

Industi
SUPERI



DELEGATURA DE PROPIEDAD INDUSTRIAL
DIRECCIÓN DE NUEVAS CREACIONES

SOLICITUD DE PATENTE DE
INVENCION

TITULO: PROMOTORES DE APOPTOSIS N-ACILSULFONAMIDAS

SOLICITANTES: ASTRAZENECA AB

DIRECCIÓN: S-151- 85 Sodertalje Suecia

APODERADO: CARLOS R. OLARTE

BOGOTÁ 08 de febrero de 2013

P2013/000020

OLARTEMOURE

OLARTE MOURE & ASOC

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 13-026618- -00000-0000

Fecha: 2013-02-08 17:12:31 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 5

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD

PATENTE PCT

ENTRADA EN FASE NACIONAL

P2013/000020

SOLICITUD DE:

1

☒

Patente de Invención.

☐

Patente de Modelo de Utilidad.

☒

Capítulo I.

☐

Capítulo II.

2

SOLICITANTE (71)

Nombre: ASTRAZENECA AB

Dirección: S-151- 85 Sodertalje Suecia

Nacionalidad o Domicilio: Suecia

Lugar de Constitución: Suecia

Teléfono: _____

Fax: _____

E-mail: _____

IDENTIFICACIÓN

C.C.

☐

NIT

☐

C.E.

☐

Otro

☐

Cual _____

Número _____

REPRESENTANTE O APODERADO

Nombre: CARLOS R. OLARTE

Dirección: Carrera 5 No. 34-03 Bogotá

Teléfono: 601-7700 Fax: 601-7799

E-mail: office@olartemoure.com

IDENTIFICACIÓN

C.C.

☒

NIT

☐

C.E.

☐

Otro

☐

Cual _____

Número 79.782.747

TP 74.295

INVENTOR (ES) (72)

Nombre: VER PAGINA ADJUNTA

Dirección: VER PAGINA ADJUNTA

Nacionalidad o Domicilio: VER PAGINA ADJUNTA

5

PCT (86)

Solicitud Internacional No. PCT/GB2011/051484

Fecha

Agosto 05, 2011

Publicación Internacional No. WO 2012/017251 A1

Fecha

Febrero 9, 2012

6

Título (54) PROMOTORES DE APOPTOSIS N-ACILSULFONAMIDAS.

Clasificación Internacional (51) C07D 211/22; A61K 31/445; A61P 35/00; A61P 35/02.

Prioridad

SI

☒

NO

☐

(33) País de Origen

US

US

(32) Fecha

Agosto 6, 2010

Septiembre 17, 2010

(31) Número de Solicitud

61/371,648

61/384,170

9

Comprobante de pago No. 13-

Fecha

10

ANEXOS☒

Comprobante de pago de la tasa de presentación de la solicitud.

☒

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

☒

Poderes, si fuere el caso.

☐

Documento de cesión del inventor al solicitante o a su causante.

☐

Declaraciones. Declaración bajo la Regla 4.17 (ii) del PCT.

☒

Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).

☒

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.

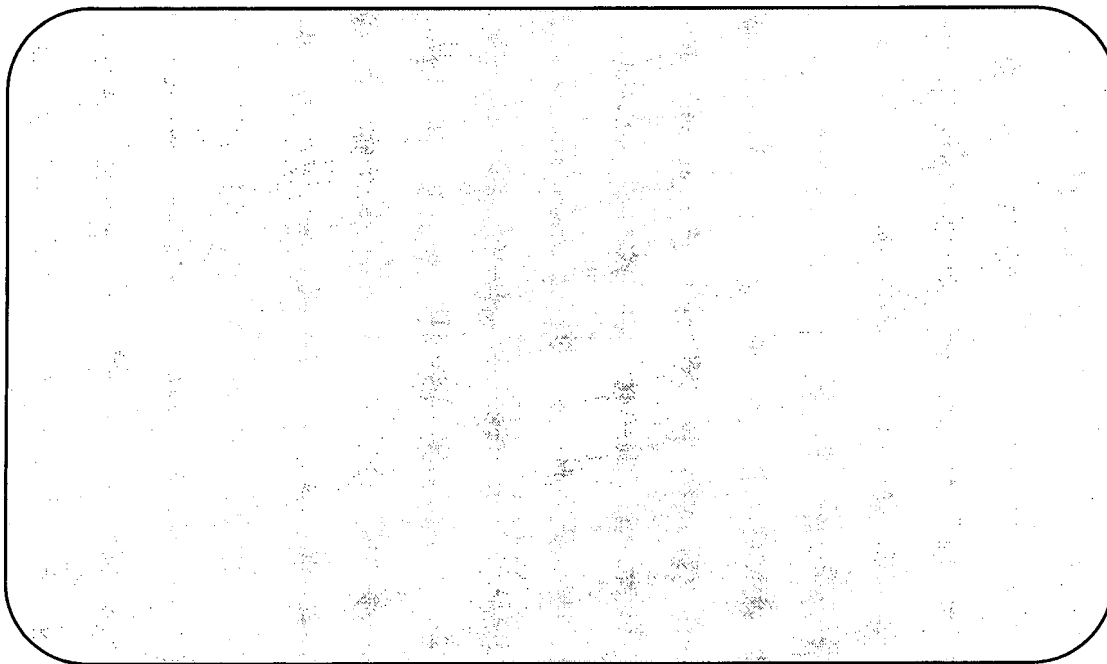
☐

De ser el caso, modificaciones efectuadas a la solicitud internacional.

☒

Otros. Búsqueda Internacional

11

FIGURA CARACTERÍSTICA:

12

Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE

FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

LISTA DE INVENTORES

PCT/GB2011/051484

Robert Bruc DIEBOLD

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35 Gatehouse Drive, Waltham,
Massachusetts 02451
Estados Unidos de América
Nacionalidad: Estadounidense

Thomas GERO

AstraZeneca R&D Boston,
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Estados Unidos de América
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Massachusetts 02451
Estados Unidos de América
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Massachusetts 02451
Estados Unidos de América
Nacionalidad: Ghanés

Jamal Carlos SAEH

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Massachusetts 02451
Estados Unidos de América
Nacionalidad: Estadounidense

Jeffrey Gilbert VARNES

AstraZeneca R&D Boston,
35 Gatehouse Drive, Waltham,
Massachusetts 02451
Estados Unidos de América
Nacionalidad: Estadounidense

PATENTE DE INVENCION ☐

MODELO DE UTILIDAD ☐

Art 33 Decisión 486/00

☐	Indicación que se solicita una patente.
☐	Datos de identificación del solicitante o de la persona que presenta la solicitud
☐	Descripción de la invención
☐	Dibujos de ser estos pertinentes
☐	Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)
Completa ☐ Incompleta ☐	

PATENTE DE INVENCION 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 ☐	

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 13-026618-00000-0000

Fecha: 2013-02-08 17:12:31

Dep. 2020 DIR.NUEVASCR

Tra. 11 PATENTEIYII

Eve: 378 FASENACIONALI

Act. 411 PRESENTACION

Folios: 5

PI02-F03 (2009-11-18)

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 Minjusticia

Apostilla adjunta:

APOSTILLE	
(Convention du La Haye du 5 octobre 1961)	
1. País:	Suecia
<u>El presente documento público</u>	
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.
<u>Certificado</u>	
5. En:	Estocolmo
6. El:	Día 26 de Octubre de 2007
7. Por:	Björn Sandin, Notario Público
8. Bajo el No.	4071
9. Sello / estampilla:	Björn Sandin, Notario Público de Estocolmo.
10. Firma:	(Firmado)

Certificación:

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

Fecha: 13 de Noviembre de 2007.

Traductor: Jorge Enrique Sierra Reyes.

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

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

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

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


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

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

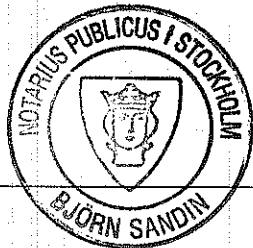
7. by Björn Sandin

Notary Public

8. No 4071

9. Seal/stamp:

10. Signature:



A handwritten signature in black ink, appearing to read "Björn Sandin", followed by a period.

OLARTE RAISBECK

OLARTE RAISBECK & FRIERI LTDA.

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

Zayde Chahí
Simón Salina
Alexander Agudela
Camilo A. Rodríguez
Lina Mosquera
Catalina Barbastefan

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

Power of Attorney

The undersigned,

domiciled in

AstraZeneca AB
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 Mour 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.

El suscrito,

domiciliado en

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

Signature/Firma:

Anders Burén
Authorized Signatory

Date/Fecha: 24 OCTOBER 2007

City/Country/Ciudad,País: SÖDERTÄLJE



I, the undersigned, Anne-Marie Bonde, Notary Public of the City of Stockholm
hereby certify that

ANDERS BURÉN

duly authorized to sign for

ASTRAZENECA AB

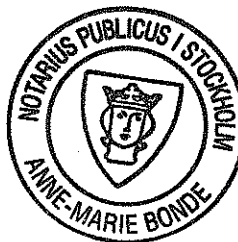
has issued and signed the foregoing document.

Fee 340:-

Stockholm 2007-10-26

Crowns

Ex officio:



Anders Burén
Authorized Signatory



MODEL OF NOTARIAL CERTIFICATION

Notarial Certification

On this date,

The undersigned Notary Public certifies:

1. That

of legal age and domiciled in

signed the foregoing document.

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

3. That ASTRAZENECA AB having its principal place of business located in SODERTALJE, SWEDEN

is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.

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

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

1. CERTIFICATE OF INCORPORATION OF ASTRAZENECA AB

2. AUTHORISATION IN FAVOUR OF SIGNATORY

NOTARY PUBLIC (Signature):

Name and Particulars (e.g. Notary's name, Jurisdiction, Date of Licence Expiration)

SEAL (optional)

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que

mayor de edad y domiciliado

suscribió el documento que antecede.

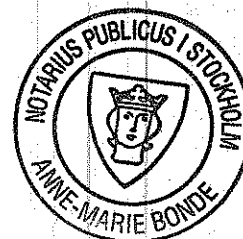
2. Que el otorgante ha suscrito el referido documento en su carácter de de

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):



Traducción oficial de un documento cuyo original está en inglés

BOLAGSVERKET

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

Certificado de Existencia

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

Registro No. 556011-7482

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

En testimonio de lo anterior, he puesto mi firma y estampado el sello oficial de Bolagsverket en Sundsvall, este día 8 de Agosto del año 2007.
(Firmado) Anna-Karin Östin.

Hay un sello de Bolagsverket

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

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



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

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

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

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

Certificación Notarial

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

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

Ex officio:

(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 Minjusticia

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

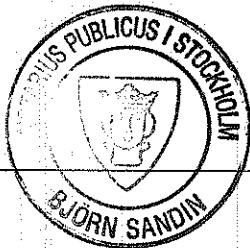
7. by Björn Sandin

Notary Public

8. No 4070

9. Seal/stamp:

10. Signature:





Certificate of Good Standing

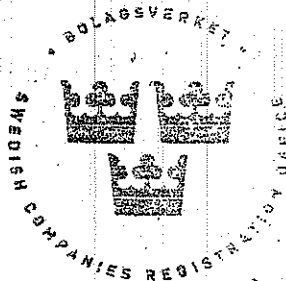
I, Anna-Karin Östin, of Bolagsverket, the Swedish Companies Registration Office, do hereby certify that

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.

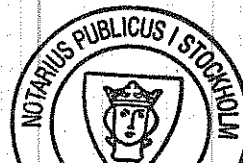

Anna-Karin Östin



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.



I, the undersigned, Anne-Marie Bonde, Notary Public of the City of Stockholm
hereby certify that

ANNA-KARIN ÖSTIN

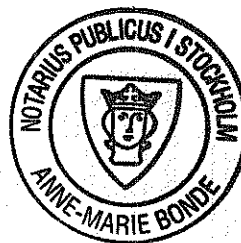
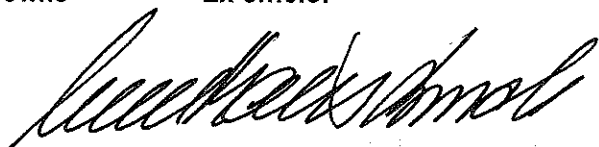
duly authorized to sign for

THE SWEDISH COMPANIES REGISTRATION OFFICE

has issued and signed the foregoing document in original of which this is a true copy.

Fee 340:- Stockholm 2007-10-26

Crowns Ex officio:



12.1142b

The Ministry for Foreign
Affairs in Stockholm, hereby
certifies that

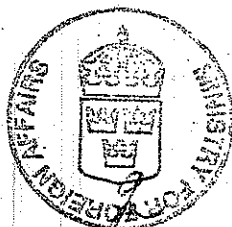
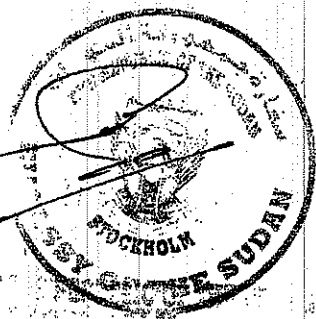
Mr. S. Anna - Karin Eric

**Swedish Companies Registration
Office, Sundsvall**

has issued and signed the
foregoing attestation in his
official capacity

For Stockholm this 14th day of August
1907- PAID

Agnete Ederlund

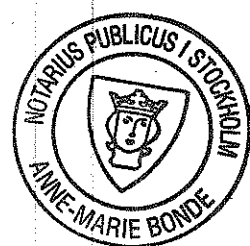


SIGNATURE OF *Agnete Ederlund*

AND STAMP OF: *Sec. MFA*

SIGNATURE: *Mohammed Husseini*

DATE: *20-08-07*





(51) International Patent Classification:

C07D 211/22 (2006.01) A61P 35/00 (2006.01)
A61K 31/445 (2006.01) A61P 35/02 (2006.01)

(21) International Application Number:

PCT/GB2011/051484

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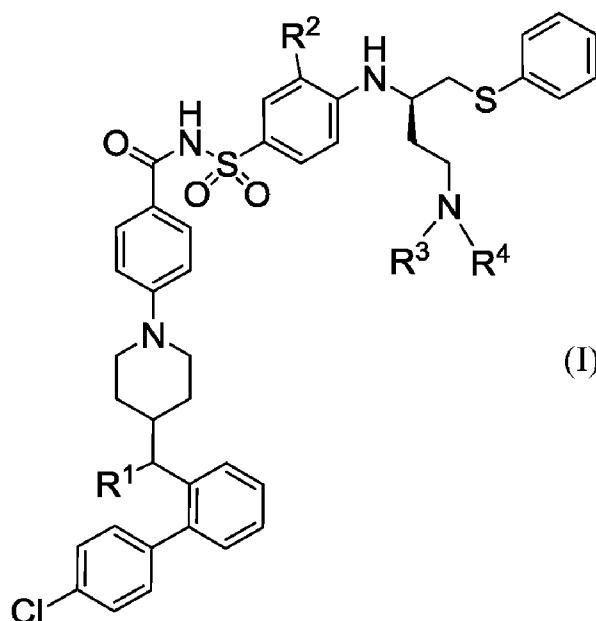
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[Continued on next page]

(54) Title: N-ACYLSULFONAMIDE APOPTOSIS PROMOTERS



(I)

(57) Abstract: The present invention relates to compounds of Formula (I): and to their salts, pharmaceutical compositions, methods of use, and methods for their preparation. These compounds inhibit Bcl-2 and/or Bcl-X_L activities and may be used for the treatment of cancer.



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N-ACYLSULFONAMIDE APOPTOSIS PROMOTERS

RELATED APPLICATIONS

[0001] This application claims priority to U.S. provisional patent application serial number 61/371648, filed August 6, 2010; and to U.S. provisional patent application serial number 61/384170, filed September 17, 2010, the entire disclosure of each of which is incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to novel compounds, their pharmaceutical compositions, and their methods of use. In addition, the present invention relates to therapeutic methods for the treatment and prevention of cancers and to use of such compounds in the manufacture of medicaments for use in the treatment and prevention of cancers.

BACKGROUND OF THE INVENTION

[0003] Apoptosis is the process by which a cell undergoes programmed cell death in response to nutrient deprivation, stress signals, death receptor signaling, DNA damage, treatment with novel targeted or cytotoxic agents or other insults from the external environment. Two forms of apoptosis have been identified: the intrinsic or mitochondrial pathway involving members of the BCL2 family of proteins and BH3 only proteins, and the extrinsic pathway where signals from death domain containing receptors trigger the activation of the caspase cascade via regulation of members of the inhibitor of apoptosis (IAP) family of proteins.

[0004] The BCL2 family of BH-3 containing proteins, comprising Bcl-2, Bcl-X_L, Mcl-1, Bcl-w and Bcl-A1 (also known as Bfl-1), is a family of adaptor molecules involved in regulating the control of mitochondrial apoptosis in a variety of different cell types (reviewed in (1)). BCL2 family members are generally considered to be anti-apoptotic because they bind to and counteract the activity of pro-apoptotic members of the BH3-only family, including Bim, tBid, and Puma, and the multidomain effector proteins Bak and Bax. Bim and tBid in turn facilitate the oligomerization and activation of Bak and Bax to form a pore in the outer mitochondrial membrane through which Smac and cytochrome c are released into the cytosol. The release of cytochrome c triggers activation of the caspase cascade via formation of a complex with Apaf-1, termed the apoptosome, ultimately leading to apoptotic cell death. Another group of BH3-only proteins, the "sentinels" are upregulated by a variety of transcriptional and post-translational mechanisms in response to the pro-apoptotic triggers mentioned above. These proteins, including Noxa, Bmf, Bad, Bik, and Hrk bind selectively to certain BCL2 family members and

alter the balance of free and bound pro-apoptotic members, through a process of sensitization (binding to anti-apoptotic BCL2 family members) and depression (displacing bound Bim, tBid, Bak and Bax), permitting permeabilization of the outer mitochondrial membrane (MOMP) to occur. In healthy cells, the balance of pro- and anti-apoptotic proteins ensures that apoptosis is held in check until needed.

[0005] The anti-apoptotic BCL2 family members are often found to be up-regulated in cancers and have been associated both with stage of disease and prognosis. Over-expression of Bcl-2, Bcl-X_L and Mcl-1 has been linked to resistance to common therapeutic agents and strategies that target BCL2 family members can restore sensitivity to cytotoxic agents by reinstating the ability of the tumor cell to undergo apoptosis. A translocation, t(14;18)(q32;q31) involving Bcl2 and IGH leads to over-expression of the Bcl-2 protein and is commonly found in tumors of hematological origin including non Hodgkin's Lymphomas (2-4). Even in the absence of a translocation, BCL2 family expression is often de-regulated (2,3,5-8). Amplifications of Bcl-X_L and Mcl-1 are also commonly seen in many tumor types (9-11) for example by activation of NFkB or by suppression of certain microRNAs (12).

[0006] In a number of tumors, including chronic lymphocytic leukemia (CLL) (4,13-15), small cell lung cancer (SCLC) (16), and prostate cancer (17), Bcl-2 expression is an independent indicator of poor prognosis. In other tumor types such as colorectal cancer Bcl-X_L expression is linked to grade and stage (18) and in hepatocellular cancer Bcl-X_L expression is an independent marker of poorer overall and disease-free survival (19). Mcl-1 expression has also been linked to stage in CLL and to prognosis, for example in myeloma, melanoma, ovarian and gastric tumors (20-22).

[0007] Redundancy has been seen among members of the BCL2 family and is believed to account at least in part for resistance to the BH3-mimetic compounds that target Bcl-2, Bcl-X_L, Bcl-w, and Bcl-A1, but not Mcl-1 (23-26). Hence, for many cancers, a combination of a selective BH-3 mimetic with another agent that targets the Bim/Noxa/Mcl-1 axis may be desirable to ensure apoptosis induction and tumor regression. Examples of such agents include but are not limited to cytotoxic chemotherapeutics, proteasome inhibitors, EGFR inhibitors, and MEK/ERK pathway inhibitors.

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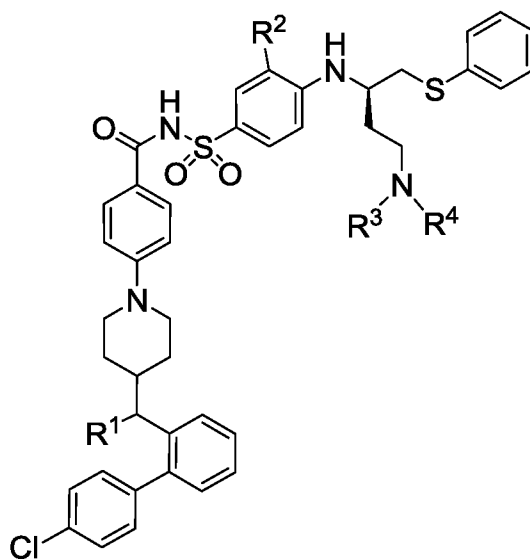
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SUMMARY OF THE INVENTION

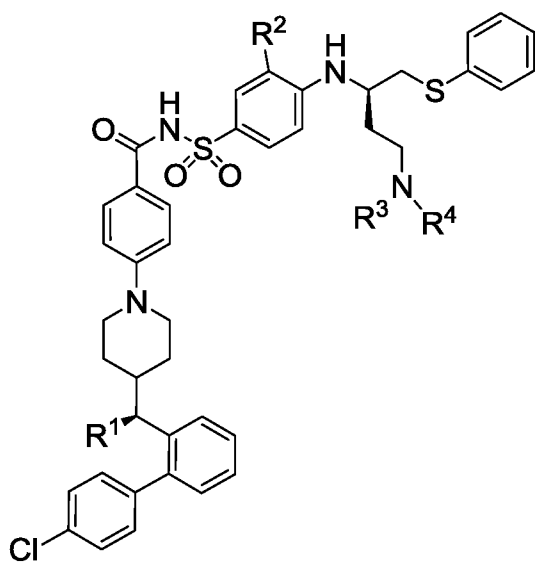
[0008] The present invention relates to compounds of Formula (I):



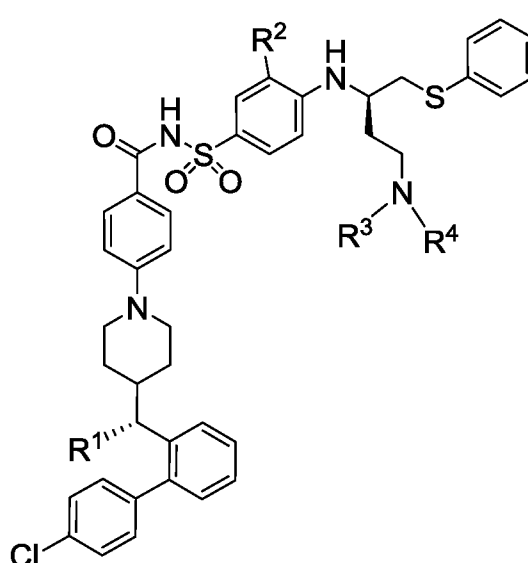
Formula (I)

and/or to pharmaceutically acceptable salts thereof.

[0009] In certain embodiments, compounds provided by the present invention have the structure set forth in Formulae (I-a) and/or (I-b):



(I-a)



(I-b)

and/or a pharmaceutically acceptable salt thereof, wherein each of R¹, R², R³, and R⁴ are as defined for compounds of formula (I) and in classes and subclasses described herein.

[00010] In some embodiments, the present invention provides a compound of formula (I-a), as depicted above, or a pharmaceutically acceptable salt thereof, wherein each R¹, R², R³, and R⁴ are as defined for compounds of formula (I) and in classes and subclasses described herein.

[00011] In some embodiments, the present invention provides a compound of formula (I-b), as depicted above, or a pharmaceutically acceptable salt thereof, wherein each R¹, R², R³, and R⁴ are as defined for compounds of formula (I) and in classes and subclasses described herein.

[00012] Compounds of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e) possess beneficial efficacious, metabolic, pharmacokinetic, and/or pharmacodynamic properties. Compounds of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e) are useful for their ability to inhibit Bcl-2 and Bcl-X_L activities and are accordingly also useful in the treatment of diseases or medical conditions mediated alone or in part by the BCL2 family. It has been found that for certain enantiomers of the present invention, there may be differences in one or more biological and or physiological property which may be advantageous.

[00013] In particular, compounds of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e) may be used for the treatment of cancer, including solid tumors, such as: bladder cancer; breast cancer; colon cancer; ovarian cancer; AML; diffuse large B-cell lymphoma (DLBCL); CLL; small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), including the non-squamous and squamous subtypes; small cell lung cancer; pancreatic cancer; Follicular lymphoma (FL), and prostate cancer.

[00014] The invention also relates to processes for the manufacture of said compounds, to pharmaceutical compositions containing them, and to their use in the manufacture of medicaments for use in the production of an anti-proliferation and/or pro-apoptotic effect in warm-blooded animals such as man. Also in accordance with the present invention there are provided methods of using said compounds or pharmaceutically acceptable salts thereof in the treatment of cancer.

DETAILED DESCRIPTION OF THE INVENTION

I. DEFINITIONS

[00015] "ALKYL": As used herein the term "alkyl" refers to both straight and branched chain saturated hydrocarbon radicals having the specified number of carbon atoms. References to individual alkyl groups such as "propyl" are specific for the straight chain version only and references to individual branched chain alkyl groups such as 'isopropyl' are specific for the

branched chain version only. In one aspect, "alkyl" may be "C₁₋₄alkyl." In another aspect, "alkyl" and "C₁₋₄alkyl" may be "C₁₋₃alkyl." In another aspect, "alkyl," "C₁₋₄alkyl," and "C₁₋₃alkyl," may be methyl. In some embodiments, the term "C₁ALKYL" refers to a saturated hydrocarbon radical having one carbon atom. In some embodiments, the term "C₂ALKYL" refers to saturated hydrocarbon radicals having two carbon atoms. In some embodiments, the term "C₃ALKYL" refers to both straight and branched chain saturated hydrocarbon radicals having one, two, or three carbon atoms. In some embodiments, the term "C₄ALKYL" refers to both straight and branched chain saturated hydrocarbon radicals having one, two, three or four carbon atoms.

[00016] "C₁₋₄ALKYL": As used herein the term "C₁₋₄alkyl" refers to both straight and branched chain saturated hydrocarbon radicals having one, two, three, or four carbon atoms. In some embodiments, "C₁₋₄alkyl" is "C₁alkyl". In some embodiments, "C₁₋₄alkyl" is "C₂alkyl". In some embodiments, "C₁₋₄alkyl" is "C₃alkyl". In some embodiments, "C₁₋₄alkyl" is "C₄alkyl".

[00017] "C₁₋₃ALKYL": As used herein the term "C₁₋₃alkyl" refers to both straight and branched chain saturated hydrocarbon radicals having one, two, or three carbon atoms. In some embodiments, "C₁₋₃alkyl" is "C₁alkyl". In some embodiments, "C₁₋₃alkyl" is "C₂alkyl". In some embodiments, "C₁₋₃alkyl" is "C₃alkyl".

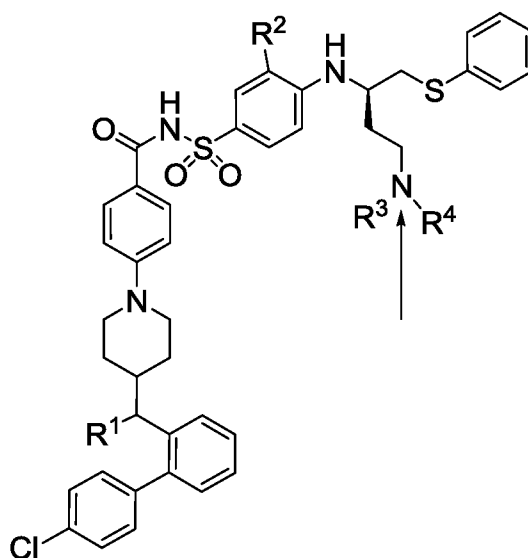
[00018] "C₁₋₂ALKYL": As used herein the term "C₁₋₂alkyl" refers to both straight and branched chain saturated hydrocarbon radicals having one, or two carbon atoms. In some embodiments, "C₁₋₂alkyl" is "C₁alkyl". In some embodiments, "C₁₋₂alkyl" is "C₂alkyl".

[00019] "EFFECTIVE AMOUNT": As used herein, the phrase "effective amount" means an amount of a compound or composition which is sufficient enough to significantly and positively modify the symptoms and/or conditions to be treated (e.g., provide a positive clinical response). The effective amount of an active ingredient for use in a pharmaceutical composition will vary with the particular condition being treated, the severity of the condition, the duration of the treatment, the nature of concurrent therapy, the particular active ingredient(s) being employed, the particular pharmaceutically-acceptable excipient(s)/carrier(s) utilized, and like factors within the knowledge and expertise of the attending physician.

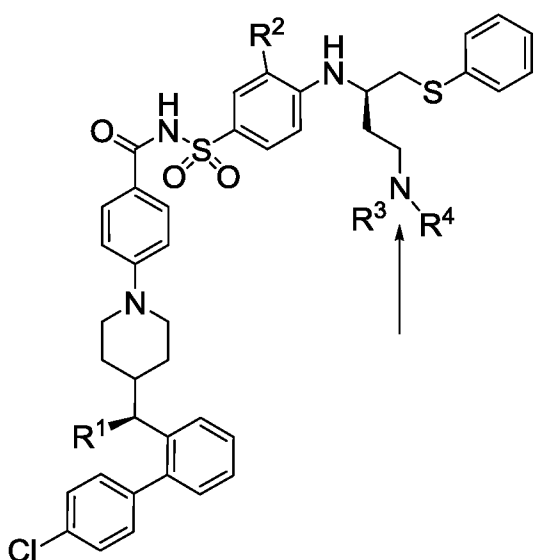
[00020] In particular, an effective amount of a compound of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e) for use in the treatment of cancer is an amount sufficient to symptomatically relieve in a warm-blooded animal such as man, the symptoms of cancer, to slow the progression of cancer, or to reduce in patients with symptoms of cancer the risk of getting worse.

[00021] "HALO": The terms "halogen" or "halo," as used herein, refers to fluoro, chloro, bromo and iodo. In certain embodiments, the term "halo" may refer to fluoro, chloro, and bromo. In certain embodiments, the term "halo" may refer to fluoro and chloro. In certain embodiments, the term "halo" may refer to fluoro. In certain embodiments, the term "halo" may refer to chloro. In certain embodiments, the term "halo" may refer to bromo.

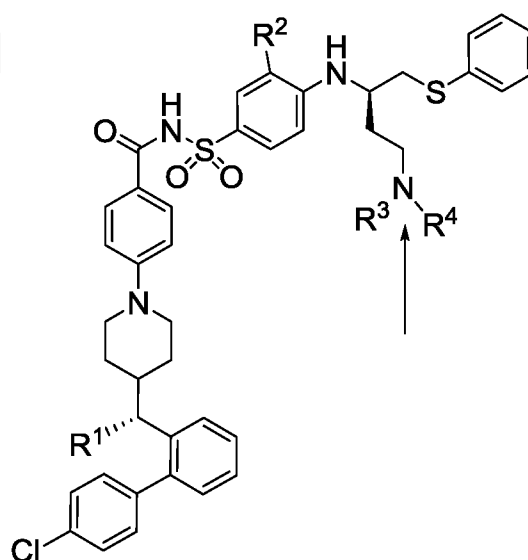
[00022] "5- or 6- MEMBERED HETEROCYCLIC RING" The term "5- or 6-membered heterocyclic ring" refers to a saturated or partially saturated monocyclic ring containing 5 or 6 ring atoms, of which one ring atom is the nitrogen indicated by the arrow below in Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e):



Formula (I)



Formula (I-a)



Formula (I-b)

[00023] The ring may include, in addition to the indicated nitrogen, one or more heteroatoms selected from nitrogen, sulfur, and oxygen. One or more -CH₂- groups may be

optionally replaced by a corresponding number of -C(O)- groups. Ring sulfur atoms may be optionally oxidized to form S-oxides. Illustrative examples of “5- or 6-membered heterocyclic ring” include azetidiny, imidazolin-1-yl, imidazolidin-1-yl, pyrazolidin-1-yl, piperazin-1-yl, piperidin-1-yl, pyrrolidin-1-yl, morpholino, and thiomorpholino.

[00024] Unless specifically stated, the bonding atom of a group may be any suitable atom of that group; for example, propyl includes prop-1-yl and prop-2-yl.

[00025] “LEAVING GROUP”: As used herein, the phrase “leaving group” is intended to refer to groups readily displaceable by a nucleophile such as an amine nucleophile, and alcohol nucleophile, or a thiol nucleophile. Examples of suitable leaving groups include halo, such as chloro, fluoro, iodo, and bromo, and sulfonyloxy group, such as methanesulfonyloxy and toluene-4-sulfonyloxy.

[00026] “OPTIONALLY SUBSTITUTED”: As used herein, the phrase “optionally substituted,” indicates that substitution is optional and therefore it is possible for the designated group to be either substituted or unsubstituted. In the event a substitution is desired, any number of hydrogens on the designated group may be replaced with a selection from the indicated substituents, provided that the normal valency of the atoms on a particular substituent is not exceeded, and that the substitution results in a stable compound.

[00027] In one aspect, when a particular group is designated as being optionally substituted with “one or more” substituents, the particular may be unsubstituted. In another aspect, the particular group may bear one substituent. In another aspect, the particular substituent may bear two substituents. In still another aspect, the particular group may bear three substituents. In yet another aspect, the particular group may bear four substituents. In a further aspect, the particular group may bear one or two substituents. In still a further aspect, the particular group may be unsubstituted, or may bear one or two substituents.

[00028] “PHARMACEUTICALLY ACCEPTABLE”: As used herein, the term “pharmaceutically acceptable” refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[00029] Examples of pharmaceutically acceptable acid addition salts include acetate, adipate, ascorbate, benzoate, benzenesulfonate, bicarbonate, bisulfate, butyrate, camphorate, camphorsulfonate, choline, citrate, cyclohexyl sulfamate, diethylenediamine, ethanesulfonate, formate, fumarate, glutamate, glycolate, hemisulfate, 2-hydroxyethylsulfonate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, hydroxymaleate, lactate, malate, maleate, methanesulfonate, meglumine, 2-naphthalenesulfonate, nitrate, oxalate, pamoate, persulfate,

phenylacetate, phosphate, diphosphate, picrate, pivalate, propionate, quinate, salicylate, stearate, succinate, sulfamate, sulfanilate, sulfate, tartrate, tosylate (p-toluenesulfonate), trifluoroacetate, and undecanoate.

[00030] Examples of pharmaceutically acceptable base salts include ammonium salts; alkali metal salts such as sodium, lithium and potassium salts; alkaline earth metal salts such as aluminum, calcium and magnesium salts; salts with organic bases such as dicyclohexylamine salts and N-methyl-D-glucamine; and salts with amino acids such as arginine, lysine, ornithine, and so forth. Also, basic nitrogen-containing groups may be quaternized with such agents as: lower alkyl halides, such as methyl, ethyl, propyl, and butyl halides; dialkyl sulfates such as dimethyl, diethyl, dibutyl; diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl halides; arylalkyl halides such as benzyl bromide and others. Non-toxic physiologically-acceptable salts are preferred, although other salts may be useful, such as in isolating or purifying the product.

[00031] “PROTECTING GROUP”: As used herein, the term “protecting group” is intended to refer to those groups used to prevent selected reactive groups (such as carboxy, amino, hydroxy, and mercapto groups) from undergoing undesired reactions.

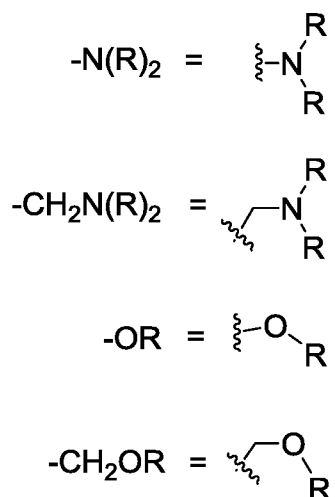
[00032] Illustrative examples of suitable protecting groups for a hydroxy group include, but are not limited to, an acyl group; alkanoyl groups such as acetyl; aroyl groups, such as benzoyl; silyl groups, such as trimethylsilyl; and arylmethyl groups, such as benzyl. The deprotection conditions for the above hydroxy 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 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.

[00033] Illustrative examples of suitable protecting groups for an amino group include, but are not limited to, acyl groups; alkanoyl groups such as acetyl; alkoxycarbonyl groups, such as methoxycarbonyl, ethoxycarbonyl, and *t*-butoxycarbonyl; arylmethoxycarbonyl groups, such as benzyloxycarbonyl; and aroyl groups, such benzoyl. The deprotection conditions for the above amino 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,

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 trichloride). 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. Another suitable protecting group for an amine is, for example, a cyclic ether such as tetrahydrofuran, which may be removed by treatment with a suitable acid such as trifluoroacetic acid.

[00034] 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.

[00035] With reference to substituent "R": for illustrative purposes, the following substituent definitions refer to the indicated structure:



[00036] "SUBSTANTIALLY ISOLATED": As used herein, the term "substantially isolated" means a specific stereoisomer is provided (whether provided by separation, by chiral synthesis, or by other methods) it is favorably provided substantially isolated from other stereoisomers of the same compound. In one aspect, a mixture containing a particular stereoisomer of a compound of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e) may contain less than 30%, particularly less than 20%, and more particularly less than 10% by weight of other stereoisomer(s) of the same compound. In another aspect, a mixture containing a particular stereoisomer of a compound of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e) may contain less than 6%, particularly less than 3%, and more particularly less than 2% by weight of other stereoisomer(s) of the compound. In another aspect, a mixture containing a particular stereoisomer of a compound of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e) may contain less than 1%, particularly less than 0.5%, and more particularly less than 0.3%, and still more particularly less 0.1% by weight of other stereoisomer(s) of the compound.

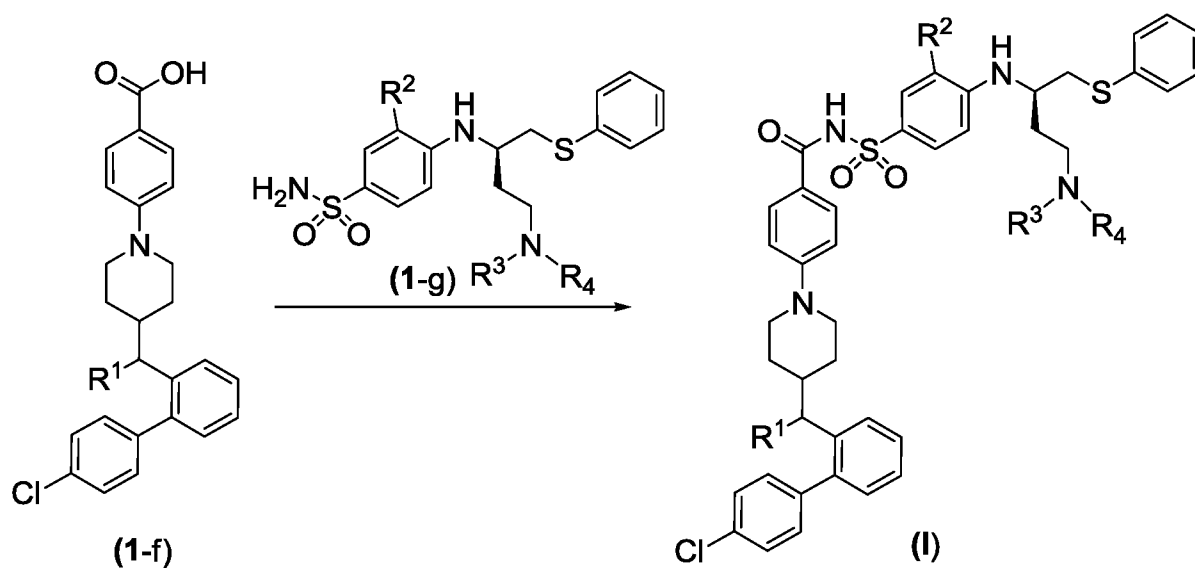
[00037] “TREAT”, “TREATING” OR “TREATMENT”: The terms “treat”, “treating” or “treatment” include administering a therapeutically effective amount of a compound sufficient to reduce or eliminate at least one symptom of the state, disease or disorder, *e.g.*, Bcl-2 related conditions and diseases, *e.g.*, cancer.

II. GENERAL METHODS OF PREPARATION

[00038] The present invention provides synthetic methodologies for preparing compounds of Formulae (I), (I-a), and/or (I-b) comprising coupling a carboxylic acid compound of formula (1-f) with a sulfonamide compound of formula (1-g) in the presence of a suitable coupling reagent and base. In certain embodiments, compounds of Formulae (I), (I-a), and/or (I-b) are further purified.

[00039] In certain embodiments, compounds of Formula (I), (I-a), and/or (I-b) are generally prepared according to the steps depicted in SCHEME 1 set forth below.

SCHEME 1



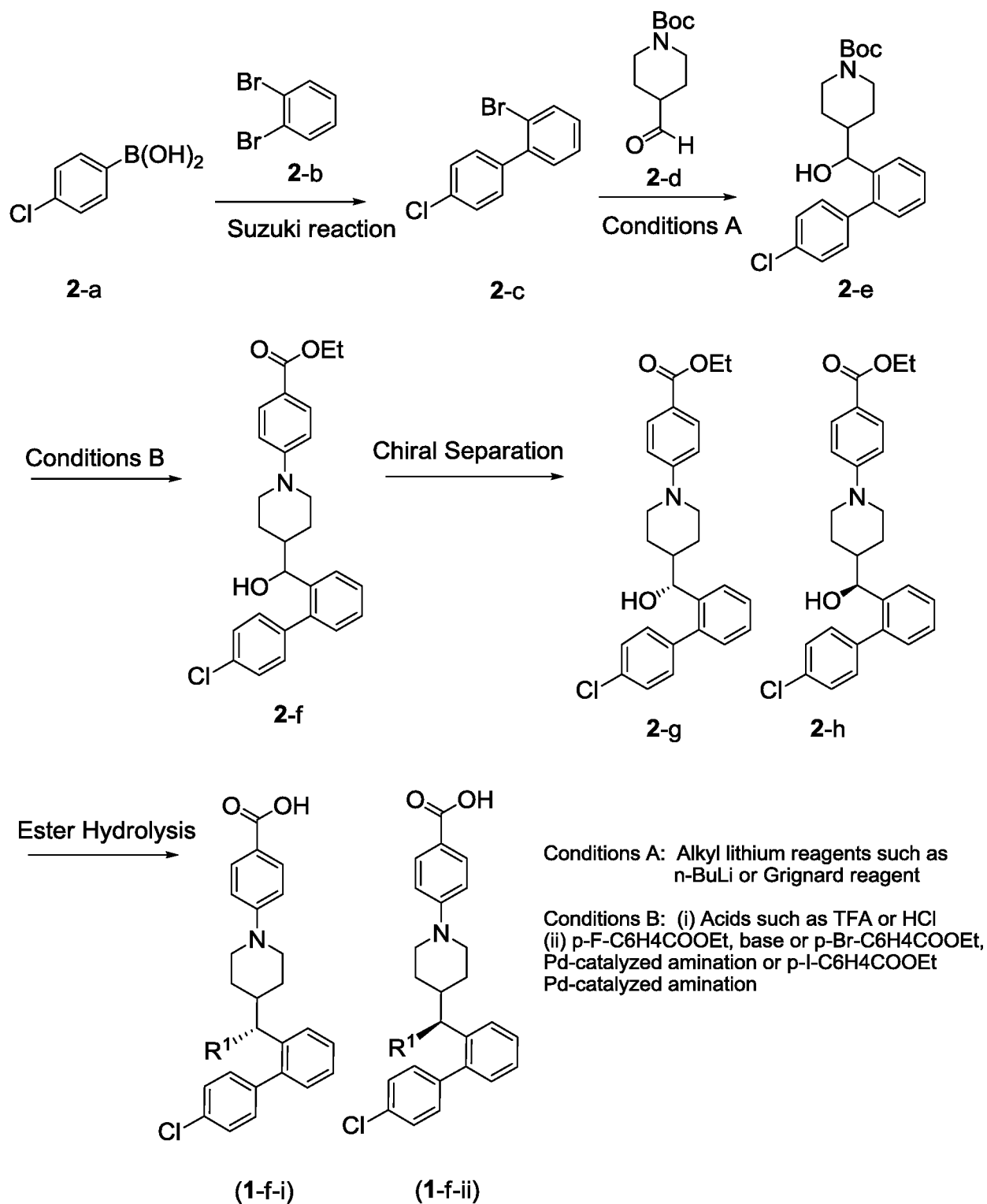
[00040] In SCHEME 1 above, R¹, R², R³, and R⁴ are defined in classes and subclasses as described herein.

[00041] A carboxylic acid compound (1-f) and a sulfonamide compound (1-g) may be reacted together in the presence of a suitable solvent, examples of which include but are not limited to dichloromethane, 1,2-dichloroethane, *N,N*-dimethyl formamide. The reaction is carried out in the presence of a suitable coupling agent such as EDC. The reaction may advantageously occur in the presence of a suitable base, examples of which include DMAP, DIPEA and TEA or combinations thereof. The reaction may be performed either at room

temperature or heating. In some embodiments, the reaction is performed at room temperature. In some embodiments, the reaction is performed at 40 °C.

[00042] A carboxylic acid compound of formula (1-f-i) and formula (1-f-ii) can be prepared according to SCHEME 2, depicted below:

SCHEME 2



[00043] In SCHEME 2 above, R¹ is as defined in classes and subclasses as described herein.

[00044] As depicted in SCHEME 2 above, a boronic acid compound of formula (2-a) is reacted with di-halogenated benzene compound of formula (2-b) under Suzuki reaction conditions known to one skilled in the art to form a biphenyl compound of formula (2-c).

[00045] A biphenyl compound of formula (2-c) is converted to a corresponding aryl lithium compound using a suitable alkyllithium reagent. In some embodiments, the alkyllithium reagent is *n*-BuLi. In some embodiments, the alkyllithium reagent is *t*-BuLi. Alternatively, a biphenyl compound of formula (2-c) may be converted to a corresponding organomagnesium Grignard reagent (see Grignard reagent, *Angew. Chem. Int. Ed.*, **2004**, 43, 3333), using a suitable alkyl magnesium bromide lithium chloride complex. In some embodiments, a suitable alkyl magnesium bromide lithium chloride complex is *i*-Pr-MgBr LiCl complex.

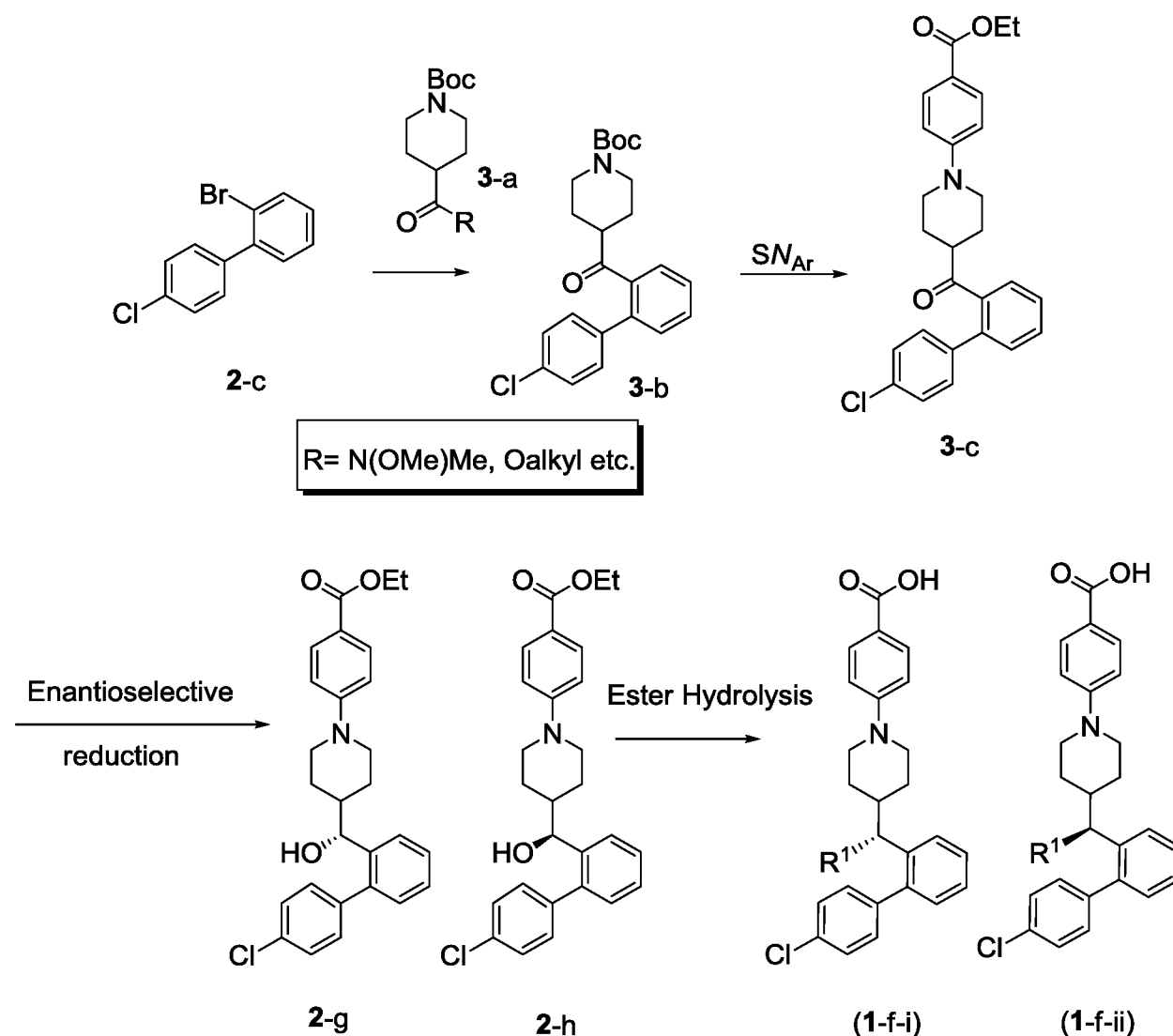
[00046] A compound of formula (2-e) as a mixture of enantiomers is prepared by *in situ* reaction of either an aryl lithium compound or a corresponding organomagnesium Grignard reagent with an N-protected carboxylate compound of formula (2-d). Further deprotection of a compound of formula (2-d) may be performed using a suitable acid. In some embodiments, the acid is TFA. In some embodiments, the acid is HCl.

[00047] A compound of formula (2-f) as a mixture of enantiomers is prepared by performing a substitution reaction using a compound of formula (2-e) and *para* substituted benzoate compound in the presence of a suitable solvent and a suitable base. In some embodiments, a suitable base is triethylamine. In some embodiments, a suitable base is DIPEA. In some embodiments, a suitable base is K₂CO₃. In some embodiments, a suitable base is Cs₂CO₃. In some embodiments, a suitable *para* substituted benzoate compound is a halogenated benzoate compound. In some embodiments, a suitable halogenated benzoate compound is *p*-F-C₆H₄COOEt.

[00048] Alternatively, a compound of formula (2-f) is prepared using Pd-catalyzed amination (see *Chem. Sci.* **2011**, 2, 27 and reference cited therein) using a suitable *para* substituted benzoate and further separating the two enantiomers (antipodes) using similar conditions to those described in the EXAMPLES, *infra*, to form compounds of formulae (2-g) and (2-h).

[00049] A carboxylic acid compound of formula (1-f-i) and/or (1-f-ii) is prepared by performing ester hydrolysis on compounds of formulae (2-g) and/or (2-h) ester using standard conditions known to one of ordinary skill in the art, as a mixture of enantiomers, or as a single enantiomer.

[00050] As an alternate embodiment, a carboxylic acid compound of formula (1-f-i) and/or (1-f-ii) can be prepared according to SCHEME 3, depicted below:



[00051] In SCHEME 3 above, R¹ is as defined in classes and subclasses as described herein.

[00052] Alternatively, the aryl lithium compound or a corresponding organomagnesium Grignard reagent described in SCHEME 2 above may be reacted with an *N*-protected compound of formula (3-a) to provide a compound of formula (3-b). A further substitution reaction using a compound of formula (3-b) and *para* substituted benzoate compound in the presence of a suitable solvent and a suitable base is performed using similar conditions to those described above for the formation of a compound of formula (3-c).

[00053] Performing enantioselective reduction to a compound of formula (3-c): (a) under CBS-conditions (*Angew. Chem. Int. Ed.* **1998**, 37, 1986); or (b) Noyori asymmetric hydrogenation conditions (*Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, **1993**, 56–82.) will provide enantio-enriched mixtures of either a compound of formula (2-g) or a compound of formula (2-h). The enantiopurity may be improved after recrystallization from a/an appropriate solvent(s).

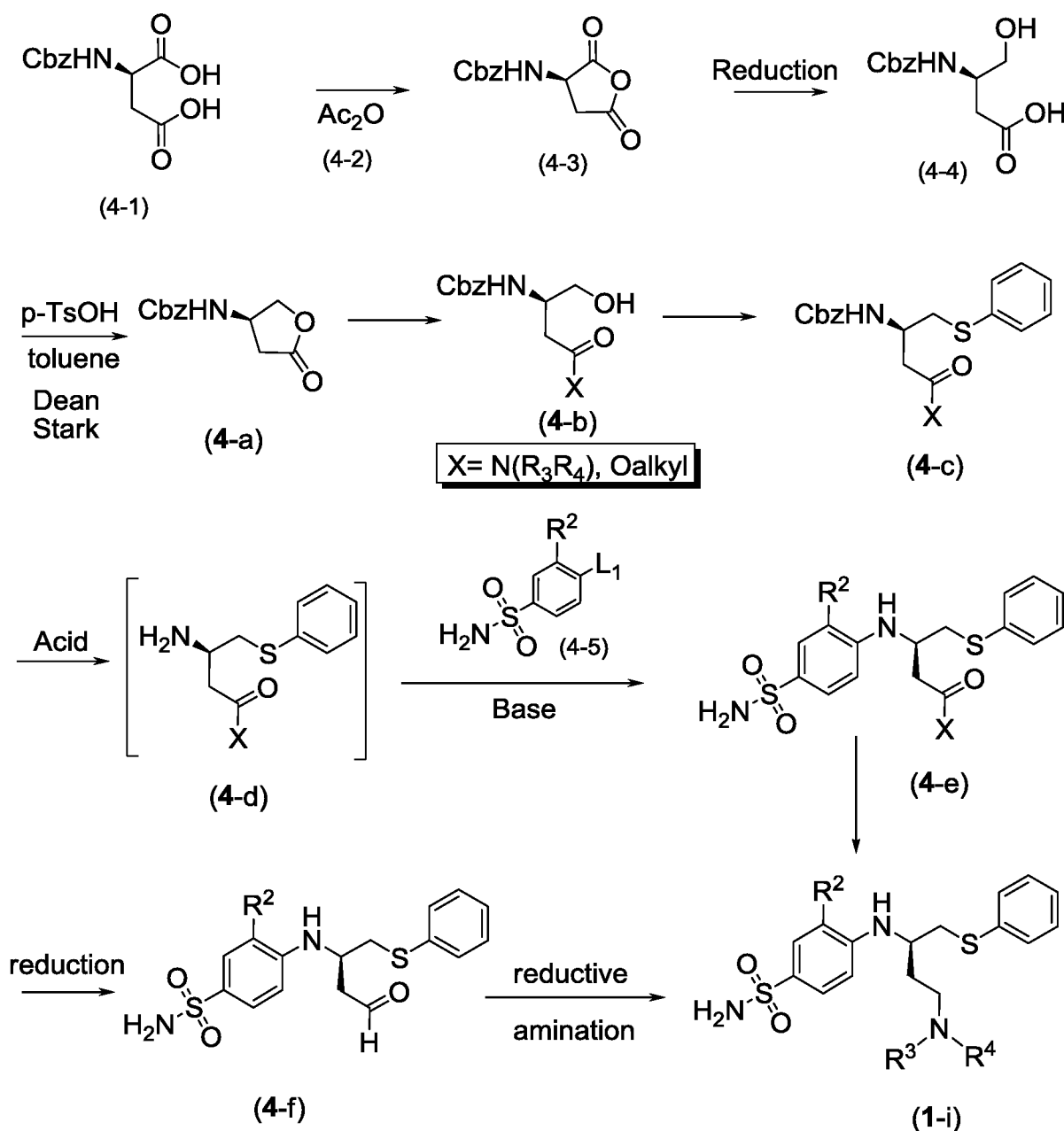
[00054] For enantioselective reduction, conversion from a compound of formula (3-c) to a compound of formula (2-g) or (2-g) may be performed by using a suitable catalyst in the presence of a suitable borane and a suitable solvent at temperatures of from about -30 °C to about 60° C. In some embodiments, a suitable catalyst is (R)-(+)-2-methyl-CBS-oxazaborolidine. In some embodiments, a suitable catalyst is (S)-(-)-2-methyl-CBS-oxazaborolidine. In some embodiments, a suitable borane is borane-tetrahydrofuran complex. In some embodiments, a suitable borane is a borane-dimethyl sulfide complex. In some embodiments, a suitable solvent is THF.

[00055] Alternatively, conversion from a compound of formula (3-c) to a compound of formula (2-g) or (2-g) may be performed using Noyori asymmetric hydrogenation. The asymmetric hydrogenation can be performed using a suitable catalyst and base in the presence of a suitable solvent mixture in a hydrogen atmosphere. In some embodiments, a suitable base is t-BuOK. In some embodiments, a suitable solvent mixture is i-PrOH and DMF.

[00056] In some embodiments, a suitable catalyst is Ru(chiral diphosphine)(chiral amine)Cl₂ wherein the chiral diphosphine portion of the catalyst may be selected from, but is not limited to, S-CIMeOBIPHEP, R-CIMeOBIPHEP, S-Segphos, R-Segphos, R-CTH-Pphos, S-CTH-Pphos, S-BINAP, and R-BINAP; and wherein the chiral amine portion of the catalyst may be selected from, but is not limited to S-Daipen, R-Daipen, S,S-DACH, and R,R-DACH. In some embodiments, the chiral diphosphine portion of the catalyst is S-CIMeOBIPHEP. In some embodiments, the chiral diphosphine portion of the catalyst is R-CIMeOBIPHEP. In some embodiments, the chiral diphosphine portion of the catalyst is S-Segphos. In some embodiments, the chiral diphosphine portion of the catalyst is R-Segphos. In some embodiments, the chiral diphosphine portion of the catalyst is S-CTH-Pphos. In some embodiments, the chiral diphosphine portion of the catalyst is R-CTH-Pphos. In some embodiments, the chiral diphosphine portion of the catalyst is S-BINAP. In some embodiments, the chiral diphosphine portion of the catalyst is R-BINAP. In some embodiments the chiral amine portion of the catalyst is S-Daipen. In some embodiments the chiral amine portion of the catalyst is R-Daipen. In some embodiments the chiral amine portion of the catalyst is S,S-DACH. In some embodiments the chiral amine portion of the catalyst is R,R-DACH.

[00057] A carboxylic acid compound of formula (1-f-i) and/or (1-f-ii) is prepared by performing ester hydrolysis on compounds of formulae (2-g) and/or (2-h) ester using standard conditions known to one of ordinary skill in the art, as a mixture of enantiomers, or as a single enantiomer.

[00058] A sulfonamide compound (1-i) can be prepared by a method disclosed herein, for example, according to SCHEME 4 below.



[00059] As depicted in SCHEME 4 above, X, L_1 , R^2 , R^3 , and R^4 are defined in classes and subclasses as described herein.

[00060] A compound of formula (4-3) may be prepared by cyclizing a commercially available *N*-protected succinic acid, for example a compound of formula (4-1), and a suitable acid anhydride, for example, a compound of formula (4-2), using conditions known to one of ordinary skill in the art. Chemoselective reduction of a compound of formula (4-3) using methods known to one of ordinary skill in the art will provide a corresponding *N*-protected acid compound of formula (4-4). A lactone compound of formula (4-a) is prepared by treating the corresponding *N*-protected acid compound of formula (4-4) with a suitable organic acid in a suitable solvent under appropriate conditions. In some embodiments, the organic acid is *p*-

TsOH. In some embodiments, the organic acid is camphorsulfonic acid. In some embodiments, a suitable solvent is toluene. In some embodiments, a distillation is performed using Dean-Stark conditions.

[00061] Ring-opening is performed by reacting a lactone compound of formula (4-a) in the presence of a suitable alcohol to provide a corresponding ester compound (for example, when X = OMe) using conditions known to one of ordinary skill in the art. In some embodiments, a suitable alcohol is methanol. Alternatively, ring opening can be performed in the presence of a suitable amine compound (for example, $\text{HN}(\text{R}_3\text{R}_4)$) to form a corresponding amide, depicted as a compound formula (4-b) in SCHEME 4.

[00062] A compound of formula (4-c) may be prepared by reacting a compound of formula (4-b) under Mitsunobu reaction conditions in the presence of a thiophenol compound, a suitable phosphine compound, azodicarbonyl reagent, a suitable solvent, at a temperature of about 0 to about 23 °C. In some embodiments, a suitable phosphine compound is a trialkyl phosphine or a triaryl phosphine. Exemplary trialkyl phosphine compounds include, but are not limited to tributyl phosphine. Exemplary triaryl phosphine compounds include, but are not limited to triphenyl phosphine. In some embodiments a suitable azodicarbonyl reagent includes, but is not limited to diisopropylazodicarboxylate. In some embodiments, a suitable solvent is *N,N*-dimethylformamide. In some embodiments, a suitable solvent is dichloromethane.

[00063] A compound of formula (4-c) is deprotected using a suitable acid to form a compound of formula (4-d). In some embodiments, a suitable acid is TFA. In some embodiments, a suitable acid is HBr in acetic acid.

