil 5-(terc-butildimetilsililoxi)pentanoato (**Producto Intermedio O4**) (2,3 g, 9,33 mmol) en THF

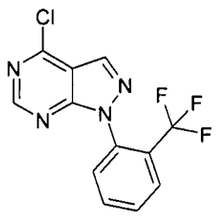
(10 mL) gota a gota durante un período de 5 minutos. La solución resultante se agitó a -78°C durante 10 minutos y luego se entibió hasta alcanzar la temperatura ambiente. La solución de enolato se agregó gota a gota durante un período de 10 minutos a yodo (2,65 g, 10,45 mmol) en THF (20 mL) a -78°C bajo nitrógeno, se agitó durante 10 minutos y se dejó entibiar hasta alcanzar la temperatura ambiente. La mezcla se enfrió nuevamente hasta alcanzar -78°C, se vertió en ácido cítrico 1M (50 mL) y se extrajo con éter (2 × 75 mL). Los extractos orgánicos se lavaron con metabisulfito de sodio 1M (50 mL), agua y salmuera, se secaron ($MgSO_4$) y se evaporaron. El residuo se disolvió en acetonitrilo de éter dietílico 1:1 (60 mL), se agregaron (2,2,2-trifluoroacetoxi)plata (2,350 g, 10,64 mmol) y óxido de plata(I) (3,46 g, 14,93 mmol) y la mezcla se agitó durante 20 horas a temperatura ambiente. La mezcla se filtró y se evaporó. El residuo se purificó mediante cromatografía instantánea en sílice, eluyendo con 30 a 60% acetato de etilo en isohexano para proporcionar el producto (1,4 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0,06 (6H, s), 0,90 (9H, s), 1,56 - 1,80 (3H, m), 1,83 - 1,95 (1H, m), 3,22 (1H, d), 3,66 (2H, t), 3,78 (3H, s), 4,23 - 4,30 (1H, m).

Producto Intermedio O4: Metil 5-(terc-butil-dimetilsilil)oxipentanoato



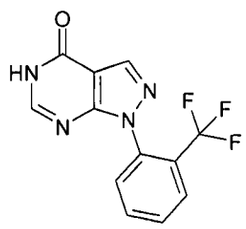
Una solución de terc-butilclorodimetilsilano (27,1 g, 179,79 mmol) en DCM (50 mL) se agregó gota a gota a una solución agitada de metil 5-hidroxipentanoato (CAS no. 14273-92-8, Huckstep, M.; Taylor, R. J. K.; Caton, M. P. L. Synthesis 1982, 10, 881) (19,8 g, 149,82 mmol) y 1H-imidazol (15,30 g, 224,73 mmol) en DCM (200 mL) a 5°C, durante un período de 10 minutos bajo nitrógeno. La suspensión resultante se agitó a temperatura ambiente durante 6 horas. La mezcla de reacción se diluyó con DCM (250 mL) y se lavó secuencialmente con agua (2 × 200 mL) y salmuera saturada (200 mL). La capa orgánica se secó ($MgSO_4$) y se evaporó. El residuo se purificó mediante cromatografía instantánea en sílice, eluyendo con 10 a 50% acetato de etilo en isohexano para proporcionar el producto (19,3 g, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0,05 (6H, s), 0,90 (9H, s), 1,50 - 1,59 (2H, m), 1,65 - 1,72 (2H, m), 2,35 (2H, t), 3,62 (2H, t), 3,65 (3H, s).

Producto Intermedio P1: 4-Cloro-1-[2-(trifluorometil)fenil]pirazolo[5,4-d]pirimidina



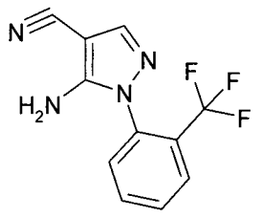
Se agregó tricloruro de fosforilo (34,2 ml, 356,88 mmol) a 1-(2-(trifluorometil)fenil)-1H-pirazolo[3,4-d]pirimidin-4-ol (**Producto Intermedio P2**) (5,0 g, 17,84 mmol). La solución resultante se agitó a 100°C durante 4 horas. La mezcla se evaporó y el residuo se agregó a hielo (~200g) con agitación vigorosa. La mezcla se agitó durante 30 mins y el sólido se recogió mediante filtración, se lavó con agua (3 × 50 mL) y se secó mediante succión. El sólido se disolvió en acetato de etilo (250 mL), se secó ($MgSO_4$) y se evaporó para proporcionar el producto (4,5g, 85%). ^{1}H NMR (400 MHz, DMSO) δ 7,75 - 7,80 (1H, m), 7,88 - 7,91 (1H, m), 7,95 - 7,98 (1H, m), 8,05 - 8,07 (1H, m), 8,79 (1H, s), 8,88 (1H, s); m/z (ESI+) (M+H)+ = 299; HPLC tR = 2,39 min.

Producto Intermedio P2: 1-[2-(trifluorometil)fenil]-5H-pirazolo[4,5-e]pirimidin-4-ona



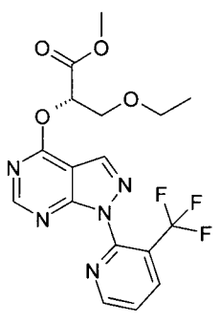
Se agregó ácido sulfúrico concentrado (5,43 mL, 101,96 mmol) a una solución agitada de 5-amino-1-(2-(trifluorometil)fenil)-1H-pirazol-4-carbonitrilo (**Producto Intermedio P3**) (14,3 g, 56,70 mmol) en ácido fórmico (100 mL). La solución resultante se agitó a 100°C durante 4 horas. La mezcla se evaporó hasta aproximadamente la mitad de su volumen original y se agregó agua (75 mL). La mezcla se agitó durante 1 hora y el sólido se recogió mediante filtración, se lavó con agua (3 × 30mL) y se secó al vacío a 50°C para proporcionar el producto (10,2g, 64%). ^{1}H NMR (400 MHz, DMSO) δ 7,67 (1H, d), 7,85 - 7,92 (1H, m), 7,93 - 7,97 (1H, m), 7,98 - 8,01 (1H, m), 8,05 (1H, s), 8,32 (1H, s), 12,37 (1H, s); m/z (ESI+) (M+H)+ = 281; HPLC tR = 1,45 min.

Producto Intermedio P3: 5-amino-1-[2-(trifluorometil)fenil]pirazol-4-carbonitrilo



Se disolvió (2-(trifluorometil)fenil)hidrazina (CAS no. 365-34-4) (10,0 g, 56,77 mmol) en MeOH (150 mL) bajo nitrógeno a 0°C. Se agregó 2-(etoximetileno)malononitrilo (6,93 g, 56,77 mmol) en porciones durante 2 mins y la mezcla se agitó a ~0°C durante 0,5 horas. La reacción se calentó a reflujo durante 2 horas. Se agregó metanol adicional (15 mL) para ayudar a la movilidad. La mezcla se dejó enfriar y se evaporó para proporcionar el producto (14,3 g, 100%) que se utilizó sin purificación adicional. ^{1}H NMR (400 MHz, DMSO) δ 6,63 (2H, s), 7,53 (1H, d), 7,73 (1H, s), 7,74 - 7,77 (1H, m), 7,82 - 7,86 (1H, m), 7,91 - 7,94 (1H, m); m/z (ESI+) (M+H)+ = 253; HPLC tR = 1,60 min.

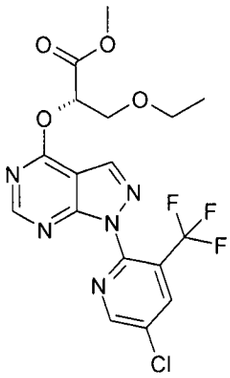
Producto Intermedio Q1: Metil (2S)-3-etoxi-2-[1-[3-(trifluorometil)piridin-2-il]pirazolo[4,5-e]pirimidin-4-il]oxipropanoato



Se agitó (2S)-metil 2-(1-(5-cloro-3-(trifluorometil)piridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-etoxipropanoato (**Producto Intermedio Q2**) (800 mg, 1,79 mmol) y 10% paladio sobre carbono (200 mg) en MeOH (30 mL) bajo una atmósfera de hidrógeno durante 24 horas. La mezcla se filtró, se agregaron 10% paladio sobre carbono (200 mg) y formiato de amonio (1,0 g) y la mezcla se calentó hasta alcanzar reflujo durante 2 horas. La mezcla se dejó enfriar y se filtró y se evaporó. El residuo se purificó mediante cromatografía instantánea en sílice, eluyendo con 50 a 100% acetato de etilo en isohexano para proporcionar el producto (400mg, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,25 (3H, t), 3,62 - 3,73 (2H, m), 3,79 (3H, s), 4,00 - 4,11 (2H, m), 5,84 (1H, dd), 7,63 - 7,66 (1H, m), 8,27 - 8,29 (1H, m), 8,38 (1H, s), 8,58 (1H, s), 8,88 - 8,89 (1H, m); m/z (ESI+) (M+H)+ = 412; HPLC tR = 2,13 min.

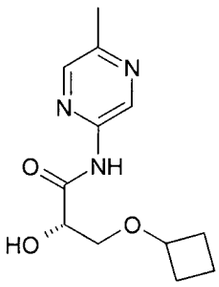
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Producto Intermedio Q2: Metil (2S)-2-[1-[5-cloro-3-(trifluorometil)piridin-2-il]pirazolo[4,5-e]pirimidin-4-il]oxi-3-etoxipropanoato



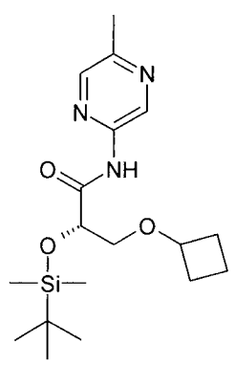
Se agregó hidruro de sodio al 60% en aceite mineral (0,316 g, 7,90 mmol) en porciones a (S)-metil 3-etoxi-2-hidroxipropanoato (**Producto Intermedio G4**) (0,976 g, 6,59 mmol) en tetrahidrofurano (50 mL) se enfrió hasta alcanzar 5°C durante un período de 1 minuto bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos. Una solución de 4-cloro-1-(5-cloro-3-(trifluorometil)piridin-2-il)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio K3**) (1,1 g, 3,29 mmol) se agregó en porciones durante un período de 1 minuto. La mezcla resultante se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 2 horas. La mezcla se enfrió hasta alcanzar 10°C, se aplacó con ácido cítrico 1M (20 mL) y se extrajo con acetato de etilo (2 × 50 mL). Los extractos orgánicos combinados se lavaron con agua (25 mL) y salmuera saturada (25 mL), se secaron ($MgSO_4$) y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 20 a 50% acetato de etilo en isohexano para proporcionar el producto (1,1 g, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,25 (3H, t), 3,72 (2H, d), 3,81 (3H, s), 3,99 - 4,13 (2H, m), 5,84 (1H, dd), 8,22 - 8,24 (1H, m), 8,38 (1H, s), 8,57 (1H, s), 8,81 - 8,82 (1H, m); m/z (ESI+) $(M+H)^+$ = 446; HPLC tR = 2,52 min.

Producto Intermedio R1: (2S)-3-ciclobutiloxi-2-hidroxi-N-(5-metilpirazin-2-il)propanamida



Una solución de fluoruro de tetrabutilamonio (1M en THF) (7,39 mL, 7,39 mmol) se agregó en una porción a una solución agitada de (S)-2-(terc-butildimetilsililoxi)-3-ciclobutoxi-N-(5-metilpirazin-2-il)propanamida (**Producto Intermedio R^2**) (2,7 g, 7,39 mmol) en tetrahidrofurano (25 mL) y la solución resultante se agitó a temperatura ambiente durante 4 horas. La mezcla de reacción se concentró al vacío, se diluyó con acetato de etilo (50 mL) y se lavó secuencialmente con agua (20 mL) y salmuera saturada (20 mL). La capa orgánica se secó ($MgSO_4$) y se evaporó. El residuo se purificó mediante cromatografía instantánea en sílice, eluyendo con acetato de etilo para proporcionar el producto (1,5g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,48 - 1,56 (1H, m), 1,70 - 1,76 (1H, m), 1,90 - 2,00 (2H, m), 2,19 - 2,26 (2H, m), 2,54 (3H, s), 3,61(1H, d), 3,67 - 3,73 (2H, m), 3,97 - 4,05 (1H, m), 4,35 - 4,38 (1H, m), 8,14 (1H, d), 9,15 (1H, s), 9,43 (1H, d); m/z (ESI+) (M+H)+ = 252; HPLC t_R = 1,31 min.

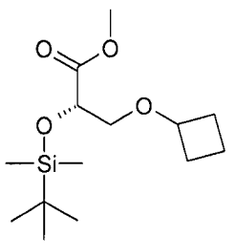
Producto Intermedio R2: (2S)-2-(terc-butil-dimetilsilil)oxi-3-ciclobutiloxi-N-(5-metilpirazin-2-il)propanamida



Una solución de trimetilaluminio (2M en hexano) (11,44 mL, 22,88 mmol) se agregó gota a gota a una solución agitada de 5-metilpirazin-2-amina (CAS no. 5521-58-4) (2,497 g, 22,88 mmol) en tolueno (50 mL) enfriado hasta alcanzar 0°C, durante un período de 5 minutos bajo nitrógeno. La solución resultante se agitó a 0°C durante 15 minutos. Una solución de (S)-metil 2-(terc-butildimetilsililoxi)-3-ciclobutoxipropanoato (**Producto**

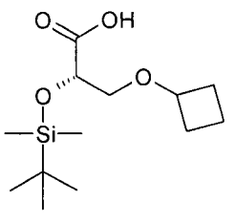
Intermedio R3) (6,0 g, 20,80 mmol) en tolueno (10 mL) se agregó gota a gota durante un período de 2 minutos. La solución resultante se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó hasta alcanzar reflujo durante 2 horas. La mezcla se dejó enfriar, se agregaron tartrato de sodio y potasio al 20% (50 mL) y agua (25 mL) y la mezcla se extrajo con acetato de etilo (25 mL). La fase acuosa se extrajo nuevamente con acetato de etilo (25 mL). Las fases orgánicas se combinaron, se lavaron con agua (5 mL) y salmuera (20 mL), se secaron ($MgSO_4$) y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 20 a 100% acetato de etilo en isohexano para proporcionar el producto (2,7 g, 36%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0,19 (3H, s), 2,00 (3H, s), 0,99 (9H, s), 1,48 - 1,51 (1H, m), 1,67 - 1,70 (1H, m), 1,91 - 1,94 (2H, m), 2,16 - 2,21 (2H, m), 2,54 (3H, s), 3,55 (1H, dd), 3,69 (1H, dd), 3,93 - 3,97 (1H, m), 4,39 - 4,41 (1H, m), 8,14 (1H, d), 9,00 (1H, s), 9,43 (1H, d); m/z (ESI+) $(M+H)^+$ = 366; HPLC t_R = 3,28 min.

Producto Intermedio R3: (S)-Metil 2-(terc-butildimetilsililoxi)-3-ciclobutoxipropanoato



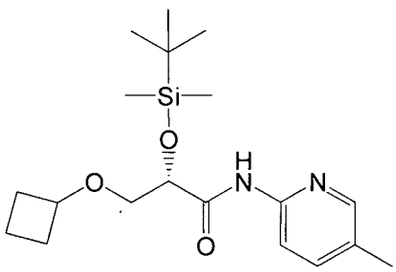
Se preparó utilizando un procedimiento análogo al descrito para el **Producto Intermedio C7a** utilizando ciclobutanol. ^{1}H NMR (400 MHz, DMSO) δ 0,00 (d, 6H), 0,81 (s, 9H), 1,31 - 1,44 (m, 1H), 1,50 - 1,60 (m, 1H), 1,65 - 1,79 (m, 2H), 2,01 - 2,11 (m, 2H), 3,35 - 3,45 (m, 2H), 3,59 (s, 3H), 3,83 - 3,92 (m, 1H), 4,27 - 4,32 (m, 1H); m/z (EI+) M-C4H9 = 231,1069; GC tR = 10,95 min.

Producto Intermedio R4: Ácido (S)-2-(terc-butildimetilsililoxi)-3-ciclobutoxipropanoico



Se agregó yoduro de litio (1,986 g, 14,84 mmol) a (S)-metil 2-(terc-butildimetilsililoxi)-3-ciclobutoxipropanoato (**Producto Intermedio R^3**) (1,07 g, 3,71 mmol) en acetato de etilo (15 mL). La suspensión resultante se protegió de la luz y se agitó a reflujo (75°C) durante 6 horas. La mezcla de reacción se diluyó con acetato de etilo (75 mL) y se lavó secuencialmente con metabisulfito de sodio 1M (25 mL), agua (25 mL) y salmuera saturada (25 mL). La capa orgánica se secó ($MgSO_4$) y se evaporó para proporcionar el producto bruto (0,920 g, 90%) que se utilizó sin purificación adicional. ^{1}H NMR (400 MHz, DMSO) δ 0,09 (d, 6H), 0,91 (s, 9H), 1,40 - 1,54 (m, 1H), 1,59 - 1,71 (m, 1H), 1,75 - 1,90 (m, 2H), 2,10 - 2,22 (m, 2H), 3,40 - 3,57 (m, 2H), 3,90 - 4,02 (m, 1H), 4,25 - 4,31 (m, 1H), 12,55 (s, 1H); m/z (EI+) M+ = 274; GC tR = 11,09 min.

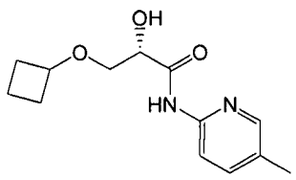
Producto Intermedio R5: (S)-2-(terc-butildimetilsililoxi)-3-ciclobutoxi-N-(5-metilpiridin-2-il)propanamida



Se agregó 1-cloro-N,N,2-trimetilprop-1-en-1-amina (0,133 mL, 1,00 mmol) a una solución agitada de ácido (S)-2-(terc-butildimetilsililoxi)-3-ciclobutoxipropanoico (**Producto Intermedio R^4**) (250 mg, 0,91 mmol) en DCM (5 mL) a temperatura ambiente bajo nitrógeno. La solución resultante se agitó a temperatura ambiente durante 30 minutos. Se agregó piridina (0,147 mL, 1,82 mmol) y luego una solución de 5-metilpiridin-2-amina (108 mg, 1,00 mmol) en DCM (5 mL) y la solución resultante se agitó a temperatura ambiente durante 1 hora. Se agregaron ácido cítrico 1M (10 mL) y DCM (50 mL) y las fases se separaron. La fase orgánica se lavó con agua (10 mL) y salmuera (10 mL), se secó ($MgSO_4$), se filtró y se evaporó. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 30% acetato de etilo en isohexano para proporcionar el producto (195 mg, 58,7 %). ^{1}H NMR (400 MHz, DMSO) δ 0,01 (d, 6H), 0,80 (s, 9H), 1,24 - 1,37 (m, 1H), 1,43 - 1,53 (m, 1H), 1,59 - 1,72 (m, 2H), 1,94 - 2,06 (m, 2H), 2,13 (s, 3H), 3,33 - 3,44 (m, 2H), 3,77 - 3,87 (m, 1H), 4,29 - 4,34 (m, 1H), 7,49 - 7,54 (m, 1H), 7,86 (d, 1H), 8,02 - 8,06 (m, 1H), 9,25 (s, 1H); m/z (ESI+) (M+H)+ = 365,47;

HPLC tR = 3,60 min.

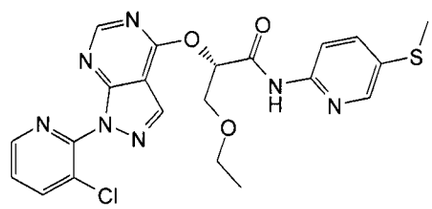
Producto Intermedio R6: (S)-3-ciclobutoxi-2-hidroxi-N-(5-metilpiridin-2-il)propanamida



Una solución de fluoruro de tetrabutilamonio (1M en THF) (0,439 mL, 0,44 mmol) se agregó a una solución agitada de (S)-2-(terc-butildimetilsililoxi)-3-ciclobutoxi-N-(5-metilpiridin-2-il)propanamida (**Producto Intermedio R5**) (80 mg, 0,22 mmol) en tetrahidrofurano (5 mL). La solución resultante se agitó a temperatura ambiente durante 4 horas. La mezcla de reacción se concentró y se diluyó con acetato de etilo (20 mL) y se lavó secuencialmente con agua (5 mL) y salmuera saturada (5 mL). La capa orgánica se secó ($MgSO_4$) y se evaporó. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 60% acetato de etilo en isohexano para proporcionar el producto (46,0 mg, 84%). ^{1}H NMR (400 MHz, DMSO) δ 1,34 - 1,49 (m, 1H), 1,52 - 1,64 (m, 1H), 1,71 - 1,85 (m, 2H), 2,05 - 2,16 (m, 2H), 2,24 (s, 3H), 3,46 - 3,56 (m, 2H), 3,87 - 3,97 (m, 1H), 4,17 - 4,24 (m, 1H), 6,02 (d, 1H), 7,59 - 7,66 (m, 1H), 7,98 (d, 1H), 8,12 - 8,17 (m, 1H), 9,48 (s, 1H)

m/z (ESI+) (M+H)+ = 251,33; HPLC tR = 1,31 min.

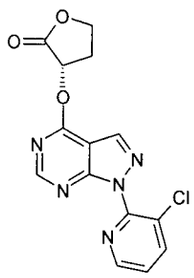
Producto Intermedio S1: (2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-etoxi-N-(5-(metiltio)piridin-2-il)propanamida



Se agregó trimetilaluminio 2M en hexano (0,457 mL, 0,91 mmol) a 5-(metiltio)piridin-2-amina (CAS no. 77618-99-6) (0,111 g, 0,79 mmol) en tolueno (22 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 20 minutos. Se agregó (2S)-metil 2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-etoxipropanoato (**Producto Intermedio L2**) (0,300 g, 0,79 mmol) en tolueno (6 mL) gota a gota a esta

temperatura. Después de que se completó la adición, la solución se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó a reflujo durante 16 horas. La mezcla se dejó enfriar hasta alcanzar la temperatura ambiente y se dejó reposar 2 días. La mezcla de reacción se concentró, se diluyó con acetato de etilo (100 mL) y luego se lavó con salmuera saturada (50 mL). La capa orgánica se secó ($MgSO_4$) y se evaporó. El residuo se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 3% MeOH en DCM para proporcionar el producto. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,14 (3H, t), 2,41 (3H, s), 3,52 - 3,61 (2H, m), 3,99 - 4,07 (2H, m), 5,99 (1H, t), 7,38 - 7,42 (1H, m), 7,57 - 7,60 (1H, m), 7,93 - 7,95 (1H, m), 8,11 - 8,15 (2H, m), 8,40 (1H, s), 8,54 - 8,56 (2H, m), 8,64 (1H, s); m/z (ES+) $(M+H)^+$ = 486; HPLC tR = 2,26 min.

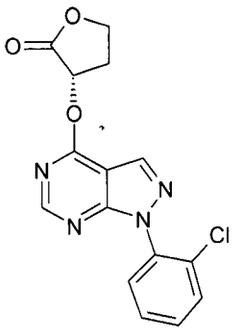
Producto Intermedio T1: (3S)-3-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)dihidrofuran-2(3H)-ona



Se agregó hidruro de sodio al 60% en aceite mineral (0,470 g, 11,75 mmol) a (S)-3-hidroxidihidrofuran-2(3H)-ona (0,764 mL, 9,80 mmol) en THF anhidro (30 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos y luego se agregó 4-cloro-1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidina (CAS no. 52079-23-9) (2,87 g, 10,77 mmol) en porciones manteniendo la temperatura por debajo de 5°C. La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 1 hora. La mezcla de reacción se neutralizó con ácido cítrico 1M y la mayor parte del THF se eliminó al vacío. La mezcla de reacción se diluyó con agua (20 mL) y acetato de etilo (50 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con acetato de etilo (2 × 100 mL). Los elementos orgánicos combinados se lavaron con salmuera saturada (75 mL), agua (75 mL) se secaron ($MgSO_4$), se filtraron y se evaporaron. El residuo se purificó mediante cromatografía instantánea en sílice, eluyendo con 50 a 100% acetato de etilo en isohexano para proporcionar el producto (1,970 g, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) 2,52 - 2,62 (1H, m), 2,92 - 3,00 (1H, m), 4,41 - 4,47 (1H, m), 4,59 - 4,64 (1H, m),

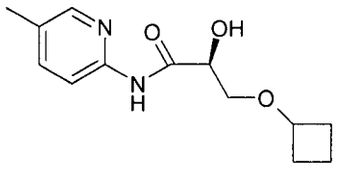
6,11 - 6,16 (1H, m), 7,46 - 7,49 (1H, m), 8,00 - 8,02 (1H, m), 8,37 (1H, s), 8,61 - 8,63 (1H, m), 8,64 (1H, s); m/z (ESI+) $(M+H)^+$ = 332; HPLC t_R = 1,51 min.

Producto Intermedio T2: (3S)-3-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)dihidrofuran-2(3H)-ona



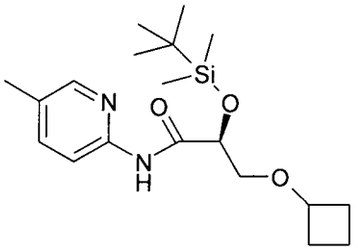
Se preparó utilizando un procedimiento análogo al descrito para el **Producto Intermedio T1** utilizando el **Producto Intermedio B1** ^{1}H NMR (400 MHz, $CDCl_3$) 2,53 - 2,63 (1H, m), 2,92 - 2,99 (1H, m), 4,41 - 4,47 (1H, m), 4,59 - 4,65 (1H, m), 6,12 - 6,16 (1H, m), 7,44 - 7,55 (3H, m), 7,60 - 7,63 (1H, m), 8,33 (1H, s), 8,60 (1H, s); m/z (ESI+) $(M+H)^+$ = 331; HPLC t_R = 1,98 min.

Producto Intermedio U1: (S)-3-ciclobutoxi-2-hidroxi-N-(5-metilpiridin-2-il)propanamida



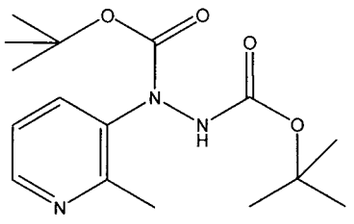
Se preparó en una forma análoga al **Producto Intermedio H1** a partir de (S)-2-(terc-butildimetilsililoxi)-3-ciclobutoxi-N-(5-metilpiridin-2-il)propanamida (**Producto Intermedio U2**) ^{1}H NMR (400 MHz, $CDCl_3$) 1,45 - 1,60 (1H, m), 1,64 - 1,74 (1H, m), 1,90 - 2,04 (2H, m), 2,17 - 2,26 (2H, m), 2,30 (3H, s), 3,63 - 3,74 (2H, m), 3,97 - 4,04 (1H, m), 4,11 - 4,17 (1H, m), 4,34 - 4,36 (1H, m), 7,51 - 7,54 (1H, m), 8,07 - 8,13 (2H, m), 9,26 (1H, s); m/z (ESI+) $(M+H)^+$ = 251; HPLC t_R = 1,30 min.

Producto Intermedio U2: (S)-2-(terc-butildimetilsililoxi)-3-ciclobutoxi-N-(5-metilpiridin-2-il)propanamida



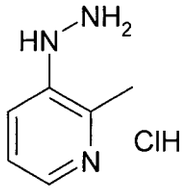
Se preparó en una forma análoga al **Producto Intermedio E2** a partir de ácido (S)-2-(terc-butildimetilsililoxi)-3-ciclobutoxipropanoico (**Producto Intermedio R[4]**). ^{1}H NMR (400 MHz, $CDCl_3$) 0,19 (6H, d), 0,99 (9H, s), 1,46 - 1,52 (1H, m), 1,67 - 1,70 (1H, m), 1,89 - 1,94 (2H, m), 2,16 - 2,20 (2H, m), 2,30 (3H, s), 3,49 - 3,54 (1H, m), 3,67 - 3,70 (1H, m), 3,93 - 3,97 (1H, m), 4,36 - 4,38 (1H, m), 7,49 - 7,52 (1H, m), 8,10 - 8,14 (2H, m), 9,01 (1H, s); m/z (ESI+) (M+H)+ = 365; HPLC t_R = 3,57min.

Producto Intermedio V1: di-terc-butil 1-(2-metilpiridin-3-il)hidrazina-1,2-dicarboxilato



Se preparó utilizando un procedimiento análogo al descrito para el **Producto Intermedio X1** utilizando 3-bromo-2-metilpiridina (CAS no. 38749-79-0). ^{1}H NMR (400 MHz, DMSO) δ 1,07 - 1,32 (m, 18H), 3,09 (s, 3H), 7,01 - 7,12 (m, 1H), 7,41 - 7,50 (m, 1H), 8,12 - 8,18 (m, 1H), 9,39 - 9,62 (m, 1H); m/z (ESI+) (M+H)+ = 324,39; HPLC t_R = 1,57 min.

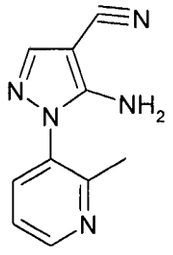
Producto Intermedio V2: 3-hidrazinil-2-metilpiridina clorhidrato



Se agregó cloruro de hidrógeno en dioxano (5,67 mL, 22,67 mmol) a una solución de di-terc-butil 1-(2-metilpiridin-3-il)hidrazina-1,2-dicarboxilato (**Producto Intermedio V1**) (733 mg, 2,27 mmol) en IPA (10 mL). La mezcla de reacción se calentó a reflujo durante 20 mins. La mezcla de reacción se dejó enfriar y luego se diluyó con éter dietílico (30 mL). El precipitado resultante se recogió mediante filtración y se secó al vacío para proporcionar

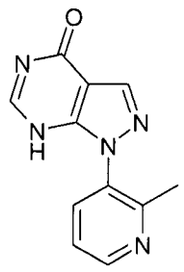
3-hidrazinil-2-metilpiridina clorhidrato (362 mg, 100 %). ^{1}H NMR (400 MHz, DMSO) δ 2,66 (3H, s), 7,80 - 7,83 (1H, m), 7,95 - 7,97 (1H, m), 8,23 - 8,25 (1H, m), 9,15 (1H, s), 11,30 (1H, s); no ion en LCMS (1NH mising).

Producto Intermedio V3: 5-amino-1-(2-metilpiridin-3-il)-1H-pirazol-4-carbonitrilo



Se agregó MP-carbonato (2,64 mmol/g) (2,6 g, 6,80 mmol) a 3-hidrazinil-2-metilpiridina clorhidrato (**Producto Intermedio V2**) (362 mg, 2,27 mmol) en DCM (10 mL). La mezcla de reacción se agitó a temperatura ambiente durante 6 horas. La mezcla de reacción se filtró y se evaporó. Se agregó 2-(etoximetileno)malononitrilo (277 mg, 2,27 mmol) a una suspensión del sólido precedente en MeOH (6 mL) bajo nitrógeno enfriado hasta alcanzar -5°C. La mezcla de reacción se agitó a 0°C durante 30 mins y luego se dejó entibiar hasta alcanzar la temperatura ambiente y se calentó a reflujo bajo nitrógeno durante 2 horas. La mezcla de reacción se dejó enfriar y se evaporó hasta secarse para proporcionar el producto (210 mg, 46,5%) que se utilizó sin purificación adicional. ^{1}H NMR (400 MHz, DMSO) δ 2,23 (3H, s), 6,65 (2H, s), 7,39 - 7,43 (1H, m), 7,74 (1H d), 7,79 (1H, s), 8,58 - 8,60 (1H, m); m/z (ESI+) (M+H)+ = 200; HPLC t_R = 1,21 min.

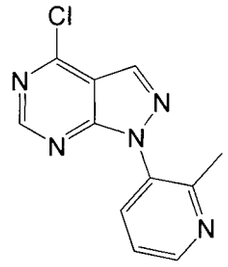
Producto Intermedio V4: 1-(2-metilpiridin-3-il)-1H-pirazolo[3,4-d]pirimidin-4(7H)-ona



Se agregó ácido sulfúrico concentrado (0,258 mL, 4,85 mmol) a una solución agitada de 5-amino-1-(2-metilpiridin-3-il)-1H-pirazol-4-carbonitrilo (**Producto Intermedio V3**) (878 mg, 4,41 mmol) en ácido fórmico (5 mL). La solución resultante se agitó a 100°C durante 1 hora. La reacción se dejó enfriar hasta alcanzar la temperatura ambiente y se evaporó hasta

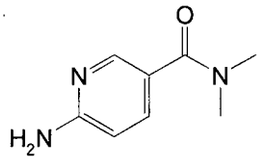
aproximadamente la mitad del volumen y se agregó agua (25 mL). La mezcla de reacción se ajustó hasta alcanzar pH 4 con NaOH 2M. El precipitado resultante se recogió mediante filtración, se lavó bien con agua y luego se secó al vacío para proporcionar 1-(2-metilpiridin-3-il)-1H-pirazolo[3,4-d]pirimidin-4(7H)-ona (525 mg, 52%). ^{1}H NMR (400 MHz, DMSO) δ 2,28 (3H, s), 7,44 - 7,47 (1H, m), 7,85 - 7,87 (1H, m), 8,09 (1H, s), 8,35 (1H, s), 8,61 - 8,63 (1H, m), 12,3 (1H, s);
m/z (ESI+) (M+H)+ = 228; HPLC t_R = 0,65 min.

Producto Intermedio V5: 4-cloro-1-(2-metilpiridin-3-il)-1H-pirazolo[3,4-d]pirimidina



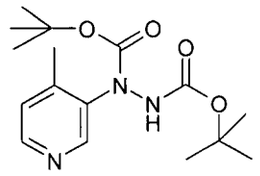
Se preparó utilizando un procedimiento análogo al descrito para el **Producto Intermedio X5** utilizando el **Producto Intermedio V4**. ^{1}H NMR (400 MHz, DMSO) δ 2,32 (s, 3H), 7,51 - 7,56 (m, 1H), 7,96 - 8,00 (m, 1H), 8,67 - 8,70 (m, 1H), 8,81 (s, 1H), 8,91 (s, 1H).
m/z (ESI+) (M+H)+ = 246,29; HPLC tR = 1,29 min

Producto Intermedio W1: 6-amino-N,N-dimetilnicotinamida



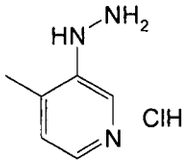
Se agregó N-etil-N-isopropilpropan-2-amina (12,61 mL, 72,40 mmol) a ácido 6-aminonicotínico (CAS no. 3167-49-5) (5 g, 36,20 mmol), dimetilamina (2M en THF) (21,72 mL, 43,44 mmol) y EDCI (9,02 g, 47,06 mmol) en THF (150 mL) bajo nitrógeno. La suspensión resultante se agitó a t.a. durante 18 horas. La mezcla de reacción se cargó deshidratada sobre sílice y se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 10% MeOH en acetato de etilo al producto (4,50 g, 75%). ^{1}H NMR (400 MHz, DMSO) δ 2,95 (6H, s), 6,28 (2H, s), 6,38 - 6,44 (1H, m), 7,42 - 7,47 (1H, m), 7,99 - 8,04 (1H, m)

Producto Intermedio X1: di-terc-butil 1-(4-metilpiridin-3-il)hidrazina-1,2-dicarboxilato



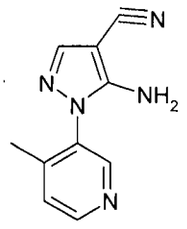
Se agregó complejo de cloruro de isopropilmagnesio. cloruro de litio (0,96 M) (23,62 mL, 22,67 mmol) a 3-bromo-4-metilpiridina (CAS no. 3430-22-6) (3 g, 17,44 mmol) en THF (60 mL) enfriado hasta alcanzar 0°C bajo nitrógeno. La solución resultante se entibió hasta alcanzar la temperatura ambiente y se agitó durante 3 horas. La temperatura de la reacción se enfrió hasta alcanzar 0°C y se agregó di-terc-butil azodicaboxilato (6,02 g, 26,16 mmol) en THF (10 ml) gota a gota manteniendo la temperatura por debajo de 10°C. La reacción se entibió hasta alcanzar la temperatura ambiente y se agitó durante 1,5 horas. La mezcla de reacción se aplacó con NH_4Cl saturado (50 mL) y se extrajo con acetato de etilo (3 × 75 mL). La capa orgánica se secó ($MgSO_4$) y se evaporó. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 90% acetato de etilo en isohexano para proporcionar el producto (4,50 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,41 - 1,49 (18H, m), 2,34 (3H, s), 6,90 (1H, s), 7,13 (1H, d), 8,36 (1H, d), 8,60 (1H, s); m/z (ESI+) $(M+H)^+$ = 324; HPLC tR = 2,15 min.

Producto Intermedio X2: 3-hidrazinil-4-metilpiridina clorhidrato



Se preparó utilizando un procedimiento análogo al descrito para el **Producto Intermedio V2** utilizando el **Producto Intermedio X1**, ^{1}H NMR (400 MHz, DMSO) δ 2,44 (3H, s), 7,79 - 7,80 (1H, m), 8,38 (2H, d), 9,07 (1H, s), 11,4 (2H, s)

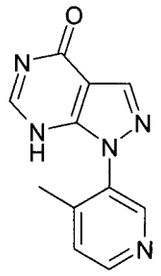
Producto Intermedio X3: 5-amino-1-(4-metilpiridin-3-il)-1H-pirazol-4-carbonitrilo



Se preparó utilizando un procedimiento análogo al descrito para el **Producto Intermedio V3** utilizando el **Producto Intermedio X2**. ^{1}H NMR (400 MHz, DMSO) δ 2,09 (3H, s),

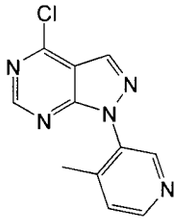
6,68 (2H, s), 7,50 (1H, d), 7,80 (1H, s), 8,44 - 8,48 (1H, m), 8,57 (1H, d); m/z (ESI+) (M+H)+ = 200; HPLC tR = 1,47 min.

Producto Intermedio X4: 1-(4-metilpiridin-3-il)-1H-pirazolo[3,4-d]pirimidin-4(7H)-ona



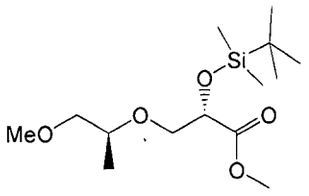
Se preparó utilizando un procedimiento análogo al descrito para el **Producto Intermedio V4** utilizando el **Producto Intermedio X3**. ^{1}H NMR (400 MHz, DMSO) δ 2,15 (3H, s), 7,51 (1H, d), 8,09 (1H, s), 8,37 (1H, s), 8,57 - 8,59 (2H, m), 12,5 (1H, s); m/z (ESI+) (M+H)+ = 228; HPLC t_R = 1,36 min.

Producto Intermedio X5: 4-cloro-1-(4-metilpiridin-3-il)-1H-pirazolo[3,4-d]pirimidina



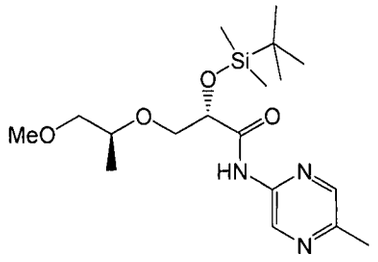
Se agregó oxicloruro de fósforo (5,10 ml, 54,75 mmol) a 1-(4-metilpiridin-3-il)-1H-pirazolo[3,4-d]pirimidin-4-ol (0,622 g, 2,74 mmol). La solución resultante se agitó a 100°C durante 2 horas. La mezcla de reacción se evaporó. Se agregó tolueno al residuo y la mezcla de reacción se concentró. Esto se repitió para eliminar el exceso de $POCl_3$. El residuo se disolvió en DMF (15 mL) y se agregó MP carbonato (~ 3g) y se dejó agitar durante toda la noche. La DMF se evaporó al vacío para proporcionar el producto bruto que se utilizó sin purificación adicional. ^{1}H NMR (400 MHz, DMSO) δ 2,1 (3H, s), 7,60 (1H, d), 8,65 (1H, d), 8,68 (1H, s), 8,82 (1H, s), 8,91 (1H, s); m/z (ES+) (M+H)+ = 246; HPLC tR = 1,69 min.

Producto Intermedio Y1: (S)-metil 2-(terc-butildimetilsililoxi)-3-((S)-1-metoxipropan-2-iloxi)propanoato



Se agregó perclorato de magnesio (2,79 g, 12,49 mmol) en una porción a (S)-metil oxirano-2-carboxilato (CAS no. 118712-39-3) (5,1 g, 49,96 mmol) y (S)-1-metoxipropan-2-ol (CAS no. 26550-55-0) (4,50 g, 49,96 mmol) a temperatura ambiente. La suspensión resultante se agitó a 50°C durante 16 horas. La mezcla de reacción se diluyó con DMF (50 mL) antes de agregar 1H-imidazol (6,80 g, 99,92 mmol) y terc-butilclorodimetilsilano (9,04 g, 59,95 mmol). La solución resultante se agitó a 40°C durante 5 horas. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en acetato de etilo (125 mL) y se lavó secuencialmente con agua (50 mL) y salmuera saturada (25 mL). La capa orgánica se secó ($MgSO_4$) y se evaporó. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 50% acetato de etilo en isohexano para proporcionar el producto (4,52 g, 30%). ^{1}H NMR (400 MHz, DMSO) δ 0,00 (d, 6H), 0,82 (s, 9H), 0,98 (d, 3H), 3,13 - 3,28 (m, 5H), 3,50 - 3,64 (m, 6H), 4,26 - 4,32 (m, 1H); m/z (ESI+) (M+H)+ = 307,19; HPLC t_R = 10,82 min.

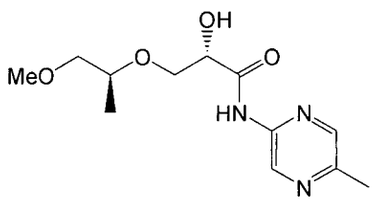
Producto Intermedio Y2: (S)-2-(terc-butildimetilsililoxi)-3-((S)-1-metoxipropan-2-iloxi)-N-(5-metilpirazin-2-il)propanamida



Se agregó trimetilaluminio (2M en hexano) (1,126 mL, 2,25 mmol) gota a gota a 5-metilpirazin-2-amina (214 mg, 1,96 mmol) en tolueno (5 mL) enfriado hasta alcanzar 0°C bajo nitrógeno. La solución resultante se agitó durante 20 minutos. Se agregó una solución de (S)-metil 2-(terc-butildimetilsililoxi)-3-((S)-1-metoxipropan-2-iloxi) propanoato (**Producto Intermedio Y1**) (600 mg, 1,96 mmol) en tolueno (2 mL) a la mezcla de reacción y la solución resultante se agitó a reflujo durante 5 horas. La reacción se dejó

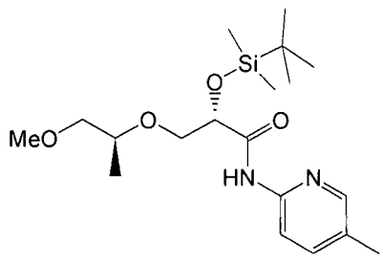
enfriar hasta alcanzar la TA antes de agregar acetato de etilo (30 mL) y solución de tartrato de sodio y potasio al 20% (30 mL), que se agitó vigorosamente durante 16 horas. Las fases se separaron y la capa orgánica se lavó con salmuera sat. (15 mL), se secó ($MgSO_4$) y se evaporó. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 60% acetato de etilo en isohexano para proporcionar el producto (230 mg, 31%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0,17 (d, 6H), 0,98 (s, 9H), 1,16 (d, 3H), 2,53 (s, 3H), 3,25 - 3,32 (m, 4H), 3,35 - 3,42 (m, 1H), 3,60 - 3,68 (m, 1H), 3,74 - 3,80 (m, 1H), 3,82 - 3,87 (m, 1H), 4,35 - 4,40 (m, 1H), 8,12 - 8,13 (m, 1H), 8,98 (s, 1H), 9,42 (d, 1H); m/z (ESI+) (M+H)+ = 384,23; HPLC t_R = 10,70 min.

Producto Intermedio Y3: (S)-2-hidroxi-3-((S)-1-metoxipropan-2-iloxi)-N-(5-metilpirazin-2-il)propanamida



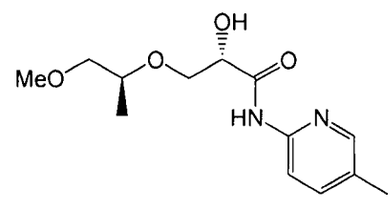
Se agregó fluoruro de tetrabutilamonio (1M en THF) (1199 µl, 1,20 mmol) a (S)-2-(terc-butildimetilsililoxi)-3-((S)-1-metoxipropan-2-iloxi)-N-(5-metilpirazin-2-il)propanamida (**Producto Intermedio Y2**) (230 mg, 0,60 mmol) en THF (3,0 mL) a 20°C. La solución resultante se agitó a temperatura ambiente durante 3 horas. La mezcla de reacción se concentró y se diluyó con acetato de etilo (50 mL) y se lavó secuencialmente con agua (25 mL) y salmuera saturada (10 mL). La capa orgánica se secó ($MgSO_4$) y se evaporó. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 100% acetato de etilo para proporcionar el producto (80 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,16 (d, 3H), 2,53 (s, 3H), 3,34 - 3,45 (m, 5H), 3,66 - 3,81 (m, 2H), 3,97 - 4,03 (m, 1H), 4,30 (d, 1H), 4,34 - 4,39 (m, 1H), 8,13 (d, 1H), 9,30 (s, 1H), 9,41 (d, 1H); m/z (ESI+) (M+H)+ = 270,29; HPLC t_R = 0,95 min.

Producto Intermedio Y4: (S)-2-(terc-butildimetilsililoxi)-3-((S)-1-metoxipropan-2-iloxi)-N-(5-metilpiridin-2-il)propanamida



Se agregó trimetilaluminio (2M en hexano) (0,938 mL, 1,88 mmol) gota a gota a 5-metilpiridin-2-amina (194 mg, 1,79 mmol) en tolueno (5 mL) enfriado hasta alcanzar 0°C bajo nitrógeno. La solución resultante se agitó durante 20 minutos. Se agregó una solución de (S)-metil 2-(terc-butildimetilsililoxi)-3-((S)-1-metoxipropan-2-iloxi) propanoato (**Producto Intermedio Y1**) (500 mg, 1,63 mmol) en tolueno (2 mL) a la mezcla de reacción y la solución resultante se agitó a reflujo durante 5 horas. La reacción se dejó enfriar hasta alcanzar la temperatura ambiente antes de agregar acetato de etilo (30 mL) y solución de tartrato de sodio y potasio al 20% (30 mL), que se agitó vigorosamente durante 16 horas. Las fases se separaron y la capa orgánica se lavó con salmuera sat. (15 mL), se secó ($MgSO_4$) y se evaporó. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 60% acetato de etilo en isohexano para proporcionar el producto (388 mg, 62%). ^{1}H NMR (400 MHz, DMSO) δ 0,01 (d, 6H), 0,81 (s, 9H), 0,93 (d, 3H), 2,13 (s, 3H), 3,06 - 3,21 (m, 5H), 3,44 - 3,53 (m, 1H), 3,57 (d, 2H), 4,29 (t, 1H), 7,49 - 7,55 (m, 1H), 7,87 (d, 1H), 8,01 - 8,05 (m, 1H), 9,25 (s, 1H); m/z (ESI+) $(M+H)^+$ = 383,24; HPLC t_R = 11,31 min.

