CSA836222 Organizacion y
Digitalizacion CSA

PCT

Industria y Comercio

SUPERINTENDENCIA

10-74457 ½

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIRECCIÓN DE NUEVAS CREACIONES

INVENTARIO

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: COMPUESTOS DE CARBAMOILO COMO INHIBIDORES DE LA DGAT1 190

SOLICITANTE: ASTRAZENECA AB

DIRECCIÓN: S-SE-151 85 Södertälje, Suecia

APODERADO: J. IAN RAISBECK

BOGOTÁ 21 de Junio de 2010

21-09-2010

P2010/000077

OLARTERAISBECK
OLARTE RAISBECK MOURE & C...

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-074457- -00000-0000
Fecha: 2010-06-21 17:00:09 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 394

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2010/000077**

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:** J. IAN RAISBECK **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** 79.376.996 **TP** 135.799
INVENTOR (ES) (72)	**Nombre:** VER PAGINA ADJUNTA **Dirección:** VER PAGINA ADJUNTA **Nacionalidad o Domicilio:** VER PAGINA ADJUNTA	

(5) **PCT (86)**

Solicitud Internacional No. PCT/GB2008/051199 Fecha Diciembre 18, 2008

Publicación Internacional No. WO 2009/081195 Fecha Julio 2, 2009

(6) **Título (54)** **COMPUESTOS DE CARBAMOILO COMO INHIBIDORES DE LA DGAT1 190**

Clasificación Internacional (51) C07D 213/81, C07D 213/82, C07D 241/24, C07d 401/04 , C07D 401/10, C07D 403/10, A61K 31/4418, A61K 31/4965, A61P 3/00

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

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Diciembre 20, 2007	61/015,397

(9) **Comprobante de pago No.** 10- **Fecha** Junio de 2010

(10) **ANEXOS**

P.

[X] Comprobante de pago de la tasa de presentación de la solicitud.

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

[X] Poderes, si fuere el caso. Adjunto copia simple Ver Expediente No. 08-129.814

[ ] 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.

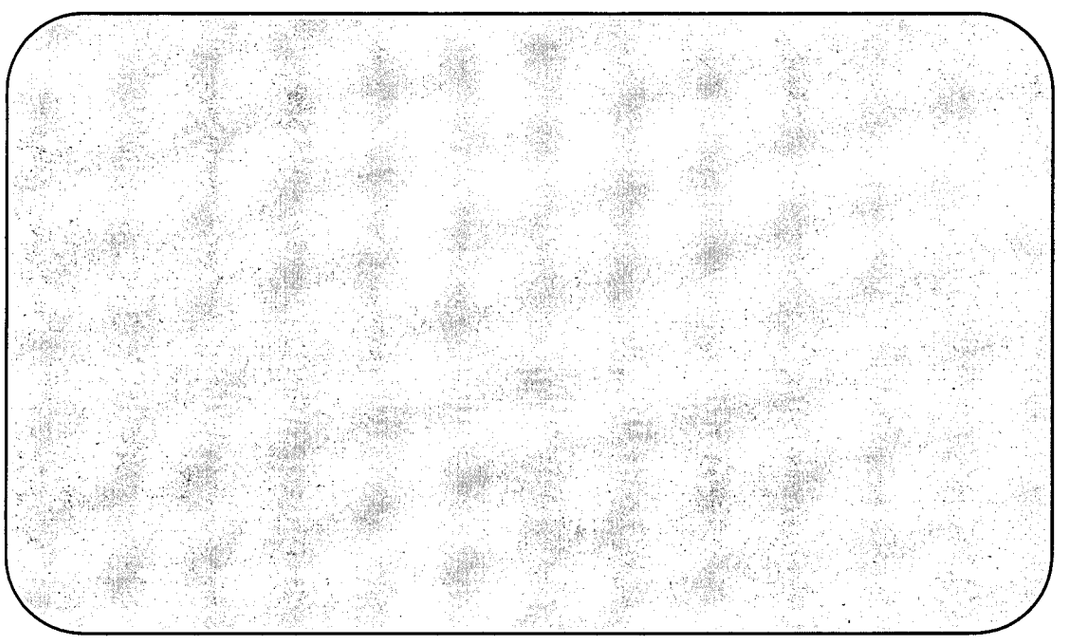
[ ] Arte final 12 x 12.

[ ] 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: J. IAN RAISBECK FIRMA:

C.C. 79.376.996 Btá T.P. 135.799

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

LISTA DE INVENTORES

PCT/GB2008/051199

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S-431 83 Mölndal
Suecia
Nacionalidad: Suecia

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 900176089-2

RECIBO OFICIAL DE CAJA : 10 - 49,668
FECHA : JUNIO 21 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-074457- -00000-0000

Fecha: 2010-06-21 17:00:09 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 394

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	174655286	21/06/2010	7,859,000.00

***** C O N C E P T O *****

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

SON: QUINIENTOS CINCUENTA Y CUATRO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Traducción oficial de un documento 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-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 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 Ministerio

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

OCT 2007

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

8

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:**

NOTARIUS PUBLICUS I STOCKHOLM
BJÖRN SANDIN

OLARTE RAISBECK
OLARTE RAISBECK & FRIERI LTDA.

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

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

Of Counsel
Guillermo Chahí
Graciela Mel
Jacqueline Chaparr
Cruz E. de Moncaleai

Power of Attorney

Poder

The undersigned, El suscrito,

AstraZeneca AB

domiciled in domiciliado en

Vastra Malarehamnen 9 S-151 85 Södertälje, Sweden

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.

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 2002

City,Country/Ciudad,País: SODERTALJE

World Trade Center - Torre A, Calle 100 No. 8A – 37, Piso 9, Bogotá D.C., Colombia
Tel + 57 1 601-7700, Fax + 57 1 601-7799, office@olarteraisbeck.com, www.olarteraisbeck.com

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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 BORGE

Traducción oficial de un documento cuyo original está en inglés

BOLAGSVERKET

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

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 Mini

- 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

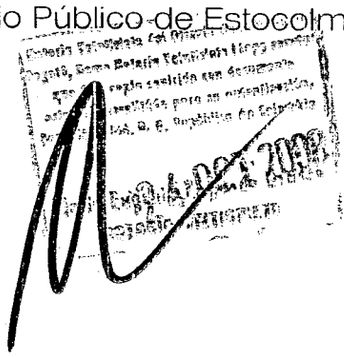
Yo, la suscrita Anne-Marie Bonde, Notario Público de la ciudad de Estocolmo, certifico por medio del presente que Anna-Karin Östin, debidamente autorizada para firmar en nombre de la Oficina de Registro de Compañías de Suecia, ha expedido y firmado el anterior documento en original, del cual la presente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

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.

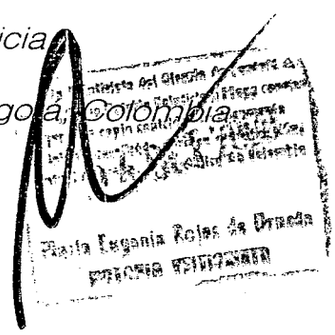
Traductor: Jorge Enrique Sierra Reyes.

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: treseser1@yahoo.com. No. 10-053





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

14

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 I STOCKHOLM
BJÖRN SANDIN

15

Bolagsverket

851 81 Sundsvall
Besökare: Badhusparken
Tel: 060-18 40 00 • Fax: 060-12 98 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 8th day of August in the year of two thousand and seven.

Anna-Karin Östin

Bolagsverket, the Swedish Companies Registration Office, is the official registrar 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 BOMAN

16

11426
The Ministry for Foreign Affairs in Stockholm, hereby certifies that
Mr. Anna-Karin Eden

Swedish Companies Registration Office, Sundsvall

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

For Stockholm this 14th day of August
Kr 60/- PAID 2007

Agneta Ödelklund

Agneta Ödelklund

SIGNATURE OF Agneta Ödelklund
AND STAMP OF : SE MFA
SIGNATURE : Mohammed Hussein
DATE : 20-08-07

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE DORÉE

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
2 July 2009 (02.07.2009)

PCT

(10) International Publication Number
WO 2009/081195 A1

(51) International Patent Classification:
C07D 213/81 (2006.01) *C07D 403/10* (2006.01)
C07D 213/82 (2006.01) *A61K 31/4418* (2006.01)
C07D 241/24 (2006.01) *A61K 31/4965* (2006.01)
C07D 401/04 (2006.01) *A61K 31/497* (2006.01)
C07D 401/10 (2006.01) *A61P 3/00* (2006.01)

(21) International Application Number:
PCT/GB2008/051199

(22) International Filing Date:
18 December 2008 (18.12.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/015,397 20 December 2007 (20.12.2007) US

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

(71) Applicant *(for MG only)*: **ASTRAZENECA UK LIMITED** [GB/GB]; 15 Stanhope Gate, London, Greater London W1K 1LN (GB).

(72) Inventors; and
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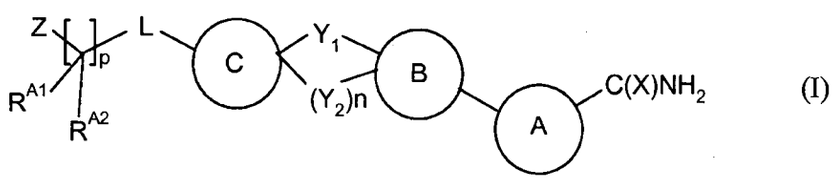
(74) Agent: **ASTRAZENECA INTELLECTUAL PROPERTY**; AstraZeneca AB, S-151 85 Södertälje (SE).

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

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(54) Title: CARBAMOYL COMPOUNDS AS DGAT1 INHIBITORS 190



(I)

(57) Abstract: DGAT-1 inhibitor compounds of formula (I), pharmaceutically-acceptable salts and pro- drugs thereof are described, together with pharmaceutical compositions, processes for making them and their use in treating, for example, obesity wherein, for example, Ring A is optionally substituted 2,6-pyrazindiyl; X is =O; Ring B is optionally substituted 1,4-phenylene; Y_1 is a direct bond or -O-; Y_2 is $-(CH_2)_r-$ wherein r is 2 or 3; n is 0 or n is 1 when Y_1 is a direct bond between Ring B and Ring C and when Ring B is 1,4-phenylene and Ring C is (4-6C)cycloalkane; Ring C is optionally substituted (4-6C)cycloalkane, (7-10C)bicycloalkane, (8-12C)tricycloalkane, phenylene or pryidindiyl; L is a direct bond or -O-; p is 0, 1 or 2 and when p is 1 or 2 R^{A1} and R^{A2} are each independently hydrogen or (1-4C)alkyl; Z is carboxy or a mimic or bioisostere thereof.

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CARBAMOYL COMPOUNDS AS DGAT1 INHIBITORS 190

The present invention relates to compounds which inhibit acetyl CoA(acetyl coenzyme A):diacylglycerol acyltransferase (DGAT1) activity, processes for their preparation, pharmaceutical compositions containing them as the active ingredient, methods for the treatment of disease states associated with DGAT1 activity, to their use as medicaments and to their use in the manufacture of medicaments for use in the inhibition of DGAT1 in warm-blooded animals such as humans. In particular this invention relates to compounds useful for the treatment of type II diabetes, insulin resistance, impaired glucose tolerance and obesity in warm-blooded animals such as humans, more particularly to the use of these compounds in the manufacture of medicaments for use in the treatment of type II diabetes, insulin resistance, impaired glucose tolerance and obesity in warm-blooded animals such as humans.

Acyl CoA:diacylglycerol acyltransferase (DGAT) is found in the microsomal fraction of cells. It catalyzes the final reaction in the glycerol phosphate pathway, considered to be the main pathway of triglyceride synthesis in cells by facilitating the joining of a diacylglycerol with a fatty acyl CoA, resulting in the formation of triglyceride. Although it is unclear whether DGAT is rate-limiting for triglyceride synthesis, it catalyzes the only step in the pathway that is committed to producing this type of molecule [Lehner & Kuksis (1996) Biosynthesis of triacylglycerols. Prog. Lipid Res. 35: 169-201].

Two DGAT genes have been cloned and characterised. Both of the encoded proteins catalyse the same reaction although they share no sequence homology. The DGAT1 gene was identified from sequence database searches because of its similarity to acyl CoA:cholesterol acyltransferase (ACAT) genes. [Cases *et al* (1998) Identification of a gene encoding an acyl CoA:diacylglycerol acyltransferase, a key enzyme in triacylglycerol synthesis. Proc. Natl. Acad. Sci. USA 95: 13018-13023]. DGAT1 activity has been found in many mammalian tissues, including adipocytes.

Because of the previous lack of molecular probes, little is known about the regulation of DGAT1. DGAT1 is known to be significantly up-regulated during adipocyte differentiation.

Studies in gene knockout mice has indicated that modulators of the activity of DGAT1 would be of value in the treatment of type II diabetes and obesity. DGAT1

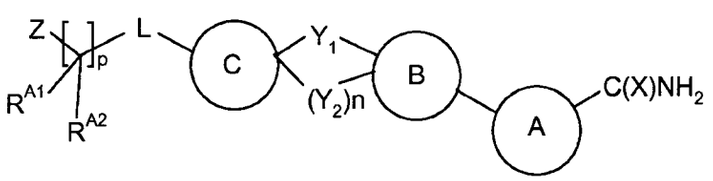
knockout (*Dgat1*$^{-/-}$) mice, are viable and capable of synthesizing triglycerides, as evidenced by normal fasting serum triglyceride levels and normal adipose tissue composition. *Dgat1*$^{-/-}$ mice have less adipose tissue than wild-type mice at baseline and are resistant to diet-induced obesity. Metabolic rate is ~20% higher in *Dgat1*$^{-/-}$ mice than in wild-type mice on both regular and high-fat diets [Smith *et al* (2000) Obesity resistance and multiple mechanisms of triglyceride synthesis in mice lacking DGAT. Nature Genetics 25: 87-90]. Increased physical activity in *Dgat1*$^{-/-}$ mice partially accounts for their increased energy expenditure. The *Dgat1*$^{-/-}$ mice also exhibit increased insulin sensitivity and a 20% increase in glucose disposal rate. Leptin levels are 50% decreased in the *Dgat1*$^{-/-}$ mice in line with the 50% decrease in fat mass.

When *Dgat1*$^{-/-}$ mice are crossed with *ob/ob* mice, these mice exhibit the *ob/ob* phenotype [Chen *et al* (2002) Increased insulin and leptin sensitivity in mice lacking acyl CoA:diacylglycerol acyltransferase J. Clin. Invest. 109:1049-1055] indicating that the *Dgat1*$^{-/-}$ phenotype requires an intact leptin pathway. When *Dgat1*$^{-/-}$ mice are crossed with *Agouti* mice a decrease in body weight is seen with normal glucose levels and 70% reduced insulin levels compared to wild type, *agouti* or *ob/ob/ Dgat1*$^{-/-}$ mice.

Transplantation of adipose tissue from *Dgat1*$^{-/-}$ mice to wild type mice confers resistance to diet-induced obesity and improved glucose metabolism in these mice [Chen *et al* (2003) Obesity resistance and enhanced glucose metabolism in mice transplanted with white adipose tissue lacking acyl CoA:diacylglycerol acyltransferase J. Clin. Invest. 111: 1715-1722].

International Application WO 2006/064189 describes certain oxadiazole compounds which inhibit DGAT-1. However, there remains a need for further DGAT-1 inhibitors possessing desirable properties, such as, for example, pharmaco-kinetic/dynamic and/or physico-chemical and/or toxicological profiles.

Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically-acceptable salt, or pro-drug thereof,



(I)

wherein

Ring A is 2,6-pyrazindiyl, 3,5-pyridindiyl or 2,6-pyridindiyl, each optionally substituted on an available carbon atom by one or two substituents independently selected from linear (1-3C)alkyl, (2-3C)alkenyl, (2-3C)alkynyl, (1-2C)alkoxy, methoxymethyl, amino and cyano;

X is =O or =S;

Ring B is 1,4-phenylene or Ring B is a di-linked (excluding links via the same or adjacent atoms) ring selected from pyridindiyl, furandiyl, thiophendiyl, pyrroldiyl, oxazoldiyl, thiazoldiyl, imidazoldiyl, isoxazoldiyl, isothiazoldiyl and pyrazoldiyl; each optionally substituted on an available carbon atom by one or two substituents independently selected from halo, amino, cyano, (1-4C)alkyl, (2-3C)alkenyl, (2-3C)alkynyl, (1-4C)alkoxy and (1-4C)alkoxy-(1-4C)alkyl;

Y_1 is a direct bond between Ring B and Ring C or Y_1 is -O-, -S- or –NRa- wherein Ra is hydrogen or (1-4C)alkyl;

Y_2 is $-(CH_2)_r-$ wherein r is 2 or 3, and Y_2 is linked at the same carbon atom as Y_1 in Ring C and Y_2 is linked at an adjacent carbon atom to Y_1 in Ring B;

n is 0 or n is 1 when Y_1 is a direct bond between Ring B and Ring C and when Ring B is 1,4-phenylene and Ring C is (4-6C)cycloalkane, so that a 5- or 6-membered spiro-ring system is formed and Ring C is tri-linked;

Ring C is a di-linked (excluding links via the same or adjacent atoms) ring or ring system chosen from (4-6C)cycloalkane, (7-10C)bicycloalkane and (8-12C)tricycloalkane each optionally substituted on an available carbon atom, including the ring carbon atom bearing the Z-containing group, by one substituent selected from hydroxy, (1-4C)alkyl, (1-4C)alkoxy and (1-4C)alkoxy(1-4C)alkyl;

or Ring C is a di-linked (excluding links via the same or adjacent atoms) ring selected from phenylene, pryidindiyl, piperidinediyl N-linked to Y_1, piperazinediyl, furandiyl, thiophendiyl, pyrroldiyl, oxazoldiyl, thiazoldiyl, imidazoldiyl, isoxazoldiyl, isothiazoldiyl, pyrazoldiyl and azabicyclo[3.1.0]hexanediyl;

each optionally substituted on an available carbon atom by up to four substituents independently selected from fluoro, chloro, bromo, cyano, (1-4C)alkyl, (1-4C)alkoxy and (1-4C)alkoxy(1-4C)alkyl;

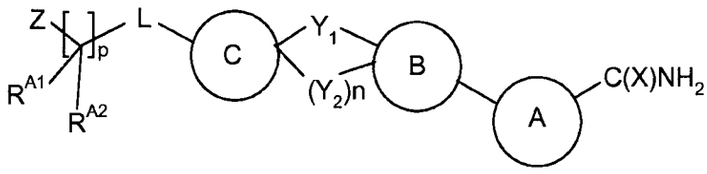
L is a direct bond to Ring C, -O-, -S- or –NH-;

p is 0 (when L is a direct bond), 1 or 2 and when p is 1 or 2 R^{A1} and R^{A2} are each independently hydrogen or (1-4C)alkyl or R^{A1} and R^{A2} are linked together to form a (3-6C)spiroalkyl ring;

Z is carboxy or a mimic or bioisostere thereof, hydroxy or –CONRbRc wherein Rb and Rc are independently selected from hydrogen and (1-4C)alkyl, which (1-4C)alkyl group may be optionally substituted by carboxy or a mimic or bioisostere thereof;

and wherein any carbon atom in a linear (1-3C)alkyl, (1-2C)alkoxy, (1-4C)alkyl or (1-4C)alkoxy containing group defined above may be optionally substituted by up to 3 fluoro atoms; with the proviso that the compound (4-(4-(6-Carbamoyl-pyridin-2-yl)phenyl)cyclohexyl)acetic acid is excluded.

In one embodiment there is provided a compound of formula (I), or a pharmaceutically-acceptable salt, or pro-drug thereof,



(I)

wherein

Ring A is 2,6-pyrazindiyl, 3,5-pyridindiyl or 2,6-pyridindiyl, each optionally substituted on an available carbon atom by one or two substituents independently selected from linear (1-3C)alkyl, (2-3C)alkenyl, (2-3C)alkynyl, (1-2C)alkoxy, methoxymethyl, amino and cyano;

X is =O or =S;

Ring B is 1,4-phenylene or Ring B is a di-linked (excluding links via the same or adjacent atoms) ring selected from pyridindiyl, furandiyl, thiophendiyl, pyrroldiyl, oxazoldiyl, thiazoldiyl, imidazoldiyl, isoxazoldiyl, isothiazoldiyl and pyrazoldiyl; each optionally substituted on an available carbon atom by one or two substituents independently selected from halo, amino, cyano, (1-4C)alkyl, (2-3C)alkenyl, (2-3C)alkynyl, (1-4C)alkoxy and (1-4C)alkoxy-(1-4C)alkyl;

Y_1 is a direct bond between Ring B and Ring C or Y_1 is -O-, -S- or –NRa- wherein Ra is hydrogen or (1-4C)alkyl;

Y_2 is $-(CH_2)_r-$ wherein r is 2 or 3, and Y_2 is linked at the same carbon atom as Y_1 in Ring C and Y_2 is linked at an adjacent carbon atom to Y_1 in Ring B;

n is 0 or n is 1 when Y_1 is a direct bond between Ring B and Ring C and when Ring B is 1,4-phenylene and Ring C is (4-6C)cycloalkane, so that a 5- or 6-membered spiro-ring system is formed;

Ring C is a di-linked (excluding links via the same or adjacent atoms) ring or ring system chosen from (4-6C)cycloalkane, (7-10C)bicycloalkane and (8-12C)tricycloalkane each optionally substituted on an available carbon atom, including the ring carbon atom bearing the Z-containing group, by one substituent selected from hydroxy, (1-4C)alkyl, (1-4C)alkoxy and (1-4C)alkoxy(1-4C)alkyl;

or Ring C is a di-linked (excluding links via the same or adjacent atoms) ring selected from phenylene, pryidindiyl, piperidinediyl N-linked to Y_1, furandiyl, thiophendiyl, pyrroldiyl, oxazoldiyl, thiazoldiyl, imidazoldiyl, isoxazoldiyl, isothiazoldiyl and pyrazoldiyl; each optionally substituted on an available carbon atom by up to four substituents independently selected from fluoro, chloro, bromo, cyano, (1-4C)alkyl, (1-4C)alkoxy and (1-4C)alkoxy(1-4C)alkyl;

L is a direct bond to Ring C, -O-, -S- or –NH-;

p is 0, 1 or 2 and when p is 1 R^{A1} and R^{A2} are each independently hydrogen or (1-4C)alkyl or R^{A1} and R^{A2} are linked together to form a (3-6C)spiroalkyl ring;

Z is carboxy or a mimic or bioisostere thereof, hydroxy or –CONRbRc wherein Rb and Rc are independently selected from hydrogen and (1-4C)alkyl, which (1-4C)alkyl group may be optionally substituted by carboxy or a mimic or bioisostere thereof;

and wherein any carbon atom in a linear (1-3C)alkyl, (1-2C)alkoxy, (1-4C)alkyl or (1-4C)alkoxy containing group defined above may be optionally substituted by up to 3 fluoro atoms.

In a further embodiment there is provided a compound of formula (I), or a pharmaceutically-acceptable salt, or pro-drug thereof, as in any embodiment hereinbefore or hereinafter, with the proviso that the compound (4-(4-(6-carbamoyl-pyridin-2-yl)phenyl)cyclohexyl)acetic acid is excluded.

A further feature is any of the above three embodiments with the proviso that any of the specific Examples herein are individually disclaimed. For example, a further feature

is any of the above embodiments with the proviso that any of the compounds selected from the following are individually disclaimed,

{trans-4-[4-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl] cyclohexyl}acetic acid;

3,5-Dimethyl-6-[4-(trans-4-{2-[(methylsulfonyl)amino]-2-oxoethyl}cyclohexyl)-phenyl]pyrazine-2-carboxamide;

6-{4-[trans-4-(2-Amino-2-oxoethyl)cyclohexyl]phenyl}-3,5-dimethylpyrazine-2-carboxamide;

N-({trans-4-[4-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl] cyclohexyl}acetyl)-2-methylalanine;

6-{4-[trans-4-(2-Hydroxyethyl)cyclohexyl]phenyl}-3,5-dimethyl pyrazine-2-carboxamide;

(trans-4-{4-[6-Carbamoyl-5-(difluoromethyl)-3-methylpyrazin-2-yl]phenyl}cyclohexyl)acetic acid;

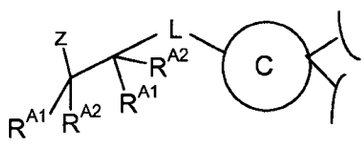
{trans-4-[4-(6-Carbamoyl-3-ethyl-5-methylpyrazin-2-yl)phenyl] cyclohexyl}acetic acid;

{trans-4-[4-(6-Carbamoyl-5-ethyl-3-methylpyrazin-2-yl)phenyl] cyclohexyl}acetic acid and {trans-4-[4-(6-Carbamoyl-3-methylpyrazin-2-yl)phenyl]cyclohexyl}acetic acid; or a pharmaceutically-acceptable salt of any of these.

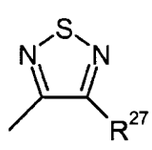
It will be understood that Ring B and Ring C as a di-linked ring or ring system excludes links to Y_1 and L via the same or adjacent atoms (i.e. -1,1- and -1,2- links are excluded).

It will be understood that Ring B is numbered clockwise towards Ring C from the dominant heteroatom in Ring B.

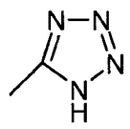
When p is 0 the group Z is connected directly to direct bond L (i.e. Z is connected directly to Ring C and L is not -O-, -S- or –NH-); when p is 2 the group Z is connected as follows to L;



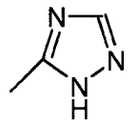
As used herein, the reference to carboxylic acid mimic or bioisostere includes groups as defined in The Practice of Medicinal Chemistry, Wermuth C.G. Ed.: Academic Press: New York, 1996, p203. Particular examples of such groups include $-SO_3H$, $-S(O)_2NHR^{13}$, $S(O)_2NHC(O)R^{13}$, $-CH_2S(O)_2R^{13}$, $-C(O)NHS(O)_2R^{13}$, -C(O)NHOH, -C(O)NHCN, $-CH(CF_3)OH$, $C(CF_3)_2OH$, $-P(O)(OH)_2$ and groups of sub-formula (a)-(i') below



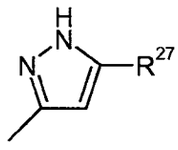
(a)



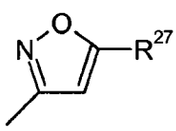
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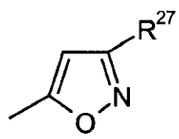
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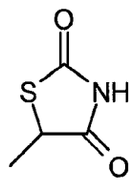
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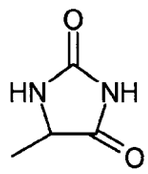
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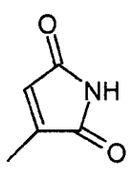
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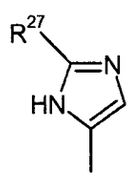
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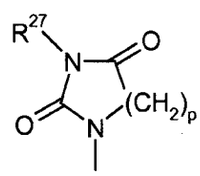
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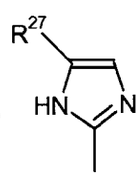
(i)



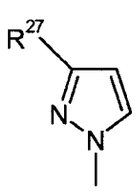
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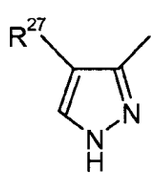
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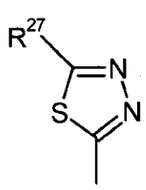
(l)



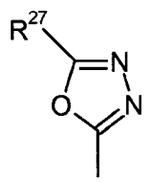
(m)



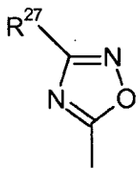
(n)



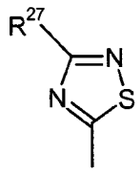
(o)



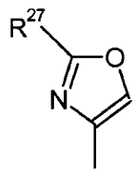
(p)



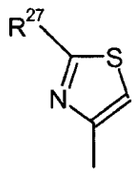
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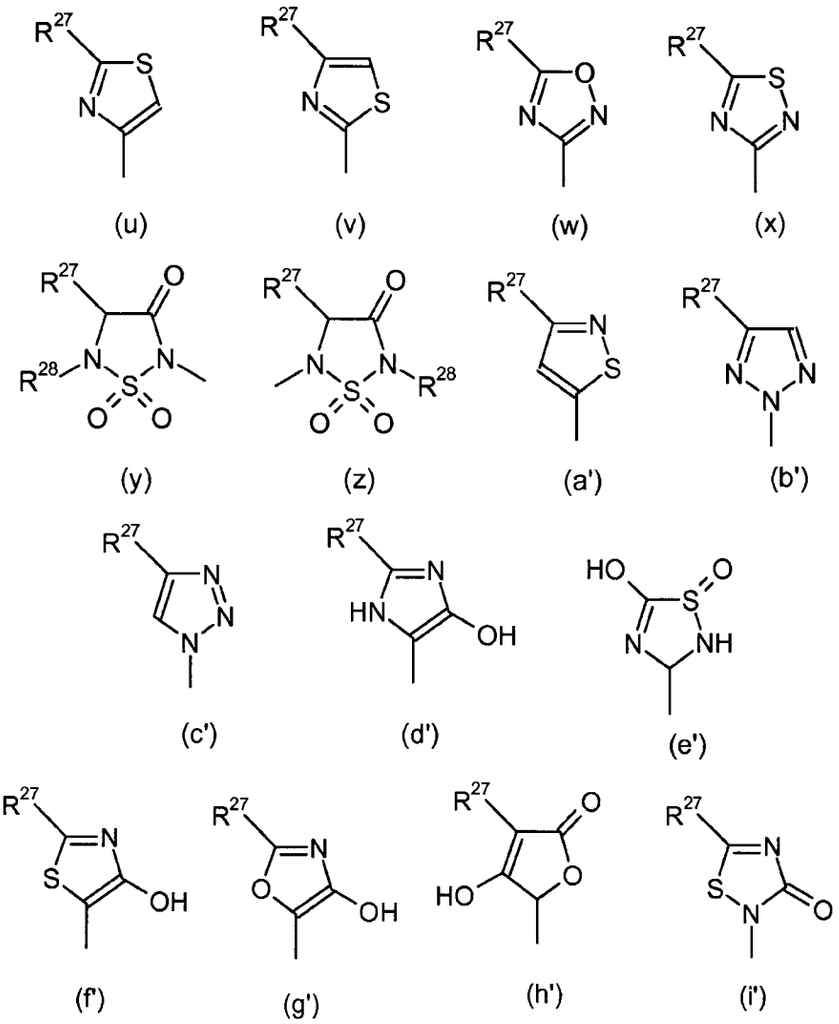
(r)



(s)



(t)



where p in sub-formula (k) is 1 or 2, R^{27} and R^{28} are independently selected from hydrogen, hydroxy, (1-6C)alkoxy, thiol, (1-6C)alkylthio, $-C(O)R^{29}$, $-S(O)R^{30}$, $-SO_2R^{31}$, $-NR^{32}R^{33}$, -NHCN, halogen and trihalomethyl, where R^{29}, R^{30} and R^{31} are $-OR^{34}$, (1-6C)alkyl, $-NR^{32}R^{33}$ or trihalomethyl, R^{32} and R^{33} are independently selected from hydrogen, (1-6C)alkyl, $-SO_2R^{34}$ and $-COR^{35}$, where R^{35} is (1-6C)alkyl or trihalomethyl, and R^{34} is hydrogen, (1-6C)alkyl or trihalomethyl and R^{13} is selected from hydrogen, (1-6C)alkyl, hydroxy, halo, amino, cyano, ((1-3C)alkyl)CONH-, carboxy, (1-6C)alkoxy, (1-6C)alkoxycarbonyl, carbamoyl, N-((1-6C)alkyl)carbamoyl, halo((1-6C)alkyl) (such as trifluoromethyl), (1-6C)alkylsulphonyl or (1-6C)alkylsulphinyl. Particular examples of R^{27} or R^{28} are hydroxy.

Particular carboxylic acid mimic or bioisosteres are a tetrazole group of sub-formula (b) and $-C(O)NHS(O)_2Me$.

In this specification the term "alkyl" includes both straight and branched chain alkyl groups, unless otherwise stated, and references to individual alkyl groups such as "propyl" are specific for the straight chain version only. An analogous convention applies to other generic terms. Unless otherwise stated the term "alkyl" advantageously refers to chains with 1-10 carbon atoms, suitably from 1- 6 carbon atoms, preferably 1-4 carbon atoms.

In this specification the term "alkoxy" means an alkyl group as defined hereinbefore linked to an oxygen atom.

Particular values include for linear (1-3C)alkyl, methyl, ethyl and propyl; for (1-4C)alkyl, methyl, ethyl, propyl and butyl; for (2-3C)alkenyl, ethenyl; for (2-3C)alkynyl, ethynyl; for (1-2C)alkoxy, methoxy and ethoxy; for (1-4C)alkoxy, methoxy, ethoxy and propoxy; for -CONRbRc, $-CONH_2$ and –CONHMe.

Particular values include for any carbon atom in a linear (1-3C)alkyl, (1-2C)alkoxy, (1-4C)alkyl or (1-4C)alkoxy group that may be optionally substituted by up to 3 fluoro atoms, a group such as, for example, trifluoromethyl, difluoromethyl, difluoromethoxy or trifluoromethoxy.

When p in formula (I) is 1 and R^{A1} and R^{A2} are linked together to form a (3-6C)spiroalkyl ring, such a ring may be, for example, a spiro-linked cyclopropyl or cyclobutyl.

When p in formula (I) is 2 and R^{A1} and R^{A2} are linked together to form a (3-6C)spiroalkyl ring, such a ring may be, for example, a spiro-linked cyclopropyl or cyclobutyl.

When Ring C is a di-linked (excluding links via the same or adjacent atoms) (4-6C)cycloalkane ring this includes 1,4-cyclohexane, 1,3-cyclopentane and 1,3-cyclobutane.

When Ring C is (7-10C)bicycloalkanediyl this includes bicyclo[2.2.1]heptanediyl, 1,4-bicyclo[2.2.2]octanediyl, 1,5-bicyclo[3.2.1]octanediyl, 1,5-bicyclo[3.2.2]nonanediyl and 1,5-bicyclo[3.3.2]decanediyl.

When Ring C is (8-12C)tricycloalkanediyl this includes adamantanediyl.

For the avoidance of doubt it is to be understood that where in this specification a group is qualified by 'hereinbefore defined' or 'defined hereinbefore' the said group encompasses the first occurring and broadest definition as well as each and all of the particular definitions for that group.

If not stated elsewhere, suitable optional substituents for a particular group are

those as stated for similar groups herein.

A compound of formula (I) may form stable acid or basic salts, and in such cases administration of a compound as a salt may be appropriate, and pharmaceutically acceptable salts may be made by conventional methods such as those described following.

Suitable pharmaceutically-acceptable salts include acid addition salts such as methanesulfonate, tosylate, α-glycerophosphate, fumarate, hydrochloride, citrate, maleate, tartrate and (less preferably) hydrobromide. Also suitable are salts formed with phosphoric and sulfuric acid. In another aspect suitable salts are base salts such as Group (I) (alkali metal) salt, Group (II) (alkaline earth) metal salt, an organic amine salt for example triethylamine, morpholine, *N*-methylpiperidine, *N*-ethylpiperidine, procaine, dibenzylamine, *N,N*-dibenzylethylamine, tris-(2-hydroxyethyl)amine, *N*-methyl d-glucamine and amino acids such as lysine. There may be more than one cation or anion depending on the number of charged functions and the valency of the cations or anions.

Other suitable pharmaceutically-acceptable salts are mentioned in, for example, Berge et al. (J. Pharm. Sci., 1977, 66, 1-19) and/or Handbook of Pharmaceutical Salts: Properties, Selection and Use by Stahl and Wermuth (Wiley-VCH, 2002).

A feature of the invention relates to a compound of the invention, such as any one of the Examples, in the free acid or free base form or as a pharmaceutically acceptable salt thereof. Such forms may be prepared by standard techniques.

However, to facilitate isolation of the salt during preparation, salts which are less soluble in the chosen solvent may be preferred whether pharmaceutically-acceptable or not.

Within the present invention it is to be understood that a compound of the formula (I) or a salt thereof may exhibit the phenomenon of tautomerism and that the formulae drawings within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which inhibits DGAT1 activity and is not to be limited merely to any one tautomeric form utilised within the formulae drawings.

Pro-drugs of compounds of formula (I), and salts thereof, are also within the scope of the invention.

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

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

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

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

Examples of such prodrugs are *in vivo* cleavable esters of a compound of the invention. An *in vivo* cleavable ester of a compound of the invention containing a carboxy group is, for example, a pharmaceutically-acceptable ester which is cleaved in the human or animal body to produce the parent acid. Suitable pharmaceutically-acceptable esters for carboxy include (1-6C)alkyl esters, for example methyl or ethyl; (1-6C)alkoxymethyl esters, for example methoxymethyl; (1-6C)alkanoyloxymethyl esters, for example pivaloyloxymethyl; phthalidyl esters; (3-8C)cycloalkoxycarbonyloxy(1-6C)alkyl esters, for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolan-2-ylmethyl esters, for example 5-methyl-1,3-dioxolan-2-ylmethyl; (1-6C)alkoxycarbonyloxyethyl esters, for example 1-methoxycarbonyloxyethyl; aminocarbonylmethyl esters and mono- or di- N-((1-6C)alkyl) versions thereof, for example N,N-dimethylaminocarbonylmethyl esters and N-ethylaminocarbonylmethyl esters; and may be formed at any carboxy group in the compounds of this invention. An *in vivo* cleavable ester of a compound of the invention containing a hydroxy group is, for example, a pharmaceutically-acceptable ester which is cleaved in the human or animal body to produce the parent hydroxy group. Suitable pharmaceutically acceptable esters for hydroxy include (1-6C)alkanoyl esters, for example acetyl esters; and benzoyl esters wherein the phenyl group may be substituted with aminomethyl or N- substituted mono- or di- (1-6C)alkyl aminomethyl, for example 4-aminomethylbenzoyl esters and 4-N,N-dimethylaminomethylbenzoyl esters.

Particular prodrugs are (1-4C)alkyl esters of the carboxylic acid in compounds of formula (I), (IA) and/or (IB).

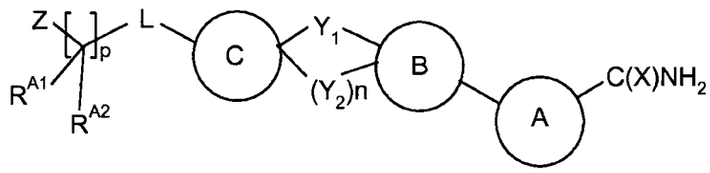
It will be appreciated by those skilled in the art that certain compounds of formula (I) contain asymmetrically substituted carbon and/or sulfur atoms, and accordingly may exist

in, and be isolated in, optically-active and racemic forms. Some compounds of formula (I) may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic or stereoisomeric form, or mixtures thereof, which form possesses properties useful in the inhibition of DGAT1 activity, it being well known in the art how to prepare optically-active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, by enzymatic resolution, by biotransformation, or by chromatographic separation using a chiral stationary phase) and how to determine efficacy for the inhibition of DGAT1 activity by the standard tests described hereinafter.

It is also to be understood that certain compounds of the formula (I) 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 inhibit DGAT1 activity.

As stated before, a range of compounds are provided that have good DGAT1 inhibitory activity. They have good physical and/or pharmacokinetic properties in general.

Thus, in one embodiment there is provided a compound of formula (I), or a pharmaceutically-acceptable salt thereof,



(I)

wherein

Ring A is 2,6-pyrazindiyl, 3,5-pyridindiyl or 2,6-pyridindiyl, each optionally substituted on an available carbon atom by one or two substituents independently selected from linear (1-3C)alkyl, (2-3C)alkenyl, (2-3C)alkynyl, (1-2C)alkoxy, methoxymethyl, amino and cyano;

X is =O or =S;

Ring B is 1,4-phenylene or Ring B is a di-linked (excluding links via the same or adjacent atoms) ring selected from pyridindiyl, furandiyl, thiophendiyl, pyrroldiyl, oxazoldiyl, thiazoldiyl, imidazoldiyl, isoxazoldiyl, isothiazoldiyl and pyrazoldiyl; each optionally substituted on an available carbon atom by one or two substituents

independently selected from halo, amino, cyano, (1-4C)alkyl, (2-3C)alkenyl, (2-3C)alkynyl, (1-4C)alkoxy and (1-4C)alkoxy-(1-4C)alkyl;

Y_1 is a direct bond between Ring B and Ring C or Y_1 is -O-, -S- or –NRa- wherein Ra is hydrogen or (1-4C)alkyl;

Y_2 is $-(CH_2)_r-$ wherein r is 2 or 3, and Y_2 is linked at the same carbon atom as Y_1 in Ring C and Y_2 is linked at an adjacent carbon atom to Y_1 in Ring B;

n is 0 or n is 1 when Y_1 is a direct bond between Ring B and Ring C and when Ring B is 1,4-phenylene and Ring C is (4-6C)cycloalkane, so that a 5- or 6-membered spiro-ring system is formed and Ring C is tri-linked;

Ring C is a di-linked (excluding links via the same or adjacent atoms) ring or ring system chosen from (4-6C)cycloalkane, (7-10C)bicycloalkane and (8-12C)tricycloalkane each optionally substituted on an available carbon atom, including the ring carbon atom bearing the Z-containing group, by one substituent selected from hydroxy, (1-4C)alkyl, (1-4C)alkoxy and (1-4C)alkoxy(1-4C)alkyl;

or Ring C is a di-linked (excluding links via the same or adjacent atoms) ring selected from phenylene, pryidindiyl, piperidinediyl N-linked to Y_1, piperazinediyl, furandiyl, thiophendiyl, pyrroldiyl, oxazoldiyl, thiazoldiyl, imidazoldiyl, isoxazoldiyl, isothiazoldiyl, pyrazoldiyl and azabicyclo[3.1.0]hexanediyl;

each optionally substituted on an available carbon atom by up to four substituents independently selected from fluoro, chloro, bromo, cyano, (1-4C)alkyl, (1-4C)alkoxy and (1-4C)alkoxy(1-4C)alkyl;

L is a direct bond to Ring C, -O-, -S- or –NH-;

p is 0, 1 or 2 and when p is 1 R^{A1} and R^{A2} are each independently hydrogen or (1-4C)alkyl or R^{A1} and R^{A2} are linked together to form a (3-6C)spiroalkyl ring;

Z is carboxy or a mimic or bioisostere thereof, hydroxy or –CONRbRc wherein Rb and Rc are independently selected from hydrogen and (1-4C)alkyl, which (1-4C)alkyl group may be optionally substituted by carboxy or a mimic or bioisostere thereof;

and wherein any carbon atom in a linear (1-3C)alkyl, (1-2C)alkoxy, (1-4C)alkyl or (1-4C)alkoxy containing group defined above may be optionally substituted by up to 3 fluoro atoms; with the proviso that the compound (4-(4-(6-Carbamoyl-pyridin-2-yl)phenyl)cyclohexyl)acetic acid is excluded.

In another embodiment there is provided a compound of formula (I), or a pharmaceutically-acceptable salt, or pro-drug thereof wherein

Ring A is 2,6-pyrazindiyl, 3,5-pyridindiyl or 2,6-pyridindiyl, each optionally substituted on an available carbon atom by one or two substituents independently selected from linear (1-3C)alkyl, (2-3C)alkenyl, (2-3C)alkynyl, (1-2C)alkoxy, methoxymethyl, amino and cyano;

X is =O or =S;

Ring B is 1,4-phenylene or Ring B is a di-linked (excluding links via the same or adjacent atoms) ring selected from pyridindiyl, furandiyl, thiophendiyl, pyrroldiyl, oxazoldiyl, thiazoldiyl, imidazoldiyl, isoxazoldiyl, isothiazoldiyl and pyrazoldiyl; each optionally substituted on an available carbon atom by one or two substituents independently selected from halo, amino, cyano, (1-4C)alkyl, (2-3C)alkenyl, (2-3C)alkynyl, (1-4C)alkoxy and (1-4C)alkoxy-(1-4C)alkyl;

Y_1 is a direct bond between Ring B and Ring C or Y_1 is -O-, -S- or –NRa- wherein Ra is hydrogen or (1-4C)alkyl;

Y_2 is $-(CH_2)_r-$ wherein r is 2 or 3, and Y_2 is linked at the same carbon atom as Y_1 in Ring C and Y_2 is linked at an adjacent carbon atom to Y_1 in Ring B;

n is 0 or n is 1 when Y_1 is a direct bond between Ring B and Ring C and when Ring B is 1,4-phenylene and Ring C is (4-6C)cycloalkane, so that a 5- or 6-membered spiro-ring system is formed;

Ring C is a di-linked (excluding links via the same or adjacent atoms) ring or ring system chosen from (4-6C)cycloalkane, (7-10C)bicycloalkane and (8-12C)tricycloalkane each optionally substituted on an available carbon atom, including the ring carbon atom bearing the Z-containing group, by one substituent selected from hydroxy, (1-4C)alkyl, (1-4C)alkoxy and (1-4C)alkoxy(1-4C)alkyl;

or Ring C is a di-linked (excluding links via the same or adjacent atoms) ring selected from phenylene, pryidindiyl, piperidinediyl N-linked to Y_1, furandiyl, thiophendiyl, pyrroldiyl, oxazoldiyl, thiazoldiyl, imidazoldiyl, isoxazoldiyl, isothiazoldiyl and pyrazoldiyl; each optionally substituted on an available carbon atom by up to four substituents independently selected from fluoro, chloro, bromo, cyano, (1-4C)alkyl, (1-4C)alkoxy and (1-4C)alkoxy(1-4C)alkyl;

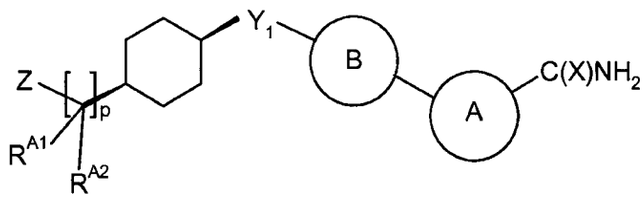
L is a direct bond to Ring C, -O-, -S- or –NH-;

p is 0, 1 or 2 and when p is 1 R^{A1} and R^{A2} are each independently hydrogen or (1-4C)alkyl or R^{A1} and R^{A2} are linked together to form a (3-6C)spiroalkyl ring;

Z is carboxy or a mimic or bioisostere thereof, hydroxy or –CONRbRc wherein Rb and Rc are independently selected from hydrogen and (1-4C)alkyl, which (1-4C)alkyl group may be optionally substituted by carboxy or a mimic or bioisostere thereof;

and wherein any carbon atom in a linear (1-3C)alkyl, (1-2C)alkoxy, (1-4C)alkyl or (1-4C)alkoxy containing group defined above may be optionally substituted by up to 3 fluoro atoms.

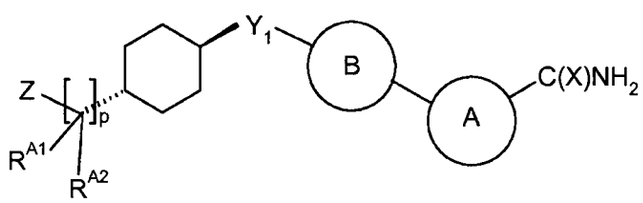
In another embodiment there is provided a compound of formula (IA), or a pharmaceutically-acceptable salt, or pro-drug thereof,



(IA)

wherein X, Ring A, Ring B, Y_1, p, R^{A1}, R^{A2} and Z are as defined in Claim 1 or 2.

In another embodiment there is provided a compound of formula (IB), or a pharmaceutically-acceptable salt, or pro-drug thereof,



(IB)

wherein X, Ring A, Ring B, Y_1, p, R^{A1}, R^{A2} and Z are as defined in Claim 1 or 2.

In another embodiment there is provided a compound as claimed in any one of Claims 1 to 4, or a pharmaceutically-acceptable salt, or pro-drug thereof, wherein X is =O; Ring A is 2,6-pyrazindiyl optionally substituted on an available carbon atom by one or two substituents independently selected from linear (1-3C)alkyl, (2-3C)alkenyl, (2-3C)alkynyl, (1-2C)alkoxy, methoxymethyl, amino and cyano;

Ring B is 1,4-phenylene optionally substituted on an available carbon atom by one or two substituents independently selected from halo, amino, cyano, (1-4C)alkyl, (2-3C)alkenyl, (2-3C)alkynyl, (1-4C)alkoxy and (1-4C)alkoxy-(1-4C)alkyl;

Ring C is 1,4-cyclohexane;

n is 0 and Y_1 is a direct bond or Y_1 is -O-;

L is a direct bond;

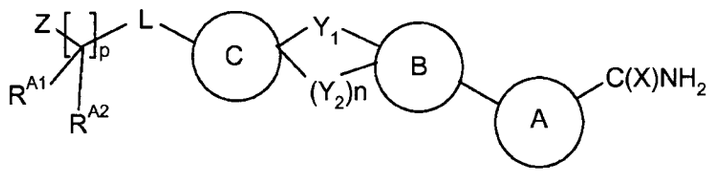
p is 1 and R^{A1} and R^{A2} are each hydrogen;

Z is carboxy, a tetrazole group, $-C(O)NHS(O)_2Me$, hydroxy or –CONRbRc wherein Rb and Rc are independently selected from hydrogen and (1-4C)alkyl, which (1-4C)alkyl group may be optionally substituted by carboxy; and wherein any carbon atom in a linear (1-3C)alkyl, (1-2C)alkoxy, (1-4C)alkyl or (1-4C)alkoxy containing group defined above may be optionally substituted by up to 3 fluoro atoms.

In another embodiment there is provided a compound as claimed in any one of Claims 1 to 5, or a pharmaceutically-acceptable salt, or pro-drug thereof, wherein Ring A is 2,6-pyrazindiyl optionally substituted on an available carbon atom by one or two linear (1-3C)alkyl substituents.

The following compounds possess particular, desirable pharmaceutical and/or physical and/or pharmacokinetic/dynamic and/or toxicological properties and/or selective activity for DGAT1.

A compound of formula (I), or a pharmaceutically-acceptable salt, or pro-drug thereof,



(I)

wherein

Ring A is 2,6-pyrazindiyl, 3,5-pyridindiyl or 2,6-pyridindiyl, each optionally substituted on an available carbon atom by one or two substituents independently selected from linear (1-3C)alkyl, (2-3C)alkenyl, (2-3C)alkynyl, (1-2C)alkoxy, methoxymethyl, amino and cyano;

X is =O or =S;

Ring B is 1,4-phenylene or Ring B is a di-linked (excluding links via the same or adjacent atoms) pyridindiyl ring; each optionally substituted on an available carbon atom by one or two substituents independently selected from halo, amino, cyano, (1-4C)alkyl, (2-3C)alkenyl, (2-3C)alkynyl, (1-4C)alkoxy and (1-4C)alkoxy-(1-4C)alkyl;

Y_1 is a direct bond between Ring B and Ring C or Y_1 is -O-, -S- or –NRa- wherein Ra is hydrogen or (1-4C)alkyl;

n is 0;

Ring C is a di-linked (excluding links via the same or adjacent atoms) (4-6C)cycloalkane ring, optionally substituted on an available carbon atom, including the ring carbon atom bearing the Z-containing group, by one substituent selected from hydroxy, (1-4C)alkyl, (1-4C)alkoxy and (1-4C)alkoxy(1-4C)alkyl;

L is a direct bond to Ring C or -O-;

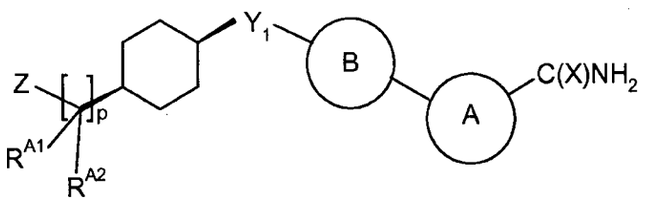
p is 0, 1 or 2 and when p is 1 R^{A1} and R^{A2} are each independently hydrogen or (1-4C)alkyl;

Z is carboxy or a mimic or bioisostere thereof, hydroxy or –CONRbRc wherein Rb and Rc are independently selected from hydrogen and (1-4C)alkyl, which (1-4C)alkyl group may be optionally substituted by carboxy or a mimic or bioisostere thereof;

and wherein any carbon atom in a linear (1-3C)alkyl, (1-2C)alkoxy, (1-4C)alkyl or (1-4C)alkoxy containing group defined above may be optionally substituted by up to 3 fluoro atoms.

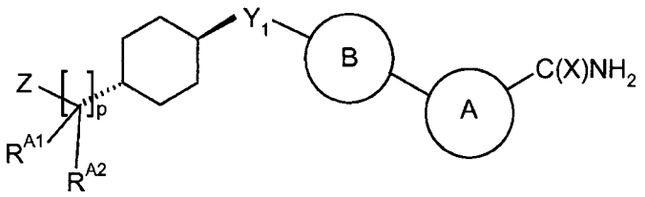
In one aspect, it will be appreciated that in certain compounds of formula (I) the Ring C substituent bearing the Z group (or suitable replacement thereof) and the $-Y_1-$ link are in either a cis- or a trans- arrangement across the ring, in relation to each other. Where appropriate the invention encompasses both the cis- and trans- isomers. Techniques for separation of such isomers are well known in the art.

Thus, in one aspect, when Ring C is cyclohexyl the Z containing group and $-Y_1-$ link are in a cis- configuration across the cyclohexyl ring, to give a compound of formula (IA), wherein the variables are as defined hereinbefore or hereinafter:



(IA)

Thus, in one aspect, when Ring C is cyclohexyl the Z containing group and $-Y_1-$ link are in a trans- configuration across the cyclohexyl ring, to give a compound of formula (IB), wherein the variables are as defined hereinbefore or hereinafter:



(IB)

References hereinbefore or hereinafter to a compound of formula (I) are taken to apply also to compounds of formulae (IA) and (IB).

In one embodiment of the invention there are provided compounds of formulae (I), (IA) and (IB), in an alternative embodiment there are provided salts, particularly pharmaceutically-acceptable salts of compounds of formulae (I), (IA) and (IB). In a further embodiment, there are provided pro-drugs, particularly in-vivo cleavable esters, of compounds of formulae (I), (IA) and (IB). In a further embodiment, there are provided salts, particularly pharmaceutically-acceptable salts of pro-drugs of compounds of formulae (I), (IA) and (IB).

Particular values of substituents in compounds of formulae (I), (IA) and (IB) are as follows (such values may be used where appropriate with any of the other values, definitions, claims or embodiments defined hereinbefore or hereinafter)...

1) X is =O;

2) X is =S;

3) Ring A is 2,6-pyrazindiyl;

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4) Ring A is 2,6-pyrazindiyl substituted with any of the substituents in the Examples;

5) Ring A is 2,6-pyrazindiyl substituted with one or two (1-3C)alkyl;

6) Ring B is 1,4-phenylene;

7) Ring B is 2,5-pyridindiyl or 3,6-pyridindiyl;

8) Ring B is optionally substituted on an available carbon atom by one or two halo substituents;

9) Ring C is 1,4-cyclohexane (i.e. 1,4-cyclohexyl);

10) n is 0 and Y_1 is a direct bond between Ring B and Ring C or Y_1 is -O-;

11) Ring B and Ring C are particularly 2,4- or 2,5-furandiyl, 2,4- or 2,5-thiophendiyl, 2,4- or 2,5-pyrroldiyl, 2,4- or 2,5-oxazoldiyl, 2,4- or 2,5-thiazoldiyl, 2,4- or 2,5-imidazoldiyl, 3,4- or 3,5-isoxazoldiyl, 3,4- or 3,5-isothiazoldiyl, 3,4- or 3,5-pyrazoldiyl;

12) L is a direct bond;

13) p is 0;

14) p is 1 and R^{A1} and R^{A2} are each hydrogen;

15) p is 2 and R^{A1} and R^{A2} are each hydrogen;

16) Z is carboxy, –CONRbRc (wherein Rb and Rc are independently selected from hydrogen and (1-4C)alkyl (which (1-4C)alkyl group may be optionally substituted by carboxy), a tetrazole group or -C(O)NHS(O)$_2$Me;

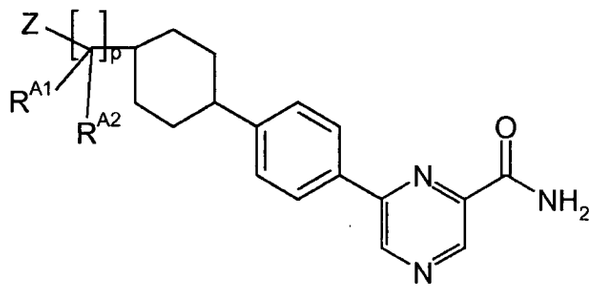
17) Z is carboxy;

18) a pro-drug for Z as carboxy is a (1-6C)alkyl ester.

Thus, for example, in one embodiment there is provided a compound of formula (I), or a pharmaceutically-acceptable salt thereof, wherein X=O; Ring A is 2,6-pyrazindiyl optionally substituted on an available carbon atom by one or two substituents independently selected from linear (1-3C)alkyl, (2-3C)alkenyl, (2-3C)alkynyl, (1-2C)alkoxy, methoxymethyl, amino and cyano; Ring B is 1,4-phenylene (optionally substituted on an available carbon atom by one or two halo substituents); n is 0 and Y_1 is a direct bond between Ring B and Ring C; p is 0 or p is 1 and R^{A1} and R^{A2} are each hydrogen; L is a direct bond and Z is carboxy, –CONRbRc (wherein Rb and Rc are independently selected from hydrogen and (1-4C)alkyl (which (1-4C)alkyl group may be

37

optionally substituted by carboxy), a tetrazole group or -C(O)NHS(O)$_2$Me; i.e. a compound of formula (IC), or a pharmaceutically-acceptable salt thereof, wherein the 2,6-pyrazindiyl ring is optionally substituted on an available carbon atom by one or two substituents independently selected from linear (1-3C)alkyl, (2-3C)alkenyl, (2-3C)alkynyl, (1-2C)alkoxy, methoxymethyl, amino and cyano and other values are as defined immediately above.



(IC)

In another embodiment there is provided a compound of formula (I), or a pharmaceutically-acceptable salt thereof, wherein X=O; Ring A is 2,6-pyrazindiyl optionally substituted on an available carbon atom by one or two substituents independently selected from linear (1-3C)alkyl, (2-3C)alkenyl, (2-3C)alkynyl, (1-2C)alkoxy, methoxymethyl, amino and cyano; Ring B is 1,4-phenylene (optionally substituted on an available carbon atom by one or two halo substituents); n is 0 and Y_1 is a direct bond between Ring B and Ring C; p is 1 and R^{A1} and R^{A2} are each hydrogen; L is a direct bond and Z is carboxy or a tetrazole group.

In another embodiment there is provided a compound of formula (I), or a pharmaceutically-acceptable salt thereof, wherein X=O; Ring A is 2,6-pyrazindiyl optionally substituted on an available carbon atom by one or two substituents independently selected from linear (1-3C)alkyl; Ring B is 1,4-phenylene (optionally substituted on an available carbon atom by one or two fluoro substituents); n is 0 and Y_1 is a direct bond between Ring B and Ring C; p is 1 and R^{A1} and R^{A2} are each hydrogen; L is a direct bond and Z is carboxy or a tetrazole group.

In another embodiment there is provided a compound of formula (I), or a pharmaceutically-acceptable salt thereof, wherein X=O; Ring A is 2,6-pyrazindiyl

optionally substituted on an available carbon atom by one or two methyl substituents; Ring B is 1,4-phenylene (optionally substituted on an available carbon atom by one or two fluoro substituents); n is 0 and Y_1 is a direct bond between Ring B and Ring C; p is 1 and R^{A1} and R^{A2} are each hydrogen; L is a direct bond and Z is carboxy or a tetrazole group.

In another embodiment there is provided a compound of formula (I), or a pharmaceutically-acceptable salt thereof, wherein X=O; Ring A is 2,6-pyrazindiyl optionally substituted on an available carbon atom by one or two methyl substituents; Ring B is 1,4-phenylene; n is 0 and Y_1 is a direct bond between Ring B and Ring C; p is 1 and R^{A1} and R^{A2} are each hydrogen; L is a direct bond and Z is carboxy or a tetrazole group.

In another embodiment there is provided a compound of formula (I), or a pharmaceutically-acceptable salt thereof, wherein X=O; Ring A is 2,6-pyrazindiyl optionally substituted on an available carbon atom by one or two methyl substituents; Ring B is 1,4-phenylene; n is 0 and Y_1 is a direct bond between Ring B and Ring C; p is 1 and R^{A1} and R^{A2} are each hydrogen; L is a direct bond and Z is carboxy.

In another embodiment there is provided a compound of formula (I), wherein X=O; Ring A is 2,6-pyrazindiyl optionally substituted on an available carbon atom by one or two methyl substituents; Ring B is 1,4-phenylene; n is 0 and Y_1 is a direct bond between Ring B and Ring C; p is 1 and R^{A1} and R^{A2} are each hydrogen; L is a direct bond and Z is carboxy.

In another embodiment there is provided a compound of formula (I) as defined in any of the seven embodiments immediately above, wherein the Z containing group and the $-Y_1-$ link are in either a cis- or a trans- arrangement across the ring, in relation to each other.

In another embodiment there is provided a compound of formula (I) as defined in any of the eight embodiments immediately above wherein a pro-drug for Z as carboxy is a (1-6C)alkyl ester.

A further feature is any of the scopes defined herein with the proviso that specific Examples, such as Example 1, 2, 3, 4 etc. are individually disclaimed.

Further particular 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 particular compounds of the Examples or a pharmaceutically-acceptable salt thereof (such as, for example, a sodium, magnesium, *tert*-butylammonium,

tris(hydroxymethyl)methylammonium, triethanolammonium, diethanolammonium, ethanolammonium, methylethanolammonium, diethylammonium or nicotinamide salt).

For example, a further feature is any of the particular compounds of the Examples or a pharmaceutically-acceptable salt thereof, such as any compound selected from

{trans-4-[4-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl] cyclohexyl}acetic acid;

3,5-Dimethyl-6-[4-(trans-4-{2-[(methylsulfonyl)amino]-2-oxoethyl}cyclohexyl)-phenyl]pyrazine-2-carboxamide;

6-{4-[trans-4-(2-Amino-2-oxoethyl)cyclohexyl]phenyl}-3,5-dimethylpyrazine-2-carboxamide;

N-({trans-4-[4-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl] cyclohexyl}acetyl)-2-methylalanine;

6-{4-[trans-4-(2-Hydroxyethyl)cyclohexyl]phenyl}-3,5-dimethyl pyrazine-2-carboxamide;

(trans-4-{4-[6-Carbamoyl-5-(difluoromethyl)-3-methylpyrazin-2-yl]phenyl}cyclohexyl)acetic acid;

{trans-4-[4-(6-Carbamoyl-3-ethyl-5-methylpyrazin-2-yl)phenyl]cyclohexyl}acetic acid;

{trans-4-[4-(6-Carbamoyl-5-ethyl-3-methylpyrazin-2-yl)phenyl]cyclohexyl}acetic acid;

{trans-4-[4-(6-Carbamoyl-3-methylpyrazin-2-yl)phenyl]cyclohexyl} acetic acid;

2-((1r,4s)-5'-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-4-yl)acetic acid;

(1r,4s)-5'-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-4-carboxylic acid;

2-((1r,4r)-4-(4-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)-2-methylpropanoic acid

2-(1-(4-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)pyrrolidin-3-yl)acetic acid;

(1R,5S,6r)-3-(4-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid;

6-(4-((1r,4r)-4-((1H-Tetrazol-5-yl)methyl)cyclohexyl)phenyl)-3,5-dimethylpyrazine-2-carboxamide;

4'-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)biphenyl-4-carboxylic acid;

Methyl *trans*-4-{4-[6-(aminocarbonyl)-3-methylpyrazin-2-yl]phenyl}-cyclohexanecarboxylate;

trans-4-{4-[6-(Aminocarbonyl)-3-methylpyrazin-2-yl]phenyl}cyclo-hexanecarboxylic acid; or a pharmaceutically-acceptable salt of any of these.

In a further aspect, the present invention also comprises any particular isomers of compounds of the Examples, such as the cis- isomer of compounds such as Examples 1 or 2, i.e. {cis-4-[4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl]cyclohexyl}acetic acid or 3,5-dimethyl-6-[4-(cis-4-{2-[(methylsulfonyl)amino]-2-oxoethylcyclohexyl)phenyl]-pyrazine-2-carboxamide or a pharmaceutically-acceptable salt of either of these; or compounds such as 6-{4-[cis-4-(2-Amino-2-oxoethyl)cyclohexyl]phenyl}-3,5-dimethylpyrazine-2-carboxamide;

N-({cis-4-[4-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl] cyclohexyl}acetyl)-2-methylalanine;

6-{4-[cis-4-(2-Hydroxyethyl)cyclohexyl]phenyl}-3,5-dimethyl pyrazine-2-carboxamide;

(cis-4-{4-[6-Carbamoyl-5-(difluoromethyl)-3-methylpyrazin-2-yl]phenyl}cyclohexyl)acetic acid;

{cis-4-[4-(6-Carbamoyl-3-ethyl-5-methylpyrazin-2-yl)phenyl] cyclohexyl}acetic acid;

{cis-4-[4-(6-Carbamoyl-5-ethyl-3-methylpyrazin-2-yl)phenyl] cyclohexyl}acetic acid;

{cis-4-[4-(6-Carbamoyl-3-methylpyrazin-2-yl)phenyl]cyclohexyl} acetic acid; or a pharmaceutically-acceptable salt of any of these.

A compound of formula (I) and its salts may be prepared by any process known to be applicable to the preparation of chemically related compounds. Such processes, when used to prepare a compound of the formula (I), or a pharmaceutically-acceptable salt thereof, are provided as a further feature of the invention.

In a further aspect the present invention also provides that the compounds of the formula (I) and salts thereof, can be prepared by the following processes, the processes of the Examples and analogous processes (wherein all variables are as hereinbefore defined for a compound of formula (I) unless otherwise stated) and thereafter if necessary any protecting groups can be removed and/or an appropriate salt formed. Any defined carboxylic acid groups may be replaced as appropriate by a mimic or bioisostere thereof.

Variables shown in the schemes are defined or can be interpreted in the context of the variants described herein for the compounds of the invention. Analogous chemistry to that shown in the schemes and Examples may be used to prepare other ring variants and linking group options within the scope of the invention.

Also included as an aspect of the invention are the compounds obtainable by any of the processes or Examples described herein.

Process a)

By modifying a substituent in, or introducing a substituent into, another compound of formula (I). Suitable methods for converting substituents into other substituents are known in the art. For example, an acid group may be converted into an amide group or reduced to an alcohol group.

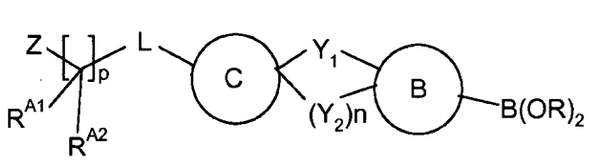
An amide in Ring A may be converted into a thioamide by use of Lawesson's reagent or P_2S_5.

Compounds of formula (I) where, for example, Z is an acylsulfonamide group or Z is a tetrazole may be prepared from the corresponding carboxylic acid. The tetrazole may be introduced early in the synthetic route via an amide (which, for primary amides, may be converted to the nitrile by standard methods) which is then in turn converted into a tetrazole by reaction with azide. The tetrazole may be carried through the rest of the synthesis in protected form, e.g. N-benzylated or N-(2-cyanoethyl)ated.

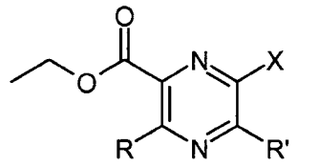
Process b)

Suzuki coupling of an appropriate iodo-, bromo- or chloro-substituted Ring A derivative (e.g. pyrazine ester (III)) with a suitably substituted intermediate boronate compound of formula (II) followed by conversion of the ring A ester group to the corresponding acid by basic hydrolysis and thence to the corresponding primary carboxamide by reaction with ammonia in the presence of a coupling agent, for example PyBOP.

A protecting group can be removed, for example, by acid catalysed hydrolysis of a tert-butyl ester to give a compound of formula (I) where Z = CO_2H.



(II)



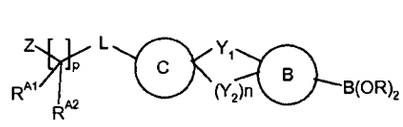
X = Cl or Br

(III)

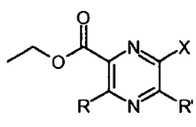
R and R' may represent any of the variables defined herein at such positions.

Analogous chemistry may be used to prepare other Ring A derivatives (e.g. pyridine compounds).

Alternatively a Suzuki coupling of an appropriate iodo-, bromo- or chloro-pyrazine amide (IV), particularly bromo- or chloro-pyrazine amide (IV), can be used followed by removal of the protecting group by basic hydrolysis of a methyl or ethyl ester.

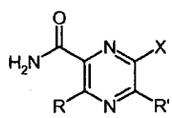


(II)



(III)

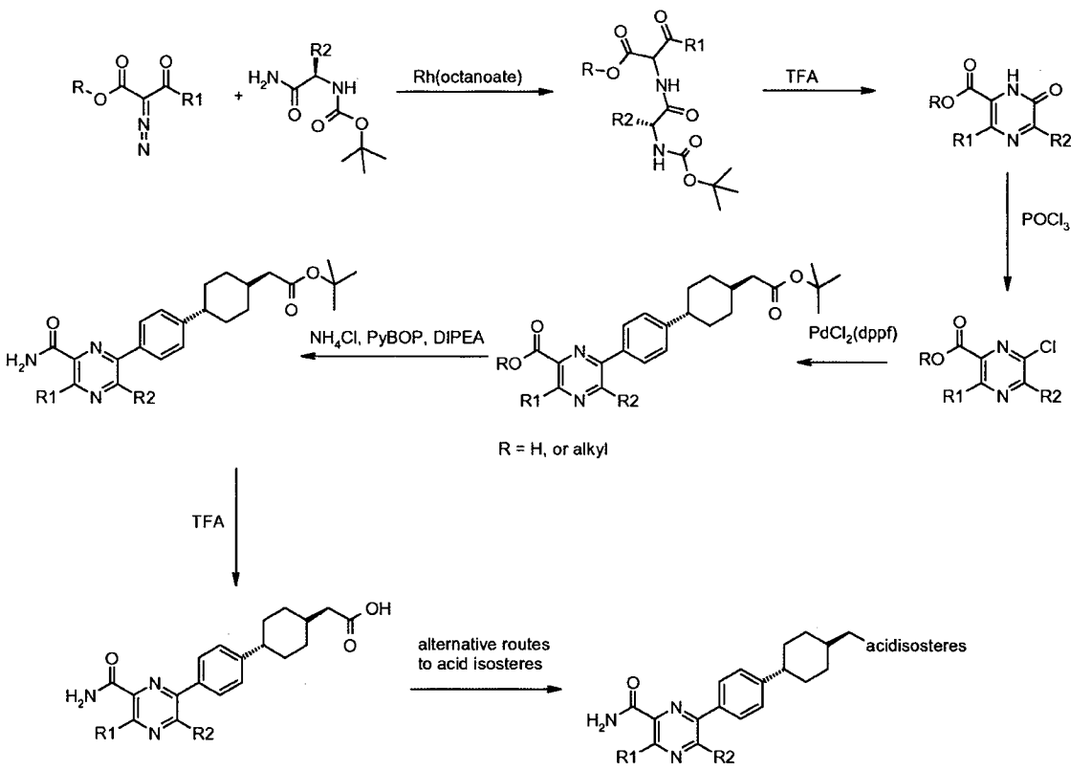
X = Cl or Br



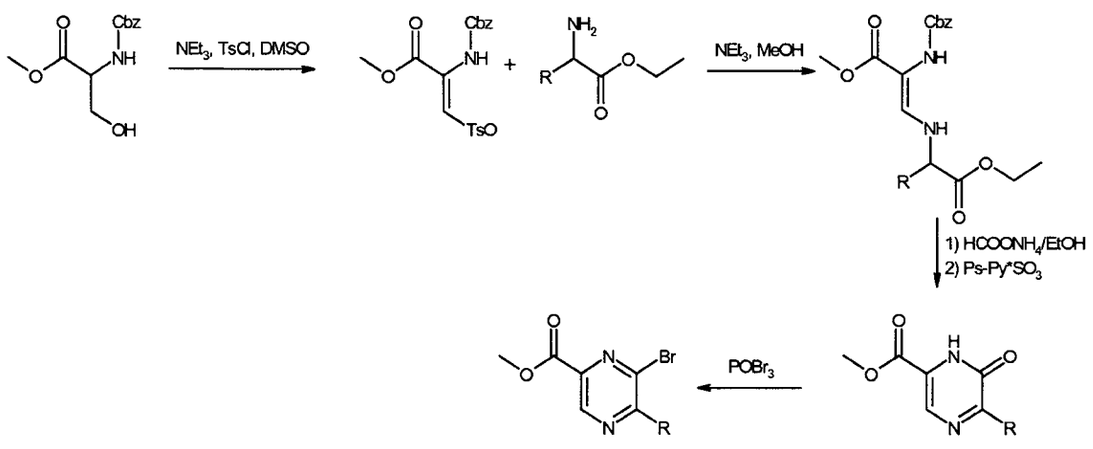
(IV)

Preparation of formula (III) compound types (Ring A)

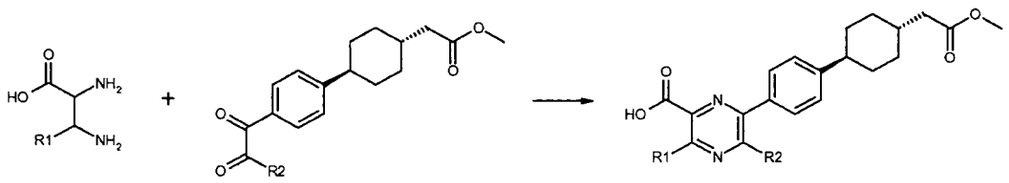
The following schemes illustrate how certain Ring A variants may be prepared. Variables shown in the schemes are defined or can be interpreted in the context of the variants described herein for the compounds of the invention. Analogous chemistry to that shown in the schemes and Examples may be used to prepare other Ring variants and linking group options within the scope of the invention.



Scheme A1: Reaction scheme for dimethylpyrazine and derivatives

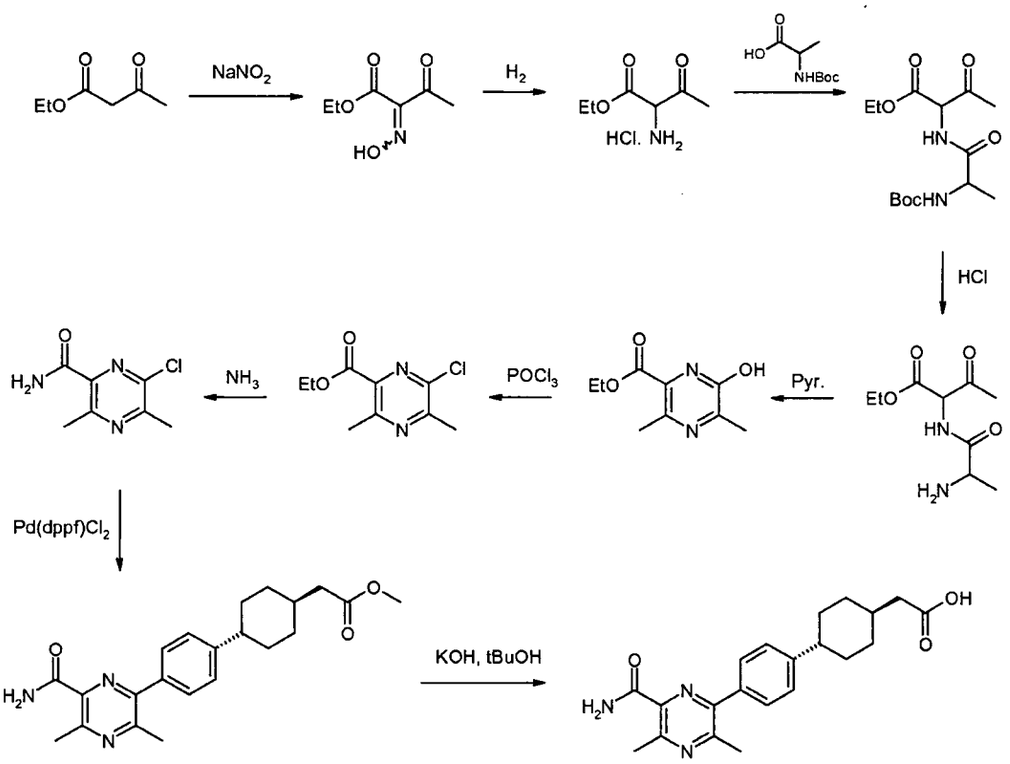


Scheme A2: Reaction scheme for mono-methylpyrazine and derivatives



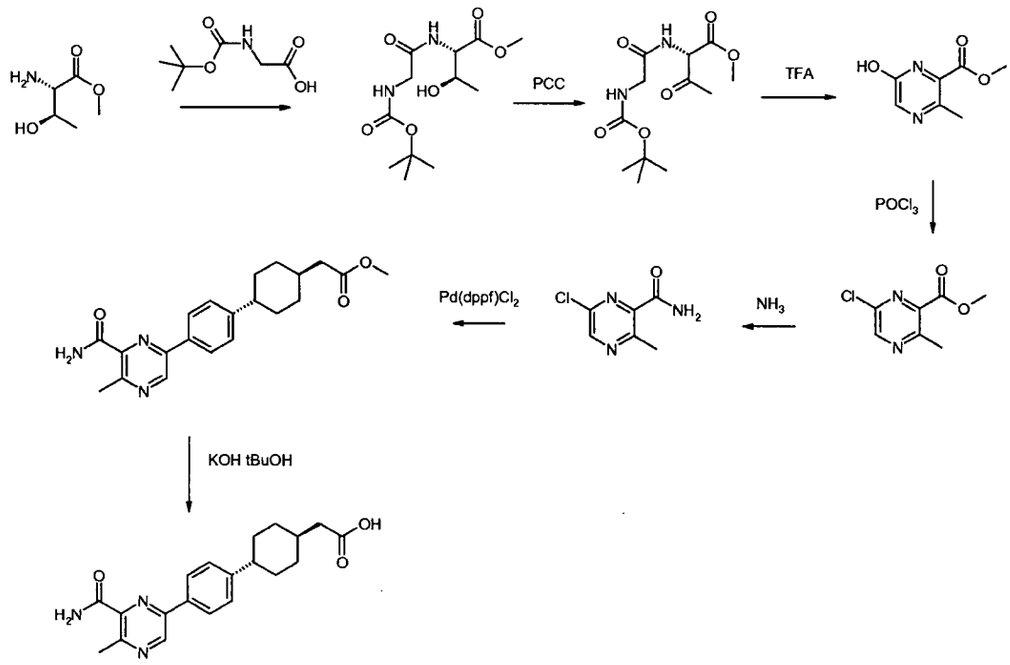
Scheme A3: Reaction scheme for condensation procedure

Preparation of formula (III) and (IV) compound types (Ring A)



Scheme A4: Reaction scheme for dimethypyrazine and derivatives

Analogues of pyrazine can be prepared using the procedure described by C. Christensen, C.W. Tornoe and M. Meldal, *QSAR & Combinatorial Science*, 2004, **23**, (2-3), 109-116, for example, 3-methylpyrazine…

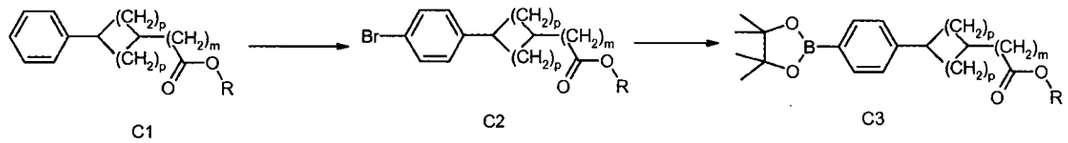


Scheme A5: Reaction scheme for 3 mono-methylpyrazine and derivatives

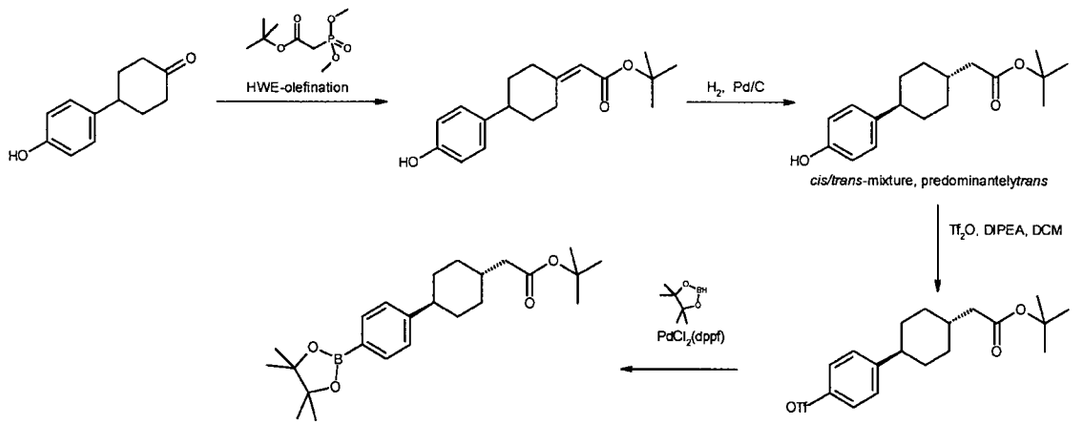
Preparation of formula (II) compound types (Ring C and Ring B)

The following schemes illustrate how certain Ring C and Ring B variants may be prepared. Variables shown in the schemes are defined or can be interpreted in the context of the variants described herein for the compounds of the invention. Analogous chemistry to that shown in the schemes and Examples may be used to prepare other ring variants and linking group options within the scope of the invention.

(i) Compounds of formula (II) in which Ring C is cyclohexane (p is 2 in structure C1) and Ring B is phenyl are described in the literature or can be made by analogy. These may be brominated to (C2) and then converted into the boronate esters (C3) using standard procedures. Alternative leaving groups to bromo in (C2) are iodo and triflate (see Scheme C1-B).



Scheme C1-A: Reaction scheme for cyclohexane variants

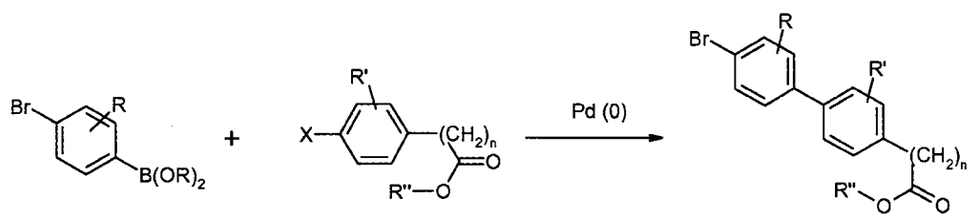


Scheme C1-B: Reaction scheme for synthesis of boronic acid ester intermediate

Scheme C1-B methyl ester has been described in WO 2004/047755.

Compounds in which a bromo-heteroaryl compound is required may not be directly obtainable via the unsubstituted heteroaryl compound. The bromo group, or other suitable alternative, may be introduced at an earlier stage in the synthetic route.

(ii) For compounds of formula (II) in which Ring C is phenyl and Ring B is phenyl many appropriate intermediates are in the literature, or can be made by analogy, and introduction of various substitution patterns may be achieved through biaryl Suzuki coupling:



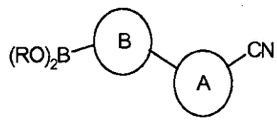
Scheme C2: Reaction scheme for biaryl variants

In Scheme C2, R and R' are any of the claimed aromatic substituents which are compatible with the reaction conditions, X is a suitable leaving group such as bromo, iodo or triflate. The bromobiaryl is then converted into the corresponding boronate derivative by standard methods.

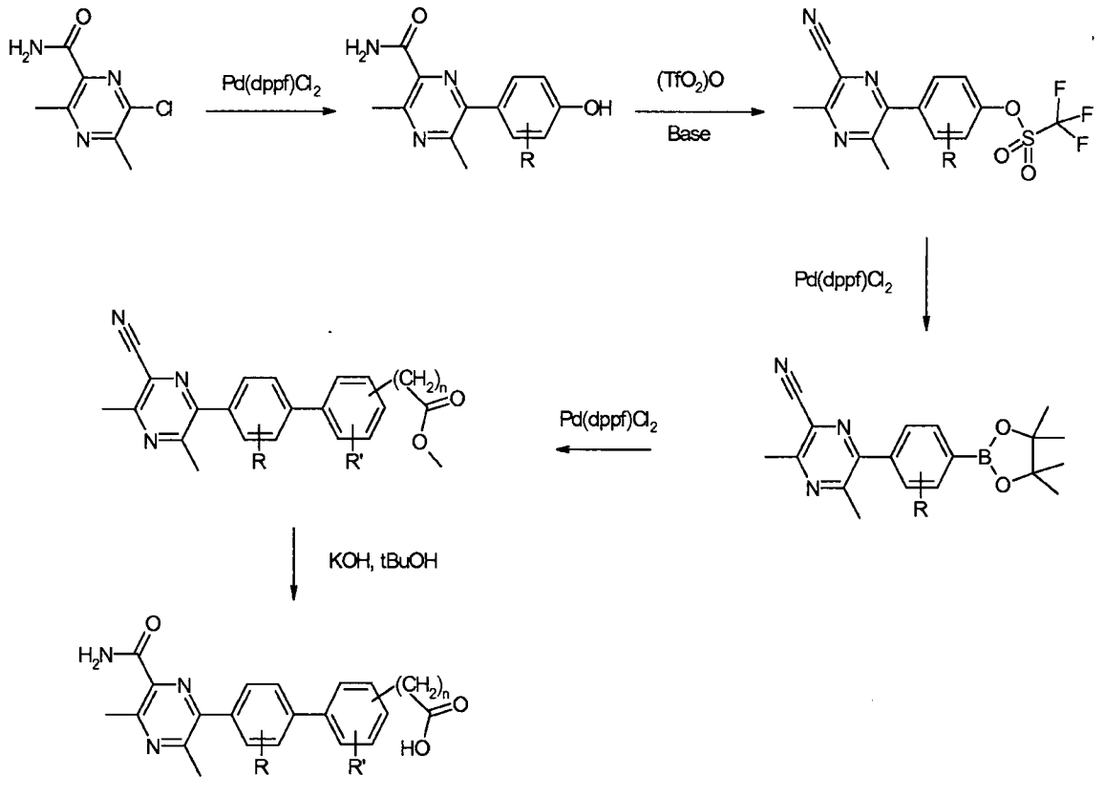
For both Scheme C1 and C2, introduction of α-alkyl and dialkyl groups is possible at the intermediate C1 or C2 stage through standard alkylation methodology, for example by deprotonation α-to the ester group using a lithium base such as LDA followed by quenching with an appropriate alkyl halide.

Preparation of formula (V) compound types (Ring A and Ring B)

(i) In an alternative sequence of Suzuki couplings a cyanoheterocyclylphenylboronic ester of type V is generated as a key intermediate, as illustrated by the scheme below. This intermediate is then used in further coupling reactions to generate biaryl compounds of the formula I.



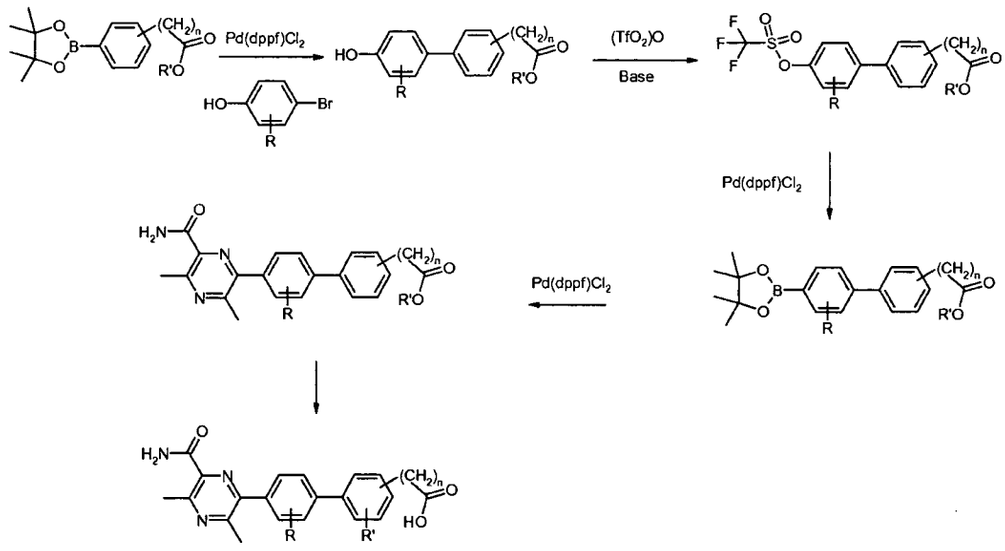
(V)



Scheme C2-A: Reaction scheme for biaryl variants

In Scheme C2, R and R' are any of the claimed aromatic substituents which are compatible with the reaction conditions. The phenol is converted into the corresponding triflate with trifluoromethanesulfonic anhydride and a suitable base, such as triethylamine, which also results in dehydration of the amide to the nitrile. The aryltriflate is converted to the corresponding boronate derivative followed by subsequent Suzuki reaction under standard methods with a suitable palladium catalyst, such as 1,1'-bis(diphenylphosphino)-

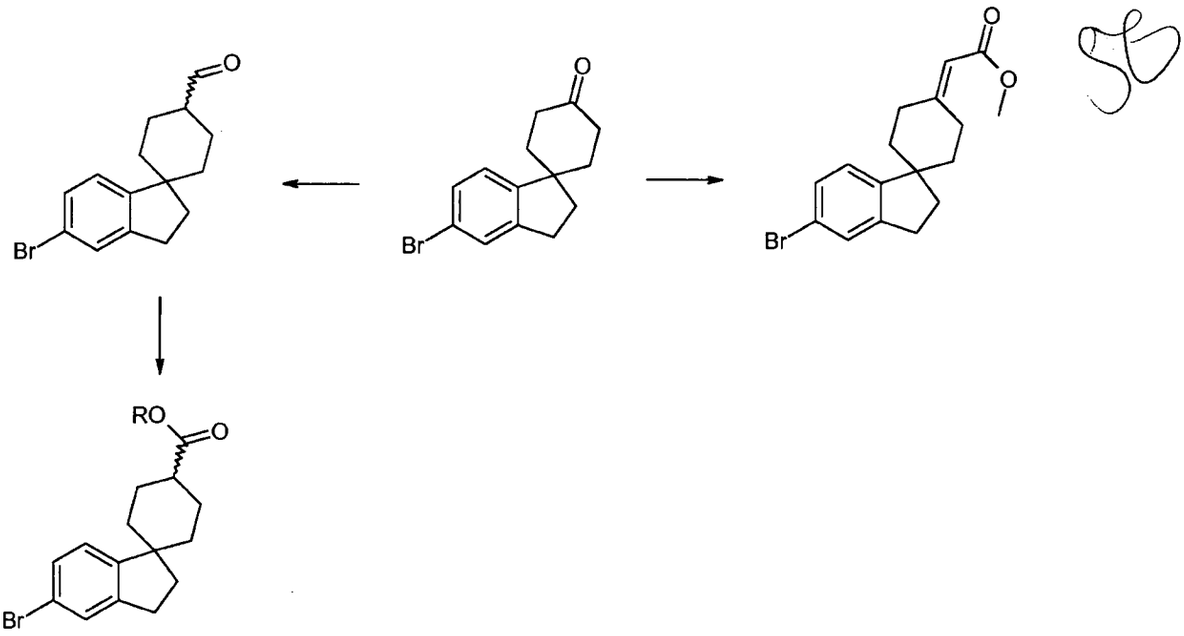
ferrocenedichloropalladium(II). Base hydrolysis, for example with potassium hydroxide in tert-butanol results in hydrolysis of the ester and nitrile.



Scheme C2-B: Reaction scheme for biaryl variants

In Scheme C2-B, R and R' are any of the claimed aromatic substituents which are compatible with the reaction conditions.

(ii) Spirocyclic compounds of formula (II) may be prepared by analogy with preparations involving the intermediates in Scheme C4 below (see WO 2004/047755 – relevant sections of which are hereby incorporated by reference).

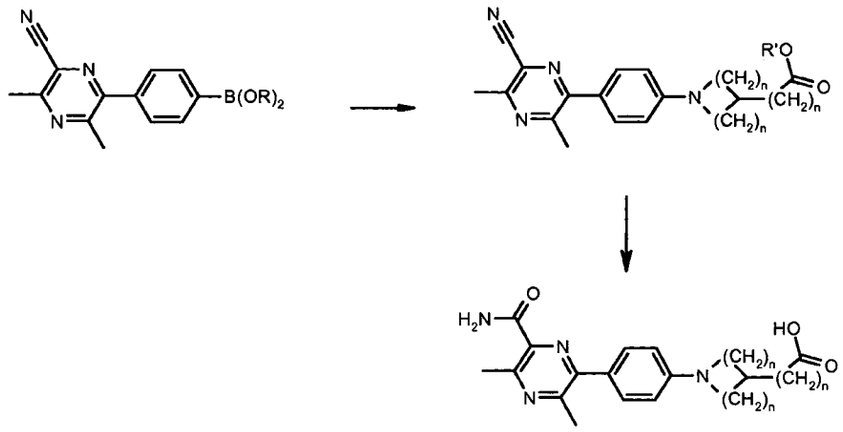


Scheme C4: Reaction scheme for spirocyclic compounds

The double bond may be reduced at a suitable stage in the synthesis and the resultant cis- and trans- isomers separated chromatographically. As above, this route may proceed by conversion of the bromo into the boronate for coupling to the appropriate Ring A (e.g. pyrazine) compound.

The cyclohexanone may be converted to the unsaturated ketone and the double bond reduced at a suitable stage in the synthesis and the cis- and trans- isomers separated chromatographically. Alternatively the cyclohexane may be converted to the aldehyde which can be oxidised to the acid, for example with oxone and the acid converted to an ester, for example a tert-butyl and the cis- and trans- isomers separated chromatographically. As above, this route may proceed by conversion of the bromo into the boronate for coupling to the appropriate Ring A (e.g. pyrazine) compound.

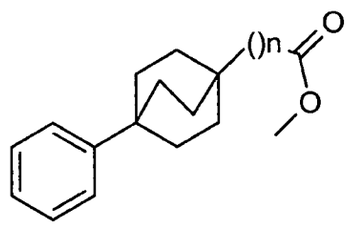
For compounds of the formula (V) in which Ring B is Phenyl and Ring C is a cyclic amine, introduction of the amine maybe achieved through transition metal coupling.



Scheme C5: Reaction scheme for cyclic amine variants

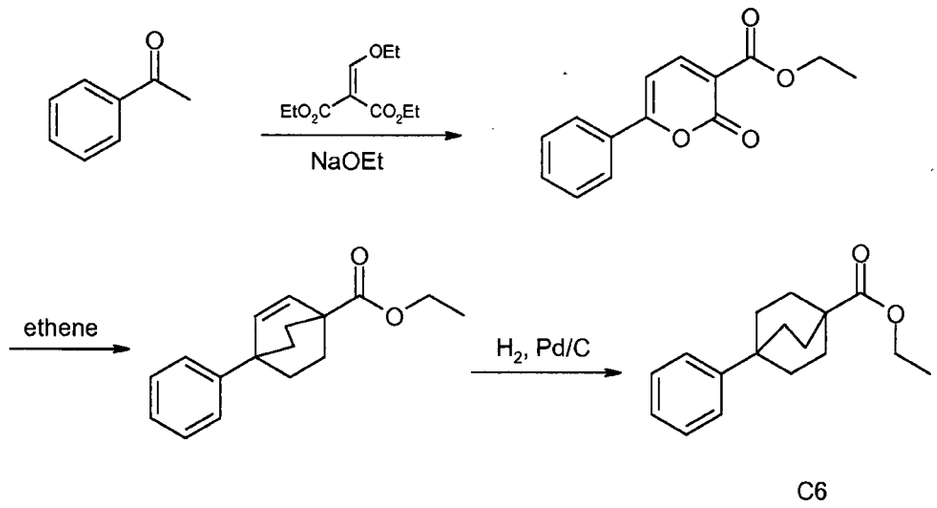
In Scheme C5 the amines may be introduced using boronic acids or esters using copper acetate as in the procedure described by D. M. T. Chan, K. L Monaco, R. Li, D. Bonne, C. G. Clark, P. Y. S Lam, *Tet. Lett.*, 2003, **44**(19), 3863-3865.

(iii) Bicyclooctane derivatives of formula (II) may be prepared by analogy with preparations involving the phenyl Intermediate C5 below (see WO 2007/071966 – relevant sections of which are hereby incorporated by reference), which is brominated and converted into the boronate for coupling to the appropriate Ring A (e.g. pyrazine) compound.



Intermediate C5

Compounds of formula C5 may be made as their ester derivative according to the process shown below in Scheme C3, or analogously thereto.

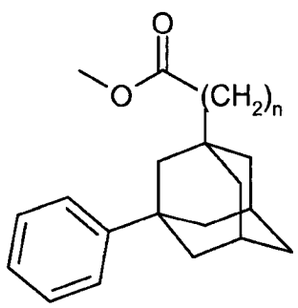


Scheme C3 : Bicyclooctane variants

Compounds such as C6 may be homologated by standard procedures such as reduction of the ester to the corresponding alcohol, conversion of this to a leaving group such as tosylate, displacing this with cyanide followed by hydrolysis and esterification, all by standard methods, to compounds such as C5 wherein n = 1.

Compounds in which Ring C is other than bicyclo[2.2.2]octane-1,4-diyl may be prepared by analogous processes.

Adamantyl derivatives of formula (II) may be prepared by analogy with preparations involving the phenyl Intermediate C7 below (see WO 2007/071966 – relevant sections are hereby incorporated by reference), which is iodinated and converted to the boronate for coupling to the appropriate Ring A (e.g. pyrazine).



Intermediate C7

If not commercially available, the necessary starting materials for the procedures such as those described above may be made by procedures which are selected from standard organic chemical techniques, techniques which are analogous to the synthesis of known, structurally similar compounds, techniques which are described or illustrated in the references given above, or techniques which are analogous to the above described procedure or the procedures described in the examples. The reader is further referred to Advanced Organic Chemistry, 5th Edition, by Jerry March and Michael Smith, published by John Wiley & Sons 2001, for general guidance on reaction conditions and reagents.

It will be appreciated that some intermediates to compounds of the formula (I) are also novel and these are provided as separate independent aspects of the invention. In particular, certain compounds of formula (IV) may form a further independent aspect of the invention. Furthermore, ester derivatives of compounds of formula (I) form a further aspect of the invention.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in compounds. The instances where protection is necessary or desirable are known to those skilled in the art, as are suitable methods for such protection. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Greene, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991).

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.

Thus, if reactants include, for example, groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

Examples of a suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, a silyl group such as trimethylsilyl or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively a silyl

group such as trimethylsilyl or SEM may be removed, for example, by fluoride or by aqueous acid; or an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation in the presence of a catalyst such as palladium-on-carbon.

A suitable protecting group for an amino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or tert-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulfuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine or 2-hydroxyethylamine, or with hydrazine.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

Resins may also be used as a protecting group.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art, or they may be removed during a later reaction step or work-up.

The skilled organic chemist will be able to use and adapt the information contained and referenced within the above references, and accompanying Examples therein and also the examples herein, to obtain necessary starting materials, and products.

The removal of any protecting groups and the formation of a pharmaceutically-acceptable salt are within the skill of an ordinary organic chemist using standard techniques. Furthermore, details on the these steps has been provided hereinbefore.

When an optically active form of a compound of the invention is required, it may be obtained by carrying out one of the above procedures using an optically active starting material (formed, for example, by asymmetric induction of a suitable reaction step), or by resolution of a racemic form of the compound or intermediate using a standard procedure, or by chromatographic separation of diastereoisomers (when produced). Enzymatic techniques may also be useful for the preparation of optically active compounds and/or intermediates.

Similarly, when a pure regioisomer of a compound of the invention is required, it may be obtained by carrying out one of the above procedures using a pure regioisomer as a starting material, or by resolution of a mixture of the regioisomers or intermediates using a standard procedure.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), (IA) or (IB) as defined hereinbefore or a pharmaceutically-acceptable salt thereof, in association with a pharmaceutically-acceptable excipient or carrier.

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).

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.

According to a further aspect of the present invention there is provided a compound of formula (I), (IA) and/or (IB), or a pharmaceutically acceptable salt, or a pro-drug thereof as defined hereinbefore for use in a method of treatment of the human or animal body by therapy.

We have found that compounds of the present invention inhibit DGAT1 activity and are therefore of interest for their blood glucose-lowering effects.

A further feature of the present invention is a compound of formula (I), (IA) and/or (IB), or a pharmaceutically-acceptable salt, or a pro-drug thereof for use as a medicament.

Conveniently this is a compound of formula (I), (IA) and/or (IB), or a pharmaceutically-acceptable salt, or a pro-drug thereof, for (use as a medicament for) producing an inhibition of DGAT1 activity in a warm-blooded animal such as a human being.

Particularly this is a compound of formula (I), (IA) and/or (IB), or a pharmaceutically-acceptable salt, or a pro-drug thereof, for (use as a medicament for) treating diabetes mellitus and/or obesity in a warm-blooded animal such as a human being.

Thus according to a further aspect of the invention there is provided the use of a compound of formula (I), (IA) and/or (IB), or a pharmaceutically-acceptable salt, or a pro-

drug thereof in the manufacture of a medicament for use in the production of an inhibition of DGAT1 activity in a warm-blooded animal such as a human being.

Thus according to a further aspect of the invention there is provided the use of a compound of formula (I), (IA) and/or (IB), or a pharmaceutically-acceptable salt, or a pro-drug thereof in the manufacture of a medicament for use in the treatment of diabetes mellitus and/or obesity in a warm-blooded animal such as a human being.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), (IA) and/or (IB) as defined hereinbefore, or a pharmaceutically-acceptable salt, or a pro-drug thereof, in association with a pharmaceutically-acceptable excipient or carrier for use in producing an inhibition of DGAT1 activity in an warm-blooded animal, such as a human being.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), (IA) and/or (IB) as defined hereinbefore, or a pharmaceutically-acceptable salt, or a pro-drug thereof, in association with a pharmaceutically-acceptable excipient or carrier for use in the treatment of diabetes mellitus and/or obesity in an warm-blooded animal, such as a human being.

According to a further feature of the invention there is provided a method for producing an inhibition of DGAT1 activity in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), (IA) and/or (IB), or a pharmaceutically-acceptable salt, or a pro-drug thereof as defined hereinbefore.

According to a further feature of the invention there is provided a method of treating diabetes mellitus and/or obesity in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), (IA) and/or (IB), or a pharmaceutically-acceptable salt, or a pro-drug thereof as defined hereinbefore.

As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular disease state will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. Preferably a daily dose in the range of 1-50 mg/kg is employed. In another embodiment a daily dose is in the range of 0.01-50 mg/kg, particularly 0.01-10 mg/kg, 0.01-1 mg/kg or 0.01-0.1mg/kg. However the daily dose will necessarily be varied depending upon the host treated, the

particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

As stated above compounds defined in the present invention are of interest for their ability to inhibit the activity of DGAT1. A compound of the invention may therefore be useful for the prevention, delay or treatment of a range of disease states including diabetes mellitus, more specifically type 2 diabetes mellitus (T2DM) and complications arising there from (for example retinopathy, neuropathy and nephropathy), impaired glucose tolerance (IGT), conditions of impaired fasting glucose, metabolic acidosis, ketosis, dysmetabolic syndrome, arthritis, osteoporosis, obesity and obesity related disorders, (which include peripheral vascular disease, (including intermittent claudication), cardiac failure and certain cardiac myopathies, myocardial ischaemia, cerebral ischaemia and reperfusion, hyperlipidaemias, atherosclerosis, infertility and polycystic ovary syndrome); the compounds of the invention may also be useful for muscle weakness, diseases of the skin such as acne, various immunomodulatory diseases (such as psoriasis), HIV infection, inflammatory bowel syndrome and inflammatory bowel disease such as Crohn's disease and ulcerative colitis.

In particular, the compounds of the present invention are of interest for the prevention, delay or treatment of diabetes mellitus and/or obesity and/or obesity related disorders. In one aspect, the compounds of the invention are used for prevention, delay or treatment of diabetes mellitus. In another aspect, the compounds of the invention are used for prevention, delay or treatment of obesity. In a further aspect, the compounds of the invention are used for prevention, delay or treatment of obesity related disorders.

The inhibition of DGAT1 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. 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 such conjoint treatment may be beneficial in the treatment of metabolic syndrome [defined as abdominal obesity (as measured by waist circumference against ethnic and gender specific cut-points) plus any <u>two</u> of the following: hypertriglyceridemia (> 150 mg/dl; 1.7mmol/l); low HDLc (<40 mg/dl or <1.03mmol/l for men and <50 mg/dl or 1.29

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mmol/l for women) or on treatment for low HDL (high density lipoprotein); hypertension (SBP ≥ 130 mmHg DBP ≥ 85 mmHg) or on treatment for hypertension; and hyperglycemia (fasting plasma glucose ≥ 100 mg/dl or 5.6 mmol/l or impaired glucose tolerance or pre-existing diabetes mellitus) - International Diabetes Federation & input from IAS/NCEP].

Such conjoint treatments may include the following main categories:

1) Anti-obesity therapies such as those that cause weight loss by effects on food intake, nutrient absorption or energy expenditure, such as orlistat, sibutramine and the like.

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, 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, glucokinase activators);

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);

8) Agents designed to treat the complications of prolonged hyperglycaemia (for example aldose reductase inhibitors);

9) Anti- dyslipidaemia agents such as, HMG-CoA reductase inhibitors (eg statins); PPAR α-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);

10) 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);

11) 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;

12) Agents which antagonise the actions of glucagon; and

13) Anti-inflammatory agents, such as non-steroidal anti-inflammatory drugs (eg. aspirin) and steroidal anti-inflammatory agents (eg. cortisone).

In addition to their use in therapeutic medicine, compounds of formula (I) and their pharmaceutically-acceptable salts are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of DGAT1 activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative, particular and preferred embodiments of the compounds of the invention described herein also apply. The alternative, particular and preferred embodiments of the invention described herein also apply to a compound of formula (I), or a pharmaceutically-acceptable salt, or a pro-drug thereof.

As indicated above, all of the compounds, and their corresponding pharmaceutically-acceptable salts, are useful in inhibiting DGAT1. The ability of the compounds of formula (I), and their corresponding pharmaceutically-acceptable (acid addition) salts, to inhibit DGAT1 may be demonstrated employing the following enzyme assay:

Human Enzyme Assay

See, for example, International Application WO 2005/044250.

The *in vitro* assay to identify DGAT1 inhibitors uses human DGAT1 expressed in insect cell membranes as the enzyme source (Proc. Natl. Acad. Sci. 1998, 95, 13018-13023). Briefly, sf9 cells were infected with recombinant baculovirus containing human DGAT1 coding sequences and harvested after 48 h. Cells were lysed by sonication and membranes isolated by centrifuging at 28000 rpm for 1 h at 4 °C on a 41% sucrose gradient. The membrane fraction at the interphase was collected, washed, and stored in liquid nitrogen.

DGAT1 activity was assayed by a modification of the method described by Coleman (Methods in Enzymology 1992, 209, 98-102). Compound at 0.0000256μM (or 0.003μM) - 33 μM (final conc.) (typically 10 μM) was incubated with 4 μg/ml (final conc)

membrane protein, 5 mM $MgCl_2$, and 100μM 1,2 dioleoyl-*sn*-glycerol (dissolved in acetone with a final assay conc. of acetone of 1.8%; other acetone concentrations may be used as appropriate, for example 10%) in a total assay volume of 200 μl in a 96 well plate. The reaction was started by adding ^{14}C oleoyl coenzyme A (30μM final concentration) and incubated at room temperature for 30 minutes. The reaction was stopped by adding 200 μl 2-propanol:heptane 7:1. Radioactive triolein product was separated into the organic phase by adding 300μl heptane and 100μl 0.1 M carbonate buffer pH 9.5. DGAT1 activity was quantified by counting aliquots of the upper heptane layer by liquid scintillography.

Using this assay the compounds generally show activity with an IC_{50} around or below 10 μM, preferably below 10 μM (i.e. IC_{50} <10 μM), preferably < 1 μM, more preferably <0.1 μM, particularly, <0.05 μM, and more particularly <0.01 μM. Stated figures are usually a mean of a number of measurements (usually 2 measurements) according to standard practice.

In some cases % inhibition data may have been provided at a particular concentration (10 μM).

Example 1 showed an IC_{50} = 0.016μM (using an assay acetone concentration of 1.8%) and 0.079μM (using an assay acetone concentration of 10%).

Examples 2 to 20 showed respectively IC_{50} = 0.071μM; 0.023μM; 0.042μM; 0.018μM; 5.71μM; 5.09μM; 0.233μM; 0.674μM; 1.34μM; 0.102μM; 0.025μM; 0.428μM; 0.159μM; 0.157μM; 1.23μM; 0.418μM; 2.85μM; 1.55μM and 6.31μM.

Examples 21 to 54 showed respectively IC_{50} = 0.27μM; 0.067μM; 0.096μM; 1μM; 0.1μM; 1.5μM; 0.31μM; 0.038μM; 0.1μM; 0.032μM; 0.17μM; 0.27μM; 1.3μM; 3μM; 0.96μM; Example 36 = 46-67% inhibition at 10μM; Example 37 = 47-50% inhibition at 10μM; 2.4μM; 3μM; 1.2μM; 0.95μM; 0.21μM; 0.066μM; 0.093μM; 0.035μM; 0.047μM; 0.056μM; 4.4μM; 0.57μM; 0.6μM; 3.4μM; 4.6μM; 4.6μM; 1.3μM.

Examples 55 to 64 showed respectively IC_{50} = 7μM; Example 56 = 15-31% inhibition at 10μM; 6.7μM; (Example 58 – no data); 0.12μM; 0.09μM; 0.15μM; 8μM; 0.18μM; 0.67μM.

Example 65 showed an IC_{50} = 7.8μM and Example 66 an IC_{50} = 0.88μM.

Example 67 showed IC_{50} = 0.18μM; Example 68 = 25% inhibition at 10μM.

Examples 69 and 70 showed respectively IC_{50} = 0.4μM and IC_{50} = 4.9μM.

The ability of the compounds of formula (I), and their corresponding pharmaceutically-acceptable (acid) salts, to inhibit DGAT1 may further be demonstrated employing the following whole cell assay.