[00064] A compound of formula (4-d) is further coupled with an amine compound of formula (4-5) in the presence of a suitable base and a suitable solvent to form a sulfonamide compound of formula (4-e), for example, wherein X = -OAlk, at a temperature of about 50 °C to about 70 °C. In some embodiments, the reaction is performed at a temperature of about 50 °C. A suitable base includes, but is not limited to DIPEA, triethylamine, *N*-methyl morpholine, or potassium carbonate. In some embodiments, a suitable base is triethylamine. In some embodiments, a suitable base is potassium carbonate. A suitable solvent includes, but is not limited to *N,N*-dimethylformamide.

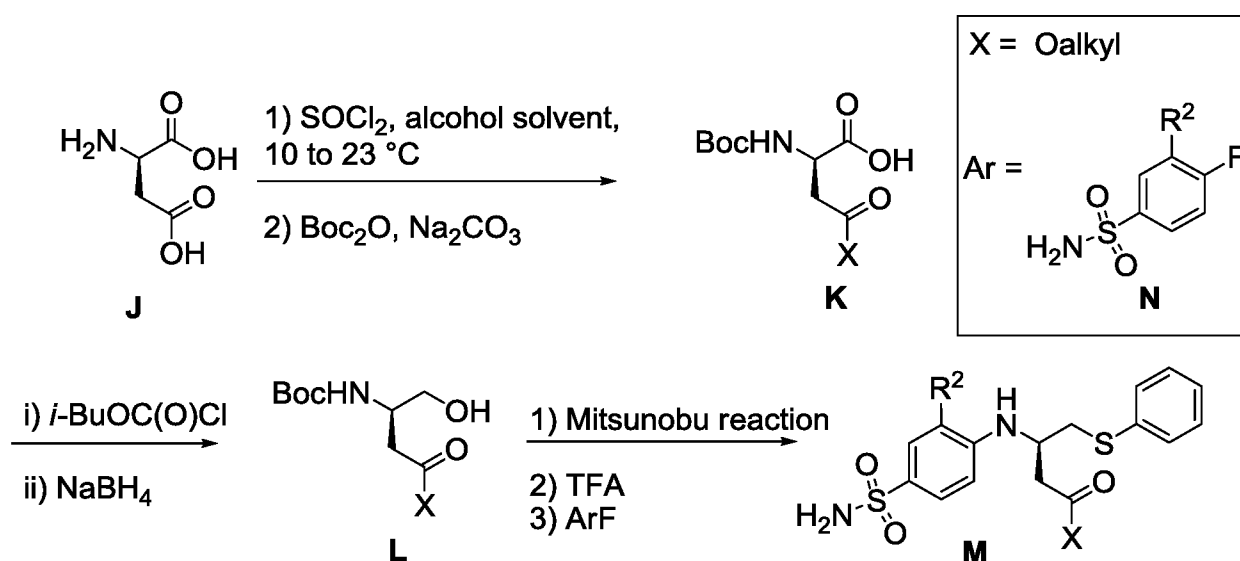
[00065] When X = $\text{N}(\text{R}_3\text{R}_4)$ in a compound of formula (4-e), an amide reduction is performed using a suitable reducing agent under conditions known to one of ordinary skill in the art to form a compound of formula (1-i). In some embodiments, a suitable reducing agent is borane-tetrahydrofuran complex.

[00066] When X = -Oalk in a compound of formula (4-e), a reduction reaction is performed to form a corresponding aldehyde compound of formula (4-f), under conditions known to one of

ordinary skill in the art. Reductive amination of a compound of formula (4-f) in the presence of an amine HNR_3R_4 using a suitable reducing agent, is performed under conditions known to one of ordinary skill in the art to form an amine compound of formula (1-i). Suitable reducing agents include, but are not limited to sodium acetoxyborohydride.

SCHEME 4A

[00067] An alternative method of preparing a compound of formula (4-e) as depicted in SCHEME 4 above, is to prepare a compound of formula M by a method disclosed herein, for example, according to SCHEME 4A below.



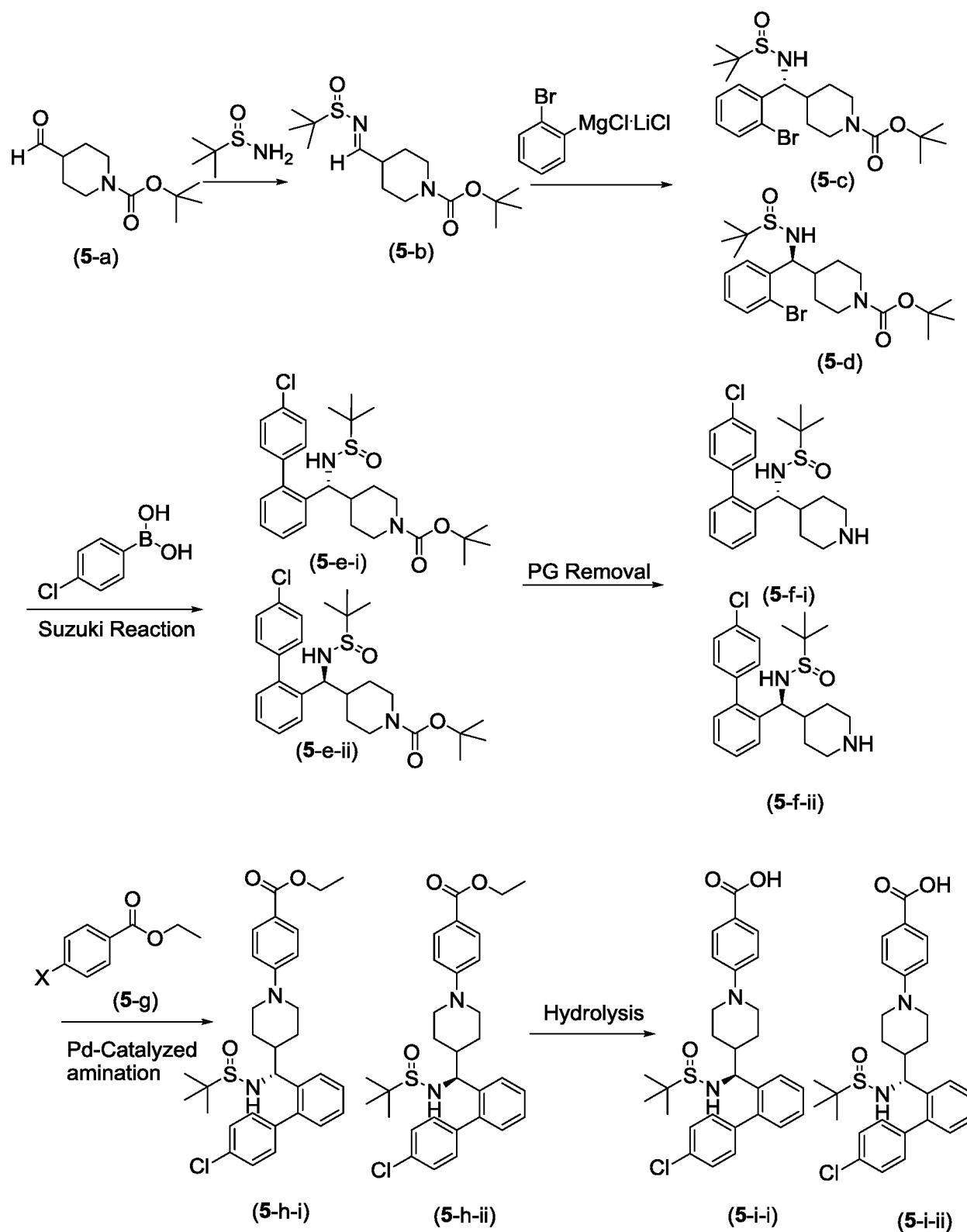
[00068] As depicted in SCHEME 4A, D-aspartic acid (J) is converted into an *N*-Boc protected methyl ester compound of formula (K) via acid catalyzed esterification in the presence of a suitable alcohol solvent followed by *t*-butylcarboxy protection of the free NH_2 . In some embodiments, a suitable alcohol solvent is methanol. Step 1) is carried out in the presence of a suitable acidic reagent at a temperature of about -10 °C to about 23° C. In some embodiments, a suitable acidic reagent is thionyl chloride. In some embodiments, a suitable acid catalyst is anhydrous HCl. In some embodiments, a suitable acid catalyst is anhydrous sulfuric acid. *N*-Boc protection is carried out in the presence of di-*tert*-butyl dicarbonate (Boc_2O) in the presence of a suitable base such potassium carbonate and in the presence of a suitable solvent mixture. Exemplary solvent mixtures include, but are not limited to ethyl acetate/water, dioxane/water, or tetrahydrofuran/water. In some embodiments, the temperature of the *N*-Boc protection reaction is -about 0° C to about 23° C. In some embodiments, a suitable base is sodium bicarbonate. In some embodiments, a suitable base is sodium carbonate.

[00069] *N*-Boc protected alkyl ester (K) is converted to primary alcohol (L) by conversion of the acid moiety of (K) into a mixed anhydride and subsequent reduction to the corresponding

alcohol. Conversion of (K) into a mixed anhydride is carried out in the presence of a suitable base. In some embodiments, a suitable base is *N*-methyl morpholine. In some embodiments, a suitable alkyl chloroformate is isobutyl chloroformate. In some embodiments, a suitable temperature is from about -20 °C to about 0 °C. In some embodiments, a suitable solvent is tetrahydrofuran. In some embodiments, a suitable solvent is 1,2-dimethoxyethane or diethyl ether. In some embodiments, a suitable base such as triethylamine or *N,N*-diisopropylethylamine is used. In some embodiments, a suitable alkyl chloroformate is ethyl chloroformate. In some embodiments, a suitable acyl chloride is pivaloyl chloride. Reduction of the mixed anhydride is carried out by adding a suitable reducing agent such as sodium borohydride using a suitable cosolvent such as methanol from about -10 to about 0 °C. In some embodiments a suitable cosolvent is water. In some embodiments a suitable cosolvent is ethanol. In some embodiments, the acid is converted directly into an alcohol using a suitable reagent such as borane-tetrahydrofuran complex in tetrahydrofuran at a temperature such as 0 to 23 °C.

[00070] Alcohol (L) is converted into sulfonamide (M) using Mitsunobu reaction conditions followed by removal of the Boc protecting group under acidic conditions and subsequent addition to aryl fluoride (N). The Mitsunobu reaction is carried out in the presence of thiophenol, a suitable trialkyl or triaryl phosphine such as tributyl phosphine, and a suitable azodicarbonyl reagent such as azodicarbonyldipiperidine at about 0 to about 23 °C using a suitable solvent such as tetrahydrofuran. In some embodiments, a suitable triarylphosphine is triphenylphosphine. In some embodiments, a suitable azodicarbonyl reagent is diisopropylazodicarboxylate. In some embodiments, a suitable solvent is ether, *N,N*-dimethylformamide, or dichloromethane. Removal of the Boc protecting group is carried out using a suitable acid such as trifluoroacetic acid, sulfuric acid, or hydrochloric acid in a suitable solvent such as dichloromethane, dioxane, or water at 23 °C. In some embodiments, the deprotection reaction is carried out from 0 to 23 °C. The crude deprotected material is then added directly to aryl fluoride (N) in the presence of a suitable base such as *N,N*-diisopropylamine in the presence of a suitable solvent such as *N,N*-dimethylformamide at a temperature such as 50 °C. In some embodiments, a suitable base is triethylamine or potassium carbonate. In some embodiments, a suitable temperature is 50 to 70 °C.

[00071] A carboxylic acid of formulae (5-i-i) and/or (5-i-ii) can be prepared by a method disclosed herein, for example, according to SCHEME 5 below.



[00072] Aldehyde (5-a) is converted to sulfinylimine (5-b) using a racemic 2-methylpropane-2-sulfinamide auxilliary group and suitable acid catalyst in a suitable solvent (*Acc. Chem. Res.* **2002**, 35, 984). In some embodiments, the auxilliary group is (S)-2-methylpropane-2-sulfinamide. In some embodiments, the auxilliary group is (R)-2-methylpropane-2-sulfinamide. In some embodiments a suitable acid catalyst is anhydrous

copper(II)sulphate. In some embodiments, a suitable acid catalyst is titanium(IV)ethoxide. The transformation is performed at about 0 to about 60 °C using a suitable solvent. In some embodiments, the suitable solvent is dichloromethane. In some embodiments, the suitable solvent is tetrahydrofuran.

[00073] Sulfinylimine (5-b) is reacted with a Grignard reagent, generated according to the procedure reported in *Angew. Chem. Int. Ed.*, 2004, 43, 3333, at a temperature of from about -20 °C to about 0 °C, in a suitable solvent (e.g., tetrahydrofuran) to provide a sulfinamide compound of formula (5-c) and/or (5-d).

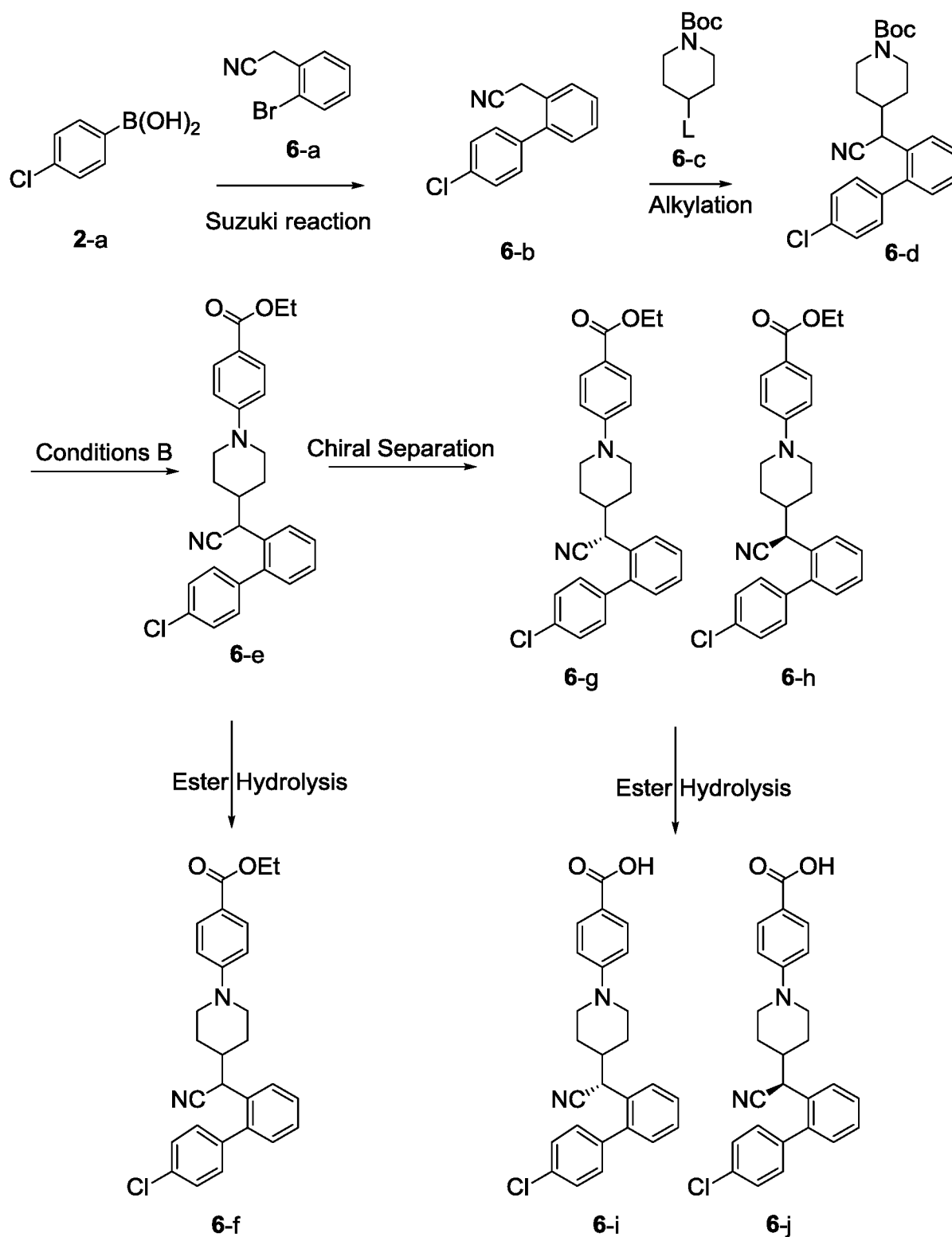
[00074] A compound of formula(e) (5-e-i) and/or (5-e-ii) is prepared by performing a Suzuki reaction on compounds of formula(e) (5-c) and/or (5-d) under conditions known to one of ordinary skill in the art (see *J. Am. Chem. Soc.* 2005, 127, 4685; and *Nature Protocols* 2007, 2, 3115. *Aldrichimica Acta* 2006, 39, 17). In some embodiments, a suitable ligand for the reaction is dicyclohexylphosphino-2',6'-dimethoxybiphenyl. In some embodiments, a suitable palladium source is tris(dibenzylideneacetone)dipalladium(0). In some embodiments a suitable base is tripotassium phosphate.

[00075] A compound of formula(e) (5-f-i) and/or (5-f-ii) is prepared by chemoselective removal of the Boc group of formula(e) (5-e-i) and/or (5-e-ii) in the presence of an acid labile t-Bu sulfinamide group. In some embodiments, the transformation is carried out in the presence of suitable acid such as TFA, in a suitable solvent such as dichloromethane, at a temperature ranging from about 0 to about 23 °C.

[00076] A compound of formula(e) (5-h-i) and/or (5-h-ii) is prepared by performing a Pd-catalyzed amination reaction on a compound of formula(e) (5-f-i) and/or (5-f-ii) in the presence of a compound of formula (5-g) under conditions known to one of ordinary skill in the art (see *Chem. Sci.* 2011, 2, 27, and reference cited therein). In some embodiments, a suitable pre-formed catalyst:ligand adduct is used such as chloro(2-dicyclophosphino-2',6'-di-isopropoxy-1,1'-biphenyl)[2-(2-aminoethylphenyl)]Pd(II) methylbutyl adduct. In some embodiments, additional dicyclohexyl(2'6'-diisopropoxybiphenyl-2-yl)phosphine is added. In some embodiments a suitable base is used, including but not limited to cesium carbonate. The transformation is performed at temperatures ranging of from about 80 to about 120 °C.

[00077] A compound of formula(e) (5-i-i) and/or (5-i-ii) is prepared is prepared by performing ester hydrolysis on a compound of formula(e) (5-h-i) and/or (5-h-ii) using standard conditions known to one of ordinary skill in the art, as a mixture of diastereomers, or as a single diastereomer.

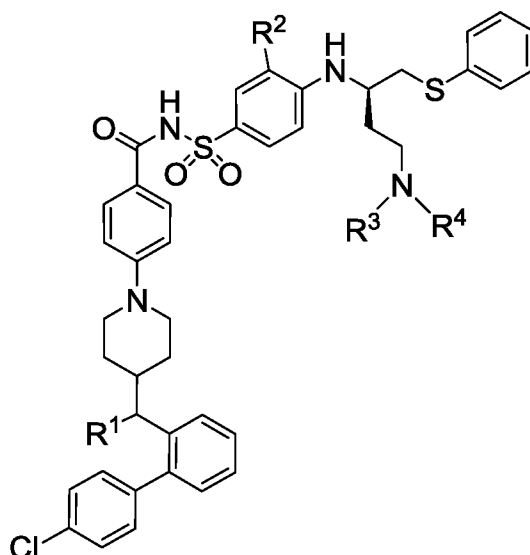
[00078] In certain embodiments, carboxylic acid (6-f), (6-i) and (6-j) are prepared according to SCHEME 6.



III. COMPOUNDS OF THE PRESENT INVENTION

[00079] Compounds provided by the present invention include those described generally above, and are further illustrated by all classes, subclasses and species of each of these compounds disclosed herein.

[00080] The present invention relates to compounds of Formula (I):



Formula (I)

and/or a pharmaceutically acceptable salt thereof, wherein:

R¹ is selected from -CN, -OR^{1a}, and -N(R^{1a})₂;

R^{1a} in each occurrence is independently selected from H, C₁₋₄alkyl, -C(O)CH₂NH₂, -C(O)CH₂NHCH₃, and when **R¹** is -OR^{1a}, then **R^{1a}** is additionally selected from -P(=O)(OH)(OCH₃), -P(=O)(OCH₂CH₃)₂, -CH₂OP(=O)(OH)[OC(CH₃)₃] and -CH₂OP(=O)[OC(CH₃)₃]₂;

R² is selected from -N(O)₂ and -S(O)₂CF₃;

R³ is selected from H and C₁₋₄alkyl, wherein said C₁₋₄alkyl is optionally substituted with one or more R⁴⁰;

R⁴ is selected from H and C₁₋₄alkyl, wherein said C₁₋₄alkyl is optionally substituted with one or more R⁴⁰;

or **R³** and **R⁴** together with the nitrogen to which they are attached form a 5- or 6-membered heterocyclic ring, wherein

- i) said 5- or 6-membered heterocyclic ring is optionally substituted on carbon with one or more R⁴⁰; and
- ii) if said 5- or 6-membered heterocyclic ring contains a nitrogen, that nitrogen is optionally substituted with R^{40*} to form a tertiary amine;

R^{40*} is C₁₋₄alkyl and -(CH₂)₂OP(=O)(OH)₂, wherein said C₁₋₄alkyl is optionally substituted with one or more R^a;

R⁴⁰ in each occurrence is selected from -OR^{40a}, -N(R^{40a})₂, -CH₂OR^{5a}, -CH₂N(R^{5a})₂,

-OP(=O)(OH)₂, and -OP(=O)[OC(CH₃)₃]₂;

R^{5a} in each occurrence is selected from H and C₁₋₃alkyl;

R^{40a} in each occurrence is independently selected from H and C₁₋₄alkyl; and

R^a is selected from halo, -OR^m, and -N(R^m)₂; and

R^m in each occurrence is independently selected from H and C₁₋₄alkyl.

[00081] Additional embodiments of the invention are as follows. These additional embodiments relate to compounds of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e) and pharmaceutically acceptable salts thereof. Such specific substituents may be used, where appropriate, with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

[00082] In some embodiments, the present invention relates to compounds of Formula (I), and/or a pharmaceutically acceptable salt thereof, wherein:

R¹ is selected from -CN, -OR^{1a}, and -N(R^{1a})₂;

R^{1a} in each occurrence is independently selected from H, C₁₋₄alkyl, -C(O)CH₂NH₂, and -C(O)CH₂NHCH₃;

R² is selected from -N(O)₂ and -S(O)₂CF₃;

R³ is selected from H and C₁₋₄alkyl, wherein said C₁₋₄alkyl is optionally substituted with one or more R⁴⁰;

R⁴ is selected from H and C₁₋₄alkyl, wherein said C₁₋₄alkyl is optionally substituted with one or more R⁴⁰;

or **R³** and **R⁴** together with the nitrogen to which they are attached form a 5- or 6-membered heterocyclic ring, wherein

- i) said 5- or 6-membered heterocyclic ring is optionally substituted on carbon with one or more R⁴⁰; and
- ii) if said 5- or 6-membered heterocyclic ring contains a nitrogen, that nitrogen is optionally substituted with R^{40*} to form a tertiary amine;

R^{40*} is C₁₋₄alkyl, wherein said C₁₋₄alkyl is optionally substituted with one or more R^a;

R⁴⁰ in each occurrence is selected from -OR^{40a}, -N(R^{40a})₂, -CH₂OR^{5a}, -CH₂N(R^{5a})₂;

R^{5a} in each occurrence is selected from H and C₁₋₃alkyl;

R^{40a} in each occurrence is independently selected from H and C₁₋₄alkyl; and

R^a is selected from halo, -OR^m, and -N(R^m)₂; and

R^m in each occurrence is independently selected from H and C₁₋₄alkyl.

[00083] In some embodiments, the present invention relates to compounds of Formula (I), and/or a pharmaceutically acceptable salt thereof, wherein:

R¹ is selected from -CN, -OR^{1a}, and -N(R^{1a})₂;

R^{1a} in each occurrence is independently selected from H, C₁₋₄alkyl, -C(O)CH₂NH₂, -C(O)CH₂NHCH₃, and when **R¹** is -OR^{1a}, then **R^{1a}** is additionally selected from -P(=O)(OH)(OCH₃), -P(=O)(OCH₂CH₃)₂, -CH₂OP(=O)(OH)[OC(CH₃)₃] and -CH₂OP(=O)[OC(CH₃)₃]₂;

R² is selected from -N(O)₂ and -S(O)₂CF₃;

R³ is selected from H and C₁₋₄alkyl, wherein said C₁₋₄alkyl is optionally substituted with one or more R⁴⁰;

R⁴ is selected from H and C₁₋₄alkyl, wherein said C₁₋₄alkyl is optionally substituted with one or more R⁴⁰;

or **R³** and **R⁴** together with the nitrogen to which they are attached form a 5- or 6-membered heterocyclic ring, wherein

- i) said 5- or 6-membered heterocyclic ring is optionally substituted on carbon with one or more R⁴⁰; and
- ii) if said 5- or 6-membered heterocyclic ring contains a nitrogen, that nitrogen is optionally substituted with R^{40*} to form a tertiary amine;

R^{40*} is selected from C₁₋₄alkyl and -(CH₂)₂OP(=O)(OH)₂, wherein said C₁₋₄alkyl is optionally substituted with one or more R^a;

R⁴⁰ in each occurrence is selected from -OR^{40a}, -N(R^{40a})₂, -CH₂OR^{5a}, -CH₂N(R^{5a})₂, -OP(=O)(OH)₂, and -OP(=O)[OC(CH₃)₃]₂;

R^{5a} in each occurrence is selected from H and C₁₋₃alkyl;

R^{40a} in each occurrence is independently selected from H and C₁₋₄alkyl; and

R^a is selected from halo, -OR^m, and -N(R^m)₂; and

R^m in each occurrence is independently selected from H and C₁₋₄alkyl;

and wherein at least one of **R¹**, **R³**, or **R⁴**, contains a -P(=O)- group.

[00084] In some embodiments, the present invention relates to compounds of Formula (I), and/or a pharmaceutically acceptable salt thereof, wherein:

R¹ is selected from -CN, -OR^{1a}, and -N(R^{1a})₂;

R^{1a} in each occurrence is independently selected from H, C₁alkyl, -C(O)CH₂NH₂, and -C(O)CH₂NHCH₃;

R² is selected from -N(O)₂ and -S(O)₂CF₃;

R³ is selected from C₁₋₂alkyl, wherein said C₁₋₂alkyl is optionally substituted with one or more R⁴⁰;

R⁴ is selected from C₁₋₂alkyl, wherein said C₁₋₂alkyl is optionally substituted with one or more R⁴⁰;

or **R³** and **R⁴** together with the nitrogen to which they are attached form a 5- or 6-membered heterocyclic ring, wherein

- i) said 5- or 6-membered heterocyclic ring is optionally substituted on carbon with one or more R⁴⁰; and
- ii) if said 5- or 6-membered heterocyclic ring contains a nitrogen, that nitrogen is optionally substituted with R^{40*} to form a tertiary amine;

R^{40*} is selected from C₂₋₃alkyl wherein said C₂₋₃alkyl is optionally substituted with one or more R^a;

R⁴⁰ in each occurrence is selected from -OR^{40a}, -CH₂OR^{5a}, and -CH₂N(R^{5a})₂;

R^{5a} in each occurrence is selected from H and C₂alkyl;

R^{40a} in each occurrence is independently H; and

R^a is selected from halo and -OR^m; and

R^m in each occurrence is independently H.

[00085] In some embodiments, the present invention relates to compounds of Formula (I), and/or a pharmaceutically acceptable salt thereof, wherein:

R¹ is -OR^{1a};

R^{1a} in each occurrence is independently selected from H, and -P(=O)(OH)(OCH₃), -P(=O)(OCH₂CH₃)₂, -CH₂OP(=O)(OH)[OC(CH₃)₃] and -CH₂OP(=O)[OC(CH₃)₃]₂;

R² is -S(O)₂CF₃;

R³ is C₁₋₂alkyl, wherein said C₁₋₂alkyl is optionally substituted with one or more R⁴⁰;

R⁴ is C₁₋₂alkyl, wherein said C₁₋₂alkyl is optionally substituted with one or more R⁴⁰;

or **R³** and **R⁴** together with the nitrogen to which they are attached form a 5- or 6-membered heterocyclic ring, wherein

- i) said 5- or 6-membered heterocyclic ring is optionally substituted on carbon with one or more R⁴⁰; and
- ii) if said 5- or 6-membered heterocyclic ring contains a nitrogen, that nitrogen is optionally substituted with R^{40*} to form a tertiary amine;

R^{40*} is $-(CH_2)_2OP(=O)(OH)_2$;

R⁴⁰ in each occurrence is selected from $-OP(=O)(OH)_2$ and $-CH_2N(R^{5a})_2$;

R^{5a} in each occurrence is selected from H and C₂alkyl;

R^a is selected from halo, $-OR^m$, and $-N(R^m)_2$; and

R^m in each occurrence is independently selected from H and C₁₋₄alkyl.

[00086] In some embodiments, the present invention relates to compounds of Formula (I), and/or a pharmaceutically acceptable salt thereof, wherein:

R¹ is $-OH$;

R² is $-S(O)_2CF_3$;

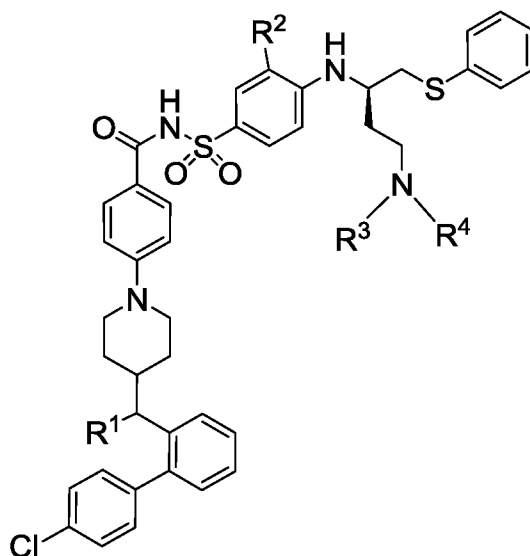
R³ is C₁₋₂alkyl, wherein said C₁₋₂alkyl is optionally substituted with one or more R⁴⁰;

R⁴ is C₁₋₂alkyl, wherein said C₁₋₂alkyl is optionally substituted with one or more R⁴⁰;

R⁴⁰ in each occurrence is selected from $-OR^{40a}$ and $-OP(=O)(OH)_2$; and

R^{40a} is H.

[00087] In certain embodiments, the present invention provides compound of Formula (I):



Formula (I)

and/or to pharmaceutically acceptable salts thereof, wherein:

R¹ is selected from -CN, -OR^{1a}, and -N(R^{1a})₂;

R^{1a} in each occurrence is independently selected from H and C₁₋₄alkyl;

R² is selected from -N(O)₂ and -S(O)₂CF₃;

R³ is selected from H and C₁₋₄alkyl, wherein said C₁₋₄alkyl is optionally substituted with one or more R⁴⁰;

R⁴ is selected from H and C₁₋₄alkyl, wherein said C₁₋₄alkyl is optionally substituted with one or more R⁴⁰;

or **R³** and **R⁴** together with the nitrogen to which they are attached form a 5- or 6-membered heterocyclic ring, wherein:

- i) said 5- or 6-membered ring is not morpholino;
- ii) said 5- or 6-membered heterocyclic ring is optionally substituted on carbon with one or more R⁴⁰; and
- iii) if said 5- or 6-membered heterocyclic ring contains an -NH- moiety, that nitrogen is optionally substituted with R^{40*};

R^{40*} is C₁₋₄alkyl, wherein said C₁₋₄alkyl is optionally substituted with one or more R^a;

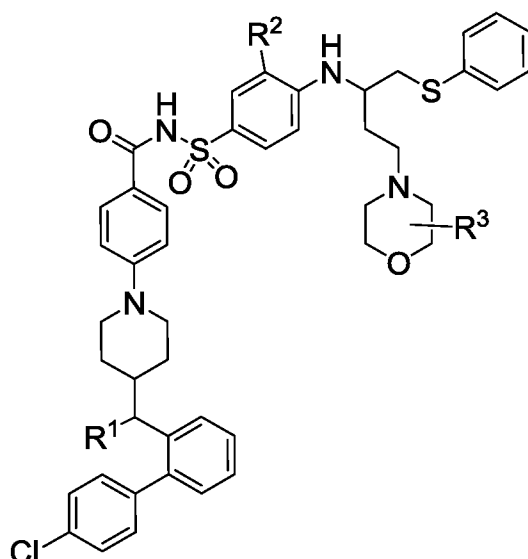
R⁴⁰ is selected from -OR^{40a} and -N(R^{40a})₂;

R^{40a} in each occurrence is independently selected from H and C₁₋₄alkyl; and

R^a is selected from halo, -OR^m, and -N(R^m)₂; and

R^m in each occurrence is independently selected from H and C₁₋₄alkyl.

[00088] In certain embodiments, the present invention provides compound of Formula (I-c):



Formula (I-c)

and/or to pharmaceutically acceptable salts thereof, wherein:

R¹ is selected from -CN, -OR^{1a}, and -N(R^{1a})₂;

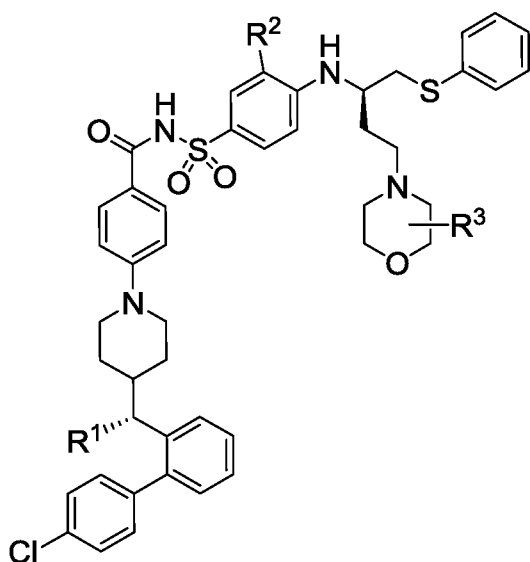
R^{1a} in each occurrence is independently selected from H and C₁₋₃alkyl;

R² is selected from -N(O)₂ and -S(O)₂CF₃;

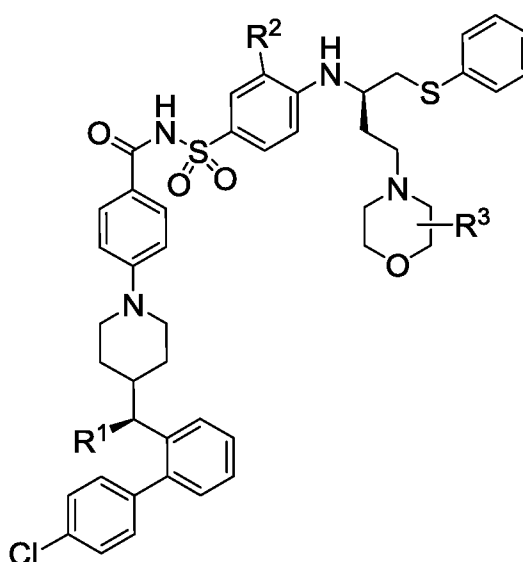
R³ is selected from -CH₂OR^{3a} and -CH₂N(R^{3a})₂; and

R^{3a} is selected from H and C₁₋₃alkyl.

[00089] In certain embodiments, compounds provided by the present invention have the structure set forth in Formulae (I-d) and/or (I-e):



Formula (I-d)



Formula (I-e)

and/or a pharmaceutically acceptable salt thereof, wherein each of R¹, R², and R³ are as defined and described in classes and subclasses herein.

[00090] R¹ EMBODIMENTS

[00091] As generally defined herein, **R¹** is selected from -CN, -OR^{1a}, and -N(R^{1a})₂.

[00092] In one aspect, **R¹** is selected from -OH and -CN.

[00093] In some embodiments, **R¹** is -OH. In some embodiments, **R¹** is -CN. In some embodiments **R¹** is -NH₂. In some embodiments **R¹** is -CH₂OP(=O)[OC(CH₃)₃]₂. In some embodiments **R¹** is -CH₂OP(=O)(OH)[OC(CH₃)₃]. In some embodiments **R¹** is -P(=O)(OCH₂CH₃)₂. In some embodiments **R¹** is -P(=O)(OH)(OCH₃). In some embodiments **R¹** is -NHC(O)CH₂NHCH₃. In some embodiments **R¹** is -NHC(O)CH₂NH₂. In some embodiments **R¹** is -N(CH₃)₂.

[00094] R² EMBODIMENTS

[00095] As generally defined above, **R²** is selected from -NO₂ and -SO₂CF₃.

[00096] In some embodiments, **R²** is -N(O)₂. In some embodiments, **R²** is -S(O)₂CF₃.

[00097] R³ EMBODIMENTS

[00098] As generally defined above, **R³** is selected from H and C₁₋₄alkyl, wherein said C₁₋₄alkyl is optionally substituted with one or more R⁴⁰.

[00099] In one aspect, **R³** is selected from -CH₂OR^{3a} and -CH₂N(R^{3a})₂.

[000100] In some embodiments, **R³** is selected from -CH₂OH and -CH₂N(R^{3a})₂. In some embodiments **R³** is methyl. In some embodiments **R³** is methyl optionally substituted with one or more R⁴⁰. In some embodiments **R³** is ethyl optionally substituted with one or more R⁴⁰. In some embodiments **R³** is ethyl. In some embodiments **R³** is -CH₂CH₂OH. In some embodiments **R³** is -CH₂CH₂OP(=O)(OH)₂.

[000101] R^{3a} EMBODIMENTS

In one aspect, **R^{3a}** in each occurrence is independently selected from H and C₁₋₃alkyl. In some embodiments, **R^{3a}** is ethyl.

[000102] R⁴ EMBODIMENTS

[000103] As generally defined above, **R⁴** is selected from H and C₁₋₄alkyl, wherein said C₁₋₄alkyl is optionally substituted with one or more R⁴⁰.

[000104] In some embodiments, **R⁴** is H. In some embodiments **R⁴** is methyl. In some

embodiments **R⁴** is methyl optionally substituted with one or more **R⁴⁰**. In some embodiments **R⁴** is ethyl optionally substituted with one or more **R⁴⁰**. In some embodiments **R⁴** is ethyl. In some embodiments **R⁴** is -CH₂CH₂OH. In some embodiments **R⁴** is -CH₂CH₂OP(=O)(OH)₂.

[000105] **R³** and **R⁴** EMBODIMENTS

[000106] In one aspect, **R³** is C₁₋₄alkyl, wherein said C₁₋₄alkyl is optionally substituted with one or more **R⁴⁰**; **R⁴** is C₁₋₄alkyl, wherein said C₁₋₄alkyl is optionally substituted with one or more **R⁴⁰**; and **R⁴⁰** is -OH.

[000107] In another aspect, **R³** is selected from methyl and ethyl, wherein said methyl and ethyl are optionally substituted with one or more **R⁴⁰**; **R⁴** is ethyl, wherein said ethyl is optionally substituted with one or more **R⁴⁰**; and **R⁴⁰** is -OH.

[000108] In another aspect, **R³** is selected from methyl, ethyl, and 2-hydroxyethyl; and **R⁴** is selected from methyl and 2-hydroxyethyl.

[000109] In another aspect, **R³** and **R⁴** together with the nitrogen to which they are attached form a 5- or 6-membered heterocyclic ring, wherein:

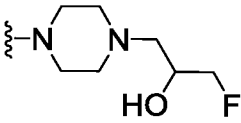
- i) said 5- or 6-membered ring is not morpholino;
- ii) if said 5- or 6-membered heterocyclic ring contains an -NH- moiety, that nitrogen is optionally substituted with **R^{40*}**; **R^{40*}** is C₁₋₄alkyl, wherein said C₁₋₄alkyl is optionally substituted with one or more **R^a**; and **R^a** in each occurrence is independently selected from halo and -OH.

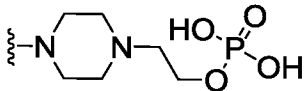
[000110] In another aspect, **R³** and **R⁴** together with the nitrogen to which they are attached form a piperazin-1-yl ring, wherein said piperazin-1-yl ring is optionally substituted on nitrogen with **R^{40*}**; **R^{40*}** is C₁₋₄alkyl, wherein said C₁₋₄alkyl is optionally substituted with one or more **R^a**; and **R^a** in each occurrence is independently selected from halo and -OH.

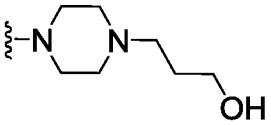
[000111] In another aspect, **R³** and **R⁴** together with the nitrogen to which they are attached form a piperazin-1-yl ring, wherein said piperazin-1-yl ring is optionally substituted on nitrogen with **R^{40*}**; **R^{40*}** is selected from ethyl and propyl, wherein said ethyl and propyl are optionally substituted with one or more **R^a**; and **R^a** in each occurrence is independently selected from fluoro and -OH.

[000112] In another aspect, **R³** and **R⁴** together with the nitrogen to which they are attached form a member selected from 4-(3-fluoro-2-hydroxypropyl)piperazin-1-yl and 4-(2-hydroxyethyl)piperazin-1-yl.

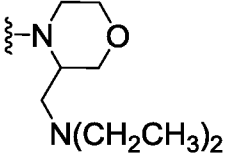
[000113] In some embodiments **R³** and **R⁴** together with the nitrogen to which they are attached form 4-(3-fluoro-2-hydroxypropyl)piperazin-1-yl. In some embodiments **R³** and **R⁴**

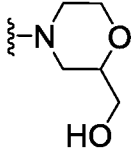
together with the nitrogen to which they are attached form  In some embodiments **R³** and **R⁴** together with the nitrogen to which they are attached form

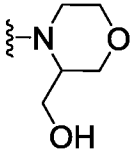
 In some embodiments **R³** and **R⁴** together with the nitrogen to which

they are attached form . In some embodiments **R³** and **R⁴** together with the

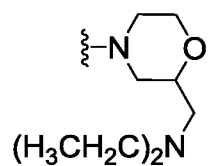
nitrogen to which they are attached form . In some embodiments **R³** and **R⁴** together

with the nitrogen to which they are attached form . In some embodiments **R³**

and **R⁴** together with the nitrogen to which they are attached form . In some

embodiments **R³** and **R⁴** together with the nitrogen to which they are attached form .

In some embodiments **R³** and **R⁴** together with the nitrogen to which they are attached form



[000114] **R¹**, **R²**, and **R³** EMBODIMENTS

[000115] In one aspect, **R¹** is selected from -OH and -CN; **R²** is selected from -NO₂ and -SO₂CF₃; **R³** is selected from -CH₂OR^{3a} and -CH₂N(R^{3a})₂; and **R^{3a}** in each occurrence is independently selected from H and C₁₋₃alkyl.

[000116] In another aspect, **R¹** is selected from -OH and -CN; **R²** is selected from -NO₂ and -SO₂CF₃; **R³** is selected from -CH₂OH and -CH₂N(R^{3a})₂; and **R^{3a}** is ethyl.

[000117] R^1 , R^2 , R^3 , and R^4 EMBODIMENTS

[000118] In one aspect, R^1 is -OH; R^2 is selected from -N(O)₂ and -S(O)₂CF₃; R^3 is C₁₋₄alkyl, wherein said C₁₋₄alkyl is optionally substituted with one or more R⁴⁰; R^4 is C₁₋₄alkyl, wherein said C₁₋₄alkyl is optionally substituted with one or more R⁴⁰; or R^3 and R^4 together with the nitrogen to which they are attached form a 5- or 6-membered heterocyclic ring, wherein:

- i) said 5- or 6-membered ring is not morpholino;
- ii) if said 5- or 6-membered heterocyclic ring contains an -NH- moiety, that nitrogen is optionally substituted with R^{40*};

R^{40*} is C₁₋₄alkyl, wherein said C₁₋₄alkyl is optionally substituted with one or more R^a; R^{40} is -OH; and R^a in each occurrence is independently selected from halo and -OH.

[000119] In another aspect, R^1 is -OH; R^2 is selected from -N(O)₂ and -S(O)₂CF₃; R^3 is selected from methyl, ethyl, and 2-hydroxyethyl; R^4 is selected from methyl and 2-hydroxyethyl; or R^3 and R^4 together with the nitrogen to which they are attached form a piperazin-1-yl ring, wherein said piperazin-1-yl ring is optionally substituted on nitrogen with R^{40*}; R^{40*} is selected from ethyl and propyl, wherein said ethyl and propyl are optionally substituted with one or more R^a; and R^a in each occurrence is independently selected from fluoro and -OH.

[000120] In some embodiments, R^1 is -OH; R^2 is -S(O)₂CF₃; R^3 is methyl; and R^4 is -CH₂CH₂OH.

[000121] In some embodiments, R^1 is -OH; R^2 is -S(O)₂CF₃; R^3 is ethyl; and R^4 is -CH₂CH₂OH.

[000122] In some embodiments, R^1 is -OH; R^2 is -S(O)₂CF₃; R^3 is -CH₂CH₂OP(=O)(OH)₂; and R^4 is ethyl.

[000123] In some embodiments, R^1 is -OH; R^2 is -S(O)₂CF₃; R^3 is -CH₂CH₂OP(=O)(OH)₂; and R^4 is methyl.

[000124] In one aspect there is provided a compound selected from:

[000125] 4-(4-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-N-(4-((R)-4-(4-(2-hydroxyethyl)piperazin-1-yl)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide;

[000126] 4-(4-((4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-N-(4-((R)-4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfonyl)benzamide;

[000127] 4-(4-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-N-(4-((R)-4-((2-hydroxyethyl)(methyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide;

[000128] 4-(4-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-N-(4-((R)-4-(ethyl(2-hydroxyethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide;

[000129] N-(4-4-(bis(2-hydroxyethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)-4-(4-((R)-4-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzamide; and

[000130] 4-(4-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-N-(4-((2R)-4-(4-(3-fluoro-2-hydroxypropyl)piperazin-1-yl)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide;
and/or a pharmaceutically acceptable salt thereof.

[000131] In another aspect, there is provided a compound selected from:

[000132] 4-{4-[(S)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl]piperidin-1-yl}-N-[(4-{[(2R)-4-(morpholin-4-yl)-1-(phenylsulfanyl)butan-2-yl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]benzamide;

[000133] 4-{4-[(R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl]piperidin-1-yl}-N-[(4-{[(2R)-4-(morpholin-4-yl)-1-(phenylsulfanyl)butan-2-yl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]benzamide;

[000134] 4-{4-[(S)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl]piperidin-1-yl}-N-[(4-{[(2R)-4-(morpholin-4-yl)-1-(phenylsulfanyl)butan-2-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

[000135] 4-{4-[(R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl]piperidin-1-yl}-N-[(4-{[(2R)-4-(morpholin-4-yl)-1-(phenylsulfanyl)butan-2-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

[000136] 4-{4-[(4'-chlorobiphenyl-2-yl)(cyano)methyl]piperidin-1-yl}-N-[(4-{[(2R)-4-(morpholin-4-yl)-1-(phenylsulfanyl)butan-2-yl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]benzamide;

[000137] 4-{4-[(S)-(4'-chlorobiphenyl-2-yl)(cyano)methyl]piperidin-1-yl}-N-[(4-{[(2R)-4-(morpholin-4-yl)-1-(phenylsulfanyl)butan-2-yl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]benzamide;

[000138] 4-{4-[(R)-(4'-chlorobiphenyl-2-yl)(cyano)methyl]piperidin-1-yl}-N-[(4-{[(2R)-4-(morpholin-4-yl)-1-(phenylsulfanyl)butan-2-yl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]benzamide;

[000139] 4-{4-[(S)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl]piperidin-1-yl}-N-[(4-{[(2R)-4-[(3S)-3-{[diethylamino]methyl}morpholin-4-yl]-1-(phenylsulfanyl)butan-2-yl]amino}-3-

[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]benzamide;

[000140] 4-{4-[(R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl]piperidin-1-yl}-N-[(4-{[(2R)-4-[(3S)-3-{[diethylamino]methyl}morpholin-4-yl]-1-(phenylsulfanyl)butan-2-yl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]benzamide;

[000141] 4-{4-[(S)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl]piperidin-1-yl}-N-[(4-{[(2R)-4-[(3R)-3-{[diethylamino]methyl}morpholin-4-yl]-1-(phenylsulfanyl)butan-2-yl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]benzamide;

[000142] 4-{4-[(R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl]piperidin-1-yl}-N-[(4-{[(2R)-4-[(3R)-3-{[diethylamino]methyl}morpholin-4-yl]-1-(phenylsulfanyl)butan-2-yl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]benzamide;

[000143] 4-{4-[(S)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl]piperidin-1-yl}-N-[(4-{[(2R)-4-[(2R)-2-(hydroxymethyl)morpholin-4-yl]-1-(phenylsulfanyl)butan-2-yl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]benzamide;

[000144] 4-{4-[(R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl]piperidin-1-yl}-N-[(4-{[(2R)-4-[(2R)-2-(hydroxymethyl)morpholin-4-yl]-1-(phenylsulfanyl)butan-2-yl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]benzamide;

[000145] 4-{4-[(S)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl]piperidin-1-yl}-N-[(4-{[(2R)-4-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-1-(phenylsulfanyl)butan-2-yl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]benzamide;

[000146] 4-{4-[(R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl]piperidin-1-yl}-N-[(4-{[(2R)-4-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-1-(phenylsulfanyl)butan-2-yl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]benzamide;

[000147] 4-{4-[(S)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl]piperidin-1-yl}-N-[(4-{[(2R)-4-[(3R)-3-(hydroxymethyl)morpholin-4-yl]-1-(phenylsulfanyl)butan-2-yl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]benzamide;

[000148] 4-{4-[(R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl]piperidin-1-yl}-N-[(4-{[(2R)-4-[(3R)-3-(hydroxymethyl)morpholin-4-yl]-1-(phenylsulfanyl)butan-2-yl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]benzamide;

[000149] 4-{4-[(S)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl]piperidin-1-yl}-N-[(4-{[(2R)-4-[(3S)-3-(hydroxymethyl)morpholin-4-yl]-1-(phenylsulfanyl)butan-2-yl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]benzamide;

[000150] 4-{4-[(R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl]piperidin-1-yl}-N-[(4-{[(2R)-4-[(3S)-3-(hydroxymethyl)morpholin-4-yl]-1-(phenylsulfanyl)butan-2-yl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]benzamide;

[000151] 4-{4-[(S)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl]piperidin-1-yl}-N-[(4-{[(2R)-4-

{(2*S*)-2-[(diethylamino)methyl]morpholin-4-yl}-1-(phenylsulfonyl)butan-2-yl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]benzamide;

[000152] 4-{4-[(*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl]piperidin-1-yl}-*N*-[(4-{[(2*R*)-4-{(2*S*)-2-[(diethylamino)methyl]morpholin-4-yl}-1-(phenylsulfonyl)butan-2-yl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]benzamide;

[000153] 4-{4-[(*S*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl]piperidin-1-yl}-*N*-[(4-{[(2*R*)-4-{(2*R*)-2-[(diethylamino)methyl]morpholin-4-yl}-1-(phenylsulfonyl)butan-2-yl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]benzamide; and

[000154] 4-{4-[(*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl]piperidin-1-yl}-*N*-[(4-{[(2*R*)-4-{(2*R*)-2-[(diethylamino)methyl]morpholin-4-yl}-1-(phenylsulfonyl)butan-2-yl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]benzamide, and/or a pharmaceutically acceptable salt thereof.

[000155] In another aspect, there is provided a compound selected from:

[000156] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-(2-hydroxyethyl)piperazin-1-yl)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl]benzamide;

[000157] 4-(4-((*S*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((*S*)-4-(2-hydroxyethyl)(methyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl]benzamide;

[000158] 4-(4-((*S*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-(2-hydroxyethyl)(methyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl]benzamide;

[000159] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((*S*)-4-(2-hydroxyethyl)(methyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl]benzamide;

[000160] 4-(4-((*S*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((*S*)-4-(ethyl(2-hydroxyethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl]benzamide;

[000161] 4-(4-((*S*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-(ethyl(2-hydroxyethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl]benzamide;

[000162] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((*S*)-4-(ethyl(2-hydroxyethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl]benzamide;

[000163] *N*-(4-((*R*)-4-(bis(2-hydroxyethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-

(trifluoromethylsulfonyl)phenylsulfonyl)-4-(4-((R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzamide;

[000164] 4-(4-((R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-N-(4-((R)-4-(4-((R)-3-fluoro-2-hydroxypropyl)piperazin-1-yl)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide;

[000165] 4-(4-((R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-N-(4-((R)-4-(4-((S)-3-fluoro-2-hydroxypropyl)piperazin-1-yl)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide;

[000166] 2,2'-((R)-3-(4-(N-(4-(4-((R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-(phenylthio)butylazanediyl)bis(ethane-2,1-diyl) bis(dihydrogen phosphate);

[000167] 2-(((R)-3-(4-(N-(4-(4-((R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-(phenylthio)butyl)(ethyl)amino)ethyl dihydrogen phosphate;

[000168] 2-(((S)-3-(4-(N-(4-(4-((S)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-(phenylthio)butyl)(ethyl)amino)ethyl dihydrogen phosphate;

[000169] 2-(((R)-3-(4-(N-(4-(4-((S)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-(phenylthio)butyl)(ethyl)amino)ethyl dihydrogen phosphate;

[000170] 2-(((S)-3-(4-(N-(4-(4-((R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-(phenylthio)butyl)(ethyl)amino)ethyl dihydrogen phosphate;

[000171] 2-(((R)-3-(4-(N-(4-(4-((R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-(phenylthio)butyl)(methyl)amino)ethyl dihydrogen phosphate;

[000172] 2-(((S)-3-(4-(N-(4-(4-((S)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-(phenylthio)butyl)(methyl)amino)ethyl dihydrogen phosphate;

[000173] 2-(((R)-3-(4-(N-(4-(4-((S)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-(phenylthio)butyl)(methyl)amino)ethyl dihydrogen phosphate;

[000174] 2-(((S)-3-(4-(N-(4-(4-((R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-(phenylthio)butyl)(methyl)amino)ethyl dihydrogen phosphate;

- [000175]** 4-(4-((*R*)-amino(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-(2-hydroxyethyl)(methyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide;
- [000176]** 4-(4-((*R*)-amino(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-(ethyl(2-hydroxyethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide;
- [000177]** 4-(4-((*R*)-amino(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-(4-(2-hydroxyethyl)piperazin-1-yl)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide;
- [000178]** 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(cyano)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide;
- [000179]** 4-(4-((*S*)-(4'-chlorobiphenyl-2-yl)(cyano)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide;
- [000180]** 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-((*R*)-2-(hydroxymethyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide;
- [000181]** 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-((*S*)-2-(hydroxymethyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide;
- [000182]** 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-((*R*)-3-(hydroxymethyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide;
- [000183]** 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-((*S*)-3-(hydroxymethyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide;
- [000184]** (*R*)-(4'-chlorobiphenyl-2-yl)(1-(4-(4-((*R*)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonylcarbamoyl)phenyl)piperidin-4-yl)methyl diethyl phosphate;
- [000185]** (*R*)-(4'-chlorobiphenyl-2-yl)(1-(4-(4-((*R*)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonylcarbamoyl)phenyl)piperidin-4-yl)methyl methyl hydrogen phosphate;
- [000186]** 4-(4-((*R*)-amino(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-

(trifluoromethylsulfonyl)phenylsulfonyl)benzamide;

[000187] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(2-(methylamino)acetamido)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-

(trifluoromethylsulfonyl)phenylsulfonyl)benzamide;

[000188] 4-(4-((*R*)-(2-aminoacetamido)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-

(trifluoromethylsulfonyl)phenylsulfonyl)benzamide;

[000189] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(dimethylamino)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-

(trifluoromethylsulfonyl)phenylsulfonyl)benzamide;

and/or a pharmaceutically acceptable salt thereof.

[000190] Exemplary compounds of the present invention include:

[000191] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-(2-hydroxyethyl)piperazin-1-yl)-1-(phenylthio)butan-2-ylamino)-3-

(trifluoromethylsulfonyl)phenylsulfonyl)benzamide, formic acid salt;

[000192] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfonyl)benzamide;

[000193] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-(2-hydroxyethyl)(methyl)amino)-1-(phenylthio)butan-2-ylamino)-3-

(trifluoromethylsulfonyl)phenylsulfonyl)benzamide;

[000194] 4-(4-((*S*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((*S*)-4-(2-hydroxyethyl)(methyl)amino)-1-(phenylthio)butan-2-ylamino)-3-

(trifluoromethylsulfonyl)phenylsulfonyl)benzamide;

[000195] 4-(4-((*S*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-(2-hydroxyethyl)(methyl)amino)-1-(phenylthio)butan-2-ylamino)-3-

(trifluoromethylsulfonyl)phenylsulfonyl)benzamide;

[000196] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((*S*)-4-(2-hydroxyethyl)(methyl)amino)-1-(phenylthio)butan-2-ylamino)-3-

(trifluoromethylsulfonyl)phenylsulfonyl)benzamide;

[000197] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-(2-hydroxyethyl)(methyl)amino)-1-(phenylthio)butan-2-ylamino)-3-

(trifluoromethylsulfonyl)phenylsulfonyl)benzamide, formic acid salt;

[000198] 4-(4-((*S*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((*S*)-4-(2-hydroxyethyl)(methyl)amino)-1-(phenylthio)butan-2-ylamino)-3-

(trifluoromethylsulfonyl)phenylsulfonyl)benzamide, formic acid salt;

- [000199]** 4-(4-((S)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-N-(4-((R)-4-((2-hydroxyethyl)(methyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide, formic acid salt;
- [000200]** 4-(4-((R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-N-(4-((S)-4-((2-hydroxyethyl)(methyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide, formic acid salt;
- [000201]** 4-(4-((R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-N-(4-((R)-4-(ethyl(2-hydroxyethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide;
- [000202]** 4-(4-((S)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-N-(4-((S)-4-(ethyl(2-hydroxyethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide;
- [000203]** 4-(4-((S)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-N-(4-((R)-4-(ethyl(2-hydroxyethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide;
- [000204]** 4-(4-((R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-N-(4-((S)-4-(ethyl(2-hydroxyethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide;
- [000205]** 4-(4-((R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-N-(4-((R)-4-(ethyl(2-hydroxyethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide, formic acid salt;
- [000206]** 4-(4-((S)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-N-(4-((S)-4-(ethyl(2-hydroxyethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide, formic acid salt;
- [000207]** 4-(4-((S)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-N-(4-((R)-4-(ethyl(2-hydroxyethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide, formic acid salt;
- [000208]** 4-(4-((R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-N-(4-((S)-4-(ethyl(2-hydroxyethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide, formic acid salt;
- [000209]** N-(4-((R)-4-(bis(2-hydroxyethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)-4-(4-((R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzamide, formic acid salt;
- [000210]** 4-(4-((R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-N-(4-((R)-4-(4-((R)-3-fluoro-2-hydroxypropyl)piperazin-1-yl)-1-(phenylthio)butan-2-ylamino)-3-

(trifluoromethylsulfonyl)phenylsulfonyl)benzamide formic acid salt;

[000211] 4-(4-((R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-N-(4-((R)-4-(4-((R)-3-fluoro-2-hydroxypropyl)piperazin-1-yl)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide formic;

[000212] 4-(4-((R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-N-(4-((R)-4-(4-((S)-3-fluoro-2-hydroxypropyl)piperazin-1-yl)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide formic acid salt, mixture of diastereomers;

[000213] 4-(4-((R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-N-(4-((R)-4-(4-((S)-3-fluoro-2-hydroxypropyl)piperazin-1-yl)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide;

[000214] 4-(4-((R)-amino(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-N-(4-((R)-4-((2-hydroxyethyl)(methyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide, formic acid salt;

[000215] 4-(4-((R)-amino(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-N-(4-((R)-4-(ethyl(2-hydroxyethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide, formic acid salt;

[000216] 4-(4-((R)-amino(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-N-(4-((R)-4-(4-(2-hydroxyethyl)piperazin-1-yl)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide, formic acid salt;

[000217] 4-(4-((S)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-N-(4-((R)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide;

[000218] 4-(4-((R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-N-(4-((R)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide;

[000219] 4-(4-((R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-N-(4-((R)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfonyl)benzamide;

[000220] 4-(4-((R)-(4'-chlorobiphenyl-2-yl)(cyano)methyl)piperidin-1-yl)-N-(4-((R)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide

[000221] 4-(4-((S)-(4'-chlorobiphenyl-2-yl)(cyano)methyl)piperidin-1-yl)-N-(4-((R)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide;

[000222] 4-(4-((R)-(4'-chlorobiphenyl-2-yl)(cyano)methyl)piperidin-1-yl)-N-(4-((R)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-

(trifluoromethylsulfonyl)phenylsulfonyl)benzamide;

[000223] 4-(4-((*S*)-(4'-chlorobiphenyl-2-yl)(cyano)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-

(trifluoromethylsulfonyl)phenylsulfonyl)benzamide;

[000224] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-((*S*)-3-((diethylamino)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-

(trifluoromethylsulfonyl)phenylsulfonyl)benzamide;

[000225] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-((*R*)-3-((diethylamino)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-

(trifluoromethylsulfonyl)phenylsulfonyl)benzamide;

[000226] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-((*R*)-2-(hydroxymethyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-

(trifluoromethylsulfonyl)phenylsulfonyl)benzamide, formic acid salt;

[000227] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-((*S*)-2-(hydroxymethyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-

(trifluoromethylsulfonyl)phenylsulfonyl)benzamide, formic acid salt;

[000228] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-((*R*)-3-(hydroxymethyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-

(trifluoromethylsulfonyl)phenylsulfonyl)benzamide, formic acid salt;

[000229] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-((*S*)-3-(hydroxymethyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-

(trifluoromethylsulfonyl)phenylsulfonyl)benzamide, hydrochloride salt;

[000230] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((2*R*)-4-(2*S*)-((diethylamino)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-

(trifluoromethylsulfonyl)phenylsulfonyl)benzamide;

[000231] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((2*R*)-4-(2*R*)-((diethylamino)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-

(trifluoromethylsulfonyl)phenylsulfonyl)benzamide;

[000232] 4-(4-((*R*)-amino(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-

(trifluoromethylsulfonyl)phenylsulfonyl)benzamide, formic acid salt;

[000233] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(2-(methylamino)acetamido)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-

(trifluoromethylsulfonyl)phenylsulfonyl)benzamide, hydrochloride salt;

[000234] 4-(4-((*R*)-(2-aminoacetamido)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-*N*-(4-

((*R*)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-

(trifluoromethylsulfonyl)phenylsulfonyl)benzamide hydrochloride salt; and

[000235] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(dimethylamino)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-

(trifluoromethylsulfonyl)phenylsulfonyl)benzamide, hydrochloride salt.