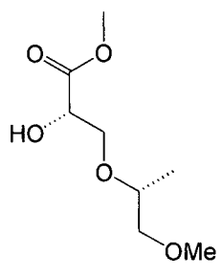
Producto Intermedio Y5: (S)-2-hidroxi-3-((S)-1-metoxipropan-2-iloxi)-N-(5-metilpiridin-2-il)propanamida



Se agregó fluoruro de tetrabutilamonio (1M en THF) (2028 µl, 2,03 mmol) a (S)-2-(terc-butildimetilsililoxi)-3-((S)-1-metoxipropan-2-iloxi)-N-(5-metilpiridin-2-il)propanamida (**Producto Intermedio Y4**) (388 mg, 1,01 mmol) en THF (5 mL) a 20°C. La solución resultante se agitó a temperatura ambiente durante 3 horas. La mezcla de reacción se

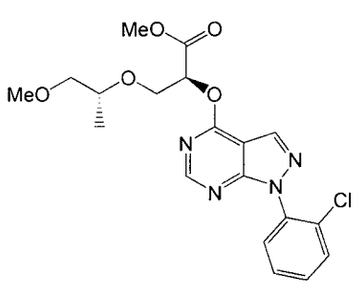
concentró, se diluyó con acetato de etilo (50 mL) y se lavó secuencialmente con agua (25 mL) y salmuera saturada (10 mL). La capa orgánica se secó ($MgSO_4$) y se evaporó. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 10% MeOH en DCM para proporcionar el producto (200 mg, 74 %). ^{1}H NMR (400 MHz, DMSO) δ 1,04 (d, 3H), 2,24 (s, 3H), 3,17 - 3,23 (m, 4H), 3,25 - 3,31 (m, 1H), 3,55 - 3,73 (m, 3H), 4,16 - 4,23 (m, 1H), 5,94 (d, 1H), 7,59 - 7,65 (m, 1H), 7,98 (d, 1H), 8,12 - 8,16 (m, 1H), 9,48 (s, 1H); m/z (ESI+) (M+H)+ = 269,31; HPLC t_R = 1,11 min.

Producto Intermedio Y6: (S)-Metil 2-hidroxi-3-((R)-1-metoxipropan-2-iloxi)propanoato



Se agregó perclorato de magnesio (2,73 g, 12,24 mmol) en una porción a (S)-metil oxirano-2-carboxilato (CAS no. 118712-39-3) (5 g, 48,98 mmol) y (R)-1-metoxipropan-2-ol (CAS no. 4984-22-9) (4,41 g, 48,98 mmol) a temperatura ambiente. La suspensión resultante se agitó a 50°C durante 16 horas. La mezcla de reacción se diluyó con acetato de etilo (50 mL) y se lavó con agua (20 mL), se secó ($MgSO_4$) y se evaporó. Esto no se aisló y se utilizó en bruto en la siguiente etapa. ^{1}H NMR (400 MHz, $CDCl_3$) δ1,11 (d, 3H), 3,31 - 3,40 (m, 5H), 3,64 - 3,72 (m, 1H), 3,75 - 3,80 (m, 4H), 3,89 - 3,95 (m, 1H), 4,27 - 4,30 (m, 1H), No se observó OH.

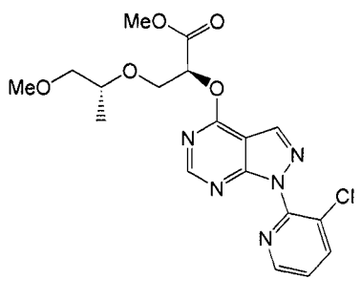
Producto Intermedio Y7: (2S)-Metil 2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-((R)-1-metoxipropan-2-iloxi)propanoato



Se agregó hidruro de sodio (94 mg, 2,34 mmol) a (S)-metil 2-hidroxi-3-((R)-1-

metoxipropan-2-iloxi)propanoato (**Producto Intermedio Y6**) (300 mg, 1,56 mmol) en THF anhidro (5 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos y luego se agregó 4-cloro-1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio B1**) (538 mg, 2,03 mmol). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 30 minutos. La mezcla de reacción se neutralizó con ácido cítrico 1M, se diluyó con acetato de etilo (20 mL) y se lavó secuencialmente con agua (10 mL) y salmuera saturada (5 mL). La capa orgánica se secó ($MgSO_4$) y se evaporó. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0-100% acetato de etilo en isohexano para proporcionar el producto (358 mg, 54,5 %). ^{1}H NMR (400 MHz, DMSO) δ 1,07 (d, 3H), 3,23 - 3,40 (m, 5H), 3,68 - 3,77 (m, 4H), 4,05 - 4,10 (m, 2H), 5,81 (t, 1H), 7,56 - 7,71 (m, 3H), 7,73 - 7,79 (m, 1H), 8,57 (s, 1H), 8,58 (s, 1H); m/z (ESI+) $(M+H)^+$ = 421,17; HPLC t_R = 1,86 min.

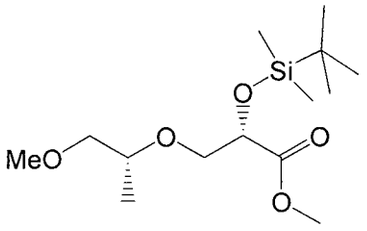
Producto Intermedio Y8: (2S)-Metil 2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-((R)-1-metoxipropan-2-iloxi)propanoato



Se agregó hidruro de sodio (62,4 mg, 1,56 mmol) a (S)-metil 2-hidroxi-3-((R)-1-metoxipropan-2-iloxi)propanoato (**Producto Intermedio Y6**) (200 mg, 1,04 mmol) en THF anhidro (5 mL) a 0°C bajo nitrógeno. La mezcla resultante se agitó durante 10 minutos a 0°C y luego se agregó 4-cloro-1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio B15**) (360 mg, 1,35 mmol) y la reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 1 hora. La mezcla de reacción se diluyó con acetato de etilo (20 mL) y se lavó secuencialmente con agua (10 mL) y salmuera saturada (5 mL). La capa orgánica se secó ($MgSO_4$) y se evaporó. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0-100% acetato de etilo en isohexano para proporcionar el producto (245 mg, 55,8 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,19 (d, 3H), 3,33 - 3,48 (m, 5H), 3,74 - 3,82 (m, 4H), 4,13 - 4,18 (m, 2H), 5,81 - 5,86 (m, 1H), 7,43 - 7,48 (m, 1H), 7,98 - 8,02 (m, 1H), 8,39 - 8,41 (m,

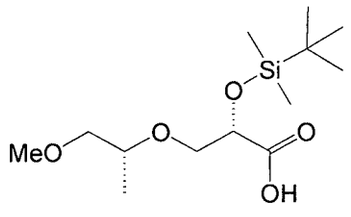
1H), 8,58 (s, 1H), 8,60 - 8,63 (m, 1H); m/z (ESI+) (M+H)+ = 422,36; HPLC t_R = 1,93 min.

Producto Intermedio Y9: (S)-Metil 2-(terc-butildimetilsililoxi)-3-((R)-1-metoxipropan-2-iloxi)propanoato



Se agregó terc-butilclorodimetilsilano (7,09 g, 47,01 mmol) a (S)-metil 2-hidroxi-3-((R)-1-metoxipropan-2-iloxi)propanoato (**Producto Intermedio Y6**) (7,53 g, 39,18 mmol) y 1H-imidazol (5,33 g, 78,35 mmol) en DMF (50 mL) a temperatura ambiente bajo nitrógeno. La solución resultante se agitó a 40°C durante 5 horas. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en acetato de etilo (125 mL) y se lavó secuencialmente con agua (50 mL) y salmuera saturada (25 mL). La capa orgánica se secó ($MgSO_4$) y se evaporó. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 50% acetato de etilo en isohexano para proporcionar el producto (2,58 g, 21,5%). ^{1}H NMR (400 MHz, DMSO) δ -0,01 (d, 6H), 0,81 (s, 9H), 0,97 (d, 3H), 3,13 - 3,29 (m, 5H), 3,49 - 3,64 (m, 6H), 4,26 - 4,31 (m, 1H); m/z (ESI+) M-C_4H_9 = 249; GC t_R = 10,92 min.

Producto Intermedio Y10: Ácido (S)-2-(terc-butildimetilsililoxi)-3-((R)-2-metoxipropoxi)propanoico

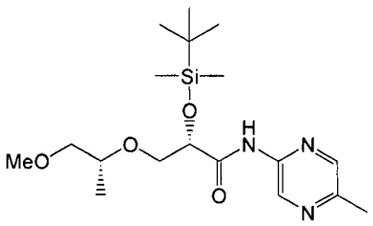


Se agregó yoduro de litio (4,51 g, 33,67 mmol) a (S)-metil 2-(terc-butildimetilsililoxi)-3-((R)-2-metoxipropoxi) propanoato (**Producto Intermedio Y9**) (2,58 g, 8,42 mmol) en acetato de etilo (15 mL). La suspensión resultante se protegió de la luz y se agitó a reflujo (75°C) durante 6 horas. La mezcla de reacción se diluyó con acetato de etilo (75 mL) se lavó secuencialmente con metabisulfito de sodio 1M (25 mL), agua (25 mL) y salmuera saturada (25 mL). La capa orgánica se secó ($MgSO_4$) y se evaporó para proporcionar el

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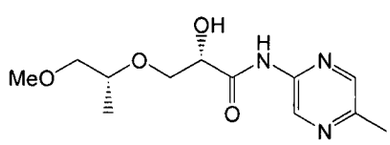
producto bruto (1,166 g, 47,4 %) que se utilizó sin purificación adicional.

Producto Intermedio Y11: (S)-2-(terc-butildimetilsililoxi)-3-((R)-1-metoxipropan-2-iloxi)-N-(5-metilpirazin-2-il)propanamida



Se agregó 1-cloro-N,N,2-trimetilprop-1-en-1-amina (0,170 mL, 1,28 mmol) a una solución agitada de ácido (S)-2-(terc-butildimetilsililoxi)-3-((R)-1-metoxipropan-2-iloxi)propanoico (**Producto Intermedio Y10**) (250 mg, 0,85 mmol) en DCM (5 mL) a temperatura ambiente bajo nitrógeno. La solución resultante se agitó a temperatura ambiente durante 30 minutos. Una solución de 5-metilpirazin-2-amina (140 mg, 1,28 mmol) en DCM (5 mL) se agregó a la mezcla de reacción y la solución resultante se agitó a temperatura ambiente durante 16 horas. La mezcla de reacción se aplacó con agua (20 mL), se extrajo con DCM (2 × 25 mL), las capas orgánicas combinadas se secaron ($MgSO_4$) y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 90% acetato de etilo en isohexano para proporcionar el producto (170 mg, 51,8 %). ^1H NMR (400 MHz, DMSO) δ 0,01 (d, 6H), 0,80 (s, 9H), 0,91 (d, 3H), 2,35 (s, 3H), 3,09 - 3,23 (m, 5H), 3,47 - 3,63 (m, 3H), 4,35 - 4,40 (m, 1H), 8,20 (s, 1H), 9,09 (s, 1H), 9,63 (s, 1H); m/z (ESI+) $(M+H)^+$ = 384,43; HPLC t_R = 2,99 min.

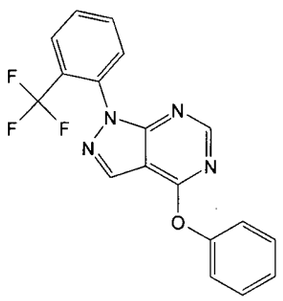
Producto Intermedio Y12: (S)-2-hidroxi-3-((R)-2-metoxipropoxi)-N-(5-metilpirazin-2-il)propanamida



Se agregó fluoruro de tetrabutilamonio (881 µl, 0,88 mmol) a (S)-2-(terc-butildimetilsililoxi)-3-((R)-2-metoxipropoxi)-N-(5-metilpirazin-2-il)propanamida (**Producto Intermedio Y11**) (169 mg, 0,44 mmol) en THF (2203 µl) a temperatura ambiente bajo nitrógeno. La solución resultante se agitó a temperatura ambiente durante 3 horas. La mezcla de reacción se aplacó con agua (5 mL), se extrajo con acetato de etilo

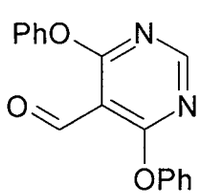
(3 × 10 mL), la capa orgánica se lavó a contracorriente con agua (5 mL), se secó ($MgSO_4$) y se evaporó. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 100% acetato de etilo en isohexano para proporcionar el producto (64,0 mg, 53,9 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,13 (d, 3H), 2,53 (s, 3H), 3,33 - 3,43 (m, 5H), 3,68 - 3,82 (m, 2H), 4,04 - 4,11 (m, 1H), 4,33 (t, 1H), 4,53 (s, 1H), 8,12 - 8,15 (m, 1H), 9,19 (s, 1H), 9,43 (d, 1H); m/z (ESI+) (M+H)+ = 270,24; HPLC t_R = 1,04 min.

Producto Intermedio Z1: 4-fenoxi-1-(2-(trifluorometil)fenil)-1H-pirazolo[3,4-d]pirimidina



Se agregó (2-(trifluorometil)fenil)hidrazina (CAS no. 365-34-4) (102 mg, 0,58 mmol) a 4,6-difenoxipirimidina-5-carbaldehído (**Producto Intermedio Z2**) (169 mg, 0,58 mmol) en THF (2 mL) y la solución resultante se agitó a temperatura ambiente durante 5 minutos. Se agregó 2-terc-butilimino-2-dietilamino-1,3-dimetil-perhidro-1,3,2-diazafosphorina en poliestireno (526 mg, 1,16 mmol) y se selló en un tubo de microondas. La reacción se calentó hasta alcanzar 150°C durante 10 horas en un reactor de microondas y se enfrió hasta alcanzar la TA. La mezcla de reacción se filtró y se evaporó hasta secarse. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 10 a 80% acetato de etilo en isohexano para proporcionar el producto (88 mg, 42,7 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7,29 - 7,33 (2H, m), 7,34 - 7,39 (1H, m), 7,49 - 7,58 (3H, m), 7,67 - 7,71 (1H, m), 7,74 - 7,78 (1H, m), 7,90 - 7,92 (1H, m), 8,08 (1H, s), 8,56 (1H, s); m/z (ES+) (M+H)+ = 357; HPLC tR = 2,66 min.

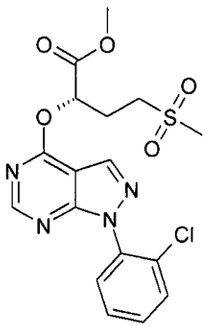
Producto Intermedio Z2: ácido (S)-2-acetoxi-4-metoxibutanoico



Se agregó carbonato de potasio (6,08 g, 44,00 mmol) un fenol (2,070 g, 22,00 mmol) en

THF (20 mL) bajo nitrógeno. La suspensión resultante se agitó a temperatura ambiente durante 30 minutos. Se agregó 4,6-dicloro-5-pirimidinacarbaldehído (1,770 g, 10 mmol) y la mezcla se agitó durante toda la noche bajo nitrógeno. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en DCM (100 mL) y se lavó secuencialmente con agua (150 mL). La capa orgánica se secó ($MgSO_4$) y se evaporó. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 50% acetato de etilo en isohexano para proporcionar el producto (2,54 g, 87 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7,19 (4H, d), 7,31 (2H, t), 7,44 - 7,48 (4H, m), 8,40 (1H, s), 10,67 (1H, s); m/z (ES+) $(M+H)^+$ = 293; HPLC tR = 2,48 min.

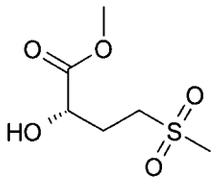
Producto Intermedio AA1: (2S)-metil 2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-4-(metilsulfonil)butanoato



Se agregó hidruro de sodio (58,7 mg, 1,47 mmol) a (S)-metil 2-hidroxi-4-(metilsulfonil)butanoato (**Producto Intermedio AA2**) (120 mg, 0,61 mmol) en THF anhidro (50 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos y luego se agregó 4-cloro-1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio B1**) (357 mg, 0,67 mmol). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 3 horas. La mezcla de reacción se neutralizó con ácido cítrico 1M y la mayor parte del THF se eliminó al vacío. La mezcla de reacción se diluyó con agua (20 mL) y acetato de etilo (50 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con acetato de etilo (2 × 100 mL). Los elementos orgánicos combinados se lavaron con salmuera saturada (75 mL), se secaron ($MgSO_4$) y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 50 a 100% acetato de etilo en isohexano para proporcionar el producto (160 mg, 61,6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2,60 - 2,75 (2H, m), 3,01 (3H, s), 3,25 - 3,38 (2H, m), 3,82 (3H, s), 5,79 - 5,82 (1H, m), 7,44 - 7,54 (3H, m), 7,61 - 7,63 (1H, m), 8,34

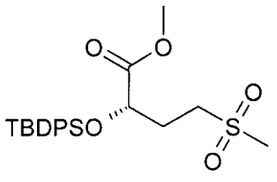
(1H, s), 8,54 (1H, s); m/z (ES+) (M+H)+ = 425; HPLC tR = 2,01 min.

Producto Intermedio AA2: (S)-metil 2-hidroxi-4-(metilsulfonil)butanoato



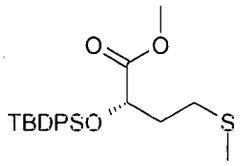
Se agregó fluoruro de tetrabutilamonio (1M en THF) (2071 µl, 2,07 mmol) a (S)-metil 2-(terc-butildifenilsililoxi)-4-(metilsulfonil)butanoato (**Producto Intermedio AA3**) (450 mg, 1,04 mmol) en THF (3106 µl) bajo nitrógeno. La mezcla resultante se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se aplacó con NH_4Cl saturado (10 mL), se extrajo con Et_2O (3 × 15 mL). Las capas orgánicas combinadas se lavaron a contracorriente con agua (10 mL), se secaron ($MgSO_4$) y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 100% acetato de etilo en isohexano para proporcionar el producto (120 mg, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2,10 - 2,20 (1H, m), 2,38 - 2,46 (1H, m), 2,94 (4H, m), 3,10 - 3,24 (2H, m), 3,84 (3H, s), 4,34 (1H, q), 7,26 (3H, s).

Producto Intermedio AA3: (S)-metil 2-(terc-butildifenilsililoxi)-4-(metilsulfonil)butanoato



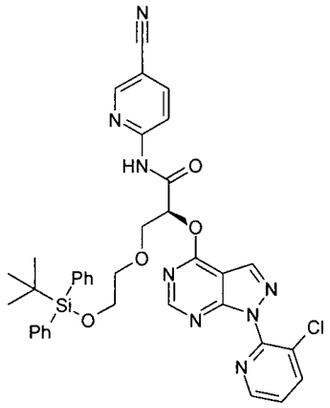
Se agregó ácido 3-cloroperoxibenzoico (753 mg, 3,05 mmol) en una porción a (S)-metil 2-(terc-butildifenilsililoxi)-4-(metiltio)butanoato (**Producto Intermedio AA4**) (410 mg, 1,02 mmol) en diclorometano (20 mL) a 25°C. La suspensión resultante se agitó a 25°C durante 2 horas. La mezcla de reacción se aplacó con $NaHCO_3$ saturado (50 mL), se lavó con agua (1 × 50 mL), la capa orgánica se secó ($MgSO_4$) y se evaporó para proporcionar el producto (420 mg, 95%) que se utilizó sin purificación adicional. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,10 (9H, s), 2,18 - 2,24 (2H, m), 2,83 (3H, s), 3,00 - 3,04 (1H, m), 3,12 - 3,18 (1H, m), 3,52 (3H, s), 4,38 (1H, t), 7,35 - 7,47 (6H, m), 7,61 - 7,65 (4H, m); m/z (ES+) $(M+NH_4)^+$ = 452; HPLC tR = 3,0 min.

Producto Intermedio AA4: (S)-metil 2-(terc-butildifenilsililoxi)-4-(metiltio)butanoato



Se agregó tiometóxido de sodio (0,187 g, 2,67 mmol) a (S)-3-(terc-butildifenilsililoxi)dihidrofuran-2(3H)-ona (CAS no. 220351-82-6: Klar, U.; Schwede, W.; Skuballa, W.; Buchmann, B.; Schirner, M. Ger. Offen. 1999 DE 19735575 A1) (0,826 g, 2,43 mmol) en DMF (2 mL) a 0°C . La solución resultante se agitó a temperatura ambiente durante 16 horas. La mezcla de reacción se neutralizó con HCl 2M y se diluyó con acetato de etilo. La capa orgánica se extrajo con agua (3 × 100 mL), la capa orgánica se secó ($MgSO_4$) y se evaporó para proporcionar ácido (S)-2-(terc-butildifenilsililoxi)-4-(metiltio)butanoico (0,160 g, 16,98 %) que se utilizó sin purificación adicional. Se agregó una solución de trimetilsilildiazometano (solución 2M en éter, 0,412 ml, 0,82 mmol) gota a gota a una solución agitada de alcohol metílico (0,167 ml, 4,12 mmol) y ácido (S)-2-(terc-butildifenilsililoxi)-4-(metiltio)butanoico (0,160 g, 0,41 mmol) en tolueno (0,174 ml) durante un período de 2 minutos. La solución resultante se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se aplacó con ácido acético (0,071 ml, 1,24 mmol) y se agitó a temperatura ambiente durante 10 minutos. La mezcla de reacción se evaporó. El residuo se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 50% acetato de etilo en isohexano para proporcionar el producto (0,120 g, 72,4%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,09 (9H, s), 1,94 - 2,05 (5H, m), 2,48 - 2,60 (2H, m), 3,47 (3H, s), 4,33 - 4,36 (1H, m), 7,34 - 7,45 (6H, m), 7,62 - 7,67 (4H, m); m/z (ES+) (M-Ph)- = 325; HPLC tR = 3,63 min

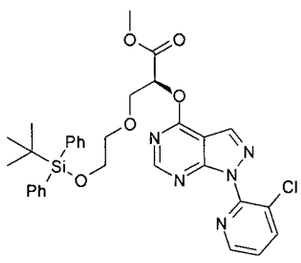
Producto Intermedio AB1: (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-cianopiridin-2-il)propanamida



Se agregó trimetilaluminio (2M en hexano) (0,455 mL, 0,91 mmol) a 6-aminonicotinonitrilo (104 mg, 0,87 mmol) en tolueno (10 mL) enfriado hasta alcanzar 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 20 minutos. Se agregó (2S)-metil 3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanoato (**Producto Intermedio AB2**) (500 mg, 0,79 mmol) en tolueno (2 mL) y la reacción se dejó entibiar hasta alcanzar la temperatura ambiente. La temperatura disminuyó hasta alcanzar 60°C y se agitó durante 4 horas, luego se calentó a reflujo durante 24 horas. La mezcla de reacción se concentró al vacío y se neutralizó con ácido cítrico (1M, ac) y luego se diluyó con agua (10ml) y DCM (10 mL). La mezcla se vertió en un separador de fases y la capa orgánica se evaporó al vacío. El producto bruto se purificó mediante HPLC preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, 50 mm de diámetro, 150 mm de longitud), utilizando mezclas cada vez menos polares de agua (que contenía ácido fórmico al 0,1%) y MeCN como eluyentes. Las fracciones que contenían el compuesto deseado se neutralizaron con MP-carbonato y se evaporaron hasta secarse para proporcionar el producto (100 mg, 17,6%).

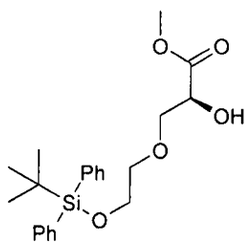
m/z (ES+) (M+H)+ = 719,51; HPLC tR = 3,58 min.

Producto Intermedio AB2: (2S)-metil 3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanoato



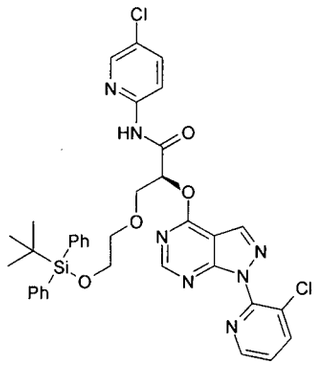
Se agregó hidruro de sodio al 60% en aceite mineral (1,013 g, 25,34 mmol) a (S)-metil 3-(2-(terc-butildifenilsililoxi)etoxi)-2-hidroxipropanoato (**Producto Intermedio AB3**) (8,5 g, 21,12 mmol) en tetrahidrofurano (150 mL) enfriado hasta alcanzar 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos. Se agregó una solución de 4-cloro-1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidina (6,18 g, 23,23 mmol) en tetrahidrofurano (20 mL) gota a gota durante un período de 5 minutos. La mezcla resultante se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 2 horas. La mezcla de reacción se aplacó con ácido cítrico 1M y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó ($MgSO_4$) y se evaporó. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 100% acetato de etilo en isohexano para proporcionar el producto (7,15 g, 53,6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,05 (9H, s), 3,68 - 3,79 (5H, m), 3,85 (2H, t), 4,08 - 4,23 (2H, m), 5,84 - 5,89 (1H, m), 7,33 - 7,48 (7H, m), 7,65 - 7,73 (4H, m), 7,97 - 8,03 (1H, m), 8,34 (1H, s), 8,58 (1H, s), 8,59 - 8,63 (1H, m); m/z (ESI+) $(M+H)^+$ = 632; HPLC tR = 3,68 min.

Producto Intermedio AB3: (S)-metil 3-(2-(terc-butildifenilsililoxi)etoxi)-2-hidroxipropanoato



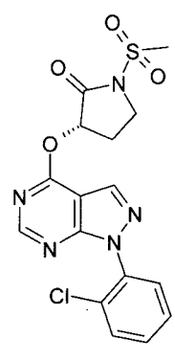
Se agregó trifluorometanosulfonato de magnesio (3,95 g, 12,24 mmol) en una porción a (S)-metil oxirano-2-carboxilato (5 g, 48,98 mmol) y 2-(terc-butildifenilsililoxi)etanol (14,72 g, 48,98 mmol) a 10°C. La suspensión resultante se agitó a 10°C durante 10 minutos y luego se entibió hasta alcanzar 45°C y se agitó durante 3 días. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 30% acetato de etilo en isohexano para proporcionar el producto (8,50 g, 43,1 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,05 (9H, s), 3,10 (1H, d), 3,62 (2H, t), 3,74 - 3,87 (7H, m), 4,26 - 4,34 (1H, m), 7,35 - 7,46 (6H, m), 7,63 - 7,71 (4H, m); m/z (ESI+) $(M+Na)^+$ = 425,37; HPLC tR = 3,15 min.

Producto Intermedio AB4: (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-N-(5-cloropiridin-2-il)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida



Se agregó trimetilaluminio (2M en hexano) (0,455 mL, 0,91 mmol) a 5-cloropiridin-2-amina (112 mg, 0,87 mmol) en tolueno (10 mL) enfriado hasta alcanzar 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 20 minutos. Se agregó (2S)-metil 3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanoato (**Producto Intermedio AB2**) (500 mg, 0,79 mmol) en tolueno (2 mL) y la reacción se calentó hasta alcanzar reflujo durante 24 horas. La mezcla de reacción se concentró al vacío y se neutralizó con ácido cítrico (1M, ac) y luego se diluyó con agua (10ml) y DCM (10 mL). La mezcla se vertió en un separador de fases y la capa orgánica se recogió y se evaporó. El material bruto se utilizó sin purificación.

Producto Intermedio AC1: (3S)-3-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-1-(metilsulfonil)pirrolidin-2-ona

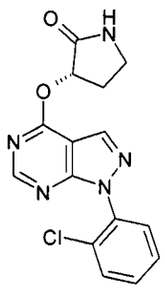


Se agregó butillitio (1,6M en hexano, 1,668 mL, 2,67 mmol) gota a gota a (3S)-3-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)pirrolidin-2-ona (**Producto Intermedio AC2**) (800 mg, 2,43 mmol) en THF (15 mL) enfriado hasta alcanzar -78°C bajo nitrógeno. La solución resultante se dejó entibiar hasta alcanzar la t.a., luego se enfrió nuevamente hasta alcanzar -78°C. Se agregó cloruro de metanosulfonilo (0,207 mL, 2,67 mmol) gota a gota y la solución resultante se agitó a t.a. durante 2 horas. La mezcla de reacción se aplacó con agua (20 mL) y se extrajo con acetato de etilo (2 × 50 mL). Las capas orgánicas

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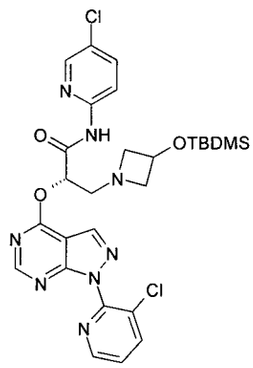
combinadas se secaron ($MgSO_4$) y se evaporaron (995 mg). El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 50 a 100% acetato de etilo en isohexano para proporcionar el producto (368 mg, 37,2%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2,35 - 2,47 (1H, m), 2,83 - 2,92 (1H, m), 3,37 (3H, s), 3,85 - 3,94 (1H, m), 4,06 - 4,16 (1H, m), 6,13 (1H, t), 7,44 - 7,56 (3H, m), 7,59 - 7,66 (1H, m), 8,32 (1H, s), 8,57 (1H, s); m/z (ES+) $(M+H)^+$ = 408,29; HPLC tR = 2,10 min.

Producto Intermedio AC2: (3S)-3-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)pirrolidin-2-ona



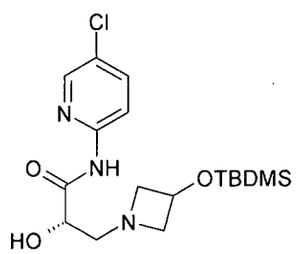
Se agregó hidruro de sodio (60% en aceite) (0,435 g, 10,88 mmol) a (S)-3-hidroxipirrolidin-2-ona (CAS no. 34368-52-0) (1 g, 9,89 mmol) en THF (50 mL) a 0°C bajo nitrógeno. La suspensión resultante se agitó a 0°C durante 10 minutos. Se agregó una solución de 4-cloro-1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio B15**) (4,01 g, 15,13 mmol) en DMF (25 mL) y la mezcla resultante se agitó a t.a. durante 16 horas. La mezcla de reacción se aplacó con agua (20 mL) y se extrajo con acetato de etilo (2 × 50 mL). Las capas orgánicas combinadas se secaron ($MgSO_4$) y se evaporaron (3,8 g). El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0-50% MeOH en acetato de etilo para proporcionar el producto (0,810 g, 24,8%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2,30 - 2,42 (1H, m), 2,81 - 2,91 (1H, m), 3,45 - 3,64 (2H, m), 6,05 (1H, t), 6,44 (1H, s), 7,42 - 7,51 (2H, m), 7,51 - 7,56 (1H, m), 7,57 - 7,66 (1H, m), 8,33 (1H, s), 8,60 (1H, s);
m/z (ES+) $(M+H)^+$ = 330,27; HPLC tR = 1,61 min.

Producto Intermedio AD1: (2S)-3-[3-(terc-butil-dimetilsilil)oxiazetidin-1-il]-N-(5-cloropiridin-2-il)-2-[1-(3-cloropiridin-2-il)pirazolo[4,5-e]pirimidin-4-il]oxipropanamida



Se agregó hidruro de sodio (0,715 g, 17,88 mmol) a (S)-3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-N-(5-cloropiridin-2-il)-2-hidroxipropanamida (**Producto Intermedio AD2**) (2,3 g, 5,96 mmol) en THF anhidro (25 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos y luego se agregó 4-cloro-1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio B15**) (2,265 g, 5,96 mmol). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 3 horas. La mezcla de reacción se neutralizó con ácido cítrico 1M y se diluyó con agua (25 mL) y EtOAc (50 mL). La capa orgánica se separó y se lavó con salmuera saturada (25 mL), se secó ($MgSO_4$) y se evaporó para proporcionar el producto (3,67g, 100%) que se utilizó para la siguiente etapa sin purificación. m/z (ESI+) $(M+H)^+ = 615$; HPLC $t_R = 2,43$ min.

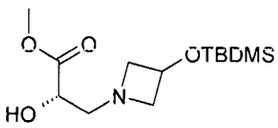
Producto Intermedio AD2: (2S)-3-[3-(terc-butil-dimetilsilil)oxiazetidin-1-il]-N-(5-cloropiridin-2-il)-2-hidroxipropanamida



Se agregó trimetilaluminio (5,75 mL, 11,50 mmol) a 5-cloropiridin-2-amina (1,285 g, 10,00 mmol) en tolueno (50 mL) enfriado hasta alcanzar 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos, se agregó (S)-metil 3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-hidroxipropanoato (**Producto Intermedio AD3**) (2,894 g, 10,00 mmol) en tolueno (20 mL), la reacción se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó a 80°C durante 4 horas. La mezcla de reacción se enfrió, se concentró al vacío y el residuo se neutralizó con ácido cítrico 1M (30 mL), se

diluyó con agua (25 mL) y se extrajo con EtOAc (2 x 30 mL). Los extractos orgánicos combinados se secaron ($MgSO_4$) y se evaporaron para proporcionar el producto bruto que se purificó mediante cromatografía instantánea en sílice con EtOAc como eluyente para proporcionar el producto (2,5g, 65%). ^{1}H NMR (400 MHz, DMSO) δ 0,01 (6H, s), 0,84 (9H, m), 2,65 - 2,70 (2H, m), 2,76 - 2,83 (2H, m), 3,56 - 3,59 (2H, m), 4,07 - 4,10 (1H, m), 4,28 - 4,34 (1H, m), 5,78 (1H, s), 7,92 (1H, dd), 8,12 (1H, dd), 8,36 - 8,37 (1H, m), 9,87 (1H, s); m/z (ESI+) $(M+H)^+$ = 386; HPLC t_R = 1,64 min.

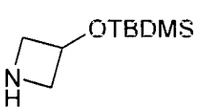
Producto Intermedio AD3: Metil (2S)-3-[3-(terc-butil-dimetilsilil)oxiazetidin-1-il]-2-hidroxipropanoato



Se disolvió 3-(terc-butildimetilsililoxi)azetidina (**Producto Intermedio AD4**) (11,0 g, 58,71 mmol) y (S)-metil oxirano-2-carboxilato (5,99 g, 58,71 mmol) en butironitrilo (75 mL) y se calentó hasta alcanzar 100°C durante 90 minutos. La reacción pasó de ser incolora a amarilla durante el período de calentamiento. La mezcla resultante se enfrió y se evaporó. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 0 a 5% MeOH en EtOAc, para proporcionar el producto (9,6g, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0,04 (6H, s), 0,85 (9H, s), 2,71 - 2,79 (2H, m), 2,87 - 2,95 (2H, m), 3,58 - 3,68 (2H, m), 3,75 (3H, s), 4,10 - 4,12 (1H, m), 4,35 - 4,39 (1H, t) (no se observó señal de OH).

El procedimiento también puede llevarse a cabo en una manera análoga utilizando azetidin-3-iloxi-terc-butil-dimetilsilano y difenilmetano (1:1) (**Producto Intermedio AD5**).

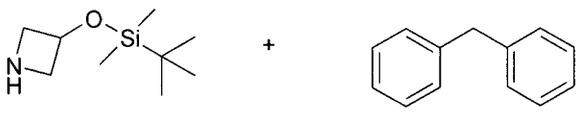
Producto Intermedio AD4: Azetidin-3-iloxi-terc-butil-dimetilsilano



Una solución de terc-butilclorodimetilsilano (12,01 g, 79,69 mmol) en DCM (20 mL) se agregó gota a gota a una solución agitada de azetidin-3-ol clorhidrato (CAS no. 18621-18-6) (8,73 g, 79,69 mmol) y N-etil-N-isopropilpropan-2-amina anhidra (34,1 mL, 199,22 mmol) en DCM (20 mL) enfriado hasta alcanzar 10°C, durante un período de 2 minutos bajo nitrógeno. La solución resultante se agitó a temperatura ambiente durante 20 horas. La

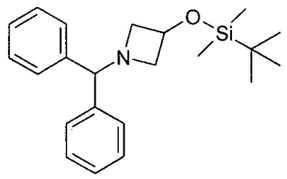
mezcla de reacción se concentró, se diluyó con EtOAc (75 mL) y se lavó secuencialmente con $NaHCO_3$ saturado (25 mL), agua (20 mL) y salmuera saturada (20 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el producto (11,1 g, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0,04 (6H, s), 0,87 (9H, m), 2,80 (1H, s), 3,57 - 3,61 (2H, m), 3,67 - 3,71 (2H, m), 4,57 - 4,64 (1H, m).

Producto Intermedio AD5: Azetidin-3-iloxi-terc-butil-dimetilsilano y difenilmetano (1:1)



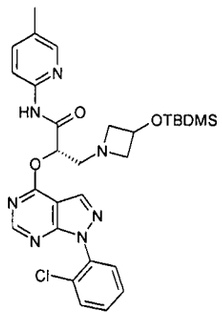
Se agitaron 1-benzhidril-3-(terc-butildimetilsililoxi)azetidina (**Producto Intermedio AD6**) (3,12 g, 8,82 mmol) y paladio sobre carbono (0,3 g, 0,28 mmol) en metanol (60 mL) bajo una atmósfera de hidrógeno a temperatura ambiente durante 18 horas. La mezcla de reacción se filtró y se concentró hasta proporcionar un líquido incoloro, compuesto de 3-(terc-butildimetilsililoxi)azetidina con difenilmetano (1:1) (3,02 g, 96 %). Esto se utilizó sin purificación adicional. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0,00 (6H, s), 0,84 (9H, s), 3,52 - 3,58 (2H, m), 3,61 - 3,67 (2H, m), 3,95 (2H, s), 4,55 - 4,63 (1H, m), 7,12 - 7,27 (10H, m), 7,64 (1H, s).

Producto Intermedio AD6: (1-Benzhidrilazetidin-3-il)oxi-terc-butil-dimetilsilano



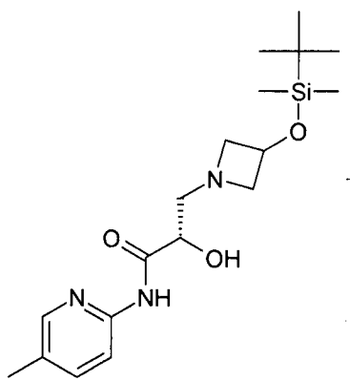
Se agregó cloruro de terc-butildimetilsililo (1,524 g, 10,11 mmol) a 1-benzhidrilazetidin-3-ol (CAS no. 18621-17-5) (2,2 g, 9,19 mmol) e imidazol (1,565 g, 22,98 mmol) en DCM (46,0 mL) a t.a. bajo nitrógeno. La solución resultante se agitó a t.a. durante 3 horas. La mezcla de reacción se aplacó con agua, se vertió en un separador de fases y se evaporó para proporcionar el producto (3,66 g, 113 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0,00 (6H, s), 0,85 (9H, s), 2,81 (2H, s), 3,52 (2H, s), 4,35 (1H, s), 4,40 - 4,49 (1H, m), 7,08 - 7,43 (10H, m); m/z (ES+) $(M+H)^+$ = 354,55; HPLC t_R = 2,04 min.

Producto Intermedio AD7: (2S)-3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-metilpiridin-2-il)propanamida



Se agregó hidruro de sodio (132 mg, 3,30 mmol) a (S)-3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-hidroxi-N-(5-metilpiridin-2-il)propanamida (**Producto Intermedio AD8**) (482 mg, 1,32 mmol) en THF anhidro (5 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos y se agregó luego 4-cloro-1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio B1**) (385 mg, 1,45 mmol). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 3 horas. La mezcla de reacción se neutralizó con ácido cítrico 1M y se diluyó con agua y EtOAc. La capa orgánica se separó y se lavó con salmuera saturada, se secó ($MgSO_4$) y se evaporó para proporcionar el producto (908 mg) que se utilizó sin purificación adicional. m/z (ES+) $(M+H)^+$ = 594,52; HPLC t_R = 1,87 min.

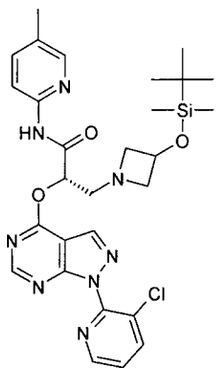
Producto Intermedio AD8: (S)-3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-hidroxi-N-(5-metilpiridin-2-il)propanamida



Se agregó trimetilaluminio (2M en tolueno) (0,993 mL, 1,99 mmol) a 5-metilpiridin-2-amina (205 mg, 1,90 mmol) en tolueno (10 mL) enfriado hasta alcanzar 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos. Se agregó (S)-metil 3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-hidroxipropanoato (**Producto Intermedio AD3**) (500 mg, 1,73 mmol) en tolueno (4 mL) y la reacción se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó a 80°C durante 4 horas. La mezcla de reacción

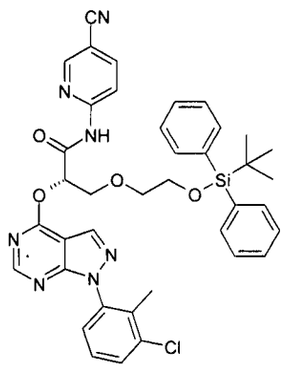
se concentró al vacío. El residuo se neutralizó con ácido cítrico (1M, ac) y luego se diluyó con agua y se extrajo con EtOAc. Los elementos orgánicos combinados se secaron ($MgSO_4$) y se evaporaron para proporcionar el producto (482 mg, 76 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0,05 (6H, s), 0,88 (9H, s), 2,30 (3H, s), 3,15 - 3,23 (1H, m), 3,37 - 3,51 (3H, m), 4,15 - 4,30 (2H, m), 4,32 - 4,39 (1H, m), 4,58 - 4,66 (1H, m), 7,48 - 7,53 (1H, m), 8,04 (1H, d), 8,12 - 8,15 (1H, m), 9,46 (1H, s); m/z (ES+) $(M+H)^+$ = 366,53; HPLC t_R = 1,50 min.

Producto Intermedio AD9: (2S)-3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-metilpiridin-2-il)propanamida



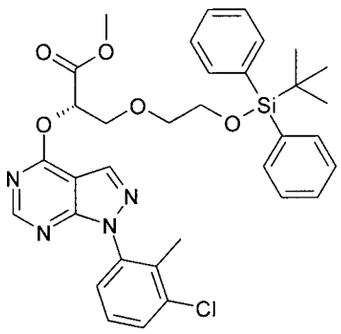
Se agregó hidruro de sodio (15,76 mg, 0,39 mmol) a (S)-3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-hidroxi-N-(5-metilpiridin-2-il)propanamida (**Producto Intermedio AD8**) (120 mg, 0,33 mmol) en THF anhidro (5 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos y luego se agregó 4-cloro-1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio B15**) (96 mg, 0,36 mmol). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 5 horas. Se agregó una porción adicional de hidruro de sodio (15,76 mg, 0,39 mmol) y se continuó agitando durante 1 hora más. La mezcla de reacción se neutralizó con ácido cítrico 1M y se diluyó con agua y EtOAc. La capa orgánica se separó y se lavó con salmuera saturada, se secó ($MgSO_4$) y se evaporó para proporcionar el producto (195 mg). m/z (ES+) $(M+H)^+$ = 595,61; HPLC t_R = 1,83 min.

Producto Intermedio AE1: (2S)-3-[2-(terc-butil-difenilsilil)oxietoxi]-2-[1-(3-cloro-2-metilfenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-cianopiridin-2-il)propanamida



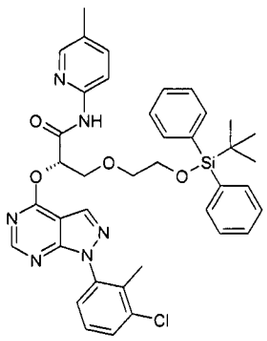
Una solución de trimetilaluminio 2M en tolueno (1,790 mL, 3,58 mmol) en tolueno (15 mL) se agregó gota a gota a una suspensión agitada de 6-aminonicotinonitrilo (0,426 g, 3,58 mmol) en tolueno (15 mL) enfriado hasta alcanzar 0°C, durante un período de 2 minutos bajo nitrógeno y la suspensión resultante se agitó durante 20 minutos a 0°C. Se agregó una solución de (2S)-metil 3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(3-cloro-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanoato (**Producto Intermedio AE2**) (1,05 g, 1,63 mmol) en tolueno (10 mL) gota a gota durante 2 minutos, la mezcla se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó hasta alcanzar 60°C durante 20hrs. Se enfrió hasta alcanzar ~5°C y se agregó una solución de sal de Rochelle al 10% (25 mL) y luego acetato de etilo (30 mL) y se agitó a temperatura ambiente durante 30 minutos. La fase orgánica se separó, se lavó con agua (20 mL) y salmuera (20 mL), se secó ($MgSO_4$), se filtró y se evaporó hasta proporcionar una goma amarilla. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 20 a 50% EtOAc en isohexano para proporcionar el producto (1,1g, 92%). ^{1}H NMR (400 MHz, DMSO) δ 0,89 (9H, s), 2,03 (3H, s), 3,71 - 3,78 (4H, m), 4,05 - 4,10 (1H, m), 4,14 - 4,19 (1H, m), 6,00 - 6,02 (1H, m), 7,34 - 7,45 (8H, m), 7,59 - 7,61 (4H, m), 7,67 - 7,69 (1H, m), 8,11 - 8,14 (1H, m), 8,20 - 8,23 (1H, m), 8,51 (1H, s), 8,84 (1H, s), 8,80 - 8,82 (1H, m), 11,55 (1H, s); m/z (ESI+) $(M+H)^+$ = 732; HPLC t_R = 3,48 min.