Measurement of Triglyceride Synthesis in HuTu 80 Cells

HuTu80 cells were cultured to confluency in 6 well plates in minimum essential media containing foetal calf serum. For the experiment, the medium was changed to serum-free medium and the cells pre-incubated with compound solubilised in DMSO (final concentration 0.1%) for 30 minutes. De novo lipogenesis was measured by the addition of 0.12 mM sodium oleate plus 1 μCi/mL ^{14}C-sodium oleate complexed to 0.03mM BSA to each well for a further 2 h. The cells were washed in phosphate buffered saline and solubilised in 1% sodium dodecyl sulfate. An aliquot was removed for protein determination using a protein estimation kit (Perbio) based on the method of Lowry (J. Biol. Chem., 1951, 193, 265-275). The lipids were extracted into the organic phase using a heptane:propan-2-ol:water (80:20:2) mixture followed by aliquots of water and heptane according to the method of Coleman (Methods in Enzymology, 1992, 209, 98-104). The organic phase was collected and the solvent evaporated under a stream of nitrogen. The extracts solubilised in iso-hexane:acetic acid (99:1) and lipids separated *via* normal phase high performance liquid chromatography (HPLC) using a Lichrospher diol-5, 4 × 250 mm column and a gradient solvent system of iso-hexane:acetic acid (99:1) and iso-hexane:propan-2-ol:acetic acid (85:15:1), flow rate of 1 mL/minute according to the method of Silversand and Haux (1997). Incorporation of radiolabel into the triglyceride fraction was analysed using a Radiomatic Flo-one Detector (Packard) connected to the HPLC machine.

Examples

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 generally 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;

(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 with flash chromatography purifications run on Biotage SP1 or SP4 instruments using Biotage Silica columns;

(vii) mass spectra were recorded on a Finnigan LCQ Duo ion trap mass spectrometer equipped with an electrospray interface (LC-MS) or LC-MS system consisting of a Waters ZQ using a LC-Agilent 1100 LC system;

(viii) ^{1}H NMR measurements were performed on a Varian Mercury VXR 300 and 400 spectrometer, operating at a 1H frequency of 300 and 400 and Varian UNITY plus 400, 500 and 600 spectrometers, operating at 1H frequencies of 400, 500 and 600 respectively. Chemical shifts are given in ppm with the solvent as internal standard. Protons on heteroatoms such as NH and OH protons are only reported when detected in NMR and can therefore be missing.

(ix) HPLC separations were performed on a Waters YMC-ODS AQS-3 120 Angstrom 3 x 500 mm or on a Waters Delta Prep Systems using Kromasil C8, 10 μm columns. Acidic HPLC was carried out using gradients of mobilephase A: 100 % ACN and mobilephase B: 5 % ACN + 95 % H_2O + 0.2 % FA. Neutral HPLC was carried out using

gradients of mobilephase A: 100 % ACN and mobilephase B: 5 % ACN + 95 % 0.1 M NH_4OAc.

(x) Reactions performed in a microwave oven were run in a Biotage Initiator Instrument.

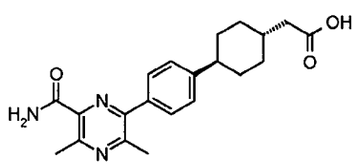
(xi) A number of chemical nomenclature software packages, such as ACDName; ACDLabs Name: Release 9:00, product version 9.04 and Struc=Name/CambridgeSoft ELN, have been used in the naming of compounds.

List of abbreviations herein:

ACN	Acetonitrile
aq	Aqueous
Boc	tert-butyloxycarbonyl
Brine	Saturated solution of sodium chloride in water
BSA	Bovine Serum Albumine
DCE	1,2-dichloroethane
DCM	Dichloromethane
DEE	Diethylether
DIPEA	N,N-Diisopropylethylamine
DMAP	Dimethylaminopyridine
DMF	N,N-dimethylformamide
DMSO	Dimethylsulphoxide
Dppf	1,1'-bis(Diphenylphosphino)ferrocene
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
EDTA	Ethylenediaminetetraacetic acid
EtOAc	Ethyl acetate
EtOH	Ethanol
FA	Formic acid
HOAc	Acetic acid
HPLC	High-performance liquid chromatography
HWE	Horner-Wadsworth-Emmons
Hz	Hertz

IPA	Isopropylalcohol
iPr	isopropyl
LC	Liquid chromatography
m-CPBA	meta-chloroperoxybenzoicacid
MeOH	Methanol
MHz	Megahertz
mL	Millilitre
MS	Mass spectra
NMM	N-methylmorpholine
NMP	N-methylpiperazine
NMR	Nuclear magnetic resonance
OAc	acetate
Ph	Phenyl
PyBOP	Benzotriazol-1-yl-oxytri-pyrrolidinophosphonium hexafluorophosphate
PyBROP	Bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
RT	Room temperature
sat	saturated
TEA	Triethylamine
Tf	trifluoromethylsulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofurane
TLC	Thin layer chromatography
Ts	p-toluenesulfonyl

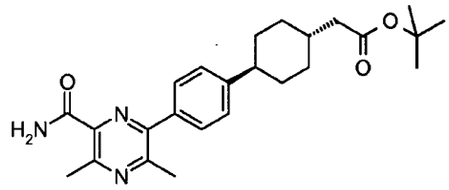
Example 1: {trans-4-[4-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl] cyclohexyl}acetic acid



To a solution of **Intermediate 1-1** (363 mg, 0.86 mmol) in DCM (30 mL) was added TFA (3 mL) dropwise. The colorless solution gradually turned into pale yellow clear solution. The reaction mixture was stirred under N_2 at RT overnight. The solvent was evaporated to give the title compound (100 %).

^{1}H NMR (600 MHz, CD_3OD) δ 1.22 (q, 2H), 1.59 (q, 2H), 1.85 (s, 1H), 1.94 (d, 4H), 2.23 (d, 2H), 2.58 (t, 1H), 2.62 (s, 3H), 2.84 (s, 3H), 7.37 (d, 2H), 7.58 (d, 2H); *m/z* 368 $(M+H)^+$.

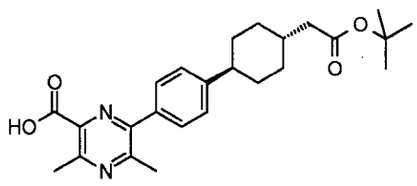
Intermediate 1-1: tert-Butyl {trans-4-[4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl]cyclohexyl}acetate



To a solution of PyBOP (717 mg, 1.38 mmol) and NH_4Cl (196.6 mg, 3.68 mmol) in DMF (50 mL) was added Intermediate 1-2 (390.0 mg, 0.92 mmol) and finally DIPEA (0.80 mL, 4.59 mmol) to initiate the reaction. The solution was stirred for 5 h at RT. The reaction was quenched by the addition of sat Na_2CO_3 and extracted with toluene (3×100 mL). The combined organics were washed with brine and water, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography using EtOAc (20-60 %) in petroleum ether. Evaporation of pure product fractions gave title compound (376 mg, 96 %) as white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (q, 2H), 1.47(s, 9H), 1.50-1.64 (m, 2H), 1.80-2.00 (m, 5H), 2.17 (d, 2H), 2.56 (t, 1H), 2.67 (t, 3H), 2.98 (t, 3H), 5.43 (s, 1H), 7.33 (d, 2H), 7.52 (d, 2H), 7.81 (d, 2H); *m/z* 424 $(M+H)^+$.

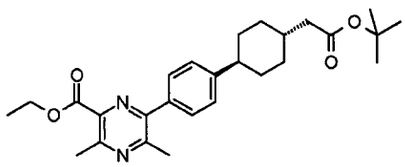
Intermediate 1-2: 6-{4-[trans-4-(2-tert-Butoxy-2-oxoethyl)cyclohexyl]phenyl}-3,5-dimethylpyrazine-2-carboxylic acid



To a solution of **Intermediate 1-3** (0.530 g, 1.17 mmol) in THF (10 mL) was added LiOH (1M, 15 mL). The reaction was stirred at room temperature for 5 h. THF was removed under vacuum and the aqueous residue was acidified with 1M HCl and extracted with EtOAc. The organic layer was dried through a phase separator and concentrated to give the title compound (0.5 g, 100 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12-1.21 (m, 2H), 1.45 (s, 9H), 1.49-1.57 (m, 2H), 1.79-1.96 (m, 5H), 2.15 (d, 2H), 2.51-2.57 (m, 1H), 2.70 (s, 3H), 2.97 (s, 3H), 7.33 (d, 2H), 7.48 (d, 2H); *m/z 425* $(M+H)^+$.

Intermediate 1-3: Ethyl 6-{4-[trans-4-(2-tert-butoxy-2-oxoethyl)cyclohexyl] phenyl}-3,5-dimethylpyrazine-2-carboxylate



To a solution of **Intermediate 1-4** (0.580 g, 2.70 mmol) in DME (22 mL), EtOH (12 mL) and water (5 mL) was added **Intermediate D** (see after Intermediate 1-7; 1.244 g, 3.11 mmol), potassium phosphate, tribasic (0.688 g, 3.24 mmol) and $PdCl_2$(dppf) (0.119 g, 0.16 mmol). The solutions degassed with nitrogen for 10 min and then heated in the microwave oven at 140 °C for 20 min. Additional amounts of **Intermediate D** and $PdCl_2$(dppf) was added to drive the reaction. The microwave heating was continued at 140 °C for an additional 30 min.

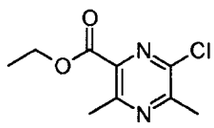
(The ethyl ester can be hydrolyzed here by prolonging the heating time and adding 3 extra equivalents of potassium phosphate, to give **Intermediate 1-2**.)

The mixtures were combined, filtered through a glass filter funnel and evaporated. The remaining black residue was dissolved in EtOAc, washed with 0.5M HCl and extracted

with 2×EtOAc. The combined organics were dried through a phase separator and concentrated. The crude was purified by flash chromatography using EtOAc (0-50 %) in heptane as eluent. Evaporation gave title compound (1.063 g, 80%) as oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13-1.22 (m, 2H), 1.42 (t, 3H), 1.47 (s, 9H), 1.49-1.58 (m, 2H), 1.80-1.95 (m, 5H), 2.16 (d, 2H), 2.49-2.56 (m, 1H), 2.66 (s, 3H), 2.81 (s, 3H), 4.45 (q, 2H), 7.30 (d, 2H), 7.53 (d, 2H); *m/z* 453 $(M+H)^+$.

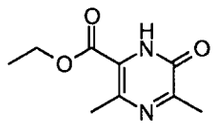
Intermediate 1-4: Ethyl 6-chloro-3,5-dimethylpyrazine-2-carboxylate



To a suspension of **Intermediate 1-5** (0.23 g, 1.17 mmol) in butyronitrile (4 mL) was added $POCl_3$ (0.27 mL, 2.93 mmol). The reaction was heated to 150 °C for 10 min in the microwave oven and cooled to RT. To the reaction mixture was added water (2 mL) and the phases were separated. The organic layer was concentrated under reduced pressure. The crude product was purified by flash chromatography using 0.5% HOAc in DCM as eluent to afford the title compound (0.18 g, 73 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (t, 3H), 2.68 (s, 3H), 2.78 (s, 3H), 4.46 (q, 2H); *m/z* 215 $(M+H)^+$.

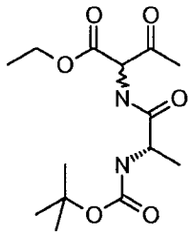
Intermediate 1-5: Ethyl 3,5-dimethyl-6-oxo-1,6-dihydropyrazine-2-carboxylate



To a solution of **Intermediate 1-6** (800 mg, 2.53 mmol) in dry DCE (40 mL) was added TFA (1.95 mL, 25.3 mmol). The reaction mixture was heated to reflux for 4 h. The solvent was evaporated and the crude product was purified by flash chromatography using EtOAc (20-80 %) in heptane as eluent. Concentration of pure fractions gave title compound (160 mg, 32 %) as white-yellow powder. The crude from this reaction can optionally be used directly in the next step without purification.

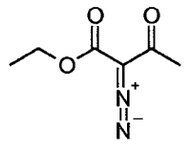
^{1}H NMR (400 Mhz, $CDCl_3$) δ 4.42 (q, 2H), 2.61 (s, 3H), 2.52 (s, 3H), 1.41 (t, 3H); *m/z* 197 $(M+H)^+$.

Intermediate 1-6: Ethyl 2-{[N-(tert-butoxycarbonyl)-L-alanyl]amino}-3-oxobutanoate



Intermediate 1-7 (500 mg, 3.2 mmol) and BOC-Ala-NH_2 (843.8 mg, 4.5 mmol, CAS 85642-13-3) were added to a round bottomed flask, sealed and backfilled with argon. Dry toluene (30 mL) was added via syringe and the resulting heterogeneous mixture was stirred at 90 °C for 10 min to get a homogeneous solution. Meanwhile, the rhodium (II) octanoate dimer (62.3 mg, 0.080 mmol, CAS 73482-96-9) was dissolved in toluene (5 mL) and put on an ultrasound bath for 5 min, to get a fine Rh-dispersion. This dispersion was then added dropwise to the reaction mixture at 80 °C (a violent N_2 effervescence was observed). After stirring another 20 min at elevated temperature the reaction mixture was concentrated under reduced pressure to give a black pasty solid. The N-H insertion product could here be purified or taken directly to the next step. The crude was purified by flash chromatography using EtOAc (20-80 %) in heptane to afford the title compound (850 mg, 84 %) (diastereomeric mixture) as a yellow oil. *m/z* 317 $(M+H)^+$.

Intermediate 1-7: Ethyl 2-diazo-3-oxobutanoate



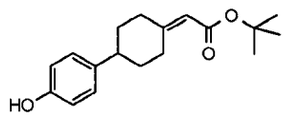
Polymer-bound tosylazide (11 g, 15.4 mmol) (typical loading 1,4 mmol/g, prepared according to Merz et al *J. Org. Chem.* **2001,** *66,* 2509-2511) was swollen in dry DCM (40 mL). Ethyl acetoacetate (1.0 g, 7.7 mmol, CAS 141-97-9) and TEA (3.2 mL, 23.1 mmol) were dissolved in DCM (10 mL) and added to the polymer containing solution. The resulting mixture was then shaken at RT under nitrogen until the reaction was judged completed by TLC, typically 6 h. The supernatant was filtered off, then the resin was washed with DCM (3×30 mL) to rinse out residual product. The reaction mixture was then evaporated to dryness to afford the title compound (1.1 g, 92 %) as yellow oil.

^{1}H NMR (400MHz, $CDCl_3$) δ 4.28 (q, 2H), 2.45 (s, 3H), 1.33 (t, 3H).

Typically these intermediates were not characterized due to their high-energetic properties (Clark et al, *Thermochimica Acta*, 386, **2002**, 73-79), but carried through to the next step as crude products.

Preparation of Intermediate D:

Intermediate A: tert-Butyl [4-(4-hydroxyphenyl)cyclohexylidene]acetate



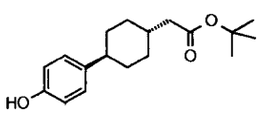
To an ice-cold solution of 4-(4-hydroxy-phenyl)-cyclohexanone (15.22 g, 78.4 mmol, CAS 105640-07-1) in THF (375 mL) under N_2 was added NaH in mineral oil (3.28 g, 79.3 mmol) to give a thick suspension.

In a separate flask NaH in mineral oil (4.06 g, 98.0 mmol) was suspended in dry THF (375 mL) under N_2. The suspension was cooled to 0 °C and tert-butyl P,P-dimethyl phosphonoacetate (16.82 mL, 82.32 mmol, CAS 62327-21-3) was added carefully.

Both mixtures were stirred for ~15 min before the ice-baths were removed. After 2 h at RT the ketone solution was transferred to the ylide solution via syringe. The combined mixture was stirred under N_2 overnight. The reaction was quenched by the addition of water (~100 mL) and THF was then removed under vacuum. More water was added (150 mL) and the aqueous solution was extracted with EtOAc (3×200 mL). The combined organic layer was washed with brine (2×200 mL) and dried through a phase separator. Concentration gave product as colorless oil (24.6 g, 99 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51 (s, 9H), 1.55-1.65 (m, 2H), 1.97-2.07 (m, 3H), 2.29-2.40 (m, 2H), 2.70-2.78 (m, 1H), 3.90-3.96 (m, 1H), 4.60 (s, 1H), 5.62 (s, 1H), 6.77 (d, 2H), 7.09 (d, 2H). *m/z* 287 $(M-H)^-$.

Intermediate B: tert-Butyl [trans-4-(4-hydroxyphenyl)cyclohexyl]acetate

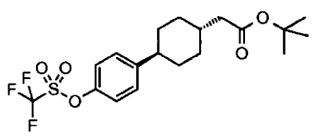


To a solution of **Intermediate A** (4.2 g, 14.56 mmol) in EtOAc (120 mL) was added 10 % Pd/C (390 mg). The reaction was hydrogenated for 3 h (5 Bar). The catalyst was filtered

off through Celite and the organic filtrate was washed with water, dried through a phase separator and concentrated to a colorless oil (4.02 g of cis:trans mixture). The crude mixture was purified by chiral HPLC (neutral) using a Chiralpak AD (250×50 mm) column and 100 % ACN as mobile phase. Purification gave pure trans phenol (2.88 g, 68 %) as white solid and also pure cis phenol. NMR analysis of both isomers confirmed that the wanted (major) isomer was trans.

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10-1.20 (m, 2H), 1.42-1.52 (m, 2H), 1.48 (s, 9H), 1.77-1.92 (m, 5H), 2.17 (d, 2H), 2.38-2.45 (m, 1H), 4.7-4.9 (m, 1H), 6.78 (d, 2H), 7.09 (d, 2H); *m/z* 289 $(M-H)^-$.

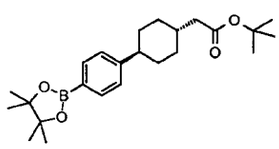
Intermediate C: tert-Butyl [trans-4-(4-{[(trifluoromethyl)sulfonyl]oxy}phenyl) cyclohexyl]acetate



To a solution of **Intermediate B** (2.86 g, 9.85 mmol) in DCM (75 mL) was added pyridine (1.59 mL, 19.7 mmol). The solution was cooled on an ice-bath and trifluoromethanesulfonic anhydride (1.99 mL, 11.82 mmol, CAS 358-23-6) was added dropwise. The ice-bath was removed and the reaction was stirred for 10 min. The reaction was quenched with 1M HCl, diluted with DCM and washed with saturated $NaHCO_3$ and brine. The organic layer was dried through a phase separator and concentrated. The crude product was filtered through silica using 8 % EtOAc in heptane as eluent. Concentration of pure product fractions gave title compound (4.06 g, 98 %) as white crystalline solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12-1.22 (m, 2H), 1.45-1.54 (m, 2H), 1.48 (s, 9H), 1.79-1.88 (m, 1H), 1.89-1.95 (m, 4H), 2.17 (d, 2H), 2.48-2.56 (m, 1H), 7.20 (d, 2H), 7.28 (d, 2H); *m/z* 421 $(M-H)^-$.

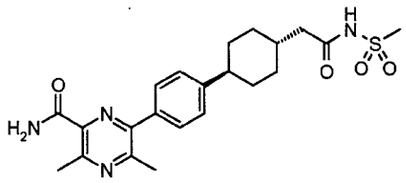
Intermediate D: tert-Butyl {trans-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]cyclohexyl}acetate



To a suspension of $PdCl_2(dppf)$ (0.93 g, 1.27 mmol, CAS 72287-26-4) in dioxane (135 mL) under N_2 was added **Intermediate C** (17.9 g, 42.4 mmol), TEA (17.7 mL, 127 mmol) and finally a 1M solution of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane in THF (72 mL, 72 mmol, CAS 25015-63-8). The mixture was refluxed for 7 h, cooled to 10 °C and quenched carefully with H_2O. The aqueous solution was extracted with 2×DCM and the combined organics were dried through a phase separator and concentrated to a black oil. Flash chromatography using 6 % EtOAc in heptane as eluent gave title compound (12.1 g, 71 %) as white powder.

^1H NMR (500 MHz, $CDCl_3$) δ 1.12-1.22 (m, 2H), 1.36 (s, 12H), 1.49 (s, 9H), 1.48-1.61 (m, 2H), 1.80-1.95 (m, 5H), 2.17 (d, 2H), 2.46-2.54 (m, 1H), 7.25 (d, 2H), 7.78 (d, 2H). *m/z* no ionization.

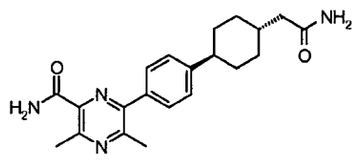
Example 2: 3,5-Dimethyl-6-[4-(trans-4-{2-[(methylsulfonyl)amino]-2-oxoethyl}cyclohexyl)phenyl]pyrazine-2-carboxamide



To a solution of **Example 1** (30 mg, 0.082 mmol) in DCM was added DMAP (2 mg, 0.02 mmol), TEA (16 μL, 0.122 mmol), EDCl (20 mg, 0.11 mmol) and finally methanesulfonamide (11 mg, 0.11 mmol, CAS 3144-09-0). The solution was stirred at RT overnight. The crude was concentrated and purified by HPLC (acidic). Evaporation and co-evaporation with toluene gave title compound (22 mg, 60 %).

^1H NMR (500 MHz, $CDCl_3$) δ 1.08-1.18 (m, 2H), 1.45-1.56 (m, 2H), 1.76-1.86 (m, 5H), 2.20 (d, 2H), 2.42-2.52 (m, 1H), 2.57 (s, 3H), 2.72 (s, 3H), 3.22 (s, 3H), 7.35 (d, 2H), 7.59 (s, 1H), 7.64 (d, 2H), 7.99 (s, 1H), 11.67 (s, 1H); *m/z* 445 $(M+H)^+$.

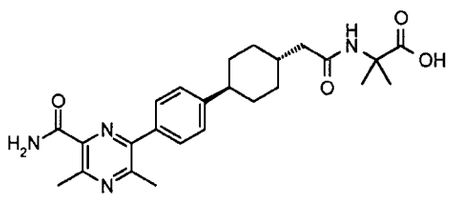
Example 3: 6-{4-[trans-4-(2-Amino-2-oxoethyl)cyclohexyl]phenyl}-3,5-dimethylpyrazine-2-carboxamide



This compound was synthesised from **Example 1** using similar conditions as described in **Intermediate 1-1** to afford title compound (40 mg, 38 %) as white solid.

^{1}H NMR (500 MHz, DMSO) δ 1.05-1.15 (m, 2H), 1.43-1.53 (m, 2H), 1.69-1.86 (m, 5H), 1.97 (d, 2H), 2.47-2.55 (m, 1H), 2.58 (s, 3H), 2.72 (s, 3H), 6.71 (s, 1H), 7.24 (s, 1H), 7.35 (d, 2H), 7.59 (s, 1H), 7.64 (d, 2H), 7.99 (s, 1H); *m/z* 367 $(M+H)^+$.

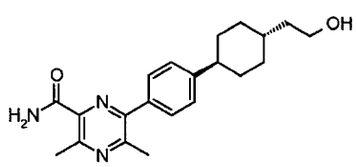
Example 4: N-({trans-4-[4-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl] cyclohexyl}acetyl)-2-methylalanine



This compound was synthesised from **Example 1** and alpha-aminoisobutyric acid methyl ester hydrochloride (CAS 15028-41-8) using similar conditions as in **Intermediate 1-1**. The intermediate methyl ester was hydrolysed to the corresponding acid using similar protocol as described in **Intermediate 1-2**.

^{1}H NMR (500 MHz, DMSO) δ 1.04-1.14 (m, 2H), 1.31 (s, 6H), 1.43-1.53 (m, 2H), 1.67-1.75 (m, 1H), 1.77-1.85 (m, 4H), 1.96 (d, 2H), 2.48-2.56 (m, 1H), 2.57 (s, 3H), 2.72 (s, 3H), 7.35 (d, 2H), 7.59 (br s, 1H), 7.64 (d, 2H), 7.77-7.82 (m, 1H), 8.00 (br s, 1H); *m/z* 453 $(M+H)^+$.

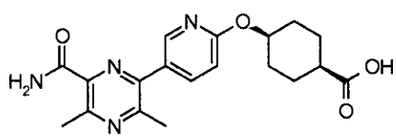
Example 5: 6-{4-[trans-4-(2-Hydroxyethyl)cyclohexyl]phenyl}-3,5-dimethyl pyrazine-2-carboxamide



To a suspension of **Example 1** (50 mg, 0.14 mmol) and NMM (71 µL, 0.64 mmol) in THF (1 mL) at 0 °C was added a solution of ethyl chloroformate (61 µL, 0.64 mmol) in THF (0.5 mL). The reaction was stirred at 0 °C for ~ 3 h, but additional equivalents of NMM and ethyl chloroformate were needed during this time to drive the reaction. The reaction mixture was added dropwise to a solution of $NaBH_4$ in water at 0-5 °C and the combined mixture was stirred for 30 min. The mixture was partitioned between EtOAc and 1M HCl and the organic layer was washed with water, dried through a phase separator and concentrated. The crude was dissolved in DMSO and purified by HPLC (neutral). Freeze-drying of pure fractions gave the title compound (8 mg, 17 %) as white powder.

^{1}H NMR (500 MHz, DMSO) δ 1.02-1.14 (m, 2H), 1.34-1.54 (m, 5H), 1.80-1.87 (m, 4H), 2.47-2.57 (m, 1H), 2.58 (s, 3H), 2.73 (s, 3H), 3.43-3.51 (m, 2H), 4.30-4.35 (m, 1H), 7.35 (d, 2H), 7.60 (br s, 1H), 7.65 (d, 2H), 7.99 (br s, 1H) ; *m/z* 354 $(M+H)^+$.

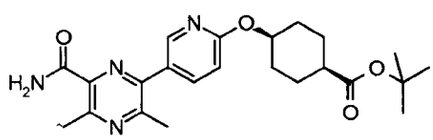
Example 6: cis-4-{[5-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)pyridin-2-yl]oxy} cyclohexanecarboxylic acid



A solution of **Intermediate 6-1** (0.0243 g, 0.06 mmol) in 10 mL of a 4.0 M solution of HCl in 1.4-dioxane and a few drops of water was stirred at 40 °C for 5 h. The solvent was evaporated and the remaining solid was purified by HPLC (acidic) to afford the title compound (8.7 mg, 42 %) as a dry film.

^{1}H NMR (500 MHz, CD_3OD) δ 1.72-1.83 (m, 4H), 1.90-2.07 (m, 4H), 2.47 (m, 1H), 2.67 (s, 3H), 2.85 (s, 3H), 5.27 (s, 1H), 6.92 (d, 1H), 8.03 (dd, 1H), 8.45 (s, 1H); *m/z* 371 $(M+H)^+$.

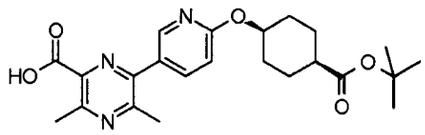
Intermediate 6-1: tert-Butyl cis-4-{[5-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)pyridin-2-yl]oxy}cyclohexanecarboxylate



This compound was synthesised from **Intermediate 6-2** using similar procedure as described in **Intermediate 1-1**. Purification gave title product (24.3 mg, 68 %) as white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45 (s, 9H), 1.67-1.79 (m, 4H), 1.85-2.07 (m, 4H), 2.34 (m, 1H), 2.68 (s, 3H), 2.96 (s, 3H), 5.28 (s, 1H), 5.77 (s, 1H), 6.84 (d, 1H), 7.76 (s, 1H), 7.82 (dd, 1H), 8.39 (s, 1H); *m/z* 427 $(M+H)^+$.

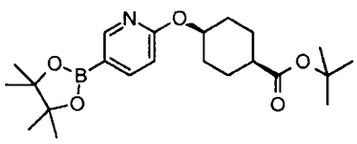
Intermediate 6-2: 6-(6-{[cis-4-(tert-Butoxycarbonyl)cyclohexyl]oxy}pyridin-3-yl)-3,5-dimethylpyrazine-2-carboxylic acid



This compound was synthesised from **Intermediate 6-3** and **Intermediate 1-4** using similar Suzuki conditions as in **Intermediate 1-3** to afford the title compound (36 mg, 45 %) as white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.67-1.79 (m, 4H), 1.84-2.05 (m, 4H), 2.34 (m, 1H), 2.72 (s, 3H), 2.97 (s, 3H), 5.27 (s, 1H), 6.85 (d, 1H), 7.80 (d, 1H), 8.37 (s, 1H); *m/z* 428 $(M+H)^+$.

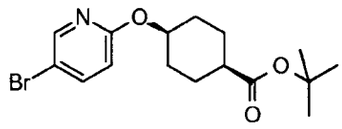
Intermediate 6-3: tert-Butyl cis-4-{[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]oxy}cyclohexanecarboxylate



Intermediate 6-4 (0.124 g, 0.35 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.121 g, 0.48 mmol, CAS 73183-34-3) and potassium acetate (0.139 g, 1.41 mmol) in 1,4-dioxane (10 mL) was degassed prior to addition of $PdCl_2$(dppf) (0.013 g, 0.02 mmol) under N_2. The reaction was heated at 85 °C for 16 h. The solvent was evaporated and the crude was dissolved in EtOAc, washed with water (2×25 mL), organics dried over Na_2SO_4, filtered and evaporated. The brownish oil was purified by flash chromatography using 5-50 % EtOAc in heptane to afford the title compound (74 mg, 52 %) as a dry film.

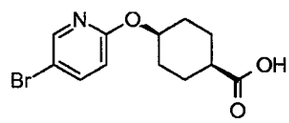
^{1}H NMR (500 MHz, CDCl3) δ 1.30 (s, 12H), 1.43 (s, 9H), 1.59-1.77 (m, 4H), 1.80-2.00 (m, 4H), 2.29 (m ,1H), 5.25 (m, 1H), 6.67 (d, 1H), 7.88 (dd, 1H), 8.48 (d, 1H).

Intermediate 6-4: tert-Butyl cis-4-[(5-bromopyridin-2-yl)oxy]cyclohexane carboxylate



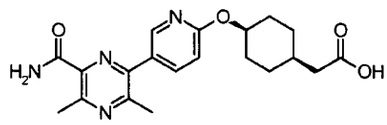
A solution of **Intermediate 6-5** (0.224 g, 0.75 mmol) in 1,1-di-tert-butoxy-N,N-dimethylmethaneamine (0.893 mL, 3.72 mmol, CAS 36805-97-7) were heated at 120 °C in a microwave oven for 45 min. The crude was purified by flash chromatography using EtOAc (5-70 %) in heptane to afford the title compound (124 mg, 46 %) as white solid.
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.58-1.75 (m, 4H), 1.82-2.00 (m, 4H), 2.3 (m, 1H), 5.13 (m, 1H), 6.61 (d, 1H), 7.59 (dd, 1H), 8.12 (d, 1H); *m/z* 357 $(M+H)^+$.

Intermediate 6-5: cis-4-[(5-Bromopyridin-2-yl)oxy]cyclohexanecarboxylic acid



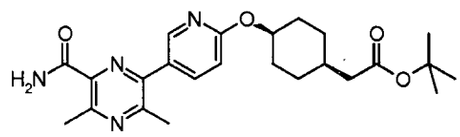
A solution of (1*S*,4*S*)-4-hydroxycyclohexanecarboxylic acid (2.14 g, 14.9 mmol) in DMA (10 mL) was added to a stirred suspension of NaH (1.32 g, 30.2 mmol) in DMA (15 mL) at 0 °C where it was stirred for 10 min. The suspension was taken off the cooling bath and 5-bromo-2-fluoropyridine (1.53 mL, 14.87 mmol, CAS 766-11-0) was added followed by DMA (10 mL). The reaction was heated at 100 °C for 2.5 h. The solvent was evaporated and DCM and 2M HCl were added, the phases separated and the aqueous phase was extracted with DCM (2x50 mL). The combined organics were dried over $MgSO_4$, filtered and evaporated. The remaining crude was purified by flash chromatography using 5-75 % EtOAc (1 % HOAc) in heptane to afford the title compound (1.86 g, 42 %) as solid.
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.70 (t, 2H), 1.75-1.86 (m, 2H), 1.90-2.06 (m, 4H), 2.49 (m, 1H), 5.18 (m, 1H), 6.64 (d, 1H), 7.62 (dd, 1H), 8.16 (d, 1H); *m/z* 301 $(M+H)^+$.

Example 7: (cis-4-{[5-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)pyridin-2-yl]oxy}cyclohexyl)acetic acid



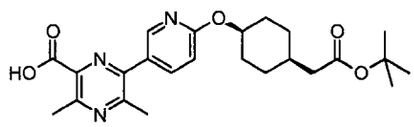
This compound was synthesised from **Intermediate 7-1** using similar conditions as described in **Example 1** to give the title compound (15 mg, 42 %) as white solid. ^{1}H NMR (500 MHz, CD_3OD) δ 1.51 (t, 2H), 1.61-1.75 (m, 4H), 1.91 (m, 1H), 2.05 (d, 2H), 2.25 (d, 2H), 2.66 (s, 3H), 2.84 (s, 3H), 5.29 (s, 1H), 6.91 (d, 1H), 8.02 (dd, 1H), 8.44 (s, 1H); *m/z* 385 $(M+H)^+$.

Intermediate 7-1: tert-Butyl (cis-4-{[5-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)pyridin-2-yl]oxy}cyclohexyl)acetate



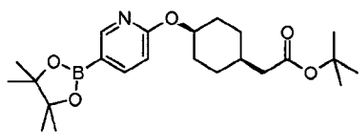
This compound was synthesised from **Intermediate 7-2** using similar conditions as described in **Intermediate 1-1** to afford the title compound (42 mg, 66 %) as white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39-1.50 (m, 11H), 1.55-1.69 (m, 4H), 1.87 (m, 1H), 2.02-2.06 (m, 2H), 2.16 (d, 2H), 2.66 (s, 3H), 2.93 (s, 3H), 5.29 (s, 1H), 6.40 (s, 1H), 6.80 (d, 1H), 7.75-7.82 (m, 2H), 8.37 (d, 1H); *m/z* 441 $(M+H)^+$.

Intermediate 7-2: 6-(6-{[cis-4-(2-tert-Butoxy-2-oxoethyl)cyclohexyl]oxy}pyridin-3-yl)-3,5-dimethylpyrazine-2-carboxylic acid



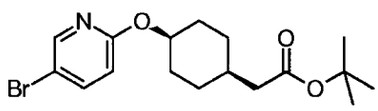
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.38-1.51 (m, 11H), 1.56-1.69 (m, 4H), 1.88 (m, 1H), 2.03 (d, 2H), 2.17 (d, 2H), 2.71 (s, 3H), 2.94 (s, 3H), 5.29 (s, 1H), 6.82 (d, 1H), 7.80 (d, 1H), 8.37 (s, 1H), 9.94 (s, 1H); *m/z* 442 $(M+H)^+$.

Intermediate 7-3: tert-Butyl (cis-4-{[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]oxy}cyclohexyl)acetate



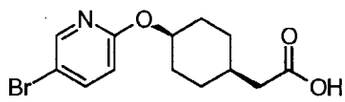
This compound was synthesised from **Intermediate 7-4** using similar conditions as described in **Intermediate 6-3** to afford the title compound (0.149 g, 43 %) as white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (s, 12H), 1.39-1.50 (m, 11H), 1.53-1.67 (m, 4H), 1.87 (m, 1H), 2.00 (d, 2H), 2.16 (d, 2H), 5.30 (s, 1H), 6.67 (d, 1H), 7.89 (dd, 1H), 8.50 (d, 1H).

Intermediate 7-4: tert-Butyl{cis-4-[(5-bromopyridin-2-yl)oxy]cyclohexyl}acetate



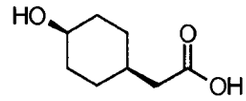
This compound was synthesised from **Intermediate 7-5** using similar conditions as described in **Intermediate 6-4** to afford the title compound (0.303 g, 43 %) as white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35-1.46 (m, 11H), 1.52-1.63 (m, 4H), 1.85 (m, 1H), 1.96 (d, 2H), 2.14 (d, 2H), 5.16 (s, 1H), 6.59 (d, 1H), 7.58 (dd, 1H), 8.13 (d, 1H); *m/z* 372 $(M+H)^+$.

Intermediate 7-5: {cis-4-[(5-Bromopyridin-2-yl)oxy]cyclohexyl}acetic acid



This compound was synthesised from **Intermediate 7-6** using similar conditions as described in **Intermediate 6-5** to afford the title compound (1.287 g, 68 %) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44-1.52 (m, 2H), 1.58-1.68 (m, 4H), 1.93 (m, 1H), 2.00 (d, 2H), 2.31 (d, 2H), 5.19 (s, 1H), 6.63 (d, 1H), 7.62 (dd, 1H), 8.16 (d, 1H); *m/z* 316 $(M+H)^+$.

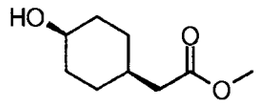
Intermediate 7-6: (cis-4-Hydroxycyclohexyl)acetic acid



This compound was synthesised from **Intermediate 7-7** using similar conditions as described in **Intermediate 1-2** to afford the title compound (0.943 g, 100 %) as white solid.

^{1}H NMR (500 MHz, CD3OD) δ 1.39-1.60 (m, 6H), 1.65-1.73 (m, 2H), 1.83 (m, 1H), 2.10 (d, 2H), 3.85 (m, 1H).

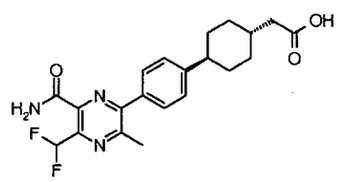
Intermediate 7-7: Methyl (cis-4-hydroxycyclohexyl)acetate



A solution of methyl 4-hydroxyphenylacetate (10.01 g, 60.2 mmol, CAS 14199-15-6), rhodium (5 % on Alumina) (0.073 g, 0.71 mmol) in MeOH (30 mL) was hydrogenated at 8 bar. The crude was filtered through Celite and concentrated at reduced pressure. The remaining colorless oil was dissolved in isohexane and EtOAc and purified by flash chromatography using EtOAc (20-50 %) in isohexane to afford the title cis compound (4.31 g, 42 %) as colorless oil. NMR analysis of both trans and cis isomers were compared to make sure that the right isomer was used in subsequent steps.

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40-1.48 (m, 2H), 1.48-1.62 (m, 4H), 1.66-1.74 (m, 2H), 1.86 (m, 1H), 2.24 (d, 2H), 3.66 (s, 3H), 3.97 (s, 1H).

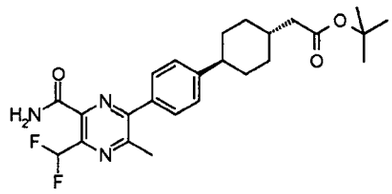
Example 8: (trans-4-{4-[6-Carbamoyl-5-(difluoromethyl)-3-methylpyrazin-2-yl]phenyl}cyclohexyl)acetic acid



This compound was synthesised from **Intermediate 8-1** using similar conditions as described in **Example 1** to give the title compound (3.8 mg, 31 %).

^{1}H NMR (500 MHz, CD_3OD) δ 1.17-1.30 (m, 2H), 1.54-1.67 (m, 2H), 1.80-2.00 (m, 5H), 2.24 (d, 2H), 2.56-2.65 (m, 1H), 2.74 (s, 3H), 7.42 (m, 2H), 7.67 (m, 2H), 7.79 (t, 1H); *m/z* 404 $(M+H)^+$.

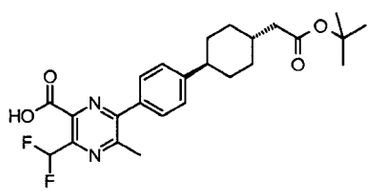
Intermediate 8-1: tert-Butyl (trans-4-{4-[6-carbamoyl-5-(difluoromethyl)-3-methylpyrazin-2-yl]phenyl}cyclohexyl)acetate



This compound was synthesised from **Intermediate 8-2** using similar conditions as described in **Intermediate 1-1** to give the title compound (11 mg, 44 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14-1.24 (m, 2H), 1.47 (s, 9H), 1.51-1.63 (m, 2H), 1.80-2.01 (m, 5H), 2.18 (d, 2H), 2.53-2.62 (m, 1H), 2.81 (s, 3H), 5.72 (s, 1H), 7.37 (m, 2H), 7.56 (m, 2H), 7.84 (s, 1H), 7.97 (t, 1H); *m/z* 460 $(M+H)^+$.

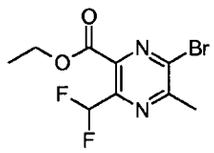
Intermediate 8-2: 6-{4-[trans-4-(2-tert-Butoxy-2-oxoethyl)cyclohexyl]phenyl}-3-(difluoromethyl)-5-methylpyrazine-2-carboxylic acid



This compound was synthesised from **Intermediate 8-3** using similar conditions as described in **Intermediate 1-3** to give the title compound (25 mg, 44 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14-1.25 (m, 2H), 1.47 (s, 9H), 1.51-1.61 (m, 2H), 1.80-2.01 (m, 5H), 2.14-2.21 (m, 2H), 2.53-2.63 (m, 1H), 2.86 (s, 3H), 7.35-7.60 (m, 4H), 7.83 (t, 1H); *m/z* 461 $(M+H)^+$.

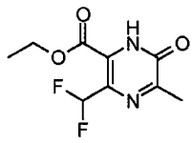
Intermediate 8-3: Ethyl 6-bromo-3-(difluoromethyl)-5-methylpyrazine-2-carboxylate



This compound was synthesised from **Intermediate 8-4** using similar procedure as described in **Intermediate 9-3** to afford the title compound (36 mg, 37 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45 (t, 3H), 2.83 (s, 3H), 4.50 (q, 2H), 7.24 (t, J = 55 Hz, 1H); *m/z* 295 $(M+H)^+$.

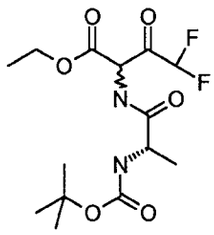
Intermediate 8-4: Ethyl 3-(difluoromethyl)-5-methyl-6-oxo-1,6-dihydropyrazine-2-carboxylate



This compound was synthesised from **Intermediate 8-5** using similar procedure as described in **Intermediate 1-5**. The cyclized intermediate product was oxidized by heating at 120 °C for 20 min in a microwave oven with Pd/C in HOAc to afford the title compound (280 mg, 38.6 %).

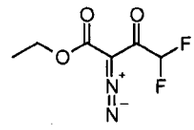
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46 (t, 3H), 2.59 (s, 3H), 4.51 (q, 2H), 7.36 (t, 1H, J = 56 Hz); *m/z* 233 $(M+H)^+$.

Intermediate 8-5: Ethyl 2-{[N-(tert-butoxycarbonyl)-L-alanyl]amino}-4,4-difluoro-3-oxobutanoate



This compound was synthesised from **Intermediate 8-6** using similar procedure as described in **Intermediate 1-6**. The crude was used directly in next step.

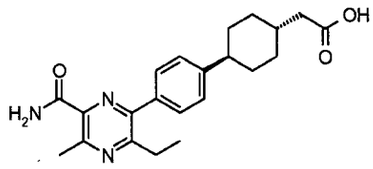
Intermediate 8-6: Ethyl 2-diazo-4,4-difluoro-3-oxobutanoate



This compound was synthesised from 4,4-difluoro-3-oxo-butyric acid ethyl ester (CAS 352-24-9) and polymer-bound tosylazide using similar conditions as described in **Intermediate 1-7**. The crude was used directly in next step.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (t, 3H), 4.35 (q, 2H), 6.59 (t, J = 56 Hz, 1H).

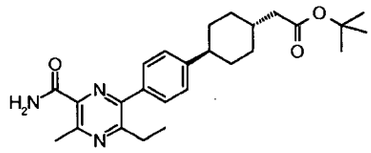
Example 9: {trans-4-[4-(6-Carbamoyl-3-ethyl-5-methylpyrazin-2-yl)phenyl] cyclohexyl}acetic acid



This compound was synthesised from **Intermediate 9-1** using similar conditions as described in **Example 1** to afford the title compound (5 mg, 29 %) as white solid.

^{1}H NMR (500MHz, $CDCl_3$) δ 1.17 (q, 2H), 1.21 (t, 3H), 1.52 (q, 2H), 1.75-1.88 (m, 1H), 1.92 (d, 4H), 2.22 (d, 2H), 2.52 (t, 1H), 2.88 (q, 2H), 2.9 (s, 3H), 6.12 (br s, 1H), 7.28 (d, 2H), 7.42 (d, 2H), 7.80 (br s, 1H); *m/z* 382 $(M+H)^+$.

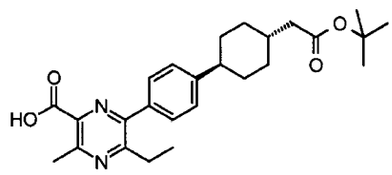
Intermediate 9-1: tert-Butyl {trans-4-[4-(6-carbamoyl-3-ethyl-5-methylpyrazin-2-yl)phenyl]cyclohexyl}acetate



This compound was synthesised from **Intermediate 9-2** using similar conditions as described in **Intermediate 1-1** to afford the title compound (20 mg, 30 %) as white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (q, 2H), 1.26 (t, 3H), 1.46 (s, 9H), 1.48-1.62 (m, 2H), 1.78-1.87 (m, 1H), 1.94 (t, 4H), 2.16 (d, 2H), 2.55 (t, 1H), 2.93 (q, 2H), 2.98 (s, 3H), 5.65 (br s, 1H), 7.31 (d, 2H), 7.46 (d, 2H), 7.80 (s, 1H); *m/z* 438 $(M+H)^+$.

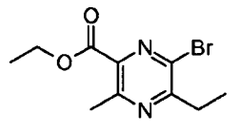
Intermediate 9-2: 6-{4-[trans-4-(2-tert-Butoxy-2-oxoethyl)cyclohexyl]phenyl}-5-ethyl-3-methylpyrazine-2-carboxylic acid



This compound was synthesised from **Intermediate 9-3** and **Intermediate D** using similar Suzuki conditions as described in **Intermediate 1-2** to afford the title compound (65.7 mg, 67 % yield) as white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14-1.23 (m, 2H), 1.28 (t, 3H), 1.47 (s, 9H), 1.55 (q, 2H), 1.78-1.98 (m, 6H), 2.17 (d, 2H), 2.55 (t, 1H), 2.93-3.01 (m, 5H), 7.29-7.36 (m, 2H), 7.40-7.47 (m, 2H); *m/z* 439 $(M+H)^+$.

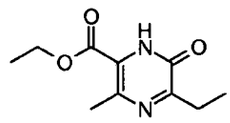
Intermediate 9-3: Ethyl 6-bromo-5-ethyl-3-methylpyrazine-2-carboxylate



To a solution of $POBr_3$ (0.307 mL, 3.02 mmol, CAS 7789-59-5) in DCE (10 mL) was added **Intermediate 9-4** (0.160 g, 0.76 mmol). The mixture was heated at 100 °C for 19 h. The reaction was cooled to RT. Saturated $NaHCO_3$ was added carefully and the mixture was extracted with DCM. The extracts were combined, dried over Na_2SO_4, filtered and concentrated. The remaining crude was purified by flash chromatography using EtOAc (0-25 %) in heptane to afford the title compound (60.4 mg, 29 %) as pale yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (t, 3H), 1.41 (t, 3H), 2.74 (s, 3H), 2.98 (q, 2H), 4.43 (q, 2H).

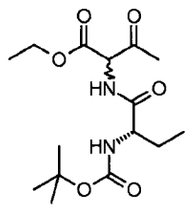
Intermediate 9-4: Ethyl 5-ethyl-3-methyl-6-oxo-1,6-dihydropyrazine-2-carboxylate



This compound was synthesised from **Intermediate 9-5** using similar conditions as described in **Intermediate 1-5** to afford the title compound (160 mg, 21 %) as white solid.

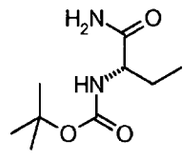
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (t, 3H), 1.39 (t, 3H), 2.61 (s, 3H), 2.85 (q, 2H), 4.40 (q, 2H).

Intermediate 9-5: Ethyl 2-({(2S)-2-[(tert-butoxycarbonyl)amino]butanoyl} amino)-3-oxobutanoate



This compound was synthesised from **Intermediate 9-6** and **Intermediate 1-7** using similar conditions as in **Intermediate 1-6.** Crude residue was taken directly to next step.

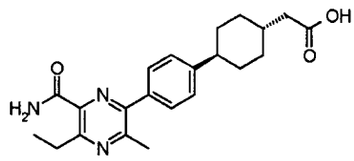
Intermediate 9-6: tert-Butyl [(1S)-1-carbamoylpropyl]carbamate



To a solution of (2*S*)-2-[(*tert*-butoxycarbonyl)amino]butanoic acid (1.01 g, 4.99 mmol) in DMF (5 mL) at –20 °C was added NMM (1.10 mL, 9.99 mmol) and isobutyl chloroformate (1.30 mL, 9.99 mmol). The reaction was stirred for 10 min at -20 °C. The precipitate was removed by filtration. 26 % NH_4OH (aq) solution (0.39 mL, 9.99 mmol) was added and the reaction was stirred at -20 °C for 3 h. The volume was reduced under vacuum and hexane was added. A white precipitate was formed after a few minutes. The precipitate was collected in a filter and washed with additional hexane. The precipitate was recrystallised from EtOAc and hexane to give the title compound (0.811 g, 80 %) as white solid.

^{1}H NMR (500 MHz, CD_3OD) δ 0.96 (t, 3H), 1.45 (s, 9H), 1.61 (m, 1H), 1.78 (m, 1H), 3.93 (t, 1H), 6.63 (s, 1H), 6.96 (s, 1H), 7.51 (s, 1H).

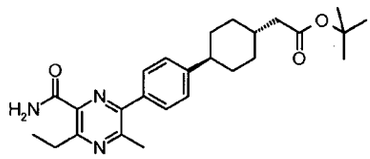
Example 10: {trans-4-[4-(6-Carbamoyl-5-ethyl-3-methylpyrazin-2-yl)phenyl] cyclohexyl}acetic acid



This compound was synthesised from **Intermediate 10-1** using similar conditions as described in **Example 1** to give title compound (13 mg, 95 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19-1.30 (2H, m), 1.36 (3H, t), 1.52-1.65 (2H, m), 1.84-2.04 (5H, m), 2.35 (2H, d), 2.54-2.64 (1H, m), 2.73 (3H, s), 3.39 (2H, q), 7.29 (1H, s), 7.36 (2H, m), 7.52 (2H, m), 8.10 (1H, s), 8.50 (1H, br s); *m/z* 382 $(M+H)^+$.

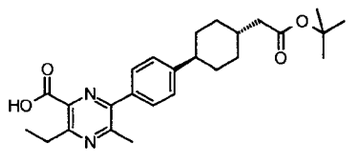
Intermediate 10-1: tert-Butyl {trans-4-[4-(6-carbamoyl-5-ethyl-3-methylpyrazin-2-yl)phenyl]cyclohexyl}acetate



This compound was synthesised from **Intermediate 10-2** using similar procedure as described in **Intermediate 1-1** to give title compound (15 mg, 50 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13-1.25 (m, 2H), 1.36 (t, 3H), 1.47 (s, 9H), 1.52-1.62 (m, 2H), 1.80-2.00 (m, 5H), 2.18 (d, 2H), 2.52-2.60 (m, 1H), 2.68 (s, 3H), 3.39 (q, 2H), 5.48 (br s, 1H), 7.33 (d, 2H), 7.52 (d, 2H), 7.81 (br s, 1H); *m/z* 438 $(M+H)^+$.

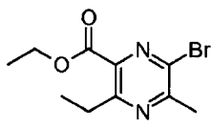
Intermediate 10-2: 6-{4-[trans-4-(2-tert-Butoxy-2-oxoethyl)cyclohexyl]phenyl}-3-ethyl-5-methylpyrazine-2-carboxylic acid



This compound was synthesised from **Intermediate 10-3** and **Intermediate D** using similar Suzuki conditions as described in **Intermediate 1-3**. Purification gave title product (30 mg, 62 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13-1.25 (m, 2H), 1.37 (t, 3H), 1.47 (s, 9H), 1.52-1.62 (m, 2H), 1.80-2.00 (m, 5H), 2.18 (d, 2H), 2.53-2.61 (m, 1H), 2.74 (s, 3H), 3.42 (q, 2H), 7.36 (d, 2H), 7.51 (d, 2H), 11.21 (br s, 1H); *m/z* 439 $(M+H)^+$.

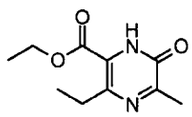
Intermediate 10-3: Ethyl 6-bromo-3-ethyl-5-methylpyrazine-2-carboxylate



This compound was synthesised from **Intermediate 10-4** using similar protocol as described in **Intermediate 9-3** to give title compound (30 mg, 8 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (t, 3H), 1.42 (t, 3H), 2.71 (s, 3H), 3.06 (q, 2H), 4.45 (q, 2H); *m/z* 275 $(M+H)^+$.

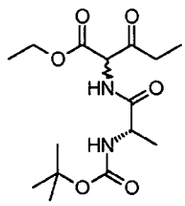
Intermediate 10-4: Ethyl 3-ethyl-5-methyl-6-oxo-1,6-dihydropyrazine-2-carboxylate



This compound was synthesised from **Intermediate 10-5** using similar protocol as described in **Intermediate 1-5**. Purification gave title compound (0.340 g, 67 %) as bright yellow oil.

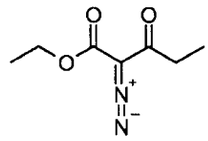
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (t, 3H), 1.43 (t, 3H), 2.54 (s, 3H), 3.02 (q, 2H), 4.44 (q, 2H), 9.20 (br s, 1H); *m/z* 211 $(M+H)^+$.

Intermediate 10-5: ethyl N-(tert-butoxycarbonyl)-L-alanyl-3-oxonorvalinate



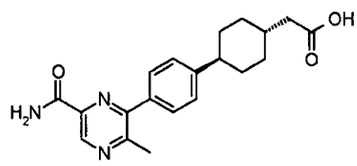
This compound was synthesised from **Intermediate 10-6** using similar conditions as described in **Intermediate 1-6**. Crude product (1 g, 46 %) was taken directly to next step. *m/z* 331 $(M+H)^+$.

Intermediate 10-6: Ethyl 2-diazo-3-oxopentanoate



This compound was synthesised from ethyl propionylacetate (CAS 4949-44-4) and polymer-bound tosylazide using similar protocol as described in **Intermediate 1-7**. Crude material (0.9 g, 95 %) was taken directly to next step.

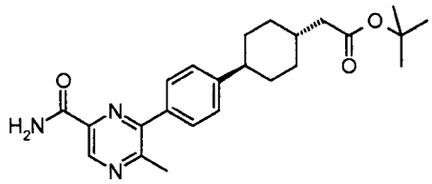
Example 11: {trans-4-[4-(6-Carbamoyl-3-methylpyrazin-2-yl)phenyl]cyclohexyl} acetic acid



This compound was synthesised from **Intermediate 11-1** using similar conditions as described in **Example 1** to give title compound (16 mg, 53 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15-1.25 (m, 2H), 1.51-1.61 (m, 2H), 1.83-2.00 (m, 5H), 2.26 (d, 2H), 2.53-2.61 (m, 1H), 2.71 (s, 3H), 7.34 (d, 2H), 7.51 (d, 2H), 9.18 (s, 1H); *m/z* 354 $(M+H)^+$.

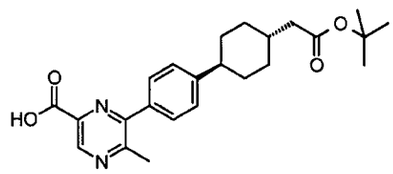
Intermediate 11-1: tert-Butyl {trans-4-[4-(6-carbamoyl-3-methylpyrazin-2-yl)phenyl]cyclohexyl}acetate



This compound was synthesised from **Intermediate 11-2** using similar conditions as described in **Intermediate 1-1**. The crude was taken directly to next step.

m/z 410 $(M+H)^+$.

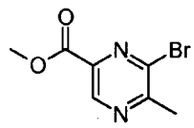
Intermediate 11-2: 6-{4-[trans-4-(2-tert-Butoxy-2-oxoethyl)cyclohexyl]phenyl}-5-methylpyrazine-2-carboxylic acid



This compound was synthesised from **Intermediate 11-3** and **Intermediate D** using similar Suzuki conditions as described in **Intermediate 1-3.** Purification gave title compound (410 mg, 66 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15-1.26 (m, 2H), 1.48 (s, 9H), 1.52-1.62 (m, 2H), 1.81-2.00 (m, 5H), 2.19 (d, 2H), 2.54-2.61 (m, 1H), 2.78 (s, 3H), 7.37 (d, 2H), 7.53 (d, 2H), 9.26 (s, 1H); *m/z* 411 $(M+H)^+$.

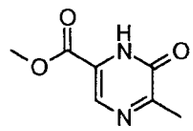
Intermediate 11-3: Methyl 6-bromo-5-methylpyrazine-2-carboxylate



This compound was synthesised from **Intermediate 11-4** using similar conditions as described in **Intermediate 9-3** to give the title compound (0.493 mg, 54 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.78 (s, 3H), 4.02 (s, 3H), 9.10 (s, 1H); *m/z* 233 $(M+H)^+$.

Intermediate 11-4: Methyl 5-methyl-6-oxo-1,6-dihydropyrazine-2-carboxylate

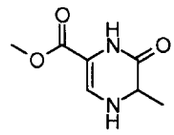


To a solution of **intermediate 11-5** (0.98 g, 5.76 mmol) in DCM (180 mL) was added polymer-bound sulfurtrioxide (7.3 g, 3 eq, CAS 26412-87-3). The mixture was stirred at RT for 4 days. The polymer was filtered off and washed with portions of DCM. Concentration of filtrate gave title compound (0.8 g, 80 %) as yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.56 (s, 3H), 4.00 (s, 3H), 7.94 (s, 1H); *m/z* 169 $(M+H)^+$.

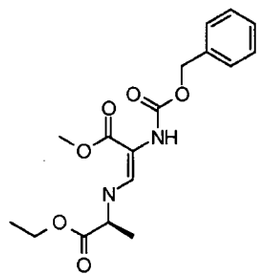
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Intermediate 11-5: Methyl 5-methyl-6-oxo-1,4,5,6-tetrahydropyrazine-2-carboxylate



To a solution of **Intermediate 11-6** (3.0 g, 8.56 mmol) in EtOH (250 mL) under N_2 was added 10 % Pd/C (1.35 g) and ammonium formate (2.43 g, 38.5 mmol). The solution was stirred at RT for 90 min. The alcohol was removed under vacuum and the black residue was dissolved in EtOAc and filtered through Celite. Concentration of filtrate gave the title compound (1.2 g, 80 %). *m/z* 171 $(M+H)^+$.

Intermediate 11-6: Ethyl N-[(1Z)-2-{[(benzyloxy)carbonyl]amino}-3-methoxy-3-oxoprop-1-en-1-yl]-L-alaninate

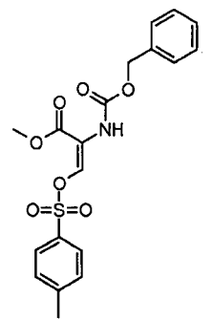


A solution of **Intermediate 11-7** (0.450 g, 0.78 mmol), L-alanine ethyl ester hydrochloride (0.179, 1.17 mmol, CAS 1115-59-9) and TEA (0.33 mL, 2.33 mmol) in MeOH (10 mL) was stirred at RT overnight. The residue was concentrated, dissolved in EtOAc (50 mL) and washed with brine (2×25 mL). The organic layer was dried through a phase separator and concentrated. The crude residue was purified by flash chromatography using a gradient of EtOAc (30-50 %) in heptane as eluent. Pure product fractions were concentrated to give the title compound (230 mg, 85 %) as colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24-1.33 (m, 6H), 3.70 (s, 3H), 3.94-4.02 (m, 1H), 4.22 (q, 2H), 5.16 (s, 2H), 5.75 (br s, 1H), 6.13 (br s, 1H), 7.25 (d, 1H), 7.30-7.45 (m, 5H); *m/z* 351 $(M+H)^+$.

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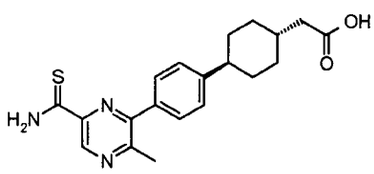
Intermediate 11-7: Methyl (2Z)-2-{[(benzyloxy)carbonyl]amino}-3-{[(4-methylphenyl)sulfonyl]oxy}acrylate



To a pre-cooled (-30 °C) solution of DMF:DMSO (1:1, 200 mL) under nitrogen was added TsCl (76.3 g, 0.4 mol) in small portions over 30 min. NOTE: This reaction is highly exothermic and careful temperature control is essential! The solution was stirred at –10 °C for 10 min, then again taken to –30 °C. A solution of cbz-L-serine methyl ester (20.3 g, 0.08 mol, CAS 1676-81-9) in DMF was added dropwise, again with careful temperature control. After stirring for 10 min at –30 °C triethylamine (110 mL, 0.79 mol) was added and the reaction was slowly taken to 0 °C and kept at this temperature for 2 h. The reaction was quenched by addition of ice-cold water. The solution was extracted with 3×EtOAc, then the combined organic layer was washed extensively with brine and water. Drying and evaporation gave product as yellow oil (30 g, 94 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.47 (s, 3H), 3.77 (s, 3H), 5.11 (s, 2H), 6.01 (br s, 1H), 7.32-7.41 (m, 7H), 7.48 (s, 1H), 7.84 (d, 2H); *m/z* 406 $(M+H)^+$.

Example 12: (trans-4-{4-[6-(Aminocarbonothioyl)-3-methylpyrazin-2-yl]phenyl}cyclohexyl)acetic acid

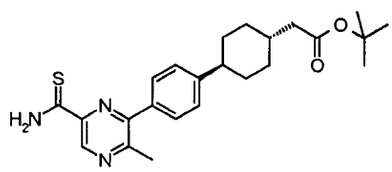


This compound was synthesised from **Intermediate 12-1** using similar procedure as in **Example 1** to afford the title compound (46 mg, 100 %).

GB

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20-1.34 (m, 2H), 1.50-1.67 (m, 2H), 1.92 (s, 1H), 2.0 (d, 4H), 2.37 (d, 2H), 2.60 (t, 1H), 2.78 (s, 3H), 7.38 (d, 2H), 7.53 (d, 2H), 7.83 (s, 1H), 9.18 (s, 1H), 9.67 (s, 1H); *m/z* 370 $(M+H)^+$.

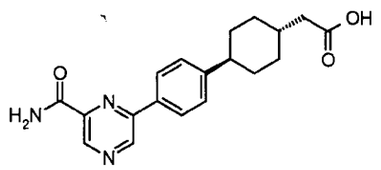
Intermediate 12-1: tert-Butyl (trans-4-{4-[6-(aminocarbonothioyl)-3-methylpyrazin-2-yl]phenyl}cyclohexyl)acetate



A solution of **Example 11** (40 mg, 0.10 mmol) and Lawesson's reagent (39.5 mg, 0.10 mmol) in toluene:THF (3:1 mL) was heated at 80 °C overnight. An additional amount (0.5 eq) of Lawesson's reagent was added followed by continued heating for another 1 h. The reaction mixture was concentrated and purified by flash chromatography using EtOAc (10-30 %) in petroleum ether as eluent to give the title compound (37 mg, 89 %) as slightly yellowish powder.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12-1.25 (m, 3H), 1.45 (s, 9H), 1.50-1.60 (m, 1H), 1.83 (s, 1H), 1.93 (t, 4H), 2.15 (d, 2H), 2.54 (t, 1H), 2.70 (s, 3H), 7.33 (d, 2H), 7.50 (d, 2H), 7.54 (s, 1H), 9.21 (s, 1H), 9.64 (s, 1H); *m/z* 426 $(M+H)^+$.

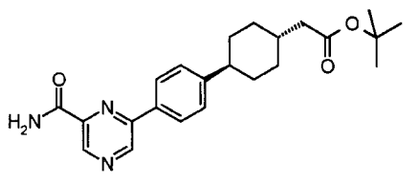
Example 13: {trans-4-[4-(6-Carbamoylpyrazin-2-yl)phenyl]cyclohexyl}acetic acid



This compound was synthesised from **Intermediate 13-1** using similar procedure as described in **Example 1** to afford the title compound (0.5 g, 95 %).

^{1}H NMR (500 MHz, DMSO) δ 1.08-1.19 (m, 2H), 1.47-1.57 (m, 2H), 1.71-1.87 (m, 5H), 2.15 (d, 2H), 2.52-2.58 (m, 1H), 7.40 (d, 2H), 8.27 (d, 2H), 9.06 (s, 1H), 9.40 (s, 1H); *m/z* 340 $(M+H)^+$.

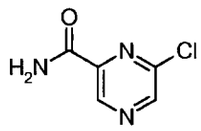
Intermediate 13-1: tert-Butyl {trans-4-[4-(6-carbamoylpyrazin-2-yl)phenyl]cyclohexyl}acetate



This compound was synthesised from **Intermediate 13-2** and **Intermediate D** using similar Suzuki conditions as described in **Intermediate 1-3**. This gave the title compound (570 mg, 45 %) as light-yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14-1.24 (m, 2H), 1.47 (s, 9H), 1.51-1.61 (m, 2H), 1.81-1.98 (m, 5H), 2.18 (d, 2H), 2.53-2.61 (m, 1H), 5.67 (br s, 1H), 7.39 (d, 2H), 7.77 (br s, 1H), 7.96 (d, 2H), 9.18 (s, 1H), 9.32 (s, 1H); *m/z* 396 $(M+H)^+$.

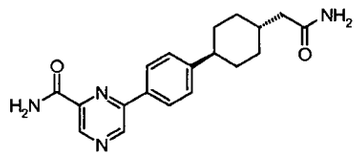
Intermediate 13-2: 6-chloropyrazine-2-carboxamide



A solution of 6-chloro-pyrazine carboxylic acid (2.00 g, 12.62 mmol) in DMF (7 mL) was cooled to –40 °C. NMP (2.77 mL, 25.23 mmol) and isobutyl chloroformate 3.27 mL, 25.23 mmol) were added. The temperature was allowed to increase to –20 °C during 20 min and then NH_4OH was added. A precipitate was rapidly formed and after 15 min it was filtered off and washed with water. Crystallization from EtOH gave the title compound (670 mg, 34 %) as light-brown needles.

^{1}H NMR (500 MHz, DMSO) δ 7.93 (br s, 1H), 8.24 (br s, 1H), 8.99 (s, 1H), 9.12 (s, 1H).

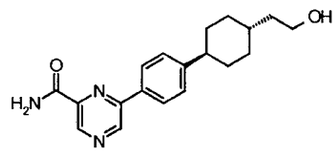
Example 14: 6-{4-[trans-4-(2-Amino-2-oxoethyl)cyclohexyl]phenyl}pyrazine-2-carboxamide



This compound was synthesised from **Example 13** using similar conditions as described in **Intermediate 1-1**. Aqueous work-up gave low yield and is not recommended here (4 mg, 10%).

^{1}H NMR (500 MHz, DMSO) δ 1.05-1.17 (m, 2H), 1.45-1.56 (m, 2H), 1.71-1.87 (m, 5H), 1.99 (d, 2H), 2.50-2.59 (m, 1H), 6.71 (s, 1H), 7.25 (s, 1H), 7.39 (d, 2H), 7.88 (s, 1H), 8.26 (d, 2H), 8.40 (s, 1H), 9.07 (s, 1H), 9.39 (s, 1H); *m/z* 339 $(M+H)^+$.

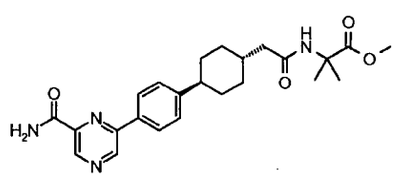
Example 15: 6-{4-[trans-4-(2-Hydroxyethyl)cyclohexyl]phenyl}pyrazine-2-carboxamide



This compound was synthesised from **Example 13** using similar conditions as in **Example 5** to afford the title compound (3 mg, 11 %) as white solid.

^{1}H NMR (500 MHz, THF) δ 1.11-1.21 (m, 2H), 1.47 (q, 2H), 1.52-1.63 (m, 3H), 1.90-1.98 (m, 4H), 2.55-2.64 (m, 1H), 3.33 (br s, 1H), 3.56-3.63 (m, 2H), 7.09 (br s, 1H), 7.40 (d, 2H), 7.95 (br s, 1H), 8.15 (d, 2H), 9.18 (s, 1H), 9.26 (s, 1H); *m/z* 326 $(M+H)^+$.

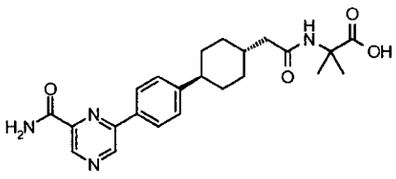
Example 16: Methyl N-({trans-4-[4-(6-carbamoylpyrazin-2-yl)phenyl]cyclohexyl}acetyl)-2-methylalaninate



This compound was synthesised from **Example 13** and alpha-aminoisobutyric acid methyl ester hydrochoride using similar conditions as in **Intermediate 1-1**. Purification gave title compound (40 mg, 76 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13-1.23 (m, 2H), 1.52-1.62 (m, 2H), 1.58 (s, 6H), 1.86-1.98 (m, 5H), 2.11 (d, 2H), 2.52-2.61 (m, 2H), 3.76 (s, 3H), 5.71 (br s, 1H), 6.02 (br s, 1H), 7.38 (d, 2H), 7.77 (br s, 1H), 7.96 (d, 2H), 9.18 (s, 1H), 9.32 (s, 1H); *m/z* 439 $(M+H)^+$.

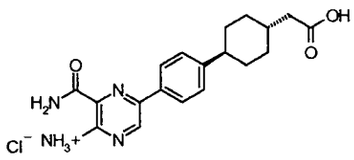
Example 17: N-({trans-4-[4-(6-Carbamoylpyrazin-2-yl)phenyl]cyclohexyl}acetyl) -2-methylalanine



The methyl ester from **Example 16** was hydrolysed to the corresponding acid using similar protocol as described in **Intermediate 1-2** to afford the title compound (21 mg, 72 %) as white solid.

^{1}H NMR (500 MHz, DMSO) δ 1.04-1.14 (m, 2H), 1.31 (s, 6H), 1.43-1.53 (m, 2H), 1.69-1.85 (m, 5H), 1.99 (d, 2H), 2.48-2.57 (m, 2H), 7.39 (d, 2H), 7.87 (br s, 1H), 7.98 (s, 1H), 8.26 (d, 2H), 8.42 (br s, 1H), 9.06 (s, 1H), 9.39 (s, 1H), 12.0 (s, 1H); *m/z* 425 $(M+H)^+$.

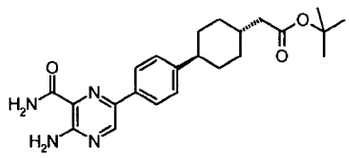
Example 18: 3-Carbamoyl-5-{4-[trans-4-(carboxymethyl)cyclohexyl]phenyl} pyrazin-2-aminium chloride



To a solution of **Intermediate 18-1** (26 mg, 0.06 mmol) in dioxane (5 mL) was added a solution of 4M HCl in dioxane (0.316 mL) in one portion. A precipitate formed. Water (1 mL) was added to dissolve the precipitate. The reaction mixture was heated in a microwave oven at 120 °C. Evaporation gave title compound (25.8 mg, 100 %) as yellow solid.

^{1}H NMR (400 MHz, DMSO) δ 1.05-1.20 (m, 2H), 1.48 (q, 2H), 1.66-1.87 (m, 5H), 2.14 (d, 2H), 2.50 (1H, covered by DMSO), 7.29 (d, 2H), 7.64 (s, 1H), 8.01 (d, 2H), 8.23 (s, 1H), 8.77 (s, 1H); *m/z* 355 $(M+H-HCl)^+$.

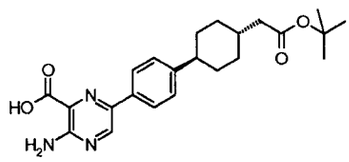
Intermediate 18-1: tert-Butyl {trans-4-[4-(5-amino-6-carbamoylpyrazin-2-yl)phenyl]cyclohexyl}acetate



This compound was synthesised from **Intermediate 18-2** using similar procedure as described in **Intermediate 1-1** to afford the title compound (26 mg, 24 %) as white-yellow powder.

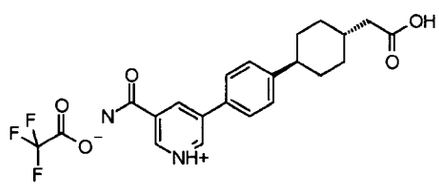
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08-1.32 (m, 4H), 1.46 (s, 9H), 1.84 (m, 1H), 2.16 (d, 2H), 2.52 (t, 1H), 5.46 (s, 1H), 7.31 (d, 2H), 7.78 (d, 2H), 7.83 (s, 1H), 8.63 (s, 1H); *m/z* 411 $(M+H)^+$.

Intermediate 18-2: 3-amino-6-{4-[trans-4-(2-tert-butoxy-2-oxoethyl)cyclohexyl]phenyl}pyrazine-2-carboxylic acid



This compound was synthesised from 3-Amino-6-bromo-pyrazine-2-carboxylic acid methyl ester (CAS 6966-01-4) and **Intermediate D** using similar Suzuki protocol as described in **Intermediate 1-3**. Crude was not isolated. *m/z* 412 $(M+H)^+$.

Example 19: 3-Carbamoyl-5-{4-[trans-4-(carboxymethyl)cyclohexyl]phenyl}pyridinium trifluoroacetate

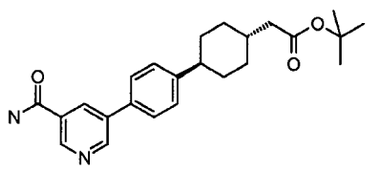


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This compound was synthesised from **Intermediate 19-1** using similar procedure as described in **Example 1**. Evaporation yielded the title compound (22 mg, 69 %) as white powder.

^{1}H NMR (600 MHz, DMSO) δ 1.12 (2H, q), 1.50 (2H, q), 1.74 (1H, s), 1.82 (4H, d), 2.13 (2H, d), 2.51 (1H, t); *m/z* 339 $(M+H-TFA)^+$.

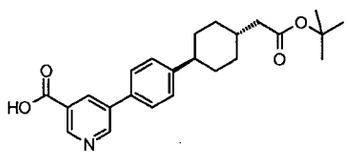
Intermediate 19-1: tert-Butyl {trans-4-[4-(5-carbamoylpyridin-3-yl)phenyl] cyclohexyl}acetate



This compound was synthesised from **Intermediate 19-2** using similar reaction conditions as described in **Intermediate 1-1**. Purification gave title compound (40 mg, 37 %) as white powder.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78-1.70 (13H, m), 1.83 (1H, s), 1.91 (4H, t), 2.15 (2H, d), 2.52 (1H, t), 5.68 (1H, s), 6.28 (1H, s), 7.33 (2H, d), 7.54 (2H, d), 8.39 (1H, t), 8.95 (1H, s), 8.99 (1H, s); *m/z* 395 $(M+H)^+$.

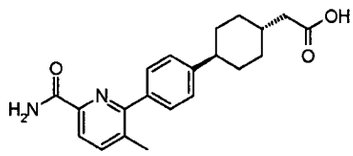
Intermediate 19-2: 5-{4-[trans-4-(2-tert-Butoxy-2-oxoethyl)cyclohexyl]phenyl} nicotinic acid



This compound was synthesised from 5-bromonicotinic acid (CAS 20826-04-4) and **Intermediate D** using similar Suzuki protocol as described in **Intermediate 1-3**. Purification gave title compound (230 mg, 74 %) as white solid.

^{1}H NMR (400 MHz, CD_3OD) δ 1.18 (2H, q), 1.44 (9H, s), 1.55 (2H, q), 1.81 (1H, s), 1.89 (4H, t), 2,14 (2H, d), 2.53 (1H, t), 7.34 (2H, d), 7.59 (2H, d), 8.50 (1H, t), 8.76 (1H, d), 8.97 (1H, d); *m/z* 396 $(M+H)^+$.

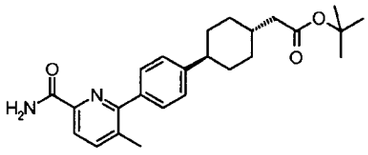
Example 20: {trans-4-[4-(6-Carbamoyl-3-methylpyridin-2-yl)phenyl]cyclohexyl} acetic acid



This compound was synthesised from **Intermediate 20-1** using similar conditions as described in **Example 1** to afford title compound (11 mg, 85 %).

^{1}H NMR (400MHz, $CDCl_3$) δ 1.02-1.18 (m, 2H), 1.37-1.51 (m, 2H), 1.62-1.82 (m, 5H), 2.08 (d, 2H), 2.32 (s, 3H), 2.40-2.51 (m, 1H), 7.27 (d, 2H), 7.49 (d, 3H), 7.81 (d, 2H), 7.86 (s, 1H); *m/z* 353 $(M+H)^+$.

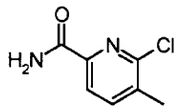
Intermediate 20-1: tert-Butyl {trans-4-[4-(6-carbamoyl-3-methylpyridin-2-yl)phenyl]cyclohexyl}acetate



This compound was synthesised from **Intermediate 20-2** and **Intermediate D** using similar Suzuki protocol as in **Intermediate 1-3**. Purification gave title product (15 mg, 21 %).

^{1}H NMR (400MHz, $CDCl_3$) δ 1.09-1.30 (m, 2H), 1.45 (s, 9H), 1.48-1.61 (m, 2H), 1.76-1.98 (m, 5H), 2.15 (d, 2H), 2.41 (s, 3H), 2.48-2.57 (m, 1H), 5.60 (s, 1H), 7.29 (d, 2H), 7.45 (d, 2H), 7.71 (d, 1H), 7.87 (s, 1H), 8.04 (d, 1H).

Intermediate 20-2: 6-chloro-5-methylpyridine-2-carboxamide

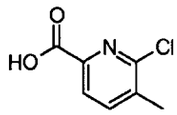


To a solution of **Intermediate 20-3** (112 mg, 0.65 mmol) in DCM (5 mL) was added PyBROP (457 mg, 0.98 mmol), NH_4Cl (70 mg, 1.30 mmol) and DIPEA (0.43 mL, 2.61 mmol). The reaction mixture was stirred at RT for 2 h. After dilution with DCM (15 mL) the solution was washed with sat $NaHCO_3$ (2 x 15 mL) and water (15 mL), dried through a

phase separator and evaporated. The crude product was purified by flash chromatography using EtOAc in heptane as eluent. Pure fractions were evaporated to dryness to afford the title compound (83 mg, 74 %).

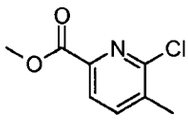
^{1}H NMR (400 MHz, DMSO) δ 2.35 (s, 3H), 7.63 (s, 1H), 7.85-7.90 (m, 3H); *m/z* 171 $(M+H)^+$.

Intermediate 20-3: 6-Chloro-5-methylpyridine-2-carboxylic acid



This compound was synthesised from the corresponding Me-ester using similar protocol as described in **Intermediate 1-2** to give title compound (0.11 g, 80 %); *m/z* 172 $(M+H)^+$.

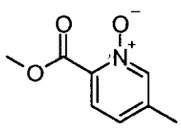
Intermediate 20-4: Methyl 6-chloro-5-methylpyridine-2-carboxylate



A solution of **Intermediate 20-5** (1.67g, 9.99mmol) in $POCl_3$ (15 mL) was heated to reflux for 3 h. After cooling to RT the reaction mixture was added to an ice-water solution, basified with 1M NaOH (aq) and extracted with DCM (3 x 30 mL). Organic layers were combined, passed through a phase separator and evaporated. The crude product was purified by flash chromatography using EtOAc (15 %) in heptane as eluent. Pure fractions were evaporated to dryness to afford the title compound (0.73 g, 39 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 3.97 (s, 3H), 7.67 (d, 1H), 7.96 (d, 1H); *m/z* 186 $(M+H)^+$.

Intermediate 20-5: Methyl 5-methylpyridine-2-carboxylate 1-oxide

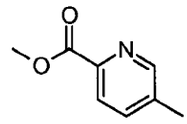


To a solution of **Intermediate 20-6** (2.11 g, 14.0 mmol) in DCM (40 mL) was added *m*-CPBA (4.70 g, 21.0 mmol) and the reaction was stirred at RT for 5 h. Sat Na_2SO_2 (15 mL) was added and the reaction was stirred for 5 min. The two phases were separated and the

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organic phase was washed with 1M $NaHCO_3$, passed through a phase separator and evaporated. The crude product was taken to the next step without further purification. *m/z* 168 $(M+H)^+$.

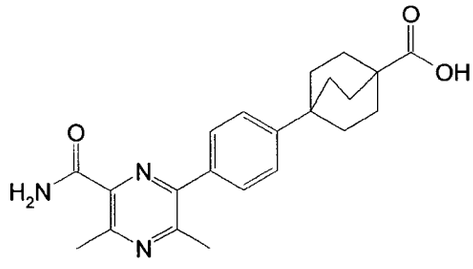
Intermediate 20-6: Methyl 5-methylpyridine-2-carboxylate



To a solution of 2,5-dimethylpyridine (3.00 g, 28.0 mmol, CAS 589-93-5) in pyridine (15 mL) was added selenium dioxide (4.66 g, 42.0 mmol, CAS 7446-08-4). The reaction mixture was heated at reflux overnight. After cooling to RT a solid was filtered off and washed with water and pyridine (2x5 mL/wash). The filtrate was evaporated and the crude retaken in methanol (100 mL). Sulphuric acid (1.34 mL, 25.0 mmol) was added and the reaction mixture was heated at reflux for 5 h. After cooling to RT the reaction mixture was basified with 20% NaOH (aq). The methanol was evaporated off and water was added (50 mL). This mixture was extracted with DEE (3 x 100 mL). The combined organics were dried (Na_2SO_4) and evaporated to afford the title compound (2.11 g, 50 %) as light-brown oil.

^1H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3H), 3.97 (s, 3H), 7.61 (d, 1H), 8.01 (d, 1H), 8.54 (s, 1H).

Example 21: 4-(4-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)bicyclo[2.2.2]octane-1-carboxylic acid

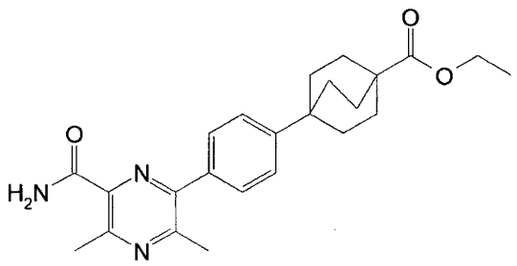


Powdered potassium hydroxide (204 mg, 3.63 mmol) was added in one portion to **Intermediate 21-1** (493 mg, 1.21 mmol) in tert-butanol (10 mL) at 40 °C under nitrogen. The resulting suspension was stirred at 45 °C for 5 h, a thick white precipitate suspension

slowly formed. Acetic acid (0.346 mL, 6.05 mmol) was added and the resulting solution stirred for a several minutes before being partitioned between EtOAc (100 mL) and 1N citric acid (50 mL). The suspension was filtered and dried to afford of desired product as a white solid (300 mg), the organic phase was separated, dried over $MgSO_4$, filtered and evaporated to afford crude product as a colourless oil which solidified on standing. The filtrate 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 and combined with the solid to afford the title compound (376 mg, 82 %) as a white solid.

^{1}H NMR (400 MHz, DMSO) δ 1.84 (12H, s), 2.58 (3H, s), 2.73 (3H, s), 7.46 (2H, d), 7.57 (1H, s), 7.66 (2H, d), 7.98 (1H, s), 12.08 (1H, s); *m/z* 380 $(M+H)^+$.

Intermediate 21-1: Ethyl 4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)bicyclo[2.2.2]octane-1-carboxylate

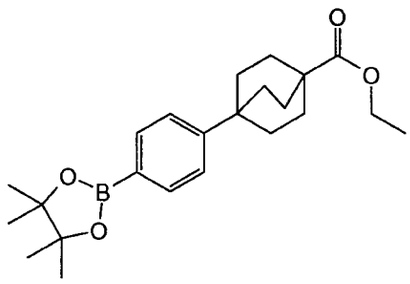


A solution of **Intermediate 21-2** (525 mg, 1.37 mmol), **Intermediate 21-4** (254 mg, 1.37 mmol), and tripotassium phosphate (348 mg, 1.64 mmol) in DME (15 mL), EtOH (5 mL) and water (2 mL) were degassed before addition of (1,1'-Bis(diphenylphosphino)ferrocene)-dichloropalladium(II) (DCM adduct) (56.2 mg, 0.07 mmol). The reaction mixture was heated to 80 °C, under nitrogen, and left to stir at 80 °C for 2 h. The reaction mixture was allowed to cool to room temperature and then evaporated. The crude product was partitioned between EtOAc (100 mL) and water (50 mL), filtered through celite and the organic phase was separated, washed with saturated brine (50 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. Pure fractions were evaporated to dryness to afford the title compound (493 mg, 89 %) as a white solid.

^{1}H NMR (400 MHz, DMSO) δ 1.18 (3H, t), 1.85 (12H, s), 2.58 (3H, s), 2.73 (3H, s), 4.05 (2H, q), 7.46 (2H, d), 7.57 (1H, s), 7.66 (2H, d), 7.97 (1H, s); *m/z* 408 $(M+H)^+$.

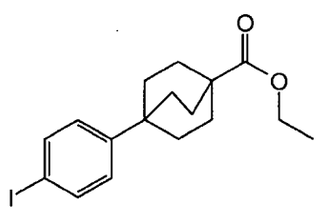
Intermediate 21-2: Ethyl 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)bicyclo[2.2.2]octane-1-carboxylate



To a degassed solution of **Intermediate 21-3** (1.66 g, 4.32 mmol) in DMSO (30 mL) was added potassium acetate (1.272 g, 12.96 mmol) and bis(pinacolato)diboron (1.207 g, 4.75 mmol), the reaction mixture was degassed for a further 20 minutes. (1,1'-Bis(diphenylphosphino)ferrocene)-dichloropalladium(II) (DCM adduct) (0.212 g, 0.26 mmol) was added and the suspension was degassed and then heated, under nitrogen at 80 °C for 3 h. The reaction mixture was allowed to cool, poured onto water (125 mL), the suspension was filtered and the solid was purified by flash silica chromatography, elution gradient 0 to 20% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the title compound (1.080 g, 65.0 %) as a white solid.

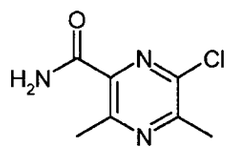
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (3H, t), 1.33 (12H, s), 1.84 – 1.93 (12H, m), 4.12 (2H, q), 7.33 (2H, d), 7.75 (2H, d); *m/z* (EI+) 384 M^+.

Intermediate 21-3: Ethyl 4-(4-iodophenyl)bicyclo[2.2.2]octane-1-carboxylate



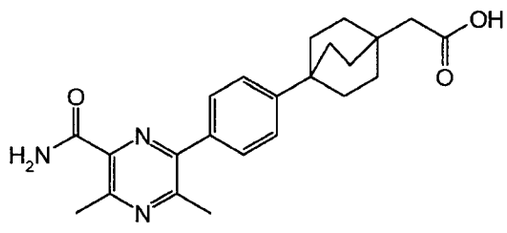
[Bis(trifluoroacetoxy)iodo]benzene (3.78 g, 8.78 mmol) and iodine (1.061 g, 4.18 mmol) were added to a stirred solution of ethyl 4-phenylbicyclo[2.2.2]octane-1-carboxylate (prepared according to the procedure described in WO 2007/071966) (2.16 g, 8.36 mmol, CAS 10207-26-8) in $CHCl_3$ (50 mL). The resulting solution was stirred at ambient temperature for 90 minutes. The reaction mixture was poured into sodium thiosulfate (100 mL), extracted with DCM (2 x 100 mL), the organic layer was washed with aqueous sodium thiosulfate (2 x 80 mL), separated, dried over $MgSO_4$, filtered and evaporated to afford a yellow oil which solidified on standing. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the title compound (2.78 g, 87 %) as a white solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (3H, t), 1.79 – 1.84 (6H, m), 1.88 – 1.93 (6H, m), 4.11 (2H, q), 7.05 (2H, d), 7.61 (2H, d); *m/z* 385 $(M+H)^+$.

Intermediate 21-4: 6-Chloro-3,5-dimethylpyrazine-2-carboxamide



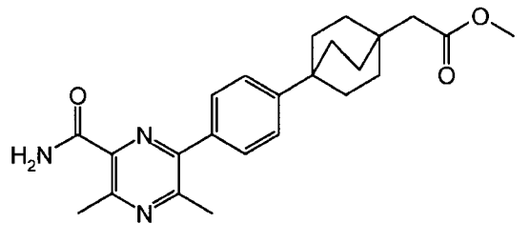
Intermediate 1-4 (227 g, 1057.54 mmol) was stirred in ammonia (7N in MeOH) (1957 mL, 89633.59 mmol) at ambient temperature overnight. The mixture was evaporated to dryness and the residue was triturated with ether and the suspension was filtered and at 40 °C under vacuum to afford the title compound (181 g, 92 %) as a light brown solid.
^{1}H NMR (400 MHz, DMSO) δ 2.59 (3H, s), 2.67 (3H, s), 7.70 (1H, s), 7.99 (1H, s)
m/z 186 $(M+H)^+$.

Example 22: 2-(4-(4-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)bicyclo-[2.2.2]octan-1-yl)acetic acid



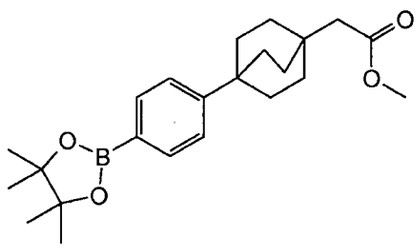
This compound was synthesised from **Intermediate 22-1** using similar conditions as described in **Example 21** to give the title compound (292 mg, 77 %) as a white solid.
^{1}H NMR (400 MHz, DMSO) δ 1.60 - 1.65 (6H, m), 1.80 - 1.84 (6H, m), 2.05 (2H, s), 2.58 (3H, s), 2.72 (3H, s), 7.45 (2H, d), 7.56 (1H, s), 7.64 (2H, d), 7.97 (1H, s), 11.91 (1H, s); *m/z* 394 $(M+H)^+$.

Intermediate 22-1: Methyl 2-(4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)bicyclo[2.2.2]octan-1-yl)acetate



This compound was synthesised from **Intermediate 21-4** and **Intermediate 22-2** using similar conditions as described in **Intermediate 21-1** to give the title compound (392 mg, 96 %) as a white solid.
^{1}H NMR (400 MHz, DMSO) δ 1.57 - 1.63 (6H, m), 1.80 - 1.86 (6H, m), 2.15 (2H, s), 2.58 (3H, s), 2.73 (3H, s), 3.58 (3H, s), 7.44 (2H, d), 7.57 (1H, s), 7.64 (2H, d), 7.97 (1H, s); *m/z* 408 $(M+H)^+$.

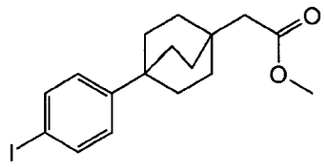
Intermediate 22-2: Methyl 2-(4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)bicyclo[2.2.2]octan-1-yl)acetate



This compound was synthesised from **Intermediate 22-3** using similar conditions as described in **Intermediate 21-2** to give the title compound (0.701 g, 55.6 %) as a white solid.

^{1}H NMR (400, $CDCl_3$) δ 1.33 (12H, s), 1.62 - 1.66 (6H, m), 1.82 - 1.87 (6H, m), 2.16 (2H, s), 3.65 (3H, s), 7.32 (2H, d), 7.74 (2H, d); *m/z* (EI+) 384 M^+.

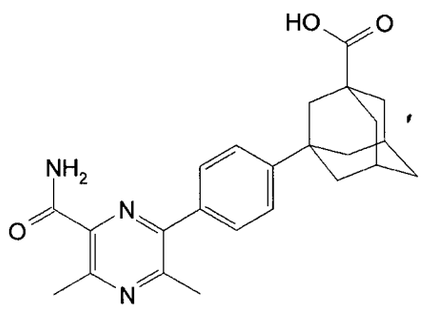
Intermediate 22-3: Methyl 2-(4-(4-iodophenyl)bicyclo[2.2.2]octan-1-yl)acetate



This compound was synthesised from methyl 2-(4-phenylbicyclo[2.2.2]octan-1-yl)acetate (prepared according to the procedure described in WO 2007/071966, CAS 70631-58-2) using similar conditions as described in **Intermediate 21-3** to give the title compound (1.320 g, 80 %) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62 - 1.66 (6H, m), 1.77 - 1.82 (6H, m), 2.16 (2H, s), 3.66 (3H, s), 7.05 (2H, d), 7.59 (2H, d); *m/z* (EI+) 384 M^+.

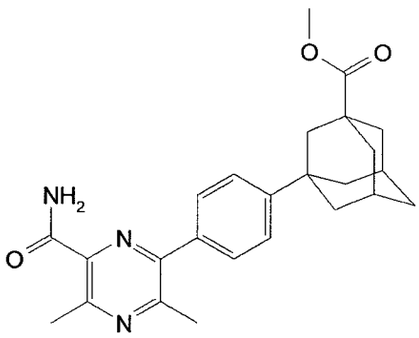
Example 23: 3-[4-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl]adamantane-1-carboxylic acid



This compound was synthesised from **Intermediate 23-1** using similar conditions as described in **Example 21**. Except after 70 minutes the reaction mixture was allowed to cool and 1N citric acid (15 mL) was added, the precipitate was collected by filtration, washed with 1N citric acid (10 mL), water (10 mL) and dried under vacuum to afford the title compound (360 mg, 90 %) as a white solid.

^{1}H NMR (400 MHz, DMSO) δ 1.69 - 1.73 (2H, m), 1.84 - 1.89 (8H, m), 1.96 (2H, s), 2.17 - 2.19 (2H, m), 2.59 (3H, s), 2.74 (3H, s), 7.50 (2H, d), 7.59 (1H, s), 7.68 (2H, d), 7.98 (1H, s), 12.07 (1H, s); *m/z* 406 $(M+H)^+$.

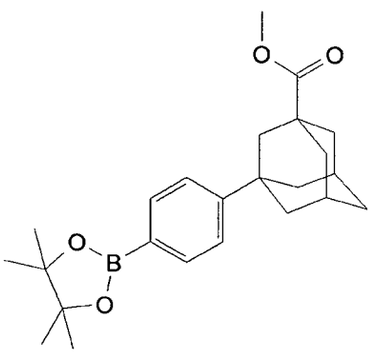
Intermediate 23-1: Methyl 3-[4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl]adamantane-1-carboxylate



This compound was synthesised from **Intermediate 21-4** and **Intermediate 23-2** using similar conditions as described in **Intermediate 21-1** to give the title compound (412 mg, 74.3 %) as a white solid.

^{1}H NMR (400 MHz, DMSO) δ 1.70 - 1.73 (2H, m), 1.85 - 1.91 (8H, m), 1.98 (2H, s), 2.18 - 2.20 (2H, m), 2.58 (3H, s), 2.73 (3H, s), 3.60 (3H, s), 7.49 (2H, d), 7.58 (1H, s), 7.68 (2H, d), 7.97 (1H, s); *m/z* 420 $(M+H)^+$.

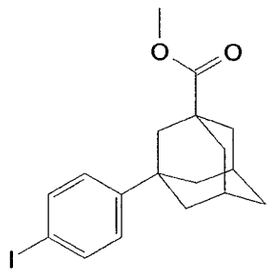
Intermediate 23-2: Methyl 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]adamantane-1-carboxylate



This compound was synthesised from **Intermediate 23-3** using similar conditions as described in **Intermediate 21-2** to give the title compound (1.758 g, 63.9 %) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (12H, s), 1.73 - 1.75 (2H, m), 1.88 - 1.95 (8H, m), 2.05 (2H, s), 2.21 - 2.25 (2H, m), 3.67 (3H, s), 7.37 (2H, d), 7.77 (2H, d); *m/z* 396 (EI+) M^+.

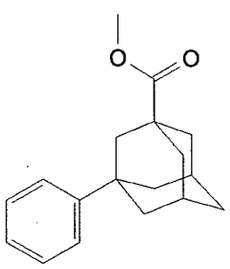
Intermediate 23-3: Methyl 3-(4-iodophenyl)adamantane-1-carboxylate



This compound was synthesised from **Intermediate 23-4** using similar conditions as described in **Intermediate 21-3** to give the title compound (2.75 g, 88 %) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72 - 1.74 (2H, m), 1.89 - 1.95 (8H, m), 1.99 (2H, s), 2.22 - 2.24 (2H, m), 3.67 (3H, s), 7.11 (2H, d), 7.63 (2H, d); *m/z* 396 (EI+) M^+.

Intermediate 23-4: Methyl 3-phenyladamantane-1-carboxylate



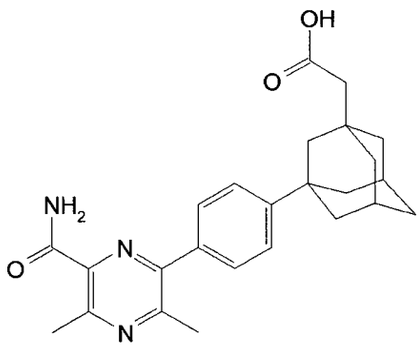
Trimethylsilyldiazomethane 2M solution in hexane (8.15 mL, 16.31 mmol) was added dropwise to a stirred solution of 3-phenyl-1-adamantanecarboxylic acid (2.09 g, 8.15 mmol, CAS 37589-22-3) in toluene (20 mL) and methanol (10 mL) over a period of 2 minutes. The resulting solution was stirred at ambient temperature for 60 minutes. The reaction mixture was evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% EtOAc in isohexane. Pure

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fractions were evaporated to dryness to afford the title compound (2.140 g, 97 %) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.73 - 1.75 (2H, m), 1.90 - 1.93 (8H, m), 2.04 (2H, s), 2.22 - 2.25 (2H, m), 3.67 (3H, s), 7.17 - 7.21 (1H, m), 7.30 - 7.38 (4H, m); *m/z* 270 (EI+) M^+.

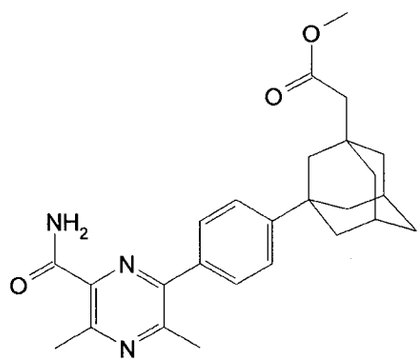
Example 24: 2-[3-[4-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl]-1-adamantyl]acetic acid



This compound was synthesised from **Intermediate 24-1** using similar conditions as described in **Example 21** to give the title compound (126 mg, 62.0 %) as a white solid.

^{1}H NMR (400 MHz, DMSO) δ 1.62 - 1.71 (6H, m), 1.75 (2H, s), 1.81 - 1.88 (4H, m), 2.07 (2H, s), 2.15 (2H, s), 2.59 (3H, s), 2.73 (3H, s), 7.47 (2H, d), 7.58 (1H, s), 7.67 (2H, d), 7.97 (1H, s), 11.89 (1H, s); *m/z* 420 $(M+H)^+$.

Intermediate 24-1: Methyl 2-[3-[4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl]-1-adamantyl]acetate

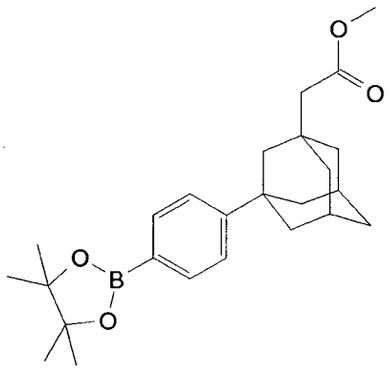


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This compound was synthesised from **Intermediate 21-4** and **Intermediate 24-2** using similar conditions as described in **Intermediate 21-1** to give the title compound (210 mg, 48.4 %) as a colourless oil which solidified on standing.

^{1}H NMR (400 MHz, DMSO) δ 1.60 - 1.70 (6H, m), 1.73 (2H, s), 1.81 - 1.89 (4H, m), 2.14 - 2.16 (2H, m), 2.16 (2H, s), 2.59 (3H, s), 2.74 (3H, s), 3.57 (3H, s), 7.47 (2H, d), 7.58 (1H, s), 7.68 (2H, d), 7.97 (1H, s); *m/z* 434 $(M+H)^+$.

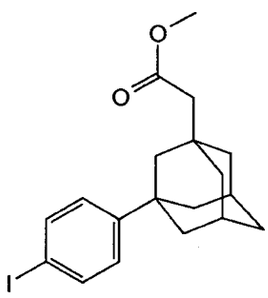
Intermediate 24-2: Methyl 2-[3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-adamantyl]acetate



This compound was synthesised from **Intermediate 24-3** using similar conditions as described in **Intermediate 21-2** to give the title compound (1.240 g, 76 %) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (12H, s), 1.61 - 1.72 (6H, m), 1.75 (2H, s), 1.82 - 1.90 (2H, m), 2.17 (2H, s), 2.17 - 2.20 (4H, m), 3.64 (3H, s), 7.36 (2H, d), 7.77 (2H, d); *m/z* 410 (EI+) M^+.

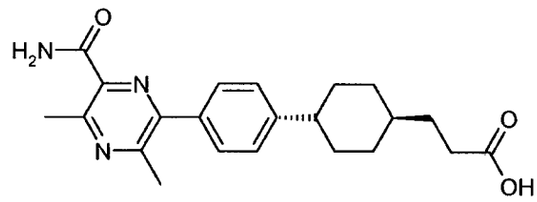
Intermediate 24-3: Methyl 2-[3-(4-iodophenyl)-1-adamantyl]acetate



This compound was synthesised from methyl 2-(3-phenyl-1-adamantyl)acetate (CAS 175721-57-0, prepared according to the procedure described in WO 2007/071966 using similar conditions as described in **Intermediate 21-3** to give the title compound (1.680 g, 81 %) as a yellow oil which solidified on standing.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62 - 1.71 (8H, m), 1.78 - 1.84 (4H, m), 2.16 (2H, s), 2.17 - 2.20 (2H, m), 3.65 (3H, s), 7.09 (2H, d), 7.62 (2H, d); *m/z* 410 (EI+) M^+.

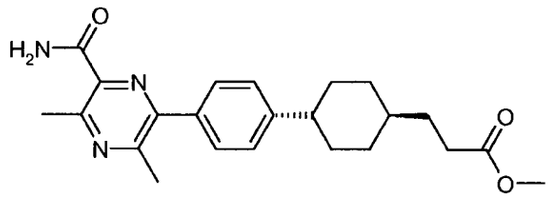
Example 25: 3-((1r,4r)-4-(4-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)propanoic acid



This compound was synthesised from **Intermediate 25-1** using similar conditions as described in **Example 21**. Except the crude product was purified by crystallisation from boiling EtOH (~10 mL) to afford the title compound (180 mg, 65.3 %) as a pale red solid.

^{1}H NMR (400 MHz, DMSO) δ 1.02 - 1.11 (2H, m), 1.27 - 1.36 (1H, m), 1.43 - 1.53 (4H, m), 1.81 - 1.87 (4H, m), 2.25 (2H, t), 2.51 - 2.55 (1H, m), 2.58 (3H, s), 2.73 (3H, s), 7.35 (2H, d), 7.57 (1H, s), 7.64 (2H, d), 7.97 (1H, s), 11.97 (1H, s); *m/z* 382 $(M+H)^+$.

Intermediate 25-1: Methyl 3-((1r,4r)-4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)propanoate

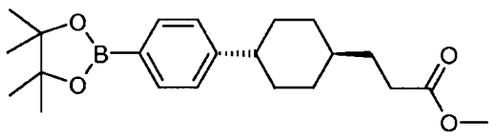


Acetonitrile (4.345 mL) added to 1,1 bis(di-tert-butylphosphino)ferrocene palladium dichloride (57.7 mg, 0.10 mmol) and stirred at room temperature for 5 min before addition of potassium carbonate (540 mg, 3.91 mmol), water (4.35 mL) and **Intermediate 25-2** (728 mg, 1.96 mmol). After a further 5 minutes **Intermediate 21-4** (364 mg, 1.96 mmol) was added and the reaction mixture heated to 80 °C for 5 hours. The reaction mixture was

partitioned between EtOAc (100 mL) and water (50 mL) and the mixture was filtered through celite, washing through with EtOAc (50 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 0 to 50% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the title compound (286 mg, 37.0 %) as a red brown solid.

^{1}H NMR (400 MHz, DMSO) δ 1.02 - 1.13 (3H, m), 1.26 - 1.37 (1H, m), 1.42 - 1.53 (4H, m), 1.80 - 1.88 (4H, m), 2.35 (2H, t), 2.58 (3H, s), 2.74 (3H, s), 3.59 (3H, s), 7.34 (2H, d), 7.57 (1H, s), 7.64 (2H, d), 7.96 (1H, s); *m/z* 396 $(M+H)^+$.

Intermediate 25-2: Methyl 3-((1r,4r)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclohexyl)propanoate

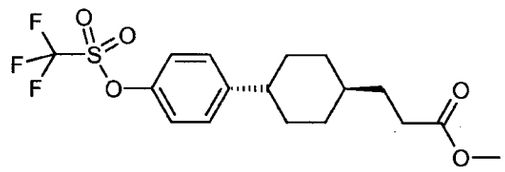


A solution of **Intermediate 25-3** (4.40 g, 11.16 mmol) in dioxane (85 mL) was degassed with nitrogen for a period of 5 minutes. Potassium acetate (3.28 g, 33.47 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (3.12 g, 12.27 mmol), (1,1'-Bis(diphenylphosphino)ferrocene)-dichloropalladium(II) (DCM adduct) (0.551 g, 0.67 mmol) and 1,1'-Bis(diphenylphosphino)ferrocene (0.375 g, 0.67 mmol) were added. The resulting mixture was stirred at 85 °C under nitrogen for 17 hours. The reaction mixture was concentrated and diluted with EtOAc (200 mL), and then mixture was filtered through celite. The filtrate was washed with saturated brine, 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 0 to 20% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the title compound (2.68 g, 64.5 %) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 - 1.13 (2H, m), 1.31 - 1.33 (1H, m), 1.33 (12H, s), 1.40 - 1.52 (2H, m), 1.59 (2H, q), 1.84 - 1.92 (4H, m), 2.36 (2H, t), 2.43 - 2.52 (1H, m), 3.68 (3H, s), 7.21 (2H, d), 7.73 (2H, d); *m/z* 372 (EI+) M^+.

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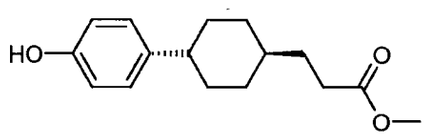
Intermediate 25-3: Methyl 3-((1r,4r)-4-(4-(trifluoromethylsulfonyloxy)phenyl)-cyclohexyl)propanoate



Triethylamine (2.59 mL, 18.57 mmol) was added to a stirred solution of **Intermediate 25-4** (3.27 g, 12.46 mmol) and trifluoromethanesulphonic anhydride (2.56 mL, 15.58 mmol) in DCM (120 mL) cooled to 0 °C, over a period of 5 minutes under nitrogen. The resulting red solution was stirred at 0 °C for 2 hours and then allowed to warm to ambient temperature overnight. The reaction mixture was diluted with DCM (100 mL), and washed sequentially with water (100 mL), saturated $NaHCO_3$ (100 mL), and saturated brine (100 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 0 to 20% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the title compound (4.42 g, 90 %) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 - 1.11 (2H, m), 1.29 - 1.35 (1H, m), 1.37 - 1.47 (2H, m), 1.58 (2H, q), 1.88 - 1.91 (4H, m), 2.36 (2H, t), 2.46 - 2.53 (1H, m), 3.68 (3H, s), 7.15 - 7.19 (2H, m), 7.23 - 7.27 (2H, m); *m/z* 394 (EI+) M^+.

Intermediate 25-4: Methyl 3-((1r,4r)-4-(4-hydroxyphenyl)cyclohexyl)propanoate

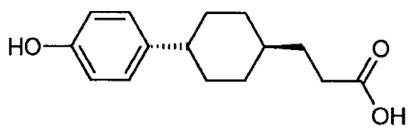


A solution of **Intermediate 25-5** (3.82 g, 15.38 mmol) in MeOH (100 mL) and concentrated H_2SO_4 (1.0 mL) was stirred at 70 °C for 3 hours and allowed to cool to ambient temperature overnight. The reaction mixture was evaporated to dryness and redissolved in EtOAc (200 mL) and washed with saturated brine (2 x 150 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 0 to 20% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the title compound (3.27 g, 81 %) as a white solid.

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^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 - 1.12 (2H, m), 1.26 - 1.33 (1H, m), 1.35 - 1.45 (2H, m), 1.58 (2H, q), 1.83 - 1.89 (4H, m), 2.36 (2H, t), 2.35 - 2.44 (1H, m), 3.68 (3H, s), 4.62 (1H, s), 6.73 - 6.77 (2H, m), 7.04 - 7.08 (2H, m); *m/z* 262 (EI+) M^+.

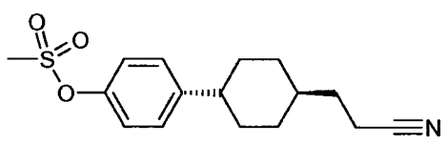
Intermediate 25-5: 3-((1r,4r)-4-(4-Hydroxyphenyl)cyclohexyl)propanoic acid



A solution of **Intermediate 25-6** (5.49 g, 17.86 mmol) and sodium hydroxide (10.71 g, 267.88 mmol) in 1,2-propanediol (65 mL) and water (16 mL) was heated to 140 °C for 1 hour. The reaction mixture was allowed to cool to ambient temperature, adjusted to pH 2 with 2M HCl and the suspension was extracted into EtOAc (2 x 200 mL). The organic extracts were combined, washed with saturated brine (200 mL), dried over $MgSO_4$, filtered and evaporated to afford crude product. This was slurried in isohexane (120 mL), filtered and air dried to afford the title compound (3.87 g, 86 %) as a white solid, which was used without further purification.

^{1}H NMR (400 MHz, DMSO) δ 0.95 - 1.05 (2H, m), 1.16 - 1.39 (3H, m), 1.44 (2H, q), 1.73 - 1.79 (4H, m), 2.23 (2H, t), 2.29 - 2.38 (1H, m), 6.62 - 6.66 (2H, m), 6.98 (2H, d), 9.03 (1H, s), 11.92 (1H, s); *m/z* 247 $(M-H)^-$.

Intermediate 25-6: 4-((1r,4r)-4-(2-Cyanoethyl)cyclohexyl)phenyl methanesulfonate

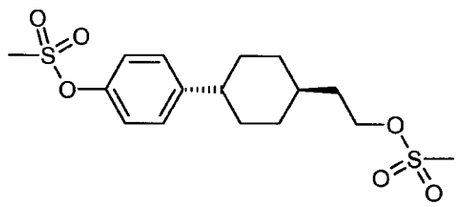


Sodium cyanide (1.669 g, 34.06 mmol) was added to a stirred solution of **Intermediate 25-7** (8.55 g, 22.71 mmol) in DMF (153 mL). The resulting mixture was stirred at 80 °C for 3 h and then allowed to cool to ambient temperature. The reaction mixture was diluted with EtOAc (150 mL), and washed with saturated brine (2 x 250 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford desired product. This still contained DMF so it was re dissolved in EtOAc (150 mL), and washed with saturated brine (2 x 200 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 30 to 60% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the title compound (4.08 g, 58.4 %) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 - 1.16 (2H, m), 1.41 - 1.52 (3H, m), 1.54 (3H, s), 1.64 (2H, q), 1.89 - 1.95 (4H, m), 2.40 (2H, t), 2.47 - 2.53 (1H, m), 3.13 (3H, s), 7.18 - 7.24 (4H, m); *m/z* 307 (EI+) M^+.