[000236] Exemplary compounds of the present invention include:

[000237] 2,2'-((*R*)-3-(4-(*N*-(4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-

(phenylthio)butylazanediy)bis(ethane-2,1-diyl) bis(dihydrogen phosphate), hydrochloride salt;

[000238] 2-(((*R*)-3-(4-(*N*-(4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-

(phenylthio)butyl)(ethyl)amino)ethyl dihydrogen phosphate, hydrochloride salt;

[000239] 2-(((*S*)-3-(4-(*N*-(4-(4-((*S*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-

(phenylthio)butyl)(ethyl)amino)ethyl dihydrogen phosphate, hydrochloride salt;

[000240] 2-(((*R*)-3-(4-(*N*-(4-(4-((*S*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-

(phenylthio)butyl)(ethyl)amino)ethyl dihydrogen phosphate, hydrochloride salt;

[000241] 2-(((*S*)-3-(4-(*N*-(4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-

(phenylthio)butyl)(ethyl)amino)ethyl dihydrogen phosphate, hydrochloride salt;

[000242] 2-(((*R*)-3-(4-(*N*-(4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-

(phenylthio)butyl)(ethyl)amino)ethyl dihydrogen phosphate;

[000243] 2-(((*S*)-3-(4-(*N*-(4-(4-((*S*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-

(phenylthio)butyl)(ethyl)amino)ethyl dihydrogen phosphate;

[000244] 2-(((*R*)-3-(4-(*N*-(4-(4-((*S*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-

(phenylthio)butyl)(ethyl)amino)ethyl dihydrogen phosphate;

[000245] 2-(((*S*)-3-(4-(*N*-(4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-

(phenylthio)butyl)(ethyl)amino)ethyl dihydrogen phosphate;

[000246] 2-(((*R*)-3-(4-(*N*-(4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-

(phenylthio)butyl)(methylamino)ethyl dihydrogen phosphate, hydrochloride salt;

[000247] 2-(((S)-3-(4-(N-(4-(4-((S)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-(phenylthio)butyl)(methylamino)ethyl dihydrogen phosphate, hydrochloride salt;

[000248] 2-(((R)-3-(4-(N-(4-(4-((S)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-(phenylthio)butyl)(methylamino)ethyl dihydrogen phosphate, hydrochloride salt;

[000249] 2-(((S)-3-(4-(N-(4-(4-((R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-(phenylthio)butyl)(methylamino)ethyl dihydrogen phosphate, hydrochloride salt;

[000250] 2-(((R)-3-(4-(N-(4-(4-((R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-(phenylthio)butyl)(methylamino)ethyl dihydrogen phosphate;

[000251] 2-(((S)-3-(4-(N-(4-(4-((S)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-(phenylthio)butyl)(methylamino)ethyl dihydrogen phosphate;

[000252] 2-(((R)-3-(4-(N-(4-(4-((S)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-(phenylthio)butyl)(methylamino)ethyl dihydrogen phosphate;

[000253] 2-(((S)-3-(4-(N-(4-(4-((R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-(phenylthio)butyl)(methylamino)ethyl dihydrogen phosphate;

[000254] 2-(4-((R)-3-(4-(N-(4-(4-((R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-(phenylthio)butyl)piperazin-1-yl)ethyl dihydrogen phosphate

[000255] Di-*tert*-butyl ((R)-(4'-chlorobiphenyl-2-yl)(1-(4-(4-((R)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonylcarbonyl)phenyl)piperidin-4-yl)methoxy)methyl phosphate;

[000256] *tert*-Butyl ((R)-(4'-chlorobiphenyl-2-yl)(1-(4-(4-((R)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonylcarbonyl)phenyl)piperidin-4-yl)methoxy)methyl hydrogen phosphate;

[000257] (R)-(4'-chlorobiphenyl-2-yl)(1-(4-(4-((R)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonylcarbonyl)phenyl)piperidin-4-yl)methyl

diethyl phosphate, hydrochloride salt;

[000258] (*R*)-(4'-chlorobiphenyl-2-yl)(1-(4-(4-((*R*)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonylcarbonyl)phenyl)piperidin-4-yl)methyl methyl hydrogen phosphate, hydrochloride salt;

[000259] Di-*tert*-butyl ((*R*)-(4'-chlorobiphenyl-2-yl)(1-(4-(4-((*R*)-4-((*S*)-3-((diethylamino)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonylcarbonyl)phenyl)piperidin-4-yl)methoxy)methyl phosphate; and

[000260] *tert*-Butyl ((*R*)-(4'-chlorobiphenyl-2-yl)(1-(4-(4-((*R*)-4-((*S*)-3-((diethylamino)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonylcarbonyl)phenyl)piperidin-4-yl)methoxy)methyl hydrogen phosphate.

[000261] In another aspect, there is provided a compound selected from:

[000262] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-((2-hydroxyethyl)(methyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide;

[000263] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-(ethyl(2-hydroxyethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide;

[000264] 2-(((*R*)-3-(4-(*N*-(4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfonyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-(phenylthio)butyl)(ethyl)amino)ethyl dihydrogen phosphate; and

[000265] 2-(((*R*)-3-(4-(*N*-(4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfonyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-(phenylthio)butyl)(methyl)amino)ethyl dihydrogen phosphate.

and/or a pharmaceutically acceptable salt thereof.

[000266] Specific exemplary compounds described herein are set forth in the EXAMPLES below. Those skilled in the art will recognize that the compounds described herein, including those set forth in EXAMPLES, can occur in the free, non-salt, form or can occur as salts.

[000267] It is understood that any embodiment described herein can be combined with any other suitable embodiment described herein to provide additional embodiments. For example, various R¹ substituent embodiments can be combined with various R² and R³ substituent embodiments; various R² substituent embodiments can be combined with various R¹ and R³ substituent embodiments; and various R³ substituent embodiments can be combined with

various R¹ and R² substituent embodiments. As would be appreciated by one skilled in the art, any combination of substituents, or group of substituents, is considered to be within the scope of the present invention.

[000268] Compounds of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e) may form stable pharmaceutically acceptable acid or base salts or zwitterions, and in such cases administration of a compound as a salt or zwitterion may be appropriate. Salts or bases of compounds of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e) can be prepared during isolation or following purification of compounds. Compounds of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e) have at least one protonatable nitrogen atom and are consequently capable of forming acid or base salts, for example about 1 to about 3, about 1.1 to about 3, about 1.2 to about 3, about 1.3 to about 3, about 1.4 to about 3, about 1.5 to about 3, about 1.6 to about 3, about 1.7 to about 3, about 1.8 to about 3, about 1.9 to about 3, about 2.0 to about 3, about 2.1 to about 3, about 2.2 to about 3, about 2.3 to about 3, about 2.4 to about 3, about 2.5 to about 3, about 2.6 to about 3, about 2.7 to about 3, about 2.8 to about 3, or about 2.9 to about 3, equivalents of acid or base per equivalent of compound.

[000269] Salts may be formed by conventional means, such as by reacting the free base form of the product with one or more equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water, which is removed *in vacuo* or by freeze drying or by exchanging the anions of an existing salt for another anion on a suitable ion-exchange resin.

[000270] Compound(s) of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e) are useful for their ability to inhibit Bcl-2 and Bcl-X_L activity. Compounds are also useful for the treatment of all cancer types such as neuroblastoma, intestine carcinoma such as rectum carcinoma, colon carcinoma, familial adenomatous polyposis carcinoma and hereditary non-polyposis colorectal cancer, esophageal carcinoma, labial carcinoma, larynx carcinoma, hypopharynx carcinoma, tongue carcinoma, salivary gland carcinoma, gastric carcinoma, adenocarcinoma, medullary thyroidea carcinoma, papillary thyroidea carcinoma, renal carcinoma, kidney parenchym carcinoma, ovarian carcinoma, cervix carcinoma, uterine corpus carcinoma, endometrium carcinoma, chorion carcinoma, pancreatic carcinoma, prostate carcinoma, testis carcinoma, breast carcinoma, urinary carcinoma, melanoma, brain tumors such as glioblastoma, astrocytoma, meningioma, medulloblastoma and peripheral neuroectodermal tumors, Hodgkin's lymphoma, non-Hodgkin's lymphoma, Diffuse Large B Cell Lymphoma (DLBCL), Follicular Lymphoma (FL), Mantle Cell Lymphoma (MCL), Mantle Zone Lymphoma (MZL), Hairy Cell Leukemia (HCL), Peripheral T-cell Lymphoma (PTCL), Burkitt lymphoma, acute lymphatic leukemia (ALL), chronic lymphocytic leukemia (CLL/SLL), acute myeloid leukemia (AML), chronic

myeloid leukemia (CML), adult T-cell leukemia lymphoma, hepatocellular carcinoma, gall bladder carcinoma, bronchial carcinoma, small cell lung carcinoma, non-small cell lung carcinoma, multiple myeloma, basalioma, teratoma, retinoblastoma, choroidea melanoma, seminoma, rhabdomyo sarcoma, craniopharyngeoma, osteosarcoma, chondrosarcoma, myosarcoma, liposarcoma, fibrosarcoma, Ewing sarcoma and plasmocytoma.

[000271] In some embodiments, compound(s) of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e) are useful for the treatment of non-Hodgkin's lymphoma. In some embodiments, compound(s) of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e) are useful for the treatment of CLL. In some embodiments, compound(s) of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e) are useful for the treatment of non-small cell lung cancer (NSCLC). In some embodiments, compound(s) of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e) are useful for the treatment of diffuse large B-cell lymphoma (DLBCL). In some embodiments, compound(s) of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e) are useful for the treatment of prostate cancer.

[000272] Compound(s) of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e) should also be useful as standards and reagents in determining the ability of a potential pharmaceutical to inhibit BH-3 containing proteins, particularly the BCL2 family. These would be provided in commercial kits comprising a compound of this invention.

[000273] Compound(s) of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e) have been shown to inhibit Bcl-2 and Bcl-X_L activities as demonstrated by an assay based on the assay description below. Although pharmacological properties of compound(s) of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e) may vary with structural change, typical compounds of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e) possess Bcl-2 and Bcl-X_L inhibitory activities at IC₅₀ concentrations (concentrations to achieve 50% inhibition) or doses at a level below 10 μ M.

[000274] The following *in vitro* binding and cellular assays may be used to determine the activity and specificity of compounds of the present invention to bind to Bcl-2 and inhibit Bcl-2 function in a cell.

A. Bcl-2 Binding Assay(s)

[000275] Bcl-x_L and Bcl-2 FP binding affinity of compound(s) of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e) may be determined using a variety of known methods. One such assay is a sensitive and quantitative *in vitro* binding assay using fluorescence polarization ("FP") described by Wang, J.-L.; Zhang, Z.-J.; Choksi, S.; Sjam, S.; Lu, Z.; Croce, C. M.; Alnemri, E. S.; Komgold, R.; Huang, Z. Cell permeable Bcl-2 binding peptides: a chemical approach to apoptosis induction in tumor cells. *Cancer Res.* 2000, 60, 1498-1502).

[000276] Additionally, the binding affinity of compound(s) of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e) to Bcl-2 protein *in vitro* was determined by a competitive binding assay based

on fluorescence polarization. For example, fluorescence polarization ("FP") assays may be developed using a c-terminal 6XHIS tagged Bcl-2 (aa 1-204) and a C-terminal 6XHIS tagged Bcl-X_L (aa 1-209). The tracer may be a synthetic peptide BH-3 peptide Bim conjugated to Fluorescein isothiocyanate (FITC- DLRPEIRIAQELRRIGDEFNETYTRR). Dilutions of either Bcl-2 (1.3 nM) or Bcl-X_L (0.8 nM) may be added to serial dilutions of antagonist and incubated for one hour prior to the addition of 2 nM of fluorescent peptide tracer (Anaspec, Fremont, CA) in the assay buffer. Final assay buffer conditions may be 20 mM HEPES, pH 7.5, 1 mM DTT, 0.005% Tween-20 and 50 mM NaCl. Samples may be read after 20-minute incubation. Fluorescence polarization values may be plotted as a function of the antagonist concentration.

[000277] When tested in an FP assay based on the FP assay described above, the inhibitory activity of the following examples were measured at the IC₅₀s (μM) shown in Table 1.

TABLE 1

Example	Bcl-X _L FP assay IC ₅₀ (μM)	Bcl-2 FP assay IC ₅₀ (μM)
1	0.001	<0.001
2	0.001	0.0003
3	0.001	<0.0003
4	0.0008	0.0005
5	0.001	0.0008
6	0.002	0.001
7	0.001	0.002
8	0.001	0.0009
9	0.001	0.0009
10	0.001	0.0007
11	0.003	0.004
12	0.003	0.003
13	0.015	0.016
14	0.078	0.253
15	0.001	0.003
16	0.001	0.0008
17	0.001	0.002
18	0.002	0.007
19	0.008	1.195

20	0.001	0.0003
21	0.0005	0.0003
22	0.003	0.0006
23	0.001	0.001
24	0.002	0.0004
25	0.002	0.0004
26	0.0005	0.0004
27	NT	NT
28	0.002	0.004
29	0.012	0.03
30	0.001	0.001
31	NT	NT
32	NT	NT
33	0.033	0.03
34	0.019	0.027
35	0.022	0.038
36	0.018	0.024

B. Cell Based Assay(s)

[000278] Certain compounds of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e) may be tested in cell-based assays using Bcl-2 and Bcl-X_L dependent cell lines to determine whether apoptosis is induced when the cell lines are treated with such compounds. Exemplary cell lines include FDCP-1 cell line transfected with and overexpressing Bcl-2, and FDCP-1 cell line transfected with and overexpressing Bcl-X_L.

[000279] In this specification the prefix C_{x-y} as used in terms such as C_{x-y}alkyl and the like (where x and y are integers) indicates the numerical range of carbon atoms that are present in the group; for example, C₁₋₄alkyl includes C₁alkyl (methyl), C₂alkyl (ethyl), C₃alkyl (propyl and isopropyl) and C₄alkyl (butyl, 1-methylpropyl, 2-methylpropyl, and *t*-butyl).

[000280] Compounds of formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e) have chiral centers, and thus exist as stereoisomers. It is to be understood that the invention encompasses all such stereoisomers, including enantiomers and diastereoisomers, as well as to mixtures of these enantiomers, and/or mixtures of these diastereoisomers. Insofar as compounds of formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e), may exist in optically active or racemic forms, the invention includes in its definition any such optically active or racemic form which possesses the

above-mentioned activity. The present invention encompasses all such stereoisomers having activity as herein defined. Throughout this application, the name of the product of this invention, where the absolute configuration of an asymmetric center is not indicated, is intended to embrace the individual stereoisomers as well as mixtures of stereoisomers.

[000281] The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Racemates may be separated into individual enantiomers using known procedures (see, for example, Advanced Organic Chemistry: 3rd Edition: author J March, p104-107). A suitable procedure involves formation of diastereomeric derivatives by reaction of the racemic material with a chiral auxiliary, followed by separation, for example by chromatography, of the diastereomers and then cleavage of the auxiliary species. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

[000282] Thus, throughout the specification, where reference is made to compounds of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e), it is to be understood that the term compound includes stereoisomers, mixtures of stereoisomers, and polymorphs that inhibit bcl-2 activity in a human or animal.

[000283] Stereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The enantiomers may be isolated by separation of a racemate for example by fractional crystallisation, resolution or HPLC. The diastereoisomers may be isolated by separation by virtue of the different physical properties of the diastereoisomers, for example, by fractional crystallisation, HPLC or flash chromatography. Alternatively particular stereoisomers may be made by chiral synthesis from chiral starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, with a chiral reagent.

[000284] When a specific stereoisomer is provided (whether provided by separation, by chiral synthesis, or by other methods) it is favorably provided substantially isolated from other stereoisomers of the same compound. In one aspect, a mixture containing a particular stereoisomer of a compound of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e) may contain less than 30%, particularly less than 20%, and more particularly less than 10% by weight of other stereoisomer(s) of the same compound. In another aspect, a mixture containing a particular stereoisomer of a compound of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e) may contain less than 6%, particularly less than 3%, and more particularly less than 2% by weight of other stereoisomer(s) of the compound. In another aspect, a mixture containing a particular stereoisomer of a compound of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e) may contain less

than 1%, particularly less than 0.5%, and more particularly less than 0.3%, and still more particularly less 0.1% by weight of other stereoisomer(s) of the compound.

[000285] It is to be understood that, insofar as certain compounds of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e) defined above may exist in tautomeric forms, the invention includes in its definition any such tautomeric form which possesses the above-mentioned activity/activities. Thus, the invention relates to all tautomeric forms of compounds of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e) which inhibit Bcl-2 and/or Bcl-X_L activities in a human or animal.

[000286] It is also to be understood that certain compounds of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e) 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.

[000287] Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures including the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ¹³C- or ¹⁴C-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents in accordance with the present invention. In some embodiments. By way of example, the R¹ group of formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e) may comprise one or more deuterium atoms. Mixtures of isomeric forms may be separated and/or purified by techniques as would be known to one skilled in this art, including but not limited to column chromatography.

[000288] Certain phosphate-bearing compounds of the present invention may be transformed by metabolic means (such as by hydrolysis, for example, with alkaline phosphatases) to a corresponding parent compound. Such phosphate-bearing compounds are designed to enhance pharmaceutically and/or pharmacokinetically based properties associated with the parent drug molecule. Exemplary advantages of a phosphate-bearing compound lie in its physical properties, such as enhanced water solubility for various types of administration (e.g., intravenous, parenteral, subcutaneous, intramuscular, etc.) at physiological pH compared to the parent drug, or it enhances absorption from the digestive tract, or it may enhance drug stability for long-term storage.

V. METHODS

[000289] In one aspect, there is provided compound(s) of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e), or a pharmaceutically acceptable salt thereof, for use as a medicament.

[000290] In another aspect, there is provided use of compound(s) of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e), or a pharmaceutically acceptable salt thereof, in the manufacture of a

medicament for the treatment or prophylaxis of at least one of: carcinoma, hematopoietic tumours of lymphoid lineage, hematopoietic tumors of myeloid lineage, tumors of mesenchymal origin, melanoma, seminoma, tetratocarcinoma, neuroblastoma, and glioma.

[000291] In another aspect, there is provided use of compound(s) of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of at least one of: bladder cancer, breast cancer, colon cancer, ovarian cancer, AML, diffuse large B-cell lymphoma (DLBCL), CLL; small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), including the non-squamous and squamous subtypes, pancreatic cancer, prostate cancer, non-Hodgkin's lymphoma, Follicular Lymphoma (FL), Mantle Cell Lymphoma (MCL), Mantle Zone Lymphoma (MZL), Hairy Cell Leukemia (HCL), and Peripheral T-cell Lymphoma (PTCL).

[000292] In some embodiments, compound(s) of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e) are useful in the manufacture of a medicament for the treatment of at least one of: non-Hodgkin's lymphoma, CLL, non-small cell lung cancer (NSCLC), diffuse large B-cell lymphoma (DLBCL), and prostate cancer.

[000293] In another aspect, there is provided use of compound(s) of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer.

[000294] In another aspect, there is provided use of compound(s) of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the production of an anti-proliferative and/or pro-apoptotic effect in a warm-blooded animal such as man.

[000295] In another aspect, there is provided use of compound(s) of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the production of a Bcl-2 and/or Bcl-X_L inhibitory effect in a warm blooded animal such as man.

[000296] In another aspect, there is provided a method for the treatment or prophylaxis of at least one of: carcinoma, hematopoietic tumours of lymphoid lineage, hematopoietic tumors of myeloid lineage, tumors of mesenchymal origin, melanoma, seminoma, tetratocarcinoma, neuroblastoma and glioma in a warm-blooded animal such as man, said method comprising administering to said animal an effective amount of compound(s) of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e), or a pharmaceutically acceptable salt thereof.

[000297] In another aspect, there is provided a method for treating at least one of: bladder cancer, breast cancer, colon cancer, ovarian cancer, AML, diffuse large B-cell lymphoma (DLBCL), CLL; small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), including

the non-squamous and squamous subtypes, pancreatic cancer, prostate cancer, non-Hodgkin's lymphoma, Follicular Lymphoma (FL), Mantle Cell Lymphoma (MCL), Mantle Zone Lymphoma (MZL), Hairy Cell Leukemia (HCL), and Peripheral T-cell Lymphoma (PTCL) in a warm-blooded animal such as man, said method comprising administering to said animal an effective amount of compound(s) of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e), or a pharmaceutically acceptable salt thereof.

[000298] In some embodiments, compound(s) of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e) are useful for treating at least one of: non-Hodgkin's lymphoma, CLL, non-small cell lung cancer (NSCLC), diffuse large B-cell lymphoma (DLBCL), and prostate cancer.

[000299] In another aspect, there is provided a method for producing an anti-proliferative and/or pro-apoptotic effect in a warm-blooded animal such as man, said method comprising administering to said animal an effective amount of compound(s) of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e), or a pharmaceutically acceptable salt thereof.

[000300] In some embodiments, an anti-proliferative and/or pro-apoptotic effect is for treating bladder cancer, breast cancer, colon cancer, ovarian cancer, AML, diffuse large B-cell lymphoma (DLBCL), CLL; small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), including the non-squamous and squamous subtypes, pancreatic cancer, prostate cancer, non-Hodgkin's lymphoma, Follicular Lymphoma (FL), Mantle Cell Lymphoma (MCL), Mantle Zone Lymphoma (MZL), Hairy Cell Leukemia (HCL), and Peripheral T-cell Lymphoma (PTCL).

[000301] In some embodiments, compound(s) of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e) have an anti-proliferative and/or pro-apoptotic effect that is useful for treating at least one of: non-Hodgkin's lymphoma, CLL, non-small cell lung cancer (NSCLC), diffuse large B-cell lymphoma (DLBCL), and prostate cancer.

[000302] In another aspect, there is provided a method for producing a Bcl-2 and/or Bcl-X_L inhibitory effect in a warm-blooded animal such as man, said method comprising administering to said animal an effective amount of compound(s) of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e), or a pharmaceutically acceptable salt thereof.

[000303] In another aspect, there is provided a method for treating cancer in a warm-blooded animal such as man, said method comprising administering to said animal an effective amount of compound(s) of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e), or a pharmaceutically acceptable salt thereof.

[000304] In another aspect, there is provided compound(s) of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e), or a pharmaceutically acceptable salt thereof, for use in the treatment of at least one of: carcinoma, hematopoietic tumours of lymphoid lineage, hematopoietic tumors of myeloid lineage, tumors of mesenchymal origin, melanoma, seminoma, tetratocarcinoma, neuroblastoma,

and glioma.

[000305] In another aspect, there is provided compound(s) of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e), or a pharmaceutically acceptable salt thereof, for use in the treatment of at least one of: bladder cancer, breast cancer, colon cancer, ovarian cancer, AML, diffuse large B-cell lymphoma (DLBCL), CLL; small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), including the non-squamous and squamous subtypes, pancreatic cancer, prostate cancer, non-Hodgkin's lymphoma, Follicular Lymphoma (FL), Mantle Cell Lymphoma (MCL), Mantle Zone Lymphoma (MZL), Hairy Cell Leukemia (HCL), and Peripheral T-cell Lymphoma (PTCL).

[000306] In some embodiments, compound(s) of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e) are useful for treating at least one of: non-Hodgkin's lymphoma, CLL, non-small cell lung cancer (NSCLC), diffuse large B-cell lymphoma (DLBCL), and prostate cancer.

[000307] In still another aspect, there is provided compound(s) of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e), or a pharmaceutically acceptable salt thereof, for use in the production of an anti-proliferative and/or pro-apoptotic effect, in a warm-blooded animal such as man.

[000308] In some embodiments, an anti-proliferative and/or pro-apoptotic effect is for treating bladder cancer, breast cancer, colon cancer, ovarian cancer, AML, diffuse large B-cell lymphoma (DLBCL), CLL; small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), including the non-squamous and squamous subtypes, pancreatic cancer, prostate cancer, non-Hodgkin's lymphoma, Follicular Lymphoma (FL), Mantle Cell Lymphoma (MCL), Mantle Zone Lymphoma (MZL), Hairy Cell Leukemia (HCL), and Peripheral T-cell Lymphoma (PTCL).

[000309] In some embodiments, compound(s) of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e) are for use in the production of an anti-proliferative and/or pro-apoptotic effect to treat at least one of: non-Hodgkin's lymphoma, CLL, non-small cell lung cancer (NSCLC), diffuse large B-cell lymphoma (DLBCL), and prostate cancer.

[000310] In another aspect, there is provided compound(s) of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e), or a pharmaceutically acceptable salt thereof, for use in the production of a Bcl-2 and/or Bcl-X_L inhibitory effect in a warm-blooded animal such as man.

[000311] In another aspect, there is provided compound(s) of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e), or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer in a warm-blooded animal such as man.

VI. COMPOSITIONS AND PHARMACEUTICAL COMPOSITIONS

[000312] In another aspect, there is provided a pharmaceutical composition comprising a compound of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, diluent, or excipient.

[000313] 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). In some embodiments, compounds and/or compositions of the present invention are administered by intravenous (I.V.) administration.

[000314] Compositions of the present 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 coloring, sweetening, flavoring and/or preservative agents.

[000315] 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.

[000316] 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.

[000317] Aqueous suspensions generally contain the active ingredient in finely powdered form or in the form of nano or micronized particles 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 polyoxyethylene 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); coloring agents; flavoring agents; and/or sweetening agents such as sucrose, saccharine or aspartame.

[000318] 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 flavoring 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.

[000319] 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, flavoring and coloring agents, may also be present.

[000320] 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, flavoring and preservative agents.

[000321] 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, flavoring and/or coloring agent.

[000322] 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.

[000323] Compositions for administration by inhalation may be in the form of a conventional pressurized 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.

[000324] 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.

[000325] 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 4 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.

[000326] 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. A daily dose in the range of 0.1-50 mg/kg may be employed. Accordingly, the optimum dosage may be determined by the practitioner who is treating any particular patient.

VII. COMBINATIONS

[000327] The anti-cancer treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to the compound of the invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents:

(i) other antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis platin, oxaliplatin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, bendamustine, busulphan, temozolamide and nitrosoureas); antimetabolites (for example gemcitabine, cpecitabine and antifolates such as fluoropyrimidines like 5 fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, and hydroxyurea); antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C,

dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine; and taxoids like taxol and taxotere; and polo kinase or kinesin motor protein inhibitors); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan, camptothecin, Pixantrone, and irinotecan); inhibitors of DNA repair mechanisms such as, but not limited to, CHK kinase, DNA-dependent protein kinase inhibitors and inhibitors of poly (ADP-ribose) polymerase (PARP inhibitors), ATM or ATR; and Hsp90 inhibitors such as tanespamycin and retaspimycin. Compounds that inhibit progression through the cell cycle such as antimitotic agents (for example, and not limited to, vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine; epothilones such as ixabepilone; and taxoids like taxol and taxotere; polo-like kinase inhibitors; and inhibitors of kinesin motor proteins such as Eg5 protein inhibitors); aurora kinase inhibitors (for example, but not limited to, AZD1152, PH739358, VX-680, MLN8054, R763, MP235, MP529, VX-528 and AX39459) and cyclin dependent kinase inhibitors such as CDK2 and/or CDK4 inhibitors (for example, flavopiridol/Alvocidib, roscovitine, seliciclib); inhibitors of centromeric protein function such as CENP-E inhibitors.

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, fulvestrant, toremifene, raloxifene, droloxifene and idoxifene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane); inhibitors of 5 α -reductase such as finasteride; and inhibitors of CYP17A1 such as abiraterone acetate;

(iii) anti-invasion agents [for example c-Src kinase family inhibitors like 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline (AZD0530; International Patent Application WO 01/94341), N-(2-chloro-6-methylphenyl)-2-{6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-ylamino}thiazole-5-carboxamide (dasatinib, BMS-354825; J. Med. Chem., 2004, 47, 6658-6661) and bosutinib (SKI-606), and metalloproteinase inhibitors like marimastat, inhibitors of urokinase plasminogen activator receptor function or antibodies to Heparanase, inhibitors of FAK or focal-adhesion kinase, inhibitors of or antibodies to MET receptor kinase or the MET ligand hepatocyte growth factor;

(iv) inhibitors of growth factor function: for example such inhibitors include growth factor antibodies and growth factor receptor antibodies (for example the anti erbB2 antibody trastuzumab [Herceptin™], the anti-EGFR antibody panitumumab, the anti erbB1 antibody cetuximab [Erbix, C225] and any growth factor or growth factor receptor antibodies disclosed by Stern et al. (Critical reviews in oncology/haematology, 2005, Vol. 54, pp11-29); such

inhibitors also include tyrosine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, ZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI 774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)-quinazolin-4-amine (CI 1033), erbB2 tyrosine kinase inhibitors such as lapatinib); inhibitors of the hepatocyte growth factor family; inhibitors of the insulin growth factor family; inhibitors of the platelet-derived growth factor family such as imatinib and/or nilotinib (AMN107); inhibitors of spleen tyrosine kinase (SYK) such as fostamatinib disodium (R788/R406), PRT062607; inhibitors of serine/threonine kinases (for example Ras/Raf signalling inhibitors such as farnesyl transferase inhibitors, for example sorafenib (BAY 43-9006), tipifarnib (R75777) and lonafarnib (SCH66336)), inhibitors of cell signaling through MEK and/or AKT kinases, c-kit inhibitors, abl kinase inhibitors, PI3 kinase inhibitors, Flt3 kinase inhibitors, CSF-1R kinase inhibitors, IGF receptor (insulin-like growth factor) kinase inhibitors; aurora kinase inhibitors (for example AZD1152, PH739358, VX-680, MLN8054, R763, MP235, MP529, VX-528 AND AX39459) and cyclin dependent kinase inhibitors such as CDK2 and/or CDK4 inhibitors; and inhibitors of JAK/STAT signaling such as Pim kinase inhibitors and Jak 1 and 2 kinase inhibitors (for example, but not limited to, AZD1480, Ruxolitinib);

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, [for example the anti vascular endothelial cell growth factor antibody bevacizumab (Avastin™) and for example, a VEGF receptor tyrosine kinase inhibitor such as vandetanib (ZD6474), vatalanib (PTK787), sunitinib (SU11248), axitinib (AG-013736), pazopanib (GW 786034) and 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (AZD2171; Example 240 within WO 00/47212), compounds such as those disclosed in International Patent Applications WO97/22596, WO 97/30035, WO 97/32856 and WO 98/13354 and compounds that work by other mechanisms (for example linomide, inhibitors of integrin $\alpha v \beta 3$ function and angiostatin)];

(vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 and WO 02/08213; and inhibitors of angiopoietins or their receptors (Tie-a and Tie-2);

(vii) an endothelin receptor antagonist, for example zibotentan (ZD4054) or atrasentan;

(viii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense; or oblimerson sodium, an anti-Bcl-2 antisense;

(ix) gene therapy approaches, including for example approaches to replace aberrant genes

such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene directed enzyme pro drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi drug resistance gene therapy;

(x) immunotherapy approaches, including for example ex vivo and in vivo approaches to increase the immunogenicity of patient tumor cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte macrophage colony stimulating factor, approaches to decrease T cell anergy, approaches using transfected immune cells such as cytokine transfected dendritic cells, approaches using cytokine transfected tumor cell lines, approaches using anti idiotypic antibodies, approaches for T-cell enhancement including CTLA4 antibodies, and antibodies directed toward CD137, PD-1 or B7-H1, toll-receptor agonists; agonistic antibodies to CD40 such as SGN-40 (Dacetuzumab) or to the Tweak receptor such as PDL-192; agonistic antibodies to FAS; approaches using antibodies to tumor associated antigens, and antibodies that deplete target cell types (e.g. unconjugated anti-CD20 antibodies such as Rituximab, ofatumumab, Obinutuzumab, anti-CD19 antibodies such as MEDI-551, anti-CD52 antibodies such as Alemtuzumab, anti-CD37 antibodies such as TRU-016, anti-CD22 antibodies such as Inotuzumab, radiolabeled anti-CD20 antibodies Bexxar and Zevalin, and anti-CD54 antibody Campath; immunotoxins such as moxetumumab pasudotox), approaches using anti-idiotypic antibodies, approaches that enhance Natural Killer cell function, and approaches that utilize antibody-toxin conjugates (e.g. anti-CD33 antibody Mylotarg). Immune modifiers such as Revlimid (Lenalidomide);

(xi) pro-apoptotic approaches, including antibodies to death receptor 4 or death receptor 5 or antibodies binding to both death receptor 4 and death receptor 5; SMAC mimetics or compounds that inhibit the protein-protein interactions of the inhibitor of apoptosis proteins such as cIAP-1, cIAP-2 and XIAP; antisense or small interfering RNA molecules to cIAP-1, cIAP-2, XIAP or surviving;

(xii) cytokine treatment, including tumor necrosis factor alpha, and recombinant Trail protein or small molecule or protein mimetics of the Trail protein; FAS or Tweak ligands or mimetics of these ligands;

(xiii) efficacy enhancers, such as leucovorin;

(xiv) radiation; Such radiotherapy may include one or more of the following categories or radiation:

(a) external radiation therapy using electromagnetic radiation, and intraoperative radiation therapy using electromagnetic radiation;

- (b) internal radiation therapy or brachytherapy; including interstitial radiation therapy or intraluminal radiation therapy; and/or
- (c) systemic radiation therapy, including but not limited to iodine 131 and strontium 89
- (xv) inhibitors of antigen receptor signaling, including spleen tyrosine kinase (Syk) inhibitors such as fostamatinib (R788/R406), PRT062607, bruton's tyrosine kinase (Btk) inhibitors such as PCI-32765, AVL-292, Protein kinase C inhibitors such as sorastaurin, IKK/NFkB inhibitors, PI3-kinase inhibitors such as CAL-101 (GS 1101), Enzastaurin, AZD8186, PI3-kinase inhibitors such as CAL-101 (GS 1101), Enzastaurin, AZD8186, BCL6 inhibitors; and
- (xvi) regulators of hematopoietic cell trafficking/homing including agents that target CXCR4 such as Plerixafor (rINN and USAN, also known as MOZOBIL, JM 3100 and AMD3100), BKT140, Syk inhibitors such as fostamatinib, agents that target VLA-4 and agents that target CD44; and
- (xvii) inhibitors of proteasome mediated protein degradation including but not limited to proteasome inhibitors such as VelcadeTM (bortezomib), carfilzomib, inhibitors of ubiquitin ligases, and inhibitors of ubiquitin proteases, inhibitors of protein Neddylation, inhibitors of protein sumoylation.

[000328] Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products employ compounds of this invention, or pharmaceutically acceptable salts thereof, within the dosage range described hereinbefore and the other pharmaceutically-active agent within its approved dosage range.

[000329] In addition to its use in therapeutic medicine, compounds of Formulae (I), (I-a), (I-b), (I-c), (I-d) and/or (I-e) and pharmaceutically acceptable salts thereof are also useful as pharmacological tools in the development and standardization of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of Bcl-2 and/or Bcl-X_L in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

[000330] In any of the above-mentioned pharmaceutical composition, process, method, use, medicament, and manufacturing features of the instant invention, any of the alternate embodiments of compounds of the present invention described herein also apply.

EXAMPLES

[000331] The invention will now be further described with reference to the following illustrative examples in which, unless stated otherwise:

- (i) temperatures are given in degrees Celsius (°C); operations are carried out at room

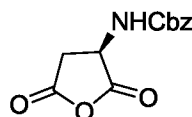
- temperature or ambient temperature, that is, in a range of 18-25 °C;
- (ii) organic solutions were dried over anhydrous magnesium sulfate unless otherwise stated; evaporation of organic solvent was carried out using a rotary evaporator under reduced pressure (4.5 – 30 mmHg) with a bath temperature of up to 60 °C;
 - (iii) column chromatography means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates;
 - (iv) in general, the course of reactions was followed by TLC or liquid chromatography/mass spectroscopy (LC/MS) and reaction times are given for illustration only;
 - (v) final products have satisfactory proton nuclear magnetic resonance (NMR) spectra and/or mass spectra data;
 - (vi) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;
 - (vii) when given, NMR data is in the form of delta values for major diagnostic protons, given in part per million (ppm) relative to tetramethylsilane (TMS) as an internal standard;
 - (viii) chemical symbols have their usual meanings;
 - (ix) in the event that the nomenclature assigned to a given compound does not correspond to the compound structure depicted herein, the structure will control;
 - (x) solvent ratio was given in volume : volume (v/v) terms;
 - (xi) “ISCO” refers to normal phase flash column chromatography using pre-packed silica gel cartridges (12 g, 40 g etc.), used according to the manufacturer’s instructions, and obtained from ISCO, Inc, 4700 Superior Street Lincoln, NE, USA;
 - (xii) A “Gilson column” refers to a YMC-AQC18 reverse phase HPLC Column with dimension 20 mm/100 and 50 mm/250 in H₂O/MeCN with 0.1% TFA as mobile phase unless otherwise stated and used according to the manufacturer’s instructions, obtained from Gilson, Inc. 3000 Parmenter Street, Middleton, WI 53562-0027, U.S.A.; or an Atlantis T3 reverse phase HPLC Column (Waters Corp., 34 Maple St., Milford, MA 01757, U.S.A) with dimension 20 mm/100 and 50 mm/250 in H₂O/MeCN with 0.1% TFA as mobile phase unless otherwise stated. Both columns were used with a preparative HPLC (High Performance Liquid Chromatography) instrument obtained from Gilson, Inc. 3000 Parmenter Street, Middleton, WI 53562-0027, U.S.A., according to the manufacturer’s instructions;
 - (xiii) “SFC (Super Critical Fluid Chromatography)” refers to Analytical SFC (ASC-1000 Analytical SFC System with Diode Array Detector, or AMS-1000 Analytical SFC/MS system with Diode Array and Mass Spectrometer detection) and/or Preparative SFC

- (APS-1000 AutoPrep Preparative SFC, or MultiGram III SFC), used with carbon dioxide according to the manufacturer's instruction, obtained from Waters Corp., 34 Maple Street, Milford, MA 01757, U.S.A;
- (xiv) Chiralpak[®] columns (e.g., type "IA", "IB" and/or "IC") are used according to the manufacturer's instruction obtained from Chiral Technologies, Inc. 800 North Five Points Road West Chester, PA19380, USA;
- (xv) Enantiomeric excess for each individual enantiomer (e.e.): > % calculated using area percent at 220 nm or 254 nm unless otherwise stated;
- (xvi) Diastereomeric excess for each individual diastereomer (d.e.): > % calculated using area percent at 220 nm or 254 nm unless otherwise stated;
- (xvii) Specific rotation(s) $[\alpha]$ were calculated based upon the equation: $[\alpha] = (100 \cdot \alpha) / (l \cdot c)$, α is the observed rotation, l is the path length and c is the compound concentration;
- (xviii) Observed optical rotations were measured using a PerkinElmer Model 341 Polarimeter, obtained from PerkinElmer, 940 Winter Street, Waltham, MA 02451, USA;
- (xix) FT-IR (Fourier transform infrared spectroscopy) spectra were measured using a Nicolet Magna 560 FTIR (Thermo Fisher Scientific 81 Wyman Street, Waltham, MA 02454 USA) equipped with a Harrick SplitPea[™] ATR assembly 32 scans, 4000-600 cm^{-1} , sample applied directly on ATR surface, background collected prior to sample being run, then sample as background subtracted;
- (xx) mass spectra were acquired when samples were separated using reverse-phase liquid chromatography (LC) and detected by electrospray ionization (ESI) mass spectrometry (MS) in positive and negative ion; values for m/z are given; generally, only ions which indicate the parent mass are reported; and unless otherwise stated, the mass ion quoted is $(M+H)^+$ or $(M-H)^+$; and
- (xxi) The following abbreviations have been used:
- | | |
|-------|--|
| Cbz | benzyloxycarbonyl; |
| DCM | dichloromethane; |
| DCE | 1,2-dichloroethane; |
| HPLC | high-performance liquid chromatography; |
| DIPEA | <i>N,N</i> -diisopropylethylamine; |
| DMF | <i>N,N</i> -dimethylformamide; |
| EDC | 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; |
| HOBt | 1-hydroxybenzotriazole hydrate; |
| THF | tetrahydrofuran; |
| DMAP | 4-dimethylaminopyridine; |

DMSO	dimethylsulfoxide;
EtOAc	ethyl acetate;
Et ₂ O	diethyl ether;
r.t./R.T.	room temperature;
o/n	overnight;
hr(s)	hour(s);
min(s)	minute(s);
DMA	<i>N,N</i> -dimethylacetamide;
TEA	triethylamine;
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate; and
HATU	2-(7-Aza-1 <i>H</i> -benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate

INTERMEDIATE 1

[000332] (*R*)-benzyl 2,5-dioxotetrahydrofuran-3-ylcarbamate



[000333] A mixture of (*R*)-2-(benzyloxycarbonylamino)succinic acid (Aldrich, 30 g, 112.26 mmol) and acetic anhydride (65.7 ml, 696.02 mmol) was stirred overnight at room temperature during which time the reaction mixture became clear. The volatiles were removed under reduced pressure (water bath temperature 65 °C) and the concentrate was azeotroped with toluene (3 x 50 ml) and obtained the title product after drying for ~48 hours at 60 °C under high vacuum pump (28.0 g, yield: almost quantitative).

[000334] ¹H NMR (400 MHz, DMSO-d₆) δ ppm 2.94 (dd, 1 H) 3.28 (dd, 1 H) 4.61 - 4.82 (m, 1 H) 5.08 (s, 2 H) 7.21 - 7.51 (m, 5 H) 8.16 (d, 1 H)

[000335] Optical rotation:

Concentration: 0.14 g/dL

Lamp: Sodium

Wavelength: 589 nm

Temperature: 20° C

Path length: 10 cm

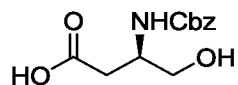
Cell volume: 1 ml

Solvent: CH₂Cl₂

[α]= +13

INTERMEDIATE 2

[000336] (R)-3-(benzyloxycarbonylamino)-4-hydroxybutanoic acid



[000337] A solution of (R)-benzyl 2,5-dioxotetrahydrofuran-3-ylcarbamate (INTERMEDIATE 1, 53.28 g, 213.79 mmol) in THF (330 ml) was added over a 4 hour period using an additional funnel to a mixture of sodium borohydride (8.09 g, 213.79 mmol) in THF (330 ml) at 0 °C. After the addition was complete, the mixture was warmed to room temperature and stirred for 2 hours. The solution was then concentrated under reduced pressure to 1/4 of the original volume, cooled to 0 °C, and carefully quenched by the slow addition of water (400 ml). The mixture was acidified to pH 4 with 1N aqueous hydrochloric acid and extracted with Et₂O (5 x 300 ml). The combined organic layers were dried (Na₂SO₄) and concentrated *in vacuo* to provide the title product (45.9 g, yield: 85%).

[000338] ¹H NMR (300 MHz, METHANOL-d₄) δ ppm 2.41 - 2.54 (m, 1 H) 2.56 - 2.70 (m, 1 H) 3.33 (dt, 2 H) 3.42 - 3.65 (m, 2 H) 3.95 - 4.12 (m, 1 H) 5.01 - 5.22 (m, 2 H) 7.14 - 7.46 (m, 5 H).

[000339] LCMS: (ESI) *m/z* 254.1 [M+H]⁺.

[000340] Optical rotation:

Concentration: 0.14 g/dL

Lamp: Sodium

Wavelength: 589 nm

Temperature: 20° C

Path length: 10 cm

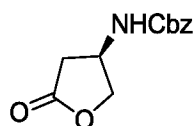
Cell volume: 1 ml

Solvent: CH₂Cl₂

[α]_D = +13

INTERMEDIATE 3

[000341] (R)-benzyl 5-oxotetrahydrofuran-3-ylcarbamate



[000342] (R)-3-(Benzyloxycarbonylamino)-4-hydroxybutanoic acid (INTERMEDIATE 2, 27.7 g, 109.38 mmol) was dissolved in toluene (648 ml). *p*-Toluenesulfonic acid (367 mg, 2.13

mmol) was added to the solution and the resulting mixture was heated at reflux under Dean-Stark conditions for 3 hours. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. Diethyl ether (200 ml) was added, and formation of crystals was observed upon standing. The crystals were filtered *in vacuo*. The mother liquors were concentrated *in vacuo* and additional diethyl ether (40 ml) was added. More crystals appeared which were filtered *in vacuo*. Both sets of crystals combined to give the title product (22.8 g, yield: 83%).

[000343] ^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 2.49 (dd, 1 H) 2.76 - 2.94 (m, 1 H) 4.24 (d, 1 H) 4.42 - 4.61 (m, 2 H) 5.03 - 5.24 (m, 3 H) 7.27 - 7.46 (m, 5 H).

[000344] LCMS: (ESI) m/z 234 $[\text{M-H}]^+$.

[000345] Optical rotation:

Concentration: 0.155 g/dL

Lamp: Sodium

Wavelength: 589 nm

Temperature: 20° C

Path length: 10 cm

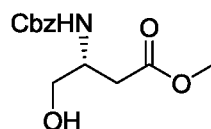
Cell volume: 1 ml

Solvent: CH_2Cl_2

$[\alpha] = +46$

INTERMEDIATE 4

[000346] (*R*)-methyl 3-(benzyloxycarbonylamino)-4-hydroxybutanoate

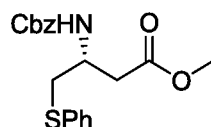


[000347] (*R*)-Benzyl 5-oxotetrahydrofuran-3-ylcarbamate (INTERMEDIATE 3, 27.0 g, 114.78 mmol) was dissolved in methanol (75 ml) and triethylamine (75 ml) was added at room temperature. The resulting mixture was allowed to stir overnight at this temperature. The mixture was concentrated *in vacuo* to provide the title product. This material was used to prepare INTERMEDIATE 5 without further purification.

[000348] ^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 2.67 (d, 2 H) 3.60 - 3.72 (m, 3 H) 3.70 - 3.78 (m, 1 H) 4.00 - 4.15 (m, 2 H) 5.03 - 5.18 (m, 2 H) 5.52 (br. s., 1 H) 7.28 - 7.42 (m, 5 H).

INTERMEDIATE 5

[000349] (*R*)-methyl 3-(benzyloxycarbonylamino)-4-(phenylthio)butanoate

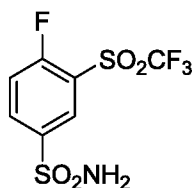


[000350] To a solution of benzenethiol (11.16 ml, 108.65 mmol), (*R*)-methyl 3-(benzyloxycarbonylamino)-4-hydroxybutanoate (INTERMEDIATE 4, 26.4 g, 98.77 mmol) and tributylphosphine (34.5 ml, 138.28 mmol) in anhydrous THF (350 ml) under nitrogen atmosphere was added. A solution of (*E*)-diazene-1,2-diylbis(piperidin-1-ylmethanone) (34.9 g, 138.22 mmol) in anhydrous THF (350 ml) was added dropwise over a 30 minute period. During the addition a white precipitate was formed and stirring was continued for 2 hours after the addition was complete. The white precipitate was filtered off and evaporation of the volatiles under reduced pressure gave a residue, which was purified by column chromatography (ISCO, eluting with 0→100% EtOAc/hexanes) to give the title product (25.0 g, yield: 70%).

[000351] ^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 2.59 - 2.73 (m, 1 H) 2.75 - 2.88 (m, 1 H) 3.04 - 3.19 (m, 1 H) 3.21 - 3.37 (m, 1 H) 3.57 - 3.69 (m, 3 H) 4.08 - 4.24 (m, 1 H) 5.00 - 5.14 (m, 2 H) 5.46 (br. s., 1 H) 7.14 - 7.48 (m, 10 H).

INTERMEDIATE 6

[000352] 4-fluoro-3-(trifluoromethylsulfonyl)benzenesulfonamide



[000353] A mixture of chlorosulfonic acid (49.3 ml, 736.31 mmol) and 1-fluoro-2-(trifluoromethylsulfonyl)benzene (60.0 g, 262.9 mg) was heated at 125 °C for 18 hours. The reaction mixture was allowed to cool to room temperature and then poured carefully onto 500 ml of crushed ice. The mixture was extracted with ethyl acetate (3 x 300 ml) and the combined organic layer was washed with water (300 ml), brine (300 ml), dried over sodium sulfate, and concentrated under reduced pressure. The concentrate was dissolved in isopropyl alcohol (1200 ml) and cooled to -65 °C. A solution of ammonium hydroxide (280 ml) was added at such rate so that the internal temperature did not rise above -60 °C. After the addition was completed, the reaction mixture was allowed to warm to 0 °C over ~1.5 hours. The solution was then cooled back to approximately -50 °C and acidified by the dropwise addition of concentrated HCl (240 ml) resulting in the formation of a white precipitate. The solid was filtered off and the filtrate was concentrated under reduced pressure to remove the volatiles. The resulting mixture was filtered and the combined collected solid was washed with water (~200 ml). The filtrate was

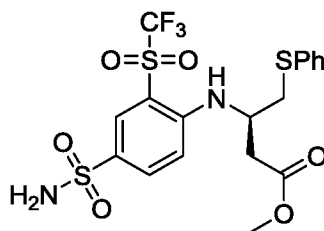
further extracted with EtOAc (2 x 250 ml) and the combined organic extracts were washed with water and brine, and dried over sodium sulfate and filtered. Concentration of the volatiles under reduced pressure gave an oil, which was crystallized from ethyl acetate/hexane to provide the title product (45.0 g, yield: 56%).

[000354] ^1H NMR (400 MHz, DMSO- d_6) δ ppm 7.70 - 7.90 (m, 2 H) 7.98 (dd, 1 H) 8.32 - 8.60 (m, 2 H).

[000355] LCMS: (ESI) m/z 306 $[\text{M}-\text{H}]^+$.

INTERMEDIATE 7

[000356] (*R*)-methyl 4-(phenylthio)-3-(4-sulfamoyl-2-(trifluoromethylsulfonyl)phenylamino)-butanoate



[000357] Step 1: A solution of (*R*)-methyl 3-(benzyloxycarbonylamino)-4-(phenylthio)butanoate (INTERMEDIATE 5, 25.6 g, 71.22 mmol), and TFA (200 ml) was heated at reflux for 1 hour. The excess reagent was removed under reduced pressure and the concentrate was azeotroped with 50 ml of DCM to give (*R*)-methyl 3-amino-4-(phenylthio)butanoate, trifluoroacetic acid salt, which was used in the preparation of INTERMEDIATE 7, STEP 2 without further purification.

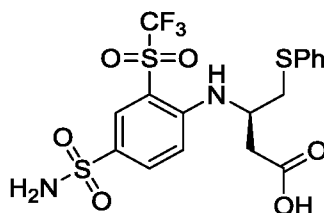
Step 2: 4-Fluoro-3-(trifluoromethylsulfonyl)benzenesulfonamide (INTERMEDIATE 6, 21.67 g, 71.22 mmol) and DIPEA (129 ml, 738 mmol) were added to a solution of (*R*)-methyl 3-amino-4-(phenylthio)butanoate, trifluoroacetic acid salt (INTERMEDIATE 7, STEP 2) in DMF (20 ml). The resulting reaction mixture was heated at 50 °C for 1.5 hours, allowed to cool to room temperature, diluted with ethyl acetate (500 ml), and washed with water (250 ml) and brine (250 ml). The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The concentrate was purified by column chromatography (ISCO, eluting with 0→30 % EtOAc/DCM over 54 minutes) to give the title product (20.5 g, yield: 56%).

[000358] ^1H NMR (300 MHz, CHLOROFORM- d) δ ppm 2.75 - 2.88 (m, 2 H) 3.06 - 3.20 (m, 2 H) 3.63 - 3.76 (m, 3 H) 4.04 - 4.21 (m, 1 H) 4.84 (s, 1 H) 6.55 (d, 1 H) 7.19 - 7.49 (m, 5 H) 7.85 (dd, 1 H) 8.28 (d, 1 H).

[000359] LCMS: (ESI) m/z 511 $[\text{M}-\text{H}]^+$.

INTERMEDIATE 8

[000360] (*R*)-4-(phenylthio)-3-(4-sulfamoyl-2-(trifluoromethylsulfonyl)phenylamino) butanoic acid



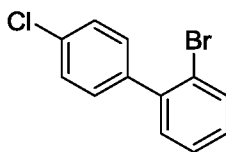
[000361] A 100 ml flask was charged with (*R*)-methyl 4-(phenylthio)-3-(4-sulfamoyl-2-(trifluoromethylsulfonyl)phenylamino)butanoate (INTERMEDIATE 7, 7.5 g, 14.63 mmol) and THF (117 ml), MeOH (39 ml) and water (39 ml) were added sequentially. LiOH (1.05 g, 43.9 mmol) was added to the solution and the reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure to remove the volatiles, and cooled to 0 °C. An aqueous solution of HCl (1N) was added dropwise to the solution and the resulting mixture was filtered. The filter cake was dried under high vacuum at 60 °C to provide the title product (6.8 g, yield: 93%).

[000362] ¹H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 2.70 - 3.02 (m, 2 H) 3.04 - 3.26 (m, 2 H) 4.01 - 4.20 (m, 1 H) 4.95 (s, 2 H) 6.54 (d, 1 H) 7.29 - 7.49 (m, 5 H) 7.85 (dd, 1 H) 8.26 (d, 1 H).

[000363] LCMS: (ESI) *m/z* 497 [M-H]⁺.

INTERMEDIATE 9

[000364] 2-bromo-4'-chlorobiphenyl



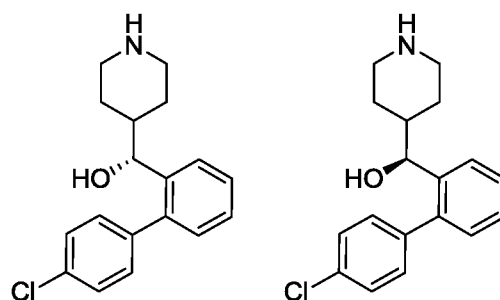
[000365] Sodium carbonate (19.8 g, 186.81 mmol) and tetrakis(triphenylphosphine)palladium(0) (1.05 g, 0.90 mmol) were added to a solution of 1,2-dibromobenzene (12.8 ml, 105.98 mmol) and 4-chlorophenylboronic acid (14.1 g, 90.08 mmol) in toluene (170 ml) and water (80 ml). The mixture was purged with nitrogen and heated at reflux overnight. The reaction mixture was allowed to cool to room temperature, and partitioned between saturated aq. NH₄Cl and ethyl acetate (500 ml). The organic layer was dried over MgSO₄, filtered and the volatiles were evaporated under reduced pressure to give a residue. The residue was purified by column chromatography (ISCO, 330g silica gel column, eluting with 100% hexanes) to give the title product (17.0 g, yield: 71 %).

[000366] ^1H NMR (400 MHz, DMSO- d_6) δ ppm 7.34 (td, 1 H) 7.37 - 7.45 (m, 3 H) 7.45 - 7.50 (m, 1 H) 7.50 - 7.56 (m, 2 H) 7.75 (d, 1 H).

[000367] GC-MS: 268 [M]

INTERMEDIATE 10

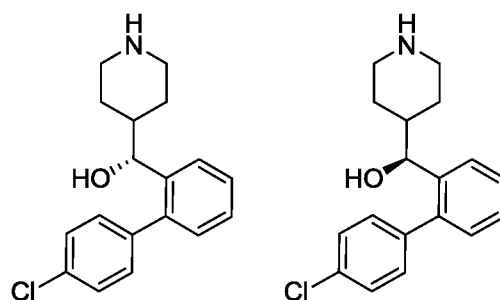
[000368] (*R*)-(4'-chlorobiphenyl-2-yl)(piperidin-4-yl)methanol and (*S*)-(4'-chlorobiphenyl-2-yl)(piperidin-4-yl)methanol, mixture of enantiomers



[000369] *n*-Butyl lithium (29.4 mL, 47.09 mmol) was added dropwise to a solution of 2-bromo-4'-chlorobiphenyl (INTERMEDIATE 9, 12 g, 44.85 mmol) in THF (220 ml) under nitrogen, at -78 °C. The resulting colored mixture was stirred at -78 °C for 30 minutes and a solution of *tert*-butyl 4-formylpiperidine-1-carboxylate (10.04 g, 47.09 mmol) in THF (15 ml) was added. The reaction mixture was allowed to warm to 0 °C during 3 hours and then was quenched with a solution of saturated aq. NH_4Cl . The aqueous layer was extracted with ethyl acetate (3 x) and the combined organic extracts and dried over MgSO_4 . The mixture was filtered and evaporation of the volatiles under reduced pressure gave a residue, which was purified by column chromatography (ISCO, 330g silica gel column, eluting with 0→40 % EtOAc/hexanes) to give *tert*-butyl 4-[(4'-chlorobiphenyl-2-yl)(hydroxy)methyl]piperidine-1-carboxylate as a mixture of enantiomers.

INTERMEDIATE 10A

[000370] (*R*)-(4'-chlorobiphenyl-2-yl)(piperidin-4-yl)methanol and (*S*)-(4'-chlorobiphenyl-2-yl)(piperidin-4-yl)methanol, mixture of enantiomers



[000371] As an alternate procedure to the preparations of INTERMEDIATE 10, (*R*)-(4'-

chlorobiphenyl-2-yl)(piperidin-4-yl)methanol and (S)-(4'-chlorobiphenyl-2-yl)(piperidin-4-yl)methanol, mixture of enantiomers, was prepared according to Steps 1 and 2 as follows.

[000372] Step 1: A heat-dried 50 ml round-bottom flask was charged, under nitrogen, with *i*-PrMgCl/LiCl complex (1.3 M in THF, 12.0 ml, 15.6 mmol). The flask was cooled to approximately -15 °C and 2-bromo-4'-chlorobiphenyl (INTERMEDIATE 9, 4.01 g, 14.99 mmol) was added. The resulting mixture was stirred at -15 °C for 1 hour, then at 0 °C for 2.5 hours and was then allowed to warm up to room temperature overnight. The reaction mixture cooled to 0 °C and *tert*-butyl 4-formylpiperidine-1-carboxylate (3.53 g, 16.35 mmol) in THF (5.0 ml) was added dropwise over approximately 5 minutes and the resulting mixture was allowed to stir for 90 minutes at this temperature. The reaction mixture was quenched by the addition of saturated aq. NH₄Cl (30 ml) and extracted with EtOAc (4 x 60 ml). The organic layer was dried (MgSO₄), filtered, and evaporated under reduced pressure. The concentrate was purified by column chromatography (ISCO, 120 g silica gel column, eluting with 100% hexanes → 50% EtOAc/hexanes and subsequently with 0 → 3% MeOH/DCM) to give (*R*)-*tert*-butyl 4-((4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidine-1-carboxylate and (*S*)-*tert*-butyl 4-((4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidine-1-carboxylate, mixture of enantiomers (2.04 g, yield: 43%).

[000373] ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.61 (qd, 1 H) 0.81 - 0.96 (m, 2 H) 1.33 (s, 9 H) 1.50 - 1.63 (m, 1 H) 1.74 - 1.85 (m, 1 H) 3.63 - 3.78 (m, 1 H) 3.81 - 3.93 (m, 1 H) 4.28 (dd, 1 H) 5.21 (d, 1 H) 7.12 (d, 1 H) 7.26 - 7.38 (m, 3 H) 7.41 (t, 1 H) 7.50 (d, 2 H) 7.56 (d, 1 H).

[000374] LCMS: (ESI) *m/z* 424 [M+Na]⁺

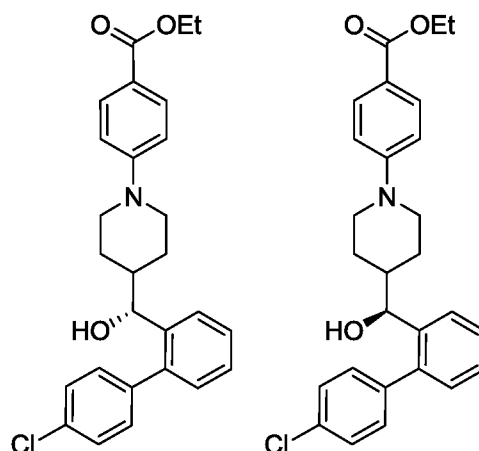
[000375] Step 2: (*R*)-*tert*-butyl 4-((4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidine-1-carboxylate and (*S*)-*tert*-butyl 4-((4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidine-1-carboxylate, mixture of enantiomers (INTERMEDIATE 10, STEP 1, 1.0 g, 2.49 mmol) were dissolved in DCM (10.0 ml) and MeOH (0.4 ml) and treated with TFA (10.0 ml) at room temperature. The resulting mixture was stirred at this temperature for 40 minutes and the volatiles were evaporated under reduced pressure. The residue was dissolved in EtOAc (50 ml), washed with saturated aq. sodium bicarbonate (100 ml) and water (50 ml), dried (MgSO₄), filtered, and evaporated under vacuum to give the title product (701 mg, yield: 92%) as clear gum, which crystallized upon standing.