Producto Intermedio AE2: (2S)-Metil 3-[2-(terc-butil-difenilsilil)oxietoxi]-2-[1-(3-cloro-2-metilfenil)pirazolo[4,5-e]pirimidin-4-il]oxipropanoato



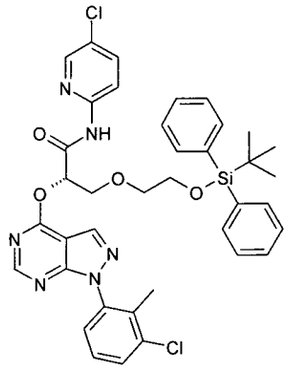
Se agregó hidruro de sodio (60% en aceite mineral) (0,191 g, 4,77 mmol) en una porción a (S)-metil 3-(2-(terc-butildifenilsililoxi)etoxi)-2-hidroxipropanoato (**Producto Intermedio AB3**) (1,6 g, 3,97 mmol) en THF (15 mL) enfriado hasta alcanzar 0°C bajo nitrógeno. Se produjo un lento desprendimiento de gas. La suspensión resultante se agitó a 0°C durante 10 minutos. Una solución de 4-cloro-1-(3-cloro-2-metilfenil)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio AE5**) (1,109 g, 3,97 mmol) en THF (10 mL) se agregó gota a gota durante 2 minutos. La suspensión resultante se agitó a 0°C durante 10 minutos, se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 72 horas para proporcionar una solución naranja. Se enfrió hasta alcanzar ~5°C, se agregó ácido cítrico 1M (30 mL), la mezcla se agitó durante 10 minutos, se diluyó con EtOAc (50 mL), la fase orgánica se separó y se lavó secuencialmente con agua (25 mL) y salmuera saturada (25 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó al vacío. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 20 a 50% EtOAc en isohexano para proporcionar el producto (2,1g, 82%). ^{1}H NMR (400 MHz, DMSO) δ 0,95 (9H, s), 2,03 (3H, s), 3,68 (3H, s), 3,67 - 3,74 (2H, m), 3,78 - 3,82 (2H, m), 4,04 - 4,07 (1H, m), 4,11 - 4,15 (1H, m), 5,87 - 5,91 (1H, m), 7,37 - 7,45 (8H, m), 7,61 - 7,65 (4H, m), 7,67 - 7,69 (1H, m), 8,48 (1H, s), 8,57 (1H, s); m/z (ESI+) $(M+H)^+$ = 645; HPLC t_R = 3,65 min.

Producto Intermedio AE3: (2S)-3-[2-(terc-butil-dimetilsilil)oxietoxi]-2-[1-(3-cloro-2-metilfenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-metilpiridin-2-il)propanamida



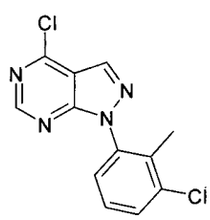
Una solución de 2M trimetilaluminio en tolueno (1,790 mL, 3,58 mmol) en tolueno (15 mL) se agregó gota a gota a una suspensión agitada de 5-metilpiridin-2-amina (0,387 g, 3,58 mmol) en tolueno (15 mL) enfriado hasta alcanzar 0°C, durante un período de 2 minutos bajo nitrógeno y la suspensión resultante se agitó a 0°C durante 20 minutos. Una solución de (2S)-metil 3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(3-cloro-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanoato (**Producto Intermedio AE2**) (1,05 g, 1,63 mmol) en tolueno (10 mL) se agregó gota a gota durante 2 minutos, la mezcla se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó hasta alcanzar 60°C durante 20hrs. La reacción se enfrió hasta alcanzar ~5°C y se agregó una solución de sal de Rochelle al 10% (25 mL) y luego acetato de etilo (30 mL). La fase orgánica se separó, se lavó con agua (20 mL) y salmuera (20 mL), se secó ($MgSO_4$), se filtró y se evaporó. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 20 a 50% EtOAc en iso-hexano para proporcionar el producto (1,1g, 94%). ^{1}H NMR (400 MHz, DMSO) δ 0,89 (9H, s), 2,03 (3H, s), 2,24 (3H, s), 3,70 - 3,79 (4H, m), 4,03 - 4,07 (1H, m), 4,12 - 4,16 (1H, m), 5,99 - 6,00 (1H, m), 7,33 - 7,47 (8H, m), 7,55 - 7,62 (5H, m), 7,67 - 7,69 (1H, m), 7,86 - 7,89 (1H, m), 8,17 - 8,18 (1H, m), 8,50 (1H, s), 8,53 (1H, s), 10,87 (1H, s); m/z (ESI+) $(M+H)^+$ = 721; HPLC t_R = 3,63 min.

Producto Intermedio AE4: (2S)-3-[2-(terc-butil-difenilsilil)oxietoxi]-2-[1-(3-cloro-2-metilfenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-cloropiridin-2-il)propanamida



Se agregó hidruro de sodio (60% en aceite mineral) (88 mg, 2,20 mmol) en una porción a (S)-3-(2-(terc-butildifenilsililoxi)etoxi)-N-(5-cloropiridin-2-il)-2-hidroxipropanamida (**Producto Intermedio AU3**) (499 mg, 1,00 mmol) en THF (25 mL) enfriado hasta alcanzar 0°C bajo nitrógeno. Se produjo un lento desprendimiento de gas y la suspensión resultante se agitó a 0°C durante 10 minutos. Se agregó 4-cloro-1-(3-cloro-2-metilfenil)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio AE5**) (279,1 mg, 1,00 mmol) en una porción, se agitó a 0°C durante 10 minutos, se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 20 horas. Se enfrió hasta alcanzar ~5°C, se agregó ácido cítrico 1M (30 mL) y la mezcla se agitó durante 10 minutos. La mezcla se diluyó con EtOAc (50 mL), la fase orgánica se separó y se lavó secuencialmente con agua (25 mL) y salmuera saturada (25 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el producto bruto que se purificó mediante cromatografía instantánea en sílice, gradiente de elución 20 a 50% EtOAc en isohexano para proporcionar el producto (550mg, 74%). ^{1}H NMR (400 MHz, DMSO) δ 0,89 (9H, s), 2,03 (3H, s), 3,70 - 3,79 (4H, m), 4,02 - 4,18(2H, m), 5,98 - 6,03 (1H, d), 7,32 - 7,47 (8H, m), 7,59 - 7,62 (4H, m), 7,67 - 7,69 (1H, m), 7,86 - 7,88 (1H, m), 8,00 - 8,03 (1H, m), 8,39 (1H, dd), 8,51 (1H, s), 8,54 (1H, s), 11,19 (1H, s); m/z (ESI+) $(M+H)^+$ = 741/743/745 (Cl_2 pattern); HPLC t_R = 3,83 min.

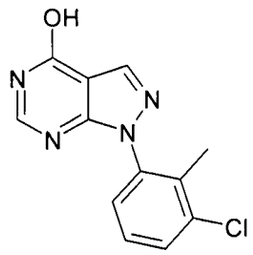
Producto Intermedio AE5: 4-Cloro-1-(3-cloro-2-metilfenil)pirazolo[5,4-d]pirimidina



Se agregó tricloruro de fosforilo (16,09 mL, 172,63 mmol) en una porción a 1-(3-cloro-2-

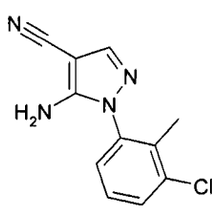
metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-ol (**Producto Intermedio AE6**) (3,0 g, 11,51 mmol) y la suspensión resultante se calentó hasta alcanzar 100°C para proporcionar una solución y se agitó durante 4 horas. Se evaporó, el residuo se vertió en hielo/agua y se agitó durante 30 minutos. Los sólidos se filtraron, se lavaron con agua (4 × 20 mL), se disolvieron en acetato de etilo (100 mL), se secaron ($MgSO_4$), se filtraron y se evaporaron para proporcionar el producto (2,8 g) que se utilizó sin purificación adicional. ^{1}H NMR (400 MHz, DMSO) δ 2,06 (3H, s), 7,41 - 7,54 (2H, m), 7,71 - 7,73 (1H, m), 8,79 (1H, s), 8,89 (1H, s); m/z (ESI+) $(M+H)^+$ = 279; HPLC t_R = 2,59 min.

Producto Intermedio AE6: 1-(3-cloro-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-ol



Se agregó ácido sulfúrico concentrado (1,595 mL, 29,93 mmol) a una solución agitada de 5-amino-1-(3-cloro-2-metilfenil)-1H-pirazol-4-carbonitrilo (**Producto Intermedio AE7**) (6,33 g, 27,21 mmol) en ácido fórmico (40 mL). La solución resultante se agitó a 100°C durante 24 horas. La reacción se dejó enfriar hasta alcanzar la temperatura ambiente y se evaporó hasta proporcionar ~la mitad del volumen, se agregó agua (100 mL) y se agitó durante 1 hora. El precipitado formado se retiró mediante filtración, se lavó bien con agua y se secó durante toda la noche en un vacío sobre P_2O_5 para proporcionar el producto (5,82 g, 82 %). ^{1}H NMR (400 MHz, DMSO) δ 2,04 (3H, s), 7,37 - 7,46 (2H, m), 7,64 - 7,68 (1H, m), 8,06 (1H, d), 8,33 (1H, s), 12,35 (1H, s); m/z (ES-) (M-H)- = 259,24; HPLC t_R = 1,68 min.

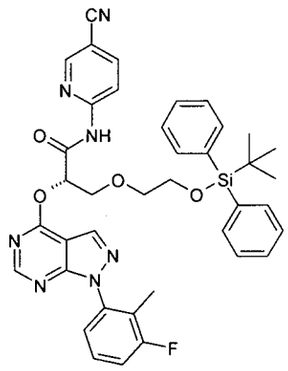
Producto Intermedio AE7: 5-amino-1-(3-cloro-2-metilfenil)-1H-pirazol-4-carbonitrilo



Se dividió (3-cloro-2-metilfenil)hidrazina clorhidrato (CAS no. 65208-12-0) (9 g, 46,61 mmol) entre EtOAc (100 mL) y NaOH (2M, ac) (60 mL). La capa orgánica se

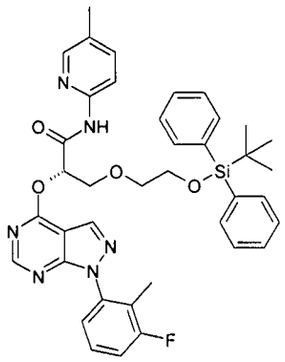
separó y se lavó con agua (50 mL), salmuera (50 mL), se secó ($MgSO_4$), se filtró y se concentró. El aceite resultante se suspendió en MeOH (100 mL) bajo nitrógeno a -5°C. Se agregó 2-(etoximetileno)malononitrilo (5,69 g, 46,61 mmol) en porciones durante 5 mins y la mezcla se agitó a ~0°C durante 30 mins. La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó a reflujo bajo nitrógeno durante 2 horas. La mezcla de reacción se dejó enfriar y se evaporó hasta secarse. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 0 a 50% EtOAc en isohexano para proporcionar el producto (6,33 g, 58,4 %). ^{1}H NMR (400 MHz, DMSO) δ 2,02 (3H, s), 6,57 (2H, s), 7,25 - 7,32 (1H, m), 7,37 (1H, t), 7,58 - 7,64 (1H, m), 7,77 (1H, s); m/z (ES+) $(M+H)^+$ = 233,28; HPLC t_R = 1,89 min.

Producto Intermedio AF1: (2S)-3-[2-(terc-butil-dimetilsilil)oxietoxi]-N-(5-cianopiridin-2-il)-2-[1-(3-fluoro-2-metilfenil)pirazolo[4,5-e]pirimidin-4-il]oxipropanamida



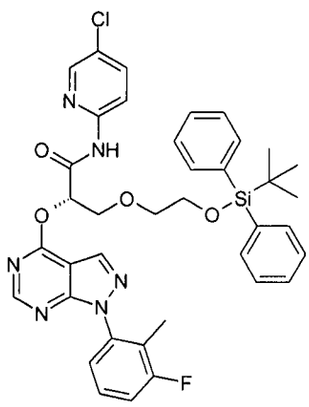
Se preparó utilizando un procedimiento análogo al descrito para el Producto Intermedio AE1 utilizando (2S)-metil 3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(3-fluoro-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanoato (**Producto Intermedio AF4**) y 6-aminonicotinonitrilo. ^{1}H NMR (400 MHz, DMSO) d 0,89 (9H, s), 1,96 (3H, d), 3,83 - 3,69 (4H, m), 4,12 - 4,04 (1H, m), 4,17 (1H, dd), 6,02 (1H, m), 7,51 - 7,27 (9H, m), 7,60 (4H, m), 8,13 (1H, d), 8,22 (1H, dd), 8,51 (1H, s), 8,55 (1H, s), 8,81 (1H, d), 11,56 (1H, s). m/z (ES+) $(M+H)^+$ = 716; HPLC t_R = 3,29 min.

Producto Intermedio AF2: (2S)-3-[2-(terc-butil-dimetilsilil)oxietoxi]-2-[1-(3-fluoro-2-metilfenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-metilpiridin-2-il)propanamida



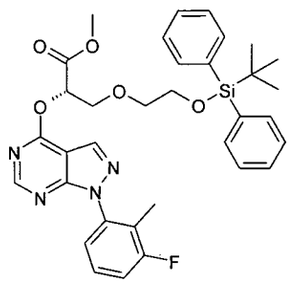
Se preparó utilizando un procedimiento análogo al descrito para el Producto Intermedio AE1 utilizando (2S)-metil 3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(3-fluoro-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanoato (**Producto Intermedio AF4**) y 5-metilpiridin-2-amina. ^{1}H NMR (400 MHz, DMSO) d 0,88 (9H, s), 1,96 (3H, d), 2,24 (3H, s), 3,75 (4H, m), 4,08 - 4,02 (1H, m), 4,14 (1H, m), 5,99 (1H, m), 7,50 - 7,29 (9H, m), 7,63 - 7,54 (5H, m), 7,89 (1H, d), 8,17 (1H, s), 8,51 (1H, s), 8,55 (1H, s), 10,94 (1H, s). m/z (ES+) $(M+H)^+$ = 705; HPLC t_R = 3,42 min.

Producto Intermedio AF3: (2S)-3-[2-(terc-butil-dimetilsilil)oxietoxi]-N-(5-cloropiridin-2-il)-2-[1-(3-fluoro-2-metilfenil)pirazolo[4,5-e]pirimidin-4-il]oxipropanamida



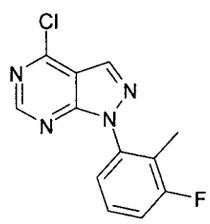
Se preparó utilizando un procedimiento análogo al descrito para el Producto Intermedio AE1 utilizando (2S)-metil 3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(3-fluoro-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanoato (**Producto Intermedio AF4**) y 5-cloropiridin-2-amina. ^{1}H NMR (400 MHz, DMSO) d 0,87 (9H, s), 1,96 (3H, d), 3,75 (4H,m), 4,10 - 4,02 (1H, m), 4,15 (1H, m), 6,00 (1H, m), 7,38 (9 H, m), 7,63 - 7,57 (4H, m), 7,88 (1H, dd), 8,03 (1H, d), 8,40 (1H, d), 8,52 (1H, s), 8,56 (1H, s), 11,25 (1H, s). m/z (ES+) $(M+H)^+$ = 725; HPLC t_R = 3,63 min.

Producto Intermedio AF4: (2S)-metil 3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(3-fluoro-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanoato



Se preparó utilizando un procedimiento análogo al descrito para el Producto Intermedio AE2 utilizando (S)-metil 3-(2-(terc-butildifenilsililoxi)etoxi)-2-hidroxipropanoato (**Producto Intermedio AB3**) y 4-cloro-1-(3-fluoro-2-metilfenil)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio AF5**). ^{1}H NMR (400 MHz, DMSO) d 0,94 (9H, s), 1,96 (3H, d), 3,81 - 3,63 (7H, m), 4,09 - 4,02 (1H, m), 4,13 (1H, m), 5,89 (1H, m), 7,50 - 7,30 (9H, m), 7,63 (4H, m), 8,49 (1H, s), 8,59 (1H, s). m/z (ES+) $(M+H)^+$ = 629; HPLC t_R = 3,43 min.

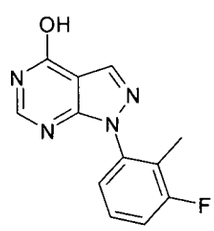
Producto Intermedio AF5: 4-cloro-1-(3-fluoro-2-metilfenil)-1H-pirazolo[3,4-d]pirimidina



Se preparó utilizando un procedimiento análogo al descrito para el **Producto Intermedio AE5** utilizando 1-(3-fluoro-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-ol (**Producto Intermedio AF6**). ^{1}H NMR (400 MHz, DMSO) d 1,99 (3H, d), 7,37 (1H, d), 7,45 (2H, m), 8,77 (1H, s), 8,89 (1H, s).

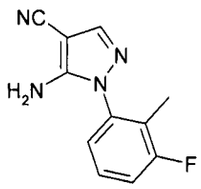
m/z (ES+) $(M+H)^+$ = 263; HPLC t_R = 2,38 min.

Producto Intermedio AF6: 1-(3-fluoro-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-ol



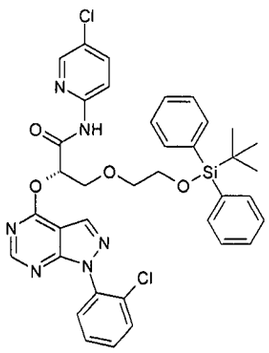
Se preparó utilizando un procedimiento análogo al descrito para el **Producto Intermedio AE6** utilizando 5-amino-1-(3-fluoro-2-metilfenil)-1H-pirazol-4-carbonitrilo (**Producto Intermedio AF7**) ^{1}H NMR (400 MHz, DMSO) d 1,97 (3H, d), 7,28 (1H, d), 7,48 - 7,35 (2H, m), 8,07 (1H, d), 8,33 (1H, s), 12,34 (1H, s); m/z (ES+) $(M+H)^+$ = 245; HPLC t_R = 1,43 min.

Producto Intermedio AF7: 5-amino-1-(3-fluoro-2-metilfenil)-1H-pirazol-4-carbonitrilo



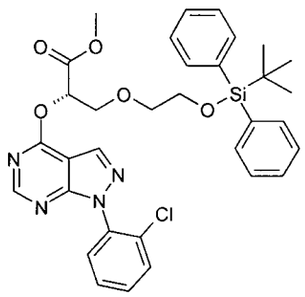
Se preparó utilizando un procedimiento análogo al descrito para el **Producto Intermedio AE7** utilizando (3-fluoro-2-metilfenil)hidrazina clorhidrato. ^{1}H NMR (400 MHz, DMSO) d 1,94 (3H, d), 6,56 (2H, s), 7,15 (1H, d), 7,42 - 7,30 (2H, m), 7,76 (1H, s); m/z (ES+) $(M+H)^+$ = 217; HPLC t_R = 1,63 min.

Producto Intermedio AG1: (2S)-3-[2-(terc-butil-dimetilsilil)oxietoxi]-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-cloropiridin-2-il)propanamida



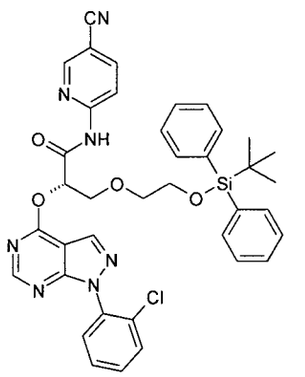
Se preparó a partir de (2S)-metil 3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanoato (**Producto Intermedio AG2**) (950mg, 1,51 mmol) de acuerdo con el método para el **Producto Intermedio AE3** utilizando 5-cloropiridin-2-amina. ^{1}H NMR (400 MHz, DMSO) δ 0,88 (9H, s), 3,71 - 3,84 (4H, m), 4,02 - 4,07 (1H, m), 4,13 - 4,18 (1H, m), 5,97 - 5,99 (1H, m), 7,34 - 7,43 (6H, m), 7,56 - 7,67 (7H, m), 7,74 - 7,77 (1H, m), 7,86 - 7,89 (1H, m), 8,00 - 8,03 (1H, m), 8,40 - 8,41 (1H, m), 8,52 (1H, s), 8,57 (1H, s), 11,25 (1H, s); m/z (ESI+) $(M+H)^+$ = 727; HPLC t_R = 3,49 min.

Producto Intermedio AG2: metil (2S)-3-[2-(terc-butil-difenilsilil)oxietoxi]-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxipropanoato



Se preparó de acuerdo con el método para el **Producto Intermedio AE2** a partir de (S)-metil 3-(2-(terc-butildifenilsililoxi)etoxi)-2-hidroxipropanoato (**Producto Intermedio AB3**) y 4-cloro-1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio B1**). ^{1}H NMR (400 MHz, DMSO) δ 0,94 (9H, s), 3,56 - 3,75 (4H, m), 3,68 (3H, s), 3,90 - 4,09 (2H, m), 5,80 - 5,85 (1H, m), 7,29 - 7,43 (6H, m), 7,50 - 7,67 (7H, m), 7,67 - 7,74 (1H, m), 8,43 (1H, s), 8,52 (1H, s); m/z (ESI+) $(M+H)^+$ = 631; HPLC t_R = 3,38 min.

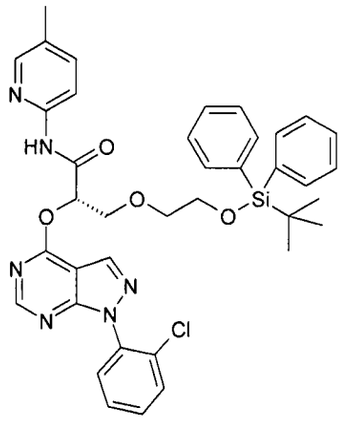
Producto Intermedio AG3: (2S)-3-[2-(terc-butil-difenilsilil)oxietoxi]-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-cianopiridin-2-il)propanamida



Se preparó de acuerdo con el método para el (**Producto Intermedio AE1**) a partir de (2S)-metil 3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanoato (**Producto Intermedio AG2**). ^{1}H NMR (400 MHz, DMSO) δ 0,91 (9H, s), 3,68 - 3,80 (4H, m), 4,09 - 4,19 (2H, m), 5,98 - 6,04 (1H, m), 7,34 - 7,48 (6H, m), 7,56 - 7,68 (7H, m), 7,74 - 7,77 (1H, m), 8,11 - 8,15 (1H, m), 8,21 - 8,24 (1H, m), 8,52 (1H, s), 8,54 (1H, s), 8,82 - 8,83 (1H, m), 11,60 (1H, s); m/z (ESI+) $(M+H)^+$ = 718; HPLC t_R = 3,13 min.

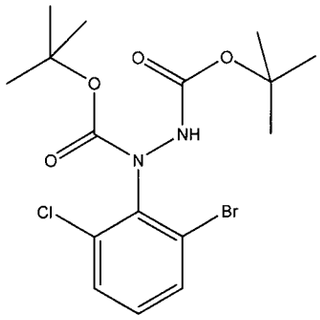
Producto Intermedio AG4: (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(2-

clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-metilpiridin-2-il)propanamida



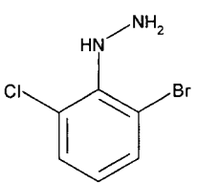
Se agregó hidruro de sodio (14,21 mg, 0,36 mmol) a (S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-hidroxi-N-(5-metilpiridin-2-il)propanamida (**Producto Intermedio AU2**) (85 mg, 0,18 mmol) en THF anhidro (5 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos y luego se agregó 4-cloro-1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidina (47,1 mg, 0,18 mmol). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 1 hora. La mezcla de reacción se neutralizó con ácido cítrico 1M y la mayor parte del THF se eliminó al vacío. La mezcla de reacción se diluyó con agua (20 mL) y EtOAc (50 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc (2 × 20 mL). Los elementos orgánicos combinados se lavaron con salmuera saturada (10 mL), se secaron ($MgSO_4$) y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 20% EtOAc en isohexano para proporcionar (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-metilpiridin-2-il)propanamida (126 mg, 100 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ0,99 (s, 9H), 2,29 (s, 3H), 3,67 - 3,73 (m, 2H), 3,77 - 3,84 (m, 2H), 4,13 - 4,25 (m, 2H), 6,07 (t, 1H), 7,29 - 7,54 (m, 10H), 7,59 - 7,69 (m, 5H), 8,06 - 8,16 (m, 2H), 8,38 (s, 1H), 8,58 (s, 1H), 8,66 (s, 1H); m/z (ES+), $(M+H)^+$ = 707,62; HPLC t_R = 3,81 min

Producto Intermedio AH1: di-terc-butil 1-(2-bromo-6-clorofenil)hidrazina-1,2-dicarboxilato



A una solución agitada de butillitio 2,5 M en hexanos (13,79 mL, 34,47 mmol) a -20°C se agregó gota a gota 2,2,6,6-tetrametilpiperidina (5,82 mL, 34,47 mmol) en THF (30 mL). Esto se agitó durante 30 minutos. Esta solución se enfrió hasta alcanzar -78°C y una solución de 1-bromo-3-clorobenceno (6 g, 31,34 mmol) en THF (20 mL) se agregó gota a gota para mantener la temperatura a <-70°C. Después de 2 horas se agregó (Z)-di-terc-butil diazeno-1,2-dicarboxilato (10,82 g, 47,01 mmol) en THF (30 mL) gota a gota a -78°C. Se agitó a esta temperatura durante 2 horas, luego se dejó entibiar hasta alcanzar la temperatura ambiente durante toda la noche. Se agregó agua (150 mL). La mezcla se extrajo con EtOAc (2 × 300 mL). Los extractos se combinaron, se lavaron con salmuera (100 mL), se secaron ($MgSO_4$) y se redujeron para proporcionar un residuo que se purificó mediante cromatografía instantánea en sílice, gradiente de elución 0-10% EtOAc en hexano. Las fracciones que contenían el producto sospechado se combinaron y se redujeron para proporcionar di-terc-butil 1-(2-bromo-6-clorofenil)hidrazina-1,2-dicarboxilato (9,59 g, 72,5 %). ^{1}H NMR (400 MHz, DMSO) δ 1,30-1,50 (18H, s), 7,28 (1H, m), 7,55 (1H, dd), 7,67 (1H, dd), 9,18 (1H, s). m/z (ES+) $(M+Na)^+$ = 443; HPLC t_R = 10,76 min.

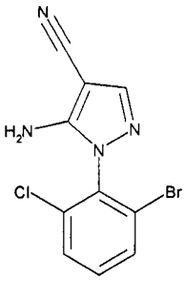
Producto Intermedio AH2: (2-bromo-6-clorofenil)hidrazina clorhidrato



Se agregó cloruro de hidrógeno 4M en dioxano (28,2 mL, 112,64 mmol) a di-terc-butil 1-(2-bromo-6-clorofenil)hidrazina-1,2-dicarboxilato (**Producto Intermedio AH1**) (9,5 g, 22,53 mmol) en iPrOH (30 mL) a temperatura ambiente. La solución resultante se calentó hasta alcanzar 60°C y se agitó durante 20 minutos. La mezcla de reacción se dejó enfriar

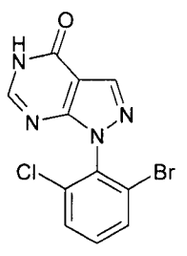
hasta alcanzar la temperatura ambiente. Se retiró un sólido mediante filtración y se secó al vacío para proporcionar el producto (4,71 g). ^{1}H NMR (400 MHz, DMSO) d 6,97 (1H, s), 7,06 (1H, t), 7,41 (1H, dd), 7,52 (1H, dd), 9,83 (3H, s). m/z M^+ = 220; GC-MS tR = 10,419 min.

Producto Intermedio AH3: 5-amino-1-(2-bromo-6-clorofenil)-1H-pirazol-4-carbonitrilo



Se dividió (2-bromo-6-clorofenil)hidrazina clorhidrato (**Producto Intermedio AH2**) (4,71 g, 18,26 mmol) entre DCM (300 mL) y NaOH 2M (20 mL). Se dejó agitar durante 1 hora. Las dos fases se separaron. La fase orgánica se redujo al vacío para proporcionar la base libre. Esto se disolvió en MeOH (60 mL) y se agitó en un baño de enfriamiento a 0°C. Se agregó (etoximetileno)malononitrilo (2,230 g, 18,26 mmol) en porciones. La mezcla de reacción luego se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 1 hora. La mezcla luego se calentó hasta alcanzar reflujo y se agitó durante 16 horas. Se dejó enfriar hasta alcanzar la temperatura ambiente. La mezcla de reacción se concentró para proporcionar un sólido, que se trituró bajo MeOH. Se retiró un sólido mediante filtración. Esto se secó para proporcionar el producto (4,59 g, 85 %). ^{1}H NMR (400 MHz, DMSO) δ 6,79 (2H, s), 7,54 - 7,47 (1H, m), 7,70 (1H, dd), 7,79 (1H, s), 7,81 (1H, d). m/z (ES+) $(M+H)^+$ = 299; HPLC t_R = 1,70 min.

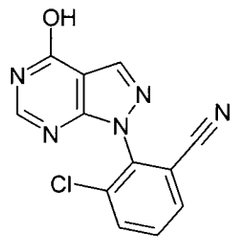
Producto Intermedio AH4: 1-(2-bromo-6-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona



Se agregó ácido sulfúrico concentrado (0,905 mL, 16,97 mmol) a una solución agitada de

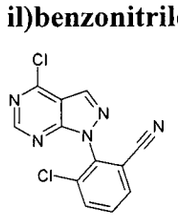
5-amino-1-(2-bromo-6-clorofenil)-1H-pirazol-4-carbonitrilo (**Producto Intermedio AH3**) (4,59 g, 15,43 mmol) en ácido fórmico (30 mL). La solución resultante se calentó hasta alcanzar 100°C y se agitó durante 4 horas. La mezcla de reacción se dejó enfriar hasta alcanzar la temperatura ambiente. La mezcla de reacción se evaporó hasta secarse. El residuo se trituró bajo agua. Se retiró un sólido mediante filtración. Esto se secó al vacío para proporcionar el producto (3,71 g, 73,8 %). ^{1}H NMR (400 MHz, DMSO) δ 7,58 (1H, t), 7,80 - 7,76 (1H, m), 7,88 (1H, dd), 8,08 (1H, d), 8,40 (1H, s), 12,44 (1H, s). m/z (ES+) $(M+H)^+$ = 327; HPLC t_R = 1,48 min.

Producto Intermedio AH5: 3-cloro-2-(4-hidroxi-1H-pirazolo[3,4-d]pirimidin-1-il)benzonitrilo



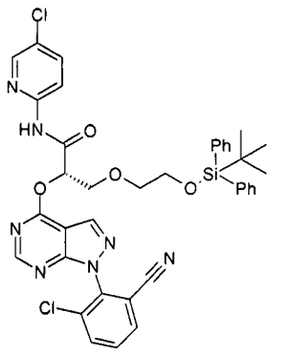
Se disolvió 1-(2-bromo-6-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona (**Producto Intermedio AH4**) (1012 mg, 3,11 mmol) y cianuro de zinc (329 mg, 2,80 mmol) en DMF (15 mL). Se selló en un tubo de microondas. El tubo se purgó con nitrógeno. Se agregó 9,9-dimetil-4,5-bis(difenilfosfino)xanteno (180 mg, 0,31 mmol) y tris(dibencilidenoacetona)dipaladio(0) (142 mg, 0,16 mmol). La reacción se calentó hasta alcanzar 160°C durante 15 minutos en el reactor de microondas, luego se dejó enfriar hasta alcanzar la temperatura ambiente. La DMF se retiró mediante evaporación. El producto bruto se absorbió en sílice y luego se purificó mediante cromatografía instantánea en sílice, gradiente de elución 0 a 10% MeOH en DCM para proporcionar el producto (769 mg, 91 %). ^{1}H NMR (400 MHz, DMSO) δ 7,89 - 7,83 (1H, t), 8,14 (1H, s), 8,15 (2H, d), 8,49 (1H, s), 12,56 (1H, s); m/z (ES+) $(M+H)^+$ = 272; HPLC t_R = 1,29 min.

Producto Intermedio AH6: 3-Cloro-2-(4-cloro-1H-pirazolo[3,4-d]pirimidin-1-il)benzonitrilo



Se agregó oxicloruro de fósforo (7,93 mL, 85,03 mmol) a 3-cloro-2-(4-hidroxi-1H-pirazolo[3,4-d]pirimidin-1-il)benzonitrilo (**Producto Intermedio AH5**) (1,155 g, 4,25 mmol). La mezcla resultante se calentó hasta alcanzar 100°C y se agitó durante 4 horas. La mezcla de reacción se dejó enfriar hasta alcanzar la temperatura ambiente. La mezcla de reacción se evaporó casi hasta secarse. Se vertió en hielo/agua con agitación. Se recogió un precipitado sólido mediante filtración. Esto se secó durante toda la noche al vacío para proporcionar el producto (0,928 g, 75 %). ^{1}H NMR (400 MHz, DMSO) δ 8,02 - 7,96 (1H, t), 8,26 (1H, d), 8,28 (1H, s), 9,05 (2H, d). m/z M^+ = 289; GCMS tR = 13,82 min.

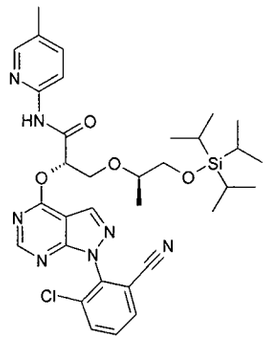
Producto Intermedio AH7: (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(2-cloro-6-cianofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-cloropiridin-2-il)propanamida



Se agregó hidruro de sodio al 60% (95 mg, 2,38 mmol) a (S)-3-(2-(terc-butildifenilsililoxi)etoxi)-N-(5-cloropiridin-2-il)-2-hidroxipropanamida (**Producto Intermedio AU3**) (540 mg, 1,08 mmol) en THF anhidro (15 mL), a 0°C, bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos. Se agregó 3-cloro-2-(4-cloro-1H-pirazolo[3,4-d]pirimidin-1-il)benzonitrilo (**Producto Intermedio AH6**) (314 mg, 1,08 mmol). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y luego se agitó durante 2 horas. La mezcla de reacción se neutralizó con ácido cítrico 1M y luego se diluyó con agua (50 mL) y EtOAc (100 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc (2 × 100 mL). Los elementos orgánicos combinados se lavaron con salmuera saturada (50 mL), se secaron ($MgSO_4$), se filtraron y se concentraron al vacío. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 30 a 50% EtOAc en isohexano. Las fracciones se evaporaron hasta secarse para proporcionar (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(2-cloro-6-cianofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-cloropiridin-2-il)propanamida (466 mg, 57,2 %). ^{1}H NMR (400 MHz, DMSO) δ 0,89 (9H, d), 3,83 - 3,66 (4H, m), 4,11 - 4,04

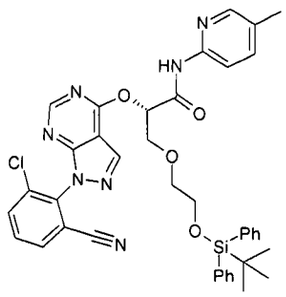
(1H, m), 4,20 - 4,12 (1H, m), 6,00 (1H, s), 7,44 - 7,31 (6H, m), 7,60 (4H, m), 7,87 (2H, m), 8,03 (1H, t), 8,22 - 8,13 (2H, m), 8,39 (1H, d), 8,62 (1H, d), 8,68 (1H, d), 11,23 (1H, s). m/z (ES+) $(M+H)^+$ = 752; HPLC t_R = 3,89 min.

Producto Intermedio AH8: (2S)-2-(1-(2-cloro-6-cianofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-metilpiridin-2-il)-3-((R)-1-(triisopropilsililoxi)propan-2-iloxi)propanamida



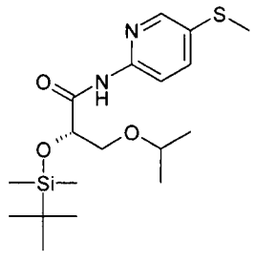
Se agregó hidruro de sodio (64,3 mg, 1,61 mmol) a (S)-2-hidroxi-N-(5-metilpiridin-2-il)-3-((R)-1-(triisopropilsililoxi)propan-2-iloxi)propanamida (**Producto Intermedio AU4**) (300 mg, 0,73 mmol) en THF anhidro (10 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos y luego se agregó 3-cloro-2-(4-cloro-1H-pirazolo[3,4-d]pirimidin-1-il)benzonitrilo (**Producto Intermedio AH6**) (212 mg, 0,73 mmol). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 2 horas. La mezcla de reacción se neutralizó con ácido cítrico 1M y luego se diluyó con agua (50 mL) y EtOAc (100 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc (2 x 100 mL). Los elementos orgánicos combinados se lavaron con salmuera saturada (50 mL), se secaron ($MgSO_4$), se filtraron y se concentraron al vacío. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 20 a 40% EtOAc en isohexano para proporcionar el producto (334 mg, 68,8 %). ^{1}H NMR (400 MHz, DMSO) δ 0,98 - 0,86 (21H, m), 1,09 (3H, d), 2,24 (3H, s), 3,58 - 3,47 (1H, m), 3,64 (1H,m), 3,81 - 3,71 (1H, m), 4,10 (2H,m), 5,92 (1H, s), 7,58 (1H, d), 7,89 (2H, t), 8,18 (3H, m), 8,59 (1H, s), 8,72 (1H, s), 10,88 (1H, s). m/z (ES+) $(M+H)^+$ = 664; HPLC t_R = 3,99 min.

Producto Intermedio AH9: (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(2-cloro-6-cianofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-metilpiridin-2-il)propanamida



Se preparó utilizando un procedimiento análogo al descrito para el **Producto Intermedio AH7** utilizando (S)-3-(2-(terc-butildifenilsililoxi)etoxi)-N-(5-metilpiridin-2-il)-2-hidroxipropanamida (**Producto Intermedio AU2**) y 3-cloro-2-(4-cloro-1H-pirazolo[3,4-d]pirimidin-1-il)benzonitrilo (**Producto Intermedio AH6**). m/z (ES+) $(M+H)^+$ = 732; HPLC t_R = 3,76 min

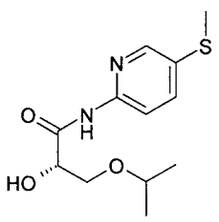
Producto Intermedio AI1: (S)-2-(terc-butildimetilsililoxi)-3-isopropoxi-N-(5-(metiltio)piridin-2-il)propanamida



Se agregó trimetilaluminio (2M en tolueno) (10,40 mL, 20,80 mmol) a 5-(metiltio)piridin-2-amina (CAS no. 77618-99-6) (2,54 g, 18,09 mmol) en tolueno (100 mL) enfriado hasta alcanzar 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 20 minutos. Se agregó (S)-metil 2-(terc-butildimetilsililoxi)-3-isopropoxipropanoato (**Producto Intermedio C7b**) (5 g, 18,09 mmol) y la reacción se dejó entibiar hasta alcanzar la temperatura ambiente. La reacción se dejó agitar a temperatura ambiente durante 1 hora. La temperatura disminuyó hasta alcanzar 60°C y se agitó durante 24 horas adicionales. La mezcla de reacción se neutralizó con ácido cítrico (1M, ac) y luego se diluyó con agua y EtOAc (200 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc (100 mL). Los elementos orgánicos combinados se secaron ($MgSO_4$), se filtraron y se evaporaron al vacío. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 0 a 50% Et_2O en isohexano para proporcionar el producto (3,95 g, 56,8 %). ^{1}H RMN (400 MHz, DMSO) δ 0,10 - 0,13 (6H, d), 0,90 - 0,92 (9H, m), 1,04 - 1,07 (6H, m), 2,40 (3H +DMSO, s), 3,54 - 3,63 (3H, m), 4,42 - 4,44 (1H, m), 7,77 -

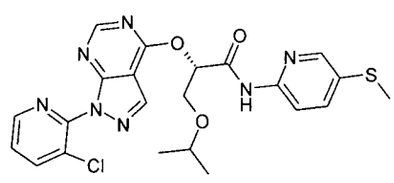
7,80 (1H, dd), 8,03 - 8,06 (1H, d), 8,26 (1H, d), 9,49 (1H, s);
m/z (ES+) $(M+H)^+ = 385$; HPLC $t_R = 3,66$ min.

Producto Intermedio AI2: (S)-2-hidroxi-3-isopropoxi-N-(5-(metiltio)piridin-2-il)propanamida



Una solución de fluoruro de tetrabutilamonio (1M en THF) (10,04 mL, 10,04 mmol) se agregó en una porción a una solución agitada de (S)-2-(terc-butildimetilsililoxi)-3-isopropoxi-N-(5-(metiltio)piridin-2-il)propanamida (**Producto Intermedio AI1**) en tetrahidrofurano (50 mL). La solución resultante se agitó a temperatura ambiente durante 30 minutos. La mayor parte del THF se evaporó al vacío. El residuo se diluyó con EtOAc (100 mL), se lavó secuencialmente con agua (25 mL) y salmuera saturada (25 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el producto bruto. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 30 a 50% EtOAc en isohexano para proporcionar el producto (2,38 g, 88 %). ^1H NMR (400 MHz, DMSO) δ 1,03 - 1,07 (6H, m), 3,28 (3H, s), 3,53 - 3,64 (3H, m), 4,19 - 4,22 (1H, m), 5,95 (1H, d), 7,77 - 7,80 (1H, d), 8,04 - 8,06 (1H, d), 8,24 - 8,25 (1H, s), 9,60 (1H, s); m/z (ES+) $(M+H)^+ = 271$; HPLC $t_R = 1,74$ min.

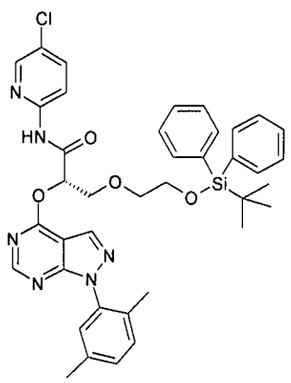
Producto Intermedio AI3: (2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-isopropoxi-N-(5-(metiltio)piridin-2-il)propanamida



Se agregó hidruro de sodio al 60% (111 mg, 2,77 mmol) a una solución de (S)-2-hidroxi-3-isopropoxi-N-(5-(metiltio)piridin-2-il)propanamida (**Producto Intermedio AI2**) (500 mg, 1,85 mmol) en THF anhidro (30 mL) a 0°C bajo nitrógeno. La suspensión resultante se agitó a 0°C durante 10 minutos y luego se agregó una solución de 4-cloro-1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio B15**) (492 mg, 1,85 mmol) en THF seco (10 mL) gota a gota, manteniendo la temperatura por debajo de 5°C.

La mezcla de reacción se agitó a 0°C durante 10 minutos y luego se dejó entibiar hasta alcanzar la temperatura ambiente. La reacción se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se neutralizó con HCl (1M, ac). La mayor parte del THF se evaporó al vacío y luego se agregó EtOAc (100 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc (2 x 100 mL). Los elementos orgánicos combinados se lavaron con salmuera saturada (75 mL), se secaron ($MgSO_4$), se filtraron y se concentraron al vacío. El producto bruto se purificó mediante cromatografía instantánea en sílice (330 g), gradiente de elución 20 a 70% EtOAc en isohexano para proporcionar el producto (609 mg, 65,9 %). ^{1}H NMR (400 MHz, DMSO) δ 1,12 (6H, dd), 3,28 (3H, s), 3,76 (1H, dt), 4,07 - 3,96 (2H, m), 5,90 (1H, s), 7,78 - 7,72 (2H, m), 7,95 (1H, d), 8,27 (1H, dd), 8,33 (1H, dd), 8,56 (1H, s), 8,65 (1H, s), 8,67 (1H, dd), 10,97 (1H, s). m/z (ES+) $(M+H)^+ = 500$; HPLC $t_R = 2,43$ min.

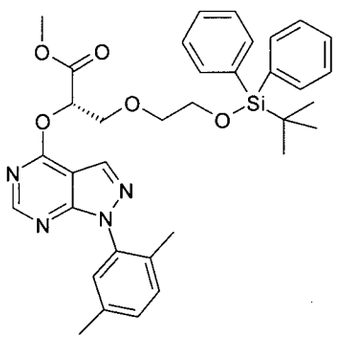
Producto Intermedio AJ1: (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-N-(5-cloropiridin-2-il)-2-(1-(2,5-dimetilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida



Se agregó trimetilaluminio (2M en tolueno) (0,692 mL, 1,38 mmol) gota a gota a una solución agitada de 5-cloropiridin-2-amina (163 mg, 1,27 mmol) en tolueno (15 mL) bajo nitrógeno a 0°C. La solución resultante se dejó agitar a esta temperatura durante 20 minutos adicionales. Se agregó (2S)-metil 3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(2,5-dimetilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanoato (**Producto Intermedio AJ2**) (721 mg, 1,15 mmol) en tolueno (6 mL) lentamente a la mezcla a 0°C. La mezcla de reacción luego se calentó hasta alcanzar 100°C y se agitó durante 5 horas utilizando el microondas. La mezcla de reacción se dejó enfriar hasta alcanzar la temperatura ambiente, luego se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía instantánea en sílice. Las fracciones se evaporaron hasta secarse

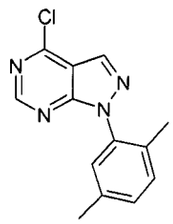
para proporcionar un producto bruto (428 mg). Se agregó trimetilaluminio (2M en tolueno) (0,258 mL, 0,52 mmol) gota a gota a una solución agitada de 5-cloropiridin-2-amina (66,3 mg, 0,52 mmol) en tolueno (6 mL), bajo nitrógeno a 0°C. La solución resultante se dejó agitar a esta temperatura durante 20 minutos adicionales. El producto bruto en tolueno (6 mL) se agregó lentamente a la mezcla a 0°C. La mezcla de reacción luego se calentó hasta alcanzar 100°C y se agitó durante 5 horas utilizando el microondas. La mezcla de reacción se dejó enfriar hasta alcanzar la temperatura ambiente, luego se evaporó para proporcionar un producto bruto. Esto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 0 a 30% EtOAc en isohexano para proporcionar el producto (328 mg). m/z (ES+) $(M+H)^+ = 721$; HPLC $t_R = 3,76$ min.

Producto Intermedio AJ2: (2S)-metil 3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(2,5-dimetilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanoato



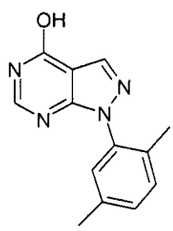
Se agregó hidruro de sodio al 60% (0,187 g, 4,67 mmol) a (S)-metil 3-(2-(terc-butildifenilsililoxi)etoxi)-2-hidroxipropanoato (**Producto Intermedio AB3**) (1,568 g, 3,90 mmol) en THF anhidro (20 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos y luego se agregó 4-cloro-1-(2,5-dimetilfenil)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio AJ3**) (1,008 g, 3,90 mmol). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 1 hora. La mezcla de reacción se neutralizó con ácido cítrico 1M y la mayor parte del THF se eliminó al vacío. El residuo se diluyó con agua (20 mL) y EtOAc (100 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc (100 mL). Los elementos orgánicos combinados se lavaron con salmuera saturada (75 mL), se secaron ($MgSO_4$) y se evaporaron para proporcionar el producto bruto. Esto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 0 a 20% EtOAc en isohexano para proporcionar el producto (1,400 g, 57,5 %). m/z (ES+) $(M+H)^+ = 625$; HPLC $t_R = 3,53$ min.

Producto Intermedio AJ3: 4-Cloro-1-(2,5-dimetilfenil)-1H-pirazolo[3,4-d]pirimidina



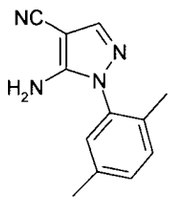
Se agregó oxicloruro de fósforo (7,76 mL, 83,24 mmol) a 1-(2,5-dimetilfenil)-1H-pirazolo[3,4-d]pirimidin-4-ol (1 g, 4,16 mmol). La solución resultante se agitó a 100°C durante 2 horas. La LCMS mostró que la reacción se completó. La mezcla de reacción se evaporó. Se agregaron hielo/agua y luego EtOAc. La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc. Los elementos orgánicos combinados se lavaron con agua, se secaron ($MgSO_4$) y se concentraron para proporcionar el producto bruto (1,077 g, 100 %) que se utilizó sin purificación. ^{1}H NMR (400 MHz, DMSO) δ 2,00 (3H, s), 2,35 (3H, s), 7,26 - 7,37 (3H, m), 8,72 (1H, s), 8,86 (1H, s); m/z (ES+) $(M+H)^+ = 259$; HPLC $t_R = 2,48$ min.