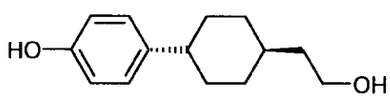
Intermediate 25-7: 4-((1r,4r)-4-(2-(Methylsulfonyloxy)ethyl)cyclohexyl)phenyl methanesulfonate



Methanesulphonyl chloride (6.56 mL, 84.58 mmol) was added to a stirred suspension of **Intermediate 25-8** (8.47 g, 38.45 mmol) and triethylamine (11.79 mL, 84.58 mmol) in DCM (300 mL). The resulting solution was stirred at ambient temperature for 16 h. The reaction mixture was washed with saturated brine (100 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 70% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the title compound (13.84 g, 96 %) as a white solid.

^{1}H NMR (400 MHz, DMSO) δ 0.99 - 1.15 (2H, m), 1.32 - 1.51 (3H, m), 1.62 (2H, q), 1.75 - 1.87 (4H, m), 2.52 - 2.56 (1H, m), 3.16 (3H, s), 3.27 (3H, 3), 4.26 (1H, t), 7.22 - 7.26 (2H, m), 7.31 - 7.35 (2H, m); *m/z* 399 $(M+Na)^+$.

Intermediate 25-8: 4-((1r,4r)-4-(2-Hydroxyethyl)cyclohexyl)phenol

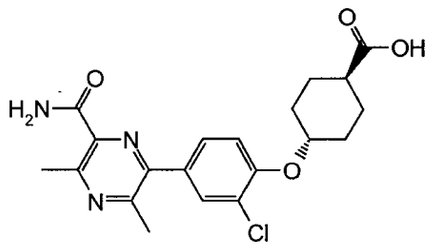


A 1M solution of lithium aluminum hydride in THF (80 mL, 79.75 mmol) was added dropwise to a stirred solution of methyl 2-((1r,4r)-4-(4-hydroxyphenyl)cyclohexyl)acetate (prepared according to WO 2004/047755) (12.3 g, 49.53 mmol, CAS 701232-67-9) in THF (280 mL) at 0 °C under nitrogen. A thick suspension formed so the mixture was removed

from the cooling bath and stirred at ambient temperature for 1 h. The reaction mixture was cooled in 0 °C and carefully quenched with saturated NH_4Cl (75 mL), water (50 mL) and 2N HCl (50 mL). The mixture was filtered through celite, washing through with MeOH (150 mL) and EtOAc (2 x 250 mL). The filtrate was concentrated, the residue was diluted with EtOAc (300 mL), washed sequentially with 2N HCl (100 mL) and saturated brine (200 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford the title compound (10.37 g, 95 %) as a white solid.

^{1}H NMR (400 MHz, DMSO) δ 0.97 - 1.06 (2H, m), 1.29 - 1.42 (5H, m), 1.71 - 1.79 (4H, m), 2.29 - 2.36 (1H, m), 3.42 - 3.47 (2H, m), 4.27 (1H, t), 6.64 (2H, d), 6.98 (2H, d), 9.03 (1H, s); *m/z* 220 (EI+) M^+.

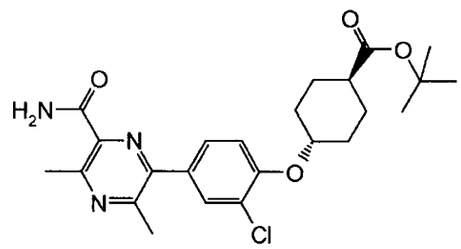
Example 26: (1r,4r)-4-(4-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)-2-chlorophenoxy)cyclohexanecarboxylic acid



A solution of **Intermediate 26-1** (561 mg, 1.22 mmol) in TFA (6.098 mL) allowed to stand at ambient temperature for 30 minutes. The reaction mixture was evaporated and ether was added to the residue to give a solid which was purified by recrystallisation from boiling absolute EtOH (~10 mL) to afford the title compound (293 mg, 59.5 %) as a yellow solid.

^{1}H NMR (400 MHz, DMSO) δ 1.45 - 1.59 (4H, m), 1.93 - 2.00 (2H, m) 2.08 - 2.10 (2H, m), 2.28 - 2.34 (1H, m), 2.59 (3H, s), 2.73 (3H, s), 4.48 - 4.52 (1H, m), 7.32 (1H, d), 7.59 (1H, s), 7.63 - 7.66 (1H, m), 7.86 (1H, d), 8.05 (1H, s), 12.10 (1H, s); *m/z* 404 $(M+H)^+$.

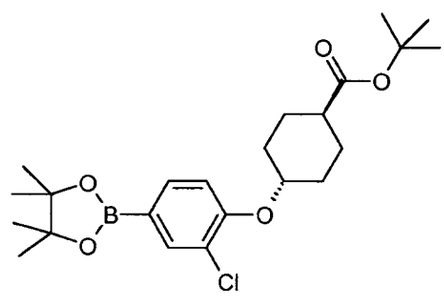
Intermediate 26-1: (1r,4r)-tert-Butyl 4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)-2-chlorophenoxy)cyclohexanecarboxylate



This compound was synthesised from **Intermediate 26-2** using similar conditions as described in **Intermediate 25-1** to give the title compound (561 mg, 71.5 %) as a yellow solid.

^{1}H NMR (400 MHz, DMSO) δ 1.47 (9H, s), 1.54 - 1.65 (4H, m), 1.96 - 2.04 (2H, m), 2.12 - 2.17 (2H, m), 2.32 - 2.39 (1H, m), 2.66 (3H, s), 2.80 (3H, s), 4.53 - 4.60 (1H, m), 7.39 (1H, d), 7.66 (1H, s), 7.71 (1H, d), 7.92 (1H, s), 8.12 (1H, s); *m/z* 460 $(M+H)^+$.

Intermediate 26-2: (1r,4r)-tert-Butyl 4-(2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)cyclohexanecarboxylate

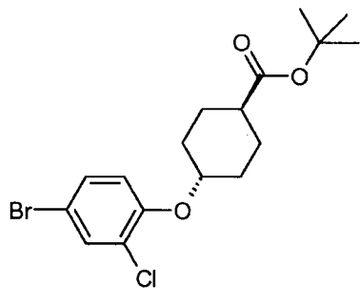


This compound was synthesised from **Intermediate 26-3** using similar conditions as described in **Intermediate 25-2** to give the title compound (4.23 g, 88 %) as a colourless oil which solidified on standing.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (12H, s), 1.45 (9H, s), 1.55 - 1.62 (4H, m), 2.03 - 2.08 (2H, m), 2.13 - 2.19 (2H, m), 2.24 - 2.31 (1H, m), 4.25 - 4.31 (1H, m), 6.92 (1H, d), 7.61 (1H, d), 7.79 (1H, s); *m/z* 436 (EI+) M^+.

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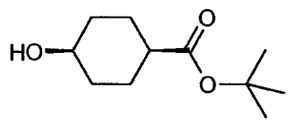
Intermediate 26-3: (1r,4r)-tert-Butyl 4-(4-bromo-2-chlorophenoxy)cyclohexane-carboxylate



To a solution of **Intermediate 26-4** (5.3 g, 26.46 mmol, CAS 931110-79-1), 4-bromo-2-chlorophenol (6.59 g, 31.76 mmol) and triphenylphosphine (8.33 g, 31.76 mmol) in THF (200 mL) was added diisopropyl azodicarboxylate (5.73 mL, 29.11 mmol). The solution was stirred at room temperature for 4 h. The reaction mixture was evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the title compound (4.27 g, 41.4 %) as a colourless oil.

^{1}H NMR (400 MHz, DMSO) δ 1.37 - 1.53 (13H, m), 1.88 - 2.03 (4H, m), 2.23 - 2.28 (1H, m), 4.35 - 4.39 (1H, m), 7.19 (1H, d), 7.42 - 7.44 (1H, m), 7.63 (1H, d); HPLC tR= 3.65 min.

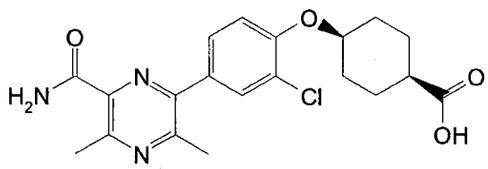
Intermediate 26-4: (1s,4s)-tert-Butyl 4-hydroxycyclohexanecarboxylate



To a suspension of (1s,4s)-4-hydroxycyclohexanecarboxylic acid (5 g, 34.68 mmol, CAS 3685-22-1) in toluene (160 mL) at 90 °C was added N,N-Dimethylformamide di-tert-butyl acetal (16.63 mL, 69.36 mmol) in one portion. The resultant solution was stirred at 90 °C for 1 h. A further portion of N,N-Dimethylformamide di-tert-butyl acetal (16.63 mL, 69.36 mmol) was then added and the reaction mixture stirred for 30 min at 90 °C and then room temperature overnight. Further N,N-Dimethylformamide di-tert-butyl acetal (10 mL) added dropwise over 10 minutes, the reaction mixture was stirred at 70 °C for 1 h and then allowed to cool. The reaction mixture was washed with 2M NaOH (100 mL), brine (100 mL) and then evaporated to give the title compound (5.30 g, 76 %) as an oil.

^{1}H NMR (400 MHz, DMSO) δ 1.36 - 1.39 (1H, m), 1.39 (9H, s), 1.41 - 1.51 (6H, m), 1.70 - 1.81 (2H, m), 2.19 - 2.25 (1H, m), 3.62 (1H, m), 4.32 (1H, d).

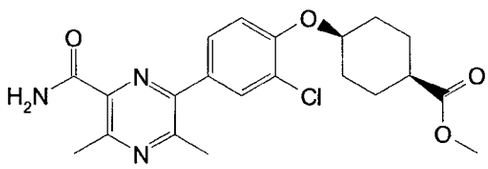
Example 27: (1s,4s)-4-(4-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)-2-chlorophenoxy)cyclohexanecarboxylic acid



This compound was synthesised from **Intermediate 27-1** using similar conditions as described in **Example 21** to give the title compound (182 mg, 50.8 %) as a white solid, which was crystallised from boiling absolute EtOH (~2 mL).

1H NMR (400 MHz, DMSO) δ 1.67 - 1.74 (4H, m), 1.76 - 1.93 (4H, m), 2.35 - 2.41 (1H, m), 2.60 (3H, s), 2.73 (3H, s), 4.77 (1H, brs), 7.28 (1H, d), 7.59 (1H, s), 7.65 (1H, dd), 7.87 (1H, d), 8.05 (1H, s), 12.07 (1H, s); *m/z* 404 $(M+H)^+$.

Intermediate 27-1: (1s,4s)-Methyl 4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)-2-chlorophenoxy)cyclohexanecarboxylate

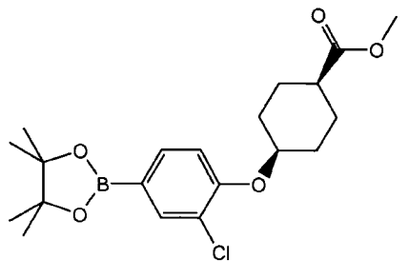


This compound was synthesised from **Intermediate 27-2** and **Intermediate 21-4** using similar conditions as described in **Intermediate 25-1** to give the title compound (371 mg, 48.1 %) as a white solid.

^{1}H NMR (400 MHz, DMSO) δ 1.68 - 1.75 (4H, m), 1.78 - 1.93 (4H, m), 2.52 - 2.54 (1H, m) 2.60 (3H, s), 2.73 (3H, s), 3.61 (3H, s), 4.76 - 4.79 (1H, m), 7.29 (1H, d), 7.59 (1H, s), 7.65 (1H, dd), 7.87 (1H, d), 8.05 (1H, s); *m/z* 418 $(M+H)^+$.

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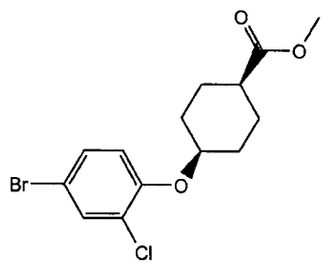
Intermediate 27-2: (1s,4s)-Methyl 4-(2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)cyclohexanecarboxylate



This compound was synthesised from **Intermediate 27-3** using similar conditions as described in **Intermediate 25-2** to give the title compound (4.73 g, 85 %) as a pale yellow oil which solidified on standing.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (12H, s), 1.60 - 1.68 (2H, m), 1.74 - 1.81 (2H, m), 1.98 - 2.09 (4H, m), 2.37 - 2.44 (1H, m), 3.69 (3H, s), 4.57 - 4.60 (1H, m), 6.90 (1H, d), 7.60 - 7.62 (1H, m), 7.80 (1H, d); *m/z* 394 (EI+) M^+.

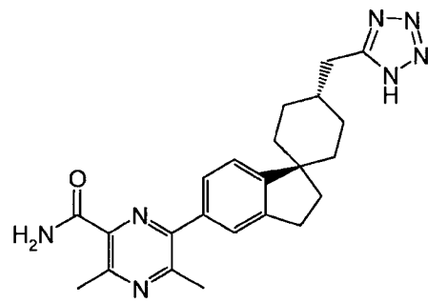
Intermediate 27-3: (1s,4s)-methyl 4-(4-bromo-2-chlorophenoxy)cyclohexane-carboxylate



This compound was synthesised from (1r,4r)-methyl 4-hydroxycyclohexanecarboxylate (CAS 6125-57-1) and 4-bromo-2-chlorophenol using similar conditions as described in **Intermediate 26-3** to give the title compound (4.88 g, 55.5 %) as a colourless oil.

^{1}H NMR (400 MHz, DMSO) δ 1.62 - 1.86 (8H, m), 3.60 (3H, s), 4.66 (1H, m), 7.15 (1H, d), 7.42 - 7.45 (1H, m), 7.64 (1H, d) one CH obscured; HPLC tR= 2.99 min.

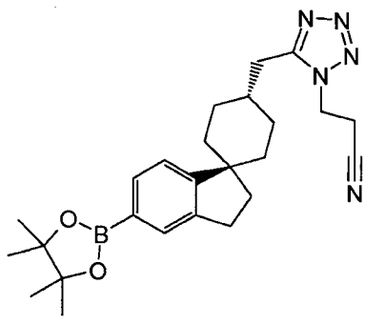
Example 28: 6-((1r,4s)-4-((2H-Tetrazol-5-yl)methyl)-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-5'-yl)-3,5-dimethylpyrazine-2-carboxamide



A solution of **Intermediate 21-4** (197 mg, 1.06 mmol), **Intermediate 28-1** (473 mg, 1.06 mmol) and tripotassium phosphate (449 mg, 2.11 mmol) in DME (10 mL), EtOH (6.25 mL) and water (2.5 mL) was degassed before addition of (1,1'-bis(diphenylphosphino)ferrocene)-dichloropalladium(II) (43.5 mg, 0.05 mmol). The reaction mixture was heated to 80 °C, under nitrogen, and left to stir overnight for 5hrs. The reaction mixture was allowed to cool to room temperature and then evaporated. The residue was acidfied with 2N HCl (3 mL), diluted with water (20 mL) and extracted into EtOAc (4 x 50 mL). The organic extracts were combined, dried over $MgSO_4$, 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 evaporated to dryness to afford the title compound (51.9 mg, 11.76 %) as a white solid.

^{1}H NMR (400 MHz, DMSO) δ 1.23 - 1.38 (2H, m), 1.58 - 1.73 (6H, m), 1.86 - 1.96 (1H, m), 2.04 (2H, t), 2.63 (3H, s), 2.79 (3H, s), 2.91 (2H, d), 2.97 (2H, t), 7.33 (1H, d), 7.55 (1H, d), 7.60 (1H, s), 7.62 (1H, s), 8.02 (1H, s); NH not seen; *m/z* 418 $(M+H)^+$.

Intermediate 28-1: 3-(5-(((1r,4s)-5'-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-4-yl)methyl)-2H-tetrazol-2-yl)propanenitrile

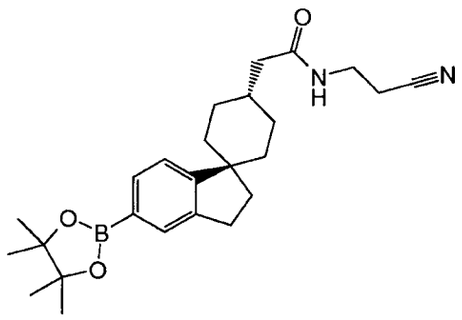


To a solution of triphenylphosphine (1.453 g, 5.54 mmol) and **Intermediate 28-2** (900 mg, 2.13 mmol) in THF (25.400 mL) in an ice bath was added diisopropyl azodicarboxylate (1.133 mL, 5.75 mmol). The resulting yellow solution was allowed to stir at 0 °C, after 2 minutes azidotrimethylsilane (0.820 mL, 6.18 mmol) was added dropwise. After 17 hours at ambient temperature further triphenylphosphine (1.453 g, 5.54 mmol), diisopropyl azodicarboxylate (1.133 mL, 5.75 mmol) and azidotrimethylsilane (0.820 mL, 6.18 mmol) were added and the suspension was stirred at ambient temperature for a further 24 hours. The reaction mixture was cooled in an ice bath and a solution of Sodium nitrite (162 mg, 2.34 mmol) in water (3 mL) was added and after 30 minutes a solution of ammonium cerium(IV) nitrate (1285 mg, 2.34 mmol) in water (10 mL) was added (CAUTION: Gas evolution). The reaction mixture was stirred for a further 45 minutes. The reaction mixture was poured into water (50 mL) and extracted with DCM (200 mL and 100 mL). The organic extracts were combined, dried over $MgSO_4$, filtered and evaporated to afford crude product.

The crude product was purified by flash silica chromatography, elution gradient 0 to 80% EtOAc in isohexane. Mixed fractions were evaporated to dryness to afford the title compound (487 mg, 51.1 %) as a cream solid.

^{1}H NMR (400 MHz, DMSO) δ 1.20 - 1.38 (14H, m), 1.40 - 1.50 (2H, m), 1.53 - 1.70 (4H, m), 1.83 - 1.97 (3H, m), 2.82 (2H, t), 2.89 (2H, d), 3.18 (2H, t), 4.69 (2H, t), 7.16 (1H, d), 7.48 (1H, d), 7.49 (1H, s); *m/z* 448 $(M+H)^+$.

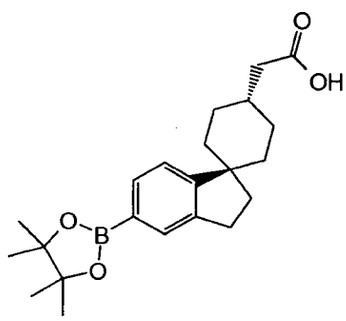
Intermediate 28-2: N-(2-Cyanoethyl)-2-((1r,4s)-5'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-4-yl)acetamide



3-Aminopropionitrile (0.215 mL, 2.94 mmol) was added to a stirred solution of **Intermediate 28-3** (725 mg, 1.96 mmol), N-ethyldiisopropylamine (1.023 mL, 5.87 mmol) and PyBROP (1.369 g, 2.94 mmol) in DCM (50 mL). The resulting solution was stirred at ambient temperature for 4 hours. The reaction mixture was evaporated to dryness and redissolved in EtOAc (125 mL), and washed sequentially with 2M HCl (75 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 0 to 100% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the title compound (900 mg, 109 %) as a white foam.

^{1}H NMR (400 MHz, DMSO) δ 1.09 - 1.20 (2H, m), 1.27 (12H, s), 1.42 - 1.46 (2H, m), 1.53 - 1.67 (4H, m), 1.72 - 1.79 (1H, m), 1.90 (2H, t), 2.03 (2H, d), 2.63 (2H, t), 2.81 (2H, t), 3.26 - 3.29 (2H, m), 7.17 (1H, d), 7.46 (1H, d), 7.48 (1H, s), 8.16 (1H, t); *m/z* 423 $(M+H)^+$.

Intermediate 28-3: 2-((1r,4s)-5'-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-4-yl)acetic acid

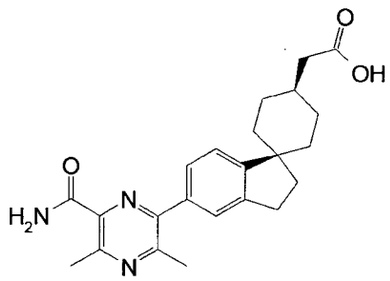


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TFA (15.90 mL) was added to a stirred solution of **Intermediate 29-3** (802 mg, 1.88 mmol) in DCM (15.90 mL) at 0 °C. The resulting solution was stirred at 0 °C for 30 minutes, the reaction mixture was evaporated and the residue was azeotroped with toluene to afford the title compound (676 mg, 97 %) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 - 1.28 (2H, m), 1.33 (12H, s), 1.56 - 1.70 (4H, m), 1.76 - 1.82 (2H, m), 1.85 - 1.93 (1H, m), 1.97 (2H, t), 2.31 (2H, d), 2.87 (2H, t), 7.15 (1H, d), 7.64 - 7.67 (2H, m); COOH not seen; *m/z* 370 (EI+) M^+.

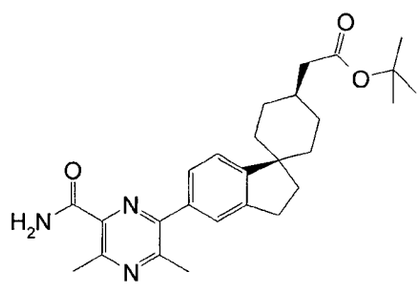
Example 29: N: 2-((1s,4r)-5'-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-4-yl)acetic acid



A solution of **Intermediate 29-1** (0.748 g, 1.66 mmol) in TFA (8 mL) allowed to stand at room temperature for 0.5 h. The reaction mixture was evaporated to a solid. The crude product was purified by recrystallisation twice from MeOH to afford the title compound (0.201 g, 30.7 %) as an off-white crystalline solid.

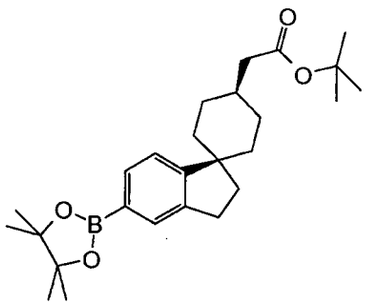
^{1}H NMR (400 MHz, DMSO) δ 1.40 - 1.56 (4H, m), 1.66 - 1.80 (4H, m), 1.96 (2H, t), 2.03 (1H, br s), 2.39 (2H, d), 2.58 (3H, s), 2.73 (3H, s), 2.89 (2H, t), 7.46 - 7.50 (2H, m), 7.54 (1H, s), 7.57 (1H, s), 7.97 (1H, s), 11.99 (1H, s); *m/z* 394 $(M+H)^+$.

Intermediate 29-1: N: *tert*-Butyl 2-((1s, 4r)-5'-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-4-yl)acetate

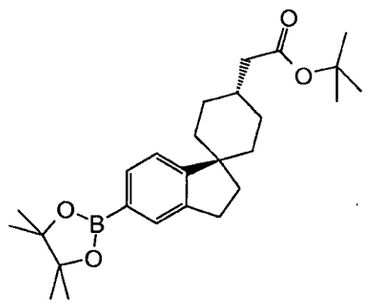


This compound was synthesised from **Intermediate 29-2** using similar conditions as described in **Intermediate 25-1** to give the title compound (0.748 g, 50.3 %) as a solid which was a 2:1 mixture with the other diastereoisomer. *m/z* 450 $(M+H)^+$.

Intermediate 29-2: N: tert-Butyl 2-((1s,4r)-5'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-4-yl)acetate and Intermediate 29-3: tert-Butyl 2-((1r,4s)-5'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-4-yl)acetate



Intermediate 29-2



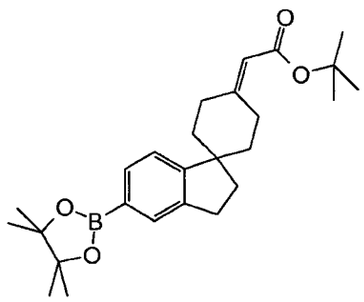
Intermediate 29-3

To a solution of **Intermediate 29-4** (5.42 g, 12.77 mmol) in THF (125 mL), under nitrogen, was added 10% (w/w) palladium on carbon (1.4 g). The atmosphere was replaced with hydrogen and the reaction stirred at room temperature overnight. The reaction mixture was filtered and evaporated to a colourless oil. This was dissolved in methanol (*ca.* 20 mL) and cooled in a dry ice/acetone bath to produce a white solid. The suspension was allowed to warm and then evaporated to give the crude product as a white solid. This was recrystallised by dissolving in DCM (*ca.* 20 mL) adding methanol (*ca.* 20 mL) and cooling in a dry ice / acetone bath. The resultant suspension was filtered and the collected solid dried to give **Intermediate 29-3** (2.290 g, 42.1 %) as a white solid.

^{1}H NMR (400 MHz, DMSO) δ 1.17 - 1.21 (2H, m), 1.26 (12H, s), 1.40 (9H, s), 1.44 - 1.67 (7H, m), 1.90 (2H, t), 2.13 (2H, d), 2.81 (2H, t), 7.18 (1H, d), 7.46 - 7.48 (2H, m).

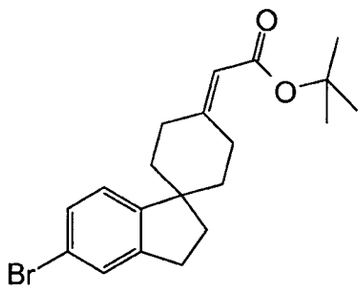
The mother liquors were evaporated to give **Intermediate 29-2** (1.610 g, 29.6 %) as a solid as a 2:1 mixture with the other diastereoisomer.

Intermediate 29-4: N: *tert*-Butyl 2-(5'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-4-ylidene)acetate



This compound was synthesised from **Intermediate 29-5** using similar conditions as described in **Intermediate 25-2** to give the title compound (5.42 g, 66.4 %) as a solid. ^{1}H NMR (400 MHz, DMSO) δ 1.28 (12H, t), 1.42 (8H, s), 1.60 - 1.73 (4H, m), 2.04 - 2.13 (3H, m), 2.26 (1H, d), 2.31 - 2.36 (1H, m), 2.87 (2H, t), 3.66 (1H, d), 5.60 (1H, s), 7.17 (1H, d), 7.45 - 7.47 (1H, m), 7.50 (1H, s) one proton obscured; *m/z* 423 $(M-H)^-$.

Intermediate 29-5: N: tert-Butyl 2-(5'-bromo-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-4-ylidene)acetate

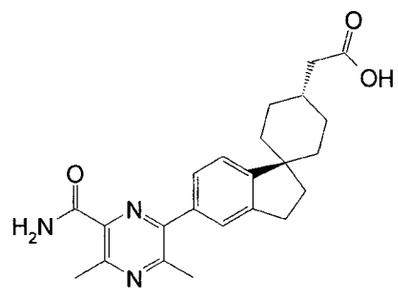


To a solution of *tert*-butyldiethylphosphonoacetate (8.80 mL, 37.47 mmol) in THF (100 mL) was added 60% w/w sodium hydride (1.498 g, 37.47 mmol). The reaction mixture was stirred at room temperature for 30 min. A solution of 5'-bromo-2',3'-dihydrospiro[cyclohexane-1,1'-inden]-4-one (prepared according to the procedure described in WO 2004/047755, CAS 701232-89-5) (8.716 g, 31.22 mmol) in THF (50 mL) was added and stirring continued at room temp for 1 hour. The reaction mixture was quenched with saturated brine (150 mL), extracted with EtOAc (2 x 200 mL), the organic layer was dried over Na_2SO_4, filtered and evaporated to afford the crude product as a brown oil (13.66g). The crude oil was triturated with isohexane to give a solid which was

collected by filtration and dried under vacuum to give the title compound (4.84 g, 41 %) as a beige solid. A second crop of the title compound (2.42 g, 21 %) was obtained from the filtrate.

^{1}H NMR (400 MHz, DMSO) δ 1.42 (9H, s), 1.59 - 1.69 (4H, m), 2.05 - 2.12 (3H, m), 2.24 - 2.35 (2H, m), 2.88 (2H, t), 3.66 (1H, d), 5.60 (1H, s), 7.14 (1H, d), 7.27 - 7.30 (1H, m), 7.38 (1H, t).

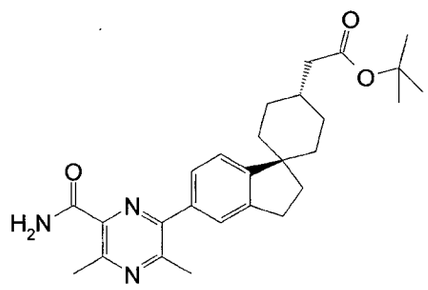
Example 30: 2-((1r,4s)-5'-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-4-yl)acetic acid



A solution of **Intermediate 30-1** (1.16 g, 2.58 mmol) in TFA (12 mL) was allowed to stand at RT for 0.5 h. The reaction mixture was evaporated to a solid. The crude product was purified by recrystallisation from MeOH to afford the title compound (0.648 g, 63.8 %) as a white crystalline solid.

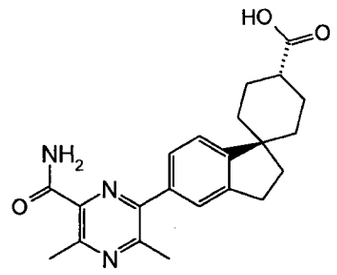
^{1}H NMR (300 MHz, DMSO) δ 1.14 - 1.27 (2H, m), 1.51 - 1.80 (7H, m), 1.98 (2H, t), 2.17 (2H, d), 2.58 (3H, s), 2.73 (3H, s), 2.90 (2H, t), 7.30 (1H, d), 7.50 (1H, d), 7.54 (1H, s), 7.62 (1H, s), 8.01 (1H, s), 12.05 (1H, s); *m/z* 394 $(M+H)^+$.

Intermediate 30-1: tert-Butyl 2-((1r,4s)-5'-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-4-yl)acetate



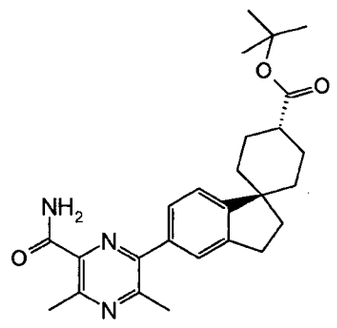
This compound was synthesised from **Intermediate 29-3** using similar conditions as described in **Intermediate 25-1** to give the title compound (1.260 g, 89 %) as a solid.
^{1}H NMR (400 MHz, DMSO) δ 1.20 - 1.23 (2H, m), 1.41 (9H, s), 1.51 - 1.69 (7H, m), 1.97 (2H, t), 2.14 (2H, d), 2.57 (3H, s), 2.73 (3H, s), 2.90 (2H, t), 7.29 (1H, d), 7.47 - 7.57 (2H, m), 7.53 (1H, s), 7.96 (1H, s); *m/z* 450 $(M+H)^+$.

Example 31: (1r,4s)-5'-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-4-carboxylic acid



4M HCl in dioxane (10 mL, 0.43 mmol) was added to **Intermediate 31-1** (188 mg, 0.43 mmol) in DCM (5 mL). The resulting solution was stirred for 16 hours. The resulting mixture was evaporated to dryness and the residue was slurried with ether then filtered to afford the title compound (158 mg, 96 %) as a pale yellow solid.
^{1}H NMR (400 MHz, DMSO) δ 1.48 - 1.73 (6H, m), 1.85 - 1.93 (2H, m), 2.00 (2H, t), 2.28 - 2.36 (1H, m), 2.58 (3H, s), 2.73 (3H, s), 2.91 (2H, t), 7.29 (1H, d), 7.50 (1H, d), 7.56 (3H, d), 7.98 (1H, s); *m/z* 380 $(M+H)^+$.

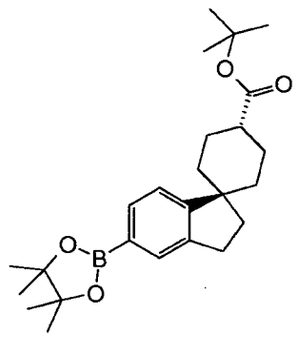
Intermediate 31-1: (1r,4s)-tert-Butyl 5'-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-4-carboxylate



This compound was synthesised from **Intermediate 31-2** and **Intermediate 21-4** using similar conditions as described in **Intermediate 25-1** to give the title compound (188 mg, 32.0 %) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (9H, s), 1.54 - 1.68 (6H, m), 1.86 - 1.96 (2H, m), 2.02 (2H, t), 2.16 - 2.28 (1H, m), 2.60 (3H, s), 2.82 - 2.95 (5H, m), 5.40 (1H, s), 7.15 (1H, d), 7.30 (1H, d), 7.33 (1H, dd), 7.72 (1H, s); *m/z* 436 $(M+H)^+$.

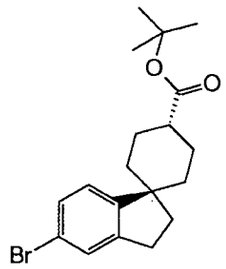
Intermediate 31-2: (1r,4s)-tert-Butyl 5'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-4-carboxylate



This compound was synthesised from **Intermediate 31-3** using similar conditions as described in **Intermediate 25-2** to give the title compound (3.13 g, 73.7 %) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (12H, s), 1.39 (19H, s), 1.50 (2H, d), 1.50 - 1.60 (6H, m), 1.80 - 1.90 (2H, m), 1.93 (2H, t), 2.15 - 2.25 (1H, m), 2.81 (2H, t), 7.07 (1H, d), 7.59 (1H, dd), 7.59 (1H, s).

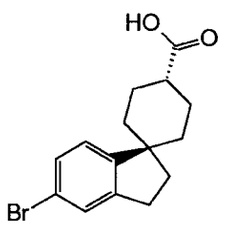
Intermediate 31-3: (1r,4s)-tert-Butyl 5'-bromo-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-4-carboxylate



To a solution of **Intermediate 31-4** (3.47 g, 11.22 mmol) in tert-butanol (100 mL) was added DMAP (0.411 g, 3.37 mmol) and di-tert-butyl dicarbonate (14.70 g, 67.34 mmol) (effervescence). The resulting solution was stirred at ambient temperature for 16 hours. Saturated $NaHCO_3$ (100 mL) was added and the reaction stirred for 30 minutes before adding EtOAc (400 mL). The organic layer was separated and washed with water (200 mL) then saturated brine (200 mL) and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the title compound (3.76 g, 92 %) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (9H, s), 1.52 - 1.67 (6H, m), 1.90 - 1.97 (2H, m), 1.98 - 2.03 (2H, m), 2.20 - 2.30 (1H, m), 2.86 (2H, t), 6.96 (1H, d), 7.28 (1H, dt), 7.32 (1H, d).

Intermediate 31-4: (1r,4s)-5'-Bromo-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-4-carboxylic acid

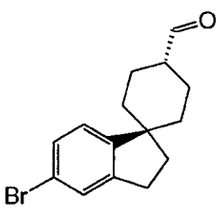


Oxone (6.98 g, 11.36 mmol) was added to **Intermediate 31-5** (3.33 g, 11.36 mmol), in DMF (70 mL). The resulting suspension was stirred for 16 hours. The reaction mixture was diluted with EtOAc (300 mL), and washed sequentially with water (3 x 150 mL) and saturated brine (150 mL). The organic layer was evaporated to afford the title compound (3.51 g, 100 %).

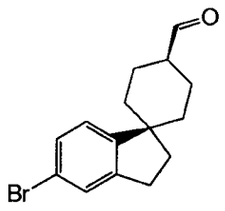
^{1}H NMR (400 MHz, DMSO) δ 1.30 - 1.73 (6H, m), 1.80 - 2.00 (4H, m), 2.20 - 2.32 (1H, m), 2.83 (2H, t), 7.12 (1H, d), 7.31 (1H, dt), 7.36 (1H, t), 12.03 (1H, s); *m/z* 309 M-H$^-$.

Intermediate 31-5: (1r,4s)-5'-Bromo-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-4-carbaldehyde and

Intermediate 31-6: (1s,4r)-5'-Bromo-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-4-carbaldehyde



Intermediate 31-5



Intermediate 31-6

(Methoxymethyl)triphenylphosphonium chloride (20.76 g, 60.55 mmol) was added to a stirred suspension of potassium tert-butoxide (6.79 g, 60.55 mmol) in 1,4-dioxane (113 mL) at ambient temperature, over a period of 10 minutes under nitrogen. The resulting red solution was stirred at ambient temperature for 2 hours and then a solution of 5'-bromo-2',3'-dihydrospiro[cyclohexane-1,1'-inden]-4-one (prepared according to the procedure described in WO 2004/047755, CAS 701232-89-5) (7.35 g, 26.33 mmol) in 1,4-dioxane (63.4 mL) was added over a period of 10 minutes under nitrogen. The resulting solution was stirred at ambient temperature for 1 hour and then heated at 70 °C for 16 hours. The reaction mixture was poured into water (200 mL), extracted with EtOAc (2 x 200 mL), the organic layer was washed with saturated brine (200 mL) and evaporated to afford a black oil. To the crude oil was added EtOAc and isohexane (1:3, 200 mL) to give a solid which was collected by filtration, washed with EtOAc and isohexane (75 mL). The filtrate was evaporated to afford a solid residue, which was added to 90% acetic acid in water (200 mL, 3493.64 mmol). The resulting solution was stirred at 70 °C for 16 hours, the mixture was allowed to cool, evaporated to dryness and the crude product was purified by flash silica chromatography, elution gradient 0 to 15% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford **Intermediate 31-5** (3.33 g, 43.1 %) and **Intermediate 31-6** (1.17g, 15%) as colourless gums.

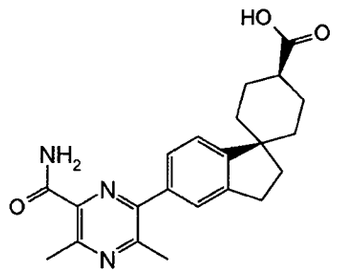
Intermediate 31-5:

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 - 1.67 (6H, m), 1.84 - 2.00 (4H, m), 2.19 - 2.29 (1H, m), 2.80 (2H, t), 6.92 (1H, m), 7.22 (1H, m), 7.23 (1H, dd), 9.61 (1H, d); *m/z* (EI+) 292 M^+.

Intermediate 31-6:

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 - 1.60 (4H, m), 1.68 - 1.80 (2H, m), 1.93 (2H, t), 2.09 (2H, dt), 2.37 - 2.44 (1H, m), 2.75 - 2.85 (2H, m), 6.90 (1H, d), 7.19 (1H, d), 7.24 (1H, d), 9.72 (1H, s); *m/z* 292 (EI+) M^+.

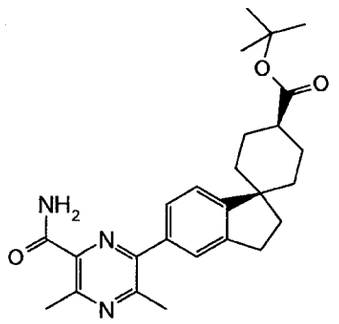
Example 32: (1s,4r)-5'-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-4-carboxylic acid



This compound was synthesised from **Intermediate 32-1** using similar conditions as described in **Example 31** to give the title compound (176 mg, 59.9 %) as a pale yellow solid.

^{1}H NMR (400 MHz, DMSO) δ 1.45 (2H, dd), 1.72 (3H, dd), 1.77 (1H, m), 1.96 (1H, s), 1.99 (3H, t), 2.58 (4H, s), 2.73 (3H, s), 2.90 (2H, t), 7.25 (1H, d), 7.49 (1H, dd), 7.55 (1H, d), 7.57 (1H, s), 7.97 (1H, s); *m/z* 380 $(M+H)^+$.

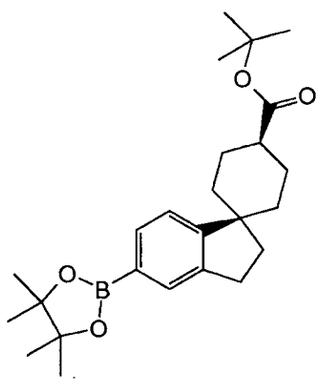
Intermediate 32-1: (1s,4r)-tert-Butyl 5'-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-4-carboxylate



This compound was synthesised from **Intermediate 32-2** and **Intermediate 21-4** using similar conditions as described in **Intermediate 25-1** to give the title compound (342 mg, 58.2 %) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 – 1.50 (2H, m), 1.44 (9H, s), 1.65 – 1.75 (2H, m), 1.75 – 1.85 (2H, m), 1.95 – 2.08 (4H, m), 2.45 – 2.51 (1H, m), 2.60 (3H, s), 2.85 – 2.93 (5H, m), 5.39 (1H, s), 7.26 – 7.35 (3H, m), 7.73 (1H, s); *m/z* 436 $(M+H)^+$.

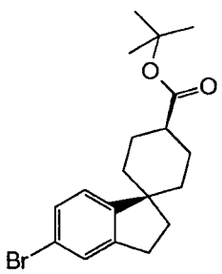
Intermediate 32-2: (1s,4r)-tert-Butyl 5'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-4-carboxylate



This compound was synthesised from **Intermediate 32-3** using similar conditions as described in **Intermediate 25-2** to give the title compound (0.935 g, 62.3 %) as a colourless oil which solidified on standing.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (12H, s), 1.44 – 1.47 (2H, m), 1.50 (9H, s), 1.67 – 1.86 (4H, m), 1.96 (2H, t), 2.01 – 2.09 (2H, m), 2.48 – 2.53 (1H, m), 2.83 – 2.90 (2H, m), 7.25 (1H, d), 7.63 (1H, d), 7.67 (1H, s); *m/z* 412 (EI+) M^+.

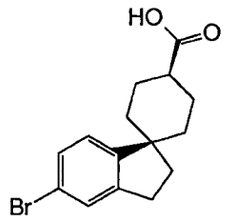
Intermediate 32-3: (1s,4r)-tert-Butyl 5'-bromo-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-4-carboxylate



This compound was synthesised from **Intermediate 32-4** using similar conditions as described in **Intermediate 31-3** to give the title compound (1.330 g, 89 %) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 – 1.46 (2H, m), 1.49 (9H, s), 1.67 – 1.81 (4H, m), 1.96 (2H, t), 2.00 – 2.06 (2H, m), 2.48 – 2.53 (1H, m), 2.85 (2H, t), 7.08 (1H, d), 7.26 – 7.28 (1H, m), 7.32 (1H, s); *m/z* 364 (EI+) M^+.

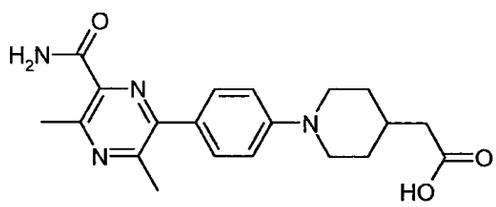
Intermediate 32-4: (1s,4r)-5'-Bromo-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-4-carboxylic acid



This compound was synthesised from **Intermediate 31-6** using similar conditions as described in **Intermediate 31-4** to give the title compound (1.27g, 100%) as a solid.

^{1}H NMR (400 MHz, DMSO) δ 1.35 – 1.44 (2H, m), 1.60 – 1.73 (4H, m), 1.85 – 2.00 (4H, m), 2.53 (1H, q), 2.82 (2H, t), 7.08 (1H, d), 7.30 (1H, dt), 7.37 (1H, t), 12.12 (1H, s); *m/z* 309 $(M-H)^-$.

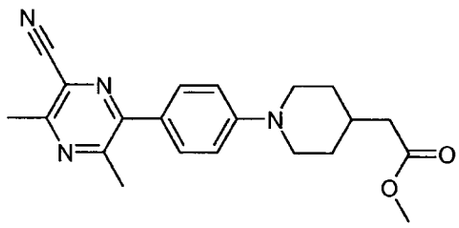
Example 33: 2-(1-(4-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)piperidin-4-yl)acetic acid



Powdered potassium hydroxide (44.5 mg, 0.79 mmol) was added in one portion to **Intermediate 33-1** (60 mg, 0.16 mmol) in tert-butanol (5 mL). The resulting pale yellow suspension was stirred at 40 °C for 30 minutes. The reaction mixture was quenched with acetic acid (0.073 mL, 1.27 mmol) in EtOH (10.0 mL) and the resulting solution stirred for a further 10 minutes before being evaporated to dryness. The resulting solid was partitioned between water (20 mL) and EtOAc (20 mL). The aqueous layer showed a pH= 6. The organic layer was separated and the aqueous re-extracted with EtOAc (2 x 25 mL). The combined organics were washed with brine (15 mL), dried over $MgSO_4$ and evaporated in vacuo to give crude product. This was recrystallised from hot EtOH (6 mL)

to give a yellow solid which was washed with ethylacetate (5 mL) and dried under vacuum at room temperature to give the title compound (41.0 mg, 70.2 %) as a yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 1.28 (2H, m), 1.76 (2H, m), 1.86 (1H, m), 2.15 (2H, d), 2.60 (3H, s), 2.71 (3H, s), 2.76 (2H, d), 3.79 (2H, d), 7.00 (2H, d), 7.55 (1H, s), 7.60 (2H, d), 7.96 (1H, s); *m/z* 369 $(M+H)^+$.

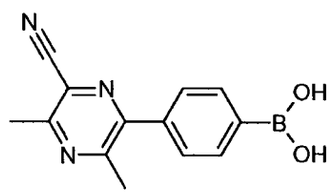
Intermediate 33-1: ethyl 2-(1-(4-(6-cyano-3,5-dimethylpyrazin-2-yl)phenyl) piperidin-4-ylacetate



Pyridine (0.050 mL, 0.62 mmol) was added dropwise to **Intermediate 33-2** (78 mg, 0.31 mmol), ethyl 2-(piperidin-4-yl)acetate (79 mg, 0.46 mmol) and Copper(II) acetate (56.0 mg, 0.31 mmol) in anhydrous DCM (10 mL) The resulting blue solution was stirred at 25 °C for 16 hours. The reaction mixture was diluted with DCM (25 mL), and washed with a 20% aqueous EDTA solution (25 mL). The organic layer was evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 70% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the title compound (53.0 mg, 45.4 %) as a pale yellow soild.

^{1}H NMR (400 MHz, DMSO) δ 1.20 (5H, m), 1.69 (2H, d), 1.84 (1H, m), 2.22 (2H, m), 2.61 (6H, s), 2.71 (2H, m), 3.77 (2H, d), 4.02 (2H, m), 6.97 (2H, m), 7.47 (2H, m); *m/z* 379 $(M+H)^+$.

Intermediate 33-2: 4-(6-Cyano-3,5-dimethylpyrazin-2-yl)phenylboronic acid

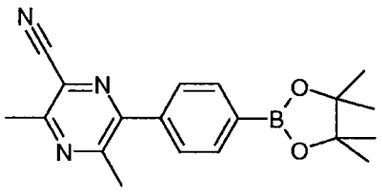


Sodium periodate (5.02 g, 23.45 mmol) was added in one portion to **Intermediate 33-3** (2.62 g, 7.82 mmol) in THF (80 mL) and water (20 mL) and the cloudy suspension was

stirred at room temperature for 30 minutes. 1M HCl (5.47 mL, 5.47 mmol) was added and the reaction mixture was stirred at room temperature for 2 hours.. The THF was evaporated under reduced pressure, the reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (2 x 100 mL). The combined extracts were washed with water (2 x 30 mL) and brine (30 mL), dried over sodium sulfate, concentrated to dryness by rotary evaporation to give the title compound (1.980 g, 100 %).

^{1}H NMR (400 MHz, DMSO) δ 2.62 (3H, s), 2.70 (3H, s), 7.60 (2H, d), 7.92 (2H, d), 8.16 (2H, s); *m/z* 254 $(M+H)^+$.

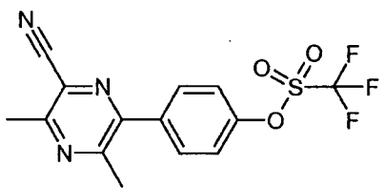
Intermediate 33-3: 3,5-Dimethyl-6-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrazine-2-carbonitrile



This compound was synthesised from **Intermediate 33-4** using similar conditions as described in **Intermediate 25-2** to give the title compound (70.0 mg, 50.4 %) as a white crystalline solid.

^{1}H NMR (400 MHz, DMSO) δ 1.39 (12H, s), 2.68 (3H, s), 2.77 (3H, s), 7.73 (2H, d), 7.88 (2H, d); HPLC tR= 2.85 min.

Intermediate 33-4: 4-(6-Cyano-3,5-dimethylpyrazin-2-yl)phenyl trifluoromethanesulfonate

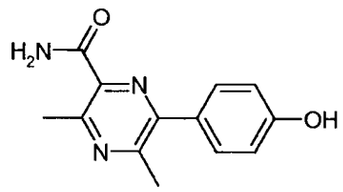


Trifluoromethanesulphonic anhydride (27.3 mL, 166.57 mmol) was added to a stirred solution of **Intermediate 33-5** (10.13 g, 41.64 mmol) in DCM (400 mL) cooled to 0 °C, over a period of 20 minutes under nitrogen. The resulting slurry was then allowed to warm to ambient temperature overnight under a nitrogen atmosphere. Triethylamine (46.4 mL, 333.14 mmol) was added dropwise over 10 minutes (under ice bath cooling, keeping

temperature between 5-10°C) and the resulting solution stirred at 30 °C for 3 hours under nitrogen. The reaction mixture was diluted with DCM (200 mL), and washed sequentially with water (200 mL), saturated $NaHCO_3$ (200 mL), and saturated brine (100 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 0 to 40% EtOAc in isohexane. Pure fractions were evaporated to dryness to the title compound (9.87 g, 66.3 %) as a yellow oil.

^{1}H NMR (400 MHz, DMSO) δ 2.68 (3H, s), 2.78 (3H, s), 7.74 (2H, d), 7.93 (2H, d); m/z = mass ion not seen; HPLC tR= 2.84 min.

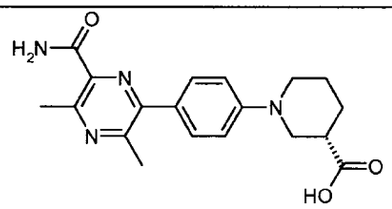
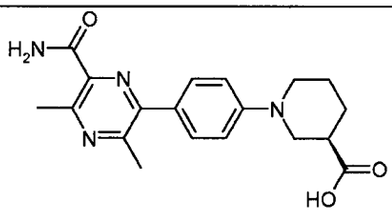
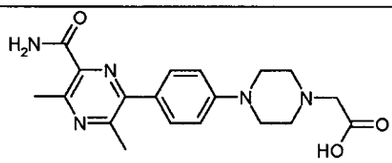
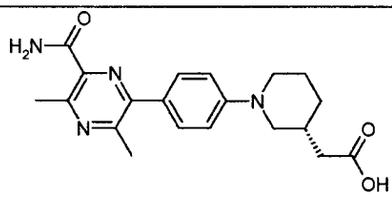
Intermediate 33-5: 6-(4-Hydroxyphenyl)-3,5-dimethylpyrazine-2-carboxamide

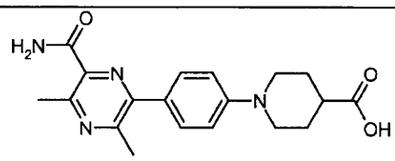
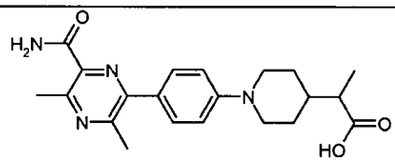


This compound was synthesised from **Intermediate 21-4** and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (CAS 269409-70-3) using similar conditions as described in **Intermediate 25-1** to give the title compound (10.13 g, 97 %) as an orange solid.

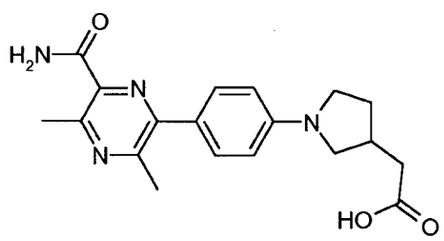
^{1}H NMR (400 MHz, DMSO) δ 2.58 (3H, s), 2.71 (3H, s), 6.87 (2H, d), 7.56 - 7.60 (3H, m), 7.95 (1H, s), 9.73 (1H, s); *m/z* 244 $(M+H)^+$.

The following examples were synthesised using similar conditions as described in **Example 33** to give the desired compounds **34-39**.

Example	Structure	^{1}H NMR (400 MHz, DMSO) δ	*m/z* $(M+H)^+$
34		1.58 (2H, m), 1.72 (1H, m), 1.92 (1H, m), 2.53 (1H, m), 2.60 (3H, s), 2.72 (3H, s), 2.90 (1H, m), 3.04 (1H, m), 3.58 (1H, m), 3.76 (1H, m), 7.02 (2H, d), 7.56 (1H, s), 7.62 (2H, d), 7.96 (1H, s)	355
35		1.66 (2H, m), 1.80 (1H, m), 2.00 (1H, m), 2.61 (1H, m), 2.67 (3H, s), 2.78 (3H, s), 2.98 (1H, t), 3.14 (1H, t), 3.65 (1H, d), 3.83 (1H, d), 7.10 (2H, d), 7.63 (1H, s), 7.69 (2H, d), 8.02 (1H, s)	355
36		2.60 (3H, s), 2.71 (7H, m), 3.20 (2H, s), 3.27 (4H, m), 7.03 (2H, d), 7.56 (1H, s), 7.63 (2H, d), 7.96 (1H, s)	370
37		1.20 (1H, m), 1.55 (1H, m), 1.69 (1H, m), 1.81 (1H, m), 1.98 (1H, m), 2.17 (1H, m), 2.28 (1H, m), 2.60 (4H, m), 2.71 (3H, s), 2.81 (1H, t), 3.73 (2H, t), 7.00 (2H, d), 7.56 (1H, s), 7.61 (2H, d), 7.96 (1H, s), 12.11 (1H, s)	369

38		1.64 (2H, m), 1.90 (2H, m), 2.45 (1H, m), 2.60 (3H, s), 2.71 (3H, s), 2.87 (2H, t), 3.76 (2H, d), 7.03 (2H, d), 7.56 (1H, s), 7.61 (2H, d), 7.96 (1H, s), 12.19 (1H, s)	355
39		1.12 (3H, d), 1.39 (2H, m), 1.75 (3H, m), 2.27 (1H, m), 2.66 (3H, s), 2.77 (5H, m), 3.91 (2H, m), 7.08 (2H, d), 7.62 (1H, s), 7.67 (2H, d), 8.02 (1H, s), 12.14 (1H, s)	383

Example 40: 2-(1-(4-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)pyrrolidin-3-yl)acetic acid

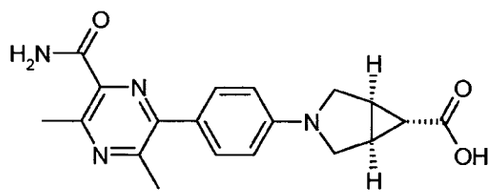


Powdered potassium hydroxide (122 mg, 2.17 mmol) was added in one portion to **Intermediate 40-1** (170 mg, 0.43 mmol) in tert-butanol (5 mL). The resulting yellow suspension was stirred at 40 °C for 90 minutes. The reaction mixture was quenched with acetic acid (0.198 mL, 3.47 mmol) in EtOH (10.0 mL) and the resulting solution stirred for a further 10 minutes before being evaporated to dryness. The resulting solid was partitioned between water (20 mL) and EtOAc (20 mL). The aqueous layer showed a pH= 6. The organic layer was separated and evaporated to dryness to afford crude product (185 mg). The crude product was dissolved in DCM (5.00 mL) and TFA (1.0 mL, 12.99 mmol) was added. The brown solution was stirred at room temperature for 2 hours. The reaction mixture was purified by ion exchange chromatography, using an SCX column. The column was eluted with DCM (100 mL) followed by MeOH (100 mL) and then the desired product

was eluted from the column using 0.35M NH_3/MeOH (100 mL) and fractions containing the product were evaporated to dryness to afford crude product as a yellow solid (110 mg). This 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 MeOH as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (76 mg, 49.5 %) as a yellow solid.

^{1}H NMR (400 MHz, DMSO) δ 1.65 (1H, m), 2.13 (1H, m), 2.38 (2H, m), 2.55 (4H, m), 2.65 (3H, s), 2.93 (1H, t), 3.26 (1H, m), 3.33 (1H, m), 3.47 (1H, m), 6.55 (2H, d), 7.50 (1H, s), 7.56 (2H, d), 7.89 (1H, s), 12.13 (1H, s); *m/z* 355 $(M+H)^+$.

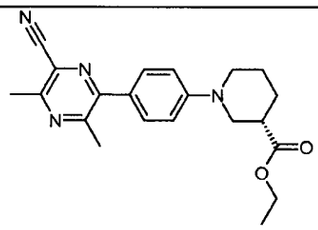
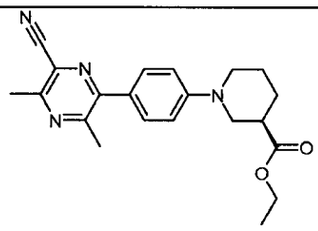
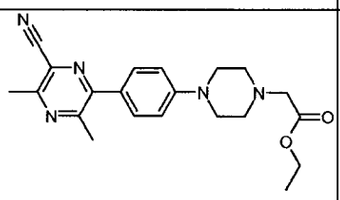
Example 41 (1R,5S,6r)-3-(4-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid

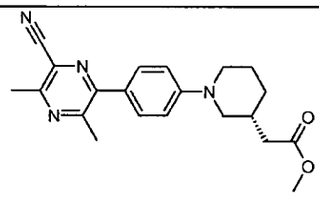
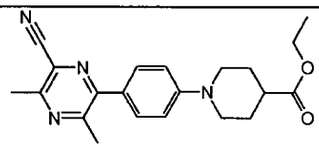
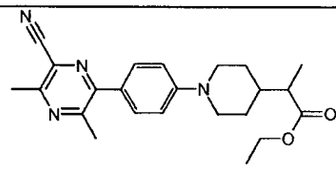
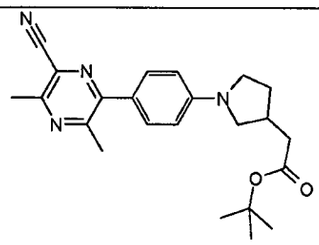
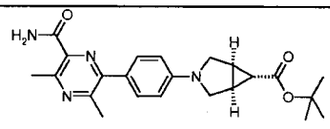


Powdered potassium hydroxide (101 mg, 1.79 mmol) was added in one portion to **Intermediate 41-1** (175 mg, 0.45 mmol) in tert-butanol (4 mL) at 40 °C under nitrogen. The resulting suspension was stirred at 40 °C for 6 hours. A thick precipitate formed so the reaction was quenched with acetic acid (0.205 mL, 3.59 mmol) in EtOH (10 mL) and the resulting solution stirred for a further 10 minutes before being evaporated to dryness. The crude material was treated with a 5% HCl in methanol solution (10 mL), and stirred overnight. The mixture was then treated with powdered potassium hydroxide (101 mg, 1.79 mmol) in tert-butanol. The resulting mixture was stirred at 40 °C for 2 hours, before being quenched with acetic acid (0.205 mL, 3.59 mmol) in EtOH (5 mL) and evaporated to 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. Fractions containing the desired compound were evaporated to dryness to afford the title compound (66.5 mg, 42.1 %) as a yellow solid.

^{1}H NMR (400 MHz, DMSO) δ 1.51 (1H, t), 2.23 - 2.26 (2H, m), 2.66 (3H, s), 2.77 (3H, s), 3.39 (2H, d), 3.72 (2H, d), 6.71 (2H, d), 7.62 (1H, s), 7.66 (2H, d), 8.01 (1H, s,) COOH not seen; *m/z* 353 $(M+H)^+$.

The following compounds were synthesised from **Intermediate 33-2** and the appropriate amine using similar conditions as described in **Intermediate 33-1** to give the desired **Intermediates 34-1** to **40-1.**

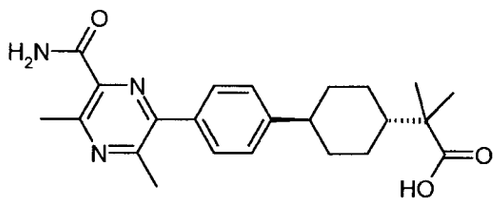
Intermediate	**Structure**	**^{1}H NMR (400 MHz, DMSO) δ**	***m/z* $(M+H)^+$**
34-1		1.27 (3H, t), 1.71 (3H, m), 1.99 (1H, m), 2.70 (7H, m), 3.04 (1H, m), 3.23 (1H, m), 3.64 (1H, d), 3.83 (1H, d), 4.16 (2H, q), 7.10 (2H, d), 7.61 (2H, d).	365
35-1		1.14 (3H, t), 1.59 (3H, m), 1.87 (1H, m), 2.58 (7H, m), 2.92 (1H, t), 3.10 (1H, t), 3.52 (1H, d), 3.71 (1H, d), 4.04 (2H, q), 6.98 (2H, d), 7.49 (2H, d).	365
36-1		2.60 (3H, s), 2.71 (7H, m), 3.20 (2H, s), 3.27 (4H, m), 7.03 (2H, d), 7.56 (1H, s), 7.63 (2H, d), 7.96 (1H, s).	370

37-1		1.23 (1H, m), 1.55 (1H, m), 1.69 (1H, m), 1.79 (1H, m), 2.00 (1H, m), 2.28 (1H, m), 2.38 (1H, m), 2.63 (7H, m), 2.83 (1H, m), 3.62 (3H, s), 3.74 (2H, m), 7.01 (2H, d), 7.53 (2H, d).	365
38-1		1.13 (3H, t), 1.60 (2H, m), 1.86 (2H, m), 2.51 (1H, m), 2.59 (3H, s), 2.61 (3H, s), 2.84 (2H, t), 3.72 (2H, d), 4.03 (2H, q), 6.98 (2H, d), 7.48 (2H, d).	365
39-1[a]		1.07 (3H, d), 1.18 (3H, t), 1.31 (2H, m), 1.68 (3H, m), 2.30 (1H, m), 2.65 (3H, s), 2.66 (3H, s), 2.73 (2H, m), 3.87 (2H, t), 4.07 (2H, m), 7.02 (2H, d), 7.52 (2H, d).	393
40-1		1.39 (1H, m), 1.42 (9H, s), 1.69 (1H, m), 2.16 (1H, m), 2.40 (2H, m), 2.59 (1H, m), 2.65 (6H, s), 2.96 (1H, t), 3.37 (1H, m), 3.50 (1H, m), 6.61 (2H, d), 7.53 (2H, d).	393
41-1[a]		1.41 (9H, s), 1.42 - 1.45 (1H, m), 2.17 - 2.19 (2H, m), 2.64 (3H, s), 2.65 (3H, s), 3.27 (2H, d), 3.66 (2H, d), 6.64 (2H, d), 7.51 (2H, d).	391

Note: **39-1**[a] ethyl 2-(piperidin-4-yl)propanoate, CAS 141060-27-7 was prepared according to the procedure described in WO 2008042925.

41-1[a] (1R,5S,6r)-tert-butyl 3-azabicyclo[3.1.0]hexane-6-carboxylate, CAS 681424-89-5 (prepared according to the procedure described in WO 2004033451).

Example 42: 2-((1r,4r)-4-(4-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)-2-methylpropanoic acid

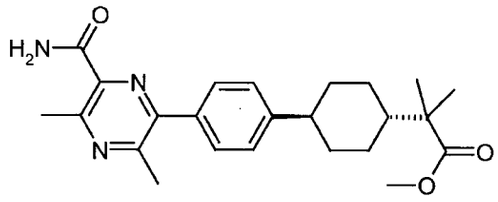


Powdered potassium hydroxide (193 mg, 3.44 mmol) was added in one portion to **Intermediate 42-1** (470 mg, 1.15 mmol) in tert-butanol (20 mL) at 40 °C under nitrogen. The resulting suspension was stirred at 40 °C for 2 hours. The reaction was incomplete so the temperature was increased to 100 °C and the reaction mixture was stirred for a further 16 hours. The reaction was quenched with acetic acid (0.329 mL, 5.74 mmol) in EtOH (10 mL) and the resulting solution stirred for a further 20 minutes before being evaporated to dryness . The resulting solid was partitioned between water (50 mL) and EtOAc (50 mL). The aqueous layer was acidified with 2M HCl (5 mL) was added and the organic layer was separated and the aqueous re-extracted with EtOAc (50 mL). The combined organics were washed with saturated brine (50 mL) and evaporated in vacuo to give crude solid product. This was recrystallised from hot EtOH (15 mL) and washed with ether (10 mL) and dried under vacuum at room temperature to give the title compound (90 mg, 19.83 %) as a pink solid.

^{1}H NMR (400.13 MHz, DMSO) δ 1.06 (6H, s), 1.15 - 1.30 (2H, m), 1.43 - 1.56 (2H, m), 1.60 - 1.80 (3H, m), 1.80 - 1.95 (2H, m), 2.40 - 2.60 (1H, m), 2.58 (3H, s), 2.73 (3H, s), 3.29 (3H, s), 7.36 (2H, d), 7.57 (1H, s), 7.64 (2H, d), 7.97 (1H, s), 12.03 (1H, s); *m/z* 396 $(M+H)^+$.

744

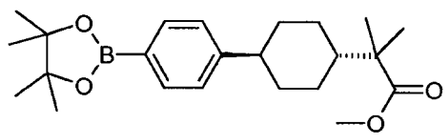
Intermediate 42-1: Methyl 2-((1r,4r)-4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)-2-methylpropanoate



This compound was synthesised from **Intermediate 42-2** and **Intermediate 21-4** using similar conditions as described in **Intermediate 25-1** to give the title compound (494 mg, 44.8 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (6H, s), 1.12 - 1.28 (2H, m), 1.40 - 1.53 (2H, m), 1.60 - 1.73 (3H, m), 1.90 - 2.00 (2H, m), 2.43 - 2.52 (1H, m), 2.60 (3H, s), 2.91 (3H, s), 3.62 (3H, s), 5.42 (1H, s), 7.25 (2H, d), 7.44 (2H, dt), 7.72 (1H, s); *m/z* 410 $(M+H)^+$.

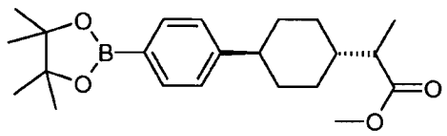
Intermediate 42-2: Methyl 2-methyl-2-((1r,4r)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclohexyl)propanoate



To a solution of diisopropylamine (4.83 mL, 34.17 mmol) in THF (50 mL) under nitrogen, cooled to -70 °C was added butyllithium (21.35 mL, 34.17 mmol) dropwise while maintaining the temperature between -70 and -60 °C. After 30 minutes **Intermediate 42-3** (3.18 g, 8.54 mmol) in THF (20 mL) was added and the mixture was allowed to warm to ~20 °C over 90 minutes. The solution was cooled to –65 °C, methyl iodide (2.129 mL, 34.17 mmol) was added and the reaction allowed to stir for 1 hour and then allowed to warm to –30 °C. The reaction was quenched with saturated ammonium chloride (100 mL), extracted with EtOAc (200 mL), the organic phase separated, washed with water (100 mL) and saturated brine (100 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product (2.99 g). The crude product was purified by flash silica chromatography, elution gradient 0 to 10% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the title compound (1.830 g, 55.5 %) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (6H, s), 1.15 - 1.28 (2H, m), 1.33 (12H, s), 1.49 (2H, dd), 1.65 - 1.75 (3H, m), 1.90 - 1.98 (2H, m), 2.42 - 2.51 (1H, m), 3.68 (3H, d), 7.21 (2H, d), 7.74 (2H, dd); *m/z* (EI+) 386 M^+.

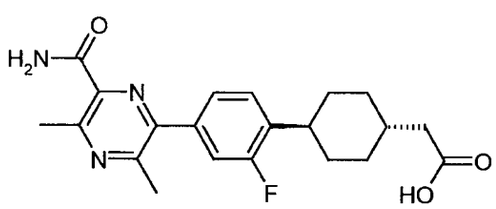
Intermediate 42-3: Methyl 2-((1r,4r)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclohexyl)propanoate



Lithium bis(trimethylsilyl)amide (16.75 mL, 16.75 mmol) was added to methyl 2-((1r,4r)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclohexyl)acetate (CAS 701232-69-1) (prepared according to the procedure described in WO 2004047755) (5 g, 13.96 mmol) in THF (50 mL) at 0 °C under nitrogen. The resulting solution was stirred at 0 °C for 30 minutes and then methyl iodide (1.304 mL, 20.93 mmol) was added and the reaction stirred for 30 minutes. The reaction was quenched with saturated ammonium chloride (50 mL), extracted with EtOAc (100 mL), the organic phase separated, washed with water (50 mL) and saturated brine (50 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 0 to 10% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the title compound (3.38 g, 65.1 %) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 - 1.30 (5H, m), 1.33 (12H, s), 1.40 - 1.70 (3H, m), 1.70 - 1.97 (4H, m), 2.31 (1H, t), 2.43 - 2.53 (1H, m), 3.68 (3H, m), 7.21 (2H, d), 7.74 (2H, d); *m/z* 395 $(M+Na)^+$.

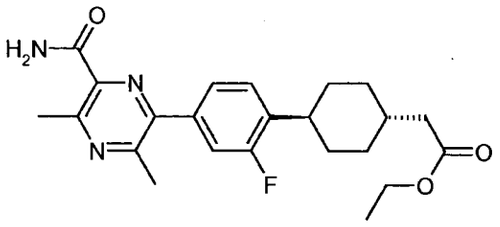
Example 43: 2-((1r,4r)-4-(4-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)-2-fluorophenyl)cyclohexyl)acetic acid



This compound was synthesised from **Intermediate 43-1** using similar conditions as described in **Example 21**. Except the crude product was purified by crystallisation from boiling EtOH (6 mL) to afford the title compound (89 mg, 43.6 %).

^{1}H NMR (400 MHz, DMSO) δ 1.09 - 1.22 (3H, m), 1.53 - 1.61 (2H, m), 1.72 - 1.89 (4H, m), 2.14 - 2.16 (2H, m), 2.60 (3H, s), 2.73 (3H, s), 2.79 - 2.87 (1H, m), 7.43 - 7.48 (1H, m), 7.53 (1H, d), 7.56 - 7.60 (2H, m), 8.04 (1H, s), 12.11 (1H, s); *m/z* 386 $(M+H)^+$.

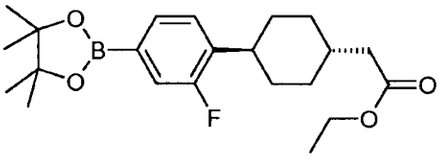
Intermediate 43-1: Ethyl 2-((1r,4r)-4-(4-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)-2-fluorophenyl)cyclohexyl)acetate



This compound was synthesised from **Intermediate 43-2** and **Intermediate 21-4** using similar conditions as described in Intermediate 21-1 to give the title compound (0.219 g, 23.90 %) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (3H, t), 1.54 - 1.64 (2H, m), 1.87 - 1.98 (7H, m), 2.26 (2H, d), 2.67 (3H, s), 2.86 - 2.94 (1H, m), 2.98 (3H, s), 4.13 - 4.18 (2H, m), 5.91 (1H, s), 7.24 - 7.36 (3H, m), 7.78 (1H, s); *m/z* 414 $(M+H)^+$.

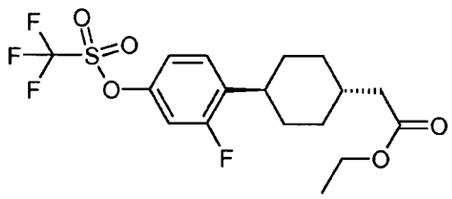
Intermediate 43-2: Ethyl 2-((1r,4r)-4-(2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclohexyl)acetate



This compound was synthesised from **Intermediate 43-3** using similar conditions as described in **Intermediate 25-2** to give the title compound (0.865 g, 43.8 %) as a white crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 - 1.17 (2H, m), 1.21 (3H, t), 1.26 (2H, s), 1.46 (12H, s), 1.48 - 1.54 (2H, m), 1.78 - 1.87 (4H, m), 2.73 - 2.81 (1H, m), 3.42 (1H, d), 4.05 - 4.11 (2H, m), 7.11 (1H, d), 7.14 (1H, d), 7.19 - 7.21 (1H, m).

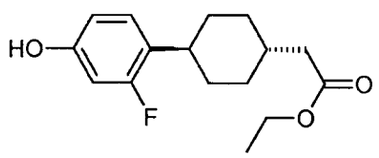
Intermediate 43-3: Ethyl 2-((1r,4r)-4-(2-fluoro-4-(trifluoromethylsulfonyloxy)-phenyl)cyclohexyl)acetate



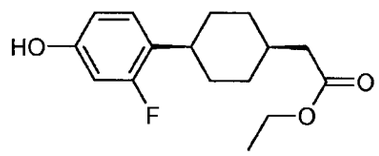
This compound was synthesised from **Intermediate 43-4** using similar conditions as described in **Intermediate 25-4** to give the title compound (2.087 g, 62.2 %) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 - 1.25 (2H, m), 1.27 (3H, t), 1.46 - 1.56 (3H, m), 1.83 - 1.94 (4H, m), 2.24 (2H, d), 2.79 - 2.87 (1H, m), 4.12 - 4.17 (2H, m), 6.96 - 6.99 (1H, m), 7.01 - 7.05 (1H, m), 7.27 - 7.31 (1H, m); *m/z* 411 $(M-H)^-$.

Intermediate 43-4: Ethyl 2-((1r,4r)-4-(2-fluoro-4-hydroxyphenyl)-cyclohexyl)acetate
and
Intermediate 43-5: Ethyl 2-((1s,4s)-4-(2-fluoro-4-hydroxyphenyl)-cyclohexyl)acetate



Intermediate 43-4



Intermediate 43-5

Intermediate 43-6 (6.29 g, 22.60 mmol) and palladium on carbon (10%) (0.6 g, 0.56 mmol) in EtOH (200 mL) was evacuated with hydrogen (4 cycles) and then stirred under a balloon of hydrogen at ambient temperature for 2 hours. The reaction mixture was filtered and evaporated to give a colourless oil. The crude product was purified by flash silica chromatography, elution gradient 10 to 20% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the desired product as a mixture of cis and trans isomers as a colourless oil which was further purified by preparative chiral-HPLC on a Chiralcel OJ

column, eluting isocratically with 10% IPA in isohexane as eluent. The fractions containing the desired compounds were evaporated to dryness to afford **Intermediate 43-4** (2.28g, 36%) as a white solid and **Intermediate 43-5** (3.08 g, 48.6 %) as a pale yellow gum.

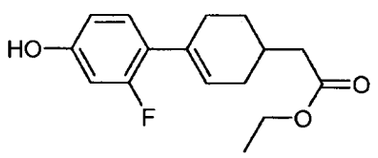
Intermediate 43-4

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 - 1.24 (2H, m), 1.26 (3H, t), 1.42 - 1.53 (2H, m), 1.80 - 1.89 (5H, m), 2.23 (2H, d), 2.69 - 2.76 (1H, m), 4.14 (2H, q), 4.82 (1H, s), 6.50 - 6.57 (2H, m), 7.04 (1H, t); *m/z* (EI+) 280 M^+.

Intermediate 43-5

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (3H, t), 1.59 - 1.76 (8H, m), 2.29 - 2.36 (1H, m), 2.45 (2H, d), 2.75 - 2.83 (1H, m), 4.15 (2H, q), 4.94 (1H, s), 6.51 - 6.57 (2H, m), 7.08 (1H, t); *m/z* (EI+) 280 M^+.

Intermediate 43-6: Ethyl 2-(4-(2-fluoro-4-hydroxyphenyl)cyclohex-3-enyl)acetate

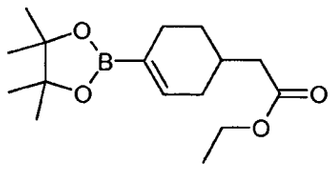


A solution of **Intermediate 43-7** (18.48 g, 62.82 mmol) in DMF (100 mL) was added to a stirred suspension of 4-bromo-3-fluorophenol (10 g, 52.36 mmol), potassium carbonate (21.71 g, 157.07 mmol) and [1,1-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (1.163 g, 1.41 mmol) in DMF (100 mL) at ambient temperature. The resulting suspension was stirred at 80 °C under nitrogen for 2 hours. The reaction was incomplete so the temperature was increased to 100 °C and the reaction mixture was stirred for a further 30 minutes and then further [1,1-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (1.163 g, 1.41 mmol) was added and the suspension was stirred at 100 °C for a further 45 minutes and then further [1,1-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (400 mg, 0.487 mmol) was added and the suspension was stirred at 100 °C for a further 45 minutes. The reaction mixture was evaporated to dryness and redissolved in EtOAc (200 mL) and 2M HCl (250 mL) was cautiously added. The aqueous layer was further extracted with EtOAc (3 x 200 mL) and the organic extracts were combined, washed saturated brine (300 mL), dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude

product was purified by flash silica chromatography, elution gradient 0 to 20% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the title compound (6.34 g, 43.5 %) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (3H, t), 1.41 - 1.50 (1H, m), 1.85 - 1.95 (2H, m), 2.14 - 2.21 (1H, m), 2.32 (2H, d), 2.32 - 2.48 (3H, m), 4.16 (2H, q), 4.98 (1H, s), 5.81 (1H, s), 6.51 - 6.56 (2H, m), 7.05 - 7.09 (1H, m); *m/z* 277 $(M-H)^-$.

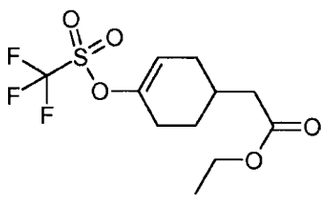
Intermediate 43-7: Ethyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enyl)acetate



This compound was synthesised from **Intermediate 43-8** using similar conditions as described in **Intermediate 25-2** to give the title compound (10.4 g, 71 %) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ1.24 - 1.28 (18H, m), 1.77 - 1.80 (2H, m), 2.18 - 2.27 (2H, m), 2.20 - 2.24 (2H, m), 4.09 - 4.16 (2H, m), 6.51 (1H, d)

Intermediate 43-8: Ethyl 2-(4-(trifluoromethylsulfonyloxy)cyclohex-3-enyl)acetate

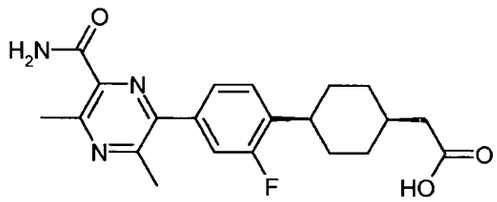


Triflouromethanesulfonic anhydride (11.9 mL, 70.86 mmol) was added portionwise to a solution of 2,6-di-tert-butyl-4-methylpyridine (18.19 g, 88.58 mmol) in DCM (250 mL). A solution of ethyl 2-(4-oxocyclohexyl)acetate (10.88 g, 59.05 mmol, CAS 58012-34-3) in DCM (100 mL) was then added dropwise and the reaction mixture was allowed to stir open to air and at room temperature overnight. The reaction mixture was washed with water, saturated Na_2CO_3, saturated brine, dried over $MgSO_4$ and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0

to 10% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the title compound (16.05 g, 86 %) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 - 1.29 (3H, m), 1.39 - 1.51 (1H, m), 1.76 - 1.85 (2H, m), 2.07 - 2.23 (4H, m), 2.29 (2H, d), 4.09 - 4.18 (2H, m), 4.96 (1H, s).

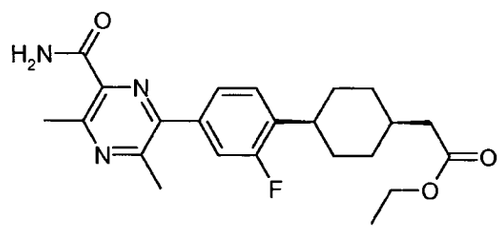
Example 44: 2-((1s,4s)-4-(4-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)-2-fluorophenyl)cyclohexyl)acetic acid



This compound was synthesized from **Intermediate 44-1** using similar conditions as described in **Example 21** to give the title compound (252 mg, 71%) as a white solid.

^{1}H NMR (400 MHz, DMSO) δ 1.65 (8H, m), 2.22 (1H, m), 2.41 (2H, d), 2.60 (3H, s), 2.74 (3H, s), 2.88 (1H, m), 7.53 (4H, m), 8.05 (1H, s), 12.03 (1H, s); *m/z* 386 $(M+H)^+$.

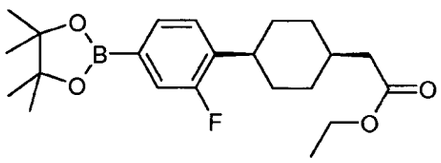
Intermediate 44-1: Ethyl 2-((1s,4s)-4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)-2-fluorophenyl)cyclohexyl)acetate



This compound was synthesized from **Intermediate 44-2** and **Intermediate 21-4** using similar conditions as described in **Intermediate 21-1** to give the title compound (453mg, 68%) as a pale yellow solid.

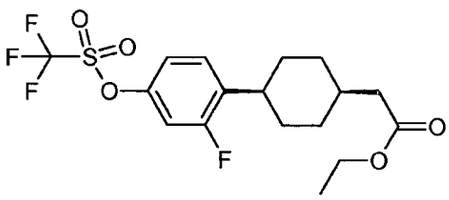
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (3H, t), 1.74 (8H, m), 2.39 (1H, m), 2.48 (2H, d), 2.68 (3H, s), 2.97 (4H, m), 4.16 (2H, q), 5.51 (1H, s), 7.26 (1H, m), 7.32 (1H, m), 7.38 (1H, t), 7.75 (1H, s); *m/z* 414 $(M+H)^+$.

Intermediate 44-2: Ethyl 2-((1s,4s)-4-(2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclohexyl)acetate



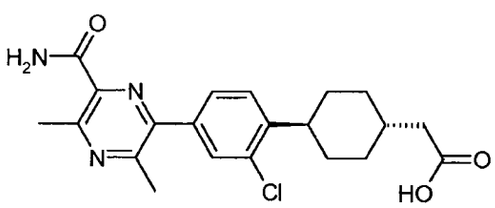
This compound was synthesized from **Intermediate 44-3** using similar conditions as described in **Intermediate 25-2** to give the title compound (1.45 g, 61%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (3H, t), 1.32 (12H, s), 1.67 (8H, m), 2.35 (1H, m), 2.46 (2H, d), 2.89 (1H, m), 4.14 (2H, q), 7.25 (1H, t), 7.42 (1H, d), 7.52 (1H, d); m/z (ES+) (M+H)+ = No mass ion; HPLC tR= 3.62 min.

Intermediate 44-3: Ethyl 2-((1s,4s)-4-(2-fluoro-4-(trifluoromethylsulfonyloxy)-phenyl)cyclohexyl)acetate



This compound was synthesized from **Intermediate 43-5** using similar conditions as described in **Intermediate 25-4** to give the title compound (2.53 g, 86 %) as a yellow oil. ^{1}H NMR (400 MHz, DMSO) δ 1.12 (3H, t), 1.55 (8H, m), 2.15 (1H, m), 2.41 (2H, d), 2.77 (1H, m), 4.00 (3H, q), 7.24 (1H, m), 7.43 (1H, m), 7.56 (1H, t); *m/z* (ES-) 411 $(M-H)^-$.

Example 45-((1r,4r)-4-(4-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)-2-chlorophenyl)cyclohexyl)acetic acid

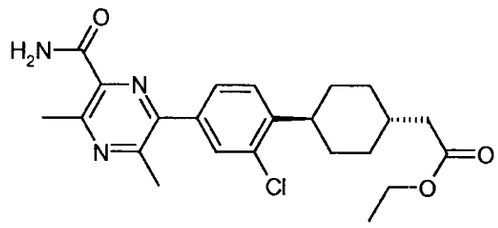


This compound was synthesised from **Intermediate 45-1** using similar conditions as described in **Example 21**. Except the crude product was recrystallised from hot EtOH (15

mL) to give a solid which was washed with Ether (10 mL) and dried under vacuum at room temperature to give the title compound (313 mg, 80 %).

^{1}H NMR (400 MHz, DMSO) δ 1.12 - 1.23 (2H, m), 1.49 - 1.60 (2H, m), 1.76 - 1.90 (5H, m), 2.18 (2H, d), 2.60 (3H, s), 2.75 (3H, s), 2.91 - 3.00 (1H, m), 7.52 (1H, d), 7.65 (1H, s), 7.67 - 7.70 (1H, m), 7.84 (1H, d), 8.10 (1H, s), 12.09 (1H, s); *m/z* 402 $(M+H)^+$.

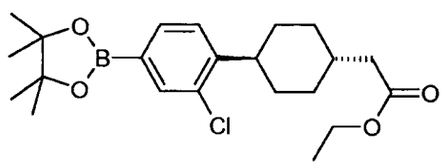
Intermediate 45-1: Ethyl 2-((1r,4r)-4-(4-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)-2-chlorophenyl)cyclohexyl)acetate



This compound was synthesized from **Intermediate 45-2** and **Intermediate 21-4** using similar conditions as described in **Intermediate 21-1** to give the title compound (482 mg, 91 %) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (3H, t), 1.40 - 1.47 (1H, m), 1.84 - 1.94 (4H, m), 2.20 (2H, d), 2.60 (3H, s), 2.91 (3H, s), 2.94 - 3.02 (1H, m), 3.42 (4H, d), 4.06 - 4.11 (2H, m), 5.40 (1H, s), 7.29 - 7.32 (1H, m), 7.36 - 7.38 (1H, m), 7.51 (1H, d), 7.67 (1H, s); *m/z* 430 $(M+H)^+$.

Intermediate 45-2: Ethyl 2-((1r,4r)-4-(2-Chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclohexyl)acetate

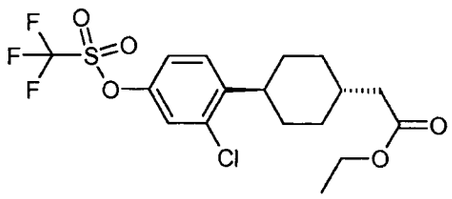


This compound was synthesized from **Intermediate 45-3** using similar conditions as described in **Intermediate 25-2** to give the title compound (1.046 g, 70.7 %) as a colourless oil which crystallised on standing.

153

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76 - 0.87 (4H, m), 1.20 (3H, t), 1.35 - 1.44 (1H, m), 1.48 (12H, s), 1.80 - 1.86 (4H, m), 2.18 (2H, d), 2.89 - 2.97 (1H, m), 4.05 - 4.10 (2H, m), 7.18 (1H, d), 7.56 (1H, d), 7.70 (1H, d); *m/z* 430 $(M+Na)^+$.

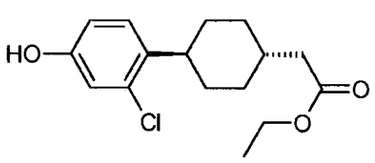
Intermediate 45-3: Ethyl 2-((1r,4r)-4-(2-Chloro-4-(trifluoromethyl-sulfonyloxy)phenyl)cyclohexyl)acetate



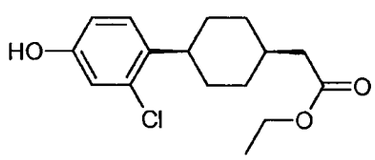
This compound was synthesized from **Intermediate 45-4** using similar conditions as described in **Intermediate 25-4** to give the title compound (1.560 g, 85 %) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 - 1.29 (4H, m), 1.39 - 1.49 (2H, m), 1.88 - 1.95 (4H, m), 2.25 (2H, d), 2.93 - 3.01 (1H, m), 3.49 (2H, d), 4.12 - 4.18 (2H, m), 7.14 - 7.17 (1H, m), 7.29 (1H, d), 7.32 (1H, d); *m/z* 427 $(M-H)^-$.

Intermediate 45-4: Ethyl 2-((1r,4r)-4-(2-chloro-4-hydroxyphenyl)-cyclohexyl)acetate and

Intermediate 45-5: Ethyl 2-((1s,4s)-4-(2-chloro-4-hydroxyphenyl)cyclohexyl)acetate



Intermediate 45-4



Intermediate 45-5

These compounds were synthesized from **Intermediate 45-6** using similar conditions as described in **Intermediate 43-4** and **43-5**, except after silica chromatography the crude product was purified by preparative HPLC (Phenomenex Gemini C18 110A (axia) column, 5μ silica, 21 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 crude product as a mixture of isomers (5.78 g, 49.9 %) as a colourless oil. The oil was purified by preparative chiral-HPLC on a Merck 50mm 20μm Chiralcel OJ column, eluting isocratically with 70% isohexane in IPA

(modified with AcOH/Et_3N) as eluent. The fractions containing the desired compound were evaporated to dryness to afford **Intermediate 45-4** (1.264 g, 21.87 %) as a white solid and **Intermediate 45-5** (3.52 g, 60.9 %) as white solid.

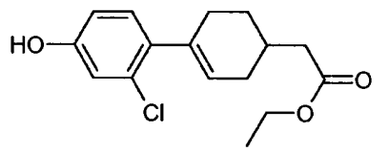
Intermediate 45-4:

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 - 1.24 (2H, m), 1.27 (3H, t), 1.34 - 1.45 (2H, m), 1.80 - 1.91 (5H, m), 2.24 (2H, d), 2.84 - 2.92 (1H, m), 4.12 - 4.18 (2H, m), 6.70 - 6.73 (1H, m), 6.86 (1H, d), 7.08 (1H, d) phenol OH not seen; m/z (ES-) (M-H)- = 295, 297

Intermediate 45-5:

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (3H, t), 1.46 - 1.58 (3H, m), 1.65 - 1.78 (5H, m), 2.33 - 2.40 (1H, m), 2.47 (2H, d), 2.89 - 2.96 (1H, m), 4.13 - 4.18 (2H, m), 6.70 - 6.73 (1H, m), 6.86 (1H, d), 7.12 (1H, d) phenol OH not seen; m/z (ES-) (M-H)- = 295, 297

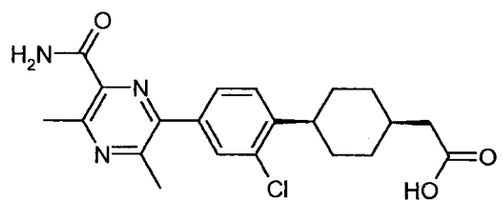
Intermediate 45-6: Ethyl 2-(4-(2-chloro-4-hydroxyphenyl)cyclohex-3-enyl)acetate



This compound was synthesized from **Intermediate 43-7** and 4-bromo-3-chlorophenol using similar conditions as described in **Intermediate 43-6** to give the title compound (5.30 g, 74.7 %) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (3H, t), 1.36 - 1.45 (1H, m), 1.58 (1H, s), 1.76 - 1.87 (2H, m), 2.07 - 2.17 (1H, m), 2.22 - 2.29 (4H, m), 4.07 - 4.12 (2H, m), 5.16 (1H, s), 5.50 - 5.52 (1H, m), 6.59 - 6.62 (1H, m), 6.78 (1H, d), 6.93 (1H, d); *m/z* 293 $(M-H)^-$.

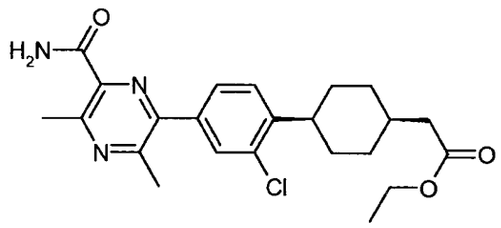
Example 46: 2-((1s,4s)-4-(4-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)-2-chlorophenyl)cyclohexyl)acetic acid



This compound was synthesized from **Intermediate 46-1** using similar conditions as described in **Example 21** to give the title compound (184 mg, 44 %) as a white solid.

^{1}H NMR (400 MHz, DMSO) δ 1.65 (8H, m), 2.24 (1H, m), 2.44 (2H, d), 2.59 (3H, s), 2.73 (3H, s), 2.99 (1H, m), 7.58 (2H, m), 7.67 (1H, d), 7.81 (1H, s), 8.05 (1H, s), 12.01 (1H, s); *m/z* 402 $(M+H)^+$.

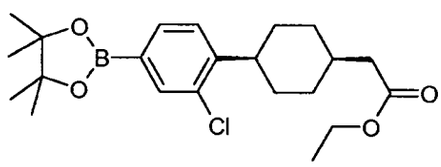
Intermediate 46-1: Ethyl 2-((1s,4s)-4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)-2-chlorophenyl)cyclohexyl)acetate



This compound was synthesized from **Intermediate 46-2** and **Intermediate 21-4** using similar conditions as described in **Intermediate 21-1** to give the title compound (365 mg, 78 %) as a colourless gum.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (3H, t), 1.67 (2H, m), 1.78 (6H, m), 2.42 (1H, m), 2.50 (2H, d), 2.67 (3H, s), 2.98 (3H, s), 3.10 (1H, m), 4.16 (2H, m), 5.53 (1H, s), 7.43 (2H, m), 7.59 (1H, d), 7.75 (1H, s); *m/z* 430 $(M+H)^+$.

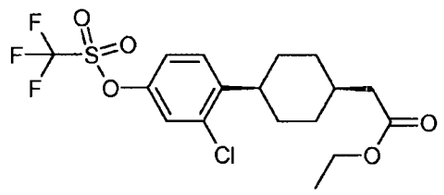
Intermediate 46-2: Ethyl 2-((1s,4s)-4-(2-Chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclohexyl)acetate



This compound was synthesized from **Intermediate 46-3** using similar conditions as described in **Intermediate 25-2** to give the title compound (1.19g, 62%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (3H, t), 1.33 (12H, s), 1.59 (2H, m), 1.72 (6H, m), 2.39 (1H, m), 2.47 (2H, d), 3.05 (1H, m), 4.15 (2H, q), 7.28 (1H, t), 7.64 (1H, d), 7.77 (1H, s); *m/z* 430 $(M+Na)^+$.

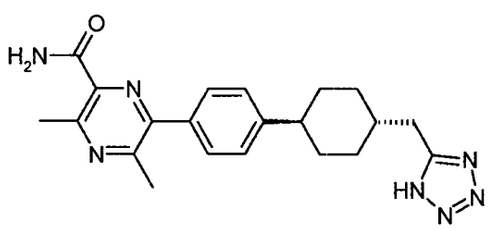
Intermediate 46-3: Ethyl 2-((1s,4s)-4-(2-chloro-4-(trifluoromethyl-sulfonyloxy)phenyl)cyclohexyl)acetate



This compound was synthesized from **Intermediate 45-5** using similar conditions as described in **Intermediate 25-4** to give the title compound (2.051 g, 71.0 %) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (3H, t), 1.56 (2H, m), 1.73 (6H, m), 2.40 (1H, m), 2.46 (2H, d), 3.02 (1H, t), 4.16 (1H, q), 7.16 (1H, m), 7.30 (1H, d), 7.37 (1H, d); *m/z* 427 $(M-H)^-$.

Example 47: 6-(4-((1r,4r)-4-((1H-Tetrazol-5-yl)methyl)cyclohexyl)phenyl)-3,5-dimethylpyrazine-2-carboxamide

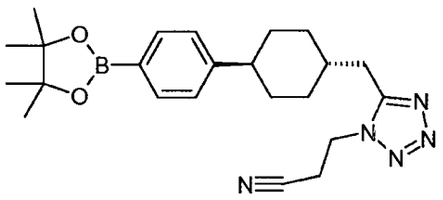


This compound was synthesised from **Intermediate 47-1** using similar conditions as described in **Example 28** to give the title compound (220 mg, 41.7 %) as a white solid. The material was recrystallised from hot Methanol, filtered off and washed with ether before drying under vacuum to give the title compound (223 mg, 42.3 %).

^{1}H NMR (300 MHz, DMSO) δ 1.13 - 1.27 (2H, m), 1.43 - 1.56 (2H, m), 1.74 - 1.88 (5H, m), 2.53 - 2.57 (1H, m), 2.58 (3H, s), 2.74 (3H, s), 2.84 (2H, d), 7.35 (2H, d), 7.58 (1H, s), 7.65 (2H, d), 7.97 (1H, s), 16.00 (1H, s); *m/z* 392 $(M+H)^+$.

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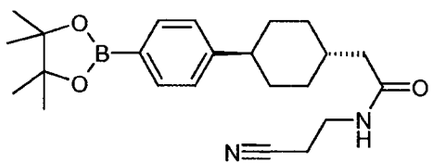
Intermediate 47-1: 3-(5-(((1r,4r)-4-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclohexyl)methyl)-1H-tetrazol-1-yl)propanenitrile



This compound was synthesised from **Intermediate 47-2** using similar conditions as described in **Intermediate 28-1** to give the title compound (1.960 g, 59.9 %) contaminated with triphenyphosphine oxide (3 mol %).

^{1}H NMR (400 MHz, DMSO) δ 0.96 - 1.05 (2H, m), 1.06 (12H, s), 1.19 - 1.30 (2H, m), 1.54 - 1.64 (5H, m), 2.67 (2H, d), 2.97 (2H, t), 3.07 (1H, s), 4.47 (2H, t), 7.02 (2H, d), 7.37 (2H, d); HPLC tR=2.81.

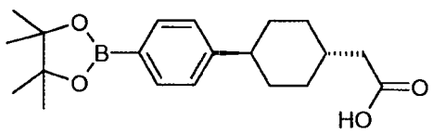
Intermediate 47-2: N-(2-Cyanoethyl)-2-((1r,4r)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclohexyl)acetamide



This compound was synthesised from **Intermediate 47-3** using similar conditions as described in **Intermediate 28-2** to give the title compound (3.08 g, 77 %).

^{1}H NMR (400 MHz, DMSO) δ 1.03 - 1.13 (2H, m), 1.27 (12H, s), 1.37 - 1.47 (2H, m), 1.71 - 1.80 (5H, m), 2.02 (2H, d), 2.63 (2H, t), 7.22 (2H, d), 7.58 (2H, d), 8.16 (1H, t), 3 x CH obscured by solvent.

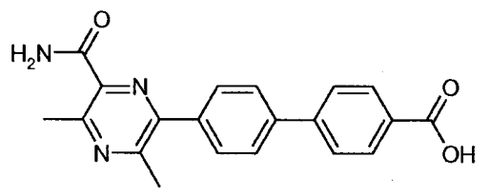
Intermediate 47-3: 2-((1r,4r)-4-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclohexyl)acetic acid



Methyl 2-((1r,4r)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclohexyl)acetate (CAS 701232-69-1, prepared according to the procedure described in WO 2004/047755) (3.6 g, 10.05 mmol) was dissolved in a solution of sodium hydroxide (1.326 g, 33.16 mmol) in methanol (36 mL) and water (4.00 mL). The reaction mixture was split in two and heated to 120 °C for 30 min in a microwave. The reaction mixtures were combined, acidified with 2M HCl and evaporated. The crude product was taken onto the next step without purification.

^{1}H NMR (400 MHz, DMSO) δ 1.08 - 1.12 (2H, m), 1.27 (12H, s), 1.42 - 1.46 (2H, m), 1.74 - 1.82 (5H, m), 2.13 (2H, d), 7.22 (2H, d), 7.58 (2H, d) one CH and COOH not seen.

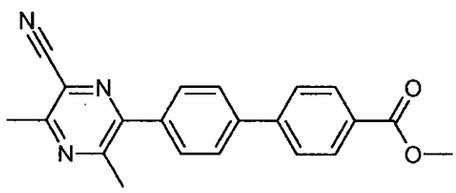
Example 48: 4'-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)biphenyl-4-carboxylic acid



This compound was synthesised from **Intermediate 48-1** using similar conditions as described in **Example 21** to give the title compound (42.2 mg, 74.5 %) as an off white solid.

^{1}H NMR (400 MHz, DMSO) δ 2.58 (3H, s), 2.70 (3H, s), 3.57 (2H, s), 7.32 (2H, d), 7.55 (1H, s), 7.64 (2H, d), 7.73 (2H, d), 7.78 (2H, d), 7.96 (1H, s), 12.29 (1H, s); *m/z* 362 $(M+H)^+$.

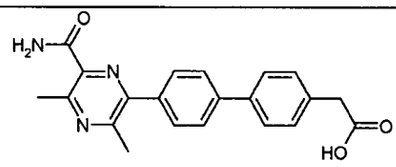
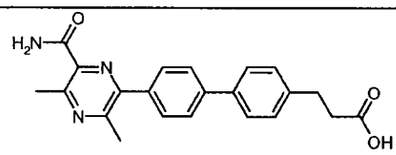
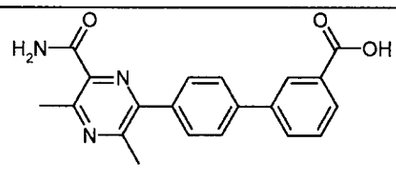
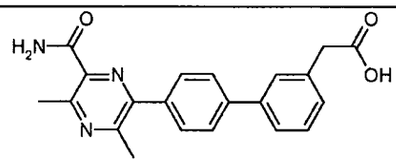
Intermediate 48-1: Methyl 4'-(6-cyano-3,5-dimethylpyrazin-2-yl)biphenyl-4-carboxylate



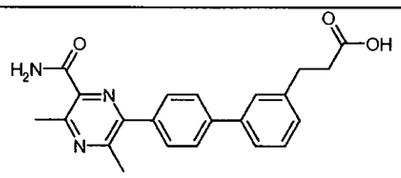
This compound was synthesised from **Intermediate 33-3** and methyl 4-bromobenzoate using similar conditions as described in **Intermediate 21-1** to give the title compound (124 mg, 72.1 %) as a white solid.

^{1}H NMR (400 MHz, DMSO) δ 2.68 (3H, s), 2.72 (3H, s), 3.89 (3H, s), 7.80 (2H, d), 7.89 - 7.93 (4H, m), 8.07 (2H, d); HPLC tR= 2.92 min.

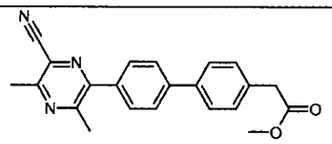
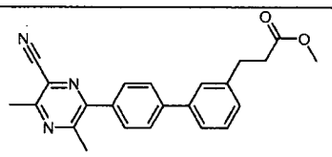
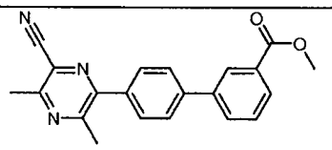
The following examples were synthesised from **Intermediates 49-1-to 53-1** using similar conditions as described in **Example 21** to give the desired compounds.

Example	Structure	^{1}H NMR (400 MHz, DMSO) δ	*m/z* $(M+H)^+$
49		2.64 (3H, s), 2.76 (3H, s), 3.63 (2H, s), 7.38 (2H, d), 7.61 (1H, s), 7.70 (2H, d), 7.79 (2H, d), 7.84 (2H, d), 8.02 (1H, s), 12.33 (1H, s).	362
50		2.55 (2H, t), 2.64 (3H, s), 2.75 (3H, s), 2.87 (2H, t), 7.35 (2H, d), 7.61 (1H, s), 7.65 (2H, d), 7.77 (2H, d), 7.83 (2H, d), 8.02 (1H, s), COOH not seen.	376
51		2.65 (3H, s), 2.76 (3H, s), 7.35 (1H, t), 7.61 (2H, d), 7.77 (2H, d), 7.82 - 7.86 (3H, m), 8.05 (1H, s), 8.19 (1H, s), COOH not seen.	348
52		2.71 (3H, s), 2.82 (3H, s), 3.74 (2H, s), 7.36 (1H, d), 7.51 (1H, t), 7.69 (3H, d), 7.85 (2H, d), 7.92 (2H, d), 8.09 (1H, s), 12.43 (1H, s).	362

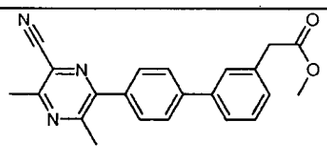
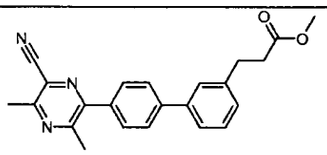
160

53		2.61 (2H, t), 2.64 (3H, s), 2.76 (3H, s), 2.92 (2H, t), 7.26 (1H, d), 7.40 (1H, t), 7.56 (1H, d), 7.60 - 7.63 (2H, m), 7.79 (2H, d), 7.84 (2H, d), 8.02 (1H, s), 12.12 (1H, s).	376

The following Intermediates were synthesised from **Intermediate 33-3** and the appropriate aryl bromide or triflate using similar conditions as described in **Intermediate 21-1** to give the desired compounds.

Intermediate	**Structure**	**^{1}H NMR (400 MHz, DMSO) δ**	***m/z*** **$(M+H)^+$**
49-1[a]		2.75 (3H, s), 2.79 (3H, s), 3.70 (3H, s), 3.81 (2H, s), 7.46 (2H, d), 7.78 (2H, d), 7.82 (2H, d), 7.89 (2H, d)	HPLC tR= 2.83 min
50-1[b]		2.73 - 2.77 (5H, m), 2.78 (3H, s), 2.98 (2H, t), 3.35 (3H, s), 7.42 (2H, d), 7.74 (2H, d), 7.81 (2H, d), 7.87 (2H, d)	HPLC tR= 2.97 min.
51-1[c]		2.75 (3H, s), 2.79 (3H, s), 3.97 (3H, s), 7.74 (1H, t), 7.86 (2H, d), 7.95 (2H, d), 8.05 - 8.08 (1H, m), 8.10 - 8.13 (1H, m), 8.34 (1H, t).	HPLC tR= 2.93 min.

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52-1[d]		2.75 (3H, s), 2.79 (3H, s), 3.70 (3H, s), 3.85 (2H, s), 7.38 (1H, d), 7.52 (1H, t), 7.70 - 7.73 (2H, m), 7.83 (2H, d), 7.88 (2H, d).	358
53-1[e]		2.74 (3H, s), 2.76 - 2.80 (5H, m), 3.02 (2H, t), 3.66 (3H, s), 7.34 (1H, d), 7.48 (1H, t), 7.64 (1H, d), 7.68 - 7.69 (1H, m), 7.82 (2H, d), 7.89 (2H, d).	372

Note: **49-1**[a] methyl 2-(4-bromophenyl)acetate, CAS 41841-16-1 was made according to the procedure described by E. E. Knaus at al, *Bioorg. Med. Chem.*, 2005, **13**, 4694-4703.

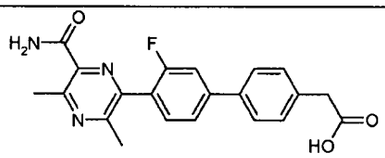
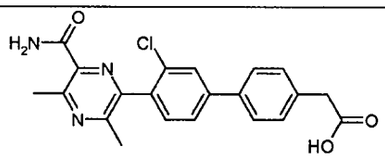
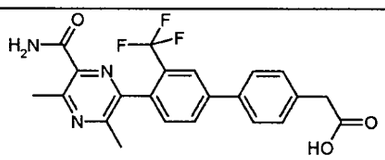
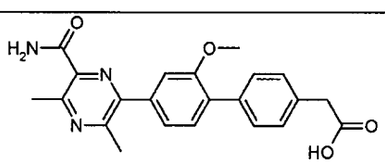
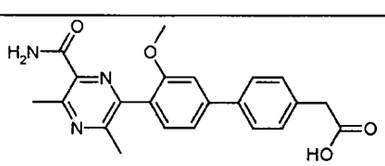
50-1[b] methyl 3-(4-(trifluoromethylsulfonyloxy)phenyl)propanoate, CAS 475272-11-8. was made according to the procedure described in WO 2002089738.

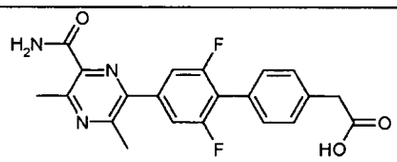
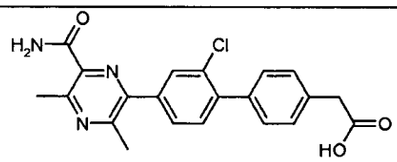
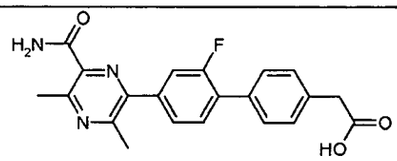
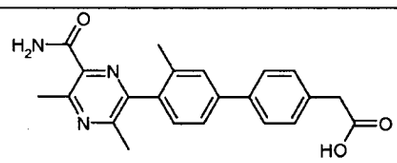
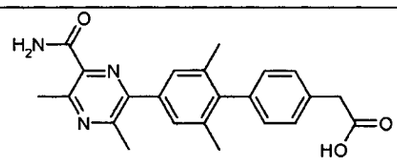
51-1[c] methyl 3-bromobenzoate, CAS 618-89-3.

52-1[d] methyl 2-(3-bromophenyl)acetate, CAS 150529-73-0.

53-1[e] methyl 3-(3-bromophenyl)propanoate, CAS 151583-29-8 was made according to the procedure described in WO 2007089667.

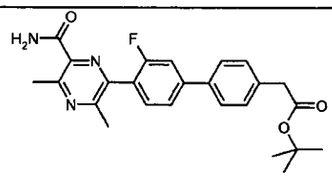
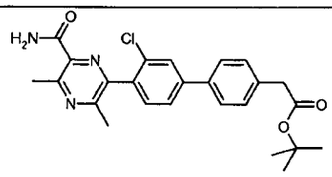
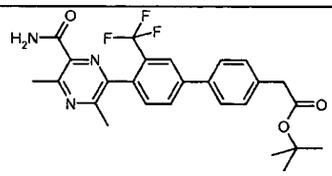
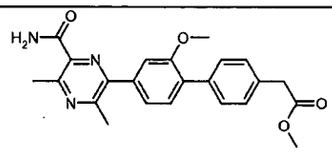
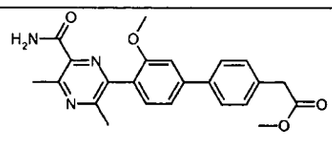
The following **Examples 54 – 56** were synthesised from **Intermediates 54-1 to 56-1** using similar conditions as described in **Example 26** and **Examples 57 to 63** were synthesised from **Intermediates 57-1 to 63-1** using similar conditions as described in **Example 21**. All crude products were 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 the desired products.