[000376] ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.59 (qd, 1 H) 0.75 - 0.94 (m, 2 H) 1.40 - 1.53 (m, 1 H) 1.71 - 1.83 (m, 1 H) 2.15 (td, 1 H) 2.22 - 2.35 (m, 1 H) 2.61 - 2.71 (m, 1 H) 2.77 - 2.87 (m, 1 H) 4.25 (dd, 1 H) 5.08 (d, 1 H) 7.11 (d, 1 H) 7.25 - 7.31 (m, 1 H) 7.31 - 7.37 (m, 2 H) 7.40 (t, 1 H) 7.47 - 7.52 (m, 2 H) 7.54 (d, 1 H).

[000377] LCMS: (ESI) *m/z* 302 [M+H]⁺.

INTERMEDIATE 11

[000378] (*R*)-Ethyl 4-(4-((4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoate and (*S*)-ethyl 4-(4-((4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoate



[000379] DIPEA (11 ml, 63 mmol) was added into a solution of (4'-chlorobiphenyl-2-yl)(piperidin-4-yl)methanol (INTERMEDIATE 10, 6.41g, 21.24 mmol) and ethyl 4-fluorobenzoate (6.25 ml, 42.59 mmol) in dry DMSO (25 ml). The resulting solution was heated at 120 °C for 20 hours, and more triethylamine (12.2 ml, 87.67 mmol) was added. The solution was heated at 120 °C for additional 24 hours and then partitioned between ethyl acetate (500 ml) and saturated aq. NH₄Cl solution (250 ml). The organic layer was washed with water, dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford a residue. This residue was purified by column chromatography (ISCO, 120 g silica column, eluting with 0→65% EtOAc/hexanes) to give the title product (5.12 g, yield: 54%) as a mixture of enantiomers.

[000380] The R and S enantiomers of the title product were separated using Chiral SFC, (Chiralpak IA column).

Column dimensions: 21 x 250 mm, 5 μ

Modifier: 35% Isopropanol

Flow rate (ml/min): 60

Outlet Pressure (bar): 100

Detection (nm): 220

INTERMEDIATE 11A (First Eluting Compound)

[000381] (*R*)-ethyl 4-(4-((4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoate

[000382] The first eluting compound had a retention time of 4.97 minutes.

[000383] ¹H NMR (400 MHz, DMSO-d₆) δ ppm 0.84 (qd, 1 H) 0.98 - 1.17 (m, 2 H) 1.27 (t, 3 H) 1.60 - 1.73 (m, 1 H) 1.85 - 1.95 (m, 1 H) 2.52 - 2.61 (m, 1 H) 2.63 - 2.74 (m, 1 H) 3.64 - 3.73

(m, 1 H) 3.80 - 3.90 (m, 1 H) 4.21 (q, 2 H) 4.31 (dd, 1 H) 5.23 (d, 1 H) 6.85 (d, 2 H) 7.14 (dd, 1 H) 7.28 - 7.38 (m, 3 H) 7.43 (td, 1 H) 7.46 - 7.52 (m, 2 H) 7.56 - 7.62 (m, 1 H) 7.71 (d, 2 H).

[000384] LCMS: (ESI) m/z 450 $[M+H]^+$.

[000385] Optical rotation:

Concentration: 0.1 g/dL

Lamp: Sodium

Wavelength: 589 nm

Temperature: 20° C

Path length: 10 cm

Cell volume: 1 ml

Solvent: DCM

$[\alpha] = +107$

INTERMEDIATE 11B (Second Eluting Compound)

[000386] (S)-ethyl 4-(4-((4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoate

[000387] The second eluting compound had a retention time of 6.72 minutes.

[000388] ^1H NMR (400 MHz, DMSO- d_6) δ ppm 0.84 (qd, 1 H) 0.98 - 1.17 (m, 2 H) 1.27 (t, 3 H) 1.61 - 1.73 (m, 1 H) 1.85 - 1.94 (m, 1 H) 2.52 - 2.61 (m, 1 H) 2.63 - 2.74 (m, 1 H) 3.65 - 3.73 (m, 1 H) 3.80 - 3.89 (m, 1 H) 4.21 (q, 2 H) 4.31 (dd, 1 H) 5.23 (d, 1 H) 6.85 (d, 2 H) 7.14 (dd, 1 H) 7.28 - 7.38 (m, 3 H) 7.43 (td, 1 H) 7.46 - 7.52 (m, 2 H) 7.56 - 7.62 (m, 1 H) 7.71 (d, 2 H).

[000389] LCMS: (ESI) m/z 450 $[M+H]^+$.

[000390] Optical rotation:

Concentration: 0.1 g/dL

Lamp: Sodium

Wavelength: 589 nm

Temperature: 20° C

Path length: 10 cm

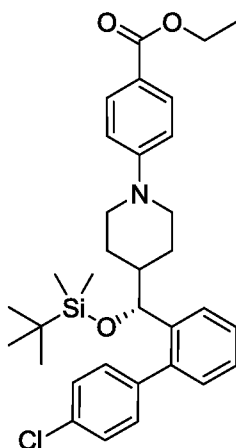
Cell volume: 1 ml

Solvent: DCM

$[\alpha] = -116$

INTERMEDIATE 12

[000391] (R)-Ethyl 4-(4-((*tert*-butyldimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)benzoate



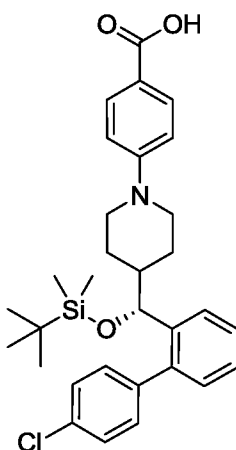
[000392] 2,6-Lutidine (1.128 ml, 9.68 mmol) was added to a solution of (R)-ethyl 4-(4-((4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoate (INTERMEDIATE 11A (First Eluting Compound), 1.74 g, 3.87 mmol) in DCM (10 ml) at 0 °C. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (1.3 ml, 5.81 mmol) was added dropwise via syringe at 0 °C and the resulting mixture was allowed to warm up to room temperature for 10 minutes. Evaporation of the volatiles under reduced pressure gave a residue, which was purified by column chromatography (ISCO, 80 g silicon column, eluting with 0→10% EtOAc/hexanes) to give the title product (2.1 g, yield: almost quantitative).

[000393] ^1H NMR (400 MHz, CHLOROFORM- d) δ ppm -0.23 (s, 3 H) -0.06 (s, 3 H) 0.86 (s, 9 H) 1.22 - 1.48 (m, 6 H) 1.73 - 1.83 (m, 1 H) 2.53 - 2.70 (m, 2 H) 3.70 - 3.78 (m, 1 H) 3.80 - 3.89 (m, 1 H) 4.32 (q, 2 H) 4.56 - 4.65 (m, 1 H) 6.82 (d, 2 H) 7.10 - 7.15 (m, 1 H) 7.22 (d, 2 H) 7.28 - 7.33 (m, 1 H) 7.36 - 7.43 (m, 3 H) 7.59 (d, 1 H) 7.89 (d, 2 H).

[000394] LCMS: (ESI) m/z 564 $[\text{M}+\text{H}]^+$.

INTERMEDIATE 13

[000395] (*R*)-4-(4-((*tert*-Butyldimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)benzoic acid



[000396] Lithium hydroxide (1.42 g, 59.29 mmol) was added to a mixture of (*R*)-ethyl 4-(4-

((*tert*-butyldimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)benzoate

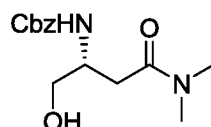
(INTERMEDIATE 12, 3.83 g, 6.78 mmol) in THF (27 ml), MeOH (9 ml) and water (1 ml). The resulting mixture was stirred at room temperature overnight and then the volatiles were removed under reduced pressure. The concentrate was purified by column chromatography (ISCO, 80g silica column, eluting with 0→80 % EtOAc/hexanes) to give the title product (3.24 g, yield: 89%).

[000397] ^1H NMR (400 MHz, DICHLOROMETHANE- d_2) δ ppm -0.23 (s, 3 H) -0.06 (s, 3 H) 0.85 (s, 9 H) 1.19 - 1.49 (m, 3 H) 1.52 - 1.64 (m, 1 H) 1.70 - 1.80 (m, 1 H) 2.57 - 2.73 (m, 2 H) 3.75 - 3.84 (m, 1 H) 3.85 - 3.94 (m, 1 H) 4.61 (d, $J=4.80$ Hz, 1 H) 6.82 (d, $J=9.09$ Hz, 2 H) 7.13 (dd, $J=7.58$, 1.26 Hz, 1 H) 7.24 (d, $J=8.34$ Hz, 2 H) 7.30 (td, $J=7.45$, 1.52 Hz, 1 H) 7.35 - 7.45 (m, 3 H) 7.60 (d, $J=7.83$ Hz, 1 H) 7.85 - 7.92 (m, 2 H).

[000398] LCMS: m/z 536 $[\text{M}+\text{H}]^+$.

INTERMEDIATE 14

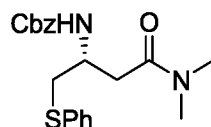
[000399] (*R*)-Benzyl 4-(dimethylamino)-1-hydroxy-4-oxobutan-2-ylcarbamate



[000400] A solution of (*R*)-benzyl-5-oxotetrahydrofuran-3-ylcarbamate (INTERMEDIATE 3, 18.4 g, 7.8 mmol) in THF (100 ml) was purged, at room temperature, with gaseous dimethylamine for 5 minutes. After stirring at room temp for 14 hours, the reaction mixture was concentrated to dryness, and purified by column chromatography (silica gel, eluting first with 50% ethyl acetate/hexanes followed by 100% acetone) to give the title product (20 g, yield: 91.5 %).

INTERMEDIATE 15

[000401] (*R*)-Benzyl 4-(dimethylamino)-4-oxo-1-(phenylthio)butan-2-ylcarbamate



[000402] Diphenyl disulfide (55.8 g, 0.3 mol) and Bu_3P (75 ml, 0.3 mol) were added sequentially to a solution of (*R*)-benzyl 4-(dimethylamino)-1-hydroxy-4-oxobutan-2-ylcarbamate (INTERMEDIATE 14, 48 g, 0.17 mol) in toluene (100 ml). The resulting mixture was heated at 80 °C for 8 hours. The reaction mixture was allowed to cool to room temperature and the volatiles were removed *in vacuo*. The residue was purified by column chromatography (silica

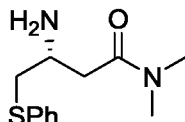
gel, 7 cm height x 14 cm width, eluting with hexanes followed by 10:1, 2:1 then 1:1 hexanes/ethyl acetate) to yield the title product (40 g, yield: 63%).

[000403] $^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ 2.59 (m, 2H), 2.79 (s, 3H), 2.89 (s, 3H), 3.12 (m, 2H), 4.71 (m, 1H), 4.02 (m, 1H), 5.01 (s, 2H), 7.18 (t, 1H), 7.26-7.41 (m, 10H).

[000404] LCMS (ESI) m/z 373 ($\text{M}+\text{H}$) $^+$.

INTERMEDIATE 16

[000405] (*R*)-3-amino-*N,N*-dimethyl-4-(phenylthio)butanamide



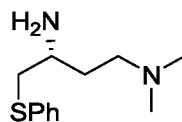
[000406] A suspension of (*R*)-benzyl 4-(dimethylamino)-4-oxo-1-(phenylthio)butan-2-ylcarbamate (INTERMEDIATE 15, 40 g, 0.10 mol) in 40 % HBr in acetic acid (100 ml) was stirred at room temperature for 16 hours and the reaction mixture became homogeneous during this time. The mixture was concentrated to dryness, diluted with water (200 ml) and AcOH (200 ml) and washed with diethyl ether (3x 50 ml). The aqueous phase was brought to approximately pH 8-9 with solid Na_2CO_3 and was extracted with CH_2Cl_2 (5x). The combined organic phases were dried (MgSO_4) and concentrated under reduced pressure to give the title product (15 g, 59 %) that was used in the preparation of INTERMEDIATE 17 without further purification.

[000407] $^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ 2.37 (dd, 1H), 2.51 (dd, 1H), 2.79 (s, 3H), 2.89 (dd, 1H), 2.91 (s, 3H), 3.05-3.20 (m, 2H), 3.32 (m, 2H), 7.16 (t, 1H), 7.30 (dd, 2H), 7.35 (d, 2H).

[000408] LCMS (ESI) m/z 239 ($\text{M}+\text{H}$) $^+$.

INTERMEDIATE 17

[000409] (3*R*)-4-*N,N*-dimethylamine-1-(phenylthio)butan-2-amine



[000410] A solution of (*R*)-3-amino-*N,N*-dimethyl-4-(phenylthio)butanamide (INTERMEDIATE 16, 1.0 g, 4.2 mmol) in THF (30 ml) was treated, dropwise via an addition funnel, with a solution of $\text{BH}_3\cdot\text{THF}$ complex (16 ml, 1 M solution in THF, 16 mmol). The resulting dark solution was stirred at room temperature overnight. The mixture was cooled to 0 °C and treated dropwise with 5 ml MeOH, resulting in vigorous gas evolution. After gas evolution had ceased, the reaction mixture was concentrated to dryness, reconstituted in MeOH (35 ml) and concentrated HCl (5 ml) and brought to reflux for 4 hours. The reaction mixture was allowed to cool to room temperature, was concentrated to dryness and partitioned between

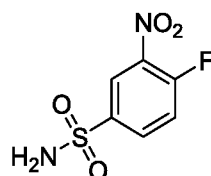
saturated aqueous NaHCO₃ and CH₂Cl₂. The aqueous phase was extracted with CH₂Cl₂ (3x) and the combined organic phases were washed with saturated aqueous NaHCO₃, brine, dried (MgSO₄) and concentrated under reduced pressure. Concentration of the volatiles under reduced pressure gave a residue that was purified by column chromatography (silica gel, eluting with a step gradient of CH₂Cl₂ saturated with NH₃(g), 5% MeOH in CH₂Cl₂ saturated with NH₃(g), 10% MeOH/CH₂Cl₂ saturated with NH₃(g) by 13% MeOH/CH₂Cl₂ saturated with NH₃(g)) to yield the title product (0.3 g, yield: 32 %).

[000411] ¹H-NMR (300 MHz, DMSO-d₆) δ 1.31 (m, 1 H), 1.64 (m, 1 H), 2.08 (m, 6 H), 2.25 (m, 2 H), 2.78 (m, 1 H), 2.98 (m, 1 H), 7.17 (m, 1 H), 7.35 (m, 4 H).

[000412] LCMS (ESI) *m/z* 225 (M+H)⁺.

INTERMEDIATE 18

[000413] 4-fluoro-3-nitrobenzenesulfonamide



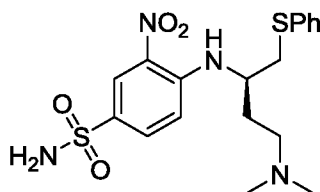
[000414] A solution of 2-fluoronitrobenzene (14.1 g, 0.10 mol) in chlorosulfonic acid (30 ml) was heated at 80 °C for 10 hours. After the reaction mixture was cooled to room temperature, it was carefully poured onto ice (about 100 g) in a 500 ml of Erlenmeyer flask cooled efficiently by ice. The resulting mixture was extracted with diethyl ether (2 x 200 ml), and the combined organic extracts concentrated under reduced pressure. The residue was dissolved in 70 ml 1:1 (v/v) THF/CH₂Cl₂, cooled to -78 °C and treated carefully with concentrated ammonium hydroxide (7.5 ml). The cold mixture was poured into 5 M aq. HCl (50 ml), the layers separated, the aqueous phase was extracted with ethyl acetate (2 x 200 ml) and the combined organic phases were washed with the 4 M aq. HCl, brine, and dried (MgSO₄). Removal of the volatiles under reduced pressure gave a solid. The resulting solid was re-crystallized from ethyl acetate and hexanes to give the title compound (15 g, 70 %).

[000415] ¹HNMR (300 MHz, DMSO-*d*₆) 8.53 (dd, 1H), 8.20 (ddd, 1H), 7.87 (dd, 1H), 7.72 (s, 2H).

[000416] LCMS (ESI) *m/z* 219 (M-H)⁻.

INTERMEDIATE 19

[000417] (*R*)-4-(4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrobenzenesulfonamide



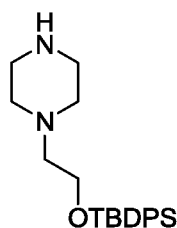
[000418] A solution of (*R*)-N¹, N¹-dimethylamine-4-(phenylthio)butane-1,3-diamine (INTERMEDIATE 17, 25 mg, 0.11 mmol) in DMF (5 ml) and DIPEA (0.01 ml) was treated with 4-fluoro-3-nitrobenzenesulfonamide (INTERMEDIATE 18, 24.9 mg, 0.11 mmol) in one portion and the resulting mixture was stirred at room temperature overnight. The reaction mixture was poured into water and extracted with EtOAc (2x 50 ml). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, eluting with a step gradient of CH₂Cl₂ saturated with NH₃(g), 5% MeOH in CH₂Cl₂ saturated with NH₃(g), 10% MeOH/CH₂Cl₂ saturated with NH₃(g) by 13 % MeOH/CH₂Cl₂ saturated with NH₃(g)) to yield the title product (31 mg, yield: 66%) after re-crystallization from EtOAc.

[000419] ¹H-NMR (300 MHz, DMSO-d₆) δ 1.83 (m, 1 H), 1.95 (m, 1 H), 2.11 (s, 6 H), 2.21 (m, 1 H), 2.43 (m, 1 H), 3.30 (br m, 2 H), 3.39 (m, 2 H), 4.10 (m, 1 H), 7.06 (d, 1 H), 7.17 (t, 2H), 7.25 (dd, 2 H), 7.30 (d, 2 H), 7.70 (dd, 1 H), 8.38 (d, 1 H), 8.62 (d, 1 H).

[000420] LCMS (ESI) *m/z* 425 (M+H)⁺.

INTERMEDIATE 20

[000421] 1-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)piperazine



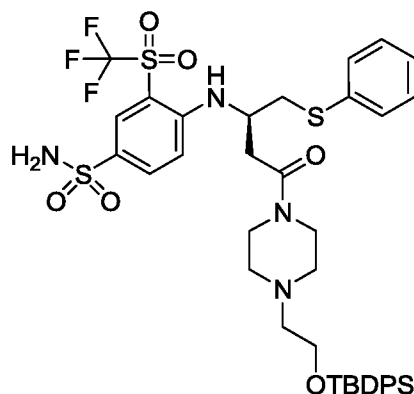
[000422] 2-(Piperazin-1-yl)ethanol (1.000 g, 7.68 mmol) was dissolved in DCM (35.1 ml) and pyridine (0.932 ml, 11.52 mmol) followed by DMAP (0.094 g, 0.77 mmol) were added. *tert*-butylchlorodiphenylsilane (2.368 ml, 9.22 mmol) was added to the solution and the reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure and the concentrate was purified by column chromatography (ISCO, eluting with 10% MeOH/DCM) to give the title product (2.73 g, yield: 96 %).

[000423] LCMS: (ESI) *m/z* 369 [M+H]⁺.

INTERMEDIATE 21

[000424] (*R*)-4-(4-(4-(2-(*tert*-butyldiphenylsilyloxy)ethyl)piperazin-1-yl)-4-oxo-1-

(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

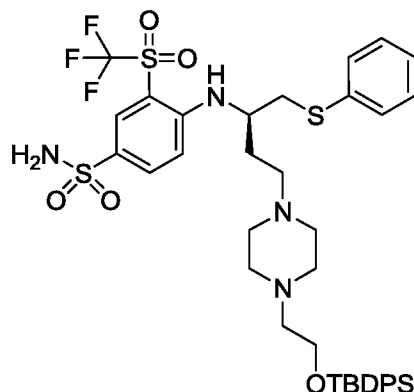


[000425] HATU (0.915 g, 2.41 mmol) and DIPEA (0.701 ml, 4.01 mmol) were added sequentially to a solution of (*R*)-4-(phenylthio)-3-(4-sulfamoyl-2-(trifluoromethylsulfonyl)phenylamino) butanoic acid (INTERMEDIATE 8, 1.0 g, 2.01 mmol) and 1-(2-(*tert*-butyldiphenylsilyloxy)ethyl)piperazine (INTERMEDIATE 20, 0.894 g, 2.21 mmol) in DMA (2.0 ml). Additional DMA (1.7 ml) was added and the resulting mixture was stirred at room temperature for 2 hrs. The mixture was diluted with EtOAc and the organic layer was washed with H₂O (2x), 1N NaHSO₄ (aq.) and saturated aq. NaHCO₃. The organic layer was dried (Na₂SO₄), and concentrated under reduced pressure to provide the title product (2.0 g, yield: quantitative), which was used in the preparation of INTERMEDIATE 22 without further purification.

[000426] LCMS: (ESI) *m/z* 849 [M+H]⁺.

INTERMEDIATE 22

[000427] (*R*)-4-(4-(4-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)piperazin-1-yl)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide



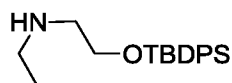
[000428] (*R*)-4-(4-(4-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)piperazin-1-yl)-4-oxo-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide (INTERMEDIATE 21, 0.98 g, 1.15 mmol) was dissolved in THF (4.6 ml), under a nitrogen atmosphere, and a solution of borane-THF complex (1M in THF; 6.93 ml, 6.93 mmol) was

added. The mixture was diluted with NH_3 in MeOH (7N, 20 ml) and stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, diluted with EtOAc (75 ml), washed with water (40 ml), and dried (Na_2SO_4). Evaporation of the volatiles under reduced pressure afforded a concentrate, which was purified by column chromatography (ISCO, 40 g silica gel column, eluting with 0→100% EtOAc/ hexanes) to provide the title compound (245 mg, yield: 25%).

[000429] LCMS: (ESI) m/z 835 $[\text{M}+\text{H}]^+$.

INTERMEDIATE 23

[000430] 2-(*tert*-butyldiphenylsilyloxy)-*N*-ethylethanamine

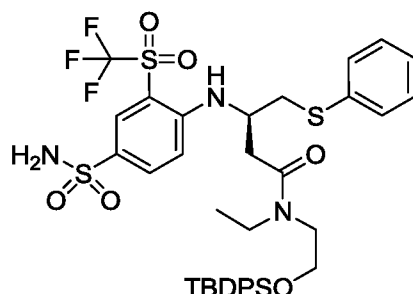


[000431] Imidazole (1.53 g, 22.44 mmol) and a solution of *tert*-butylchlorodiphenylsilane (4.63 g, 16.83 mmol) in DCM (10 ml) were added sequentially to a solution of 2-(ethylamino)ethanol (1.099 ml, 11.22 mmol) in DCM (30 ml) and the resulting reaction mixture was stirred at room temperature overnight. The mixture was diluted with DCM and washed with 1N aq. NaHSO_4 and saturated aq. NaHCO_3 . The organic layer was dried (Na_2SO_4), concentrated under reduced pressure to give a residue which was purified by column chromatography (ISCO, 40 g silica gel column, eluting with 0→100% EtOAc/ hexanes) to provide the title compound (2.95 g, yield: 80 %).

[000432] LCMS: (ESI) m/z 328 $[\text{M}+\text{H}]^+$.

INTERMEDIATE 24

[000433] (*R*)-*N*-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-*N*-ethyl-4-(phenylthio)-3-(4-sulfamoyl-2-(trifluoromethylsulfonyl)phenylamino)butanamide



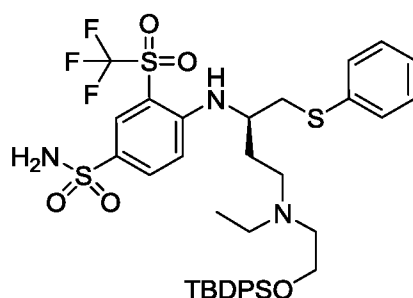
[000434] 2-(*tert*-Butyldiphenylsilyloxy)-*N*-ethylethanamine (INTERMEDIATE 23, 0.263 g, 0.80 mmol) in THF (2.5 ml), diethyl 4-oxobenzo[d][1,2,3]triazin-3(4H)-yl phosphate (0.480 g, 1.60 mmol) and DIPEA (0.280 ml, 1.60 mmol) were added sequentially to a solution of (*R*)-4-(phenylthio)-3-(4-sulfamoyl-2-(trifluoromethylsulfonyl)phenylamino)butanoic acid

(INTERMEDIATE 8, 0.4 g, 0.80 mmol) in THF (5.0 ml) and the mixture was stirred at room temperature for 3 hrs. The reaction mixture was then concentrated under reduced pressure, diluted with EtOAc and the organic layer was washed with 1N aq. NaHSO₄ and saturated aq. NaHCO₃. The organic layer was dried (Na₂SO₄), concentrated under reduced pressure to give a residue, which was purified by column chromatography (ISCO, 40 g silica gel column, eluting with 0→100% EtOAc/ hexanes) to provide the title product (590 mg, yield: 91%).

[000435] LCMS: (ESI) m/z 808 [M+H]⁺.

INTERMEDIATE 25

[000436] (*R*)-4-(4-((2-(*tert*-butyldiphenylsilyloxy)ethyl)(ethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

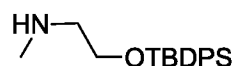


[000437] (*R*)-*N*-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)-*N*-ethyl-4-(phenylthio)-3-(4-sulfamoyl-2-(trifluoromethylsulfonyl)phenylamino)butanamide (INTERMEDIATE 24, 0.59 g, 0.73 mmol) was dissolved in THF (4.6 ml), under a nitrogen atmosphere, and a solution of borane-THF complex (1M in THF; 2.2 ml, 2.2 mmol) was added and the resulting solution was stirred at ambient temperature overnight. An additional solution of borane-THF complex (1M in THF; 2.2 ml, 2.2 mmol) was added. The resulting mixture was stirred at ambient for further 6 hrs. The mixture was diluted with NH₃ in MeOH (7N, 20 ml) and stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, diluted with EtOAc (75 ml), washed with water (40 ml), and dried (Na₂SO₄). Evaporation of the volatiles under reduced pressure afforded a concentrate, which was purified by column chromatography (ISCO, 40 g silica gel column, eluting with 0→100% EtOAc/ hexanes) to provide the title compound (280 mg, yield: 48%).

[000438] LCMS: (ESI) m/z 796 [M+H]⁺.

INTERMEDIATE 26

[000439] 2-(*tert*-Butyldiphenylsilyloxy)-*N*-methylethanamine



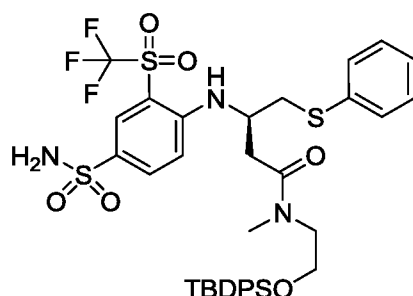
[000440] The title compound (4.1 g, yield: 49%) was prepared using a procedure similar to the

one described for the synthesis of INTERMEDIATE 23 utilizing 2-(methylamino)ethanol (2.0 g, 26.6 mmol) as starting material. The title product was purified by column chromatography (ISCO, 40 g silica gel column, eluting with 0→100 % DCM/ 10% MeOH in DCM with 1% NH₄OH).

[000441] LCMS: (ESI) m/z 314 [M+H]⁺.

INTERMEDIATE 27

[000442] (*R*)-N-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-*N*-methyl-4-(phenylthio)-3-(4-sulfamoyl-2-(trifluoromethylsulfonyl)phenylamino)butanamide

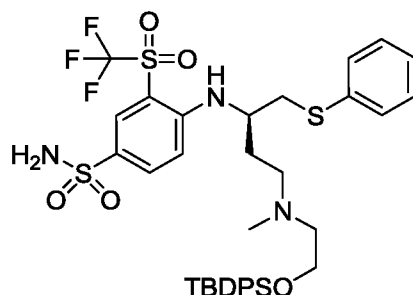


[000443] The title product (590 mg, yield: 93%) was prepared using a procedure similar to the one described for the synthesis of INTERMEDIATE 24 utilizing (*R*)-4-(phenylthio)-3-(4-sulfamoyl-2-(trifluoromethylsulfonyl)phenylamino)butanoic acid (INTERMEDIATE 8, 400 mg, 0.8 mmol) and 2-(*tert*-butyldiphenylsilyloxy)-*N*-methylethanamine (INTERMEDIATE 26, 251 mg, 0.8 mmol) as starting materials. The title product was purified by column chromatography (ISCO, 12 g silica gel column, eluting with 0→100 % EtOAc/hexanes).

[000444] LCMS: (ESI) m/z 794 [M+H]⁺.

INTERMEDIATE 28

[000445] (*R*)-4-(4-((2-(*tert*-butyldiphenylsilyloxy)ethyl)(methyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide



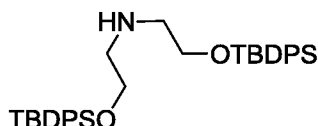
[000446] The title compound (230 mg, yield: 40%) was prepared using a procedure similar to the one described for the synthesis of INTERMEDIATE 25 utilizing (*R*)-N-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-*N*-methyl-4-(phenylthio)-3-(4-sulfamoyl-2-

(trifluoromethylsulfonyl)phenylamino)butanamide (INTERMEDIATE 27, 590 mg, 0.74 mmol) as starting material. The title compound was purified by column chromatography (ISCO, 12 g silica gel column, eluting with 0→100 % EtOAc/hexanes).

[000447] LCMS: (ESI) m/z 780 $[M+H]^+$.

INTERMEDIATE 29

[000448] Bis(2-(*tert*-butyldiphenylsilyloxy)ethyl)amine

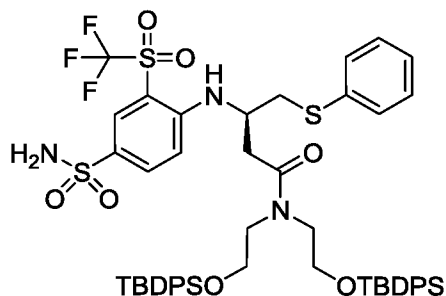


[000449] The title compound (4.8 g, yield: 87%) was prepared using a procedure similar to the one described for the synthesis of INTERMEDIATE 23 utilizing 2,2'-azanediethanol (1.0 g, 9.51 mmol) as starting material. The title product was purified by column chromatography (ISCO, 40 g silica gel column, eluting with 0→50 % EtOAc/hexanes).

[000450] LCMS: (ESI) m/z 582 $[M+H]^+$.

INTERMEDIATE 30

[000451] (*R*)-*N,N*-Bis(2-(*tert*-butyldiphenylsilyloxy)ethyl)-4-(phenylthio)-3-(4-sulfamoyl-2-(trifluoromethylsulfonyl)phenylamino)butanamide

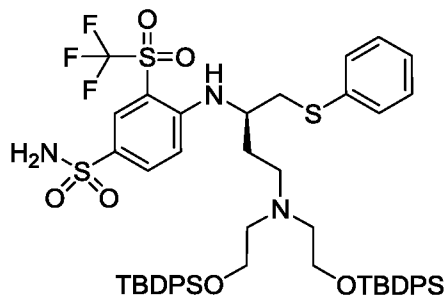


[000452] The title product (1.06 g, yield: 83%) was prepared using a procedure similar to the one described for the synthesis of INTERMEDIATE 24 utilizing (*R*)-4-(phenylthio)-3-(4-sulfamoyl-2-(trifluoromethylsulfonyl)phenylamino)butanoic acid (INTERMEDIATE 8, 600 mg, 1.2 mmol) and bis(2-(*tert*-butyldiphenylsilyloxy)ethyl)amine (INTERMEDIATE 29, 0.700 g, 1.20 mmol) as starting materials. The title product was purified by column chromatography (ISCO, 40 g silica gel column, eluting with 0→100% EtOAc/hexanes).

[000453] LCMS: (ESI) m/z 1062 $[M+H]^+$.

INTERMEDIATE 31

[000454] (*R*)-4-(4-(Bis(2-(*tert*-butyldiphenylsilyloxy)ethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

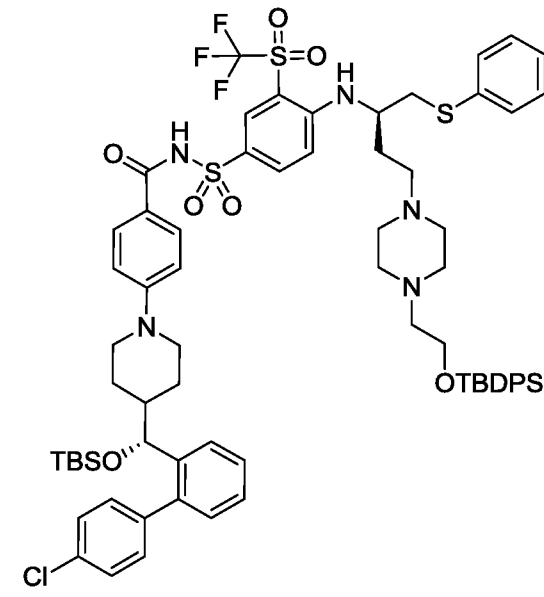


[000455] The title product (800 mg, yield: 77 %) was prepared using a procedure similar to the one described for the synthesis of INTERMEDIATE 25 utilizing (*R*)-*N,N*-bis(2-(*tert*-butyldiphenylsilyloxy)ethyl)-4-(phenylthio)-3-(4-sulfamoyl-2-(trifluoromethylsulfonyl)phenylamino)butanamide (INTERMEDIATE 30, 1.05 g, 0.99 mmol) as starting material. The title product was purified by column chromatography (ISCO, 40 g silica gel column, eluting with 0→50 % EtOAc/hexanes).

[000456] LCMS: (ESI) m/z 1048 $[M+H]^+$.

INTERMEDIATE 32

[000457] 4-(4-((*R*)-(2-(*tert*-butyldimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-(4-(2-(*tert*-butyldiphenylsilyloxy)ethyl)piperazin-1-yl)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide



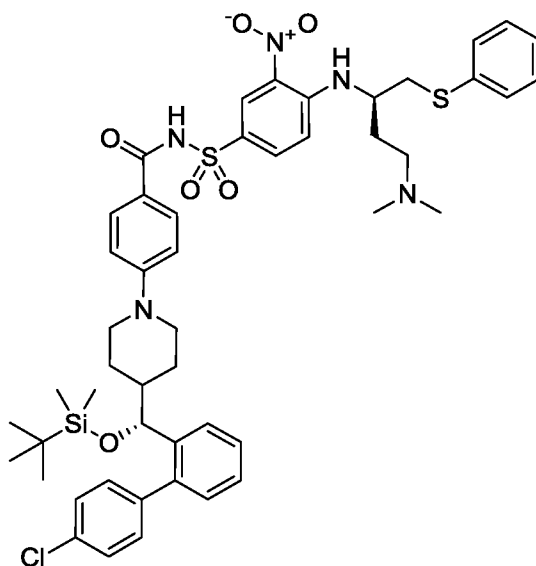
[000458] (*R*)-4-(4-((*tert*-butyldimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)benzoic acid (INTERMEDIATE 13, 56.5 mg, 0.11 mmol), (*R*)-4-(4-(4-(2-(*tert*-butyldiphenylsilyloxy)ethyl)piperazin-1-yl)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide (INTERMEDIATE 22, 80 mg, 0.1 mmol), DMAP (35.1 mg, 0.29 mmol), and EDC (36.7 mg, 0.19 mmol) were placed in a 50 ml flask and flushed with nitrogen. DCM (0.96 ml) was added, and the solution was stirred at room temperature

overnight. The reaction mixture was diluted with DCM (40 ml) and washed with 1N sodium bisulfate (35 ml) followed by a saturated aq. sodium bicarbonate (40 ml). The organic layer was dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give the title product (147 mg, yield: quantitative), that was used in the preparation of EXAMPLE 1 without further purification.

[000459] LCMS: (ESI) m/z 1354 $[\text{M}+\text{H}]^+$.

INTERMEDIATE 33

[000460] 4-(4-((*R*)-(tert-butyl)dimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfonyl)benzamide



[000461] The title product (162.8 mg, yield: 32%) was prepared using a procedure similar to the one described for the synthesis of INTERMEDIATE 32 utilizing (*R*)-4-(4-((tert-butyl)dimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)benzoic acid (INTERMEDIATE 13, 249.6 mg, 0.47 mmol) and (*R*)-4-(4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrobenzenesulfonamide (INTERMEDIATE 19, 208.8 mg, 0.49 mmol). The title product was purified by column chromatography (ISCO, 12 g silica gel column, eluting with 0→10 % MeOH/DCM).

[000462] ^1H NMR (300 MHz, $\text{DICHLOROMETHANE-}d_2$) δ ppm -0.24 (s, 3 H) -0.07 (s, 3 H) 0.86 (s, 9 H) 1.47 - 1.62 (m, 1 H) 1.68 - 1.81 (m, 1 H) 2.04 - 2.18 (m, 1 H) 2.43 (s, 6 H) 2.50 - 2.77 (m, 4 H) 3.15 (d, $J=5.84$ Hz, 2 H) 3.65 - 3.87 (m, 2 H) 4.07 (s, 1 H) 4.60 (d, 1 H) 6.68 - 6.82 (m, 3 H) 7.08 - 7.45 (m, 12 H) 7.54 - 7.63 (m, 1 H) 7.70 (d, 2 H) 7.75 - 7.84 (m, 1 H) 8.64 (s, 2 H).

[000463] LCMS: m/z 942 $[\text{M}+\text{H}]^+$.

[000464] Optical rotation:

Concentration: 0.1 g/dL

Lamp: Sodium

Wavelength: 589 nm

Temperature: 20° C

Path length: 10 cm

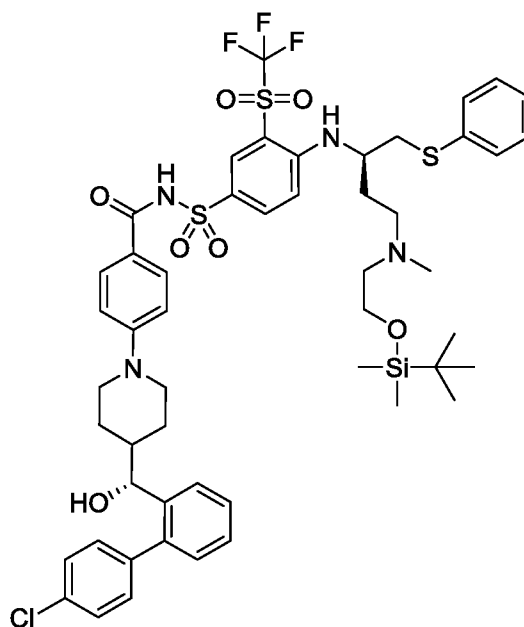
Cell volume: 1 ml

Solvent: CH₂Cl₂

[α] = -13°

INTERMEDIATE 34

[000465] *N*-(4-((*R*)-4-((2-(*tert*-butyldimethylsilyloxy)ethyl)(methyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)-4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzamide



[000466] To a yellow solution of (*R*)-4-(4-((4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoic acid (INTERMEDIATE 40, 1.64 g, 3.89 mmol), (*R*)-4-(4-((2-(*tert*-butyldimethylsilyloxy)ethyl)(methyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide (INTERMEDIATE 67, 2.68 g, 4.09 mmol), DMAP (0.95 g, 7.78 mmol) and dichloromethane (41 ml) was added EDC (1.492 g, 7.78 mmol). After stirring for 16 hours, the mixture was diluted with saturated aqueous sodium bicarbonate. The layers were separated and the aqueous layer was extracted with dichloromethane (x2). The combined organic layers were washed with saturated aqueous sodium chloride, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The concentrate was purified by column chromatography (ISCO, 330 g SiO₂, isocratic 50% ethyl acetate in hexanes for 50 minutes, then 50→65% ethyl acetate in hexanes over 30 minutes followed by 65→100% ethyl

acetate in hexanes over 20 min and then 0→10% methanol in ethyl acetate over 20 minutes) to afford the title product (3.25 g, yield: 79%).

[000467] ^1H NMR (300 MHz, DMSO- d_6 , at 27 °C) δ 10.09 (br. s, 0.4H), 8.11 (d, 1H), 7.90 - 8.00 (m, 1H), 7.68 (d, 2H), 7.59 (d, 1H), 7.10 - 7.54 (m, 12H), 6.89 (d, 2H), 6.75 (d, 2H), 5.21 (d, 1H), 4.24 - 4.39 (m, 1H), 4.04 (d, 1H), 3.73 (br. s., 3H), 3.52 - 3.66 (m, 1H), 3.19 - 3.38 (m, 2H), 2.67 - 3.01 (m, 4H), 2.39 - 2.66 (m, 5H), 2.00 (s, 3H), 1.53 - 1.71 (m, 1H), 0.96 - 1.15 (m, 2H), 0.83 - 0.93 (m, 1H), 0.81 (s, 9H), 0.00 (s, 6H).

[000468] ^{19}F NMR (282 MHz, DMSO- d_6) δ -78.91 (3F).

LCMS: (ESI) m/z 1059.4, 1061.4 $[\text{M}+\text{H}]^+$.

[000469] Optical rotation:

Concentration: 0.14 g/dL

Lamp: Sodium

Wavelength: 589 nm

Temperature: 20° C

Path length: 10 cm

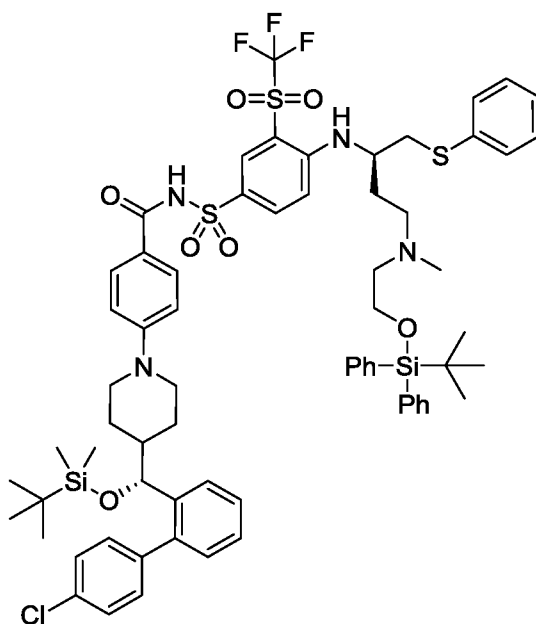
Cell volume: 1 ml

Solvent: CH_2Cl_2

$[\alpha] = -2$

INTERMEDIATE 34A

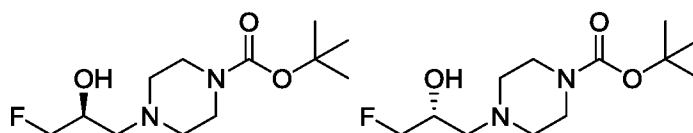
[000470] 4-(4-((*R*)-(tert-butyldimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-N-(4-((*R*)-4-((2-(tert-butyldiphenylsilyloxy)ethyl)(methyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide



[000471] The title product (110 mg, yield: 88 %) was prepared using a procedure similar to the one described for the synthesis of INTERMEDIATE 32 utilizing 4-(4-((*tert*-butyldimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)benzoic acid (INTERMEDIATE 13, 56.7 mg, 0.11 mmol) and (*R*)-4-(4-((2-(*tert*-butyldiphenylsilyloxy)ethyl)(methyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide (INTERMEDIATE 28, 75 mg, 0.10 mmol) as starting materials. The title product was purified by column chromatography (ISCO, 12 g silica gel column, eluting with 0→30 % EtOAc/hexanes).

INTERMEDIATE 35

[000472] (*S*)-*tert*-butyl 4-(3-fluoro-2-hydroxypropyl)piperazine-1-carboxylate and (*R*)-*tert*-butyl 4-(3-fluoro-2-hydroxypropyl)piperazine-1-carboxylate, mixture of enantiomers



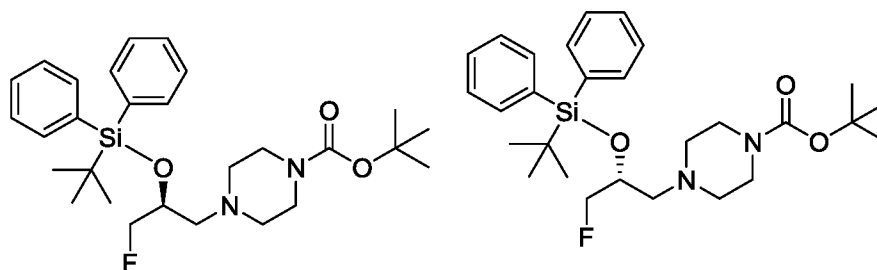
[000473] *Tert*-butyl piperazine-1-carboxylate (2.448 g, 13.15 mmol) was dissolved in ethanol (44.0 ml) and epifluorohydrin (1.00 g, 13.15 mmol) was added to the solution and the resulting reaction mixture was stirred at 50 °C overnight. The reaction mixture was cooled to room temperature, concentrated under reduced pressure and dried under high vacuum overnight to give the title products (0.345 g, yield: quantitative) as a mixture of enantiomers.

[000474] ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 4.59 – 4.46 (m, 1 H), 4.45 – 4.32 (m, 1 H), 3.98 (m, 1 H), 3.52 – 3.46 (m, 4 H), 2.66 – 2.55 (m, 3 H), 2.47 – 2.38 (m, 3 H), 1.47 (s, 9 H).

[000475] LCMS:(ESI) *m/z* 263[M+H]⁺.

INTERMEDIATE 36

[000476] (*S*)-*tert*-butyl 4-(2-(*tert*-butyldiphenylsilyloxy)-3-fluoropropyl)piperazine-1-carboxylate and (*R*)-*tert*-butyl 4-(2-(*tert*-butyldiphenylsilyloxy)-3-fluoropropyl)piperazine-1-carboxylate mixture of enantiomers



[000477] (*S*)-*tert*-butyl 4-(3-fluoro-2-hydroxypropyl)piperazine-1-carboxylate and (*R*)-*tert*-

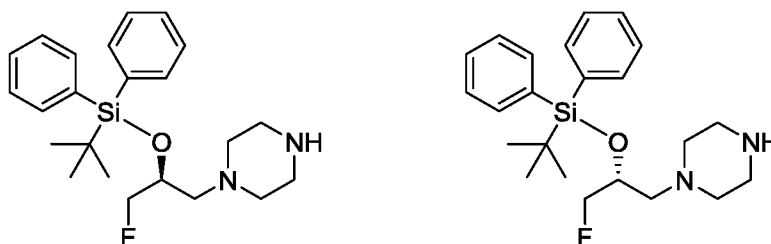
butyl 4-(3-fluoro-2-hydroxypropyl)piperazine-1-carboxylate, mixture of enantiomers (INTERMEDIATE 35, 3.45 g, 13.15 mmol) were dissolved in DMF (39.0 ml) and imidazole (1.790 g, 26.30 mmol) was added. *tert*-Butyldiphenylchlorosilane (5.06 ml, 19.73 mmol) was added to the solution and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc and washed with H₂O (2x). The organic layer was dried (Na₂SO₄) and purified by SFC chromatography eluting with 90% CO₂/10% MeOH to provide the title products, as a mixture of enantiomers (3.77 g, yield: 57%).

[000478] ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.73 – 7.70 (m, 4H), 7.46 – 7.40 (m, 6H), 4.49 – 4.37 (m, 2 H), 3.92 (m, 1 H), 3.50 (m, 1H), 3.30 – 3.20 (m, 4 H), 2.45 – 2.32 (m, 2 H), 2.22 – 2.14 (m, 3 H), 1.44 (s, 9 H), 1.07 (s, 9H).

[000479] LCMS: (ESI) *m/z* 501[M+H]⁺.

INTERMEDIATE 37

[000480] (S)-1-(2-(*tert*-butyldiphenylsilyloxy)-3-fluoropropyl)piperazine compound and (R)-1-(2-(*tert*-butyldiphenylsilyloxy)-3-fluoropropyl)piperazine, mixture of enantiomers



[000481] (*S*)-*tert*-butyl 4-(2-(*tert*-butyldiphenylsilyloxy)-3-fluoropropyl)piperazine-1-carboxylate and (*R*)-*tert*-butyl 4-(2-(*tert*-butyldiphenylsilyloxy)-3-fluoropropyl)piperazine-1-carboxylate mixture of enantiomers (INTERMEDIATE 36, 3.7 g, 7.39 mmol) were dissolved in DCM (31.0 ml) and TFA (5.69 ml, 73.89 mmol) was added. The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure, diluted with DCM and was washed with saturated aq. NaHCO₃. The organic layer was dried (Na₂SO₄), concentrated under reduced pressure and dried under high vacuum overnight to provide the title products (3.12 g, yield: 82%).

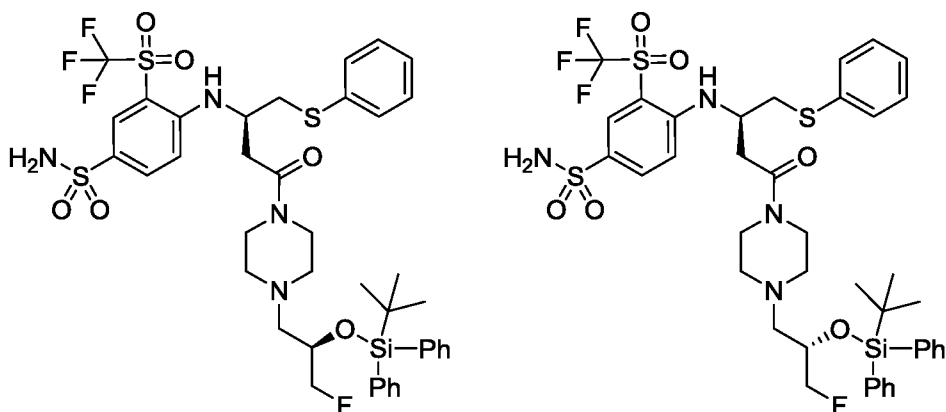
[000482] ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.68 – 7.63 (m, 4 H), 7.50 – 7.41 (m, 6H), 4.48 (m, 1H), 4.36 (m, 1H), 3.97 (m, 1H), 2.72 (m, 4H), 2.40 – 2.27 (m, 2H), 2.24 – 2.20 (m, 4H), 1.00 (s, 9H).

[000483] LCMS: (ESI) *m/z* 401 [M+H]⁺.

INTERMEDIATE 38

[000484] 4-((R)-4-(4-((R)-2-(*tert*-butyldiphenylsilyloxy)-3-fluoropropyl)piperazin-1-yl)-4-oxo-

1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide and 4-((R)-4-(4-((S)-2-(tert-butyldiphenylsilyloxy)-3-fluoropropyl)piperazin-1-yl)-4-oxo-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide, mixture of diastereomers



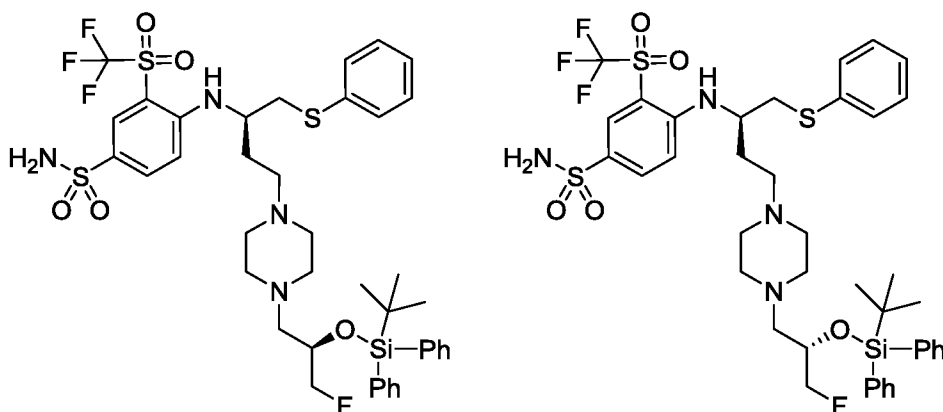
[000485] (*S*)-1-(2-(*tert*-butyldiphenylsilyloxy)-3-fluoropropyl)piperazine compound and (*R*)-1-(2-(*tert*-butyldiphenylsilyloxy)-3-fluoropropyl)piperazine, mixture of enantiomers (INTERMEDIATE 37, 0.194 g, 0.48 mmol) in THF (1.5 ml), diethyl 4-oxobenzo[d][1,2,3]triazin-3(4H)-yl phosphate (0.276 g, 0.92 mmol) and DIPEA (0.161 ml, 0.92 mmol) were added sequentially to a solution of (*R*)-4-(phenylthio)-3-(4-sulfamoyl-2-(trifluoromethylsulfonyl)phenylamino)butanoic acid (INTERMEDIATE 8, 0.23 g, 0.46 mmol) in THF (3.0 ml) and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, diluted with EtOAc and the organic layer was washed with 1N aq. NaHSO₄ and saturated aq. NaHCO₃. The organic layer was dried (Na₂SO₄), concentrated under reduced pressure to give a residue which was purified by column chromatography (ISCO, 40 g silica gel column, eluting with 0→100% EtOAc/ hexanes) to provide the title products (280 mg, yield: 69%).

[000486] ¹H NMR (400 MHz, DICHLOROMETHANE-*d*₂) δ ppm 8.18 (d, 1H), 7.83 - 7.79 (m, 2 H), 7.73 - 7.68 (m, 4 H), 7.48 - 7.23 (m, 11H), 6.62 (d, 1 H), 4.51 - 4.44 (m, 1H), 4.39 - 4.32 (m, 1H), 4.19 - 4.09 (m, 1H), 3.98 - 3.88 (m, 1H), 3.37 - 3.22 (m, 4H), 3.15 - 3.10 (m, 2H), 2.78 (dd, 1H), 2.56 (dd, 1H), 2.42 - 2.32 (m, 2H), 2.20 - 2.08 (m, 4H), 1.05 (s, 9H).

[000487] LCMS: (ESI) *m/z* 881 [M+H]⁺.

INTERMEDIATE 39

[000488] 4-((*R*)-4-(4-((*R*)-2-(*tert*-butyldiphenylsilyloxy)-3-fluoropropyl)piperazin-1-yl)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide and 4-((*R*)-4-(4-((*S*)-2-(*tert*-butyldiphenylsilyloxy)-3-fluoropropyl)piperazin-1-yl)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide mixture of diastereomers

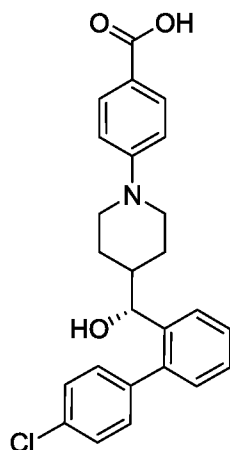


[000489] The title product (130 mg, yield: 55 %) was prepared using a procedure similar to the one described for the synthesis of INTERMEDIATE 25 utilizing 4-((R)-4-(4-((R)-2-(tert-butyldiphenylsilyloxy)-3-fluoropropyl)piperazin-1-yl)-4-oxo-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide and 4-((R)-4-(4-((S)-2-(tert-butyldiphenylsilyloxy)-3-fluoropropyl)piperazin-1-yl)-4-oxo-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide, mixture of diastereomers (INTERMEDIATE 38, 0.24 g, 0.27 mmol) as starting materials. The title products were purified by column chromatography (ISCO, 12 g silica gel column, eluting with 0→50 % DCM/MeOH/NH₃ (10:1:0.1).

[000490] LCMS: (ESI) m/z 867 $[M+H]^+$.

INTERMEDIATE 40

[000491] (*R*)-4-(4-((4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoic acid



[000492] A solution of (*R*)-ethyl 4-(4-((4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoate (INTERMEDIATE 11A (First Eluting Compound), 5.37 g, 11.93 mmol) in THF (160 ml), water (40 ml), and methanol (40 ml) was stirred at 50 °C overnight. The volatiles were removed under reduced pressure and the resulting residue was diluted with water (100 ml). The pH of the solution was adjusted to ~5 with 1N aq. HCl (35 ml) promoting the formation of a precipitate. The white solid was collected via filtration and washed with water (~150 ml). The

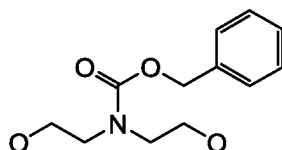
filter cake was dried overnight under high vacuum at 50 °C to provide the title product (4.0 g, yield: 79%).

[000493] ^1H NMR (400 MHz, DMSO- d_6) δ ppm 0.63 (qd, 3.79 Hz, 1 H) 0.72 - 1.00 (m, 2 H) 1.35 - 1.49 (m, 1 H) 1.67 (d, 1 H) 2.28 - 2.39 (m, 1 H) 2.46 (t, 1 H) 3.43 (d, 1 H) 3.59 (d, 1 H) 4.09 (d, 1 H) 6.63 (d, 2 H) 6.91 (dd, 1 H) 7.05 - 7.23 (m, 4 H) 7.23 - 7.29 (m, 2 H) 7.36 (d, 1 H) 7.47 (d, 2 H).

[000494] LCMS: (ESI) m/z 422 $[\text{M}+\text{H}]^+$.

INTERMEDIATE 41

[000495] Benzyl bis(2-hydroxyethyl)carbamate



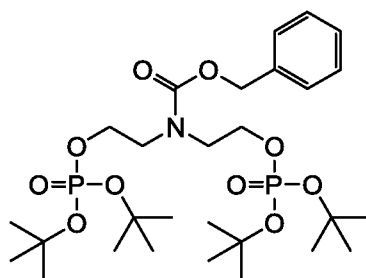
[000496] A suspension of 2,2'-azanediyldiethanol (7.3 ml, 76.09 mmol), sodium carbonate (18.33 g, 172.94 mmol), acetone (125 ml), and water (125 ml) at 0 °C was treated dropwise over a 15 minute period with Cbz-Cl (10.25 ml, 69.17 mmol). The suspension was stirred an additional 3 hours at 0 °C. The suspension was diluted with water (500 ml) and extracted with CHCl_3 (2 x 250 ml). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure. The concentrate was purified by column chromatography (ISCO, eluting with MeOH/DCM, 0 $\rightarrow$ 10% over 40 minutes) to give the title compound (12.5 g, yield: 76 %).

[000497] ^1H NMR (400 MHz, DICHLOROMETHANE- d_2) δ ppm 3.04 - 3.22 (m, 1 H) 3.28 - 3.43 (m, 1 H) 3.51 (br. s., 4 H) 3.80 (d, 4 H) 5.16 (s, 2 H) 7.24 - 7.60 (m, 5 H).

[000498] LCMS: (ESI) m/z 262 $[\text{M}+\text{Na}]^+$.

INTERMEDIATE 42

[000499] Benzyl bis(2-(di-tert-butoxyphosphoryloxy)ethyl)carbamate



[000500] A solution of benzyl bis(2-hydroxyethyl)carbamate (INTERMEDIATE 41, 1.8 g, 7.52 mmol), di-*tert*-butyl diethylphosphoramidite (5.6 ml, 18.81 mmol), and THF (80 ml), was treated

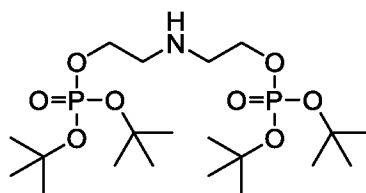
with 1*H*-tetrazole (1.58 g, 22.57 mmol). The mixture was stirred for 30 min at ambient temperature, subsequently cooled to -78 °C and *m*-CPBA (7.42 g, 30.09 mmol) was added portion-wise over a 2 minute period. The mixture was stirred for 20 minutes at -78 °C and allowed to warm to room temperature. The volatiles were reduced to 2/3 of the total volume under reduced pressure while the water bath was kept at 30 °C. The concentrate was diluted with ethyl acetate (300 ml), washed with 10% aq. sodium bisulfite (100 ml), saturated aq. NaHCO₃ (4x 100 ml), dried over sodium sulfate. Evaporation of the volatiles under reduced pressure gave a residue that was purified by column chromatography (ISCO, 330g silica gel column, eluting with 0→20% MeOH in DCM over 53 minutes) to give the title compound (2.5 g, yield: 53 %).

[000501] ¹H NMR (400 MHz, DICHLOROMETHANE-*d*₂) δ ppm 1.42 - 1.51 (m, 36 H) 3.58 - 3.66 (m, 4 H) 3.99 - 4.12 (m, 4 H) 5.16 (s, 2 H) 7.39 (d, 5 H).

[000502] LCMS: (ESI) *m/z* 624 [M+H]⁺.