Producto Intermedio AJ4: 1-(2,5-dimetilfenil)-1H-pirazolo[3,4-d]pirimidin-4-ol



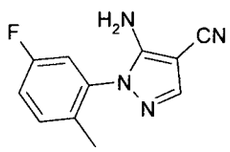
Se agregó ácido sulfúrico concentrado (3,06 mL, 57,37 mmol) a una solución agitada de 5-amino-1-(2,5-dimetilfenil)-1H-pirazol-4-carbonitrilo (**Producto Intermedio AJ5**) (11,07 g, 52,16 mmol) en ácido fórmico (70 mL). La solución resultante se agitó a 100°C durante 24 horas. La reacción se dejó enfriar hasta alcanzar la temperatura ambiente y se evaporó hasta proporcionar ~la mitad del volumen, se agregó agua (100 mL) y se agitó durante 1 hora. El precipitado formado se retiró mediante filtración, se lavó bien con agua y se secó durante toda la noche en un vacío sobre P_2O_5 para proporcionar el producto (8,71 g, 69,5 %) que se utilizó sin purificación. ^{1}H NMR (400 MHz, DMSO) δ 2,00 (3H, s), 2,33 (3H, s), 3,43 (2H, s), 7,18 (1H, s), 7,24 - 7,31 (2H, m), 8,04 (1H, d), 8,28 (1H, s), 12,27 (1H, s); m/z (ES+) $(M+H)^+ = 241$; HPLC $t_R = 1,6$ min.

Producto Intermedio AJ5: 5-amino-1-(2,5-dimetilfenil)-1H-pirazol-4-carbonitrilo



Se dividió 2,5-dimetilfenilhidrazina clorhidrato (CAS no. 56737-78-1) (10 g, 57,92 mmol) entre EtOAc (100 mL) y NaOH (2M, ac) (60 mL). La capa orgánica se separó y se lavó con agua (50 mL), salmuera (50 mL), se secó ($MgSO_4$), se filtró y se concentró para proporcionar la base libre del material de partida. El aceite resultante se suspendió en MeOH (100 mL) bajo nitrógeno a -5°C. Se agregó 2-(etoximetileno)malononitrilo (7,07 g, 57,92 mmol) en porciones durante 5 mins y la mezcla se agitó a ~0°C durante 30 mins. La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó a reflujo bajo nitrógeno durante 2 horas. La mezcla de reacción se dejó enfriar y se evaporó hasta secarse para proporcionar el producto (11,07 g, 90 %) que se utilizó sin purificación. ^{1}H NMR (400 MHz, DMSO) δ 1,98 (3H, s), 2,31 (3H, s), 6,39 (2H, s), 7,07 (1H, s), 7,21 - 7,28 (2H, m), 7,72 (1H, s); m/z (ES+) $(M+H)^+$ = 213; HPLC t_R = 1,79 min.

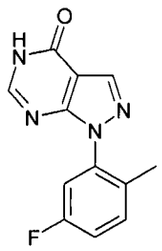
Producto Intermedio AK1: 5-amino-1-(5-fluoro-2-metilfenil)-1H-pirazol-4-carbonitrilo



Se agregó (etoximetileno)malononitrilo (CAS no. 123-06-8) (3,18 g, 26,04 mmol) en porciones a la solución agitada de (5-fluoro-2-metilfenil)hidrazina clorhidrato (CAS no. 325-50-8) (4,6 g, 26,04 mmol) y N,N-diisopropiletilamina (5,90 mL, 33,86 mmol) en MeOH (50 mL), bajo nitrógeno a 5°C. La solución resultante se dejó agitar durante unos 30 minutos adicionales a esta temperatura. La mezcla de reacción luego se calentó hasta alcanzar reflujo y se agitó durante 3 horas. La mezcla de reacción se dejó enfriar hasta alcanzar la temperatura ambiente. La mezcla de reacción se evaporó hasta secarse, se disolvió nuevamente en EtOAc (200 mL), se lavó con agua (50 mL) y salmuera saturada (50 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el producto bruto. Esto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 0 a 50% EtOAc en isohexano para proporcionar el producto (1,076 g, 19,11 %). ^{1}H NMR (400 MHz, DMSO) δ 2,00 (3H, s), 6,56 (2H, s), 7,20 (1H, dd), 7,29 (1H, td), 7,43

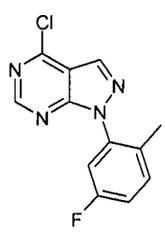
(1H, t), 7,75 (1H, s); m/z (ES+) $(M+H)^+ = 217$; HPLC $t_R = 1,61$ min.

Producto Intermedio AK2: 1-(5-fluoro-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona



Se agregó ácido sulfúrico (0,353 mL, 6,61 mmol) a una solución agitada de 5-amino-1-(5-fluoro-2-metilfenil)-1H-pirazol-4-carbonitrilo (**Producto Intermedio AK1**) (1,3 g, 6,01 mmol) en ácido fórmico (10 mL), bajo nitrógeno a 5°C. La mezcla de reacción luego se calentó hasta alcanzar 100°C y se agitó durante 16 horas. La mezcla de reacción se dejó enfriar hasta alcanzar la temperatura ambiente, luego se evaporó hasta proporcionar la mitad del volumen. Se retiró un precipitado mediante filtración. Este sólido se lavó con agua, luego se secó al vacío para proporcionar el producto (0,713 g, 48,6 %). ^{1}H NMR (400 MHz, DMSO) δ 2,05 (3H, s), 7,30 - 7,36 (2H, m), 7,45 - 7,51 (1H, m), 8,08 (1H, s), 8,32 (1H, s), 12,33 (1H, s). m/z (ES+) $(M+H)^+ = 245$; HPLC $t_R = 1,43$ min.

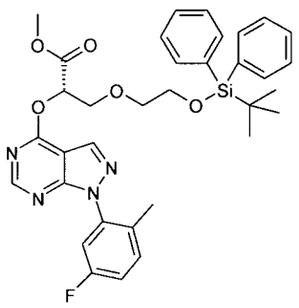
Producto Intermedio AK3: 4-cloro-1-(5-fluoro-2-metilfenil)-1H-pirazolo[3,4-d]pirimidina



Se agregó oxicloruro de fósforo (5442 µl, 58,39 mmol) a 1-(5-fluoro-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona (**Producto Intermedio AK2**) (713 mg, 2,92 mmol), a temperatura ambiente. La mezcla resultante se calentó hasta alcanzar 100°C y se agitó durante 4 horas. La mezcla se dejó enfriar hasta alcanzar la temperatura ambiente. La mezcla de reacción se evaporó casi hasta secarse. Se disolvió en tolueno, se evaporó, se disolvió en tolueno y se evaporó hasta secarse nuevamente. El sólido se secó al vacío para proporcionar el producto bruto. Esto se dividió entre EtOAc (70 mL) y agua (25 mL). La fase orgánica se secó ($MgSO_4$), se evaporó, luego se secó al vacío para proporcionar el

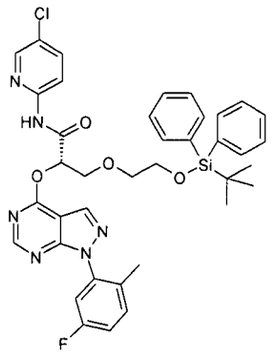
producto (732 mg, 95 %). ^{1}H NMR (400 MHz, DMSO) δ 2,13 (3H, s), 7,52 - 7,42 (2H, m), 7,64 - 7,58 (1H, m), 8,83 (1H, s), 8,96 (1H, s); m/z (ES+) $(M+H)^+$ = 263; HPLC t_R = 2,39 min.

Producto Intermedio AK4: (2S)-metil 3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(5-fluoro-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanoato



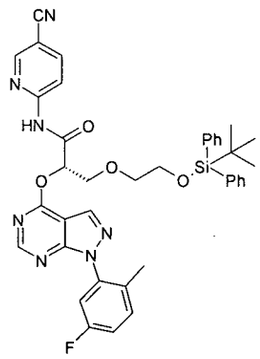
Se agregó hidruro de sodio al 60% (156 mg, 3,89 mmol) a (S)-metil 3-(2-(terc-butildifenilsililoxi)etoxi)-2-hidroxipropanoato (**Producto Intermedio AB3**) (1119 mg, 2,78 mmol) en THF anhidro (15 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos y luego se agregó 4-cloro-1-(5-fluoro-2-metilfenil)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio AK3**) (730 mg, 2,78 mmol). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 1 hora. La mezcla de reacción se neutralizó con ácido cítrico 1M y la mayor parte del THF se eliminó al vacío. El residuo se diluyó con agua (20 mL) y EtOAc (100 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc (100 mL). Los elementos orgánicos combinados se lavaron con salmuera saturada (75 mL), se secaron ($MgSO_4$) y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice (120 g), gradiente de elución 0 a 20% EtOAc en isohexano para proporcionar el producto (932 mg, 53,3 %). ^{1}H NMR (400 MHz, DMSO) δ 0,94 (9H, s), 2,03 (3H, s), 3,80 - 3,65 (7H, m), 4,16 - 4,03 (2H, m), 5,89 (1H, dd), 7,46 - 7,33 (8H, m), 7,54 - 7,48 (1H, m), 7,65 - 7,61 (4H, m), 8,48 (1H, s), 8,59 (1H, s); m/z (ES+) $(M+H)^+$ = 629; HPLC t_R = 3,41 min.

Producto Intermedio AK5: (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-N-(5-cloropiridin-2-il)-2-(1-(5-fluoro-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida



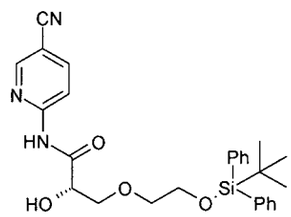
Se agregó trimetilaluminio (2M en tolueno) (0,556 mL, 1,11 mmol) gota a gota a una solución agitada de 5-cloropiridin-2-amina (143 mg, 1,11 mmol) en tolueno (10 mL), bajo nitrógeno a 0°C. La solución resultante se dejó agitar a esta temperatura durante 20 minutos adicionales. Se agregó (2S)-metil 3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(5-fluoro-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanoato (**Producto Intermedio AK4**) (466 mg, 0,74 mmol) en tolueno (5 mL) lentamente a la mezcla a 0°C. La mezcla de reacción luego se calentó hasta alcanzar 100°C y se agitó durante 6 horas utilizando el microondas. La mezcla de reacción se dejó enfriar hasta alcanzar la temperatura ambiente, luego se evaporó para proporcionar una goma. Esto se disolvió en EtOAc (75 mL) y se lavó secuencialmente con solución de Rochelle (20 mL) y agua (20 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el producto bruto. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 10 a 30% EtOAc en isohexano para proporcionar el producto (390 mg, 72,6 %). ^{1}H NMR (400 MHz, DMSO) δ 0,88 (9H, s), 2,03 (3H, s), 3,82 - 3,67 (4H, m), 4,05 (1H, m), 4,15 (1H, m), 6,00 (1H, m), 7,45 - 7,31 (8H, m), 7,50 (1H, t), 7,60 (4H, m), 7,87 (1H, dd), 8,02 (1H, d), 8,40 (1H, d), 8,51 (1H, s), 8,56 (1H, s), 11,25 (1H, s); m/z (ES+) $(M+H)^+$ = 725; HPLC t_R = 3,63 min.

Producto Intermedio AK6: (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-N-(5-cianopiridin-2-il)-2-(1-(5-fluoro-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida



Se preparó en una forma análoga al **Producto Intermedio AL1** utilizando el **Producto Intermedio AK3** y el **Producto Intermedio AK7**. ^{1}H NMR (400 MHz, $CDCl_3$) 0,99 (9H, s), 2,13 (3H, s), 3,70 - 3,73 (2H, m), 3,84 (2H, t), 4,19 - 4,21 (2H, m), 6,04 (1H, t), 7,13 - 7,17 (2H, m), 7,32 - 7,42 (7H, m), 7,63 - 7,66 (4H, m), 7,91 - 7,94 (1H, m), 8,35 (1H, s), 8,36 - 8,38 (1H, m), 8,51 (1H, q), 8,57 (1H, s), 9,02 (1H, s); m/z (ES+) $(M+H)^+$ = 716,5; HPLC t_R = 3,69 min.

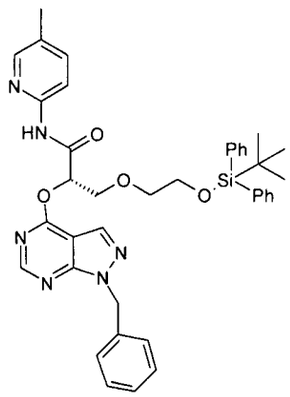
Producto Intermedio AK7: (S)-3-(2-(terc-butildifenilsililoxi)etoxi)-N-(5-cianopiridin-2-il)-2-hidroxipropanamida



Se agregó trimetilaluminio (2M en tolueno) (0,621 mL, 1,24 mmol) a una solución de 6-aminonicotinonitrilo (148 mg, 1,24 mmol) en tolueno (10 mL) a 0°C bajo nitrógeno. La mezcla de reacción se agitó a 0°C durante 20 mins y luego se agregó (S)-metil 3-(2-(terc-butildifenilsililoxi)etoxi)-2-hidroxipropanoato (**Producto Intermedio AB3**) (250 mg, 0,62 mmol). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó a reflujo bajo nitrógeno durante 4 horas. La mezcla de reacción se dejó enfriar hasta alcanzar la temperatura ambiente y luego se concentró al vacío. El residuo se neutralizó con ácido cítrico (1M, ac) y luego se diluyó con agua y DCM (50 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con DCM (30 mL). Los elementos orgánicos combinados se secaron ($MgSO_4$), se filtraron y se evaporaron al vacío. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 20 a 50% EtOAc en isohexano para proporcionar el producto (202 mg, 66,4 %). ^{1}H NMR (400 MHz, $CDCl_3$) 1,04 (9H, s), 3,65 - 3,67 (2H, m), 3,81 - 3,91 (4H, m), 4,36

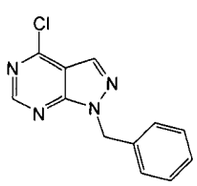
(1H, t), 7,35 - 7,45 (6H, m), 7,65 - 7,67 (4H, m), 7,92 - 7,95 (1H, m), 8,36 - 8,39 (1H, m), 8,54 - 8,56 (1H m), 9,43 (1H, s); m/z (ES+) $(M+H)^+$ = 490; HPLC t_R = 3,08 min.

Producto Intermedio AL1: (S)-2-(1-bencil-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-(2-(terc-butildifenilsililoxi)etoxi)-N-(5-metilpiridin-2-il)propanamida



Se agregó hidruro de sodio (90 mg, 2,25 mmol) a (S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-hidroxi-N-(5-metilpiridin-2-il)propanamida (538 mg, 1,12 mmol) **(Producto Intermedio AU2)** en THF anhidro (20 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos y luego se agregó 1-bencil-4-cloro-1H-pirazolo[3,4-d]pirimidina **(Producto Intermedio AL2)** (250 mg, 1,02 mmol). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante toda la noche. La mezcla de reacción se neutralizó con ácido cítrico 1M, se diluyó con agua (20 mL) y EtOAc (50 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc (2 x 50 mL). Los elementos orgánicos combinados se lavaron con salmuera saturada (75 mL),se secaron ($MgSO_4$), se filtraron y se concentraron al vacío. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 30 a 50% EtOAc en isohexano para proporcionar el producto (540 mg, 77 %). m/z (ES+) $(M+H)^+$ = 687; HPLC t_R = 3,89 min.

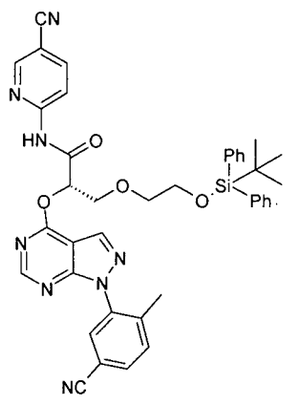
Producto Intermedio AL2: 1-bencil-4-cloro-1H-pirazolo[3,4-d]pirimidina



Se agregó trietilamina (1,181 mL, 8,48 mmol) a 4,6-dicloropirimidina-5-carbaldehído (CAS no. 5305-40-8) (500 mg, 2,83 mmol) y bencilhidrazina diclorhidrato (CAS no.

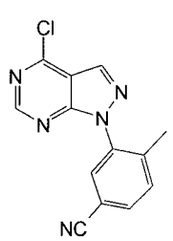
20570-96-1) (551 mg, 2,83 mmol) en THF (15 mL) a temperatura ambiente bajo nitrógeno. La suspensión resultante se agitó a temperatura ambiente durante 10 minutos y luego se calentó a 65°C durante 50 mins. Se agregó sílice a la mezcla de reacción y se concentró al vacío. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 20 a 50% EtOAc en isohexano para proporcionar el producto (500 mg, 72,3 %). ^{1}H NMR (400 MHz, $CDCl_3$) 5,67 (2H, s), 7,28 - 7,38 (5H, m), 8,16 (1H, s), 8,79 (1H, s); m/z (ES+) $(M+H)^+$ = 245; HPLC t_R = 2,29 min.

Producto Intermedio AM1: (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(5-ciano-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-cianopiridin-2-il)propanamida



Se preparó en una forma análoga al **Producto Intermedio AL1** utilizando el **Producto Intermedio AM2** y el **Producto Intermedio AK7**. ^{1}H NMR (400 MHz, $CDCl_3$) 1,00 (9H, s), 2,28 (3H, s), 3,70 - 3,74 (2H, m), 3,84 (2H, t), 4,12 4,20 - 4,21 (2H, m), 6,04 (1H, t), 7,32 - 7,43 (6H, m), 7,52 - 7,54 (1H, m), 7,63 - 7,73 (6H, m), 7,91 - 7,94 (1H, m), 8,35 - 8,38 (2H, m), 8,51 (1H, q), 8,57 (1H, s), 9,02 (1H, s); m/z (ES+) $(M+H)^+$ = 723,5; HPLC t_R = 3,57 min.

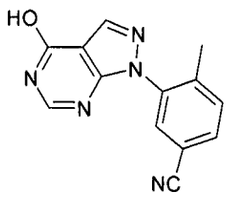
Producto Intermedio AM2: 3-(4-cloro-1H-pirazolo[3,4-d]pirimidin-1-il)-4-metilbenzonitrilo



Se agregó oxicloruro de fósforo (8,90 mL, 95,52 mmol) a 3-(4-hidroxi-1H-pirazolo[3,4-d]pirimidin-1-il)-4-metilbenzonitrilo (**Producto Intermedio AM3**) (1,2 g, 4,78 mmol). La

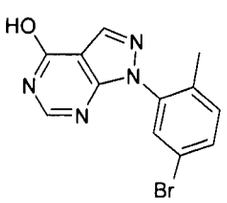
solución resultante se agitó a 100°C durante 4 horas. La mezcla de reacción se evaporó y luego se sometió a azeotropía con tolueno para eliminar todo $POCl_3$ residual. Se agregó hielo/agua y el precipitado formado se filtró lavando bien con agua y se secó durante toda la noche al vacío sobre P_2O_5 para proporcionar 3-(4-cloro-1H-pirazolo[3,4-d]pirimidin-1-il)-4-metilbenzonitrilo (1,16g, 90%). ^{1}H NMR (400 MHz, DMSO) 2,21 (3H, s), 7,73 (1H, d), 7,97 - 8,00 (1H, m), 8,06 (1H, d), 8,81 (1H, s), 8,91 (1H, s); HPLC t_R = 2,05 min.

Producto Intermedio AM3: 3-(4-hidroxi-1H-pirazolo[3,4-d]pirimidin-1-il)-4-metilbenzonitrilo



Se disolvió 1-(5-bromo-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-ol (**Producto Intermedio AM4**) (1,38 g, 4,52 mmol) y cianuro de zinc (0,478 g, 4,07 mmol) en DMF (15 mL) y se selló en un tubo de microondas. La mezcla de reacción se vació y se lavó a contracorriente con nitrógeno varias veces. Se agregaron 9,9-dimetil-4,5-bis(difenilfosfino)xanteno (0,262 g, 0,45 mmol) y tris(dibencilidenoacetona)dipaladio(0) (0,207 g, 0,23 mmol). La reacción se calentó hasta alcanzar 160°C durante 10 minutos en el reactor de microondas y se enfrió hasta alcanzar la TA. La mezcla de reacción se diluyó con EtOAc (100 mL) y agua (50 mL) y luego se filtró. Se recogió el sólido en metanol caliente, se filtró y se secó al vacío para proporcionar el producto (0,99g, 89 %) que se utilizó sin purificación adicional. ^{1}H NMR (400 MHz, DMSO) 2,19 (3H, s), 7,67 (1H, d), 7,92 - 7,96 (2H, m), 8,10 (1H, s), 8,35 (1H, s), 12,38 (1H, s); m/z (ES-) (M-H)- = 250; HPLC t_R = 1,23 min.

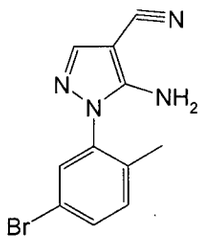
Producto Intermedio AM4: 1-(5-bromo-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4(7H)-ona



Se agregó ácido sulfúrico concentrado (1,160 mL, 21,76 mmol) a una solución agitada de 5-amino-1-(5-bromo-2-metilfenil)-1H-pirazol-4-carbonitrilo (**Producto Intermedio AM5**)

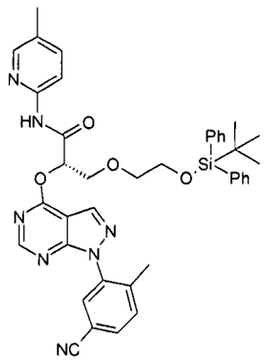
(5,481 g, 19,78 mmol) en ácido fórmico (35 mL). La solución resultante se agitó a 100°C durante 24 horas. La reacción se dejó enfriar hasta alcanzar la temperatura ambiente y se evaporó hasta proporcionar aproximadamente la mitad del volumen, se agregó agua (50 mL) y se agitó durante 1 hora. El precipitado formado se retiró mediante filtración, se lavó bien con agua y se secó durante toda la noche al vacío sobre P_2O_5 para proporcionar el producto (4,47 g, 74,0 %). ^{1}H NMR (400 MHz, DMSO)2,05 (3H, s), 7,40 - 7,42 (1H, m), 7,63 - 7,67 (2H, m), 8,08 - 8,09 (1H, m), 8,32 (1H, s), 12,34 (1H, s); m/z (ES-) (M-H)- = 305, 303; HPLC t_R = 1,62 min.

Producto Intermedio AM5: 5-amino-1-(5-bromo-2-metilfenil)-1H-pirazol-4-carbonitrilo



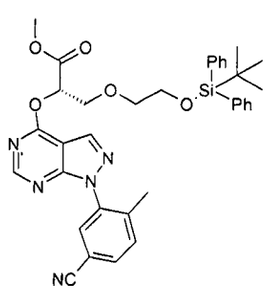
Se dividió (5-bromo-2-metilfenil)hidrazina clorhidrato (CAS no. 214915-80-7) (5 g, 21,05 mmol) entre EtOAc (50 mL) y NaOH (2M, ac) (30 mL). La capa orgánica se separó y se lavó con agua (50 mL), salmuera (50 mL), se secó ($MgSO_4$), se filtró y se concentró para proporcionar la base libre del material de partida. El aceite resultante se suspendió en MeOH (50 mL) bajo nitrógeno a -5°C. Se agregó 2-(etoximetileno)malononitrilo (2,57 g, 21,05 mmol) en porciones durante 5 mins y la mezcla se agitó a ~0°C durante 30 mins. La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó a reflujo bajo nitrógeno durante 2 horas. La mezcla de reacción se dejó enfriar y se evaporó hasta secarse para proporcionar el producto (5,48 g, 94 %). ^{1}H NMR (400 MHz, DMSO) 1,99 (3H, s), 6,59 (2H, s), 7,36 (1H, d), 7,49 (1H, d), 7,60 - 7,63 (1H, m), 7,76 (1H, s); m/z (ES+) $(M+H)^+$ = 277+279; HPLC t_R = 2,01 min.

Producto Intermedio AM6: (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(5-ciano-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-metilpiridin-2-il)propanamida



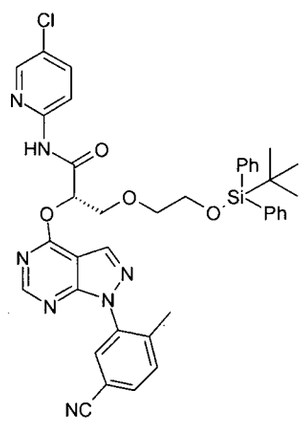
Se agregó trimetilaluminio (2M en tolueno) (0,472 mL, 0,94 mmol) a una solución de 5-metilpiridin-2-amina (102 mg, 0,94 mmol) en tolueno (10 mL) a 0°C bajo nitrógeno en un vial de microondas. La mezcla de reacción se agitó a 0°C durante 20 mins y luego se agregó (2S)-metil 3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(5-ciano-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanoato (**Producto Intermedio AM7**) (300 mg, 0,47 mmol). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó en el microondas a 120°C durante 2 horas. La mezcla de reacción se dejó enfriar hasta alcanzar la temperatura ambiente y luego se concentró al vacío. El residuo se neutralizó con ácido cítrico (1M, ac) y luego se diluyó con agua y DCM (50 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con DCM (30 mL). Los elementos orgánicos combinados se secaron ($MgSO_4$), se filtraron y se evaporaron al vacío. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 20 a 50% Et_2O en isohexano para proporcionar el producto (125 mg, 37,2 %). ^1H NMR (400 MHz, $CDCl_3$) 0,99 (9H, s), 2,27 (3H, s), 2,29 (3H, s), 3,69 - 3,72 (2H, m), 3,81 (2H, t), 4,16 - 4,24 (2H, m), 6,07 - 6,09 (1H, m), 7,16 - 7,41 (6H, m), 7,51 (1H, s), 7,53 (1H, s), 7,63 - 7,65 (4H, m), 7,68 - 7,72 (2H, m), 8,08 - 8,08 (1H, m), 8,14 (1H, d), 8,37 (1H, s), 8,57 (1H, s), 8,67 (1H, s); m/z (ES+) $(M+H)^+$ = 712,6; HPLC t_R = 3,65 min.

Producto Intermedio AM7: (2S)-metil 3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(5-ciano-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanoato



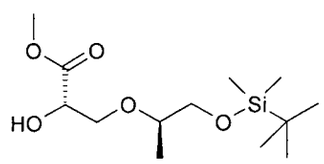
Se agregó hidruro de sodio (108 mg, 2,69 mmol) a (S)-metil 3-(2-(terc-butildifenilsililoxi)etoxi)-2-hidroxipropanoato (795 mg, 1,97 mmol) (**Producto Intermedio AB3**) en THF anhidro (20 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos y luego se agregó 3-(4-cloro-1H-pirazolo[3,4-d]pirimidin-1-il)-4-metilbenzonitrilo (**Producto Intermedio AM2**) (484 mg, 1,79 mmol). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 1 hora. La mezcla de reacción se neutralizó con ácido cítrico 1M y la mezcla de reacción se diluyó con agua (10 mL) y EtOAc (30 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc (2 × 30 mL). Los elementos orgánicos combinados se lavaron con salmuera saturada (75 mL), se secaron ($MgSO_4$), se filtraron y se concentraron al vacío. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 30 a 50% Et_2O en isohexano para proporcionar el producto (300 mg, 26,3 %). m/z (ES+) $(M+H)^+$ = 636,5; HPLC t_R = 3,65 min.

Producto Intermedio AM8: (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-N-(5-cloropiridin-2-il)-2-(1-(5-ciano-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida



Se preparó en una forma análoga al **Producto Intermedio AM6** utilizando 5-cloropiridil-2-amina. m/z (ES+) $(M+H)^+$ = 732,5; HPLC t_R = 3,77 min.

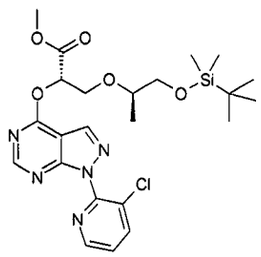
Producto Intermedio AN1: (S)-Metil 3-((R)-1-(terc-butildimetilsililoxi)propan-2-iloxi)-2-hidroxipropanoato



Se agregó trifluorometanosulfonato de magnesio (1,165 g, 3,61 mmol) en una porción a

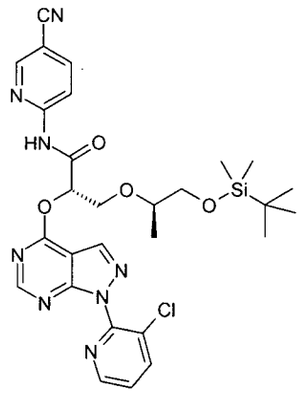
(S)-metil oxirano-2-carboxilato (1,475 g, 14,45 mmol) y (R)-1-(terc-butildimetilsililoxi)propan-2-ol (CAS no. 136918-07-5) (2,75 g, 14,45 mmol) enfriado hasta alcanzar 10°C. La suspensión resultante se agitó a 10°C durante 10 minutos y luego se entibió hasta alcanzar 45°C y se agitó durante 2 días. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 30% EtOAc en isohexano para proporcionar el producto (1,680 g, 39,8 %). ^{1}H NMR (400 MHz, DMSO) δ0,00 (s, 6H), 0,83 (s, 9H), 0,98 (d, 3H), 3,35 - 3,45 (m, 2H), 3,47 - 3,65 (m, 3H), 3,66 (s, 3H), 4,09 - 4,15 (m, 1H), 5,37 (d, 1H).

Producto Intermedio AN2: (2S)-metil 3-((R)-1-(terc-butildimetilsililoxi)propan-2-iloxi)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanoato



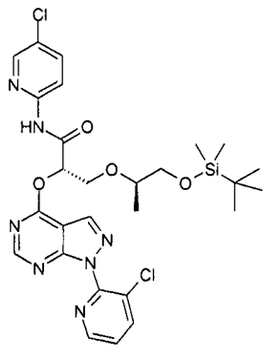
Se agregó hidruro de sodio (0,164 g, 4,10 mmol) a (S)-metil 3-((R)-1-(terc-butildimetilsililoxi)propan-2-iloxi)-2-hidroxipropanoato (**Producto Intermedio AN1**) (1 g, 3,42 mmol) en THF anhidro (20 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos y luego se agregó 4-cloro-1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio B15**) (0,910 g, 3,42 mmol). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 1 hora. La mezcla de reacción se neutralizó con ácido cítrico 1M y la mayor parte del THF se eliminó al vacío. La mezcla de reacción se diluyó con agua (20 mL) y EtOAc (50 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc (2 × 50 mL). Los elementos orgánicos combinados se lavaron con salmuera saturada (25 mL), se secaron ($MgSO_4$) y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 40 a 70% EtOAc en isohexano para proporcionar el producto (0,911 g, 51,0%). ^{1}H NMR (400 MHz, DMSO) δ0,00 (d, 6H), 0,81 (s, 9H), 1,04 (d, 3H), 3,47 - 3,62 (m, 3H), 3,68 (s, 3H), 4,08 (d, 2H), 5,81 (t, 1H), 7,71 - 7,77 (m, 1H), 8,29 - 8,34 (m, 1H), 8,54 - 8,58 (m, 2H), 8,64 - 8,67 (m, 1H); m/z (ES+), $(M+H)^+$ = 522,50; HPLC t_R = 3,38 min

Producto Intermedio AN3: (2S)-3-((R)-1-(terc-butildimetilsililoxi)propan-2-iloxi)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-cianopiridin-2-il)propanamida



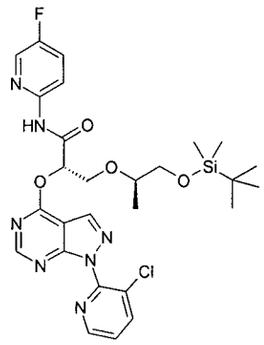
Se agregó trimetilaluminio (2M en hexanos) (1,839 mL, 3,68 mmol) a 6-aminonicotinonitrilo (CAS no. 4214-73-7) (411 mg, 3,45 mmol) en DCM (8 mL) enfriado hasta alcanzar 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 20 minutos. Se agregó (2S)-metil 3-((R)-1-(terc-butildimetilsililoxi)propan-2-iloxi)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanoato (**Producto Intermedio AN2**) (600 mg, 1,15 mmol) en tolueno (8 mL) y la reacción se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó hasta alcanzar 100°C durante 5 horas en el reactor de microondas. La reacción se dejó enfriar hasta alcanzar la temperatura ambiente antes de agregar EtOAc (50 mL) y solución de tartrato de sodio y potasio al 20% (30 mL), que se agitó vigorosamente durante 16 horas. Las fases se separaron y la capa orgánica se lavó con salmuera sat. (15 mL), se secó ($MgSO_4$) y se evaporó. El producto bruto se purificó mediante cromatografía instantánea en alúmina, eluyendo con 0 a 50% EtOAc en isohexano para proporcionar el producto (395 mg, 56,4 %). ^{1}H NMR (400 MHz, DMSO) δ-0,01 (d, 6H), 0,80 (s, 9H), 1,08 (d, 3H), 3,47 - 3,62 (m, 2H), 3,67 - 3,77 (m, 1H), 4,09 - 4,21 (m, 2H), 5,92 - 5,97 (m, 1H), 7,75 - 7,80 (m, 1H), 8,13 - 8,17 (m, 1H), 8,22 - 8,29 (m, 1H), 8,34 - 8,37 (m, 1H), 8,58 (s, 1H), 8,63 (s, 1H), 8,67 - 8,71 (m, 1H), 8,83 - 8,85 (m, 1H), 11,55 (s, 1H); m/z (ES+), $(M+H)^+$ = 607,47; HPLC t_R = 3,27 min

Producto Intermedio AN4: (2S)-3-((R)-1-(terc-butildimetilsililoxi)propan-2-iloxi)-N-(5-cloropiridin-2-il)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida



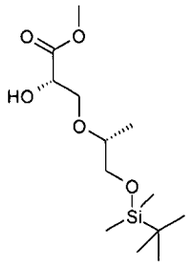
Se agregó trimetilaluminio (2M en Hexanos) (0,551 mL, 1,10 mmol) a 5-cloropiridin-2-amina (135 mg, 1,05 mmol) en tolueno (5 mL) enfriado hasta alcanzar 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 20 minutos. Se agregó (2S)-metil 3-((R)-1-(terc-butildimetilsililoxi)propan-2-iloxi)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanoato (**Producto Intermedio AN2**) (500 mg, 0,96 mmol) en tolueno (5 mL) y la reacción se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó hasta alcanzar 100°C durante 5 horas en el reactor de microondas. La reacción se dejó enfriar hasta alcanzar la temperatura ambiente antes de agregar EtOAc (50 mL) y solución de tartrato de sodio y potasio al 20% (30 mL), que se agitó vigorosamente durante 16 horas. Las fases se separaron y la capa orgánica se lavó con salmuera sat. (15 mL), se secó ($MgSO_4$) y se evaporó. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 30 a 50% EtOAc en isohexano lo que proporcionó el producto (460 mg, 78 %). ^{1}H NMR (400 MHz, DMSO) δ-0,01 (d, 6H), 0,80 (s, 9H), 1,08 (d, 3H), 3,47 - 3,63 (m, 2H), 3,67 - 3,76 (m, 1H), 4,07 - 4,19 (m, 2H), 5,89 - 5,96 (m, 1H), 7,75 - 7,80 (m, 1H), 7,89 - 7,94 (m, 1H), 8,02 - 8,07 (m, 1H), 8,33 - 8,37 (m, 1H), 8,41 - 8,43 (m, 1H), 8,58 (s, 1H), 8,63 (s, 1H), 8,67 - 8,72 (m, 1H), 11,18 (s, 1H); m/z (ES+), $(M+H)^+$ = 618,44; HPLC t_R = 3,53 min

Producto Intermedio AN5: (2S)-3-((R)-1-(terc-butildimetilsililoxi)propan-2-iloxi)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-fluoropiridin-2-il)propanamida



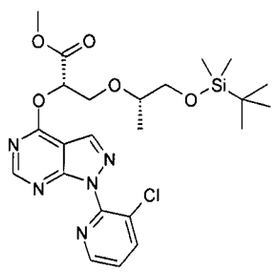
Se agregó trimetilaluminio (2M en hexano) (0,474 mL, 0,95 mmol) a 5-fluoropiridin-2-amina (102 mg, 0,91 mmol) en tolueno (7 mL) enfriado hasta alcanzar 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 20 minutos. Se agregó (2S)-metil 3-((R)-1-(terc-butildimetilsililoxi)propan-2-iloxi)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanoato (**Producto Intermedio AN2**) (430 mg, 0,82 mmol) en tolueno (7 mL) y la reacción se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó hasta alcanzar 100°C durante 5 horas en el reactor de microondas. La reacción se dejó enfriar hasta alcanzar la temperatura ambiente antes de agregar EtOAc (30 mL) y solución de tartrato de sodio y potasio al 20% (30 mL), que se agitó vigorosamente durante 16 horas. Las fases se separaron y la capa orgánica se lavó con salmuera sat. (15 mL), se secó ($MgSO_4$) y se evaporó. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 30 a 50% EtOAc en isohexano para proporcionar (2S)-3-((R)-1-(terc-butildimetilsililoxi)propan-2-iloxi)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-fluoropiridin-2-il)propanamida (303 mg, 61,1 %). ^{1}H NMR (400 MHz, DMSO) δ-0,01 (d, 6H), 0,80 (s, 9H), 1,09 (d, 3H), 3,46 - 3,63 (m, 2H), 3,67 - 3,77 (m, 1H), 4,07 - 4,20 (m, 2H), 5,90 - 5,95 (m, 1H), 7,71 - 7,80 (m, 2H), 8,02 - 8,08 (m, 1H), 8,33 - 8,39 (m, 2H), 8,58 (s, 1H), 8,63 (s, 1H), 8,67 - 8,71 (m, 1H), 11,09 (s, 1H); m/z (ES+), $(M+H)^+$ = 602,48; HPLC t_R = 3,33 min

Producto Intermedio AO1: (S)-metil 3-((S)-1-(terc-butildimetilsililoxi)propan-2-iloxi)-2-hidroxipropanoato



Se agregó trifluorometanosulfonato de magnesio (0,974 g, 3,02 mmol) en una porción a (S)-metil oxirano-2-carboxilato (1,234 g, 12,08 mmol) y (S)-1-(terc-butildimetilsililoxi)propan-2-ol (CAS no. 113534-13-7) (2,30 g, 12,08 mmol) en EtOAc (5 mL) enfriado hasta alcanzar 10°C. La suspensión resultante se agitó a 10°C durante 10 minutos y luego se entibió hasta alcanzar 45°C y se agitó durante 2 días. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 30% EtOAc en isohexano para proporcionar el producto (1,336 g, 37,8 %). ^{1}H NMR (400 MHz, DMSO) δ0,00 (s, 6H), 0,83 (s, 9H), 0,98 (d, 3H), 3,34 - 3,53 (m, 3H), 3,55 - 3,64 (m, 5H), 4,11 (q, 1H), 5,39 (d, 1H)

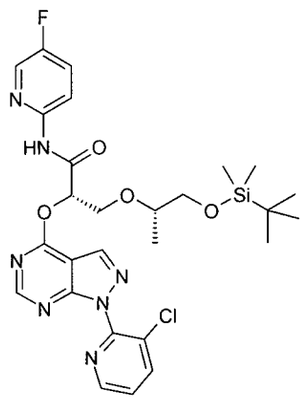
Producto Intermedio AO2: (2S)-metil 3-((S)-1-(terc-butildimetilsililoxi)propan-2-iloxi)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanoato



Se agregó hidruro de sodio (0,219 g, 5,48 mmol) a (S)-metil 3-((S)-1-(terc-butildimetilsililoxi)propan-2-iloxi)-2-hidroxipropanoato (**Producto Intermedio AO1**) (1,336 g, 4,57 mmol) en THF anhidro (30 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos y luego se agregó 4-cloro-1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidina (1,216 g, 4,57 mmol). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 1 hora. La mezcla de reacción se neutralizó con ácido cítrico 1M y la mayor parte del THF se eliminó al vacío. La mezcla de reacción se diluyó con agua (20 mL) y EtOAc (50 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc (2 × 50 mL). Los elementos orgánicos combinados se lavaron con salmuera saturada (25 mL), se secaron ($MgSO_4$) y se

evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 30 a 60% EtOAc en isohexano para proporcionar (2S)-metil 3-((S)-1-(terc-butildimetilsililoxi)propan-2-iloxi)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanoato (1,658g, 69,5%). m/z (ES+), $(M+H)^+$ = 522,50; HPLC t_R = 3,35 min

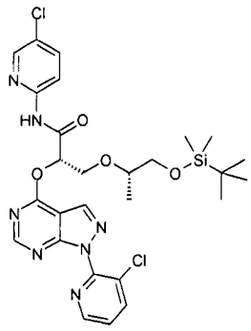
Producto Intermedio AO3: (2S)-3-((S)-1-(terc-butildimetilsililoxi)propan-2-iloxi)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-fluoropiridin-2-il)propanamida



Se agregó trimetilaluminio (2M en hexanos) (0,608 mL, 1,22 mmol) a 5-fluoropiridin-2-amina (130 mg, 1,16 mmol) en tolueno (8 mL) enfriado hasta alcanzar 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 20 minutos. Se agregó (2S)-metil 3-((S)-1-(terc-butildimetilsililoxi)propan-2-iloxi)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanoato (**Producto Intermedio AO2**) (552 mg, 1,06 mmol) en tolueno (8 mL) y la reacción se calentó hasta alcanzar 100°C durante 5 horas en el reactor de microondas. La reacción se dejó enfriar hasta alcanzar la temperatura ambiente antes de agregar EtOAc (30 mL) y solución de tartrato de sodio y potasio al 20% (30 mL), que se agitó vigorosamente durante 16 horas. Las fases se separaron y la capa orgánica se lavó con salmuera sat. (15 mL), se secó ($MgSO_4$) y se evaporó para proporcionar el producto (638 mg, 100 %) que se utilizó sin purificación adicional. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0,05 (d, 6H), 0,87 (s, 9H), 1,17 (d, 3H), 3,51 - 3,58 (m, 1H), 3,60 - 3,69 (m, 2H), 4,18 - 4,22 (m, 2H), 6,00 (t, 1H), 7,40 - 7,49 (m, 2H), 7,98 - 8,03 (m, 1H), 8,13 (d, 1H), 8,22 - 8,28 (m, 1H), 8,44 (s, 1H), 8,60 - 8,64 (m, 2H), 8,94 (s, 1H); m/z (ES+), $(M+H)^+$ = 602,55; HPLC t_R = 3,35 min

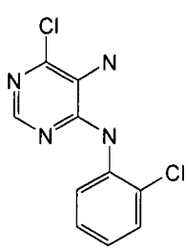
Producto Intermedio AO4: (2S)-3-((S)-1-(terc-butildimetilsililoxi)propan-2-iloxi)-N-(5-cloropiridin-2-il)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-

iloxi)propanamida



Se agregó trimetilaluminio (2M en hexanos) (0,551 mL, 1,10 mmol) a 5-cloropiridin-2-amina (135 mg, 1,05 mmol) en tolueno (8 mL) enfriado hasta alcanzar 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 20 minutos. Se agregó (2S)-metil 3-((S)-1-(terc-butildimetilsililoxi)propan-2-iloxi)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanoato (**Producto Intermedio AO2**) (500 mg, 0,96 mmol) en tolueno (8 mL) y la reacción se calentó hasta alcanzar 100°C durante 5 horas en el reactor de microondas. La reacción se dejó enfriar hasta alcanzar la temperatura ambiente antes de agregar EtOAc (30 mL) y solución de tartrato de sodio y potasio al 20% (30 mL), que se agitó vigorosamente durante 16 horas. Las fases se separaron y la capa orgánica se lavó con salmuera sat. (15 mL), se secó ($MgSO_4$) y se evaporó para proporcionar el producto bruto (300 mg) que se utilizó sin purificación adicional. m/z (ES+), $(M+H)^+$ = 618,44; HPLC t_R = 23,55 min

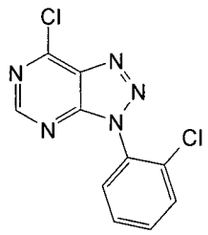
Producto Intermedio AP1: 6-cloro-N4-(2-clorofenil)pirimidina-4,5-diamina



Se disolvió 4,6-dicloropirimidin-5-amina (CAS no. 5413-85-4) (2 g, 12,20 mmol) y 2-cloroanilina (CAS no. 95-51-2) (1,556 g, 12,20 mmol) en etilenglicol (12 mL) y se selló en un tubo de microondas. La reacción se calentó hasta alcanzar 100°C durante 1 hora en el reactor de microondas y se enfrió hasta alcanzar la temperatura ambiente. La mezcla de reacción se aplacó con agua (50 mL), se extrajo con EtOAc (3 × 50 mL), la capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el producto bruto. El producto

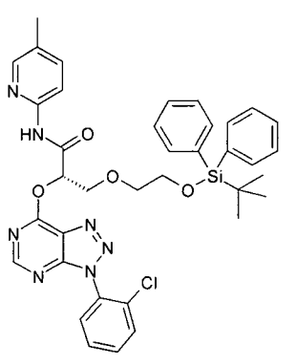
bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 60% EtOAc en isohexano para proporcionar el producto (2,65 g, 85 %). ^{1}H NMR (400 MHz, DMSO) δ5,38 (s, 2H), 7,19 - 7,25 (m, 1H), 7,32 - 7,38 (m, 1H), 7,49 - 7,54 (m, 1H), 7,57 - 7,62 (m, 1H), 7,73 (s, 1H), 8,38 (s, 1H); m/z (ES+), $(M+H)^+$ = 255,25; HPLC t_R = 1,82 min.