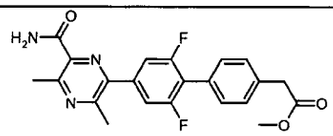
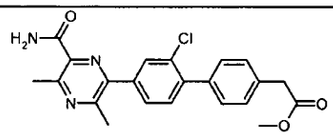
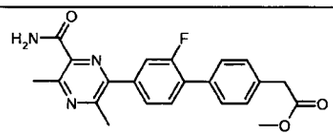
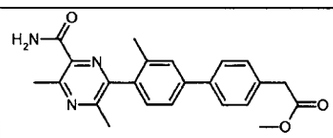
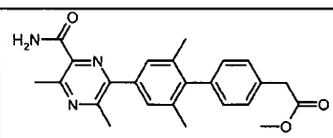
Example	Structure	^{1}H NMR (400 MHz, DMSO) δ	*m/z* $(M+H)^+$
54		2.45 (3H, s), 2.75 (3H, s), 3.62 (2H, s), 7.38 (2H, d), 7.60 (1H, s), 7.66 - 7.68 (3H, m), 7.73 (2H, d), 7.96 (1H, s), 12.33 (1H, s)	380
55		2.40 (3H, s), 2.78 (3H, s), 3.64 (2H, s), 7.39 (2H, d), 7.60 - 7.62 (2H, m), 7.73 (2H, d), 7.78 - 7.81 (1H, m), 7.90 (1H, d), 7.92 (1H, s), 12.35 (1H, s)	396
56		2.41 (3H, s), 2.87 (3H, s), 3.72 (2H, s), 7.49 (2H, d), 7.65 (1H, s), 7.75 (1H, d), 7.84 (3H, d), 8.17 (2H, t), COOH not seen.	430
57		2.65 (3H, s), 2.76 (3H, s), 3.60 (2H, s), 3.83 (3H, s), 7.31 (2H, d), 7.34 - 7.43 (3H, m), 7.47 (2H, d), 7.60 (1H, s), 8.05 (1H, s), COOH not seen.	392
58		2.37 (3H, s), 2.75 (3H, s), 3.63 (2H, s), 3.87 (3H, s), 7.35 - 7.40 (4H, m), 7.45 (1H, d), 7.55 (1H, s), 7.72 (2H, d), 7.91 (1H, s), 12.34 (1H, s).	392

59		2.75 (3H, s), 2.84 (3H, s), 3.72 (2H, s), 7.48 (2H, d), 7.53 (2H, d), 7.70 (1H, s), 7.74 - 7.80 (2H, m), 8.20 (1H, s), 12.47 (1H, s)	398
60		2.59 (3H, s), 2.71 (3H, s), 3.59 (2H, s), 7.32 - 7.34 (2H, m), 7.39 - 7.41 (2H, m), 7.48 (1H, d), 7.57 (1H, s), 7.73 - 7.75 (1H, m), 7.92 (1H, d), 8.04 (1H, s), 12.31 (1H, s).	396
61		2.68 (3H, s), 2.78 (3H, s), 3.66 (2H, s), 7.42 (2H, d), 7.59 (2H, dd), 7.64 (1H, m), 7.69 (2H, dd), 7.80 (1H, dd), 8.10 (1H, s), 12.40 (1H, s).	380
62		2.15 (3H, s), 2.37 (3H, s), 2.77 (3H, s), 3.62 (2H, s), 7.37 (3H, m), 7.54 (1H, s), 7.58 (1H, d), 7.67 (3H, m), 7.90 (1H, s), 12.34 (1H, s).	376
63		2.04 (6H, s), 2.63 (3H, s), 2.75 (3H, s), 3.63 (2H, s), 7.14 (2H, d), 7.37 (2H, d), 7.47 (2H, s), 7.60 (1H, s), 8.00 (1H, s), 12.33 (1H, s).	390

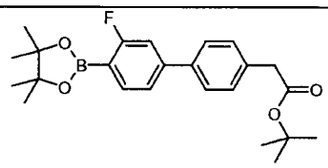
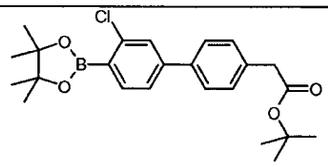
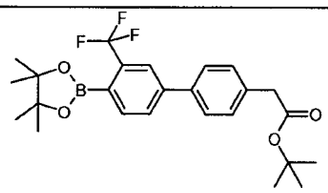
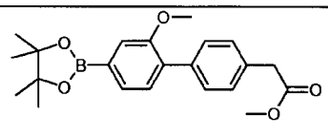
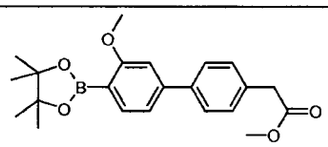
The following **Intermediates 54-1 to 63-1** were synthesised from **Intermediates 54-2** to **63-2** and **Intermediate 21-4** using similar conditions as described in **Intermediate 21-1** to afford the desired compounds.

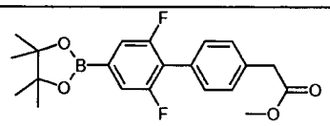
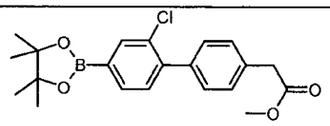
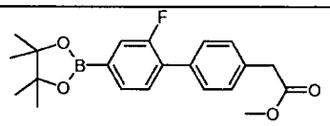
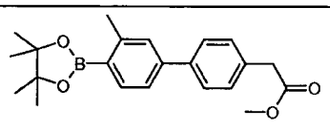
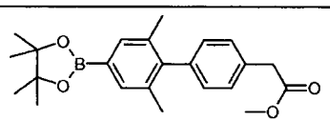
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Intermediate	Structure	^{1}H NMR (400 MHz, DMSO) δ	*m/z* $(M+H)^+$
54-1		1.48 (9H, s), 2.53 (3H, s), 2.83 (3H, s), 3.69 (2H, s), 7.45 (2H, d), 7.69 (1H, s), 7.74 - 7.78 (3H, m), 7.82 (2H, d), 8.05 (1H, s)	436
55-1		1.42 (9H, s), 2.40 (3H, s), 2.78 (3H, s), 3.63 (2H, s), 7.38 (2H, d), 7.59 - 7.62 (2H, m), 7.74 (2H, d), 7.78 - 7.81 (1H, m), 7.90 - 7.91 (2H, m)	452
56-1		1.42 (9H, s), 2.34 (3H, s), 2.80 (3H, s), 3.64 (2H, s), 7.41 (2H, d), 7.59 (1H, s), 7.68 (1H, d), 7.75 (1H, s), 7.79 (2H, d), 8.09 - 8.11 (2H, m)	486
57-1		2.65 (3H, s), 2.77 (3H, s), 3.64 (3H, s), 3.72 (2H, s), 3.84 (3H, s), 7.31 (2H, d), 7.36 - 7.42 (3H, m), 7.49 (2H, d), 7.61 (1H, s), 8.05 (1H, s)	406
58-1		2.37 (3H, s), 2.75 (3H, s), 3.64 (3H, s), 3.75 (2H, s), 3.87 (3H, s), 7.36 - 7.40 (4H, m), 7.45 (1H, d), 7.55 (1H, s), 7.73 (2H, d), 7.90 (1H, s)	406

59-1		2.75 (3H, s), 2.84 (3H, s), 3.72 (3H, s), 3.84 (2H, s), 7.49 (2H, d), 7.55 (2H, d), 7.71 (1H, s), 7.75 - 7.80 (2H, m), 8.20 (1H, s).	412
60-1		2.71 (3H, s), 2.83 (3H, s), 3.72 (3H, s), 3.95 (2H, s), 7.46 (2H, d), 7.52 - 7.54 (2H, m), 7.60 (1H, d), 7.69 (1H, s), 7.85 - 7.87 (1H, m), 8.05 (1H, d), 8.16 (1H, s).	410
61-1		($CDCl_3$) δ 2.65 (3H, s), 2.93 (3H, s), 3.63 (2H, s), 3.66 (3H, s), 5.58 (1H, s), 7.31 - 7.39 (4H, m), 7.46 - 7.53 (3H, m), 7.69 (1H, s).	394
62-1		2.16 (3H, s), 2.36 (3H, s), 2.78 (3H, s), 3.64 (3H, s), 3.74 (2H, s), 7.38 (3H, d), 7.55 (1H, s), 7.59 (1H, d), 7.67 (3H, m), 7.90 (1H, s).	390
63-1		2.05 (6H, s), 2.63 (3H, s), 2.75 (3H, s), 3.66 (3H, s), 3.76 (2H, s), 7.15 (2H, d), 7.38 (2H, d), 7.47 (2H, s), 7.60 (1H, s), 8.00 (1H, s).	404

The following **Intermediates 54-2 to 63-2** were synthesised from **Intermediates 54-3** to **63-3** using similar conditions as described in **Intermediate 25-2** to afford the desired compounds.

Intermediate	Structure	^{1}H NMR (400 MHz)	*m/z*
54-2		($CDCl_3$) δ 1.38 (12H, s), 1.45 (9H, s), 3.56 (2H, s), 7.24 - 7.27 (1H, m), 7.33 - 7.38 (3H, m), 7.55 (2H, d), 7.77 - 7.80 (1H, m)	412 $M^{+\cdot}$ (EI+)
55-2		($CDCl_3$) δ 1.39 (12H, s), 1.45 (9H, s), 3.56 (2H, s), 7.34 (2H, d), 7.43 - 7.45 (1H, m), 7.53 (2H, d), 7.58 (1H, s), 7.75 (1H, d)	428 $M^{+\cdot}$ (EI+)
56-2		($CDCl_3$) δ 1.38 (12H, s), 1.46 (9H, s), 3.57 (2H, s), 7.37 (2H, d), 7.56 (2H, d), 7.72 (1H, d), 7.80 (1H, d), 7.87 (1H, s)	462 $M^{+\cdot}$ (EI+)
57-2		($CDCl_3$) δ 1.36 (12H, s), 3.65 (2H, s), 3.71 (3H, s), 3.85 (3H, s), 7.31 - 7.33 (3H, m), 7.39 (1H, s), 7.47 - 7.51 (3H, m)	382 $M^{+\cdot}$ (EI+)
58-2		(DMSO) δ 1.34 (12H, s), 3.35 (3H, s), 3.80 (2H, s), 3.89 (3H, s), 7.24 (1H, d), 7.26 - 7.28 (1H, m), 7.43 (2H, d), 7.67 (1H, d), 7.72 (2H, d)	mass ion not seen; HPLC tR= 3.01 min.

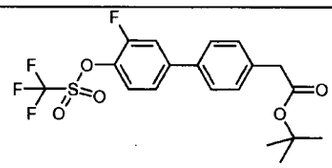
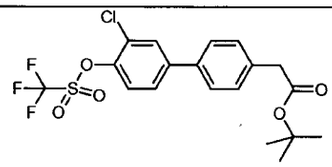
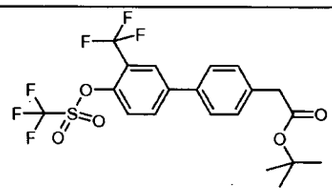
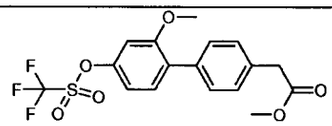
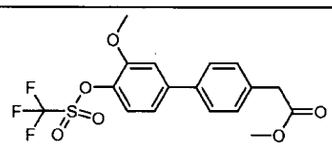
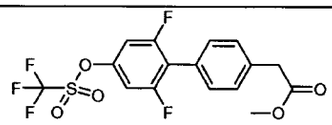
59-2		(DMSO) δ 1.38 (12H, s), 3.70 (3H, s), 3.82 (2H, s), 7.40 (2H, d), 7.46 (4H, s)	mass ion not seen; HPLC tR= 3.30 min.
60-2		(DMSO) δ 1.31 (12H, s), 3.64 (3H, s), 3.75 (2H, s), 7.35 - 7.41 (4H, m), 7.42 (1H, d), 7.65 - 7.67 (1H, m), 7.72 (1H, d).	mass ion not seen; HPLC tR= 3.42 min.
61-2		(DMSO) δ 1.31 (12H, s), 3.63 (3H, s), 3.74 (2H, s), 7.36 - 7.46 (3H, m), 7.52 (2H, dd), 7.55 (2H, d).	388 $M+Na^+$
62-2		(DMSO) δ 1.30 (12H, s), 2.52 (3H, s), 3.62 (3H, s), 3.72 (2H, s), 7.26 (1H, m), 7.40 (3H, m), 7.62 (2H, d), 7.70 (1H, d).	no mass ion seen HPLC tR= 3.44 min
63-2		(DMSO) δ 1.28 (12H, s), 1.94 (6H, s), 3.64 (3H, s), 3.74 (2H, s), 7.06 (2H, d), 7.34 (2H, d), 7.41 (2H, s).	no mass ion seen HPLC tR= 3.39 min.

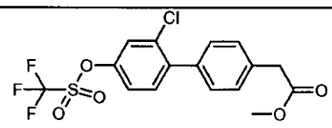
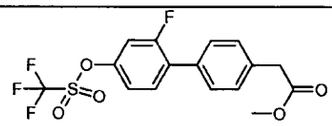
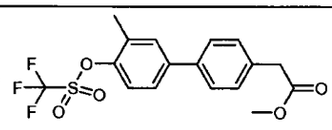
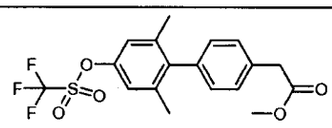
The following **Intermediates 54-3 to 63-3** were synthesised from **Intermediates 54-4 to 63-4** either using similar conditions as described in **Intermediate 25-4** (Method A) or by Method B (the procedure described by A. Bengtson, A. Hallberg and M. Larhed, *Org. Lett.*, 2002, **4**, 1231-1233) to afford the desired compounds.

Representative example of Method B:

Intermediate 54-3: tert-Butyl 2-(3'-fluoro-4'-(trifluoromethylsulfonyl-oxy)biphenyl-4-yl)acetate

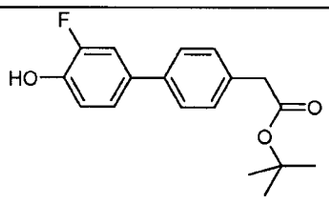
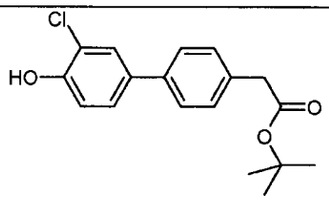
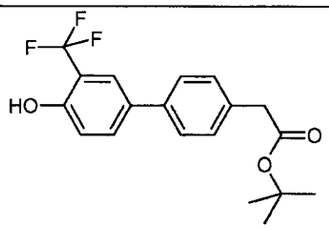
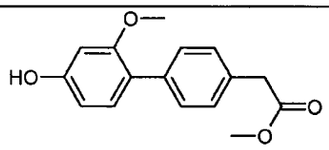
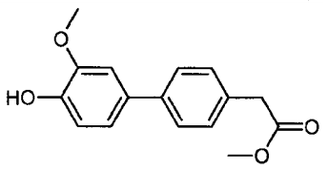
Intermediate 54-4 (637 mg, 2.11 mmol), 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (753 mg, 2.11 mmol) and potassium carbonate (874 mg, 6.32 mmol) were suspended in THF (11 mL) and sealed into a microwave tube. The reaction was heated to 120 °C for 6 minutes in the microwave reactor and cooled to RT. The suspension was filtered, the solid was washed with EtOAc (20 mL) and the filtrate was evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the title compound (690 mg, 75 %) as a colourless oil.

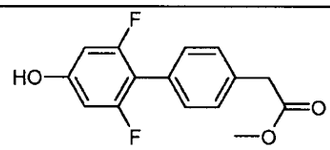
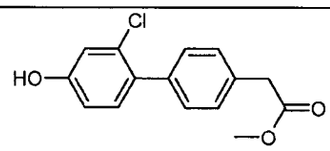
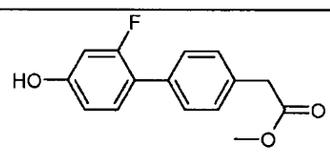
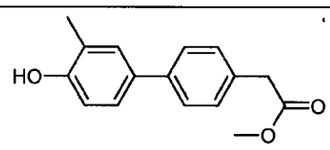
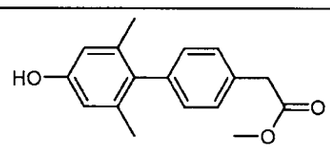
Intermediate	Structure	^{1}H NMR (400 MHz)	*m/z* $(M-H)^-$
54-3		($CDCl_3$) δ 1.46 (9H, s), 3.58 (2H, s), 7.35 - 7.39 (4H, m), 7.43 - 7.51 (3H, m)	433
55-3		($CDCl_3$) δ 1.46 (9H, s), 3.57 (2H, s), 7.36 - 7.41 (3H, m), 7.48 - 7.53 (3H, m), 7.71 (1H, s)	449
56-3		($CDCl_3$) δ 1.46 (9H, s), 3.59 (2H, s), 7.40 (2H, d), 7.52 (2H, d), 7.56 (1H, d), 7.80 - 7.83 (1H, m), 7.92 (1H, d)	483
57-3		($CDCl_3$) δ 3.67 (2H, s), 3.72 (3H, s), 3.83 (3H, s), 6.85 (1H, d), 6.92 - 6.95 (1H, m), 7.33 - 7.35 (3H, m), 7.44 (2H, d)	404
58-3		(DMSO) δ 3.63 (3H, s), 3.74 (2H, s), 3.99 (3H, s), 7.30 - 7.33 (1H, m), 7.38 (2H, d), 7.48 (1H, d), 7.52 (1H, d), 7.69 (2H, d)	403
59-3		(DMSO) δ 3.70 (3H, s), 3.83 (2H, s), 7.46 - 7.52 (4H, m), 7.74 (2H, d).	409

60-3		(DMSO) δ 3.71 (3H, s), 3.82 (2H, s), 7.43 - 7.50 (4H, m), 7.64 - 7.69 (2H, m), 7.95 (1H, d).	mass ion not seen; HPLC tR= 3.14 min.
61-3		(DMSO) δ 3.63 (3H, s), 3.75 (2H, s), 7.41 (2H, dd), 7.53 (2H, dt), 7.72 (1H, d), 7.73 (1H, t).	391
62-3		(DMSO) δ 2.40 (3H, s), 3.63 (3H, s), 3.73 (2H, s), 7.27 (1H, m), 7.40 (3H, m), 7.65 (2H, m), 7.77 (1H, s).	387
63-3		(DMSO) δ 2.01 (6H, s), 3.64 (3H, s), 3.73 (2H, s), 7.12 (2H, d), 7.26 (2H, s), 7.37 (2H, d).	401

Notes: Method A **58-3, 59-3, 60-3**; Method B **54-3, 55-3, 56-3, 57-3, 61-3, 62-3, 63-3**

The following **Intermediates 54-4 to 63-4** were synthesised from either **Intermediate 54-5 or 54-7** and the appropriate bromophenol using similar conditions as described in **Intermediate 21-1** to afford the desired compounds.

Intermediate	Structure	^{1}H NMR (400 MHz)	*m/z* $(M-H)^-$
54-4[a]		($CDCl_3$) δ 1.45 (9H, s), 3.55 (2H, s), 5.11 (1H, d), 7.04 (1H, t), 7.24 - 7.27 (1H, m), 7.28 - 7.33 (3H, m), 7.46 (2H, d).	301
55-4[b]		($CDCl_3$) δ 1.45 (9H, s), 3.55 (2H, s), 5.54 (1H, s), 7.07 (1H, d), 7.31 - 7.33 (2H, m), 7.38 - 7.41 (1H, m), 7.45 - 7.47 (2H, m), 7.54 (1H, d).	317
56-4[c]		($CDCl_3$) δ 1.45 (9H, s), 3.55 (2H, s), 5.11 (1H, d), 7.04 (1H, t), 7.24 - 7.27 (1H, m), 7.28 - 7.33 (3H, m), 7.46 (2H, d)	351
57-4[d]		($CDCl_3$) δ 3.65 (2H, s), 3.71 (3H, s), 3.78 (3H, s), 4.88 (1H, s), 6.45 - 6.47 (1H, m), 6.51 (1H, s), 7.15 (1H, d), 7.29 (2H, d), 7.44 (2H, d)	271
58-4[e]		(DMSO) δ 3.69 (3H, s), 3.75 (2H, s), 3.91 (3H, s), 6.90 (1H, d), 7.11 - 7.13 (1H, m), 7.23 (1H, d), 7.35 (2H, d), 7.61 (2H, d), 9.10 (1H, s).	mass ion not seen; HPLC tR= 2.20

			min.
59-4[f]		(DMSO) δ 3.38 (3H, s), 3.47 (2H, s), 6.28 - 6.34 (2H, m), 7.05 - 7.10 (4H, m), 10.18 (1H, s).	277
60-4[g]		(DMSO) δ 3.63 (3H, s), 3.71 (2H, s), 6.80 - 6.83 (1H, m), 6.92 (1H, d), 7.20 (1H, d), 7.28 - 7.33 (4H, m), 9.93 (1H, s).	275
61-4[h]		(DMSO) δ 3.62 (3H, s), 3.70 (2H, s), 6.65 (1H, dd), 6.70 (1H, dd), 7.30 (1H, d), 7.32 (2H, dd), 7.41 (2H, dd), 9.96 (1H, s).	259
62-4[i]		(DMSO) δ 2.18 (3H, s), 3.62 (3H, s), 3.67 (2H, s), 6.83 (1H, d), 7.27 (3H, d), 7.36 (1H, s), 7.50 (2H, d), 9.35 (1H, s).	no mass ion seen HPLC tR= 2.28 min.
63-4[j]		(DMSO) δ 1.87 (6H, s), 3.64 (3H, s), 3.71 (2H, s), 6.50 (2H, s), 7.03 (2H, d), 7.29 (2H, d), 9.12 (1H, s).	no mass ion seen HPLC tR= 2.31 min.

Notes: **54-4**[a] 4-Bromo-2-fluorophenol and **Intermediate 54-5**

55-4[b] 4-Bromo-2-chlorophenol and **Intermediate 54-5.**

56-4c 4-Bromo-2-(trifluoromethyl)benzenol and **Intermediate 54-5.**

57-4[d] 4-Bromo-3-methoxyphenol and **Intermediate 54-5.**

58-4[e] 4-Bromo-2-methoxyphenol and **Intermediate 54-7.**

59-4[f] 4-Bromo-3,5-Difluorophenol and **Intermediate 54-7.**

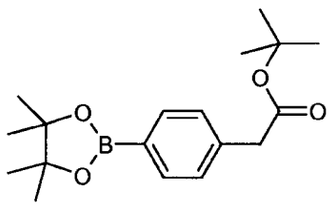
60-4[g] 4-Bromo-3-chlorophenol and **Intermediate 54-7.**

61-4[h] 4-Bromo-3-fluorophenol and **Intermediate 54-7.**

62-4[i] 4-Bromo-2-methylphenol and **Intermediate 54-7.**

63-4[j] 4-Bromo-3,5-dimethylphenol and **Intermediate 54-7.**

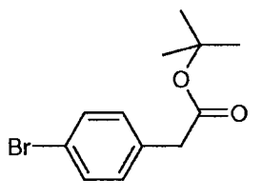
Intermediate 54-5: tert-Butyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate



This compound was synthesised from **Intermediate 54-6** using similar conditions as described in **Intermediate 25-2** to give the title compound (8.37 g, 69.3 %) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (12H, s), 1.42 (9H, s), 3.53 (2H, s), 7.27 (2H, d), 7.75 (2H, d); *m/z* (EI+) 318 M^+.

Intermediate 54-6 :tert-Butyl 2-(4-bromophenyl)acetate CAS 33155-58-7

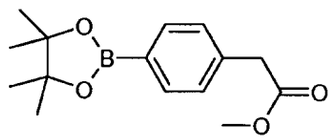


N,N-Dimethylformamide di-tert-butyl acetal (29.8 mL, 124.44 mmol) was added portionwise over 10 minutes to a stirred solution of 4-bromophenylacetic acid (13.38 g, 62.22 mmol) in toluene (400 mL) at 85 °C. The resulting solution was stirred at 85 °C for 4 hours and allowed to cool to ambient temperature. The reaction mixture was evaporated afford crude product which was purified by flash silica chromatography, elution gradient 0

to 20% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the title compound (10.29 g, 61.0 %) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (9H, s), 3.46 (2H, s), 7.14 (2H, d), 7.44 (2H, d); *m/z* (EI+) 270 M^+.

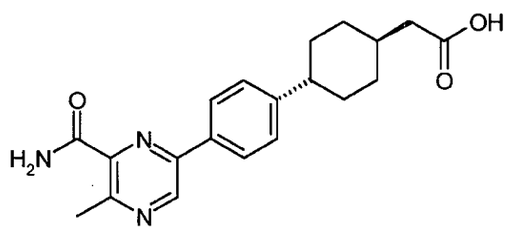
Intermediate 54-7: Methyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (CAS 454185-98-9)



This compound was synthesised from methyl 2-(4-bromophenyl)acetate (CAS 41841-16-1 made according to the procedure described by E. E. Knaus at al, *Bioorg. Med. Chem.*, 2005, **13**, 4694-4703) using similar conditions as described in **Intermediate 25-2** to afford the title compound (2.140 g, 100 %) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (12H, s), 3.64 (2H, s), 3.68 (3H, s), 7.28 (2H, d), 7.77 (2H, d); *m/z* (EI+) 276 M^+.

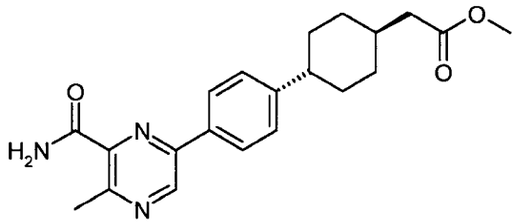
Example 64: 2-((1r,4r)-4-(4-(6-Carbamoyl-5-methylpyrazin-2-yl)phenyl)cyclohexyl)acetic acid



This compound was synthesised from **Intermediate 64-1** using similar conditions as described in **Example 21** to afford the title compound (120 mg, 64.3 %) as a white solid.

^{1}H NMR (400 MHz, DMSO) δ 1.10 - 1.18 (2H, m), 1.49 - 1.53 (2H, m), 1.84 (4H, d), 2.15 (2H, d), 2.31 - 2.33 (1H, m), 2.65 - 2.67 (1H, m), 2.75 (3H, s), 7.38 (2H, d), 7.70 (1H, s), 8.14 (2H, d), 8.22 (1H, s), 9.18 (1H, s), 11.97 (1H, s); *m/z* 395 $(M+H)^+$.

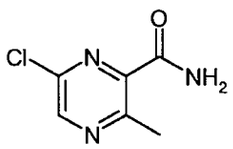
Intermediate 64-1: Methyl 2-((1r,4r)-4-(4-(6-Carbamoyl-5-methylpyrazin-2-yl)phenyl)cyclohexyl)acetate



This compound was synthesised from **Intermediate 64-2** and methyl 2-((1r,4r)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclohexyl)acetate (CAS 701232-69-1: see also **Intermediate 64-8**) using similar conditions as described in **Intermediate 21-1** to afford the title compound (194 mg, 83 %) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (3H, m), 1.60 (2H, m) 1.87 (4H, s), 2.20 - 2.22 (2H, m), 2.40 - 2.50 (1H, m) 2.94 (3H, s), 3.63 (3H, s), 5.5 (1H, s), 7.29 (2H, d), 7.80 (1H, s), 7.85 (2H, d), 8.95 (1H, s); *m/z* 368 $(M+H)^+$.

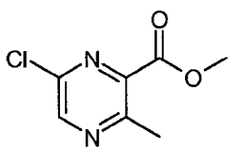
Intermediate 64-2: 6-Chloro-3-methylpyrazine-2-carboxamide



This compound was synthesised from **Intermediate 64-3** using similar conditions as described in **Intermediate 21-4** to afford the title compound (109 mg, 83 %) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.89 (3H, s), 5.45-5.55 (1H, s), 7.45-7.55 (1H, s), 8.56 (1H, s).

Intermediate 64-3: Methyl 6-chloro-3-methylpyrazine-2-carboxylate

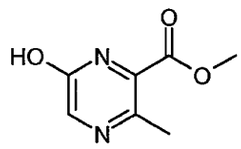


A suspension of **Intermediate 64-4** (314 mg, 1.87 mmol) and Phosphorus oxychloride (2.088 mL, 22.40 mmol) stirred at 90 °C for 70 minutes. The reaction mixture was added

dropwise to water (20 mL) over 2-3 hours while maintaining the temperature below 40 °C (external cooling required). The mixture was extracted with DCM (5 x 50 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford a yellow oil. This was then purified by flash silica chromatography, elution gradient 0 to 20% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the title compound (142 mg, 40.8 %) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.76 (3H, s), 3.94 (3H, s), 8.56 (1H, s); *m/z*187 $(M+H)^+$.

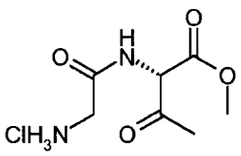
Intermediate 64-4: Methyl 6-hydroxy-3-methylpyrazine-2-carboxylate



A solution of **Intermediate 64-5** (1.3 g, 5.79 mmol) in pyridine (58.5 mL) was stirred at 60 °C for 90 minutes. The reaction mixture was evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 50 to 80% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the title compound (0.340 g, 34.9 %) as a yellow solid.

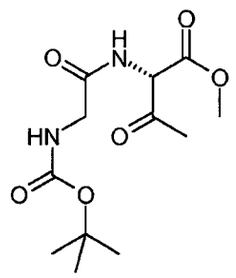
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.59 (3H, s), 3.94 (3H, s), 8.27 (1H, s); *m/z* 169 $(M+H)^+$.

Intermediate 64-5: (S)-Methyl 2-(2-aminoacetamido)-3-oxobutanoate hydrochloric acid salt



A 4M solution of Hydrogen chloride (7.98 mL, 31.91 mmol) in dioxane was added to **Intermediate 64-6** (2.3 g, 7.98 mmol). The resulting solution was stirred at ambient temperature for 4 hours. The reaction mixture was evaporated to afford the title compound (1.790 g, 119 %) as a cream solid, which was used without further purification. *m/z* 189 $(M+H)^+$.

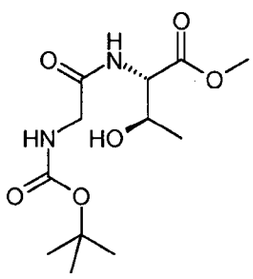
Intermediate 64-6: (S)-Methyl 2-(2-(tert-butoxycarbonylamino)acetamido)-3-oxobutanoate



A solution of **Intermediate 64-7** (12.9 g, 44.43 mmol) in DCM (72 mL) was added to a stirred suspension of pyridinium chlorochromate (22.99 g, 106.64 mmol) in DCM (43 mL) at 0 °C, over a period of 15 minutes under air. The resulting mixture was stirred at ambient temperature for 24 hours. The reaction mixture was evaporated to dryness and ether (400 mL) and water (300 mL) were added. The suspension was filtered through celite and the flask was rinsed with ether (4 x 300 mL) and water (3 x 200 mL). The washings were filtered through celite and the organic layers were combined, washed with saturated brine (200 mL), The aqueous phase was re extracted with EtOAc (2 x 500 mL), the organic layers were combined dried over $MgSO_4$, filtered and evaporated to afford 5.5g of crude product. The crude product was purified by flash silica chromatography, elution gradient 50 to 80% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the title compound (18.29 %) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (9H, d), 1.97 - 2.01 (3H, m), 2.31 (2H, s), 3.68 (1H, t), 3.75 (3H, s), 3.76 - 3.82 (3H, m), 4.05 (2H, q), 5.19 (1H, d).

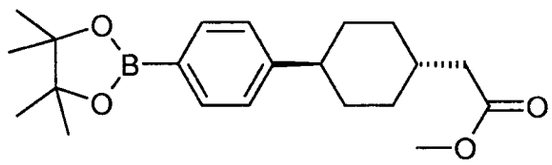
Intermediate 64-7: Methyl 2-(2-(tert-butoxycarbonylamino)acetamido)-3-hydroxybutanoate



HATU (46.9 g, 123.30 mmol) was added to a stirred solution of 2-(tert-butoxycarbonylamino)acetic acid (18 g, 102.75 mmol) DMA (230 mL) at ambient temperature. After 5 minutes a solution of (2S,3R)-methyl 2-amino-3-hydroxybutanoate hydrochloride (17.43 g, 102.75 mmol) and DIPEA (71.8 mL, 411.00 mmol) in DMA (230 mL) was added and the resulting solution was stirred at ambient temperature for 20 hours, The reaction mixture was diluted with EtOAc (300 mL), and washed with 1N citric acid (300 mL), salt was added to the aqueous layer which was re extracted with EtOAc (4 x 400 mL). The organic extracts were combined, washed with saturated $NaHCO_3$ (200 mL), dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 50 to 100% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the title compound (12.97 g, 43.5 %) as a yellow glass which formed a solid on standing.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (3H, t), 1.38 (9H, d), 3.70 (3H, s), 3.80 - 3.81 (2H, m), 4.25 - 4.28 (1H, m), 4.51 - 4.54 (1H, m), 5.36 (1H, s), 6.96 (1H, d); *m/z* 291 $(M+H)^+$.

Intermediate 64-8: Methyl 2-((1r,4r)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclohexyl)acetate



Trimethylphosphonoacetate (1.05X-1.06X) was added dropwise to a suspended solution of t-BuOK (0.70X-0.71X) in 2-MeTHF (10 vol) at 5-10°C. The resulting solution was stirred at 15-20°C for 3.5-4.0 hours. The reaction mixture was cooled to 5-10°C and DIPEA (0.81-0.82X) was added to the reaction at 10-15°C. 4-(4-Hydroxyphenyl)cyclohexanone (1.0 X) was added in portions to the above reaction mixture at 10-15°C and the resulting solution was stirred at 15-20°C for 3-6 hours and then sampled for HPLC analysis. NH4Cl-sol (5.0X-6.0X) was added to the reaction mixture at 0-15°C, and the reaction was quenched. The organic layer was separated and the aqueous layer was extracted with 2-MeTHF (2.5X-3.0X). The two organic extracts were combined and washed with $NaHSO_3$ aq. and then NaCl-solution (2.5X-3.0X) twice. The organic layer was concentrated to 2~3 vol and n-heptane was added to give a suspended solution, and the above mixture was

concentrated to below 3% of 2-MeTHF residue to give a suspended solution. The mixture was cooled to 0~5 °C, stirred for 1.0-2.0 h, filtered and the cake washed with n-heptane (2 vol X2). Dry in vacuum at below 45°C to give the desired phenoxyacrylate product.

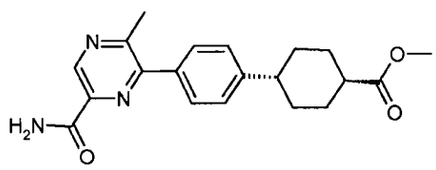
AcOH (0.05X) and Toluene (20vol) were added to a pressure reactor, then the above phenoxyacrylate (1.0X) was added to the mixture. The reactor was carefully inertised, then 10% Pd/C (0.15X) was added to the reaction mixture under nitrogen protection. The agitation was slowed down and the nitrogen-atmosphere was exchanged by hydrogen three times, and hydrogenation was performed at 1200 mbar at 25-28°C. The resulting solution was stirred at 25-28 °C for 14-18 h. HPLC showed conversion of >98%. The reaction mixture was filtered, and the cake was washed with EtOH (1.5X x2), then the filtrate was concentrated in vacuo to 2-3 vol, n-heptane(10vol) was added to precipitate, then concentrated until toluene residue <1.0%, cooled to 0-5 °C, filtered, the cake was dried in vacuo to dryness. The crude product was dissolved in EtOH:H_2O=2:1 (1.09X of crude product) by heating to reflux and stirred at this temperature for ~5 min, then cooled slowly to 20 °C over 3 h and stirred at 20 °C for 1 h, followed by cooling slowly to 0~5 °C over 90 min and stirred at 0~5 °C for 1 h. After filtering the filter cake was washed with cold EtOH:H_2O=2:1 (0.18X x2 of crude product, 0~5 °C). The filter cake was dried in vacuo at 45-50 °C for 24 h to give the pure trans-ester product.

The above trans ester (1.0X) was dissolved in anhydrous CH_2Cl_2 (12vol), NMM (0.57X,1.4 eq) was added dropwise to the mixture under N_2. The resulting solution was cooled to -10~ 0 °C and stirred for 10min, then Tf_2O (1.36X, 1.2 eq) was added dropwise at -10~0 °C (N.B. CF_3SO_2Cl can be appropriately used in place of triflic anhydride Tf_2O). The resulting solution was stirred at -10~0 °C for 30 min, warmed to 0~10 °C and stirred for 30 min. (sampled for HPLC analysis, conversion was >98%). 10% citric acid solution (10.0X) was added dropwise to the mixture. The mixture was stirred for 10 min, the organic layer was separated, washed with 10% citric acid (10.0X) and brine(10.0X), dried with anhydrous $MgSO_4$ (0.5X) for 2 hrs, filtered and concentrated to remove CH_2Cl_2. Heptane (10X) was added and concentrated to remove the residual CH_2Cl_2 (expectation <1.0%), then the suspension in heptane was concentrated to 1.5~2.0 vol, the mixture was cooled to

0~5 °C and stirred for 30~60min at 0~5 °C. After filtering the cake was dried under vacuum at 30~40 °C to give the desired triflate as a white solid.

Pinacoldiboron ester (0.8X, 1.2 eq), TBAF(0.13X, 0.2 eq) and KOAc(0.38X, 1.5eq) were dissolved in CH_3CN (5 vol), then PCy_3 (1.5%X, 0.02eq) and $PdCl_2$ (0.47%X, 0.01eq) were added. The mixture was degassed with nitrogen. A solution of the triflate (1.0X, 1.0 eq) in CH_3CN (7vol) was added to the mixture at 20-25 °C. Then the resulting solution was heated to reflux and stirred for 16 hrs (overnight - sampled for HPLC analysis, conversion was >98%). The mixture was filtered via a pad of 20 um cellulose, activated carbon (0.2X) was added to the filtrate and the resulting solution was heated to reflux for 2~3 hrs. The mixture was cooled to 40~50 °C and then filtered and the filtrate was concentrated to dryness. The residue solid was dissolved in EtOAc, and the EtOAc solution was washed with water (10 vol), 1N HCl (10 vol) and brine (10 vol). The organic layer was separated and concentrated to 1~2 vol, then heptane (5~6vol) was added to the solution and concentrated until EtOAc was removed (EtOAc/Heptane=0-1%), heptane (5~6vol) was added to the resulting solution and heated to 50~60 °C for 30 min. There were two layers (a clear upper heptane layer and a yellowish bottom layer). The heptane layer was separated, heptane (5~6vol) was added to the yellowish bottom layer and heated to 50~60 °C for 30 min, and the heptane layer was separated again. The heptane layers were combined and filtered via silica gel. The filtrate was concentrated to 1~1.5vol and the precipitate was filtered and dried in vacuo to give the desired boronate ester as a white solid.

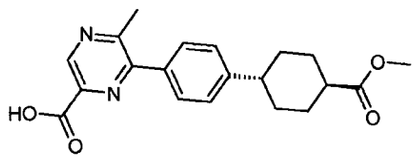
Example 65: Methyl *trans*-4-{4-[6-(aminocarbonyl)-3-methylpyrazin-2-yl]phenyl}-cyclohexanecarboxylate



Ethyl chloroformate (245 µl, 2.54 mmol) was added dropwise to a stirred solution of 6-{4-[trans-4-(methoxycarbonyl)cyclohexyl]phenyl}-5-methylpyrazine-2-carboxylic acid (Intermediate 65-1, 751 mg, 2.12 mmol) and N-methylmorpholine (350 µl, 3.18 mmol) in DCM (20 mL) at 0 °C. Ammonia (5 mL of a 7M solution in MeOH) was added. The

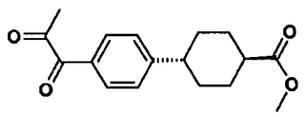
reaction mixture was allowed to warm up over 1 h then was concentrated and the residue was purified by chromatography eluting with 0-10% MeOH/DCM to give the title compound (226 mg, 30%) as a solid; ^{1}H NMR δ 9.00 (1H, s), 8.08 (1H, s), 7.74 (1H, s), 7.70 (2H, d), 7.40 (2H, d), 3.63 (3H, s), 2.70-2.55 (1H, m), 2.67 (3H, s), 2.50-2.35 (1H, m), 2.10-1.98 (2H, m), 1.96-1.83 (2H, m), 1.65-1.43 (4H, m); MS 354.

Intermediate 65-1: 6-{4-[*trans*-4-(Methoxycarbonyl)cyclohexyl]phenyl}-5-methylpyrazine-2-carboxylic acid



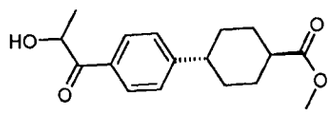
Diaminopropionic acid hydrochloride (496 mg, 3.52 mmol) was added to a stirred solution of methyl *trans*-4-(4-pyruvoylphenyl)cyclohexanecarboxylate (Intermediate 65-2, 844 mg, 2.93 mmol) and triethylamine (1.6 mL, 11.72 mmol) in MeOH (6 mL). After 48 h the reaction mixture was concentrated and the residue was triturated with ether to give the title compound (751 mg, 72%) as a solid that was used without further purification; ^{1}H NMR δ 9.04 (1H, s), 7.62 (2H, d), 7.40 (2H, d), 3.64 (3H, obs. s), 2.70-2.55 (1H, m), 2.66 (3H, s), 2.50-2.36 (1H, m), 2.08-1.96 (2H, m), 1.95-1.85 (2H, m), 1.65-1.45 (4H, m); MS 355.

Intermediate 65-2: Methyl *trans*-4-(4-pyruvoylphenyl)cyclohexanecarboxylate



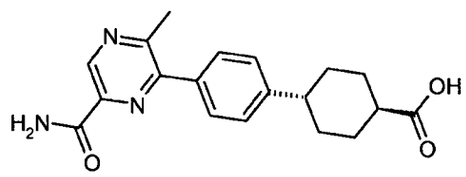
1,1,1-*tris*(Acetoxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one (5.14 g, 12.12 mmol) was added to a stirred solution of methyl *trans*-4-(4-lactoylphenyl)cyclohexanecarboxylate (Intermediate 65-3, 1.758 g, 6.06 mmol) in DCM (25 mL). The mixture was stirred for 1 h, hexanes (50mL) was added and the mixture was filtered through a pad of diatomaceous earth. Volatile material was removed by evaporation to give the title compound (1.55 g, 88%) as a solid that was used without further purification; ^{1}H NMR δ 7.88 (2H, d), 7.45 (2H, d), 3.63 (3H, s), 2.70-2.57 (1H, m), 2.50 (3H, s), 2.48-2.36 (1H, m), 2.08-1.94 (2H, m), 1.90-1.80 (2H, m), 1.60-1.40 (4H, m); MS 311 $(M+Na)^+$.

Intermediate 65-3: Methyl *trans*-4-(4-lactoylphenyl)cyclohexanecarboxylate



Sodium hydroxide (370 mg, 9.25 mmol) in water (2 mL) was added to a stirred solution of methyl *trans*-4-[4-(2-bromopropanoyl)phenyl]cyclohexanecarboxylate (prepared as described in Patent Application WO2004/047755) (3.264 g, 9.25 mmol) in DMF (10 mL). The mixture was stirred for 40 minutes then extracted with ether (5 x 20 mL). The extracts were combined, dried and concentrated. The crude product was purified by flash column chromatography eluting with 20-40% EtOAc/hexanes to give the title compound (1.76 g, 66%) as a solid; ^{1}H NMR δ 7.94 (2H, d), 7.39 (2H, d), 5.29 (1H, d), 5.08-4.98 (1H, m), 3.62 (3H, s), 2.68-2.54 (1H, m), 2.48-2.35 (1H, m), 2.08-1.94 (2H, m), 1.90-1.79 (2H, m), 1.60-1.40 (4H, m), 1.28 (3H, s); MS 313 $(M+Na)^+$.

Example 66: *trans*-4-{4-[6-(Aminocarbonyl)-3-methylpyrazin-2-yl]phenyl}cyclohexanecarboxylic acid



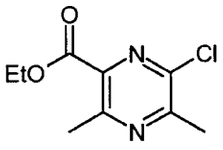
Lithium hydroxide monohydrate (42 mg, 1.00 mmol) was added to a stirred solution of methyl trans-4-{4-[6-(aminocarbonyl)-3-methylpyrazin-2-yl]phenyl}-cyclohexanecarboxylate (Example 65, 71 mg, 0.20 mmol) in MeOH (2 mL), THF (1 mL) and water (0.5 mL). After 16 h the reaction mixture was concentrated in vacuo and purified by reverse phase HPLC (150mm x 21mm Phenomenex Column packed with Luna 10u C18 silica, eluting with 5-95% acetonitrile/water) to give the title compound as a yellow solid (6 mg, 9%); ^{1}H NMR δ 9.01 (1H, s), 8.08 (1H, s), 7.73 (1H, s), 7.70 (2H, d), 7.40 (2H, d), 2.70-2.50 (1H, m), 2.65 (3H, s), 2.37-2.25 (1H, m), 2.10-2.00 (2H, m), 1.95-1.85 (2H, m), 1.65-1.40 (4H, m); MS 340.

Examples 67 to 70

Other compounds which have been made by processes analogous to those described herein are 2-(4'-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)-2'-methylbiphenyl-4-yl)acetic acid; 2-(4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)naphthalen-1-yl)phenyl)acetic acid; 2-(4'-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)-2'-cyanobiphenyl-4-yl)acetic acid and 2-(4'-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)-3',5'-difluorobiphenyl-4-yl)acetic acid.

Alternative Preparations

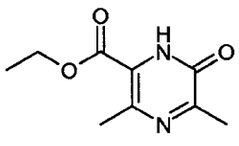
Intermediate 1-4: Ethyl 6-chloro-3,5-dimethylpyrazine-2-carboxylate



A suspension of **Intermediate 1-5** (268 g, 1365.93 mmol) in phosphorus oxychloride (1273 mL, 13659.31 mmol) was heated at 90 °C under nitrogen for 1 hour then cooled to ambient temperature. The reaction was cautiously added to water (6 L) with vigorous stirring keeping the temperature between 17 °C and 20 °C. The mixture was then extracted with DCM (5 x 2.5 L), washed with water, saturated brine and dried over $MgSO_4$ and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 25% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the title compound (227 g, 77%) as a yellow oil which solidified on standing.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (3H, t), 2.68 (3H, s), 2.77 (3H, s), 4.46 (2H, q); *m/z* 215 $(M+H)^+$.

Intermediate 1-5: Ethyl 6-hydroxy-3,5-dimethylpyrazine-2-carboxylate



A solution of 2M Hydrochloric acid in 1,4-dioxane (1177 mL, 4709.97 mmol) was added to **Intermediate 1-6** (745 g, 2354.99 mmol) and stirred at room temperature for 15 minutes then warmed to 40 °C for a further 40 minutes. Pyridine (6500 mL) was then slowly added

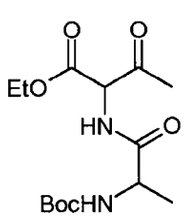
and then the reaction was heated to 80 °C for 2 hours in the presence of air. The reaction was then allowed to cool to ambient temperature and evaporated to dryness to afford a viscous oil. This was suspended in DCM (2.5 L) and washed water (1.5 L). The DCM was then dried over $MgSO_4$, filtered and concentrated to afford an orange semi-solid, which was triturated with 1:1 EtOAc/iso-hexane (250 mL) to afford ethyl 6-hydroxy-3,5-dimethyl-1,4-dihydropyrazine-2-carboxylate (127 g, 27.1 %) as a cream solid. The mother liqours were then purified by flash silica chromatography (gradient from 20% ethyl acetate/iso-hexane to 80% ethyl acetate/iso-hexane). Fractions containing the desired product were concentrated and the residue was triturated with a small volume of 1:1 EtOAc/iso-hexane to afford the title compound (9.00 g, 1.948 %).

Manganese dioxide (150 g) was added to a suspension of ethyl 6-hydroxy-3,5-dimethyl-4,5-dihydropyrazine-2-carboxylate (121 g, 610.44 mmol) in DCM (1.8 L) at ambient temperature giving rise to a 2 °C exotherm. The reaction was stirred for 10 minutes then warmed to 35 °C for 1 hour. The reaction was incomplete so an additional 115g of Manganese dioxide was added and the reaction stirred for 1 hour at 35 °C then stirred to cool to ambient temperature. The reaction was filtered through a short bed of silica and washed through with 2 L of 1:1 EtOAc/iso-hexane and finally 2 x 2 L EtOAc. The fractions were then combined and reduce in-vacuo to give an orange solid, which was slurried in 300 mL of 1:1 EtOAc/iso-hexane, filtered and washed with iso-hexane to afford the title compound (87 g, 72.6 %) as an orange solid.

^{1}H NMR (400 MHz, DMSO) δ 1.31 (3H, t), 2.35 (3H, s), 2.50 (3H, s), 4.31 (2H, q), 11.93 (1H, s); *m/z* 197 $(M+H)^+$

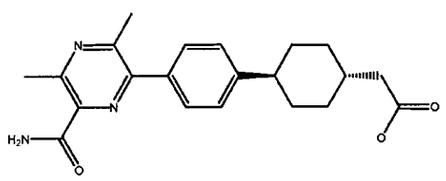
Intermediate 1-6 can also be prepared by the following procedure:

Intermediate 1-6: Ethyl 2-(2-(tert-butoxycarbonylamino)propanamido)-3-oxobutanoate



A solution of 4-methylmorpholine (900g) in THF (15 L) was added to 2-(tert-butoxycarbonylamino)propanoic acid (1690 g, 8933.17 mmol). The mixture was cooled to –25 °C and isobutyl chloroformate (1.164 L, 8933.17 mmol) was added. After 20 minutes the second equivalent of 4-methylmorpholine (900g) was added followed by ethyl 2-amino-3-oxobutanoate Tosylate salt (see J-P. Genet et al, *Eur. J. Org. Chem.*, 2004, 3017-3026) (2700 g, 8507.78 mmol) suspended in THF (2.5 L). The mixture was stirred at –25 °C for 30 minutes and then left to warm to ambient temperature overnight. The reaction was quenched with water (15 L), extracted with EtOAc (3 x 5 L) and the combined extracts washed with 50% saturated brine (5 L). 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 50 to 80% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford ethyl 2-(2-(tert-butoxycarbonylamino)propanamido)-3-oxobutanoate (1850 g, 68.7 %).

Example 1: 2-((1r,4r)-4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)acetic acid

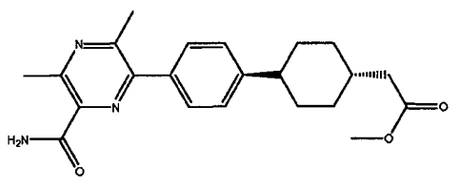


Powdered potassium hydroxide (2.81 g, 50.10 mmol) was added in one portion to **Intermediate 1-8** (6.37 g, 16.70 mmol) in *tert*-butanol (150 mL) at 40°C under nitrogen. The resulting suspension was stirred at 40°C for 20 minutes. A thick precipitate formed so the reaction was quenched with acetic acid (4.78 mL, 83.49 mmol) in ethanol (100.0 mL) and the resulting solution stirred for a further 20 minutes before being evaporated to dryness. The resulting solid was partitioned between water (500 mL) and EtOAc (500 mL). The aqueous layer showed a pH=4~5. The organic layer was separated and the aqueous re-extracted with EtOAc (2 x 250 mL). The combined organics were washed with brine (100 mL), dried over $MgSO_4$ and evaporated in vacuo to give crude product. This was recrystallised from hot ethanol (250 mL) to give a yellow solid which was washed with ether (100 mL) and dried under vacuum at room temperature to give the title compound (4.82 g, 79 %).

[^{1}H NMR (400.132 MHz, DMSO) δ 1.09 - 1.19 (2H, m), 1.46 - 1.57 (2H, m), 1.70 - 1.78 (1H, m), 1.81 - 1.87 (4H, m), 2.15 (2H, d), 2.58 (3H, s), 2.73 (3H, s), 3.29 (1H, s), 7.36 (2H, d), 7.57 (1H, s), 7.64 (2H, d), 7.98 (1H, s), 11.98 (1H, s)].

A melting point with an onset value of approximately 225°C has been determined for {trans-4-[4-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl] cyclohexyl}acetic acid.

Intermediate 1-8: methyl 2-((1s,4s)-4-(4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)acetate

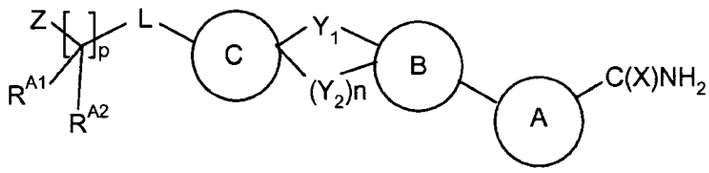


A solution of 6-chloro-3,5-dimethylpyrazine-2-carboxamide (see **Intermediate 21-4**) (3.15 g, 16.97 mmol), methyl 2-((1s,4s)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclohexyl)acetate (see **Intermediate 64-8**) (6.08 g, 16.97 mmol) and tripotassium phosphate (4.32 g, 20.37 mmol) in DME (120 mL), ethanol (75 mL) and water (30.0 mL) were degassed before addition of (1,1'-bis(diphenylphosphino)ferrocene)-dichloropalladium(II) (0.698 g, 0.85 mmol). The reaction mixture was heated to 80 °C, under nitrogen, and left to stir overnight for 16 hrs. The reaction mixture was allowed to cool to room temperature and then evaporated. The crude product was partitioned between water (250 mL) and EtOAc (250 mL). The catalyst was filtered off from the biphasic mixture. The organic phase was separated and washed with brine (100 mL), dried (Na_2SO_4) and evaporated. The crude product was purified by flash silica chromatography, elution gradient 5 to 90% EtOAc in isohexane on 330g silicyle column. Pure fractions were evaporated to dryness to afford the title compound (6.47 g, 100 %) as a yellow solid.

[^{1}H NMR (400.132 MHz, DMSO) δ 1.10 - 1.21 (2H, m), 1.46 - 1.56 (2H, m), 1.73 - 1.86 (5H, m), 2.25 (2H, d), 2.58 (3H, s), 2.73 (3H, s), 3.28 (1H, s), 3.60 (3H, s), 7.35 (2H, d), 7.58 (1H, s), 7.64 (2H, d), 7.97 (1H, s); HPLC tR= 2.53 min.]

Claims

1. A compound of formula (I), or a pharmaceutically-acceptable salt, or pro-drug thereof,



(I)

wherein

Ring A is 2,6-pyrazindiyl, 3,5-pyridindiyl or 2,6-pyridindiyl, each optionally substituted on an available carbon atom by one or two substituents independently selected from linear (1-3C)alkyl, (2-3C)alkenyl, (2-3C)alkynyl, (1-2C)alkoxy, methoxymethyl, amino and cyano;

X is =O or =S;

Ring B is 1,4-phenylene or Ring B is a di-linked (excluding links via the same or adjacent atoms) ring selected from pyridindiyl, furandiyl, thiophendiyl, pyrroldiyl, oxazoldiyl, thiazoldiyl, imidazoldiyl, isoxazoldiyl, isothiazoldiyl and pyrazoldiyl; each optionally substituted on an available carbon atom by one or two substituents independently selected from halo, amino, cyano, (1-4C)alkyl, (2-3C)alkenyl, (2-3C)alkynyl, (1-4C)alkoxy and (1-4C)alkoxy-(1-4C)alkyl;

Y_1 is a direct bond between Ring B and Ring C or Y_1 is -O-, -S- or –NRa- wherein Ra is hydrogen or (1-4C)alkyl;

Y_2 is $-(CH_2)_r-$ wherein r is 2 or 3, and Y_2 is linked at the same carbon atom as Y_1 in Ring C and Y_2 is linked at an adjacent carbon atom to Y_1 in Ring B;

n is 0 or n is 1 when Y_1 is a direct bond between Ring B and Ring C and when Ring B is 1,4-phenylene and Ring C is (4-6C)cycloalkane, so that a 5- or 6-membered spiro-ring system is formed and Ring C is tri-linked;

Ring C is a di-linked (excluding links via the same or adjacent atoms) ring or ring system chosen from (4-6C)cycloalkane, (7-10C)bicycloalkane and (8-12C)tricycloalkane each optionally substituted on an available carbon atom, including the ring carbon atom bearing the Z-containing group, by one substituent selected from hydroxy, (1-4C)alkyl, (1-4C)alkoxy and (1-4C)alkoxy(1-4C)alkyl;

or Ring C is a di-linked (excluding links via the same or adjacent atoms) ring selected from phenylene, pryidindiyl, piperidinediyl N-linked to Y_1, piperazinediyl, furandiyl, thiophendiyl, pyrroldiyl, oxazoldiyl, thiazoldiyl, imidazoldiyl, isoxazoldiyl, isothiazoldiyl, pyrazoldiyl and azabicyclo[3.1.0]hexanediyl;

each optionally substituted on an available carbon atom by up to four substituents independently selected from fluoro, chloro, bromo, cyano, (1-4C)alkyl, (1-4C)alkoxy and (1-4C)alkoxy(1-4C)alkyl;

L is a direct bond to Ring C, -O-, -S- or –NH-;

p is 0 (when L is a direct bond), 1 or 2 and when p is 1 or 2 R^{A1} and R^{A2} are each independently hydrogen or (1-4C)alkyl or R^{A1} and R^{A2} are linked together to form a (3-6C)spiroalkyl ring;

Z is carboxy or a mimic or bioisostere thereof, hydroxy or –CONRbRc wherein Rb and Rc are independently selected from hydrogen and (1-4C)alkyl, which (1-4C)alkyl group may be optionally substituted by carboxy or a mimic or bioisostere thereof;

and wherein any carbon atom in a linear (1-3C)alkyl, (1-2C)alkoxy, (1-4C)alkyl or (1-4C)alkoxy containing group defined above may be optionally substituted by up to 3 fluoro atoms; with the proviso that the compound (4-(4-(6-carbamoyl-pyridin-2-yl)phenyl)cyclohexyl)acetic acid is excluded.

2. A compound of formula (I), or a pharmaceutically-acceptable salt, or pro-drug thereof, as claimed in Claim 1, wherein

Ring A is 2,6-pyrazindiyl, 3,5-pyridindiyl or 2,6-pyridindiyl, each optionally substituted on an available carbon atom by one or two substituents independently selected from linear (1-3C)alkyl, (2-3C)alkenyl, (2-3C)alkynyl, (1-2C)alkoxy, methoxymethyl, amino and cyano;

X is =O or =S;

Ring B is 1,4-phenylene or Ring B is a di-linked (excluding links via the same or adjacent atoms) ring selected from pyridindiyl, furandiyl, thiophendiyl, pyrroldiyl, oxazoldiyl, thiazoldiyl, imidazoldiyl, isoxazoldiyl, isothiazoldiyl and pyrazoldiyl; each optionally substituted on an available carbon atom by one or two substituents independently selected from halo, amino, cyano, (1-4C)alkyl, (2-3C)alkenyl, (2-3C)alkynyl, (1-4C)alkoxy and (1-4C)alkoxy-(1-4C)alkyl;

Y_1 is a direct bond between Ring B and Ring C or Y_1 is -O-, -S- or –NRa- wherein Ra is hydrogen or (1-4C)alkyl;

Y_2 is $–(CH_2)_r-$ wherein r is 2 or 3, and Y_2 is linked at the same carbon atom as Y_1 in Ring C and Y_2 is linked at an adjacent carbon atom to Y_1 in Ring B;

n is 0 or n is 1 when Y_1 is a direct bond between Ring B and Ring C and when Ring B is 1,4-phenylene and Ring C is (4-6C)cycloalkane, so that a 5- or 6-membered spiro-ring system is formed;

Ring C is a di-linked (excluding links via the same or adjacent atoms) ring or ring system chosen from (4-6C)cycloalkane, (7-10C)bicycloalkane and (8-12C)tricycloalkane each optionally substituted on an available carbon atom, including the ring carbon atom bearing the Z-containing group, by one substituent selected from hydroxy, (1-4C)alkyl, (1-4C)alkoxy and (1-4C)alkoxy(1-4C)alkyl;

or Ring C is a di-linked (excluding links via the same or adjacent atoms) ring selected from phenylene, pryidindiyl, piperidinediyl N-linked to Y_1, furandiyl, thiophendiyl, pyrroldiyl, oxazoldiyl, thiazoldiyl, imidazoldiyl, isoxazoldiyl, isothiazoldiyl and pyrazoldiyl;

each optionally substituted on an available carbon atom by up to four substituents independently selected from fluoro, chloro, bromo, cyano, (1-4C)alkyl, (1-4C)alkoxy and (1-4C)alkoxy(1-4C)alkyl;

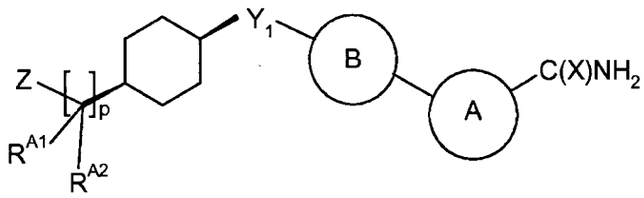
L is a direct bond to Ring C, -O-, -S- or –NH-;

p is 0, 1 or 2 and when p is 1 R^{A1} and R^{A2} are each independently hydrogen or (1-4C)alkyl or R^{A1} and R^{A2} are linked together to form a (3-6C)spiroalkyl ring;

Z is carboxy or a mimic or bioisostere thereof, hydroxy or –CONRbRc wherein Rb and Rc are independently selected from hydrogen and (1-4C)alkyl, which (1-4C)alkyl group may be optionally substituted by carboxy or a mimic or bioisostere thereof;

and wherein any carbon atom in a linear (1-3C)alkyl, (1-2C)alkoxy, (1-4C)alkyl or (1-4C)alkoxy containing group defined above may be optionally substituted by up to 3 fluoro atoms.

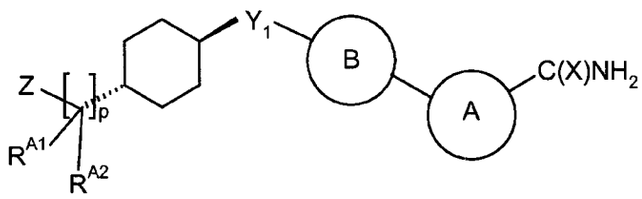
3. A compound of formula (IA) as claimed in Claim 1 or 2, or a pharmaceutically-acceptable salt, or pro-drug thereof,



(IA)

wherein X, Ring A, Ring B, Y_1, p, R^{A1}, R^{A2} and Z are as defined in Claim 1 or 2.

4. A compound of formula (IB) as claimed in Claim 1 or 2, or a pharmaceutically-acceptable salt, or pro-drug thereof,



(IB)

wherein X, Ring A, Ring B, Y_1, p, R^{A1}, R^{A2} and Z are as defined in Claim 1 or 2.

5. A compound as claimed in any one of Claims 1 to 4, or a pharmaceutically-acceptable salt, or pro-drug thereof, wherein X is =O;

Ring A is 2,6-pyrazindiyl optionally substituted on an available carbon atom by one or two substituents independently selected from linear (1-3C)alkyl, (2-3C)alkenyl, (2-3C)alkynyl, (1-2C)alkoxy, methoxymethyl, amino and cyano;

Ring B is 1,4-phenylene optionally substituted on an available carbon atom by one or two substituents independently selected from halo, amino, cyano, (1-4C)alkyl, (2-3C)alkenyl, (2-3C)alkynyl, (1-4C)alkoxy and (1-4C)alkoxy-(1-4C)alkyl;

Ring C is 1,4-cyclohexane;

n is 0 and Y_1 is a direct bond or Y_1 is -O-;

L is a direct bond;

p is 1 and R^{A1} and R^{A2} are each hydrogen;

Z is carboxy, a tetrazole group, -C(O)NHS(O)$_2$Me, hydroxy or –CONRbRc wherein Rb and Rc are independently selected from hydrogen and (1-4C)alkyl, which (1-4C)alkyl group may be optionally substituted by carboxy; and wherein any carbon atom in a linear (1-3C)alkyl, (1-2C)alkoxy, (1-4C)alkyl or (1-4C)alkoxy containing group defined above may be optionally substituted by up to 3 fluoro atoms.

6. A compound as claimed in any one of Claims 1 to 5, or a pharmaceutically-acceptable salt, or pro-drug thereof, wherein Ring A is 2,6-pyrazindiyl optionally substituted on an available carbon atom by one or two linear (1-3C)alkyl substituents.

7. A compound as claimed in Claim 1 or 2 selected from
{trans-4-[4-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl] cyclohexyl}acetic acid;
3,5-Dimethyl-6-[4-(trans-4-{2-[(methylsulfonyl)amino]-2-oxoethyl}cyclohexyl)-phenyl]pyrazine-2-carboxamide;
6-{4-[trans-4-(2-Amino-2-oxoethyl)cyclohexyl]phenyl}-3,5-dimethylpyrazine-2-carboxamide;
N-({trans-4-[4-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl] cyclohexyl}acetyl)-2-methylalanine;
6-{4-[trans-4-(2-Hydroxyethyl)cyclohexyl]phenyl}-3,5-dimethyl pyrazine-2-carboxamide;
(trans-4-{4-[6-Carbamoyl-5-(difluoromethyl)-3-methylpyrazin-2-yl]phenyl}cyclohexyl)acetic acid;
{trans-4-[4-(6-Carbamoyl-3-ethyl-5-methylpyrazin-2-yl)phenyl] cyclohexyl}acetic acid;
{trans-4-[4-(6-Carbamoyl-5-ethyl-3-methylpyrazin-2-yl)phenyl] cyclohexyl}acetic acid and {trans-4-[4-(6-Carbamoyl-3-methylpyrazin-2-yl)phenyl]cyclohexyl} acetic acid;
2-((1r,4s)-5'-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-4-yl)acetic acid;
(1r,4s)-5'-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-4-carboxylic acid;
2-((1r,4r)-4-(4-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)cyclohexyl)-2-methylpropanoic acid
2-(1-(4-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)pyrrolidin-3-yl)acetic acid;

(1R,5S,6r)-3-(4-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid;

6-(4-((1r,4r)-4-((1H-Tetrazol-5-yl)methyl)cyclohexyl)phenyl)-3,5-dimethylpyrazine-2-carboxamide;

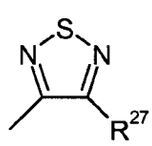
4'-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)biphenyl-4-carboxylic acid;

Methyl *trans*-4-{4-[6-(aminocarbonyl)-3-methylpyrazin-2-yl]phenyl}-cyclohexanecarboxylate;

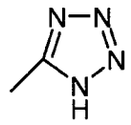
trans-4-{4-[6-(Aminocarbonyl)-3-methylpyrazin-2-yl]phenyl}cyclo-hexanecarboxylic acid; or a pharmaceutically-acceptable salt of any of these.

8. A compound as claimed in any one of Claims 1 to 6 wherein a pro-drug thereof is an ester of a carboxy group selected from a (1-6C)alkyl ester, a (1-6C)alkoxymethyl ester, a (1-6C)alkanoyloxymethyl ester, a phthalidyl ester, a (3-8C)cycloalkoxycarbonyloxy(1-6C)alkyl ester, a 1,3-dioxolan-2-ylmethyl ester, a (1-6C)alkoxycarbonyloxyethyl ester, an aminocarbonylmethyl ester and a mono- or di- N-((1-6C)alkyl) version of an aminocarbonylmethyl ester.

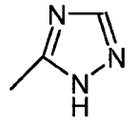
9. A compound as claimed in any one of Claims 1 to 6 wherein a mimic or bioisostere of a carboxy group is selected from $-SO_3H$, $-S(O)_2NHR^{13}$, $S(O)_2NHC(O)R^{13}$, $-CH_2S(O)_2R^{13}$, $-C(O)NHS(O)_2R^{13}$, -C(O)NHOH, -C(O)NHCN, $-CH(CF_3)OH$, $C(CF_3)_2OH$, $-P(O)(OH)_2$ and groups of sub-formula (a)-(i') below



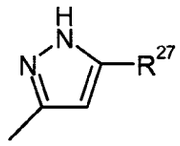
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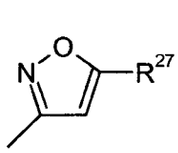
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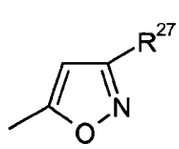
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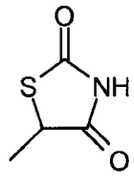
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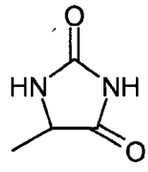
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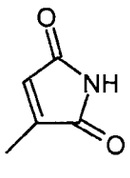
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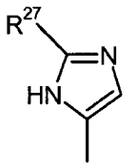
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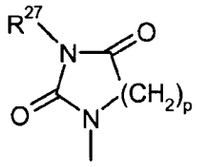
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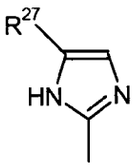
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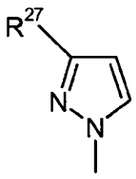
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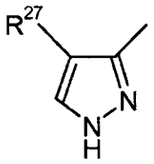
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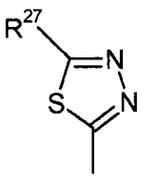
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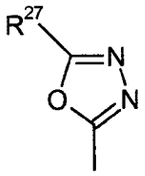
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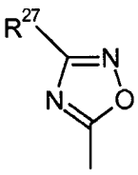
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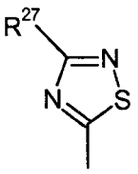
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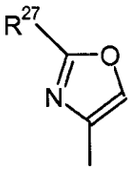
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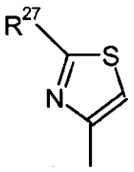
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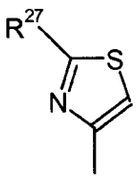
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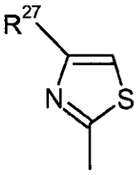
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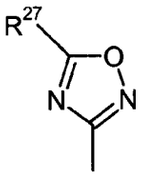
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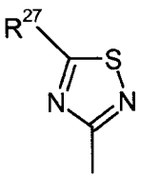
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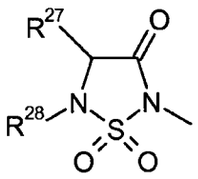
(v)



(w)



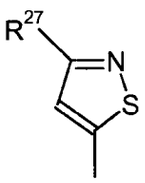
(x)



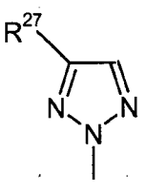
(y)



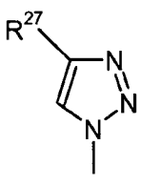
(z)



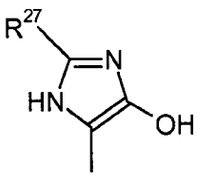
(a')



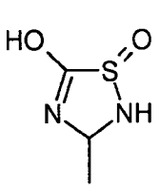
(b')



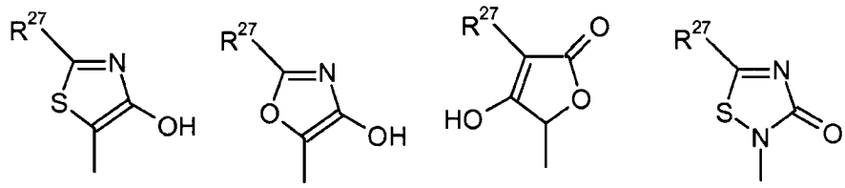
(c')



(d')



(e')



(f') (g') (h') (i')

wherein where p in sub-formula (k) is 1 or 2, R^{27} and R^{28} are independently selected from hydrogen, hydroxy, (1-6C)alkoxy, thiol, (1-6C)alkylthio, $-C(O)R^{29}$, $-S(O)R^{30}$, $-SO_2R^{31}$, $-NR^{32}R^{33}$, -NHCN, halogen and trihalomethyl, where R^{29}, R^{30} and R^{31} are $-OR^{34}$, (1-6C)alkyl, $-NR^{32}R^{33}$ or trihalomethyl, R^{32} and R^{33} are independently selected from hydrogen, (1-6C)alkyl, $-SO_2R^{34}$ and $-COR^{35}$, where R^{35} is (1-6C)alkyl or trihalomethyl, and R^{34} is hydrogen, (1-6C)alkyl or trihalomethyl and R^{13} is selected from hydrogen, (1-6C)alkyl, hydroxy, halo, amino, cyano, ((1-3C)alkyl)CONH-, carboxy, (1-6C)alkoxy, (1-6C)alkoxycarbonyl, carbamoyl, N-((1-6C)alkyl)carbamoyl, halo((1-6C)alkyl) (such as trifluoromethyl), (1-6C)alkylsulphonyl or (1-6C)alkylsulphinyl.

10. A compound according to any one of Claims 1 to 9 or a pharmaceutically-acceptable salt, or pro-drug thereof for use as a medicament.

11. A compound, or a pharmaceutically-acceptable salt, or pro-drug thereof, for use as a medicament as claimed in Claim 10 for treating diabetes mellitus and/or obesity in a warm-blooded animal such as a human being.

12. The use of a compound according to any one of Claims 1 to 9, or a pharmaceutically-acceptable salt, or pro-drug thereof, in the manufacture of a medicament for use in the production of an inhibition of DGAT-1 activity in a warm-blooded animal such as a human being.

13. The use of a compound of formula (I), or a pharmaceutically-acceptable salt, or pro-drug thereof, as claimed in Claim 12, in the manufacture of a medicament for use in the treatment of diabetes mellitus and/or obesity in a warm-blooded animal such as a human being.

14. A method of treating diabetes mellitus and/or obesity in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound according to any one of Claims 1 to 9, or a pharmaceutically-acceptable salt, or pro-drug thereof.

15. A pharmaceutical composition which comprises a compound of formula (I) as claimed in any one of Claims 1 to 9, or a pharmaceutically-acceptable salt, or pro-drug thereof, in association with a pharmaceutically-acceptable excipient or carrier.

Compuestos de Carbamoilo como Inhibidores de la DGAT1 190

El presente invento se relaciona con compuestos que inhiben la actividad de la acetil CoA (acetil coenzima A): diacilglicerol aciltransferasa (DGAT1), procesos para su preparación, composiciones farmacéuticas que los contienen como el ingrediente activo, métodos para el tratamiento de estados patológicos con actividad DGAT1, con su uso como medicamentos y su uso en la fabricación de medicamentos para utilizar en la inhibicición de la actividad de DGAT1 en animales de sangre caliente tales como los seres humanos. En particular, este invento se relaciona con compuestos útiles para el tratamiento de diabetes tipo II, resistencia a la insulina, tolerancia deteriorada a la glucosa y obesidad en animales de sangre caliente tales como los humanos, más particularmente se relaciona con el uso de estos compuestos en la fabricación de medicamentos para el uso en el tratamiento de diabetes tipo II, resistencia a la insulina, tolerancia deteriorada a la glucosa y obesidad en animales de sangre caliente tales como los humanos.

La acil CoA:diacilglicerol aciltransferasa (DGAT) se encuentra en la fracción microsomal de las células. Esta cataliza la reacción final en la ruta de fosfato, considerada como la principal ruta de síntesis de triglicéridos en células al facilitar la unión de un diacilglicerol con un acil CoA graso, resultando en la formación de triglicéridos. Aunque no está claro si la DGAT es un limitante de tasa para la síntesis de triglicéridos, ésta cataliza el único paso en la ruta que es ejecutado para producir este tipo de molécula [Lehner & Kuksis (1996) *Biosynthesis of triacylglycerols*. Prog. Lipid Res. 35: 169-201].

Dos genes DGAT se han clonado y caracterizado. Ambas proteínas codificadas catalizan la misma reacción aunque no comparten homología de secuencia. El gen DGAT1 fue identificado a partir de búsquedas de bases de datos de secuencias debido a su similitud con genes de acil CoA: colesterol aciltransferasa (ACAT). (Cases (1998) Identificación de un gen que codifica una Acil CoA:diacilglicerol aciltransferasa, una enzima clave en la síntesis de triacilglicerol. Proc. Natl. Acad. Sci. USA 95: 13018-13023]. La actividad de la DGAT1 se ha encontrado en muchos tejidos mamíferos, incluyendo los adipocitos.

Debido a la carencia previa de sondas moleculares, poco se sabe acerca de la regulación de la DGAT1. La DGAT1 se conoce por ser significativamente regulada de manera positiva durante diferenciación de adipositos.

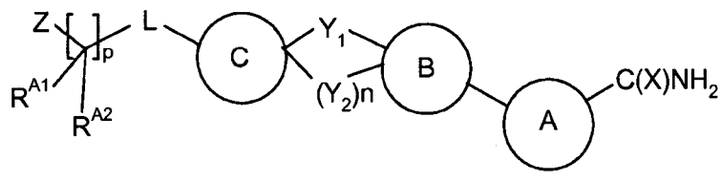
Estudios en ratones knockout han indicado que los moduladores de actividad de la DGAT1 serían de valor en el tratamiento de la diabetes tipo II y la obesidad. Los ratones DGAT1 knockout (*Dgat1*$^{-/-}$), son viables y capaces de sintetizar triglicéridos, como se evidenció por niveles normales en ayuno de triglicéridos séricos y composición de tejidos adiposos normales. Los ratones *Dgat1*$^{-/-}$ tienen menos tejido adiposo que los ratones tipo silvestre al inicio del estudio y son resistentes a la obesidad producida por dietas. La tasa metabólica es 20% mayor aproximadamente en ratones *Dgat1*$^{-/-}$ que en ratones tipo silvestre tanto en dietas regulares como en dietas altas en grasa [Smith (2000) Resistencia a Obesidad y múltiples mecanismos de síntesis de triglicéridos en ratones sin DGAT. Nature Genetics 25: 87-90]. La actividad física aumentada en ratones *Dgat1*$^{-/-}$ explica parcialmente su aumentado gasto de energía. Los ratones *Dgat1*$^{-/-}$ también exhiben sensibilidad a insulina aumentada y un aumento del 20% en tasa de eliminación de glucosa. Los niveles de leptina son disminuidos 50% en ratones *Dgat1*$^{-/-}$ de acuerdo con la disminución del 50% en masa de grasa.

Cuando los ratones *Dgat1*$^{-/-}$ son cruzados con ratones *ob/ob*, estos ratones exhiben el fenotipo *ob/ob* [Chen (2002). Sensibilidad aumentada a la insulina y leptina en ratones que carecen de Acil CoA:diacilglicerol aciltransferasa J. Clin. Invest. 109:1049-1055] indicando que el fenotipo *Dgat1*$^{-/-}$ require una ruta de leptina intacta. Cuando los ratones *Dgat1-/-* son cruzados con ratones *Agouti* se observa una disminución del peso corporal con niveles normales de glucosa y niveles de insulina reducidos en 70%> en comparación con ratones tipo silvestre, *agouti* o *ob/ob Dgat1*$^{-/-}$.

El transplante de tejido adiposo de ratones *Dgat1-/-* a ratones tipo silvestre confiere resistencia a la obesidad inducida por la dieta y metabolismo de glucosa mejorado en estos ratones [Chen (2003) Resistencia a Obesidad y metabolismo de glucosa aumentado en ratones transplantados con tejido adiposo blanco careciendo de acil CoA:diacilglicerol aciltransferasa J. Clin. Invest. 111:1715-1722].

La Solicitud Internacional WO 2006/064189 describe ciertos compuestos los cuales inhiben la DGAT1. Sin embargo, sigue existiendo la necesidad de inhibidores de la DGAT1 adicionales que posean las propiedades deseables, tales como, por ejemplo, perfiles fármaco-cinéticos/dinámicos y/o físico/químicos y/o toxicológicos.

Por consiguiente, el presente invento proporciona un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable, o pro-fármaco del mismo,



(I)

en donde

El anillo A es 2,6-pirazindiilo, 3,5-piridindiilo o 2,6-piridindiilo, cada uno opcionalmente sustituido sobre un átomo de carbono disponible, por uno o dos sustituyentes independientemente seleccionados a partir de (1-3C)alquilo, (2-3C)alquenilo, (2-3C)alquinilo, (l-2C)alcoxilo, metoximetilo, amino and ciano;

X es =O ó =S;

El Anillo B es 1,4-fenileno o el Anillo B es un anillo di-enlazado (excluyendo enlaces vía los mismos átomos o átomos adyacentes) seleccionado a partir de piridindiilo, furandiilo, tiofendiilo, pirroldiilo, oxazoldiilo, tiazoldiilo, imidazoldiilo, isoxazoldiilo, isotiazoldiilo y pirazoldiilo; cada uno opcionalmente sustituido sobre un átomo de carbono disponible por uno o dos sustituyentes independientemente seleccionados a partir de halo, amino, ciano, (l-4C)alkilo, (2-3C)alquenilo, (2- 3C)alquinilo, (l-4C)alcoxilo y (l-4C)alcoxi-(l-4C)alquilo;

Y_1 es un enlace directo entre el Anillo B y el Anillo C o Y_1 es –O-, -S-, o –NRa- en donde Ra es hidrógeno o (l-4C)alquilo;

Y_2 is $-(CH_2)_r$ en donde r is 2 o 3, y Y_2 está unido al mismo átomo de carbono que Y_1 en el Anillo C y Y_2 está unido en un átomo de carbono adyacente a Y_1 en el Anillo B;

n es 0 o n es 1 cuando Y_1 es un enlace directo entre el Anillo B y el Anillo C y cuando el Anillo B es 1,4-fenileno y el Anillo C es (4-6C)cicloalcano, de manera que se forma un sistema espiro-cíclico de 5 o 6 miembros y el Anillo C es tri-enlazado;

El Anillo C es un sistema di-enlazado (excluyendo enlaces vía los mismos átomos o átomos adyacentes) o un sistema cíclico elegido a partir de (4-6C)cicloalcano, (7-10C)bicicloalcano y (8-12C)tricicloalcano cada uno opcionalmente sustituido sobre un átomo de carbono disponible, incluyendo el átomo de carbono cíclico que lleva el grupo que contiene Z, por un sustituyente seleccionado a partir de hidroxilo, (l-4C)alquilo, (1-4C)alcoxilo y (l-4C)alcoxilo(l-4C)alquilo; o el Anillo C es un anillo di-enlazado (excluyendo enlaces vía los mismos átomos o átomos adyacentes) seleccionado a partir de fenileno, priidindiilo,

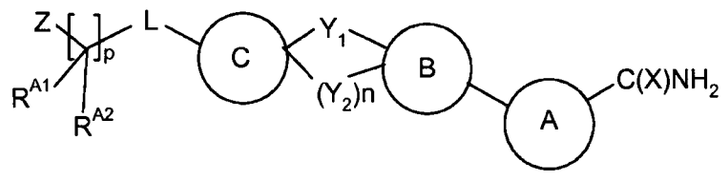
piperidinediilo N-enlazado a Y1, piperazinediilo, furandiilo, tiofendiilo, pirroldiilo, oxazoldiilo, tiazoldiilo, imidazoldiilo, isoxazoldiilo, isotiazoldiilo, pirazoldiilo y azabiciclo[3.1.0]hexanediilo; cada uno opcionalmente sustituido sobre un átomo de carbono disponible por hasta cuatro sustituyentes independientemente seleccionados a partir de fluoro, cloro, bromo, ciano, (1-4C)alquilo, (1-4C)alcoxilo y (1-4C)alcoxilo(1-4C)alquilo;

L es un enlace directo al Anillo C, -O-, -S- o -NH-;

p es 0 (cuando L es un enlace directo), 1 o 2 y cuando p es 1 o 2 R^{A1} y R^{A2} son cada uno independientemente hidrógeno o (1-4C)alquilo o R^{A1} y R^{A2} son enlazados juntos para formar un anillo (3-6C)espiroalquilo;

Z es carboxilo o un mimético o biosóstero del mismo, hidroxilo o -CONRbRc en donde Rb y Rc son independientemente seleccionados a partir de hidrógeno y (1-4C)alquilo, tal grupo (1-4C)alquilo puede ser opcionalmente sustituido por carboxilo o un mimético o biosóstero del mismo; y en donde cualquier átomo de carbono en un grupo lineal conteniendo (1-3C)alquilo, (1-2C)alcoxilo, (1-4C)alquilo o (1-4C)alcoxilo definido anteriormente puede ser opcionalmente sustituido por hasta 3 átomos de fluoro; con la condición que el compesto ácido (4-(4-(6-carbamoil-piridin-2-il)fenil)ciclohexil)acético sea excluido.

En una realización se proporciona un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable, o profármaco del mismo,



(I)

en donde

El Anillo A es 2,6-pirazindiilo, 3,5-piridindiilo o 2,6-piridindiilo, cada uno opcionalmente sustituido sobre un átomo de carbono disponible por uno o dos sustituyentes independientemente seleccionados a partir de (1-3C)alquilo lineal, (2-3C)alquenilo, (2-3C)alquinilo, (1-2C)alcoxilo, metoximetilo, amino y ciano;

X es =O o =S;

El Anillo B es 1,4-fenileno o el Anillo B es un anillo di-enlazado (excluyendo enlaces vía los mismos átomos o átomos adyacentes) seleccionado a partir de piridindiilo, furandiilo,

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División de Nuevas Creaciones

SOLICITUD
PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 10-74457

54. **TÍTULO** _____

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51. **CLASIFICACIÓN INTERNACIONAL** _____

71. **SOLICITANTE** _____

DOMICILIO _____

74. **APODERADO** _____

22. **BOGOTÁ, D.C.,** _____

(FORMA P-10)

Organizacion y
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Industria y Comercio

SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

SOLICITUD
PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 10-744571 2/2.

54. **TÍTULO** _____

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51. **CLASIFICACIÓN INTERNACIONAL** _____

71. **SOLICITANTE** _____

DOMICILIO _____

74. **APODERADO** _____

22. **BOGOTÁ, D.C.,** _____

(FORMA P-10)

tiofendiilo, pirroldiilo,oxazoldiilo, tiazoldiilo, imidazoldiilo, isoxazoldiilo, isotiazoldiilo y pirazoldiilo; cada uno opcionalmente sustituido sobre un átomo de carbono disponible, por uno o dos sustituyentes independientemente seleccionados a partir de halo, amino, ciano, (l-4C)alquilo, (2-3C)alquenilo, (2-3C)alquinilo, (l-4C)alcoxilo y (l-4C)alcoxilo-(l-4C)alquilo;

Y_1 es un enlace directo entre el Anillo B y el Anillo C o Y1 es -O-, -S- o -NRa- en donde Ra es hidrógeno o (l-4C)alquilo;

Y_2 es $-(CH_2)_r-$ en donde r es 2 o 3, y Y_2 está unido al mismo átomo de carbono que Y_1 en el Anillo C y Y_2 está unido en un átomo de carbono adyacente a Y_1 en el Anillo B;

n es 0 o n es 1 cuando Y_1 es un enlace directo entre el Anillo B y el Anillo C y cuando el Anillo B es 1,4-fenileno y el Anillo C es (4-6C)cicloalcano, de manera que un sistema espiro-cíclico de 5 o 6 miembros es formado;

El Anillo C es un anillo di-enlazado (excluyendo enlaces vía los mismos átomos o átomos adyacentes) o sistema cíclico elegido a partir de (4-6C)cicloalcano, (7-10C)bicicloalcano y (8-12C)tricicloalcano cada uno opcionalmente sustituido sobre un átomo de carbono disponible, incluyendo el átomo de carbono cíclico que lleva el grupo que contiene Z, por un sustituyente seleccionado a partir de hidroxilo, (l-4C)alquilo, (1-4C)alcoxilo y (l-4C)alcoxilo(l-4C)alquilo; o el Anillo C es un anillo di-enlazado (excluyendo enlaces vía los mismos átomos o átomos adyacentes) seleccionado a partir de fenileno, priidindiilo, piperidinediilo N-enlazado a Y_1, furandiilo, tiofendiilo, pirroldiilo, oxazoldiilo, tiazoldiilo, imidazoldiilo, isoxazoldiilo, isotiazoldiilo y pirazoldiilo; cada uno opcionalmente sustituido sobre un átomo de carbono disponible, por hasta cuatro sustituyentes independientemente seleccionados a partir de fluoro, cloro, bromo, ciano, (l-4C)alquilo, (l-4C)alcoxilo y (1-4C)alcoxilo(l-4C)alquilo;

L es un enlace directo al Anillo C, -O-, -S- o -NH-;

p es 0, 1 o 2 y cuando p es 1 R^{A1} y R^{A2} son cada uno independientemente hidrógeno o (l-4C)alquilo o R^{A1}y R^{A2} son enlazados juntos para formar un anillo (3-6C)espiroalquilo;

Z es carboxilo o un mimético o biosóstero del mismo, hidroxilo o -CONRbRc en donde Rb y Rc son independientemente seleccionados a partir de hidrógeno y (l-4C)alquilo, tal grupo (l-4C)alquilo puede ser opcionalmente sustituido por carboxilo o un mimético o biosóstero del mismo; y en donde cualquier átomo de carbono en un (l-3C)alquilo lineal, (l-2C)alcoxilo, (l-4C)alquilo o (1-4C)alcoxilo conteniendo el grupo definido anteriormente puede ser opcionalmente sustituido por hasta 3 átomos de fluoro.

En una realización adicional se proporciona un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable, o profármaco del mismo, como en cualquiera de las realizaciones anteriores o posteriores, con la condición que el compuesto ácido (4-(4-(6-carbamoil-piridin-2-il)fenil)ciclohexil)acético sea excluido.

Una característica adicional puede ser cualquiera de las tres realizaciones anteriores con la condición de que cualquiera de los Ejemplos específicos en la presente sean individualmente rechazados. Por ejemplo, una característica adicional es cualquiera de las realizaciones anteriores con la condición que cualquiera de los compuestos seleccionados a partir de los siguientes sean individualmente rechazados,

Ácido {trans-4-[4-(6-Carbamoil-3,5-dimetilpirazin-2-il)fenil] ciclohexil}acético;

3,5-Dimetill-6-[4-(trans-4-{2-[(metilsulfonil)amino]-2-oxoetil}ciclohexil)-fenil]pirazina-2-carboxamida;

6-{4-[trans-4-(2-Amino-2-oxoetil)ciclohexil]fenil}-3,5-dimetilpirazina-2-carboxamida;

N-({trans-4-[4-(6-Carbamoil-3,5-dimetilpirazin-2-il)fenil] ciclohexil}acetil)-2-metilalanina;

6-{4-[trans-4-(2-Hidroxiloetil)ciclohexil]fenil}-3,5-dimetilpirazina-2-carboxamida;

Ácido (trans-4-{4-[6-Carbamoil-5-(difluorometil)-3-metilpirazin-2-yl]fenil}ciclohexil)acético;

Ácido {trans-4-[4-(6-Carbamoil-3-etil-5-metilpirazin-2-yl)fenil] ciclohexil} acético;

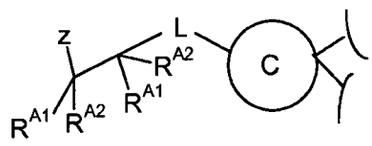
Ácido {trans-4-[4-(6-Carbamoil-5-etil-3-metilpirazin-2-yl)fenil] ciclohexil} acético

y ácido {trans-4-[4-(6-Carbamoil-3-metilpirazin-2-il)fenil]ciclohexil}acético; o una sal farmacéuticamente aceptable de cualquiera de estos.

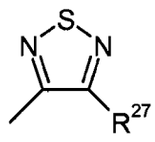
Se entenderá que el Anillo B y el Anillo C como un anillo di-enlazado o sistema cíclico excluye enlaces a Y_1 y L vía los mismos átomos o átomos adyacentes (es decir los enlaces -1,1- y -1,2- son excluidos).

Se entenderá que el Anillo B es numerado en dirección de las manecillas del reloj hacia el Anillo C a partir del heteroátomo dominante en el Anillo B.

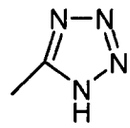
Cuando p es 0 el grupo Z es conectado directamente al enlace directo L (es decir Z es conectado directamente al Anillo C y L no es -O-, -S- o -NH-); cuando p es 2 el grupo Z es conectado como sigue a L;



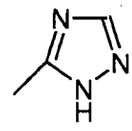
Como se utiliza en la presente, la referencia a mimético o biosóstero de ácido carboxílico incluye grupos como se definió en The Practice of Medicinal Chemistry, Wermuth C.G. Ed.: Academic Press: New York, 1996, p203. Ejemplos particulares de tales grupos incluyen -SO3H, -S(O)2NHR^{13}, S(O)$_2$NHC(O)R^{13}, -CH$_2$S(O)$_2$R^{13}, -C(O)NHS(O)$_2$R^{13}, -C(O)NHOH, -C(O)NHCN, -CH(CF$_3$)OH, C(CF$_3$)$_2$OH, -P(O)(OH)$_2$ y grupos de las sub-fórmulas (a)-(i') a continuación



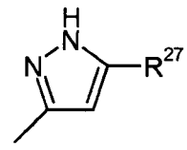
(a)



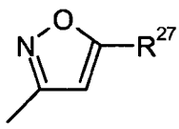
(b)



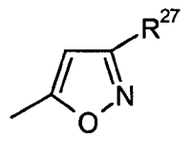
(c)



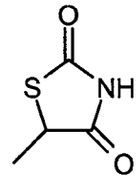
(d)



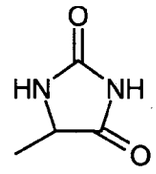
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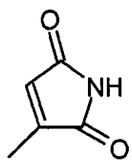
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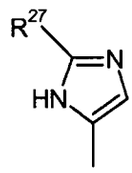
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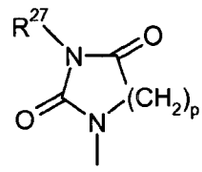
(h)



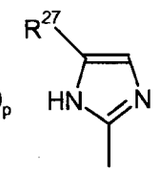
(i)



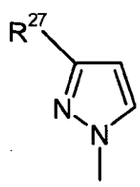
(j)



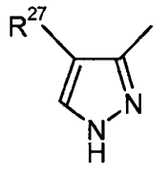
(k)



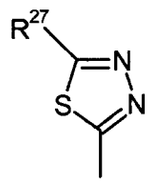
(l)



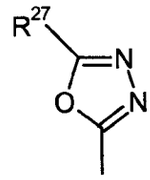
(m)



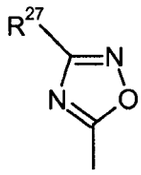
(n)



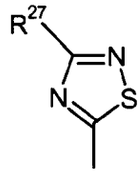
(o)



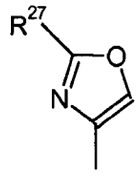
(p)



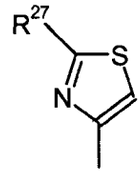
(q)



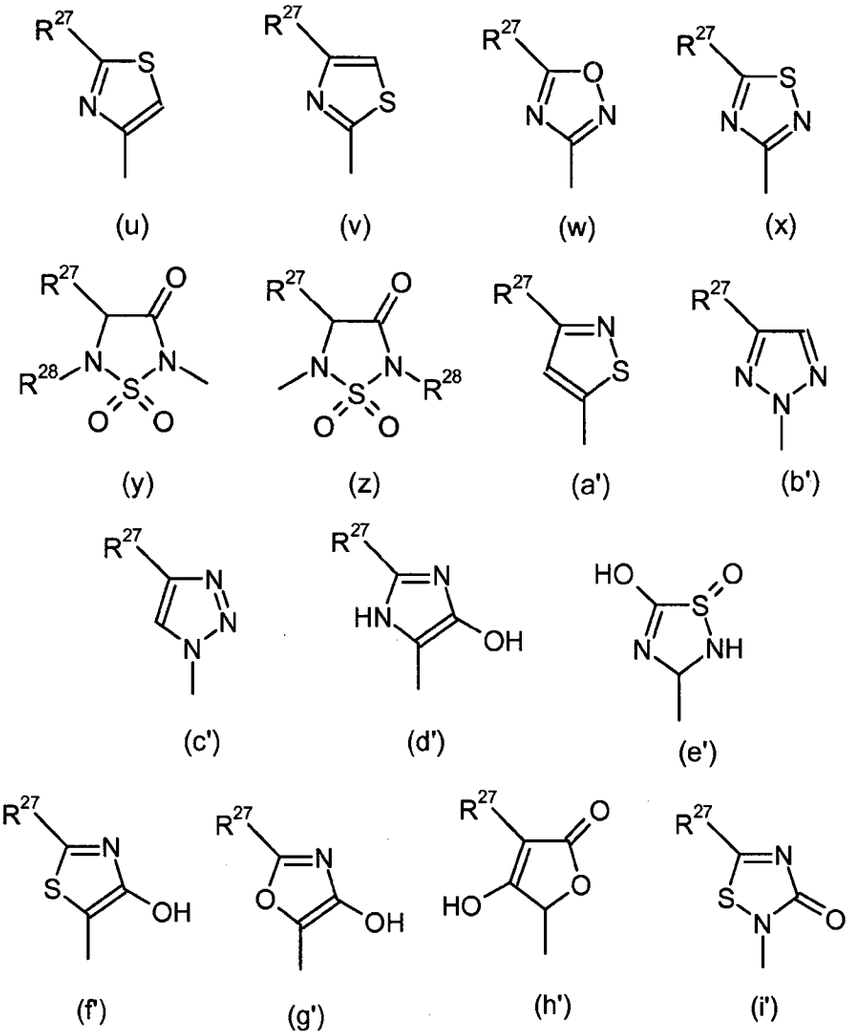
(r)



(s)



(t)



donde p en la sub-fórmula (k) es 1 o 2, R^{27} y R^{28} son independientemente seleccionados a partir de hidrógeno, hidroxilo, (l-6C)alcoxilo, tiol, (l-6C)alquiltio, $-C(O)R^{29}$, $-S(O)R^{30}$, $-S0_2R^{31}$, $-NR^{32}R^{33}$, -NHCN, halógeno y trihalometilo, donde R^{29}, R^{30} y R^{31} son $-OR^{34}$, (1-6C)alquilo, -NR R o trihalometilo, R^{32} y R^{33} son independientemente seleccionados a partir de hidrógeno, (l-6C)alquilo, $-S0_2R^{34}$ y $-COR^{35}$, donde R^{35} es (l-6C)alquilo o trihalometilo, y R^{34} es hidrógeno, (l-6C)alquilo o trihalometilo y R^{13} es seleccionado a partir de hidrógeno, (1-6C)alquilo, hidroxilo, halo, amino, ciano, ((l-3C)alquilo)CONH-, carboxilo, (l-6C)alcoxilo, (1-6C)alcoxilocarbonilo, carbamoilo, N-((l-6C)alquilo)carbamoilo, halo((l-6C)alquilo) (tal como trifluorometilo), (l-6C)alquilsulfonilo o (l-6C)alquilsulfinilo. Ejemplos particulares de R^{27} o R^{28} son hidroxilo.

Miméticos o bioisósteros de ácido carboxílico particulares son un grupo tetrazol de la subfórmula (b) y -C(O)NHS(O)$_2$Me.

En esta especificación, el término "alquilo" incluye grupos alquilo tanto de cadena lineal como ramificada, a menos que se especifique lo contrario, y referencias a grupos alquilo individuales tal como "propilo" son específicas para la versión de cadena lineal solamente. Una convención análoga se aplica a otros términos genéricos. A menos que se especifique lo contrario el término "alquilo" de manera ventajosa se refiere a cadenas con 1-10 átomos de carbono, apropiadamente 1-6 átomos de carbono, preferiblemente 1-4 átomos de carbono.

En esta especificación, el término "alcoxilo" significa un grupo alquilo como se definió anteriormente enlazado a un átomo de oxigeno.

Valores particulares incluyen para (1-3C)alquilo lineal, metilo, etilo y propilo; para (1-4C)alquilo, metilo, etilo, propilo y butilo; para (2-3C)alquenilo, etenilo; para (2-3C)alquinilo, etinilo; para (1-2C)alcoxilo, metoxilo y etoxilo; para (1-4C)alcoxilo, metoxilo, etoxilo y propoxilo; para -CONRbRc, -CONH$_2$ y -CONHMe.

Valores particulares incluyen para cualquier átomo de carbono en un grupo lineal (1-3C)alquilo, (1-2C)alcoxilo, (1-4C)alquilo o (1-4C)alcoxilo que puede ser opcionalmente sustituido por hasta 3 átomos de fluoro, un grupo tal como, por ejemplo, trifluorometilo, difluorometilo, difluorometoxilo o trifluorometoxilo.

Cuando p en la fórmula (I) es 1 y R^{A1} y R^{A2} son enlazados juntos para formar un anillo (3-6C)espiroalquilo, tal anillo puede ser, por ejemplo, un ciclopropilo o ciclobutilo espiro-enlazado.

Cuando p en la fórmula (I) es 2 y R^{A1} y R^{A2} son enlazados juntos para formar un anillo (3-6C)espiroalquilo, tal anillo puede ser, por ejemplo, un ciclopropilo o ciclobutilo espiro-enlazado.

Cuando el Anillo C es un anillo (4-6C)cicloalcano di-enlazado (excluyendo enlaces vía los mismos átomos o átomos adyacentes) este incluye 1,4-ciclohexano, 1,3-ciclopentano y 1,3-ciclobutano.

Cuando el Anillo C es (7-10C)bicicloalcanodiilo este incluye biciclo[2.2.1]heptanodiilo, 1,4-biciclo[2.2.2]octanodiilo, 1,5-biciclo[3.2.1]octanodiilo, 1,5-biciclo[3.2.2]nonanodiilo y 1,5-biciclo[3.3.2]decanodiilo.

Cuando el Anillo C es (8-12C)tricicloalcanodiilo este incluye adamantanodiilo.

Para evitar dudas se debe entender que donde en esta especificación se califica un grupo como 'definido anteriormente' o 'definido antes' dicho grupo incluye la primera definición que

ocurra y la más amplia así como también cada una y todas las definiciones particulares para ese grupo.

Si no se afirma en otra parte, los sustituyentes opcionales apropiados para un grupo particular son aquellos declarados para grupos similares en la presente.

Un compuesto de la fórmula (I) puede formar sales ácidas o alcalinas estables, y en tales casos puede ser apropiado la administración de un compuesto como una sal , y las sales farmacéuticamente apropiadas pueden ser preparadas mediante métodos convencionales tales como aquellos descritos más adelante.

Sales farmacéuticamente aceptables apropiadas incluyen sales de adición ácida tales como metanosulfonato, tosilato, α-glicerofosfato, fumarato, hidrocloruro, citrato, maleato, tartrato y (menos preferiblemente) hidrobromuro. También apropiadas son las sales formadas con ácido fosfórico y sulfúrico. En otro aspecto, sales apropiadas son sales alcalinas tales como sal de Grupo (I) (metal alcalino), sal metálica de Grupo (II) (alcalinoterrea), una sal de aminaorgánica por ejemplo trietilamina, morfolina, *N*-metilpiperidina, *N*-etilpiperidina, procaina, dibencilamina, N,N-dibenciletilamina, tris-(2-hidroxiletil)amina, N-metil-d-glucamina y aminoácidos tales como lisina. Pueden existir más de un catión o anión dependiendo del número de funciones cargadas y la valencia de los cationes o aniones.

Otras sales farmacéuticamente aceptables apropiadas son mencionadas en, por ejemplo, Berge et al. (J. Pharm. Sci., 1977, 66, 1-19) y/o *Handbook de Pharmaceutical Salts*: *Properties, Selection and Use* de Stahl y Wermuth (Wiley-VCH, 2002).

Una característica del invento se relaciona con un compuesto del invento, tal como cualquiera de los Ejemplos, en la forma ácida libre o alcalina libre o como una sal farmacéuticamente aceptable del mismo. Tales formas se pueden preparar mediante técnicas estándares.

Sin embargo, para facilitar la separación de la sal durante la preparación, las sales menos solubles en el solvente elegido pueden ser preferidas ya sean farmacéuticamente aceptables o no.

Dentro del presente invento se debe entender que un compuesto de la fórmula (I) o una sal del mismo puede exhibir el fenómeno de tautomerismo y que las ilustraciones de fórmulas dentro de esta especificación pueden representar solamente una de las formas tautoméricas posibles. Se debe entender que el invento incluye cualquier forma tautomérica que inhibe la actividad DGAT1

y no está limitado meramenta a cualquier forma tautomérica utilizada dentro de las ilustraciones de fórmulas.

Pro-fármacos de compuestos de fórmula (I), y sales de los mismos, también están dentro del alcance del invento.

Varias formas de profármacos son conocidas en el estado de la técnica. Para ejemplos de tales derivados de profármacos, ver:

a) Diseño de Profármacos, editado por H. Bundgaard, (Elsevier, 1985) y Métodos en Enzimología, Vol. 42, p. 309-396, editado por K. Widder. (Academic Press, 1985);

b) Un Manual de Diseño y Desarrollo Farmacológico, editado por Krogsgaard-Larsen and H. Bundgaard, Capitulo 5 "Diseño y Aplicación de Profármacos", de H. Bundgaard p. 113-191(1991);

c) H. Bundgaard, Reseñas de Liberación Avanzada de Fármacos, 8, 1-38 (1992);

d) H. Bundgaard, Diario de Ciencias Farmacéuticas, 77, 285 (1988); y

e) N. Kakeya, Chem Pharm Bull, 32, 692 (1984).

Ejemplos de tales profármacos son ésteres escindibles *in vivo* de un compuesto del invento. Un éster escindible *in vivo* de un compuesto del invento que contiene un grupo carboxilo es, por ejemplo, un éster farmacéuticamente aceptable el cual es escindido en el cuerpo humano o animal para producir el ácido precursor. Ésteres farmacéuticamente aceptables apropiados para carboxilo incluyen ésteres (1-6C)alquilo, por ejemplo metilo o etilo; ésteres de (1-6C)alcoximetilo, por ejemplo metoximetilo; ésteres de (1-6C)alcanoiloximetilo por ejemplo pivaloiloximetilo; ésteres de ftalidilo; ésteres de (3-8C)cicloalcoxilocarboniloxi(l-6C)alquilo, por ejemplo 1-ciclohexilcarboniloxietilo; ésteres de l,3-dioxolan-2-ilmetilo, por ejemplo 5-metil-l,3-dioxolan-2-ilmetilo; ésteres de (l-6C)alcoxilocarboniloxietilo, por ejemplo 1-metoxilocarboniloxietilo; ésteres de aminocarbonilmetilo y versiones mono- o di- N-((l-6C)alquilo) de los mismos, por ejemplo ésteres N,N-dimetilaminocarbonilmetilo y ésteres N-etilaminocarbonilmetilo; y se pueden formar en cualquier grupo carboxilo en los compuestos de este invento. Un éster escindible *in vivo* de un compuesto del invento que contiene un grupo carboxilo es, por ejemplo, un éster farmacéuticamente aceptable el cual es escindido en el cuerpo humano o animal para producir el ácido precursor. Ésteres farmacéuticamente aceptables apropiados para hidroxilo incluyen ésteres de (1-6C)alcanolilo, por ejemplo ésteres de acetilo; y ésteres de benzoilo en donde el grupo fenilo puede ser sustituido con aminometilo o mono- o di-

(1-6C)alquilo aminometilo N-sustituido, por ejemplo ésteres de 4- aminometilbenzoilo y ésteres de 4-N,N-dimetilaminometilbenzoilo.

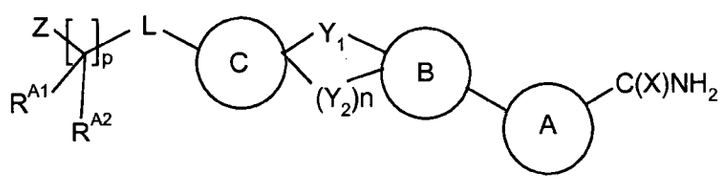
Profármacos particulares son ésteres de (1-4)alquilo del ácido carboxílico en compuestos de las fórmulas (I), (IA) y/o (IB).

Se apreciará por aquellos con experiencia en el estado de la técnica que ciertos compuestos de la fórmula (I) contienen átomos de carbono y/o azufre asimetricamente sustituidos, y por consiguiente pueden existir en, y ser aislados en formas ópticamente activas y racémicas. Algunos compuestos de la formula (I) pueden exhibir polimorfismo. Se debe entender que el presente invento incluye cualquier forma racémica, óptimamente activa, polimórfica o estereoisomérica, o mezclas de las mismas, tal forma posee propiedades útiles en la inhibición de actividad DGAT1, siendo bien conocido en el estado de la técnica cómo preparar formas ópticamente activas (por ejemplo, mediante resolución de la forma racémica mediante técnicas de recristalización, mediante síntesis a partir de materiales de inicio ópticamente activos, mediante síntesis quiral, mediante resolución enzimática, mediante biotransformación, o mediante separación cromatográfica utilizando una fase quiral estacionaria) y cómo determinar la eficacia para la inhibición de actividad DGAT1 mediante las pruebas éstardares descritas más adelante.

También se debe entender que ciertos compuestos de la fórmula (I) y sales de los mismos pueden existir tanto en formas solvatadas como no solvatadas tales como, por ejemplo, formas hidratadas. Se debe entender que el invento incluye todas estas formas solvatadas las cuales inhiben la actividad DGAT1.

Como se afirmó anteriormente, se proporciona un rango de los compuestos los cuales tienen buena actividad inhibitoria DGAT1. Estos tienen buenas propiedades físicas y/o farmacocinéticas en general.

Por lo tanto, en una realización se proporciona un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo,



(I)

en donde

El Anillo A es 2,6-pirazindiilo, 3,5-piridindiilo o 2,6-piridindiilo, cada uno opcionalmente sustituido sobre un átomo de carbono disponible, por uno o dos sustituyentes independientemente seleccionados a partir de (1-3C)alquilo lineal, (2-3C)alquenilo, (2-3C)alquinilo, (l-2C)alcoxilo, metoximetilo, amino y ciano;

X es =0 or =S;

El Anillo B es 1,4-fenileno o el Anillo B es un anillo di-enlazado (excluyendo enlaces vía los mismos átomos o átosmos diferentes) seleccionado a partir de piridindiilo, furandiilo, tiofendiilo, pirroldiilo,oxazoldiilo, tiazoldiilo, imidazoldiilo, isoxazoldiilo, isotiazoldiilo y pirazoldiilo; cada uno opcionalmente sustituido sobre un átomo de carbono disponible, por uno o dos sustituyentes independientemente seleccionados a partir de halo, amino, ciano, (l-4C)alquilo, (2-3C)alquenilo, (2-3C)alquinilo, (l-4C)alcoxilo y (l-4C)alcoxilo-(l-4C)alquilo;

Y_1 es un enlace directo entre el Anillo B y el Anillo C o Y_1 es -O-, -S- o -NRa- en donde Ra es hidrógeno o (l-4C)alquilo;

Y_2 es $-(CH_2)_r-$ en donde r es 2 o 3, y Y_2 está unido al mismo átomo de carbono que Y_1 en el Anillo C y Y_2 está unido en un átomo de carbono adyacente a Y_1 en el Anillo B;

n es 0 o n es 1 cuando Y_1 es un enlace directo entre el Anillo B y el Anillo C y cuando el Anillo B es 1,4-fenileno y el Anillo C es (4-6C)cicloalcano, de manera que un sistema espiro-ciclico de 5- o 6-miembros es formado y el Anillo C es tri-enlazado;

Anillo C es un sistema cíclico di-enlazado (excluyendo enlaces vía los mismos átomos o átomos adyacentes) o un sistema cíclico elegido a partir de (4-6C)cicloalcano, (7-10C)bicicloalcano y (8-12C)tricicloalcano cada uno opcionalmente sustituido sobre un átomo de carbono disponible, incluyendo el átomo de carbono cíclico llevando el grupo que contiene Z, por un sustituyente seleccionado a partir de hidroxilo, (l-4C)alquilo, (1-4C)alcoxilo y (l-4C)alcoxi(l-4C)alquilo;

o el Anillo C es un anillo di-enlazado (excluyendo enlaces vía los mismos átomos o átomos adyacentes) seleccionado a partir de fenileno, priidindiilo, piperidinadiilo N-enlazado a Y_1, piperazinediilo, furandiilo, tiofendiilo, pirroldiilo, oxazoldiilo, tiazoldiilo, imidazoldiilo, isoxazoldiilo, isotiazoldiilo, pirazoldiilo y azabiciclo[3.1.0]hexanodiilo; cada uno opcionalmente sustituido sobre un átomo de carbono disponible por hasta cuatro sustituyentes independientemente seleccionado a partir de fluoro, cloro, bromo, ciano, (l-4C)alquilo, (l-4C)alcoxilo y (l-4C)alcoxilo(l-4C)alquilo;

L es un enlace directo al Anillo C, -O-, -S- o -NH-;

P es 0, 1 o 2 y cuando p es 1, R^{A1} y R^{A2} son cada uno independientemente hidrógeno o (1-4C)alquilo o RA1 y RA2 son unidos juntos para formar un anillo (3-6C)espiroalquilo; Z es carboxilo o un mimético o biosóstero del mismo, hidroxilo o -CONRbRc en donde Rb y Rc son independientemente seleccionados a partir de hidrógeno y (l-4C)alquilo, tal grupo (l-4C)alquilo puede ser opcionalmente sustituido por carboxilo o un mimético o biosóstero del mismo;

y en donde cualquier átomo de carbono en un (l-3C)alquilo, (l-2C)alcoxilo, (l-4C)alquilo o (1-4C)alcoxilo lineal conteniendo el grupo definido anteriormente puede ser opcionalmente sustituido por hasta 3 'atomos de fluoro; con la condición que el compuesto ácido (4-(4-(6-carbamoil-piridin-2-il)fenil)ciclohexil)acético sea excluido.