INTERMEDIATE 43

[000503] 2,2'-azanediylbis(ethane-2,1-diyl) di-*tert*-butyl diphosphate



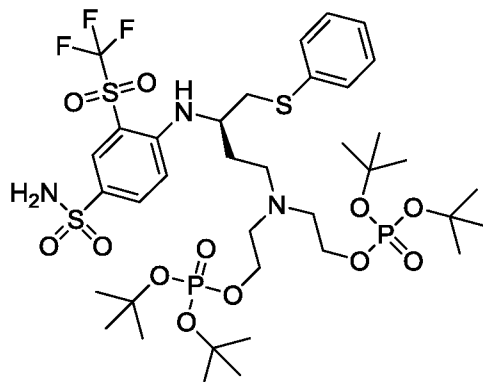
[000504] A mixture of Pd on carbon (5%, 0.64 g, 0.30 mmol), benzyl bis(2-(di-*tert*-butoxyphosphoryloxy)ethyl)carbamate (INTERMEDIATE 42, 2.500 g, 4.01 mmol), and MeOH (50 ml) was stirred under an atmosphere of hydrogen for 2 hours. The catalyst was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure to give the title compound (1.65 g, 84 %), which was used in the preparation of INTERMEDIATE 44 without further purification.

[000505] ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 1.48 - 1.58 (m, 36 H) 2.93 (s, 4 H) 3.99 - 4.22 (m, 4 H)

[000506] LCMS: *m/z* 490 [M+H]⁺.

INTERMEDIATE 44

[000507] (R)-Di-*tert*-butyl 2,2'-(4-(phenylthio)-3-(4-sulfamoyl-2-(trifluoromethylsulfonyl)phenylamino)butylazanediyl)bis(ethane-2,1-diyl) diphosphate



[000508] 2,2'-azanediybis(ethane-2,1-diyl) di-tert-butyl diphosphate

A solution of 2,2'-azanediybis(ethane-2,1-diyl) di-tert-butyl diphosphate (INTERMEDIATE 43, 336 mg, 0.69 mmol), (*R*)-4-(4-oxo-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide (INTERMEDIATE 45, 276 mg, 0.57 mmol), and DCM (10 ml) was treated with sodium triacetoxyborohydride (242 mg, 1.14 mmol). The resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with DCM (20 ml) and washed with sodium bicarbonate (saturated, 30 ml). The organic phase was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The concentrate was purified by column chromatography (ISCO, eluting with 0→10% MeOH in DCM over 19 minutes) to give the title compound (311 mg, yield: 57 %).

[000509] ^1H NMR (300 MHz, $\text{DICHLOROMETHANE-}d_2$) δ ppm 1.36 - 1.52 (m, 36 H) 1.65 (s, 1 H) 2.04 (s, 1 H) 2.45 - 2.94 (m, 6 H) 3.21 (d, 2 H) 3.83 (q, 4 H) 4.05 - 4.31 (m, 1 H) 5.76 (s, 2 H) 6.95 (d, 2 H) 7.19 - 7.49 (m, 5 H) 7.96 - 8.09 (m, 1 H) 8.19 (d, 1 H).

[000510] LCMS: (ESI) m/z 956 $[\text{M}+\text{H}]^+$.

[000511] Optical rotation:

Concentration: 0.1 g/dL

Lamp: Sodium

Wavelength: 589 nm

Temperature: 20° C

Path length: 10 cm

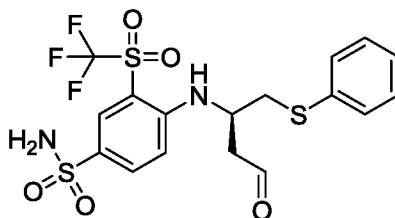
Cell volume: 1 ml

Solvent: Dichloromethane

$[\alpha] = +12$

INTERMEDIATE 45

[000512] (*R*)-4-(4-oxo-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide



[000513] A mixture of (*R*)-methyl 4-(phenylthio)-3-(4-sulfamoyl-2-(trifluoromethylsulfonyl)phenylamino)butanoate (INTERMEDIATE 7, 3.1 g, 6.05 mmol) in DCM (155 ml) was cooled to -78 °C and DIBAL-H in heptane (18.1 ml, 18.1 mmol) was added dropwise. After addition was complete, the mixture was stirred for 3 hours at -78 °C. Methanol (8 ml) and an aqueous solution of Rochelle's salt (15.0 ml) were added sequentially, and the reaction mixture was warmed to r.t. Water (150 ml) was added to the reaction, and the layers were separated. The organic layer was washed with water, dried (Na₂SO₄), and concentrated *in vacuo* to afford the title compound (2.9g, yield: almost quantitative).

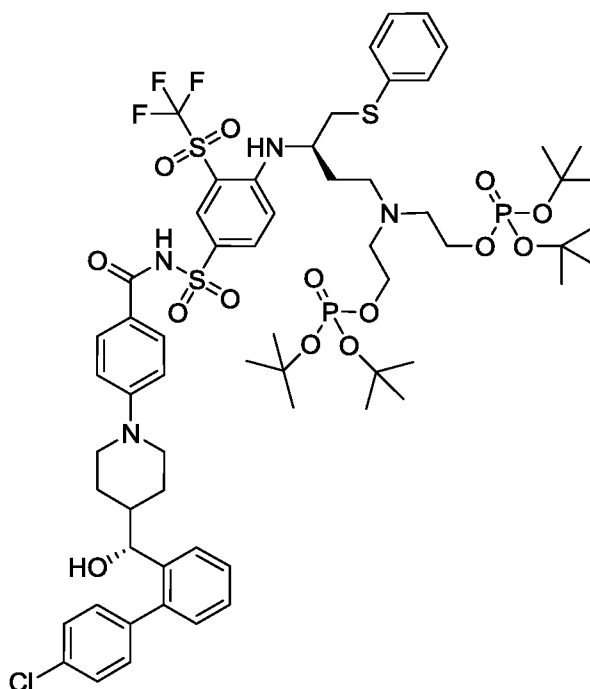
[000514] ¹H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 2.99 (dd, 2 H) 3.09 - 3.23 (m, 2 H) 4.22 (br. s., 1 H) 4.78 (s, 1 H) 6.59 (d, 1 H) 7.19 (d, 1 H) 7.30 - 7.50 (m, 3 H) 7.88 (dd, 1 H) 8.28 (d, 1 H) 9.77 (s, 1 H).

[000515] LCMS: (ESI) *m/z* 481 [M-H]⁺.

[000516] On scales larger than 3.1 g, INTERMEDIATE 7 crashed out of solution in dichloromethane at -78 °C. Hence, for reductions involving > 3.1 g of INTERMEDIATE 7, the order of addition was reversed such that a solution of INTERMEDIATE 7 in tetrahydrofuran was added to a solution of DIBAL-H at -78 °C while maintaining an internal reaction temperature of ≤ -70 °C. Once addition of INTERMEDIATE 7 was completed, the reaction was stirred and worked up in a manner identical to that described above.

INTERMEDIATE 46

[000517] Di-tert-butyl 2,2'-((*R*)-3-(4-(N-(4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxymethyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-(phenylthio)butylazanediyl)bis(ethane-2,1-diyl) diphosphate



[000518] A solution of (*R*)-di-*tert*-butyl 2,2'-(4-(phenylthio)-3-(4-sulfamoyl-2-(trifluoromethylsulfonyl)phenylamino)butylazanediyl)bis(ethane-2,1-diyl) diphosphate (INTERMEDIATE 44, 311 mg, 0.33 mmol), (*R*)-4-(4-((4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoic acid (INTERMEDIATE 40, 137 mg, 0.33 mmol), EDC (125 mg, 0.65 mmol), DMAP (79 mg, 0.65 mmol), triethylamine (0.1 ml, 0.65 mmol), and DCM (10 ml) was stirred at ambient temperature for 72 hours. The volatiles were removed under reduced pressure and the concentrate was purified by column chromatography (ISCO, 80g silica gel column, eluting with 0→10% MeOH in DCM over 19 minutes) to give the title compound (258 mg, yield: 58 %).

[000519] ^1H NMR (400 MHz, $\text{DICHLOROMETHANE-}d_2$) δ ppm 0.92 - 1.37 (m, 3 H) 1.37 - 1.55 (m, 37 H) 1.56 - 1.89 (m, 3 H) 2.04 (s, 2 H) 2.54 - 2.89 (m, 8 H) 3.20 (dd, 2 H) 3.68 - 3.80 (m, 1 H) 3.85 - 4.00 (m, 5 H) 4.02 - 4.10 (m, 1 H) 4.40 - 4.60 (m, 1 H) 6.67 - 6.92 (m, 3 H) 7.09 - 7.55 (m, 13 H) 7.56 - 7.73 (m, 3 H) 8.07 - 8.21 (m, 1 H) 8.40 (d, 1 H).

[000520] LCMS: (ESI) m/z 1359 $[\text{M}+\text{H}]^+$.

[000521] Optical rotation:

Concentration: 0.1 g/dL

Lamp: Sodium

Wavelength: 589 nm

Temperature: 20° C

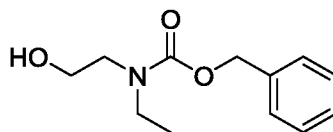
Path length: 10 cm

Cell volume: 1 ml

Solvent: Dichloromethane

[α]= +14

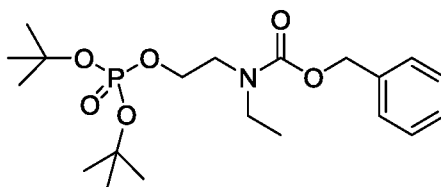
INTERMEDIATE 47

[000522] Benzyl ethyl(2-hydroxyethyl)carbamate

[000523] Benzylchloroformate (5.91 g, 34.67 mmol) and triethylamine (5.2 ml) were added sequentially to a solution of 2-(ethylamino)ethanol (3.0 g, 33.66 mmol) in DCM (180 ml) at 0 °C. The ice bath was removed and the reaction mixture was allowed to stir overnight at ambient temperature. The solution was washed with 10% citric acid (100 ml) and H₂O (2 x 100 ml) and concentrated *in vacuo*. The organic phase was dried (MgSO₄), concentrated under reduced pressure, and the concentrate was purified by column chromatography (ISCO, silica gel column, eluting with 60→100% EtOAc/hexanes for 14 minutes) to give the title compound (7.29 g, yield: 97%).

[000524] ¹H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.16 (t, 3 H) 3.29 - 3.53 (m, 4 H) 3.79 (br. s., 2 H) 5.17 (s, 2 H) 7.27 - 7.45 (m, 5 H).

INTERMEDIATE 48

[000525] Benzyl 2-(di-*tert*-butoxyphosphoryloxy)ethyl(ethyl)carbamate

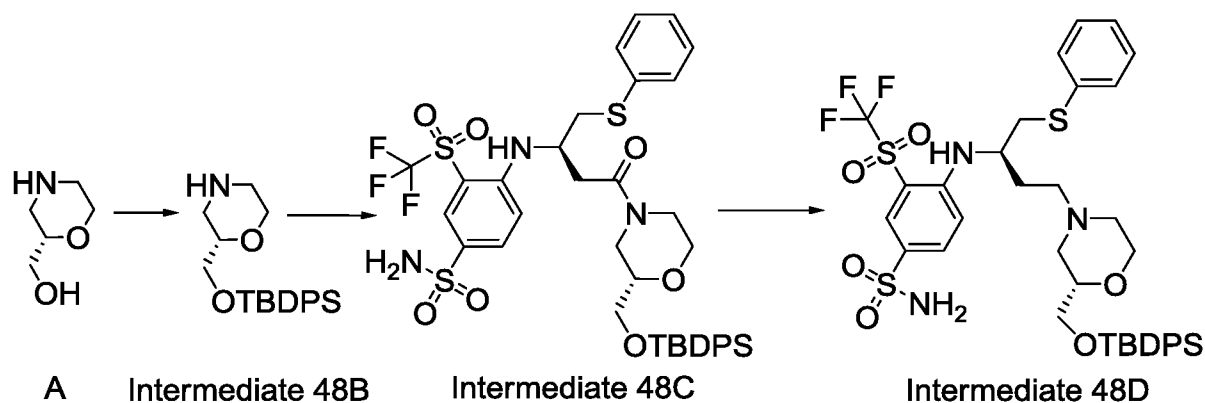
[000526] A solution of benzyl ethyl(2-hydroxyethyl)carbamate (INTERMEDIATE 47, 1.0 g, 4.48 mmol) and di-*tert*-butyl diethylphosphoramidite (4.47 ml, 16.1 mmol) in THF (146 ml) was treated with tetrazole (1.57 g, 22.39 mmol) in one portion. The resulting mixture was stirred at r.t for 50 minutes and the clear solution became cloudy. The mixture was cooled using an acetone / dry ice bath (~ -77 °C) and *m*-CPBA (6.96 g) was added over the course of ~1 minute. The mixture was stirred under these conditions for 20 minutes and subsequently allowed to warm to r.t. over 10 minutes. Sodium bisulfite (aq., 10% w/v, 3.41 ml) was added and the mixture was stirred for 10 minutes, concentrated *in vacuo*, diluted with EtOAc (200 ml), and washed with sodium bisulfite (aq., 100 ml), and NaHCO₃ (aq., 5% w/v, 100 ml). The organic layer was dried (Na₂SO₄), filtered, and evaporated under reduced pressure. The concentrate was purified by

column chromatography (ISCO, silica gel column, eluting with 0→100% EtOAc in hexanes) to give the title compound (1.1 g, yield: 60%).

[000527] ^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.28 (t, 3 H) 1.40 - 1.53 (s, 18 H) 2.97 - 3.08 (m, 2 H) 3.56 (d, 2 H) 3.97 - 4.17 (m, 2 H) 5.15 (s, 2 H) 7.29 - 7.42 (m, 5 H).

INTERMEDIATE 48A

[000528] The stereochemistry for INTERMEDIATE 48 was assigned based upon the procedure described below:



[000529] Step 1: Pyridine (0.207 ml, 2.56 mmol) and DMAP (0.021 g, 0.17 mmol) were added to a solution of (S)-morpholin-2-ylmethanol (A, Tyger Scientific Inc, 0.2 g, 1.71 mmol) in DCM (5.0 ml) followed by tert-butyldichlorodiphenylsilane (0.526 ml, 2.05 mmol). The reaction mixture was stirred at room temperature for 48 hours. The reaction mixture was concentrated under reduced pressure and the concentrate was purified by column chromatography (ISCO, eluting with 10% MeOH/DCM) to provide (S)-2-((tert-butyldiphenylsilyloxy)methyl)morpholine B (INTERMEDIATE 48B, 0.26 g, yield: 43 %).

[000530] LCMS: m/z 356 $[\text{M}+\text{H}]^+$.

[000531] Step 2: (R)-4-(Phenylthio)-3-(4-sulfamoyl-2-(trifluoromethylsulfonyl)phenylamino)butanoic acid (INTERMEDIATE 8, 1.51 g, 3.03 mmol) was added to a solution of (S)-2-((tert-butyldiphenylsilyloxy)methyl)morpholine (INTERMEDIATE 48B, 1.185 g, 3.33 mmol) in DMF (9.04 ml) followed by sequential addition of DIPEA (1.058 ml, 6.06 mmol), EDC (0.871 g, 4.54 mmol) and HOBt (0.696 g, 4.54 mmol). The resulting reaction mixture was stirred at room temperature overnight and was then diluted with EtOAc. The organic phase was washed with H_2O (2x), 1N aq. NaHSO_4 , saturated aq. NaHCO_3 and brine. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give a residue which was purified by column chromatography (ISCO, eluting with 50% EtOAc/hexanes) to provide 4-((2R)-4-(2-((tert-butyldiphenylsilyloxy)methyl)morpholino)-4-phenylthio)butanoic acid.

4-oxo-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide (INTERMEDIATE 48C, 2.380 g, yield: 94 %).

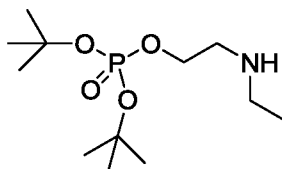
[000532] LCMS: m/z 837 $[M+H]^+$.

[000533] Step 3: A solution of $BH_3 \cdot THF$ complex (0.6 ml, 0.6 mmol) was added slowly to a solution of 4-((2R)-4-(2-((tert-butyldiphenylsilyloxy)methyl)morpholino)-4-oxo-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide (INTERMEDIATE 48C, 0.083 g, 0.10 mmol) and THF (0.4 ml) and the resulting reaction mixture was stirred at room temperature overnight. The mixture was diluted with a solution of NH_3 in MeOH (7N, 20 mL) and was stirred at room temperature overnight. Evaporation of the volatiles under reduced pressure gave a residue, which was diluted with EtOAc. The organic phase was washed with H_2O (2x), dried (Na_2SO_4), filtered and concentrated under reduced pressure to provide 4-((R)-4-((S)-3-((tert-butyldiphenylsilyloxy)methyl)morpholino-1-yl)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide (INTERMEDIATE 48D, 0.030 g, 37 %), which matched INTERMEDIATE 48 upon examination on the chiral HPLC conditions previously tested.

[000534] LCMS: m/z 822 $[M+H]^+$.

INTERMEDIATE 49

[000535] Di-tert-butyl 2-(ethylamino)ethyl phosphate

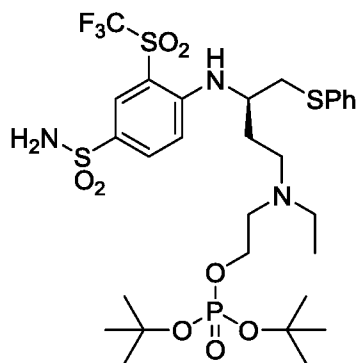


[000536] Benzyl 2-(di-tert-butoxyphosphoryloxy)ethyl(ethyl)carbamate (INTERMEDIATE 48, 0.9 g, 2.17 mmol) was dissolved in methanol (5 ml), and 5% Pd on charcoal (0.10 g) was added. The reaction mixture was stirred at r.t under a hydrogen atmosphere overnight. The reaction mixture was filtered and concentrated *in vacuo* to give the title compound (0.57 g, yield: 94%).

[000537] ^1H NMR (300 MHz, $CHLOROFORM-d$) δ ppm 1.15 (t, 3 H) 1.42 - 1.55 (m, 18 H) 2.72 (d, 2 H) 2.84 - 2.96 (m, 2 H) 4.04 - 4.14 (m, 2 H).

INTERMEDIATE 50

[000538] (R)-di-tert-butyl 2-(ethyl(4-(phenylthio)-3-(4-sulfamoyl-2-(trifluoromethylsulfonyl)phenylamino)butyl)amino)ethyl phosphate



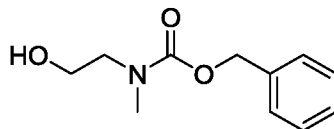
[000539] A solution of di-*tert*-butyl 2-(ethylamino)ethyl phosphate (INTERMEDIATE 49, 455 mg, 1.62 mmol) in 1,2-dichloroethane (0.5 ml) at r.t was added to a solution (*R*)-4-(4-oxo-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide (INTERMEDIATE 45, 0.78 g, 1.62 mmol) and 1,2-dichloroethane (10.0 ml). The resulting reaction mixture was stirred for 15 minutes at r.t and solid sodium triacetoxyborohydride (0.514 g, 2.42 mmol) was added. The resulting mixture was stirred at r.t for 4 hours. A solution of NaOH (aq., 0.5 N, 40 ml) and DCM (20 ml) were added to the reaction mixture. After stirring for 15 min at r.t, the layers were separated. After separation, the organic layer was washed with saturated NaHCO₃, brine, dried (Na₂SO₄), and concentrated *in vacuo*. The concentrate was purified by column chromatography (ISCO, silica gel, eluting with 0→100% EtOAc/hexanes) to give the title compound (610 mg, yield: 50%).

[000540] ¹H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.96 (t, 3 H) 1.32 - 1.53 (m, 18 H) 1.58 (s, 3 H) 2.37 - 2.60 (m, 4 H) 3.10 (d, 2 H) 3.71 (d, 2 H) 3.91 - 4.08 (m, 1 H) 5.43 (s, 2 H) 6.75 (d, 1 H) 6.98 (d, 1 H) 7.27 - 7.44 (m, 4 H) 7.93 (dd, 1 H) 8.26 (d, 1 H).

[000541] LCMS: (ESI) *m/z* 746 [M-H]⁺.

INTERMEDIATE 51

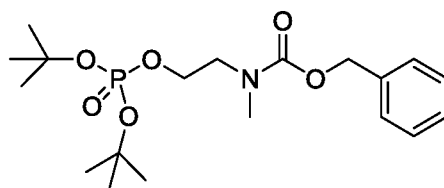
[000542] Benzyl 2-hydroxyethyl(methyl)carbamate



[000543] A similar procedure to that described for INTERMEDIATE 47 utilizing 2-(methylamino)ethanol (2.3 g, 30.62 mmol) as starting material was followed, with subsequent purification by column chromatography (ISCO, silica gel column, eluting with 60→100% EtOAc/hexanes for 14 minutes) to give the title product (5.96 g, yield: 93%).

[000544] ¹H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 2.25 (br. s., 1 H) 3.02 (s, 3 H) 3.48 (t, 2 H) 3.78 (br. s., 2 H) 5.15 (s, 2 H) 7.21 - 7.44 (m, 5 H).

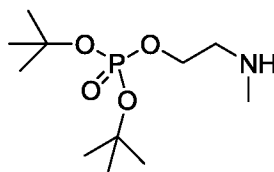
INTERMEDIATE 52

[000545] Benzyl 2-(di-*tert*-butoxyphosphoryloxy)ethyl(methyl)carbamate

[000546] A similar procedure to that described for INTERMEDIATE 48 utilizing benzyl 2-hydroxyethyl(methyl)carbamate (INTERMEDIATE 51, 0.46 g, 2.20 mmol) as starting material was followed, with subsequent purification by column chromatography (ISCO, 12 g silica gel column, eluting with 0→100% EtOAc/hexanes) to give the title product (590 mg, yield: 67%).

[000547] ^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.39 - 1.53 (m, 18 H) 2.95 - 3.09 (m, 3 H) 3.56 (d, 2 H) 4.07 (dd, 2 H) 5.15 (s, 2 H) 7.25 - 7.43 (m, 5 H).

INTERMEDIATE 53

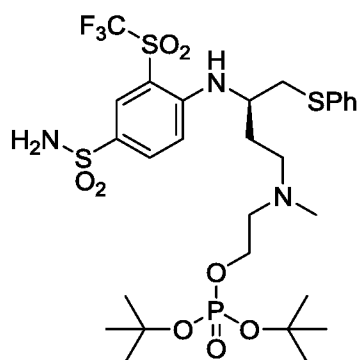
[000548] Di-*tert*-butyl 2-(methylamino)ethyl phosphate

[000549] A similar procedure to that described for INTERMEDIATE 49 utilizing benzyl 2-(di-*tert*-butoxyphosphoryloxy)ethyl(methyl)carbamate (INTERMEDIATE 52, 0.59 g, 1.47 mmol) as starting material was followed, to give the title product (370 mg, yield: 95%).

[000550] ^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.48 - 1.55 (m, 18 H) 2.67 (s, 3 H) 3.11 - 3.22 (m, 2 H) 4.21 - 4.36 (m, 2 H).

INTERMEDIATE 54

[000551] (*R*)-di-*tert*-butyl 2-(methyl(4-(phenylthio)-3-(4-sulfamoyl-2-(trifluoromethylsulfonyl)phenylamino)butyl)amino)ethyl phosphate



[000552] A similar procedure to that described for INTERMEDIATE 50 utilizing (*R*)-4-(4-oxo-

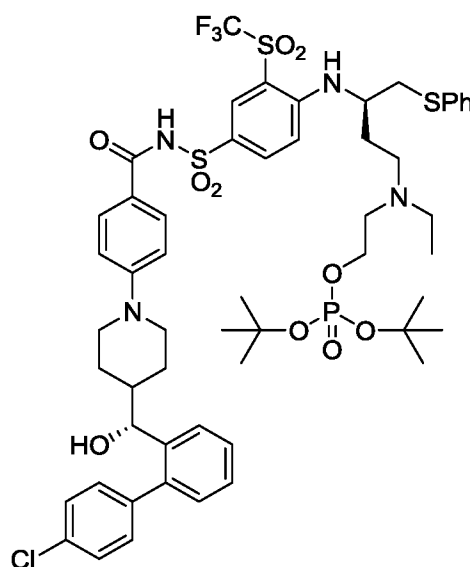
1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide (INTERMEDIATE 45, 0.68 g, 1.4 mmol) and di-*tert*-butyl 2-(methylamino)ethyl phosphate (INTERMEDIATE 53 0.37 mg, 1.4 mmol) as starting materials was followed, with subsequent purification by column chromatography (ISCO, 12 g silica gel column, eluting with 0→100% EtOAc/hexanes) to give the title product (640 mg, yield: 62%).

[000553] ^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.35 - 1.52 (m, 18 H) 2.21 (s, 3 H) 2.54 (br. s., 2 H) 3.10 (t, 2 H) 3.80 (br. s., 3 H) 3.96 - 4.11 (m, 2 H) 5.45 (br. s., 2 H) 6.84 (d, 1 H) 7.04 (s, 1 H) 7.27 - 7.44 (m, 4 H) 7.98 (dd, 1 H) 8.25 (d, 1 H).

[000554] LCMS: (ESI) m/z 732 $[\text{M}-\text{H}]^+$.

INTERMEDIATE 55

[000555] Di-*tert*-butyl 2-(((*R*)-3-(4-(N-(4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-(phenylthio)butyl)(ethylamino)ethyl phosphate



[000556] To a solution of (*R*)-4-(4-((4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoic acid (INTERMEDIATE 40, 88 mg, 0.20 mmol), EDC (77 mg, 0.40 mmol), and DMAP (49 mg, 0.40 mmol), triethylamine (28 μl , 0.20 mmol) in 5 ml of DCM was added (*R*)-di-*tert*-butyl 2-(ethyl(4-(phenylthio)-3-(4-sulfamoyl-2-(trifluoromethylsulfonyl)phenylamino)butyl)amino)ethyl phosphate (INTERMEDIATE 50, 150 mg, 0.20 mmol). The mixture was stirred at r.t overnight. The reaction solution was diluted with DCM (20 ml) and washed with water (30 ml). The aqueous layer was extracted with DCM (30 ml) and the combined organic layers were dried over sodium sulfate, and concentrated *in vacuo* to an oil. This material was purified by column chromatography (ISCO, 0→100%

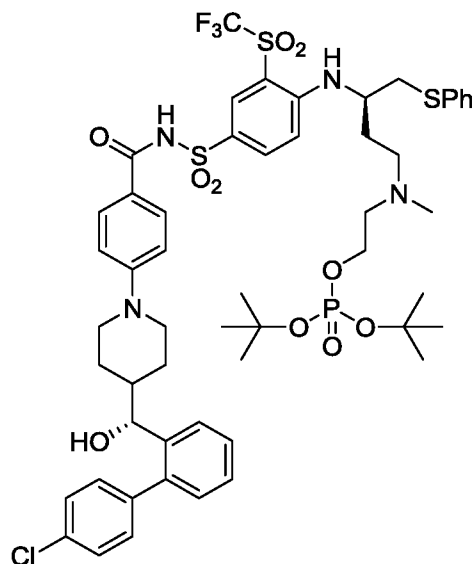
EtOAc/hexane followed by 0→10%MeOH/EtOAc) to provide the title compound (137 mg, yield: 59%).

[000557] ^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.85 - 1.10 (m, 4 H) 1.16 - 1.35 (m, 1 H) 1.48 (d, 18 H) 1.81 (br. s., 3 H) 2.40 - 2.88 (m, 8 H) 3.11 (d, 2 H) 3.62 - 3.76 (m, 1 H) 3.93 (d, 4 H) 4.50 (d, 1 H) 6.58 - 6.70 (m, 1 H) 6.77 (d, 2 H) 7.11 - 7.51 (m, 12 H) 7.54 - 7.70 (m, 3 H) 8.12 (br. s., 1 H) 8.38 (s, 1 H).

[000558] LCMS: (ESI) m/z 1150 $[\text{M}-\text{H}]^+$.

INTERMEDIATE 56

[000559] Di-*tert*-butyl 2-(((*R*)-3-(4-(*N*-(4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-(phenylthio)butyl)(methyl)amino)ethyl phosphate



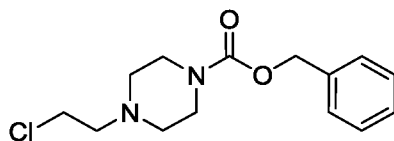
[000560] A similar procedure to that described for INTERMEDIATE 55 utilizing (*R*)-4-(4-((4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoic acid (INTERMEDIATE 40, 63 mg, 0.14 mmol) and (*R*)-di-*tert*-butyl 2-(methyl(4-(phenylthio)-3-(4-sulfamoyl-2-(trifluoromethylsulfonyl)phenylamino)butyl)amino)ethyl phosphate (INTERMEDIATE 54, 105 mg, 0.14 mmol) as starting materials was followed, with subsequent purification by column chromatography (ISCO, 0→100% EtOAc/hexane followed by 0→10%MeOH/EtOAc) to give the title product (98 mg, yield: 60%).

[000561] ^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.97 - 1.12 (m, 2 H) 1.48 (d, 21 H) 1.79 (br. s., 4 H) 2.27 (br. s., 3 H) 2.68 (br. s., 7 H) 3.10 (br. s., 2 H) 3.69 (br. s., 1 H) 3.81 - 4.09 (m, 4 H) 4.50 (d, 1 H) 6.55 - 6.68 (m, 1 H) 6.78 (d, 2 H) 7.12 - 7.52 (m, 12 H) 7.53 - 7.67 (m, 3 H) 8.13 (d, 1 H) 8.39 (d, 1 H).

[000562] LCMS: (ESI) m/z 1138 $[\text{M}+\text{H}]^+$.

INTERMEDIATE 57

[000563] Benzyl 4-(2-chloroethyl)piperazine-1-carboxylate



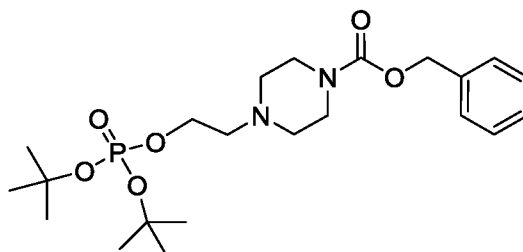
[000564] Benzyl piperazine-1-carboxylate (1.00 g, 4.54 mmol) and K_2CO_3 (1.255 g, 9.08 mmol) were dissolved in acetonitrile (12.87 ml) to form a suspension. 1-bromo-2-chloroethane (2.3 ml, 27.24 mmol) was added to the reaction mixture at r.t and the resulting mixture was stirred at this temperature for 96 hours. The reaction mixture was filtered, and the filtrate concentrated under reduced pressure. Purification by column chromatography (ISCO, silica gel column, eluting with 0→100% EtOAc in hexanes) gave the title compound (0.64 g, yield: 50 %).

[000565] ^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.28 - 7.43 (m, 5 H) 5.15 (s, 2 H) 3.48 - 3.65 (m, 6 H) 2.76 (t, 2 H) 2.42 - 2.57 (m, 4 H).

[000566] LCMS: (ESI) m/z 283[M+H] $^+$.

INTERMEDIATE 58

[000567] Benzyl 4-(2-(di-tert-butoxyphosphoryloxy)ethyl)piperazine-1-carboxylate



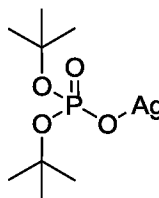
[000568] A solution of benzyl 4-(2-chloroethyl)piperazine-1-carboxylate (INTERMEDIATE 57, 0.12 g, 0.42 mmol) in toluene (1.415 ml) was treated with silver di-*tert*-butyl phosphate (INTERMEDIATE 59, 0.148 g, 0.47 mmol). The reaction mixture was stirred at 100 °C for 100 mins. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give the title compound (0.14 g, yield: 73%), which was used in the preparation of INTERMEDIATE 60, without further purification.

[000569] ^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.31 - 7.43 (m, 5 H) 5.15 (s, 2 H) 4.01 - 4.14 (m, 2 H) 3.47 - 3.60 (m, 4 H) 2.69 (t, 2 H) 2.44 - 2.57 (m, 4 H) 1.50 (s, 18 H).

[000570] LCMS: (ESI) m/z 457 [M+H] $^+$.

INTERMEDIATE 59

[000571] Silver di-*tert*-butyl phosphate

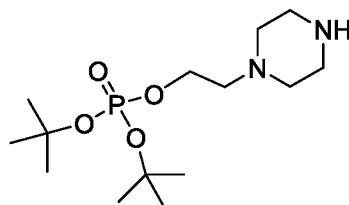


[000572] Potassium di-*tert*-butyl phosphate (18.94 g, 76.28 mmol) was dissolved in water (140 ml) and cooled in an ice bath. The solution was swirled by hand and treated dropwise with concentrated HCl (~28 ml), which resulted in a white precipitate. The precipitate was collected on a Büchner funnel, washed with water (70 ml), and air-dried for several minutes. In a 2 L beaker, the resulting damp powder (15.09 g) was dissolved in a mixture of barium hydroxide octahydrate (24.12 g, 76.45 mmol) in water (400 ml). Carbon dioxide (g) was bubbled through the solution resulting in copious formation of white precipitate. The mixture was filtered through Büchner funnel, and the cloudy filtrate was evaporated to give a white solid (~21 g). Most of the material was dissolved in MeOH (~250 ml). A white, powdery suspension was removed by filtration through Celite® and the clear filtrate was evaporated to give damp white solid (~20 g). The material was dissolved in MeOH (25-30 ml), and precipitated by the addition of acetone (900 ml). The white precipitate was collected on a Buchner funnel and washed with acetone to give barium di-*tert*-butyl phosphate as a white solid (14.60 g, 26.27 mmol). The barium di-*tert*-butyl phosphate was dissolved in water (100 ml), and added to a solution of silver sulfate (8.19 g, 26.27 mmol) in water (1100 ml), which resulted in formation of a white precipitate. The mixture was filtered through Celite® and the clear filtrate was evaporated to give a white solid. Most of the material was dissolved in MeOH (~600 ml) and a white powdery suspension was removed by filtration through Celite®. The filtrate was concentrated, treated with toluene (~200 ml) and evaporated to dryness to give the title compound (15.1 g, yield: 62%).

[000573] LCMS: (ESI) m/z 209 [M-Ag].

INTERMEDIATE 60

[000574] Di-*tert*-butyl 2-(piperazin-1-yl)ethyl phosphate



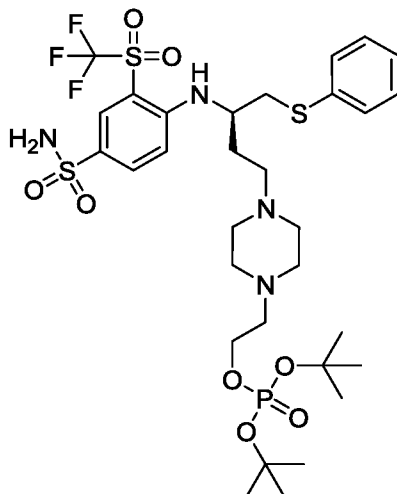
[000575] A 100 ml flask was charged with benzyl 4-(2-(di-*tert*-butoxyphosphoryloxy)ethyl)piperazine-1-carboxylate (INTERMEDIATE 58, 0.90 g, 1.97 mmol) in MeOH (19.7 ml) and 10% palladium on charcoal (0.042 g, 0.04 mmol). The reaction mixture was stirred under a hydrogen atmosphere overnight. The reaction mixture was filtered and the

filtrate concentrated *in vacuo* to give the title compound (0.63 g, yield: 99 %), which was used in the preparation of INTERMEDIATE 61 without further purification.

[000576] ^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 4.08 (d, 2 H) 3.50 (s, 3 H) 2.89 - 2.99 (m, 4 H) 2.67 (t, 2 H) 2.51 - 2.61 (m, 4 H) 1.50 (s, 18 H). LCMS: (ESI) m/z 323 $[\text{M}+\text{H}]^+$.

INTERMEDIATE 61

[000577] (R)-di-*tert*-butyl 2-(4-(4-(phenylthio)-3-(4-sulfamoyl-2-(trifluoromethylsulfonyl)phenylamino)butyl)piperazin-1-yl)ethyl phosphate



[000578] A solution of di-*tert*-butyl 2-(piperazin-1-yl)ethyl phosphate (INTERMEDIATE 60, 0.31 g, 0.95 mmol) in 1,2-dichloroethane (4 ml) was added to a solution of (*R*)-4-(4-oxo-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide (INTERMEDIATE 45, 0.46 g, 0.95 mmol) in dichloroethane (5.0 ml) at room temperature. The reaction mixture was allowed to stir for 15 minutes at r.t, and solid sodium triacetoxyborohydride (0.30 g, 1.43 mmol) was added. The mixture was stirred for 1 hour at ambient temperature. To the reaction mixture was added 0.5 N NaOH (10 ml) and DCM (20 ml). After stirring for 15 mins at r.t, the layers were separated and the organic layer was washed with NaHCO_3 (saturated aq.) and brine, and dried (Na_2SO_4). The volatiles were removed under reduced pressure. Purification by column chromatography (ISCO, silica gel, eluting with 0→100% EtOAc/hexanes) gave the title compound (0.71 g, yield: 94 %).

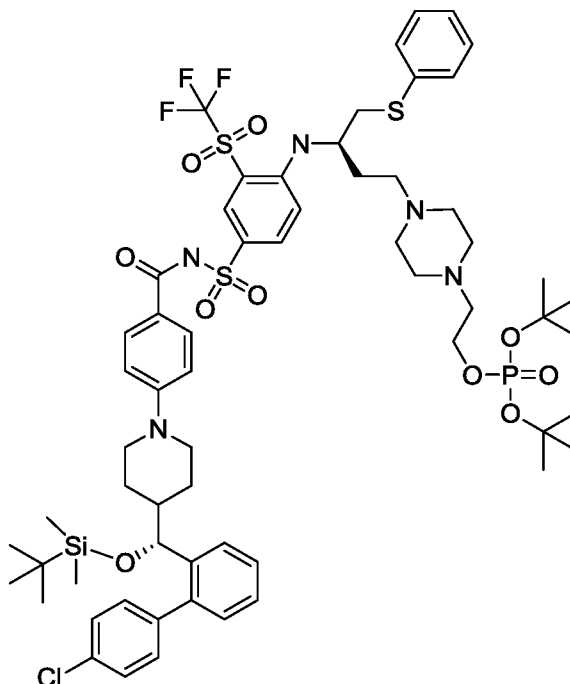
[000579] ^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 8.26 (d, 1 H) 7.91 (dd, 1 H) 7.29 - 7.44 (m, 6 H) 5.24 (br. s., 2 H) 4.07 (br. s., 2 H) 3.94 (br. s., 1 H) 3.10 (d, 2 H) 2.74 (br. s., 3 H) 2.57 (br. s., 4 H) 2.41 (br. s., 5 H) 2.07 (br. s., 1 H) 1.51 (d, 18 H).

[000580] LCMS: (ESI) m/z 790 $[\text{M}+\text{H}]^+$.

INTERMEDIATE 62

[000581] di-*tert*-butyl

2-(4-((*R*)-3-(4-(N-(4-(4-((*R*)-(tert-butyl)dimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-(phenylthio)butyl)piperazin-1-yl)ethyl phosphate

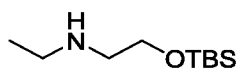


[000582] (*R*)-4-(4-((*tert*-butyl)dimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)benzoic acid (INTERMEDIATE 13, 170 mg, 0.32 mmol), (*R*)-di-*tert*-butyl 2-(4-(4-(phenylthio)-3-(4-sulfamoyl-2-(trifluoromethylsulfonyl)phenylamino)butyl)piperazin-1-yl)ethyl phosphate (INTERMEDIATE 61, 275 mg, 0.35 mmol), DMAP (116 mg, 0.95 mmol) and EDC (122 mg, 0.63 mmol) were dissolved in DCM (3.2 ml). The reaction mixture was stirred at r.t. for 72 hours. The mixture was diluted with DCM (10 ml) and washed with NaHCO₃ solution (saturated, aq., 5 ml) and brine (5 ml). The collected organic layer was dried over Na₂SO₄ and concentrated to give the title compound (446 mg, yield: almost quantitative). The title compound was used in the preparation of EXAMPLE 10 without further purification.

[000583] LCMS: (ESI) 1307 [M+H]⁺.

INTERMEDIATE 63

[000584] 2-(tert-butyl)dimethylsilyloxy)-N-ethylethanamine



[000585] DIPEA (5.48 ml, 31.38 mmol) and tert-butylchlorodimethylsilane (6.76 g, 22.42 mmol) were added to a solution of 2-(ethylamino)ethanol (1.998 g, 22.42 mmol) in DCM (39.3 ml) at room temperature. The mixture was stirred at room temperature for 20 hours, partitioned between H₂O/Et₂O (50 ml/50 ml). The aqueous phase was extracted with ether (3 x 30 ml). The

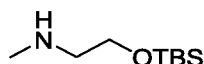
combined organic layers were concentrated under reduced pressure to give a residue which was re-dissolved in DCM (50 ml), dried (Na_2SO_4), filtered and concentrated under vacuum to give the title compound (3.9 g, yield: 85%).

[000586] ^1H NMR (300 MHz, $\text{CHLOROFORM-}d$) δ ppm 3.66 (t, 2 H) 2.55 - 2.69 (m, 4 H) 1.43 (br. s., 1 H) 1.05 (t, 3 H) 0.80 - 0.86 (m, 9 H) -0.03 - 0.05 (m, 6 H).

[000587] LCMS: m/z 204 $[\text{M}+\text{H}]^+$.

INTERMEDIATE 64

[000588] 2-(*tert*-butyldimethylsilyloxy)-*N*-methylethanamine



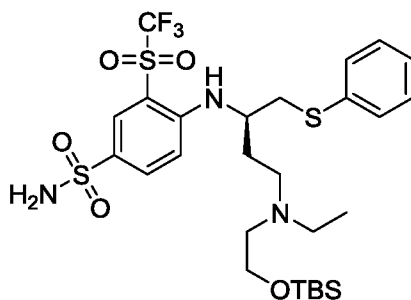
[000589] A similar procedure to that described for INTERMEDIATE 63 utilizing 2-(methylamino)ethanol (2.0 g, 26.68 mmol) as starting material was followed, to give the title product (4.17 g, yield: 83%).

[000590] LCMS: m/z 190 $[\text{M}+\text{H}]^+$.

[000591] ^1H NMR (300 MHz, $\text{CHLOROFORM-}d$) δ ppm 3.61 - 3.69 (m, 2 H) 2.57 - 2.65 (m, 2 H) 2.39 (s, 3 H) 1.47 (br. s., 1 H) 0.80 - 0.87 (m, 9 H) -0.04 - 0.01 (m, 6 H).

INTERMEDIATE 65

[000592] (*R*)-4-(4-((2-(*tert*-butyldimethylsilyloxy)ethyl)(ethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide



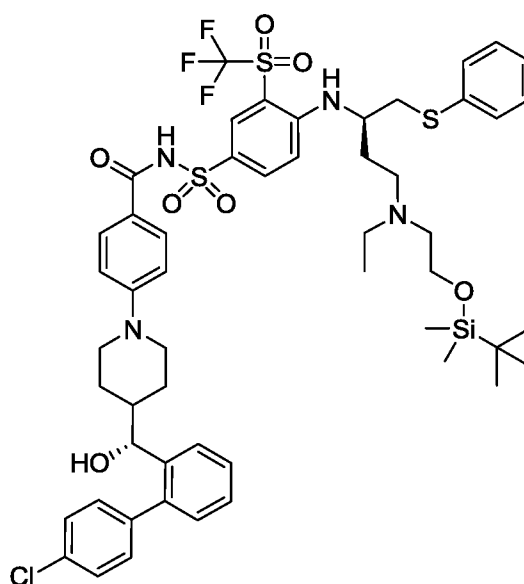
[000593] To a solution of (*R*)-4-(4-oxo-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide (INTERMEDIATE 45, 3.98 g, 8.25 mmol) and 2-(*tert*-butyldimethylsilyloxy)-*N*-ethylethanamine (INTERMEDIATE 63, 1.68 g, 8.25 mmol) in 1,2-dichloroethane (27.5 ml) was added sodium triacetoxyborohydride (2.62 g, 12.37 mmol). The resulting mixture was stirred in the dark for 11.5 h and was then quenched with 0.5 M aqueous sodium hydroxide (50 ml). After vigorous stirring for 10 min, the opaque mixture became clear. The layers were diluted with ethyl acetate and then separated. The organic layer was washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride

before being dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography (ISCO, 330 g SiO₂, 50→100% ethyl acetate in hexanes for 20 mins then 0→20% methanol in ethyl acetate for 20 mins followed by 0→20% methanol in ethyl acetate over 20 min) to afford the title product (3.41 g, yield: 62%).

[000594] LCMS: (ESI) m/z 670 $[M+H]^+$.

INTERMEDIATE 66

[000595] N-(4-((R)-4-((2-(tert-butyldimethylsilyloxy)ethyl)(ethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)-4-(4-((R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzamide



[000596] (*R*)-4-(4-((4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoic acid (INTERMEDIATE 40, 2.15 g, 5.10 mmol), (*R*)-4-(4-((2-(tert-butyldimethylsilyloxy)ethyl)(ethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide (INTERMEDIATE 65, 3.41 g, 5.10 mmol), DMAP (1.87 g, 15.29 mmol) and EDC (1.954 g, 10.19 mmol) were dissolved in DCM (17 ml). The reaction mixture was stirred at r.t. overnight, diluted with DCM (50 ml) and washed with NH₄Cl solution (saturated, aq., 20 ml), saturated aq. NaHCO₃ (20 ml) and brine (20 ml). The collected organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The concentrate was purified by column chromatography (ISCO, 12 g silica gel, eluted with 0→20% MeOH in EtOAc) to provide the title compound (3.41 g, yield: 62%).

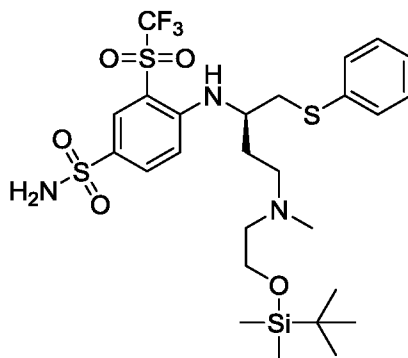
[000597] ¹H NMR (300 MHz, DICHLOROMETHANE-*d*₂) δ ppm 8.27 (s, 1 H) 7.92 (d, 1 H) 7.63 (d, 2 H) 7.55 - 7.59 (m, 1 H) 7.30 - 7.45 (m, 5 H) 7.15 - 7.30 (m, 6 H) 7.06 (d, 1 H) 6.74 (d, 2 H) 6.63 (d, 1 H) 4.46 (d, 1 H) 3.94 (d, 1 H) 3.83 (d, 1 H) 3.62 - 3.72 (m, 3 H) 3.08 (d, 2 H) 2.55 - 2.78 (m, 9 H) 2.00 (br. s., 2H) 1.88 (br. s., 1 H) 1.69 - 1.83 (m, 2 H) 1.20 - 1.35 (m, 1 H) 1.15

(br. s., 1 H) 0.94 - 1.06 (m, 4 H) 0.80 - 0.87 (m, 9 H) 0.00 (s, 6 H).

[000598] LCMS: (ESI) m/z 1074 $[M+H]^+$.

INTERMEDIATE 67

[000599] (R)-4-(4-((2-(tert-butyldimethylsilyloxy)ethyl)(methyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide



[000600] To a solution of (R)-4-(4-oxo-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide (INTERMEDIATE 45, 3.98 g, 8.25 mmol) and 2-(tert-butyldimethylsilyloxy)-N-methylethanamine (INTERMEDIATE 64, 1.56 g, 8.25 mmol) in 1,2-dichloroethane (27.5 ml) was added sodium triacetoxyborohydride (2.62 g, 12.37 mmol). The resulting mixture was stirred in the dark for 11.5 hours and then sodium hydroxide (0.5 M, aq., 50 ml) was added. The mixture was diluted with dichloromethane (70 ml) and stirred vigorously for 10 min. The layers were separated, and the organic layer was washed with saturated aqueous sodium bicarbonate. The organic layer was then diluted heavily with ethyl acetate and washed with saturated aqueous sodium chloride (x2) before being dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography (ISCO, 330 g SiO₂, 0→50% ethyl acetate in hexanes over 30 min, then isocratic hold for 30 min, then 50→100% ethyl acetate in hexanes over 20 min) to afford the title product (2.68 g, yield: 49.5 %). Additional impure title product was also obtained (1.65 g), which was further purified by reverse phase HPLC (Column: Xbridge Phenyl OBD 19mm x 100mm, 5μm; eluting with 65→80% acetonitrile in water (10 mM NH₄OAc, pH 8) over 15 min). Product fractions were combined, diluted with saturated aqueous sodium bicarbonate, and extracted with ethyl acetate (x3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford additional title product (1.05 g, yield: 19%).

[000601] ¹H NMR (300 MHz, CHLOROFORM-d) δ 8.21 (d, 1H), 7.75 (dd, 1H), 7.33 - 7.47 (m, 3H), 7.20 - 7.32 (m, 3H), 6.56 (d, 1H), 4.74 (br. s., 2H), 3.80 - 3.97 (m, 1H), 3.52 - 3.71 (m, 2H), 3.04 (d, 2H), 2.31 - 2.65 (m, 4H), 2.21 (br. s., 3H), 2.01 (s, 1H), 1.61 - 1.80 (m, 1H), 0.79 -

0.88 (m, 9H), 0.00 (s, 6H).

[000602] LCMS: (ESI) m/z 654 $[M-H]^+$.

[000603] Optical rotation:

Concentration: 0.15 g/dL

Lamp: Sodium

Wavelength: 589 nm

Temperature: 20° C

Path length: 10 cm

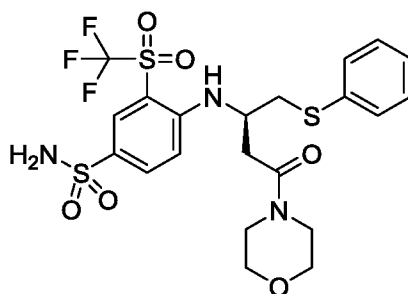
Cell volume: 1 ml

Solvent: CH₂Cl₂

$[\alpha] = -111$

INTERMEDIATE 68

[000604] (*R*)-4-(4-morpholino-4-oxo-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl) benzenesulfonamide



[000605] A solution of (*R*)-4-(phenylthio)-3-(4-sulfamoyl-2-(trifluoromethylsulfonyl)phenylamino) butanoic acid (INTERMEDIATE 8, 1.99 g, 4.01 mmol) and HATU (1.83 g, 4.82 mmol) in DMA (18.0 ml) was treated with morpholine (0.35 ml, 4.02 mmol) and DIPEA (1.40 ml, 8.02 mmol). The resulting reaction mixture was stirred at room temperature for 1 hour and then diluted with EtOAc (250 ml). The organic layer was washed with water (3 x 250 ml), 1M aq. NaHSO₄ (200 ml), and saturated aq. NaHCO₃ (200 ml). The organic layer was dried (Na₂SO₄), filtered, and evaporated under reduced pressure to provide a sticky foam. The foam was dissolved in EtOAc (40 ml) and washed with water (2 x 250 ml). During the second wash material precipitated. EtOAc (80 ml) was added and the resulting mixture was shaken, resulting in redissolution of the precipitate. The mixture was further dried (Na₂SO₄), filtered, and evaporated under reduced pressure. The residue was dissolved in a few ml of DCM resulting in the formation of a precipitate. Finally, evaporation of the volatiles under reduced pressure afforded the title product (2.02 g, yield: 89%).

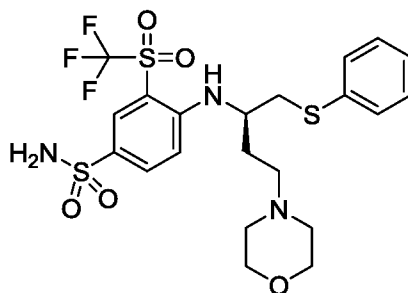
[000606] LCMS: (ESI) m/z 568 $[M+H]^+$.

[000607] Optical rotation:

Concentration:	0.1 g/dL
Lamp:	Sodium
Wavelength:	589 nm
Temperature:	20° C
Path length:	10 cm
Cell volume:	1 ml
Solvent:	CH ₂ Cl ₂
[α]=	-122

INTERMEDIATE 69

[000608] (*R*)-4-(4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl) benzenesulfonamide



[000609] (*R*)-4-(4-morpholino-4-oxo-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl) benzenesulfonamide (INTERMEDIATE 68, 2.01 g, 3.5 mmol) was dissolved in a solution of borane-THF complex (1M in THF, 8.0 ml, 8.0 mmol) and the resulting solution was stirred at room temperature overnight. The flask was opened to atmosphere and cautiously treated with MeOH (4.0 ml) followed by concentrated HCl (1.55 ml). The resulting mixture was heated at reflux for 3 hours and was then allowed to cool to room temperature. The pH of the mixture was adjusted to approximately 10 by the addition of aqueous solution of Na₂CO₃ (2 M) resulting in a precipitate. The mixture was dissolved in EtOAc (250 ml) and washed with water (125ml), brine (125 ml), and dried (Na₂SO₄). Evaporation of the volatiles under reduced pressure afforded a concentrate, which was purified by column chromatography (ISCO, 80 g silica gel column, eluting with 0→100% EtOAc/ hexanes) to provide the title product (1.33 g, yield: 68%).

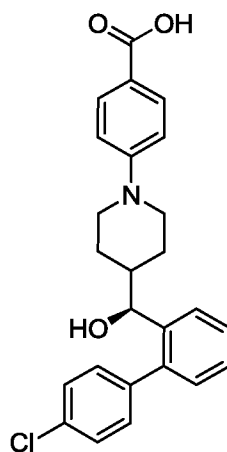
[000610] ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 1.65 - 1.81 (m, 1 H) 1.87 - 2.02 (m, 1 H) 2.09 - 2.40 (m, 6 H) 3.43 - 3.57 (m, 4 H) 4.02 - 4.18 (m, 1 H) 6.91 (d, 1 H) 7.06 (d, 1 H) 7.16 - 7.42 (m, 7 H) 7.85 (dd, 1 H) 7.98 (d, 1 H).

[000611] LCMS: (ESI) *m/z* : 554 [M+H]⁺.

[000612] Optical rotation:

Concentration: 0.1 g/dL
 Lamp: Sodium
 Wavelength: 589 nm
 Temperature: 20° C
 Path length: 10 cm
 Cell volume: 1 ml
 Solvent: CH₂Cl₂
 [α]= -147

INTERMEDIATE 70

[000613] (*S*)-4-(4-((4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoic acid

[000614] (*S*)-Ethyl 4-(4-((4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoate (INTERMEDIATE 11B, 150.0 mg, 0.33 mmol) was dissolved in THF (6.0 ml) and methanol (1.4 ml). A solution of LiOH (40.6 mg) in water (1.4 ml) was added. The solution was heated at 50° overnight. The reaction mixture was allowed to cool to room temperature and then concentrated under reduced pressure. The residue was diluted with water (5 ml), acidified with 1N aq. HCl (2.0 ml), and extracted with DCM (2 x 5 ml). The extract was dried (MgSO₄), filtered through cotton, and evaporated under vacuum to provide the title product as a substantially separated enantiomer (155 mg, yield: almost quantitative) ¹H NMR (400 MHz, DICHLOROMETHANE-*d*₂) δ ppm 0.79 - 0.94 (m, 1 H) 0.98 - 1.12 (m, 1 H) 1.14 - 1.40 (m, 4 H) 2.04 (m, 1 H) 2.67 (td, *J*=12.51, 2.78 Hz, 1 H) 2.78 (td, 1 H) 3.74 (d, 1 H) 3.91 (m, 1 H) 4.48 (d, 1 H) 6.81 (d, 2 H) 7.17 - 7.29 (m, 3 H) 7.31 - 7.49 (m, 4 H) 7.61 (dd, 1 H) 7.84 - 7.93 (m, 2 H).

[000615] LCMS: (ESI) *m/z* 420 [M-H]⁺.

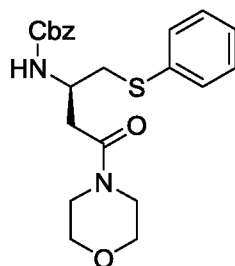
[000616] Optical rotation:

Concentration: 0.1 g/dL

Lamp:	Sodium
Wavelength:	589 nm
Temperature:	20 °C
Path length:	10 cm
Cell volume:	1 ml
Solvent:	CH ₂ Cl ₂
[α]=	-107

INTERMEDIATE 71

[000617] (*R*)-benzyl 4-morpholino-4-oxo-1-(phenylthio)butan-2-ylcarbamate

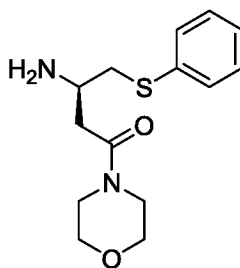


[000618] Morpholine (130 g, 1.49 mol) was added to a solution of (*R*)-benzyl 5-oxotetrahydrofuran-3-ylcarbamate (INTERMEDIATE 3, 34.46g, 0.147 mmol) in THF, and the resulting mixture was allowed to stir at room temperature overnight. The reaction mixture was concentrated to dryness under reduced pressure and the concentrate was re-dissolved in EtOAc. The organic layer was washed with dilute HCl, dried over Na₂SO₄ and concentrated under reduced pressure to give a thick, colorless oil (24.2g). A solution of the resulting oil (27.2 g, 84 mmol) in toluene (250 ml) was treated with diphenyl disulfide (20.3 g, 109.2 mmol) followed by Bu₃P (27.2 ml, 109.2 mmol). The reaction mixture was heated at 80 °C overnight under a nitrogen atmosphere. Evaporation of the volatiles under reduced pressure gave a residue, which was purified by column chromatography (silica gel, 7 cm height x 14 cm width, eluting with hexanes followed by 10:1, 2:1 then 1:1 v/v hexanes/EtOAc) to give the title product (25 g, yield: 71.5 %).

[000619] LCMS: (ESI) *m/z* 413 [M-H]⁺.

INTERMEDIATE 72

[000620] (*R*)-3-amino-1-morpholino-4-(phenylthio)butan-1-one



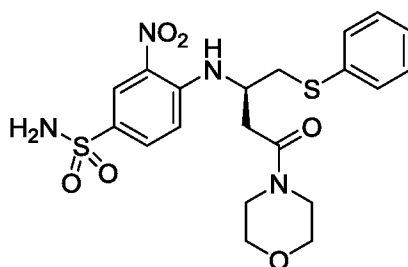
[000621] A suspension of (*R*)-benzyl 4-morpholino-4-oxo-1-(phenylthio)butan-2-ylcarbamate (INTERMEDIATE 71, 25 g, 60 mmol) in 40% HBr in acetic acid (500 ml) was stirred at room temperature for 50 hrs. The reaction mixture became homogeneous during this time. The reaction mixture was concentrated to dryness, diluted with water (400 ml) and 5 % aq. HCl (200 ml) and washed with diethyl ether (3 x 100 ml). The aqueous phase was brought to pH ~8-9 with solid Na₂CO₃ and extracted vigorously with CH₂Cl₂ (5x). The combined organic layers were dried (MgSO₄) and concentrated under reduced pressure to give the title product (16.9 g, yield: almost quantitative), which was used in the preparation of Intermediate 73 without further purification.

[000622] ¹H-NMR (300 MHz, DMSO-*d*₆) δ 2.42 (dd, 1 H), 2.57 (dd, 1 H), 2.77 (m 3 H), 2.97-3.02 (m, 1 H), 3.06-3.14 (m, 1 H), 3.37 (m, 2 H), 3.59(m, 6 H), 7.18 (t, 1H), 7.27 (d, 2H), 7.37 (d, 2H).

[000623] LCMS: (ESI) *m/z* 281 (M+H)⁺.

INTERMEDIATE 73

[000624] (*R*)-4-(4-morpholino-4-oxo-1-(phenylthio)butan-2-ylamino)-3-nitrobenzenesulfonamide



[000625] To a solution of (*R*)-3-amino-1-morpholino-4-(phenylthio)butan-1-one (INTERMEDIATE 72, 375.5 mg, 1.34 mmol) in DMF (2.5 ml) and DIPEA (1.20 ml, 6.87 mmol) was added 4-fluoro-3-nitrobenzenesulfonamide (INTERMEDIATE 18, 325.8 mg, 1.48 mmol), and the resulting dark solution was stirred at 50 °C overnight, under a nitrogen atmosphere. The mixture was diluted with EtOAc (50 ml) and washed with water and brine (30 ml each), dried (Na₂SO₄), filtered, and evaporated under reduced pressure. The concentrate was purified by column chromatography (ISCO, 40 g silica gel column, eluting with 0→100%

EtOAc/DCM) to give the title product (532.5 mg, yield: 83%).

[000626] ^1H NMR (400 MHz, DICHLOROMETHANE- d_2) δ ppm 2.72 (dd, 1 H) 2.85 - 2.97 (m, 1 H) 3.25 - 3.44 (m, 4 H) 3.48 - 3.68 (m, 6 H) 4.26 - 4.39 (m, 1 H) 4.96 (s, 2 H) 6.76 (d, 1 H) 7.23 - 7.37 (m, 3 H) 7.37 - 7.46 (m, 2 H) 7.74 (dd, 1 H) 8.61 (d, 1 H) 9.08 (d, 1 H).

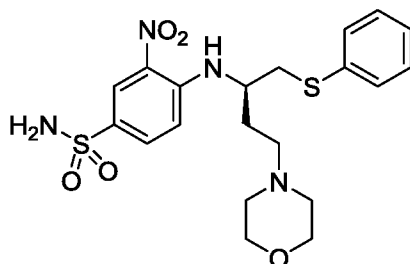
[000627] LCMS:(ESI) m/z 481 $[\text{M}+\text{H}]^+$.