Producto Intermedio AP2: 7-cloro-3-(2-clorofenil)-3H-[1,2,3]triazolo[4,5-d]pirimidina



Se agregó nitrito de sodio (0,298 g, 4,31 mmol) a 6-cloro-N4-(2-clorofenil)pirimidina-4,5-diamina (**Producto Intermedio AP1**) (1 g, 3,92 mmol) en ácido acético (50%Aq, 25 mL) y DCM (25 mL) a temperatura ambiente. La solución resultante se agitó a temperatura ambiente durante 15 minutos. La mezcla de reacción se separó y la fase orgánica se lavó con agua (10 mL), se secó ($MgSO_4$) y se evaporó para proporcionar el producto bruto (0,600 g) que se utilizó sin purificación adicional. ^{1}H NMR (400 MHz, $CDCl_3$) δ δ7,52 - 7,65 (m, 3H), 7,68 - 7,73 (m, 1H), 8,97 (s, 1H); m/z (ES+), $(M+H)^+$ = 266,21; HPLC t_R = 2,33 min

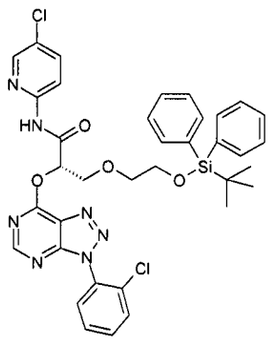
Producto Intermedio AP3: (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-(3-(2-clorofenil)-3H-[1,2,3]triazolo[4,5-d]pirimidin-7-iloxi)-N-(5-cloropiridin-2-il)propanamida



Se agregó hidruro de sodio (50,1 mg, 1,25 mmol) a (S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-hidroxi-N-(5-metilpiridin-2-il)propanamida (**Producto Intermedio AU2**) (250 mg, 0,52 mmol) en THF anhidro (5 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos y luego se agregó 7-cloro-3-(2-

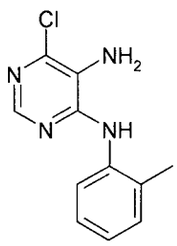
clorofenil)-3H-[1,2,3]triazolo[4,5-d]pirimidina (**Producto Intermedio AP2**) (278 mg, 1,04 mmol). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 1 hora. La mezcla de reacción se neutralizó con ácido cítrico 1M y la mayor parte del THF se eliminó al vacío. La mezcla de reacción se diluyó con agua (20 mL) y EtOAc (50 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc (2 × 50 mL). Los elementos orgánicos combinados se lavaron con salmuera saturada (15 mL), se secaron ($MgSO_4$) y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 50% EtOAc en isohexano para proporcionar (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-(3-(2-clorofenil)-3H-[1,2,3]triazolo[4,5-d]pirimidin-7-iloxi)-N-(5-metilpiridin-2-il)propanamida (335 mg, 91 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ0,97 (s, 9H), 2,28 (s, 3H), 3,67 - 3,84 (m, 4H), 4,26 (d, 2H), 6,15 (t, 1H), 7,30 - 7,41 (m, 5H), 7,48 - 7,71 (m, 10H), 8,06 - 8,14 (m, 2H), 8,68 (s, 1H), 8,76 (s, 1H); m/z (ES+), $(M+H)^+$ = 708,65; HPLC t_R = 3,84 min

Producto Intermedio AP4: (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-(3-(2-clorofenil)-3H-[1,2,3]triazolo[4,5-d]pirimidin-7-iloxi)-N-(5-cloropiridin-2-il)propanamida



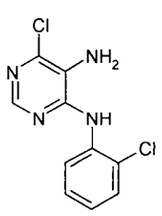
Se agregó hidruro de sodio (38,5 mg, 0,96 mmol) a (S)-3-(2-(terc-butildifenilsililoxi)etoxi)-N-(5-cloropiridin-2-il)-2-hidroxipropanamida (**Producto Intermedio AU3**) (200 mg, 0,40 mmol) en THF anhidro (5 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos y luego se agregó 7-cloro-3-(2-clorofenil)-3H-[1,2,3]triazolo[4,5-d]pirimidina (**Producto Intermedio AP2**) (107 mg, 0,40 mmol). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 1 hora. La mezcla de reacción se neutralizó con ácido cítrico 1M y la mayor parte del THF se eliminó al vacío. La mezcla de reacción se diluyó con agua (20 mL) y EtOAc (50 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc (2 × 50 mL). Los elementos orgánicos combinados se lavaron con salmuera

saturada (25 mL), se secaron ($MgSO_4$) y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 50% EtOAc en isohexano para proporcionar (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-(3-(2-clorofenil)-3H-[1,2,3]triazolo[4,5-d]pirimidin-7-iloxi)-N-(5-cloropiridin-2-il)propanamida (290 mg, 99 %). m/z (ES+), $(M+H)^+$ = 728,38 : HPLC t_R = 3,91 min**Producto Intermedio AP5: 6-cloro-N4-o-tolilpirimidina-4,5-diamina**



Se disolvió 4,6-dicloropirimidin-5-amina (2 g, 12,20 mmol) y o-toluidina (1,309 mL, 12,20 mmol) en etilenglicol (10 mL) y se selló en un tubo de microondas. La reacción se calentó hasta alcanzar 100°C durante 1 hora en el reactor de microondas y se enfrió hasta alcanzar la temperatura ambiente. La mezcla de reacción se aplacó con agua (20 mL), se extrajo con EtOAc (3 x 20 mL), la capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el producto bruto. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 50% EtOAc en isohexano para proporcionar el producto (2,300 g, 80 %). ^{1}H NMR (400 MHz, DMSO) δ2,15 (s, 3H), 5,28 (s, 2H), 7,08 - 7,33 (m, 4H), 7,68 (s, 1H), 8,18 (s, 1H); m/z (ES+), $(M+H)^+$ = 235,34; HPLC t_R = 1,54 min.

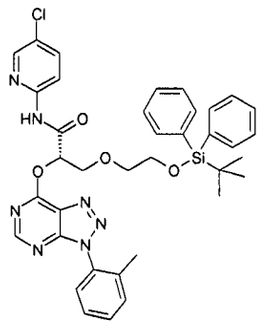
Producto Intermedio AP6: 7-cloro-3-o-tolil-3H-[1,2,3]triazolo[4,5-d]pirimidina



Se agregó nitrito de sodio (0,323 g, 4,69 mmol) a 6-cloro-N4-o-tolilpirimidina-4,5-diamina (**Producto Intermedio AP5**) (1 g, 4,26 mmol) en ácido acético (50% ac.) (25 mL) y DCM (25 mL) a temperatura ambiente. La solución resultante se agitó a temperatura ambiente durante 15 minutos. La mezcla de reacción se separó y la fase orgánica se lavó con agua (10 mL), se secó ($MgSO_4$) y se evaporó para proporcionar 7-cloro-3-o-tolil-3H-[1,2,3]triazolo[4,5-d]pirimidina bruta (0,980 g, 94 %) que se utilizó sin purificación

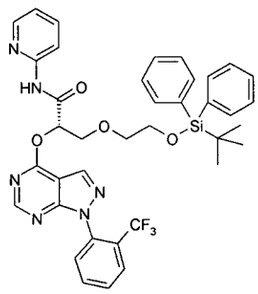
adicional. ^{1}H NMR (400 MHz, $CDCl_3$) δ2,19 (s, 3H), 7,42 - 7,57 (m, 4H), 8,95 (s, 1H) m/z (ES+), $(M+H)^+$ = 246,29; HPLC t_R = 2,28 min

Producto Intermedio AP7: (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-N-(5-cloropiridin-2-il)-2-(3-o-tolil-3H-[1,2,3]triazolo[4,5-d]pirimidin-7-iloxi)propanamida



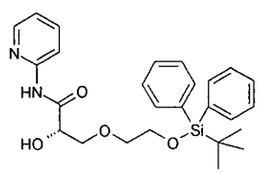
Se agregó hidruro de sodio (57,7 mg, 1,44 mmol) a (S)-3-(2-(terc-butildifenilsililoxi)etoxi)-N-(5-cloropiridin-2-il)-2-hidroxipropanamida (**Producto Intermedio AU3**) (300 mg, 0,60 mmol) en THF anhidro (7 ml) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos y luego se agregó 7-cloro-3-o-tolil-3H-[1,2,3]triazolo[4,5-d]pirimidina (148 mg, 0,60 mmol). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 1 hora. La mezcla de reacción se neutralizó con ácido cítrico 1M y la mayor parte del THF se eliminó al vacío. La mezcla de reacción se diluyó con agua (20 mL) y EtOAc (50 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc (2 x 50 mL). Los elementos orgánicos combinados se lavaron con salmuera saturada (15 mL), se secaron ($MgSO_4$) y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 50% EtOAc en isohexano para proporcionar (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-N-(5-cloropiridin-2-il)-2-(3-o-tolil-3H-[1,2,3]triazolo[4,5-d]pirimidin-7-iloxi)propanamida (410 mg, 100 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ0,97 (s, 9H), 2,19 (s, 3H), 3,67 - 3,85 (m, 4H), 4,26 (d, 2H), 6,14 (t, 1H), 7,31 - 7,54 (m, 10H), 7,60 - 7,68 (m, 5H), 8,18 - 8,23 (m, 2H), 8,66 (s, 1H), 8,91 (s, 1H); m/z (ES+), $(M+H)^+$ = 708,61; HPLC t_R = 4,02 min

Producto Intermedio AQ1: (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-N-(piridin-2-il)-2-(1-(2-(trifluorometil)fenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida



Se agregó hidruro de sodio (117 mg, 2,93 mmol) a (S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-hidroxi-N-(piridin-2-il)propanamida (618mg, 1,33 mmol) (**Producto Intermedio AQ2**) en THF anhidro (20 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos y luego se agregó 4-cloro-1-(2-(trifluorometil) fenil)-1H-pirazolo[3,4-d]pirimidina (514 mg, 1,46 mmol) (**Producto Intermedio B4**) . La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 1 hora. La mezcla de reacción se neutralizó con ácido cítrico 1M y la mayor parte del THF se eliminó al vacío. La mezcla de reacción se diluyó con agua (20 mL) y EtOAc (50 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc (2 x 100 mL). Los elementos orgánicos combinados se lavaron con salmuera saturada (75 mL), se secaron ($MgSO_4$) y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 50 a 100% EtOAc en isohexano para proporcionar el producto (919 mg, 95 %). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 0,99 (9H, t), 3,70 - 3,72 (2H, m), 3,82 (2H, t), 4,16 - 4,25 (2H, m), 6,05 - 6,07 (1H, m), 7,04 - 7,07 (1H, m), 7,31 - 7,75 (14H, m), 7,89 - 7,92 (1H, m), 8,24 - 8,28 (2H, m), 8,36 (1H, s), 8,55 (1H, s), 8,73 (1H, s); m/z (ES+) $(M+H)^+$ = 279,1; HPLC TA = 3,71 min.

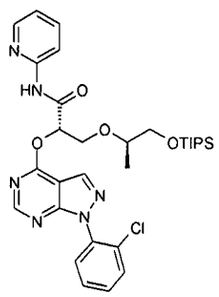
Producto Intermedio AQ2: (S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-hidroxi-N-(piridin-2-il)propanamida



Se agregó trimetilaluminio (3,73 mL, 7,45 mmol) a piridin-2-amina (0,701 g, 7,45 mmol) en tolueno (6 ml) enfriado hasta alcanzar 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 20 minutos. Se agregó (S)-metil 3-(2-(terc-butildifenilsililoxi)etoxi)-2-hidroxipropanoato (1,5 g, 3,73 mmol) (**Producto Intermedio AB3**) en tolueno (6 ml) y la

reacción se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó hasta alcanzar 110 durante 5 horas en un microondas. La mezcla de reacción se dejó enfriar y se concentró al vacío. El residuo se neutralizó con ácido cítrico (1M, ac) y luego se diluyó con agua (25mL) y se extrajo con EtOAc (2 x 50 mL). Los elementos orgánicos combinados se lavaron con salmuera (20ml), luego se secaron ($MgSO_4$), se filtraron y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 30 a 50% EtOAc en isohexano para proporcionar el producto (1,085 g, 62,7 %). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 1,05 (9H, t), 3,60 - 3,66 (2H, m), 3,67 (1H, d), 3,82-3,84 (2H d, *m*), 3,80 - 3,85 (2H, m), 4,33 - 4,35 (1H, m), 7,03 - 7,06 (1H, m), 7,35 - 7,68 (10H, m), 7,70 (1H, d), 8,22 (1H, d), 8,29 - 8,30 (1H, m),9,15 (1H,s); m/z (ES+) $(M+H)^+$ = 465,42; HPLC t_R = 3,13 min.

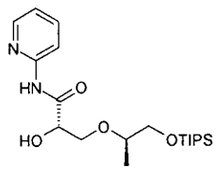
Producto Intermedio AQ3: (2S)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(piridin-2-il)-3-((R)-1-(triisopropilsililoxi)propan-2-iloxi)propanamida



Se agregó hidruro de sodio (78 mg, 1,95 mmol) a (S)-2-hidroxi-N-(piridin-2-il)-3-((R)-1-(triisopropilsililoxi)propan-2-iloxi)propanamida (**Producto Intermedio AQ4**) (387 mg, 0,98 mmol) en THF anhidro (20 mL). La solución resultante se agitó a 0°C durante 10 minutos y luego se agregó 4-cloro-1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio B1**) (250 mg, 0,89 mmol) . La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 1 hora. La mezcla de reacción se neutralizó con ácido cítrico 1M y la mayor parte del THF se eliminó al vacío. La mezcla de reacción se diluyó con agua (20 mL) y EtOAc (50 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc (2 x 100 mL). Los elementos orgánicos combinados se lavaron con salmuera saturada (75 mL), se secaron ($MgSO_4$) y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 50 a 100% EtOAc en isohexano para proporcionar el producto (329 mg, 59,4 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,01 - 1,15 (24H, m), 3,55 - 3,78 (3H, m), 4,19 - 4,35

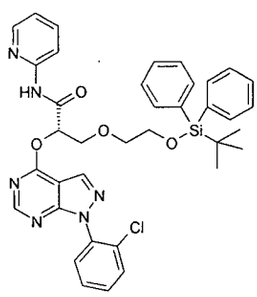
(2H, m), 6,03 (1H, t), 7,05 (1H, t) 7,40 - 7,65 (4H, m), 7,7 (1H, t), 8,2- 8,3 (2H, m), 8,43 (1H, s), 8,58 (1H, s), 8,75 (1H, s); m/z (ES+) M+ = 625,44; HPLC t_R = 4,02 min.

Producto Intermedio AQ4: (S)-2-hidroxi-N-(piridin-2-il)-3-((R)-1-(triisopropilsililoxi)propan-2-iloxi)propanamida



Se agregó trimetilaluminio (2M en tolueno) (2,99 ml, 5,98 mmol) a piridin-2-amina (0,563 g, 5,98 mmol) en tolueno (20,18 ml) enfriado hasta alcanzar 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 20 minutos. Se agregó (S)-metil 2-hidroxi-3-((R)-1-(triisopropilsililoxi)propan-2-iloxi)propanoato (1 g, 2,99 mmol) (**Producto Intermedio AN1**) en tolueno (6,73 mL) y la reacción se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó a reflujo durante 5 horas. La mezcla de reacción se dejó enfriar y se concentró al vacío. El residuo se neutralizó con ácido cítrico (1M, ac) y luego se diluyó con agua (25mL) y se extrajo con EtOAc (2 × 50 mL). Los elementos orgánicos combinados se lavaron con salmuera (20ml), luego se secaron ($MgSO_4$), se filtraron y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 30 a 50% EtOAc en isohexano para proporcionar el producto (0,657 g, 55,4 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,03 - 1,17 (24H, m), 3,61 - 3,69 (3H, m), 3,82 - 3,86 (1H, m), 4,00 - 4,04 (1H, m), 4,13 (1H, d), 4,32 (1H, q), 7,02 - 7,06 (1H, m), 7,67 - 7,72 (1H, m), 8,23 (1H, d), 8,29 - 8,31 (1H, m), 9,20 (1H, s); m/z (ES+) $(M+H)^+$ = 397,44; HPLC t_R = 3,36 min.

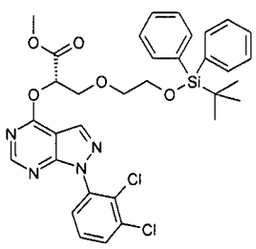
Producto Intermedio AQ5: (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(piridin-2-il)propanamida



Se agregó hidruro de sodio (91 mg, 2,27 mmol) a (S)-3-(2-(terc-butildifenilsililoxi)etoxi)-

2-hidroxi-N-(piridin-2-il)propanamida (**Producto Intermedio AQ4**) (480 mg, 1,03 mmol) (**Producto Intermedio 3**) en THF anhidro (20 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos y luego se agregó 4-cloro-1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio B1**) (320 mg, 1,14 mmol). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 1 hora. La mezcla de reacción se neutralizó con ácido cítrico 1M y la mayor parte del THF se eliminó al vacío. La mezcla de reacción se diluyó con agua (20 mL) y EtOAc (50 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc (2 x 100 mL). Los elementos orgánicos combinados se lavaron con salmuera saturada (75 mL), se secaron ($MgSO_4$) y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 50 a 100% EtOAc en isohexano para proporcionar el producto (682 mg, 95 %). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 0,98 - 1,00 (9H, m), 3,69 - 3,72 (2H, m), 3,81 (2H, t), 4,16 - 4,25 (2H, m), 6,06 - 6,09 (1H, m), 7,04 - 7,07 (1H, m), 7,31 - 7,66 (14H, m), 7,68 - 7,73 (1H, m), 8,24 - 8,28 (2H, m), 8,38 (1H, s), 8,58 (1H, s), 8,75 (1H, s); m/z (ES+) M+ = 693,61; HPLC t_R = 3,79 min.

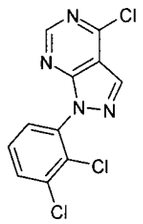
Producto Intermedio AR1: (2S)-metil 3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(2,3-diclorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanoato



Se agregó hidruro de sodio (0,167 g, 4,17 mmol) a (S)-metil 3-(2-(terc-butildifenilsililoxi)etoxi)-2-hidroxipropanoato (**Producto Intermedio AB3**) (1,4 g, 3,48 mmol) en THF anhidro (25 ml) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos y luego se agregó 4-cloro-1-(2,3-diclorofenil)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio AR2**) (1,432 g, 3,83 mmol). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 1 hora. La mezcla de reacción se neutralizó con ácido cítrico 1M y la mayor parte del THF se eliminó al vacío. La mezcla de reacción se diluyó con agua (20 mL) y EtOAc (50 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc (2 x 100 mL). Los elementos orgánicos combinados se lavaron con salmuera saturada (75 mL), se secaron

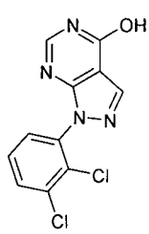
($MgSO_4$) y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 50 a 100% EtOAc en isohexano. Las fracciones que contenían el producto se evaporaron hasta secarse para proporcionar el producto bruto que desafortunadamente se contaminó con el alcohol y metil glicidato de partida. El producto bruto se purificó nuevamente mediante cromatografía instantánea en sílice, gradiente de elución 0 a 30% EtOAc en tolueno para proporcionar el producto (0,860 g, 37,1 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,04 (9H, s), 3,80 – 3,69 (5H, m), 3,85 (2H, t), 4,15 – 4,08 (1H, m), 4,20 (1H, dd), 5,87 (1H, dd), 7,48 – 7,33 (8H, m), 7,75 – 7,60 (5H, m), 8,32 (1H, s), 8,54 (1H, s). m/z (ES+) $(M+H)^+$ = 667; HPLC t_R = 3,8 min.

Producto Intermedio AR2: 4-cloro-1-(2,3-diclorofenil)-1H-pirazolo[3,4-d]pirimidina



Se agregó oxicloruro de fósforo (26,5 ml, 284,60 mmol) a 1-(2,3-diclorofenil)-1H-pirazolo[3,4-d]pirimidin-4-ol (**Producto Intermedio AR3**) (4 g, 14,23 mmol) a temperatura ambiente. La mezcla resultante se agitó a 100°C durante 4 horas. Se dejó enfriar hasta alcanzar la temperatura ambiente. La mezcla de reacción se evaporó casi hasta secarse, se disolvió en tolueno, se evaporó, se disolvió nuevamente en tolueno y se evaporó hasta secarse nuevamente. El sólido se trituró con EtOH. Se retiró un sólido mediante filtración y se secó al vacío para proporcionar el producto (2,450 g, 57,5 %). ^{1}H NMR (400 MHz, DMSO) δ 7,65 (1H, m), 7,73 - 7,75 (1H, dd), 7,94 - 7,97 (1H, dd), 8,83 (1H, s), 8,91 (1H, s); m/z (ES+) $(M+H)^+$ = 518; HPLC t_R = 1,89 min.

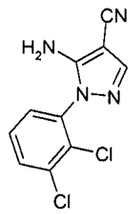
Producto Intermedio AR3: 1-(2,3-Diclorofenil)-1H-pirazolo[3,4-d]pirimidin-4-ol



Se agregó ácido sulfúrico concentrado (1,666 mL, 31,25 mmol) a una solución agitada de 5-amino-1-(2,3-diclorofenil)-1H-pirazol-4-carbonitrilo (**Producto Intermedio AR4**) (7,19 g, 28,41 mmol) en ácido fórmico (40 mL). La solución resultante se agitó a 100°C durante

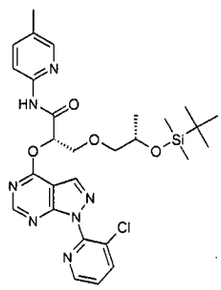
16 horas. Se dejó enfriar hasta alcanzar la temperatura ambiente. La mezcla de reacción se evaporó hasta secarse. El residuo se trituró bajo agua. Se retiró un sólido mediante filtración y se secó al vacío para proporcionar el producto (6,64 g, 83 %). ^{1}H NMR (400 MHz, DMSO) δ 7,57 - 7,61 (1H, m), 7,63 - 7,66 (1H, m), 7,88 - 7,91 (1H, dd), 8,09 (1H, d), 8,36 (1H, s), 12,40 (1H, s); m/z (ES$^+$) $(M+H)^+$ = 281; HPLC t_R = 1,61 min.

Producto Intermedio AR4: 5-amino-1-(2,3-diclorofenil)-1H-pirazol-4-carbonitrilo



Se dividió (2,3-diclorofenil)hidrazina clorhidrato (CAS no. 21938-47-6) (6,06 g, 28,4 mmol) entre EtOAc y NaOH 2M. Se separó. La solución orgánica se secó ($MgSO_4$), se filtró y se redujo para proporcionar la base libre. Se agregó 2-(etoximetileno)malononitrilo (3,47 g, 28,39 mmol) en porciones a una solución agitada de (2,3-diclorofenil)hidrazina en MeOH (50 mL), bajo nitrógeno a 5°C. La solución resultante se dejó agitar durante 1 hora más. La mezcla de reacción luego se calentó hasta alcanzar reflujo y se agitó durante 3 horas. La mezcla de reacción se dejó enfriar hasta alcanzar la temperatura ambiente, luego se evaporó para proporcionar el producto (7,19 g, 100 %) que se utilizó sin purificación adicional. ^{1}H NMR (400 MHz, DMSO) δ 6,75 (2H, s), 7,48 - 7,53 (2H, m), 7,77 (1H, s), 7,79 - 7,84 (1H, m).

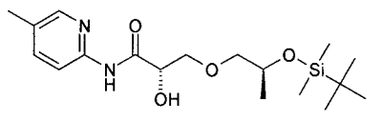
Producto Intermedio AS1: (2S)-3-((S)-2-(terc-butildimetilsililoxi)propoxi)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-metilpiridin-2-il)propanamida



Se agregó hidruro de sodio (134 mg, 3,36 mmol) a (S)-3-((S)-2-(terc-butildimetilsililoxi)propoxi)-2-hidroxi-N-(5-metilpiridin-2-il)propanamida (**Producto Intermedio AS2**) (495 mg, 1,34 mmol) en THF anhidro (5 mL) a 0°C bajo nitrógeno. La

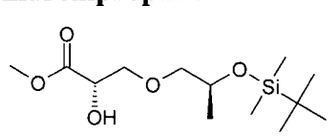
solución resultante se agitó a 0°C durante 10 minutos y luego se agregó 4-cloro-1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio B15**) (393 mg, 1,48 mmol). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 2 horas. La mezcla de reacción se neutralizó con ácido cítrico 1M y se diluyó con agua y EtOAc. La capa orgánica se separó y se lavó con salmuera saturada, se secó ($MgSO_4$) y se evaporó para proporcionar (2S)-3-((S)-2-(terc-butildimetilsililoxi)propoxi)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-metilpiridin-2-il)propanamida (843 mg, 105 %). m/z (ES+) $(M+H)^+$ = 598,58; HPLC t_R = 3,36 min.

Producto Intermedio AS2: (S)-3-((S)-2-(terc-Butildimetilsililoxi)propoxi)-2-hidroxi-N-(5-metilpiridin-2-il)propanamida



Se agregó trimetilaluminio (1,966 mL, 3,93 mmol) lentamente a 5-metilpiridin-2-amina (0,407 g, 3,76 mmol) en tolueno (20 mL) enfriado hasta alcanzar 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos. Se agregó (S)-metil 3-((S)-2-(terc-butildimetilsililoxi)propoxi)-2-hidroxipropanoato (**Producto Intermedio AS3**) (1 g, 3,42 mmol) en tolueno (4 mL) y la reacción se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó a reflujo durante 4 horas (se agregaron 5ml adicionales de tolueno para favorecer la agitación). La mezcla de reacción se concentró al vacío. El residuo se neutralizó con ácido cítrico (1M, ac) y luego se diluyó con agua y se extrajo con EtOAc. Los elementos orgánicos combinados se secaron ($MgSO_4$) y se evaporaron para proporcionar el producto (0,994 g) que se utilizó sin purificación adicional. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0,07 (6H, d), 0,88 (9H, s), 1,15 (3H, d), 2,30 (3H, s), 2,79 - 3,11 (1H, m), 3,39 - 3,51 (2H, m), 3,80 - 3,91 (2H, m), 3,94 - 4,03 (1H, m), 4,31 - 4,36 (1H, m), 7,49 - 7,56 (1H, m), 8,09 - 8,16 (2H, m), 9,20 (1H, s); m/z (ES+) $(M+H)^+$ = 369,52; HPLC t_R = 2,73 min.

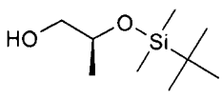
Producto Intermedio AS3: (S)-Metil 3-((S)-2-(terc-butildimetilsililoxi)propoxi)-2-hidroxipropanoato



Se agregó trifluorometanosulfonato de magnesio (1,779 g, 5,52 mmol) en una porción a

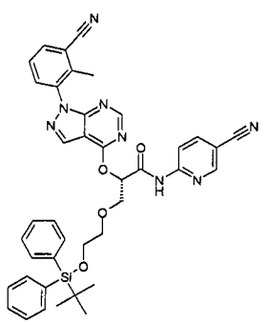
(S)-2-(terc-butildimetilsililoxi)propan-1-ol (**Producto Intermedio AS4**) (4,2 g, 22,06 mmol) y (S)-metil oxirano-2-carboxilato (2,252 g, 22,06 mmol) en EtOAc (25 mL). La suspensión resultante se agitó a 80°C durante 24 horas. Se agregaron 1,5g adicionales del oxirano y la reacción se agitó durante 4 días. La mezcla de reacción se diluyó con EtOAc, se filtró a través de celite y se evaporó hasta secarse. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 0 a 30% EtOAc en isohexano para proporcionar el producto (2,70 g, 41,8 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0,00 (6H, d), 0,82 (9H, s), 1,06 (3H, d), 3,04 (1H, d), 3,25 - 3,39 (2H, m), 3,65 - 3,78 (5H, m), 3,83 - 3,92 (1H, m), 4,19 - 4,27 (1H, m)

Producto Intermedio AS4: (S)-2-(terc-butildimetilsililoxi)propan-1-ol



Se agregó hidruro de diisobutilaluminio (1M en DCM) (41,4 mL, 41,42 mmol) gota a gota a una solución agitada de (S)-etil 2-(terc-butildimetilsililoxi)propanoato (CAS no. 106513-42-2) (5 mL, 18,83 mmol) en éter dietílico (25 mL) a -78°C bajo nitrógeno. La mezcla resultante se agitó a t.a. durante 2 horas. La mezcla de reacción se aplacó cuidadosamente con solución de Rochelle al 20% (>100 ml) y a -78°C y se dejó entibiar hasta alcanzar la t.a.. Después de 2 horas de agitación vigorosa la mezcla se extrajo con Et_2O x2, la capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un líquido incoloro, (S)-2-(terc-butildimetilsililoxi)propan-1-ol (3,50 g, 98 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0,00 (6H, s), 0,81 (9H, s), 1,03 (3H, d), 1,71 - 1,90 (1H, m), 3,24 - 3,33 (1H, m), 3,35 - 3,44 (1H, m), 3,78 - 3,87 (1H, m).

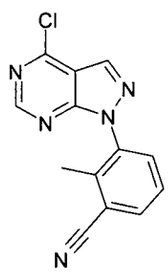
Producto Intermedio AT1: (2S)-3-(2-(terc-Butildifenilsililoxi)etoxi)-2-(1-(3-ciano-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-cianopiridin-2-il)propanamida



Se agregó hidruro de sodio (60% en aceite) (87 mg, 2,17 mmol) a (S)-3-(2-(terc-

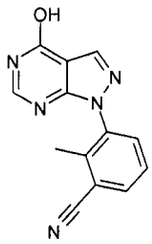
butildifenilsililoxi)etoxi)-N-(5-cianopiridin-2-il)-2-hidroxipropanamida (**Producto Intermedio AU1**) (484 mg, 0,99 mmol) en THF anhidro (25 ml) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos y luego se agregó 3-(4-cloro-1H-pirazolo[3,4-d]pirimidin-1-il)-2-metilbenzonitrilo (**Producto Intermedio AT2**) (267 mg, 0,99 mmol). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 4 horas. La mezcla de reacción se neutralizó con ácido cítrico 1M y se diluyó con agua y EtOAc. La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc. Los elementos orgánicos combinados se lavaron con salmuera saturada, se secaron ($MgSO_4$) y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 50% EtOAc en isohexano para proporcionar el producto (251 mg, 35,1 %). m/z (ES+) $(M+H)^+$ = 723,67; HPLC t_R = 3,75 min.

Producto Intermedio AT2: 3-(4-cloro-1H-pirazolo[3,4-d]pirimidin-1-il)-2-metilbenzonitrilo



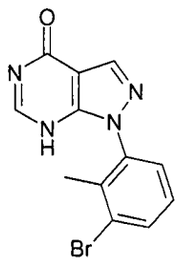
Se agregó tricloruro de fosforilo (9,92 ml, 103,49 mmol) a 3-(4-hidroxi-1H-pirazolo[3,4-d]pirimidin-1-il)-2-metilbenzonitrilo (**Producto Intermedio AT3**) (1,3 g, 5,17 mmol). La solución resultante se agitó a 100°C durante 2 horas. La mezcla de reacción se evaporó (sometiendo a azeotropía con tolueno x3) proporcionando un aceite marrón que se trituró con hielo/agua para proporcionar el producto (1,200 g) que se utilizó sin purificación adicional. ^{1}H NMR (400 MHz, DMSO) δ 2,28 (3H, s), 7,65 (1H, t), 7,86 (1H, d), 8,06 (1H, d), 8,81 (1H, s), 8,90 (1H, s)

Producto Intermedio AT3: 3-(4-hidroxi-1H-pirazolo[3,4-d]pirimidin-1-il)-2-metilbenzonitrilo



Se disolvió 1-(3-bromo-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-ol (**Producto Intermedio AT4**) (2 g, 6,55 mmol) y cianuro de zinc (0,693 g, 5,90 mmol) en DMF (30 mL) y se selló en un tubo de microondas. El tubo se purgó con nitrógeno. Se agregó 9,9-dimetil-4,5-bis(difenilfosfino)xanteno (0,379 g, 0,66 mmol) y tris(dibencilidenoacetona)dipaladio(0) (0,300 g, 0,33 mmol). La reacción se calentó hasta alcanzar 160ºC durante 10 minutos en el reactor de microondas y se enfrió hasta alcanzar la TA. La mezcla de reacción se filtró y el sólido se lavó con DMF (hasta que el filtrado quedó incoloro) para proporcionar el producto (1,340 g, 81 %) que se utilizó sin purificación adicional. ^{1}H NMR (400 MHz, DMSO) δ 2,19 (3H, s), 7,54 (1H, t), 7,71 (1H, d), 7,94 (1H, d), 8,02 (1H, s), 8,30 (1H, s), 12,32 (1H, s)

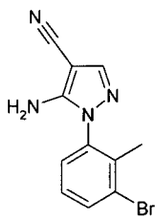
Producto Intermedio AT4: 1-(3-bromo-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4(7H)-ona



Se agregó ácido sulfúrico concentrado (2,67 mL, 50,01 mmol) a una solución agitada de 5-amino-1-(3-bromo-2-metilfenil)-1H-pirazol-4-carbonitrilo (**Producto Intermedio AT5**) (12,6 g, 45,47 mmol) en ácido fórmico (80 mL). La solución resultante se agitó a 100ºC durante 18 horas. La reacción se dejó enfriar hasta alcanzar la temperatura ambiente y se evaporó hasta proporcionar ~la mitad del volumen, se agregó agua (100 mL) y se agitó durante 2 horas. El precipitado formado se retiró mediante filtración, se lavó bien con agua y se secó durante toda la noche en un vacío sobre P_2O_5. El sólido resultante luego se suspendió en DCM (100 mL), se filtró y se secó para proporcionar el producto (9,30 g, 67,0 %) que se utilizó sin purificación adicional. ^{1}H NMR (400 MHz, DMSO) δ 2,06 (3H, s), 7,34 (1H, t), 7,43 (1H, d), 7,82 (1H, d), 8,06 (1H, d), 8,33 (1H, s), 12,34 (1H, s); m/z

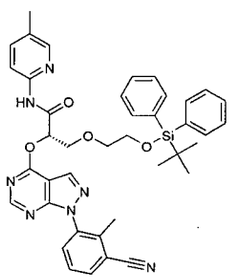
(ES-) (M-H)- = 303,26, 305,21; HPLC t_R = 1,72 min.

Producto Intermedio AT5: 5-amino-1-(3-bromo-2-metilfenil)-1H-pirazol-4-carbonitrilo



Se suspendió (3-bromo-2-metilfenil)hidrazina (CAS no. 459817-67-5) (10 g, 49,74 mmol) en MeOH (100 mL) bajo nitrógeno a 0°C. Se agregó 2-(etoximetileno)malononitrilo (6,07 g, 49,74 mmol) en porciones durante 5 mins y la mezcla se agitó a ~0°C durante 2 horas. La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó a reflujo bajo nitrógeno durante 2 horas. No se produjo reacción. El material de partida se sometió a NMR y se encontró que era una sal, por lo que se agregó N-etil-N-isopropilpropan-2-amina (17,33 mL, 99,47 mmol) y se agitó durante unas 16 horas adicionales. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en EtOAc y se lavó secuencialmente con agua x2 y salmuera saturada. La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el producto bruto, 5-amino-1-(3-bromo-2-metilfenil)-1H-pirazol-4-carbonitrilo (12,60 g, 91 %). m/z (ES+) $(M+H)^+$ = 279,25; HPLC t_R = 1,95 min.

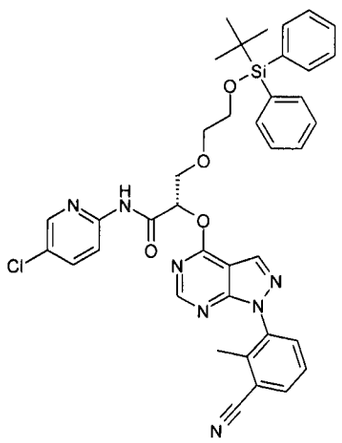
Producto Intermedio AT6: (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(3-ciano-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-metilpiridin-2-il)propanamida



Se agregó hidruro de sodio (60% en aceite) (92 mg, 2,30 mmol) a (S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-hidroxi-N-(5-metilpiridin-2-il)propanamida (**Producto Intermedio AU2**) (500 mg, 1,04 mmol) en THF anhidro (25 ml) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos y luego se agregó 3-(4-cloro-1H-pirazolo[3,4-d]pirimidin-1-il)-2-metilbenzonitrilo (**Producto Intermedio AT2**) (282 mg,

1,04 mmol). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 4 horas. La mezcla de reacción se neutralizó con ácido cítrico 1M y se diluyó con agua y EtOAc. La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc. Los elementos orgánicos combinados se lavaron con salmuera saturada, se secaron ($MgSO_4$) y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 0 a 50% EtOAc en isohexano. No se logró la separación. La columna se repitió con un gradiente 0-10% MeOH/DCM. Tampoco se consiguió la separación. Las fracciones mezcladas se evaporaron hasta secarse para proporcionar (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(3-ciano-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-metilpiridin-2-il)propanamida (313 mg, 42,1 %). m/z (ES+) $(M+H)^+$ = 712,63; HPLC t_R = 3,85 min.

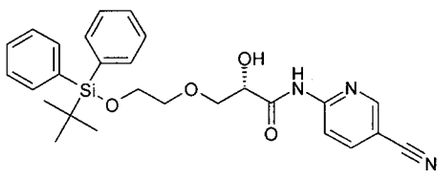
Producto Intermedio AT7: (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-N-(5-cloropiridin-2-il)-2-(1-(3-ciano-2-metilfenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida



Se agregó trimetilaluminio (2M en tolueno) (1,850 mL, 3,70 mmol) a 5-cloropiridin-2-amina (260 mg, 2,02 mmol) en tolueno (8 mL) enfriado hasta alcanzar 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 15 minutos. Se agregó (S)-3-(2-(terc-butildifenilsililoxi)etoxi)-N-(5-cloropiridin-2-il)-2-hidroxipropanamida (**Producto Intermedio AU3**) en tolueno (2 mL) y la reacción se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó a reflujo durante 18 horas. La mezcla de reacción se dejó enfriar y se concentró al vacío. El residuo se neutralizó con ácido cítrico (1M, ac) y luego se diluyó con agua y se extrajo con EtOAc x2. Los elementos orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$) y se evaporaron para proporcionar el producto (860 mg) que se utilizó sin purificación adicional. m/z (ES+) $(M+H)^+$ = 732,66;

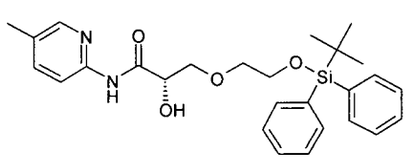
HPLC t_R = 3,89 min.

Producto Intermedio AU1: (S)-3-(2-(terc-butildifenilsililoxi)etoxi)-N-(5-cianopiridin-2-il)-2-hidroxipropanamida



Se agregó trimetilaluminio (2M en tolueno) (6,21 mL, 12,42 mmol) a 6-aminonicotinonitrilo (1,480 g, 12,42 mmol) en tolueno (80 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 15 minutos. Se agregó (S)-metil 3-(2-(terc-butildifenilsililoxi)etoxi)-2-hidroxipropanoato (**Producto Intermedio AB3**) (2,5 g, 6,21 mmol) en tolueno (20 mL). La reacción se calentó hasta alcanzar 110°C durante 2 horas y se enfrió hasta alcanzar la TA. La mezcla de reacción se concentró. El residuo se neutralizó con ácido cítrico (1M, ac) y luego se diluyó con agua y se extrajo con EtOAc. Los elementos orgánicos combinados se secaron ($MgSO_4$) y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 20 a 50% EtOAc en isohexano para proporcionar el producto (1,780 g, 58,5 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,04 (9H, s), 3,65 - 3,69 (3H, m), 3,81 - 3,91 (4H, m), 4,35 (1H, q), 7,35 - 7,45 (6H, m), 7,65 - 7,67 (4H, m), 7,92 - 7,95 (1H, m), 8,36 - 8,38 (1H, m), 8,55 - 8,56 (1H, m), 9,40 (1H, s); m/z (ES+) $(M+H)^+$ = 490; HPLC t_R = 3,07 min.

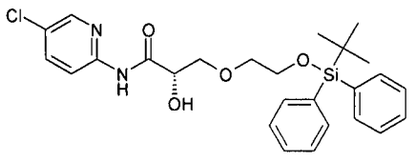
Producto Intermedio AU2: (S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-hidroxi-N-(5-metilpiridin-2-il)propanamida



Se agregó cuidadosamente trimetilaluminio (2M en tolueno) (4,97 mL, 9,94 mmol) a 5-metilpiridin-2-amina (1,075 g, 9,94 mmol) en tolueno (20 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 15 minutos. Se agregó (S)-metil 3-(2-(terc-butildifenilsililoxi)etoxi)-2-hidroxipropanoato (**Producto Intermedio AB3**) (2 g, 4,97 mmol) en tolueno (4 mL). La reacción se calentó hasta alcanzar 120°C durante 1 hora en el reactor de microondas y se enfrió hasta alcanzar la TA. La mezcla de reacción se concentró. El residuo se neutralizó con ácido cítrico (1M, ac) y luego se diluyó con agua y

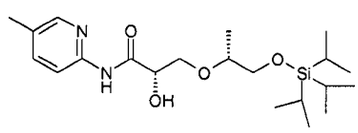
se extrajo con EtOAc. Los elementos orgánicos combinados se secaron ($MgSO_4$) y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 0 a 50% EtOAc en isohexano, para proporcionar el producto (1,800 g, 76 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,04 (9H, s), 2,29 (3H, s), 3,65 (2H, t), 3,76 - 3,90 (5H, m), 4,31 - 4,37 (1H, m), 7,34 - 7,45 (6H, m), 7,48 - 7,54 (1H, m), 7,64 - 7,71 (4H, m), 8,07 - 8,13 (2H, m), 9,13 (1H, s); m/z (ES+) $(M+H)^+$ = 479,60; HPLC t_R = 3,16 min.

Producto Intermedio AU3: (S)-3-(2-(terc-Butildifenilsililoxi)etoxi)-N-(5-cloropiridin-2-il)-2-hidroxipropanamida



Se agregó cuidadosamente trimetilaluminio (2M en tolueno) (4,97 mL, 9,94 mmol) a 5-cloropiridin-2-amina (1,277 g, 9,94 mmol) en tolueno (10 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 15 minutos. Se agregó (S)-metil 3-(2-(terc-butildifenilsililoxi)etoxi)-2-hidroxipropanoato (**Producto Intermedio AB3**) (2 g, 4,97 mmol) en tolueno (2 mL). La reacción se calentó hasta alcanzar 120°C durante 2 horas en el reactor de microondas. La mezcla de reacción se dejó enfriar. El residuo se neutralizó con ácido cítrico (1M, ac) y luego se diluyó con agua y se extrajo con EtOAc. Los elementos orgánicos combinados se secaron ($MgSO_4$) y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 0 a 50% EtOAc en isohexano para proporcionar el producto (1,52 g, 61,3 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,04 (9H, s), 3,63 - 3,68 (3H, m), 3,79 - 3,83 (2H, m), 3,85 (2H, d), 4,33 (1H, q), 7,34 - 7,46 (6H, m), 7,63 - 7,69 (5H, m), 8,18 - 8,25 (2H, m), 9,19 (1H, s); m/z (ES+) $(M+H)^+$ = 499,55; HPLC t_R = 3,43 min.

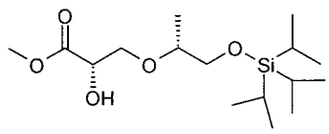
Producto Intermedio AU4: (S)-2-hidroxi-N-(5-metilpiridin-2-il)-3-((R)-1-(triisopropilsililoxi)propan-2-iloxi)propanamida



Se agregó trimetilaluminio (2M en tolueno) (8,97 ml, 17,94 mmol) a 5-metilpiridin-2-amina (1,940 g, 17,94 mmol) en tolueno (70 ml) enfriado hasta alcanzar 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 20 minutos. Se agregó (S)-metil 2-

hidroxi-3-((R)-1-(triisopropilsililoxi)propan-2-iloxi)propanoato (**Producto Intermedio AU5**) (3,0 g, 8,97 mmol) en tolueno (20 ml) y la reacción se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó a reflujo durante 5 horas. La mezcla de reacción se dejó enfriar y se concentró al vacío. El residuo se neutralizó con ácido cítrico (1M, ac) y luego se diluyó con agua (50 mL) y se extrajo con EtOAc (2 × 100 mL). Los elementos orgánicos combinados se secaron ($MgSO_4$) se filtraron y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 30 a 50% EtOAc en isohexano para proporcionar el producto (2,40 g, 65,2 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,03 - 1,15 (24H, m), 2,29 (3H, s), 3,60 - 3,68 (3H, m), 3,82 - 3,86 (1H, m), 3,98 - 4,02 (1H, m), 4,14 - 4,15 (1H, m), 4,30 - 4,34 (1H, m), 7,49 - 7,52 (1H, m), 8,11 - 8,13 (2H, m), 9,14 (1H, s); m/z (ES+) $(M+H)^+$ = 411,44; HPLC t_R = 3,46 min.

Producto Intermedio AU5: (S)-Metil 2-hidroxi-3-((R)-1-(triisopropilsililoxi)propan-2-iloxi)propanoato

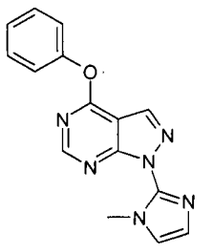


Se preparó utilizando un procedimiento análogo al descrito para el **Producto Intermedio AN1** utilizando (R)-1-(triisopropilsililoxi)propan-2-ol (CAS no. 871657-72-6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,04 - 1,16 (24H, m), 3,39 (1H, d), 3,54 - 3,59 (2H, m), 3,67 - 3,72 (1H, m), 3,78 (3H, s), 3,80 - 3,91 (2H, m), 4,27 - 4,31 (1H, m).

Producto Intermedio AU5: (R)-metil 2-hidroxi-3-((S)-1-(triisopropilsililoxi)propan-2-iloxi)propanoato Procedimiento alternativo

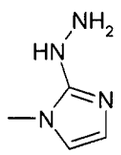
Se agregó trifluorometanosulfonato de magnesio (1,263 g, 3,92 mmol) a una mezcla de (S)-1-(triisopropilsililoxi)propan-2-ol (4,55 g, 19,59 mmol) y (R)-metil oxirano-2-carboxilato (2 g, 19,59 mmol) en acetato de etilo (40 mL). La suspensión resultante se calentó hasta alcanzar 80°C durante 72 horas. Se agregó (R)-metil oxirano-2-carboxilato adicional (2 g, 19,59 mmol) y la mezcla se agitó a 80°C durante 48 hrs. Se agregó (R)-metil oxirano-2-carboxilato adicional (2 g, 19,59 mmol) y la mezcla se agitó durante 24hrs. La mezcla se dejó enfriar, se filtró a través de un lecho de sílice (~10g), se lavó con EtOAc y se evaporó. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 10 a 50% EtOAc en isohexano, para proporcionar el producto (2,7g, 41%).