En otra realización se proporciona un compuesto de fórmula (I), o una sal farmacéuticamente aceptable, o profármaco del mismo en donde el Anillo A es 2,6-pirazindiilo, 3,5-piridindiilo o 2,6-piridindiilo, cada uno opcionalmente sustituido sobre un átomo de carbono disponible por uno o dos sustituyentes independientemente seleccionados a partir de (1-3C)alquilo lineal, (2-3C)alquenilo, (2-3C)alquinilo, (l-2C)alcoxilo, metoximetilo, amino y ciano;

X es =0 o =S;

El Anillo B es 1,4-fenileno o el Anillo B es un anillo di-enlazado (excluyendo enlaces vía los mismos átomos o átomos adyacentes) seleccionado a partir de piridindiilo, furandiilo, tiofendiilo, pirroldiilo, oxazoldiilo, tiazoldiilo, imidazoldiilo, isoxazoldiilo, isotiazoldiilo y pirazoldiilo; cada uno opcionalmente sustituido sobre un átomo de carbono disponible por uno o dos sustituyentes independientemente seleccionados a partir de halo, amino, ciano, (l-4C)alquilo, (2-3C)alquenilo, (2-3C)alquinilo, (l-4C)alcoxilo y (l-4C)alcoxi-(l-4C)alquilo;

Y_1 es un enlace directo entre el Anillo B y el Anillo C o Y_1 es -O-, -S- o -NRa- en donde Ra es hidrógeno o (l-4C)alquilo;

Y_2 es $-(CH_2)_r-$ en donde r es 2 o 3, y Y_2 está unido al mismo átomo de carbono que Y_1 en el Anillo C y Y_2 está unido en un átomo de carbono adyacente a Y1 en el Anillo B;

n es 0 o n es 1 cuando Y_1 es un enlace directo entre el Anillo B y el Anillo C y cuando el Anillo B es 1,4-fenileno y el Anillo C es (4-6C)cicloalcano, de manera que un sistema espiro-cíclico de 5 o 6 miembros es formado;

el Anillo C es un sistema cíclico di-enlazado (excluyendo enlaces vía los mismos átomos o átomos adyacentes) o un sistema cíclico elegido a partir de (4-6C)cicloalcano, (7-

10C)bicicloalcano y (8-12C)tricicloalcano cada uno opcionalmente sustituido sobre un átomo de carbono disponible, incluyendo el átomo de carbono cíclico que lleva el grupo que contiene Z, por un sustituyente seleccionado a partir de hidroxilo, (l-4C)alquilo, (1-4C)alcoxilo y (l-4C)alcoxi(l-4C)alquilo;

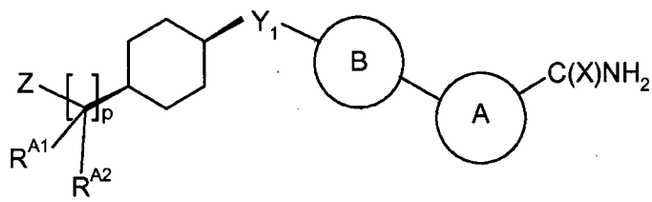
o el Anillo C es un anillo di-enlazado (excluyendo enlaces vía los mismos átomos o átomos adyacentes) seleccionado a partir de fenileno, priidindiilo, piperidinadiilo N-enlazado a Y_1, furandiilo, tiofendiilo, pirroldiilo, oxazoldiilo, tiazoldiilo, imidazoldiilo, isoxazoldiilo, isotiazoldiilo y pirazoldiilo; cada uno opcionalmente sustituido sobre un átomo de carbono disponible, por hasta cuatro sustituyentes independientemente seleccionados a partir de fluoro, cloro, bromo, ciano, (l-4C)alquilo, (l-4C)alcoxilo y (l-4C)alcoxi(l-4C)alquilo; L es un enlace directo al Anillo C, -O-, -S- o -NH-;

p es 0, 1 o 2 y cuando p es 1, R^{A1} y R^{A2} son cada uno independientemente hidrógeno o (l-4C)alquilo o R^{A1}andR^{A2} son enlazados juntos para formar un anillo (3-6C)espiroalquilo;

Z es carboxilo o un mimético o biosóstero del mismo, hidroxilo o -CONRbRc en donde Rb y Rc son independientemente seleccionados a partir de hidrógeno y (l-4C)alquilo, tal grupo (l-4C)alquilo puede ser opcionalmente sustituido por carboxilo o un mimético o biosóstero del mismo;

y en donde cualquier átomo de carbono en un (l-3C)alquilo lineal, (l-2C)alcoxilo, (l-4C)alquilo o (1-4C)alcoxilo conteniendo el grupo definido anteriormente puede ser opcionalmente sustituido por hasta 3 átomos de fluoro.

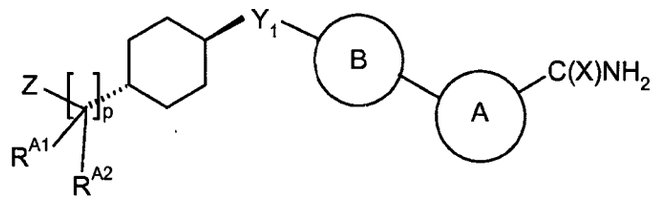
En otra realización se proporciona un compuesto de la fórmula (IA), o una sal farmacéuticamente aceptable, o profármaco del mismo,



(IA)

en donde X, Anillo A, Anillo B, Y1, p, R \ R ^{2} y Z son como se definió en la Reivindicación 1 o 2.

En otra realización se proporciona un compuesto de la fórmula (IB), o una sal farmacéuticamente aceptable, o profármaco del mismo,



(IB)

en donde X, Anillo A, Anillo B, Y_1, p, R^{A1}, R^{A2} y Z son como se definió en la Reivindicación 1 o 2.

En otra realización se proporciona un compuesto como se reivindicó en cualquiera de las Reivindicaciones 1 a 4, o una sal farmacéuticamente aceptable, o profármaco del mismo, en donde X es =0; el Anillo A es 2,6-pirazindiilo opcionalmente sustituido sobre un átomo de carbono disponible, por uno o dos sustituyentes independientemente seleccionados a partir de (1-3C)alquilo lineal, (2-3C)alquenilo, (2-3C)alquinilo, (1-2C)alcoxilo, metoximetilo, amino y ciano;

elAnillo B es 1,4-fenileno opcionalmente sustituido sobre un átomo de carbono disponible, por uno o dos sustituyentes independientemente seleccionados a partir de halo, amino, ciano, (1-4C)alquilo, (2-3C)alquenilo, (2-3C)alquinilo, (1-4C)alcoxilo y (1-4C)alcoxilo-(1-4C)alquilo;

el Anillo C es 1,4-ciclohexano;

n es 0 y Y_1 es un enlace directo o Y_1 es -O-;

L es un enlace directo;

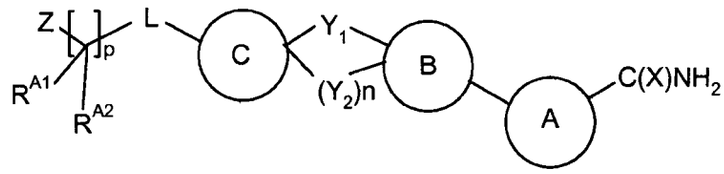
p es 1 y R^{A1} y R^{A2} son cada uno hidrógeno;

Z es carboxilo, un grupo tetrazol, -C(O)NHS(O)2Me, hidroxilo o -CONRbRc en donde Rb y Rc son independientemente seleccionados a partir de hidrógeno y (1-4C)alquilo, tal grupo (1-4C)alquilo puede ser opcionalmente sustituido por carboxilo; y en donde cualquier átomo de carbono en un (1-3C)alquilo lineal, (1-2C)alcoxilo, (1-4C)alquilo o (1-4C)alcoxilo conteniendo el grupo definido anteriormente puede ser opcionalmente sustituido por hasta 3 átomos de fluoro.

En otra realización se proporciona un compuesto como se reivindicó en cualquiera de las Reivindicaciones 1 a 5, o una sal farmacéuticamente aceptable, o profármaco del mismo, en donde el Anillo A es 2,6-pirazindiilo opcionalmente sustituido sobre un átomo de carbono disponible por uno o dos sustituyentes (1-3C)alquilo lineales.

Los siguientes compuestos poseen propiedades farmacéuticas y/o físicas y/o farmacocinéticas/dinámicas y/o toxicológicas particulares deseables y/o actividad selectiva para DGAT1.

Un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable, o profármaco del mismo,



(I)

en donde

el Anillo A es 2,6-pirazindiilo, 3,5-piridindiilo o 2,6-piridindiilo, cada uno opcionalmente sustituido sobre un átomo de carbono disponible por uno o dos sustituyentes independientemente seleccionados a partir de linear (1-3C)alquilo, (2-3C)alquenilo, (2-3C)alquinilo, (l-2C)alcoxilo, metoximetilo, amino y ciano;

X es =0 o =S;

el Anillo B es 1,4-fenileno o Anillo B es un anillo di-enlazado (excluyendo enlaces vía los mismos átomos o átomos adyacentes) piridindiilo; cada uno opcionalmente sustituido sobre un átomo de carbono disponible, por uno o dos sustituyentes independientemente seleccionados a partir de halo, amino, ciano, (l-4C)alquilo, (2-3C)alquenilo, (2-3C)alquinilo, (l-4C)alcoxilo y (l-4C)alcoxilo-(l-4C)alquilo;

Y_1 es un enlace directo entre el Anillo B y el Anillo C o Y1 es -O-, -S- o -NRa- en donde Ra es hidrógeno o (l-4C)alquilo;

n is 0;

el Anillo C es un anillo di-enlazado (excluyendo enlaces vía los mismos átomos o átomos adyacentes) (4-6C)cicloalcanoanillo, opcionalmente sustituido sobre un átomo de carbono disponible, incluyendo el átomo de carbono cíclico que lleva el grupo que contiene Z, por un sustituyente seleccionado a partir de hidroxilo, (l-4C)alquilo, (1-4C)alcoxilo y (l-4C)alcoxilo(l-4C)alquilo;

L es un enlace directo al Anillo C o -O-;

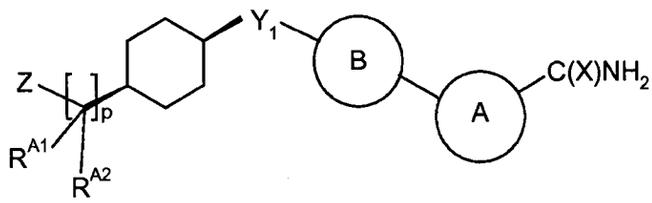
p es 0, 1 o 2 y cuando p es 1, R^{A1} y R^{A2} son cada uno independientemente hidrógeno o (1-4C)alquilo;

Z es carboxilo o un mimético o biosóstero del mismo, hidroxilo o -CONRbRc en donde Rb y Rc son independientemente seleccionados a partir de hidrógeno y (1-4C)alquilo, tal grupo (1-4C)alquilo puede ser opcionalmente sustituido por carboxilo o un mimético o biosóstero del mismo;

y en donde cualquier átomo de carbono en un (1-3C)alquilo lineal, (1-2C)alcoxilo, (1-4C)alquilo o (1-4C)alcoxilo conteniendo el grupo definido anteriormente puede ser opcionalmente sustituido por hasta 3 átomos de fluoro.

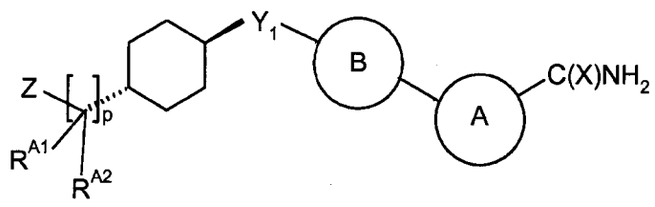
En un aspecto, se apreciará que en ciertos compuestos de la fórmula (I) el sustituyente del Anillo C que lleva el grupo Z (o reemplazo apropiado del mismo) y el enlace Y son un arreglo cis- o un arreglo trans- a través del anillo, en relación entre si. Donde es apropiado el invento incluye ambos isómeros cis- y trans-. Técnicas para la separación de tales isómeros son bien conocidas en el estado de la técnica.

Por lo tanto, en un aspecto, cuando el Anillo C es ciclohexilo, el grupo que contiene Z y el enlace Y_1 están en una configuración cis- a través del anillo de ciclohexilo, para proporcionar un compuesto de la fórmula (IA), en donde las variables son como se definieron anteriormente o más adelante.



(IA)

Por lo tanto, en un aspecto, cuando el Anillo C es ciclohexilo, el grupo que contiene Z y el enlace Y_1 están en una configuración trans- a través del anillo de ciclohexilo, para proporcionar un compuesto de la fórmula (IB), en donde las variables son como se definieron anteriormente o más adelante.



(IB)

Las referencias anteriores o posteriores a un compuesto de la fórmula (I) son tomadas para aplicar también a compuestos de las fórmulas (IA) y (IB).

En una realización del invento se proporcionan compuestos de las fórmulas (I), (IA) y (IB), en una realización alternativa se proporcionan sales, particularmente sales farmacéuticamente aceptables de compuestos de las fórmulas (I), (IA) y (IB). En una realización adicional, se proporcionan pro-fármacos, particularmente ésteres escindibles *in vivo*, de compuestos de las fórmulas (I), (IA) y (IB). En una realización adicional, se proporcionan sales, particularmente sales farmacéuticamente aceptables de pro-fármacos de compuestos de las fórmulas (I), (IA) y (IB).

Valores particulares de sustituyentes en compuestos de las fórmulas (I), (IA) y (IB) son como siguen (tales valores se pueden utilizar donde sea apropiado con cualquiera de los otros valores, definiciones, reivindicaciones o realizaciones definidos antes o después)...

1) X es =O;

2) X es =S;

3) El Anillo A es 2,6-pirazindiilo;

4) El Anillo A es 2,6-pirazindiilo sustituido con cualquiera de los sustituyentes en los Ejemplos;

5) El Anillo A es 2,6-pirazindiilo sustituido con uno o dos (1-3C)alquilo;

6) El Anillo B es 1,4-fenileno;

7) El Anillo B es 2,5-piridindiilo o 3,6-piridindiilo;

8) El Anillo B es opcionalmente sustituido sobre un átomo de carbono disponible, por uno o dos sustituyentes halo;

9) El Anillo C es 1,4-ciclohexano (es decir 1,4-ciclohexilo);

10) n es 0 y Y_1 es un enlace directo entre el Anillo B y el Anillo C o Y_1 es -O-;

11) El Anillo B y el Anillo C son particularmente 2,4- o 2,5-furandiilo, 2,4- o 2,5-tiofendiilo, 2,4- o 2,5-pirroldiilo, 2,4- o 2,5-oxazoldiilo, 2,4- o 2,5-tiazoldiilo, 2,4- o 2,5-imidazoldiilo, 3,4- o 3,5-isoxazoldiilo, 3,4- o 3,5-isotiazoldiilo, 3,4- o 3,5-pirazoldiilo;

12) L es un enlace directo;

13) p es 0;

14) p es 1 y R^{A1} y R^{A2} son cada uno hidrógeno;

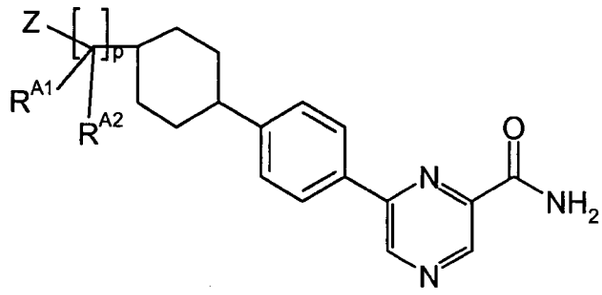
15) p es 2 y R^{A1} y R^{A2} son cada uno hidrógeno;

16) Z es carboxilo, -CONRbRc (en donde Rb y Rc son independientemente seleccionados a partir de hidrógeno y (l-4C)alquilo (tal grupo (l-4C)alquilo puede ser opcionalmente sustituido por carboxilo), un grupo tetrazol o -C(O)NHS(O)2Me;

17) Z es carboxilo;

18) un profármaco para Z como carboxilo es un éster de (l-6C)alquilo.

Por lo tanto, por ejemplo, en una realización se proporciona un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, en donde X=0; el Anillo A es 2,6-pirazindiilo opcionalmente sustituido sobre un átomo de carbono disponible, por uno o dos sustituyentes independientemente seleccionados a partir de (l-3C)alquilo lineal, (2-3C)alquenilo, (2-3C)alquinilo, (1-2C)alcoxilo, metoximetilo, amino y ciano; el Anillo B es 1,4-fenileno (opcionalmente sustituido sobre un átomo de carbono disponible, por uno o dos sustituyentes halo); n es 0 y Y_1 es un enlace directo entre el Anillo B y el Anillo C; p es 0 o p es 1 y R^{A1} y R^{A2} son cada uno hidrógeno; L es un enlace directo y Z es carboxilo, -CONRbRc (en donde Rb y Rc son independientemente seleccionados a partir de hidrógeno y (l-4C)alquilo (tal grupo (l-4C)alquilo puede ser opcionalmente sustituido por carboxilo), un grupo tetrazol o -C(O)NHS$(O)_2$Me; es decir un compuesto de la fórmula (IC), o una sal farmacéuticamente aceptable del mismo, en donde el anillo 2,6-pirazindiilo es opcionalmente sustituido sobre un átomo de carbono disponible, por uno o dos sustituyentes independientemente seleccionados a partir de (l-3C)alquilo lineal, (2-3C)alquenilo, (2-3C)alquinilo, (1-2C)alcoxilo, metoximetilo, amino y ciano y otros valores son como se definieron inmediatamente antes.



(IC)

En otra realización se proporciona un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, en donde X=0; el Anillo A es 2,6-pirazindiilo opcionalmente sustituido sobre un átomo de carbono disponible por uno o dos sustituyentes independientemente seleccionados a partir de (1-3C)alquilo lineal, (2-3C)alquenilo, (2-3C)alquinilo, (1-2C)alcoxilo, metoximetilo, amino y ciano; el Anillo B es 1,4-fenileno (opcionalmente sustituido sobre un átomo de carbono disponible por uno o dos sustituyentes halo); n es 0 y Y1 es un enlace directo entre el Anillo B y el Anillo C; p es 1 y R^{A1} y R^{A2} son cada uno hidrógeno; L es un enlace directo y Z es carboxilo o un grupo tetrazol.

En otra realización se proporciona un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, en donde X=0; el Anillo A es 2,6-pirazindiilo opcionalmente sustituido sobre un átomo de carbono disponible por uno o dos sustituyentes independientemente seleccionados a partir de (1-3C)alquilo lineal; el Anillo B es 1,4-fenileno (opcionalmente sustituido sobre un átomo de carbono disponible por uno o dos sustituyentes fluoro); n es 0 y Y_1 es un enlace directo entre el Anillo B y el Anillo C; p es 1 y R^{A1} y R^{A2} son cada uno hidrógeno; L es un enlace directo y Z es carboxilo o un grupo tetrazol.

En otra realización se proporciona un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, en donde X=0; el Anillo A es 2,6-pirazindiilo opcionalmente sustituido sobre un átomo de carbono disponible, por uno o dos sustituyentes metilo; el Anillo B es 1,4-fenileno (opcionalmente sustituido sobre un átomo de carbono disponible por uno o dos sustituyentes fluoro); n es 0 y Y_1 es un enlace directo entre el Anillo B y el Anillo C; p es 1 y R^{A1} y R^{A2} son cada uno hidrógeno; L es un enlace directo y Z es carboxilo o un grupo tetrazol.

En otra realización se proporciona un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, en donde X=0; el Anillo A es 2,6-pirazindiilo opcionalmente sustituido sobre un átomo de carbono disponible por uno o dos sustituyentes metilo; el Anillo B es 1,4-fenileno; n es 0 y Y_1 es un enlace directo entre el Anillo B y el Anillo C; p es 1 y R^{A1} y R^{A2} son cada uno hidrógeno; L es un enlace directo y Z es carboxilo o un grupo tetrazol.

En otra realización se proporciona un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, en donde X=0; el Anillo A es 2,6-pirazindiilo opcionalmente sustituido sobre un átomo de carbono disponible por uno o dos sustituyentes metilo; el Anillo B es 1,4-fenileno; n es 0 y Y_1 es un enlace directo entre el Anillo B y el Anillo C; p es 1 y R^{A1} y R^{A2} son cada uno hidrógeno; L es un enlace directo y Z es carboxilo.

En otra realización se proporciona un compuesto de la fórmula (I), en donde X=0; el Anillo A es 2,6-pirazindiilo opcionalmente sustituido sobre un átomo de carbono disponible por uno o dos sustituyentes metilo; el Anillo B es 1,4-fenileno; n es 0 y Y_1 es un enlace directo entre el Anillo B y el Anillo C; p es 1 y R^{A1} y R^{A2} son cada uno hidrógeno; L es un enlace directo y Z es carboxilo.

En otra realización se proporciona un compuesto de la fórmula (I) como se definió en cualquiera de las siete realizaciones inmediatamente anteriores, en donde el grupo que contiene Z y el enlace Y_1 están en ya sea una configuración cis- o trans- a través del anillo, entre si.

En otra realización se proporciona un compuesto de la fórmula (I) como se definió en cualquiera de las ocho realizaciones inmediatamente anteriores en donde un profármaco para Z como carboxilo es un éster (1-6C)alquilo.

Una característica adicional es cualquiera de los propósitos definidos en la presente con la condición que Ejemplos específicos, tales como el Ejemplo 1, 2, 3, 4 etc. sean individualmente rechazados.

Compuestos particulares adicionales del invento son cada uno de los Ejemplos, cada uno de los cuales proporciona un aspecto independiente adicional del invento. En aspectos adicionales, el presente invento también comprende cualquiera de los compuestos particulares de los Ejemplos o una sal farmacéuticamente aceptable de los mismos (tal como, por ejemplo, una sal de sodio, magnesio, tert-butilamonio, tris(hidroximetil)metilamonio, trietanolamonio, dietanolamonio, etanolamonio, metiletanolamonio, dietilamonio o nicotinamida).

Por ejemplo, una característica adicional es cualquiera de los compuestos particulares de los Ejemplos o una sal farmacéuticamente aceptable de los mismos, tal como cualquier compuesto seleccionado a partir de

Ácido {trans-4-[4-(6-Carbamoil-3,5-dimetilpirazin-2-il)fenil]ciclohexil}acético;

3,5-Dimetil-6-[4-(trans-4-{2-[(metilsulfonil)amino]-2-oxoetil}ciclohexil)-fenil]pirazina-2-carboxamida;

6-{4-[trans-4-(2-Amino-2-oxoetil)ciclohexil]fenil}-3,5-dimetilpirazina-2-carboxamida;

N-({trans-4-[4-(6-Carbamoil-3,5-dimetilpirazin-2-il)fenil]ciclohexil}acetil)-2-metilalanina;

6-{4-[trans-4-(2-Hidroxiloetil)ciclohexil]fenil}-3,5-dimetilpirazina-2-carboxamida;

Ácido {trans-4-[4-(6-Carbamoil-5-difluorometil)-3-metilpirazin-2-il]fenil}ciclohexil}acético;

Ácido {trans-4-[4-(6-Carbamoil-3-etil-5-metilpirazon-2i-l)fenil]ciclohexil}acético;

Ácido {trans-4-[4-(6-Carbamoil-5-etil-3-metilpirazin-2-il)fenil]ciclohexil}acético;

Ácido {trans-4-[4-(6-Carbamoil-3-metilpirazin-2-il)fenil]ciclohexil} acético;

Ácido 2-((lr,4s)-5'-(6-Carbamoil-3,5-dimetilpirazin-2-il)-2',3'-dihydrospiro[ciclohexano-l,r-indeno]-4-il)acético;

Ácido (lr,4s)-5'-(6-Carbamoil-3,5-dimetilpirazin-2-il)-2',3'-dihidroespiro[ciclohexano-l,r-indeno]-4-carboxílico;

Ácido 2-((lr,4r)-4-(4-(6-Carbamoil-3,5-dimetilpirazin-2-il)fenil)ciclohexil)-2-metilpropanóico

Ácido 2-(l-(4-(6-Carbamoil-3,5-dimetilpirazin-2-il)fenil)pirrolidin-3-il)acético;

Ácido (lR,5S,6r)-3-(4-(6-Carbamoil-3,5-dimetilpirazin-2-il)fenil)-3-azabiciclo[3.1.0]hexano-6-carboxílico;

6-(4-((lr,4r)-4-((lH-Tetrazol-5-il)metil)ciclohexil)fenil)-3,5-dimetilpirazina-2-carboxamida;

Ácido 4'-(6-Carbamoil-3,5-dimetilpirazin-2-il)bifenil-4-carboxílico;

trans-4- {4-[6-(aminocarbonyl)-3-metilpirazin-2-il]fenil}-ciclohexanocarboxilato de metilo;

Ácido *trans*-4-{4-[6-(Aminocarbonyl)-3-metilpirazin-2-il]fenil}ciclo-hexanocarboxílico; o una sal farmacéuticamente aceptable de cualquiera de estos.

En un aspecto adicional, el presente invento también comprende cualquiera de los isómeros particulares de los compuestos de los Ejemplos, tal como el isómero cis- de compuestos tal como los Ejemplos 1 o 2, es decir ácido {cis-4-[4-(6-Carbamoil-3,5-dimetilpirazin-2-il)fenil]ciclohexil}acético o 3,5-dimetil-6-[4-(cis-4-{2-[(metilsulfonil)amino]-2-oxoetilciclohexil)fenil]-pirazina-2-carboxamida o una sal farmacéuticamente aceptable de

cualquiera de estos; o compuestos tales como 6-{4-[cis-4-(2-Amino-2-oxoetil)ciclohexil]fenil}-3,5-dimetilpirazina-2-carboxamida;
N-({cis-4-[4-(6-Carbamoil-3,5-dimetilpirazin-2-il)fenil] ciclohexil}acetil)-2-metilalanina;
6-{4-[cis-4-(2-Hidroxiloetil)ciclohexil]fenil}-3,5-dimetilpirazina-2-carboxamida;
Ácido (cis-4-{4-[6-Carbamoil-5-(difiuorometil)-3-metilpirazin-2-il]fenil}ciclohexil)acético;
Ácido {cis-4-[4-(6-Carbamoil-3-etil-5-metilpirazin-2-il)fenil] ciclohexil}acético; ácido {cis-4-[4-(6-Carbamoil-5-etil-3-metilpirazin-2-il)fenil] ciclohexil}acético; ácido {cis-4-[4-(6-Carbamoil-3-metilpirazin-2-il)fenil]ciclohexil}acético; o una sal farmacéuticamente aceptable de cualquiera de estos.

Un compuesto de la fórmula (I) y sus sales se pueden preparar mediante cualquier proceso conocido como aplicable a la preparación de compuestos químicamente relacionados. Tales procesos, cuando se utilizan para preparar un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, son proporcionados como una característica adicional del invento.

En un aspecto adicional el presente invento también dispone que los compuestos de la fórmula (I) y sales de los mismos, se puedan preparar mediante los siguientes procesos, los procesos de los Ejemplos y procesos análogos (en donde todas las variables son como se definieron anteriormente para un compuesto de la fórmula (I) a menos que se especifique lo contrario) y luego si es necesario cualquiera de los grupos protectores puede ser retirado y/o una sal apropiada puede ser formada. Cualquiera de los grupos de ácido carboxílico puede ser reemplazado según sea apropiado por un mimético o biosóstero del mismo.

Las variables mostradas en los esquemas son definidas o se pueden interpretar en el contexto de las variantes descritas en la presente para los compuestos del invento. Se puede utilizar química análoga a aquella mostrada en los esquemas y Ejemplos para preparar otras variantes cíclicas y opciones de grupos enlazadores dentro del alcance del invento.

También incluidos como un aspecto del invento son los compuestos obtenibles mediante cualquiera de los procesos o Ejemplos descritos en la presente.

Proceso a)

Al modificar o introducir un sustituyente en otro compuesto de la fórmula (I). Métodos apropiados para convertir sustituyentes en otros sustituyentes son conocidos en el estado de la

técnica. Por ejemplo, un grupo ácido se puede convertir en un grupo amida o se puede reducir a un grupo alcohol.

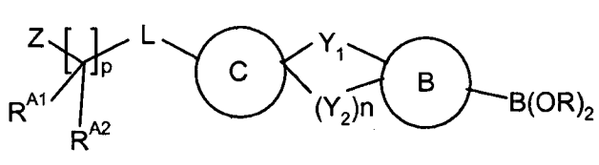
Una amida en el Anillo A se puede invertir en una tioamida mediante el uso del reactivo de Lawesson o P_2S_5.

Los compuestos de la fórmula (I) donde, por ejemplo, Z es un grupo acilsulfonamida o Z es un tetrazol se pueden preparar a partir del correspondiente ácido carboxílico. El tetrazol se puede introducir temprano en la ruta sintética vía una amida (la cual, para amidas primarias, se puede convertir en el nitrilo mediante métodos estándares) la cual luego es a su vez convertida en un tetrazol mediante la reacción con azida. El tetrazol puede ser llevado a través del resto de la síntesis en forma protegida, ej., N-bencilado o N-(2-cianoetil)ado.

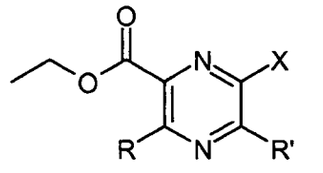
Proceso b)

Acoplamiento de Suzuki de un derivado de Anillo A yodo-, bromo—o cloro- sustituido (ej., éster de pirazina (III) con un compuesto de boronato intermedio apropiadamente sustituido de la fórmula (II) seguido por la conversión del grupo éster de anillo A en el ácido correspondiente mediante hidrólisis básica y de allí a la carboxamida primaria correspondiente mediante la reacción con amoníaco en presencia de un agente acoplador, como por ejemplo PyBOP.

Un grupo protector puede ser retirado, por ejemplo, mediante hidrólisis catalizada por ácido de un éster Pert-butílico para proporcionar un compuesto de la fórmula (I) en donde Z = CO_2H.



(II)



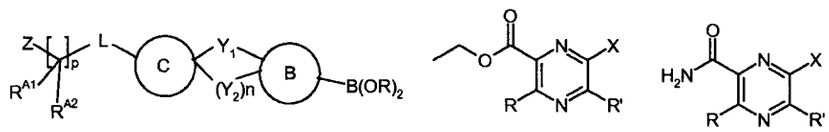
X = Cl or Br

(III)

R y R' pueden representar cualquiera de las variables definidas en la presente en tales posiciones.

Se puede utilizar química análoga para preparar otros derivados de Anillo A (ej., compuestos de piridina).

Alternativamente un acoplamiento de Suzuki de una yodo-, bromo-, o cloro- pirazina amida (IV), particularmente bromo- o cloro-pirazina amida (IV), se puede utilizar seguido por el retiro del grupo protector para hidrólisis alcalina de un éster de metilo o etilo.

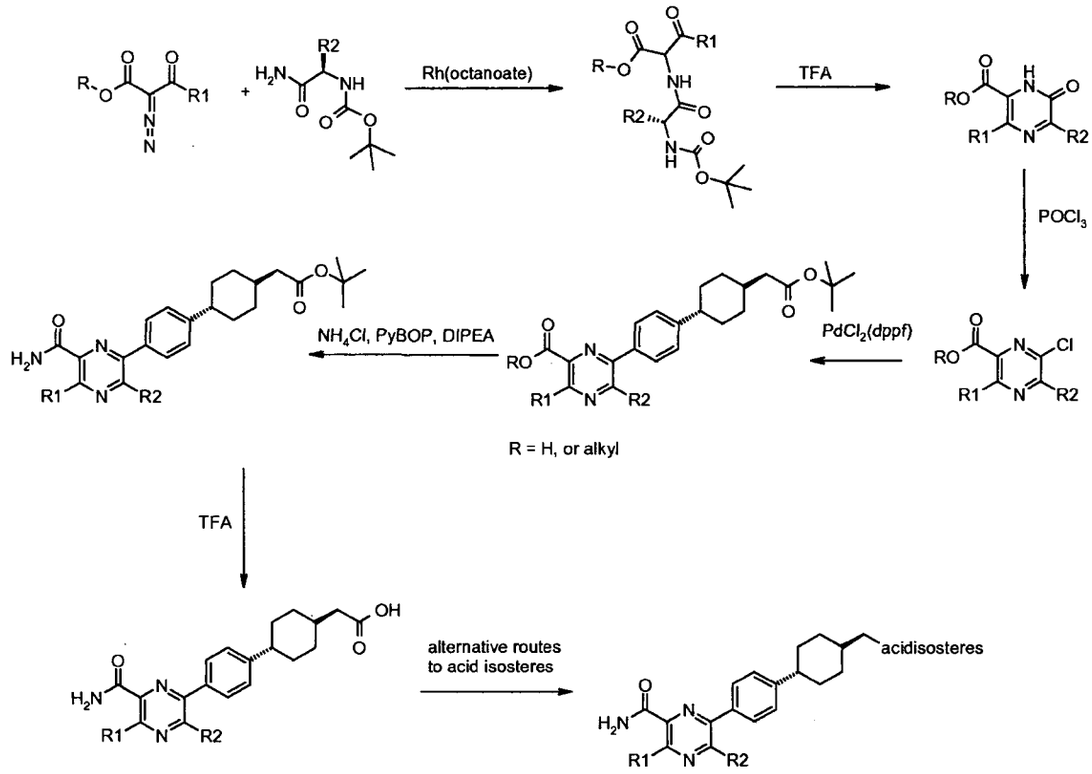


X = Cl or Br

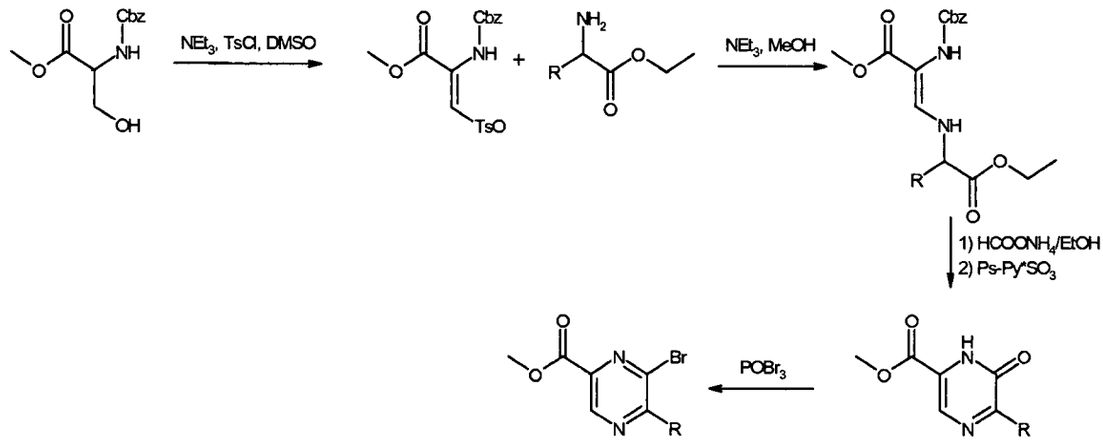
(II) (III) (IV)

Preparación de tipos de compuestos de la fórmula (III) (Anillo A)

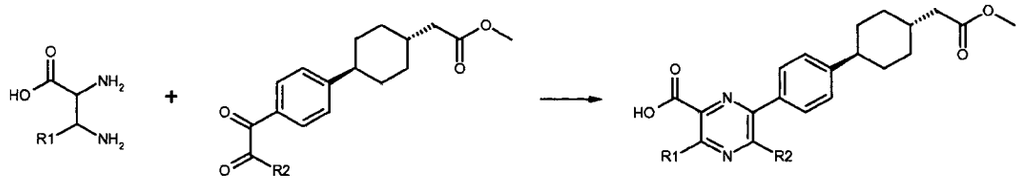
Los siguientes esquemas ilustran cómo se pueden preparar ciertas variantes del Anillo A. Las variables mostradas en los esquemas son definidas o se pueden interpretar en el contexto de las variantes descritas en la presente para los compuestos del invento. Se puede utilizar química análoga a aquella mostrada en los esquemas y Ejemplos para preparar otras variantes cíclicas y opciones de grupos enlazadores dentro del alcance del invento.



Esquema A1: Esquema de Reacción para dimetilpirazina y derivados

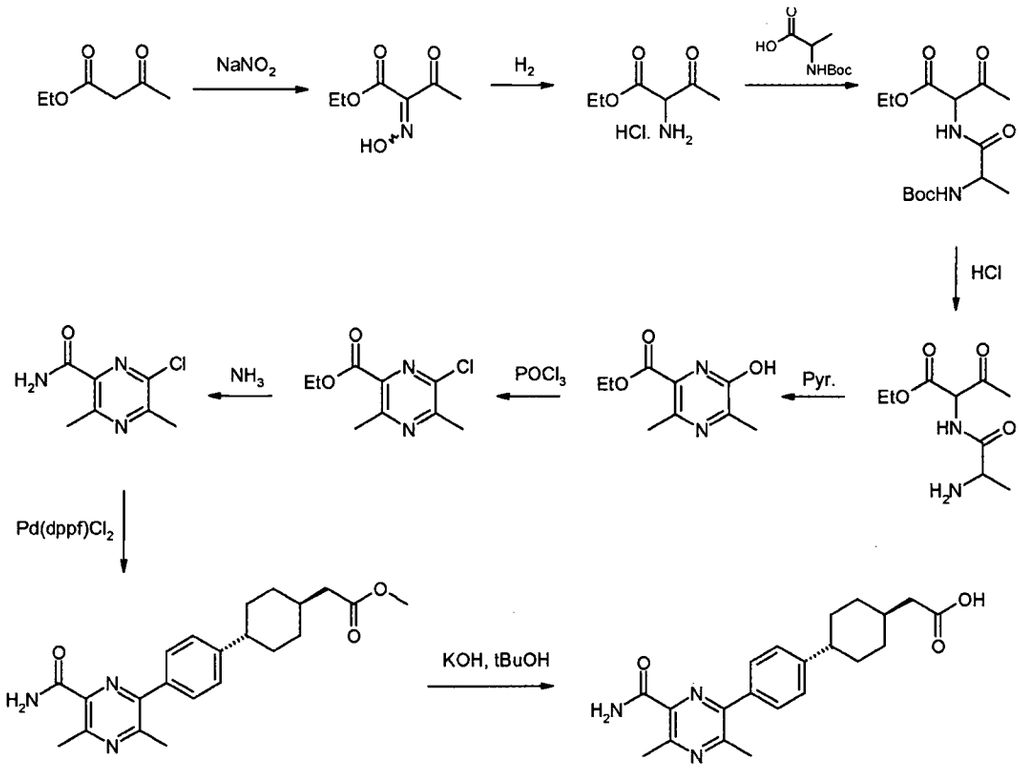


Esquema A2: Esquema de Reacción para mono-metilpirazina y derivados



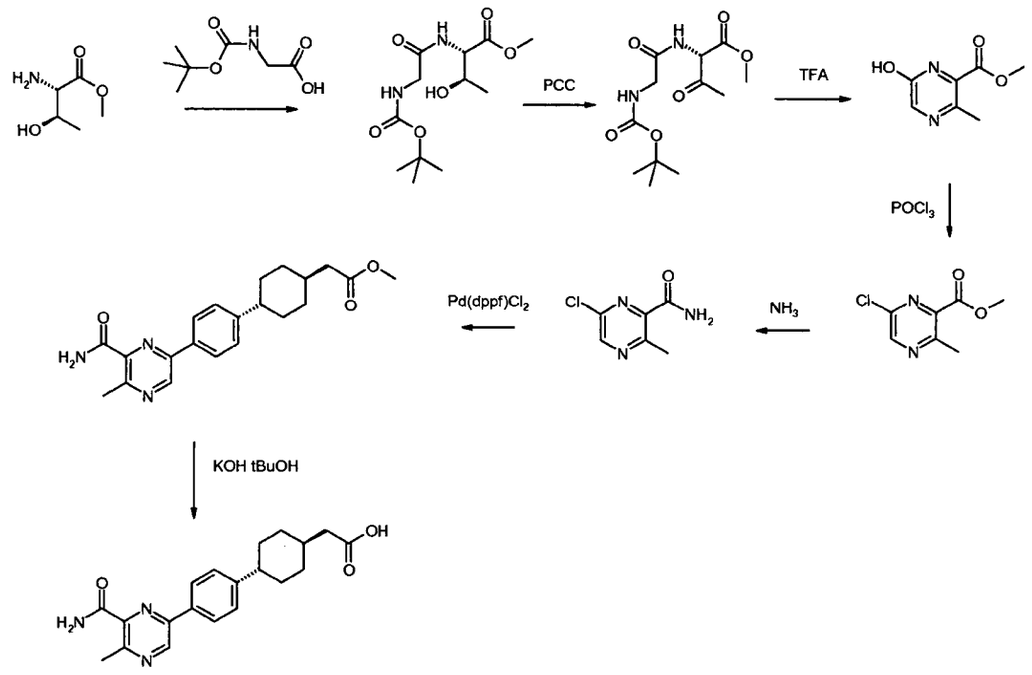
Esquema A3: Esquema de Reacción para procedimiento de condensación

Preparación de tipos de compuestos de las fórmulas (IV) (Anillo A)



Esquema A4: Esquema de Reacción para dimetilpirazina y derivados

Se pueden preparar análogos de pirazina utilizando el procedimiento descrito por C. Christensen, C.W. Tornoe y M. Meldal, *QSAR & Combinatorial Science,* 2004, 23, (2-3), 109-116, por ejemplo, 3-metilpirazina...

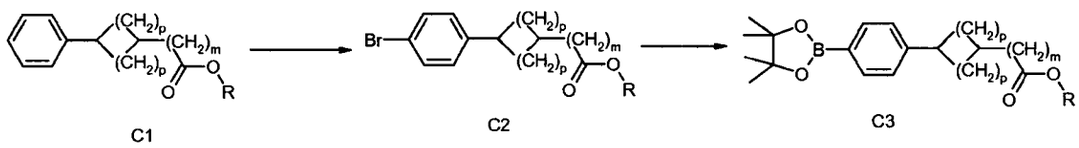


Esquema A5: Esquema de Reacción para 3 mono-metilpirazina y derivados

Preparación de tipos de compuestos de la fórmula (II) (Anillo C y Anillo B)

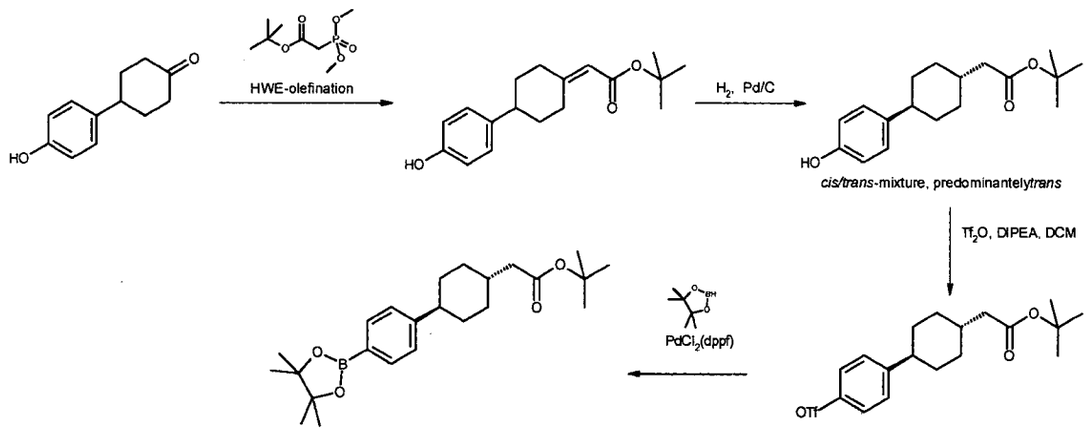
Los siguientes esquemas ilustran cómo se pueden preparar ciertas variantes del Anillo A y Anillo B. Las variables mostradas en los esquemas son definidas o se pueden interpretar en el contexto de las variantes descritas en la presente para los compuestos del invento. Se puede utilizar química análoga a aquella mostrada en los esquemas y Ejemplos para preparar otras variantes cíclicas y opciones de grupos enlazadores dentro del alcance del invento.

(i) Los compuestos de la fórmula (II) en los cuales el Anillo C es ciclohexano (p es 2 en la estructura C1) y el Anillo B es fenilo se describen en la literatura o se pueden preparar mediante analogía. Estos pueden ser bromados hasta llegar a (C2) y luego pueden ser convertidos en los ésteres de boronato (C3) utilizando procedimientos estándares. Grupos salientes alternativos a bromo en (C2) son yodo y triflato (ver Esquema C1-B).



C1 C2 C3

Esquema Cl-A: Esquema de Reacción para variantes de ciclohexano

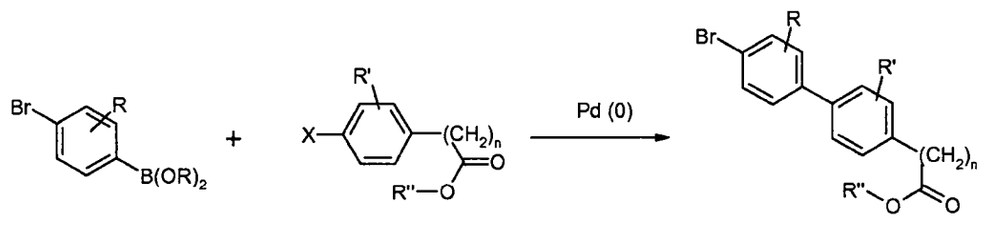


Esquema Cl-B: Esquema de reacción para síntesis de intermedio de éster de ácido borónico

El éster de metilo del esquema C1-B se ha descrito en WO 2004/047755.

Los compuestos en los cuales se requiere el compuesto bromo-heteroarilo no se pueden obtener directamente vía el compuesto de heteroarilo no sustituido. El grupo bromo, u otro grupo alternativo apropiado, se puede introducir en una etapa temprana en la ruta sintética.

(ii) Para compuestos de la fórmula (II) en los cuales el Anillo C es fenilo y el Anillo B es fenilo muchos intermedios apropiados están en la literatura, o se pueden preparar mediante analogía, y la introducción de varios modelos de sustitución se puede lograr a través de acoplamiento de Suzuki de biarilo:



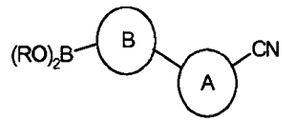
Esquema C2: Esquema de reacción para variantes de biarilo

En el Esquema C2, R y R' son cualquiera de los sustituyentes aromáticos reivindicados los cuales son compatibles con las condiciones de reacción, X es un grupo saliente apropiado tal como bromo, yodo o triflato. Luego el bromobiarilo es convertido en el derivado de boronato correspondiente mediante métodos estándares.

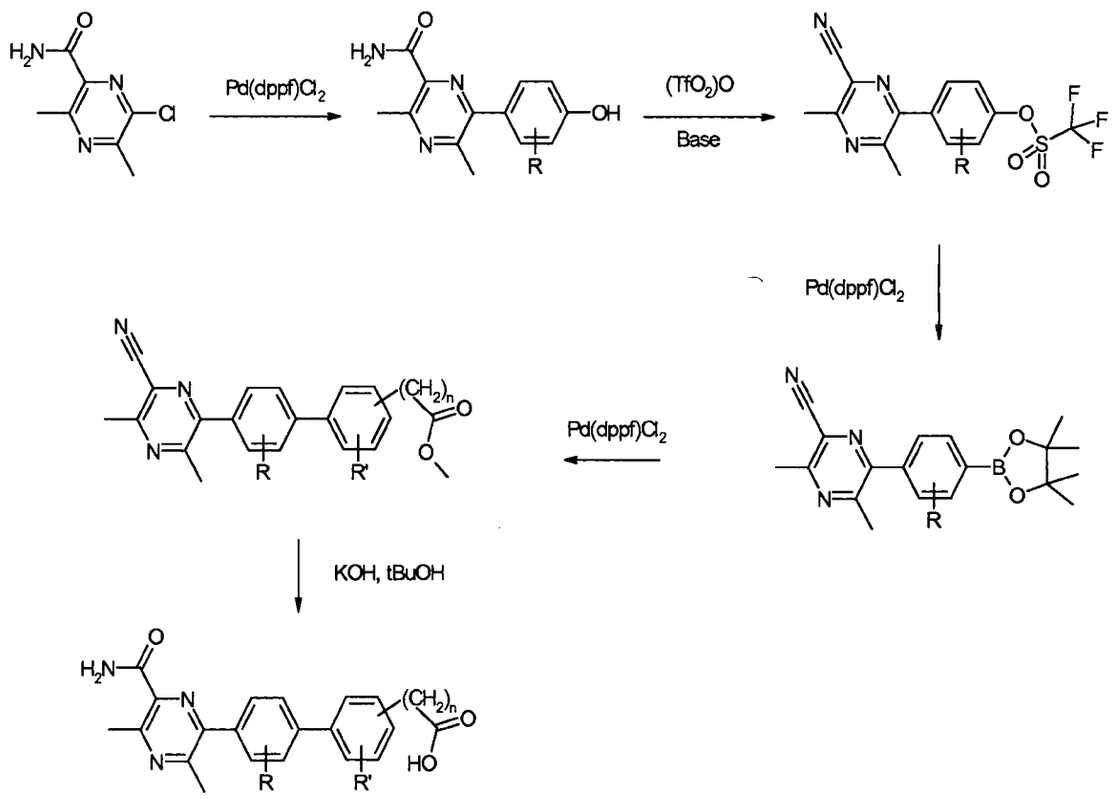
Para ambos el Esquema C1 y C2, la introducción de grupos α-alquilo y dialquilo es posible en la etapa intermedia C1 o C2 a través de metodología de alquilación estándar, por ejemplo mediante desprotonación α al grupo éster utilizando una base de litio tal como LDA seguido por apagado con un haluro de alquilo apropiado.

Preparación de tipos de compuestos de la fórmula (V) (Anillo A y Anillo B)

(i) En una secuencia alternativa de acoplamientos de Suzuki un éster cianoheterociclilfenilborónico del tipo V es generado como un intermedio clave, como se ilustra mediante el Esquema a continuación. Este intermedio luego se utiliza en reacciones de acoplamiento adicionales para generar compuestos de biarilo de la fórmula I.



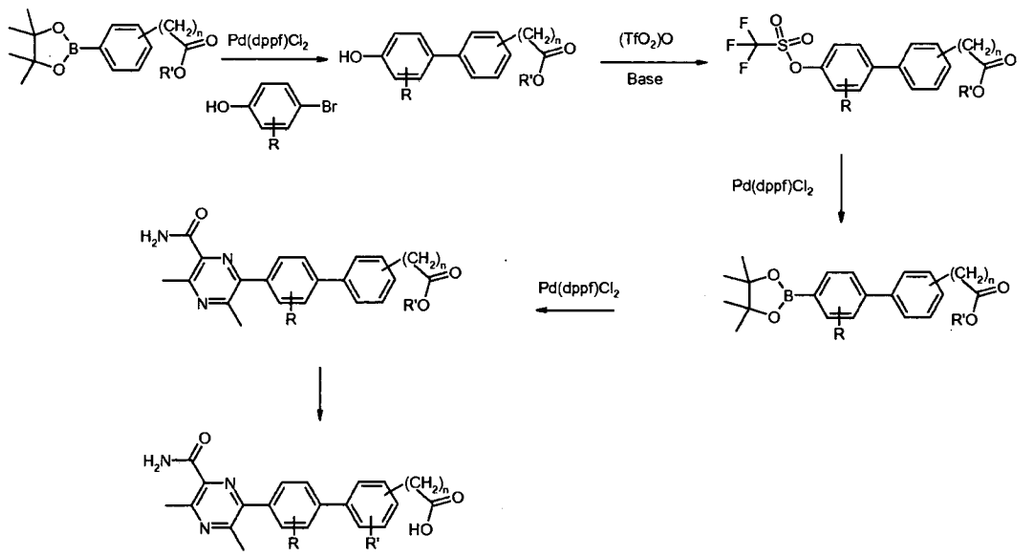
(V)



Esquema C2-A: Esquema de reacción para variantes de biarilo

En el Esquema C2, R y R' son cualquiera de los sustituyentes aromáticos reivindicados los cuales son compatibles con las condiciones de reacción. El fenol es convertido en el correspondiente triflato con anhídrido trifluorometanosulfónico y una base apropiada, tal como trietilamina, lo cual también resulta en deshidratación de la amida al nitrilo. El ariltriflato es convertido en el correspondiente derivado de boronato seguido por la reacción subsiguiente de

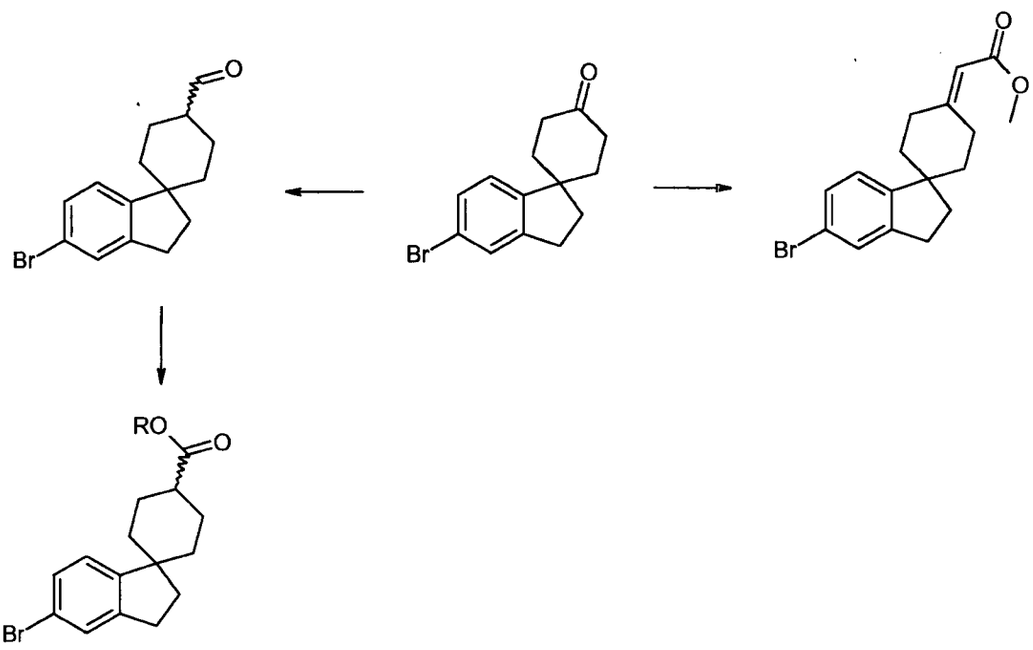
Suzuki bajo métodos estándares con un catalizador de paladio apropiado, tal como 1,1'-bis(difenilfosfino)-ferrocenodicloropaladio(II). Hidrólisis base, por ejemplo con hidróxido de potasio en tert-butanol resulta en hidrólisis del éster y nitrilo.



Esquema C2-B: Esquema de reacción para variantes de biarilo

En el Esquema C2-B, R y R' son cualquiera de los sustituyentes aromáticos reivindicados los cuales son compatibles con las condiciones de reacción.

(ii) Los compuestos espirocíclicos de la fórmula (II) se pueden preparar por analogía con preparaciones que involucran intermedios en el Esquema C4 a continuación ver WO 2004/047755 – secciones relevantes las cuales se incorporan en la presente como referencia).

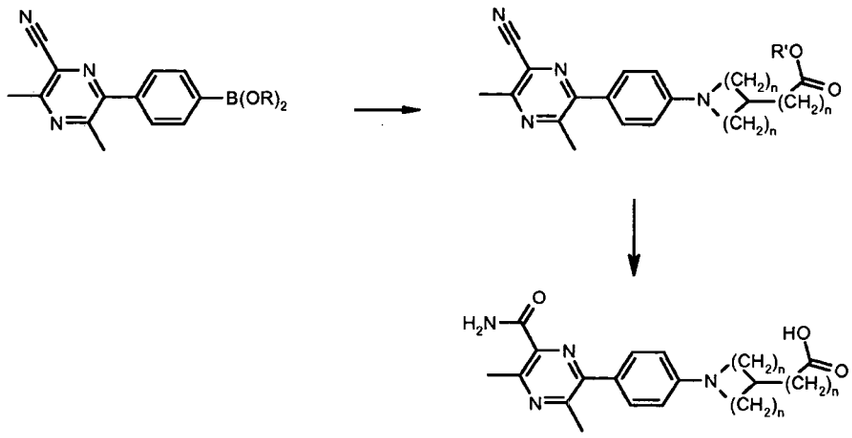


Esquema C4: Esquema de reacción para compuestos espirocíclicos

El enlace doble se puede reducir en una etapa apropiada en la síntesis y los isómeros cis- y trans- resultantes se pueden separar de forma cromatográfica. Como antes, esta ruta puede proceder por la conversión del bromo en el boronato para acoplar al compuesto de Anillo A apropiado (ej., pirazina).

El ciclohexano se puede convertir en la cetona no saturada y el enlace doble se puede reducir en una etapa apropiada en la síntesis y los isómeros cis- y trans- resultantes se pueden separar de forma cromatográfica. Alternativamente el ciclohexano se puede convertir en el aldehído el cual se puede oxidar al ácido, por ejemplo con ozono y el ácido se puede convertir en un éster, por ejemplo un tert-butilo y los isómeros cis- y trans- resultantes se pueden separar de forma cromatográfica. Como antes, esta ruta puede proceder por la conversión del bromo en el boronato para acoplar al compuesto de Anillo A apropiado (ej., pirazina).

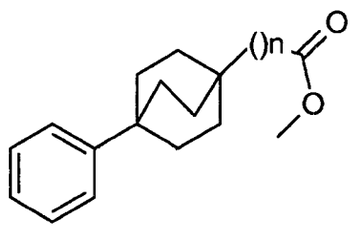
Para compuestos de la fórmula (V) en la cual el Anillo B es fenilo y el Anillo C es una amina cíclica, la introducción de la amina se puede lograr a través de acoplamiento por metales de transición.



Esquema C5: Esquema de reacción para variantes de amina cíclica

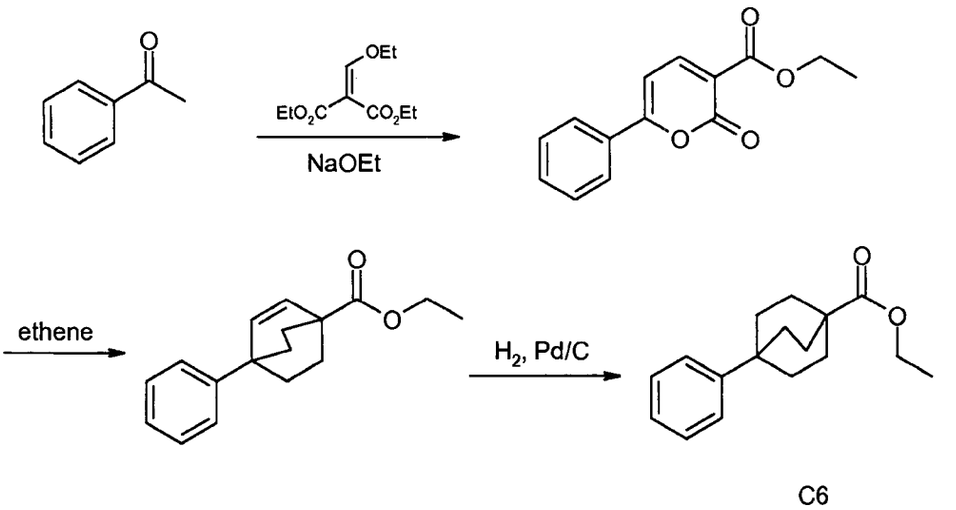
En el Esquema C5 las aminas se pueden introducir utilizando ácidos o ésteres borónicos utilizando acetato de cobre como en el procedimiento descrito por D. M. T. Chan, K. L Monaco, R. Li, D. Bonne, C. G. Clark, P. Y. S Lam, *Tet. Lett.*, 2003, 44(19), 3863-3865.

(iii) Los derivados de biciclooctano de la fórmula (II) se pueden preparar por analogía con preparaciones que involucran el Intermedio de fenilo C5 a continuación (ver WO 2007/071966 – secciones relevantes las cuales se incorporan en la presente como referencia), el cual es brominado y convertido en el boronato para acoplamiento al compuesto del Anillo A apropiado (ej., pirazina).



Intermedio C5

Los compuestos de la fórmula C5 se pueden preparar como su derivado de éster según el proceso mostrado a continuación en el Esquema C3, o de manera análoga al mismo.

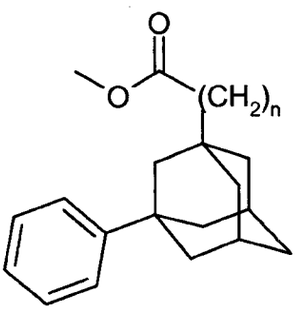


Esquema C3 : Variantes de biciclooctano

Los compuestos tales como C6 se pueden homologar mediante procedimientos estándares tal como la reducción del éster al correspondiente alcohol, la conversión de este en un grupo saliente tal como tosilato, desplazando este con cianuro seguido por hidrólisis y esterificación, todo mediante métodos estándares, a compuestos tales como C5 en donde n=1.

Los compuestos en los cuales el Anillo C es diferente de biciclo [2.2.2]octano-1,4-diilo se pueden preparar mediante procesos análogos.

(iii) Los derivados de adamantilo de la fórmula (II) se pueden preparar por analogía con preparaciones que involucran el Intermedio de fenilo C7 a continuación (ver WO 2007/071966 – secciones relevantes las cuales se incorporan en la presente como referencia), el cual es yodado y convertido en el boronato para acoplamiento al Anillo A apropiado (ej., pirazina).



Intermedio C7

Si los materiales de inicio necesarios no están comercialmente disponibles para los procedimientos descritos anteriormente, se pueden preparar mediante procedimientos que son seleccionados a partir de técnicas químicas orgánicas, técnicas que son análogas a la síntesis de compuestos estructuralmente similares, técnicas que son descritas o ilustradas en las referencias anteriores, o técnicas que son análogas al procedimientos antes descrito o los procedimientos descritos en los Ejemplos. El lector además es remitido a *Advanced Organic Chemistry*, Quinta Edición, de Jerry March y Michael Smith, publicada por John Wiley & Sons 2001, para guía general sobre condiciones y reactivos de reacción.

Se apreciará que algunos intermedios a compuestos de la fórmula (I) también son novedosos y estos son proporcionados como aspectos independientes separados del invento. En particular, ciertos compuestos de la fórmula (IV) pueden formar un aspecto independiente adicional del invento. Además, derivados de éster de compuestos de la fórmula (I) forman un aspecto adicional del invento.

También se apreciará que en algunas de las reacciones mencionadas en la presente, puede ser necesario/deseable proteger cualquiera de los grupos sensibles en los compuestos. Las instancias donde la protección es necesaria o deseable son conocidas por aquellos con experiencia en el estado de la técnica, como son los métodos apropiados para tal protección. Se pueden utilizar grupos protectores convencionales según la práctica estándar (para ilustración ver T.W. Greene, *Protective Groups in Organic Synthesis*, John Wiley and Sons, 1991).

Los grupos protectores se pueden retirar mediante cualquier método conveniente como se describe en la literatura ,o mediante cualquier método conocido por el químico con experiencia como apropiado para el retiro del grupo protector en cuestión, tales métodos escogidos para realizar el retiro del grupo protector con mínima alteración de grupos en otra parte de la molécula.

Por lo tanto, si los reactivos incluyen, por ejemplo, grupos tales como amino, carboxilo o hidroxilo, puede ser deseable proteger el grupo en algunas de las reacciones mencionadas en la presente.

Ejemplos de un grupo protector apropiado para un grupo hidroxilo es, por ejemplo, un grupo acilo, por ejemplo un grupo alcanoilo tal como acetilo, un grupo aroilo, por ejemplo benzoilo, un grupo sililo tal como trimetilsililo o un grupo arilmetilo, por ejemplo bencilo. Las

condiciones de desprotección para los anteriores grupos protectores necesariamente variarán con la elección del grupo protector. Por lo tanto, por ejemplo, un grupo acilo tal como un alcanoilo o un grupo aroilo se puede retirar, por ejemplo, mediante hidrólisis con una base apropiada tal como un hidróxido alcalino metálico, por ejemplo hidróxido de litio o sodio. Alternativamente un grupo sililo tal como trimetilsililo o SEM se puede retirar, por ejemplo, por fluoruro o ácido acuoso; o un grupo arilmetilo tal como un grupo bencilo se puede retirar, por ejemplo, por hidrogenación en presencia de un catalizador tal como paladio sobre carbono.

Un grupo protector apropiado para un grupo amino es, por ejemplo, un grupo acilo, por ejemplo un grupo alcanoilo tal como acetilo, un grupo alcoxicarbonilo, por ejemplo un grupo metoxicarbonilo, etoxicarbonilo o tert-butoxicarbonilo, un grupo arilmetoxicarbonilo, por ejemplo benciloxicarbonilo, o un grupo aroilo, por ejemplo benzoilo. Las condiciones de desprotección para los anteriores grupos protectores necesariamente variarán con la elección del grupo protector. Por lo tanto, por ejemplo, un grupo acilo tal como un grupo alcanoilo o alcoxilocarbonilo o un grupo aroilo se puede retirar, por ejemplo, mediante hidrólisis con una base apropiada tal como un hidróxido alcalino metálico, por ejemplo hidróxido de litio o sodio. Alternativamente un grupo acilo tal como un grupo t-butoxicarbonilo se puede retirar, por ejemplo, mediante tratamiento con un ácido apropiado como ácido clorhídrico, sulfúrico o fosfórico o ácido trifluoroacético y un grupo arilmetoxicarbonilo tal como un grupo benciloxicarbonilo se puede retirar, por ejemplo, mediante hidrogenación sobre un catalizador tal como paladio sobre carbono, o mediante tratamiento con un ácido Lewis por ejemplos tris(trifluroacetato) de boro. Un grupo protector apropiado alternativo para un grupo amino primario, es por ejemplo, un grupo ftaloilo el cual se puede retirar mediante tratamiento con una alquilamina, por ejemplo dimetilaminopropilamina o 2-hidroxietilamina, o con hidrazina.

Un grupo protector apropiado para un grupo carboxilo es, por ejemplo, un grupo esterificante, por ejemplo un grupo metilo o etilo el cual puede ser retirado, por ejemplo, mediante hidrólisis con una base tal como hidróxido de sodio, o por ejemplo un grupo t-butilo el cual se puede retirar, por ejemplo, mediante tratamiento con un ácido, por ejemplo un ácido orgánico tal como ácido trifluoroacético, o por ejemplo un grupo bencilo el cual se puede retirar, por ejemplo, mediante hidrogenación sobre un catalizador tal como paladio sobre carbono.

Las resinas también se pueden utilizar como un grupo protector.

Los grupos protectores se pueden retirar en cualquier etapa conveniente en la síntesis utilizando técnicas convencionales bien conocidas en el estado de la técnica, o se pueden retirar durante un paso de reacción posterior o procedimientos de tratamiento final.

El químico orgánico con experiencia podrá utilizar y adaptar la información contenida y citada dentro de las anteriores referencias, y Ejemplos anexos y también los Ejemplos en la presente, para obtener los productos y materiales de inicio necesarios.

El retiro de cualquiera de los grupos protectores y la formación de una sal farmacéuticamente aceptable están dentro de la experiencia de un químico orgánico común utilizando técnicas estándares. Además, los detalles sobre estos pasos se han proporcionado anteriormente.

Cuando se requiere una forma ópticamente activa de un compuesto del invento, ésta se puede obtener al ejecutar uno de los procedimientos anteriores utilizando un material de inicio ópticamente activo (formado, por ejemplo, mediante inducción asimétrica de un paso de reacción apropiado), o por resolución de una forma racémica del compuesto o intermedio utilizando un procedimiento estándar, o mediante separación cromatográfica de diastereoisómeros (cuando se producen). Las técnicas estándares también pueden ser útiles para la preparación de compuestos y/o intermedios ópticamente activos.

De manera similar, cuando se requiere un regioisómero puro de un compuesto del invento, éste se puede obtener al ejecutar uno de los procedimientos anteriores utilizando un regioisómero puro como un material de inicio, o mediante resolución de una mezcla de regioisómeros o intermedios utilizando un procedimiento estándar.

Según un aspecto adicional del invento, se proporciona una composición farmacéutica la cual comprende un compuesto de la fórmula (I), (IA) o (IB) como se definió anteriormente o una sal farmacéuticamente aceptable del mismo, en asociación un excipiente o vehículo farmacéuticamente aceptable.

Las composiciones del invento pueden estar en una forma apropiada para uso oral (por ejemplo como tabletas, pastillas, cápsulas duras o blandas, suspensiones acuosas o aceitosas, emulsiones, polvos o gránulos dispersables, jarabes o elíxires), para uso tópico (por ejemplo como cremas, ungüentos, geles, o soluciones o suspensiones acuosas o aceitosas), para administración por inhalación (por ejemplo como un polvo finamente dividido o un aerosol líquido), para administración por insuflación (por ejemplo como un polvo finamente dividido) o

para administración parenteral (por ejemplo como una solución acuosa o aceitosa estéril para dosificación intravenosa, subcutánea, intramuscular o como un supositorio para dosificación rectal.

Las composiciones del invento se pueden obtener mediante procedimientos convencionales utilizando excipientes farmacéuticos convencionales, bien conocidos en el estado de la técnica. Por lo tanto, las composiciones diseñadas para uso oral pueden contener, por ejemplo, uno o más agentes colorantes, endulzantes, saborizantes y/o preservativos.

Los excipientes farmacéuticamente aceptables para una formulación en tableta incluyen, por ejemplo, diluyentes inertes tales como lactosa, carbonato de sodio, fosfato de calcio o carbonato de calcio, agentes granulantes o desintegrantes tales como almidón de maíz o ácido algénico; aglutinantes tales como almidón; agentes lubricantes tal como estearato de magnesio, ácido esteárico o talco; agentes preservativos tal como p-hidroxibenzoato de etilo o propilo, y antioxidantes, tal como ácido ascórbico. Las formulaciones en tableta pueden ser recubiertas o no 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, en cualquier caso, utilizando agentes de recubrimiento convencionales y procedimientos bien conocidos en el estado de la técnica.

Las composiciones para uso oral pueden ser en la forma de cápsulas de gelatina dura en las cuales el ingrediente activo es mezclado con un diluyente sólido inerte, por ejemplo, carbonato de calcio, fosfato de calcio o caolina, o como cápsulas de gelatina blanda en las cuales el ingrediente activo es mezclado con agua o un aceite tal como aceite de cacahuate, parafina líquida, o aceite de oliva.

Las suspensiones acuosas generalmente contienen el ingrediente activo en forma de polvo fino junto con uno o más ingredientes de suspensión, tales como carboximetilcelulosa de sodio, metilcelulosa, hidroxipropilmetilcelulosa, alginato de sodio, polivinil-pirrolidona, goma tragacanto y goma acacia; agentes dispersantes o humectantes tales lecitina o productos de condensación de un óxido de alquileno con ácidos grasos (por ejemplo estearato de polioxietileno), o productos de condensación de óxido de etileno con alcoholes alifáticos de cadena larga, por ejemplo heptadecaetilenooxicetanol, o productos de condensación de óxido de etileno con Ésteres parciales derivados de ácidos grasos y un hexitol tal como monooletato de sorbital, o productos de condensación de óxido de etileno con alcoholes alifáticos de cadena

larga, por ejemplo heptadecaetilenooxicetanol, o productos de condensación de óxido de etileno con ésteres parciales derivados a partir de ácidos grasos y un hexitol tal como monooleato de sorbitol de polioxietileno, o productos de condensación de óxido de etileno con ésteres parciales derivados a partir de ácidos grasos, anhídridos de hexitol, por ejemplo sorbital monooleato de polietileno. Las suspensiones acuosas también pueden contener uno o más preservativos (tal como p-hidroxibenzoato de etilo o propilo), anti-oxidantes (tal como ácido ascórbico), agentes saborizantes, y/o agentes endulzantes (tal como sacarosa, sacarina o aspartame).

Las suspensiones aceitosas se pueden formular al suspender el ingrediente activo en un aceite vegetal (tal como aceite de cacahuate, aceite de oliva, aceite de ajonjolí o aceite de coco) o en un aceite mineral (tal como parafina líquida). Las suspensiones aceitosas también pueden contener un agente espesante tal como cera de abejas, parafina dura o alcohol cetílico. Se pueden agregar agentes endulzantes y agentes saborizantes tales como aquellos divulgados anteriormente para proporcionar una preparación oral de sabor agradable. Estas composiciones se pueden preservar mediante la adición de un anti-oxidante tal como ácido ascórbico.

Los polvos y gránulos dispersables apropiados para la preparación de una suspensión acuosa mediante la adición de agua generalmente contienen el ingrediente activo junto con un agente de dispersión o humectante, agente de suspensión y uno o más preservativos. Los agentes humectantes o de dispersión apropiados y agentes de suspensión son ejemplificados por aquellos mencionados anteriormente. Excipientes adicionales tales como agentes endulzantes, saborizantes y colorantes, también pueden estar presentes.

Las composiciones farmacéuticas del invento también pueden estar en la forma de emulsiones de aceite en agua. La fase aceitosa puede ser un aceite vegetal, tal como aceite de oliva o aceite de cacahuate, tal como por ejemplo parafina líquida o una mezcla de cualquiera de estos. Agentes emulsificantes apropiados pueden ser, por ejemplo, gomas naturales tales como goma acacia o goma tragacanto, fosfatidas naturales tales como soya, lecitina, ésteres o ésteres parciales derivados de ácidos grasos y anhídridos de hexitol (por ejemplo sorbitan monooleato) y productos de condensación de dichos ésteres parciales con óxido de etileno tal como sorbitan monooleato de polioxietileno. Las emulsiones también pueden contener agentes endulzantes, saborizantes y preservativos.

Los jarabes y elíxires se pueden formular con agentes endulzantes tales como glicerol, glicol de propileno, aspartame o sacarosa, y también pueden contener un demulcente, preservativo, agente saborizante y/o colorante.

Las composiciones farmacéuticas también pueden estar en la forma de una suspensión acuosa o aceitosa inyectable estéril, la cual se puede formular según los procedimientos conocidos utilizando uno o más de los agentes dispersantes o humectantes y agentes de suspensión, los cuales se han mencionado anteriormente. Una preparación inyectable estéril también puede ser una solución o suspensión inyectable estéril en diluyente o solvente no tóxico parenteralmente aceptable, por ejemplo una solución en 1,3-butanediol.

Las composiciones para administración por inhalación pueden estar en la forma de un aerosol presurizado convencional configurado para dispensar el ingrediente activo ya sea como un aerosol que contiene un sólido finamente dividido o gotitas líquidas. Se pueden utilizar propelantes de aerosol convencionales tales como hidrocarburos o hidrocarburos fluorados volátiles y el dispositivo de aerosol es convenientemente configurado para dispensar una cantidad medida del ingrediente activo.

Para información adicional sobre formulación, el lector es remitido al Capítulo 25.2 en Volumen 5 de *Comprehensive Medicinal Chemistry* (Corwin Hansch; Chairman de Editorial Board), Pergamon Press 1990.

La cantidad del ingrediente activo que es combinado con uno o más excipientes para producir una única forma de dosificación necesariamente variará dependiendo del huésped tratado y la ruta particular de administración. Por ejemplo, una formulación diseñada para administración oral a humanos generalmente contendrá, por ejemplo, entre 0.5 mg y 2 mg del agente activo en composición con una cantidad apropiada y conveniente de excipientes la cual variará entre 5% y 98% aproximadamente por peso de la composición total. Las formas unitarias de dosificación generalmente contendrán entre 1 mg y 500 mg aproximadamente de un ingrediente activo. Para información adicional sobre Rutas de Administración y Regímenes de Dosificación el lector es remitido al Capítulo 25,3 en Volumen 5 de *Comprehensive Medicinal Chemistry* (Corwin Hansch; Chairman de Editorial Board), Pergamon Press 1990.

Según un aspecto adicional del presente invento se proporciona un compuesto de las fórmulas (I), (IA), y/o (IB), o una sal farmacéuticamente aceptable, o un profármaco del mismo

como se definió anteriormente para utilizar en un método de tratamiento del cuerpo humano o animal mediante terapia.

Se ha encontrado que los compuestos del presente invento inhiben la actividad DGAT1 y por lo tanto son de interés por sus efectos reductores de glucosa en sangre.

Una característica adicional del presente invento es un compuesto de la fórmula (I), (IA) y/o (IB), o una sal farmacéuticamente aceptable, o un profármaco del mismo para utilizar como un medicamento.

Convenientemente este es un compuesto de la fórmula (I), (IA) y/o (IB), o una sal farmacéuticamente aceptable, o un profármaco del mismo, para (utilizar como un medicamento para) producir inhibición de actividad DGAT1 en un animal de sangre caliente tal como un ser humano.

Particularmente este es un compuesto de la fórmula (I), (IA) y/o (IB), o una sal farmacéuticamente aceptable, o un profármaco del mismo, para (utilizar como un medicamento para) tratar diabetes mellitus y/o obesidad en un animal de sangre caliente tal como un ser humano.

Por lo tanto, según un aspecto adicional del invento se proporciona el uso de un compuesto de la fórmula (I), (IA), y/o (IB), o una sal farmacéuticamente aceptable, o un profármaco del mismo en la fabricación de un medicamento para utilizar en la producción de inhibición de actividad DGAT1 en un animal de sangre caliente tal como un ser humano.

Por lo tanto, según un aspecto adicional del invento se proporciona el uso de un compuesto de la fórmula (I), (IA), y/o (IB), o una sal farmacéuticamente aceptable, o un profármaco del mismo en la fabricación de un medicamento para utilizar en el tratamiento de diabetes mellitus y/o obesidad en un animal de sangre caliente tal como un ser humano.

Según un aspecto adicional del invento, se proporciona una composición farmacéutica la cual comprende un compuesto de la fórmula (I), (IA) o (IB) como se definió anteriormente o una sal farmacéuticamente aceptable, o un profármaco del mismo, en asociación un excipiente o vehículo farmacéuticamente aceptable para utilizar en la producción de inhibición de actividad DGAT1 en un animal de sangre caliente, tal como un ser humano.

Según un aspecto adicional del invento, se proporciona una composición farmacéutica la cual comprende un compuesto de la fórmula (I), (IA) o (IB) como se definió anteriormente, o una sal farmacéuticamente aceptable, o un profármaco del mismo, en asociación con un excipiente o

vehículo farmacéuticamente aceptable para utilizar en el tratamiento de diabetes mellitus y/o obesidad en un animal de sangre caliente, tal como un ser humano.

Según una característica adicional del invento se proporciona un método para producir inhibición de actividad DGAT1 en un animal de sangre caliente, tal como un ser humano, en necesidad de tal tratamiento el cual comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), (IA), y/o (IB), o una sal farmacéuticamente aceptable, o un profármaco del mismo como se definió anteriormente.

Según una característica adicional del invento se proporciona un método para tratar diabetes mellitus y/o obesidad en un animal de sangre caliente, tal como un ser humano, en necesidad de tal tratamiento el cual comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), (IA), y/o (IB), o una sal farmacéuticamente aceptable, o un profármaco del mismo como se definió anteriormente.

Como se afirmó anteriormente, el tamaño de la dosis requerida para el tratamiento terapéutico o profiláctico de un estado patológico particular necesariamente variará dependiendo del huésped tratado, la ruta de administración y la severidad de la enfermedad tratada. Preferiblemente se emplea una dosis diaria en el rango entre 1-50 mg/kg. En otra realización una dosis diaria está en el rango entre 0.01-50 mg/kg, particularmente 0.01-10 mg/kg, 0.01-1 mg/kg o 0.01-0.1 mg/kg. Sin embargo la dosis diaria necesariamente variará dependiendo del huésped tratado, la ruta particular de administración, y la severidad de la enfermedad tratada. Por consiguiente la dosis óptima puede ser determinada por el medico tratando un paciente particular.

Como se afirmó anteriormente, los compuestos definidos en el presente invento son de interés por su capacidad para inhibir la actividad de DGAT1. Por lo tanto un compuesto del invento puede ser útil para la prevención, retardo o tratamiento de un rango de estados patológicos incluyendo diabetes mellitus, más específicamente diabetes mellitus tipo 2 (T2DM) y complicaciones que se originan a partir de (por ejemplo retinopatía, neuropatía y nefropatía), tolerancia deteriorada a glucosa (IGT por su sigla en inglés), condiciones de glucosa en ayunas deteriorada, acidosis metabólica, cetosis, síndrome dismetabólico, artritis, osteoporosis, obesidad y trastornos relacionados con obesidad, (los cuales incluyen enfermedad vascular periférica, (incluyendo claudicación intermitente), falla cardiaca y ciertas miopatías cardiacas, isquemia miocardial, isquemia cerebral, y reperfusión, hiperlipidemias, aterosclerosis, infertilidad y síndrome de ovario policístico); el compuesto del invento también puede ser útil para debilidad

muscular, enfermedades de la piel tal como acné, varias enfermedades inmunomoduladoras (tal como soriasis), infección por VIH, síndrome de intestino inflamatorio y enfermedad intestinal inflamatoria tal como enfermedad de Crohn y colitis ulcerativa.

En particular, los compuestos del presente invento son de interés para la prevención, retardo o tratamiento de diabetes mellitus y/o trastornos relacionados con obesidad. En un aspecto, los compuestos del invento se utilizan para la prevención, retardo o tratamiento de diabetes mellitus. En otro aspecto, los compuestos del invento se utilizan para la prevención, retardo o tratamiento de diabetes mellitus. En un aspecto adicional, los compuestos del invento se utilizan para la prevención, retardo o tratamiento de trastornos relacionados con obesidad.

La inhibición de actividad DGAT1 descrita en la presente se puede aplicar como una terapia única o en combinación con una o más sustancias y/o tratamientos para la indicación tratada. Tal tratamiento conjunto se puede lograr mediante la administración simultánea, secuencial o separada de los componentes individuales del tratamiento. El tratamiento simultáneo puede ser en una única tableta o en tabletas separadas. Por ejemplo tal tratamiento conjunto puede ser benéfico en el tratamiento de síndrome metabólico [definido como obesidad abdominal (como se midió por la circunferencia de cintura contra puntos de corte específicos étnicos y de género) más cualquiera dos de los siguientes: hipertrigliceridemia (> 150 mg/dl; 1.7mmol/l); HDLc baja (<40 mg/dl o <1.03mmol/l para hombres y <50 mg/dl o 1.29 mmol/1 para mujeres) o en tratamiento para HDL baja (lipoproteína de alta densidad); hipertensión (SBP > 130 mmHg DBP > 85 mmHg) o en tratamiento para hipertensión; e hiperglicemia (glucosa de plasma en ayunas > 100 mg/dl o 5.6 mmol/l o tolerancia deteriorada a glucosa o diabetes mellitus pre-existente) – Federación Internacional de Diabetes & entrada desde IAS/NCEP].

Tales tratamientos conjuntos pueden incluir las siguientes características principales:

1) Terapias anti-obesidad tales como aquellas que producen pérdida de peso mediante efectos sobre la ingesta alimenticia, absorción de nutrientes o gasto de energía, tal como orlistat, sibutramina y similares.

2) Secretagogos de insulina incluyendo sulfonilureas (por ejemplo glibenclamide, glipizide), reguladores pandriales de la glicemia (por ejemplo repaglinide, nateglinide);

Agentes que mejoran la acción de la incretina (por ejemplo inhibidores de la dipeptidil peptidasa IV, y agonistas del GLP-1);

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4) Agentes sensibilizadores de la insulina incluyendo agonistas del PPAR gama (por ejemplo pioglitazona y rosiglitazona) y agentes con actividad PPARalfa y gama combinada;

5) Agentes que modulan el balance de glucosa hepática (por ejemplo metformina, fructosa 1, inhibidores de la 6 bisfosfatasa, inhibidores de la glicógeno fosforilasa, inhibidores de la glicógeno sintasa quinasa, activadores de la glucoquinasa);

6) Agentes diseñados para reducir la absorción de glucosa desde el intestino (por ejemplo acarbosa);

7) Agentes que evitan la reabsorción de glucosa por parte del riñón (inhibidores SGLT);

8) Agentes diseñados para tratar complicaciones de hiperglicemia prolongada (por ejemplo, inhibidores de la aldosa reductasa);

9) Agentes anti-dislipidemia tales como, inhibidores de la HMG-CoA reductasa (ej., estaninas); PPAR α-agonistas (fibratos, ej., gemfibrozil); secuestrantes de ácido biliar (colestiramina); inhibidores de absorción de colesterol (estanoles vegetales, inhibidores sintéticos); inhibidores de absorción de ácido biliar (IBATi) y ácido nicotínico y análogos (niacina y formulaciones de liberación lenta);

10) Agentes antihipertensivos tales como β-bloqueadores (ej., atenolol, inderal); inhibidores ACE (ej., lisinopril); antagonistas de calcio (ej., nifedipina); antagonistas de receptores de angiotensina (ej., candesartan, α-antagonistas y agentes diuréticos (ej., furosemide, benztiazide);

11) Moduladores de la haemostasis tales como, antitrombóticos, activadores de fibrinólisis y agentes antiplaquetarios; antagonistas de trombina; inhibidores de factor Xa; inhibidores de factor VIIa);agentes antiplaquetas (ej., asparina, clopidogrel); anticoagulantes (heparina y análogos de bajo peso molecular, hirudin) y warfarina;

12) Agentes que antagonizan las acciones del glucagón; y

13) Agentes anti-inflamatorios, tales como fármacos anti-inflamatorios no esteroidales (ej., aspirina) y agentes anti-inflamatorios esteroidales (ej., cortisona).

Además de su uso en medicina terapéutica, los compuestos de la fórmula (I) y sus sales farmacéuticamente aceptables son útiles como herramientas farmacológicas en el desarrollo y estandarización de sistemas de prueba *in vitro* y *in vivo* para la evaluación de los efectos de inhibidores de actividad DGAT1 en animales de laboratorio tales como gatos, perros, conejos, monos, ratas, y ratones, como parte de la investigación para nuevos agentes terapéuticos.

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En la anterior composición farmacéutica, proceso, método, uso y características de manufactura del medicamento, también aplican las realizaciones particulares y preferidas de los compuestos del invento descritas en la presente. Las realizaciones alternativas, particulares y preferidas del invento descritas en la presente también aplican para un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable, o un profármaco del mismo.

Como se indicó anteriormente, todos los compuestos, y sus correspondientes sales farmacéuticamente aceptables, son útiles para inhibir DGAT1. La capacidad de los compuestos de la fórmula (I), y sus correspondientes sales farmacéuticamente aceptables (adición ácida), para inhibir DGAT1 se puede demostrar empleando el siguiente ensayo enzimático:

Ensayo Enzimático Humano

Ver, por ejemplo, la Solicitud Internacional WO 2005/044250.

Para identificar inhibidores la DGAT1, el ensayo *in vitro* utiliza la DGAT1 humana expresada en membranas de células de insectos como la fuente de enzimas (Proc. Natl. Acad. Sci. 1998, 95, 13018-13023). Brevemente, se infectaron células sf9 con baculovirus recombinante conteniendo secuencias codificadoras de la DGAT1 humana y se cosecharon después de 48 h. Las células fueron sometidas a lisis mediante sonicación y las membranas se aislaron mediante centrifugación a 28000 rpm durante 1h a 4° sobre un gradiente de sacarosa al 41%. La fracción de membrana en la interfase fue recolectada, lavada, y almacenada en nitrógeno líquido.

La actividad de la DGAT1 fue probada mediante una modificación del método descrito por Coleman (*Methods in Enzymology* 1992, 209, 98-102). El compuesto a 0.0000256μM (o 0.003μM) - 33 μM (concentración final) (típicamente 10 μM) fue incubado con 4 μg/ml (concentración final) de proteína de membrana, 5 mM MgCb, y 100μM 1,2 dioleoil-sn-glicerol (disuelto en acetone con una concentración de ensayo final, de acetona de 1.8%; se pueden utilizar otras concentraciones de acetona según sea apropiado, por ejemplo 10%) en un volumen de ensayo total de 200 μl en una placa de 96 pozos. La reacción fue iniciada mediante la adición de ^{14}C oleoilo coenzima A (30μM concentración final) e incubada a temperatura ambiente durante 30 minutos. La reacción fue detenida mediante la adición de 200 μl de 2-propanol:heptano 7:1 y 100μl de 0.1 M buffer de carbonato pH 9.5. La actividad la DGAT1 fue cuantificada contando alícuotas de la capa de heptano superior mediante cintilografía líquida.

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Utilizando este ensayo los compuestos generalmente muestran actividad con un IC50 alrededor o por debajo de 10 μM, preferiblemente por debajo de 10 μM (es decir, IC50 <10 μM, más preferiblemente <0.1 μM, particularmente <0.05 μM, y más particularmente <0.01 μM. Las cifras citadas usualmente son un promedio de un número de mediciones (usualmente 2 mediciones) según la práctica estándar.

En algunos casos los datos de porcentaje de inhibición se han proporcionado a una concentración particular (10 μM).

El Ejemplo 1 mostró un IC50 = 0.06μM (utilizando una concentración de acetona de ensayo de 1.8%) y 0.079μM (utilizando una concentración de acetona de ensayo de 10%).

Los Ejemplos 2 a 20 mostraron respectivamente IC50 = 0.071μM; 0.023μM; 0.042μM; 0.018μM; 5.71μM; 5.09μM; 0.233μM; 0.674μM; 1.34μM; 0.102μM; 0.025μM; 0.428μM; 0.159μM; 0.157μM; 1.23μM; 0.418μM; 2.85μM; 1.55μM y 6.31μM.

Los Ejemplos 21 a 54 mostraron respectivamente IC50 = 0.27μM; 0.067μM; 0.096μM; 1μM; 0.1μM; 1.5μM; 0.31μM; 0.038μM; 0.1μM; 0.032μM; 0.17μM; 0.27μM; 1.3μM; 3μM; 0.96μM; Ejemplo 36 = inhibición de 46-67% 10μM; Ejemplo 37 ≡ inhibición de 47-50% a 10μM; 2.4μM; 3μM; 1.2μM; 0.95μM; 0.21μM; 0.066μM; 0.093μM; 0.035μM; 0.047μM; 0.056μM; 4.4μM; 0.57μM; 0.6μM; 3.4μM; 4.6μM; 4.6μM; 1.3μM.

Los Ejemplos 55 a 64 mostraron respectivamente IC_{50} = 7μM; Ejemplo 56 = inhibición de 15-31% a 10μM; 6.7μM; (Ejemplo 58 – sin datos); 0.12μM; 0.09μM; 0.15μM; 8μM; 0.18μM; 0.67μM.

El Ejemplos 65 mostró un IC50 = 7.8μM y el Ejemplo 66 un IC50 = 0.88μM.

El Ejemplo 67 mostró IC50 = 0.18μM; El Ejemplo 68 = inhibición del 25% a 10μM.

Los Ejemplos 69 y 70 mostraron respectivamente IC50 = 0.4μM y IC50 = 4.9μM.

La capacidad de los compuestos de la fórmula (I), y sus correspondientes sales farmacéuticamente aceptables (ácidas), para inhibir la DGAT1 se puede demostrar adicionalmente empleando el siguiente ensayo de células enteras:

Medición de Síntesis de Triglicéridos en Células HuTu 80

Células HuTu80 fueron cultivadas a confluencia en placas de 6 pozos en medio esencial mínimo conteniendo suero de ternero fetal. Para el experimento, el medio fue cambiado a medio

libre de suero y las células se pre-incubaron con compuesto solubilizado en DMSO (concentración final 0.1%) durante 30 minutos. La lipogénesis de novo fue medida mediante la adición de 0.12 mM oleato de sodio más 1μCi/mL ^{14}C-sodio oleato formando complejo con 0.03 mM de BSA a cada pozo durante 2 h más. Las células fueron lavadas en solución salina, amortiguada con fosfato y solubilizadas en dodecilsulfato sódico al 1%. Se retiró una alícuota para determinación de proteínas utilizando un kit de estimación de proteínas (Perbio) con base en el método de Lowry (J. Biol. Chem., 1951, 193, 265-275). Los lípidos fueron extraídos en la fase orgánica utilizando una mezcla de heptano:propan-2-ol: agua (80:20:2) seguido por alícuotas de agua y heptano según el método de Coleman (*Methods in Enzymology*, 1992, 209, 98-104). La fase orgánica fue recolectada y el solvente evaporado bajo una corriente de nitrógeno. Los extractos se solubilizaron en iso-hexano:ácido acético (99:1) y los lípidos se separaron vía cromatografía líquida de alto desempeño de fase normal (HPLC) utilizando una columna Lichrospher diol-5, 4 x 250 mm y un sistema solvente gradiente de iso-hexano: ácido acético (99:1) y iso-hexano:propan-2-ol: ácido acético (85:15:1), tasa de flujo de 1 mL/minuto según el método de Silversand y Aux. (1997). La incorporación de radiorótulo en la fracción de triglicéridos fue analizada utilizando un Radiomatic Flo-one Detector (Packard) conectado a la maquina HPLC.

Ejemplos

Los siguientes Ejemplos son para fines de ilustración y no tienen la intención de limitar el alcance de esta solicitud. Cada compuesto ejemplificado representa un aspecto individual e independiente del invento. En los siguientes Ejemplos no limitantes, a menos que se afirme lo contrario:

(i) las evaporaciones se realizaron mediante evaporación rotatoria bajo presión reducida y los procedimientos de tratamiento final se realizaron después de retirar los sólidos residuales tales como agentes de secado mediante filtración;

(ii) las operaciones se realizaron a temperatura ambiente, es decir en el rango 18-25°C y generalmente bajo una atmósfera de un gas inerte tal como argón o nitrógeno;

(iii) los rendimientos son dados solamente para ilustración y no son necesariamente el máximo alcanzable;

(iv) las estructuras de los productos finales de la fórmula (I) fueron confirmadas mediante resonancia magnética nuclear (NMR) (generalmente de protones) y técnicas espectrales de masa; los valores de desplazamiento químico por resonancia magnética de protones fueron medidos sobre la escala delta y las multiplicidades son como sigue: s, sencillo; d, doblete; t, triplete; m, múltiple; br; ancho; q, cuarteto, quin, quinteto;

(v) los intermedios generalmente no fueron completamente caracterizados y la pureza se evaluó mediante cromatografía de capa delgada (TLC), cromatografía líquida de alto desempeño (HPLC), análisis infra-rojo (IR) o RMN;

(vi) la cromatografía flash fue realizada sobre sílice a menos que se especifique lo contrario con purificaciones de cromatografía flash corridas sobre instrumentos Biotage SP1 o SP4 utilizando columnas Biotage Silica;

(vii) los espectros de masa fueron registrados sobre un espectrómetro de masas de tipo trampa iónica Finnigan LCQ equipado con una interfase de electrospray (LC-MS) o sistema LC-MS con un WatersZQ utilizando un sistema LC-Agilent 1100 LC;

(viii) las mediciones ^{1}H RMN fueron realizadas sobre un espectrómetro Varian Mercury VXR 300 y 400, operando a una frecuencia 1H de 300 y 400 y espectrómetros Varian UNITY plus 400, 500 y 600, operando a frecuencias 1H de 400, 500 y 600 respectivamente. Los cambios químicos son dados en ppm con el solvente como estándar interno. Los protones sobre heteroátomos tales como protones NH y OH solamente son reportados cuando se detectan en RMN y por lo tanto pueden ser omitidos.

(ix) las separaciones HPLC fueron realizadas sobre una Waters YMC-ODS AQS-3 120 Angstrom 3 x 500 mm o sobre una Waters Delta Prep Systems utilizando columnas Kromasil C8, 10 μm. HPLC ácida fue realizada utilizando gradientes de fase móvil A: 100 % ACN y fase

móvil B: 5 % ACN + 95 % H_20 + 0.2 % FA. HPLC neutral se realizó utilizando gradientes de fase móvil A: 100 % ACN y fase móvil B: 5 % ACN + 95 % 0.1 M NH_4OAc.

(x) Las reacciones realizadas en un horno microondas fueron corridas en un Instrumento Iniciador Biotage.

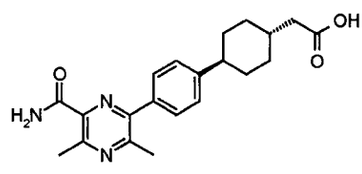
(xi) Se utilizó un número de paquetes de software de nomenclatura química, tales como ACDName; ACDLabsName; Release 9:00, versión de producto 9.04 y Struc=Name/CambridgeSoft ELN, para nombrar los compuestos.

Lista de abreviaturas utilizadas en la presente:

ACN	Acetonitrilo
aq	Acuoso
Boc	tert-butiloxicarbonil
Brine	Solución saturada de cloruro de sodio en agua
BSA	Albumina de Suero Bovino
DCE	1,2-dicloroetano
DCM	Diclorometano
DEE	Dietiléter
DIPEA	N,N-Diisopropiletilamina
DMAP	Dimetilaminopiridina
DMF	N,N-dimetilformamida
DMSO	Dimetilsulfoxido
Dppf	1,1 '-bis(Difenilfosfino)ferroceno
EDCI	hidrocloruro de 1 -Etil-3-(3-dimetilaminopropil)carbodiimide
EDTA	Acido etilendiaminotetraacético
EtOAc	Acetato de etilo
EtOH	Etanol
FA	Acido fórmico
HO Ac	Acético acid
HPLC	Cromatografia líquida de alto desempeño
HWE	Horner-Wadsworth-Emmons
Hz	Hertz

IPA	Isopropilalcohol
iPr	isopropil
LC	Cromatografía Líquida
m-CPBA	Acido meta-cloroperoxibenzóico
MeOH	Metanol
MHz	Megahertz
mL	Mililitro
MS	Espectro de Masa
NMM	N-metilmorfolina
NMP	N-metilpiperazina
NMR(RMN)	Resonancia Magnética Nuclear
OAc	Acetato
Ph	Fenilo
PyBOP	hexafluorofosfato de Benzotriazol-1-il-oxitri-pirrolidinofosfonio
PyBROP	hexafluorofosfato de Bromo-tris-pirrolidino-fosfonio
RT	temperatura ambiente
sat	saturado
TEA	Trietilamina
Tf	trifluorometilsulfonilo
TFA	ácido trifluroacético
THF	Tetrahidrofurano
TLC	Cromatografia de capa delgada
Ts	p-toluensulfonilo

Ejemplo 1: Acido {trans-4-[4-(6-Carbamoil-3,5-dimetilpirazin-2-il)fenil]ciclohexil}acético

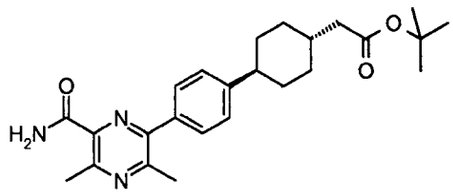


A una solución del **Intermedio 1-1** (363 mg, 0.86 mmol) en DCM (30 mL) se agregó TFA

(3 mL) por goteo. La solución incolora gradualmente se volvió una solución transparente de color amarillo claro . La mezcla de reacción se agitó bajo N2 a RT durante la noche. El solvente fue evaporado para proporcionar el compuesto del título (100 %).

^{1}H NMR (600 MHz, CD_3OD) δ 1.22 (q, 2H), 1.59 (q, 2H), 1.85 (s, 1H), 1.94 (d, 4H), 2.23 (d, 2H), 2.58 (t, 1H), 2.62 (s, 3H), 2.84 (s, 3H), 7.37 (d, 2H), 7.58 (d, 2H); *m/z* 368 $(M+H)^+$.

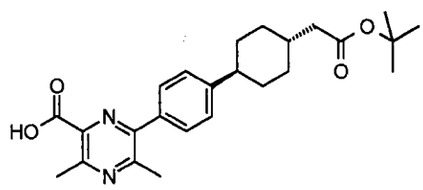
Intermedio 1-1: tert-Butil {trans-4-[4-f6-Carbamoil-3,5-dimetilpirazin-2-il)fenil]ciclohexil}acetate



A una solución de PyBOP (717 mg, 1.38 mmol) y NH_4Cl (196.6 mg, 3.68 mmol) en DMF (50 mL) se agregó el Intermedio 1-2 (390.0 mg, 0.92 mmol) y finalmente DIPEA (0.80 mL, 4.59 mmol) para iniciar la reacción. La solución fue agitada durante 5 h a temperatura ambiente. La reacción fue apagada mediante la adición de Na_2CO_3 saturado y extraída con tolueno (3 x 100 mL). Los orgánicos combinados fueron lavados con salmuera y agua, secados sobre Na_2SO_4, filtrados y concentrados bajo presión reducida. El material crudo fue purificado mediante cromatografía flash utilizando EtOAc (20-60 %) en éter de petróleo. La evaporación de fracciones de producto puro proporcionó el compuesto del título (376 mg, 96 %) como un sólido blanco.

^{1}H NMR (400 MHz, $CDC1_3$) δ 1.20 (q, 2H), 1.47(s, 9H), 1.50-1.64 (m, 2H), 1.80-2.00 (m, 5H), 2.17 (d, 2H), 2.56 (t, 1H), 2.67 (t, 3H), 2.98 (t, 3H), 5.43 (s, 1H), 7.33 (d, 2H), 7.52 (d, 2H), 7.81 (d, 2H); *m/z* 424 $(M+H)^+$.

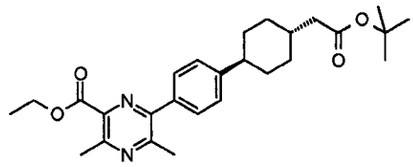
Intermedio 1-2: ácido 6-{4-[trans-4-(2-tert-Butoxi-2-oxoetil)ciclohexil]fenil}-3,5-dimetilpirazina-2-carboxílico



A una solución del Intermedio **1-3** (0.530 g, 1.17 mmol) en THF (10 mL) se agregó LiOH (1M, 15 mL). La reacción se agitó a temperatura ambiente durante 5 h. El THF fue retirado al vacio y el residuo acuoso fue acidificado con 1M HCL y extraído con EtOAc. La capa orgánica fue secada a través de un separador de fase y concentrada para proporcionar el compuesto del título (0.5 g, 100 %).

^{1}HNMR(500MHz,$CDCl_3$) δ 1.12-1.21 (m, 2H), 1.45 (s, 9H), 1.49-1.57 (m, 2H), 1.79-1.96 (m, 5H), 2.15 (d, 2H), 2.51-2.57 (m, 1H), 2.70 (s, 3H), 2.97 (s, 3H), 7.33 (d, 2H), 7.48 (d, 2H); *m/z* *425* $(M+H)^+$.

<u>Intermedio 1-3: Etil 6-{4-[trans-4-(2-tert-butoxi-2-oxoetil)ciclohexil] fenil}-3,5-dimetilpirazina-2-carboxilato</u>



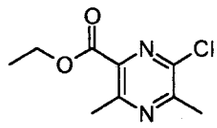
A una solución del Intermedio **1-4** (0.580 g, 2.70 mmol) en DME (22 mL), EtOH (12 mL) y agua (5 mL) se agregó el **Intermedio D** (ver luego Intermedio 1 -7; 1.244 g, 3.11 mmol), fosfato de potasio, tribásico (0.688 g, 3.24 mmol) y $PdCl_2$(dppf) (0.119 g, 0.16 mmol). Las soluciones se degasificaron con nitrógeno durante 10 min y luego se calentaron en el horno microondas a 140 °C durante 20 min. Cantidades adicionales del **Intermedio D** y PdCl2(dppf) se agregaron para impulsar la reacción. El calentamiento microondas continuó a 140 °C durante 30 minutos más.

(El éster etílico se puede hidrolizar aquí prolongando el tiempo de calentamiento y agregando 3 equivalentes extra de fosfato de potasio, para proporcionar el **Intermedio 1-2.)**

Las mezclas fueron combinadas, filtradas a través de un embudo de filtro de vidrio y evaporadas. El residuo negro restante fue disuelto en EtOAc, lavado con 0.5M HCl y extraído con 2xEtOAc. Los orgánicos combinados fueron secados mediante un separador de fase y

concentrados. El crudo fue purificado mediante cromatografía flash utilizando EtOAc (0-50 %) en heptano como eluente. La evaporación proporcionó el compuesto del título (1.063 g, 80%) como aceite. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13-1.22 (m, 2H), 1.42 (t, 3H), 1.47 (s, 9H), 1.49-1.58 (m, 2H), 1.80-1.95 (m, 5H), 2.16 (d, 2H), 2.49-2.56 (m, 1H), 2.66 (s, 3H), 2.81 (s, 3H), 4.45 (q, 2H), 7.30 (d, 2H), 7.53 (d, 2H); *m/z* 453 $(M+H)^+$.

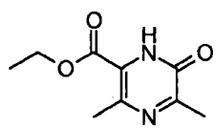
Intermedio 1-4: Etil 6-cloro-3,5-dimetilpirazina-2-carboxilato



A una suspensión del **Intermedio 1-5** (0.23 g, 1.17 mmol) en butironitrilo (4 mL) se agregó $POCl_3$ (0.27 mL, 2.93 mmol). La reacción fue calentada a 150 °C durante 10 min en el horno microondas y enfriada a temperatura ambiente. A la mezcla de reacción se agregó agua (2 mL) y las fases fueron separadas. La capa orgánica se concentró bajo presión reducida. El producto crudo se purificó mediante cromatografía flash utilizando 0.5% HOAc en DCM como eluente para proporcionar el compuesto del título (0.18 g, 73 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (t, 3H), 2.68 (s, 3H), 2.78 (s, 3H), 4.46 (q, 2H); *m/z* 215 $(M+H)^+$.

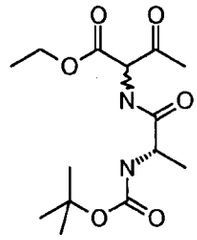
Intermedio 1-5: Etil 3,5-dimetil-6-oxo-1,6-dihidropirazina-2-carboxilato



A una solución del Intermedio **1-6** (800 mg, 2.53 mmol) en DCE seco (40 mL) se agregó TFA (1.95 mL, 25.3 mmol). La mezcla de reacción se calentó a reflujo durante 4 h. El solvente fue evaporado y el producto crudo se purificó mediante cromatografía flash utilizando EtOAc (20-80 %) en heptano como eluente. La concentración de las fracciones puras proporcionó el compuesto del título (160 mg, 32 %) como un polvo blanco-amarillo. El crudo de esta reacción se puede opcionalmente utilizar directamente en el siguiente paso sin purificación.

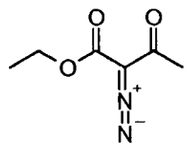
^{1}H NMR (400 Mhz, $CDCl_3$) δ 4.42 (q, 2H), 2.61 (s, 3H), 2.52 (s, 3H), 1.41 (t, 3H); *m/z* 197$(M+H)^+$.

Intermedio 1-6: 2-{[N-(tert-butoxicarbonil)-L-alanil]amino}-3-oxobutanoato de Etilo



Se agregó el **Intermedio 1-7** (500 mg, 3.2 mmol) y BOC-Ala-NH_2 (843.8 mg, 4.5 mmol, CAS 85642-13-3) a una matraz de fondo redondo, se selló y lleno con argón. Se agregó tolueno seco (30 mL) vía jeringa y la mezcla heterogenea resultante se agitó a 90 °C durante 10 min para obtener una solución homogénea. Entre tanto, se disolvió el dimero de octanoato de rodio (II) (62.3 mg, 0.080 mmol, CAS 73482-96-9) en tolueno (5 mL) y se colocó sobre un baño de ultrasonido durante 5 min, para obtener una dispersión Rh fina. Luego ésta dispersión se agregó por goteo a la mezcla de reacción a 80 °C (se observó una efervescencia de N_2 violenta). Después de agitar 20 min más a temperatura elevada la mezcla de reacción fue concentrada bajo presión reducida para proporcionar un sólido negro pálido. El producto de inserción N-H se podría purificar aquí o llevar directamente al siguiente paso. El crudo fue purificado mediante cromatografía flash utilizando EtOAc (20-80 %) en heptano para proporcionar el compuesto del título (850 mg, 84 %) (mezcla diastereomérica) como un aceite amarillo. *m/z* 317 $(M+H)^+$.

Intermedio 1-7: 2-diazo-3-oxobutanoato de Etilo

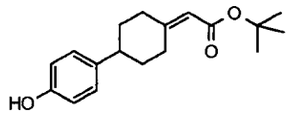


Tosilazida fijada a polímero (11 g, 15.4 mmol) (carga típica 1,4 mmol/g, preparada según Merz *J. Org. Chem.* **2001,** *66,* 2509-2511) fue dilatada en DCM seco (40 mL). Se disolvió acetoacetato de etilo (1.0 g, 7.7 mmol, CAS 141-97-9) y TEA (3.2 mL, 23.1 mmol) en DCM (10 mL) y se agregó a la solución conteniendo el polímero . Luego la mezcla resultante se agitó a temperatura ambiente bajo nitrógeno hasta que se determinó mediante TLC que la reacción estaba completa, típicamente 6 h. El sobrenadante fue filtrado, luego la resina se lavó con DCM

(3x30 mL) para enjuagar el producto residual. Luego la mezcla de reacción se evaporó hasta sequedad para proporcionar el compuesto del título (1.1 g, 92 %) como un aceite amarillo. ^{1}H NMR (400MHz, $CDCl_3$) δ 4.28 (q, 2H), 2.45 (s, 3H), 1.33 (t, 3H). Típicamente estos intermedios no fueron caracterizados debido a sus altas propiedades energéticas (Clark , *Thermochimica Ada,* 386, **2002,** 73-79), pero se llevaron a través del siguiente paso como productos crudos.

Preparación del Intermedio D:

Intermedio A: [4-(4-hidroxifenil)ciclohexilideno]acetate de tert-butilo

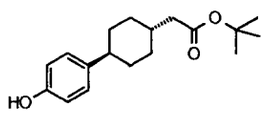


A una solución helada de 4-(4-hidroxilo-fenil)-ciclohexanone (15.22 g, 78.4 mmol, CAS 105640-07-1) en THF (375 mL) bajo N_2 se agregó NaH en aceite mineral (3.28 g, 79.3 mmol) para proporcionar una suspensión espesa.