[000628] Optical rotation:

Concentration:	0.1 g/dL
Lamp:	Sodium
Wavelength:	589 nm
Temperature:	20° C
Path length:	10 cm
Cell volume:	1 ml
Solvent:	CH_2Cl_2
$[\alpha]=$	-212

INTERMEDIATE 74

[000629] (*R*)-4-(4-morpholino-1-(phenylthio)butan-2-ylamino)-3-nitrobenzenesulfonamide



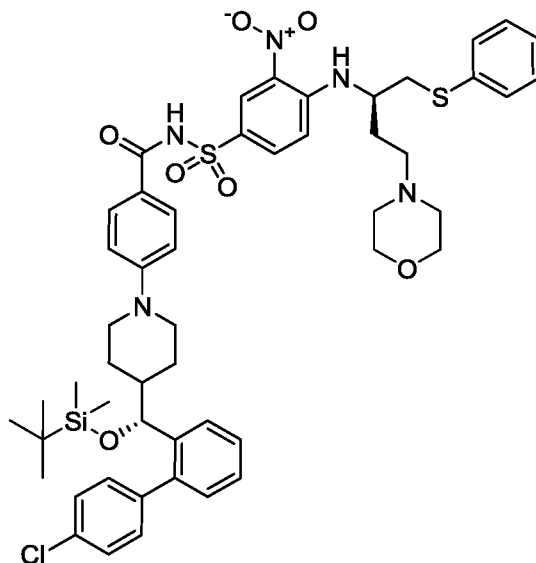
[000630] (*R*)-4-(4-Morpholino-4-oxo-1-(phenylthio)butan-2-ylamino)-3-nitrobenzenesulfonamide (INTERMEDIATE 73, 523.6 mg, 1.09 mmol) was dissolved under a nitrogen atmosphere in a solution of borane-THF complex (1M in THF; 2.4 ml, 2.4 mmol) and the resulting solution was stirred at room temperature overnight. The flask was opened to atmosphere and cautiously treated with MeOH (1.20 ml) followed by concentrated HCl (0.48 ml). The resulting mixture was heated at reflux for 3 hours and was then allowed to cool to room temperature. The pH of the mixture was adjusted to approximately 10 by the addition of aqueous solution of Na_2CO_3 (4 M) resulting in a precipitate. The mixture was dissolved in EtOAc (75 ml) and washed with water (40 ml), brine (40 ml), and dried (Na_2SO_4). Evaporation of the volatiles under reduced pressure afforded a concentrate, which was purified by column chromatography (ISCO, 40 g silica gel column, eluting with 0→100% EtOAc/ hexanes) to provide the title product (406.6 mg, yield: 80 %).

[000631] ^1H NMR (400 MHz, DMSO- d_6) δ ppm 1.75 - 1.87 (m, 1 H) 1.93 - 2.06 (m, 1 H) 2.14 - 2.43 (m, 6 H) 3.37 (m, 2 H) 3.45 - 3.59 (m, 4 H) 4.16 (m, 1 H) 7.12 (d, 1 H) 7.16 - 7.22 (m, 1 H) 7.23 - 7.29 (m, 2 H) 7.29 - 7.35 (m, 4 H) 7.71 (dd, 1 H) 8.36 - 8.45 (m, 2 H).

[000632] LCMS: (ESI) m/z 467 $[\text{M}+\text{H}]^+$.

INTERMEDIATE 75

[000633] 4-(4-((*R*)-(tert-butyl)dimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfonyl)benzamide



[000634] The title product (346.6 mg, yield: 75%) was prepared using a procedure similar to the one described for the synthesis of INTERMEDIATE 33. (*R*)-4-(4-((tert-Butyl)dimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)benzoic acid (INTERMEDIATE 13, 250.7 mg, 0.47 mmol) and (*R*)-4-(4-morpholino-1-(phenylthio)butan-2-ylamino)-3-nitrobenzenesulfonamide (INTERMEDIATE 74, 229.0 mg, 0.49 mmol) were used as starting materials. The resulting product was purified by column chromatography (ISCO, 12 g silica gel column, eluting with 0→10 % MeOH/DCM), providing the title product.

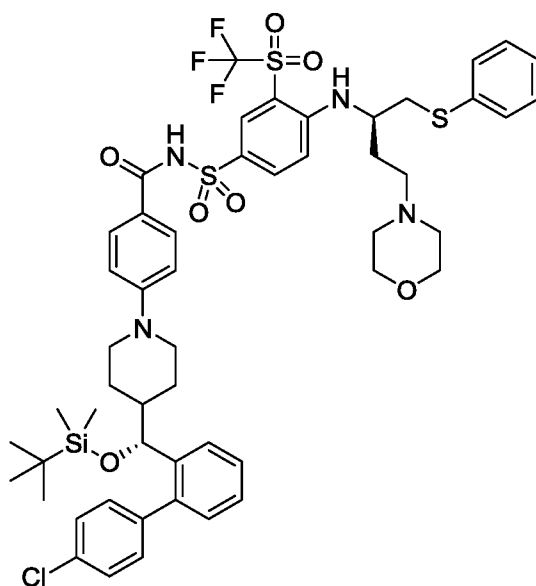
[000635] ^1H NMR (400 MHz, DICHLOROMETHANE- d_2) δ ppm -0.24 (s, 3 H) -0.07 (s, 3 H) 0.84 (s, 9 H) 1.50 - 1.62 (m, 1 H) 1.68 - 1.84 (m, 2 H) 2.04 - 2.15 (m, 1 H) 2.23 - 2.49 (m, 6 H) 2.56 - 2.72 (m, 2 H) 3.18 (d, 2 H) 3.55 - 3.69 (m, 4 H) 3.72 - 3.80 (m, 1 H) 3.81 - 3.90 (m, 1 H) 4.55 - 4.63 (m, 1 H) 6.78 (d, 2 H) 6.84 (d, 1 H) 7.12 (dd, 1 H) 7.17 - 7.44 (m, 11 H) 7.59 (d, 3 H) 7.93 (dd, 1 H) 8.55 - 8.63 (m, 1 H) 8.77 (d, 1 H).

[000636] LCMS:(ESI) m/z 984 $[\text{M}+\text{H}]^+$.

INTERMEDIATE 76

[000637] 4-(4-((*R*)-(tert-butyl)dimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-

N-(4-((*R*)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide



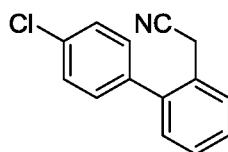
[000638] The title product (71.4 mg, yield: 33%) was prepared using a procedure similar to the one described for the synthesis of INTERMEDIATE 33. (*R*)-4-(4-((*tert*-Butyldimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)benzoic acid (INTERMEDIATE 13, 106.7 mg, 0.2 mmol) and (*R*)-4-(4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl) benzenesulfonamide (INTERMEDIATE 69, 117 mg, 0.21 mmol) were used as starting materials. The resulting product was purified by column chromatography (ISCO, 4 g silica gel column, eluting with 0→100 % EtOAc/hexanes), providing the title product.

[000639] ^1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm -0.24 (s, 3 H) -0.07 (s, 3 H) 0.85 (s, 9 H) 1.38 (m, 2 H) 1.47 - 1.80 (m, 5 H) 2.08 - 2.19 (m, 1 H) 2.25 - 2.51 (m, 6 H) 2.57 - 2.73 (m, 2 H) 2.99 - 3.15 (m, 2 H) 3.60 - 3.72 (m, 4 H) 3.72 - 3.80 (m, 1 H) 3.81 - 3.89 (m, 1 H) 3.89 - 3.98 (m, 1 H) 4.56 - 4.63 (m, 1 H) 6.59 - 6.66 (m, 1 H) 6.78 (d, 2 H) 7.06 - 7.15 (m, 2 H) 7.20 (d, 2 H) 7.35 - 7.43 (m, 5 H) 7.53 - 7.65 (m, 3 H) 8.10 - 8.16 (m, 1 H) 8.35 - 8.40 (m, 1 H).

[000640] LCMS: (ESI) m/z 1071 $[\text{M}+\text{H}]^+$.

INTERMEDIATE 77

[000641] 2-(4'-chlorobiphenyl-2-yl)acetonitrile



[000642] 2-(2-bromophenyl)acetonitrile (5.00 g, 25.5 mmol), 4-chlorophenylboronic acid (4.30

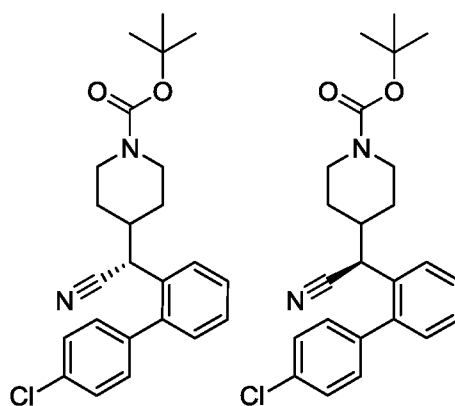
g, 27.5 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.48 g 0.42 mmol) were mixed with toluene (57 ml) in a 250 ml 3-necked flask. A reflux condenser was attached and the flask was purged with nitrogen. Aqueous solution of Na₂CO₃ (2M, 29 ml, 58 mmol) was added by syringe, and the atmosphere was evacuated and replaced with nitrogen. The reaction mixture was heated at reflux overnight, and then allowed to cool at ambient temperature. The mixture was partitioned between saturated aq. NH₄Cl and EtOAc (200 ml each). The organic phase was separated, dried (MgSO₄), filtered through diatomaceous earth and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography (ISCO, 120 g silica gel column, 0→20% EtOAc/ hexanes) to give the tile compound (5.44 g, yield: 94%).

[000643] ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.91 (s, 2 H), 7.26 - 7.33 (m, 1 H), 7.36 - 7.49 (m, 4 H), 7.50 - 7.59 (m, 3 H).

[000644] LCMS:(ESI) *m/z* 228 [M+H]⁺.

INTERMEDIATE 78

[000645] (*R*)-*tert*-butyl 4-((4'-chlorobiphenyl-2-yl)(cyano)methyl)piperidine-1-carboxylate and (*S*)-*tert*-butyl 4-((4'-chlorobiphenyl-2-yl)(cyano)methyl)piperidine-1-carboxylate, mixture of enantiomers



[000646] NaH (0.84 g, 60% oil dispersion, 21 mmol) was suspended in DMF (5.0 ml) and the suspension was treated with 2-(4'-chlorobiphenyl-2-yl)acetonitrile (INTERMEDIATE 77, 4.1 g, 17.9 mmol) causing the mixture to turn red. The reaction mixture was stirred at room temperature for 1 hour, during which time more precipitate was observed. The mixture was cooled to 0 °C and *tert*-butyl 4-iodopiperidine-1-carboxylate (5.59 g, 17.97 mmol) was added along with more DMF (5.0 ml) in order to facilitate stirring. The mixture was stirred at 0 °C for 2 hours and was then allowed to warm to room temperature for 36 hours. The mixture was diluted with saturated aq. NH₄Cl (50 ml) and water (50 ml) and extracted with DCM (3 x 50 ml). The extracts were washed with water (150 ml), dried (MgSO₄), filtered, and evaporated under reduced pressure. The concentrate was purified by column chromatography (ISCO, 330 g silica

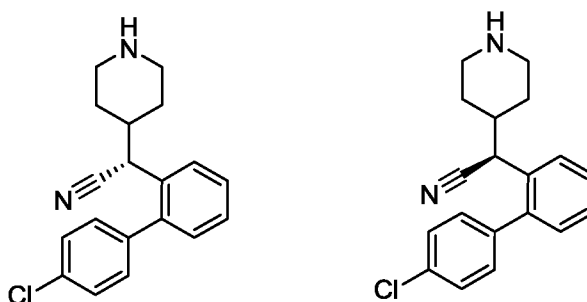
gel column, 0→25% EtOAc/hexanes) to give the title products as a mixture of enantiomers.

[000647] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 0.73 (qd, 1 H), 1.06 - 1.20 (m, 2 H), 1.35 (s, 9 H), 1.65 - 1.73 (m, 1 H), 1.83 - 1.95 (m, 1 H), 2.54 - 2.69 (m, 1 H), 3.72 - 3.82 (m, 1 H), 3.85 (d, 1 H), 3.88 - 3.97 (m, 1 H), 7.27 (dd, 1 H), 7.30 - 7.37 (m, 2 H), 7.42 - 7.48 (m, 1 H), 7.48 - 7.61 (m, 4 H).

[000648] LCMS:(ESI) m/z 433 $[\text{M}+\text{Na}]^+$

INTERMEDIATE 79

[000649] (*R*)-2-(4'-chlorobiphenyl-2-yl)-2-(piperidin-4-yl)acetonitrile and (*S*)-2-(4'-chlorobiphenyl-2-yl)-2-(piperidin-4-yl)acetonitrile, mixture of enantiomers



[000650] (*R*)-*tert*-butyl 4-((4'-chlorobiphenyl-2-yl)(cyano)methyl)piperidine-1-carboxylate and (*S*)-*tert*-butyl 4-((4'-chlorobiphenyl-2-yl)(cyano)methyl)piperidine-1-carboxylate, mixture of enantiomers (INTERMEDIATE 78, 501 mg, 1.22 mmol) were mixed with DCM (3.0 ml) and MeOH (0.12 ml) and treated with TFA (3.0 ml). The reaction mixture was stirred at room temperature for 15 minutes whereupon the volatiles were removed under reduced pressure. The resulting mixture was mixed with water (~15 ml) and made basic (pH ~11) by the addition of small portions of K_2CO_3 solid, with cautious (but ultimately vigorous) swirling. The resulting cloudy mixture was extracted with DCM (3 x 15 ml), and the combined extracts were washed with water (20 ml), dried (MgSO_4), filtered, and evaporated under reduced pressure to provide the title products (397 mg, yield: quantitative) as a mixture of enantiomers.

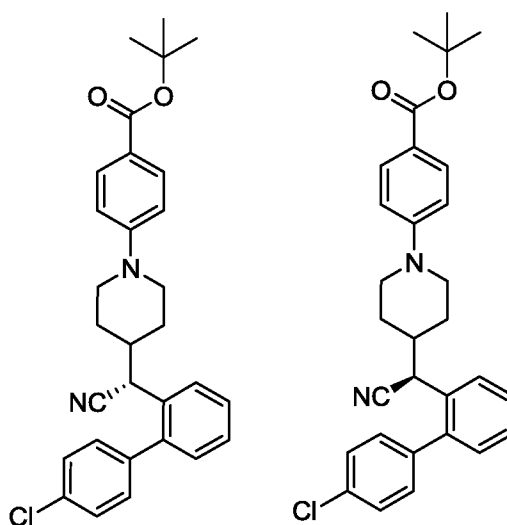
[000651] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 0.75 (qd, 1 H), 1.02 - 1.15 (m, 2 H), 1.57 - 1.66 (m, 1 H), 1.67 - 1.78 (m, 1 H), 2.18 (td, 1 H), 2.32 (td, 2 H), 2.69 - 2.78 (m, 1 H), 2.83 - 2.91 (m, 1 H), 3.80 (d, 1 H), 7.26 (d, 1 H), 7.33 (d, 2 H), 7.44 (t, 1 H), 7.50 (t, 1 H), 7.53 - 7.59 (m, 3 H).

[000652] FTIR shows nitrile stretch at 2238 /cm .

INTERMEDIATE 80

[000653] (*R*)-*tert*-butyl 4-(4-((4'-chlorobiphenyl-2-yl)(cyano)methyl)piperidin-1-yl)benzoate

and (*S*)-*tert*-butyl 4-((4'-(4-chlorobiphenyl-2-yl)(cyano)methyl)piperidin-1-yl)benzoate, mixture of enantiomers



[000654] (*R*)-2-(4'-chlorobiphenyl-2-yl)-2-(piperidin-4-yl)acetonitrile and (*S*)-2-(4'-chlorobiphenyl-2-yl)-2-(piperidin-4-yl)acetonitrile, mixture of enantiomers (INTERMEDIATE 79, 196.4 mg, 0.63 mmol) were added to a mixture of *tert*-butyl 4-fluorobenzoate (152.2 mg, 1.39 mmol) in DMSO (0.6 ml), and DIPEA (0.132 ml, 1.49 mmol). The resulting mixture was heated at 120 °C for 8 hours, whereupon more *tert*-butyl 4-fluorobenzoate (121.0 mg) was added and heating was continued for an additional 24 hours. Additional DIPEA (0.13 ml) was added and heating was continued for another 48 hours. The mixture was diluted with EtOAc (20 ml), washed with water (3 x 20 ml) and brine (20 ml), dried (MgSO₄), filtered, and evaporated under reduced pressure. The concentrate was purified by column chromatography (ISCO, 4 g silica gel column, 0→20%, eluting with EtOAc/hexanes) to provide the title products (62.6 mg, yield: 20%) as a mixture of enantiomers.

[000655] ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.90 - 1.02 (m, 1 H), 1.21 - 1.39 (m, 2 H), 1.49 (s, 9 H), 1.72 - 1.81 (m, 1 H), 2.53 - 2.63 (m, 1 H), 2.65 - 2.77 (m, 1 H), 3.74 (d, 1 H), 3.89 (d, 2 H), 6.86 (d, 2 H), 7.26 - 7.31 (m, 1 H), 7.32 - 7.38 (m, 2 H), 7.46 (td, 1 H), 7.50 - 7.57 (m, 3 H), 7.58 - 7.63 (m, 1 H), 7.67 (d, 2 H).

[000656] LCMS: (ESI) *m/z* 487 [M+H]⁺.

[000657] The R and S enantiomers of the title product were separated using Chiral SFC, (Chiralpak IA column), providing INTERMEDIATE 81 and INTERMEDIATE 82 as substantially separated enantiomers.

Column dimensions: 21 x 250 mm, 5 μ

Modifier: 25 % Methanol/ 0.1 % dimethylethylamine

Flow rate (ml/min): 60

Outlet Pressure (bar): 100

Detection (nm):

210

INTERMEDIATE 81 (First Eluting Compound)

[000658] (*R*)-*tert*-butyl 4-(4-((4'-chlorobiphenyl-2-yl)(cyano)methyl)piperidin-1-yl)benzoate

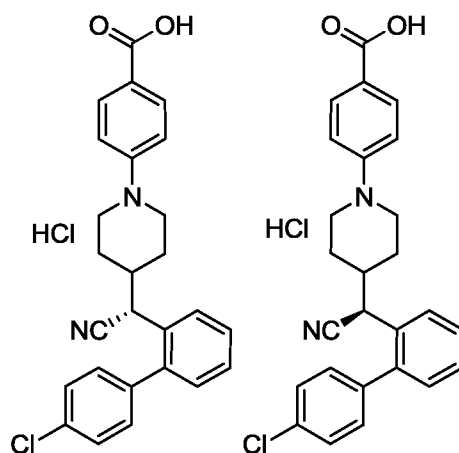
The first eluting compound had a retention time of 9.62 minutes.

[000659] ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.89 - 1.02 (m, 1 H), 1.21 - 1.39 (m, 2 H), 1.49 (s, 9 H), 1.72 - 1.81 (m, 1 H), 1.91 - 2.03 (m, 1 H), 2.53 - 2.63 (m, 1 H), 2.65 - 2.77 (m, 1 H), 3.74 (d, 1 H), 3.84 - 3.94 (m, 2 H), 6.86 (d, 2 H), 7.25 - 7.31 (m, 1 H), 7.32 - 7.38 (m, 2 H), 7.43 - 7.49 (m, 1 H), 7.50 - 7.57 (m, 3 H), 7.58 - 7.63 (m, 1 H), 7.64 - 7.70 (m, 2 H).**[000660]** LCMS: (ESI) *m/z* 487 [M+H]⁺.

INTERMEDIATE 82 (Second Eluting Compound)

[000661] (*S*)-*tert*-butyl 4-(4-((4'-chlorobiphenyl-2-yl)(cyano)methyl)piperidin-1-yl)benzoate**[000662]** The second eluting compound had a retention time of 12.95 minutes.**[000663]** ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.96 (qd, 1 H), 1.21 - 1.39 (m, 2 H), 1.49 (s, 9 H), 1.72 - 1.81 (m, 1 H), 1.91 - 2.03 (m, 1 H), 2.58 (td, 1 H), 2.65 - 2.77 (m, 1 H), 3.70 - 3.78 (m, 1 H), 3.84 - 3.94 (m, 2 H), 6.87 (d, 2 H), 7.28 (dd, 1 H), 7.32 - 7.38 (m, 2 H), 7.46 (td, 1 H), 7.50 - 7.57 (m, 3 H), 7.58 - 7.63 (m, 1 H), 7.67 (d, 2 H).**[000664]** LCMS: (ESI) *m/z* 487 [M+H]⁺.

INTERMEDIATE 83

[000665] (*R*)-4-(4-((4'-chlorobiphenyl-2-yl)(cyano)methyl)piperidin-1-yl)benzoic acid and (*S*)-4-(4-((4'-chlorobiphenyl-2-yl)(cyano)methyl)piperidin-1-yl)benzoic acid hydrochloride salts, mixture of enantiomers**[000666]** (*R*)-*tert*-Butyl 4-(4-((4'-chlorobiphenyl-2-yl)(cyano)methyl)piperidin-1-yl)benzoate and (*S*)-*tert*-butyl 4-(4-((4'-chlorobiphenyl-2-yl)(cyano)methyl)piperidin-1-yl)benzoate, mixture

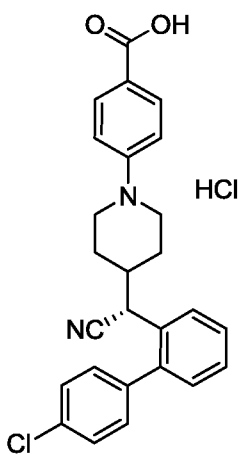
of enantiomers (INTERMEDIATE 80, 213.5 mg, 0.44 mmol) were dissolved in DCM (2.0 ml) and MeOH (0.1 ml) and treated with TFA (2.0 ml, 25.96 mmol). The mixture was stirred at room temperature for 30 minutes and then the solvent was evaporated under reduced pressure. The residue was dissolved sequentially and evaporated to dryness with toluene and DCM to provide the corresponding trifluoroacetate salts (251.3 mg). The material was dissolved in MeOH (6 ml), and 2 M HCl in ether (2 ml) was added. After stirring the solution for 10 minutes, the volatiles were removed under reduced pressure to give the title products (182 mg, yield: 89 %) as a mixture of enantiomers.

[000667] ^1H NMR (300 MHz, DMSO- d_6) δ ppm 0.89 - 1.08 (m, 1 H), 1.19 - 1.45 (m, 2 H), 1.71 - 1.85 (m, 1 H), 1.89 - 2.07 (m, 1 H), 2.55 - 2.68 (m, 1 H), 2.69 - 2.82 (m, 1 H), 3.66 - 3.80 (m, 1 H), 3.82 - 3.94 (m, 2 H), 6.91 (d, 2 H), 7.28 (d, 1 H), 7.35 (d, 2 H), 7.40 - 7.50 (m, 1 H), 7.49 - 7.57 (m, 3 H), 7.57 - 7.64 (m, 1 H), 7.73 (d, 2 H).

[000668] LCMS: (ESI) m/z 431 $[\text{M}+\text{H}]^+$.

INTERMEDIATE 84

[000669] (*R*)-4-(4-((4'-chlorobiphenyl-2-yl)(cyano)methyl)piperidin-1-yl)benzoic acid, hydrochloride salt



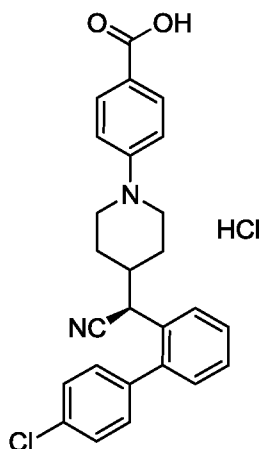
[000670] The title product (215 mg, yield: quantitative) was obtained using a procedure similar to the one described for the synthesis of INTERMEDIATE 83. (*R*)-*tert*-Butyl 4-(4-((4'-chlorobiphenyl-2-yl)(cyano)methyl)piperidin-1-yl)benzoate (INTERMEDIATE 81, 103.8 mg, 0.21 mmol) was used as a starting material.

[000671] ^1H NMR (400 MHz, DMSO- d_6) δ ppm 0.97 (qd, 1 H), 1.21 - 1.42 (m, 2 H), 1.73 - 1.83 (m, 1 H), 1.91 - 2.03 (m, 1 H), 2.56 - 2.65 (m, 1 H), 2.69 - 2.80 (m, 1 H), 3.68 - 3.79 (m, 1 H), 3.83 - 3.93 (m, 2 H), 7.27 (d, 1 H), 7.34 (d, 2 H), 7.42 - 7.48 (m, 1 H), 7.49 - 7.56 (m, 3 H), 7.57 - 7.62 (m, 1 H), 7.72 (d, 2 H).

[000672] LCMS: (ESI) m/z 431 $[\text{M}+\text{H}]^+$.

INTERMEDIATE 85

[000673] (*S*)-4-(4-((4'-chlorobiphenyl-2-yl)(cyano)methyl)piperidin-1-yl)benzoic acid, HCl salt



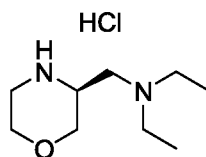
[000674] The title product (215 mg, yield: quantitative) was obtained using a procedure similar to the one described for the synthesis of INTERMEDIATE 83. (*S*)-*tert*-Butyl 4-(4-((4'-chlorobiphenyl-2-yl)(cyano)methyl)piperidin-1-yl)benzoate (INTERMEDIATE 82, 101.8 mg, 0.21 mmol) was used as starting material.

[000675] ^1H NMR (400 MHz, DMSO- d_6) δ ppm 0.90 - 1.03 (m, 1 H), 1.21 - 1.40 (m, 3 H), 1.73 - 1.82 (m, 1 H), 1.91 - 2.03 (m, 1 H), 2.55 - 2.65 (m, 1 H), 2.69 - 2.80 (m, 1 H), 3.68 - 3.80 (m, 1 H), 3.84 - 3.95 (m, 2 H), 6.89 (d, 2 H), 7.27 (dd, 1 H), 7.31 - 7.39 (m, 2 H), 7.45 (td, 1 H), 7.49 - 7.57 (m, 3 H), 7.58 - 7.63 (m, 1 H), 7.69 - 7.79 (m, 2 H).

[000676] LCMS:(ESI) m/z 431 $[\text{M}+\text{H}]^+$.

INTERMEDIATE 86

[000677] (*S*)-*N*-ethyl-*N*-(morpholin-3-ylmethyl)ethanamine hydrochloride salt



[000678] Step 1: A solution of (*S*)-*tert*-butyl 3-(aminomethyl)morpholine-4-carboxylate (1.0 g, 4.62 mmol) in MeOH (15 ml) was treated with acetaldehyde (0.204 g, 4.62 mmol). The reaction mixture was stirred at 0 °C for 15 minutes and sodium triacetoxyborohydride (2.450 g, 11.56 mmol) was added all at once. The resulting mixture was stirred for 24 h and the mixture was diluted with DCM (15 ml) and washed with saturated aq. sodium bicarbonate (15 ml). The organic phase dried over sodium sulfate, filtered, and concentrated under pressure to give a residue which was purified by column chromatography (ISCO, 12 g silica gel column, eluting with 0→20 % MeOH in DCM) to give (*S*)-*tert*-butyl 3-((diethylamino)methyl)morpholine-4-

carboxylate (INTERMEDIATE 86, STEP 1).

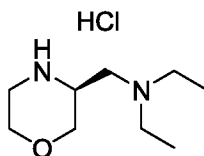
[000679] LCMS: (ESI) m/z 273 $[M+H]^+$.

[000680] Step 2: (*S*)-*tert*-butyl 3-((diethylamino)methyl)morpholine-4-carboxylate (INTERMEDIATE 86, STEP 1) was dissolved with TFA/DCM, (10 ml, 1:1 v/v) and the resulting mixture was stirred for 1 hour at room temperature. The volatiles were removed under reduced pressure and the concentrate was treated with 4N HCl in dioxane (5 ml), stirred for 10 minutes and the volatiles were removed under reduced pressure. The resulting semi solid was triturated with diethyl ether (2x 30 ml), filtered and dried to give the title product (0.65 g, yield: 67%).

[000681] LCMS: (ESI) m/z 173 $[M+H]^+$.

[000682] INTERMEDIATE 86A

[000683] Intermediate 86 was also prepared according to the following procedure:



[000684] Step 1: To a solution of (*S*)-*tert*-butyl 3-(aminomethyl)morpholine-4-carboxylate (commercially available, 0.62 g, 2.87 mmol) in dichloromethane (28.0 ml) were added sequentially pyridine (0.5 ml, 5.73 mmol) and acetyl chloride (0.25 ml, 3.44 mmol). After 30 min the reaction was diluted with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride. The resulting mixture was extracted with ethyl acetate (x3), and the combined organic layers were then dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resulting light yellow oil was purified by flash column chromatography (ISCO, SiO₂, 0-10% methanol in ethyl acetate over 10 min) to afford (*S*)-*tert*-butyl 3-(acetamidomethyl)morpholine-4-carboxylate (0.741 g, yield: almost quantitative, INTERMEDIATE 86A STEP 1).

[000685] ¹H NMR (300 MHz, CHLOROFORM-*d*) δ 5.85 (br. s., 1H), 3.92 - 4.26 (m, 2H), 3.67 - 3.91 (m, 3H), 3.56 - 3.64 (m, 1H), 3.46 (dt, 1H), 3.09 - 3.32 (m, 2H), 1.96 (s, 3H), 1.49 (s, 9H).

[000686] LCMS: (ESI) m/z 259 $[M+H]^+$.

[000687] Step 2: To a degassed solution of (*S*)-*tert*-butyl 3-(acetamidomethyl)morpholine-4-carboxylate (INTERMEDIATE 86A, Step 1, 0.69 g, 2.68 mmol) and DMF (20 ml) was added sequentially iodoethane (1.297 ml, 16.05 mmol) and 60% sodium hydride in mineral oil (0.118 g, 2.94 mmol) in one portion. After 15 min, the reaction was diluted with ethyl acetate and washed with water (x2). The aqueous layer were extracted with ethyl acetate, and then the combined

organic layers were washed with saturated aqueous sodium chloride. The organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resulting light yellow oil was purified by flash column chromatography (SiO₂, ISCO, 0-100% ethyl acetate in hexanes over 10 min, then 10% methanol in ethyl acetate for 5 min) to afford (S)-tert-butyl 3-((N-ethylacetamido)methyl)morpholine-4-carboxylate (0.586 g, yield : 76 %, INTERMEDIATE 86A, Step 2).

[000688] ¹H NMR (300 MHz, DMSO-d₆, 87 °C) δ 4.07 (br. s., 1H), 3.80 (d, 1H), 3.05 - 3.74 (m, 9H), 2.00 (s, 3H), 1.38 - 1.46 (m, 9H), 1.10 (t, 3H).

[000689] LCMS: (ESI) *m/z* 287 [M+H]⁺.

[000690] Step 3: To a solution of (S)-tert-butyl 3-((N-ethylacetamido)methyl)morpholine-4-carboxylate (INTERMEDIATE 86A, Step 2, 0.04 g, 0.14 mmol) and diphenylsilane (0.052 ml, 0.28 mmol) in tetrahydrofuran (1.345 ml) at rt was added carbonyltris(triphenylphosphine)rhodium(I)hydride (6.42 mg, 6.98 μmol). After a brief surge of gas evolution, the now yellow reaction was stirred for 30 min and then quenched with 1N aqueous hydrogen chloride. The mixture was extracted with ether, and the aqueous layer was basified with 50% aqueous sodium hydroxide. The aqueous layer was the extracted with ethyl acetate (x4), and the combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford (S)-tert-butyl 3-((diethylamino)methyl)morpholine-4-carboxylate (0.038 g, yield: almost quantitative) (INTERMEDIATE 86A, Step 3).

[000691] ¹H NMR (300 MHz, CHLOROFORM-d) δ 3.98 (d, 1H), 3.58 - 3.82 (m, 3H), 3.29 - 3.46 (m, 2H), 2.90 - 3.04 (m, 1H), 2.71 - 2.86 (m, 1H), 2.36 - 2.63 (m, 4H), 2.21 (d, 1H), 1.36 - 1.42 (m, 9H), 0.87 - 1.01 (m, 6H).

[000692] LCMS: (ESI) *m/z* 273 [M+H]⁺.

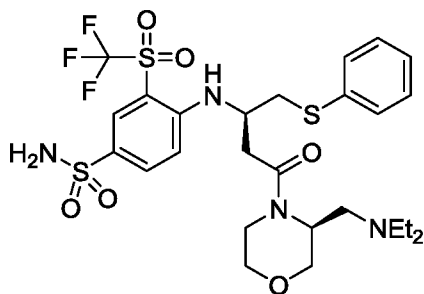
[000693] Step 4: To (S)-tert-butyl 3-((diethylamino)methyl)morpholine-4-carboxylate (0.348 g, 1.28 mmol INTERMEDIATE 86A, Step 3) was added 32 wt% hydrochloric acid in water (1.5 ml, 15.80 mmol). After gas evolution ceased, the mixture was concentrated under reduced pressure. The resulting yellow residue was treated with 5% methanol in dichloromethane and reconcentrated (x3) to afford (S)-N-ethyl-N-(morpholin-3-ylmethyl)ethanamine hydrochloride salt (INTERMEDIATE 86, yield: almost quantitative).

[000694] ¹H NMR (300 MHz, METHANOL-d₄) δ 4.20 (dd, 1H), 3.99 - 4.13 (m, 2H), 3.79 - 3.96 (m, 2H), 3.60 - 3.70 (m, 1H), 3.27 - 3.54 (m, 6H), 1.43 (t, 6H).

[000695] LCMS: (ESI) *m/z* 173 [M+H]⁺.

INTERMEDIATE 87

[000696] 4-((*R*)-4-((*S*)-3-((diethylamino)methyl)morpholino)-4-oxo-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

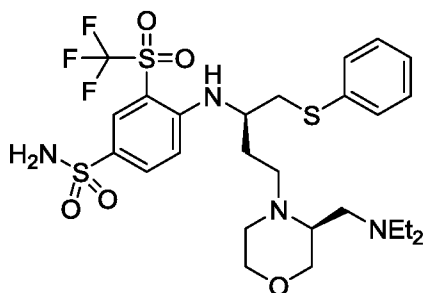


[000697] To a solution of (*R*)-4-(phenylthio)-3-(4-sulfamoyl-2-(trifluoromethylsulfonyl)phenylamino) butanoic acid (INTERMEDIATE 8, 500 mg, 1.00 mmol), (*S*)-*N*-ethyl-*N*-(morpholin-3-ylmethyl)ethanamine hydrochloride salt (INTERMEDIATE 86, 50 mg, 1.2 mmol), DIPEA (0.526 ml, 3.01 mmol), in DMA (5 ml) was added HATU (458 mg, 1.20 mmol). The mixture was stirred for 1 hour at room temperature and diluted with ethyl acetate (200 ml). The mixture was washed successively with 1 M aq. sodium bisulfate, saturated sodium bicarbonate, and brine. The organic phase was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The concentrate was purified column chromatography (ISCO, eluting with 0→100 % DCM/10 % 2 M ammonia in MeOH in DCM over 24 minutes) to give the title product (380 mg, yield: 58 %).

[000698] LCMS: (ESI) m/z 653 $[M+H]^+$.

INTERMEDIATE 88

[000699] 4-((*R*)-4-((*S*)-3-((diethylamino)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide



[000700] A mixture of 4-((*R*)-4-((*S*)-3-((diethylamino)methyl)morpholino)-4-oxo-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide (INTERMEDIATE 87, 360 mg, 0.55 mmol) and 1 M borane-tetrahydrofuran complex in THF (1191 μ l, 1.19 mmol) was stirred at room temperature for 16 hours. The reaction mixture was treated carefully with MeOH (5 ml) and concentrated HCl (1 ml). The mixture was heated at 80

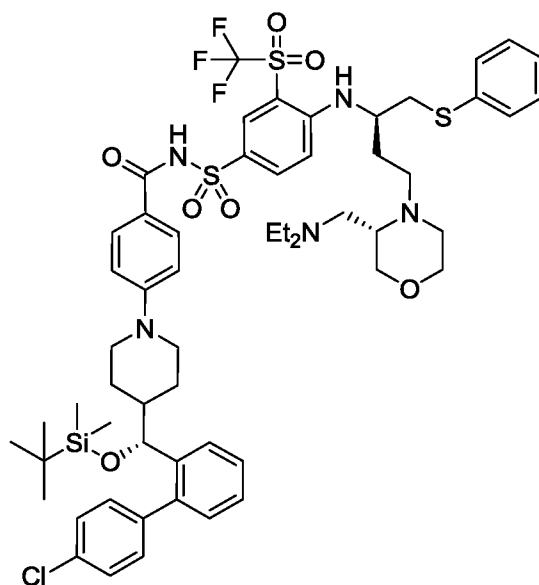
°C for 3 hours, cooled to r.t, and the pH was adjusted to pH 10 with 4 N aqueous sodium carbonate. The mixture was diluted with ethyl acetate (300 ml), washed successively with water (150 ml) and brine (150 ml), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The concentrate was purified by column chromatography (ISCO, eluting with 0→20% MeOH/DCM over 15 minutes) to give the title product (130 mg, yield: 37 %).

[000701] ^1H NMR (400 MHz, METHANOL- d_4) δ ppm 0.79 (t, 6 H) 1.53 - 1.69 (m, 1 H) 1.91 - 2.45 (m, 11 H) 2.63 - 2.87 (m, 2 H) 2.98 - 3.24 (m, 5 H) 3.43 (ddd, 1 H) 3.60 (dt, 1 H) 3.68 (dd, 1 H) 3.87 - 4.05 (m, 1 H) 6.68 (d, 1 H) 7.07 - 7.26 (m, 3 H) 7.26 - 7.39 (m, 2 H) 7.75 (dd, 1 H) 8.04 (d, 1 H).

[000702] LCMS: (ESI) m/z 639 $[\text{M}+\text{H}]^+$.

INTERMEDIATE 89

[000703] 4-(4-((*R*)-(tert-butyldimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-((*S*)-3-((diethylamino)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide



[000704] A solution of (*R*)-4-(4-((tert-butyldimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)benzoic acid, (INTERMEDIATE 13, 109 mg, 0.20 mmol), 4-((*R*)-4-((*S*)-3-((diethylamino)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide (INTERMEDIATE 88, 130 mg, 0.20 mmol), EDC (78 mg, 0.41 mmol), DMAP (49.7 mg, 0.41 mmol), TEA (0.028 ml, 0.20 mmol) and DCM (5 ml) was stirred overnight at room temperature. The reaction mixture was diluted with DCM (50 ml) and washed successively with water (2 x 50 ml) and brine (50 ml). The organic phase was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The concentrate

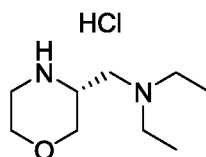
was purified by column chromatography (ISCO, eluting with 0→20 MeOH/DCM over 19 minutes) to give the title product (100 mg, yield: 42.5 %).

[000705] ^1H NMR (400 MHz, DICHLOROMETHANE- d_2) δ ppm 0.00 (s, 3 H) 0.17 (s, 3 H) 1.09 (s, 9 H) 1.19 (t, 6 H) 1.51 (br. s., 5 H) 1.69 - 1.93 (m, 2 H) 1.92 - 2.05 (m, 1 H) 2.24 - 2.38 (m, 1 H) 2.41 - 2.53 (m, 1 H) 2.59 - 3.05 (m, 11 H) 3.30 (t, 2 H) 3.54 - 3.65 (m, 1 H) 3.71 - 3.80 (m, 1 H) 3.92 (d, 3 H) 3.99 - 4.09 (m, 1 H) 4.10 - 4.24 (m, 1 H) 4.84 (br. s., 1 H) 6.86 (d, 1 H) 7.00 (d, $J=8.84$ Hz, 2 H) 7.13 (d, 1 H) 7.36 (dd, 1 H) 7.40 - 7.72 (m, 11 H) 7.76 - 7.88 (m, 1 H) 7.95 (d, 2 H) 8.24 (s, 1 H) 8.53 (d, 1 H).

[000706] LCMS: (ESI) m/z 1156 $[\text{M}+\text{H}]^+$.

INTERMEDIATE 90

[000707] (*R*)-*N*-ethyl-*N*-(morpholin-3-ylmethyl)ethanamine hydrochloride salt



[000708] Step 1: A solution of (*R*)-*tert*-butyl 3-(aminomethyl)morpholine-4-carboxylate (commercially available, 250 mg, 1.16 mmol) and DCM (7 ml) at 0 °C was treated with acetaldehyde (0.162 ml, 2.89 mmol). The reaction mixture was stirred at 0 °C for 15 minutes and sodium triacetoxyborohydride (612 mg, 2.89 mmol) was added all at once. The resulting mixture was stirred for 24 h and the mixture was diluted with 20 ml of DCM (20 ml) and washed with saturated aq. sodium bicarbonate (20 ml). The organic phase was dried over sodium sulfate, filtered, and concentrate under pressure to give (*R*)-*tert*-butyl 3-((diethylamino)methyl)morpholine-4-carboxylate (INTERMEDIATE 90, STEP 1)

[000709] LCMS: (ESI) m/z 273 $[\text{M}+\text{H}]^+$.

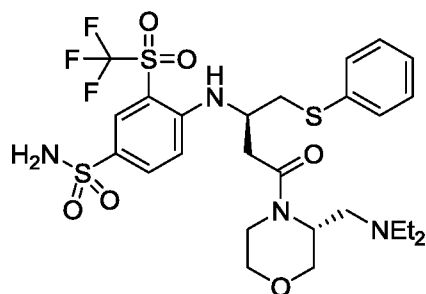
[000710] Step 2: (*R*)-*tert*-butyl 3-((diethylamino)methyl)morpholine-4-carboxylate (INTERMEDIATE 90, STEP 1) was dissolved with TFA/DCM, (6 ml, 1:1 v/v) and the resulting mixture was stirred for 1 h at room temperature. The volatiles were removed under reduced pressure and the concentrate was treated with 4N HCl in dioxane (3 ml), stirred for 10 minutes and the volatiles were removed under reduced pressure. The resulting semi solid was triturated with diethyl ether (2x 30 ml) and dried to give the title product (140 mg, yield: 58 %).

[000711] LCMS: (ESI) m/z 173 $[\text{M}+\text{H}]^+$.

INTERMEDIATE 91

[000712] 4-((*R*)-4-((*R*)-3-((diethylamino)methyl)morpholino)-4-oxo-1-(phenylthio)butan-2-

ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide



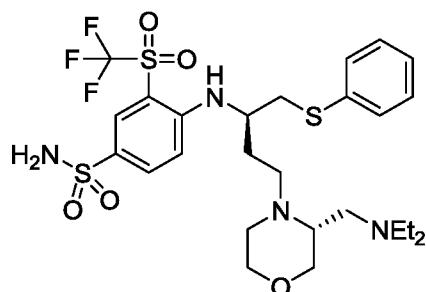
[000713] To a solution of (*R*)-4-(phenylthio)-3-(4-sulfamoyl-2-(trifluoromethylsulfonyl)phenylamino) butanoic acid (INTERMEDIATE 8, 500 mg, 1.00 mmol), (*R*)-*N*-ethyl-*N*-(morpholin-3-ylmethyl)ethanamine hydrochloride salt (INTERMEDIATE 90, 209 mg, 1.00 mmol), DIPEA (0.701 ml, 4.01 mmol) in DMA (5 ml) was added HATU (458 mg, 1.20 mmol). The mixture was stirred for 1 h at room temperature and diluted with ethyl acetate (200 ml). The mixture was washed successively with 1M aq. sodium bisulfate, saturated sodium bicarbonate, and brine. The organic phase was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The concentrate was purified column chromatography (ISCO, eluting with 0→100 % DCM/ 10 % 2 M ammonia in MeOH in DCM over 24 minutes) to give the title product (200 mg, yield: 30.5 %).

[000714] ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 0.75 - 1.06 (m, 6 H) 2.32 - 2.67 (m, 6 H) 2.69 - 2.89 (m, 3 H) 3.11 - 3.42 (m, 7 H) 3.45 - 3.57 (m, 1 H) 3.67 - 3.92 (m, 3 H) 4.26 (d, 2 H) 6.73 (d, 1 H) 7.08 - 7.26 (m, 3 H) 7.27 - 7.37 (m, 2 H) 7.65 - 7.83 (m, 1 H) 7.96 - 8.12 (m, 1 H).

[000715] LCMS: (ESI) *m/z* 653 [M+H]⁺.

INTERMEDIATE 92

[000716] 4-((*R*)-4-((*R*)-3-((diethylamino)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide



[000717] A mixture of 4-((*R*)-4-((*R*)-3-((diethylamino)methyl)morpholino)-4-oxo-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide (INTERMEDIATE 91, 200 mg, 0.31 mmol) and 1 M borane-tetrahydrofuran complex (662 μl,

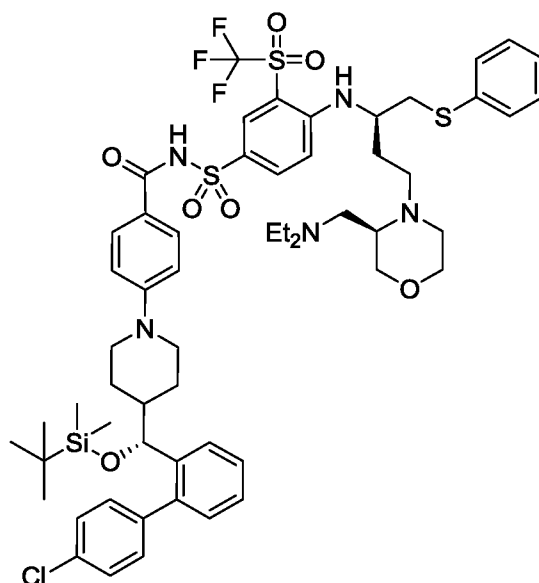
0.66 mmol) was stirred at room temperature for 16 hours. The reaction mixture was treated carefully with MeOH (5 ml) and concentrated HCl (1 ml). The mixture was heated at 80 °C for 3 hours, cooled to r.t, and the pH was adjusted to pH 10 with 4 N aqueous sodium carbonate. The mixture was diluted with ethyl acetate (300 ml), washed successively with water (150 ml) and brine (150 ml), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The concentrate was purified by column chromatography (ISCO, eluting with 0→20% MeOH/DCM over 15 minutes) to give the title product (109 mg, yield: 56 %).

[000718] ^1H NMR (400 MHz, METHANOL- d_4) δ ppm 0.79 - 0.91 (m, 6 H) 1.54 - 1.74 (m, 1 H) 1.89 - 2.07 (m, 1 H) 2.13 - 2.48 (m, 10 H) 2.58 (ddd, 1 H) 2.75 (ddd, 1 H) 3.02 - 3.24 (m, 3 H) 3.36 (dd, 1 H) 3.46 - 3.65 (m, 3 H) 3.95 (dd, 1 H) 6.74 (d, 1 H) 7.08 - 7.26 (m, 3 H) 7.26 - 7.38 (m, 2 H) 7.78 (dd, 1 H) 8.04 (d, 1 H).

[000719] LCMS: (ESI) m/z 639 $[\text{M}+\text{H}]^+$.

INTERMEDIATE 93

[000720] 4-(4-((*R*)-(tert-butyl)dimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-((*R*)-3-((diethylamino)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide



[000721] The title product (100 mg, yield: 55 %) was prepared using a procedure similar to the one described for the synthesis of INTERMEDIATE 89. (*R*)-4-(4-((tert-Butyl)dimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)benzoic acid, (INTERMEDIATE 13, 84 mg, 0.16 mmol) and 4-((*R*)-4-((*R*)-3-((diethylamino)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide (INTERMEDIATE 92, 100 mg, 0.16 mmol) were used as starting materials. The resulting product was purified by column chromatography (ISCO,

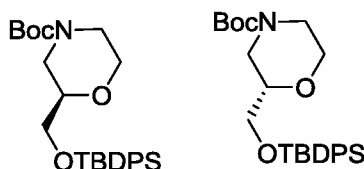
eluting with 0→20% MeOH/DCM for 19 minutes), providing the title product.

[000722] ^1H NMR (400 MHz, $\text{DICHLOROMETHANE-}d_2$) δ ppm 0.00 (s, 3 H) 0.17 (s, 3 H) 1.09 (s, 9 H) 1.29 (t, 6 H) 1.40 - 1.69 (m, 4 H) 1.71 - 1.92 (m, 2 H) 1.92 - 2.06 (m, 1 H) 2.24 (s, 1 H) 2.58 (br. s., 3 H) 2.71 - 3.09 (m, 10 H) 3.35 (dd, 2 H) 3.71 (br. s., 3 H) 3.84 (br. s., 1 H) 3.90 - 3.99 (m, 1 H) 3.99 - 4.09 (m, 1 H) 4.16 - 4.30 (m, 1 H) 4.76 - 4.96 (m, 1 H) 6.76 - 7.11 (m, 5 H) 7.36 (dd, 1 H) 7.41 - 7.70 (m, 13 H) 7.74 - 7.87 (m, 1 H) 7.91 (d, 2 H) 8.19 (s, 1 H) 8.53 (d, 1 H).

[000723] LCMS: (ESI) m/z 1158 $[\text{M}+\text{H}]^+$.

INTERMEDIATE 94

[000724] (*R*)-*tert*-Butyl 2-((*tert*-butyldiphenylsilyloxy)methyl)morpholine-4-carboxylate and (*S*)-*tert*-butyl 2-((*tert*-butyldiphenylsilyloxy)methyl)morpholine-4-carboxylate, mixture of enantiomers

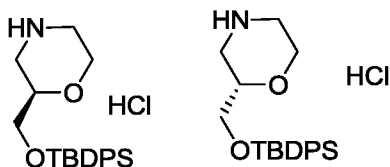


[000725] Pyridine (0.313 ml, 3.87 mmol) and DMAP (0.031 g, 0.26 mmol) were added to a solution of (*R*)-*tert*-butyl 2-(hydroxymethyl)morpholine-4-carboxylate and (*S*)-*tert*-butyl 2-(hydroxymethyl)morpholine-4-carboxylate, mixture of enantiomers (commercially available, 0.560 g, 2.58 mmol) in DCM (7.48 ml) at ambient temperature. *tert*-Butylchlorodiphenylsilane (0.795 ml, 3.09 mmol) was added and the reaction mixture was stirred at room temperature overnight. The mixture was concentrated under reduced pressure and the concentrate was purified by column chromatography (ISCO, eluting with 0→100% EtOAc/hexanes) to give the title products as a mixture of enantiomers (0.853 g, yield: 73 %).

[000726] LCMS: (ESI) m/z 456 $[\text{M}+\text{H}]^+$.

INTERMEDIATE 95

[000727] (*R*)-2-((*tert*-butyldiphenylsilyloxy)methyl)morpholine compound and (*S*)-2-((*tert*-butyldiphenylsilyloxy)methyl)morpholine hydrochloride salts, mixture of enantiomers



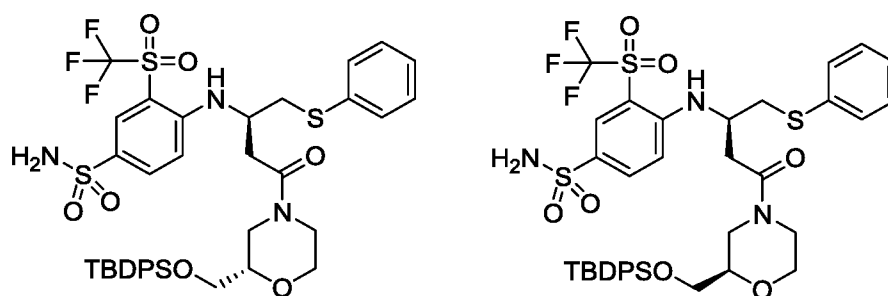
[000728] HCl (4M in Dioxane, 3.24 ml, 93.27 mmol) was added dropwise into a solution of (*R*)-*tert*-Butyl 2-((*tert*-butyldiphenylsilyloxy)methyl)morpholine-4-carboxylate and (*S*)-*tert*-butyl 2-((*tert*-butyldiphenylsilyloxy)methyl)morpholine-4-carboxylate, mixture of enantiomers

(INTERMEDIATE 94, 0.85 g, 1.87 mmol) in DCM (2.98 ml), and the resulting reaction mixture was stirred at room temperature for 30 minutes. The volatiles were removed under reduced pressure to afford the title product as a mixture of enantiomers (0.73 g, yield: quantitative).

[000729] LCMS: (ESI) m/z 356 $[M+H]^+$.

INTERMEDIATE 96

[000730] 4-((*R*)-4-((*R*)-2-((*tert*-butyldiphenylsilyloxy)methyl)morpholino)-4-oxo-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide and 4-((*R*)-4-((*S*)-2-((*tert*-butyldiphenylsilyloxy)methyl)morpholino)-4-oxo-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

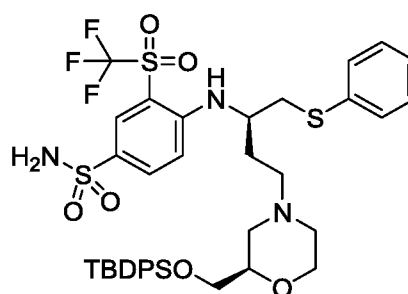
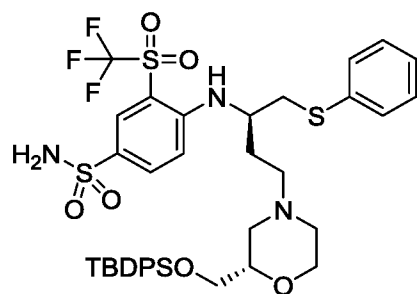


[000731] (*R*)-4-(phenylthio)-3-(4-sulfamoyl-2-(trifluoromethylsulfonyl)phenylamino)butanoic acid (INTERMEDIATE 8, 0.850 g, 1.71 mmol) was added to a solution of (*R*)-2-((*tert*-butyldiphenylsilyloxy)methyl)morpholine compound and (*S*)-2-((*tert*-butyldiphenylsilyloxy)methyl)morpholine hydrochloride salts, mixture of enantiomers (INTERMEDIATE 95, 0.735 g, 1.88 mmol) in DMF (5.09 ml) followed by sequential addition of DIPEA (0.596 ml, 3.41 mmol), EDC (0.490 g, 2.56 mmol) and HOBt (0.392 g, 2.56 mmol). The resulting reaction mixture was stirred at room temperature overnight. The mixture was diluted with EtOAc and washed with H₂O (2x), 1N aq. NaHSO₄, saturated aq. NaHCO₃ and brine. The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure. The concentrate was purified by column chromatography (ISCO, eluting with 50% EtOAc/ hexanes) to provide the title products as a mixture of enantiomers (1.6 g, yield: quantitative).

[000732] LCMS: (ESI) m/z 836 $[M+H]^+$.

INTERMEDIATE 97

[000733] 4-((*R*)-4-((*R*)-2-((*tert*-butyldiphenylsilyloxy)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide and 4-((*R*)-4-((*S*)-2-((*tert*-butyldiphenylsilyloxy)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide



[000734] A solution of $\text{BH}_3 \cdot \text{THF}$ complex in THF (10.23 ml, 10.23 mmol) was added slowly to a solution of 4-((*R*)-4-((*R*)-2-((*tert*-butyldiphenylsilyloxy)methyl)morpholino)-4-oxo-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide and 4-((*R*)-4-((*S*)-2-((*tert*-butyldiphenylsilyloxy)methyl)morpholino)-4-oxo-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide (INTERMEDIATE 96, 1.43 g, 1.71 mmol) and THF (4 ml) and the resulting reaction mixture was stirred at room temperature overnight. The mixture was diluted with a solution of NH_3 in MeOH (7N, 20 ml) and stirred at room temperature overnight. Evaporation of the volatiles under reduced pressure gave a residue, which was diluted with EtOAc. The organic phase was washed with H_2O (2x), dried (Na_2SO_4), filtered and concentrated under reduced pressure to provide the title products (0.52 g, 37 %) as a mixture of diastereomers.

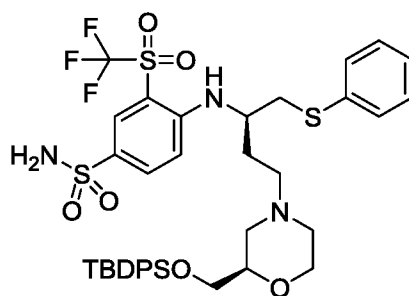
[000735] LCMS: (ESI) m/z 822 $[\text{M}+\text{H}]^+$.

[000736] The resulting two diastereomers of the title product were separated using Chiral HPLC providing INTERMEDIATE 98 and INTERMEDIATE 99 as substantially separated diastereomers.

Column:	Chiralpak IC column
Column dimensions:	4.6x 100mm, 5 μ
Mobile phase:	80% hexanes, 20% isopropanol
Flow rate (ml/min):	1.0 ml/min
Detection (nm):	220 nm

INTERMEDIATE 98

[000737] 4-((*R*)-4-((*R*)-2-((*tert*-butyldiphenylsilyloxy)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide



[000738] The first eluting compound had a retention time of 5.84 minutes, 86% d.e. (294 mg, yield: 21%).

[000739] ^1H NMR (300 MHz, METHANOL- d_4) δ ppm 1.07 (s, 5 H) 1.02 (s, 5 H) 1.73 - 1.91 (m, 2 H) 2.04 - 2.16 (m, 2 H) 2.36 - 2.45 (m, 2 H) 2.53 (d, 1 H) 2.73 (d, 1 H) 2.92 (d, 1 H) 3.12 - 3.29 (m, 2 H) 3.50 - 3.64 (m, 4 H) 3.71 (dd, 1 H) 3.81 (t, 1 H) 4.06 (d, 1 H) 6.86 (d, 1 H) 7.22 - 7.33 (m, 3 H) 7.35 - 7.48 (m, 9 H) 7.62 - 7.73 (m, 4 H) 7.87 (dt, 1 H) 8.15 (s, 1 H).

[000740] LCMS: (ESI) m/z 822 $[\text{M}+\text{H}]^+$.

[000741] Optical rotation:

Concentration: 0.1 g/dL

Lamp: Sodium

Wavelength: 589 nm

Temperature: 20° C

Path length: 10 cm

Cell volume: 1 ml

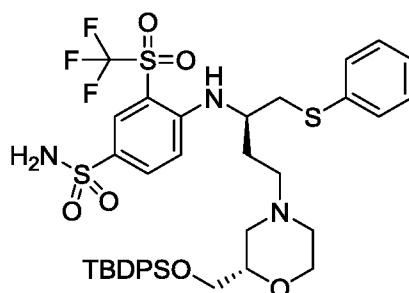
Solvent: Methanol

$[\alpha]_D^{20} = -88$

INTERMEDIATE 99

[000742]

4-((*R*)-4-((*S*)-2-((*tert*-butyldiphenylsilyloxy)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide



[000743] The second eluting compound had a retention time of 6.86 minutes, 92% d.e. (223 mg, yield: 16%).

[000744] ^1H NMR (300 MHz, METHANOL- d_4) δ ppm 1.07 (s, 5 H) 1.02 (s, 5 H) 1.73 - 1.91 (m, 2 H) 2.04 - 2.16 (m, 2 H) 2.36 - 2.45 (m, 2 H) 2.53 (d, 1 H) 2.73 (d, 1 H) 2.92 (d, 1 H) 3.12 - 3.29 (m, 2 H) 3.50 - 3.64 (m, 4 H) 3.71 (dd, 1 H) 3.81 (t, 1 H) 4.06 (d, 1 H) 6.86 (d, 1 H) 7.22 - 7.33 (m, 3 H) 7.35 - 7.48 (m, 9 H) 7.62 - 7.73 (m, 4 H) 7.87 (dt, 1 H) 8.15 (s, 1 H).

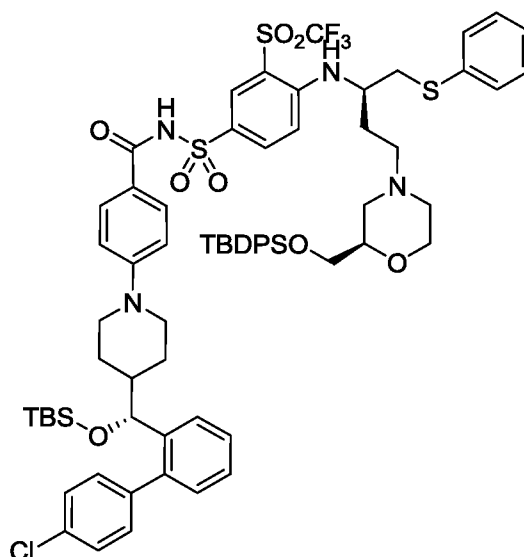
[000745] LCMS: (ESI) m/z 822 $[\text{M}+\text{H}]^+$.