Producto Intermedio AV1: 1-(1-metil-1H-imidazol-2-il)-4-fenoxi-1H-pirazolo[3,4-d]pirimidina



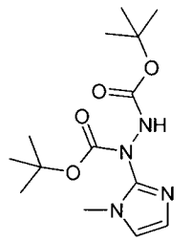
Se agregó 2-hidrazinil-1-metil-1H-imidazol clorhidrato (**Producto Intermedio AV2**) (305 mg, 2,05 mmol) a 4,6-difenoxipirimidina-5-carbaldehído (**Producto Intermedio Z2**) (600 mg, 2,05 mmol) en THF (15 mL) y la solución resultante se agitó a temperatura ambiente durante 5 minutos. Se agregó 2-terc-butilimino-2-dietilamino-1,3-dimetil-perhidro-1,3,2-diazafosforina en poliestireno (2,8 g, 6,2 mmol) y se selló en un tubo de microondas. La reacción se calentó hasta alcanzar 120°C durante 10 horas en el reactor de microondas y se enfrió hasta alcanzar la TA. La mezcla de reacción se filtró y se evaporó hasta secarse. El producto bruto se purificó mediante cromatografía instantánea en sílice eluyendo con 0 a 5% MeOH en DCM para proporcionar el producto (190 mg, 32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3,59 (3H, s), 6,95 (1H, d), 7,11 (1H, d), 7,24 - 7,20 (2H, m), 7,32 - 7,26 (1H, m), 7,44 (2H, m), 8,03 (1H, s), 8,59 (1H, s); m/z (ES$^+$) $(M+H)^+$ = 293; HPLC t_R = 1,65 min.

Producto Intermedio AV2: 2-Hidrazinil-1-metil-1H-imidazol clorhidrato



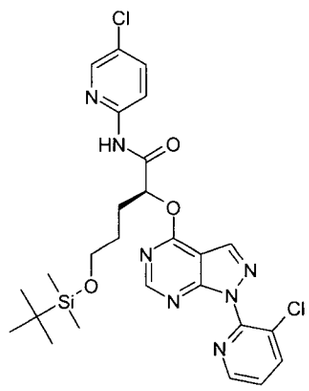
Se agregó cloruro de hidrógeno 4 M en dioxano (50 mL, 200,00 mmol) a di-terc-butil 1-(1-metil-1H-imidazol-2-il)hidrazina-1,2-dicarboxilato (**Producto Intermedio AV3**) (5,9 g, 18,89 mmol) en acetato de etilo (50 mL) a 22°C. La solución resultante se agitó a 22°C durante 20 horas. La mezcla de reacción se evaporó hasta secarse para proporcionar el producto (2,80 g) que se utilizó sin purificación. ^{1}H NMR (400 MHz, DMSO) δ 3,38 (3H, s), 6,90 (1H, d), 6,96 (1H, d).

Producto Intermedio AV3: di-terc-butil 1-(1-metil-1H-imidazol-2-il)hidrazina-1,2-dicarboxilato



Se agregó n-butillitio (1,6M en hexano, 20,76 mL, 33,22 mmol) gota a gota a 1-metil-1H-imidazol (CAS no. 616-47-7) (3 g, 36,54 mmol) en THF (10 mL) enfriado hasta alcanzar –70°C durante un período de 10 minutos bajo nitrógeno. La solución resultante se agitó a –70°C durante 10 minutos. Se agregó di-terc-butil diazeno-1,2-dicarboxilato (CAS no. 870-50-8) (7,65 g, 33,22 mmol) en THF (6 ml) gota a gota durante 10 minutos, sin permitir que la solución aumentara por encima de -65°C. Después de que se completó la adición la solución se dejó entibiar hasta alcanzar la temperatura ambiente durante toda la noche. Se agregó agua (20 mL) a TA. El THF se retiró al vacío. Se extrajo con EtOAc (2 × 40mL). Los extractos orgánicos se combinaron, se lavaron con salmuera (15 mL), se secaron sobre $MgSO_4$ y se redujeron para proporcionar el producto bruto. El producto bruto se purificó mediante cromatografía instantánea en sílice eluyendo con 20 a 100% EtOAc en isohexano para proporcionar el producto (6,17 g, 59,5%). m/z (ESI+) $(M+H)^+$ = 313; HPLC t_R = 1,36 min.

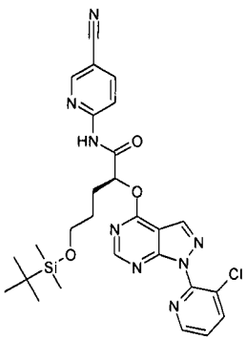
Producto Intermedio AW1: (2S)-5-(terc-butildimetilsililoxi)-N-(5-cloropiridin-2-il)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)pentanamida



Una solución de trimetilaluminio (2M en tolueno) (0,795 mL, 1,59 mmol) se agregó gota a gota a una solución agitada de 5-cloropiridin-2-amina (178 mg, 1,38 mmol) en tolueno (5 mL) enfriado hasta alcanzar 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 15 minutos. Se agregó gota a gota una solución de (2S)-metil 5-(terc-

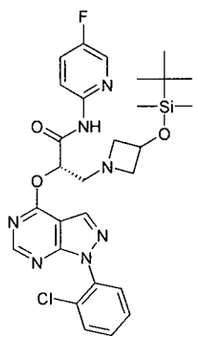
butildimetilsililoxi)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin- 4-iloxi)pentanoato (**Producto Intermedio O2**) (680 mg, 1,38 mmol) en tolueno (5 mL). La solución resultante se agitó a 0°C durante 10 minutos, se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó a reflujo durante 18 horas. La mezcla de reacción se dejó enfriar hasta alcanzar la t.a. y se concentró. El residuo se diluyó con acetato de etilo y se trató con ácido cítrico 1M (2ml). Las capas se separaron y los elementos orgánicos se lavaron con agua y salmuera, se secaron ($MgSO_4$) y se concentraron hasta proporcionar una espuma amarilla, (2S)-5-(terc-butildimetilsililoxi)-N-(5-cloropiridin-2-il)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)pentanamida (693 mg, 85 %). m/z (ES+) $(M+H)^+$ = 588,46; HPLC t_R = 3,54 min.

Producto Intermedio AW2: (2S)-5-(terc-butildimetilsililoxi)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-cianopiridin-2-il)pentanamida



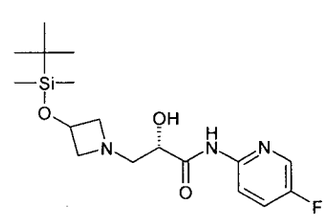
Una solución de trimetilaluminio (2M en tolueno) (0,795 mL, 1,59 mmol) se agregó gota a gota a una solución agitada de 6-aminonicotinonitrilo (165 mg, 1,38 mmol) en tolueno (5 mL) enfriado hasta alcanzar 0°C, durante un período de 1 minuto bajo nitrógeno. La solución resultante se agitó a 0°C durante 20 minutos. Se agregó gota a gota una solución de (2S)-metil 5-(terc-butildimetilsililoxi)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)pentanoato (**Producto Intermedio O2**) (680 mg, 1,38 mmol) en tolueno (5 mL). La solución resultante se agitó a 0°C durante 10 minutos se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó a reflujo durante 18 horas. La mezcla de reacción se dejó enfriar hasta alcanzar la t.a. y se concentró. El residuo se diluyó con acetato de etilo y se trató con ácido cítrico 1M (2ml). Las capas se separaron y los elementos orgánicos se lavaron con agua y salmuera, se secaron ($MgSO_4$) y se evaporaron para proporcionar el producto (797 mg) que se utilizó sin purificación adicional. m/z (ES-) (M-H)- = 577,45; HPLC t_R = 3,29 min.

Producto Intermedio AX1: (2S)-3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-fluoropiridin-2-il)propanamida



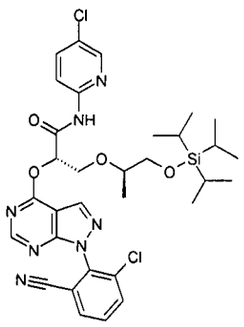
Se agregó hidruro de sodio (dispersión al 60% en aceite mineral) (0,682 g, 17,05 mmol) a (S)-3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-N-(5-fluoropiridin-2-il)-2-hidroxipropanamida (**Producto Intermedio AX2**) (3,0 g, 8,12 mmol) en THF anhidro (80 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos y luego se agregó 4-cloro-1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio B1**) (2,63 g, 8,93 mmol). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 3 horas. La mezcla de reacción se neutralizó con ácido cítrico 1M y luego se diluyó con agua (50 mL) y EtOAc (100 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc (100 mL). Los elementos orgánicos combinados se lavaron con salmuera saturada (75 mL), se secaron ($MgSO_4$), se filtraron y se concentraron al vacío. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 30 a 70% EtOAc en isohexano para proporcionar el producto (4,29 g, 88 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0,04 (6H, s), 0,88 (9H, s), 3,06 - 3,10 (2H, m), 3,15 - 3,19 (1H, m), 3,27 - 3,31 (1H, m), 3,87 - 3,90 (2H, m), 4,41 - 4,48 (1H, m), 5,89 - 5,92 (1H, m), 7,40 - 7,55 (4H, m), 7,61 - 7,63 (1H, m), 8,15 (1H, d), 8,22 - 8,26 (1H, m), 8,36 (1H, s), 8,59 (1H, s), 9,82 (1H, s); m/z (ES^+) $(M+H)^+$ = 598; HPLC t_R = 2,82 min.

Producto Intermedio AX2: (S)-3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-N-(5-fluoropiridin-2-il)-2-hidroxipropanamida



Se agregó trimetilaluminio (solución 2M en tolueno) (15,89 mL, 31,79 mmol) a 5-fluoropiridin-2-amina (3,10 g, 27,64 mmol) en tolueno (80 mL) enfriado hasta alcanzar 0°C bajo nitrógeno durante un período de 10 minutos. La solución resultante se agitó a 0°C durante 10 minutos. Se agregó (S)-metil 3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-hidroxipropanoato (**Producto Intermedio AD3**) (8 g, 27,64 mmol) en tolueno (20 mL) durante 10 minutos y la reacción se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó a 90°C durante 2 horas. La mezcla de reacción se enfrió y se vertió en una solución de sal de Rochelle al 20% (50 mL), se diluyó con acetato de etilo (200 mL) y se agitó durante 2 horas. La fase orgánica se separó, se lavó con agua y salmuera, se secó ($MgSO_4$) se filtró y se evaporó. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 80 a 100% EtOAc en isohexano para proporcionar el producto (5,28 g, 51,7 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0,028 (3H, s), 0,033 (3H, s), 0,87 (9H, s), 2,90 (2H, d), 3,02 - 3,08 (2H, m), 3,68 - 3,74 (2H, m), 4,00 (1H, t), 4,41 - 4,48 (1H, m), 7,41 - 7,45 (1H, m), 8,15 (1H, d), 8,21 - 8,24 (1H, m), 9,85 (1H, s); m/z (ES^+) $(M+H)^+$ = 370; HPLC t_R = 1,97 min.

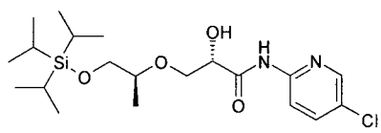
Producto Intermedio AY1: (2S)-2-(1-(2-cloro-6-cianofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-cloropiridin-2-il)-3-((R)-1-(triisopropilsililoxi)propan-2-iloxi)propanamida



Se agregó hidruro de sodio (dispersión al 60% en aceite mineral) (93 mg, 2,32 mmol) a (S)-N-(5-cloropiridin-2-il)-2-hidroxi-3-((R)-1-(triisopropilsililoxi)propan-2-iloxi)propanamida (**Producto Intermedio AY2**) (500 mg, 1,16 mmol) en THF anhidro (25 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos y luego se agregó 3-cloro-2-(4-cloro-1H-pirazolo[3,4-d]pirimidin-1-il)benzonitrilo (**Producto Intermedio AH6**) (370 mg, 1,28 mmol). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante toda la noche. La mezcla de reacción

se ajustó hasta alcanzar pH 7 mediante adición de ácido cítrico 1M y luego se diluyó con agua (20 mL) y EtOAc (50 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc (2 × 50 mL). Los elementos orgánicos combinados se lavaron con salmuera saturada (75 mL), se secaron ($MgSO_4$), se filtraron y se concentraron al vacío. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 50 a 100% EtOAc en isohexano para proporcionar el producto (626 mg, 79 %). ^1H NMR (400 MHz, $CDCl_3$) δ 0,98 - 1,09 (21H, m), 1,13 - 1,17 (3H, m), 3,60 - 3,77 (3H, m), 4,20 - 4,33 (2H, m), 5,99 - 6,03 (1H, m), 7,60 - 7,70 (2H, m), 7,78 - 7,81 (1H, m), 7,85 - 7,87 (1H, m), 8,22 - 8,25 (2H, m), 8,50 (1H, d), 8,60 (1H, d), 8,82 (1H, s); m/z (ES^-) $(M-H)^-$ = 682; HPLC t_R = 4,04 min.

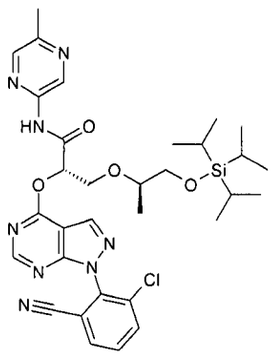
Producto Intermedio AY2: (S)-N-(5-cloropiridin-2-il)-2-hidroxi-3-((R)-1-(triisopropilsililoxi)propan-2-iloxi)propanamida



Se agregó trimetilaluminio (solución 2M en tolueno) (2,99 mL, 5,98 mmol) a una solución de 5-cloropiridin-2-amina (0,769 g, 5,98 mmol) en tolueno (20 mL) a 0°C bajo nitrógeno. La mezcla de reacción se agitó a 0°C durante 20 mins y luego se agregó (S)-metil 2-hidroxi-3-((R)-1-(triisopropilsililoxi)propan-2-iloxi)propanoato (**Producto Intermedio AU5**) (1 g, 2,99 mmol). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó a reflujo bajo nitrógeno durante 4 horas. La mezcla de reacción se dejó enfriar hasta alcanzar la temperatura ambiente y luego se concentró al vacío. El residuo se neutralizó con ácido cítrico (1M, ac.) y luego se diluyó con agua y DCM (50 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con DCM (30 mL). Los elementos orgánicos combinados se secaron ($MgSO_4$), se filtraron y se evaporaron al vacío. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 20 a 50% EtOAc en isohexano para proporcionar el producto (0,935 g, 72,6 %). ^1H NMR (400 MHz, $CDCl_3$) δ 1,05 - 1,13 (24H, m), 3,62 - 3,67 (3H, m), 3,81 - 3,84 (1H, m), 4,02 - 4,06 (1H, m), 4,20 (1H, d), 4,31 (1H, q), 7,65 - 7,67 (1H, m), 8,22 - 8,25 (2H, m), 9,23 (1H, s); m/z (ES^-) $(M-H)^-$ = 429; HPLC t_R = 3,81 min.

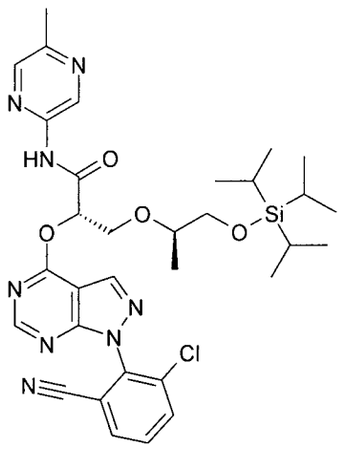
Producto Intermedio AZ1: (2S)-2-(1-(2-cloro-6-cianofenil)-1H-pirazolo[3,4-

d]pirimidin-4-iloxi)-N-(5-metilpirazin-2-il)-3-((R)-1-(triisopropilsililoxi)propan-2-iloxi)propanamida



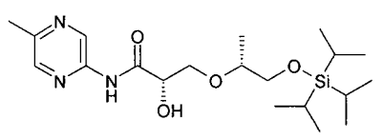
Se agregó hidruro de sodio (dispersión al 60% en aceite mineral) (0,116 g, 2,89 mmol) a (S)-2-hidroxi-N-(5-metilpirazin-2-il)-3-((R)-1-(triisopropilsililoxi)propan-2-iloxi)propanamida (**Producto Intermedio AZ2**) (0,595 g, 1,45 mmol) en THF anhidro (20 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos y luego se agregó 3-cloro-2-(4-cloro-1H-pirazolo[3,4-d]pirimidin-1-il)benzonitrilo (**Producto Intermedio AH6**) (0,438 g, 1,31 mmol). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 1 hora. La mezcla de reacción se ajustó hasta alcanzar pH 7 mediante adición de ácido cítrico 1M y la mayor parte del THF se eliminó al vacío. La mezcla de reacción se diluyó con agua (20 mL) y EtOAc (50 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc (2 × 100 mL). Los elementos orgánicos combinados se lavaron con salmuera saturada (75 mL), se secaron ($MgSO_4$) y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 50 a 100% EtOAc en isohexano para proporcionar el producto (0,590 g, 67,5 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0,98 - 1,08 (21H, m), 1,12 - 1,17 (3H, m), 2,54 (3H, s), 3,59 - 3,78 (3H, m), 4,21 - 4,26 (1H, m), 4,29 - 4,36 (1H, m), 6,02 - 6,06 (1H, m), 7,60 - 7,65 (1H, m), 7,78 - 7,81 (1H, m), 7,85 - 7,87 (1H, m), 8,11 - 8,13 (1H, m), 8,50 (1H, d), 8,61 (1H, d), 8,71 (1H, d), 9,44 (1H, t); m/z (ES^+) M^+ = 665,26; HPLC t_R = 4,02 min.

Producto Intermedio AZ1: (2S)-2-[1-(2-cloro-6-cianofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-metilpirazin-2-il)-3-[(2R)-1-tri(propan-2-il)sililoxipropan-2-il]oxipropanamida. Preparación alternativa.



Se agregó tris(dibencilidenoacetona)dipaladio(0) (0,261 g, 0,29 mmol) en una porción a una mezcla desgasificada de (2S)-2-(1-(2-bromo-6-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-metilpirazin-2-il)-3-((R)-1-(triisopropilsililoxi)propan-2-iloxi)propanamida (**Producto Intermedio BO1**) (4,1 g, 5,70 mmol), cianuro de zinc (0,335 g, 2,85 mmol) y 9,9-dimetil-4,5-bis(difenilfosfino)xanteno (0,330 g, 0,57 mmol) en N-metilpirrolidona (41 mL) a 20°C bajo nitrógeno. La suspensión resultante se desgasificó al vacío con entrada de nitrógeno cuatro veces y luego se calentó hasta alcanzar 110°C (temperatura interna) durante 1 hora. La mezcla se enfrió, se vertió en agua (100 mL) y se extrajo con acetato de etilo (2 × 50 mL). Se combinaron las capas orgánicas y se lavaron con agua (4 × 50 mL) y salmuera (50 mL), se secaron sobre $MgSO_4$, se filtraron y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 30 a 100% EtOAc en isohexano para proporcionar el producto (3,0 g, 79%). ^{1}H NMR (400,13 MHz, DMSO-d_6) δ 0,90 - 1,08 (21H, m), 1,09 - 1,11 (3H, m), 2,45 (3H, s), 3,53 - 3,58 (1H, m), 3,60 - 3,66 (1H, m), 3,75 - 3,78 (1H, m), 4,10 - 4,15 (2H, m), 5,94 - 5,99 (1H, m), 7,87 - 7,91 (1H, m), 8,16 - 8,19 (2H, m), 8,31 - 8,33 (1H, m), 8,60 - 8,61 (1H, m), 8,73 (1H, s), 9,10 - 9,12 (1H, d), 11,20 (1H, s); m/z (ES$^-$) $(M-H)^-$ = 663; HPLC t_R = 3,79 min.

Producto Intermedio AZ2: (S)-2-hidroxi-N-(5-metilpirazin-2-il)-3-((R)-1-(triisopropilsililoxi)propan-2-iloxi)propanamida



Se agregó trimetilaluminio (solución 2M en tolueno) (5,98 mL, 11,96 mmol) a 5-

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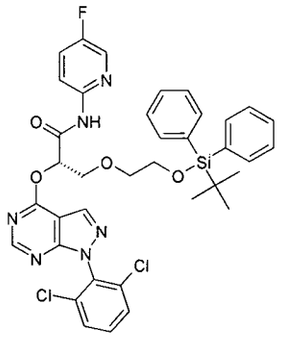
metilpirazin-2-amina (1,305 g, 11,96 mmol) en tolueno (20 mL) enfriado hasta alcanzar 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 20 minutos. Se agregó (R)-metil 2-hidroxi-3-((S)-1-(triisopropilsililoxi)propan-2-iloxi)propanoato (**Producto Intermedio AU5**) (2 g, 5,98 mmol) en tolueno (6 mL) y la reacción se dejó entibiar hasta alcanzar la temperatura ambiente y luego se sometió a reflujo durante 6 horas. La mezcla de reacción se dejó enfriar y se concentró al vacío. El residuo se neutralizó con ácido cítrico (1M, ac.) y luego se diluyó con agua (25 mL) y se extrajo con EtOAc (2 x 50 mL). Los elementos orgánicos combinados se lavaron con salmuera (20mL), luego se secaron ($MgSO_4$) y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 30 a 50% EtOAc en isohexano para proporcionar el producto (1,390 g, 56,5 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,04 - 1,17 (24H, m), 2,54 (3H, s), 3,62 - 3,67 (3H, m), 3,81 - 3,85 (1H, m), 4,05 - 4,09 (1H, m), 4,22 (1H, d), 4,34 (1H, q), 8,13 (1H, d), 9,12 (1H, s), 9,44 (1H, d); m/z (ES$^+$) $(M+H)^+$ = 412,34; HPLC t_R = 3,82 min.

Producto Intermedio AZ2: (S)-2-hidroxi-N-(5-metilpirazin-2-il)-3-((R)-1-(triisopropilsililoxi)propan-2-iloxi)propanamida. Preparación alternativa.

Se agregó trimetilaluminio (solución 2M en tolueno) (72,5 mL, 145 mmol) a 5-metilpirazin-2-amina (13,64 g, 125,0 mmol) en tolueno (520 mL) enfriado hasta alcanzar 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 20 minutos. Se agregó (R)-metil 2-hidroxi-3-((S)-1-(triisopropilsililoxi)propan-2-iloxi)propanoato (**Producto Intermedio AU5**) (33,5 g, 100,0 mmol) en tolueno (130 mL) y la reacción se dejó entibiar hasta alcanzar la temperatura ambiente y luego se agitó a 72°C durante 2,5 horas. La mezcla de reacción se dejó enfriar, luego se vertió en una mezcla agitada de acetato de etilo (500 mL) y solución acuosa de sal de Rochelle (20% p/v, 500 mL). La mezcla se agitó durante 15 minutos y luego los elementos orgánicos se separaron y se lavaron con agua (500 mL) y luego salmuera (500 mL), luego se secaron ($MgSO_4$), se filtraron y se concentraron. Los residuos se disolvieron en iso-hexano (300 mL) y se dejaron reposar durante 15 minutos a 20°C antes de enfriarse hasta alcanzar 5°C en 30 minutos. El sólido formado se aisló mediante filtración, se lavó con iso-hexano enfriado hasta alcanzar 5°C (200 mL) y se secó a 40°C al alto vacío para proporcionar el producto (26,7 g, 64%). Los filtrados se combinaron y se concentraron hasta proporcionar un volumen total de 100 mL y la mezcla se dejó reposar durante 16 horas. El sólido formado se aisló mediante filtración, se lavó con iso-hexano enfriado hasta alcanzar 5°C (100 mL), se secó a 40°C al

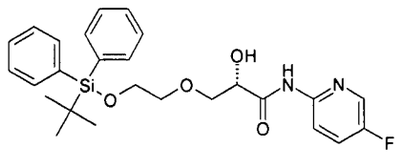
alto vacío y se combinó con el lote inicial para proporcionar el producto (30,1 g, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,04 - 1,17 (24H, m), 2,54 (3H, s), 3,62 - 3,67 (3H, m), 3,81 - 3,85 (1H, m), 4,05 - 4,09 (1H, m), 4,22 (1H, d), 4,34 (1H, q), 8,13 (1H, d), 9,12 (1H, s), 9,44 (1H, d); m/z (ES^+) $(M+H)^+$ = 412,34; HPLC t_R = 3,82 min.

Producto Intermedio BA1: (S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(2,6-diclorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-fluoropiridin-2-il)propanamida



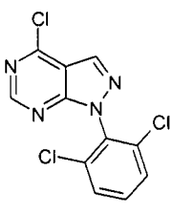
Se agregó hidruro de sodio (dispersión al 60% en aceite mineral) (83 mg, 2,07 mmol) a (S)-3-(2-(terc-butildifenilsililoxi)etoxi)-N-(5-fluoropiridin-2-il)-2-hidroxipropanamida (**Producto Intermedio BA2**) (500 mg, 1,04 mmol) en THF anhidro (20 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos y luego se agregó 4-cloro-1-(2,6-diclorofenil)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio BA3**) (310 mg, 1,04 mmol). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante toda la noche. La mezcla de reacción se ajustó hasta alcanzar pH 7 mediante adición de ácido cítrico 1M y la mezcla de reacción se diluyó con agua (20 mL) y EtOAc (50 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc (2 × 50 mL). Los elementos orgánicos combinados se lavaron con salmuera saturada (75 mL), se secaron ($MgSO_4$), se filtraron y se concentraron al vacío. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 25 a 100% EtOAc en isohexano para proporcionar el producto (637 mg, 82 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0,99 (9H, t), 3,69 - 3,72 (2H, m), 3,82 (2H, t), 4,16 - 4,24 (2H, m), 6,06 (1H, t), 7,31 - 7,47 (8H, m), 7,52 - 7,55 (2H, m), 7,63 - 7,66 (4H, m), 8,12 (1H, d), 8,26 - 8,29 (1H, m), 8,42 (1H, s), 8,58 (1H, s), 8,79 (1H, s).

Producto Intermedio BA2: (S)-3-(2-(terc-butildifenilsililoxi)etoxi)-N-(5-fluoropiridin-2-il)-2-hidroxipropanamida



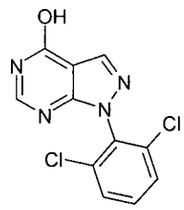
Se agregó trimetilaluminio (solución 2M en tolueno) (2,86 mL, 5,71 mmol) a 5-fluoropiridin-2-amina en tolueno (8 mL) enfriado hasta alcanzar 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 20 minutos. Se agregó (S)-metil 3-(2-(terc-butildifenilsililoxi)etoxi)-2-hidroxipropanoato (**Producto Intermedio AB3**) en tolueno (8 mL) y la reacción se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó a reflujo durante 24 horas. La mezcla de reacción se dejó enfriar y se concentró al vacío. El residuo se neutralizó con ácido cítrico (1M, ac.) y luego se diluyó con agua (30 mL) y se extrajo con EtOAc (2 × 50 mL). Los elementos orgánicos combinados se secaron ($MgSO_4$) y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 30 a 50% EtOAc en isohexano para proporcionar el producto (1,32 g, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,05 (s, 9H), 3,60 - 3,68 (m, 3H), 3,79 - 3,83 (m, 2H), 3,86 (d, 2H), 4,31 - 4,35 (m, 1H), 7,34 - 7,46 (m, 7H), 7,64 - 7,69 (m, 4H), 8,14 (d, 1H), 8,22 - 8,28 (m, 1H), 9,18 (s, 1H); m/z (ES$^+$), $(M+H)^+$ = 483,63; HPLC t_R = 3,08 min.

Producto Intermedio BA3: 4-cloro-1-(2,6-diclorofenil)-1H-pirazolo[3,4-d]pirimidina



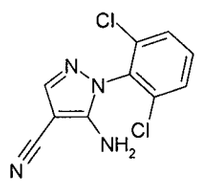
Se agregó oxicloruro de fósforo (7,96 mL, 85,38 mmol) a 1-(2,6-diclorofenil)-1H-pirazolo[3,4-d]pirimidin-4-ol (**Producto Intermedio BA4**) (1,2 g, 4,27 mmol). La solución resultante se agitó a 100°C durante 20 horas. La LCMS mostró que la reacción se había completado. La mezcla de reacción se evaporó. Se agregaron hielo/agua y luego EtOAc. La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc. Los elementos orgánicos combinados se lavaron con agua, se secaron ($MgSO_4$) y se concentraron para proporcionar el producto (1,110 g, 87 %) que se utilizó sin purificación adicional. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7,46 - 7,58 (3H, m), 8,45 (1H, s), 8,82 (1H, s); m/z (ES$^+$) $(M+H)^+$ = 299; HPLC t_R = 2,77 min.

Producto Intermedio BA4: 1-(2,6-diclorofenil)-1H-pirazolo[3,4-d]pirimidin-4-ol



Se agregó ácido sulfúrico concentrado (1,297 mL, 24,34 mmol) a una solución agitada de 5-amino-1-(2,6-diclorofenil)-1H-pirazol-4-carbonitrilo (**Producto Intermedio BA5**) (5,6 g, 22,13 mmol) en ácido fórmico (35 mL). La solución resultante se agitó a 100°C durante 24 horas. La reacción se dejó enfriar hasta alcanzar la temperatura ambiente y se evaporó hasta proporcionar ~la mitad del volumen, se agregó agua (100 mL) y se agitó durante 1 hora. El precipitado formado se retiró mediante filtración, se lavó bien con agua y se secó durante toda la noche en un vacío sobre P_2O_5 para proporcionar el producto (4,07 g, 65,4 %) que se utilizó sin purificación adicional. ^{1}H NMR (400 MHz, DMSO) δ 7,65 - 7,69 (1H, m), 7,75 - 7,78 (2H, m), 8,09 (1H, d), 8,41 (1H, s), 12,44 (1H, s); m/z (ES^-) $(M-H)^-$ = 279; HPLC t_R = 1,41 min.

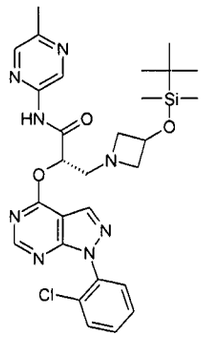
Producto Intermedio BA5: 5-amino-1-(2,6-diclorofenil)-1H-pirazol-4-carbonitrilo



Se dividió (2,6-diclorofenil)hidrazina clorhidrato (5 g, 23,42 mmol) entre EtOAc (100 mL) y NaOH (2M, ac) (40 mL). La capa orgánica se separó y se lavó con agua (50 mL), salmuera (50 mL), se secó ($MgSO_4$), se filtró y se concentró. El aceite resultante se suspendió en metanol (50 mL) bajo nitrógeno a -5°C. Se agregó 2-(etoximetileno)malononitrilo (2,86 g, 23,42 mmol) en porciones durante 5 mins y la mezcla se agitó a 0°C durante 30 mins. La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó a reflujo bajo nitrógeno durante 2 horas. La mezcla de reacción se dejó enfriar y se evaporó hasta secarse para proporcionar el producto (5,60 g, 94 %) que se utilizó sin purificación adicional. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4,47 (2H, s), 7,43 - 7,47 (1H, m), 7,51 - 7,53 (2H, m), 7,73 (1H, s); m/z (ES^+) $(M+H)^+$ = 253; HPLC t_R = 1,62 min.

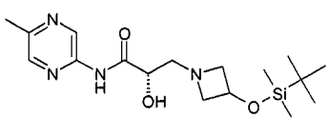
Producto Intermedio BB1: (2S)-3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-(1-(2-

clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-metilpirazin-2-il)propanamida



Se agregó hidruro de sodio (87 mg, 2,18 mmol) a (S)-3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-hidroxi-N-(5-metilpirazin-2-il)propanamida (**Producto Intermedio BB2**) (400 mg, 1,09 mmol) en tetrahidrofurano anhidro (15 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos y luego se agregó 4-cloro-1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidina (318 mg, 1,20 mmol). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 2 horas. La mezcla de reacción se ajustó hasta alcanzar pH 7 mediante adición de ácido cítrico 1M y luego se diluyó con agua (30 mL) y acetato de etilo (50 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con acetato de etilo (50 mL). Los elementos orgánicos combinados se lavaron con salmuera saturada (75 mL), se secaron ($MgSO_4$), se filtraron y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 40 a 100% acetato de etilo en isohexano y luego 0-20% metanol en acetato de etilo para proporcionar el producto (532 mg, 82 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0,00 (6H, s), 0,83 (9H, s), 2,45 (3H, s), 3,61 - 3,90 (4H, m), 4,47 - 4,60 (2H, m), 4,69 (1H, m), 6,22 (1H, m), 7,36 - 7,48 (3H, m), 7,51 - 7,57 (1H, m), 8,03 (1H, s), 8,38 (1H, s), 8,50 (1H, s), 9,27 (1H, s), 10,31 (1H, s); m/z (ES$^+$) $(M+H)^+$ = 595; HPLC t_R = 2,63 min.

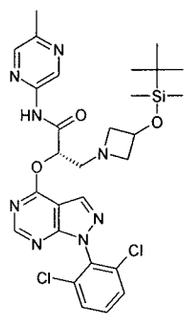
Producto Intermedio BB2: (S)-3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-hidroxi-N-(5-metilpirazin-2-il)propanamida



Se agregó trimetilaluminio (6,22 mL, 12,44 mmol) a 5-metilpirazin-2-amina (1,357 g, 12,44 mmol) en tolueno anhidro (20 mL) enfriado hasta alcanzar 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos. Se agregó (S)-metil 3-(3-(terc-

butildimetilsililoxi)azetidin-1-il)-2-hidroxipropanoato (**Producto Intermedio AD3**) (2 g, 6,91 mmol) en tolueno anhidro (10 mL) y la solución resultante se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó a 80°C durante toda la noche. La reacción se dejó enfriar hasta alcanzar la temperatura ambiente y se agregó una solución de sal de Rochelle en agua (20%, 75ml). La mezcla se diluyó con agua (25 mL) y acetato de etilo (75 mL) y se dejó agitar durante 2 horas. La capa orgánica se separó y la acuosa se extrajo con acetato de etilo (75 mL). Los elementos orgánicos combinados se lavaron con salmuera (75 mL), se secaron ($MgSO_4$), se filtraron y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 20 a 50% acetato de etilo en isohexano. Esto se purificó adicionalmente mediante cromatografía instantánea en sílice, eluyendo con 0 a 10% metanol en diclorometano, para proporcionar el producto (1,50 g, 59,2 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0,03 (3H, d), 0,04 (3H, s), 0,87 (9H, q), 2,54 (3H, s), 2,93 (2H, d), 3,09 (2H, q), 3,71 - 3,77 (2H, m), 4,04 (1H, t), 4,46 (1H, t), 8,13 (1H, d), 9,39 (1H, d), 9,81 (1H, s); m/z (ES^+) $(M+H)^+ = 367,34$; HPLC t_R = 1,76 min.

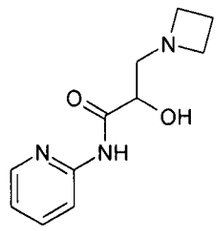
Producto Intermedio BB3: (S)-3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-(1-(2,6-diclorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-metilpirazin-2-il)propanamida



Se agregó hidruro de sodio (87 mg, 2,18 mmol) a (S)-3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-hidroxi-N-(5-metilpirazin-2-il)propanamida (**Producto Intermedio BB2**) (400 mg, 1,09 mmol) en tetrahidrofurano anhidro (15 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos y luego se agregó 4-cloro-1-(2,6-diclorofenil)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio BA3**) (360 mg, 1,20 mmol). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 2 horas. La mezcla de reacción se neutralizó con ácido cítrico 1M y luego se diluyó con agua (30 mL) y acetato de etilo (50 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con acetato de etilo (50 mL). Los elementos orgánicos combinados se lavaron con salmuera saturada (75 mL), se secaron ($MgSO_4$), se

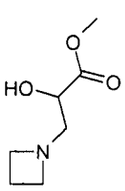
filtraron y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 40 a 80% acetato de etilo en isohexano, para proporcionar el producto (395 mg, 57,5 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0,04 (6H, s), 0,88 (9H, s), 2,54 (3H, s), 3,09 - 3,13 (2H, m), 3,16 - 3,21 (1H, m), 3,29 - 3,34 (1H, m), 3,87 - 3,92 (2H, m), 4,51 (1H, qn), 5,92 - 5,95 (1H, m), 7,43 - 7,47 (1H, m), 7,52 - 7,55 (2H, m), 8,14 (1H, d), 8,41 (1H, s), 8,59 (1H, s), 9,42 (1H, d), 9,96 (1H, s); m/z (ES^+) $(M+H)^+$ = 631; HPLC t_R = 2,94 min.

Producto Intermedio BC1: (S)-3-(azetidin-1-il)-2-hidroxi-N-(piridin-2-il)propanamida



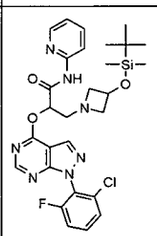
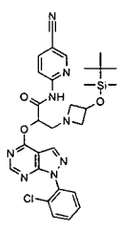
Se agregó trimetilaluminio (8,31 mL, 16,62 mmol) a piridin-2-amina (1,360 g, 14,45 mmol) en tolueno (30 mL) enfriado hasta alcanzar 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos. Se agregó (S)-metil 3-(azetidin-1-il)-2-hidroxipropanoato (**Producto Intermedio BC2**) (2,3 g, 14,45 mmol) en tolueno (10 mL) y THF (5 mL) y la solución resultante se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó a 60°C durante 8 horas. La reacción se enfrió y se agregó sal de Rochelle al 20% (50 mL) y luego EtOAc (50 mL) y la mezcla se agitó a temperatura ambiente durante toda la noche. La fase orgánica se separó y la fase acuosa se extrajo nuevamente con EtOAc (2×50 mL). Las fases orgánicas se combinaron, se secaron ($MgSO_4$) y se evaporaron para proporcionar el producto (2,7g) que se utilizó sin purificación adicional. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2,10 - 2,17 (2H, m), 2,86 (2H, d), 3,36 (4H, t), 4,00 (1H, t), 7,02 - 7,06 (1H, m), 7,67 - 7,72 (1H, m), 8,19 - 8,23 (1H, m), 8,29 - 8,32 (1H, m), 9,91 (1H, s)

Producto Intermedio BC2: (S)-metil 3-(azetidin-1-il)-2-hidroxipropanoato

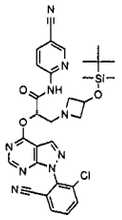
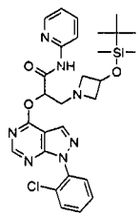
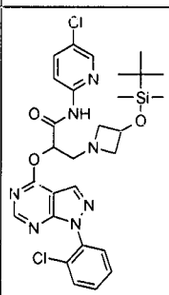
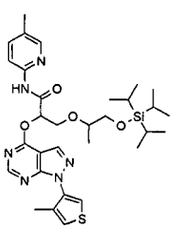


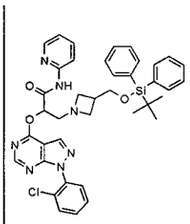
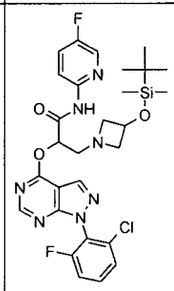
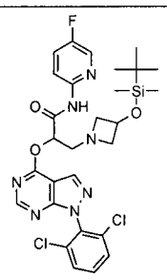
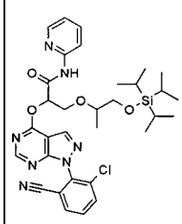
Se agregó (S)-metil oxirano-2-carboxilato (1475 mg, 14,45 mmol) en acetonitrilo (2 mL) a azetidina (825 mg, 14,45 mmol) en acetonitrilo (8 mL). La reacción se calentó hasta alcanzar 100°C durante 60 minutos en el reactor de microondas y se enfrió hasta alcanzar la temperatura ambiente. La mezcla se evaporó para proporcionar el producto bruto (2,3 g) que se utilizó sin purificación adicional. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2,04 - 2,14 (2H, m), 2,71 - 2,81 (2H, m), 3,27 (4H, t), 3,77 (3H, s), 4,11 - 4,13 (1H, m)

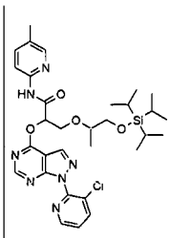
Los siguientes Productos Intermedios se prepararon utilizando un procedimiento análogo al descrito para el **Producto Intermedio BB1** utilizando los productos intermedios apropiados.

Número de producto intermedio	**Estructura**	**^{1}H NMR (400 MHz) δ**	**LCMS**	**Refs. producto intermedio**
BD1		(DMSO-d6) 0,02 (6H, s), 0,84 (9H, q), 3,02 - 3,25 (4H, s), 3,70 - 3,79 (2H, m), 4,35 - 4,42 (1H, m), 5,75 - 5,79 (1H, m), 7,11 - 7,14 (1H, m), 7,54 - 7,60 (1H, m), 7,65 - 7,67 (1H, m), 7,71 - 7,78 (2H, m), 7,94 - 7,99 (1H, m), 8,33 - 8,35 (1H, m), 8,56 (1H, d), 8,67 (1H, d), 10,94 (1H, d)	m/z (ES+) (M+H)+ = 598; HPLC tR = 3,19 min.	BI1, BH1
BD2			m/z (ES+) (M+H)+ = 605; HPLC tR = 1,95 min.	BE1, B1

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BD3			m/z (ES+) (M+H)+ = 630; HPLC tR = 1,89 min.	BE1, aH6
BD4			m/z (ES+) (M+H)+ = 580; HPLC tR = 2,46 min.	BE2, B1
BD5		(DMSO-d6) 0,03 (6H, s), 0,85 (9H, s), 2,90 - 2,95 (1H, m), 3,00 - 3,06 (1H, m), 3,10 - 3,16 (1H, m), 3,62 - 3,69 (2H, m), 4,30 - 4,39 (1H, m), 5,71 - 5,77 (1H, d), 7,54 - 7,65 (3H, m), 7,74 - 7,77 (1H, m), 7,87 - 7,90 (1H, m), 7,99 - 8,03 (1H, d), 8,39 - 8,40 (1H, m), 8,52 (1H, s), 8,58 (1H, s), 11,12 (1H, s)	m/z (ES+) (M+H)+ = 614; HPLC tR = 2,91 min.	AD2, B1
BD6		(DMSO-d6) 0,91 - 1,04 (18H, m), 1,08 (3H, d), 2,09 (3H, d), 2,24 (3H, s), 3,50 - 3,54 (1H, m), 3,62 - 3,66 (1H, m), 3,68 - 3,74 (1H, m), 4,06 - 4,14 (2H, m), 5,87 - 5,94 (1H, m), 7,40 - 7,41 (1H, m), 7,57 - 7,60 (1H, m), 7,82 (1H, d), 7,86 - 7,89 (1H, m), 8,17 - 8,17 (1H, m), 8,50 (1H, s), 8,55 (1H, s), 10,82 (1H, s)	m/z (ES+) (M+H)+ = 625; HPLC tR = 3,77 min.	AU4, BF1

BD7			m/z (ES+) (M+H)+ = 718; HPLC tR = 3,17 min.	BG1, B1
BD8		($CDCl_3$) 0,04 (6H, s), 0,88 (9H, s), 3,06 - 3,10 (2H, m), 3,15 - 3,20 (1H, m), 3,26 - 3,32 (1H, m), 3,86 - 3,91 (2H, m), 4,49 - 4,52 (1H, m), 5,89 - 5,92 (1H, m), 7,22 - 7,27 (1H, m), 7,40 - 7,44 (2H, m), 7,44 - 7,52 (1H, m), 8,15 - 8,16 (1H, m), 8,22 - 8,26 (1H, m), 8,41 (1H, d), 8,59 (1H, s), 9,83 (1H, d)	m/z (ES+) (M+H)+ = 616; HPLC tR = 3,02 min.	AX2, BH1
BD9		($CDCl_3$) 0,05 (6H, s), 0,89 (9H, s), 3,07 - 3,11 (2H, m), 3,17 - 3,21 (1H, m), 3,28 - 3,33 (1H, m), 3,89 - 3,92 (2H, m), 4,52 (1H, qn), 5,90 - 5,93 (1H, m), 7,42 - 7,48 (2H, m), 7,53 - 7,56 (2H, m), 8,17 (1H, d), 8,24 - 8,28 (1H, m), 8,42 (1H, s), 8,59 (1H, s), 9,85 (1H, s)	m/z (ES+) (M+H)+ = 632; HPLC tR = 3,05 min.	AX2, BA3
BD10		(DMSO-d6) 0,91 - 1,01 (21H, m), 1,10 (3H, d), 3,52 - 3,57 (1H, m), 3,62 - 3,68 (1H, m), 3,75 - 3,78 (1H, m), 4,11 - 4,14 (2H, m), 5,94 (1H, s), 7,11 - 7,14 (1H, m), 7,74 - 7,79 (1H, m), 7,87 - 7,91 (1H, m), 7,99 (1H, t), 8,16 - 8,19 (2H, m), 8,33 - 8,36 (1H, m), 8,60 (1H, s), 8,73 (1H, s), 10,99 (1H, s)	m/z (ES+) (M+H)+ = 650; HPLC tR = 4,07 min.	AQ4, aH6

BD11		($CDCl_3$) 1,00 - 1,04 (21H, m), 1,13 (3H, d), 2,29 (3H, s), 3,56 - 3,74 (3H, m), 4,20 - 4,31 (2H, m), 6,00 - 6,03 (1H, m), 7,45 - 7,48 (1H, m), 7,51 - 7,53 (1H, m), 7,99 - 8,02 (1H, m), 8,08 - 8,09 (1H, m), 8,13 (1H, d), 8,46 (1H, s), 8,61 - 8,62 (2H, m), 8,65 (1H, s)	m/z (ES+) (M+H)+ = 640; HPLC tR = 3,90 min.	AU2, B15

Producto Intermedio BD1 (2S)-3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-(1-(2-cloro-6-fluorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(piridin-2-il)propanamida

Producto Intermedio BD2 (2S)-3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-cianopiridin-2-il)propanamida

Producto Intermedio BD3 (2S)-3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-(1-(2-cloro-6-cianofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-cianopiridin-2-il)propanamida

Producto Intermedio BD4 (2S)-3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(piridin-2-il)propanamida

Producto Intermedio BD5 (2S)-3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-cloropiridin-2-il)propanamida

Producto Intermedio BD6 (2S)-N-(5-metilpiridin-2-il)-2-(1-(4-metiltiofen-3-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-((R)-1-(triisopropilsililoxi)propan-2-iloxi)propanamida

Producto Intermedio BD7 (2S)-3-(3-((terc-butildifenilsililoxi)metil)azetidin-1-il)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(piridin-2-il)propanamida

Producto Intermedio BD8 (2S)-3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-(1-(2-cloro-6-fluorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-fluoropiridin-2-il)propanamida

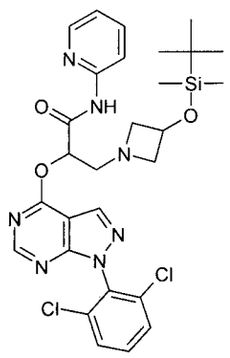
Producto Intermedio BD9 (S)-3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-(1-(2,6-diclorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-fluoropiridin-2-il)propanamida

Producto Intermedio BD10 (2S)-2-(1-(2-cloro-6-cianofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(piridin-2-il)-3-((R)-1-(triisopropilsililoxi)propan-2-iloxi)propanamida

Producto Intermedio BD11 (2S)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-metilpiridin-2-il)-3-((R)-1-(triisopropilsililoxi)propan-2-iloxi)propanamida

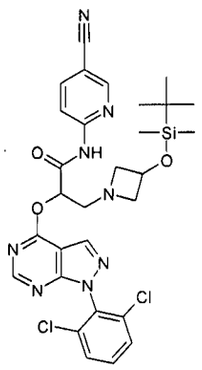
Producto Intermedio BD12: (S)-3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-(1-(2,6-

diclorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(piridin-2-il)propanamida



Se agregó trimetilaluminio (0,362 mL, 0,72 mmol) a una solución de piridin-2-amina (68,1 mg, 0,72 mmol) en tolueno (8 mL) a 0°C bajo nitrógeno. La mezcla de reacción se agitó a 0°C durante 20 mins y luego se agregó (S)-metil 3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-(1-(2,6-diclorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanoato (**Producto Intermedio BJ1**) (200 mg, 0,36 mmol) en tolueno (4 mL). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó a reflujo bajo nitrógeno durante 4 horas. La mezcla de reacción se dejó enfriar hasta alcanzar la temperatura ambiente y luego se concentró. El residuo se neutralizó hasta alcanzar pH 7 con ácido cítrico (1M, ac) y luego se diluyó con agua y DCM (50 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con DCM (30 mL). Los elementos orgánicos combinados se secaron ($MgSO_4$), se filtraron y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 20 a 50% EtOAc en isohexano para proporcionar el producto (151 mg, 67,9 %). ^1H NMR (400 MHz, $CDCl_3$) δ 0,04 (6H, s), 0,88 (9H, s), 3,05 - 3,09 (2H, m), 3,17 - 3,31 (2H, m), 3,86 - 3,91 (2H, m), 4,50 (1H, t), 5,89 - 5,92 (1H, m), 7,04 - 7,07 (1H, m), 7,42 - 7,47 (1H, m), 7,52 - 7,55 (2H, m), 7,68 - 7,72 (1H, m), 8,22 - 8,24 (1H, m), 8,29 - 8,31 (1H, m), 8,42 (1H, s), 8,58 (1H, s), 9,63 (1H, s); m/z (ES^+) $(M+H)^+ = 616$; HPLC $t_R = 1,95$ min.