En una matraz separada, NaH en aceite mineral (4.06 g, 98.0 mmol) se suspendió en THF seco (375 mL) bajo N_2. La suspensión se enfrió a 0 °C y se agregó cuidadosamente P,P-dimetil fosfonoacetate de tert-butilo (16.82 mL, 82.32 mmol, CAS 62327-21-3). Ambas mezclas fueron agitadas durante ~15 min antes de retirar los baños de hielo. After 2 h a temperatura ambiente the ketone solution was transferred to the ylide solution vía jeringa. The combined mixture was stirred bajo N2 durante la noche. La reacción fue apagada mediante la adición de agua (-100 mL) y THF was then removed bajo vacuum. More agua se agregó (150 mL) y the aqueous solution was extraída con EtOAc (3x200 mL). The combined organic layer was lavado con salmuera (2x200 mL) y dried through a phase separator. Concentración gave product como colorless aceite (24.6 g, 99 %).

^{J}H NMR (500 MHz, $CDCl_3$) 8 1.51 (s, 9H), 1.55-1.65 (m, 2H), 1.97-2.07 (m, 3H), 2.29-2.40 (m, 2H), 2.70-2.78 (m, 1H), 3.90-3.96 (m, 1H), 4.60 (s, 1H), 5.62 (s, 1H), 6.77 (d, 2H), 7.09 (d, 2H). *m/z* 287 (M-H)".

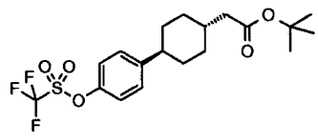
Intermedio B: [trans-4-(4-hidroxifenil)ciclohexil] acetato de tert-butilo



A una solución del Intermedio A (4.2 g, 14.56 mmol) en EtOAc (120 mL) se agregó 10 % Pd/C (390 mg). La reacción fue hidrogenada durante 3 h (5 Bar). El catalizador fue filtrado a través de Celite y el filtrado orgánico fue lavado con agua, secado a través de un separador de fase y concentrado a un aceite incoloro (4.02 g de mezcla cis:trans). La mezcla cruda fue purificada mediante HPLC quiral (neutral) utilizando una columna Chiralpak AD (250x50 mm) y 100 % ACN como fase móvil. La purificación proporcionó trans fenol puro (2.88 g, 68 %) como un sólido blanco y también cis phenol puro. El análisis NMR de ambos isómeros confirmó que el isómero deseado (principal) fue trans.

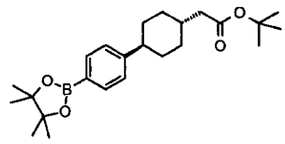
^{1}H NMR (500 MHz, $CDC1_3$) δ 1.10-1.20 (m,2H), 1.42-1.52 (m, 2H), 1.48 (s,9H), 1.77-1.92 (m, 5H), 2.17 (d, 2H), 2.38-2.45 (m, 1H), 4.7-4.9 (m, 1H), 6.78 (d, 2H), 7.09 (d, 2H); *m/z* 289 (M-H)~.

Intermedio C: [trans-4-(4-{[(trifluorometil)sulfonil]oxi}fenil) ciclohexil] acetato de tert-butilo



A una solución del Intermedio **B** (2.86 g, 9.85 mmol) en DCM (75 mL) se agregó piridina (1.59 mL, 19.7 mmol). La solución fue enfriada sobre un baño de hielo y se agregó por goteo anhidrido trifluorometanosulfónico (1.99 mL, 11.82 mmol, CAS 358-23-6) . El baño de hielo fue retirado y la reacción fue agitada durante 10 min. La reacción fue apagada con 1M HCl, diluida con DCM y lavada con $NaHCO_3$ saturado y salmuera. La capa orgánica fue secada a través de un separador de fase y concentrada. El producto crudo fue filtrado a través de sílice utilizando 8 % EtOAc en heptano como eluente. La concentración de fracciones de producto puro proporcionó el compuesto del título (4.06 g, 98 %) como sólido cristalino blanco. ^{1}H NMR (500 MHz, CDCI3) δ 1.12-1.22 (m,2H), 1.45-1.54 (m, 2H), 1.48 (s,9H), 1.79-1.88 (m, 1H), 1.89-1.95 (m, 4H), 2.17 (d, 2H), 2.48-2.56 (m, 1H), 7.20 (d, 2H), 7.28 (d, 2H); m/z 421 $(M-H)^-$.

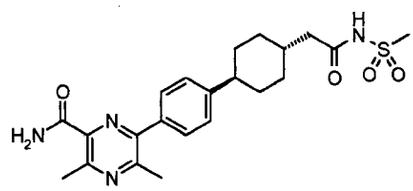
Intermedio D: {trans-4-[4-(4,4.,5.,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil]ciclohexil}acetato de tert-Butilo



A una suspensión de $PdCl_2(dppf)$ (0.93 g, 1.27 mmol, CAS 72287-26-4) en dioxano (135 mL) bajo N_2 se agregó el **Intermedio** C (17.9 g, 42.4 mmol), TEA (17.7 mL, 127 mmol) y finalmente una solución 1M de 4,4,5,5-tetrametil-l,3,2-dioxaborolano en THF (72 mL, 72 mmol, CAS 25015-63-8). La mezcla se sometió a reflujo durante 7 h, se enfrió a 10 °C y se apagó cuidadosamente con H_2O. La solución acuosa fue extraída con 2xDCM y los orgánicos combinados fueron secados mediante un separador de fase y concentrados a un aceite negro. La cromatografía flash utilizando 6 % EtOAc en heptano como eluente proporcionó el compuesto del título (12.1 g, 71 %) como polvo blanco.

^{1}H NMR (500 MHz, CDCI3) 8 1.12-1.22 (m,2H), 1.36 (s, 12H), 1.49 (s,9H), 1.48-1.61 (m, 2H), 1.80-1.95 (m, 5H), 2.17 (d, 2H), 2.46-2.54 (m, 1H), 7.25 (d, 2H), 7.78 (d, 2H). *m/z* no ionization.

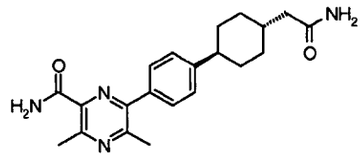
Ejemplo 2: 3,5-Dimetil-6-[4-(trans-4-{2-[(metilsulfonil)aminol-2-oxoetil} ciclohexil)fenil]pirazina-2-carboxamida



A una solución del **Ejemplo 1** (30 mg, 0.082 mmol) en DCM se agregó DMAP (2 mg, 0.02 mmol), TEA (16 uL, 0.122 mmol), EDCl (20 mg, 0.11 mmol) y finalmente metanosulfonamida (11 mg, 0.11 mmol, CAS 3144-09-0). La solución fue agitada a temperatura ambiente durante la noche. El crudo fue concentrado y purificado mediante HPLC (ácida). La Evaporación y co-evaporación con tolueno proporcionó el compuesto del título (22 mg, 60 %).

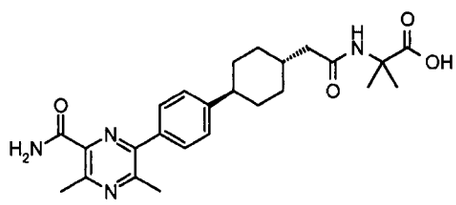
^{1}H NMR (500 MHz, $CDC1_3$) δ 1.08-1.18 (m, 2H), 1.45-1.56 (m, 2H), 1.76-1.86 (m, 5H), 2.20 (d, 2H), 2.42-2.52 (m, 1H), 2.57 (s, 3H), 2.72 (s, 3H), 3.22 (s, 3H), 7.35 (d, 2H), 7.59 (s, 1H), 7.64 (d, 2H), 7.99 (s, 1H), 11.67 (s, 1H); *m/z* 445 $(M+H)^+$.

Ejemplo 3: 6-{4-[trans-4-(2-Amino-2-oxoetil)ciclohexil]fenil}-3,5-dimetilpirazina-2-carboxamida



Este compuesto se sintetizó a partir del **Ejemplo** 1 utilizando condiciones similares como se describió en el Intermedio **1-1** para proporcionar el compuesto del título (40 mg, 38 %) como un sólido blanco. ^{1}H NMR (500 MHz, DMSO) δ 1.05-1.15 (m, 2H), 1.43-1.53 (m, 2H), 1.69-1.86 (m, 5H), 1.97 (d, 2H), 2.47-2.55 (m, 1H), 2.58 (s, 3H), 2.72 (s, 3H), 6.71 (s, 1H), 7.24 (s, 1H), 7.35 (d, 2H), 7.59 (s, 1H), 7.64 (d, 2H), 7.99 (s, 1H); *m/z* 367 $(M+H)^+$.

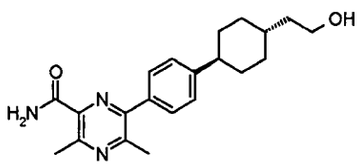
Ejemplo 4: N-({trans-4-[4-(6-Carbamoil-3,5-dimetilpirazin-2-il)fenil] ciclohexil}acetil)-2-metilalanina



Este compuesto se sintetizó a partir del **Ejemplo** 1 e hidrocloruro del éster metílico del ácido alfa-aminoisobutírico(CAS 15028-41-8) utilizando condiciones similares a aquellas en el **Intermedio 1-1.** El éster metílico intermedio fue hidrolizado al ácido correspondiente utilizando un protocolo similar al descrito en el Intermedio **1-2.**

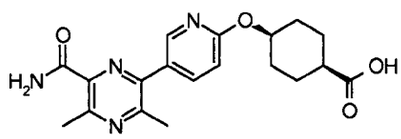
^{1}HNMR (500 MHz, DMSO) δ 1.04-1.14 (m,2H), 1.31 (s, 6H), 1.43-1.53 (m, 2H), 1.67-1.75 (m, 1H), 1.77-1.85 (m, 4H), 1.96 (d, 2H), 2.48-2.56 (m, 1H), 2.57 (s, 3H), 2.72 (s, 3H), 7.35 (d, 2H), 7.59 (br s, 1H), 7.64 (d, 2H), 7.77-7.82 (m, 1H), 8.00 (br s, 1H); *m/z* 453 $(M+H)^+$.

Ejemplo 5: 6-{4-[trans-4-(2-Hidroxietil)ciclohexil]fenil}-3,5-dimetil pirazina-2-carboxamida



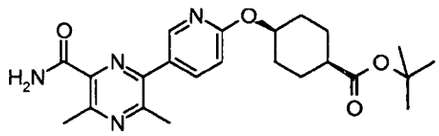
A una suspensión del **Ejemplo 1** (50 mg, 0.14 mmol) y NMM (71 uL, 0.64 mmol) en THF (1 mL) a 0 °C se agregó una solución de cloroformato de etilo (61 µL, 0.64 mmol) en THF (0.5 mL). La reacción se agitó a 0 °C durante ~ 3 h, pero equivalentes adicionales de NMM y cloroformato de etilo fueron necesarios durante este tiempo para impulsar la reacción. La mezcla de reacción se agregó por goteo a una solución de $NaBH_4$ en agua a 0-5 °C y la mezcla combinada fue agitada durante 30 min. La mezcla fue particionada entre EtOAc y 1M HCL y la capa orgánica fue lavada con agua, secada a través de un separador de fase y concentrada. El crudo fue disuelto en DMSO y purificado mediante HPLC (neutral). La liofilización de fracciones puras proporcionó el compuesto del título (8 mg, 17 %) como polvo blanco.
^{1}H NMR (500 MHz, DMSO) 8 1.02-1.14 (m, 2H), 1.34-1.54 (m, 5H), 1.80-1.87 (m, 4H), 2.47-2.57 (m, 1H), 2.58 (s, 3H), 2.73 (s, 3H), 3.43-3.51 (m, 2H), 4.30-4.35 (m, 1H), 7.35 (d, 2H), 7.60 (br s, 1H), 7.65 (d, 2H), 7.99 (br s, 1H) ; *m/z* 354 $(M+H)^+$.

Ejemplo 6: Acido cis-4-{[5-(6-Carbamoil-3,5-dimetilpirazin-2-il)piridin-2-il]oxi} ciclohexanocarboxílico



A solución de **Intermedio 6-1** (0.0243 g, 0.06 mmol) en 10 mL de una solución 4M de HCl en 1.4-dioxano y unas pocas gotas de agua se agitó a 40 °C durante 5 h. El solvente se evaporó y el sólido restante se purificó mediante HPLC (ácida) para proporcionar el compuesto del título (8.7 mg, 42 %) como una película seca.
^{1}H NMR (500 MHz, CD_3OD) 8 1.72-1.83 (m, 4H), 1.90-2.07 (m, 4H), 2.47 (m, 1H), 2.67 (s, 3H), 2.85 (s, 3H), 5.27 (s, 1H), 6.92 (d, 1H), 8.03 (dd, 1H), 8.45 (s, 1H); *m/z* 371 $(M+H)^+$.

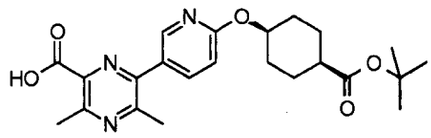
Intermedio 6-1: cis-4-{[5-(6-carbamoil-3,5-dimetilpirazin-2-il)piridin-2-il] oxi}ciclohexanocarboxilato de tert-Butilo



Este compuesto se sintetizó a partir del **Intermedio 6-2** utilizando un procedimiento similar al descrito en el **Intermedio 1-1.** La purificación proporcionó producto del título (24.3 mg, 68 %) como un sólido blanco.

^{1}H NMR (500 MHz, $CDCl_3$) 8 1.45 (s, 9H), 1.67-1.79 (m, 4H), 1.85-2.07 (m, 4H), 2.34 (m, 1H), 2.68 (s, 3H), 2.96 (s, 3H), 5.28 (s, 1H), 5.77 (s, 1H), 6.84 (d, 1H), 7.76 (s, 1H), 7.82 (dd, 1H), 8.39 (s, 1H); *m/z* 427 $(M+H)^+$.

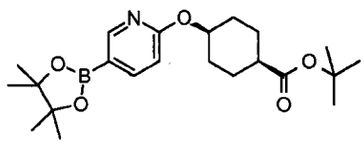
Intermedio 6-2: 6-(6-{[cis-4-ftert-Butoxicarbonil)ciclohexil]oxv}piridin-3-il)-3,5-dimetilpirazina-2-carboxílico acid



Este compuesto se sintetizó a partir del **Intermedio 6-3** y el **Intermedio 1-4** utilizando condiciones de Suzuki similares como en el **Intermedio 1-3** para proporcionar el compuesto del título (36 mg, 45 %) como un sólido blanco.

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.67-1.79 (m, 4H), 1.84-2.05 (m, 4H), 2.34 (m, 1H), 2.72 (s, 3H), 2.97 (s, 3H), 5.27 (s, 1H), 6.85 (d, 1H), 7.80 (d, 1H), 8.37 (s, 1H); *m/z* 428 $(M+H)^+$.

Intermedio 6-3: cis-4-{[5-(4,4,5.,5-tetrametil-1,3,2-dioxaborolan-2-il)piridin-2-il] oxi}ciclohexanocarboxilato de tert-Butilo

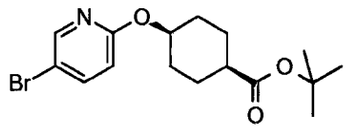


El **Intermedio 6-4** (0.124 g, 0.35 mmol), 4,4,4',4',5,5,5',5'-octametil-2,2'-bi(l,3,2-dioxaborolano) (0.121 g, 0.48 mmol, CAS 73183-34-3) y acetato de potasio (0.139 g, 1.41 mmol)

en 1,4-dioxano (10 mL) se degasificaron antes de la adición de $PdCl_2(dppf)$ (0.013 g, 0.02 mmol) bajo N_2. La reacción se calentó a 85 °C durante 16 h. El solvente fue evaporado y el crudo fue disuelto en EtOAc, lavado con agua (2x25 mL), los orgánicos se secaron sobre Na_2SO_4, se filtraron y evaporaron. El aceite pardusco castaño se purificó mediante cromatografía flash utilizando 5-50 % EtOAc en heptano para proporcionar el compuesto del título (74 mg, 52 %) como una película seca.

^{1}H NMR (500 MHz, CDC13) δ 1.30 (s, 12H), 1.43 (s, 9H), 1.59-1.77 (m, 4H), 1.80-2.00 (m, 4H), 2.29 (m ,1H), 5.25 (m, 1H), 6.67 (d, 1H), 7.88 (dd, 1H), 8.48 (d, 1H).

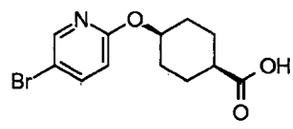
Intermedio 6-4: cis-4-[(5-bromopiridin-2-il)oxi]ciclohexano carboxilato de tert-Butilo



Una solución del **Intermedio 6-5** (0.224 g, 0.75 mmol) en l,l-di-tert-butoxi-N,N-dimetilmetanoamina (0.893 mL, 3.72 mmol, CAS 36805-97-7) se calentó a 120 °C en un horno microondas durante 45 min. El crudo fue purificado mediante cromatografía flash utilizando EtOAc (5-70 %) en heptano para proporcionar el compuesto del título (124 mg, 46 %) como un sólido blanco.

^{1}H NMR (500 MHz, $CDC1_3$) δ 1.43 (s, 9H), 1.58-1.75 (m, 4H), 1.82-2.00 (m, 4H), 2.3 (m, 1H), 5.13 (m, 1H), 6.61 (d, 1H), 7.59 (dd, 1H), 8.12 (d, 1H); *m/z* 357 $(M+H)^+$.

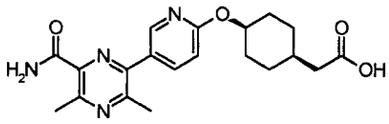
Intermedio 6-5: Acido cis-4-[(5-Bromopiridin-2-il)oxi]ciclohexanocarboxílico



Una solución de ácido (15',45)-4-hidroxi]ociclohexanocarboxílico (2.14 g, 14.9 mmol) en DMA (10 mL) se agregó to una suspensión agitada de NaH (1.32 g, 30.2 mmol) en DMA (15 mL) a 0 °C donde se agitó durante 10 min. La suspensión fue retirada del baño de enfriamiento y se agregó 5-bromo-2-fluoropiridina (1.53 mL, 14.87 mmol, CAS 766-11-0) seguido por DMA

(10 mL). La reacción se calentó a 100 °C durante 2.5 h. El solvente fue evaporado y se agregó DCM y 2M HCl , las fases se separaron y la fase acuosa fue extraída con DCM (2x50 mL). Las capas orgánicas combinadas fueron secadas sobre $MgSO_4$, filtradas y evaporadas . El crudo restante se purificó mediante cromatografía flash utilizando 5-75 % EtOAc (1 % HOAc) en heptano para proporcionar el compuesto del título (1.86 g, 42 %) como un sólido ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.70 (t, 2H), 1.75-1.86 (m, 2H), 1.90-2.06 (m, 4H), 2.49 (m, 1H), 5.18 (m, 1H), 6.64 (d, 1H), 7.62 (dd, 1H), 8.16 (d, 1H); *m/z* 301 $(M+H)^+$.

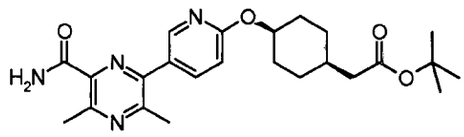
Ejemplo 7: Acido (cis-4-{[5-(6-Carbamoil-3,5-dimetilpirazin-2-il)piridin-2-il]oxi}ciclohexil)acético



Este compuesto se sintetizó a partir del **Intermedio 7-1** utilizando condiciones similares como se describió en el **Ejemplo** 1 para proporcionar el compuesto del título (15 mg, 42 %) como un sólido blanco.

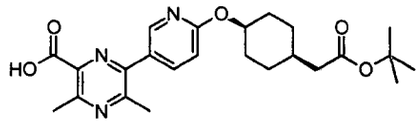
^{1}H NMR (500 MHz, CD_3OD) δ 1.51 (t, 2H), 1.61-1.75 (m, 4H), 1.91 (m, 1H), 2.05 (d, 2H), 2.25 (d, 2H), 2.66 (s, 3H), 2.84 (s, 3H), 5.29 (s, 1H), 6.91 (d, 1H), 8.02 (dd, 1H), 8.44 (s, 1H); *m/z* 385 $(M+H)^+$.

Intermedio 7-1: (cis-4-{[5-(6-Carbamoil-3,5-dimetilpirazin-2-il)piridin-2-il] oxi} ciclohexil)acetato de tert-Butilo



Este compuesto se sintetizó a partir del **Intermedio 7-2** utilizando condiciones similares como se describió en el Intermedio **1-1** para proporcionar el compuesto del título (42 mg, 66 %) como un sólido blanco. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39-1.50 (m, 11H), 1.55-1.69 (m, 4H), 1.87 (m, 1H), 2.02-2.06 (m, 2H), 2.16 (d, 2H), 2.66 (s, 3H), 2.93 (s, 3H), 5.29 (s, 1H), 6.40 (s, 1H), 6.80 (d, 1H), 7.75-7.82 (m, 2H), 8.37 (d, 1H); *m/z* 441 $(M+H)^+$.

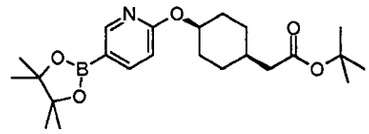
Intermedio 7-2: Acido 6-(6-{[cis-4-(2-tert-Butoxi-2-oxoetil)ciclohexil]oxi}piridin-3-il)-3,5-dimetilpirazina-2-carboxílico



Este compuesto se sintetizó a partir del Intermedio **7-3** y el Intermedio **1-4** utilizando condiciones similares como se describió en el Intermedio **1-3** para proporcionar el compuesto del título (64 mg, 44 %) como un sólido blanco.

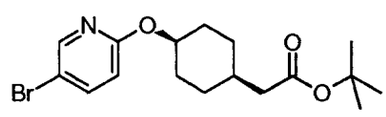
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.38-1.51 (m, 11H), 1.56-1.69 (m, 4H), 1.88 (m, 1H), 2.03 (d, 2H), 2.17 (d, 2H), 2.71 (s, 3H), 2.94 (s, 3H), 5.29 (s, 1H), 6.82 (d, 1H), 7.80 (d, 1H), 8.37 (s, 1H), 9.94 (s, 1H); *m/z* 442 $(M+H)^+$.

Intermedio 7-3: (cis-4-{[5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)piridin-2-il] oxi} ciclohexil)acetato de tert-Butilo



Este compuesto se sintetizó a partir del Intermedio **7-4** utilizando condiciones similares como se describió en el Intermedio **6-3** para proporcionar el compuesto del título (0.149 g, 43 %) como un sólido blanco. ^{1}HNMR(500MHz,$CDCl_3$) δ 1.43 (s, 12H), 1.39-1.50 (m, 11H), 1.53-1.67 (m, 4H), 1.87 (m, 1H), 2.00 (d, 2H), 2.16 (d, 2H), 5.30 (s, 1H), 6.67 (d, 1H), 7.89 (dd, 1H), 8.50 (d, 1H).

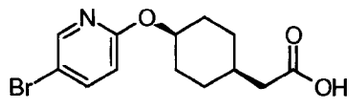
Intermedio 7-4: {cis-4- [(5-bromopiridin-2-il)oxi] ciclohexil} acetato de tert-Butilo



Este compuesto se sintetizó a partir del Intermedio **7-5** utilizando condiciones similares como se describió en el Intermedio **6-4** para proporcionar el compuesto del título (0.303 g, 43 %) como un sólido blanco.

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35-1.46 (m, 11H), 1.52-1.63 (m, 4H), 1.85 (m, 1H), 1.96 (d, 2H), 2.14 (d, 2H), 5.16 (s, 1H), 6.59 (d, 1H), 7.58 (dd, 1H), 8.13 (d, 1H); *m/z* 372 $(M+H)^+$.

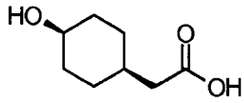
Intermedio ácido 7-5: {cis-4-[(5-Bromopiridin-2-il)oxi]ciclohexil}acético



Este compuesto se sintetizó a partir del Intermedio **7-6** utilizando condiciones similares como se describió en el Intermedio **6-5** para proporcionar el compuesto del título (1.287 g, 68 %) como un sólido blanco.

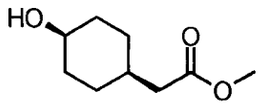
^{1}HNMR(400MHz, CDCI3) δ 1.44-1.52 (m,2H), 1.58-1.68 (m, 4H), 1.93 (m, 1H), 2.00 (d, 2H), 2.31 (d, 2H), 5.19 (s, 1H), 6.63 (d, 1H), 7.62 (dd, 1H), 8.16 (d, 1H); *m/z* 316 $(M+H)^+$.

Intermedio 7-6: Acido (cis-4-Hidroxiciclohexil)acético



Este compuesto se sintetizó a partir del Intermedio **7-7** utilizando condiciones similares como se describió en el Intermedio **1-2** para proporcionar el compuesto del título (0.943 g, 100 %) como un sólido blanco ^{1}HNMR (500 MHz, $CDCl_3$) δ 1.39-1.60 (m, 6H), 1.65-1.73 (m, 2H), 1.83 (m, 1H), 2.10 (d, 2H), 3.85 (m, 1H).

Intermedio 7-7: (cis-4-hidroxiciclohexil)acetato de metilo

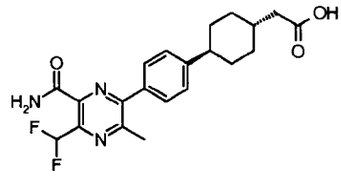


Una solución de 4-hidroxi]ofenilacetato de metilo (10.01 g, 60.2 mmol, CAS 14199-15-6), rodio (5 % sobre Alumina) (0.073 g, 0.71 mmol) en MeOH (30 mL) se hidrogenó a 8 bar. El crudo fue filtrado a través de Celite y concentrado a presión reducida. El aceite incoloro restante fue disuelto en isohexano y EtOAc y purificado mediante cromatografía flash utilizando EtOAc (20-50 %) en isohexano para proporcionar el compuesto cis del título (4.31 g, 42 %) como aceite

incoloro. Los análisis NMR de ambos isómeros trans y cis se compararon para asegurar que el isómero correcto fue utilizado en los pasos subsiguientes.

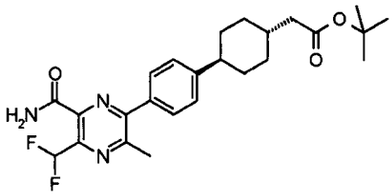
^{1}HNMR(500MHz, $CDC1_3$) δ 1.40-1.48 (m,2H), 1.48-1.62 (m, 4H), 1.66-1.74 (m, 2H), 1.86 (m, 1H), 2.24 (d, 2H), 3.66 (s, 3H), 3.97 (s, 1H).

Ejemplo 8: Acido (trans-4-{4-[6-Carbamoil-5-(difluorometil)-3-metilpirazin-2-il]fenil]ciclohexil)acético



Este compuesto se sintetizó a partir del Intermedio **8-1** utilizando condiciones similares como se describió en el **Ejemplo 1** para proporcionar el compuesto del título (3.8 mg, 31 %). ^{1}H NMR (500 MHz, CD_3OD) 8 1.17-1.30 (m, 2H), 1.54-1.67 (m, 2H), 1.80-2.00 (m, 5H), 2.24 (d, 2H), 2.56-2.65 (m, 1H), 2.74 (s, 3H), 7.42 (m, 2H), 7.67 (m, 2H), 7.79 (t, 1H); *m/z* 404 $(M+H)^+$.

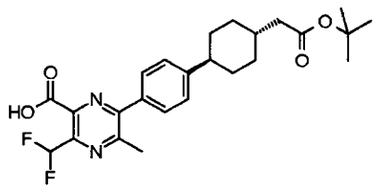
Intermedio 8-1: (trans-4-{4-r6-Carbamoil-5-(difluorometil)-3-metilpirazin-2-il] fenil}ciclohexil)acetato de tert-Butilo



Este compuesto se sintetizó a partir del Intermedio **8-2** utilizando condiciones similares como se describió en el Intermedio **1-1** para proporcionar el compuesto del título (11 mg, 44 %). ^{1}H NMR (500 MHz, $CDC1_3$) δ 1.14-1.24 (m,2H), 1.47 (s,9H), 1.51-1.63 (m, 2H), 1.80-2.01 (m, 5H), 2.18 (d, 2H), 2.53-2.62 (m, 1H), 2.81 (s, 3H), 5.72 (s, 1H), 7.37 (m, 2H), 7.56 (m, 2H), 7.84 (s, 1H), 7.97 (t, 1H); *m/z* 460 $(M+H)^+$.

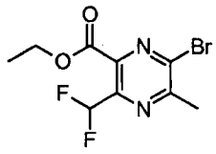
Intermedio 8-2: Acido 6-{4-[trans-4-(2-tert-Butoxi-2-oxoetil)ciclohexil]fenil}-3-(difluorometil)-5-metilpirazina-2-carboxílico acid

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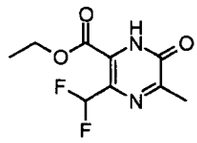
Este compuesto se sintetizó a partir del Intermedio **8-3** utilizando condiciones similares como se describió en el Intermedio **1-3** para proporcionar el compuesto del título (25 mg, 44 %).
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14-1.25 (m, 2H), 1.47 (s, 9H), 1.51-1.61 (m, 2H), 1.80-2.01 (m, 5H), 2.14-2.21 (m, 2H), 2.53-2.63 (m, 1H), 2.86 (s, 3H), 7.35-7.60 (m, 4H), 7.83 (t, 1H); *m/z* 461 $(M+H)^+$.

Intermedio 8-3: 6-bromo-3-(difluorometil)-5-metilpirazina-2-carboxilato de etilo



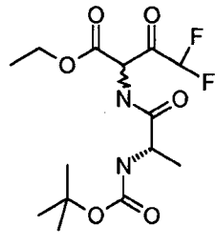
Este compuesto se sintetizó a partir del Intermedio **8-4** utilizando un procedimiento similar al descrito en el Intermedio **9-3** para proporcionar el compuesto del título (36 mg, 37 %).
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45 (t, 3H), 2.83 (s, 3H), 4.50 (q, 2H), 7.24 (t, *J*= 55 Hz, 1H); m/z 295$(M+H)^+$.

Intermedio 8-4: 3-(difluorometil)-5-metil-6-oxo-1,6-dihidropirazina-2-carboxilato de etilo



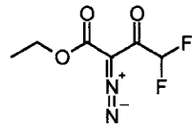
Este compuesto se sintetizó a partir del Intermedio **8-5** utilizando un procedimiento similar al descrito en el Intermedio **1-5.** El producto intermedio ciclizado fue oxidado mediante calentamiento a 120 °C durante 20 min en un horno microondas con Pd/C en HOAc para proporcionar el compuesto del título (280 mg, 38.6 %).
^{1}H NMR (500 MHz, $CDCl_3$) 8 1.46 (t, 3H), 2.59 (s, 3H), 4.51 (q, 2H), 7.36 (t, 1H, *J*= 56 Hz); *m/z* 233 $(M+H)^+$.

Intermedio 8-5: 2-{[N-ftert-butoxicarbonyl)-L-alanil]amino}-4,4-difluoro-3-oxobutanoato de etilo



Este compuesto se sintetizó a partir del Intermedio **8-6** utilizando un procedimiento similar al descrito en el Intermedio **1-6.** El crudo se utilizó directamente en el siguiente paso.

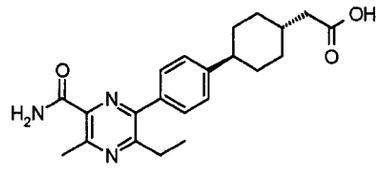
Intermedio 8-6: 2-diazo-4,4-difluoro-3-oxobutanoato de etilo



Este compuesto se sintetizó a partir de éster etílico del ácido 4,4-difluoro-3-oxo-butírico (CAS 352-24-9) y tosilazida fijada a polímero utilizando condiciones similares como se describió en el Intermedio **1-7.** El crudo se utilizó directamente en el siguiente paso.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (t, 3H), 4.35 (q, 2H), 6.59 (t, *J*= 56 Hz, 1H).

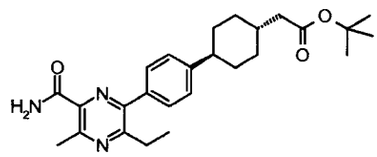
Ejemplo 9: Acido {trans-4-[4-(6-Carbamoil-3-etil-5-metilpirazin-2-il)fenil] ciclohexil]acético



Este compuesto se sintetizó a partir del Intermedio **9-1** utilizando condiciones similares como se describió en **Ejemplo** 1 para proporcionar el compuesto del título (5 mg, 29 %) como un sólido blanco.

^{1}H NMR (500MHz, $CDCl_3$) δ 1.17 (q, 2H), 1.21 (t, 3H), 1.52 (q, 2H), 1.75-1.88 (m, 1H), 1.92 (d, 4H), 2.22 (d, 2H), 2.52 (t, 1H), 2.88 (q, 2H), 2.9 (s, 3H), 6.12 (br s, 1H), 7.28 (d, 2H), 7.42 (d, 2H), 7.80 (br s, 1H); *m/z* 382 $(M+H)^+$.

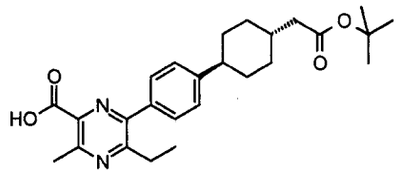
Intermedio 9-1: {trans-4-[4-(6-carbamoil-3-etil-5-metilpirazin-2-il)fenil]ciclohexil}acetato de tert-butilo



Este compuesto se sintetizó a partir del Intermedio **9-2** utilizando condiciones similares como se describió en el Intermedio **1-1** para proporcionar el compuesto del título (20 mg, 30 %) como un sólido blanco.

^{1}H NMR (400 MHz, $CDCl_3$) 8 1.18 (q, 2H), 1.26 (t, 3H), 1.46 (s, 9H), 1.48-1.62 (m, 2H), 1.78-1.87 (m, 1H), 1.94 (t, 4H), 2.16 (d, 2H), 2.55 (t, 1H), 2.93 (q, 2H), 2.98 (s, 3H), 5.65 (br s, 1H), 7.31 (d, 2H), 7.46 (d, 2H), 7.80 (s, 1H); *m/z* 438 $(M+H)^+$.

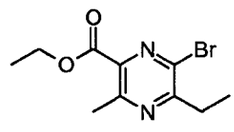
Intermedio 9-2: Acido 6-{4-[trans-4-(2-tert-Butoxi-2-oxoetil)ciclohexil]fenil}-5-etil-3-metilpirazina-2-carboxílico



Este compuesto se sintetizó a partir del Intermedio **9-3** y el Intermedio **D** utilizando condiciones de Suzuki similares como se describió en el Intermedio **1-2** para proporcionar el compuesto del título (65.7 mg, 67 % rendimiento) como un sólido blanco.

^{1}HNMR (500 MHz, $CDCl_3$) δ 1.14-1.23 (m, 2H), 1.28 (t, 3H), 1.47 (s, 9H), 1.55 (q, 2H), 1.78-1.98 (m, 6H), 2.17 (d, 2H), 2.55 (t, 1H), 2.93-3.01 (m, 5H), 7.29-7.36 (m, 2H), 7.40-7.47 (m, 2H); *m/z* 439 $(M+H)^+$.

Intermedio 9-3: 6-bromo-5-etil-3-metilpirazina-2-carboxilato de etilo

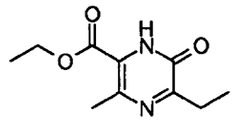


A una solución de $POBr_3$ (0.307 mL, 3.02 mmol, CAS 7789-59-5) en DCE (10 mL) se agregó el **Intermedio 9-4** (0.160 g, 0.76 mmol). La mezcla se calentó a 100 °C durante 19 h. La

reacción fue enfriada a temperatura ambiente. Se agregó NaHCO3 cuidadosamente y la mezcla fue extraída con DCM. Los extractos fueron combinados, secados sobre Na_2SO_4, filtrados y concentrados. El crudo restante se purificó mediante cromatografía flash utilizando EtOAc (0-25 %) en heptano para proporcionar el compuesto del título (60.4 mg, 29 %) como sólido amarillo pálido

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (t, 3H), 1.41 (t, 3H), 2.74 (s, 3H), 2.98 (q, 2H), 4.43 (q, 2H).

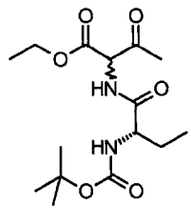
Intermedio 9-4: 5-etil-3-metil-6-oxo-l,6-dihidropirazina-2-carboxilato de etilo



Este compuesto se sintetizó a partir del Intermedio **9-5** utilizando condiciones similares como se describió en el Intermedio **1-5** para proporcionar el compuesto del título (160 mg, 21 %) como un sólido blanco.

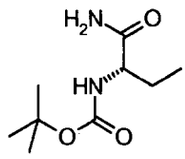
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (t, 3H), 1.39 (t, 3H), 2.61 (s, 3H), 2.85 (q, 2H), 4.40 (q, 2H).

Intermedio 9-5: 2-({(2S)-2-[(tert-butoxicarbonil)amino]butanoil} amino)-3-oxobutanoato de etilo



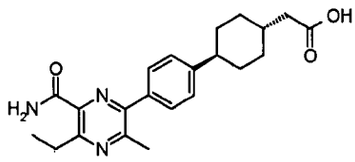
Este compuesto se sintetizó a partir del Intermedio **9-6** y el Intermedio **1-7** utilizando condiciones similares a aquellas en el Intermedio **1-6.** El residuo crudo fue llevado directamente al siguiente paso.

Intermedio 9-6: [(1S)-1-carbamoilpropil]carbamato de tert-butilo



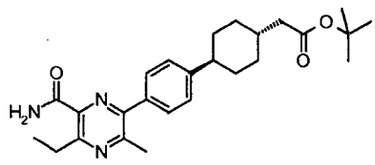
A una solución de ácido (2S)-2-[(*tert*-butoxicarbonil)amino]butanoico (1.01 g, 4.99 mmol) en DMF (5 mL) a -20 °C se agregó NMM (1.10 mL, 9.99 mmol) y cloroformado de isobutilo (1.30 mL, 9.99 mmol). La reacción fue agitada durante 10 min a -20 °C. El precipitado fue retirado mediante filtración. Se agregó solución de NH_4OH 26 %(acuosa) (0.39 mL, 9.99 mmol) y la reacción se agitó a -20 °C durante 3 h. El volumen fue reducido al vacío y se agregó hexano . Se formó un precipitado blanco después de pocos minutos . El precipitado se recolectó en un filtro y se lavó con hexano adicional. El precipitado se recristalizó a partir de EtOAc y hexano para proporcionar el compuesto del título (0.811 g, 80 %) como un sólido blanco. ^{1}H NMR (500 MHz, CD_3OD) δ 0.96 (t, 3H), 1.45 (s, 9H), 1.61 (m, 1H), 1.78 (m, 1H), 3.93 (t, 1H), 6.63 (s, 1H), 6.96 (s, 1H), 7.51 (s, 1H).

Ejemplo 10: Acido {trans-4-[4-(6-Carbamoil-5-etil-3-metilpirazin-2-il)fenil] ciclohexil]acético



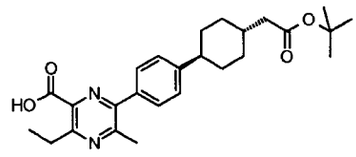
Este compuesto se sintetizó a partir de Intermedio **10-1** utilizando condiciones similares como se describió en Ejemplo 1 para proporcionar el compuesto del título (13 mg, 95 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19-1.30 (2H, m), 1.36 (3H, t), 1.52-1.65 (2H, m), 1.84-2.04 (5H, m), 2.35 (2H, d), 2.54-2.64 (1H, m), 2.73 (3H, s), 3.39 (2H, q), 7.29 (1H, s), 7.36 (2H, m), 7.52 (2H, m), 8.10 (1H, s), 8.50 (1H, br s); *m/z* 382 $(M+H)^+$.

Intermedio 10-1: {trans-4-[4-(6-carbamoil-5-etil-3-metilpirazin-2-il)fenil]ciclohexil}acetato de tert-Butilo



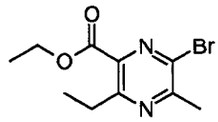
Este compuesto se sintetizó a partir del Intermedio **10-2** utilizando un procedimiento similar al descrito en el Intermedio **1-1** para proporcionar el compuesto del título (15 mg, 50 %).
^{1}H NMR (500 MHz, CDCI3) δ 1.13-1.25 (m,2H), 1.36 (t,3H), 1.47 (s,9H), 1.52-1.62 (m, 2H), 1.80-2.00 (m, 5H), 2.18 (d, 2H), 2.52-2.60 (m, 1H), 2.68 (s, 3H), 3.39 (q, 2H), 5.48 (br s, 1H), 7.33 (d, 2H), 7.52 (d, 2H), 7.81 (br s, 1H); *m/z* 438 $(M+H)^+$.

Intermedio 10-2: Acido 6-{4-[trans-4-(2-tert-Butoxi-2-oxoetil)ciclohexil]fenil}-3-etil-5-metilpirazina-2-carboxílico



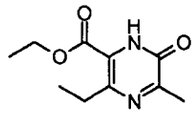
Este compuesto se sintetizó a partir del Intermedio **10-3** y el Intermedio D utilizando condiciones de Suzuki similares como se describió en el Intermedio 1-3. La purificación proporcionó el producto del título (30 mg, 62 %).
^{1}H NMR (500 MHz, $CDC1_3$) δ 1.13-1.25 (m, 2H), 1.37 (t,3H), 1.47 (s,9H), 1.52-1.62 (m, 2H), 1.80-2.00 (m, 5H), 2.18 (d, 2H), 2.53-2.61 (m, 1H), 2.74 (s, 3H), 3.42 (q, 2H), 7.36 (d, 2H), 7.51 (d, 2H), 11.21 (br s, 1H); *m/z* 439 $(M+H)^+$.

Intermedio 10-3: 6-bromo-3-etil-5-metilpirazina-2-carboxilato de etilo



Este compuesto se sintetizó a partir del Intermedio **10-4** utilizando un protocolo similar al descrito en el Intermedio **9-3** para proporcionar el compuesto del título (30 mg, 8 %).
^{1}H NMR (500 MHz, $CDC1_3$) δ 1.30 (t, 3H), 1.42 (t, 3H), 2.71 (s, 3H), 3.06 (q, 2H), 4.45 (q, 2H); *m/z* 275 $(M+H)^+$.

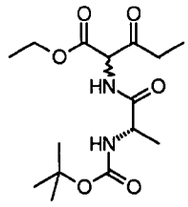
Intermedio 10-4: 3-etil-5-metil-6-oxo-l,6-dihidropirazina-2-carboxilato de etilo



Este compuesto se sintetizó a partir del Intermedio **10-5** utilizando un protocolo similar al descrito en el Intermedio **1-5. La** purificación proporcionó el compuesto del título (0.340 g, 67 %) como un aceite amarillo brillante.

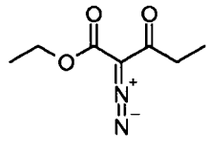
^{1}H NMR (500 MHz, $CDC1_3$) δ 1.23 (t, 3H), 1.43 (t, 3H), 2.54 (s, 3H), 3.02 (q, 2H), 4.44 (q, 2H), 9.20 (br s, 1H); *m/z* 211 $(M+H)^+$.

Intermedio 10-5: N-(tert-butoxicarbonil)-L-alanil-3-oxonorvalinato de etilo



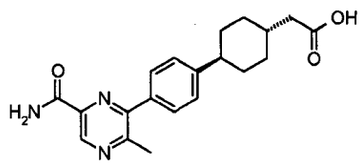
Este compuesto se sintetizó a partir del Intermedio **10-6** utilizando condiciones similares como se describió en el Intermedio **1-6.** El producto crudo (1 g, 46 %) fue llevado directamente al siguiente paso. *m/z* 331 $(M+H)^+$.

Intermedio 10-6: 2-diazo-3-oxopentanoato de etilo



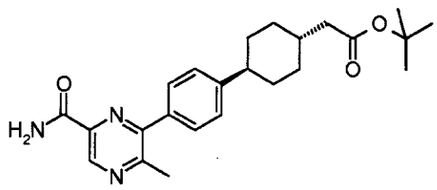
Este compuesto se sintetizó a partir de propionilacetato de etilo (CAS 4949-44-4) y tosilazida fijada a polímero utilizando un protocolo similar al descrito en el Intermedio **1-7.** El material crudo (0.9 g, 95 %) fue llevado directamente al siguiente paso.

Ejemplo 11: Acido {trans-4-[4-(6-Carbamoil-3-metilpirazin-2-il)fenil]ciclohexil} acético



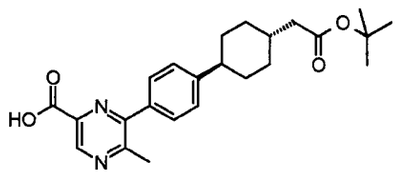
Este compuesto se sintetizó a partir del Intermedio **11-1** utilizando condiciones similares como se describió en **Ejemplo** 1 para proporcionar el compuesto del título (16 mg, 53 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15-1.25 (m, 2H), 1.51-1.61 (m, 2H), 1.83-2.00 (m, 5H), 2.26 (d, 2H), 2.53-2.61 (m, 1H), 2.71 (s, 3H), 7.34 (d, 2H), 7.51 (d, 2H), 9.18 (s, 1H); *m/z* 354 $(M+H)^+$.

Intermedio 11-1: {trans-4-[4-(6-Carbamoil-3-metilpirazin-2-il)fenil]ciclohexil}acetato de tert-Butilo



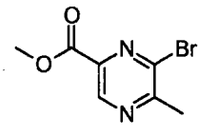
Este compuesto se sintetizó a partir del Intermedio **11-2** utilizando condiciones similares como se describió en el Intermedio **1-1.** El crudo fue llevado directamente al siguiente paso. *m/z* 410$(M+H)^+$.

Intermedio 11-2: Acido 6-{4-[trans-4-(2-tert-Butoxi-2-oxoetil)ciclohexil]fenil}-5-metilpirazina-2-carboxílico



Este compuesto se sintetizó a partir del Intermedio **11-3** y el Intermedio **D** utilizando condiciones de Suzuki similares como se describió en el Intermedio **1-3.** La purificación proporcionó el compuesto del título (410 mg, 66 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15-1.26 (m,2H), 1.48 (s,9H), 1.52-1.62 (m, 2H), 1.81-2.00 (m, 5H), 2.19 (d, 2H), 2.54-2.61 (m, 1H), 2.78 (s, 3H), 7.37 (d, 2H), 7.53 (d, 2H), 9.26 (s, 1H); *m/z* 411 $(M+H)^+$.

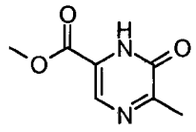
Intermedio 11-3: 6-bromo-5-metilpirazina-2-carboxilato de metilo



Este compuesto se sintetizó a partir del Intermedio **11-4** utilizando condiciones similares como se describió en el Intermedio **9-3** para proporcionar el compuesto del título (0.493 mg, 54 %).

^{1}H NMR (500 MHz, $CDC1_3$) δ 2.78 (s, 3H), 4.02 (s, 3H), 9.10 (s, 1H); *m/z* 233 $(M+H)^+$.

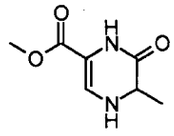
Intermedio 11-4: 5-metil-6-oxo-l,6-dihidropirazina-2-carboxilato de metilo



A una solución del **Intermedio 11-5** (0.98 g, 5.76 mmol) en DCM (180 mL) se agregó trióxido de azufre fijado a polímero (7.3 g, 3 eq, CAS 26412-87-3). La mezcla fue agitada a temperatura ambiente durante 4 días. El polímero fue filtrado y lavado con porciones de DCM. La concentración del filtrado proporcionó el compuesto del título (0.8 g, 80 %) como un sólido amarillo

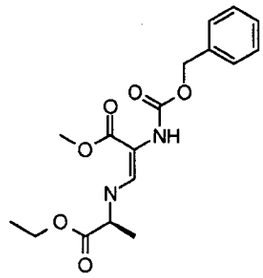
^{1}H NMR (500 MHz, $CDC1_3$) δ 2.56 (s, 3H), 4.00 (s, 3H), 7.94 (s, 1H); *m/z* 169 $(M+H)^+$.

Intermedio 11-5: 5-metil-6-oxo-l,4,5,6-tetrahidropirazina-2-carboxilato de metilo



A una solución del Intermedio **11-6** (3.0 g, 8.56 mmol) en EtOH (250 mL) bajo N_2 se agregó 10 % Pd/C (1.35 g) y formato de amonio (2.43 g, 38.5 mmol). La solución fue agitada a temperatura ambiente durante 90 min. El alcohol se retiró al vacio y el residuo negro se disolvió en EtOAc y se filtró a través de Celite. La concentración del filtrado proporcionó el compuesto del título (1.2 g, 80 %). *m/z* 171 $(M+H)^+$.

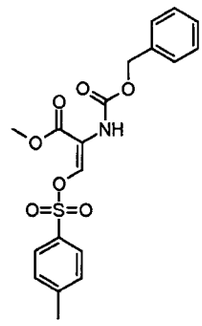
Intermedio 11-6: N-[(lZ)-2-{[(benziloxi)carbonil]amino}-3-metoxi-3-oxoprop-1-en-1-il]-L-alaninato de etilo



Una solución del **Intermedio 11-7** (0.450 g, 0.78 mmol), Hidrocloruro del éster etílico de L-alanina (0.179, 1.17 mmol, CAS 1115-59-9) y TEA (0.33 mL, 2.33 mmol) en MeOH (10 mL) fue agitada a temperatura ambiente durante la noche. El residuo fue concentrado, disuelto en EtOAc (50 mL) y lavado con salmuera (2x25 mL). La capa orgánica fue secada a través de un separador de fase y concentrada. El residuo crudo se purificó mediante cromatografía flash utilizando un gradiente de EtOAc (30-50 %) en heptano como eluente. Las fracciones de producto crudo se concentraron para proporcionar el compuesto del título (230 mg, 85 %) como un aceite incoloro.

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24-1.33 (m, 6H), 3.70 (s, 3H), 3.94-4.02 (m, 1H), 4.22 (q, 2H), 5.16 (s, 2H), 5.75 (br s, 1H), 6.13 (br s, 1H), 7.25 (d, 1H), 7.30-7.45 (m, 5H); *m/z* 351 $(M+H)^+$.

Intermedio 11-7: (2Z)-2-{r(benziloxi)carbonil]amino}-3-{[(4-metilfenil)sulfonil]oxi]acrilato de metilo

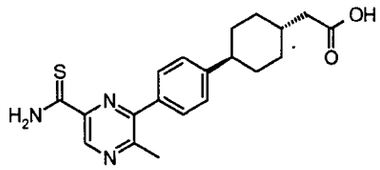


A una solución pre-enfriada (-30 °C) de DMF:DMSO (1:1, 200 mL) bajo nitrógeno se agregó TsCl (76.3 g, 0.4 mol) en porciones pequeñas durante 30 min. NOTA: Esta reacción es

altamente exotérmica y el control cuidadoso de la temperatura es esencial. La solución se agitó a -10 °C durante 10 min, luego nuevamente llevada a -30 °C. Se agregó por goteo una solución de éster metílico de cbz-L-serina (20.3 g, 0.08 mol, CAS 1676-81-9) en DMF, nuevamente con control cuidadoso de la temperatura. Después de agitar durante 10 min a -30 °C, se agregó trietilamina (110 mL, 0.79 mol) y la reacción fue llevada lentamente a 0 °C y mantenida a esta temperatura durante 2 h. La reacción fue apagada mediante la adición de agua helada. La solución fue extraída con 3xEtOAc, luego la capa orgánica combinada fue lavada ampliamente con salmuera y agua. El secado y evaporación proporcionó el producto como un aceite amarillo (30 g, 94 %).

^{1}H NMR (500 MHz, $CDCl_3$) 8 2.47 (s, 3H), 3.77 (s, 3H), 5.11 (s, 2H), 6.01 (br s, 1H), 7.32-7.41 (m, 7H), 7.48 (s, 1H), 7.84 (d, 2H); *m/z* 406 $(M+H)^+$.

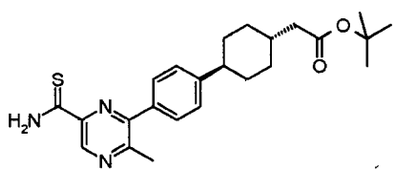
Ejemplo 12: Acido (trans-4-{4-[6-(Aminocarbonotioil)-3-metilpirazin-2-il]fenil}ciclohexil)acético



Este compuesto se sintetizó a partir del Intermedio **12-1** utilizando un procedimiento similar como en el **Ejemplo 1** para proporcionar el compuesto del título (46 mg, 100%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20-1.34 (m, 2H), 1.50-1.67 (m, 2H), 1.92 (s, 1H), 2.0 (d, 4H), 2.37 (d, 2H), 2.60 (t, 1H), 2.78 (s, 3H), 7.38 (d, 2H), 7.53 (d, 2H), 7.83 (s, 1H), 9.18 (s, 1H), 9.67 (s, 1H); *m/z* 370 $(M+H)^+$.

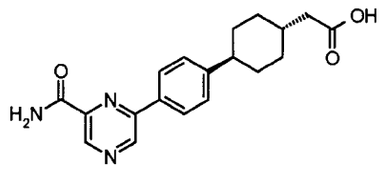
Intermedio 12-1: (trans-4-{4-[6-(aminocarbonotioil)-3-metilpirazin-2-il]fenil}ciclohexil)acetato de tert-Butilo



Una solución del **Ejemplo 11** (40 mg, 0.10 mmol) y Reactivo de Lawesson (39.5 mg, 0.10 mmol) en tolueno:THF (3:1 mL) se calentó a 80 °C durante la noche. Se agregó una cantidad adicional (0.5 eq) de Reactivo de Lawesson se seguido por calentamiento continuado durante otra 1 h. La mezcla de reacción fue concentrada y purificada mediante cromatografía flash utilizando EtOAc (10-30 %) en éter de petróleo como eluente para proporcionar el compuesto del título (37 mg, 89 %) como polvo levamente amarillento.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12-1.25 (m, 3H), 1.45 (s,9H), 1.50-1.60 (m, 1H), 1.83 (s, 1H), 1.93 (t, 4H), 2.15 (d, 2H), 2.54 (t, 1H), 2.70 (s, 3H), 7.33 (d, 2H), 7.50 (d, 2H), 7.54 (s, 1H), 9.21 (s, 1H), 9.64 (s, 1H); *m/z* 426 $(M+H)^+$.

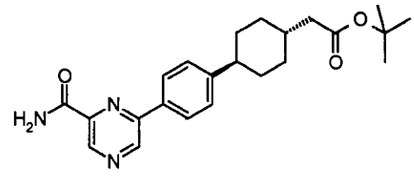
Ejemplo 13: Acido {trans-4-[4-(6-Carbamoilpirazin-2-il)fenil]ciclohexil}acético



Este compuesto se sintetizó a partir del Intermedio **13-1** utilizando un procedimiento similar como se describió en el **Ejemplo** 1 para proporcionar el compuesto del título (0.5 g, 95 %).

^{1}H NMR (500 MHz, DMSO) δ 1.08-1.19 (m, 2H), 1.47-1.57 (m, 2H), 1.71-1.87 (m, 5H), 2.15 (d, 2H), 2.52-2.58 (m, 1H), 7.40 (d, 2H), 8.27 (d, 2H), 9.06 (s, 1H), 9.40 (s, 1H); *m/z* 340 $(M+H)^+$.

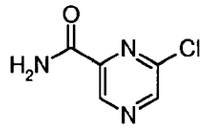
Intermedio 13-1: {trans-4-[4-(6-Carbamoilpirazin-2-il)fenil]ciclohexil]acetato de tert-butilo



Este compuesto se sintetizó a partir del Intermedio **13-2** y el Intermedio **D** utilizando las condiciones de Suzuki similares como se describió en el Intermedio **1-3.** Este proporcionó el compuesto del título (570 mg, 45 %) como un sólido amarillo claro.

^{1}H NMR (500 MHz, $CDC1_3$) δ 1.14-1.24 (m, 2H), 1.47 (s, 9H), 1.51-1.61 (m, 2H), 1.81-1.98 (m, 5H), 2.18 (d, 2H), 2.53-2.61 (m, 1H), 5.67 (br s, 1H), 7.39 (d, 2H), 7.77 (br s, 1H), 7.96 (d, 2H), 9.18 (s, 1H), 9.32 (s, 1H); *m/z* 396 $(M+H)^+$.

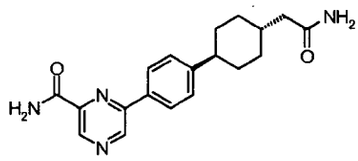
Intermedio 13-2: 6-cloropirazina-2-carboxamida



Una solución de ácido 6-cloro-pirazina-carboxílico (2.00 g, 12.62 mmol) en DMF (7 mL) se enfrió a -40 °C. Se agregó NMP (2.77 mL, 25.23 mmol) y cloroformato de isobutilo 3.27 mL, 25.23 mmol). La temperatura se dejo aumentar a -20 °C during 20 min y luego se agregó NH_4OH. Rapidamente se formó un precipitado y después de 15 minutos éste se filtró y lavó con agua. La cristalización a partir de EtOH proporcionó el compuesto del título (670 mg, 34 %) como agujas castade color café claro .

^{1}H NMR (500 MHz, DMSO) δ 7.93 (br s, 1H), 8.24 (br s, 1H), 8.99 (s, 1H), 9.12 (s, 1H).

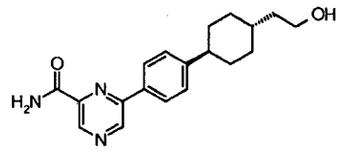
Ejemplo 14: 6-{4-[trans-4-(2-Amino-2-oxoetil)ciclohexil]fenil}pirazina-2-carboxamida



Este compuesto se sintetizó a partir del **Ejemplo** 13 utilizando condiciones similares como se describió en el **Intermedio 1-1.** Un procedimiento de tratamiento final acuoso proporcionó rendimiento bajo y no se recomienda aquí (4 mg, 10%).

^{1}H NMR (500 MHz, DMSO) δ 1.05-1.17 (m, 2H), 1.45-1.56 (m, 2H), 1.71-1.87 (m, 5H),1.99 (d, 2H), 2.50-2.59 (m, 1H), 6.71 (s, 1H), 7.25 (s, 1H), 7.39 (d, 2H), 7.88 (s, 1H), 8.26 (d, 2H), 8.40 (s, 1H), 9.07 (s, 1H), 9.39 (s, 1H); *m/z* 339 $(M+H)^+$.

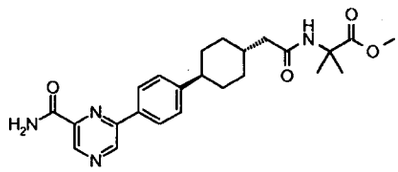
Ejemplo 15:6- {4- [trans-4-(2-Hidroxietil)ciclohexil] fenil}pirazina-2-carboxamida



Este compuesto se sintetizó a partir del **Ejemplo** 13 utilizando condiciones similares a aquellas en el **Ejemplo** 5 para proporcionar el compuesto del título (3 mg, 11 %) como un sólido blanco.

^{1}NMR (500 MHz, THF) δ 1.11-1.21 (m, 2H), 1.47 (q, 2H), 1.52-1.63 (m, 3H), 1.90-1.98 (m, 4H), 2.55-2.64 (m, 1H), 3.33 (br s, 1H), 3.56-3.63 (m, 2H), 7.09 (br s, 1H), 7.40 (d, 2H), 7.95 (br s, 1H), 8.15 (d, 2H), 9.18 (s, 1H), 9.26 (s, 1H); *m/z* 326 $(M+H)^+$.

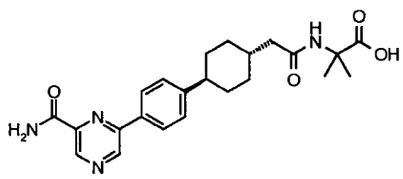
Ejemplo 16: N-({trans-4-[4-(6-carbamoilpirazin-2-il)fenil]ciclohexil} acetil)-2-metilalaninato de metilo



Este compuesto se sintetizó a partir del **Ejemplo 13** e hidrocloruro de éster metílico del ácido alpha-aminoisobutírico utilizando condiciones similares a aquellas en el Intermedio **1-1.** La purificación proporcionó el compuesto del título (40 mg, 76 %).

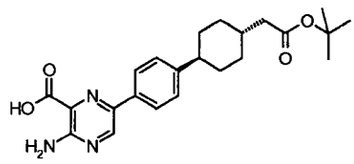
^{1}H NMR (500 MHz, $CDC1_3$) δ 1.13-1.23 (m,2H), 1.52-1.62 (m, 2H), 1.58 (s,6H), 1.86-1.98 (m, 5H), 2.11 (d, 2H), 2.52-2.61 (m, 2H), 3.76 (s, 3H), 5.71 (br s, 1H), 6.02 (br s, 1H), 7.38 (d, 2H), 7.77 (br s, 1H), 7.96 (d, 2H), 9.18 (s, 1H), 9.32 (s, 1H); *m/z* 439 $(M+H)^+$.

Ejemplo 17: N-({trans-4-[4-(6-Carbamoilpirazin-2-il)fenil]ciclohexil}acetil) -2-metilalanina



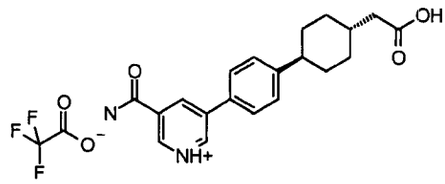
El éster metílico del **Ejemplo 16** fue hidrolizado al ácido correspondiente utilizando un protocolo similar al descrito en el Intermedio **1-2** para proporcionar el compuesto del título (21 mg, 72 %) como un sólido blanco.

^{1}H NMR (500 MHz, DMSO) δ 1.04-1.14 (m, 2H), 1.31 (s, 6H), 1.43-1.53 (m, 2H), 1.69-1.85 (m, 5H), 1.99 (d, 2H), 2.48-2.57 (m, 2H), 7.39 (d, 2H), 7.87 (br s, 1H), 7.98 (s, 1H), 8.26 (d, 2H), 8.42 (br s, 1H), 9.06 (s, 1H), 9.39 (s, 1H), 12.0 (s, 1H); *m/z* 425 $(M+H)^+$.



Este compuesto se sintetizó a partir de éster metílico del ácido 3-amino-6-bromo-pirazina-2-carboxílico (CAS 6966-01-4) y el Intermedio **D** utilizando el protocolo de Suzuki similar al descrito en el Intermedio **1-3.** Crudo no fue aislado, *m/z* 412 $(M+H)^+$.

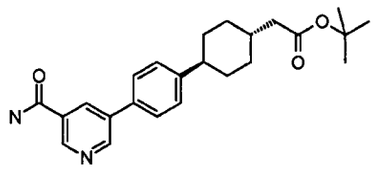
Ejemplo 19: Trifluoroacetato de 3-Carbamoil-5-{4-[trans-4-(carboximetil)ciclohexil]fenil}piridinio



Este compuesto se sintetizó a partir del Intermedio **19-1** utilizando un procedimiento similar como se describió en el **Ejemplo** 1. La evaporación rindió el compuesto del título (22 mg, 69 %) como un polvo blanco.

TiNMR (600 MHz, DMSO) 8 1.12 (2H, q), 1.50 (2H, q), 1.74 (1H, s), 1.82 (4H, d), 2.13 (2H, d), 2.51 (1H, t); *m/z* 339 $(M+H\text{-}TFA)^+$.

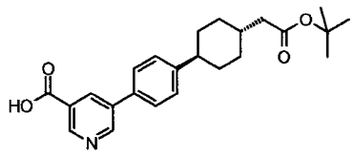
Intermedio 19-1: {trans-4-[4-(5-carbamoilpiridin-3-il)fenil] ciclohexil]acetato de tert-Butilo



Este compuesto se sintetizó a partir del Intermedio **19-2** utilizando condiciones de reacción similares como se describió en el Intermedio **1-1.** La purificación proporcionó el compuesto del título (40 mg, 37 %) como un polvo blanco.

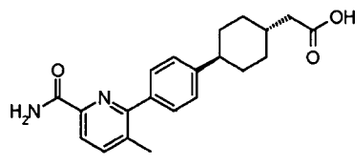
^{1}HNMR (400 MHz, $CDC1_3$) 8 0.78-1.70 (13H, m), 1.83 (1H, s), 1.91 (4H, t), 2.15 (2H, d), 2.52 (1H, t), 5.68 (1H, s), 6.28 (1H, s), 7.33 (2H, d), 7.54 (2H, d), 8.39 (1H, t), 8.95 (1H, s), 8.99 (1H, s); *m/z* 395 $(M+H)^+$.

Intermedio 19-2: Acido 5-{4-[trans-4-(2-tert-Butoxi-2-oxoetil)ciclohexil]fenil} nicotínico



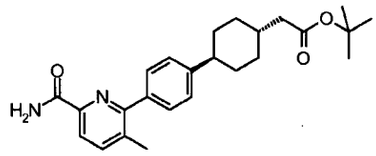
Este compuesto se sintetizó a partir de ácido 5-bromonicotínico (CAS 20826-04-4) y el Intermedio **D** utilizando el protocolo de suzuki similar al descrito en el Intermedio **1-3.** La purificación proporcionó el compuesto del título (230 mg, 74 %) como un sólido blanco. ^{1}H NMR (400 MHz, CD_3OD) 8 1.18 (2H, q), 1.44 (9H, s), 1.55 (2H,q), 1.81 (1H, s), 1.89 (4H, t), 2,14 (2H, d), 2.53 (1H, t), 7.34 (2H, d), 7.59 (2H, d), 8.50 (1H, t), 8.76 (1H, d), 8.97 (1H, d); *m/z* 396 $(M+H)^+$.

Ejemplo 20: Acido {trans-4-[4-(6-Carbamoil-3-metilpiridin-2-il)fenil]ciclohexil} acético



Este compuesto se sintetizó a partir del Intermedio **20-1** utilizando condiciones similares como se describió en el **Ejemplo 1** para proporcionar el compuesto del título (11 mg, 85 %). ^{1}H NMR (400MHz, $CDCl_3$) δ 1.02-1.18 (m, 2H), 1.37-1.51 (m, 2H), 1.62-1.82 (m, 5H), 2.08 (d, 2H), 2.32 (s, 3H), 2.40-2.51 (m, 1H), 7.27 (d, 2H), 7.49 (d, 3H), 7.81 (d, 2H), 7.86 (s, 1H); *m/z* 353 $(M+H)^+$.

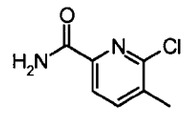
Intermedio 20-1: {trans-4-[4-(6-carbamoil-3-metilpiridin-2-il)fenil]ciclohexil}acetato de tert-Butilo



Este compuesto se sintetizó a partir del Intermedio **20-2** y el Intermedio **D** utilizando el protoloco de Suzuki similar al Intermedio **1-3.** La purificación proporcionó el producto del título (15 mg, 21%).

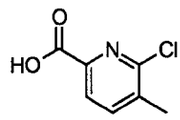
^{1}H NMR (400MHz, $CDCl_3$) δ 1.09-1.30 (m, 2H), 1.45 (s, 9H), 1.48-1.61 (m, 2H), 1.76-1.98 (m, 5H), 2.15 (d, 2H), 2.41 (s, 3H), 2.48-2.57 (m, 1H), 5.60 (s, 1H), 7.29 (d, 2H), 7.45 (d, 2H), 7.71 (d, 1H), 7.87 (s, 1H), 8.04 (d, 1H).

Intermedio 20-2: 6-cloro-5-metilpiridina-2-carboxamida



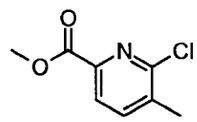
A una solución del Intermedio **20-3** (112 mg, 0.65 mmol) en DCM (5 mL) se agregó PyBROP (457 mg, 0.98 mmol), NH_4Cl (70 mg, 1.30 mmol) y DIPEA (0.43 mL, 2.61 mmol). La mezcla de reacción fue agitada a temperatura ambiente for 2 h. Después de dilución con DCM (15 mL) la solución fue lavada con $NaHCO_3$ saturado (2x15 mL) y agua (15 mL), se secó a través de un separador de fase y se evaporó. El producto crudo se purificó mediante cromatografía flash utilizando EtOAc en heptano como eluente. Fracciones puras fueron evaporadas hasta sequedad para proporcionar el compuesto del título (83 mg, 74 %).
^{1}H NMR (400 MHz, DMSO) 8 2.35 (s, 3H), 7.63 (s, 1H), 7.85-7.90 (m, 3H); *m/z* 171 $(M+H)^+$.

Intermedio 20-3: Acido 6-Cloro-5-metilpiridina-2-carboxílico acid



Este compuesto se sintetizó a partir del correspondiente Me-éster utilizando un protocolo similar al descrito en el Intermedio **1-2** para proporcionar el compuesto del título (0.11 g, 80 %); *m/z* 172 $(M+H)^+$.

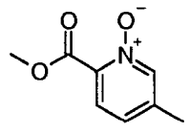
Intermedio 20-4: 6-cloro-5-metilpiridina-2-carboxilato de metilo



Una solución del **Intermedio 20-5** (1.67g, 9.99mmol) en POCL3 (15 mL) se calentó a reflujo durante 3 h. Después de enfriar a RT, la mezcla de reacción se agregó a una solución de agua

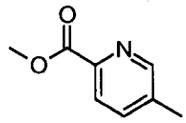
helada, se basificó con 1M NaOH (aq) y se extrajo con DCM (3x30 mL). Las capas orgánicas fueron combinadas, pasadas a través de un separador de fase y evaporadas. El producto crudo se purificó mediante cromatografía flash utilizando EtOAc (15 %) en heptano como eluente. Las fracciones puras fueron evaporadas hasta sequedad para proporcionar el compuesto del título (0.73 g, 39 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 3.97 (s, 3H), 7.67 (d, 1H), 7.96 (d, 1H); *m/z* 186$(M+H)^+$.

Intermedio 20-5: 5-metilpiridina-2-carboxilato-1-oxido de metilo



A una solución del Intermedio **20-6** (2.11 g, 14.0 mmol) en DCM (40 mL) se agregó *m*-CPBA (4.70 g, 21.0 mmol) y la reacción fue agitada a temperatura ambiente durante 5 h. Se agregó Na_2SO_2 saturado (15 mL) y la reacción fue agitada durante 5 min. Las dos fases fueron separadas y la fase orgánica fue lavada con 1M $NaHCO_3$, pasadas a través de un separador de fase y evaporadas. El producto crudo fue llevado al siguiente paso sin purificación adicional, *m/z* 168 $(M+H)^+$.

Intermedio 20-6: 5-metilpiridina-2-carboxilato de metil

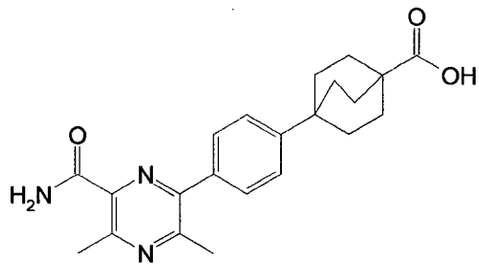


A una solución de 2,5-dimetilpiridina (3.00 g, 28.0 mmol, CAS 589-93-5) en piridina (15 mL) se agregó dióxido de selenio (4.66 g, 42.0 mmol, CAS 7446-08-4). La mezcla de reacción se calentó a reflujo durante la noche. Después enfriar a temperatura ambiente un solido fue filtrado y lavado con agua y piridina (2x5 mL/lavado). El filtrado fue evaporado y el crudo tomado nuevamente en metanol (100 mL). Se agregó ácido sulfúrico (1.34 mL, 25.0 mmol) y la mezcla de reacción se calentó a reflujo durante 5 h. Después de enfriar a temperatura ambiente la mezcla de reacción fue alcalinizada con NaOH al 20% (acuoso). El metanol fue evaporado y se agregó agua (50 mL). Esta mezcla fue extraída con DEE (3 x 100 mL). Los orgánicos combinados

fueron secados (Na_2SO_4) y evaporados para proporcionar el compuesto del título (2.11 g, 50 %) como un aceite de color café claro.

^{1}H NMR (400 MHz, $CDC1_3$) δ 2.40 (s, 3H), 3.97 (s, 3H), 7.61 (d, 1H), 8.01 (d, 1H), 8.54 (s, 1H).

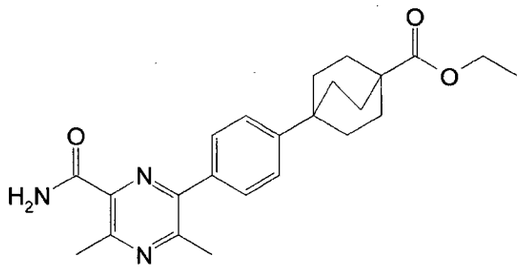
Ejemplo 21: Acido 4-(4-(6-Carbamoil-3,5-dimetilpirazin-2-il)fenil)biciclo[2.2.21octano-1-carboxílico



Se agregó hidróxido de potasio en polvo (204 mg, 3.63 mmol) en una porción al **Intermedio 21-1** (493 mg, 1.21 mmol) en tert-butanol (10 mL) a 40 °C bajo nitrógeno. La suspensión resultante se agitó a 45 °C durante 5 h, se formó una suspensición de precipitado blanca espesa. Se agregó ácido acético (0.346 mL, 6.05 mmol) y la solución resultante se agitó durante varios minutos antes de ser particionada entre EtOAc (100 mL) y ácido cítrico 1N (50 mL). La suspensión fue filtrada y secada para proporcionar el producto deseado como un sólido blanco (300 mg), la fase orgánica fue separada, secada sobre MgSO4, filtrada y evaporada para proporcionar el producto crudo como un aceite incoloro el cual se solidificó al sentar. El filtrado fue purificado mediante HPLC preparativa (Columna Waters XBridge Prep C18 OBD, sílice 5μ, 50 mm de diámeter, 150 mm de longitud), utilizando mezclas decrecientemente polares de agua (conteniendo ácido fórmico al 0.1%) y MeCN como eluentes. Las fracciones conteniendo el compuesto deseado fueron evaporadas hasta sequedad y combinadas con el sólido para proporcionar el compuesto del título (376 mg, 82 %) como un sólido blanco.

^{1}H NMR (400 MHz, DMSO) δ 1.84 (12H, s), 2.58 (3H, s), 2.73 (3H, s), 7.46 (2H, d), 7.57 (1H, s), 7.66 (2H, d), 7.98 (1H, s), 12.08 (1H, s); *m/z* 380 $(M+H)^+$.

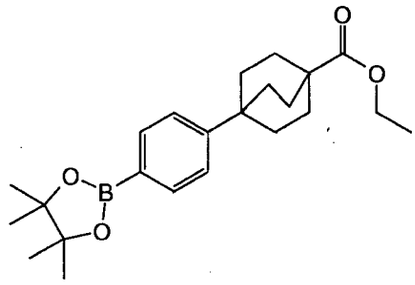
Intermedio 21-1: 4-(4-(6-Carbamoil-3,5-dimetilpirazin-2-il)fenil)biciclo[2.2.21octano-l-carboxilato de etilo



Una solución del **Intermedio 21-2** (525 mg, 1.37 mmol), **Intermedio 21-4** (254 mg, 1.37 mmol), y trifosfato de potasio (348 mg, 1.64 mmol) en DME (15 mL), EtOH (5 mL) y agua (2 mL) se degasificaron antes de la adición de (1,1'-Bis(difenilfosfino)ferrocene)-dicloropaladio(II) (aducto de DCM) (56.2 mg, 0.07 mmol). La mezcla de reacción fue calentada a 80 °C, bajo nitrógeno, y dejada agitar a 80 °C durante 2 h. La mezcla de reacción fue dejada enfriar a temperatura ambiente y luego evaporada. El producto crudo fue particionado entre EtOAc (100 mL) y agua (50 mL), filtrado a través de Celite y la fase orgánica fue separada, lavada con salmuera saturada (50 mL). La capa orgánica fue secada sobre $MgSO_4$, filtrada y evaporada para proporcionar el producto crudo. El producto crudo se purificó mediante cromatografía flash de sílice, gradiente de elución entre 20 y 50% EtOAc en isohexano. Las fracciones puras fueron evaporadas hasta sequedad para proporcionar el compuesto del título (493 mg, 89 %) como un sólido blanco.

^{1}H NMR (400 MHz, DMSO) δ 1.18 (3H, t), 1.85 (12H, s), 2.58 (3H, s), 2.73 (3H, s), 4.05 (2H, q), 7.46 (2H, d), 7.57 (1H, s), 7.66 (2H, d), 7.97 (1H, s); *m/z* 408 $(M+H)^+$.

Intermedio 21-2: 4-(4-(4,4,5-,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)biciclo[2.2.21octano-l-carboxilato de etilo

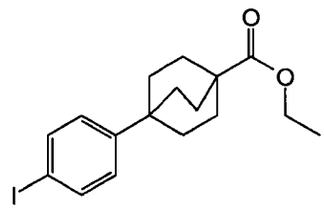


A una solución degasificada del **Intermedio 21-3** (1.66 g, 4.32 mmol) en DMSO (30 mL) se agregó acetato de potasio (1.272 g, 12.96 mmol) y bis(pinacolato)diboro (1.207 g, 4.75 mmol),

la mezcla de reacción fue degasificada durante 20 minutos más. Se agregó (1,1'-Bis(difenilfosfino)ferroceno)-dicloropaladio(II) (aducto de DCM) (0.212 g, 0.26 mmol) y la suspensión fue degasificada y luego calentada, bajo nitrógeno a 80 °C durante 3 h. La mezcla de reacción fue dejada enfriar, vertida en agua (125 mL), la suspensión fue filtrada y el sólido fue purificado mediante cromatografía flash de sílice, gradiente de elución entre 0 y 20% EtOAc en isohexano. Las fracciones puras fueron evaporadas hasta sequedad para proporcionar el compuesto del título (1.080 g, 65.0 %) como un sólido blanco.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (3H, t), 1.33 (12H, s), 1.84 - 1.93 (12H, m), 4.12 (2H, q), 7.33 (2H, d), 7.75 (2H, d); *m/z* (EI+) 384 M^+.

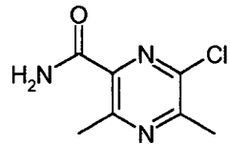
Intermedio 21-3: 4-(4-yodofenil)biciclo[2.2.2]octano-1-carboxilato de etilo



Se agregó [Bis(trifluoroacetoxi)yodo]benceno (3.78 g, 8.78 mmol) y yodo (1.061 g, 4.18 mmol) a una solución agitada de 4-fenilbiciclo[2.2.2]octano-l-carboxilato de etilo (preparada según el procedimiento descrito en WO 2007/071966) (2.16 g, 8.36 mmol, CAS 10207-26-8) en $CHCl_3$ (50 mL). La solución resultante se agitó a temperatura ambiente durante 90 minutos. La mezcla de reacción fue vertida en tiosulfato de sodio (100 mL), extraída con DCM (2 x 100 mL), la capa orgánica fue lavada con tiosulfato de sodio acuoso (2 x 80 mL), separada, secada sobre $MgSO_4$, filtrada y evaporada para proporcionar un aceite amarillo el cual se solidificó al sentar. El producto crudo se purificó mediante cromatografía flash de sílice, gradiente de elución entre 0 y 20% EtOAc en isohexano. Las fracciones puras fueron evaporadas hasta sequedad para proporcionar el compuesto del título (2.78 g, 87 %) como un sólido blanco.

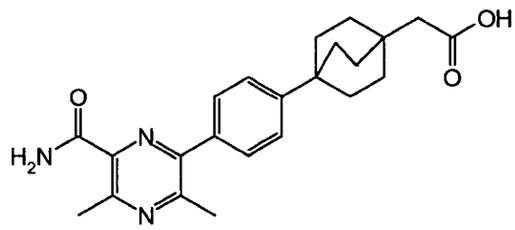
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (3H, t), 1.79 - 1.84 (6H, m), 1.88 - 1.93 (6H, m), 4.11 (2H, q), 7.05 (2H, d), 7.61 (2H, d); *m/z* 385 $(M+H)^+$.

Intermedio 21-4: 6-Cloro-3,5-dimetilpirazina-2-carboxamida



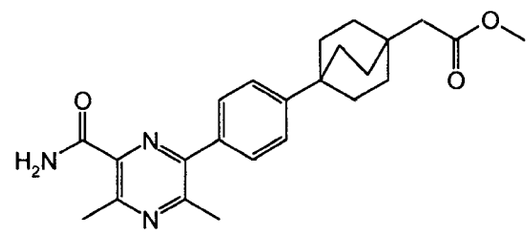
El **Intermedio 1-4** (227 g, 1057.54 mmol) fue agitado en amoniaco (7N en MeOH) (1957 mL, 89633.59 mmol) a temperatura ambiente durante la noche. La mezcla fue evaporada hasta sequedad y el residuo fue triturado con éter y la suspensión fue filtrada a 40 °C al vacío para proporcionar el compuesto del título (181 g, 92 %) como un sólido castaño claro ^{1}H NMR (400 MHz, DMSO) δ 2.59 (3H, s), 2.67 (3H, s), 7.70 (1H, s), 7.99 (1H, s) *m/z* 186 $(M+H)^+$.

Ejemplo 22: Acido 2-(4-(4-(6-Carbamoil-3,5-dimetilpirazin-2-il)fenil)biciclo-[2.2.21 octan-1-il)acético



Este compuesto se sintetizó a partir del Intermedio **22-1** utilizando condiciones similares como se describió en el Ejemplo **21** para proporcionar el compuesto del título (292 mg, 77 %) como un sólido blanco. ^{1}H NMR (400 MHz, DMSO) δ 1.60 - 1.65 (6H, m), 1.80 - 1.84 (6H, m), 2.05 (2H, s), 2.58 (3H, s), 2.72 (3H, s), 7.45 (2H, d), 7.56 (1H, s), 7.64 (2H, d), 7.97 (1H, s), 11.91 (1H, s); *m/z* 394 $(M+H)^+$.

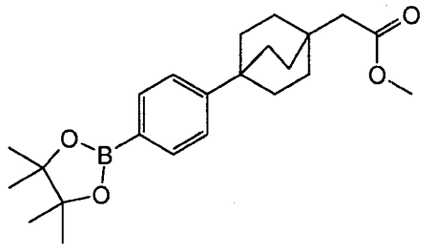
Intermedio 22-1: 2-(4-(4-(6-Carbamoil-3,5-dimetilpirazin-2-il)fenil)biciclo[2.2.21octan-l-il)acetato de metilo



Este compuesto se sintetizó a partir del Intermedio **21-4** y el Intermedio **22-2** utilizando condiciones similares como se describió en el Intermedio **21-1** para proporcionar el compuesto del título (392 mg, 96 %) como un sólido blanco.

^{1}H NMR (400 MHz, DMSO) δ 1.57 - 1.63 (6H, m), 1.80 - 1.86 (6H, m), 2.15 (2H, s), 2.58 (3H, s), 2.73 (3H, s), 3.58 (3H, s), 7.44 (2H, d), 7.57 (1H, s), 7.64 (2H, d), 7.97 (1H, s); *m/z* 408 $(M+H)^+$.

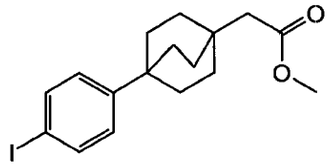
Intermedio 22-2: 2-(4-(4-(4,4,5,5-tetrametil-l,3v2-dioxaborolan-2-il)fenil)biciclo[2.2.21octan-l-il)acetato de metilo



Este compuesto se sintetizó a partir del Intermedio **22-3** utilizando condiciones similares como se describió en el Intermedio **21-2** para proporcionar el compuesto del título (0.701 g, 55.6 %) como un sólido blanco.

^{1}H NMR (400, $CDCl_3$) δ 1.33 (12H, s), 1.62 - 1.66 (6H, m), 1.82 - 1.87 (6H, m), 2.16 (2H, s), 3.65 (3H, s), 7.32 (2H, d), 7.74 (2H, d); *m/z* (EI+) 384 M^+.

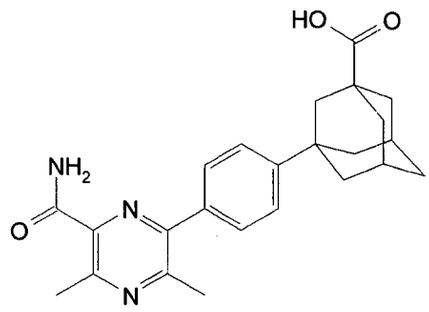
Intermedio 22-3: 2-(4-(4-iodofenil)biciclo[2.2.2] octan-l-il)acetato de metilo



Este compuesto se sintetizó a partir de 2-(4-fenilbiciclo[2.2.2]octan-l-il)acetato de metilo (preparado según el procedimiento descrito en WO 2007/071966, CAS 70631-58-2) utilizando condiciones similares como se describió en el Intermedio **21-3** para proporcionar el compuesto del título (1.320 g, 80 %) como un sólido blanco.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62 - 1.66 (6H, m), 1.77 - 1.82 (6H, m), 2.16 (2H, s), 3.66 (3H, s), 7.05 (2H, d), 7.59 (2H, d); *m/z* (EI+) 384 M^+.

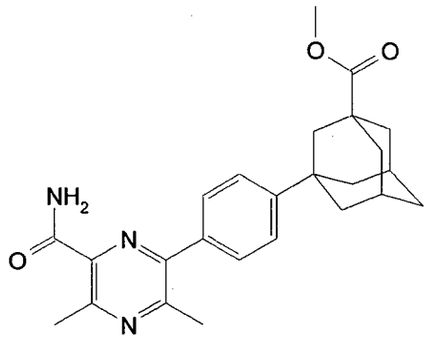
Ejemplo 23: Acido 3-[4-(6-Carbamoil-3,5-dimetilpirazin-2-il)fenil] adamantano-1-carboxílico



Este compuesto se sintetizó a partir del Intermedio **23-1** utilizando condiciones similares como se describió en **Ejemplo 21.** Excepto que después de 70 minutos la mezcla de reacción fue dejada enfriar y se agregó ácido cítrico 1N (15 mL), el precipitado se recolectó mediante filtración, se lavó ácido cítrico 1N (10 mL), agua (10 mL) y se secó al vacío para proporcionar el compuesto del título (360 mg, 90 %) como un sólido blanco.

^{1}H NMR (400 MHz, DMSO) δ 1.69 - 1.73 (2H, m), 1.84 - 1.89 (8H, m), 1.96 (2H, s), 2.17 - 2.19 (2H, m), 2.59 (3H, s), 2.74 (3H, s), 7.50 (2H, d), 7.59 (1H, s), 7.68 (2H, d), 7.98 (1H, s), 12.07 (1H, s); *m/z* 406 $(M+H)^+$.

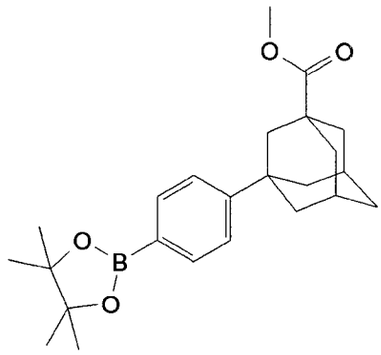
Intermedio 23-1: Metil 3-(4-(6-Carbamoil-3,5-dimetilpirazin-2-il)fenil]adamantano-l-carboxilato



Este compuesto se sintetizó a partir del Intermedio **21-4** y el Intermedio **23-2** utilizando condiciones similares como se describió en el Intermedio **21-1** para proporcionar el compuesto del título (412 mg, 74.3 %) como un sólido blanco.

^{1}H NMR (400 MHz, DMSO) δ 1.70 - 1.73 (2H, m), 1.85 - 1.91 (8H, m), 1.98 (2H, s), 2.18 - 2.20 (2H, m), 2.58 (3H, s), 2.73 (3H, s), 3.60 (3H, s), 7.49 (2H, d), 7.58 (1H, s), 7.68 (2H, d), 7.97 (1H, s); *m/z* 420 $(M+H)^+$.

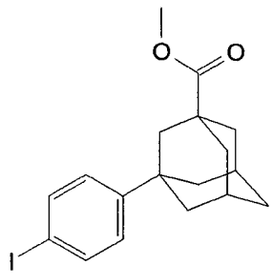
Intermedio 23-2: 3-[4-(4,4,5,5-tetrametil-l,3,2-dioxaborolan-2-il)fenil]adamantano-l-carboxilato de metilo



Este compuesto se sintetizó a partir del Intermedio **23-3** utilizando condiciones similares como se describió en el Intermedio **21-2** para proporcionar el compuesto del título (1.758 g, 63.9 %) como un sólido blanco.

^{1}H NMR (400 MHz, $CDC1_3$) δ 1.33 (12H, s), 1.73 - 1.75 (2H, m), 1.88 - 1.95 (8H, m), 2.05 (2H, s), 2.21 - 2.25 (2H, m), 3.67 (3H, s), 7.37 (2H, d), 7.77 (2H, d); *m/z* 396 (EI+) M^+.

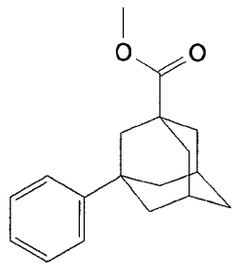
Intermedio 23-3: 3-(4-iodofenil)adamantano-l-carboxilato de metilo



Este compuesto se sintetizó a partir del Intermedio **23-4** utilizando condiciones similares como se describió en el Intermedio **21-3** para proporcionar el compuesto del título (2.75 g, 88 %) como un aceite incoloro.

^{1}H NMR (400 MHz, $CDCl_3$) 8 1.72 - 1.74 (2H, m), 1.89 - 1.95 (8H, m), 1.99 (2H, s), 2.22 - 2.24 (2H, m), 3.67 (3H, s), 7.11 (2H, d), 7.63 (2H, d); *m/z* 396 (EI+) M^+.

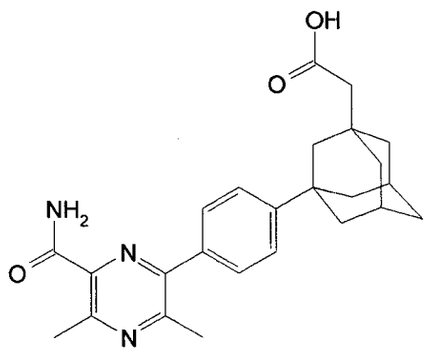
Intermedio 23-4: 3-feniladamantano-l-carboxilato de metilo



Se agregó una solución de trimetilsilildiazometano 2M en hexano (8.15 mL, 16.31 mmol) por goteo a una solución agitada de ácido 3-fenil-l-adamantano carboxílico (2.09 g, 8.15 mmol, CAS 37589-22-3) en tolueno (20 mL) y metanol (10 mL) durante un periodo de 2 minutos. La solución resultante se agitó a temperatura ambiente durante 60 minutos. La mezcla de reacción fue evaporada para proporcionar el producto crudo. El producto crudo se purificó mediante cromatografía flash de sílice, gradiente de elución entre 0 y 20% EtOAc en isohexano. Las fracciones puras fueron evaporadas hasta sequedad para proporcionar el compuesto del título (2.140 g, 97 %) como un aceite incoloro.

^{1}H NMR (400 MHz, $CDCl_3$) 8 1.73 - 1.75 (2H, m), 1.90 - 1.93 (8H, m), 2.04 (2H, s), 2.22 -2.25 (2H, m), 3.67 (3H, s), 7.17 - 7.21 (1H, m), 7.30 - 7.38 (4H, m); *m/z* 270 (EI+) M^+.

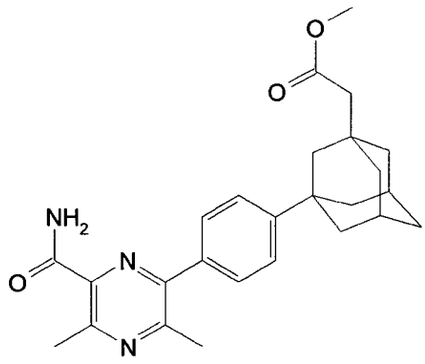
Ejemplo 24: Acido 2-[3-[4-(6-Carbamoil-3,5-dimetilpirazin-2-il)fenil]-l-adamantil]-acético



Este compuesto se sintetizó a partir del Intermedio **24-1** utilizando condiciones similares como se describió en **Ejemplo 21** para proporcionar el compuesto del título (126 mg, 62.0 %) como un sólido blanco.

^{1}H NMR (400 MHz, DMSO) δ 1.62 -1.71 (6H, m), 1.75 (2H,s), 1.81 - 1.88 (4H, m), 2.07 (2H, s), 2.15 (2H, s), 2.59 (3H, s), 2.73 (3H, s), 7.47 (2H, d), 7.58 (1H, s), 7.67 (2H, d), 7.97 (1H, s), 11.89 (1H, s); *m/z* 420 $(M+H)^+$.

Intermedio 24-1: 2-[3-[4-(6-carbamoil-3,5-dimetilpirazin-2-il)fenil]-l-adamantil] acetato de metilo

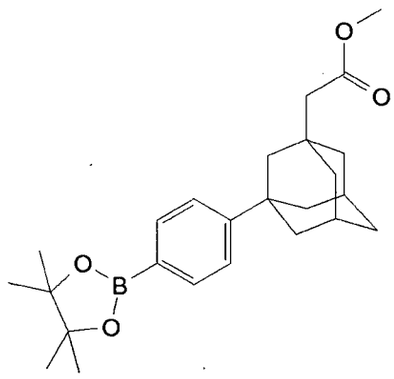


Este compuesto se sintetizó a partir del Intermedio **21-4** y el Intermedio **24-2** utilizando condiciones similares como se describió en el Intermedio **21-1** para proporcionar el compuesto del título (210 mg, 48.4 %) como un aceite incoloro el cual se solidificó al sentar.

^{1}H NMR (400 MHz, DMSO) 8 1.60 - 1.70 (6H, m), 1.73 (2H, s), 1.81-1.89 (4H, m), 2.14 - 2.16 (2H, m), 2.16 (2H, s), 2.59 (3H, s), 2.74 (3H, s), 3.57 (3H, s), 7.47 (2H, d), 7.58 (1H, s), 7.68 (2H, d), 7.97 (1H, s); *m/z* 434 $(M+H)^+$.

Intermedio 24-2: 2-(3-[4-(4,4,5,5-tetrametil-l,3,2-dioxaborolan-2-il)fenil]-1-adamantil]acetato de metilo

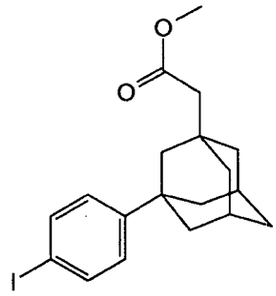
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Este compuesto se sintetizó a partir del Intermedio **24-3** utilizando condiciones similares como describió en el Intermedio **21-2** para proporcionar el compuesto del título (1.240 g, 76 %) como un sólido blanco.

^{1}H NMR (400 MHz, $CDCl_3$) 8 1.33 (12H, s), 1.61-1.72 (6H, m), 1.75 (2H, s), 1.82 - 1.90 (2H, m), 2.17 (2H, s), 2.17 - 2.20 (4H, m), 3.64 (3H, s), 7.36 (2H, d), 7.77 (2H, d); *m/z* 410 (EI+) M^+.

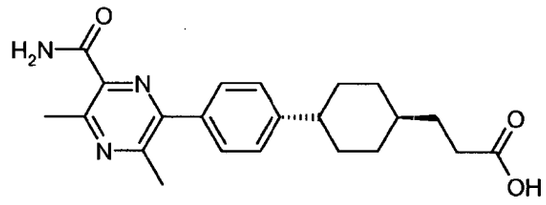
Intermedio 24-3: 2-[3-(4-yodofenil)-l-adamantil]acetato de metilo



Este compuesto se sintetizó a partir de 2-(3-fenil-l-adamantil)acetato de metilo(CAS 175721-57-0, preparado según el procedimiento descrito en WO 2007/071966 utilizando condiciones similares como se describió en el Intermedio **21-3** para proporcionar el compuesto del título (1.680 g, 81 %) como un aceite amarillo el cual se solidificó al sentar.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62 - 1.71 (8H, m), 1.78 - 1.84 (4H, m), 2.16 (2H, s), 2.17 -2.20 (2H, m), 3.65 (3H, s), 7.09 (2H, d), 7.62 (2H, d); *m/z* 410 (EI+) M^+.

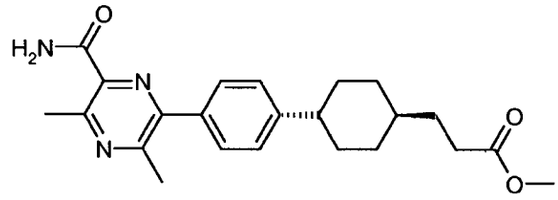
Ejemplo 25: Acido 3-((lr,4r)-4-(4-(6-Carbamoil-3,5-dimetilpirazin-2-il)fenil)ciclohexil)propanóico



Este compuesto se sintetizó a partir del Intermedio **25-1** utilizando condiciones similares como se describió en el Ejemplo **21.** Excepto que el producto crudo se purificó mediante cristalización a partir de EtOH en bullición (-10 mL) para proporcionar el compuesto del título (180 mg, 65.3 %) como un sólido rojo claro

^{1}H NMR (400 MHz, DMSO) δ 1.02 - 1.11 (2H, m), 1.27 - 1.36 (1H, m), 1.43 - 1.53 (4H, m), 1.81-1.87 (4H, m), 2.25 (2H, t), 2.51 - 2.55 (1H, m), 2.58 (3H, s), 2.73 (3H, s), 7.35 (2H, d), 7.57 (1H, s), 7.64 (2H, d), 7.97 (1H, s), 11.97 (1H, s); *m/z* 382 $(M+H)^+$.

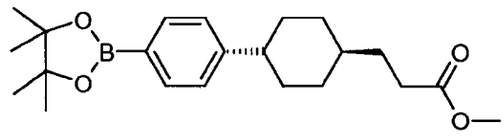
Intermedio 25-1: 3-((1r,4r)-4-(4-(6-Carbamoil-3,5-dimetilpirazin-2-il)fenil)ciclohexil)propanoato de metilo



Se agregó acetonitrilo (4.345 mL) a paladio dicloruro de 1,1 bis(di-tert-butilfosfino)ferroceno (57.7 mg, 0.10 mmol) y se agitó a temperatura ambiente durante 5 min antes de la adición de carbonato de potasio (540 mg, 3.91 mmol), agua (4.35 mL) y el Intermedio **25-2** (728 mg, 1.96 mmol). Después de 5 minutos adicionales se agregó el **Intermedio 21-4** (364 mg, 1.96 mmol) y la mezcla de reacción se calentó a 80 °C durante 5 horas. La mezcla de reacción se particionó entre EtOAc (100 mL) y agua (50 mL) y se filtró a través de Celite, lavando con EtOAc (50 mL). La capa orgánica fue secada sobre MgSO4, filtrada y evaporada para proporcionar el producto crudo. El producto crudo se purificó mediante cromatografía flash de sílice, gradiente de elución entre 0 y 50% EtOAc en isohexano. Las fracciones puras fueron evaporadas hasta sequedad para proporcionar el compuesto del título (286 mg, 37.0 %) como un sólido castaño rojo

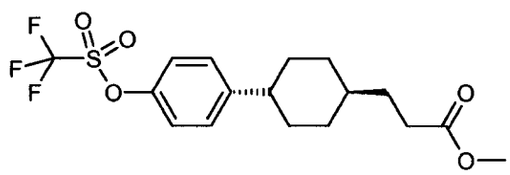
^{1}H NMR (400 MHz, DMSO) δ 1.02 - 1.13 (3H, m), 1.26 - 1.37 (1H, m), 1.42 - 1.53 (4H, m), 1.80 - 1.88 (4H, m), 2.35 (2H, t), 2.58 (3H, s), 2.74 (3H, s), 3.59 (3H, s), 7.34 (2H, d), 7.57 (1H, s), 7.64 (2H, d), 7.96 (1H, s); *m/z* 396 $(M+H)^+$.

Intermedio 25-2: 3-((1r,4r)-4-(4-(4,4,5,5-tetrametil-l,3,2-dioxaborolan-2-il)phenil)ciclohexil)propanoato de metilo



A solución del **Intermedio 25-3** (4.40 g, 11.16 mmol) en dioxano (85 mL) fue degasificada con nitrógeno durante un periodo de 5 minutos. Se agregó acetato de potasio (3.28 g, 33.47 mmol), 4,4,4',4',5,5,5',5-octametil-2,2'-bi(l,3,2-dioxaborolano) (3.12 g, 12.27 mmol), (1,1'-Bis(difenilfosfino)ferroceno)-dicloropaladio(II) (aducto de DCM) (0.551 g, 0.67 mmol) y 1,l'-Bis(difenilfosfino)ferroceno (0.375 g, 0.67 mmol). La mezcla resultante se agitó a 85 °C bajo nitrógeno durante 17 horas. La mezcla de reacción fue concentrada y diluida con EtOAc (200 mL), y luego la mezcla fue filtrada a través de Celite. El filtrado fue lavado con salmuera saturada, la capa orgánica fue secada sobre MgSO4, filtrada y evaporada para proporcionar el producto crudo. El producto crudo se purificó mediante cromatografía flash de sílice, gradiente de elución entre 0 y 20% EtOAc en isohexano. Las fracciones puras fueron evaporadas hasta sequedad para proporcionar el compuesto del título (2.68 g, 64.5 %>) como un sólido blanco. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 - 1.13 (2H, m), 1.31-1.33 (1H, m), 1.33 (12H, s), 1.40 - 1.52 (2H, m), 1.59 (2H, q), 1.84 - 1.92 (4H, m), 2.36 (2H, t), 2.43 - 2.52 (1H, m), 3.68 (3H, s), 7.21 (2H, d), 7.73 (2H, d); *m/z* 372 (EI+) M^+.

Intermedio 25-3: 3-((1r,4r)-4-(4-(trifluorometilsulfoniloxi)fenil)-ciclohexil)propanoato de metilo

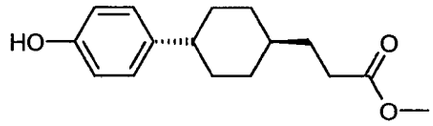


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Se agregó trietilamina (2.59 mL, 18.57 mmol) a una solución agitada del **Intermedio 25-4** (3.27 g, 12.46 mmol) y anhidrido trifluorometanosulfónico (2.56 mL, 15.58 mmol) en DCM (120 mL) enfriada a 0 °C, durante un periodo de 5 minutos bajo nitrógeno. La solución roja resultante se agitó a 0 °C durante 2 horas y luego se dejo calentar a temperatura ambiente durante la noche. La mezcla de reacción fue diluida con DCM (100 mL), y lavada secuencialmente con agua (100 mL), $NaHCO_3$ saturado (100 mL), y salmuera saturada (100 mL). La capa orgánica fue secada sobre $MgSO_4$, filtrada y evaporada para proporcionar el producto crudo. El producto crudo se purificó mediante cromatografía flash de sílice, gradiente de elución entre 0 y 20% EtOAc en isohexano. Las fracciones puras fueron evaporadas hasta sequedad para proporcionar el compuesto del título (4.42 g, 90 %) como un aceite amarillo.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 - 1.11 (2H, m), 1.29 - 1.35 (1H, m), 1.37 - 1.47 (2H, m), 1.58 (2H, q), 1.88 - 1.91 (4H, m), 2.36 (2H, t), 2.46 - 2.53 (1H, m), 3.68 (3H, s), 7.15 -7.19 (2H, m), 7.23 - 7.27 (2H, m); *m/z* 394 (EI+) M^+.

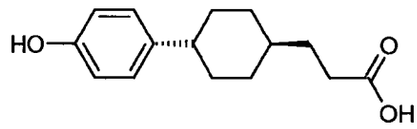
Intermedio 25-4: 3-((lr,4r)-4-(4-hidroxifenil)ciclohexil)propanoato de metilo



Una solución del **Intermedio 25-5** (3.82 g, 15.38 mmol) en MeOH (100 mL) y H_2SO4 concentrado (1.0 mL) se agitó a 70 °C durante 3 horas y se dejo enfriar a temperatura ambiente durante la noche. La mezcla de reacción fue evaporada hasta sequedad y redisuelta en EtOAc (200 mL) y lavado con salmuera saturada (2 x 150 mL). La capa orgánica fue secada sobre MgSO4, filtrada y evaporada para proporcionar el producto crudo. El producto crudo se purificó mediante cromatografía flash de sílice, gradiente de elución entre 0 y 20% EtOAc en isohexano. Las fracciones puras fueron evaporadas hasta sequedad para proporcionar el compuesto del título (3.27 g, 81 %>) como un sólido blanco.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 - 1.12 (2H, m), 1.26 - 1.33 (1H, m), 1.35 - 1.45 (2H, m), 1.58 (2H, q), 1.83 - 1.89 (4H, m), 2.36 (2H, t), 2.35 - 2.44 (1H, m), 3.68 (3H, s), 4.62 (1H, s), 6.73 - 6.77 (2H, m), 7.04 - 7.08 (2H, m); *m/z* 262 (EI+) M^+.

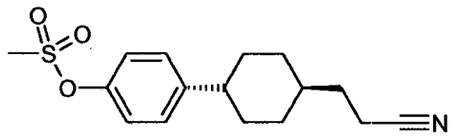
Intermedio 25-5: Acido 3-((1r,4r)-4-(4-Hidroxifenil)ciclohexil)propanóico



Una solución del **Intermedio 25-6** (5.49 g, 17.86 mmol) e hidróxido de sodio (10a.71 g, 267.88 mmol) en 1,2-propanediol (65 mL) y agua (16 mL) se calentó a 140 °C durante 1 hora. La mezcla de reacción se dejo enfriar temperatura ambiente, se ajustó a pH 2 con 2M HCl y la suspensión se extrajo en EtOAc (2 x 200 mL). Los extractos orgánicos fueron combinados, lavados con salmuera saturada (200 mL), secados sobre MgSO4, filtrados y evaporados para proporcionar el producto crudo. Este se convirtió en pasta aguada en isohexano (120 mL), se filtró y se secó al aire para proporcionar el compuesto del título (3.87 g, 86 %) como un sólido blanco, el cual se utilizó sin purificación adicional.

^{1}H NMR (400 MHz, DMSO) δ 0.95 - 1.05 (2H, m), 1.16 - 1.39 (3H, m), 1.44 (2H, q), 1.73 - 1.79 (4H, m), 2.23 (2H, t), 2.29 - 2.38 (1H, m), 6.62 - 6.66 (2H, m), 6.98 (2H, d), 9.03 (1H, s), 11.92 (1H, s); *m/z* 247 (M-H)".

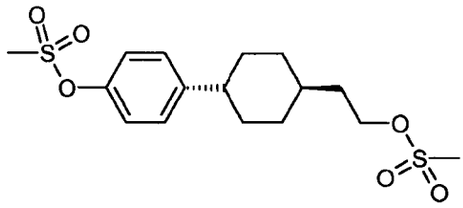
Intermedio 25-6: 4-((1r,4r)-4-(2-Cianoetil)ciclohexil)fenil-metanosulfonato



Se agregó cianuro de sodio (1.669 g, 34.06 mmol) a una solución agitada del **Intermedio 25-7** (8.55 g, 22.71 mmol) en DMF (153 mL). La mezcla resultante se agitó a 80 °C durante 3 h y luego se dejo enfriar a temperatura ambiente. La mezcla de reacción fue diluida con EtOAc (150 mL), y lavada con salmuera saturada (2 x 250 mL). La capa orgánica fue secada sobre $MgSO_4$, filtrada y evaporada para proporcionar el producto deseado. Esta aún contenía DMF de manera que se disolvió nuevamente en en EtOAc (150 mL), y se lavó con salmuera saturada (2 x 200 mL), la capa orgánica fue secada sobre $MgSO_4$, filtrada y evaporada para proporcionar el producto crudo. El producto crudo se purificó mediante cromatografía flash de sílice, gradiente de elución entre 30 y 60% EtOAc en isohexano. Las fracciones puras fueron evaporadas hasta sequedad para proporcionar el compuesto del título (4.08 g, 58.4 %) como un sólido blanco.

^{1}H NMR (400 MHz, $CDC1_3$) δ 1.06 - 1.16 (2H, m), 1.41-1.52 (3H, m), 1.54 (3H, s), 1.64 (2H, q), 1.89 - 1.95 (4H, m), 2.40 (2H, t), 2.47 - 2.53 (1H, m), 3.13 (3H, s), 7.18 - 7.24 (4H, m); *m/z* 307 (EI+) M^+.

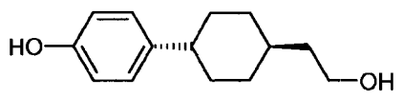
Intermedio 25-7: 4-((1r,4r)-4-(2-(Metilsulfoniloxi)etil)ciclohexil))fenil metanosulfonato



Se agregó cloruro de metanosulfonilo (6.56 mL, 84.58 mmol) a una suspensión agitada del **Intermedio 25-8** (8.47 g, 38.45 mmol) y trietilamina (11.79 mL, 84.58 mmol) en DCM (300 mL). La solución resultante se agitó a temperatura ambiente durante 16 h. La mezcla de reacción fue lavada con salmuera saturada (100 mL), la capa orgánica fue secada sobre $MgSO_4$, filtrada y evaporada para proporcionar el producto crudo. El producto crudo se purificó mediante cromatografía flash de sílice, gradiente de elución entre 20 y 70% EtOAc en isohexano. Las fracciones puras fueron evaporadas hasta sequedad para proporcionar el compuesto del título (13.84 g, 96 %>) como un sólido blanco.

^{1}H NMR (400 MHz, DMSO) δ 0.99 - 1.15 (2H, m), 1.32-1.51 (3H, m), 1.62 (2H, q), 1.75 -1.87 (4H, m), 2.52 - 2.56 (1H, m), 3.16 (3H, s), 3.27 (3H, 3), 4.26 (1H, t), 7.22 - 7.26 (2H, m), 7.31 - 7.35 (2H, m); *m/z* 399 $(M+Na)^+$.

Intermedio 25-8: 4-((1r,4r)-4-(2-Hidroxietil)ciclohexil)fenol

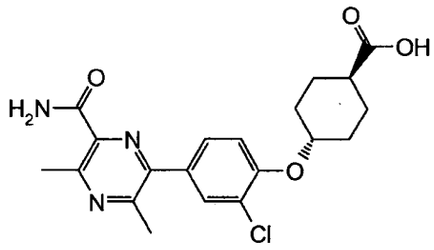


Una solución 1M de aluminio hidruro de litio en THF (80 mL, 79.75 mmol) se agregó por goteo a una solución agitada de 2-((lr,4r)-4-(4-hidroxifenil)ciclohexil)acetato de metilo (preparada según WO 2004/047755) (12.3 g, 49.53 mmol, CAS 701232-67-9) en THF (280 mL) a 0 °C bajo nitrógeno. Se formó una suspensión espesa de manera que la mezcla fue retirada a partir del baño de enfriamiento y agitada a temperatura ambiente durante 1 h. La mezcla de reacción fue enfriada a 0 °C y cuidadosamente apagada con NH_4Cl (75 mL), agua (50 mL) y 2N HCl (50 mL). La mezcla fue filtrada a través de Celite, lavando con MeOH (150 mL) y EtOAc

(2 x 250 mL). El filtrado fue concentrado, el residuo fue diluido con EtOAc (300 mL), lavado secuencialmente con 2N HCl (100 mL) y salmuera saturada (200 mL). La capa orgánica fue secada sobre $MgSO_4$, filtrada y evaporada para proporcionar el compuesto del título (10.37 g, 95 %) como un sólido blanco.