[000746] Optical rotation:

Concentration:	0.1 g/dL
Lamp:	Sodium
Wavelength:	589 nm
Temperature:	20° C
Path length:	10 cm
Cell volume:	1 ml
Solvent:	Methanol
$[\alpha]_D$	-65

INTERMEDIATE 100

[000747] 4-(4-((*R*)-(tert-butyl)dimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-((*R*)-2-((tert-butyl)diphenylsilyloxy)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide



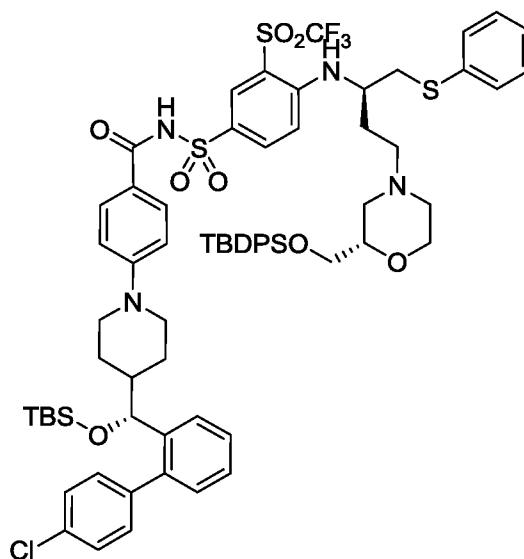
[000748] The title product (77 mg, 66 %) was prepared using a procedure similar to the one described for the synthesis of INTERMEDIATE 33. (*R*)-4-(4-((tert-Butyl)dimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)benzoic acid (INTERMEDIATE 13, 51.7 mg, 0.10 mmol) and 4-((*R*)-4-((*R*)-2-((tert-butyl)diphenylsilyloxy)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

(INTERMEDIATE 98, 72 mg, 0.09 mmol) were used as starting materials. The title product was used in the preparation of EXAMPLE 22 without further purification.

[000749] LCMS:(ESI) m/z 1340 $[M+H]^+$.

INTERMEDIATE 101

[000750] 4-(4-((*R*)-(tert-butyl)dimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-((*S*)-2-((tert-butyl)diphenylsilyloxy)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide

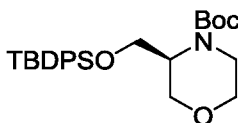


[000751] The title product (99 mg, yield: almost quantitative) was prepared using a procedure similar to the one described for the synthesis of INTERMEDIATE 33. (*R*)-4-(4-((tert-butyl)dimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)benzoic acid (INTERMEDIATE 13, 43.6 mg, 0.08 mmol) and 4-((*R*)-4-((*S*)-2-((tert-butyl)diphenylsilyloxy)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide (INTERMEDIATE 99, 61 mg, 0.07 mmol) were used as starting materials. The title product was used in the preparation of EXAMPLE 23 without further purification.

[000752] LCMS: (ESI) m/z 1340 $[M+H]^+$.

INTERMEDIATE 102

[000753] (*S*)-tert-butyl 3-((tert-butyl)diphenylsilyloxy)methyl)morpholine-4-carboxylate



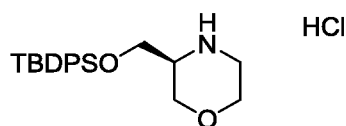
[000754] To a solution of (*S*)-tert-butyl 3-(hydroxymethyl)morpholine-4-carboxylate (1.00 g, 4.60 mmol) in DCM (10 ml) were added sequentially triethylamine (1.3 ml, 9.21 mmol), *tert*-

butylchlorodiphenylsilane (1.414 ml, 5.52 mmol) and DMAP (0.56 g, 4.60 mmol) and the resulting mixture was stirred overnight at ambient temperature. The mixture was diluted with water and the aqueous phase was extracted with DCM. The organic layer was separated and concentrated under reduced pressure. The concentrate was purified by column chromatography (ISCO, eluting with 0→50% EtOAc/hexanes) to afford the title product (1.0 g, yield: 48 %).

[000755] LCMS:(ESI) m/z 478 $[M+Na]^+$.

Intermediate 103

[000756] (*S*)-3-((*tert*-butyldiphenylsilyloxy)methyl)morpholine, HCl salt

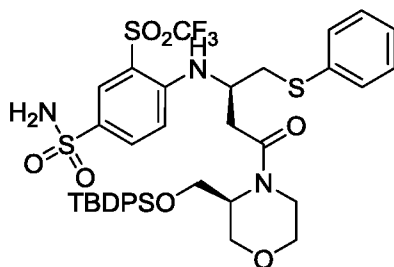


[000757] (*S*)-*tert*-Butyl 3-((*tert*-butyldiphenylsilyloxy)methyl)morpholine-4-carboxylate (INTERMEDIATE 102, 1.0 g, 2.19 mmol) in 1,4-dioxane (10 ml) was treated with HCl (4M in Dioxane, 0.76 ml, 21.95 mmol) and the resulting mixture was stirred at room temperature overnight. Evaporation of the volatiles under reduced pressure gave the title product (0.8 g, yield: 93 %).

[000758] LCMS: (ESI) m/z 356 $[M+H]^+$.

INTERMEDIATE 104

[000759] 4-((*R*)-4-((*S*)-3-((*tert*-butyldiphenylsilyloxy)methyl)morpholino)-4-oxo-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide



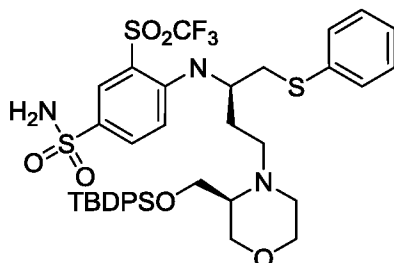
[000760] (*R*)-4-(Phenylthio)-3-(4-sulfamoyl-2-(trifluoromethylsulfonyl)phenylamino)butanoic acid (INTERMEDIATE 8, 0.8 g, 1.60 mmol) was added to a solution of (*S*)-3-((*tert*-butyldiphenylsilyloxy)methyl)morpholine, hydrochloride salt (INTERMEDIATE 103, 0.57 g, 1.60 mmol), DIPEA (0.84 ml, 4.81 mmol) and HATU (0.92 g, 2.41 mmol) in DCM (10 ml) and the resulting mixture was stirred at room temperature for 2 hours. The mixture was diluted with DCM and washed with H₂O (2x), 1N aq. NaHSO₄ and saturated aq. NaHCO₃. The organic layer was dried (Na₂SO₄), concentrated under reduced pressure and purified by column chromatography (ISCO, eluting with 0→100% DCM/ 10% MeOH in DCM) to provide the title

product (0.5 g, yield: 37 %).

[000761] LCMS: (ESI) m/z 834 $[M-H]^+$.

INTERMEDIATE 105

[000762] 4-((*R*)-4-((*S*)-3-((*tert*-butyldiphenylsilyloxy)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

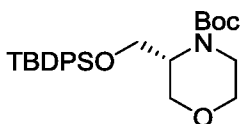


[000763] The title product (0.1 g, yield: 51 %) was prepared using a procedure similar to the one described for the synthesis of INTERMEDIATE 97. 4-((*R*)-4-((*S*)-3-((*tert*-Butyldiphenylsilyloxy)methyl)morpholino)-4-oxo-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide (INTERMEDIATE 104, 0.2 g, 0.24 mmol) was as starting material. The title product was purified by column chromatography (ISCO, eluting with 0→50 % EtOAc/hexanes).

[000764] LCMS: (ESI) m/z 822 $[M+H]^+$.

INTERMEDIATE 106

[000765] (*R*)-*tert*-butyl 3-((*tert*-butyldiphenylsilyloxy)methyl)morpholine-4-carboxylate

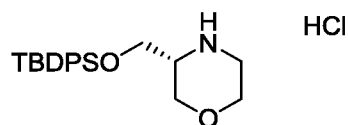


[000766] The title product (2.0 g, yield: 95%) was prepared using a procedure similar to the one described for the synthesis of INTERMEDIATE 102. (*R*)-*tert*-Butyl 3-(hydroxymethyl)morpholine-4-carboxylate (commercially available, 1.0 g, 4.60 mmol) and *tert*-butylchlorodiphenylsilane (1.4 ml, 5.52 mmol) were used as starting materials. The title product was purified by column chromatography (ISCO, eluting with 0→50 % EtOAc/hexanes).

[000767] LCMS: (ESI) m/z 478 $[M+Na]^+$.

INTERMEDIATE 107

[000768] (*R*)-3-((*tert*-butyldiphenylsilyloxy)methyl)morpholine, hydrochloride salt

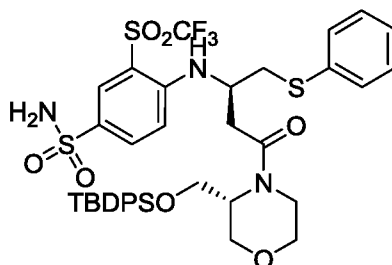


[000769] The title product (1.2 g, yield: 77%) was prepared using a procedure similar to the one described for the synthesis of INTERMEDIATE 103. (*R*)-*tert*-Butyl 3-((*tert*-butyldiphenylsilyloxy)methyl)morpholine-4-carboxylate (INTERMEDIATE 106, 2.0 g, 4.39 mmol) was used as starting material. The title product was obtained as a hydrochloride salt after evaporation of the volatiles under reduced pressure.

[000770] LCMS: (ESI) m/z 356 $[M+H]^+$.

INTERMEDIATE 108

[000771] 4-((*R*)-4-((*R*)-3-((*tert*-butyldiphenylsilyloxy)methyl)morpholino)-4-oxo-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

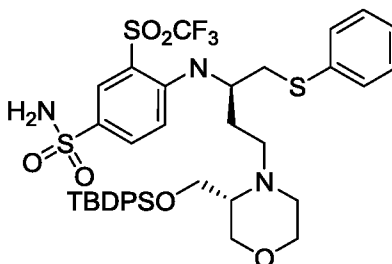


[000772] The title product (0.2 g, yield: 24 %) was prepared using a procedure similar to the one described for the synthesis of INTERMEDIATE 104. (*R*)-3-((*tert*-Butyldiphenylsilyloxy)methyl)morpholine, hydrochloride salt (INTERMEDIATE 107, 0.200 g, 0.24 mmol) and (*R*)-4-(phenylthio)-3-(4-sulfamoyl-2-(trifluoromethylsulfonyl)phenylamino)butanoic acid (INTERMEDIATE 8, 0.500 g, 1.00 mmol) were used as starting material. The title product was purified by column chromatography (ISCO, eluting with 0→100 % DCM/ 10% MeOH in DCM).

[000773] LCMS:(ESI) m/z 834 $[M-H]^+$.

INTERMEDIATE 109

[000774] 4-((*R*)-4-((*R*)-3-((*tert*-butyldiphenylsilyloxy)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

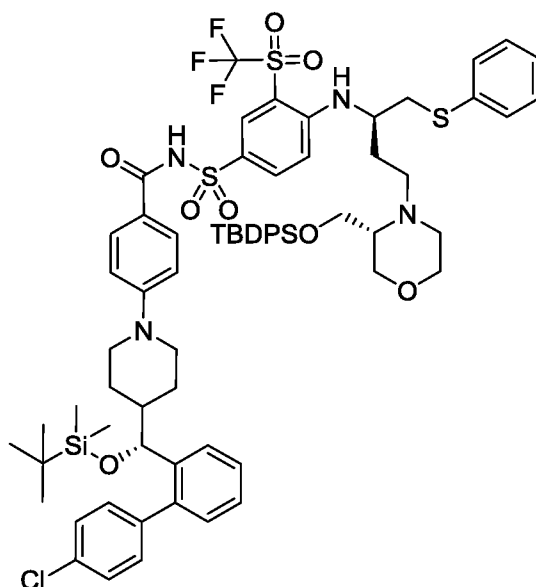


[000775] The title product (0.082 g, yield: 75 %) was prepared using a procedure similar to the one described for the synthesis of INTERMEDIATE 97. 4-((*R*)-4-((*R*)-3-((*tert*-Butyldiphenylsilyloxy)methyl)morpholino)-4-oxo-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide (INTERMEDIATE 108, 0.120 g, 0.14 mmol) was used as starting material. The title product was purified by column chromatography (ISCO, eluting with 0→50 % EtOAc/hexanes).

[000776] LCMS: (ESI) m/z 822 $[M+H]^+$.

INTERMEDIATE 110

[000777] 4-(4-((*R*)-(*tert*-butyldimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-((*R*)-3-((*tert*-butyldiphenylsilyloxy)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide

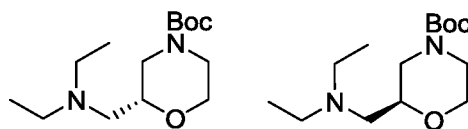


[000778] The title product (134 mg, yield: 77%) was prepared using a procedure similar to the one described for the synthesis of INTERMEDIATE 33. (*R*)-4-(4-((*tert*-Butyldimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)benzoic acid (INTERMEDIATE 13, 67.7 mg, 0.13 mmol) and 4-((*R*)-4-((*R*)-3-((*tert*-butyldiphenylsilyloxy)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide (INTERMEDIATE 109, 94.4 mg, 0.11 mmol) were used as starting materials. The resulting product was purified by column chromatography (ISCO, 12 g silica gel column, eluting with 0→30 % EtOAc/hexanes), providing the title compound.

INTERMEDIATE 111

[000779] (*R*)-*tert*-butyl 2-((diethylamino)methyl)morpholine-4-carboxylate and (*S*)-*tert*-butyl 2-

((diethylamino)methyl)morpholine-4-carboxylate, mixture of enantiomers



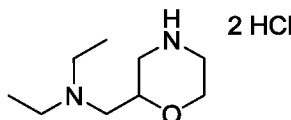
[000780] Potassium carbonate (3.20 g, 23.12 mmol) and iodoethane (1.9 ml, 23.12 mmol) were added sequentially to a solution of (*R*)-*tert*-butyl 2-(aminomethyl)morpholine-4-carboxylate and (*S*)-*tert*-butyl 2-(aminomethyl)morpholine-4-carboxylate, mixture of enantiomers (commercially available, 1.0 g, 4.62 mmol) in EtOH (21.25 ml) was added and the resulting mixture was heated at 80 °C for 3 hours. The reaction mixture was cooled to r.t, diluted with EtOAc and filtered over a pad of Celite® with copious washings (EtOAc). The filtrate was concentrated under reduced pressure and the concentrate by column chromatography (ISCO, eluting with 100% DCM → 100 % DCM/MeOH/NH₃ (10:1:0.1 v/v/v)) to give the title product as a mixture of enantiomers (1.1 g, yield: 85%).

[000781] ¹H NMR (400 MHz, DICHLOROMETHANE-*d*₂) δ ppm 4.0 – 3.75 (m, 4H), 3.56 (m, 1H), 3.00 – 2.55 (m, 8H), 1.48 (s, 9H), 1.26 (m, 6H).

[000782] LCMS: (ESI) *m/z* 273 [M+H]⁺.

INTERMEDIATE 112

[000783] (*R*)-*N*-ethyl-*N*-(morpholin-2-ylmethyl)ethanamine and (*S*)-*N*-ethyl-*N*-(morpholin-2-ylmethyl)ethanamine, mixture of enantiomers



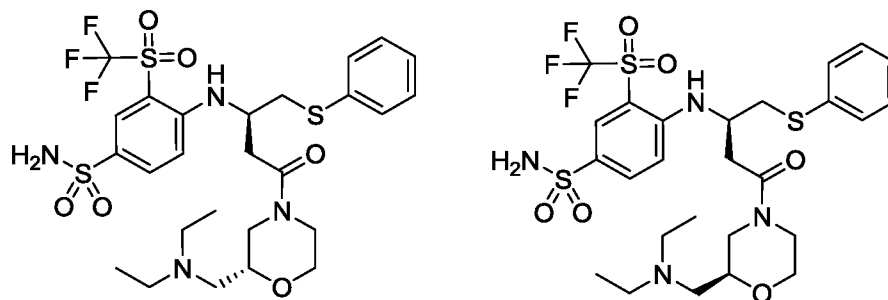
[000784] To a solution of (*R*)-*tert*-butyl 2-((diethylamino)methyl)morpholine-4-carboxylate and (*S*)-*tert*-butyl 2-((diethylamino)methyl)morpholine-4-carboxylate, mixture of enantiomers (INTERMEDIATE 111, 1.03 g, 3.78 mmol) in MeOH (15.8 ml) was added HCl (4M in dioxane, 9.45 ml, 37.81 mmol) and the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure and dried under vacuum overnight to provide the title product as a mixture of enantiomers in the form of a dihydrochloride salt (0.92 g, yield: 99 %).

[000785] ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 4.34 (m, 1H), 3.99 (m, 1H), 3.88– 3.82 (m, 3H), 3.27 (d, 2H), 3.20 – 3.10 (m, 4H), 2.94 (m, 1H), 2.82 (m, 1H), 1.21 (m, 6H).

INTERMEDIATE 113

[000786] 4-((*R*)-4-((*R*)-2-((diethylamino)methyl)morpholino)-4-oxo-1-(phenylthio)butan-2-

ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide and 4-((*R*)-4-((*S*)-2-((diethylamino)methyl)morpholino)-4-oxo-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide hydrochloride salts, mixture of diastereomers



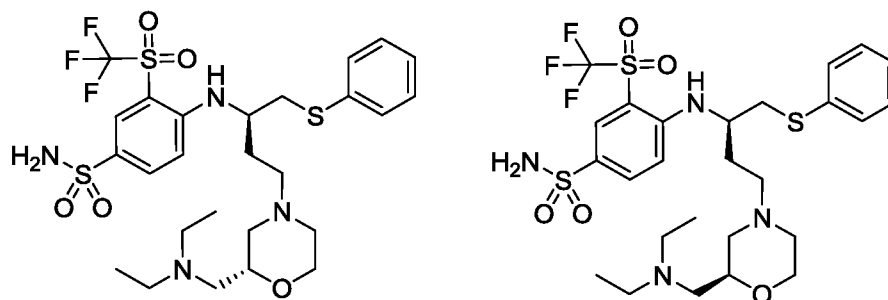
[000787] The title product (1.05 g, yield: 43 %) was prepared using a procedure similar to the one described for the synthesis of INTERMEDIATE 104. (*R*)-*N*-ethyl-*N*-(morpholin-2-ylmethyl)ethanamine and (*S*)-*N*-ethyl-*N*-(morpholin-2-ylmethyl)ethanamine hydrochloride salts, mixture of enantiomers (INTERMEDIATE 112, 0.91 g, 3.71 mmol) and (*R*)-4-(phenylthio)-3-(4-sulfamoyl-2-(trifluoromethylsulfonyl)phenylamino)butanoic acid (INTERMEDIATE 8, 1.850 g, 3.71 mmol) were used as starting material. The title product was purified by column chromatography (ISCO, eluting with 0→100 % DCM to 10% MeOH/0.1% NH₃ in DCM) as a mixture of diastereomers.

[000788] ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.15 (s, 1 H), 7.85 – 7.70 (m, 2 H), 7.43 (m, 2 H), 7.35 – 7.27 (m, 2 H), 6.58 (m, 1 H), 4.40 (m, 1 H), 4.16 (m, 1 H), 3.91 (m, 1 H), 3.55 – 3.40 (m, 2 H), 3.35 – 3.05 (m, 3 H), 3.00 – 2.37 (m, 10 H), 1.04 (m, 6 H).

[000789] LCMS: (ESI) *m/z* 653 [M+H]⁺.

INTERMEDIATE 114

[000790] 4-((*R*)-4-((*R*)-2-((diethylamino)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide and 4-((*R*)-4-((*S*)-2-((diethylamino)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide, mixture of diastereomers



[000791] The title product (0.75 g, yield: 83 %) was prepared using a procedure similar to the one described for the synthesis of INTERMEDIATE 97. 4-((*R*)-4-((*R*)-2-

((diethylamino)methyl)morpholino)-4-oxo-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide and 4-((*R*)-4-((*S*)-2-((diethylamino)methyl)morpholino)-4-oxo-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide, mixture of diastereomers (INTERMEDIATE 113, 0.92 g, 1.41 mmol) was used as starting material. The title product was obtained as a mixture of diastereomers after evaporation of the volatiles under reduced pressure.

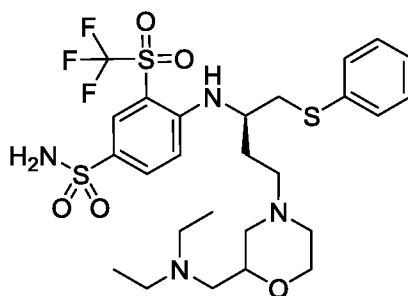
[000792] LCMS: (ESI) m/z 639 $[M+H]^+$.

[000793] The resulting two diastereomers of the title product were separated using were separated using Chiral SFC, providing INTERMEDIATES 115 and 116 as substantially separated diastereomers.

Column:	Chiralpak IB column
Column dimensions:	21 x 250 mm, 5 μ
Modifier:	15 % Methanol, 0.1% dimethylethylamine
Flow rate (ml/min):	60
Outlet Pressure (bar):	100
Detection (nm):	220

INTERMEDIATE 115

[000794] 4-((2*R*)-4-(2-((diethylamino)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide, first eluting compound

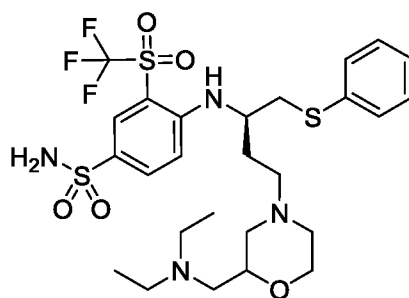


[000795] The first eluting compound had a retention time of 17.41 minutes.

[000796] LCMS: (ESI) m/z 639 $[M+H]^+$.

INTERMEDIATE 116

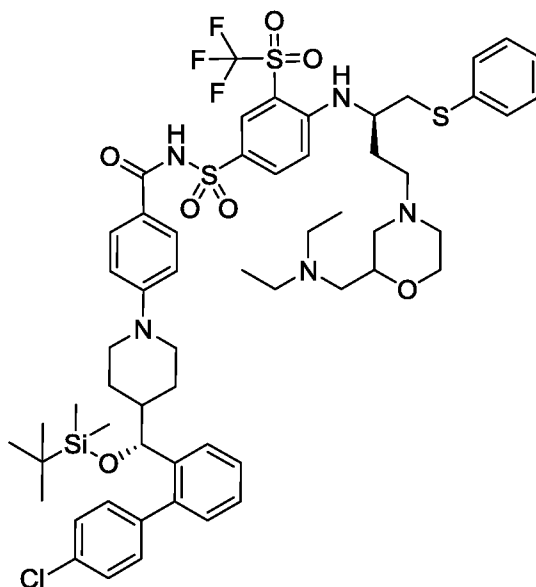
[000797] 4-((2*R*)-4-(2-((diethylamino)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide, second eluting compound



[000798] The second eluting compound had a retention time of 19.18 minutes.

INTERMEDIATE 117

[000799] 4-(4-((*R*)-(tert-butyl dimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-*N*-(4-((2*R*)-4-(2-((diethylamino)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide, single diastereomer

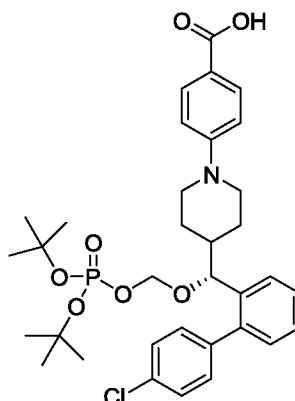


[000800] The title product (199 mg, yield: 74 %) was prepared using a procedure similar to the one described for the synthesis of INTERMEDIATE 33. (*R*)-4-(4-((tert-Butyl dimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)benzoic acid (INTERMEDIATE 13, 125 mg, 0.23 mmol) and 4-((2*R*)-4-(2-((diethylamino)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide (INTERMEDIATE 115, first eluting compound 149 mg, 0.23 mmol) were used as starting materials. The title product was obtained after evaporating the volatiles under reduced pressure, and was used in the preparation of EXAMPLE 26 without further purification.

[000801] LCMS: (ESI) m/z 1156 $[M+H]^+$.

INTERMEDIATE 118

[000802] (*R*)-4-(4-((4'-chlorobiphenyl-2-yl)(di-*tert*-butoxyphosphonooxymethoxy)methyl)piperidin-1-yl)benzoic acid



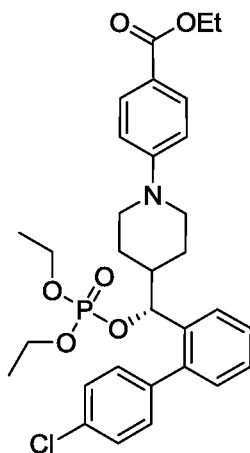
[000803] A solution of (*R*)-4-(4-((4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoic acid (INTERMEDIATE 40, 360 mg, 0.85 mmol) in toluene (4.0 ml) was treated with paraformaldehyde (128 mg, 4.27 mmol) and the resulting mixture was cooled at 0 °C. HCl (g) was slowly bubbled in the solution through a pipet. The mixture was allowed to stir for 1 hour whereupon it was dried over CaCl₂ pellets, resulting in effervescence. The solution was removed by pipet and then spun under reduced pressure (40 mbar) for a few minutes to remove excess HCl. The clear yellow solution was stirred and treated with silver di-*tert*-butyl phosphate (INTERMEDIATE 59, 0.90 g). At 0.25 hours the reaction was filtered through Celite® using a Büchner funnel, and the filter cake was washed with several portions of toluene. Evaporation of the filtrate under reduced pressure afforded a residue that was purified by column chromatography (ISCO, eluting with 0→50% EtOAc/CH₂Cl₂ for 14 minutes) to provide the title product (150 mg, yield: 25%).

[000804] ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 0.93 - 1.43 (m, 21 H) 1.68 - 1.93 (m, 2 H) 2.52 - 2.75 (m, 2 H) 3.66 - 3.78 (m, 1 H) 3.78 - 3.90 (m, 1 H) 4.53 (d, 1 H) 4.71 - 4.83 (m, 1 H) 5.04 - 5.15 (m, 1 H) 6.86 (d, 2 H) 7.20 (d, 1 H) 7.26 - 7.53 (m, 7 H) 7.71 (d, 2 H) 12.17 (s, 1 H).

[000805] LCMS: *m/z* 644 [M + H]⁺.

INTERMEDIATE 119

[000806] (*R*)-ethyl 4-(4-((4'-chlorobiphenyl-2-yl)(diethoxyphosphoryloxy)methyl)piperidin-1-yl)benzoate



[000807] A solution of (*R*)-ethyl 4-(4-((4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoate (INTERMEDIATE 11A, 600 mg, 1.33 mmol), CBr₄ (575 mg, 1.73 mmol), and pyridine (2 ml) at 0°C was treated dropwise over a 10 minute period with triethyl phosphite (0.56 ml, 3.33 mmol). The solution was stirred at 0 °C for about 10 minutes and then the ice bath was removed. The reaction was stirred overnight at r.t. whereupon the excess pyridine was removed under reduced pressure and the concentrate was taken up in 50 ml of DCM. The organic layer was washed successively with 50 ml each of 0.5 N aq. HCl, saturated aqueous sodium bicarbonate, and water. The organic layers were dried over sodium sulfate, filtered and adsorbed onto silica gel. Purification by column chromatography (ISCO, 80 g silica gel column, eluting with 0→100 % EtOAc/hexanes over 24 minutes) gave the title compound (500 mg, yield: 64 %).

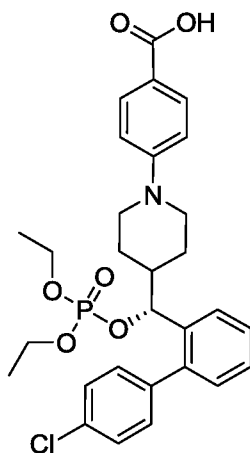
[000808] ¹H NMR (400 MHz, DICHLOROMETHANE-*d*₂) δ ppm 1.00 - 1.16 (m, 1 H) 1.18 - 1.29 (m, 7 H) 1.28 - 1.46 (m, 4 H) 1.74 - 1.92 (m, 1 H) 2.01 (dt, 1 H) 2.61 (td, 1 H) 2.73 (td, 1 H) 3.71 (d, 1 H) 3.79 - 3.91 (m, 1 H) 3.91 - 4.00 (m, 3 H) 4.07 (dt, 1 H) 4.31 (q, 2 H) 5.25 (t, 1 H) 6.82 (d, 2 H) 7.24 (dd, 1 H) 7.34 - 7.54 (m, 6 H) 7.63 (dd, 1 H) 7.79 - 7.97 (m, 2 H).

[000809] ³¹P NMR (121 MHz, DICHLOROMETHANE-*d*₂) δ ppm -1.76 (s, 2 P).

[000810] LCMS: (ESI) *m/z* 586, [M+H]⁺.

INTERMEDIATE 120

[000811] (*R*)-4-(4-((4'-chlorobiphenyl-2-yl)(diethoxyphosphoryloxy)methyl)piperidin-1-yl)benzoic acid



[000812] A solution of (R)-ethyl 4-(4-((4'-chlorobiphenyl-2-yl)(diethoxyphosphoryloxy)methyl)piperidin-1-yl)benzoate (INTERMEDIATE 119, 500 mg, 0.85 mmol) in THF (10 ml) and MeOH (2.5 ml), at room temperature, was treated with a solution of lithium hydroxide (102 mg, 4.27 mmol) in water (2.5 ml). The reaction was heated to 30 °C overnight and subsequently warmed to 40 °C for about 5 hours. The mixture was allowed to cool to room temperature whereupon the volatiles were removed under reduced pressure. The concentrate was diluted with 30 ml of water, acidified with a few drops of 6N HCl to provide a white precipitate. The precipitate was collected by vacuum filtration to give the title compound (410 mg, yield: 86%).

[000813] ^1H NMR (400 MHz, DICHLOROMETHANE- d_2) δ ppm 1.01 - 1.15 (m, 1 H) 1.21 (tdd, 7 H) 1.28 - 1.44 (m, 1 H) 1.81 - 1.94 (m, 1 H) 1.94 - 2.07 (m, 1 H) 2.64 (d, 1 H) 2.76 (m, 1 H) 3.68 - 3.81 (m, 1 H) 3.85 - 4.01 (m, 4 H) 4.01 - 4.15 (m, 1 H) 5.24 (t, 1 H) 6.83 (d, 2 H) 7.23 (dd, 1 H) 7.37 - 7.54 (m, 6 H) 7.58 - 7.68 (m, 1 H) 7.86 - 7.95 (m, 2 H).

[000814] ^{31}P NMR (121 MHz, DICHLOROMETHANE- d_2) δ ppm -1.45 (s, 2 P).

[000815] LCMS: (ESI) m/z 558 $[\text{M}+\text{H}]^+$.

[000816] Optical rotation:

Concentration: 0.1 g/dL

Lamp: Sodium

Wavelength: 589 nm

Temperature: 20° C

Path length: 10 cm

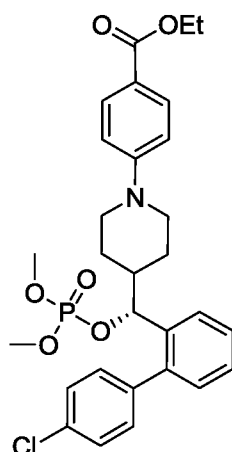
Cell volume: 1 ml

Solvent: Dichloromethane

$[\alpha] = +76$

INTERMEDIATE 121

[000817] (*R*)-ethyl 4-(4-((4'-chlorobiphenyl-2-yl)(dimethoxyphosphoryloxy)methyl)piperidin-1-yl)benzoate



[000818] A similar procedure to that described for INTERMEDIATE 119 utilizing (*R*)-ethyl 4-(4-((4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoate (INTERMEDIATE 11A, 600 mg, 1.33 mmol) and trimethyl phosphite (0.473 ml, 4.0 mmol) as starting material was followed, with subsequent purification by column chromatography (ISCO, 0→100% EtOAc/hexane over 24 minutes) to give the title compound (500 mg, yield: 67%). The title compound was used in the preparation of INTERMEDIATE 122 without further purification.

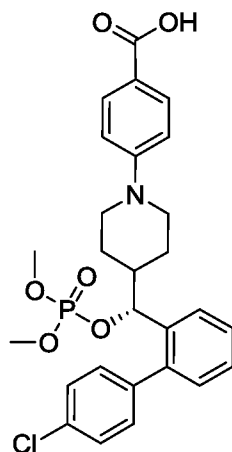
[000819] ^1H NMR (400 MHz, DICHLOROMETHANE- d_2) δ ppm 0.88 - 1.02 (m, 1 H) 1.06 - 1.12 (m, 1 H) 1.17 - 1.31 (m, 5 H) 1.63 - 1.79 (m, 1 H) 1.80 - 1.89 (m, 1 H) 2.48 (td, 1 H) 2.60 (td, 1 H) 3.42 - 3.56 (m, 7 H) 3.58 (d, 1 H) 3.65 - 3.80 (m, 1 H) 4.17 (q, 2 H) 5.11 (t, 1 H) 6.58 - 6.75 (m, 2 H) 7.11 (dd, 1 H) 7.25 - 7.40 (m, 6 H) 7.51 (dd, 1 H) 7.68 - 7.85 (m, 2 H).

[000820] ^{31}P NMR (121 MHz, DICHLOROMETHANE- d_2) δ ppm 0.68 (s, 1 P).

[000821] LCMS: (ESI) m/z 558, $[\text{M}+\text{H}]^+$.

INTERMEDIATE 122

[000822] (*R*)-4-(4-((4'-chlorobiphenyl-2-yl)(dimethoxyphosphoryloxy)methyl)piperidin-1-yl)benzoic acid



[000823] A mixture of lithium hydroxide (107 mg, 4.48 mmol), (*R*)-ethyl 4-(4-((4'-chlorobiphenyl-2-yl)(dimethoxyphosphoryloxy)methyl)piperidin-1-yl)benzoate (INTERMEDIATE 121, 500 mg, 0.9 mmol), THF (10 ml), water (2.5 ml), and MeOH (2.5 ml) was heated at 35 °C overnight. The reaction mixture was concentrated under reduced pressure, diluted with water (10 ml) and acidified with an aqueous solution of 6 N HCl, resulting in a precipitate. The solid was collected by filtration to give the title compound (270 mg, yield: 57 %). The title compound was used in the preparation of EXAMPLE 30 without further purification.

[000824] ¹H NMR (400 MHz, DICHLOROMETHANE-*d*₂) δ ppm 0.91 - 1.40 (m, 4 H) 1.70 - 2.05 (m, 2 H) 2.48 - 2.62 (m, 1 H) 2.70 (m, 1 H) 3.19 - 3.63 (m, 7 H) 3.69 - 3.83 (m, 1 H) 5.16 (t, 1 H) 6.77 (m, 1 H) 7.12 (m, 1 H) 7.21 - 7.46 (m, 7 H) 7.52 (m, 1 H) 7.79 (m, 2 H).

[000825] LCMS: (ESI) *m/z* 530 [M+H]⁺.

[000826] Optical rotation:

Concentration: 0.2 g/dL

Lamp: Sodium

Wavelength: 589 nm

Temperature: 20° C

Path length: 10 cm

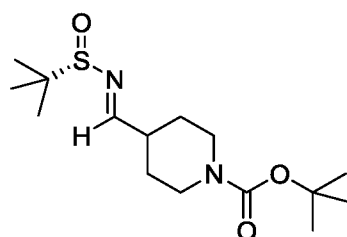
Cell volume: 1 ml

Solvent: Dichloromethane

[α]_D = +51

INTERMEDIATE 123

[000827] (*S,E*)-*tert*-butyl 4-((*tert*-butylsulfinylimino)methyl)piperidine-1-carboxylate



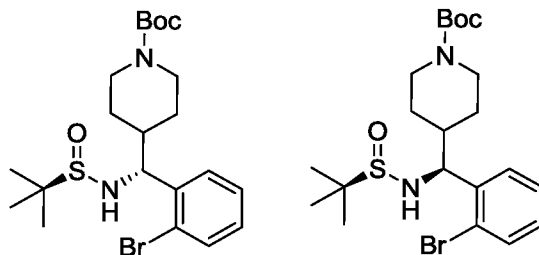
[000828] A solution of (*S*)-2-methylpropane-2-sulfinamide (2.0 g, 16.50 mmol) in THF (8.0 ml) and titanium(IV) ethoxide (17.3 ml, 82.51 mmol) were added sequentially to a solution of *tert*-butyl 4-formylpiperidine-1-carboxylate (3.70 g, 17.33 mmol) in THF (8.0 ml). The resulting mixture was stirred at r.t for 2 hours. The reaction mixture was poured into ice/water and the suspension filtered. The filtrate was extracted with EtOAc and the organic layer was dried with MgSO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was dried

under vacuum to provide the title compound (4.45 g, yield: 85%).

[000829] LCMS: (ESI) m/z 317 $[M+H]^+$.

INTERMEDIATE 124

[000830] *tert*-Butyl 4-((*R*)-(2-bromophenyl)((*S*)-1,1-dimethylethylsulfinamido)methyl)piperidine-1-carboxylate and *tert*-butyl 4-((*S*)-(2-bromophenyl)((*S*)-1,1-dimethylethylsulfinamido)methyl)piperidine-1-carboxylate, mixture of diastereomers

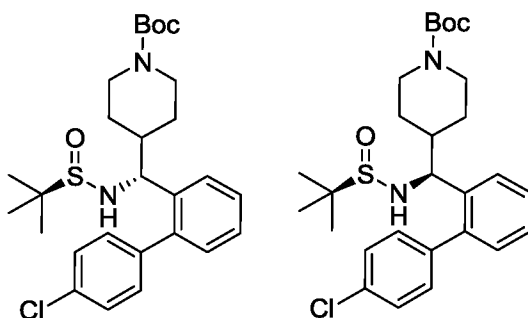


[000831] A solution of isopropylmagnesium chloride lithium chloride complex (24.9 ml, 32.39 mmol, 1.3 M THF) was cooled to -15 °C. 1,2-dibromobenzene (3.80 ml, 31.60 mmol) was added and the mixture was stirred at -15 °C for 2 hours. A solution of (*S,E*)-*tert*-butyl 4-((*tert*-butylsulfinylimino)methyl)piperidine-1-carboxylate (INTERMEDIATE 123, 2.50 g, 3.90 mmol) in THF (10.8 ml) was added dropwise to the first mixture and the resulting reaction mixture was stirred at -15 °C overnight. The reaction mixture was allowed to warm to 0 °C and quenched with saturated. aq. NH_4Cl . The mixture was diluted with EtOAc and washed with H_2O . The organic layer was dried over Na_2SO_4 , filtered and the filtrate concentrated under reduced pressure to give a residue which was purified by column chromatography (ISCO, silica gel column, eluting with 0→100% EtOAc/ hexanes) to provide the title compounds (3.0 g, yield: 80%) as a mixture of diastereomers (ratio of 2:1 in favor of *tert*-butyl 4-((*R*)-(2-bromophenyl)((*S*)-1,1-dimethylethylsulfinamido)methyl)piperidine-1-carboxylate).

[000832] LCMS: (ESI) m/z 474 $[M+H]^+$.

Intermediate 125

[000833] *tert*-Butyl 4-((*R*)-(4'-chlorobiphenyl-2-yl)((*S*)-1,1-dimethylethylsulfinamido)methyl)piperidine-1-carboxylate and *tert*-butyl 4-((*S*)-(4'-chlorobiphenyl-2-yl)((*S*)-1,1-dimethylethylsulfinamido)methyl)piperidine-1-carboxylate, mixture of diastereomers

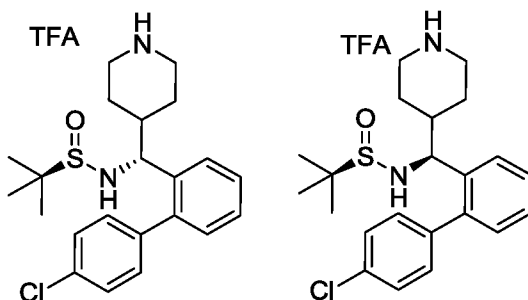


[000834] A suspension of the diastereomeric mixture of *tert*-butyl 4-((*R*)-(2-bromophenyl)((*S*)-1,1-dimethylethylsulfonamido)methyl)piperidine-1-carboxylate and *tert*-butyl 4-((*S*)-(2-bromophenyl)((*S*)-1,1-dimethylethylsulfonamido)methyl)piperidine-1-carboxylate (INTERMEDIATE 124, 2.98 g, 6.29 mmol), 4-chlorophenylboronic acid (1.48 g, 9.44 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (0.258 g, 0.63 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.231 g, 0.25 mmol) and tripotassium phosphate (4.01 g, 18.88 mmol) in degassed toluene (15.0 ml) and H₂O (6.0 ml) was stirred at 100 °C for 5 hours. The reaction mixture was cooled to r.t, diluted with EtOAc and filtered through a pad of Celite®. The organic layer was separated and dried over Na₂SO₄, filtered and the filtrate concentrated to provide a residue which was purified by column chromatography (ISCO, silica gel column, eluting with 0→100% EtOAc/ hexanes) to provide the title compounds (2.42 g, yield: 76%), as a mixture of diastereomers.

[000835] LCMS: (ESI) m/z 505[M+H]⁺.

INTERMEDIATE 126

[000836] (*S*)-*N*-((*R*)-(4'-chlorobiphenyl-2-yl)(piperidin-4-yl)methyl)-2-methylpropane-2-sulfonamide and (*S*)-*N*-((*S*)-(4'-chlorobiphenyl-2-yl)(piperidin-4-yl)methyl)-2-methylpropane-2-sulfonamide trifluoroacetic salt, mixture of diastereomers



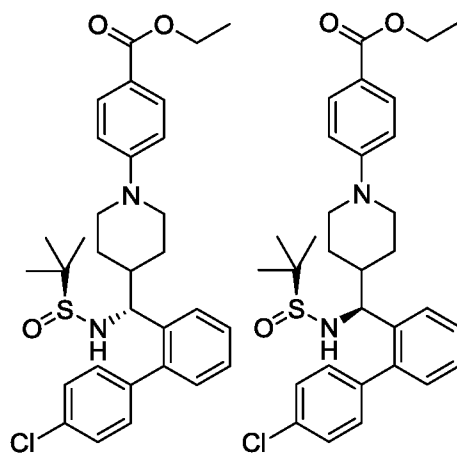
[000837] TFA (3.55 ml, 46.13 mmol) was added to a solution of *tert*-butyl 4-((*R*)-(4'-chlorobiphenyl-2-yl)((*S*)-1,1-dimethylethylsulfonamido)methyl)piperidine-1-carboxylate and *tert*-butyl 4-((*S*)-(4'-chlorobiphenyl-2-yl)((*S*)-1,1-dimethylethylsulfonamido)methyl)piperidine-1-carboxylate, mixture of diastereomers (INTERMEDIATE 125, 2.33 g, 4.61 mmol) in DCM (43 ml) and the reaction mixture was stirred at r.t for 1 hour. The reaction mixture was concentrated

under reduced pressure, diluted with EtOAc and washed with saturated aq. NaHCO₃ (2x). The organic layer was dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue obtained was dried under vacuum to provide title compounds (2.44 g, yield: almost quantitative) as a mixture of diastereomers.

[000838] LCMS: (ESI) m/z 405[M+H]⁺.

INTERMEDIATE 127

[000839] Ethyl 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)((*S*)-1,1-dimethylethylsulfonamido)methyl)piperidin-1-yl)benzoate and Ethyl 4-(4-((*S*)-(4'-chlorobiphenyl-2-yl)((*S*)-1,1-dimethylethylsulfonamido)methyl)piperidin-1-yl)benzoate, mixture of diastereomers



[000840] A suspension of (*S*)-*N*-((*R*)-(4'-chlorobiphenyl-2-yl)(piperidin-4-yl)methyl)-2-methylpropane-2-sulfonamide and (*S*)-*N*-((*S*)-(4'-chlorobiphenyl-2-yl)(piperidin-4-yl)methyl)-2-methylpropane-2-sulfonamide trifluoroacetic salt, mixture of diastereomers (INTERMEDIATE 126, 2.39 g, 4.61 mmol), chloro(2-dicyclohexylphosphino-2',6'-di-isopropoxy-1,1'-biphenyl)[2-(2-aminoethylphenyl)]Pd(II) methylbutyl ether adduct (0.168 g, 0.23 mmol), dicyclohexyl(2',6'-diisopropoxybiphenyl-2-yl)phosphine (0.108 g, 0.23 mmol), ethyl 4-iodobenzoate (0.77 ml, 4.61 mmol), and cesium carbonate (5.26 g, 16.14 mmol) in degassed toluene (22.3 ml) was stirred at 110 °C for 1.5 hours. The reaction mixture was cooled to r.t, diluted with EtOAc and filtered over a pad of Celite. The filtrate was concentrated under reduced pressure to provide a residue which was purified by column chromatography (ISCO, silica gel column, eluting with 0→100% EtOAc/ hexanes) to provide title compound (2.10 g, yield: 82%), as a mixture of diastereomers.

[000841] LCMS: (ESI) m/z 553[M+H]⁺.

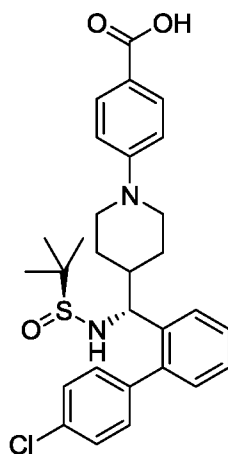
[000842] The two diastereomers were separated using Chiral SFC providing

ethyl 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)((*S*)-1,1-dimethylethylsulfonamido)methyl)piperidin-1-yl)benzoate (INTERMEDIATE 128) as the major diastereomer (1.23 g) and ethyl 4-(4-((*S*)-(4'-chlorobiphenyl-2-yl)((*S*)-1,1-dimethylethylsulfonamido)methyl)piperidin-1-yl)benzoate (INTERMEDIATE 129) as the minor diastereomer (0.59g)

Column: Chiralpak AD column
 Column dimensions: 30 x 250mm, 5 μ
 Mobile phase: CO₂ 75% and EtOH 25%.
 Flow rate (ml/min): 120 ml/min
 Detection (nm): 220 nm

INTERMEDIATE 130

[000843] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)((*S*)-1,1-dimethylethylsulfonamido)methyl)piperidin-1-yl)benzoic acid

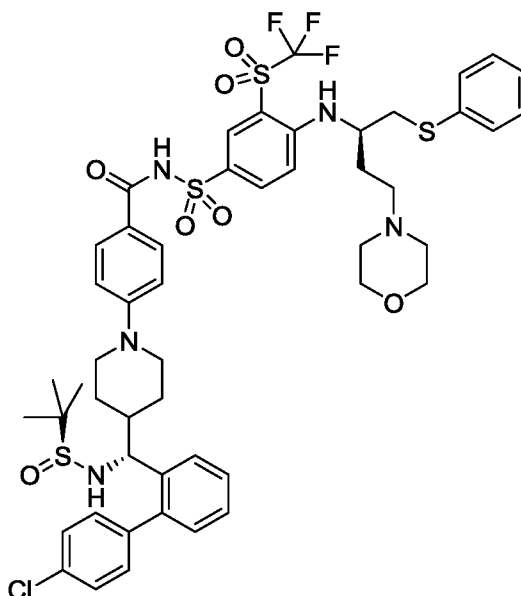


[000844] To a solution of ethyl 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)((*S*)-1,1-dimethylethylsulfonamido)methyl)piperidin-1-yl)benzoate (INTERMEDIATE 128, 0.40 g, 0.62 mmol) in THF (4.3 ml) was added MeOH (1.4 ml) and a solution of LiOH (0.09 g, 4.44 mmol) in water (1.4 ml). The reaction mixture was stirred at 40 °C overnight. The reaction mixture was cooled to rt, concentrated under reduced pressure, and the residue suspended in water. The suspension was cooled to 0 °C, acidified to pH ~2 using 1N HCl aq., filtered, and the filtercake dried in a vacuum oven to provide the title compound (0.38 g, yield: almost quantitative).

[000845] LCMS: (ESI) m/z 525 [M+H]⁺.

INTERMEDIATE 131

[000846] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)((*S*)-1,1-dimethylethylsulfonamido)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide



[000847] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)((*S*)-1,1-dimethylethylsulfinamido)methyl)piperidin-1-yl)benzoic acid (INTERMEDIATE 130, 0.150 g, 0.29 mmol), DMAP (70 mg, 0.57 mmol), and EDC (0.110 g, 0.57 mmol) were placed in a 40 ml vial and flushed with nitrogen. DCM (4.0 ml) and DIPEA (0.10 ml, 0.57 mmol) were added, and the solution was stirred at r.t for 10 minutes. A solution of (*R*)-4-(4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide (INTERMEDIATE 69, 0.158 g, 0.29 mmol) in DCM (1.6 ml) was added to the solution and the reaction mixture was stirred at r.t overnight. The mixture was diluted with DCM and washed with 1N sodium bisulfate (aq.) followed by a saturated aq. sodium bicarbonate. The organic layer was dried (Na₂SO₄), filtered, and evaporated under reduced pressure to give a residue which was purified by column chromatography (ISCO, silica gel column, eluting with 0→100 % DCM/MeOH/NH₃ (10:1:0.1 v/v/v)) to provide the title compound (0.21 g, yield: 69%).

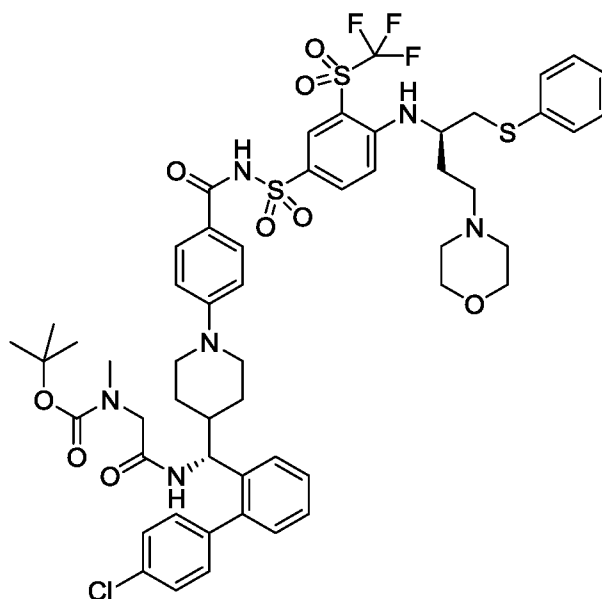
[000848] ¹H NMR (400 MHz, DICHLOROMETHANE-*d*₂) δ ppm 8.30 (d, 1 H), 8.01 (dd, 1 H), 7.70 – 7.67 (m, 2H), 7.45 – 7.18(m, 14 H), 6.96 – 6.93 (m, 1H), 6.70 – 6.65 (m, 3H), 4.29 (m, 1H), 3.96 (m, 1H), 3.76 – 3.73 (m, 1H), 3.62 – 3.55 (m, 6H), 3.11 – 3.06 (m, 2H), 2.65 – 2.48 (m, 2H), 2.38 – 2.25 (m, 6H), 2.06 (m, 2H), 1.81 (m, 1H), 1.69 – 1.62 (m, 2H), 1.17 (s, 9H), 1.11 – 0.95 (m, 3H).

[000849] LCMS: (ESI) *m/z* 1060 [M+H]⁺.

INTERMEDIATE 132

[000850] *tert*-Butyl 2-((*R*)-(4'-chlorobiphenyl-2-yl)(1-(4-(4-((*R*)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonylcarbamoyl)phenyl)piperidin-4-yl)methylamino)-2-

oxoethyl(methyl)carbamate.

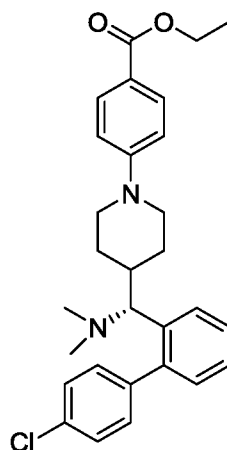


[000851] DIPEA (0.08 ml, 0.46 mmol) was added to a solution of 4-(4-((*R*)-amino(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide, formic acid salt (EXAMPLE 33, 0.11 g, 0.11 mmol), 2-(*tert*-butoxycarbonyl(methyl)amino)acetic acid (22 mg, 0.11 mmol) and HATU (52 mg, 0.14 mmol) in DMF (2.2 ml) and the resulting mixture was stirred at r.t for 1 hour. The reaction mixture was concentrated under reduced pressure, diluted with DCM and washed with H₂O, 1N NaHSO₄ (aq.) and saturated aq. NaHCO₃. The organic layer was dried with Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure to provide a residue which was purified by column chromatography (ISCO, silica gel column, eluting with 0→100 % DCM/MeOH/NH₃ (10:1:0.1)) to provide the title compound (94 mg, yield: 73%).

[000852] LCMS: (ESI) *m/z* 1127 [M+H]⁺.

INTERMEDIATE 133

[000853] (*R*)-ethyl 4-(4-((4'-chlorobiphenyl-2-yl)(dimethylamino)methyl)piperidin-1-yl)benzoate.



[000854] Step 1: HCl (1.16 ml, 4.63 mmol, 4.0M in dioxane) was added to a solution of ethyl 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)((*S*)-1,1-dimethylethylsulfinamido)methyl)piperidin-1-yl)benzoate (INTERMEDIATE 128, 0.128 g, 0.23 mmol) in MeOH (3.5 ml) and the reaction mixture was stirred at r.t. for 3 hours. The reaction mixture was concentrated under reduced pressure and dried under vacuum to provide (*R*)-ethyl 4-(4-(amino(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)benzoate hydrochloride salt (INTERMEDIATE 133, STEP 1, 0.12 g), which was used in the preparation of INTERMEDIATE 133, STEP 2 without further purification.

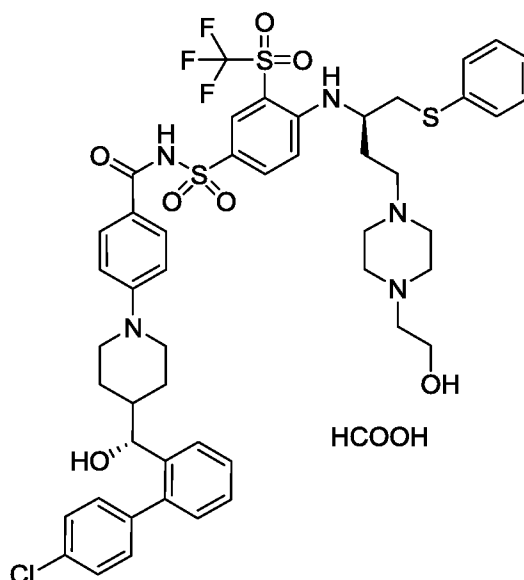
[000855] LCMS: (ESI) m/z 449 $[M+H]^+$.

[000856] Step 2: Formaldehyde (0.17 ml, 2.3 mmol, 37 wt% in MeOH) and sodium triacetoxyborohydride (0.49 g, 2.30 mmol) were added sequentially to a solution of (*R*)-ethyl 4-(4-(amino(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)benzoate hydrochloride salt (INTERMEDIATE 133, STEP 1, 0.12 g, 0.23 mmol) in DCM (2.1 ml) and the reaction mixture was stirred for 2 hours. The reaction mixture was diluted with DCM and washed with saturated aq. NaHCO_3 . The organic layer was dried (Na_2SO_4), filtered and the filtrate was concentrated under reduced pressure to give the title compound (0.11 g, yield: almost quantitative) after drying under vacuum.

[000857] LCMS: (ESI) m/z 477 $[M+H]^+$.

EXAMPLE 1

[000858] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-N-(4-((*R*)-4-(4-(2-hydroxyethyl)piperazin-1-yl)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide, formic acid salt



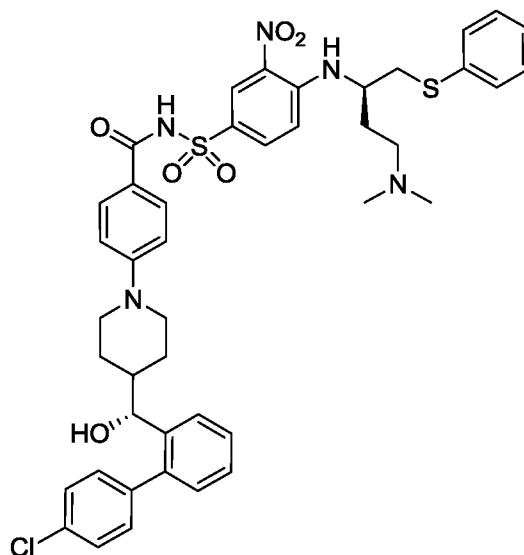
[000859] TBAF (1M solution in THF, 192 μ l, 0.19 mmol) was added dropwise to a solution of 4-(4-((*R*)-(tert-butyl)dimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-(4-(2-(tert-butyl)phenylsilyloxy)ethyl)piperazin-1-yl)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide (INTERMEDIATE 32, 130 mg, 0.10 mmol) in THF (702 μ l) and the resulting reaction mixture was stirred at room temperature overnight. HCl (1 ml, 4M in dioxane) was added to the mixture and stirred for an additional 1 hour at room temperature. The reaction mixture was diluted with EtOAc and the organic layer washed with H₂O (2x) and dried (Na₂SO₄). Evaporation of the volatiles under reduced pressure gave a residue, which was purified by reverse phase HPLC (Gilson column, eluting with 15 $\rightarrow$ 70% H₂O/MeCN with 0.1% formic acid for 14 minutes) to provide the title product (78 mg, yield: 78 %).

[000860] ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 8.07 (d, 1 H) 7.95 (dd, 1 H) 7.67 (d, 2 H) 7.59 (d, 1 H) 7.49 (d, 2 H) 7.43 (t, 1 H) 7.25 - 7.38 (m, 7 H) 7.07 - 7.23 (m, 3 H) 6.90 (d, 1 H) 6.73 (d, 3 H) 5.21 (br. s., 1 H) 4.25 - 4.36 (m, 2 H) 4.02 (d, 1 H) 3.73 (d, 1 H) 3.61 - 3.68 (m, 3 H) 3.22 - 3.33 (m, 4 H) 2.83 - 3.03 (m, 6 H) 2.69 - 2.82 (m, 2 H) 2.61 (dd, 4 H) 2.43 (d, 3 H) 1.90 (d, 2 H) 1.74 (d, 1 H) 1.60 (d, 1 H) 1.14 - 1.22 (m, 2 H) 0.95 - 1.08 (m, 2 H) 0.86 (d, 1 H).

[000861] LCMS: (ESI) *m/z* 1001 [M+H]⁺.

EXAMPLE 2

[000862] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfonyl)benzamide



[000863] The title compound (77.2 mg, yield: 59%) was prepared using a procedure similar to the one described for EXAMPLE 1 utilizing 4-(4-((*R*)-(tert-butyl)dimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfonyl)benzamide (INTERMEDIATE 33, 147.5 mg, 0.16 mmol) as starting material. The title product was purified by column chromatography (ISCO, 4 g silica gel column, eluting with 0→4.5% MeOH/DCM) followed by [ISCO, 12 g silica gel column, eluting with 0→8% MeOH/DCM and 0→100% (10% 2M NH₃ in MeOH/90 % DCM)].

[000864] ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.85 (m, 1 H) 0.96 - 1.05 (m, 1 H) 1.05 - 1.17 (m, 1 H) 1.53 - 1.66 (m, 1 H) 1.84 - 2.13 (m, 3 H) 2.73 - 2.96 (m, 2 H) 3.55 (d, 1 H) 3.71 (m, 1 H) 4.06 (m, 1 H) 4.31 (dd, 1 H) 5.20 (d, 1 H) 6.71 (d, 2 H) 6.89 (d, 1 H) 7.09 - 7.20 (m, 2 H) 7.24 (t, 2 H) 7.28 - 7.39 (m, 5 H) 7.42 (t, 1 H) 7.49 (d, 2 H) 7.58 (d, 1 H) 7.67 (d, 2 H) 7.79 (dd, 1 H) 8.24 (d, 1 H) 8.44 (d, 1 H).

[000865] LCMS: (ESI) *m/z* 828 [M+H]⁺.

[000866] Optical rotation:

Concentration: 0.1 g/dL

Lamp: Sodium

Wavelength: 589 nm

Temperature: 20° C

Path length: 10 cm

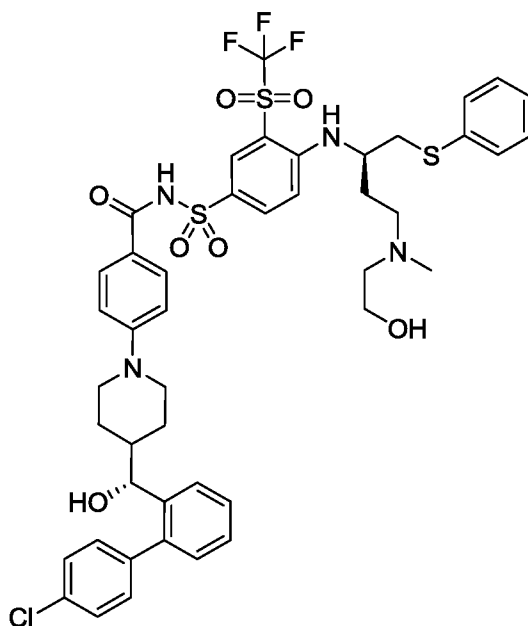
Cell volume: 1 ml

Solvent: CH₂Cl₂

[α] = -16°

EXAMPLE 3

[000867] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-((2-hydroxyethyl)(methyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide



[000868] To a solution of *N*-(4-((*R*)-4-((2-(*tert*-butyldimethylsilyloxy)ethyl)(methyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)-4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzamide (INTERMEDIATE 34, 2.96 g, 2.51 mmol) in dioxane (5.03 ml) and methanol (5.03 ml) was added slowly HCl (4M in dioxane, 15.08 ml, 60.33 mmol). Approximately half way through addition, a slight exotherm was noted, and the reaction was cooled to 0 °C. Addition of hydrochloric acid in dioxane (4M) continued, and once complete, the ice bath was removed. The resulting yellow solution was allowed to warm to r.t. and stirred for 3 min before being concentrated under reduced pressure to half volume and diluted with ethyl acetate. The resulting mixture was washed with sodium bicarbonate (saturated, aqueous) and sodium chloride (saturated, aqueous) before being dried over sodium sulfate, filtered, and concentrated. Upon concentration, a thick oily residue precipitated out of solution and this material was redissolved in acetone before being reconcentrated to a beige film. This film was dissolved in 10% methanol in ethyl acetate and purified by column chromatography (ISCO, 330 g SiO₂, isocratic 15% methanol in ethyl acetate for 30 min) to afford the title compound (1.90 g, yield: 80%).