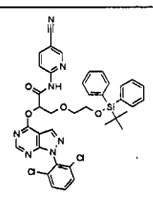
Producto Intermedio BD13: (S)-3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-N-(5-cianopiridin-2-il)-2-(1-(2,6-diclorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida

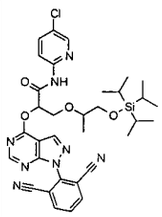
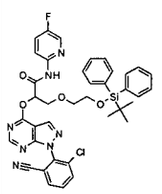
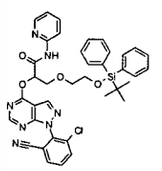
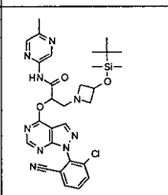
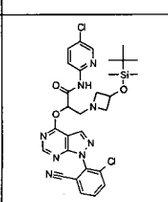


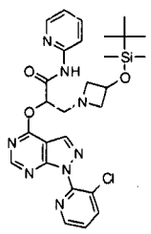
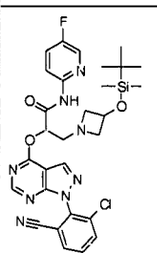
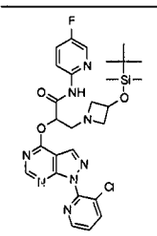
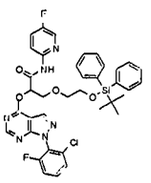
Se utilizó un procedimiento análogo al descrito para el Producto Intermedio **BD12**, utilizando 6-aminonicotinonitrilo y (S)-metil 3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-(1-(2,6-diclorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanoato (**Producto Intermedio BJ1**).

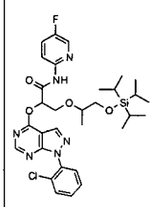
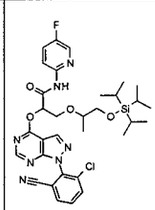
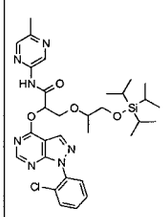
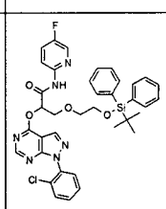
^{1}H NMR (400 MHz, $CDCl_3$) δ 0,06 (6H, s), 0,89 (9H, s), 3,11 - 3,19 (3H, m), 3,30 - 3,35 (1H, m), 3,90 - 3,94 (2H, m), 4,54 (1H, t), 5,87 - 5,91 (1H, m), 7,43 - 7,47 (1H, m), 7,52 - 7,55 (2H, m), 7,92 - 7,94 (1H, m), 8,33 - 8,36 (1H, m), 8,40 (1H, s), 8,57 (1H, s), 8,59 (1H, q), 10,57 (1H, s); m/z (ES^+) M^+ = 639; HPLC t_R = 2,02 min.

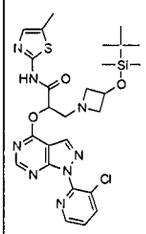
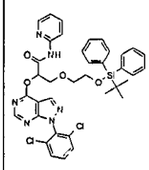
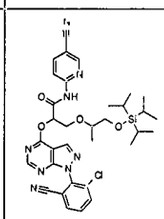
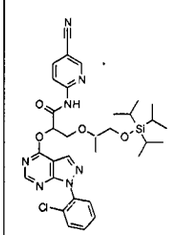
Los siguientes Productos Intermedios se prepararon utilizando un procedimiento análogo al descrito para el **Producto Intermedio BB1** utilizando los productos intermedios apropiados.

Número de producto intermedio	**Estructura**	**^{1}H NMR (400 MHz) δ**	**LCMS**	**Refs. prod. intermedio**
BD14			m/z (ES+) (M+H)+ = 752; HPLC tR = 3,78 min.	AK7, BA3

BD15		($CDCl_3$) 0,95 - 1,09 (m, 21H), 1,15 (d, 3H), 3,58 - 3,79 (m, 3H), 4,18 - 4,25 (m, 1H), 4,27 - 4,34 (m, 1H), 6,01 (t, 1H), 7,65 - 7,70 (m, 1H), 7,78 (t, 1H), 8,10 (d, 2H), 8,20 - 8,25 (m, 2H), 8,56 (s, 1H), 8,66 (s, 1H), 8,78 (s, 1H)		AY2, BK1
BD16		(DMSO-d6) 0,88 (s, 9H), 3,62 - 3,78 (m, 4H), 3,93 - 4,12 (m, 2H), 5,93 - 5,99 (m, 1H), 7,24 - 7,35 (m, 6H), 7,50 - 7,59 (m, 5H), 7,73 - 7,80 (m, 1H), 7,89 - 7,96 (m, 1H), 7,98 - 8,04 (m, 2H), 8,17 - 8,21 (m, 1H), 8,47 - 8,52 (m, 2H), 10,50 (s, 1H)	m/z (ES+), (M+H)+ = 736,55; HPLC tR = 3,66 min	BA1, aH6
BD17		(DMSO-d6) 0,97 (s, 9H), 3,71 - 3,90 (m, 4H), 4,08 - 4,22 (m, 2H), 6,03 - 6,10 (m, 1H), 7,07 - 7,13 (m, 1H), 7,33 - 7,45 (m, 6H), 7,60 - 7,66 (m, 5H), 7,71 - 7,78 (m, 1H), 7,85 (t, 1H), 7,94 - 7,99 (m, 1H), 8,06 - 8,13 (m, 2H), 8,30 - 8,34 (m, 1H), 8,57 - 8,60 (m, 1H), 10,43 (s, 1H)	m/z (ES+), (M+H)+ = 718,58; HPLC tR = 3,59 min	AQ2, aH6
BD18		($CDCl_3$) 0,00 (6H, s),0,81 (9H, s),2,47 (3H, s),2,99 - 3,09 (2H, m),3,11 (2H, d),4,40 - 4,50 (1H, m),3,81 - 3,88 (2H, m),5,83 - 5,88 (1H, m),7,53 - 7,58 (1H, m),7,70 - 7,74 (1H, m),7,77 - 7,81 (1H, m),8,07 (1H, s),8,33 - 8,41 (1H, m),8,54 (1H, d),9,32 - 9,36 (1H, m),10,08 (1H, s),9,71 (0H, s)	m/z (ES+), (M+H)+ = 620; 5min, Ácido, HPLC tR = 1,81 min	BB2, aH6
BD19		($CDCl_3$) 0,00 (6H, d), 0,78 - 0,82 (9H, m), 3,06 (2H, q), 3,23 (1H, d), 3,85 (2H, d), 4,43 - 4,46 (1H, m), 5,81 - 5,84 (1H, m), 7,19 (1H, s), 7,54 (1H, d), 7,57 - 7,61 (1H, m), 7,70 - 7,74 (1H, m), 7,77 - 7,80 (1H,	m/z (ES+), (M+H)+ = 639; 5min Ácido, HPLC tR =	AD2, aH6

		m), 8,11 - 8,14 (1H, m), 8,18 - 8,19 (1H, m), 8,38 (1H, d), 8,53 (1H, d), 10,00 (1H, s)	2,01 min	
BD20		($CDCl_3$) 0,05 (6H, t), 0,89 (9H, t), 3,05 - 3,10 (2H, m), 3,17 - 3,22 (1H, m), 3,30 (1H, q), 3,86 - 3,91 (2H, m), 4,50 (1H, t), 5,91 - 5,94 (1H, m), 7,04 - 7,08 (1H, m), 7,42 - 7,49 (1H, m), 7,68 - 7,73 (1H, m), 8,00 - 8,03 (1H, m), 8,21 - 8,24 (1H, m), 8,30 - 8,32 (1H, m), 8,42 (1H, s), 8,62 - 8,64 (2H, m), 9,59 (1H, s)	m/z (ES+) M+ = 581,36; HPLC tR = 2,57 min.	BE2, B15
BD21		($CDCl_3$) 0,03 - 0,06 (6H, m), 0,88 - 0,89 (9H, m), 3,07 - 3,33 (4H, m), 3,91 (2H, s), 4,50 - 4,54 (1H, m), 5,89 (1H, d), 7,40 - 7,46 (1H, m), 7,62 (1H, t), 7,77 - 7,81 (1H, m), 7,84 - 7,87 (1H, m), 8,16 (1H, d), 8,22 - 8,26 (1H, m), 8,45 (1H, d), 8,60 (1H, d), 9,74 - 10,00 (1H, m)	m/z (ES+) M+ = 623,20; HPLC tR = 2,81 min.	AX2, aH6
BD22		($CDCl_3$) 0,04 (6H s), 0,88 (9H s), 3,07 - 3,29 (4H, m), 3,89 (2H, s), 4,50 (1H, t), 5,91 (1H, t), 7,40 - 7,52 (2H, m), 8,00 - 8,02 (1H, m), 8,15 (1H, d), 8,22 - 8,25 (1H, m), 8,40 (1H, s), 8,61 - 8,63 (2H, m), 9,79 (1H, s)	m/z (ES+) (M+H)+ = 623,20; HPLC tR = 2,81 min.	AX2, B15
BD23		($CDCl_3$) 0,99 (9H, d), 3,68 - 3,72 (2H, m), 3,81 - 3,84 (2H, m), 4,18 - 4,21 (2H, m), 6,06 (1H, t), 7,22 - 7,27 (1H, m), 7,31 - 7,52 (9H, m), 7,63 - 7,68 (4H, m), 8,11 (1H, t), 8,25 - 8,29 (1H, m), 8,42 (1H, d), 8,58 (1H, d), 8,77 (1H, d)	m/z (ES+) (M+H)+ = 729,22; HPLC tR = 3,76 min.	BA2, BH1

BD24		($CDCl_3$) 0,98 - 1,07 (21H, m), 1,14 (3H, d), 3,59 - 3,67 (1H, m), 3,61 - 3,66 (1H, m), 3,71 - 3,75 (1H, m), 4,20 - 4,24 (1H, m), 4,28 - 4,32 (1H, m), 6,02 (1H, t), 7,42 - 7,45 (1H, m), 7,46 - 7,49 (2H, m), 7,52 - 7,55 (1H, m), 7,61 - 7,63 (1H, m), 8,13 (1H, d), 8,26 - 8,29 (1H, m), 8,42 (1H, s), 8,58 (1H, s), 8,79 (1H, s)	m/z (ES+) M+ = 643,39; HPLC tR = 3,96 min.	BL1, B1
BD25		($CDCl_3$) 0,98 - 1,07 (21H, m), 1,13 - 1,17 (3H, m), 3,59 - 3,77 (3H, m), 4,21 - 4,33 (2H, m), 6,00 - 6,04 (1H, m), 7,43 - 7,47 (1H, m), 7,60 - 7,65 (1H, m), 7,78 - 7,81 (1H, m), 7,85 - 7,87 (1H, m), 8,14 (1H, t), 8,25 - 8,29 (1H, m), 8,51 (1H, d), 8,60 (1H, d), 8,80 (1H, s)		BL1, aH6
BD26		($CDCl_3$) 0,98 - 1,08 (21H, m), 1,15 (3H, d), 2,04 (3H, s), 2,54 (3H, s), 3,59 - 3,68 (2H, m), 3,71 - 3,75 (1H, m), 4,21 - 4,33 (2H, m), 6,04 (1H, t), 7,46 - 7,50 (2H, m), 7,51 - 7,55 (1H, m), 7,61 - 7,63 (1H, m), 8,11 (1H, d), 8,41 (1H, s), 8,59 (1H, s), 8,70 (1H, s), 9,44 (1H, d)	m/z (ES+) = 641,87; HPLC tR = 4,08 min.	AZ2, B1
BD27		($CDCl_3$) 0,99 (9H, s), 3,69 - 3,72 (2H, m), 3,81 - 3,86 (2H, m), 4,16 - 4,24 (2H, m), 6,07 (1H, t), 7,31 - 7,68 (15H, m), 8,11 (1H, s), 8,25 - 8,28 (1H, m), 8,37 (1H, s), 8,58 (1H, s), 8,77 (1H, s)	m/z (ES+) (M+H)+ = 711,41; HPLC tR = 3,79 min.	BA2, B1

BD28		($CDCl_3$) 0,05 (6H, s), 0,88 (9H, s), 2,38 - 2,41 (3H, m), 3,05 - 3,16 (3H, m), 3,29 - 3,36 (1H, m), 3,90 - 3,96 (2H, m), 4,50 - 4,58 (1H, m), 5,96 - 6,01 (1H, m), 7,08 - 7,12 (1H, m), 7,44 - 7,49 (1H, m), 7,98 - 8,02 (1H, m), 8,37 (1H, s), 8,60 - 8,64 (2H, m), 11,11 - 11,47 (1H, m)	m/z (ES+) (M+H)+ = 601,39; HPLC tR = 2,61 min.	BM1, B15
BD29		($CDCl_3$) 0,99 (9H, t), 3,69 - 3,72 (2H, m), 3,82 (2H, t), 4,16 - 4,25 (2H, m), 6,06 - 6,08 (1H, m), 7,04 - 7,07 (1H, m), 7,31 - 7,46 (7H, m), 7,51 - 7,54 (2H, m), 7,63 - 7,73 (5H, m), 8,26 - 8,29 (1H, m), 8,43 (1H, s), 8,58 (1H, s), 8,76 (1H, s)	m/z (ES+) (M+H)+ = 727,48; HPLC tR = 3,98 min.	AQ2, BA3
BD30		(DMSO-d6) 0,88 - 1,01 (21H, m), 1,09 (3H, d), 3,52 - 3,56 (1H, m), 3,65 (1H, q), 3,73 - 3,77 (1H, m), 4,10 - 4,16 (2H, m), 5,93 - 5,95 (1H, m), 7,87 - 7,91 (1H, m), 8,12 - 8,19 (3H, m), 8,23 - 8,27 (1H, m), 8,60 (1H, s), 8,73 (1H, d), 8,82 - 8,83 (1H, m), 11,57 (1H, s)	m/z (ES+) (M+H)+ = 673,49 & 675,57; HPLC tR = 4 min.	BN1, aH6
BD31		($CDCl_3$) 0,98 - 1,08 (21H, m), 1,15 (3H, t), 3,61 - 3,76 (3H, m), 4,20 - 4,24 (1H, m), 4,30 - 4,34 (1H, m), 6,00 (1H, t), 7,46 - 7,54 (3H, m), 7,61 - 7,64 (1H, m), 7,94 - 7,97 (1H, m), 8,37 - 8,41 (2H, m), 8,56 - 8,58 (2H, m), 9,05 (1H, s)	m/z (ES+) (M+H)+ = 648,54 & 650,50; HPLC tR = 4,08 min.	BN1, B1

Producto Intermedio BD14 (S)-3-(2-(terc-butildifenilsililoxi)etoxi)-N-(5-cianopiridin-2-il)-2-(1-(2,6-diclorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanamida

Producto Intermedio BD15 (S)-N-(5-cloropiridin-2-il)-2-(1-(2,6-dicianofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-((R)-1-(triisopropilsililoxi)propan-2-iloxi)propanamida

Producto Intermedio BD16 (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(2-cloro-6-

cianofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-fluoropiridin-2-il)propanamida

Producto Intermedio BD17 (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(2-cloro-6-cianofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(piridin-2-il)propanamida

Producto Intermedio BD18 (2S)-3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-(1-(2-cloro-6-cianofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-metilpirazin-2-il)propanamida

Producto Intermedio BD19 (2S)-3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-(1-(2-cloro-6-cianofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-cloropiridin-2-il)propanamida

Producto Intermedio BD20 (2S)-3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(piridin-2-il)propanamida

Producto Intermedio BD21 (2S)-3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-(1-(2-cloro-6-cianofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-fluoropiridin-2-il)propanamida

Producto Intermedio BD22 (2S)-3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-fluoropiridin-2-il)propanamida

Producto Intermedio BD23 (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(2-cloro-6-fluorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-fluoropiridin-2-il)propanamida

Producto Intermedio BD24 (2S)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-fluoropiridin-2-il)-3-((R)-1-(triisopropilsililoxi)propan-2-iloxi)propanamida

Producto Intermedio BD25 (2S)-2-(1-(2-cloro-6-cianofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-fluoropiridin-2-il)-3-((R)-1-(triisopropilsililoxi)propan-2-iloxi)propanamida

Producto Intermedio BD26 (2S)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-metilpirazin-2-il)-3-((R)-1-(triisopropilsililoxi)propan-2-iloxi)propanamida

Producto Intermedio BD27 (2S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-fluoropiridin-2-il)propanamida

Producto Intermedio BD28 (2S)-3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-metiltiazol-2-il)propanamida

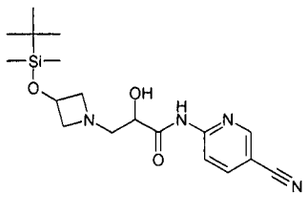
Producto Intermedio BD29 (S)-3-(2-(terc-butildifenilsililoxi)etoxi)-2-(1-(2,6-diclorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(piridin-2-il)propanamida

Producto Intermedio BD30 (2S)-2-(1-(2-cloro-6-cianofenil)-1H-pirazolo[3,4-d]pirimidin-

4-iloxi)-N-(5-cianopiridin-2-il)-3-((R)-1-(triisopropilsililoxi)propan-2-iloxi)propanamida

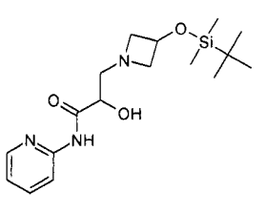
Producto Intermedio BD31 (2S)-2-(1-(2-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-cianopiridin-2-il)-3-((R)-1-(triisopropilsililoxi)propan-2-iloxi)propanamida

Producto Intermedio BE1: (S)-3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-N-(5-cianopiridin-2-il)-2-hidroxipropanamida



Se agregó trimetilaluminio (7,95 mL, 15,89 mmol) a 6-aminonicotinonitrilo (1,646 g, 13,82 mmol) en tolueno (50 mL) enfriado hasta alcanzar 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos. Se agregó (S)-metil 3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-hidroxipropanoato (**Producto Intermedio AD3**) (4,0 g, 13,82 mmol) en tolueno (20 mL) y la solución resultante se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó a 60°C durante 3 horas. La mezcla se enfrió hasta alcanzar ~10°C y se aplacó mediante la adición de solución de sal de Rochelle al 20%. Esto luego se diluyó con EtOAc (50 mL) y se agitó durante 2 horas. La fase orgánica se separó, se lavó con agua y salmuera, se secó ($MgSO_4$), se filtró y se evaporó. El residuo se purificó mediante cromatografía instantánea sobre sílice con EtOAc como eluyente para proporcionar el producto que contenía algo de 6-aminonicotinonitrilo (4,1 g). Esto se utilizó sin purificación adicional. ^{1}H NMR (400 MHz, DMSO-d6) δ 0,02 (6H, s), 0,83 (9H, s), 2,69 - 2,71 (2H, m), 2,76 - 2,82 (2H, m), 3,56 - 3,61 (2H, m), 4,12 - 4,14 (1H, m), 4,30 - 4,38 (1H, m), 5,85 (1H, s, ancho), 8,20 - 8,32 (3H, m), 10,30 (1H, s, ancho); m/z (ES$^+$) $(M+H)^+$ = 377; HPLC t_R = 1,43 min.

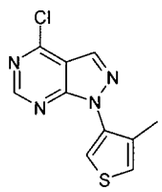
Producto Intermedio BE2: (S)-3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-hidroxi-N-(piridin-2-il)propanamida



Se agregó trimetilaluminio (2,384 mL, 4,77 mmol) a piridin-2-amina (0,390 g, 4,15 mmol) en tolueno (30 mL) enfriado hasta alcanzar 0°C bajo nitrógeno. La solución resultante se

agitó a 0°C durante 10 minutos. Se agregó (S)-metil 3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-hidroxipropanoato (**Producto Intermedio AD3**) (1,2 g, 4,15 mmol) en tolueno (10 mL) y la reacción se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó a 80°C durante 4 horas. La mezcla de reacción se enfrió, se agregó sal de Rochelle al 20% en agua (75 mL) y se agitó durante 2 horas. La mezcla se extrajo con acetato de etilo (2×5 mL) y los extractos orgánicos combinados se lavaron con agua (50 mL) y salmuera (50 mL), se secaron ($MgSO_4$), se filtraron y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 0 a 10% MeOH en EtOAc para proporcionar el producto (1,25g). ^{1}H NMR (400 MHz, DMSO-d6) δ 0,03 (6H, s), 0,83 (9H, m), 2,65 - 2,74 (2H, m), 2,78 - 2,88 (2H, m), 3,56 - 3,60 (2H, m), 4,07 - 4,12 (1H, m), 4,27 - 4,36 (1H, m), 5,77 - 5,83 (1H, m), 7,11 - 7,14 (1H, m), 7,78 - 7,82 (1H, m), 8,05 - 8,10 (1H, m), 8,30 - 8,32 (1H, m), 9,65 (1H, s) m/z (ES^+) $(M+H)^+ = 352$; HPLC $t_R = 1,25$ min.

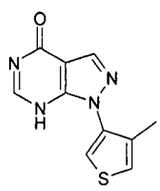
Producto Intermedio BF1: 4-cloro-1-(4-metiltiofen-3-il)-1H-pirazolo[3,4-d]pirimidina



Se agregó tricloruro de fosforilo (4,2 mL, 45 mmol) en una porción a 1-(4-metiltiofen-3-il)-1H-pirazolo[3,4-d]pirimidin-4-ol (**Producto Intermedio BF2**) (700 mg, 3,01 mmol). La suspensión resultante se calentó hasta alcanzar 100°C para proporcionar una solución y se agitó durante 2 horas. La mezcla se evaporó y se agregó hielo al residuo y se agitó durante 30 minutos. Esto luego se filtró y los sólidos se lavaron con agua (3 × 10 mL). El producto bruto se disolvió en acetato de etilo (40 mL), se secó con $MgSO_4$, se filtró y se evaporó para proporcionar el producto (700 mg, 93%). ^{1}H NMR (400 MHz, DMSO-d6) δ 2,09 (3H, d), 7,43 - 7,45 (1H, m), 7,89 (1H, d), 8,72 (1H, s), 8,90 (1H, s); m/z (ES^+) $(M+H)^+ = 251$; HPLC $t_R = 2,26$ min.

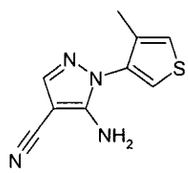
Producto Intermedio BF2: 1-(4-metiltiofen-3-il)-1H-pirazolo[3,4-d]pirimidin-4(7H)-ona

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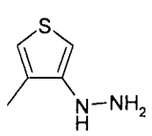
Se agregó ácido sulfúrico concentrado (0,237 mL, 4,46 mmol) a una solución agitada de 5-amino-1-(4-metiltiofen-3-il)-1H-pirazol-4-carbonitrilo (**Producto Intermedio BF3**) (910 mg, 4,46 mmol) en ácido fórmico (15 mL). La solución resultante se agitó a 100°C durante 20 horas. Esto luego se enfrió y se evaporó hasta proporcionar ~la mitad del volumen. Se agregó agua (10 mL) y se agitó durante 1 hora. Esto luego se filtró, se lavó con agua (3 × 5mL) y se secó al alto vacío a 45°C para proporcionar el producto (700 mg, 67%) que se utilizó sin purificación adicional. ^{1}H NMR (400 MHz, DMSO-d6) δ 2,07 (3H, d), 7,36 - 7,38 (1H, m), 7,77 (1H, d), 8,09 (1H, s), 8,28 (1H, s), 12,31 (1H, s); m/z (ES$^+$) $(M+H)^+$ = 233; HPLC t_R = 1,29 min.

Producto Intermedio BF3: 5-amino-1-(4-metiltiofen-3-il)-1H-pirazol-4-carbonitrilo



Se suspendió (4-metiltiofen-3-il)hidrazina (**Producto Intermedio BF4**) (910 mg, 7,10 mmol) en MeOH (30 mL) bajo nitrógeno, se agregó 2-(etoximetileno)malononitrilo (867 mg, 7,10 mmol) en una porción y la mezcla se agitó a temperatura ambiente durante 1 hora y luego se calentó a reflujo durante 2 horas. La mezcla se enfrió, se evaporó y se secó al alto vacío. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 30 a 100% EtOAc en isohexano para proporcionar el producto (780 mg, 54%). ^{1}H NMR (400 MHz, DMSO-d6) δ 1,97 (3H, s), 6,51 (2H, s), 7,34 - 7,35 (1H, m), 7,69 - 7,72 (1H, m), 7,73 (1H, s); m/z (ES$^+$) $(M+H)^+$ = 205; HPLC t_R = 1,40 min.

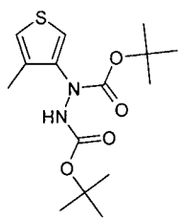
Producto Intermedio BF4: (4-metiltiofen-3-il)hidrazina



Una solución de HCl 4M en dioxano (43,4 mL, 173,55 mmol) se agregó gota a gota a una solución agitada de di-terc-butil 1-(4-metiltiofen-3-il)hidrazina-1,2-dicarboxilato (**Producto Intermedio BF5**) (5,7 g, 17,36 mmol) en isopropanol (50 mL) durante un

período de 1 minuto. La solución resultante se agitó a reflujo durante 2 horas. La mezcla se evaporó, se co-evaporó con 1,4-dioxano (3×50 mL) y se secó al alto vacío. El residuo se suspendió en DCM y se lavó con NaOH 1M. La fase orgánica se lavó con agua, se secó mediante pasaje a través de una membrana separadora de fases y se evaporó para proporcionar el producto (910mg) que se utilizó sin purificación adicional. ^{1}H NMR (400 MHz, DMSO-d6) δ 1,96 (3H, s), 3,85 (2H, s), 6,14 (1H, s), 6,17 (1H, d), 6,91 - 6,92 (1H, m).

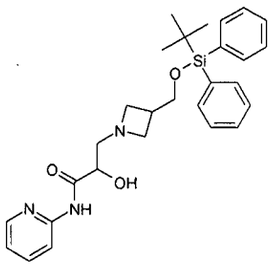
Producto Intermedio BF5: di-terc-butil 1-(4-metiltiofen-3-il)hidrazina-1,2-dicarboxilato



Se agregó complejo de cloruro de isopropilmagnesio – cloruro de litio (0,96M) (40,5 mL, 38,91 mmol) a 3-bromo-4-metiltiofeno (CAS no. 30318-99-1) (5,3 g, 29,93 mmol) en THF (60 mL) enfriado hasta alcanzar 0°C bajo nitrógeno. La solución resultante se entibió hasta alcanzar la temperatura ambiente y se agitó durante 3 horas. La temperatura de reacción se enfrió hasta alcanzar 0°C y se agregó di-terc-butil azodicarboxilato (10,34 g, 44,90 mmol) en THF (30 mL) gota a gota manteniendo la temperatura por debajo de 10°C. La reacción se entibió hasta alcanzar la temperatura ambiente y se agitó durante 20 horas. La mezcla de reacción se enfrió hasta alcanzar ~10°C, se agregó NH_4Cl saturado (150 mL) y se extrajo con EtOAc (3 × 75 mL). Las capas orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron y se evaporaron. El residuo se purificó mediante cromatografía instantánea en sílice, gradiente de elución 20 a 50% Et_2O en isohexano para proporcionar el producto (7,0 g). ^{1}H NMR (400 MHz, DMSO-d6) δ 1,37 - 1,40 (18H, m), 2,08 (3H, s), 7,06 (1H, d), 7,26 (1H, d), 8,68 (1H, s)

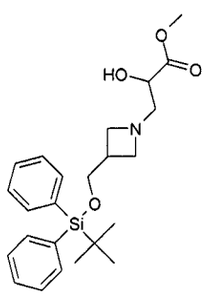
Producto Intermedio BG1: (S)-3-(3-((terc-butildifenilsililoxi)metil)azetidin-1-il)-2-hidroxi-N-(piridin-2-il)propanamida

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Se agregó trimetilaluminio (1,344 mL, 2,69 mmol) a piridin-2-amina (220 mg, 2,34 mmol) en tolueno (20 mL) enfriado hasta alcanzar 0°C bajo nitrógeno durante un período de 10 minutos. La solución resultante se agitó a 0°C durante 10 minutos. Se agregó (S)-metil 3-(3-((terc-butildifenilsililoxi)metil)azetidin-1-il)-2-hidroxipropanoato (**Producto Intermedio BG2**) (1,43 g, 2,34 mmol) en tolueno (5 mL) durante 10 minutos y la reacción se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó a 110°C durante 2 horas. La mezcla de reacción se enfrió y se vertió en una solución de sal de Rochelle al 20% (30 mL), se diluyó con acetato de etilo (80 mL) y se agitó durante 1 hora. La fase orgánica se separó, se lavó con agua y salmuera, se secó sobre $MgSO_4$, se filtró y se evaporó. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 0 a 100% (10% MeOH en DCM) en DCM para proporcionar el producto (681 mg, 59,5 %). m/z (ES^+) $(M+H)^+$ = 491; HPLC t_R = 2,67 min.

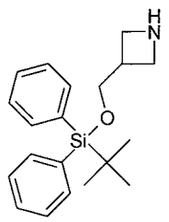
Producto Intermedio BG2: (S)-metil 3-(3-((terc-butildifenilsililoxi)metil)azetidin-1-il)-2-hidroxipropanoato



Se disolvió 3-((terc-butildifenilsililoxi)metil)azetidina (**Producto Intermedio BG3**) (7,461 g, 22,92 mmol) y (S)-metil oxirano-2-carboxilato (2,340 g, 22,92 mmol) en acetonitrilo (50 mL) y se calentó hasta alcanzar 85°C durante 90 minutos. La mezcla resultante se enfrió y se evaporó hasta secarse. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 0 a 5% MeOH en DCM para proporcionar el producto (9,6 g, 56%). ^{1}H(400 MHz, $CDCl_3$) δ 1,05 (9H s), 2,69 (1H, t), 2,73 - 2,82 (2H, m), 3,08 (2H, q), 3,38 (2H, q), 3,70 - 3,78 (5H, m), 4,09 - 4,12 (1H, m), 7,36 - 7,45 (6H, m), 7,62 -

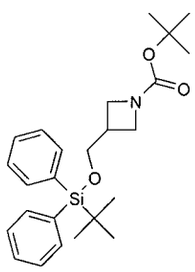
7,66 (4H, m); m/z (ES^+) $(M+H)^+$ = 428,41; HPLC t_R = 2,43 min.

Producto Intermedio BG3: 3-((terc-butildifenilsililoxi)metil)azetidina



Se agregó ácido 2,2,2-trifluoroacético (42,9 mL, 556,53 mmol) a terc-butil 3-((terc-butildifenilsililoxi)metil)azetidina-1-carboxilato (**Producto Intermedio BG4**) (9,87 g, 23,19 mmol) en DCM anhidro (50 mL) a 0°C y luego se dejó agitar a temperatura ambiente durante 1 hora. La solución se concentró y se volvió básica utilizando hidróxido de sodio (250 mL, 2M). La suspensión se extrajo con DCM y se secó con Na_2SO_4 para proporcionar el producto (7,46 g, 99 %). ^1H(400 MHz, $CDCl_3$) δ 1,03 - 1,07 (9H, m), 2,87 - 2,95 (1H, m), 3,47 - 3,51 (2H, m), 3,60 (2H, t), 3,77 (2H, d), 7,35 - 7,45 (6H, m), 7,62 - 7,73 (4H, m); m/z (ES^+) $(M+H)^+$ = 326,22; HPLC t_R = 2,45 min.

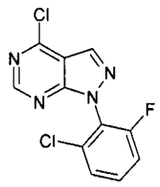
Producto Intermedio BG4: terc-butil 3-((terc-butildifenilsililoxi)metil)azetidina-1-carboxilato



Una solución de terc-butilclorodifenilsilano (5,56 mL, 21,36 mmol) en DCM (20 mL) se agregó gota a gota a una solución agitada de terc-butil 3-(hidroximetil)azetidina-1-carboxilato (CAS no. 142253-56-3) (4,0 g, 21 mmol) y anhidro N-etil-N-isopropilpropan-2-amina (9,1 mL, 53 mmol) en DCM (45 mL) enfriado hasta alcanzar 10°C, durante un período de 2 minutos bajo nitrógeno. La solución resultante se agitó a temperatura ambiente durante 3 horas, se agregó 4-dimetilaminopiridina (100 mg) y la reacción se dejó durante toda la noche. La mezcla de reacción se concentró y se diluyó con EtOAc (75 mL) y se lavó secuencialmente con $NaHCO_3$ saturado (25 mL), agua (20 mL) y salmuera saturada (20 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar el producto bruto (9,87 g) que se utilizó sin purificación adicional. ^1H(400

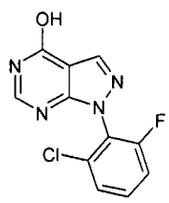
MHz, $CDCl_3$) δ 1,06 (9H, q), 1,44 (9H, d), 2,68 (1H, s), 3,72 - 3,75 (4H, m), 3,92 (2H, t), 7,36 - 7,45 (6H, m), 7,63 - 7,73 (4H, m); HPLC t_R = 3,75 min.

Producto Intermedio BH1: 4-cloro-1-(2-cloro-6-fluorofenil)-1H-pirazolo[3,4-d]pirimidina



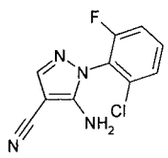
Se agregó oxicloruro de fósforo (17,54 mL, 188,18 mmol) a 1-(2-cloro-6-fluorofenil)-1H-pirazolo[3,4-d]pirimidin-4-ol (**Producto Intermedio BH2**) (2,49 g, 9,41 mmol). La solución resultante se agitó a 100°C durante 1 hora. La mezcla de reacción se evaporó. Se agregaron hielo/agua (100 mL) y luego EtOAc (100 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc (100 mL) . Los elementos orgánicos combinados se lavaron con agua (100 mL), se secaron ($MgSO_4$) y se concentraron para proporcionar el producto bruto (2,48 g) que se utilizó sin purificación adicional. ^{1}H(400 MHz, DMSO-d6) δ 7,60 - 7,65 (1H, m), 7,67 - 7,70 (1H, m), 7,75 - 7,81 (1H, m), 8,89 (1H, s), 8,92 - 8,95 (1H, m).

Producto Intermedio BH2: 1-(2-cloro-6-fluorofenil)-1H-pirazolo[3,4-d]pirimidin-4-ol



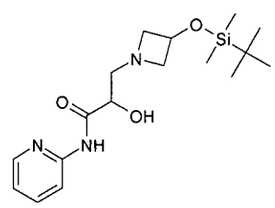
Se agregó ácido sulfúrico concentrado (0,867 mL, 16,27 mmol) a una solución agitada de 5-amino-1-(2-cloro-6-fluorofenil)-1H-pirazol-4-carbonitrilo (**Producto Intermedio BH3**) (3,5 g, 14,79 mmol) en ácido fórmico (25 mL). La solución resultante se agitó a 100°C durante 24 horas. La reacción se dejó enfriar hasta alcanzar la temperatura ambiente y se evaporó hasta aproximadamente la mitad del volumen, se agregó agua (100 mL) y se agitó durante 1 hora. El precipitado formado se retiró mediante filtración, se lavó bien con agua y se secó durante toda la noche en un vacío sobre P_2O_5 para proporcionar el producto (2,51 g, 64,1 %) que se utilizó sin purificación adicional. ^{1}H(400 MHz, DMSO-d6) δ 7,53 - 7,58 (1H, m), 7,61 - 7,64 (1H, m), 7,68 - 7,74 (1H, m), 8,09 - 8,10 (1H, m), 8,41 (1H, s), 12,46 (1H, s); m/z (ES^+) $(M+H)^+$ = 265; HPLC t_R = 1,79 min.

Producto Intermedio BH3: 5-amino-1-(2-cloro-6-fluorofenil)-1H-pirazol-4-carbonitrilo



Se dividió (2-cloro-6-fluorofenil)hidrazina clorhidrato (CAS no. 529512-79-6) (5 g, 25,38 mmol) entre EtOAc (100 mL) y NaOH (2M, ac) (40 mL). La capa orgánica se separó y se lavó con agua (50 mL), salmuera (50 mL), se secó ($MgSO_4$), se filtró y se concentró. El aceite resultante se suspendió en MeOH (50 mL) bajo nitrógeno a -5°C. Se agregó 2-(etoximetileno)malononitrilo (3,10 g, 25,38 mmol) en porciones durante 5 mins y la mezcla se agitó a ~0°C durante 30 mins. La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó a reflujo bajo nitrógeno durante 2 horas. La mezcla de reacción se dejó enfriar y se evaporó hasta secarse para proporcionar el producto (3,52 g) que se utilizó sin purificación adicional. ^1H(400 MHz, $CDCl_3$) δ 4,51 (2H, s), 7,21 - 7,26 (1H, m), 7,39 - 7,42 (1H, m), 7,47 - 7,53 (1H, m), 7,72 (1H, s); m/z (ES^+) $(M+H)^+ = 237$; HPLC $t_R = 1,54$ min.

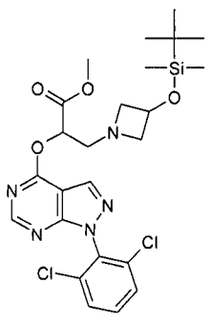
Producto Intermedio BI1: (S)-3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-hidroxi-N-(piridin-2-il)propanamida



Se agregó trimetilaluminio (7,60 mL, 15,20 mmol) a piridin-2-amina (1,431 g, 15,20 mmol) en tolueno anhidro (30 mL) enfriado hasta alcanzar 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos. Se agregó (S)-metil 3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-hidroxipropanoato (**Producto Intermedio AD3**) (2,2 g, 7,60 mmol) en tolueno anhidro (10 mL) y la solución resultante se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó a 80°C durante 4 horas. La mezcla se enfrió hasta alcanzar la temperatura ambiente, se neutralizó con sal de Rochelle en agua (20%, 75 mL), se diluyó con agua (50 mL) y se extrajo con EtOAc (2 × 50 mL). La fase orgánica se separó, se lavó con salmuera, se secó sobre $MgSO_4$, se filtró y se evaporó. El

producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 20 a 50% EtOAc en isohexano para proporcionar un producto impuro. Se determinó que esto contenía la amina de partida, por lo que se purificó nuevamente mediante cromatografía instantánea en sílice, gradiente de elución 0 a 10% MeOH en DCM para proporcionar el producto (1,928 g, 72,2%). ^{1}H(400 MHz, $CDCl_3$) δ 0,02 - 0,04 (6H, m), 0,87 (9H s), 2,90 - 2,92 (2H, m), 3,05 (2H, q), 3,69 - 3,77 (2H, m), 4,02 (1H, t), 4,41 - 4,48 (1H, m), 7,03 - 7,06 (1H, m), 7,67 - 7,72 (1H, m), 8,19 - 8,21 (1H, m), 8,30 - 8,32 (1H, m), 9,78 (1H, s); m/z (ES$^+$) $(M+H)^+$ = 353,12; HPLC t_R = 1,93 min.

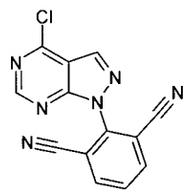
Producto Intermedio BJ1: (S)-metil 3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-(1-(2,6-diclorofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)propanoato



Se agregó hidruro de sodio (dispersión al 60% en aceite mineral) (127 mg, 3,17 mmol) a (S)-metil 3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-hidroxipropanoato (**Producto Intermedio AD3**) (765 mg, 2,64 mmol) en THF anhidro (30 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos y luego se agregó 4-cloro-1-(2,6-diclorofenil)-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio BA3**) (871 mg, 2,91 mmol). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante toda la noche. La mezcla de reacción se neutralizó con ácido cítrico 1M y la mezcla de reacción se diluyó con agua (20 mL) y EtOAc (50 mL). La capa orgánica se separó y la capa acuosa se extrajo nuevamente con EtOAc (2 × 50 mL). Los elementos orgánicos combinados se lavaron con salmuera saturada (75 mL), se secaron ($MgSO_4$), se filtraron y se concentraron al vacío. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 50 a 100% EtOAc en isohexano para proporcionar el producto (445 mg, 30,5 %). ^{1}H(400 MHz, $CDCl_3$) δ 0,05 (6H, s), 0,89 (9H, s), 3,03 - 3,11 (3H, m), 3,18 - 3,23 (1H, m), 3,77 - 3,79 (1H, m), 3,80 (3H, s), 3,86 (1H, d), 4,46 (1H, t), 5,66 (1H, q), 7,45 (1H, t), 7,51 - 7,55 (2H, m), 8,37 (1H, s), 8,53 (1H, s); m/z

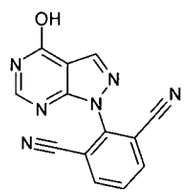
(ES^+) $(M+H)^+$ = 554,8; HPLC t_R = 1,95 min.

Producto Intermedio BK1: 2-(4-cloro-1H-pirazolo[3,4-d]pirimidin-1-il)isoftalonitrilo



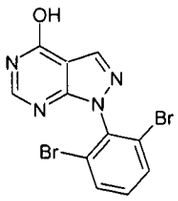
Se agregó tricloruro de fosforilo (6842 µl, 71,40 mmol) a 2-(4-hidroxi-1H-pirazolo[3,4-d]pirimidin-1-il)isoftalonitrilo (**Producto Intermedio BK2**) (1872 mg, 7,14 mmol). La solución resultante se agitó a 100°C durante 4 horas. La mezcla de reacción se evaporó y se agregó hielo/agua al residuo. Después de agitar durante 1 hora se formó un precipitado que se retiró mediante filtración y se lavó con agua (3 × 5 mL) para proporcionar un sólido amarillo. Esto se secó al alto vacío durante 20 horas para proporcionar el producto (879 mg, 43,9 %) que se utilizó sin purificación adicional. ^{1}H NMR (400 MHz, DMSO) δ 8,01 (t, 1H), 8,49 (d, 2H), 9,01 (d, 2H); m/z (ES^-), $(M-H)^-$ = 279,15; HPLC t_R = 2,17 min.

Producto Intermedio BK2: 2-(4-hidroxi-1H-pirazolo[3,4-d]pirimidin-1-il)isoftalonitrilo



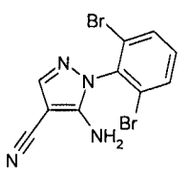
Se disolvió 1-(2,6-dibromofenil)-1H-pirazolo[3,4-d]pirimidin-4-ol (**Producto Intermedio BK3**) (686 mg, 1,85 mmol) y cianuro de zinc (392 mg, 3,34 mmol) en DMF (9270 µl) y se selló en un tubo de microondas. El tubo se purgó con nitrógeno. Se agregaron 9,9-dimetil-4,5-bis(difenilfosfino)xanteno (215 mg, 0,37 mmol) y tris(dibencilidenoacetona)dipaladio(0) (170 mg, 0,19 mmol). La reacción se calentó hasta alcanzar 150°C durante 5 minutos en el reactor de microondas y se enfrió hasta alcanzar la temperatura ambiente. El disolvente se evaporó. El producto bruto se absorbió en celite y se purificó mediante cromatografía instantánea en sílice, gradiente de elución 0 a 10% MeOH en DCM para proporcionar el producto (420 mg, 86 %). ^{1}H NMR (400 MHz, DMSO) δ 8,02 (t, 1H), 8,23 (s, 1H), 8,49 (d, 2H), 8,58 (s, 1H), 12,67 (s, 1H); m/z (ES^-) $(M-H)^-$ = 261,13; HPLC t_R = 1,42 min.

Producto Intermedio BK3: 1-(2,6-dibromofenil)-1H-pirazolo[3,4-d]pirimidin-4-ol



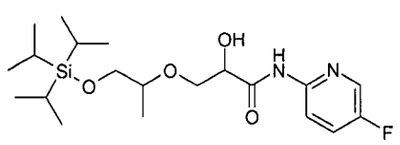
Se agregó ácido sulfúrico conc. (1,323 mL, 24,83 mmol) a una solución agitada de 5-amino-1-(2,6-dibromofenil)-1H-pirazol-4-carbonitrilo (**Producto Intermedio BK4**) (5,66 g, 16,55 mmol) en ácido fórmico (50 mL). La solución resultante se agitó a 100°C durante 3 horas. La mezcla de reacción se enfrió y se evaporó hasta aproximadamente la mitad del volumen, se agregó agua (20 mL) y se agitó durante 1 hora. El precipitado resultante se filtró, se lavó con agua (3 × 10 mL) y se secó al vacío a 50°C para proporcionar el producto (3,60 g, 58,8 %) que se utilizó sin purificación adicional. ^{1}H NMR (400 MHz, DMSO) δ 7,49 (t, 1H), 7,90 (d, 2H), 8,07 - 8,10 (m, 1H), 8,39 (s, 1H), 12,43 (s, 1H); m/z (ES$^+$), $(M+H)^+$ = 371,07; HPLC t_R = 1,92 min.