^{1}H NMR (400 MHz, DMSO) δ 0.97 - 1.06 (2H, m), 1.29 - 1.42 (5H, m), 1.71-1.79 (4H, m), 2.29 - 2.36 (1H, m), 3.42 - 3.47 (2H, m), 4.27 (1H, t), 6.64 (2H, d), 6.98 (2H, d), 9.03 (1H, s); m/z 220 (EI+) M^+.

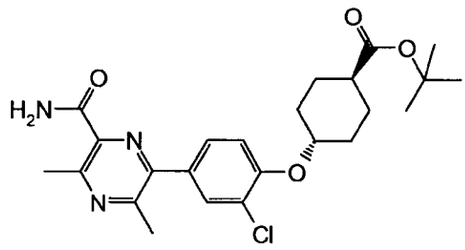
Ejemplo 26: Ácido (1r,4r)-4-(4-(6-Carbamoil-3,5-dimetilpirazin-2-il)-2-clorofenoxi)ciclohexanocarboxílico



Una solución del **Intermedio 26-1** (561 mg, 1.22 mmol) en TFA (6.098 mL) se dejo sentar a temperatura ambiente durante 30 minutos. La mezcla de reacción fue evaporada y se agregó éter al residuo para proporcionar un sólido el cual se purificó mediante recristalización a partir de EtOH en bullición absoluto (-10 mL) para proporcionar el compuesto del título (293 mg, 59.5 %) como un sólido amarillo

^{1}H NMR (400 MHz, DMSO) δ 1.45 - 1.59 (4H, m), 1.93 - 2.00 (2H, m) 2.08 - 2.10 (2H, m), 2.28 - 2.34 (1H, m), 2.59 (3H, s), 2.73 (3H, s), 4.48 - 4.52 (1H, m), 7.32 (1H, d), 7.59 (1H, s), 7.63 - 7.66 (1H, m), 7.86 (1H, d), 8.05 (1H, s), 12.10 (1H, s); *m/z* 404 $(M+H)^+$.

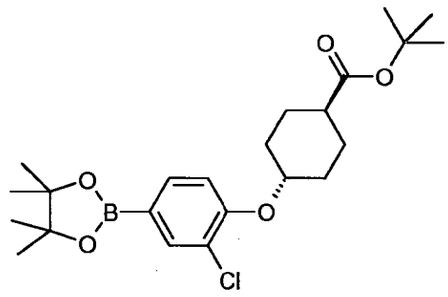
Intermedio 26-1: (1r,4r)-tert-Butil 4-(4-(6-Carbamoil-3,5-dimetilpirazin-2-il)-2-clorofenoxi)ciclohexanocarboxilato



Este compuesto se sintetizó a partir del Intermedio **26-2** utilizando condiciones similares como se describió en el Intermedio **25-1** para proporcionar el compuesto del título (561 mg, 71.5 %) como un sólido amarillo.

^{1}H NMR (400 MHz, DMSO) δ 1.47 (9H, s), 1.54 - 1.65 (4H, m), 1.96 - 2.04 (2H, m), 2.12- 2.17 (2H, m), 2.32 - 2.39 (1H, m), 2.66 (3H, s), 2.80 (3H, s), 4.53 - 4.60 (1H, m), 7.39 (1H, d), 7.66 (1H, s), 7.71 (1H, d), 7.92 (1H, s), 8.12 (1H, s); *m/z* 460 $(M+H)^+$.

Intermedio 26-2: (lr,4r)-tert-Butil 4-(2-cloro-4-(4,4,5,5-tetrametil-l,3,2-dioxaborolan-2-il)fenoxi)ciclohexanocarboxilato

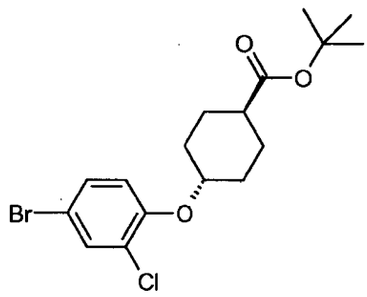


Este compuesto se sintetizó a partir del Intermedio **26-3** utilizando condiciones similares como se describió en el Intermedio **25-2** para proporcionar el compuesto del título (4.23 g, 88 %) como un aceite incoloro el cual se solidificó al sentar.

^{1}H NMR (400 MHz, $CDC1_3$) δ 1.33 (12H, s), 1.45 (9H, s), 1.55-1.62 (4H, m), 2.03 - 2.08 (2H, m), 2.13 - 2.19 (2H, m), 2.24 - 2.31 (1H, m), 4.25 - 4.31 (1H, m), 6.92 (1H, d), 7.61 (1H, d), 7.79 (1H, s); *m/z* 436 (EI+) M^+.

Intermedio 26-3: (1r,4r)-tert-Butil 4-(4-bromo-2-clorofenoxi)ciclohexano-carboxilato

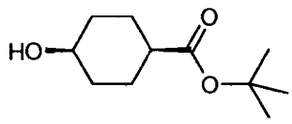
294



A una solución del Intermedio **26-4** (5.3 g, 26.46 mmol, CAS 931110-79-1), 4-bromo-2-clorofenol (6.59 g, 31.76 mmol) y trifenilfosfina (8.33 g, 31.76 mmol) en THF (200 mL) se agregó azodicarboxilato de diisopropilo (5.73 mL, 29.11 mmol). La solución se agitó a temperatura ambiente durante 4 h. La mezcla de reacción fue evaporada. El producto crudo se purificó mediante cromatografía flash de sílice, gradiente de elución entre 0 y 20% EtOAc en isohexano. Las fracciones puras fueron evaporadas hasta sequedad para proporcionar el compuesto del título (4.27 g, 41.4 %) como un aceite incoloro.

^{1}H NMR (400 MHz, DMSO) δ 1.37 - 1.53 (13H, m), 1.88 - 2.03 (4H, m), 2.23 - 2.28 (1H, m), 4.35 - 4.39 (1H, m), 7.19 (1H, d), 7.42 - 7.44 (1H, m), 7.63 (1H, d); HPLC tR= 3.65 min.

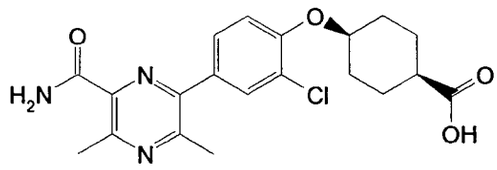
Intermedio 26-4: (ls,4s)-tert-Butil 4-hidroxiciclohexanocarboxilato



A una suspensión de ácido (1s,4s)-4-hidroxiciclohexanocarboxílico (5 g, 34.68 mmol, CAS 3685-22-1) en tolueno (160 mL) a 90 °C se agregó di-tert-butil acetal de N,N-Dimetilformamida (16.63 mL, 69.36 mmol) en una porción. La solución resultante se agitó a 90 °C durante 1 h. Luego se agregó una porción adicional de di-tert-butil acetal de N,N-Dimetilformamida (16.63 mL, 69.36 mmol) y la mezcla de reacción se agitó durante 30 min a 90 °C y luego a temperatura ambiente durante la noche. Se agregó por goteo di-tert-butil acetal de N,N-Dimetilformamida (10 mL) adicional durante10 minutos, la mezcla de reacción se agitó a 70 °C durante 1 h y luego se dejo enfriar. La mezcla de reacción se lavó con 2M NaOH (100 mL), salmuera (100 mL) y luego se evaporó para proporcionar el compuesto del título (5.30 g, 76 %) como un aceite.

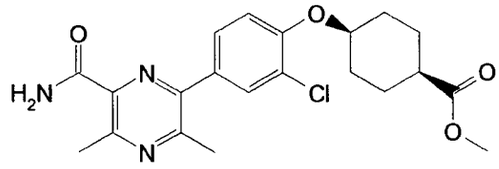
^{1}H NMR (400 MHz, DMSO) δ 1.36 - 1.39 (1H, m), 1.39 (9H, s), 1.41-1.51 (6H, m), 1.70 - 1.81 (2H, m), 2.19 - 2.25 (1H, m), 3.62 (1H, m), 4.32 (1H, d).

Ejemplo 27: Ácido (1s,4s)-4-(4-(6-Carbamoil-3,5-dimetilpirazin-2-il)-2-clorofenoxi)ciclohexanocarboxílico



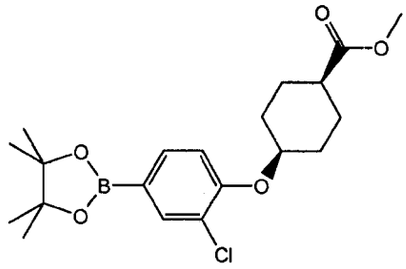
Este compuesto se sintetizó a partir del Intermedio **27-1** utilizando condiciones similares como se describió en **Ejemplo 21** para proporcionar el compuesto del título (182 mg, 50.8 %) como un sólido blanco, el cual se cristalizó a partir de EtOH absoluto en bullición (~2 mL).
^{1}H NMR (400 MHz, DMSO) δ 1.67 - 1.74 (4H, m), 1.76 - 1.93 (4H, m), 2.35 - 2.41 (1H, m), 2.60 (3H, s), 2.73 (3H, s), 4.77 (1H, brs), 7.28 (1H, d), 7.59 (1H, s), 7.65 (1H, dd), 7.87 (1H, d), 8.05 (1H, s), 12.07 (1H, s); *m/z* 404 $(M+H)^+$.

Intermedio 27-1: (ls,4s)-Metil-4-(4-(6-carbamoil-3,5-dimetilpirazin-2-il)-2-clorofenoxi)ciclohexanocarboxilato



Este compuesto se sintetizó a partir del Intermedio **27-2** y el Intermedio **21-4** utilizando condiciones similares como se describió en el Intermedio **25-1** para proporcionar el compuesto del título (371 mg, 48.1 %) como un sólido blanco.
^{1}H NMR (400 MHz, DMSO) 8 1.68 - 1.75 (4H, m), 1.78 - 1.93 (4H, m), 2.52 - 2.54 (1H, m) 2.60 (3H, s), 2.73 (3H, s), 3.61 (3H, s), 4.76 - 4.79 (1H, m), 7.29 (1H, d), 7.59 (1H, s), 7.65 (1H, dd), 7.87 (1H, d), 8.05 (1H, s); *m/z* 418 $(M+H)^+$.

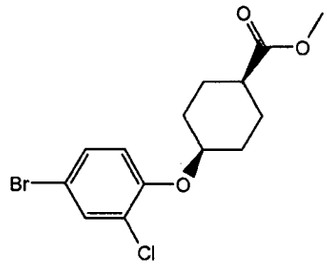
Intermedio 27-2: (1s,4s)-Metil 4-(2-cloro-4-(4,4,5,5-tetrametil-l,3,2-dioxaborolan-2-il)fenoxi)ciclohexanocarboxilato



Este compuesto se sintetizó a partir del Intermedio **27-3** utilizando condiciones similares como se describió en el Intermedio **25-2** para proporcionar el compuesto del título (4.73 g, 85 %) como un aceite amarillo claro el cual se solidificó al sentar.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (12H, s), 1.60 - 1.68 (2H, m), 1.74-1.81 (2H, m), 1.98 - 2.09 (4H, m), 2.37 - 2.44 (1H, m), 3.69 (3H, s), 4.57 - 4.60 (1H, m), 6.90 (1H, d), 7.60 -7.62 (1H, m), 7.80 (1H, d); *m/z* 394 (EI+) M^+.

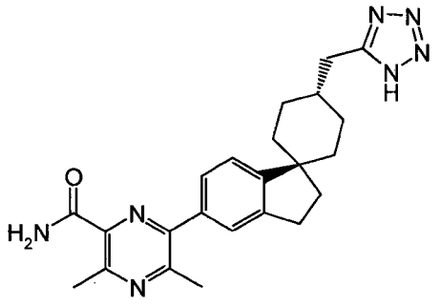
Intermedio 27-3: (1s,4s)-metil 4-(4-bromo-2-clorofenoxi)ciclohexano-carboxilato



Este compuesto se sintetizó a partir de (lr,4r)-metil 4-hidroxiciclohexanocarboxilato (CAS 6125-57-1) y 4-bromo-2-clorofenol utilizando condiciones similares como se describió en el Intermedio **26-3** para proporcionar el compuesto del título (4.88 g, 55.5 %) como un aceite incoloro.

^{1}H NMR (400 MHz, DMSO) δ 1.62 - 1.86 (8H, m), 3.60 (3H, s), 4.66 (1H, m), 7.15 (1H, d), 7.42 - 7.45 (1H, m), 7.64 (1H, d) un CH oscuro; HPLC tR= 2.99 min.

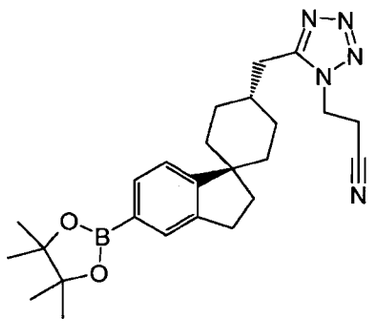
Ejemplo 28: 6-((1 r,4s)-4-((2H-Tetrazol-5-il)metil)-2',3'-dihidroespiro[ciclohexano-1,1'-indeno]-5'-il)-3,5-dimetilpirazina-2-carboxamida



A solución del **Intermedio 21-4** (197 mg, 1.06 mmol), **Intermedio 28-1** (473 mg, 1.06 mmol) y trifosfato de potasio (449 mg, 2.11 mmol) en DME (10 mL), EtOH (6.25 mL) y agua (2.5 mL) fue degasificada antes de la adición de (1,1'-bis(difenilfosfino)ferroceno)-dicloropaladio(II) (43.5 mg, 0.05 mmol). La mezcla de reacción fue calentada a 80 °C, bajo nitrógeno, y dejada agitar durante la noche durante 5hrs. La mezcla de reacción fue dejada enfriar a temperatura ambiente y luego evaporada. El residuo fue acidificado con 2N HCl (3 mL), diluido con agua (20 mL) y extraído into EtOAc (4 x 50 mL). Los extractos orgánicos fueron combinados, secados sobre $MgSO_4$, filtrados y evaporados para proporcionar el producto crudo. El producto crudo se purificó mediante HPLC preparativa (Columna Waters XBridge Prep C18 OBD, 5µ sílice, 50 mm de diámetro , 150 mm de longitud), utilizando mezclas decrecientemente polares de agua (conteniendo ácido fórmico al 0.1%) y MeCN como eluentes. Las fracciones conteniendo el compuesto deseado fueron evaporadas hasta sequedad para proporcionar el compuesto del título (51.9 mg, 11.76 %) como un sólido blanco.

^{1}H NMR (400 MHz, DMSO) δ 1.23 - 1.38 (2H, m), 1.58 - 1.73 (6H, m), 1.86 - 1.96 (1H, m), 2.04 (2H, t), 2.63 (3H, s), 2.79 (3H, s), 2.91 (2H, d), 2.97 (2H, t), 7.33 (1H, d), 7.55 (1H, d), 7.60 (1H, s), 7.62 (1H, s), 8.02 (1H, s); NH no observado; *m/z* 418 $(M+H)^+$.

Intermedio 28-1: 3-(5-(((1r,4s)-5'-(4,4,5,5--Tetrametil-1,3,2-dioxaborolan-2il)-2',3'--dihidroespiro[ciclohexano-1,1'-indenol -4-il)metil)-2H-tetrazol-2-il)propanonitrilo



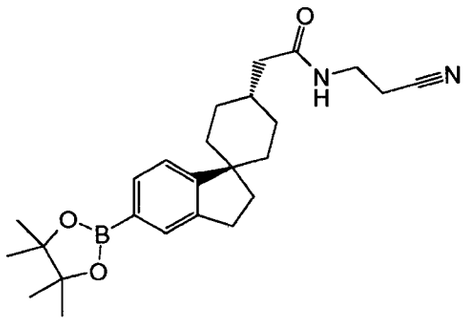
A una solución de trifenilfosfina (1.453 g, 5.54 mmol) y el Intermedio **28-2** (900 mg, 2.13 mmol) en THF (25.400 mL) en un baño de hielo se agregó azodicarboxilato de diisopropilo (1.133 mL, 5.75 mmol). La solución amarillo resultante fue dejada agitar a 0 °C, después 2 minutos se agregó azidotrimetilsilano (0.820 mL, 6.18 mmol) por goteo. Después de 17 horas a temperatura ambiente se agregó más trifenilfosfina (1.453 g, 5.54 mmol), azodicarboxilato de diisopropilo (1.133 mL, 5.75 mmol) y azidotrimetilsilano (0.820 mL, 6.18 mmol) y la suspensión se agitó a temperatura ambiente durante 24 horas más. La mezcla de reacción se enfrió en un baño de hielo y se agregó una solución de nitrito de sodio (162 mg, 2.34 mmol) en agua (3 mL) y después 30 minutos se agregó una solución de nitrato de amonio y cerio (IV) (1285 mg, 2.34 mmol) en agua (10 mL) (CUIDADO: Evolución de Gas). La mezcla de reacción fue agitada durante 45 minutos más. La mezcla de reacción fue vertida en agua (50 mL) y extraída con DCM (200 mL y 100 mL). Los extractos orgánicos fueron combinados, secados sobre $MgSO_4$, filtrados y evaporados para proporcionar el producto crudo.

El producto crudo se purificó mediante cromatografía flash de sílice, gradiente de elución entre 0 y 80% EtOAc en isohexano. Las fracciones mezcladas fueron evaporadas hasta sequedad para proporcionar el compuesto del título (487 mg, 51.1 %) como sólido crema.

^{1}H NMR (400 MHz, DMSO) δ 1.20 - 1.38 (14H, m), 1.40 - 1.50 (2H, m), 1.53-1.70 (4H, m), 1.83 - 1.97 (3H, m), 2.82 (2H, t), 2.89 (2H, d), 3.18 (2H, t), 4.69 (2H, t), 7.16 (1H, d), 7.48 (1H, d), 7.49 (1H, s); *m/z* 448 $(M+H)^+$.

Intermedio 28-2: N-(2-Cianoetil)-2-(1r,4s)-5'-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-2',3'-dihidroespiro[ciclohexano-l,l'-indenol-4-il)acetamida

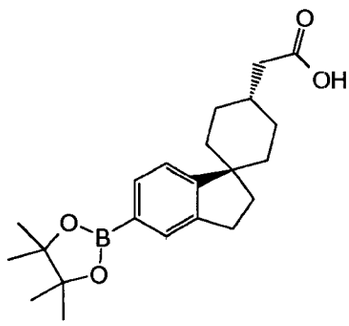
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Se agregó 3-Aminopropionitrilo (0.215 mL, 2.94 mmol) a una solución agitada del Intermedio 28-3 (725 mg, 1.96 mmol), N-etildiisopropilamina (1.023 mL, 5.87 mmol) y PyBROP (1.369 g, 2.94 mmol) en DCM (50 mL). La solución resultante se agitó a temperatura ambiente durante 4 horas. La mezcla de reacción fue evaporada hasta sequedad y redisuelta en EtOAc (125 mL), y lavada secuencialmente con 2M HCl (75 mL) y salmuera saturada (75 mL). La capa orgánica fue secada sobre $MgSO_4$, filtrada y evaporada para proporcionar el producto crudo. El producto crudo se purificó mediante cromatografía flash de sílice, gradiente de elución entre 0 y 100% en isohexano. Las fracciones puras fueron evaporadas hasta sequedad para proporcionar el compuesto del título (900 mg, 109 %) como una espuma blanca .

^{1}H NMR (400 MHz, DMSO) δ 1.09 - 1.20 (2H, m), 1.27 (12H, s), 1.42 - 1.46 (2H, m), 1.53 - 1.67 (4H, m), 1.72 - 1.79 (1H, m), 1.90 (2H, t), 2.03 (2H, d), 2.63 (2H, t), 2.81 (2H, t), 3.26 - 3.29 (2H, m), 7.17 (1H, d), 7.46 (1H, d), 7.48 (1H, s), 8.16 (1H, t); *m/z* 423 $(M+H)^+$.

Intermedio 28-3: Ácido 2-(1r,4s)-5'-(4,4,5,5-Tetrametil-l,3,2-dioxaborolan-2-il)-2',3'-dihidroespiro [ciclohexano-1,1'-indenol -4-il)acético

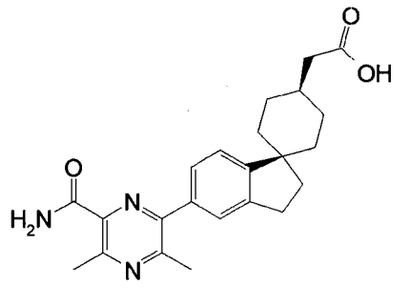


Se agregó TFA (15.90 mL) a una solución agitada del **Intermedio 29-3** (802 mg, 1.88 mmol) en DCM (15.90 mL) a 0 °C. La solución resultante se agitó a 0 °C durante 30 minutos, la

mezcla de reacción fue evaporada y el residuo fue azeotropizado con tolueno para proporcionar el compuesto del título (676 mg, 97 %) como un sólido blanco.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 - 1.28 (2H, m), 1.33 (12H, s), 1.56 - 1.70 (4H, m), 1.76 - 1.82 (2H, m), 1.85 - 1.93 (1H, m), 1.97 (2H, t), 2.31 (2H, d), 2.87 (2H, t), 7.15 (1H, d), 7.64 - 7.67 (2H, m); COOH no se observó; *m/z* 370 (EI+) M^+.

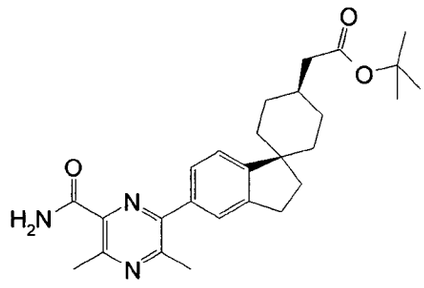
Ejemplo 29: N: Ácido 2-((ls,4r)-5'-(6-Carbamoil-3,5-dimetilpirazin-2-il)-2',3'-dihidroespiro[ciclohexano-l,l'-indeno]-4-il)acético



Una solución del **Intermedio 29-1** (0.748 g, 1.66 mmol) en TFA (8 mL) se dejo sentar a temperatura ambiente durante 0.5 h. La mezcla de reacción fue evaporadas a un sólido. El producto crudo se purificó mediante recristalización dos veces a partir de MeOH para proporcionar el compuesto del título (0.201 g, 30.7 %) como un sólido cristalino blancuzco.

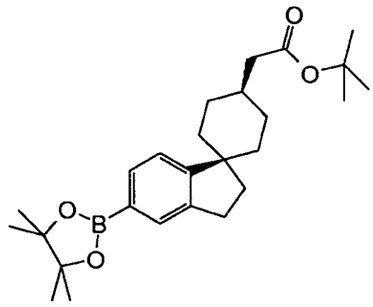
^{1}H NMR (400 MHz, DMSO) δ 1.40 - 1.56 (4H, m), 1.66 - 1.80 (4H, m), 1.96 (2H, t), 2.03 (1H, br s), 2.39 (2H, d), 2.58 (3H, s), 2.73 (3H, s), 2.89 (2H, t), 7.46 - 7.50 (2H, m), 7.54 (1H, s), 7.57 (1H, s), 7.97 (1H, s), 11.99 (1H, s); *m/z* 394 $(M+H)^+$.

Intermedio 29-1: N: 2-((ls, 4r)-5'-(6-carbamoil-3,5-dimetilpirazin-2-il)-2 ',3 '-dihidroespiro[ciclohexano-1,1'-indenol -4-il)acetato de tert-Butilo

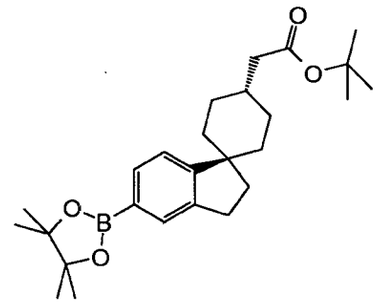


Este compuesto se sintetizó a partir del Intermedio **29-2** utilizando condiciones similares como se describió en el Intermedio **25-1** para proporcionar el compuesto del título (0.748 g, 50.3 %) como un sólido el cual fue una mezcla 2:1 con el otro diastereoisómero. *m/z* 450 $(M+H)^+$.

Intermedio 29-2: N: 2-((ls,4r)-5'-(4,4,5,5-tetrametil-l,3,2-dioxaborolan-2-il)-2',3'-dihidrospiro[ciclohexano-l.,l'-indenol-4-il)acetato de tert-Butilo y el Intermedio 29-3: 2-((1r,4s)-5'-(4,4,5,5-tetrametil-l,3,2-dioxaborolan-2-il)-2 ',3 '-dihidroespiro [ciclohexano-1,1 '-indenol -4-il)acetato de tert-Butilo



Intermedio 29-2



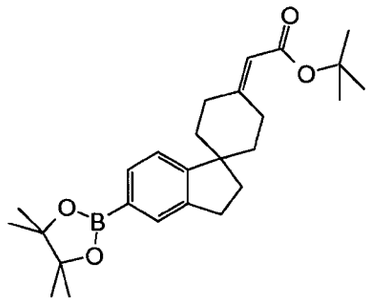
Intermedio 29-3

A una solución del Intermedio **29-4** (5.42 g, 12.77 mmol) en THF (125 mL), bajo nitrógeno, se agregó paladio sobre carbono al 10% por peso (1.4 g). La atmosfera fue reemplazada con hidrógeno y la reacción se agitó a temperatura ambiente durante la noche. La mezcla de reacción fue filtrada y evaporada a un aceite incoloro. Este fue disuelto en metanol *(ca.* 20 mL) y enfriado en un baño de hielo seco/acetona para producir un sólido blanco. La suspensión se dejo calentar y luego se evaporó para proporcionar el producto crudo como un sólido blanco. Este fue recristalizado al disolver en DCM *(ca.* 20 mL) agregando metanol *(ca.* 20 mL) y enfriando en un baño de hielo seco/acetona . La suspensión resultante fue filtrada y el sólido recolectado fue secado para proporcionar el **Intermedio 29-3** (2.290 g, 42.1 %) como a sólido blanco. ^{1}H NMR (400 MHz, DMSO) δ 1.17 - 1.21 (2H, m), 1.26 (12H, s), 1.40 (9H, s), 1.44 - 1.67 (7H, m), 1.90 (2H, t), 2.13 (2H, d), 2.81 (2H, t), 7.18 (1H, d), 7.46 - 7.48 (2H, m).

Las aguas madre fueron evaporadas para proporcionar el **Intermedio 29-2** (1.610 g, 29.6 %) como un sólido como una mezcla 2:1 con el otro diastereoisómer.

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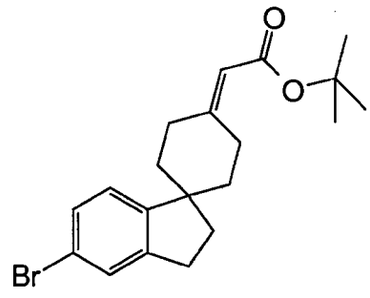
Intermedio 29-4: N: 2-(5'-(4,4,5,5-tetrametil-l,3,2-dioxaborolan-2-il)-2 ',3 '-dihidroespiro[ciclohexano-1,1'-indenol -4-ilideno)acetato de tert-butilo



Este compuesto se sintetizó a partir del Intermedio **29-5** utilizando condiciones similares como se describió en el Intermedio **25-2** para proporcionar el compuesto del título (5.42 g, 66.4 %) como un sólido

^{1}H NMR (400 MHz, DMSO) δ 1.28 (12H, t), 1.42 (8H, s), 1.60 - 1.73 (4H, m), 2.04 - 2.13 (3H, m), 2.26 (1H, d), 2.31 - 2.36 (1H, m), 2.87 (2H, t), 3.66 (1H, d), 5.60 (1H, s), 7.17 (1H, d), 7.45 - 7.47 (1H, m), 7.50 (1H, s) un protón oscuro ; *m/z* 423 (M-H)".

Intermedio 29-5: N: tert-Butil 2-(5'-bromo-2',3'-dihidroespiro[ciclohexano-1,1'-indeno] -4-ilideno)acetato

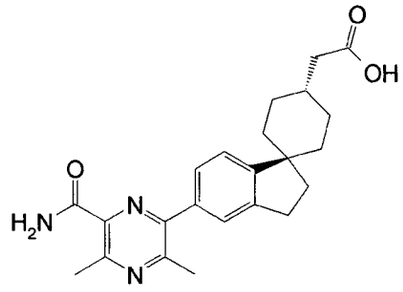


A una solución de *tert*-butildietilfosfonoacetato (8.80 mL, 37.47 mmol) en THF (100 mL) se agregó hidruro de sodio al 60% por peso (1.498 g, 37.47 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 30 minutos. Una solución de 5'-bromo-2',3'-dihidroespiro[ciclohexano-1,1'-inden]-4-ona (preparada según el procedimiento descrito en WO 2004/047755, CAS 701232-89-5) (8.716 g, 31.22 mmol) en THF (50 mL) se agregó y la agitación continuó a temperatura ambiente durante 1 hora. La mezcla de reacción fue apagada con salmuera saturada (150 mL), extraída con EtOAc (2 x 200 mL), la capa orgánica fue secada sobre $Na2SO_4$, filtrada y evaporada para proporcionar el producto crudo como un aceite marrón

(13.66g). El aceite crudo se trituró con isohexano para proporcionar un sólido el cual se recolectó mediante filtración y se secó al vacío para proporcionar el compuesto del título (4.84 g, 41 %) como un sólido amarillento. Un segundo cultivo del compuesto del título (2.42 g, 21 %) se obtuvo a partir del filtrado.

^{1}H NMR (400 MHz, DMSO) 8 1.42 (9H, s), 1.59 - 1.69 (4H, m), 2.05 - 2.12 (3H, m), 2.24 - 2.35 (2H, m), 2.88 (2H, t), 3.66 (1H, d), 5.60 (1H, s), 7.14 (1H, d), 7.27 - 7.30(1H, m), 7.38 (lH,t).

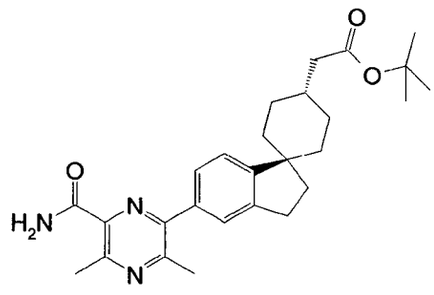
Ejemplo 30: Ácido 2-((1r,4s)-5'-(6-Carbamoil-3,5-dimetilpirazin-2-il)-2',3'-dihidroespiro[ciclohexano-1,1'-indenol-4-il)acético



Se dejo reposar una solución de **Intermedio 30-1** (1.16 g, 2.58 mmol) en TFA (12 mL) a temperatura ambiente durante 0.5 h. La mezcla de reacción se evaporó a un sólido. El producto crudo se purificó mediante recristalización a partir de MeOH para proporcionar el compuesto del título (0.648 g, 63.8 %) como un sólido cristalino blanco.

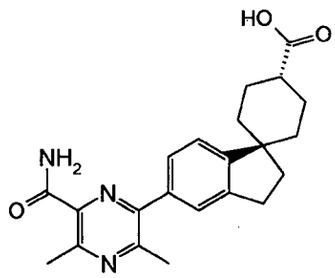
^{1}H NMR (300 MHz, DMSO) 8 1.14 - 1.27 (2H, m), 1.51-1.80 (7H, m), 1.98 (2H, t), 2.17 (2H, d), 2.58 (3H, s), 2.73 (3H, s), 2.90 (2H, t), 7.30 (1H, d), 7.50 (1H, d), 7.54 (1H, s), 7.62 (1H, s), 8.01 (1H, s), 12.05 (1H, s); *m/z* 394 $(M+H)^+$.

Intermedio 30-1: tert-Butil 2-((1r,4s)-5'-(6-carbamoil-3,5-dimetilpirazin-2-il)-2 ',3'-dihidroespiro[ciclohexano-1,1'-indenol -4-il)acetato



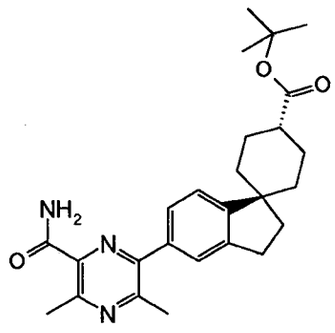
El compuesto se sintetizó a partir del **Intermedio 29-3** utilizando condiciones similares a las descritas en el **Intermedio 25-1** para proporcionar el compuesto del título (1.260 g, 89 %) como un sólido. ^{1}H NMR (400 MHz, DMSO) 8 1.20-1.23 (2H,m), 1.41 (9H, s), 1.51 - 1.69(7H,m), 1.97 (2H, t), 2.14 (2H, d), 2.57 (3H, s), 2.73 (3H, s), 2.90 (2H, t), 7.29 (1H, d), 7.47 - 7.57 (2H, m), 7.53 (1H, s), 7.96 (1H, s); *m/z* 450 $(M+H)^+$.

Examnle 31: Ácido (1r,4s)-5' (6-Carbamoil-3.5-dimetilpirazin-2-il)-2',3'-dihidroespirorciclohexano-1,1'-indeno]-4-carboxílico



Se agregó 4M HCL en dioxano (10 mL, 0.43 mmol) al **Intermedio 31-1** (188 mg, 0.43 mmol) en DCM (5 mL). La solución resultante fue agitada durante 16 horas. La mezcla resultante se evaporó hasta sequedad y el residuo se convirtió en pasta aguada con éter luego se filtró para proporcionar el compuesto del título (158 mg, 96 %) como un sólido amarillo pálido. ^{1}H NMR (400 MHz, DMSO) 8 1.48 - 1.73 (6H, m), 1.85 - 1.93 (2H, m), 2.00 (2H, t), 2.28 - 2.36 (1H, m), 2.58 (3H, s), 2.73 (3H, s), 2.91 (2H, t), 7.29 (1H, d), 7.50 (1H, d), 7.56 (3H, d), 7.98 (1H, s); *m/z* 380 $(M+H)^+$.

Intermedio 31-1: 5'-(6-Carbamoil-3,5-dimetilpirazin-2-il)-2',3'-dihidroespiro [ciclohexano-1.1'-indeno]-4-carboxilato de (1r,4s)- tert-butilo

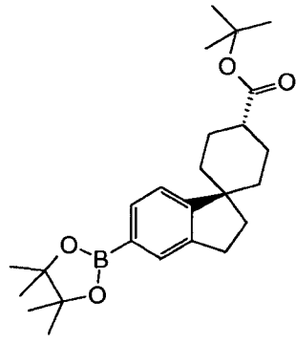


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El compuesto se sintetizó a partir del **Intermedio 31-2** y el **Intermedio 21-4** utilizando condiciones similares a las descritas en el **Intermedio 25-1** para proporcionar el compuesto del título (188 mg, 32.0 %) como un sólido.

^{1}H NMR (400 MHz, $CDCl_3$) 8 1.40 (9H, s), 1.54 - 1.68 (6H, m), 1.86 - 1.96 (2H, m), 2.02 (2H, t), 2.16 - 2.28 (1H, m), 2.60 (3H, s), 2.82 - 2.95 (5H, m), 5.40 (1H, s), 7.15 (1H, d), 7.30 (1H, d), 7.33 (1H, dd), 7.72 (1H, s); *m/z* 436 $(M+H)^+$.

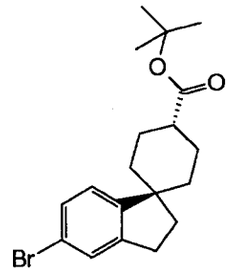
Intermedio 31-2: 5'-(4,4,5,5-Tetrametil-1,3,2-dioxaborolan-2-il)-2',3'-dihidroespiro [ciclohexano-1,1'-indeno]-4-carboxilato de (1r,4s)-tert-butilo



El compuesto se sintetizó a partir del **Intermedio 31-3** utilizando condiciones similares a las descritas en el **Intermedio 25-2** para proporcionar el compuesto del título (3.13 g, 73.7 %) como un sólido blanco.

^{1}H NMR (400 MHz, $CDCl_3$) 8 1.26 (12H, s), 1.39 (19H, s), 1.50 (2H, d), 1.50 - 1.60 (6H, m), 1.80 - 1.90 (2H, m), 1.93 (2H, t), 2.15 - 2.25 (1H, m), 2.81 (2H, t), 7.07 (1H, d), 7.59(1H, dd), 7.59 (1H, s).

Intermedio 31-3: 5'-Bromo-2'.3'-dihidroespiro[ciclohexano-1,1'-indeno] -4-carboxilato de (1r,4s)-tert-butilo

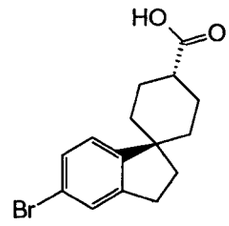


A una solución del **Intermedio 31-4** (3.47 g, 11.22 mmol) en tert-butanol (100 mL) se agregó DMAP (0.411 g, 3.37 mmol) y dicarbonato de di-tert-butilo (14.70 g, 67.34 mmol)

(efervecencia). La solución resultante se agitó a temperatura ambiente durante 16 horas. Se agregó $NaHCO_3$ saturado (100 mL) y la reacción se agitó durante 30 minutos antes de agregar EtOAc (400 mL). La capa orgánica se separó y lavó con agua (200 mL) luego salmuera saturada (200 mL) y se evaporó para proporcionar el producto crudo. El producto crudo se purificó mediante cromatografía flash de gel de sílice, gradiente de elución entre 0 y 10% EtOAc en isohexano. Las fracciones puras se evaporaron hasta sequedad para proporcionar el compuesto del título (3.76 g, 92 %) como un aceite incoloro.

^{1}H NMR (400 MHz, $CDCl_3$) 8 1.46 (9H, s), 1.52-1.67 (6H, m), 1.90 - 1.97 (2H, m), 1.98 -2.03 (2H, m), 2.20 - 2.30 (1H, m), 2.86 (2H, t), 6.96 (1H, d), 7.28 (1H, dt), 7.32 (1H, d).

Intermedio 31-4: Ácido (1r,4s)-5'-bromo-2',3'-dihidroespiro[ciclohexano-1.1'-indeno]-4-carboxílico

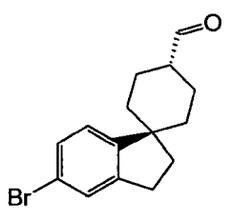


Se agregó oxona (6.98 g, 11.36 mmol) al **Intermedio 31-5** (3.33 g, 11.36 mmol), en DMF (70 mL). La suspensión resultante fue agitada durante 16 horas. La mezcla de reacción se diluyó con EtOAc (300 mL), y se lavó secuencialmente con agua (3 x 150 mL) y salmuera saturada (150 mL). La capa orgánica se evaporó para proporcionar el compuesto del título (3.51 g, 100%).

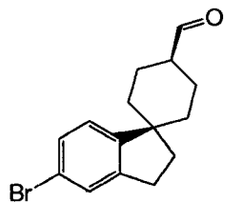
^{1}H NMR (400 MHz, DMSO) 8 1.30 - 1.73 (6H, m), 1.80 - 2.00 (4H, m), 2.20 - 2.32 (1H, m), 2.83 (2H, t), 7.12 (1H, d), 7.31 (1H, dt), 7.36 (1H, t), 12.03 (1H, s); *m/z* 309 M-H".

Intermedio 31-5: (1r,4s)-5'-Bromo-2',3'-dihidroespiro[ciclohexano-1.1'-indeno]-4-carbaxaldehido y

Intermedio 31-6: (1s,4r)-5'-Bromo-2',3'-dihidroespiro[ciclohexano-1.1'-indeno]-4-carbaxaldehido



Intermedio 31-5



Intermedio 31-6

Se agregó cloruro de (metoximetilo)trifenilfosfonio (20.76 g, 60.55 mmol) a una suspensión agitada de tert-butoxido de potasio (6.79 g, 60.55 mmol) en 1,4-dioxano (113 mL) a temperatura ambiente, durante un periodo de 10 minutos bajo nitrógeno. La solución roja resultante se agitó a temperatura ambiente durante 2 horas y luego se agregó una solución de 5'-bromo-2',3'-dihidroespiro[ciclohexano-1,1'-inden]-4-ona (preparada según el procedimiento descrito en WO 2004/047755, CAS 701232-89-5) (7.35 g, 26.33 mmol) en 1,4-dioxano (63.4 mL) durante un periodo de 10 minutos bajo nitrógeno. La solución resultante se agitó a temperatura ambiente durante 1 hora y y luego se calentó a 70 °C durante 16 horas. La mezcla de reacción se vertió en agua (200 mL), se extrajo con EtOAc (2 x 200 mL), la capa orgánicase lavó con salmuera saturada (200 mL) y evaporó para proporcionar un aceite negro. Al aceite crudo se agregó EtOAc e isohexano (1:3, 200 mL) para proporcionar un sólido el cual se recolectó mediante filtración, lavado con EtOAc e isohexano (75 mL). El filtrado se evaporó para proporcionar un residuo sólido, el cual se agregó a ácido aético al 90% en agua (200 mL, 3493.64 mmol). La solución resultante se agitó a 70 °C durante 16 horas, la mezcla se dejo enfriar, se evaporó hasta sequedad y el producto crudo se purificó mediante cromatografía flash de gel de sílice, gradiente de elución entre 0 y 15% en isohexano. Las fracciones puras se evaporaron hasta sequedad para proporcionar el **Intermedio 31-5** (3.33 g, 43.1 %) y el **Intermedio 31-6** (1.17g, 15%>) como gomas incoloras.

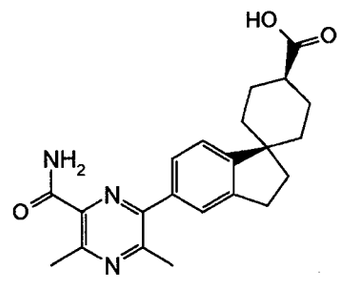
Intermedio 31-5:

^{1}H NMR (400 MHz, $CDCl_3$) 8 1.36 - 1.67 (6H, m), 1.84 - 2.00 (4H, m), 2.19 - 2.29 (1H, m), 2.80 (2H, t), 6.92 (1H, m), 7.22 (1H, m), 7.23 (1H, dd), 9.61 (1H, d); *m/z* (EI+) 292 M^+.

Intermedio 31-6:

^{1}H NMR (400 MHz, $CDCl_3$) 8 1.35 - 1.60 (4H, m), 1.68 - 1.80 (2H, m), 1.93 (2H, t), 2.09 (2H, dt), 2.37 - 2.44 (1H, m), 2.75 - 2.85 (2H, m), 6.90 (1H, d), 7.19 (1H, d), 7.24 (1H, d), 9.72 (1H, s); *m/z* 292 (EI+) M^+.

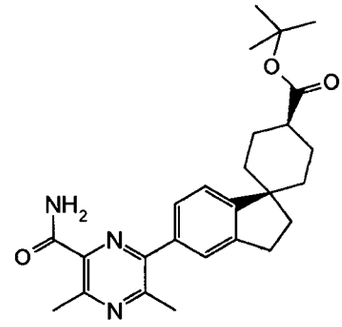
Examnle 32: Ácido (1s,4r)-5'-(6-carbamoil-3,5-dimetilpirazin-2-il)-2',3'-dihidroespiro[ciclohexano-1.1'-indeno]-4-carboxílico



El compuesto se sintetizó a partir del **Intermedio 32-1** utilizando condiciones similares a las descritas en el **Ejemplo 31** para proporcionar el compuesto del título (176 mg, 59.9 %) como un sólido amarillo pálido.

^{1}H NMR (400 MHz, DMSO) 8 1.45 (2H, dd), 1.72 (3H, dd), 1.77 (1H, m), 1.96 (1H, s), 1.99 (3H, t), 2.58 (4H, s), 2.73 (3H, s), 2.90 (2H, t), 7.25 (1H, d), 7.49 (1H, dd), 7.55 (1H, d), 7.57 (1H, s), 7.97 (1H, s); *m/z* 380 $(M+H)^+$.

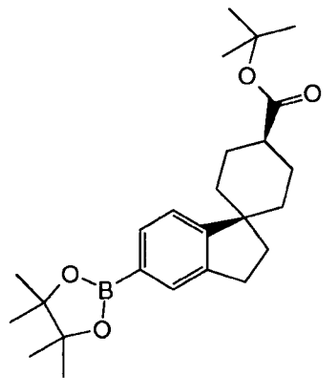
Intermedio 32-1: 5'-(6-Carbamoil-3.5-dimetilpirazin-2-il)-2',3'-dihidroespiro[ciclohexano-1,1'-indeno]-4-carboxilato de (1s.4r)-tert-butilo



El compuesto se sintetizó a partir del **Intermedio 32-2** y el **Intermedio 21-4** utilizando condiciones similares a las descritas en el **Intermedio 25-1** para proporcionar el compuesto del título (342 mg, 58.2 %) como un sólido.

^{1}H NMR (400 MHz, $CDCl_3$) 8 1.40 - 1.50 (2H, m), 1.44 (9H, s), 1.65 - 1.75 (2H, m), 1.75 - 1.85 (2H, m), 1.95 - 2.08 (4H, m), 2.45 - 2.51 (1H, m), 2.60 (3H, s), 2.85 - 2.93 (5H, m), 5.39 (1H, s), 7.26 - 7.35 (3H, m), 7.73 (1H, s); *m/z* 436 $(M+H)^+$.

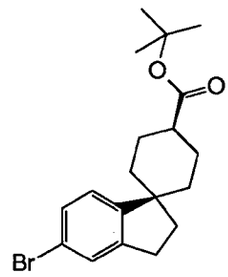
Intermedio 32-2: 5'-(4,4,5,5-Tetrametil-1,3,2-dioxaborolan-2-il)-2',3'-dihidroespiro[ciclohexano-1,1'-indeno]-4-carboxilato de (1s,4r)-tert-butilo



El compuesto se sintetizó a partir del **Intermedio 32-3** utilizando condiciones similares a las descritas en el **Intermedio 25-2** para proporcionar el compuesto del título (0.935 g, 62.3 %) como un aceite incoloro el cual se solidificó al sentar.

^{1}H NMR (400 MHz, $CDCl_3$) 8 1.32 (12H, s), 1.44 - 1.47 (2H, m), 1.50 (9H, s), 1.67 - 1.86 (4H, m), 1.96 (2H, t), 2.01 - 2.09 (2H, m), 2.48 - 2.53 (1H, m), 2.83 - 2.90 (2H, m), 7.25 (1H, d), 7.63 (1H, d), 7.67 (1H, s); *m/z* 412 (EI+) M^+.

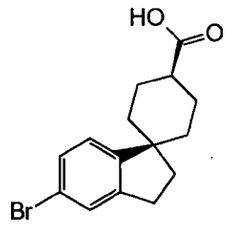
Intermedio 32-3: 5'-Bromo-2',3'-dihidroespiro[ciclohexano-1.1'-indeno]-4-carboxilato de (ls.4r)-tert-butilo



El compuesto se sintetizó a partir del **Intermedio 32-4** utilizando condiciones similares a las descritas en el **Intermedio 31-3** para proporcionar el compuesto del título (1.330 g, 89 %) como un aceite incoloro.

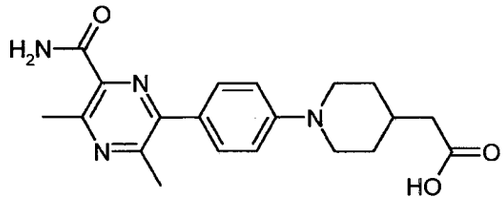
^{1}H NMR (400 MHz, $CDCl_3$) 8 1.42 - 1.46 (2H, m), 1.49 (9H, s), 1.67 - 1.81 (4H, m), 1.96 (2H, t), 2.00 - 2.06 (2H, m), 2.48 - 2.53 (1H, m), 2.85 (2H, t), 7.08 (1H, d), 7.26 - 7.28 (1H, m), 7.32 (1H, s); *m/z* 364 (EI+) M^+.

Intermedio 32-4: Ácido (1s,4r)-5'-Bromo-2'.3'-dihidroespiro[ciclohexano-1.1'-indeno]-4-carboxílico



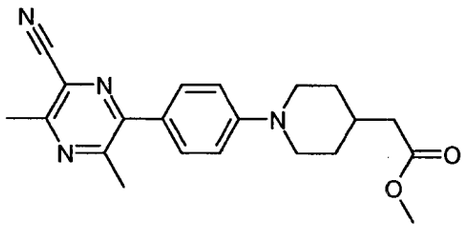
El compuesto se sintetizó a partir del **Intermedio 31-6** utilizando condiciones similares a las descritas en el **Intermedio 31-4** para proporcionar el compuesto del título (1.27g, 100%) como un sólido. ^{1}H NMR (400 MHz, DMSO) 8 1.35 - 1.44 (2H, m), 1.60 - 1.73 (4H, m), 1.85 - 2.00 (4H, m), 2.53 (1H, q), 2.82 (2H, t), 7.08 (1H, d), 7.30 (1H, dt), 7.37 (1H, t), 12.12 (1H, s); *m/z* 309 $(M-H)^-$.

Ejemplo 33: Ácido 2-(1-(4-(6-carbamoil-3,5-dimetilpirazin-2-il)fenil)piperidin-4-il)acético



Se agregó hidroxido de potasio en polvo (44.5 mg, 0.79 mmol) en una porción al **Intermedio 33-1** (60 mg, 0.16 mmol) en tert-butanol (5 mL). La sustancia color amarillo pálido resultante se agitó a 40 °C durante 30 minutos. La mezcla de reacción fue apagada con ácido acético (0.073 mL, 1.27 mmol) en EtOH (10.0 mL) y la solución resultante se agitó durante 10 minutos adicionales antes de ser evaporada hasta sequedad. El sólido resultante se particionó entre agua (20 mL) y EtOAc (20 mL). La capa acuosa mostró un pH= 6. La capa orgánica fue separada y la capa acuosa fue re-extraida con EtOAc (2 x 25 mL). Los orgánicos combinados fueron lavados con salmuera (15 mL), secados sobre $MgSO_4$ y evaporados al vacío para proporcionar el producto crudo. Este fue recristalizado a partir de EtOH caliente (6 mL) para proporcionar un sólido amarillo el cual fue lavado con etilacetato (5 mL) y secado al vacío a temperatura ambiente para proporcionar el compuesto del título (41.0 mg, 70.2 %) como un sólido amarillo. ^{1}H NMR (400 MHz, DMSO) 8 1.28 (2H, m), 1.76 (2H, m), 1.86 (1H, m), 2.15 (2H, d), 2.60 (3H, s), 2.71 (3H, s), 2.76 (2H, d), 3.79 (2H, d), 7.00 (2H, d), 7.55 (1H, s), 7.60 (2H, d), 7.96 (1H, s); *m/z* 369 $(M+H)^+$.

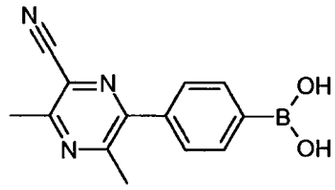
Intermedio 33-1: Piperidin-4-ilacetato de etil 2-(1-(4-(6-ciano-3,5-dimetilpirazin-2-il)fenil)



Se agregó piridina (0.050 mL, 0.62 mmol) por goteo al **Intermedio 33-2** (78 mg, 0.31 mmol), etil 2-(piperidin-4-il)acetato (79 mg, 0.46 mmol) y acetato de cobre(II) (56.0 mg, 0.31 mmol) en DCM anhidro (10 mL). La solución azul resultante se agitó a 25 °C durante 16 horas. La mezcla de reacción se diluyó con DCM (25 mL), y se lavó con una solución EDTA acuosa al 20% (25 mL). La capa orgánica se evaporó para proporcionar el producto crudo. El producto crudo se purificó mediante cromatografía flash de gel de sílice, gradiente de elución entre 0 y 70% EtOAc en isohexano. Las fracciones puras se evaporaron hasta sequedad para proporcionar el compuesto del título (53.0 mg, 45.4 %) como un sólido amarillo pálido.

^{1}H NMR (400 MHz, DMSO) 8 1.20 (5H, m), 1.69 (2H, d), 1.84 (1H, m), 2.22 (2H, m), 2.61 (6H, s), 2.71 (2H, m), 3.77 (2H, d), 4.02 (2H, m), 6.97 (2H, m), 7.47 (2H, m); *m/z* 379 $(M+H)^+$.

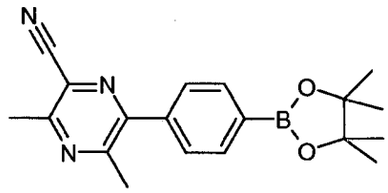
Intermedio 33-2: Ácido 4-(6-ciano-3,5-dimetilpirazin-2-il)fenilborónico



Se agregó periodato de sodio (5.02 g, 23.45 mmol) en una porción al **Intermedio 33-3** (2.62 g, 7.82 mmol) en THF (80 mL) y agua (20 mL) y la suspensión turbia se agitó a temperatura ambiente durante 30 minutos. Se agregó 1M HCl (5.47 mL, 5.47 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 2 horas. El THF se evaporó bajo presión reducida, la mezcla de reacción se diluyó con agua (100 mL) y extrajo con acetato de etilo (2 x 100 mL). Los extractos combinados fueron lavados con agua (2 x 30 mL) y salmuera (30 mL), secados sobre sulfato de sodio, concentrados hasta sequedad mediante evaporación rotatoria para proporcionar el compuesto del título (1.980 g, 100 %).

^{1}H NMR (400 MHz, DMSO) 8 2.62 (3H, s), 2.70 (3H, s), 7.60 (2H, d), 7.92 (2H, d), 8.16 (2H, s); *m/z* 254 $(M+H)^+$.

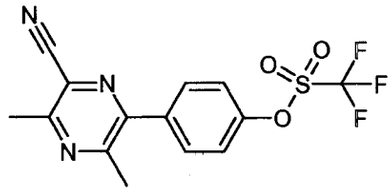
Intermedio 33-3: 3,5-Dimetil-6-(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)pirazina-2-carbonitrilo



El compuesto se sintetizó a partir del **Intermedio 33-4** utilizando condiciones similares a las descritas en el **Intermedio 25-2** para proporcionar el compuesto del título (70.0 mg, 50.4 %) como un sólido cristalino blanco.

^{1}H NMR (400 MHz, DMSO) 8 1.39 (12H, s), 2.68 (3H, s), 2.77 (3H, s), 7.73 (2H, d), 7.88 (2H, d); HPLC tR= 2.85 min.

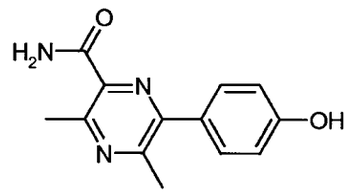
Intermedio 33-4: Trifluorometanosulfonato de 4-(6-ciano-3,5-dimetilpirazin-2-il)fenilo



Se agregó anhidruro trifluorometanosulfónico (27.3 mL, 166.57 mmol) a una solución agitada del **Intermedio 33-5** (10.13 g, 41.64 mmol) en DCM (400 mL) enfriada a 0 °C, durante un periodo de 20 minutos bajo nitrógeno. La pasta aguada resultante se dejó calentar a temperatura ambiente durante la noche bajo una atmósfera de nitrógeno. Se agregó trietilamina (46.4 mL, 333.14 mmol) por goteo durante 10 minutos (bajo enfriamiento con baño de hielo, manteniendo la temperatura en 5-10°C) y la solución resultante se agitó a 30 °C durante 3 horas bajo nitrógeno. La mezcla de reacción se diluyó con DCM (200 mL), y se lavó secuencialmente con agua (200 mL), $NaHCO_3$ saturado (200 mL), y salmuera saturada (100 mL). La capa orgánica fue secada sobre $MgSCO_4$, filtrada y evaporada para proporcionar el producto crudo. El producto crudo se purificó mediante cromatografía flash de gel de sílice, gradiente de elución entre 0 y 40% EtOAc en isohexano. Las fracciones puras se evaporaron hasta sequedad al compuesto del título (9.87 g, 66.3 %) como un aceite amarillo.

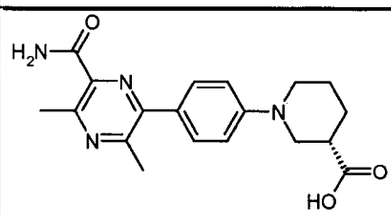
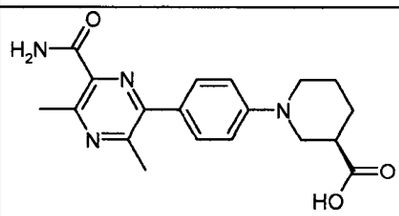
^{1}H NMR (400 MHz, DMSO) 8 2.68 (3H, s), 2.78 (3H, s), 7.74 (2H, d), 7.93 (2H, d); m/z = no se observó ión de masa; HPLC tR= 2.84 min.

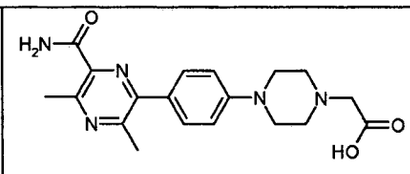
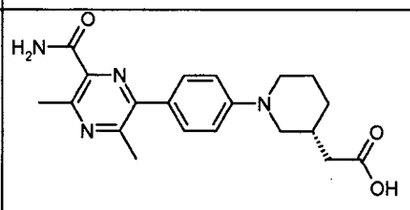
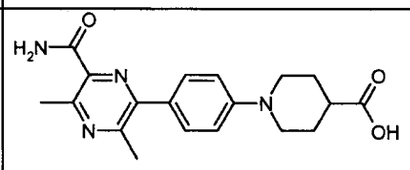
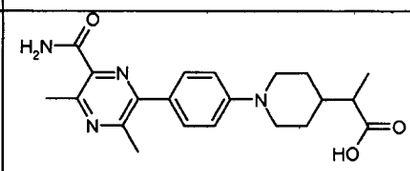
Intermedio 33-5: 6-(4-Hidroxifenil)-3,5-dimetilpirazina-2-carboxamida



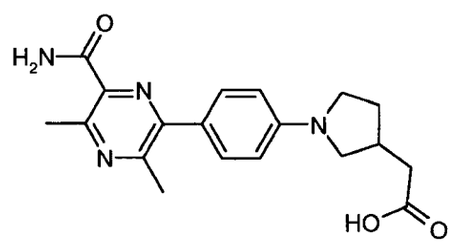
El compuesto se sintetizó a partir del **Intermedio 21-4** y 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenol (CAS 269409-70-3) utilizando condiciones similares a las descritas en el **Intermedio 25-1** para proporcionar el compuesto del título (10.13 g, 97 %) como un sólido naranja. ^{1}H NMR (400 MHz, DMSO) 8 2.58 (3H, s), 2.71 (3H, s), 6.87 (2H, d), 7.56 - 7.60 (3H, m), 7.95 (1H, s), 9.73 (1H, s); *m/z* 244 $(M+H)^+$.

Los siguientes Ejemplos se sintetizaron utilizando condiciones similares a las descritas en el **Ejemplo 33** para proporcionar los compuestos deseados **34-39.**

Ejemplo	Estructura	*H NMR (400 MHz, DMSO) 5	*m/z* $(M+H)^+$
34		1.58 (2H,m), 1.72 (lH,m), 1.92 (lH,m), 2.53 (lH,m), 2.60 (3H, s), 2.72 (3H, s), 2.90 (lH,m), 3.04 (lH,m), 3.58 (lH,m), 3.76 (lH,m), 7.02 (2H, d), 7.56 (1H, s), 7.62 (2H, d), 7.96 (1H, s)	355
35		1.66 (2H,m), 1.80 (lH,m), 2.00 (lH,m), 2.61 (lH,m), 2.67 (3H, s), 2.78 (3H, s), 2.98 (lH,t), 3.14 (lH,t), 3.65 (1H, d), 3.83 (1H, d), 7.10 (2H, d), 7.63 (1H, s), 7.69 (2H, d), 8.02 (1H, s)	355

36		2.60 (3H,s), 2.71 (7H,m), 3.20 (2H, s), 3.27 (4H,m), 7.03 (2H, d), 7.56 (1H, s), 7.63 (2H, d), 7.96 (1H, s)	370
37		1.20 (lH,m), 1.55 (lH,m), 1.69 (lH,m), 1.81 (lH,m), 1.98 (lH,m), 2.17 (lH,m), 2.28 (1H, m), 2.60 (4H, m), 2.71 (3H,s), 2.81 (lH,t), 3.73 (2H,t), 7.00 (2H,d), 7.56 (1H, s), 7.61 (2H, d), 7.96 (lH,s), 12.11 (1H, s)	369
38		1.64 (2H,m), 1.90 (2H,m), 2.45 (1H, m), 2.60 (3H, s), 2.71 (3H,s), 2.87 (2H,t), 3.76 (2H, d), 7.03 (2H, d), 7.56 (1H, s), 7.61 (2H, d), 7.96 (lH,s), 12.19 (1H, s)	355
39		1.12 (3H, d), 1.39 (2H,m), 1.75 (3H,m), 2.27 (lH,m), 2.66 (3H, s), 2.77 (5H, m), 3.91 (2H,m), 7.08 (2H,d), 7.62 (1H, s), 7.67 (2H, d), 8.02 (lH,s), 12.14 (1H, s)	383

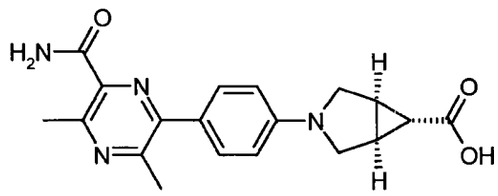
Ejemplo 40: Ácido 2-(1-(4-(6-carbamoil-3,5-dimetilpirazin-2-il)fenil)pirrolidin-3- il) acético



Se agregó hidroxido de potasio en polvo (122 mg, 2.17 mmol) en una porción al **Intermedio 40-1** (170 mg, 0.43 mmol) en tert-butanol (5 mL). La suspensión amarilla resultante se agitó a 40 °C durante 90 minutos. La mezcla de reacción fue apagada con ácido acético (0.198 mL, 3.47 mmol) en EtOH (10.0 mL) y la solución resultante fue agitada durante 10 minutos adicionales antes de ser evaporada hasta sequedad. El sólido resultante se particionó entre agua (20 mL) y EtOAc (20 mL). La capa acuosa mostró un pH= 6. La capa orgánica se separó y evaporó hasta sequedad para proporcionar el producto crudo (185 mg). El producto crudo se disolvió en DCM (5.00 mL) y se agregó TFA (1.0 mL, 12.99 mmol). La solución marrón se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se purificó mediante cromatografía de intercambio de iones, utilizando una columna SCX. La columna se eluyó con DCM (100 mL) seguido por MeOH (100 mL) y luego el producto deseado se eluyó de la columna utilizando 0.35M NH_3/MeOH (100 mL) y las fracciones que contienen el producto se evaporaron hasta sequedad para proporcionar el producto crudo como un sólido amarillo (110 mg). Este producto se purificó mediante HPLC preparativa (columnas Waters XBridge Prep C18 OBD, 5µ sílice, 50 mm diametro, 150 mm longitud), utilizando mezclas decrecientemente polares de agua (conteniendo 0.1% de ácido fórmico) y MeOH como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para proporcionar el compuesto del título (76 mg, 49.5 %) como un sólido amarillo.

^{1}H NMR (400 MHz, DMSO) 8 1.65 (1H, m), 2.13 (1H, m), 2.38 (2H, m), 2.55 (4H, m), 2.65 (3H, s), 2.93 (1H, t), 3.26 (1H, m), 3.33 (1H, m), 3.47 (1H, m), 6.55 (2H, d), 7.50 (1H, s), 7.56 (2H, d), 7.89 (1H, s), 12.13 (1H, s); *m/z* 355 $(M+H)^+$.

Ejemplo 41 Ácido(1R,5S,6r)-3-(4-(6-carbamoil-3,5-dimetilpirazin-2-il)fenil)-3-azabiciclo[3,1,0]hexano-6-carboxílico



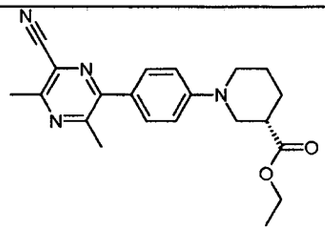
Se agregó hidroxido de potasio en polvo (101 mg, 1.79 mmol) en una porción al **Intermedio 41-1** (175 mg, 0.45 mmol) en tert-butanol (4 mL) a 40 °C bajo nitrógeno. La suspensión resultante se agitó a 40 °C durante 6 horas. Se formó un precipitado espeso de manera que la reacción fue apagada con ácido acético (0.205 mL, 3.59 mmol) en EtOH (10 mL) y la

321

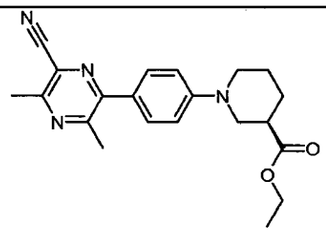
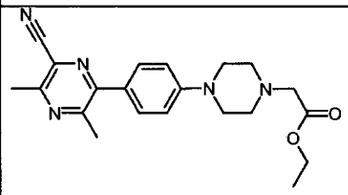
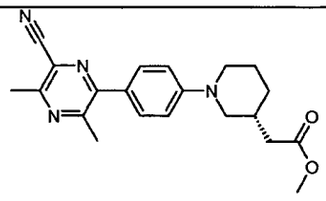
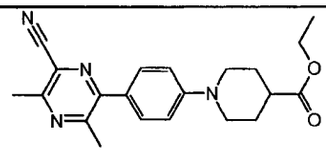
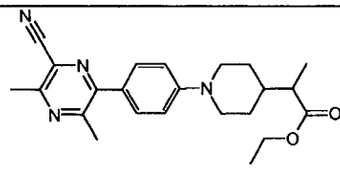
solución resultante se agitó durante 10 minutos adicionales antes de ser evaporadas hasta sequedad. El material crudo se trató conuna solución de HCl al 5% en metanol (10 mL), y se agitó durante la noche. Luego la mezcla se trató con hidroxido de potasio en polvo (101 mg, 1.79 mmol) en tert-butanol. La mezcla resultante se agitó a 40 °C durante 2 horas, antes de apagarse con ácido acético (0.205 mL, 3.59 mmol) en EtOH (5 mL) y evaporarse a una goma. El producto crudo se purificó mediante HPLC preparativa (Columna Waters XBridge Prep C18 OBD, 5p, sílice, 50 mm diametro, 150 mm longitud), utilizando mezclas decrecientemente polares de agua (conteniendo 0.1% ácido fórmico) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para proporcionar el compuesto del título (66.5 mg, 42.1 %) como un sólido amarillo.

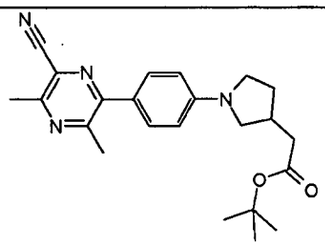
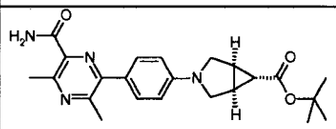
^{1}H NMR (400 MHz, DMSO) 8 1.51 (1H, t), 2.23 - 2.26 (2H, m), 2.66 (3H, s), 2.77 (3H, s), 3.39 (2H, d), 3.72 (2H, d), 6.71 (2H, d), 7.62 (1H, s), 7.66 (2H, d), 8.01 (1H, s,) COOH no se observó; *m/z* 353 $(M+H)^+$.

Los siguientes compuestos se sintetizaron a partir del **Intermedio 33-2** y la amina apropiada utilizando condiciones similares a las descritas en el **Intermedio 33-1** para proporcionar los **Intermedios** deseados **34-1** a **40-1.**

Intermedio	**Estructura**	***H NMR (400 MHz, DMSO) 5**	***m/z*** **$(M+H)^+$**
34-1		1.27 (3H,t), 1.71 (3H,m), 1.99 (lH,m), 2.70 (7H,m), 3.04 (lH,m), 3.23 (lH,m), 3.64 (1H, d), 3.83 (1H, d), 4.16 (2H, q), 7.10 (2H, d), 7.61 (2H, d).	365

322

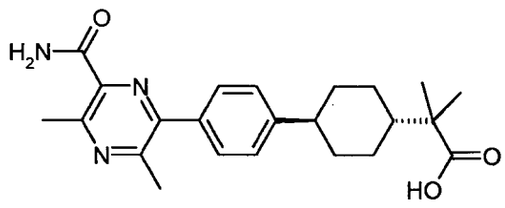
35-1		1.14 (3H,t), 1.59 (3H,m), 1.87 (lH,m), 2.58 (7H,m), 2.92 (lH,t), 3.10 (lH,t), 3.52 (1H, d), 3.71 (1H, d), 4.04 (2H, q), 6.98 (2H, d), 7.49 (2H, d).	365
36-1		2.60 (3H,s), 2.71 (7H,m), 3.20 (2H, s), 3.27 (4H,m), 7.03 (2H, d), 7.56 (1H, s), 7.63 (2H, d), 7.96 (1H, **s).**	370
37-1		1.23 (lH,m), 1.55 (lH,m), 1.69 (lH,m), 1.79 (lH,m), 2.00 (1H, m), 2.28 (1H, m), 2.38 (1H, m), 2.63 (7H, m), 2.83 (lH,m), 3.62 (3H,s), 3.74 (2H,m), 7.01 (2H, d), 7.53 (2H, d).	365
38-1		1.13 (3H,t), 1.60 (2H,m), 1.86 (2H,m), 2.51 (1H, m), 2.59 (3H, s), 2.61 (3H, s), 2.84 (2H,t), 3.72 (2H,d), 4.03 (2H, q), 6.98 (2H, d), 7.48 (2H, d).	365
39-l[a]		1.07 (3H, d), 1.18 (3H,t), 1.31 (2H,m), 1.68 (3H,m), 2.30 (1H, m), 2.65 (3H, s), 2.66 (3H, s), 2.73 (2H, m), 3.87 (2H,t), 4.07 (2H,m), 7.02 (2H, d), 7.52 (2H, d).	393

40-1		1.39 (lH,m), 1.42 (9H,s), 1.69 (lH,m), 2.16 (lH,m), 2.40 (2H, m), 2.59 (1H, m), 2.65 (6H, s), 2.96 (1H, t), 3.37 (lH,m), 3.50 (lH,m), 6.61 (2H, d), 7.53 (2H, d).	393
41-1[a]		1.41 (9H,s), 1.42-1.45 (1H, m), 2.17-2.19 (2H, m), 2.64 (3H, s), 2.65 (3H, s), 3.27 (2H,d), 3.66 (2H, d), 6.64 (2H,d), 7.51 (2H,d).	391

Nota: 39-1[a] 2-(piperidin-4-il)propanoato de etilo, CAS 141060-27-7 se preparó según el procedimiento descrito en WO 2008042925.

41-1[a] 3-azabiciclo[3.1.0]hexano-6-carboxilato de (1R,5S,6r)-tert-butilo, CAS 681424-89-5 (preparada según el procedimiento descrito en WO 2004033451).

Ejemplo 42: Ácido 2-((1r,4r)-4-(4-(6-Carbamoil-3,5-dimetilpirazin-2-il)fenil)clohexil)-2-metilpropanóico

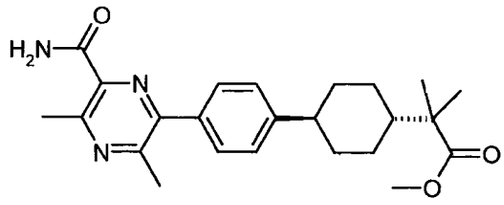


Se agregó hidroxido de potasio en polvo (193 mg, 3.44 mmol) en una porción al **Intermedio 42-1** (470 mg, 1.15 mmol) en tert-butanol (20 mL) a 40 °C bajo nitrógeno. La suspensión resultante se agitó a 40 °C durante 2 horas. La reacción estaba incompleta de manera que la temperatura se incrementó a 100 °C y la mezcla de reacción fue agitada durante 16 horas adicionales. La reacción fue apagada con ácido acético (0.329 mL, 5.74 mmol) en EtOH (10 mL) y la solución resultante se agitó durante 20 minutos adicionales antes de ser evaporadas hasta sequedad . El sólido resultante se particionó entre agua (50 mL) y EtOAc (50 mL). La solución

acuosa fue acidificada con 2M HCl (5 mL) y la capa orgánica se separó y la acuosa se re-extrajo con EtOAc (50 mL). Los orgánicos combinados fueron lavados con salmuera saturada (50 mL) y evaporados al vacío para proporcionar producto sólido crudo. Este fue recristalizado a partir de EtOH caliente (15 mL) y lavado con éter (10 mL) y secado al vacío a temperatura ambiente para proporcionar el compuesto del título (90 mg, 19.83 %) como un sólido rosa.

^{1}H NMR (400.13 MHz, DMSO) 8 1.06 (6H, s), 1.15 - 1.30 (2H, m), 1.43 - 1.56 (2H, m), 1.60 - 1.80 (3H, m), 1.80 - 1.95 (2H, m), 2.40 - 2.60 (1H, m), 2.58 (3H, s), 2.73 (3H, s), 3.29 (3H, s), 7.36 (2H, d), 7.57 (1H, s), 7.64 (2H, d), 7.97 (1H, s), 12.03 (1H, s); *m/z* 396 $(M+H)^+$.

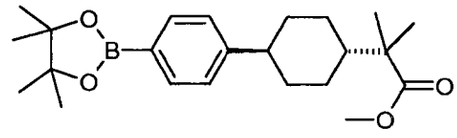
Intermedio 42-1: Metil 2-((1r,4r)-4-(4-(6-Carbamoil-3,5-dimetilpirazin-2-il)fenil)ciclohexil)-2-metilpropanoato



El compuesto se sintetizó a partir del **Intermedio** 42-2 y **Intermedio** 21-4 utilizando condiciones similares a las descritas en el **Intermedio** 25-1 para proporcionar el compuesto del título (494 mg, 44.8 %).

^{1}H NMR (400 MHz, $CDCl_3$) 8 1.10 (6H, s), 1.12 - 1.28 (2H, m), 1.40 - 1.53 (2H, m), 1.60 -1.73 (3H, m), 1.90 - 2.00 (2H, m), 2.43 - 2.52 (1H, m), 2.60 (3H, s), 2.91 (3H, s), 3.62 (3H, s), 5.42 (1H, s), 7.25 (2H, d), 7.44 (2H, dt), 7.72 (1H, s); *m/z* 410 $(M+H)^+$.

Intermedio 42-2: 2-metil-2-((1r,4r)-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)ciclohexil)propanoato de metilo

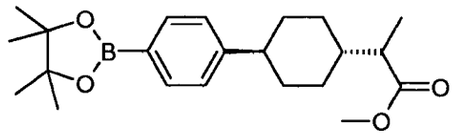


A una solución de diisopropilamina (4.83 mL, 34.17 mmol) en THF (50 mL) bajo nitrógeno, enfriada a -70 °C se agregó butilitio (21.35 mL, 34.17 mmol) por goteo mientras se mantenía la temperatura entre -70 y -60 °C. Luego de 30 minutos se agregó el **Intermedio 42-3** (3.18 g, 8.54 mmol) en THF (20 mL) y la mezcla se dejo calentar a-20 °C durante 90 minutos. La solución fue enfriada a -65 °C, se agregó yoduro de metilo (2.129 mL, 34.17 mmol) y se dejo agitar la reacción durante 1 hora y luego se dejo calentar a -30 °C. La reacción fue apagada con

cloruro de amonio saturado (100 mL), extraída con EtOAc (200 mL), la fase orgánicafue separada, lavads con agua (100 mL) y salmuera saturada (100 mL). La capa orgánica fue secada sobre $MgSO_4$, filtrada y evaporada para proporcionar el producto crudo (2.99 g). El producto crudo se purificó mediante cromatografía flash de gel de sílice, gradiente de elución entre 0 y 10% EtOAc en isohexano. Las fracciones puras se evaporaron hasta sequedad para proporcionar el compuesto del título (1.830 g, 55.5 %) como un sólido blanco.

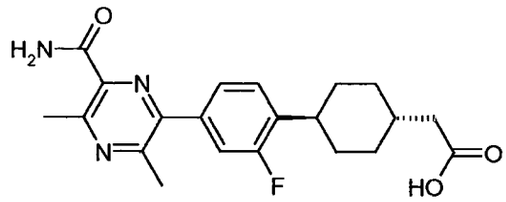
^{1}H NMR (400 MHz, $CDCl_3$) 8 1.15 (6H, s), 1.15 - 1.28 (2H, m), 1.33 (12H, s), 1.49 (2H, dd), 1.65 - 1.75 (3H, m), 1.90 - 1.98 (2H, m), 2.42 - 2.51 (1H, m), 3.68 (3H, d), 7.21 (2H, d), 7.74 (2H, dd); *m/z* (EI+) 386 M^+.

Intermedio 42-3: 2-((1r,4r)-4-(4-(4,4,5,5-tetrametil-1,3,2 -dioxaborolan-2-il)fenil)clohexil)propanoato de metilo



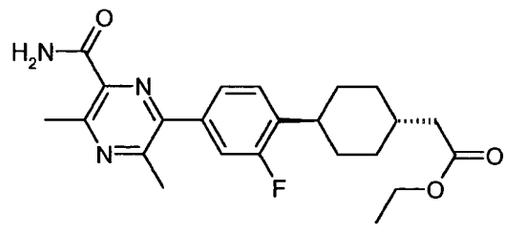
Se agregó bis(trimetilsilil)amida de litio (16.75 mL, 16.75 mmol) a 2-((1r,4r)-4-(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)ciclohexil)acetato de metilo (CAS 701232-69-1) (preparada según el procedimiento descrito en WO 2004047755) (5 g, 13.96 mmol) en THF (50 mL) a 0 °C bajo nitrógeno. La solución resultante se agitó a 0 °C durante 30 minutos y luego se agregó yoduro de metilo (1.304 mL, 20.93 mmol) y la reacción se agitó durante 30 minutos. La reacción fue apagada con cloruro de amonio saturado (50 mL), extraída con EtOAc (100 mL), la fase orgánicafue separada, lavada con agua (50 mL) y salmuera saturada (50 mL). La capa orgánica fue secada sobre $MgSO_4$, filtrada y evaporada para proporcionar el producto crudo. El producto crudo se purificó mediante cromatografía flash de gel de sílice, gradiente de elución entre 0 y 10% EtOAc en isohexano. Las fracciones puras se evaporaron hasta sequedad para proporcionar el compuesto del título (3.38 g, 65.1 %) como un sólido blanco. ^{1}H NMR (400 MHz, $CDCl_3$) 8 1.08 - 1.30 (5H, m), 1.33 (12H, s), 1.40 - 1.70 (3H, m), 1.70 -1.97 (4H, m), 2.31 (1H, t), 2.43 - 2.53 (1H, m), 3.68 (3H, m), 7.21 (2H, d), 7.74 (2H, d); *m/z* 395 $(M+Na)^+$.

Ejemplo 43: Ácido 2-((1r,4r)-4-(4-(6-carbamoil-3,5-dimetilpirazin-2-il)-2-fluorofenil)ciclohexilacético



El compuesto se sintetizó a partir del **Intermedio 43-1** utilizando condiciones similares a las descritas en el **Ejemplo 21.** Excepto que el producto crudo se purificó mediante recristalización a partir de EtOH en bullición (6 mL) para proporcionar el compuesto del título (89 mg, 43.6 %). ^{1}H NMR(400 MHz, DMSO) 8 1.09 - 1.22 (3H, m), 1.53-1.61 (2H, m), 1.72 - 1.89 (4H, m), 2.14 - 2.16 (2H, m), 2.60 (3H, s), 2.73 (3H, s), 2.79 - 2.87 (1H, m), 7.43 - 7.48 (1H, m), 7.53 (1H, d), 7.56 - 7.60 (2H, m), 8.04 (1H, s), 12.11 (1H, s); *m/z* 386 $(M+H)^+$.

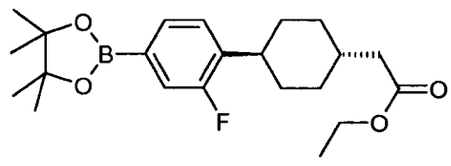
Intermedio 43-1: 2-((1r,4r)-4-(4-(6-Carbamoil-3,5-dimetilpirazin-2-il)-2-fluorofenil)ciclohexilacetato de etilo



El compuesto se sintetizó a partir del **Intermedio 43-2** y **Intermedio 21-4** utilizando condiciones similares a las descritas en el **Intermedio 21-1** para proporcionar el compuesto del título (0.219 g, 23.90 %) como un aceite incoloro.

^{1}H NMR (400 MHz, $CDCl_3$) 8 1.21 (3H, t), 1.54 - 1.64 (2H, m), 1.87 - 1.98 (7H, m), 2.26 (2H, d), 2.67 (3H, s), 2.86 - 2.94 (1H, m), 2.98 (3H, s), 4.13 - 4.18 (2H, m), 5.91 (1H, s), 7.24 - 7.36 (3H, m), 7.78 (1H, s); *m/z* 414 $(M+H)^+$.

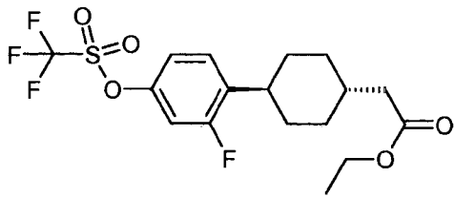
Intermedio 43-2: 2-((1r,4r)-4-(2-fluoro-4-(4,4,5,5-tetrametil-l,3,2-dioxaborolan-2-il)fenil)ciclohexil)acetato de etilo



El compuesto se sintetizó a partir del **Intermedio 43-3** utilizando condiciones similares a las descritas en el **Intermedio 25-2** para proporcionar el compuesto del título (0.865 g, 43.8 %) como un sólido cristalino blanco.

^{1}H NMR (400 MHz, $CDCl_3$) 8 1.09 - 1.17 (2H, m), 1.21 (3H, t), 1.26 (2H, s), 1.46 (12H, s), 1.48 - 1.54 (2H, m), 1.78 - 1.87 (4H, m), 2.73 - 2.81 (1H, m), 3.42 (1H, d), 4.05 - 4.11 (2H, m), 7.11 (1H, d), 7.14 (1H, d), 7.19 - 7.21 (1H, m).

Intermedio 43-3: 2-((1r,4r)-4-(2-fluoro-4-(trifluorometilsulfoniloxi)-fenil)ciclohexil)acetato de etilo



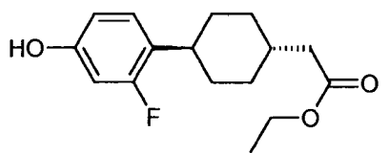
El compuesto se sintetizó a partir del **Intermedio 43-4** utilizando condiciones similares a aquellas descritas en el **Intermedio 25-4** para proporcionar el compuesto del título (2.087 g, 62.2 %) como un aceite amarillo.

^{1}H NMR (400 MHz, $CDCl_3$) 8 1.14 - 1.25 (2H, m), 1.27 (3H, t), 1.46 - 1.56 (3H, m), 1.83 -1.94 (4H, m), 2.24 (2H, d), 2.79 - 2.87 (1H, m), 4.12 - 4.17 (2H, m), 6.96 - 6.99 (1H, m), 7.01 - 7.05 (1H, m), 7.27 - 7.31 (lH,m); *m/z* 411 (M-H)".

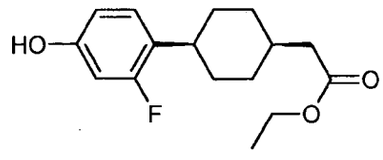
Intermedio 43-4: 2-((1r,4r)-4-(2-fluoro-4-hidroxifenil)-ciclohexil)acetato de etilo

y

Intermedio 43-5: 2-((1s,4s)-4-(2-fluoro-4-hidroxifenil)-ciclohexil)acetato de etilo



Intermedio 43-4



Intermedio 43-5

Se evacuó **Intermedio 43-6** (6.29 g, 22.60 mmol) y paladio sobre carbono (10%) (0.6 g, 0.56 mmol) en EtOH (200 mL) (4 ciclos) y luego se agitó bajo un globo de hidrógeno a temperatura ambiente durante 2 horas. La mezcla de reacción fue filtrada y evaporada para proporcionar un aceite incoloro. El producto crudo se purificó mediante cromatografía flash de gel de sílice, gradiente de elución entre 10 y 20% EtOAc en isohexano. Las fracciones puras se

evaporaron hasta sequedad para proporcionar el producto deseado como una mezcla de isomeros cis y trans como un aceite incoloro el cual se purificó adicionalmente mediante quiral-HPLC preparativa sobre una columna Chiralcel OJ, eluyendo isocraticamente con 10% IPA en isohexano como eluente. Las fracciones conteniendo los compuestos deseados se evaporaron hasta sequedad para proporcionar el **Intermedio 43-4** (2.28g, 36%) como un sólido blanco y el **Intermedio 43-5** (3.08 g, 48.6 %) como una goma color amarillo pálido.

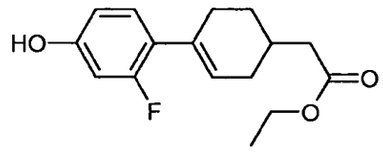
Intermedio 43-4

^{1}H NMR (400 MHz, $CDCl_3$) 8 1.11 - 1.24 (2H, m), 1.26 (3H, t), 1.42 - 1.53 (2H, m), 1.80 -1.89 (5H, m), 2.23 (2H, d), 2.69 - 2.76 (1H, m), 4.14 (2H, q), 4.82 (1H, s), 6.50 - 6.57 (2H, m), 7.04 (1H, t); *m/z* (EI+) 280 M^+.

Intermedio 43-5

^{1}H NMR (400 MHz, $CDCl_3$) 8 1.27 (3H, t), 1.59 - 1.76 (8H, m), 2.29 - 2.36 (1H, m), 2.45(2H, d), 2.75 - 2.83 (1H, m), 4.15 (2H, q), 4.94 (1H, s), 6.51 - 6.57 (2H, m), 7.08 (1H, t); *m/z* (EI+) 280 M^+.

Intermedio 43-6: 2-(4-(2-fluoro-4-hidroxifenil)ciclohex-3-enil)acetato de etilo

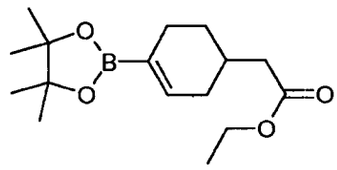


Se agregó una solución del **Intermedio 43-7** (18.48 g, 62.82 mmol) en DMF (100 mL) a una suspensión agitada de 4-bromo-3-fluorofenol (10 g, 52.36 mmol), carbonato de potasio (21.71 g, 157.07 mmol) y [1,1-Bis(difenilfosfino)ferroceno]dicloropaladio(II) (1.163 g, 1.41 mmol) en DMF (100 mL) a temperatura ambiente. La suspensión resultante se agitó a 80 °C bajo nitrógeno durante 2 horas. La reacción estaba incompleta de manera que la temperatura se incrementó a 100 °C y la mezcla de reacción se agitó durante 30 minutos adicionales y luego se agregó [1,1-Bis(difenilfosfino) ferroceno]dicloropaladio(II) adicional (1.163 g, 1.41 mmol) y la suspensión se agitó a 100 °C durante 45 minutos adicionales y luego se agregó [1,1-Bis(difenilfosfino)ferroceno]dicloropaladio(II) adicional (400 mg, 0.487 mmol) y la suspensión se agitó a 100 °C durante 45 minutos adicionales. La mezcla de reacción se evaporó hasta sequedad y redisolvió en EtOAc (200 mL) y se agregó 2M HCl (250 mL) cuidadosamente. La solución acuosa se extrajo adicionalmente con EtOAc (3 x 200 mL) y los extractos organicos se combinaron, lavaron con salmuera saturada (300 mL), secaron sobre $MgSO_4$, filtraron y

evaporaron para proporcionar el producto crudo. El producto crudo se purificó mediante cromatografía flash de gel de sílice, gradiente de elución entre 0 y 20% EtOAc en isohexano. Las fracciones puras se evaporaron hasta sequedad para proporcionar el compuesto del título (6.34 g, 43.5 %) como un aceite amarillo pálido.

^{1}H NMR (400 MHz, $CDCl_3$) 8 1.27 (3H, t), 1.41 - 1.50 (1H, m), 1.85 - 1.95 (2H, m), 2.14 -2.21 (1H, m), 2.32 (2H, d), 2.32 - 2.48 (3H, m), 4.16 (2H, q), 4.98 (1H, s), 5.81 (1H, s), 6.51 - 6.56 (2H, m), 7.05 - 7.09 (1H, m); *m/z* 277 (M-H)".

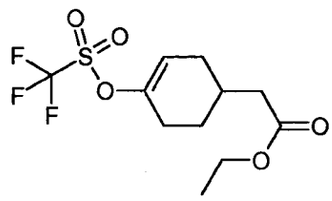
Intermedio 43-7: 2-(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)ciclohex-3-enil)acetato de etilo



El compuesto se sintetizó a partir del **Intermedio 43-8** utilizando condiciones similares a las descritas en el **Intermedio 25-2** para proporcionar el compuesto del título (10.4 g, 71 %) como un aceite incoloro.

^{1}H NMR (300 MHz, $CDCl_3$) 81.24 - 1.28 (18H, m), 1.77 - 1.80 (2H, m), 2.18 - 2.27 (2H, m), 2.20 - 2.24 (2H, m), 4.09 - 4.16 (2H, m), 6.51 (1H, d)

Intermedio 43-8: 2-(4-(trifluorometilsulfoniloxi)ciclohex-3-enil)acetato de etilo

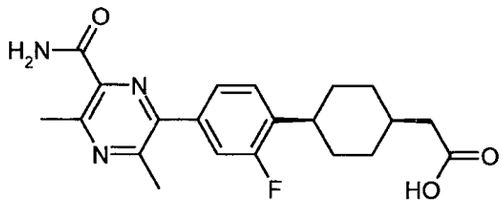


Se agregó anhidruro triflurpmetanesulfonico (11.9 mL, 70.86 mmol) por porción a una solución de 2,6-di-tert-butil-4-metilpiridina (18.19 g, 88.58 mmol) en DCM (250 mL). Luego se agregó una solución de 2-(4-oxociclohexil)acetato de etilo (10.88 g, 59.05 mmol, CAS 58012-34-3) en DCM (100 mL) por goteo y se dejo agitar la mezcla de reacción destapada y a temperatura ambiente durante la noche. La mezcla de reacción se lavó con agua, saturada Na_2CO_3, salmuera saturada, secada sobre $MgSO_4$ y evaporada para proporcionar el producto crudo. El producto crudo se purificó mediante cromatografía flash de gel de sílice, gradiente de elución entre 0 y

10% EtOAcen isohexano. Las fracciones puras se evaporaron hasta sequedad para proporcionar el compuesto del título (16.05 g, 86 %) como un aceite amarillo.

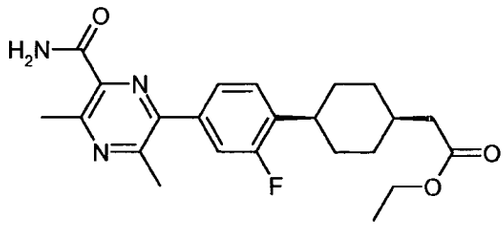
^{1}H NMR (300 MHz, $CDCl_3$) 8 1.22 - 1.29 (3H, m), 1.39 - 1.51 (1H, m), 1.76 - 1.85 (2H, m), 2.07 - 2.23 (4H, m), 2.29 (2H, d), 4.09 - 4.18 (2H, m), 4.96 (1H, s).

Ejemplo 44: Ácido 2-((1s,4s)-4-(4-(6-Carbamoil-3,5-dimetilpirazin-2-il)-2-fluorofenil)ciclohexil)acético



Este compuesto se sintetizó a partir del **Intermedio 44-1** utilizando condiciones similares a las descritas en el **Ejemplo 21** para proporcionar el compuesto del título (252 mg, 71%) como un sólido blanco. ^{1}H NMR (400 MHz, DMSO) 8 1.65 (8H, m), 2.22 (1H, m), 2.41 (2H, d), 2.60 (3H, s), 2.74 (3H, s), 2.88 (1H, m), 7.53 (4H, m), 8.05 (1H, s), 12.03 (1H, s); *m/z* 386 $(M+H)^+$.

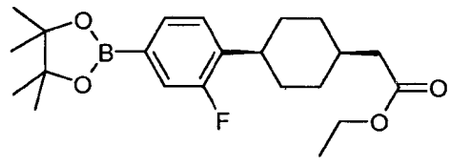
Intermedio 44-1: 2-((1s,4s)-4-(4-(6-Carbamoil-3,5-dimetilpirazin-2-il)-2-fluorofenil)ciclohexilacetato de etilo



Este compuesto se sintetizó a partir del **Intermedio 44-2** y **Intermedio 21-4** utilizando condiciones similares a las descritas en el **Intermedio 21-1** para proporcionar el compuesto del título (453 mg, 68%) como un sólido amarillo pálido.

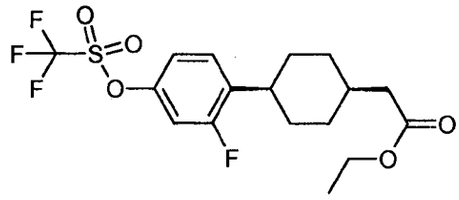
^{1}H NMR (400 MHz, $CDCl_3$) 8 1.28 (3H, t), 1.74 (8H, m), 2.39 (1H, m), 2.48 (2H, d), 2.68 (3H, s), 2.97 (4H, m), 4.16 (2H, q), 5.51 (1H, s), 7.26 (1H, m), 7.32 (1H, m), 7.38 (1H, t), 7.75 (1H, s); *m/z* 414 $(M+H)^+$.

Intermedio 44-2: 2-((1s,4s)-4-(2-fluoro-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)ciclohexil)acetato de etilo



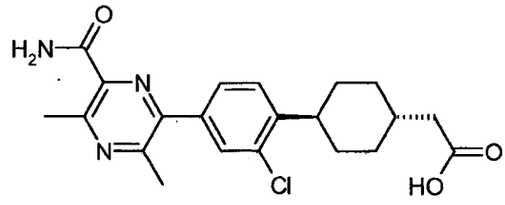
Este compuesto se sintetizó a partir del **Intermedio 44-3** utilizando condiciones similares a las descritas en el **Intermedio 25-2** para proporcionar el compuesto del título (1.45 g, 61%) como un sólido blanco. ^{1}H NMR (400 MHz, $CDCl_3$) 8 1.27 (3H, t), 1.32 (12H, s), 1.67 (8H, m), 2.35 (1H, m), 2.46 (2H, d), 2.89 (1H, m), 4.14 (2H, q), 7.25 (1H, t), 7.42 (1H, d), 7.52 (1H, d); m/z (ES+) (M+H)+ = no ión de masa; HPLC tR= 3.62 min.

Intermedio 44-3: 2-((1s,4s)-4-(2-fluoro-4-(trifluorometilsulfoniloxi)-fenil)ciclohexil)acetato de etilo



Este compuesto se sintetizó a partir del **Intermedio 43-5** utilizando condiciones similares a las descritas en el **Intermedio 25-4** para proporcionar el compuesto del título (2.53 g, 86 %) como un aceite amarillo. ^{1}H NMR (400 MHz, DMSO) 8 1.12 (3H, t), 1.55 (8H, m), 2.15 (1H, m), 2.41 (2H, d), 2.77 (1H, m), 4.00 (3H, q), 7.24 (1H, m), 7.43 (1H, m), 7.56 (1H, t); *m/z* (ES-) 411 $(M-H)^-$.

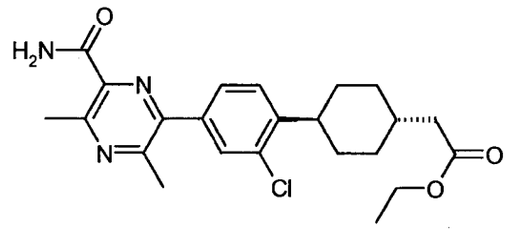
Ejemplo 45: 2-((1r,4r)-4-(4-(6-Carbamoil-3,5-dimetilpirazin-2-il)-2-clorofenil)ciclohexil)acético



El compuesto se sintetizó a partir del **Intermedio 45-1** utilizando condiciones similares a las descritas en el **Ejemplo 21.** Excepto que el producto crudo se recristalizó a partir de EtOH caliente (15 mL) para proporcionar un sólido el cual se lavó con éter (10 mL) y secó al vacío a temperatura ambiente para proporcionar el compuesto del título (313 mg, 80 %).

^{1}H NMR (400 MHz, DMSO) 8 1.12 - 1.23 (2H, m), 1.49 - 1.60 (2H, m), 1.76 - 1.90 (5H, m), 2.18 (2H, d), 2.60 (3H, s), 2.75 (3H, s), 2.91 - 3.00 (1H, m), 7.52 (1H, d), 7.65 (1H, s), 7.67 -7.70 (1H, m), 7.84 (1H, d), 8.10 (1H, s), 12.09 (1H, s); *m/z* 402 $(M+H)^+$.

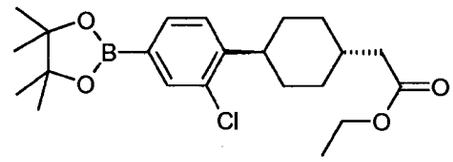
Intermedio 45-1: 2-((1r,4r)-4-(4-(6-Carbamoil-3,5-dimetilpirazin-2-il)-2-clorofenil)ciclohexil)acetato de etilo



Este compuesto se sintetizó a partir del **Intermedio 45-2** y **Intermedio 21-4** utilizando condiciones similares como descrito en el **Intermedio 21-1** para proporcionar el compuesto del título (482 mg, 91%) como un sólido amarillo.

^{1}H NMR (400 MHz, $CDCl_3$) 8 1.21 (3H, t), 1.40 - 1.47 (1H, m), 1.84 - 1.94 (4H, m), 2.20 (2H, d), 2.60 (3H, s), 2.91 (3H, s), 2.94 - 3.02 (1H, m), 3.42 (4H, d), 4.06 - 4.11 (2H, m), 5.40 (1H, s), 7.29 - 7.32 (1H, m), 7.36 - 7.38 (1H, m), 7.51 (1H, d), 7.67 (1H, s); *m/z* 430 $(M+H)^+$.

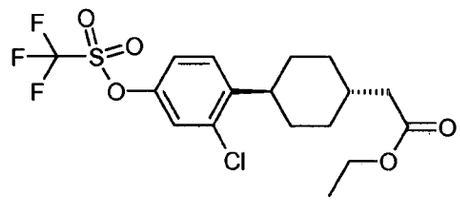
Intermedio 45-2: 2-((1r,4r)-4-(2-Cloro-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)ciclohexil)acetato de etilo



Este compuesto se sintetizó a partir del **Intermedio 45-3** utilizando condiciones similares a las descritas en el **Intermedio 25-2** para proporcionar el compuesto del título (1.046 g, 70.7 %) como un aceite incoloro el cual se recristalizó al sentarse.

^{1}H NMR (400 MHz, $CDCl_3$) 8 0.76 - 0.87 (4H, m), 1.20 (3H, t), 1.35-1.44 (1H, m), 1.48 (12H, s), 1.80 - 1.86 (4H, m), 2.18 (2H, d), 2.89 - 2.97 (1H, m), 4.05 - 4.10 (2H, m), 7.18 (1H, d), 7.56 (1H, d), 7.70 (1H, d); *m/z* 430 $(M+Na)^+$.

Intermedio 45-3: Etil 2-((1r,4r)-4-(2-Cloro-4-(trifluorometil-sulfoniloxy)fenil)ciclohexil)acetato

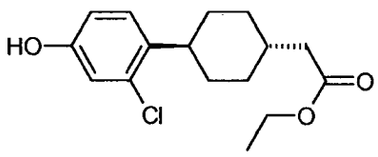


Este compuesto se sintetizó a partir del **Intermedio 45-4** utilizando condiciones similares a las descritas en el **Intermedio 25-4** para proporcionar el compuesto del título (1.560 g, 85 %) como un aceite amarillo. ^{1}H NMR (400 MHz, $CDCl_3$) 8 1.18 - 1.29 (4H, m), 1.39 - 1.49 (2H, m), 1.88 - 1.95 (4H, m), 2.25 (2H, d), 2.93 - 3.01 (1H, m), 3.49 (2H, d), 4.12 - 4.18 (2H, m), 7.14 - 7.17 (1H, m), 7.29 (1H, d), 7.32 (1H, d); *m/z* 427 $(M-H)^-$.

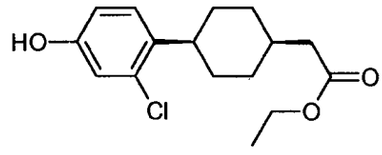
Intermedio 45-4: 2-((1r,4r)-4-(2-cloro-4-hidroxifenil)-ciclohexil)acetato de etilo

y

Intermedio 45-5: 2-((1s,4s)-4-(2-cloro-4-hidroxifenil)ciclohexil)acetato de etilo



Intermedio 45-4



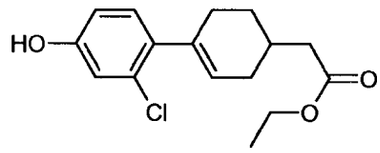
Intermedio 45-5

Estos compuestos se sintetizaron a partir del **Intermedio 45-6** utilizando condiciones similares a las descritas en el **Intermedio 43-4** y **43-5,** excepto quedespues de la cromatografía de sílice el producto crudo se purificó mediante HPLC preparativa (columna Phenomenex Gemini C18 110A (axia), 5p, sílice, 21 mm diametro, 150 mm longitud), utilizando mezclas decrecientemente polares de agua (conteniendo 0.1% ácido fórmico) y MeCN como eluentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para proporcionar el producto crudo como una mezcla de isómeros (5.78 g, 49.9 %) como un aceite incoloro. El aceite se purificó mediante quiral-HPLC preparativa sobre una columna Merck 50mm 20uM Chiralcel OJ, eluyendo isocraticamente con 70% isohexano en IPA (modificado con AcOH/Et_3N) como eluente. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para proporcionar **Intermedio 45-4** (1.264 g, 21.87 %) como un sólido blanco y el **Intermedio 45-5** (3.52 g, 60.9 %) como un sólido blanco. **Intermedio 45-4:**

^{1}H NMR (400 MHz, $CDCl_3$) 8 1.13 - 1.24 (2H, m), 1.27 (3H, t), 1.34 - 1.45 (2H, m), 1.80 - 1.91 (5H, m), 2.24 (2H, d), 2.84 - 2.92 (1H, m), 4.12 - 4.18 (2H, m), 6.70 - 6.73 (1H, m), 6.86 (1H, d), 7.08 (1H, d) fenol OH no se observó; m/z (ES-) (M-H)- = 295, 297 **Intermedio 45-5:**

^{1}H NMR (400 MHz, $CDCl_3$) 8 1.27 (3H, t), 1.46 - 1.58 (3H, m), 1.65 - 1.78 (5H, m), 2.33 - 2.40 (1H, m), 2.47 (2H, d), 2.89 - 2.96 (1H, m), 4.13 - 4.18 (2H, m), 6.70 - 6.73 (1H, m), 6.86 (1H, d), 7.12 (1H, d) fenol OH no observado; m/z (ES-) (M-H)- = 295, 297

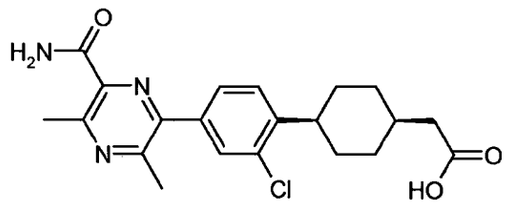
Intermedio 45-6: 2-(4-(2-cloro-4-hidroxifenil)ciclohex-3-enil)acetato de etilo



Este compuesto se sintetizó a partir del **Intermedio 43-7** y 4-bromo-3-clorofenol utilizando condiciones similares a las descritas en el **Intermedio 43-6** para proporcionar el compuesto del título (5.30 g, 74.7 %) como un aceite incoloro.

^{1}H NMR (400 MHz, $CDCl_3$) 8 1.21 (3H, t), 1.36 - 1.45 (1H, m), 1.58 (1H, s), 1.76 - 1.87 (2H, m), 2.07 - 2.17 (1H, m), 2.22 - 2.29 (4H, m), 4.07 - 4.12 (2H, m), 5.16 (1H, s), 5.50 -5.52 (1H, m), 6.59 - 6.62 (1H, m), 6.78 (1H, d), 6.93 (1H, d); *m/z* 293 $(M-H)^-$.

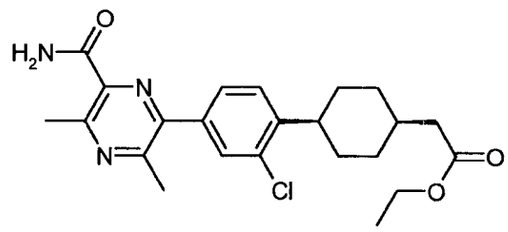
Ejemplo 46: Ácido 2-((1s,4s)-4-(4-(6-Carbamoil-3,5-dimetilpirazin-2-il)-2-clorofenil)ciclohexil)acético



Este compuesto se sintetizó a partir del **Intermedio 46-1** utilizando condiciones similares a las descritas en el **Ejemplo 21** para proporcionar el compuesto del título (184 mg, 44 %) como un sólido blanco.

^{1}H NMR (400 MHz, DMSO) 8 1.65 (8H, m), 2.24 (1H, m), 2.44 (2H, d), 2.59 (3H, s), 2.73 (3H, s), 2.99 (1H, m), 7.58 (2H, m), 7.67 (1H, d), 7.81 (1H, s), 8.05 (1H, s), 12.01 (1H, s); *m/z* 402 $(M+H)^+$.

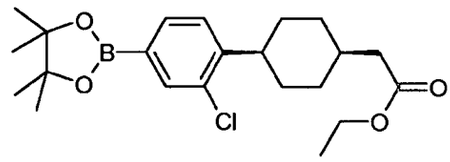
Intermedio 46-1: 2-((1s,4s)-4-(4-(6-Carbamoil-3,5-dimetilpirazin-2-il)-2-clorofenil)ciclohexil)acetato de etilo



Este compuesto se sintetizó a partir del **Intermedio 46-2** y **Intermedio 21-4** utilizando condiciones similares a las descritas en el **Intermedio 21-1** para proporcionar el compuesto del título (365 mg, 78 %) como una goma incolora.

^{1}H NMR (400 MHz, $CDCl_3$) 8 1.28 (3H, t), 1.67 (2H, m), 1.78 (6H, m), 2.42 (1H, m), 2.50 (2H, d), 2.67 (3H, s), 2.98 (3H, s), 3.10 (1H, m), 4.16 (2H, m), 5.53 (1H, s), 7.43 (2H, m), 7.59 (1H, d), 7.75 (1H, s); *m/z* 430 $(M+H)^+$.

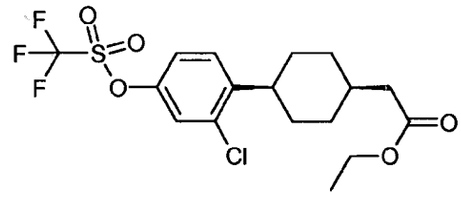
Intermedio 46-2: 2-((1s,4s)-4-(2-Cloro-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)ciclohexil)acetato de etilo



Este compuesto se sintetizó a partir del **Intermedio 46-3** utilizando condiciones similares a aquellas descritas en el **Intermedio 25-2** para proporcionar el compuesto del título (1.19g, 62%) como un aceite incoloro.

^{1}H NMR (400 MHz, $CDCl_3$) 8 1.27 (3H, t), 1.33 (12H, s), 1.59 (2H, m), 1.72 (6H, m), 2.39 (1H, m), 2.47 (2H, d), 3.05 (1H, m), 4.15 (2H, q), 7.28 (1H, t), 7.64 (1H, d), 7.77 (1H, s); *m/z* 430 $(M+Na)^+$.

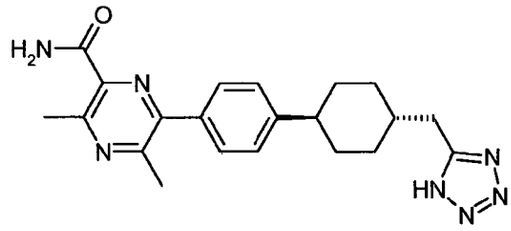
Intermedio 46-3: 2-((1s,4s)-4-(2-cloro-4-(trifluorometil-sulfoniloxi)fenil)ciclohexil)acetato de etilo



Este compuesto se sintetizó a partir del **Intermedio 45-5** utilizando condiciones similares a las descritas en el **Intermedio 25-4** para proporcionar el compuesto del título (2.051 g, 71.0 %) como un aceite incoloro.

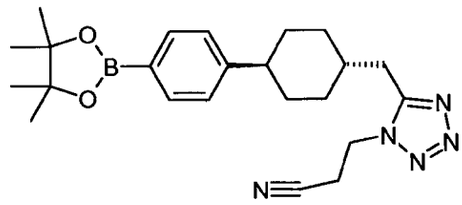
^{1}H NMR (400 MHz, $CDCl_3$) 8 1.26 (3H, t), 1.56 (2H, m), 1.73 (6H, m), 2.40 (1H, m), 2.46 (2H, d), 3.02 (1H, t), 4.16 (1H, q), 7.16 (1H, m), 7.30 (1H, d), 7.37 (1H, d); *m/z* 427 (M-H)".

Ejemplo 47: 6-(4-((1r,4r)-4-((1H-Tetrazol-5-il)metil)clohexil)fenil)-3,5-dimetilpirazina-2-carboxamida



El compuesto se sintetizó a partir del **Intermedio 47-1** utilizando condiciones similares a las descritas en el **Ejemplo 28** para proporcionar el compuesto del título (220 mg, 41.7 %) como un sólido blanco. El material fue recristalizado a partir de metanol caliente, filtrado y lavado con éter antes de secarlo al vacío para proporcionar el compuesto del título (223 mg, 42.3 %). ^{1}H NMR (300 MHz, DMSO) 8 1.13 - 1.27 (2H, m), 1.43 - 1.56 (2H, m), 1.74 - 1.88 (5H, m), 2.53 - 2.57 (1H, m), 2.58 (3H, s), 2.74 (3H, s), 2.84 (2H, d), 7.35 (2H, d), 7.58 (1H, s), 7.65 (2H, d), 7.97 (1H, s), 16.00 (1H, s); *m/z* 392 $(M+H)^+$.

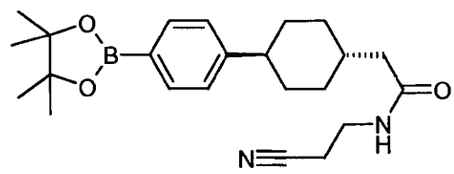
Intermedio 47-1: 3-(5-(((1r,4r)-4-(4-(4,4,5,5-Tetrametil-1,3,2-dioxaborolan-2-il)fenil)ciclohexil)metil)-1H-tetrazol-1-il)propanonitrilo



El compuesto se sintetizó a partir del **Intermedio 47-2** utilizando condiciones similares a las descritas en el **Intermedio 28-1** para proporcionar el compuesto del título (1.960 g, 59.9 %) contaminado con oxido de trifenilfosfina (3 mol %).

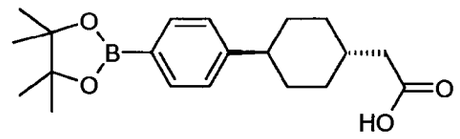
^{1}H NMR (400 MHz, DMSO) 8 0.96-1.05 (2H,m), 1.06 (12H, s), 1.19- 1.30 (2H,m), 1.54 - 1.64 (5H, m), 2.67 (2H, d), 2.97 (2H, t), 3.07 (1H, s), 4.47 (2H, t), 7.02 (2H, d), 7.37 (2H, d);HPLCtR=2.81.

Intermedio 47-2: N-(2-Cianoetil)-2-((1r,4r)-4-(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)ciclohexil)acetamida



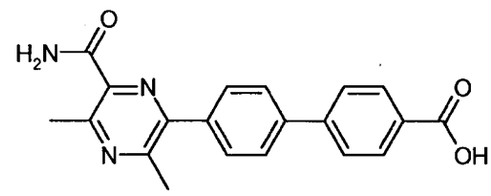
El compuesto se sintetizó a partir del **Intermedio 47-3** utilizando condiciones similares a las descritas en el **Intermedio 28-2** para proporcionar el compuesto del título (3.08 g, 77 %). ^{1}H NMR (400 MHz, DMSO) 8 1.03 - 1.13 (2H, m), 1.27 (12H, s), 1.37 - 1.47 (2H, m), 1.71 - 1.80 (5H, m), 2.02 (2H, d), 2.63 (2H, t), 7.22 (2H, d), 7.58 (2H, d), 8.16 (1H, t), 3 x CH opacado por solvente.

Intermedio 47-3: Ácido 2-((1r,4r)-4-(4-(4,4,5,5-Tetrametil-1,3,2-dioxaborolan-2-il)fenil)ciclohexil)acético



Se disolvió 2-((1r,4r)-4-(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)ciclohexil)acetato de metilo (CAS 701232-69-1, preparada según el procedimiento descrito en WO 2004/047755) (3.6 g, 10.05 mmol) en una solución de hidroxido de sodio (1.326 g, 33.16 mmol) en metanol (36 mL) y agua (4.00 mL). La mezcla de reacción se partió en dos y se calento a 120 °C durante 30 min en un microondas. La mezcla de reaccións se combinó, acidificó con 2M HCl y evaporó. El producto crudo se llevó al siguiente paso sin purificación. ^{1}H NMR (400 MHz, DMSO) 8 1.08 - 1.12 (2H, m), 1.27 (12H, s), 1.42 - 1.46 (2H, m), 1.74 - 1.82 (5H, m), 2.13 (2H, d), 7.22 (2H, d), 7.58 (2H, d) un CH y COOH no observados.

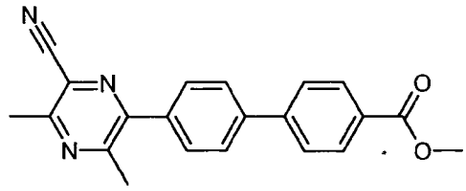
Ejemplo 48: Ácido 4'-(6-Carbamoil-3,5-dimetilpirazin-2-il)bifenil-4-carboxílico



El compuesto se sintetizó a partir del **Intermedio 48-1** utilizando condiciones similares aa las descritas en el **Ejemplo 21** para proporcionar el compuesto del título (42.2 mg, 74.5 %) como un sólido blancuzco.

^{1}H NMR (400 MHz, DMSO) 8 2.58 (3H, s), 2.70 (3H, s), 3.57 (2H, s), 7.32 (2H, d), 7.55 (1H, s), 7.64 (2H, d), 7.73 (2H, d), 7.78 (2H, d), 7.96 (1H, s), 12.29 (1H, s); *m/z* 362 $(M+H)^+$.

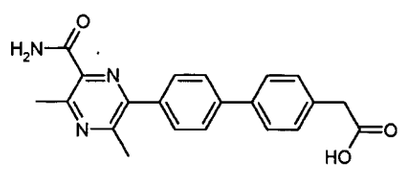
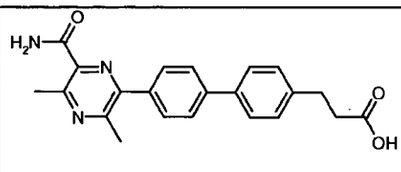
Intermedio 48-1: 4'-(6-Ciano-3,5-dimetilpirazin-2-il)bifenil-4-carboxilato de metilo

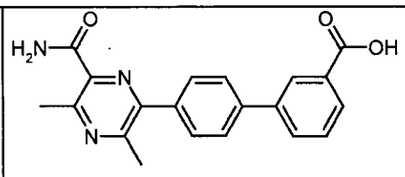
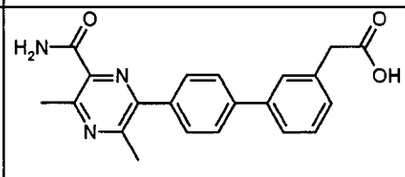
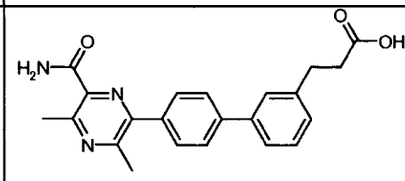


El compuesto se sintetizó a partir del **Intermedio 33-3** y 4-bromobenzoato de metiloutilizando condiciones similares a las descritas en el **Intermedio 21-1** para proporcionar el compuesto del título (124 mg, 72.1 %) como un sólido blanco.

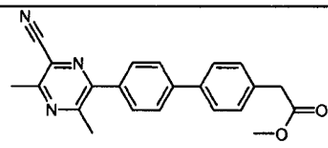
^{1}H NMR (400 MHz, DMSO) 8 2.68 (3H, s), 2.72 (3H, s), 3.89 (3H, s), 7.80 (2H, d), 7.89 -7.93 (4H, m), 8.07 (2H, d); HPLC tR= 2.92 min.

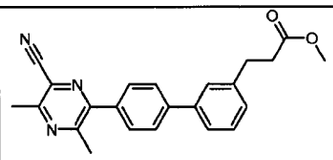
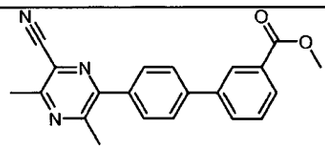
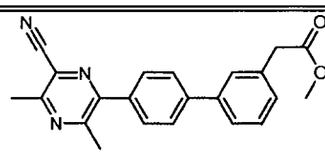
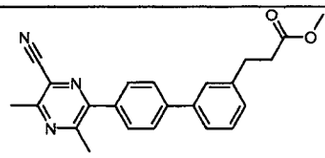
Los siguientes **Ejemplos** se sintetizaron a partir de los **Intermedios 49-1-a 53-1** utilizando condiciones similares a las descritas en el **Ejemplo 21** para proporcionar los compuestos deseados.

Ejemplo	**Estructura**	**^{1}H NMR (400 MHz, DMSO) δ**	***m/z* $(M+H)^+$**
49		2.64 (3H, s), 2.76 (3H, s), 3.63 (2H, s), 7.38 (2H, d), 7.61 (1H, s), 7.70 (2H, d), 7.79 (2H, d), 7.84 (2H, d), 8.02 (lH,s), 12.33 (1H, s).	362
50		2.55 (2H, t), 2.64 (3H, s), 2.75 (3H, s), 2.87 (2H, t), 7.35 (2H, d), 7.61 (1H, s), 7.65 (2H, d), 7.77 (2H, d), 7.83 (2H, d), 8.02 (1H, s), COOH no se observó.	376

51		2.65 (3H, s), 2.76 (3H, s), 7.35 (lH,t), 7.61 (2H,d), 7.77 (2H, d), 7.82 - 7.86 (3H,m), 8.05 (lH,s), 8.19 (1H, s), COOH no se observó.	348
52		2.71 (3H, s), 2.82 (3H, s), 3.74 (2H, s), 7.36 (1H, d), 7.51 (lH,t), 7.69 (3H,d), 7.85 (2H, d), 7.92 (2H, d), 8.09 (1H, s), 12.43 (1H, s).	362
53		2.61 (2H,t), 2.64 (3H,s), 2.76 (3H, s), 2.92 (2H, t), 7.26 (1H, d), 7.40 (1H, t), 7.56 (1H, d), 7.60 - 7.63 (2H, m), 7.79 (2H, d), 7.84 (2H, d), 8.02 (lH,s), 12.12 (1H, s).	376

Los siguientes **Intermedios** se sintetizaron a partir del **Intermedio 33-3** y el bromuro de arilo apropiado o triflato utilizando condiciones similares a las descritas en el **Intermedio 21-1** para proporcionar los compuestos deseados.

Intermedio	**Estructura**	^{1}H NMR (**400** MHz, DMSO)δ	*m/z* $(M+H)^+$
49-l[a]		2.75 (3H, s), 2.79 (3H, s), 3.70 (3H, s), 3.81 (2H, s), 7.46 (2H, d), 7.78 (2H, d), 7.82 (2H, d), 7.89 (2H, d)	HPLC tR= 2.83 min

50-l[b]		2.73 - 2.77 (5H, m), 2.78 (3H, s), 2.98 (2H,t), 3.35 (3H, s), 7.42 (2H, d), 7.74 (2H, d), 7.81 (2H,d), 7.87 (2H, d)	HPLC tPv= 2.97 min.
51-l[c]		2.75 (3H, s), 2.79 (3H, s), 3.97 (3H, s), 7.74 (lH,t), 7.86 (2H, d), 7.95 (2H, d), 8.05-8.08 (lH,m), 8.10-8.13 (lH,m), 8.34 (lH,t).	HPLC **tPv=** 2.93 min.
52-l[d]		2.75 (3H, s), 2.79 (3H, s), 3.70 (3H, s), 3.85 (2H, s), 7.38 (1H, d), 7.52 (lH,t), 7.70 - 7.73 (2H, m), 7.83 (2H, d), 7.88 (2H, d).	358
53-l[e]		2.74 (3H, s), 2.76 - 2.80 (5H,m), 3.02 (2H,t), 3.66 (3H, s), 7.34 (1H, d), 7.48 (1H, t), 7.64 (1H, d), 7.68 - 7.69 (1H, m), 7.82 (2H, d), 7.89 (2H, d).	372

Nota: **49-l**[a] 2-(4-bromofenil)acetato de metilo, CAS 41841-16-1 se preparó según el procedimiento descrito por E. E. Knaus, *Bioorg. Med. Chem.,* 2005, **13,** 4694-4703.

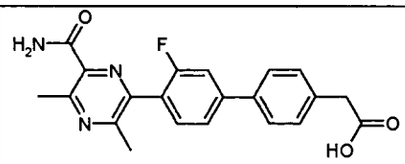
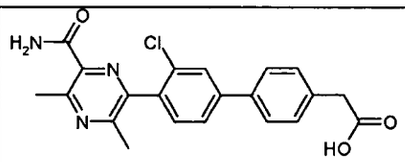
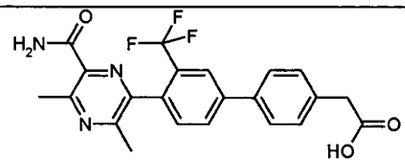
50-l[b] 3-(4-(trifluorometilsulfoniloxi)fenil)propanoato de metilo, CAS 475272-11-8. se preparó según el procedimiento descrito en WO 2002089738.

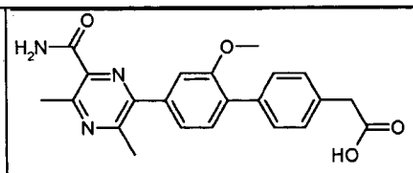
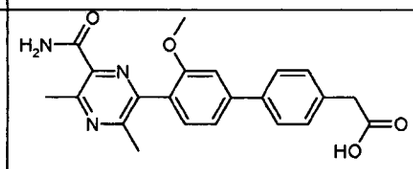
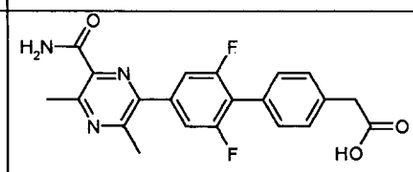
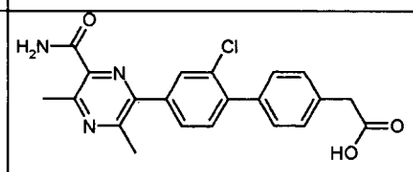
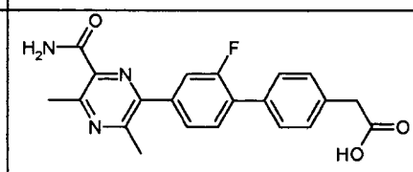
51-l[c] 3-bromobenzoato de metilo, CAS 618-89-3.

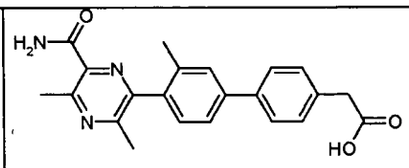
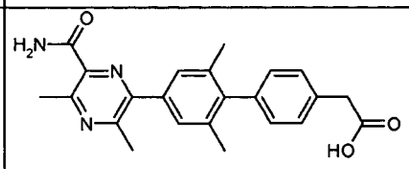
52-l[d] 2-(3-bromofenil)acetato de metilo, CAS 150529-73-0.

53-l[e] 3-(3-bromofenil)propanoato de metilo, CAS 151583-29-8 se preparó según el procedimiento descrito en WO 2007089667.

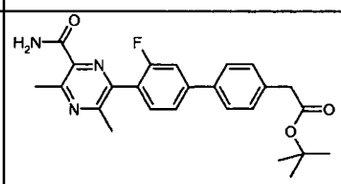
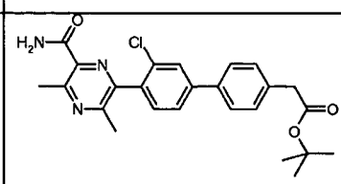
Los siguientes **Ejemplos 54 - 56** se sintetizaron a partir de los **Intermedios 54-1** a **56-1** utilizando condiciones similares a las descritas en el **Ejemplo 26** y los **Ejemplos 57** a **63** se sintetizaron a partir de los **Intermedios 57-1** a **63-1** utilizando condiciones similares a las descritas en el **Ejemplo 21.** Todos los productos crudos se purificaron mediante HPLC preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, 50 mm diametro, 150 mm longitud), utilizando mezclas decrecientemente polares de agua (conteniendo 0.1% ácido fórmico) y MeCN como eluentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para proporcionar los productos deseados.

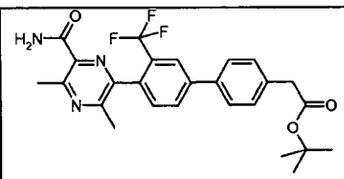
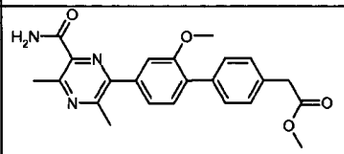
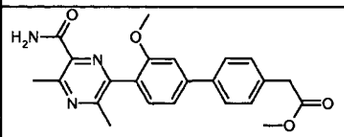
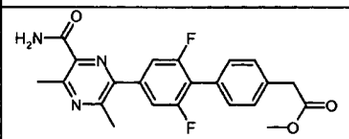
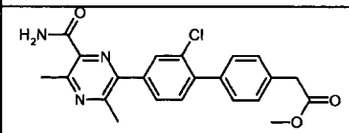
Ejemplo	**Estructura**	**^{1}H NMR (400 MHz, DMSO) δ**	***m/z*** **$(M+H)^+$**
54		2.45 (3H, s), 2.75 (3H, s), 3.62 (2H, s), 7.38 (2H, d), 7.60 (1H, s), 7.66 - 7.68 (3H, m), 7.73 (2H, d), 7.96 (1H, s), 12.33 (1H, s)	380
55		2.40 (3H, s), 2.78 (3H, s), 3.64 (2H, s), 7.39 (2H, d), 7.60 - 7.62 (2H, m), 7.73 (2H, d), 7.78-7.81 (1H, m), 7.90 (1H, d), 7.92 (1H, s), 12.35 (1H, s)	396
56		2.41 (3H, s), 2.87 (3H, s), 3.72 (2H, s), 7.49 (2H, d), 7.65 (1H, s), 7.75 (1H, d), 7.84 (3H, d), 8.17 (2H,t), COOH no se observó.	430

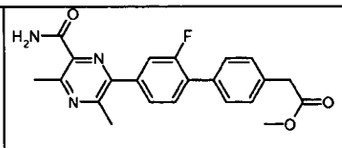
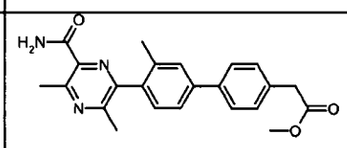
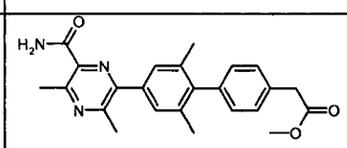
57		2.65 (3H, s), 2.76 (3H, s), 3.60 (2H, s), 3.83 (3H, s), 7.31 (2H,d), 7.34-7.43 (3H, m), 7.47 (2H, d), 7.60 (1H, s), 8.05 (1H, s), COOH no se observó.	392
58		2.37 (3H, s), 2.75 (3H, s), 3.63 (2H, s), 3.87 (3H, s), 7.35 - 7.40 (4H, m), 7.45 (1H, d), 7.55 (1H, s), 7.72 (2H,d),7.91(lH,s), 12.34 (lH,s).	392
59		2.75 (3H, s), 2.84 (3H, s), 3.72 (2H, s), 7.48 (2H, d), 7.53 (2H, d), 7.70 (1H, s), 7.74 - 7.80 (2H, m), 8.20 (1H, s), 12.47 (1H, s)	398
60		2.59 (3H, s), 2.71 (3H, s), 3.59 (2H, s), 7.32 - 7.34 (2H,m), 7.39-7.41 (2H, m), 7.48 (1H, d), 7.57 (1H, s), 7.73 - 7.75 (1H, m), 7.92 (1H, d), 8.04 (1H, s), 12.31 (lH,s).	396
61		2.68 (3H, s), 2.78 (3H, s), 3.66 (2H, s), 7.42 (2H, d), 7.59 (2H, dd), 7.64 (1H, m), 7.69 (2H, dd), 7.80 (1H, dd), 8.10 (1H, s), 12.40 (1H, s).	380

62		2.15 (3H,s), 2.37 (3H,s), 2.77 (3H, s), 3.62 (2H, s), 7.37 (3H, m), 7.54 (1H, s), 7.58 (1H, d), 7.67 (3H, m), 7.90 (1H, s), 12.34 (1H, s).	376
63		2.04 (6H, s), 2.63 (3H, s), 2.75 (3H, s), 3.63 (2H, s), 7.14 (2H, d), 7.37 (2H, d), 7.47 (2H, s), 7.60 (1H, s), 8.00 (lH,s), 12.33 (1H, s).	390

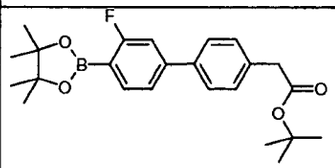
Los siguientes **Intermedios 54-1** a **63-1** se sintetizaron a partir de los **Intermedios 54-2** a **63-2** y el **Intermedio 21-4** utilizando condiciones similares a las descritas en el **Intermedio 21-1** para proporcionarlos compuestos deseados.

Intermedio	**Estructura**	**^{1}H NMR (400 MHz, DMSO) δ**	***m/z*** **$(M+H)^+$**
54-1		1.48 (9H,s), 2.53 (3H,s), 2.83 (3H, s), 3.69 (2H, s), 7.45 (2H, d), 7.69 (1H, s), 7.74 - 7.78 (3H, m), 7.82 (2H, d), 8.05 (1H, s)	436
55-1		1.42 (9H,s), 2.40 (3H,s), 2.78 (3H, s), 3.63 (2H, s), 7.38 (2H, d), 7.59 - 7.62 (2H, m), 7.74 (2H, d), 7.78 - 7.81 (lH,m), 7.90-7.91 (2H,m)	452

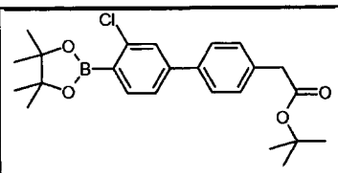
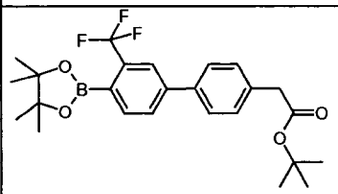
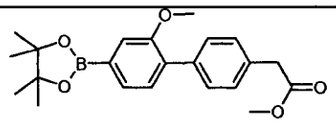
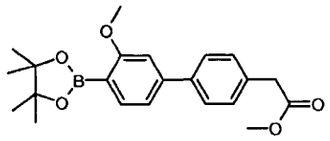
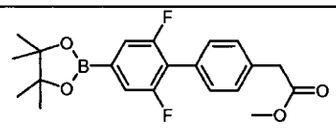
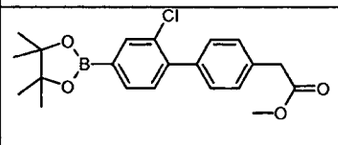
56-1		1.42 (9H,s), 2.34 (3H,s), 2.80 (3H, s), 3.64 (2H, s), 7.41 (2H, d), 7.59 (1H, s), 7.68 (1H, d), 7.75 (1H, s), 7.79 (2H,d), 8.09-8.11 (2H,m)	486
57-1		2.65 (3H, s), 2.77 (3H, s), 3.64 (3H, s), 3.72 (2H, s), 3.84 (3H, s), 7.31 (2H, d), 7.36 - 7.42 (3H, m), 7.49 (2H, d), 7.61 (1H, s), 8.05 (1H, s)	406
58-1		2.37 (3H, s), 2.75 (3H, s), 3.64 (3H, s), 3.75 (2H, s), 3.87 (3H, s), 7.36 - 7.40 (4H, m), 7.45 (1H, d), 7.55 (1H, s), 7.73 (2H, d), 7.90 (1H, s)	406
59-1		2.75 (3H, s), 2.84 (3H, s), 3.72 (3H, s), 3.84 (2H, s), 7.49 (2H, d), 7.55 (2H, d), 7.71 (lH,s), 7.75-7.80 (2H, m), 8.20 (1H, s).	412
60-1		2.71 (3H, s), 2.83 (3H, s), 3.72 (3H, s), 3.95 (2H, s), 7.46 (2H, d), 7.52 - 7.54 (2H, m), 7.60 (1H, d), 7.69 (1H, s), 7.85-7.87 (1H, m), 8.05 (lH,d), 8.16 (1H, s).	410

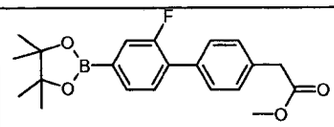
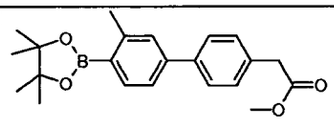
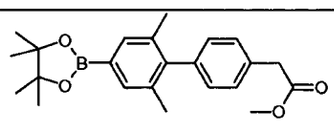
61-1		($CDCl_3$) 8 2.65 (3H, s), 2.93 (3H, s), 3.63 (2H, s), 3.66 (3H, s), 5.58 (1H, s), 7.31 - 7.39 (4H,m), 7.46-7.53 (3H, m), 7.69 (1H, s).	394
62-1		2.16 (3H,s), 2.36 (3H,s), 2.78 (3H, s), 3.64 (3H, s), 3.74 (2H, s), 7.38 (3H, d), 7.55 (1H, s), 7.59 (1H, d), 7.67 (3H, m), 7.90 (1H, s).	390
63-1		2.05 (6H, s), 2.63 (3H, s), 2.75 (3H, s), 3.66 (3H, s), 3.76 (2H, s), 7.15(2H, d), 7.38 (2H, d), 7.47 (2H, s), 7.60 (1H, s), 8.00 (1H, s).	404

Los siguientes **Intermedios 54-2 to 63-2** se sintetizaron a partir de los **Intermedios 54-3** a **63-3** utilizando condiciones similares a las descritas en el **Intermedio 25-2** para proporcionar los compuestos deseados.

Intermedio	**Estructura**	**^{1}H NMR (400 MHz)**	*m/z*
54-2		($CDCl_3$)8 1.38(12H,s), 1.45 (9H,s), 3.56 (2H,s), 7.24 - 7.27 (1H, m), 7.33 -7.38 (3H, m), 7.55 (2H, d), 7.77 - 7.80 (1H, m)	412 M^+-(EI+)

346

55-2		($CDCl_3$)8 1.39(12H,s), 1.45 (9H, s), 3.56 (2H, s), 7.34 (2H, d), 7.43 - 7.45 (1H, m), 7.53 (2H, d), 7.58 (1H, s), 7.75 (1H, d)	428 M^+-(EI+)
56-2		($CDCl_3$)8 1.38(12H,s), 1.46 (9H, s), 3.57 (2H, s), 7.37 (2H, d), 7.56 (2H, d), 7.72 (1H, d), 7.80 (1H, d), 7.87 (lH,s)	462 M^+-(EI+)
57-2		($CDCl_3$)8 1.36(12H,s), 3.65 (2H, s), 3.71 (3H, s), 3.85 (3H,s), 7.31-7.33 (3H, m), 7.39 (1H, s), 7.47 - 7.51(3H,m)	382 M^+-(EI+)
58-2		(DMSO)8 1.34(12H,s), 3.35 (3H, s), 3.80 (2H, s), 3.89 (3H, s), 7.24 (1H, d), 7.26 - 7.28 (lH,m), 7.43 (2H, d), 7.67 (lH,d), 7.72 (2H,d)	no se observó ión de masa; HPLC tR=3.01 min.
59-2		(DMSO)8 1.38(12H,s), 3.70 (3H, s), 3.82 (2H, s), 7.40 (2H, d), 7.46 (4H, s)	no se observó ión de masa; HPLC tR=3.30 min.
60-2		(DMSO)8 1.31(12H, s), 3.64 (3H, s), 3.75 (2H, s), 7.35-7.41 (4H,m), 7.42 (1H, d), 7.65 - 7.67 (1H, m), 7.72 (1H, d).	no se observó ión de masa; HPLC tR=3.42 min.

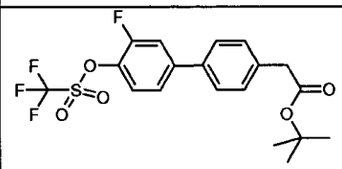
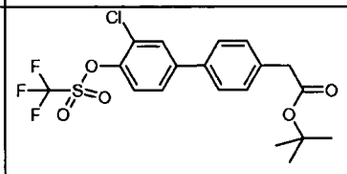
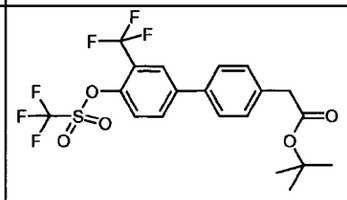
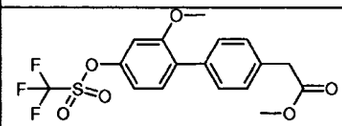
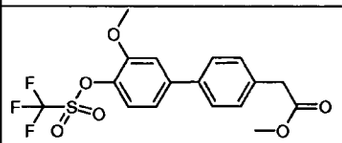
61-2		(DMSO)8 1.31(12H,s), 3.63 (3H, s), 3.74 (2H, s), 7.36 - 7.46 (3H, m), 7.52 (2H, dd), 7.55 (2H, d).	388 $M+Na^+$
62-2		(DMSO)8 1.30(12H,s), 2.52 (3H, s), 3.62 (3H, s), 3.72 (2H, s), 7.26 (lH,m), 7.40 (3H, m), 7.62 (2H, d), 7.70 (1H, d).	No se observó ión de masa HPLC tR=3.44 min
63-2		(DMSO)8 1.28(12H,s), 1.94 (6H, s), 3.64 (3H, s), 3.74 (2H, s), 7.06 (2H, d), 7.34 (2H, d), 7.41 (2H, s).	No se observó ión de masa HPLC tR=3.39 min.

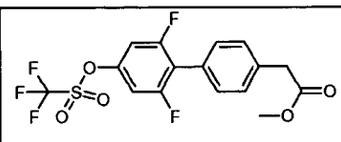
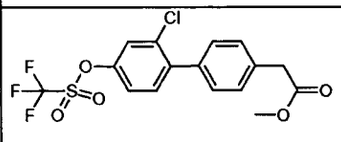
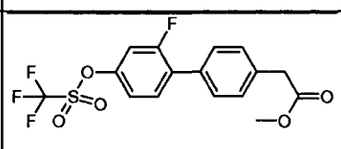
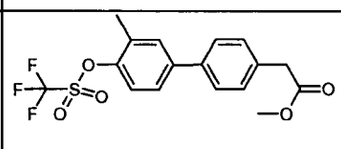
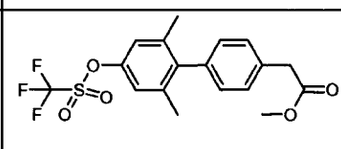
T

Los siguientes **Intermedios 54-3** a **63-3** se sintetizaron a partir de los **Intermedios 54-4** a **63-4** ya sea utilizando condiciones similares a las descritas en el **Intermedio 25-4** (Método A) o mediante Método B (el procedimiento descrito por A. Bengtson, A. Hallberg y M. Larhed, *Org. Lett.*, 2002, 4, 1231-1233) para proporcionar los compuestos deseados. Ejemplo Representativo del Método B:

Intermedio 54-3: 2-(3'-fluoro-4'-(trifluorometilsulfonil-oxi)bifenil-4-il)acetato de tert-butilo

Se suspendió **Intermedio 54-4** (637 mg, 2.11 mmol), 1,1,1-trifluoro-N-fenil-N-(trifluorometilsulfonil)metanosulfonamida (753 mg, 2.11 mmol) y carbonato de potasio (874 mg, 6.32 mmol) en THF (11 mL) y sellaron en un tubo microondas. La reacción fue calentada a 120 °C durante 6 minutos en el reactor de microondas y enfriada a temperatura ambiente. La suspensión se filtró, el sólido se lavó con EtOAc (20 mL) y el filtrado se evaporó para proporcionar el producto crudo. El producto crudo se purificó mediante cromatografía flash de gel de sílice, gradiente de elución entre 0 y 10% EtOAc en isohexano. Las fracciones puras se evaporaron hasta sequedad para proporcionar el compuesto del título (690 mg, 75 %) como un aceite incoloro.

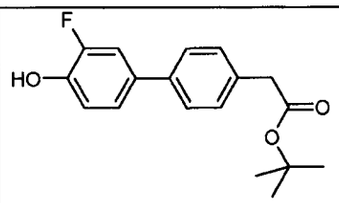
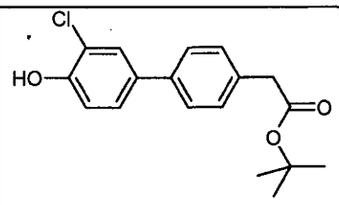
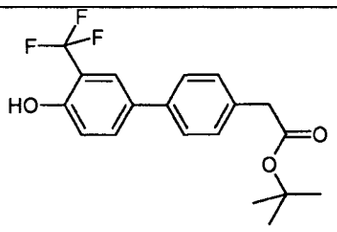
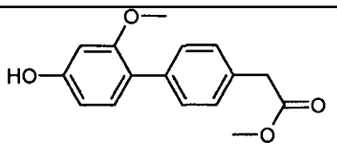
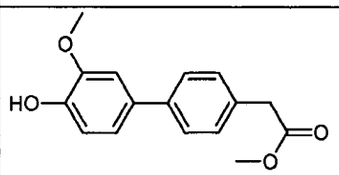
Intermedio	Estructura	^{1}H NMR (400 MHz)	*m/z* (M-H)
54-3		($CDCl_3$)8 1.46(9H,s), 3.58 (2H, s), 7.35 - 7.39 (4H,m), 7.43-7.51 (3H, m)	433
55-3		($CDCl_3$)8 1.46(9H,s), 3.57 (2H, s), 7.36 - 7.41 (3H, m), 7.48 - 7.53 (3H, m), 7.71 (1H, s)	449
56-3		($CDCl_3$)8 1.46(9H,s), 3.59 (2H, s), 7.40 (2H, d), 7.52 (2H, d), 7.56 (1H, d), 7.80 - 7.83 (lH,m), 7.92 (1H, d)	483
57-3		($CDCl_3$) 8 3.67 (2H, s), 3.72 (3H, s), 3.83 (3H, s), 6.85 (1H, d), 6.92 - 6.95 (1H, m), 7.33 - 7.35 (3H, m), 7.44 (2H, d)	404
58-3		(DMSO) 8 3.63 (3H, s), 3.74 (2H, s), 3.99 (3H, s), 7.30 - 7.33 (lH,m), 7.38 (2H, d), 7.48 (lH,d), 7.52 (1H, d), 7.69 (2H, d)	403

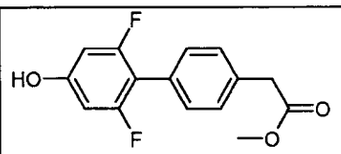
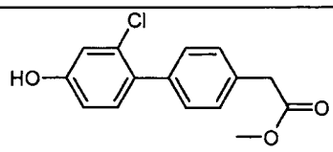
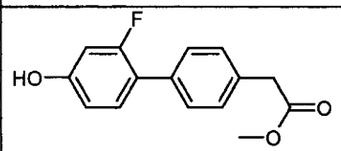
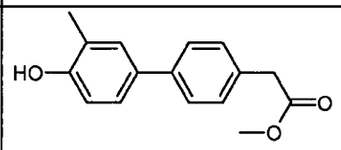
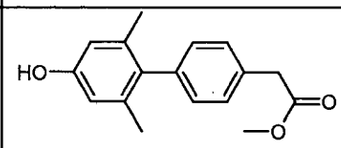
59-3		(DMSO) 8 3.70 (3H, s), 3.83 (2H, s), 7.46 - 7.52 (4H, m), 7.74 (2H, d).	409
60-3		(DMSO) 8 3.71 (3H, s), 3.82 (2H, s), 7.43 - 7.50 (4H, m), 7.64 - 7.69 (2H, m), 7.95 (1H, d).	No se observó ión de masa; HPLC tR= 3.14 min.
61-3		(DMSO) 8 3.63 (3H, s), 3.75 (2H, s), 7.41 (2H, dd), 7.53 (2H, dt), 7.72 (1H, d), 7.73 (1H, t).	391
62-3		(DMSO) 8 2.40 (3H, s), 3.63 (3H, s), 3.73 (2H, s), 7.27 (1H, m), 7.40 (3H, m), 7.65 (2H, m), 7.77 (1H, s).	387
63-3		(DMSO) 8 2.01 (6H, s), 3.64 (3H, s), 3.73 (2H, s), 7.12 (2H, d), 7.26 (2H, s), 7.37 (2H, d).	401

Notas: Metodo A **58-3, 59-3, 60-3;** Metodo B **54-3, 55-3,56-3, 57-3, 61-3, 62-3, 63-3**

Los siguientes **Intermedios 54-4 to 63-4** se sintetizaron a partir de ya sea **Intermedio 54-5** o **54-7** y el bromofenol apropiado utilizando condiciones similares a las descritas en el **Intermedio 21-1** para proporcionar los compuestos deseados.

Intermedio	**Estructura**	^{1}H NMR (**400** MHz)	*m/z* (M-H)

54-4[a]		($CDCl_3$)8 1.45(9H,s), 3.55 (2H,s), 5.11 (1H, d), 7.04 (1H, t), 7.24 - 7.27 (1H, m), 7.28 - 7.33 (3H, m), 7.46 (2H, d).	301
55-4[b]		($CDCl_3$)8 1.45(9H,s), 3.55 (2H, s), 5.54 (1H, s), 7.07 (1H, d), 7.31 -7.33 (2H,m), 7.38-7.41 (1H, m), 7.45 - 7.47 (2H, m), 7.54 (1H, d).	317
56-4[c]		($CDCl_3$)8 1.45(9H,s), 3.55 (2H, s), 5.11 (1H, d), 7.04 (1H, t), 7.24 - 7.27 (1H, m), 7.28 - 7.33 (3H, m), 7.46 (2H, d)	351
57-4[d]		($CDCl_3$) 8 3.65 (2H, s), 3.71 (3H, s), 3.78 (3H, s), 4.88 (1H, s), 6.45 - 6.47 (lH,m), 6.51 (lH,s), 7.15 (1H, d), 7.29 (2H, d), 7.44 (2H, d)	271
58-4[e]		(DMSO) 8 3.69 (3H, s), 3.75 (2H, s), 3.91 (3H, s), 6.90 (lH,d), 7.11-7.13 (1H, m), 7.23 (1H, d), 7.35 (2H, d), 7.61 (2H,d), 9.10 (1H, s).	No se observó ion de masa ; HPLC tR= 2.20 min

59-4[i]		(DMSO) 8 3.38 (3H, s), 3.47 (2H, s), 6.28 - 6.34 (2H,m), 7.05-7.10 (4H, m), 10.18 (lH,s).	277
60-4[g]		(DMSO) 8 3.63 (3H, s), 3.71 (2H, s), 6.80 - 6.83 (1H, m), 6.92 (1H, d), 7.20 (1H, d), 7.28 - 7.33 (4H, m), 9.93 (1H, s).	275
61-4[h]		(DMSO) 8 3.62 (3H, s), 3.70 (2H, s), 6.65 (1H, dd), 6.70 (1H, dd), 7.30 (1H, d), 7.32 (2H, dd), 7.41 (2H, dd), 9.96 (1H, s).	259
62-4'		(DMSO) 8 2.18 (3H, s), 3.62 (3H, s), 3.67 (2H, s), 6.83 (1H, d), 7.27 (3H, d), 7.36 (1H, s), 7.50 (2H, d), 9.35 (1H, s).	no se observó ión de masa HPLC tR= 2.28 min.
63-4[J]		(DMSO) 8 1.87 (6H, s), 3.64 (3H, s), 3.71 (2H, s), 6.50 (2H, s), 7.03 (2H, d), 7.29 (2H, d), 9.12 (1H, s).	no se observó ión de masa HPLC tPv= 2.31 min.

Notas: **54-4[a]** 4-Bromo-2-fluorofenol y el **Intermedio 54-5**

55-4[b] 4-Bromo-2-clorofenol y el **Intermedio 54-5.**

56-4[c] 4-Bromo-2-(trifluorometil)benzenol y el **Intermedio 54-5.**

57-4[d] 4-Bromo-3-metoxilofenol y el **Intermedio 54-5.**

58-4[e] 4-Bromo-2-metoxilofenol y el **Intermedio 54-7.**

59-4[f] 4-Bromo-3,5-Difluorofenol y el **Intermedio 54-7.**

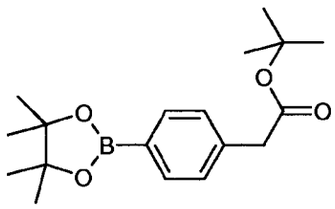
60-4[g] 4-Bromo-3-clorofenol y el **Intermedio 54-7.**

61-4[h] 4-Bromo-3-fluorofenol y el **Intermedio 54-7.**

62-4[i] 4-Bromo-2-metilfenol y el **Intermedio 54-7.**

63-4[j] 4-Bromo-3,5-dimetilfenol y el **Intermedio 54-7.**

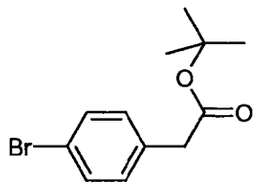
Intermedio 54-5: 2-(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)acetato de tert-butilo



El compuesto se sintetizó a partir del **Intermedio 54-6** utilizando condiciones similares a las descritas en el **Intermedio 25-2** para proporcionar el compuesto del título (8.37 g, 69.3 %) como un aceite amarillo pálido.

^{1}H NMR (400 MHz, $CDCl_3$) 8 1.34 (12H, s), 1.42 (9H, s), 3.53 (2H, s), 7.27 (2H, d), 7.75 (2H, d);m/z(EI+)318M^+.

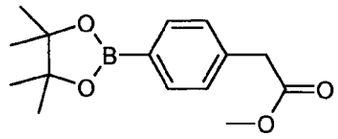
Intermedio 54-6 : 2-(4-bromofenil)acetato de tert-butilo CAS 33155-58-7



Se agregó acetal de di-tert-butilo de N,N-dimetilformamida (29.8 mL, 124.44 mmol) por porción durante 10 minutos a una solución agitada de ácido 4-bromofenilacético (13.38 g, 62.22 mmol) en tolueno (400 mL) a 85 °C. La solución resultante se agitó a 85 °C durante 4 horas y se dejo enfriar a temperatura ambiente. La mezcla de reacción se evaporó para proporcionar el producto crudo el cual se purificó mediante cromatografía flash de gel de sílice, gradiente de elución entre 0 y 20% EtOAc en isohexano. Las fracciones puras se evaporaron hasta sequedad para proporcionar el compuesto del título (10.29 g, 61.0 %) como un aceite incoloro.

^{1}H NMR (400 MHz, $CDCl_3$) 8 1.43 (9H, s), 3.46 (2H, s), 7.14 (2H, d), 7.44 (2H, d); *m/z* (EI+) 270 M^+.

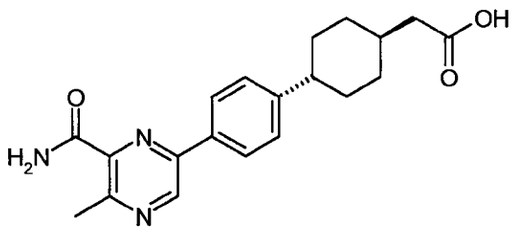
Intermedio 54-7: 2-(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)acetato de metilo (CAS 454185-98-9)



El compuesto se sintetizó a partir de 2-(4-bromofenil)acetato de metilo (CAS 41841-16-1 preparado según el procedimiento descrito por E. E. Knaus a al, *Bioorg. Med. Chem.*, 2005,**13,** 4694-4703) utilizando condiciones similares a las descritas en el **Intermedio 25-2** para proporcionar el compuesto del título (2.140 g, 100 %) como un sólido blanco.

^{1}H NMR (400 MHz, $CDCl_3$) 8 1.34 (12H, s), 3.64 (2H, s), 3.68 (3H, s), 7.28 (2H, d), 7.77 (2H, d); *m/z* (EI+) 276 M^+.

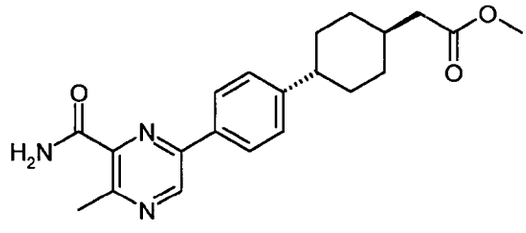
Ejemplo 64: Ácido 2-((1r,4r)-4-(4-(6-Carbamoil-5-metilpirazin-2-il)fenil)ciclohexil)acético



El compuesto se sintetizó a partir del **Intermedio 64-1** utilizando condiciones similares a las descritas en el **Ejemplo 21** para proporcionar el compuesto del título (120 mg, 64.3 %) como un sólido blanco.

^{1}H NMR (400 MHz, DMSO) 8 1.10-1.18 (2H, m), 1.49 - 1.53 (2H, m), 1.84 (4H, d), 2.15 (2H, d), 2.31 - 2.33 (1H, m), 2.65 - 2.67 (1H, m), 2.75 (3H, s), 7.38 (2H, d), 7.70 (1H, s), 8.14 (2H, d), 8.22 (1H, s), 9.18 (1H, s), 11.97 (1H, s); *m/z* 395 $(M+H)^+$.

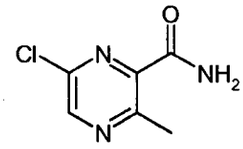
Intermedio 64-1: 2-((1r,4r)-4-(4-(6-Carbamoil-5-metilpirazin-2-il)fenil)ciclohexil)acetato de metilo



El compuesto se sintetizó a partir del **Intermedio 64-2** y 2-((1r,4r)-4-(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)ciclohexil)acetato de metilo (CAS 701232-69-1: vea

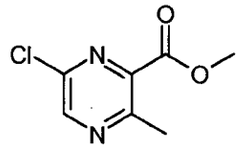
también **Intermedio 64-8**) utilizando condiciones similares a las descritas en el **Intermedio 21-1** para proporcionar el compuesto del título (194 mg, 83 %) como un sólido blanco.
^{1}H NMR (400 MHz, $CDCl_3$) 8 1.15 (3H, m), 1.60 (2H, m) 1.87 (4H, s), 2.20 - 2.22 (2H, m), 2.40 - 2.50 (1H, m) 2.94 (3H, s), 3.63 (3H, s), 5.5 (1H, s), 7.29 (2H, d), 7.80 (1H, s), 7.85 (2H, d), 8.95 (1H, s); *m/z* 368 $(M+H)^+$.

Intermedio 64-2: 6-Cloro-3-metilpirazina-2-carboxamida



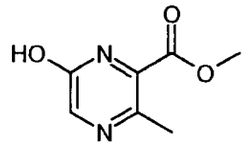
El compuesto se sintetizó a partir del **Intermedio 64-3** utilizando condiciones similares a aquellas descritas en el **Intermedio 21-4** para proporcionar el compuesto del título (109 mg, 83 %) como un sólido blanco.
^{1}H NMR (400 MHz, $CDCl_3$) 8 2.89 (3H, s), 5.45-5.55 (1H, s), 7.45-7.55 (1H, s), 8.56 (1H, s).

Intermedio 64-3: 6-cloro-3-metilpirazina-2-carboxilato de metilo



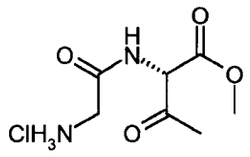
Una suspensión del **Intermedio 64-4** (314 mg, 1.87 mmol) y oxicloruro de fosforo (2.088 mL, 22.40 mmol) se agitó a 90 °C durante 70 minutos. La mezcla de reacción se agregó por goteo al agua (20 mL) durante 2-3 horas mientras se mantenía la temperatura bajo 40 °C (enfriamiento externo requerido). La mezcla fue extraída con DCM (5 x 50 mL), la capa orgánica fue secada sobre $MgSO_4$, filtrada y evaporada para proporcionar un aceite amarillo. Esto se purificó luego mediante cromatografía flash de gel de sílice, gradiente de elución entre 0 y 20% EtOAc en isohexano. Las fracciones puras se evaporaron hasta sequedad para proporcionar el compuesto del título (142 mg, 40.8 %) como un sólido blanco. ^{1}H NMR (400 MHz, $CDCl_3$) 8 2.76 (3H, s), 3.94 (3H, s), 8.56 (1H, s); m/z 187 $(M+H)^+$.

Intermedio 64-4: 6-hidroxi-3-metilpirazina-2-carboxilato de metilo



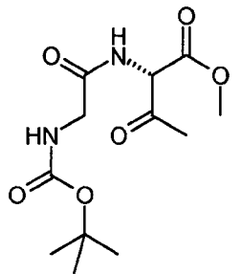
Una solución del **Intermedio 64-5** (1.3 g, 5.79 mmol) en Piridina (58.5 mL) se agitó a 60 °C durante 90 minutos. La mezcla de reacción se evaporó para proporcionar el producto crudo. El producto crudo se purificó mediante cromatografía flash de gel de sílice, gradiente de elución entre 50 y 80% EtOAc en isohexano. Las fracciones puras se evaporaron hasta sequedad para proporcionar el compuesto del título (0.340 g, 34.9 %) como un sólido amarillo. ^{1}H NMR (400 MHz, $CDCl_3$) 8 2.59 (3H, s), 3.94 (3H, s), 8.27 (1H, s); *m/z* 169 $(M+H)^+$.

Intermedio 64-5: Sal de ácido clorhídrico de 2-(2-aminoacetamido)-3-oxobutanoato de (S)-metilo



Se agregó una solución 4M de cloruro de hidrogeno (7.98 mL, 31.91 mmol) en dioxano al **Intermedio 64-6** (2.3 g, 7.98 mmol). La solución resultante se agitó a temperatura ambiente durante 4 horas. La mezcla de reacción se evaporó para proporcionar el compuesto del título (1.790 g, 119 %) como un sólido cremoso, el cual se utilizó sin purificación adicional, *m/z* 189 $(M+H)^+$.

Intermedio 64-6: 2-(2-(tert-Butoxicarbonylamino)acetamido)-3-oxobutanoato de (S)-metilo

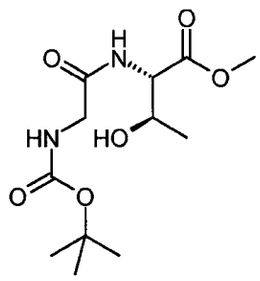


Se agregó una solución del **Intermedio 64-7** (12.9 g, 44.43 mmol) en DCM (72 mL) a una suspensión agitada de clorocromato de piridino (22.99 g, 106.64 mmol) en DCM (43 mL) a 0 °C, durante un periodo de 15 minutos bajo aire. La mezcla resultante se agitó a temperatura ambiente durante 24 horas. La mezcla de reacción se evaporó hasta sequedad y se agregó éter (400 mL) y agua (300 mL). La suspensión se filtró a traves de Celite y la matraz se juagó con éter (4 x 300 mL) y agua (3 x 200 mL). Los lavados se filtraron a traves de Celite y la capa orgánicas se combinó, lavaroncon salmuera saturada (200 mL). La capa acuosa fue re-extraída con EtOAc (2 x 500 mL), las capas orgánicas se secaron combinadas sobre $MgSO_4$, filtraron y evaporaron

para proporcionar 5.5g del producto crudo. El producto crudo se purificó mediante cromatografía flash de gel de sílice, gradiente de elución entre 50 y 80% EtOAc en isohexano. Las fracciones puras se evaporaron hasta sequedad para proporcionar el compuesto del título (18.29 %) como un aceite amarillo.

^{1}H NMR (400 MHz, $CDCl_3$) 8 1.39 (9H, d), 1.97 - 2.01 (3H, m), 2.31 (2H, s), 3.68 (1H, t), 3.75 (3H, s), 3.76 - 3.82 (3H, m), 4.05 (2H, q), 5.19 (1H, d).

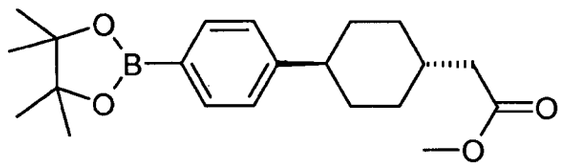
Intermedio 64-7: 2-(2-(tert-butoxicarbonylamino)acetamido)-3-hidroxilobutanoato de metilo



Se agregó HATU (46.9 g, 123.30 mmol) a una solución agitada de ácido 2-(tert-butoxicarbonylamino)acético (18 g, 102.75 mmol) DMA (230 mL) a temperatura ambiente. Después de 5 minutos se agregó una solución de hidrocloruro de (2S,3R)-metil 2-amino-3-hidroxilobutanoato (17.43 g, 102.75 mmol) y DIPEA (71.8 mL, 411.00 mmol) en DMA (230 mL) y la solución resultante se agitó a temperatura ambiente durante 20 horas, La mezcla de reacción se diluyó con EtOAc (300 mL), y se lavó con 1N ácido cítrico (300 mL), se agregó sal a la solución acuosa la cual fue re-extraída con EtOAc (4 x 400 mL). Los extractos orgánicos se combinaron, lavaron con $NaHCO_3$ saturado (200 mL), secaron sobre $MgSO_4$, filtraron y evaporaron para proporcionar el producto crudo. El producto crudo se purificó mediante cromatografía flash de gel de sílice, gradiente de elución entre 50 y 100% EtOAc en isohexano. Las fracciones puras se evaporaron hasta sequedad para proporcionar el compuesto del título (12.97 g, 43.5 %) como un vidrio amarillo el cual formo un sólido al sentarse.

^{1}H NMR (400 MHz, $CDCl_3$) 8 1.16 (3H, t), 1.38 (9H, d), 3.70 (3H, s), 3.80 - 3.81 (2H, m), 4.25 - 4.28 (1H, m), 4.51 - 4.54 (1H, m), 5.36 (1H, s), 6.96 (1H, d); *m/z* 291 $(M+H)^+$.

Intermedio 64-8: 2-((1r,4r)-4-(4(4,4,5,5-tetrametil-1,3, 2-dioxaborolan-2-il)fenil)ciclohexil)acetato de metilo



Se agregó trimetilfosfonoacetato (1.05X-1.06X) por goteo a una solución suspendida de t-BuOK (0.70X-0.71X) en 2-MeTHF (10 vol) a 5-10°C. La solución resultante se agitó a 15-20°C durante 3.5-4.0 horas. La mezcla de reacción se enfrio a 5-10°C y se agregó DIPEA (0.81-0.82X) a la reacción a 10-15°C. Se agregó 4-(4-hidroxilofenil)ciclohexanona (1.0 X) en porciones a la mezcla de reacción anterior a 10-15°C y la solución resultante se agitó a 15-20°C durante 3-6 horas y luego se tomó durante el análisis HPLC. Se agregó NH_4Cl-sol (5.0X-6.0X) a la mezcla de reacción a 0-15°C, y la reacción se apagó. La capa orgánica se separó y la solución acuosa se extrajo con 2-MeTHF (2.5X-3.0X). Los dos extractos orgánicos se combinaron y lavaron con $NaHSO_3$ acuoso y luego solución de NaCl (2.5X-3.0X) dos veces. La capa orgánica se concentró a 2~3 vol y n-heptano se agregó para proporcionar una solución suspendida, y la mezcla anterior se concentró a bajo 3% de residuo de 2-MeTHF para proporcionar una solución suspendida. La mezcla fue enfriada a 0-5 °C, agitada durante 1.0-2.0 h, filtrada y la torta lavada con n-heptano (2 vol X2). Secada al vacío a bajo 45°C para proporcionar el producto de fenoxiacrilato deseado.

Se agregó AcOH (0.05X) y Tolueno (20vol) a un reactor de presión, luego el fenoxiacrilato anterior (1.0X) se agregó a la mezcla. El reactor fue cuidadosamente inertizado, luego se agregó 10% Pd/C (0.15X) a la mezcla de reacción bajo protección de nitrógeno. La agitación fue retardada y la atmosfera de nitrógeno se intercambió por hidrógeno tres veces, y la hidrogenación se realizó a 1200 mbar a 25-28°C. La solución resultante se agitó a 25-28 °C durante 14-18 h. La HPLC mostró conversión de >98%. La mezcla de reacción se filtró, y la torta se lavó con EtOH (1.5X x2), luego el filtrado se concentró al vacío a 2-3 vol, se agregó n-heptano (10vol) para precipitar, luego se concetro hasta que residuo de tolueno <1.0%, se enfrió a 0-5 °C, filtró, la torta se secó al vacío hasta sequedad. El producto crudo se disolvió en EtOH:H_2O=2:1 (1.09X del producto crudo) al calentar a reflujo y se agitó a esta temperatura durante ~5 min, luego se enfrió lentamente a 20 °C durante 3 h y se agitó a 20 °C durante 1 h, seguido por enfriamiento lento a 0-5 °C durante 90 min y se agitó a 0-5 °C durante 1 h. Luego de filtrar, la torta de filtrado se lavó con EtOH:H_2O=2:1 frío (0.18X x2 del producto crudo, 0-5 °C). la torta de

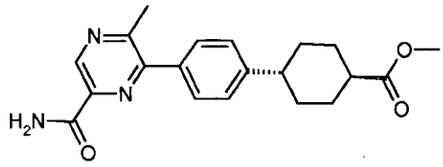
filtrado se secó al vacío a 45-50 °C durante 24 h para proporcionar el producto de trans-éster puro.

El trans-éster anterior (1.0X) se disolvió en CH_2Cl_2 anhidro (12vol), se agregó NMM (0.57X,1.4 eq) por goteo a la mezcla bajo N_2. La solución resultante se enfrió a -10-0°C y se agitó durante 10 min, luego Hf_2O (1.36X, 1.2 eq) se agregó por goteo a -10-0 °C (N.B. CF_3SO_2Cl se puede utilizar apropiadamente en lugar de anhidruro triflico Tf_2O). La solución resultante se agitó a -10-0 °C durante 30 min, se calentó a 0-10 °C y se agitó durante 30 min. (se tomaron muestras durante el análisis HPLC, la conversión fue de >98%). Se agregó solución de ácido cítrico al 10% (10.0X) por goteo a la mezcla. La mezcla fue agitada durante 10 min, la capa orgánica fue separada, lavada con ácido cítrico al 10% (10.0X) y salmuera(10.0X), secada con $MgSO_4$ anhidro (0.5X) durante 2 horas, filtrada y concentrada para remover CH_2Cl_2. Se agregó heptano (10X) y se concentró para remover el CH_2Cl_2 residual (expectativa <1.0%>), luego la suspensión en heptano se concentró a 1.5-2.0 vol, la mezcla se enfrió a 0-5 °C y se agitó durante 30~60min a 0-5 °C. Luego de filtrar la torta se secó al vacío a 30-40 °C para proporcionar el triflato deseado como un sólido blanco.

Se disolvió éster de pinacoldiborono (0.8X, 1.2 eq), TBAF(0.13X, 0.2 eq) y KOAc(0.38X, 1.5eq) en CH_3CN (5 vol), luego se agregó PCy_3 (1.5%X, 0.02eq) y $PdCl_2$ (0.47%X, 0.01eq). La mezcla se degasificó con nitrógeno. Se agregó una solución del triflato (1 .OX, 1.0 eq) en CH_3CN (7vol) a la mezcla a 20-25 °C. Luego la solución resultante se calentó a reflujo y se agitó durante 16 horas (durante la noche – se tomaron muestras durante el análisis HPLC, la conversion fue >98%). La mezcla se filtró mdeiante un cojín de celulosa 20 um, se agregó carbono activado (0.2X) al filtrado y la solución resultante se calentó a reflujo durante 2-3 horas. La mezcla fue enfriada a 40-50 °C y luego fue filtrada y el filtrado se concentró hasta sequedad. El sólido residuo fue disuelto en EtOAc, y la solución EtOAc se lavó con agua (10 vol), 1N HCl (10 vol) y salmuera (10 vol). La capa orgánica se separó y concentró a 1-2 vol, luego se agregó heptano (5~6vol)a la solución y se concentró hasta que se removió EtOAc (EtOAc/Heptano=0-l%), se agregó heptano (5~6vol) a la solución resultante y se calentó a 50-60 °C durante 30 min. Habián dos capas (un capa de heptano superior clara y una capa inferior amarillenta). La capa de heptano se separó, se agregó heptano (5~6vol) a la capa inferior

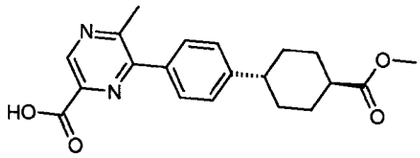
amarillenta y se calentó a 50-60 °C durante 30 min, y la capa de heptano se separó nuevamente. Las capas de heptano se combinron y filtraron mediante gel de sílice. El filtrado se concentro a 1-1.5vol y el precipitado se filtró y secó al vacío para proporcionar el éster de boronato deseado como un sólido blanco.

Ejemplo 65: *trans*-4-{4-[6-(aminocarbonil)-3-metilpirazin-2-il]fenil}-ciclohexanocarboxilato de metilo



Se agregó cloroformato de etilo (245 µl, 2.54 mmol) por goteo a una solución agitada de ácido 6-{4-[trans-4-(metoxilocarbonil)ciclohexil]fenil}-5-metilpirazina-2-carboxílico (**Intermedio 65-1**, 751 mg, 2.12 mmol) y N-metilmorfolina (350 µl, 3.18 mmol) en DCM (20 mL) a 0 °C. se agregó amoníaco (5 mL de una solución 7M en MeOH). La mezcla de reacción se dejo calentar durante 1 h luego se concentró y el residuo se purificó mediante cromatografía eluendo con 0-10% MeOH/DCM para proporcionar el compuesto del título (226 mg, 30%) como un sólido; ^{1}H NMR 8 9.00 (1H, s), 8.08 (1H, s), 7.74 (1H, s), 7.70 (2H, d), 7.40 (2H, d), 3.63 (3H, s), 2.70-2.55 (1H, m), 2.67 (3H, s), 2.50-2.35 (1H, m), 2.10-1.98 (2H, m), 1.96-1.83 (2H, m), 1.65-1.43 (4H, m); MS 354.

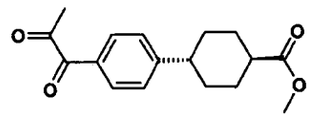
Intermedio 65-1: Ácido 6-{4-[trans-4-(metoxicarbonil)ciclohexil]fenil}-5-metilpirazina-2-carboxílico



Se agregó ácido diaminopriónico de hdrocloruro (496 mg, 3.52 mmol) a una solución agitada de *trans*-4-(4-piruvoilfenil)ciclohexanocarboxilato de metilo (**Intermedio 65-2**, 844 mg, 2.93 mmol) y trietilamina (1.6 mL, 11.72 mmol) en MeOH (6 mL). Después de 48 h la mezcla de reacción se concentró y el residuo se trituró con éter para proporcionar el compuesto del título (751 mg, 72%) como un sólido que se utilizó sin purificación adicional; ^{1}H NMR 8 9.04 (1H, s), 7.62 (2H, d), 7.40 (2H, d), 3.64 (3H, obs. s), 2.70-2.55 (1H, m), 2.66 (3H, s), 2.50-2.36 (1H, m), 2.08-1.96 (2H, m), 1.95-1.85 (2H, m), 1.65-1.45 (4H, m); MS 355.

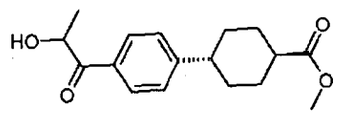
360

Intermedio 65-2: *trans*-4-(4-piruvoilfenil)ciclohexanocarboxilato de metilo



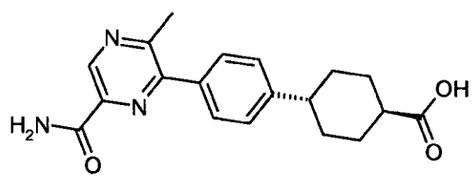
Se agregó 1,1,1-*tris*(Acetoxi)-1,1-dihidro-2,2-benziodoxol-3-(1*H*)-ona (5.14 g, 12.12 mmol) a una solución agitada de *trans*-4-(4-lactoilfenil)ciclohexanocarboxilato de metilo (**Intermedio 65-3**, 1.758 g, 6.06 mmol) en DCM (25 mL). La mezcla fue agitada durante 1 h, se agregó hexanos (50mL) y la mezcla se filtró a través de un cojín de tierra diatómacea. se removió material volátil mediante evaporación para proporcionar el compuesto del título (1.55 g, 88%) como un sólido que se utilizó sin purificación adicional; ^{1}H NMR 8 7.88 (2H, d), 7.45 (2H, d), 3.63 (3H, s), 2.70-2.57 (1H, m), 2.50 (3H, s), 2.48-2.36 (1H, m), 2.08-1.94 (2H, m), 1.90-1.80 (2H, m), 1.60-1.40 (4H, m); MS 311 $(M+Na)^+$.

Intermedio 65-3: *trans* -4-(4-lactoilfenil)ciclohexanocarboxilato de metilo



Se agregó hidroxido de sodio (370 mg, 9.25 mmol) en agua (2 mL) a una solución agitada de *trans*-4-[4-(2-bromopropanoil)fenil]ciclohexanocarboxilato de metilo (preparada como se describió en Solicitud de Patente WO2004/047755) (3.264 g, 9.25 mmol) en DMF (10 mL). La mezcla fue agitada durante 40 minutos luego extraída con éter (5 x 20 mL). Los extractos se combinaron, secaron y concentraron. El producto crudo se purificó mediante cormatografía flash de columna eluendo con 20-40% EtOAc/hexanos para proporcionar el compuesto del título (1.76 g, 66%) como un sólido; ^{1}H NMR 8 7.94 (2H, d), 7.39 (2H, d), 5.29 (1H, d), 5.08-4.98 (1H, m), 3.62 (3H, s), 2.68-2.54 (1H, m), 2.48-2.35 (1H, m), 2.08-1.94 (2H, m), 1.90-1.79 (2H, m), 1.60-1.40 (4H, m), 1.28 (3H, s); MS 313 $(M+Na)^+$.

Ejemplo 66: Ácido *trans*-4-{4- [6-(Aminocarbonil)-3-metilpirazin-2-il] fenil} ciclo-hexanocarboxílico



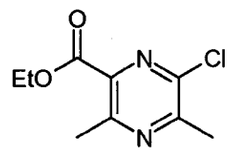
Se agregó monohidrato de hidroxido de litio (42 mg, 1.00 mmol) a una solución agitada de *trans*-4- {4-[6-(aminocarbonil)-3-metilpirazin-2-il]fenil}-ciclohexanocarboxilato de metilo (**Ejemplo 65**, 71 mg, 0.20 mmol) en MeOH (2 mL), THF (1 mL) y agua (0.5 mL). Después de 16 h la mezcla de reacción se concentró al vacío y se purificó mediante HPLC de fase inversa (150mm x 21mm Phenomenex Column empacada con sílice Luna 10u C18, eluendo con 5-95% acetonitrilo/agua) para proporcionar el compuesto del título como un sólido amarillo (6 mg, 9%); ^{1}HNMR 8 9.01 (1H, s), 8.08 (1H, s), 7.73 (1H, s), 7.70 (2H, d), 7.40 (2H, d), 2.70-2.50 (1H, m), 2.65 (3H, s), 2.37-2.25 (1H, m), 2.10-2.00 (2H, m), 1.95-1.85 (2H, m), 1.65-1.40 (4H, m); MS 340.

Ejemplos 67 a 70

Otros compuestos los cuales han sido preparados mediante procesos análogos a aquellos descritos en la presente son ácido 2-(4'-(6-Carbamoil-3,5-dimetilpirazin-2-il)-2'-metilbifenil-4-il)acético; ácido 2-(4-(4-(6-Carbamoil-3,5-dimetilpirazin-2-il)naftalen-1-il)fenil) acético; ácido2-(4'-(6-Carbamoil-3,5-dimetilpirazin-2-il)-2'-cianobifenil-4-il) acético y ácido 2-(4'-(6-Carbamoil-3,5-dimetilpirazin-2-il)-3',5'-difluorobifenil-4-il)acético.

Preparaciones Alternativas

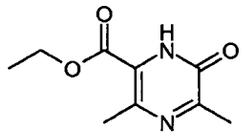
Intermedio 1-4: 6-Cloro-3,5-dimetilpirazine-2-carboxilato de etilo



Se calentó una suspensión del **Intermedio 1-5** (268 g, 1365.93 mmol) en oxicloruro de fósforo (1273 mL, 13659.31 mmol) a 90 °C bajo nitrógeno durante 1 hora, luego se enfrió a temperatura ambiente. Se agregó la reacción cuidadosamente en agua (6 L) con agitación vigorosa manteniendo la temperatura entre 17 °C y 20 °C. Luego la mezcla se extrajo con DCM (5 x 2.5 L), lavó con agua, salmuera saturada y secó sobre $MgSO_4$ y evaporó para proporcionar el producto crudo. El producto crudo se purificó mediante cromatografía flash de gel de sílice, gradiente de elución entre 0 y 25% EtOAc en isohexano. Las fracciones puras se evaporaron hasta sequedad para proporcionar el compuesto del título (227 g, 77%) como un aceite amarillo el cual se solidificó al sentar.

^{1}H NMR (400 MHz, $CDCl_3$) 8 1.43 (3H, t), 2.68 (3H, s), 2.77 (3H, s), 4.46 (2H, q); *m/z* 215 $(M+H)^+$.

Intermedio 1-5: 6-hydroxi-3,5-dimetilpirazina-2-carboxilato de etilo

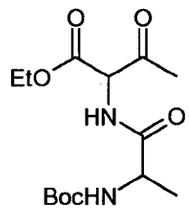


Se agregó una solución de ácido clorhídrico2M en 1,4-dioxano (1177 mL, 4709.97 mmol) al **Intermedio 1-6** (745 g, 2354.99 mmol) y se agitó a temperatura ambiente durante 15 minutos luego se calentó a40 °C durante 40 minutos adicionales. Luego se agregó piridina (6500 mL) lentamente y luego la reacción se calentó a 80 °C durante 2 horas en la presencia de aire. Luego la reacción se dejo enfriar a temperatura ambiente y se evaporó hasta sequedad para proporcionar un aceite viscoso. Esto se suspendió en DCM (2.5 L) y se lavó con agua (1.5 L). Luego el DCM se secó sobre $MgSO_4$, filtró y concentró para proporcionar un semi-sólido naranja, el cual se trituró con 1:1 EtOAc/iso-hexano (250 mL) para proporcionar 6-hidroxilo-3,5-dimetil-1,4-dihydropirazina-2-carboxilato de etilo (127 g, 27.1 %) como un sólido cremoso. Luego las aguas madre se purificaron mediante cromatografía flash de gel de sílice (gradiente a partir de 20% acetato de etilo/iso-hexano a 80% acetato de etilo/iso-hexano). Las fracciones que contienen el producto deseado se concentraron y el residuo se trituró con un pequeño volumen de 1:1 EtOAc/iso-hexano para proporcionar el compuesto del título (9.00 g, 1.948 %). Se agregó dioxido de manganeso (150 g) a una suspensión de 6-hidroxilo-3,5-dimetil-4,5-dihidropirazina-2-carboxilato de etilo 121 g, 610.44 mmol) en DCM (1.8 L) a temperatura ambiente dando origen a una exóterma de 2 °C. La reacción fue agitada durante 10 minutos luego calentada a 35 °C durante 1 hora. La reacción estaba incompleta de manera que se agregó 115g de dioxido de manganeso y la reacción se agitó durante 1 hora a 35 °C luego se agitó para enfriar a temperatura ambiente. La reacción se filtró a través de un lecho de sílice y se lavó con 2 L de 1:1 EtOAc/iso-hexano y finalmente 2 x 2 L EtOAc. Luego se combinaron las fracciones y se redujeron al vacío para proporcionar un sólido naranja, el cual se convirtió en pasta aguada en 300 mL de 1:1 EtOAc/iso-hexano, filtró y lavó con iso-hexano para proporcionar el compuesto del título (87 g, 72.6 %) como un sólido naranja.

^{1}H NMR (400 MHz, DMSO) 8 1.31 (3H, t), 2.35 (3H, s), 2.50 (3H, s), 4.31 (2H, q), 11.93 (1H, s); *m/z* 197 $(M+H)^+$

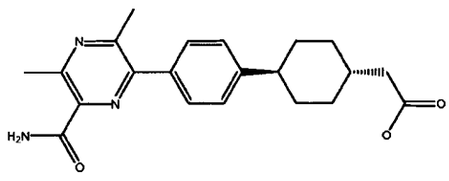
El **Intermedio 1-6** también puede preparase mediante el siguiente procedimiento:

Intermedio 1-6: 2-(2-tert-butoxicarbonilamino)propanamido)-3-oxobutanoato de etilo



Se agregó una solución de 4-metilmorfolina (900g) en THF (15 L) a ácido2-(tert-butoxicarbonilamino)propánoico (1690 g, 8933.17 mmol). La mezcla se enfrió a -25 °C y se agregó cloroformato de isobutilo (1.164 L, 8933.17 mmol).Después de 20 minutos el segundo equivalente de 4-metilmorfolina (900g) se agregó seguido por sal de Tocilato de 2-amino-3-oxobutanoato de etilo (ver J-P. Genet, *Eur. J. Org. Chem.*, 2004, 3017-3026) (2700 g, 8507.78 mmol) suspendido en THF (2.5 L). La mezcla se agitó a -25 °C durante 30 minutos y luego se dejo calentar a temperatura ambiente durante la noche. La reacción se apagó con agua (15 L), y se extrajo con EtOAc (3 x 5 L) y los extractos combinados se lavaron con 50% salmuera saturada (5 L). La capa orgánica se secó sobre $MgSO_4$, filtró y evaporó para proporcionar el producto crudo. El producto crudo se purificó mediante cromatografía flash de gel de sílice, gradiente de elución entre 50 y 80% EtOAc en isohexano. Las fracciones puras se evaporaron hasta sequedad para proporcionar 2-(2-(tert-butoxicarbonilamino)propanamido)-3-oxobutanoato de etilo (1850 g, 68.7 %).

Ejemplo 1: Ácido 2-((1r,4r)-4-(4-(6-carbamoil-3,5-dimetilpirazin-2-il)fenil)ciclohexil) acético



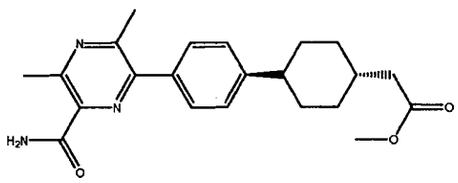
Se agregó hidroxido de potasio en polvo (2.81 g, 50.10 mmol) en una porción al **Intermedio 1-8** (6.37 g, 16.70 mmol) en *tert*-butanol (150 mL) a 40°C bajo nitrógeno. La suspensión resultante se agitó a 40°C durante 20 minutos. Un precipitado espeso se formó de manera que la reacción fue apagada con ácido acético (4.78 mL, 83.49 mmol) en etanol (100.0 mL) y la solución resultante fue agitada durante 20 minutos adicionales antes de ser evaporada

hasta sequedad. El sólido resultante se particionó entre agua (500 mL) y EtOAc (500 mL). La capa acuosa mostró un pH=4~5. La capa orgánica se separó y la acuosa se re-extrajo con EtOAc(2 x 250 mL). Los orgánicos combinados fueron lavados con salmuera (100 mL), secados sobre $MgSO_4$ y evaporados al vacío para proporcionar el producto crudo. Este fue recristalizado a partir de etanol caliente (250 mL) para proporcionar un sólido amarillo el cual se lavó con éter (100 mL) y se secó al vacío a temperatura ambiente para proporcionar el compuesto del título (4.82 g, 79 %).

[^{1}HNMR (400.132 MHz, DMSO) 8 1.09 - 1.19 (2H, m), 1.46 - 1.57 (2H, m), 1.70 - 1.78 (1H, m), 1.81 - 1.87 (4H, m), 2.15 (2H, d), 2.58 (3H, s), 2.73 (3H, s), 3.29 (1H, s), 7.36 (2H, d), 7.57 (1H, s), 7.64 (2H, d), 7.98 (1H, s), 11.98 (1H, s)].

Un punto de fusión con un valor de inicio de aproximadamente 225°C ha sido determinado para el ácido {trans-4-[4-(6-Carbamoil-3,5-dimetilpirazin-2-il)fenil] ciclohexil}acético.

Intermedio 1-8: 2-((1s,4s)-4-(4-(6-carbamoil-3,5-dimetilpirazin-2-il)fenil)ciclohexil)acetato de metilo



Se degasificó una solución de 6-cloro-3,5-dimetilpirazina-2-carboxamida (ver **Intermedio 21-4)** (3.15 g, 16.97 mmol), 2-((1s,4s)-4-(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)ciclohexil)acetato de metilo (ver **Intermedio 64-8)** (6.08 g, 16.97 mmol) y trifosfato de potasio (4.32 g, 20.37 mmol) en DME (120 mL), etanol (75 mL) y agua (30.0 mL) antes de la adición de (1,1'-bis(difenilfosfino)ferroceno)-dicloropaladio(II) (0.698 g, 0.85 mmol). La mezcla de reacción se calentó a 80 °C, bajo nitrógeno, y se dejo agitar durante la noche durante 16 horas. La mezcla de reacción se dejo enfriar a temperatura ambiente y luego se evaporó. El producto crudo se particionó entre agua (250 mL) y EtOAc (250 mL). El catalizador se filtró a partir de la mezcla bifásica. La fase orgánica se separó y se lavó con salmuera (100 mL), se secó (Na_2SO_4) y evaporó. El producto crudo se purificó mediante cromatografía flash de gel de sílice, gradiente de elución entre 5 y 90% EtOAc en isohexano sobre columna de sílice 330g. Las fracciones puras

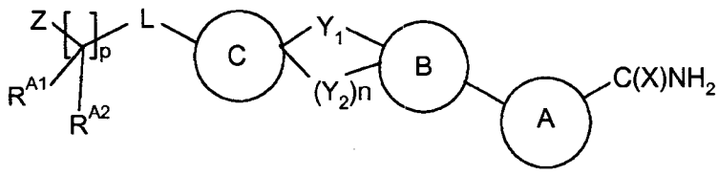
se evaporaron hasta sequedad para proporcionar el compuesto del título (6.47 g, 100 %) como un sólido amarillo.

[^{1}HNMR (400.132 MHz, DMSO) 8 1.10 - 1.21 (2H, m), 1.46 - 1.56 (2H, m), 1.73 - 1.86 (5H, m), 2.25 (2H, d), 2.58 (3H, s), 2.73 (3H, s), 3.28 (1H, s), 3.60 (3H, s), 7.35 (2H, d), 7.58 (1H, s), 7.64 (2H, d), 7.97 (1H, s); HPLC tR= 2.53 min.]

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Reivindicaciones

1. Un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable, o profármaco del mismo,



(I)

en donde

El Anillo A es 2,6-pirazindiilo, 3,5-piridindiilo o 2,6-piridindiilo, cada uno opcionalmente sustituido sobre un átomo de carbono disponible, por uno o dos sustituyentes independientemente seleccionados a partir de (1-3C)alquilo lineal, (2-3C)alquenilo, (2-3C)alquinilo, (l-2C)alcoxilo, metoximetilo, amino y ciano;

X es =0 o =S;

El Anillo B es 1,4-fenileno o el Anillo B es un anillo di-enlazado (excluyendo enlaces vía los mismos átomos o átomos adyacentes) seleccionado a partir de piridindiilo, furiilo, tiofendiilo, pirroldiilo, oxazoldiilo, tiazoldiilo, imidazoldiilo, isoxazoldiilo, isotiazoldiilo y pirazoldiilo; cada uno opcionalmente sustituido sobre un átomo de carbono disponible, por uno o dos sustituyentes independientemente seleccionados a partir de halo, amino, ciano, (l-4C)alquilo, (2-3C)alquenilo, (2-3C)alquinilo, (l-4C)alcoxilo y (l-4C)alcoxilo-(l-4C)alquilo;

Y_1 es un enlace directo entre el Anillo B y el Anillo C o Y1 es -O-, -S- o -NRa- en donde Ra es hidrógeno o (l-4C)alquilo;

Y_2 es -(CH2)r en donde r es 2 o 3, y Y_2 está unido al mismo átomo de carbono como Y_1 en el Anillo C y Y_2 está unido en un átomo de carbono adyacente a Y1 en el Anillo B;

n es 0 o n es 1 cuando Y_1 es un enlace directo entre el Anillo B y el Anillo C y cuando el Anillo B es 1,4-fenileno y el Anillo C es (4-6C)cicloalcano, de manera que un sistema espirocíclico de 5- o 6-miembros es formado y el Anillo C es tri-enlazado;

El Anillo C es un anillo di-enlazado (excluyendo enlaces vía los mismos átomos o átomos adyacentes) o sistema cíclico elegido a partir de (4-6C)cicloalcano, (7-10C)bicicloalcano y (8-12C)tricicloalcano cada uno opcionalmente sustituido sobre un átomo de carbono disponible,

incluyendo el átomo de carbono cíclico que porta el grupo que contiene Z, por un sustituyente seleccionado a partir de hidroxilo, (l-4C)alquilo, (1-4C)alcoxilo y (l-4C)alcoxi(l-4C)alquilo;

o el Anillo C es un anillo di-enlazado (excluyendo enlaces vía los mismos átomos o átomos adyacentes) seleccionado a partir de fenileno, priidindiilo, piperidinadiilo N-enlazado a Y_1, piperazinediilo, furyiilo, tiofendiilo, pirroldiilo, oxazoldiilo, tiazoldiilo, imidazoldiilo, isoxazoldiilo, isotiazoldiilo, pirazoldiilo y azabiciclo[3.1.0]hexanodiilo;

cada uno opcionalmente sustituido sobre un átomo de carbono disponible, por hasta cuatro sustituyentes independientemente seleccionados a partir de fluoro, cloro, bromo, ciano, (l-4C)alquilo, (l-4C)alcoxilo y (l-4C)alcoxilo(l-4C)alquilo;

L es un enlace directo al Anillo C, -O-, -S- o -NH-;

p es 0 (cuando L es un enlace directo), 1 o 2 y cuando p es 1 o 2 R^{A1} y R^{A2} son cada uno independientemente hidrógeno o (l-4C)alquilo o R^{A1} y R^{A2} son enlazados juntos para formar un anillo (3-6C)spiroalquilo;

Z es carboxilo o un mimético o biosóstero del mismo, hidroxilo o -CONRbRc en donde Rb y Rc son independientemente seleccionados a partir de hidrógeno y (l-4C)alquilo, tal grupo (l-4C)alquilo puede ser opcionalmente sustituido por carboxilo o un mimético o biosóstero del mismo;

y en donde cualquier átomo de carbono en un (l-3C)alquilo lineal, (l-2C)alcoxilo, (l-4C)alquilo o (1-4C)alcoxilo conteniendo el grupo definido anteriormente puede opcionalmente ser sustituido por hasta 3 átomos de fluoro; con la condición que el compound ácido (4-(4-(6-Carbamoil-piridin-2-il)fenil)ciclohexil)acético sea excluido.

2. Un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable, o pro-fármaco del mismo, como se reivindicó en Reivindicación 1, en donde

El Anillo A es 2,6-pirazindiilo, 3,5-piridindiilo o 2,6-piridindiilo, cada uno opcionalmente sustituido sobre un átomo de carbono disponible, por uno o dos sustituyentes independientemente seleccionados a partir de (1-3C)alquilo lineal, (2-3C)alquenilo, (2-3C)alquinilo, (l-2C)alcoxilo, metoximetilo, amino y ciano;

X es =0 o =S;

el Anillo B es 1,4-fenileno o el Anillo B es un anillo di-enlazado (excluyendo enlaces vía los mismos átomos o átomos adyacentes) seleccionado a partir de piridindiilo, furiilo, tiofendiilo,

pirroldiilo, oxazoldiilo, tiazoldiilo, imidazoldiilo, isoxazoldiilo, isotiazoldiilo y pirazoldiilo; cada uno opcionalmente sustituido sobre un átomo de carbono disponible por uno o dos sustituyentes independientemente seleccionados a partir de halo, amino, ciano, (l-4C)alquilo, (2-3C)alquenilo, (2-3C)alquinilo, (l-4C)alcoxilo y (l-4C)alcoxi-(l-4C)alquilo;

Y_1 es un enlace directo entre el Anillo B y el Anillo C o Y_1 es -O-, -S- o -NRa- en donde Ra es hidrógeno o (l-4C)alquilo;

Y_2 es -(CH2)r en donde r es 2 o 3, y Y_2 está unido al mismo átomo de carbono como Y_1 en el Anillo C y Y_2 está unido en un átomo de carbono adyacente a Y1 en el Anillo B;

n es 0 o n es 1 cuando Y_1 es un enlace directo entre el Anillo B y el Anillo C y cuando el Anillo B es 1,4-fenileno y el Anillo C es (4-6C)cicloalcano, de manera que un sistema espirocíclico de 5- o 6-miembros es formado;

El Anillo C es un anillo di-enlazado (excluyendo enlaces vía los mismos átomos o átomos adyacentes) o sistema cíclico elegido a partir de (4-6C)cicloalcano, (7-10C)bicicloalcano y (8-12C)tricicloalcano cada uno opcionalmente sustituido sobre un átomo de carbono disponible, incluyendo el átomo de carbono cíclico que porta el grupo que contiene Z, por un sustituyente seleccionado a partir de hidroxilo, (l-4C)alquilo, (1-4C)alcoxilo y (l-4C)alcoxi(l-4C)alquilo; o el Anillo C es un anillo di-enlazado (excluyendo enlaces vía los mismos átomos o átomos adyacentes) seleccionado a partir de fenileno, priidindiilo, piperidinadiilo N-enlazado a Y_1, furiilo, tiofendiilo, pirroldiilo, oxazoldiilo, tiazoldiilo, imidazoldiilo, isoxazoldiilo, isotiazoldiilo y pirazoldiilo; cada uno opcionalmente sustituido sobre un átomo de carbono disponible, por hasta cuatro sustituyentes independientemente seleccionados a partir de fluoro, cloro, bromo, ciano, (l-4C)alquilo, (l-4C)alcoxilo y (l-4C)alcoxi(l-4C)alquilo;

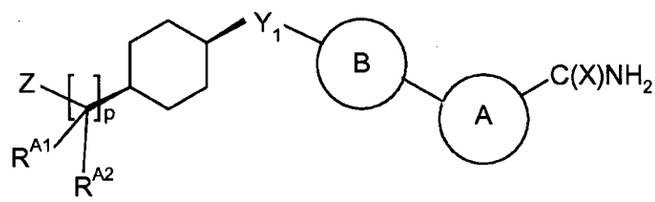
L es un enlace directo al Anillo C, -O-, -S- o -NH-;

p es 0, 1 o 2 y cuando p es 1, R^{A1} y R^{A2} son cada uno independientemente hidrógeno o (l-4C)alquilo o R^{A1} y R^{A2} son enlazados juntos for formar un anillo (3-6C)espiroalquilo;

Z es carboxilo o un mimético o biosóstero del mismo, hidroxilo o -CONRbRc en donde Rb y Rc son independientemente seleccionados a partir de hidrógeno y (l-4C)alquilo, tal grupo (l-4C)alquilo puede ser opcionalmente sustituido por carboxilo o un mimético o biosóstero del mismo;

y en donde cualquier átomo de carbono en un (l-3C)alquilo lineal, (l-2C)alcoxilo, (l-4C)alquilo o (1-4C)alcoxilo conteniendo el grupo definido anteriormente puede ser opcionalmente sustituido por hasta 3 átomos de fluoro.

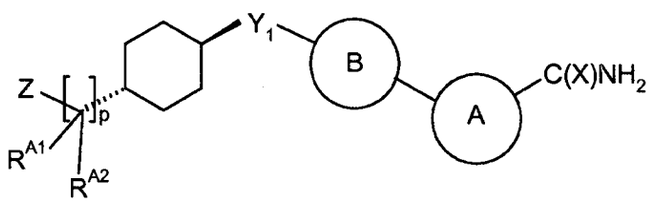
3. Un compuesto de la fórmula (IA) como se reivindicó en Reivindicación 1 o 2, o una sal farmacéuticamente aceptable, o pro-fármaco del mismo,



(IA)

en donde X, Anillo A, Anillo B, Y1, p, R^1, R^2 y Z son como se definió en Reivindicación 1 o 2.

4. Un compuesto de la fórmula (IB) como se reivindicó en Reivindicación 1 o 2, o una sal farmacéuticamente aceptable, o profármaco del mismo,



(IB)

en donde X, Anillo A, Anillo B, Y1, p, R^{A1}, R^{A2} y Z son como se definió en Reivindicación 1 o 2.

5. Un compuesto como se reivindicó en cualquiera de las Reivindicaciones 1 A 4, o una sal farmacéuticamente aceptable o profármaco del mismo , en donde X es =0;

el Anillo A es 2,6-pirazindiilo opcionalmente sustituido sobre un átomo de carbono disponible, por uno o dos sustituyentes independientemente seleccionados a partir de (l-3C)alquilo lineal, (2-3C)alquenilo, (2-3C)alquinilo, (l-2C)alcoxilo, metoximetilo, amino y ciano;

el Anillo B es 1,4-fenileno opcionalmente sustituido sobre un átomo de carbono disponible por uno o dos sustituyentes independientemente seleccionados a partir de halo, amino, ciano, (1-4C)alquilo, (2-3C)alquenilo, (2-3C)alquinilo, (1-4C)alcoxilo y (1-4C)alcoxilo-(1-4C)alquilo;

el Anillo C es 1,4-ciclohexano;

n es 0 y Y_1 es un enlace directo o Y_1 es -O-;

L es un enlace directo;

p es 1 y R^{A1} y R^{A2} son cada uno hidrógeno;

Z es carboxilo, un grupo tetrazol, $-C(O)NHS(O)_2Me$, hidroxilo o -CONRbRc en donde Rb y Rc son independientemente seleccionados a partir de hidrógeno y (1-4C)alquilo, tal grupo (1-4C)alquilo puede ser opcionalmente sustituido bPOR carboxilo; y en donde cualquier átomo de carbono en un (1-3C)alquilo lineal, (1-2C)alcoxilo, (1-4C)alquilo o (1-4C)alcoxilo conteniendo el grupo definido anteriormente puede ser opcionalmente sustituido, por hasta 3 átomos de fluoro.

6. Un compuesto como se reivindicó en cualquiera de las Reivindicaciones 1 a 5, o una sal farmacéuticamente aceptable, o profármaco del mismo, en donde el Anillo A es 2,6-pirazindiilo opcionalmente sustituido sobre un átomo de carbono disponible por uno o dos sustituyentes de (1-3C)alquilo lineal.

7. Un compuesto como se reivindicó en la Reivindicación 1 o 2 seleccionado a partir de
ácido {trans-4-[4-(6-Carbamoil-3,5-dimetilpirazin-2-il)fenil] ciclohexil}acético;
3,5-Dimetil-6-[4-(trans-4-{2-[(metilsulfonil)amino]-2-oxoetil}ciclohexil)-fenil]pirazina-2-carboxamida;
6-{4-[trans-4-(2-Amino-2-oxoetil)ciclohexil]fenil}-3,5-dimetilpirazina-2-carboxamida;
N-({trans-4-[4-(6-Carbamoil-3,5-dimetilpirazin-2-il)fenil] ciclohexil}acetil)-2-metilalanina;
6-{4-[trans-4-(2-Hidroxiloetil)ciclohexil]fenil}-3,5-dimetilpirazina-2-carboxamida;
Ácido (trans-4-{4-[6-Carbamoil-5-(difluorometil)-3-metilpirazin-2-il]fenil} ciclohexil)acético;
Ácido {trans-4-[4-(6-Carbamoil-3-etil-5-metilpirazin-2-il)fenil] ciclohexil} acético;
Ácido {trans-4-[4-(6-Carbamoil-5-etil-3-metilpirazin-2-il)fenil] ciclohexil} acético y
Ácido {trans-4-[4-(6-Carbamoil-3-metilpirazin-2-il)fenil]ciclohexil} acético;

Ácido 2-((1r,4s)-5'-(6-Carbamoil-3,5-dimetilpirazin-2-il)-2',3'-dihidroespiro[ciclohexano-l,r-indeno]-4-il)acético;

Ácido (lr,4s)-5'-(6-Carbamoil-3,5-dimetilpirazin-2-il)-2',3'-dihidroespiro[ciclohexano-l,r-indeno]-4-carboxílico;

Ácido 2-((lr,4r)-4-(4-(6-Carbamoil-3,5-dimetilpirazin-2-il)fenil)ciclohexil)-2-metilpropanóico

Ácido 2-(l-(4-(6-Carbamoil-3,5-dimetilpirazin-2-il)fenil)pirrolidin-3-il)acético;

Ácido (lR,5S,6r)-3-(4-(6-Carbamoil-3,5-dimetilpirazin-2-il)fenil)-3-azabiciclo[3.1.0]hexano-6-carboxílico;

6-(4-((1r,4r)-4-((lH-Tetrazol-5-il)metil)ciclohexil)fenil)-3,5-dimetilpirazina-2-carboxamida;

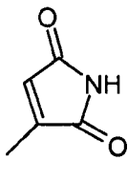
ácido 4'-(6-Carbamoil-3,5-dimetilpirazin-2-il)bifenil-4-carboxílico;

trans-4- {4-[6-(aminocarbonyl)-3-metilpirazin-2-il]fenil}-ciclohexanocarboxilato de metilo;

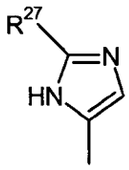
Ácido trans-4-{4-[6-(Aminocarbonil)-3-metilpirazin-2-il]fenil}ciclo-hexanocarboxílico; o una sal farmacéuticamente aceptable de cualquiera de estos.

8. Un compuesto como se reivindicó en cualquiera de las Reivindicaciones 1 a 6 en donde un profármaco del mismo es un éster de un grupo carboxilo seleccionado a partir de un éster (l-6C)alquilo, un éster (l-6C)alcoxilometilo, un éster (1-6C)alcanoiloximetilo, un éster aftalidilo, un éster (3-8C)cicloalcoxicarboniloxi(l-6C)alquilo, un éster l,3-dioxolan-2-ilmetilo , un éster (l-6C)alcoxicarboniloxietilo, un éster aminocarbonilmetilo y una versión mono- o di- N-((l-6C)alquilo) de un éster aminocarbonilmetilo.

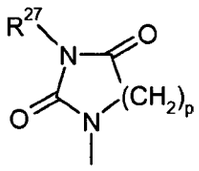
9. Un compuesto como se reivindicó en cualquiera de las Reivindicaciones 1 a 6 en donde un imitador o bioisóstero de un grupo carboxilo es seleccionado a partir de $-SO_3H$, $-S(O)_2NHR^{13}$, $S(O)_2NHC(O)R^{13}$, $-CH_2S(O)_2R^{13}$, $-C(O)NHS(O)_2R^{13}$, -C(O)NHOH, -C(O)NHCN, $-CH(CF_3)OH$, $C(CF_3)_2OH$, $-P(O)(OH)_2$ y grupos de la sub-fórmula (a)-(i') a continuación



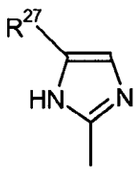
(i)



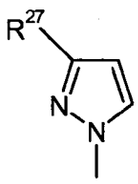
(j)



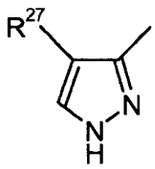
(k)



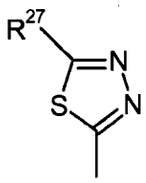
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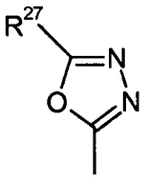
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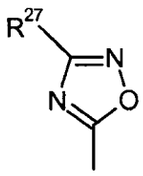
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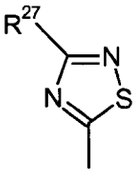
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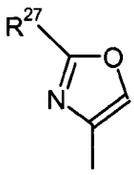
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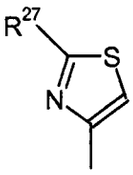
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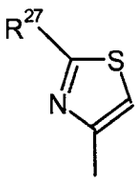
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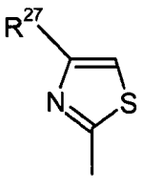
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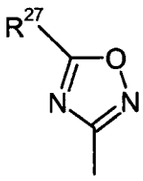
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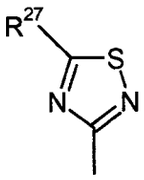
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(v)



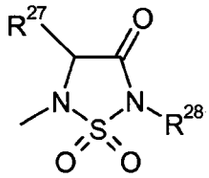
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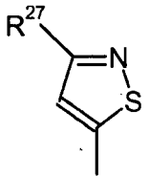
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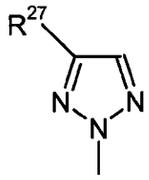
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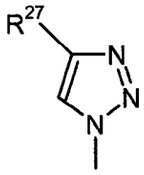
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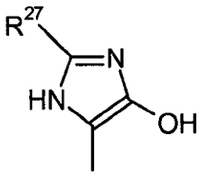
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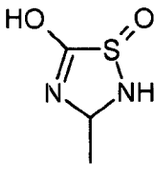
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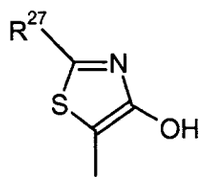
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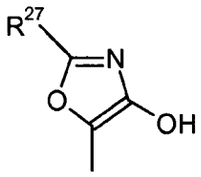
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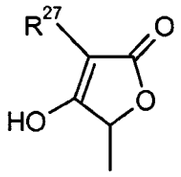
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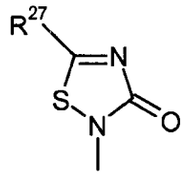
(f')



(g')



(h')



(i')

en donde donde p en la sub-fórmula (k) es 1 o 2, R^{27} y R^{28} son independientemente seleccionados a partir de hidrógeno, hidroxilo, (1-6C)alcoxilo, tiol, (1-6C)alquiltio, $-C(O)R^{29}$, $-S(O)R^{30}$, $-S0_2R^{31}$, $-NR^{32}R^{33}$, -NHCN, halógeno y trihalometilo, donde R^{29}, R^{30} y R^{31} son $-OR^{34}$, (1-6C)alquilo, $-NR^{32}R^{33}$ o trihalometilo, R^{32} y R^{33} son independientemente seleccionados a partir de hidrógeno, (1-6C)alquilo, $-SO_2R^{34}$ y $-COR^{35}$, donde R^{35} es (1-6C)alquilo o trihalometilo, y R^{34} es hidrógeno, (1-6C)alquilo o trihalometilo y R^{13} es seleccionado a partir de hidrógeno, (1-6C)alquilo, hidroxilo, halo, amino, ciano, ((1-3C)alquilo)CONH-, carboxilo, (1-6C)alcoxilo, (1-6C)alcoxilocarbonyl, Carbamoilo, N-((1-6C)alquilo)Carbamoilo, halo((1-6C)alquilo) (such como trifluorometili), (1-6C)alquilsulfonilo o (1-6C)alquilosulfinilo.

10. Un compuesto según cualquiera de las Reivindicaciones 1 a 9 o una sal farmacéuticamente aceptable, o profármaco del mismo para utilizar como un medicamento.

11. Un compuesto, o una sal farmacéuticamente aceptable, o profármaco del mismo, para utilizar como un medicamento como se reivindicó en la Reivindicación 10 para tratar diabetes mellitus y/o obesidad en un animal de sangre caliente tal como un ser humano.

12. El uso de un compuesto según cualquiera de las Reivindicaciones 1 a 9, o una sal farmacéuticamente aceptable, o profármaco del mismo, en la manufactura de un medicamento para utilizar en la producción de una inhibición de actividad DGAT-1 en un animal de sangre caliente tal como un ser humano.

13. El uso de un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable, o profármaco del mismo, como se reivindicó en la Reivindicación 12, en la manufactura de un medicamento para utilizar en el tratamiento de diabetes mellitus y/o obesidad en un animal de sangre caliente tal como un ser humano.

14. Un método para tratar diabetes mellitus y/o obesidad en un animal de sangre caliente, tal como un ser humano, en necesidad de tal tratamiento el cual comprende administrar a dicho animal una cantidad efectiva de un compuesto según cualquiera de las Reivindicaciones 1 a 9, o una sal farmacéuticamente aceptable, o profármaco del mismo.

15. Una composición farmacéutica la cual comprende un compuesto de la fórmula (I) como se reivindicó en cualquiera de las Reivindicaciones 1 a 9, o una sal farmacéuticamente aceptable, o profármaco del mismo, en asociación con un excipiente o vehículo farmacéuticamente aceptable.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

To:
ASTRAZENECA AB
Attn. ASTRAZENECA INTELLECTUAL PROPERTY
Astrazeneca Intellectual Property
SE-151 85 Södertälje
SUEDE

ANKOM/SCANNED
31 MAR 2009
Page(s) Scanned
FINAL CHECK

Date of mailing (day/month/year)	31/03/2009
Applicant's or agent's file reference: 103190-1P WO	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No.: PCT/GB2008/051199	International filing date (day/month/year) 18/12/2008
Applicant: ASTRAZENECA AB	

1. [X] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Fascimile No.: (41-22) 338.82.70

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority: European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer: Emmanuel Cherqui

Form PCT/ISA/220 (October 2005) *(See notes on accompanying sheet)*

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the International application (claims,description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the International application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1–10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

If a demand for international preliminary examination is made, the written opinion of the International Searching Authority will, except in certain cases where the International Preliminary Examining Authority did not act as International Searching Authority and where it has notified the International Bureau under Rule 66.1*bis*(b), be considered to be a written opinion of the International Preliminary Examining Authority. If a demand is made, the applicant may submit to the International Preliminary Examining Authority a reply to the written opinion together, where appropriate, with amendments before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later (Rule 43*bis*.1(c)).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, Volume II.

PATENT COOPERATION TREATY

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31 MAR 2009
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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
103190-1P WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB2008/051199	18/12/2008	20/12/2007
Applicant		
ASTRAZENECA AB		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title**,
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [X] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2008/051199

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/81 C07D213/82 C07D241/24 C07D401/04 C07D401/10
C07D403/10 A61K31/4418 A61K31/4965 A61K31/497 A61P3/00

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/126957 A (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; SERRANO-WU MICHAEL H [US]) 8 November 2007 (2007-11-08) abstract; claim 1; examples 8-1,8-2,8-3,8-4	1-15
A	WO 2007/141545 A (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; BENNETT STUART NORMAN LI) 13 December 2007 (2007-12-13) the whole document	1-15
A	WO 2007/141502 A (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; BUTLIN ROGER JOHN [GB];) 13 December 2007 (2007-12-13) the whole document	1-15

-/--

[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
23 March 2009	31/03/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Fritz, Martin

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2008/051199

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2007/138304 A (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; JOHNSTONE CRAIG [GB]; PL) 6 December 2007 (2007-12-06) the whole document	1-15

2

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2008/051199

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007126957 A	08-11-2007	AR 060220 A1	04-06-2008
		AU 2007245059 A1	08-11-2007
		CA 2647819 A1	08-11-2007
		CL 8852007 A1	23-05-2008
		EP 2004607 A2	24-12-2008
		KR 20080109784 A	17-12-2008
WO 2007141545 A	13-12-2007	EP 2032547 A1	11-03-2009
WO 2007141502 A	13-12-2007	EP 2035397 A1	18-03-2009
WO 2007138304 A	06-12-2007	AU 2007266890 A1	06-12-2007

PATENT COOPERATION TREATY

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From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

ANKOM/SCANNED
31 MAR 2009
Page(s) Scanned
FINAL CHECK

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2008/051199	18.12.2008	20.12.2007

International Patent Classification (IPC) or both national classification and IPC
INV. C07D213/81 C07D213/82 C07D241/24 C07D401/04 C07D401/10 C07D403/10 A61K31/4418 A61K31/4965 A61K31/497 A61P3/00

Applicant
ASTRAZENECA AB

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	see form PCT/ISA/210	Fritz, Martin Telephone No. +31 70 340-3024

Form PCT/ISA/237 (Cover Sheet) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2008/051199

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 1-4(part),6(part),8-15(part)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☒ the claims, or said claims Nos. 1-4(part),6(part),8-15(part) are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

see separate sheet

☒ no international search report has been established for the whole application or for said claims Nos. 1-4(part),6(part),8-15(part)

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-15
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-15
Industrial applicability (IA)	Yes:	Claims	1-15
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Present claims 1-4,6,8-15 relate to an extremely large number of possible products and their use. Support and disclosure in the sense of Article 6 and 5 PCT is to be found however for only a very small proportion of the products claimed, as there are only 66 compounds actually exemplified in the description.
The non-compliance with the substantive provisions is to such an extent, that the search was performed taking into con-sideration the non-compliance in restricting the extent of the search of the above-mentioned claims to those claimed products which appear to be supported and a generalisation of their structural formulae (PCT Guidelines 9.19 and 9.23), i.e.

compounds (I), wherein ring B is 1,4-phenylene or a 2,5-pyridindiyl

compositions and uses thereof.

Claims or parts thereof relating to inventions in respect of which no International search Report has been established need not be subject of the Written Opinion of the International Searching Authority (Rule 43bis.1(b) PCT in combination with Rule 66.1(e) PCT.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1: WO 2007/126957 A (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; SERRANO-WU MICHAEL H [US]) 8 November 2007 (2007-11-08)

The following comments with regard to novelty and inventive step of claims 1-4,6,8-15 only relate to that part of subject-matter thereof which was actually searched (Art. 17(2) PCT), vide supra

The patentability of claim 14 is inter alia dependent upon its formulation as well as upon national and regional laws, and no unifying criteria is provided in this field in the PCT. Its assessment will be carried out based on the alleged effects of the compounds and compositions as searched in the international Search Report.

The compound according to ex. 8.3 of D1 (p. 143) is a representative of the compounds (I), but excluded from the subject-matter claimed by a proviso.

The subject-matter of claims 1-15 according to the present case is therefore novel in the sense of Article 33(2) PCT.

Closest prior art is D1.

The problem underlying the present application was to provide further compounds which are inhibitors of DGAT1 and thus suitable for the treatment of diabetes and obesity.

This problem has been solved by selected representatives of the compounds (I), as can be seen in the description.

The compound according to ex. 8-3 of D1 which is a representative of the compounds claimed in the present case is not within the scope of the compounds as defined in claim 1 of D1, as in the latter the terminal group L1-A which is bound to ring B cannot designate an unsubstituted amide group:

The compounds claimed in D1 are, due to the definition of A, structurally comparable, but not identical to those compounds claimed in the present case, wherein ring A is a 2,6-pyridindiyl.

Although the compound according to example 8.3 of D1 is not within the scope of the subject-matter claimed therein, it is stated in this prior art on p. 69 that the compounds disclosed therein show DGAT1-inhibitory activity, i.e. a skilled man being aware of D1 and trying to solve the above-formulated problem would have to assume, that also the

compound according to ex. 8-3 is active against DGAT1.

Consequently those compounds (I) according to the present case, wherein ring A is a 2,6-pyridindiyl (sub-group a), have to be considered obvious for the skilled man.

Those compounds (I), wherein ring A is a 3,5-pyridindiyl (sub-group b) and 2,6-pyrazindiyl (sub-group c) are structurally more remote from the compounds disclosed in D1. The compounds according to sub-groups b and c which are indeed a solution to the problem can thus not be considered obvious for the skilled man.

In this respect the following is noted:

The Applicant is entitled to claim all obvious modifications of what was described (cf. Guidelines C-III, 6.2); alternative variations have to be supported by a certain number of examples (s. Guidelines C-II, 4.9) so that the breadth of the main claim represents a reasonable generalisation of what has been exemplified, and it can be assumed, that every compound falling within its scope actually provides a solution to the problem underlying the invention.

In the present case the scope of the compounds (I) is deemed to be far too broad, the reasoning therefor being as follows

i) all compounds (I)

The expression "or mimic or bioisoster thereof" (the meaning of which is not clear, see below) includes a countless number of structural alternatives.
Support for this term can be found only in one concrete example which is a representative of the compounds of sub-group c comprising a "mimic" of COOH which is tetrazolyl.

ii) with respect to the compounds of the sub-groups a and b:

Only one representative of each group was actually synthesized (cf. ex. 19 and 20), and in both of these examples X is oxygen, B is a 1,4-phenylene, rings B and C are connected by

a direct bond, L is a bond, p is 1, R^{A1} and R^{A2} are both hydrogen and Z is COOH, i.e. it is hardly plausible that all possible compounds within these two sub-groups are a solution to the problem.

The reasoning of ii) deos not apply for the compounds of sub-group c, as many different structural variants have been synthesized.

The applicant could - in order to overcome the above objections - submit all information available to substantiate that all claimed compounds are an non-obvious solution to the problem underlying the application (cf. Article 33(3) PCT in conjunction with Articles 5 and 6 PCT) or, alternatively, restrict the claims concerned appropriately.

An inventive step in the sense of Article 33(3) PCT can therefore not be acknowledged for the subject-matter of claims 1-15.

Further objections:

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclo-sed in the document D1 is not mentioned in the description, nor is this document identified therein.

Claims 1-6, 8, and 10-15 encompass a large number of compounds which are defined only by reference to a desired functional activity (compound being a "pro-drug"). This functional term does not give a specific technical guidance for the selection of the suitable derivatives, without proven general knowledge, to show which derivatives are suitable "pro-drugs" in the particular case of the current problem and thus could be seen as a mere invitation to the skilled person to perform a research program in order to find the suitable variants.

The description does not provide support and disclosure within the meaning of Article 6 PCT and, in addition, does not appear to be sufficiently disclosed under Art. 5 PCT for any of such compounds having the desired function and there is no general common knowledge of this kind available to the skilled person. In such a situation, the invention

cannot be carried out over the whole claimed area without imposing an undue burden, even when simple in vivo or in vitro tests are available to determine whether or not a particular compound is covered by the claims.

The same objection as of above applies for the term "mimic".

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2008/051199

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/81 C07D213/82 C07D241/24 C07D401/04 C07D401/10
C07D403/10 A61K31/4418 A61K31/4965 A61K31/497 A61P3/00

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/126957 A (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; SERRANO-WU MICHAEL H [US]) 8 November 2007 (2007-11-08) abstract; claim 1; examples 8-1,8-2,8-3,8-4	1-15
A	WO 2007/141545 A (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; BENNETT STUART NORMAN LI) 13 December 2007 (2007-12-13) the whole document	1-15
A	WO 2007/141502 A (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; BUTLIN ROGER JOHN [GB];) 13 December 2007 (2007-12-13) the whole document	1-15

-/--

[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
23 March 2009	31/03/2009

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Fritz, Martin

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2008/051199

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2007/138304 A (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; JOHNSTONE CRAIG [GB]; PL) 6 December 2007 (2007-12-06) the whole document	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2008/051199

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007126957 A	08-11-2007	AR 060220 A1	04-06-2008
		AU 2007245059 A1	08-11-2007
		CA 2647819 A1	08-11-2007
		CL 8852007 A1	23-05-2008
		EP 2004607 A2	24-12-2008
		KR 20080109784 A	17-12-2008
WO 2007141545 A	13-12-2007	EP 2032547 A1	11-03-2009
WO 2007141502 A	13-12-2007	EP 2035397 A1	18-03-2009
WO 2007138304 A	06-12-2007	AU 2007266890 A1	06-12-2007

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-074457- -00000-0000
Fecha: 2010-06-21 17:00:09 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 394

PATENTE DE INVENCIÓN ☐ **MODELO** ☐ **Art 33 Decisión 486/00**

- ☐ Indicación que se solicita una patente.
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Descripción de la invención
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

PATENTE DE INVENCIÓN PCT ☑ **MODELO DE UTILIDAD PCT** ☐ **Art.33 Decisión 486/00, Circular Única**

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

Completa ☐ Incompleta ☐

DISEÑO INDUSTRIAL ☐ **(Art. 119 Decisión 486/00)**

- ☐ Indicación que se solicita Diseño industrial
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

ESQUEMA DE TRAZADO ☐ **(Art. 92 Decisión 486/00)**

- ☐ Indicación que se solicita un esquema de trazado
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica de un esquema de trazado
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

Doctor(a)
RAISBECK J. IAN
Apoderado(a) y/o Representante de
ASTRAZENECA AB

REFERENCIA	Radicación No.	10 074457
	Solicitud internacional	PCT/GB2008/051199
	Fecha inicio fase nacional	20/07/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	10536

Como resultado del examen de forma, realizado con fundamento en el artículo 38 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. 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 k) 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 X 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.

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.

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

20 AGO. 2010

El anterior requerimiento fue notificado por fijación en lista de fecha_____.
adpa11

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Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

Doctor(a)
RAISBECK J. IAN
Apoderado(a) y/o Representante de
ASTRAZENECA AB

REFERENCIA		
	Radicación No.	10 074457
	Solicitud internacional	PCT/GB2008/051199
	Fecha inicio fase nacional	20/07/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	

№ 10537

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 titulo primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 20 AGO. 2010.
adpa11