Producto Intermedio BK4: 5-amino-1-(2,6-dibromofenil)-1H-pirazol-4-carbonitrilo



Se agregó 2-(etoximetileno)malononitrilo (197 mg, 1,62 mmol) en porciones a una solución agitada de (2,6-dibromofenil)hidrazina (CAS no. 14763-29-2) (430 mg, 1,62 mmol) en MeOH (8085 µl), bajo nitrógeno a 5°C. La solución resultante se dejó agitar durante 1 hora más. La mezcla de reacción luego se calentó hasta alcanzar reflujo y se agitó durante 3 horas. La mezcla de reacción se dejó enfriar hasta alcanzar la temperatura ambiente, luego se evaporó para proporcionar el producto bruto que se utilizó sin purificación adicional. m/z (ES$^+$), $(M+H)^+$ = 343,06; HPLC t_R = 1,91 min.

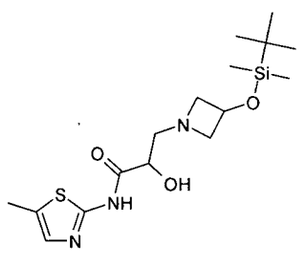
Producto Intermedio BL1: (S)-N-(5-fluoropiridin-2-il)-2-hidroxi-3-((S)-1-(triisopropilsililoxi)propan-2-iloxi)propanamida



Se agregó trimetilaluminio (5,98 mL, 11,96 mmol) a 5-fluoropiridin-2-amina (1,340 g, 11,96 mmol) en tolueno (20 mL) enfriado hasta alcanzar 0°C bajo nitrógeno. La solución

resultante se agitó a 0°C durante 20 minutos. Se agregó (S)-metil 2-hidroxi-3-((R)-1-(triisopropilsililoxi)propan-2-iloxi)propanoato (**Producto Intermedio AU5**) (2 g, 5,98 mmol) en tolueno (6 mL) y la reacción se dejó entibiar hasta alcanzar la temperatura ambiente y luego se sometió a reflujo durante 6 horas. La mezcla de reacción se dejó enfriar y se concentró al vacío. El residuo se neutralizó con ácido cítrico (1M, ac) y luego se diluyó con agua (25mL) y se extrajo con EtOAc (2 × 50 mL). Los elementos orgánicos combinados se lavaron con salmuera (20 mL), luego se secaron ($MgSO_4$) y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 30 a 50% EtOAc en isohexano para proporcionar el producto (1,863 g, 75 %). ^{1}H(400 MHz, $CDCl_3$) δ 1,03 - 1,17 (24H, m), 3,61 - 3,68 (3H, m), 3,81 - 3,85 (1H, m), 4,02 - 4,06 (1H, m), 4,16 (1H, d), 4,31 (1H, t), 7,40 - 7,45 (1H, m), 8,14 (1H, d), 8,25 - 8,28 (1H, m), 9,22 (1H, s); m/z (ES^+) $(M+H)^+$ = 415,31; HPLC t_R = 3,9 min.

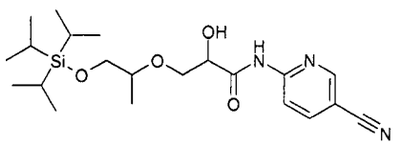
Producto Intermedio BM1: (S)-3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-hidroxi-N-(5-metiltiazol-2-il)propanamida



Se agregó trimetilaluminio (1M en heptano) (3,97 mL, 3,97 mmol) a 5-metiltiazol-2-amina (0,434 g, 3,80 mmol) en DCM (40 mL) enfriado hasta alcanzar 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos. Se agregó (S)-metil 3-(3-(terc-butildimetilsililoxi)azetidin-1-il)-2-hidroxipropanoato (**Producto Intermedio AD3**) (1 g, 3,45 mmol) en DCM (10 mL) y la reacción se dejó entibiar hasta alcanzar la temperatura ambiente y luego se calentó a reflujo durante 2 horas, luego se dejó enfriar hasta alcanzar la temperatura ambiente durante toda la noche. Se agregó solución de Rochelle (20%; 50mL) y la mezcla resultante se agitó vigorosamente durante 90 mins. La mezcla se diluyó con DCM (50 mL) y las capas se separaron. Los elementos orgánicos se secaron ($MgSO_4$) y se evaporaron (733mg). El residuo se purificó mediante cromatografía instantánea en sílice, gradiente de elución 0 a 5% MeOH en EtOAc para proporcionar el producto (0,300 g, 23,37 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0,03 (6H, s), 0,87 (9H, s), 2,40 (3H, s), 2,90 (2H, d), 2,99 - 3,10 (2H, m), 3,66 - 3,79 (2H, m), 4,04 (1H, t), 4,41 - 4,50 (1H, m),

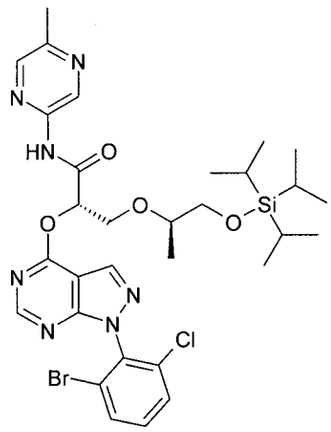
7,08 - 7,10 (1H, m); m/z (ES^+) $(M+H)^+$ = 372,39; HPLC t_R = 2,13 min.

Producto Intermedio BN1: (S)-N-(5-cianopiridin-2-il)-2-hidroxi-3-((R)-1-(triisopropilsililoxi)propan-2-iloxi)propanamida



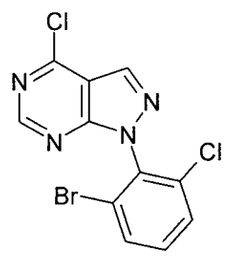
Se agregó trimetilaluminio (5,98 mL, 11,96 mmol) a 6-aminonicotinonitrilo (1,424 g, 11,96 mmol) en tolueno (20 mL) enfriado hasta alcanzar 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 20 minutos. Se agregó (S)-metil 2-hidroxi-3-((R)-1-(triisopropilsililoxi)propan-2-iloxi)propanoato (**Producto Intermedio AU5**) (2 g, 5,98 mmol) en tolueno (6 mL) y la reacción se dejó entibiar hasta alcanzar la temperatura ambiente y luego se sometió a reflujo durante 6 horas. La mezcla de reacción se dejó enfriar y se concentró al vacío. El residuo se neutralizó con ácido cítrico (1M, ac) y luego se diluyó con agua (25mL) y se extrajo con EtOAc (2 × 50 mL). Los elementos orgánicos combinados se lavaron con salmuera (20 mL), luego se secaron ($MgSO_4$) y se evaporaron. El producto bruto se purificó mediante cromatografía instantánea en sílice, eluyendo con 30 a 50% EtOAc en isohexano para proporcionar el producto (1,760 g, 69,8 %). ^1H(400 MHz, $CDCl_3$) δ 1,05 - 1,18 (27H, m), 1,25 (2H, q), 1,53 (11H, s), 2,04 (1H, s), 2,26 (1H, d), 3,63 - 3,67 (3H, m), 3,81 - 3,84 (1H, m), 4,08 - 4,15 (1H, m), 4,32 (2H, d), 7,92 - 7,95 (1H, m), 8,38 - 8,40 (1H, m), 8,58 (1H, q), 9,45 (1H, s); m/z (ES^+) $(M+H)^+$ = 422,26; HPLC t_R = 3,85 min.

Producto Intermedio BO1: (2S)-2-[1-(2-bromo-6-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-metilpirazin-2-il)-3-[(2R)-1-tri(propan-2-il)sililoxipropan-2-il]oxipropanamida



Se agregó hidruro de sodio (0,875 g, 21,87 mmol) a (S)-2-hidroxi-N-(5-metilpirazin-2-il)-3-((R)-1-(triisopropilsililoxi)propan-2-iloxi)propanamida (**Producto Intermedio AZ2**) (3,0 g, 7,29 mmol) en THF anhidro (35 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos y luego se agregó una solución de 1-(2-bromo-6-clorofenil)-4-cloro-1H-pirazolo[3,4-d]pirimidina (**Producto Intermedio BO2**) (2,507 g, 7,29 mmol) en THF anhidro (20 mL) gota a gota durante 1 minuto. La mezcla se agitó a 0°C durante 10 minutos y luego se dejó entibiar hasta alcanzar la temperatura ambiente durante 6 horas. Esto luego se enfrió hasta alcanzar ~0°C, La mezcla se vertió en ácido cítrico helado 1M y se diluyó con EtOAc (50 mL). Esto se agitó vigorosamente durante 10 minutos. La fase orgánica se separó, se lavó con agua y salmuera, se secó sobre $MgSO_4$, se filtró y se evaporó. El producto bruto se purificó mediante cromatografía instantánea en sílice, gradiente de elución 20 a 50% EtOAc en isohexano para proporcionar el producto (4,90 g, 93 %). ^{1}H NMR (400,13 MHz, DMSO-d_6) δ 0,88 - 1,03 (21H, m), 1,09 - 1,11 (3H, m), 2,44 (3H, s), 3,52 - 3,57 (1H, m), 3,63 - 3,67 (1H, m), 3,73 - 3,78 (1H, m), 4,09 - 4,18 (2H, m), 5,92 - 5,98 (1H, m), 7,60 - 7,64 (1H, m), 7,80 - 7,83 (1H, m), 7,91 - 7,93 (1H, m), 8,30 - 8,31 (1H, m), 8,53 - 8,54 (1H, m), 8,63 (1H, s), 9,11 (1H, s), 11,19 (1H, s); m/z (ES^-) $(M-H)^-$ = 718; HPLC t_R = 3,95 min.

Producto Intermedio BO2: 1-(2-bromo-6-clorofenil)-4-cloropirazolo[4,5-e]pirimidina



Se agregó tricloruro de fosforilo (30,4 ml, 326,37 mmol) en una porción a 1-(2-bromo-6-clorofenil)-1H-pirazolo[3,4-d]pirimidin-4-ol (**Producto Intermedio AH4**) (4,25 g, 13,05 mmol) y la suspensión resultante se agitó a 100°C durante 2 horas. Esto luego se enfrió y se evaporó. El residuo se disolvió en tolueno (60 mL), se vertió en hielo, se diluyó con acetato de etilo (40 mL) y se agitó durante 1 hora. La fase orgánica se separó, se lavó con agua (4 × 25 mL) y salmuera (25 mL), se secó sobre $MgSO_4$, se filtró y se evaporó hasta proporcionar un aceite claro amarillo que cristalizó en reposo para proporcionar el producto (4,3g, 95%) que se utilizó sin purificación adicional. ^{1}H NMR (400,13 MHz, DMSO-d_6) δ 7,66 (1H, dd), 7,84 (1H, dd), 7,94 (1H, dd), 8,89 (1H, s), 8,93 (1H, s); m/z (ES$^+$) $(M+H)^+$ = 345; HPLC t_R = 2,90 min.

SECCIÓN BIOLÓGICA

Pruebas:

Los efectos biológicos de los compuestos de fórmula (I) pueden evaluarse de la siguiente manera:

(1) Actividad enzimática

La actividad enzimática de la GLK pancreática humana recombinante puede medirse mediante incubación de GLK, ATP y glucosa. La tasa de formación de producto puede determinarse mediante acoplamiento del ensayo a un sistema NADP/NADPH de G-6-P deshidrogenasa y medición del aumento lineal con el tiempo de la densidad óptica a 340nm como se describe en Brocklehurst et al (Diabetes 2004, **53**, 535-541).

Los compuestos de la invención generalmente activan la glucoquinasa con un valor de CE_{50} menor que aproximadamente 100μM con excepción de los Ejemplos 2, 5, 8, 11, 14, 23, 32, 36 y 76.

Se ha encontrado que los ejemplos de la invención tienen los siguientes valores promedio de CE_{50}s (μM):

Ej. No.	CE50 / uM	Ej. No.	CE50 / uM	Ej. No.	CE50 / uM	Ej. No.	CE50 / uM	Ej. No.	CE50 / uM
1	0,62	56	3,1	112a	0,22	149	0,66	204	1,3
2	>93	57	30	113	0,3	150	1	205	0,24

3	0,17	58	1,95	113a	0,3	151	1,7	206	0,57
4	3,4	59	0,65	114	2,1	152	0,49	207	5
5	>100	60	1,7	115	0,11	153	0,28	208	2,8
6	0,68	61	1,7	115a	0,098	154	1,2	209	1,5
7	3,7	62	12	116	2,3	155	0,76	210	1,2
8	91	63	>4,5	117	6,8	156	0,087	211	1,1
9	0,52	64	10	118	0,15	157	0,14	212	0,49
10	2,7	65	>91	118a	0,12	158	0,15	213	1,1
11	>52	66	>91	119	1,2	159	0,85	214	0,32
12	2,4	67	2,4	120	0,54	160	0,28	215	0,2285
13	1,4	68	>8,4	125	0,31	161	0,61	216	0,1634
14	>82	69	0,52	126	0,57	162	1,5	217	0,4415
15	2,7	70	15	127	6	163	0,58	218	0,2147
16	0,29	71	1,6	127a	1,1	164	0,93	219	0,28
17	0,064	72	2,9	127b	0,84	165	0,37	220	0,22
18	32	73	>18	127c	0,67	166	2,9	221	0,31
19	0,095	74	>100	127d	0,67	167	1,1	222	0,14
20	9,3	75	>100	127e	0,55	168	3,9	223	0,31
21	0,032	76	>36	127f	1,1	169	1,7	224	0,51
22	0,19	81	4,7	127g	0,3	170	1,5	225	0,22
23	>100	82	0,1	127h	6,4	171	0,33	226	0,13
24	0,12	83	0,87	127i	0,36	172	0,81	227	0,32
25	1,2	84	0,47	127j	0,58	173	0,92	228	0,46
26	35	85	9,5	127k	0,56	174	0,23	229	0,11
27	1	86	1,5	127l	0,5	175	0,27	230	0,11
28	0,11	87	0,32	128	0,92	176	0,38	231	0,26
29	0,058	88	5,1	128a	0,62	177	1,5	232	0,54
30	4,8	89	1,5	129	1,3	178	4,3	233	0,21
31	0,35	90	5,4	130	1,1	179	0,62	234	0,21
32	>80	91	0,16	131	0,41	180	0,94	235	0,4
33	>1,7	92	0,42	132	0,47	181	3,3	236	0,74

34	1,9	93	3,3	133	1,1	182	3	237	0,47
35	2,1	94	9,2	134	0,44	183	7,7	238	0,42
36	>82	95	39	135	5,9	184	1,5	239	0,49
37	1,3	96	1,3	136	2,1	185	3,7	240	0,45
38	0,02	97	1,2	137	0,35	186	1,8	241	0,35
39	11	97a	0,46	138	0,81	187	1,7	242	0,22
40	0,14	98	0,11	139	1,4	188	1,1	243	0,57
41	0,12	99	9,3	140	1,2	189	0,6	244	0,33
42	0,41	100	1	141	0,34	190	0,37	245	0,47
43	4,2	101	5	142	2,4	191	0,84	246	0,22
44	3,4	102	0,13	143	0,18	192	0,36	247	0,59
45	1,4	103	0,28	143a	2,6	193	3,3	248	0,64
46	1,6	104	1,2	143b	0,26	194	0,58	249	0,59
47	1	105	0,51	143c	0,61	195	2	250	0,23
48	11	106	6,9	143d	0,59	196	1,7	251	0,35
49	34	107	3,6	143e	0,53	197	0,6	252	0,45
50	0,59	108	1,3	143f	0,98	198	2,2		
51	4,4	109	3,2	144	0,51	199	1,1		
52	2,9	110	1	145	0,23	200	0,44		
53	0,78	111	0,33	146	0,96	201	0,65		
54	4	111a	0,21	147	7,8	202	0,34		
55	>20	112	0,26	148	0,93	203	0,83		

También se encontró que los siguientes compuestos tienen una valor promedio de CE_{50} mayor de aproximadamente 100μM:

2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]sulfanil-N-(5-metil-2-piridil)octanamida;

2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]sulfanil-4-(2-metoxietoxi)-N-(5-metil-2-piridil)butanamida;

2-(1-metilpirazolo[4,5-e]pirimidin-4-il)oxi-N-(5-metil-2-piridil)-4-metilsulfonil-butanamida;

(P.)-4-metoxi-N-(5-metil-2-piridil)-2-[1-(2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-

butanamida;
(R)-2-[1-(2-metoxifenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-metil-2-piridil)propanamida;
2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-isopropoxi-N-(5-metil-1,3,4-oxadiazol-2-il)propanamida;
2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(4-ciano-2-piridil)-3-isopropoxi-propanamida;
2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-isopropoxi-N-pirimidin-2-il-propanamida;
(2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-isopropoxi-N-(3-metil-2-piridil)propanamida;
(2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-isopropoxi-N-(4-metoxi-2-piridil)propanamida;
(2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(1,5-dimetil-1,2,4-triazol-3-il)-3-isopropoxi-propanamida.

Producción de GLK recombinante:

Se obtuvo GLK humana mediante PCR a partir de ARNm pancreático utilizando técnicas consabidas descritas en Sambrook J, Fritsch EF & Maniatis T, 1989. Los cebadores de la PCR se diseñaron de acuerdo con las secuencias del ADNc de la GLK descritas en Tanizawa et al 1991 y Bonthron, D.T. et al 1994 (corregidas más tarde en Warner, J.P. 1995).

Clonación en vectores Bluescript II

La GLK se clonó en E. coli utilizando el PBluescript II (Short et al 1998), un sistema de vectores de clonación recombinante similar al utilizado por Yanisch-Perron C et al (1985), que comprende un replicón basado en colEI con un fragmento de ADN poliligador que contiene múltiples sitios de restricción únicos flanqueado por secuencias promotoras de bacteriófagos T3 y T7, un origen de replicación de fago filamentoso y un gen marcador de resistencia a la ampicilina.

Transformaciones

Las transformaciones de E. Coli generalmente se llevaron a cabo mediante electroporación. Se cultivaron cultivos de 400 mL de las cepas DH5a o BL21(DE3) en

caldo L hasta una OD 600 de 0,5 y se cosecharon mediante centrifugación a 2.000g. Las células se lavaron dos veces en agua desionizada helada, se resuspendieron en 1mL de glicerol al 10% y almacenaron en alícuotas a -70°C. Las mezclas de ligación se desalinizaron utilizando membranas Millipore V series™ (0,0025mm de tamaño de poro). Se incubaron 40mL de células con 1mL de mezcla de ligación o ADN plásmido en hielo durante 10 minutos en cubetas de electroporación de 0,2cm y luego se sometieron a impulsos con un aparato Gene Pulser™ (BioRad) a 0,5kVcm^{-1}, 250mF. Las células transformables se seleccionaron en L-agar complementado con tetracilina a 10mg/mL o ampicilina a 100mg/mL.

Expresión

La GLK se expresó a partir del vector pTB375NBSE en células BL21 de E.coli, produciendo una proteína recombinante que contenía una cola 6-His inmediatamente adyacente a la metionina en el extremo N. Alternativamente, otro vector adecuado es pET21(+)DNA, Novagen, Cat. número 697703. La cola 6-His se utilizó para permitir la purificación de la proteína recombinante en una columna con níquel-ácido nitriloacético-agarosa comercializada por Qiagen (cat. no. 30250).

(2) Prueba oral de tolerancia a la glucosa (OGTT) o perfil de glucosa

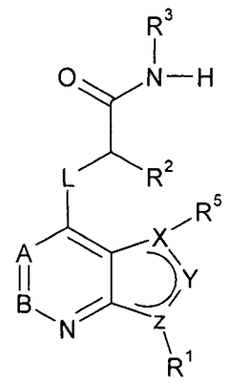
Las pruebas orales de tolerancia a la glucosa se llevaron a cabo en ratas fa/fa obesas Zucker conscientes (al menos 12-13 semanas de edad). Los animales no ingirieron alimentos en las 2 horas previas a los experimentos. Se administró oralmente un compuesto de prueba o un vehículo 120 minutos antes de la administración oral de una solución de glucosa a una dosis de 2 g/kg de peso corporal. Los niveles de glucosa en sangre se midieron utilizando un glucómetro Accucheck con muestras de sangre extraídas de la cola en diferentes puntos de tiempo antes y después de la administración de la glucosa (período total de 60 minutos). Se generó una curva de tiempo para los niveles de glucosa en sangre y se calculó el área bajo la curva (AUC) para 120 minutos (siendo el momento de la administración de la glucosa el tiempo cero). El porcentaje de reducción de la fluctuación de la glucosa se determinó utilizando el AUC en el grupo testigo con vehículo como reducción del cero por ciento.

Para el perfil de glucosa se administró un compuesto de prueba o vehículo 60 minutos antes de que las ratas fa/fa obesas Zucker conscientes (al menos 12-13 semanas de edad)

entraran en un ciclo de oscuridad (12 horas). Los niveles de glucosa en sangre se midieron utilizando un glucómetro Accucheck con muestras de sangre extraídas de la cola en diferentes puntos de tiempo durante el ciclo de oscuridad de 12 horas. Se generó una curva de tiempo para los niveles de glucosa en sangre y se calculó el área bajo la curva (AUC) para 12 horas (siendo el comienzo del ciclo de oscuridad el tiempo cero). El porcentaje de reducción de la fluctuación de la glucosa se determinó utilizando el AUC en el grupo testigo con vehículo como reducción del cero por ciento.

Reivindicaciones:

1. Un compuesto de fórmula (I):



(I)

o una sal farmacéuticamente aceptable del mismo en donde:

A y B son cada uno N o CR^6, siempre que al menos uno de A y B sea CR^6;

X es C o N;

Y es CH o N;

Z es C o N;

en donde X, Y y Z se seleccionan de forma tal que al menos dos de X, Y y Z son N, el anillo que los contiene es aromático y ningún átomo de nitrógeno del anillo está cuaternizado;

R^1 es alquilo(1-6C), arilo, arilalquilo(1-6C) o HET-1 en donde el arilo, arilalquilo(1-6C) y HET-1 están opcionalmente sustituidos por uno, dos o tres grupos que se seleccionan independientemente de halo, alquilo(1-4C), alcoxi(1-4C), trifluorometilo, alquil(1-6C)tio, alquil(1-6C)sulfinilo, alquil(1-6C)sulfonilo, ciano, carboxi, alcoxi(1-6C)carbonilo, carbamoilo, *N*-alquil(1-4C)carbamoilo, *N,N*-dialquil(1-4C)carbamoilo, aminosulfonilo, alquil(1-6C)aminosulfonilo, dialquil(1-6C)aminosulfonilo, alcanoil(1-4C)amino, hidroxialquilo(1-4C), alcoxi(1-4C)alquilo(1-4C), alquil(1-4C)S(O)palquilo(1-4C), aminoalquilo(1-4C), alquil(1-4C)aminoalquilo(1-4C), dialquil(1-4C)aminoalquilo(1-4C), alcoxi(1-6C)carbonilalquilo(1-4C)-, alquil(1-6C)sulfoniloxi, cicloalquil(3-6C)sulfonilo, alquil(1-6C)sulfonilamino, azetidinilcarbonilo, pirrolidinilcarbonilo y HET-3A;

en donde HET-1 es un anillo heteroarilo unido a C de 5 ó 6 miembros, o un sistema de anillos bicíclico fusionado de fórmula –D-E,

en donde el anillo D está unido a Z y es un anillo arilo o heteroarilo de 6 miembros y un anillo E es un anillo heteroarilo, heterociclilo o cicloalquilo de 5 ó 6 miembros que está fusionado al anillo D en cualquier posición disponible;

R^2 es alquilo(1-6C) opcionalmente sustituido por uno o dos hidroxi o por uno de los siguientes: carboxi, carbamoilo, *N,N*-dialquil(1-4C)carbamoilo, alcoxi(1-6C)carbonilo, un grupo $-N(R^7)COR^8$ o un grupo NR^9R^{10};

o R^2 es un grupo $-(CHR^4)_n$-P-Q en donde n es 1, 2, 3 ó 4;

P es un enlazante que se selecciona de O, SO_2, CONH y NHCO;

Q se selecciona de alquilo(1-6C), cicloalquilo(3-6C) y un heterociclilo de 4, 5 ó 6 miembros (en donde dicho anillo heterociclilo contiene 1, 2 ó 3 heteroátomos que se seleccionan independientemente de O, N y S, siempre que no haya enlaces O-O, S-S ni O-S, en donde un átomo de carbono disponible en el anillo puede oxidarse para convertirse en un grupo carbonilo, un átomo de azufre disponible en el anillo puede oxidarse para convertirse en un grupo SO o SO_2 y en donde opcionalmente hay un enlace doble en el anillo) y Q está opcionalmente sustituido en un átomo de carbono disponible por hidroxi o alcoxi(1-4C);

R^3 es un grupo HET-2 en donde HET-2 es un anillo heteroarilo monocíclico unido a C de 5 ó 6 miembros, que contiene un átomo de nitrógeno en la posición 2 y opcionalmente 1 ó 2 heteroátomos del anillo adicionales que se seleccionan independientemente de O, N y S; o HET-2 es un anillo heteroarilo bicíclico unido a C de 8, 9 ó 10 miembros que contiene un átomo de nitrógeno en la posición 2 con hasta cinco heteroátomos del anillo adicionales que se seleccionan independientemente de O, N y S;

en donde HET-2 está opcionalmente sustituido en un átomo de carbono disponible, o en un átomo de nitrógeno del anillo siempre que no quede de este modo cuaternizado, con 1 ó 2 sustituyentes que se seleccionan independientemente de R^{11};

cada R^4 se selecciona independientemente de hidrógeno, hidroxi, metilo y etilo; siempre que cuando n es >1, entonces no más de dos grupos R^4 son hidroxi;

R^5 es H, alcoxi(1-4C) o alquilo(1-4C);

R^6 es H, alcoxi(1-4C) o alquilo(1-4C);

R^7 es H o alquilo(1-4C);

R^8 es alquilo(1-4C);

R^9 es H o alquilo(1-4C) opcionalmente sustituido por hidroxi o metoxi;

R^{10} es H o alquilo(1-4C);

o $-NR^9R^{10}$ forma una azetidina opcionalmente sustituida por hidroxi;

R^{11} se selecciona independientemente de halo, alquilo(1-4C), alcoxi(1-4C), trifluorometilo, alquil(1-6C)tio, alquil(1-6C)sulfinilo, alquil(1-6C)sulfonilo, ciano, carboxi, alcoxi(1-6C)carbonilo, carbamoilo, *N*-alquil(1-4C)carbamoilo, *N,N*-dialquil(1-4C)carbamoilo, aminosulfonilo, alquil(1-6C)aminosulfonilo, dialquil(1-6C)aminosulfonilo, alcanoil(1-4C)amino, hidroxialquilo(1-4C), alcoxi(1-4C)alquilo(1-4C), alquil(1-4C)S(O)palquilo(1-4C) (en donde p es 0, 1 ó 2), aminoalquilo(1-4C), alquil(1-4C)aminoalquilo(1-4C), dialquil(1-4C)aminoalquilo(1-4C), alcoxi(1-6C)carbonilalquilo(1-4C)-, alquil(1-6C)sulfoniloxi, cicloalquil(3-6C)sulfonilo, alquil(1-6C)sulfonilamino, azetidinilcarbonilo, pirrolidinilcarbonilo y HET-3;

HET-3 y HET-3A son cada uno independientemente un anillo heteroarilo insustituido unido a C o N de 5 ó 6 miembros que contiene 1, 2 ó 3 heteroátomos del anillo que se seleccionan independientemente de O, N y S, o un anillo heterociclilo saturado insustituido unido a C o N de 4, 5 ó 6 miembros que contiene un heteroátomo del anillo que se selecciona de O, N y S;

L es S, O o NR^{12}; y

R^{12} es H o alquilo(1-4C);

pero excluyendo

N-(5-cloro-2-piridinil)-2-[(1-fenil-1H-pirazolo[3,4-d]pirimidin-4-il)tio]propanamida;

N-[1-(1-metiletil)-1H-pirazol-5-il]-2-[(1-fenil-1H-pirazolo[3,4-d]pirimidin-4-il)tio]propanamida,

N-(5-(metil)isoxazol-3-il)-2-[[1-(4-fluorofenil)-1H-pirazolo[3,4-d]pirimidin-4-il]tio]butanamida;

N-(5-(metil)isoxazol-3-il)-2-[[1-(4-fluorofenil)-1H-pirazolo[3,4-d]pirimidin-4-il]tio]propanamida;

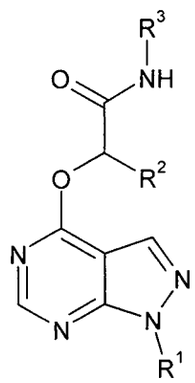
(2P)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-5-hidroxi-N-(5-metil-2-piridil)pentanamida;

(2R)-N-(5-cloro-2-piridil)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-5-hidroxi-pentanamida;

(2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-ciano-2-piridil)-3-[(1S)-2-hidroxi-1-metil-etoxi]propanamida;

(2R)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-ciano-2-piridil)-3-(2-hidroxietoxi)propanamida;
(2S)-N-(5-ciano-2-piridil)-2-[1-(2,5-dimetilfenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-(2-hidroxietoxi)propanamida;
(2S)-3-(2-hidroxietoxi)-N-(5-metil-2-piridil)-2-(9-fenilpurin-6-il)oxi-propanamida;
(2R)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-3-(2-hidroxietoxi)propanamida;
(2S)-N-(5-cloro-2-piridil)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-[(2R)-2-hidroxipropoxi]propanamida;
(2R)-N-(5-cloro-2-piridil)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-[(2R)-2-hidroxipropoxi]propanamida;
(2S)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-ciano-2-piridil)-3-(3-hidroxiciclobutoxi)propanamida; y
(2S)-N-(5-cloro-2-piridil)-2-[1-(3-cloro-2-piridil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-(3-hidroxiciclobutoxi)propanamida.

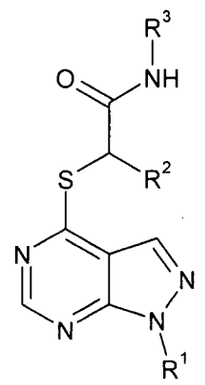
2. Un compuesto de fórmula (I) como se reivindica en la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, que es un compuesto de fórmula (IA)



(IA)

en donde R^1, R^2 y R^3 son tal como se definen en reivindicación 1.

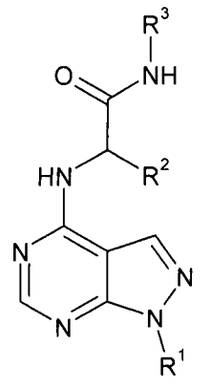
3. Un compuesto de fórmula (I) como se reivindica en la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, que es un compuesto de fórmula (IB)



(IB)

en donde R^1, R^2 y R^3 son tal como se definen en reivindicación 1.

4. Un compuesto de fórmula (I) como se reivindica en la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, que es un compuesto de fórmula (IC).



(IC)

en donde R^1, R^2 y R^3 son tal como se definen en reivindicación 1.

5. Un compuesto de fórmula (I) como se reivindica en la reivindicación 1 o la reivindicación 2, o una sal farmacéuticamente aceptable del mismo, en donde R^1 es HET-1 opcionalmente sustituido por uno o dos sustituyentes que se seleccionan independientemente de halo (particularmente cloro), alquilo(1-4C), alcoxi(1-4C), trifluorometilo, alquil(1-6C)sulfonilo y ciano.

6. Un compuesto de fórmula (I) como se reivindica en la reivindicación 1, la reivindicación 2 o la reivindicación 5, o una sal farmacéuticamente aceptable del mismo, en donde

R^2 es alquilo(1-6C) opcionalmente sustituido por uno o dos hidroxi o R^2 es un grupo –$(CHR^4)_n$-P-Q;

n es 1, 2, 3 ó 4;

un R^4 es opcionalmente hidroxi y los otros grupos R^4 (donde corresponda) son hidrógeno o metilo;

P es un enlazante de oxígeno;

Q es alquilo(1-6C), cicloalquilo(3-6C) o un heterociclilo de 4, 5 ó 6 miembros y Q está opcionalmente sustituido en un átomo de carbono disponible por hidroxi o alcoxi(1-4C).

7. Un compuesto de fórmula (I) como se reivindica en la reivindicación 1, la reivindicación 2, la reivindicación 5 o la reivindicación 6, o una sal farmacéuticamente aceptable del mismo, en donde

R^3 es piridilo, sustituido en la posición para con relación al punto de unión al grupo CONH con un sustituyente que se selecciona de halo, alquilo(1-4C), alquil(1-6C)sulfonilo, N,N-dialquilcarbamoilo y ciano.

8. Un compuesto de la fórmula (I) como se reivindica en la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, que es un compuesto de los ejemplos de la presente, o una sal farmacéuticamente aceptable del mismo.

9. Un compuesto de la fórmula (I) como se reivindica en la reivindicación 1 que se selecciona de uno o más de los siguientes:

(2S)-N-(5-cloropiridin-2-il)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]-pirimidin-4-iloxi)-3-(3-hidroxiazetidin-1-il)propanamida;

(2S)-2-(1-(2-cloro-6-cianofenil)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-N-(5-cloropiridin-2-il)-3-(2-hidroxietoxi)propanamida;

(2S)-N-(5-cloropiridin-2-il)-2-(1-(3-cloropiridin-2-il)-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-((R)-1-hidroxipropan-2-iloxi)propanamida;

(2S)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-3-(3-hidroxiazetidin-1-il)propanamida;

(2S)-2-[1-(2-cloro-6-ciano-fenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-cloro-2-piridil)-3-[(1R)-2-hidroxi-1-metil-etoxi]propanamida;

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(2S)-2-[1-(2-cloro-6-ciano-fenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-[(1R)-2-hidroxi-1-metil-etoxi]-N-(5-metilpirazin-2-il)propanamida;
(2S)-2-[1-(2,6-diclorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-3-(2-hidroxietoxi)propanamida;
(2S)-2-[1-(2-clorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-(3-hidroxiazetidin-1-il)-N-(5-metilpirazin-2-il)propanamida;
(2S)-2-[1-(2,6-diclorofenil)pirazolo[4,5-e]pirimidin-4-il]oxi-3-(3-hidroxiazetidin-1-il)-N-(5-metilpirazin-2-il)propanamida;
(2S)-2-[1-(2-clorofenil)pirazolo[3,4-d]pirimidin-4-il]oxi-N-(5-cloro-2-piridil)-3-(3-hidroxiazetidin-1-il)propanamida;
(2S)-2-[1-(2,6-diclorofenil)pirazolo[3,4-d]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-3-(3-hidroxiazetidin-1-il)propanamida; y
(2S)-2-[1-(2-cloro-6-ciano-fenil)pirazolo[3,4-d]pirimidin-4-il]oxi-N-(5-fluoro-2-piridil)-3-(3-hidroxiazetidin-1-il)propanamida;
o una sal farmacéuticamente aceptable del mismo.

10. Una composición farmacéutica que comprende un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 9, o una sal farmacéuticamente aceptable del mismo, junto con un diluyente o portador farmacéuticamente aceptable.

11. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 9, o una sal farmacéuticamente aceptable del mismo, para su uso como un medicamento.

12. El uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 9, o una sal farmacéuticamente aceptable del mismo, para la preparación de un medicamento para el tratamiento de la diabetes tipo 2.

13. Un método de tratamiento de enfermedades mediadas por GLK mediante la administración de una cantidad efectiva de un compuesto de fórmula (I) como se reivindica en cualquiera de las reivindicaciones 1 a 9, o una sal farmacéuticamente aceptable del mismo, a un mamífero que necesita dicho tratamiento.

14. El método de la reivindicación 13 en donde la enfermedad mediada por GLK es diabetes tipo 2.

15. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 9, o una sal farmacéuticamente aceptable del mismo, para su uso como un medicamento para el tratamiento de una enfermedad mediada por GLK .

16. Un compuesto de acuerdo con la reivindicación 15 en donde la enfermedad mediada por GLK es diabetes tipo 2.

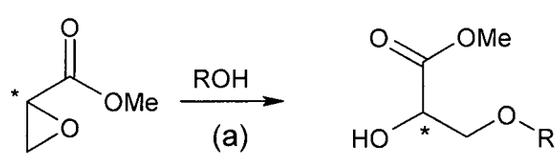
17. Un proceso para la preparación de un compuesto de fórmula (I) como se describe en la presente.

18. Una combinación farmacéutica que comprende un compuesto como se reivindica en cualquiera de las reivindicaciones 1 a 9 y otra sustancia farmacológicamente activa.

19. Una combinación farmacéutica como se reivindica en la reivindicación 18 en donde la otra sustancia farmacológicamente activa es un medicamento para el tratamiento de la diabetes tipo 2.

20. Un compuesto de acuerdo con la reivindicación 15 en donde la enfermedad mediada por GLK es obesidad.

21. La reacción de metil oxirano-2-carboxilato (IX) con un alcohol ROH (en donde R es alquilo(1-6C), cicloalquilo(3-6C) o R^x_3SiO(2-4C)alquilo (en donde cada R^x se selecciona independientemente de alquilo(1-6C) y fenilo) en presencia de magnesiotrifluorometanosulfonato en acetato de etilo, para proporcionar un compuesto de fórmula (X).

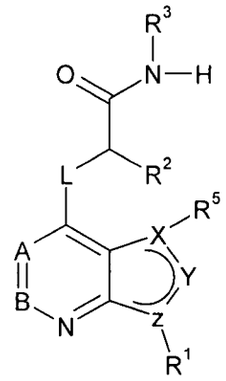


(IX) (X)

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RESUMEN

Un compuesto de fórmula (I):



(I)

es útil en el tratamiento o prevención de una enfermedad o afección médica mediada por glucoquinasa (GLK o GK), que conduce a una reducción del umbral de glucosa para la secreción de insulina.

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(74) Agent: **ASTRAZENECA INTELLECTUAL PROPERTY**; AstraZeneca AB, S-151 85 Södertälje (SE).

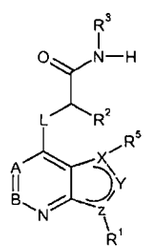
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(I)

(57) Abstract: A compound of Formula (I) is useful in the treatment or prevention of a disease or medical condition mediated through glucokinase (GLK or GK), leading to a decreased glucose threshold for insulin secretion.

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THERAPEUTIC AGENTS 414

The present invention relates to a group of 2-{[1-substituted-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl](thio,oxy or amino)-*N*-(heteroaryl)alkanamides which are useful in the treatment or prevention of a disease or medical condition mediated through glucokinase (GLK or GK). GK Activators (GKAs) are known to activate GK in the pancreatic b-cell leading to a decreased glucose threshold for insulin secretion. In addition GKAs activate hepatic GK thereby stimulating hepatic glucose uptake and suppressing hepatic glucose output. The net pharmacological effect of GKAs is to lower blood glucose levels Therefore, such compounds may have utility in the treatment of Type 2 diabetes and obesity. The invention also relates to pharmaceutical compositions comprising said compounds and to methods of treatment of diseases mediated by GLK using said compounds.

The biology of glucokinase and the mechanisms by which GKAs might deliver potential therapeutic benefit in Type 2 diabetes have been extensively reviewed in the literature (see for example Matschinsky FM et al. (2006) Diabetes 55: 1-12, Leighton B, Atkinson A, Coghlan MP (2005) Biochemical Society Transactions 33: 371-374 and "Glucokinase and Glycemic Disease: From Basics to Novel Therapeutics." Frontiers in Diabetes vol 16, eds. Matschinsky FM and Magnuson MA, Karger (Basel) 2005). In the pancreatic β-cell and liver parenchymal cells the main plasma membrane glucose transporter is GLUT2. Under physiological glucose concentrations the rate at which GLUT2 transports glucose across the membrane is not rate limiting to the overall rate of glucose uptake in these cells. The rate of glucose uptake is limited by the rate of phosphorylation of glucose to glucose-6-phosphate (G-6-P), which is catalysed by glucokinase (GLK). GLK has a high (6-10mM) Km for glucose and is not inhibited by physiological concentrations of G-6-P. GLK expression is limited to a few tissues and cell types, most notably pancreatic β-cells and liver cells (hepatocytes). In these cells GLK activity is rate limiting for glucose utilisation and therefore regulates the extent of glucose induced insulin secretion and hepatic glycogen synthesis. These processes are critical in the maintenance of whole body glucose homeostasis and both are dysfunctional in diabetes.

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International application No
PCT/GB2009/050970

A. CLASSIFICATION OF SUBJECT MATTER
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427

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2006/125958 A1 (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; CAULKETT PETER WILLIAM R) 30 November 2006 (2006-11-30) pages 1,73; example 1	1-21
A	ISMAIL ZEINAB H ET AL: "Synthesis of Some New Biologically Active Sulfur Compounds Containing Pyrazolo[3,4-d]pyrimidine Moiety" PHOSPHORUS, SULFUR AND SILICON AND THE RELATED ELEMENTS, GORDON AND BREACH SCIENCE PUBLISHERS, AMSTERDAM, GB, vol. 178, no. 8, 1 August 2003 (2003-08-01), pages 1795-1805, XP008117207 ISSN: 1042-6507 [retrieved on 2003-08-01] page 1797; example 17	1-21

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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
28 January 2010	05/02/2010

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) 340-2016	Bourghida, E

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2009/050970

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	READY J M: "Asymmetric catalytic synthesis of alpha-aryloxy alcohols: kinetic resolution of terminal epoxides via highly enantioselective ring-opening with phenols" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, NEW YORK, USA, vol. 121, no. 25, 30 June 1999 (1999-06-30), XP002122951 ISSN: 0002-7863 table 1; compound 2f	1-21

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2009/050970

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006125958 A1	30-11-2006	EP 1891069 A1	27-02-2008
		JP 2008542247 T	27-11-2008

430

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-011423- -00000-0000
Fecha: 2011-02-01 18:17:17 Dep: 2020 DIR NUEVASCR
Tra: 11 PATENTEIYII Eve: 373 FASENACIONALI
Act: 411 PRESENTACION Folios: 429

PATENTE DE INVENCIÓN ☐ **MODELO DE UTI**

- ☐ Indicación que se solicita una patente.
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Descripción de la invención
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

PATENTE DE INVENCIÓN PCT ☒ **MODELO DE UTILIDAD PCT** ☐ **Art.33 Decisión 486/00, Circular Única**

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

Completa ☒ Incompleta ☐

DISEÑO INDUSTRIAL ☐ **(Art. 119 Decisión 486/00)**

- ☐ Indicación que se solicita Diseño industrial
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

ESQUEMA DE TRAZADO ☐ **(Art. 92 Decisión 486/00)**

- ☐ Indicación que se solicita un esquema de trazado
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica de un esquema de trazado
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

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Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
ASTRAZENECA AB

REFERENCIA	Radicación No.	11 011423
	Solicitud internacional	PCT/GB2009/050970
	Fecha inicio fase nacional	04/03/2011
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	05728

Como resultado del examen de forma, realizado con fundamento en el artículo 39 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. Con respecto al resumen y de conformidad con lo dispuesto en el artículo 31 D. 486 en el cual se establece que el resumen consiste en una síntesis de la divulgación técnica contenida en la solicitud de patente, debe adecuar el resumen a los dispuesto en dicha norma, teniendo en cuenta que el extracto permitirá precisar el objeto de la invención, sus elementos característicos y el campo de aplicación.
Anexo al presente requerimiento se sugieren los lineamientos principales para la presentación adecuada del resumen.

2. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal b) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título XII de la Circular Única de Superintendencia de Industria y Comercio.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Continua en la página siguiente...

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

JOSE LUIS SALAZAR LOPEZ
Director de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 31 MAR 2011
adpa11

433

Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

Doctor(a)
OLARTE GARCIA CARLOS REINALDO
Apoderado(a) y/o Representante de
ASTRAZENECA AB

REFERENCIA	Radicación No.	11 011423
	Solicitud internacional	PCT/GB2009/050970
	Fecha inicio fase nacional	04/03/2011
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	05729

Teniendo en cuenta que el capítulo reivindicatorio presentado excede de diez reivindicaciones, es necesario que cancele la tasa establecida por cada reivindicación adicional presentada, de conformidad con lo dispuesto en la resolución de tasas vigente para la fecha de presentación de la solicitud, so pena de que no sean tenidas en cuenta dentro del presente trámite administrativo.

En consecuencia, con fundamento en lo previsto por el artículo 12 del Código Contencioso Administrativo, se le requiere para que dentro del término de dos (2) meses siguientes a la fecha de notificación del presente oficio atienda el requerimiento aquí señalado. Lo anterior, con el alcance que para tal efecto establece el artículo 13 de la misma codificación, respecto de las reivindicaciones adicionales.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

JOSE LUIS SALAZAR LOPEZ
Director de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 31 MAR. 2011.
adpa11

ANEXO INFORMATIVO

Presentación

El resumen debe ser claro y tan conciso como lo permita la descripción. No debe exceder de 250 palabras, debiendo contener preferentemente de 50 a 150 palabras y puede incluir fórmulas químicas y matemáticas, cuadros o figuras, en tamaño 12x12.

Contenido

El resumen debe tratar esencialmente de lo que es nuevo y aporta la invención al estado de la técnica al que pertenece. De esta manera, si la naturaleza de la invención es la modificación de un aparato, o la presentación de un procedimiento, producto o compuesto, el resumen debe enfocarse hacia la descripción técnica de la modificación.

En el caso de que el documento de patente reivindique un producto, particularmente un compuesto o componente y también contenga un procedimiento o método de preparación, éste también debe ser incluido en el resumen.

En lo que concierne a los compuestos o composiciones químicas, el resumen debe contener la naturaleza química del compuesto o de la composición, así como el campo de aplicación. El resumen debe indicar la fórmula química que mejor caracterice la invención.

En lo que respecta a los procedimientos, el resumen debe explicar el tipo de reacción, los reactivos y las condiciones para llevar a cabo el procedimiento.

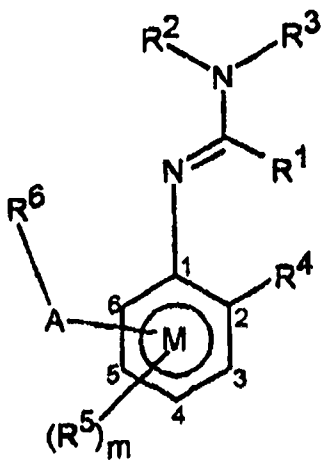
El resumen no debe contener declaraciones relativas a las ventajas asociadas a la invención.

Ejemplo:

Objeto de la Invención: Derivados de fenilamidina de fórmula (I) con aplicación como antifúngicos.

Características de la Invención: Compuestos fungicidas de fórmula (I) y sales donde: R1 es hidrógeno, alquilo, alquenilo, alquinilo, carbocíclico o heterocíclico cada uno de los cuales se encuentra sustituido; R2 y R3 son iguales o diferentes y se eligen entre: ciano, acilo, -ORa o –OSRa donde Ra es alquilo, alquenilo, alquinilo, carbociclilo o heterociclilo, o bien, R2 y R3 forman conjuntamente con el átomo al cual se unen un anillo que puede sustituirse por R4 que es alquilo, alquenilo, alquinilo, carbocicliclo o heterociclilo y que pueden sustituirse por hidroxi, mercapto, azido, nitro, halógeno, ciano, acilo. R5 es igual a la definición contemplada para R4, R6 es un anillo carbocíclico o heterocíclico opcionalmente sustituido y A es un grupo enlazante o AR6 y AR5 forman un anillo fusionado con el anillo de benceno M.

Figura característica:



Campo de aplicación: Producción de agentes antifúngicos con aplicación farmacéutica