[000869] ¹H NMR (300 MHz, METHANOL-*d*₄) δ 8.27 (s, 1H), 8.04 (dd, 1H), 7.82 (d, 2H), 7.62 (d, 1H), 7.09 - 7.50 (m, 12H), 6.66 - 6.86 (m, 3H), 4.44 (d, 1H), 3.99 (br. s., 1H), 3.69 - 3.85 (m, 3H), 3.62 (d, 1H), 3.12 - 3.29 (m, 2H), 2.86 - 3.05 (m, 4H), 2.60 - 2.75 (m, 4H), 2.46 - 2.58 (m, 1H), 2.11 - 2.28 (m, 1H), 1.88 - 2.12 (m, 2H), 1.65 - 1.84 (m, 1H), 1.08 - 1.35 (m, 2H), 0.88 - 1.07 (m, 1H).

[000870] ^{19}F NMR (282 MHz, METHANOL- d_4) δ -80.88 (3F).

[000871] LCMS: (ESI) m/z 945.4, 947.4 $[\text{M}+\text{H}]^+$.

[000872] Optical rotation:

Concentration: 0.305 g/dL

Lamp: Sodium

Wavelength: 589 nm

Temperature: 20° C

Path length: 10 cm

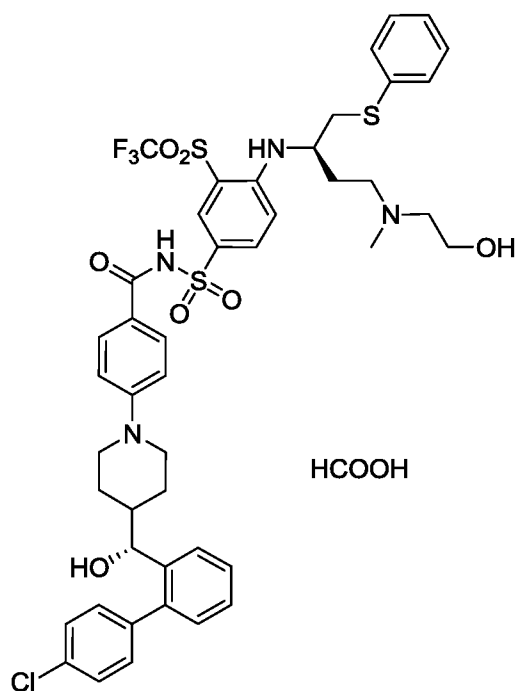
Cell volume: 1 ml

Solvent: CH_2Cl_2

$[\alpha] = +28$

EXAMPLE 3A

[000873] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-((2-hydroxyethyl)(methyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide, formic acid salt



[000874] As an alternate procedure to Example 3, a solution of 4-(4-((*R*)-(tert-butyltrimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-((2-(tert-butyltrimethylsilyloxy)ethyl)(methyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide (INTERMEDIATE 34A, 110 mg, 0.08 mmol) in THF was treated with a solution of TBAF (0.169 mL, 0.17 mmol, 1M in THF) and the resulting solution was stirred at room temperature overnight. HCl (2 ml, 4N in dioxane) was

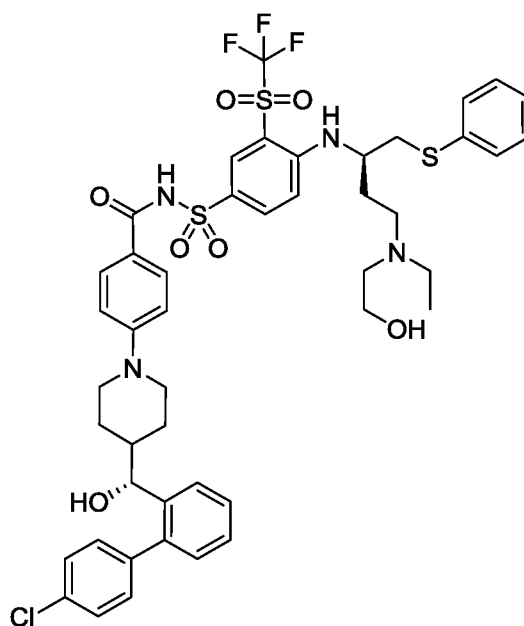
added to the solution and the mixture was allowed to stir for 30 minutes at ambient temperature. Evaporation of the volatiles under reduced pressure gave a residue, which was purified by reverse phase HPLC (Gilson column, eluting with 10→70% H₂O/MeCN with 0.1% formic acid for 14 minutes) to provide the title product (53.3 mg, yield: 66 %).

[000875] ¹H NMR (DMSO-d₆, 300Mz) δ 8.14 (s, 1H) 8.10 (s, 1H) 7.97(d, 1H) 7.67 (d, 2 H) 7.59 (d, 1H) 7.49 (d, 2H) 7.43 (t, 1H) 7.26-7.37 (m, 7H) 7.21 (d, 1H) 7.14 (d, 1H) 6.93 (d, 1H) 6.74 (d, 2H) 5.20 (d, 1H) 4.28-4.33 (m, 1H) 3.99-4.09 (m, 1H) 3.71-3.79 (m, 1H) 3.55-3.66 (m, 3H) 2.93-3.14 (m, 4H) 2.65 (s, 3H) 2.40-2.61 (m, 3H) 1.99-2.14 (m, 2H) 1.88-1.95 (m, 1H) 1.56-1.68 (m, 1H) 0.96-1.26 (m, 2H) 0.79-0.93 (m, 1H).

[000876] LCMS: (ESI) *m/z* 946 [M+H]⁺.

EXAMPLE 4

[000877] 4-(4-((R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-N-(4-((R)-4-(ethyl(2-hydroxyethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide



[000878] A solution of HCl in dioxane (4M, 11.18 ml, 44.70 mmol) was added slowly to a light yellow solution of *N*-(4-((R)-4-((2-(tert-butyldimethylsilyloxy)ethyl)(ethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)-4-(4-((R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzamide (INTERMEDIATE 66, 2.4 g, 2.24 mmol) in DCM (11.2 ml) at 0 °C. Once the addition was complete, the ice bath was removed. The resulting solution was allowed to warm to r.t. and stirred for 1 hour before being concentrated under reduced pressure to half volume and diluted with ethyl acetate. The resulting mixture was washed with sodium bicarbonate (saturated, aqueous) and sodium chloride

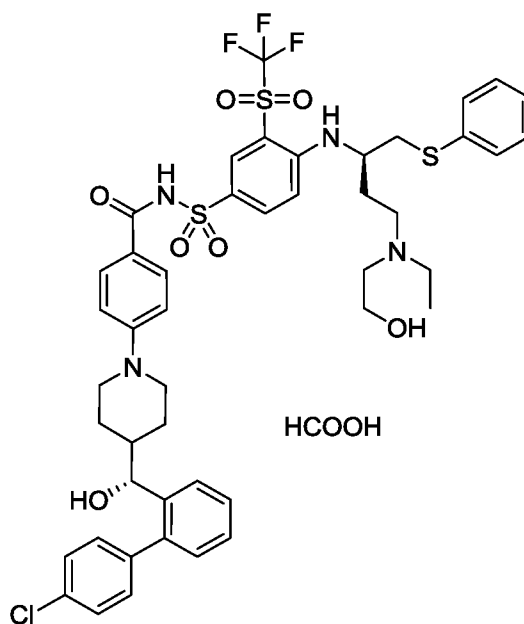
(saturated, aqueous) before being dried over sodium sulfate, filtered, and concentrated under reduced pressure. The concentrate was purified by column chromatography (ISCO, silica gel, 0→20% methanol in ethyl acetate for 30 min) to provide the title compound (1.64 g, yield: 76%).

[000879] ^1H NMR (300 MHz, DICHLOROMETHANE- d_2) δ ppm 8.25 (s, 1 H) 8.03 (d, 1 H) 7.77 (d, 2 H) 7.61 (d, 1 H) 7.39 - 7.48 (m, 2 H) 7.31 - 7.39 (m, 4 H) 7.17 - 7.30 (m, 6 H) 6.90 (d, 1 H) 6.69 (d, 3 H) 4.49 (d, 1 H) 3.91 (br.s., 2 H) 3.55 - 3.81 (m, 5 H) 3.09 (d, 2 H) 2.76 - 2.96 (m, 6 H) 2.47 - 2.72 (m, 3 H) 2.04 - 2.15 (m, 1 H) 1.84 - 1.99 (m, 2 H) 1.76 (dd, 1 H) 1.23 - 1.36 (m, 2 H) 1.13 - 1.23 (m, 1 H) 1.01 - 1.13 (m, 4 H).

[000880] LCMS: (ESI) m/z 959 $[\text{M}+\text{H}]^+$.

EXAMPLE 4A

[000881] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-(ethyl(2-hydroxyethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide, formic acid salt



[000882] Step 1: (*R*)-4-(4-((*tert*-butyldimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)benzoic acid (INTERMEDIATE 13, 160 mg, 0.3 mmol), (*R*)-4-(4-((2-(*tert*-butyldiphenylsilyloxy)ethyl)(ethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide (INTERMEDIATE 25, 216 mg, 0.27 mmol), DMAP (100 mg, 0.82 mmol), and EDC (104 mg, 0.54 mmol) were placed in a 50 ml flask and flushed with nitrogen. DCM (3 ml) was added, and the solution was stirred at room temperature overnight. The reaction mixture was diluted with DCM (40 ml) and washed with 1N aq. sodium bisulfate (35 ml) followed by a saturated aq. sodium bicarbonate (40 ml). The organic layer was dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give a residue, which was

purified by column chromatography (ISCO, 40 g silica gel column, eluting with 0→25 % EtOAc/hexanes) to give 4-(4-((R)-(tert-butyldimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-N-(4-((R)-4-((2-(tert-butyldiphenylsilyloxy)ethyl)(ethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide (EXAMPLE 4A, STEP 1, 140 mg), that was used in the preparation of EXAMPLE 4A, STEP 2, without further purification.

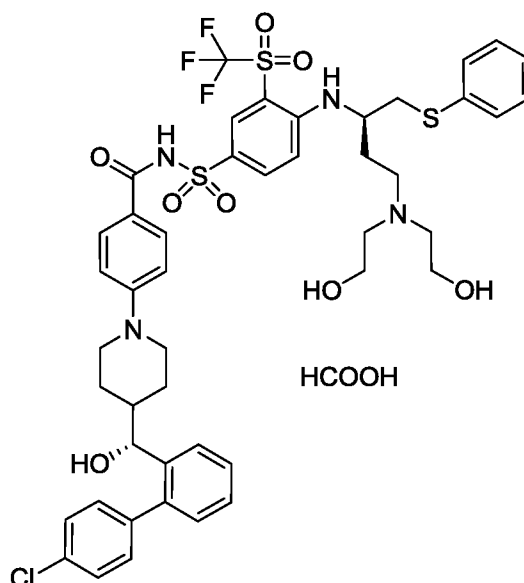
[000883] Step 2: TBAF (0.54 ml 0.54 mmol, 1M in THF) was added dropwise to a solution of 4-(4-((R)-(tert-butyldimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-N-(4-((R)-4-((2-(tert-butyldiphenylsilyloxy)ethyl)(ethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide (EXAMPLE 4A, STEP 1, 140 mg), in THF (2 ml) and the resulting reaction mixture was stirred at room temperature overnight. HCl (2 ml, 4M in dioxane) was added to the mixture and stirred for an additional 30 minutes at room temperature. The reaction mixture was diluted with EtOAc and the organic layer was washed with H₂O (2x) and dried (Na₂SO₄). Evaporation of the volatiles under reduced pressure gave a residue, which was purified by reverse phase HPLC (Gilson column, eluting with 10→70% H₂O/MeCN with 0.1% formic acid for 14 minutes) to provide the title product (60.4 mg, yield: 23 %).

[000884] ¹H NMR(DMSO-*d*₆, 300Mz) δ 8.09 (d, 1H) 7.97 (s, 1H) 7.67 (d, 2 H) 7.59 (d, 1H) 7.49 (d, 2H) 7.43 (t, 1H) 7.26-7.36 (m, 7 H) 7.20 (d, 1H) 7.14 (d, 1H) 6.90-6.96 (m, 1H) 6.73 (d, 1H) 5.28 (bs, 1 H) 5.19 (d, 1H) 4.31 (t, 1H) 4.05 (t, 1H) 3.53-3.76 (m, 4H) 2.96-3.21 (m, 4H) 2.38-2.69 (m, 5H) 2.0-2.14 (m, 2H) 1.90 (d, 1H) 1.53-1.68 (m, 1H) 0.98-1.23 (m, 6H) 0.81-0.91 (m, 1H).

[000885] LCMS: m/z 960 [M+H]⁺.

EXAMPLE 5

[000886] N-(4-((R)-4-(bis(2-hydroxyethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)-4-(4-((R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzamide, formic acid salt



[000887] Step 1: (R)-4-(4-((*tert*-butyldimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)benzoic acid (INTERMEDIATE 13, 225 mg, 0.22 mmol), DMAP (140 mg, 1.14 mmol), (R)-4-(4-(bis(2-(*tert*-butyldiphenylsilyloxy)ethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide (INTERMEDIATE 31, 400 mg, 0.38 mmol), and EDC (146 mg, 0.76 mmol) were placed in a 50 ml flask and flushed with nitrogen. DCM (3 ml) was added and the solution was stirred at room temperature overnight. The reaction mixture was diluted with DCM (40 ml) and washed with sodium bisulfate (1N, 35 ml) followed by a sodium bicarbonate (saturated, aq., 40 ml). The organic layer was dried (Na₂SO₄), filtered, and evaporated under reduced pressure to give a residue, which was purified by column chromatography (ISCO, 40 g silica gel column, eluting with 0→25 % EtOAc/hexanes) to give 4-(4-((R)-(*tert*-butyldimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-N-(4-((R)-4-((2-(*tert*-butyldiphenylsilyl)ethyl)(2-(*tert*-butyldiphenylsilyloxy)ethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide (EXAMPLE 5, STEP 1, 252 mg), that was used in the preparation of EXAMPLE 5, STEP 2 without further purification.

[000888] Step 2: A solution of TBAF (0.76 ml 0.76 mmol, 1M in THF) was added dropwise to a solution of 4-(4-((R)-(*tert*-butyldimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-N-(4-((R)-4-((2-(*tert*-butyldiphenylsilyl)ethyl)(2-(*tert*-butyldiphenylsilyloxy)ethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide (EXAMPLE 5, STEP 1, 252 mg) in THF (2 ml) and the resulting reaction mixture was stirred at room temperature overnight. HCl (2 ml, 4M in dioxane) was added to the mixture and stirred for an additional 30 minutes at room temperature. The reaction mixture was diluted with EtOAc and the organic layer was washed with H₂O (2x) and dried (Na₂SO₄). Evaporation of the volatiles under reduced pressure gave a residue, which was purified by reverse phase HPLC (Gilson

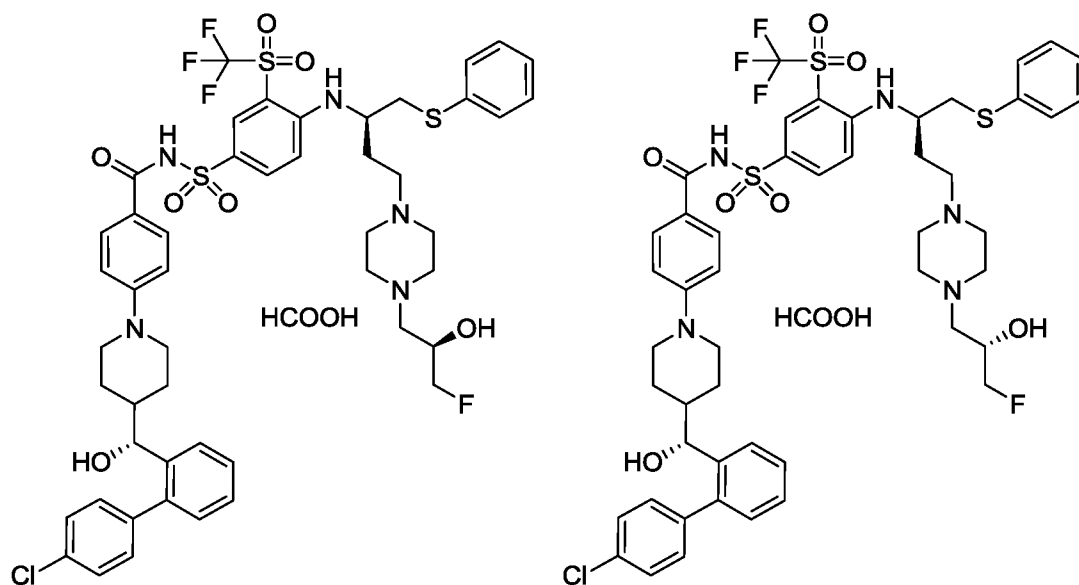
column, eluting with 10→70% H₂O/MeCN with 0.1% formic acid for 14 minutes) to provide the title product (150.2 mg, yield: 40%).

[000889] ¹H NMR(DMSO-d₆, 300Mz) δ 8.10 (s, 2H) 7.97 (d, 1H) 7.67 (d, 2 H) 7.59 (d, 1H) 7.49 (d, 2H) 7.43 (t, 1H) 7.24-7.37 (m, 7H) 7.19 (d, 1H) 7.15(d, 1H) 6.93-6.99 (m, 1H) 6.75 (d, 2H) 5.20 (d, 1H) 5.05 (bs, 1H) 4.28-4.33 (m, 1H) 4.02-4.12 (m, 1H) 3.72-3.79 (m, 1H) 3.54-3.69 (m, 5H) 2.98-3.18 (m, 5H) 2.40-2.68 (m, 4H) 1.84-2.16 (m, 3H) 1.56-1.68 (m, 1H) 0.98-1.18 (m, 2H) 0.78-0.93 (m, 1H).

[000890] LCMS: (ESI) *m/z* 975 [M+H]⁺.

EXAMPLE 6

[000891] 4-(4-((R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-N-(4-((R)-4-(4-((R)-3-fluoro-2-hydroxypropyl)piperazin-1-yl)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide and 4-(4-((R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-N-(4-((R)-4-(4-((S)-3-fluoro-2-hydroxypropyl)piperazin-1-yl)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide formic acid salt, mixture of diastereomers



[000892] Step 1: (R)-4-(4-((4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoic acid (INTERMEDIATE 40, 58 mg, 0.14 mmol), 4-((R)-4-(4-((R)-2-(tert-butyl)diphenylsilyloxy)-3-fluoropropyl)piperazin-1-yl)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide and 4-((R)-4-(4-((S)-2-(tert-butyl)diphenylsilyloxy)-3-fluoropropyl)piperazin-1-yl)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide mixture of diastereomers (INTERMEDIATE 39, 120 mg, 0.14 mmol), DMAP (34 mg, 0.28 mmol), and EDC (53 mg, 0.28 mmol) were placed in a 40 ml vial and flushed with nitrogen. DCM (2.8 ml) was added, and the solution was stirred at

room temperature overnight. The reaction mixture was diluted with DCM and washed with 1N aq. sodium bisulfate followed by a saturated aq. sodium bicarbonate. The organic layer was dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give *N*-(4-((2*R*)-4-(4-(2-(*tert*-butyldiphenylsilyloxy)-3-fluoropropyl)piperazin-1-yl)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)-4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzamide (EXAMPLE 6, STEP 1, 180 mg), which was used in the preparation of EXAMPLE 6, STEP 2, without further purification.

[000893] LCMS: m/z 1270 $[\text{M}+\text{H}]^+$.

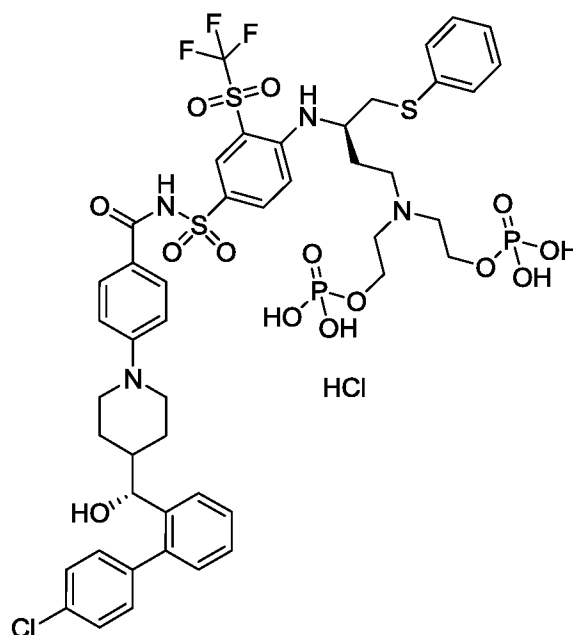
[000894] Step 2: A solution of TASF (0.43 ml, 0.43 mmol, 1M in DMF) was added dropwise to a solution of *N*-(4-((2*R*)-4-(4-(2-(*tert*-butyldiphenylsilyloxy)-3-fluoropropyl)piperazin-1-yl)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)-4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzamide (EXAMPLE 6, STEP 1, 180 mg) in DMF (1 ml) and the resulting reaction mixture was stirred at room temperature for 1h. The reaction mixture was diluted with DCM/MeOH (10:1 v/v), washed with H_2O , dried (Na_2SO_4), filtered, and evaporation of the volatiles under reduced pressure gave a residue, which was purified by reverse phase HPLC (Gilson column, eluting with 40→60 % H_2O /MeCN with 0.1% formic acid for 5 minutes) to provide the title product (48.0 mg, yield: 33 %).

[000895] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.08 (d, 1 H), 7.94 – 7.90 (m, 1H), 7.66 (d, J = 8.80 Hz, 2 H), 7.60 – 7.55 (m, 1 H), 7.51 – 7.46 (m, 2H), 7.45 – 7.40 (m, 1 H), 7.37 – 7.26 (m, 8 H), 7.21 – 7.12 (m, 2 H), 6.93 – 6.88 (m, 1 H), 6.77 – 6.71 (m, 3 H), 5.21 (d, J = 4.3 Hz, 1 H), 4.41 – 4.20 (m, 4 H), 4.05 – 3.85 (m, 3 H), 3.77 – 3.70 (m, 1 H), 3.60 – 3.55 (m, 2 H), 2.66 – 2.53 (m, 8 H), 2.45 – 2.42 (m, 5 H), 2.00 – 1.85 (m, 2 H), 1.75 (m, 1 H), 1.15 – 0.99 (m, 3 H), 0.90 – 0.81 (m, 1 H).

[000896] LCMS: (ESI) m/z 1032 $[\text{M}+\text{H}]^+$.

EXAMPLE 7

[000897] 2,2'-((*R*)-3-(4-(*N*-(4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-(phenylthio)butylazanediyl)bis(ethane-2,1-diyl) bis(dihydrogen phosphate), hydrochloride salt



[000898] A solution of di-*tert*-butyl 2,2'-((*R*)-3-(4-(*N*-(4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-(phenylthio)butylazanediy)bis(ethane-2,1-diyl) diphosphate (INTERMEDIATE 46, 250 mg, 0.18 mmol) and DCM (5 ml) was treated with a solution of HCl (4M in dioxane, 0.92 ml, 3.68 mmol). A white precipitate was observed and the mixture was allowed to stir vigorously for 45 minutes. The title compound was collected by filtration (185 mg, yield: 89%).

[000899] ^1H NMR (400 MHz, METHANOL- d_4) δ ppm 1.41 (br. s., 2 H) 1.54 - 1.71 (m, 1 H) 1.91 - 2.09 (m, 1 H) 2.31 (br. s., 3 H) 3.29 (br. s., 1 H) 3.36 - 3.51 (m, 4 H) 3.53 - 3.66 (m, 5 H) 3.70 - 3.83 (m, 1 H) 4.12 - 4.24 (m, 1 H) 4.35 (br. s., 4 H) 4.56 (d, 1 H) 7.05 (d, 1 H) 7.13 - 7.28 (m, 4 H) 7.32 - 7.41 (m, 5 H) 7.42 - 7.52 (m, 3 H) 7.58 (d, 2 H) 7.68 (d, 1 H) 7.96 (d, 2 H) 8.11 (dd, 1 H) 8.35 (d, 1 H).

[000900] ^{31}P NMR (121 MHz, METHANOL- d_4) δ ppm 0.05 (t, 2 P).

[000901] ^{31}P NMR (121 MHz, METHANOL- d_4) δ ppm 0.05 (s, 2 P) (decoupled)

[000902] Optical rotation:

Concentration: 0.2 g/dL

Lamp: Sodium

Wavelength: 589 nm

Temperature: 20° C

Path length: 10 cm

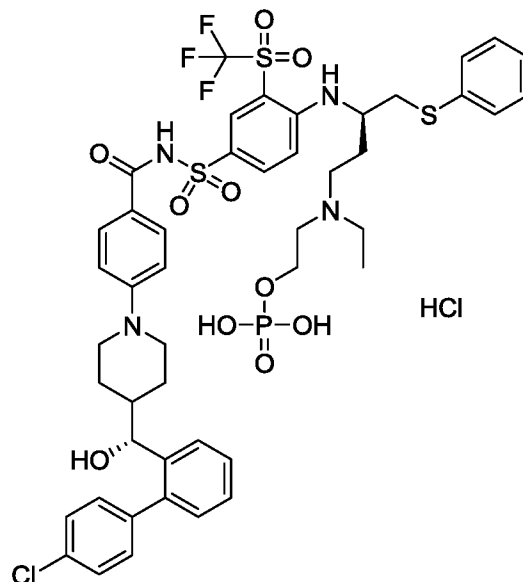
Cell volume: 1 ml

Solvent: MeOH

$[\alpha] = +3$

EXAMPLE 8

[000903] 2-(((*R*)-3-(4-(*N*-(4-(4-(((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-(phenylthio)butyl)(ethyl)amino)ethyl dihydrogen phosphate, hydrochloride salt



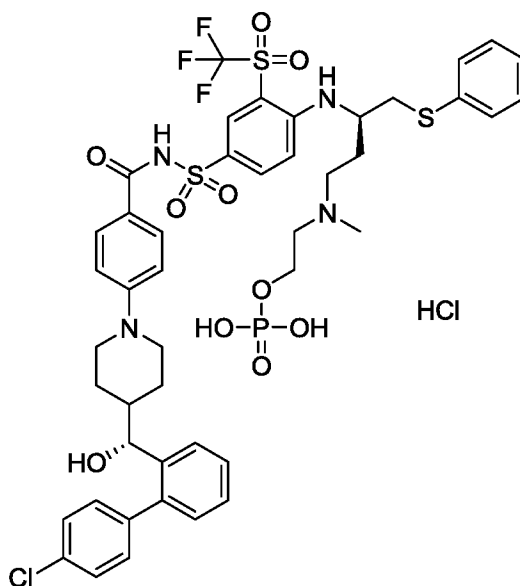
[000904] A solution of di-*tert*-butyl 2-(((*R*)-3-(4-(*N*-(4-(4-(((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-(phenylthio)butyl)(ethyl)amino)ethyl phosphate (INTERMEDIATE 55, 147 mg, 0.14 mmol) in DCM (3.17 ml) was treated with a solution of HCl (4M in dioxane, 0.60 ml). When the addition was completed, a white precipitate was observed. The mixture was diluted with MeOH after an hour and the volatiles were evaporated under reduced pressure to give a gummy residue. The material was dissolved in MeOH, and diluted with ~20 ml DCM, resulting in a white precipitate. The mixture was concentrated under reduced pressure to provide a white solid. The material was triturated in 10-15 ml CH₂Cl₂, and dried under high vacuum to provide the title compound (108 mg, 95%).

[000905] ¹H NMR (300 MHz, METHANOL-*d*₄) δ ppm 1.34 (t, 5 H) 1.46 - 1.66 (m, 1 H) 1.87 - 2.05 (m, 1 H) 2.07 - 2.38 (m, 3 H) 3.12 - 3.40 (m, 8 H) 3.42 - 3.52 (m, 2 H) 3.52 - 3.65 (m, 1 H) 3.70 - 3.84 (m, 1 H) 4.04 - 4.21 (m, 1 H) 4.23 - 4.37 (m, 2 H) 4.46 - 4.59 (m, 1 H) 6.94 - 7.10 (m, 2 H) 7.21 (d, 4 H) 7.30 - 7.52 (m, 9 H) 7.58 - 7.73 (m, 1 H) 7.92 (d, 2 H) 8.04 - 8.16 (m, 1 H) 8.27 - 8.40 (m, 1 H).

[000906] LCMS: (ESI) *m/z* 1037 [M-H]⁺.

EXAMPLE 9

[000907] 2-(((*R*)-3-(4-(*N*-(4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-(phenylthio)butyl)(methyl)amino)ethyl dihydrogen phosphate, hydrochloride salt



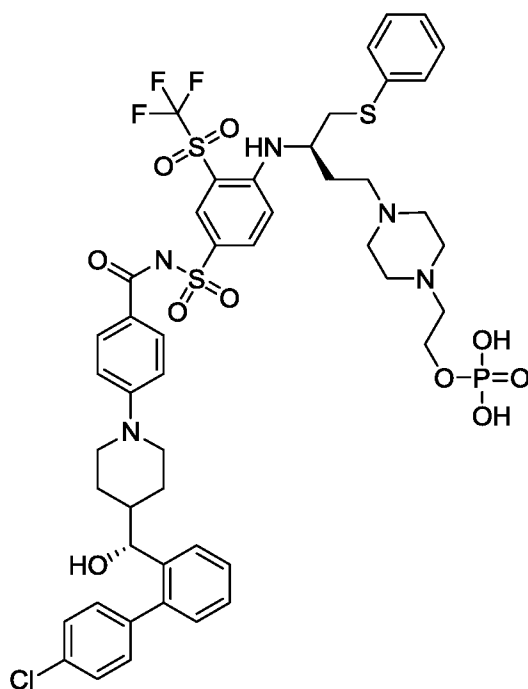
[000908] A solution of di-*tert*-butyl 2-(((*R*)-3-(4-(*N*-(4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-(phenylthio)butyl)(methyl)amino)ethyl phosphate (INTERMEDIATE 56, 140 mg, 0.13 mmol) in DCM (3 ml) was treated with a solution of HCl (4M in dioxane, 0.6 ml). When the addition was completed, a white precipitate was observed. The mixture was diluted with MeOH after an hour and the volatiles were evaporated under reduced pressure to give a gummy residue. The material was dissolved in MeOH, and diluted with ~20 ml DCM, resulting in a white precipitate. The mixture was concentrated under reduced pressure to provide a white solid. The material was triturated in 10-15 ml CH₂Cl₂, and dried under high vacuum to provide the title compound (120 mg, yield: 95%).

[000909] ¹H NMR (300 MHz, METHANOL-*d*₄) δ ppm 1.07 - 1.39 (m, 4 H) 1.83 - 2.00 (m, 1 H) 2.08 - 2.38 (m, 3 H) 2.99 - 3.38 (m, 8 H) 3.40 - 3.52 (m, 2 H) 3.57 - 3.69 (m, 1 H) 3.74 - 3.90 (m, 1 H) 4.03 - 4.19 (m, 1 H) 4.19 - 4.36 (m, 2 H) 4.45 - 4.58 (m, 1 H) 6.92 - 7.09 (m, 2 H) 7.10 - 7.52 (m, 13 H) 7.59 - 7.71 (m, 1 H) 7.77 - 7.94 (m, 2 H) 8.02 - 8.17 (m, 1 H) 8.28 - 8.41 (m, 1 H).

[000910] LCMS: (ESI) *m/z* 1023[M-H]⁺.

EXAMPLE 10

[000911] 2-(4-((*R*)-3-(4-(*N*-(4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-(phenylthio)butyl)piperazin-1-



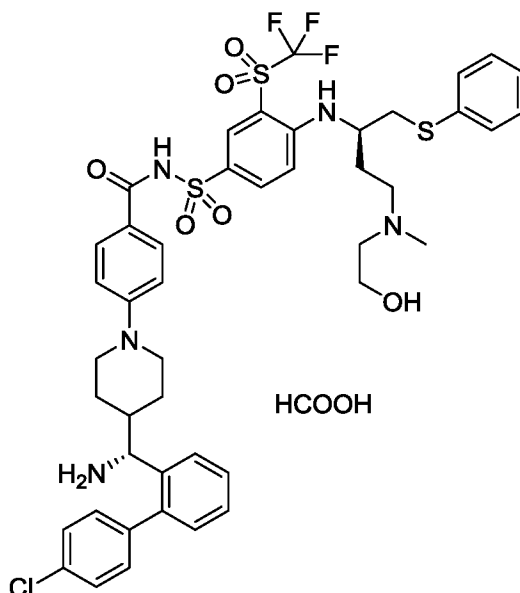
[000912] Di-*tert*-butyl 2-(4-((*R*)-3-(4-(*N*-(4-(4-((*R*)-(tert-butyl)dimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-(phenylthio)butyl)piperazin-1-yl)ethyl phosphate (INTERMEDIATE 62,414 mg, 0.32 mmol) was dissolved in DCM (0.5 ml) and treated with a solution of HCl (4M in dioxane, 4.0 ml, 15.84 mmol) at rt, to provide a cloudy solution. The reaction mixture was concentrated under reduced pressure to provide an oily residue which was purified by reverse phase HPLC (Gilson column, eluting with 20→95% MeCN in 10mM NH₄OAc with 5% MeCN over 15 min). The collected fractions were concentrated and washed with water and filtered to remove NH₄OAc and provide the title compound (120 mg, yield: 35%).

[000913] ¹H NMR (300 MHz, METHANOL-*d*₄) δ ppm 8.28 (d, 1 H) 8.04 (dd, 1 H) 7.78 (d, 2 H) 7.59 - 7.66 (m, 1 H) 7.34 - 7.47 (m, 5 H) 7.24 - 7.34 (m, 5 H) 7.16 - 7.23 (m, 2 H) 6.83 (d, 3 H) 4.44 (d, 1 H) 4.01 - 4.15 (m, 3 H) 3.83 (d, 1 H) 3.66 (d, 1 H) 3.08 - 3.26 (m, 7 H) 2.63 - 2.79 (m, 3 H) 2.41 - 2.63 (m, 5 H) 1.99 - 2.16 (m, 2 H) 1.69 - 1.85 (m, 2 H) 1.10 - 1.35 (m, 3 H) 0.98 (dd, 1 H).

[000914] LCMS: (ESI) m/z 1080 $[M+H]^+$.

EXAMPLE 11

[100915] 4-(4-((*R*)-amino(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-((2-hydroxyethyl)(methyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide, formic acid salt



[000916] Step 1: 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)((*S*)-1,1-dimethylethylsulfinamido)methyl)piperidin-1-yl)benzoic acid (INTERMEDIATE 130, 0.12 g, 0.23 mmol), DMAP (56 mg, 0.46 mmol), and EDC (88 mg, 0.46 mmol) were placed in a 40 ml vial and flushed with nitrogen. DCM (3.0 ml) and DIPEA (0.08 ml, 0.46 mmol) were added and the solution was stirred at r.t for 15 min. A solution of (*R*)-4-(4-((2-(*tert*-butyldiphenylsilyloxy)ethyl)(methyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide (INTERMEDIATE 28, 0.178 g, 0.23 mmol) in DCM (1.5 ml) was added to the solution and the reaction mixture was stirred at r.t overnight. The reaction mixture was diluted with DCM and washed with sodium bisulfate (1N, aq.) followed by a sodium bicarbonate (saturated, aq.). The organic layer was dried (Na₂SO₄), filtered, and evaporated under reduced pressure to give a residue which was dried under vacuum to provide *N*-(4-((*R*)-4-((2-(*tert*-butyldiphenylsilyloxy)ethyl)(methyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)-4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)((*S*)-1,1-dimethylethylsulfinamido)methyl)piperidin-1-yl)benzamide (EXAMPLE 11, STEP 1, 0.26 g) which was used in the preparation of EXAMPLE 11, STEP 2 without further purification.

[000917] Step 2: A solution of TASF (0.40 ml, 0.40 mmol, 1.0M in DMF) was added to a solution of *N*-(4-((*R*)-4-((2-(*tert*-butyldiphenylsilyloxy)ethyl)(methyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)-4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)((*S*)-1,1-dimethylethylsulfinamido)methyl)piperidin-1-yl)benzamide (EXAMPLE 11, STEP 1, 0.26 g, 0.20 mmol) in DMF (1.6 ml) and the reaction mixture was stirred at r.t for 1 hour. The reaction mixture was concentrated under reduced pressure, diluted with DCM and washed with H₂O. The organic layer was dried (Na₂SO₄), concentrated under reduced pressure and dried under vacuum to give 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)((*S*)-1,1-

dimethylethylsulfinamido)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-((2-hydroxyethyl)(methyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide (EXAMPLE 11, STEP 2, 0.25 g) which was used in the preparation of EXAMPLE 11, STEP 3, without further purification.

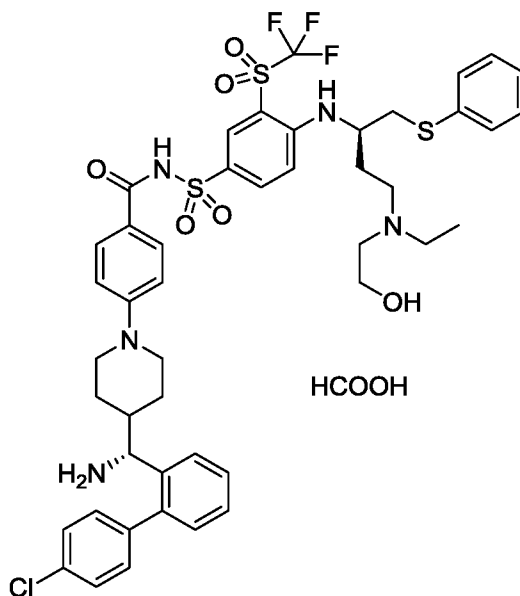
[000918] Step 3: A solution of HCl (1.00 ml, 4.00 mmol, 4.0M in dioxane) was added to a solution of 4-(4-((*R*)-4'-chlorobiphenyl-2-yl)((*S*)-1,1-dimethylethylsulfinamido)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-((2-hydroxyethyl)(methyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide (EXAMPLE 11, STEP 2, 0.21 g, 0.20 mmol) in MeOH (1.0 ml) and the reaction mixture was stirred at r.t for 1 hour. The reaction mixture was concentrated under reduced pressure to provide a residue that was purified by reverse phase HPLC (Gilson column, eluting with 30→50% H₂O/MeCN with 0.1% formic acid for 10 minutes) to provide the title compound (0.1 g, yield: 51% for 3 steps).

[000919] ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.05 (d, 1 H), 7.92 (dd, 1 H), 7.71 – 7.67 (m, 3H), 7.59 – 7.52 (m, 3H), 7.49 – 7.45 (m, 1H), 7.37 – 7.34 (m, 4 H), 7.30 – 7.26 (m, 3H), 7.20 – 7.17 (m, 1 H), 6.83 (d, 1 H), 6.78 – 6.72 (m, 3H), 4.00 (m, 1H), 3.87 – 3.84 (m, 1H), 3.78 – 3.75 (m, 1H), 3.32 – 3.16 (m, 5H), 2.67 – 2.54 (m, 5H), 2.46 – 2.43 (m, 1H), 2.31 (s, 3H), 1.98 – 1.90 (m, 2H), 1.83 – 1.75 (m, 2H), 1.19 – 1.08 (m, 2H), 0.82 – 0.74 (m, 1H).

[000920] LCMS: (ESI) *m/z* 944 [M+H]⁺.

EXAMPLE 12

[000921] 4-(4-((*R*)-amino(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-(ethyl(2-hydroxyethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide, formic acid salt



[000922] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)((*S*)-1,1-dimethylethylsulfonamido)methyl)piperidin-1-yl)benzoic acid (INTERMEDIATE 130, 0.12 g, 0.23 mmol), DMAP (56 mg, 0.46 mmol), and EDC (88 mg, 0.46 mmol) were placed in a 40 ml vial and flushed with nitrogen. DCM (3.0 ml) and DIPEA (0.08 ml, 0.46 mmol) were added, and the solution was stirred at r.t for 15 min. A solution of (*R*)-4-(4-((2-(*tert*-butyldiphenylsilyloxy)ethyl)(ethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide (INTERMEDIATE 25, 0.18 g, 0.23 mmol) in DCM (1.5 ml) was added to the solution and the reaction mixture was stirred at r.t overnight. The reaction mixture was diluted with DCM and washed with sodium bisulfate (1N, aq.) followed by sodium bicarbonate (saturated, aq). The organic layer was dried (Na₂SO₄), filtered, and evaporated under reduced pressure to give a residue that was dried under vacuum to provide *N*-(4-((*R*)-4-((2-(*tert*-butyldiphenylsilyloxy)ethyl)(ethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)-4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)((*S*)-1,1-dimethylethylsulfonamido)methyl)piperidin-1-yl)benzamide (EXAMPLE 12, STEP 1, 0.31 g) which was used in the preparation of EXAMPLE 12, STEP 2 without further purification.

[000923] Step 2: A solution of TASF (0.46 ml, 0.46 mmol, 1 M in DMF) was added to a solution of *N*-(4-((*R*)-4-((2-(*tert*-butyldiphenylsilyloxy)ethyl)(ethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)-4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)((*S*)-1,1-dimethylethylsulfonamido)methyl)piperidin-1-yl)benzamide (EXAMPLE 12, STEP 1, 0.30 g, 0.23 mmol) in DMF (1.9 ml) and the reaction mixture was stirred at r.t for 1 hour. The reaction mixture was concentrated under reduced pressure, diluted with DCM and washed with H₂O. The organic layer was dried (Na₂SO₄), concentrated under reduced pressure and dried under vacuum to give 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)((*S*)-1,1-dimethylethylsulfonamido)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-(ethyl(2-hydroxyethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide (EXAMPLE 12, STEP 2, 0.28 g) which was used in the preparation of EXAMPLE 12, STEP 3, without further purification.

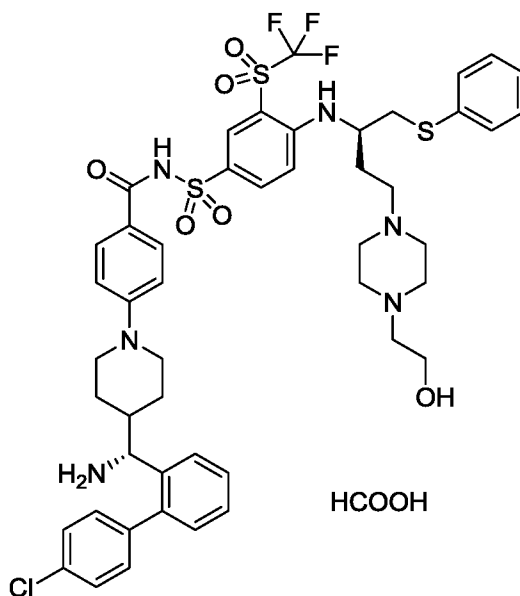
[000924] Step 3: A solution of HCl (1.15 ml, 4.60 mmol, 4 M in dioxane) was added to a solution of 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)((*S*)-1,1-dimethylethylsulfonamido)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-(ethyl(2-hydroxyethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide (EXAMPLE 12, STEP 2, 0.244 g, 0.23 mmol) in MeOH (1.2 ml) and the reaction mixture was stirred at r.t for 1 hour. The reaction mixture was concentrated under reduced pressure to provide a residue which was purified by reverse phase HPLC (Gilson column, eluting with 30→50% H₂O/MeCN with 0.1% formic acid for 10 minutes) to provide the title compound (0.12 g, yield: 52% for 3 steps).

[000925] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.05 (d, 1 H), 7.91 (dd, 1 H), 7.71 – 7.67 (m, 3H), 7.59 – 7.53 (m, 3H), 7.49 – 7.45 (m, 1H), 7.37 – 7.34 (m, 4 H), 7.30 – 7.26 (m, 3H), 7.21 – 7.17 (m, 1 H), 6.82 (d, 1 H), 6.74 – 6.68 (m, 3H), 4.00 (m, 1H), 3.87 – 3.84 (m, 1H), 3.78 – 3.75 (m, 1H) 3.58 – 3.55 (m, 1H), 3.32– 3.19 (m, 4H), 2.65 – 2.55 (m, 7H), 2.46 – 2.43 (m, 1H), 1.99 – 1.90 (m, 2H), 1.84 – 1.73 (m, 2H), 1.18 – 1.08 (m, 2H), 0.93 (t, 3 H), 0.82 – 0.73 (m, 1H).

[000926] LCMS: (ESI) m/z 958 $[\text{M}+\text{H}]^+$.

EXAMPLE 13

[000927] 4-(4-((*R*)-amino(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-(4-(2-hydroxyethyl)piperazin-1-yl)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide, formic acid salt



[000928] Step 1: 4-(4-((*R*)-4-(4-(2-(*tert*-butyldiphenylsilyloxy)ethyl)piperazin-1-yl)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamido)methyl)piperidin-1-yl)benzoic acid (INTERMEDIATE 130, 0.150 g, 0.29 mmol), DMAP (70 mg, 0.57 mmol), and EDC (0.110 g, 0.57 mmol) were placed in a 40 ml vial and flushed with nitrogen. DCM (4.0 ml) and DIPEA (0.10 ml, 0.57 mmol) were added, and the solution was stirred at r.t for 15 min. A solution of (*R*)-4-(4-(4-(2-(*tert*-butyldiphenylsilyloxy)ethyl)piperazin-1-yl)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide (INTERMEDIATE 22, 0.24 g, 0.29 mmol) in DCM (1.6 ml) was added to the solution and the reaction mixture was stirred at r.t overnight. The reaction mixture was diluted with DCM and washed with sodium bisulfate (1N, aq.) followed by sodium bicarbonate (saturated, aq.). The organic layer was dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give a residue which was dried under vacuum to provide *N*-(4-((*R*)-4-(4-(2-(*tert*-butyldiphenylsilyloxy)ethyl)piperazin-1-yl)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)-4-(4-((*R*)-4-(4'-chlorobiphenyl-2-yl)((*S*)-1,1-

1,1-dimethylethylsulfonamido)methyl)piperidin-1-yl)benzamide (EXAMPLE 13, STEP 1, 0.40 g) which was used in the preparation of EXAMPLE 13, STEP 2, without further purification.

[000929] Step 2: A solution of TASF (0.58 ml, 0.58 mmol, 1.0M in DMF) was added to a solution of *N*-(4-((*R*)-4-(4-(2-(*tert*-butyldiphenylsilyloxy)ethyl)piperazin-1-yl)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)-4-(4-((*R*)-(4'-chlorobiphenyl-2-yl))-(*S*)-1,1-dimethylethylsulfonamido)methyl)piperidin-1-yl)benzamide (EXAMPLE 13, STEP 2, 0.39 g, 0.29 mmol) in DMF (2.3 ml) and the reaction mixture was stirred at r.t for 1 hour. The reaction mixture was concentrated under reduced pressure, diluted with DCM and washed with H₂O. The organic layer was dried (Na₂SO₄), concentrated under reduced pressure, after filtration, and dried under vacuum to give 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl))-(*S*)-1,1-dimethylethylsulfonamido)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-(4-(2-hydroxyethyl)piperazin-1-yl)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide (EXAMPLE 13, STEP 2, 0.41g) which was used in the preparation of EXAMPLE 13, STEP 3 without further purification.

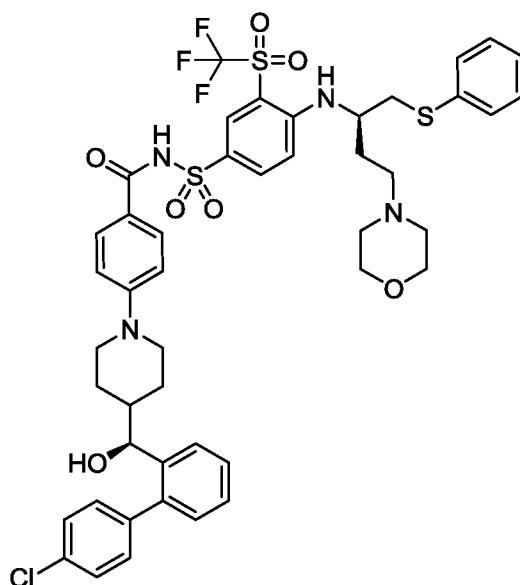
[000930] Step 3: A solution of HCl (1.45 ml, 5.80 mmol, 4.0M in dioxane) was added to a solution of 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl))-(*S*)-1,1-dimethylethylsulfonamido)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-(4-(2-hydroxyethyl)piperazin-1-yl)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide (EXAMPLE 13, STEP 2, 0.4 g, 0.29 mmol) in MeOH (1.5 ml) and the reaction mixture was stirred at r.t for 1 hour. The reaction mixture was concentrated under reduced pressure to provide a residue which was purified by reverse phase HPLC (Gilson column, eluting with 30→45% H₂O/MeCN with 0.1% formic acid for 10 minutes) to provide the title compound (0.16 g, yield: 49% for 3 steps).

[000931] ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.05 (d, 1 H), 7.91 (dd, 1 H), 7.72 – 7.68 (m, 3H), 7.60 – 7.53 (m, 3H), 7.50 – 7.46 (m, 1H), 7.38 - 7.34 (m, 4 H), 7.31 – 7.27 (m, 3H), 7.21 - 7.18 (m, 1 H), 6.84 (d, 1 H), 6.74 (d, 2 H), 6.67 (d, 1 H), 4.00 (m, 1H), 3.88 – 3.86 (m, 1H), 3.79 – 3.76 (m, 1H), 3.34– 3.21 (m, 4H), 2.69 – 2.54 (m, 7H), 2.47 – 2.44 (m, 2H), 2.40 – 2.29 (m, 5H), 1.99 – 1.91 (m, 2H), 1.84 – 1.81 (m, 1H), 1.73 – 1.66 (m, 1H), 1.20 – 1.08 (m, 3H), 0.83 – 0.74 (m, 1H).

[000932] LCMS:(ESI) *m/z* 999 [M+H]⁺.

EXAMPLE 14

[000933] 4-(4-((*S*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide



[000934] (*S*)-4-(4-((4'-Chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoic acid (INTERMEDIATE 70, 137.4 mg, 0.33 mmol), (*R*)-4-(4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl) benzenesulfonamide (INTERMEDIATE 69, 190.3 mg, 0.34 mmol), DMAP (81.0 mg, 0.66 mmol), and EDC (134.5 mg, 0.70 mmol) were placed in a 50 ml flask and flushed with nitrogen. DCM (6.5 ml) was added, and the solution was stirred at room temperature overnight. The reaction mixture was diluted with DCM (40 ml) and washed with 1N aq. sodium bisulfate (35 ml) followed by a saturated aq. sodium bicarbonate (40 ml). The organic layer was dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The concentrate was purified by column chromatography (ISCO, 12 g silica gel column, eluting with 0→10 % MeOH in DCM). Clean fractions were combined, evaporated under vacuum, and dried overnight in a 40 °C vacuum oven to provide the title product as a substantially separated isomer (129.3 mg, yield: 41.5%).

[000935] ^1H NMR (400 MHz, DMSO-d_6) δ ppm 0.74 - 0.90 (m, 1 H) 0.95 - 1.15 (m, 2 H) 1.65 (m, 1 H) 1.88 (m, 2 H) 2.60 - 2.71 (m, 1 H) 3.45 - 3.61 (m, 4 H) 3.66 (m, 1 H) 3.82 (m, 1 H) 4.05 - 4.14 (m, 1 H) 4.30 (dd, 1 H) 5.21 (d, 1 H) 6.79 (d, 2 H) 6.91 (m, 1 H) 7.02 (d, 1 H) 7.11 - 7.21 (m, 2 H) 7.23 - 7.38 (m, 7 H) 7.42 (t, 1 H) 7.48 (d, 2 H) 7.58 (d, 1 H) 7.67 (d, 2 H) 7.94 (dd, 1 H) 8.13 (d, 1 H).

[000936] LCMS:(ESI) m/z 957 $[\text{M}+\text{H}]^+$.

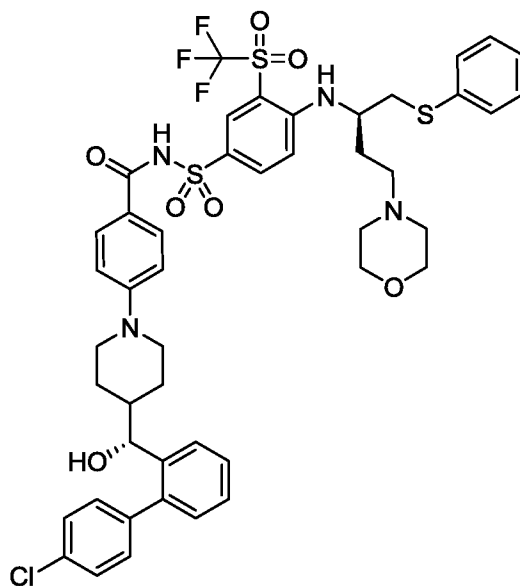
[000937] Optical rotation:

Concentration:	0.1 g/dL
Lamp:	Sodium
Wavelength:	589 nm
Temperature:	20 °C
Path length:	10 cm

Cell volume: 1 ml
 Solvent: CH₂Cl₂
 [α]= -128

EXAMPLE 15

[000938] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide



[000939] The title product (34.1 mg, yield: 59 %) was prepared using a procedure similar to the one described for the synthesis of EXAMPLE 16. 4-(4-((*R*)-(tert-butyl)dimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide (INTERMEDIATE 76, 64.7 mg, 0.06 mmol) was used as starting material. The resulting product was purified by column chromatography (ISCO, 4 g silica gel column, eluting with 0→5% MeOH/DCM) followed by further purification by column chromatography (ISCO, 4 g silica gel column, eluting with 0→100% DCM/ [10% 2M NH₃ in MeOH/90 % DCM]), providing the title product.

[000940] ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.76 - 1.17 (m, 4 H) 1.57 - 1.69 (m, 1 H) 1.69 - 1.81 (m, 1 H) 1.84 - 2.02 (m, 2 H) 2.57 - 2.69 (m, 2 H) 3.44 - 3.57 (m, 5 H) 3.58 - 3.67 (m, 1 H) 3.74 - 3.83 (m, 1 H) 3.99 - 4.11 (m, 1 H) 4.27 - 4.33 (m, 1 H) 5.19 - 5.23 (m, 1 H) 6.72 - 6.80 (m, 2 H) 6.80 - 6.88 (m, 1 H) 6.90 - 6.99 (m, 1 H) 7.11 - 7.22 (m, 2 H) 7.23 - 7.38 (m, 8 H) 7.39 - 7.45 (m, 1 H) 7.48 (d, 2 H) 7.56 - 7.61 (m, 1 H) 7.66 (d, 2 H) 7.89 - 7.95 (m, 1 H) 8.08 - 8.13 (m, 1 H).

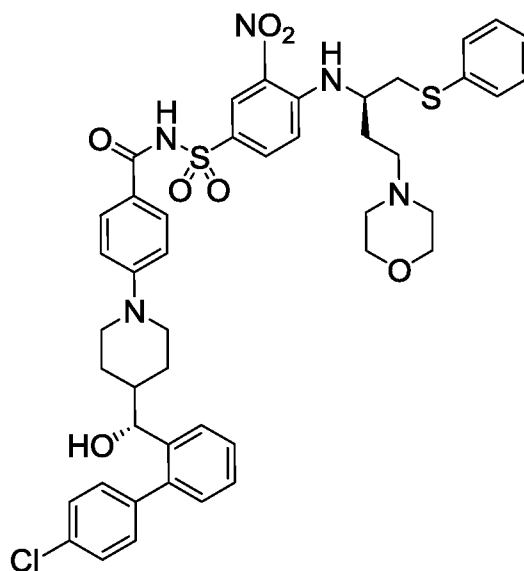
[000941] LCMS: *m/z* 957 [M+H]⁺.

[000942] Optical rotation:

Concentration:	0.1 g/dL
Lamp:	Sodium
Wavelength:	589 nm
Temperature:	20 °C
Path length:	10 cm
Cell volume:	1 ml
Solvent:	CH ₂ Cl ₂
[α]=	-9

EXAMPLE 16

[000943] 4-(4-((R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-N-(4-((R)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfonyl)benzamide



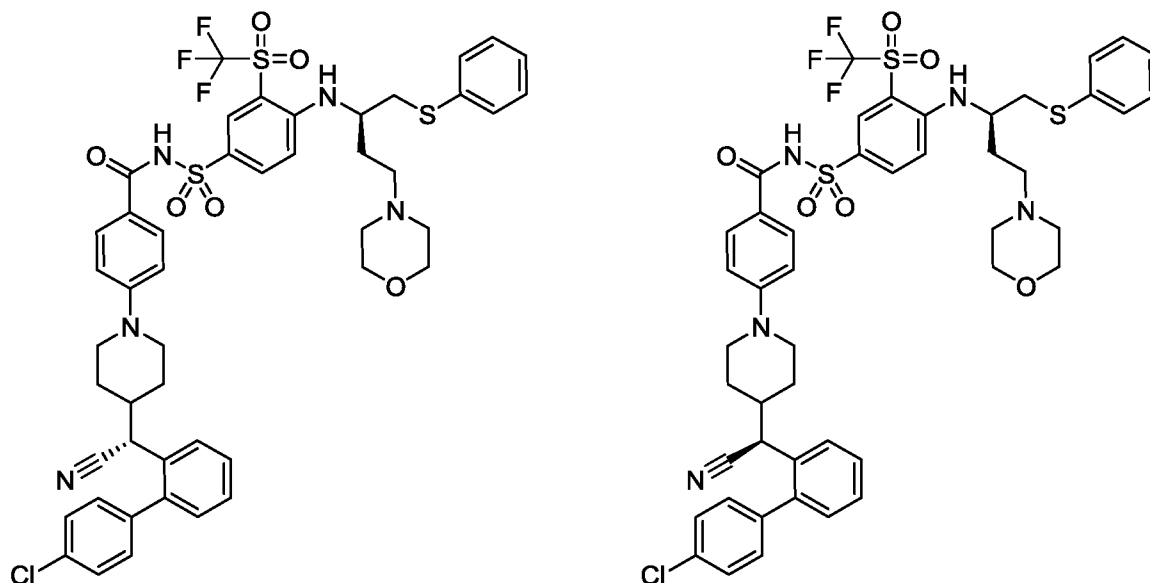
[000944] 4-(4-((R)-(tert-butyldimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-N-(4-((R)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfonyl)benzamide (INTERMEDIATE 75, 329.0 mg, 0.33 mmol) was charged in a 100 ml flask under nitrogen and treated with TBAF (10.0 ml, 1.0 M in THF, 10 mmol). The resulting solution was stirred at room temperature for 35 minutes whereupon the volatiles were removed under reduced pressure. The concentrate was diluted with DCM (100 ml) and washed with 1N aq. NaHSO₄ (100 ml), and saturated aq. NaHCO₃ (30 ml), then dried (Na₂SO₄), filtered, and evaporated under vacuum. The concentrate was purified by column chromatography (ISCO, 12 g silica gel column, eluting with 0→5% MeOH/DCM) followed by further purification by column chromatography (ISCO, 12 g silica gel column, eluting with 0→90% DCM/ [10% of 2M NH₃ in MeOH/90 % DCM]) to provide the title product (228 mg, yield: 78%)

[000945] ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ ppm 0.84 (br. s., 1 H) 1.01 (d, 2 H) 1.56 - 1.72 (m, 1 H) 1.88 (m, 2 H) 1.94 - 2.09 (m, 1 H) 3.36 (d, 2 H) 3.45 - 3.59 (m, 4 H) 3.64 (m, 1 H) 3.75 - 3.87 (m, 1 H) 4.07 - 4.21 (m, 1 H) 4.30 (dd, 1 H) 5.20 (d, 1 H) 6.78 (d, 2 H) 7.05 (d, 1 H) 7.10 - 7.25 (m, 4 H) 7.25 - 7.38 (m, 5 H) 7.38 - 7.52 (m, 3 H) 7.58 (d, 1 H) 7.67 (d, Hz, 2 H) 7.75 - 7.84 (m, 1 H) 8.38 (d, 1 H) 8.50 (d, 1 H).

[000946] LCMS: (ESI) m/z 870 $[\text{M}+\text{H}]^+$.

EXAMPLE 17

[000947] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(cyano)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide and 4-(4-((*S*)-(4'-chlorobiphenyl-2-yl)(cyano)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide, mixture of diastereomers



[000948] (*R*)-4-(4-((4'-chlorobiphenyl-2-yl)(cyano)methyl)piperidin-1-yl)benzoic acid and (*S*)-4-(4-((4'-chlorobiphenyl-2-yl)(cyano)methyl)piperidin-1-yl)benzoic acid hydrochloride salts (INTERMEDIATE 83, 67.8 mg, 0.15 mmol), (*R*)-4-(4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl) benzenesulfonamide (INTERMEDIATE 69, 81.4 mg, 0.15 mmol), DMAP (38.1 mg, 0.31 mmol), and EDC (59.0 mg, 0.31 mmol) were combined and sealed in a microwave tube. The tube was purged with nitrogen, and DCM (3.0 ml) and DIPEA (0.05 ml, 0.29 mmol) were added. The reaction mixture was stirred at room temperature for 4 days and was then diluted with water (5 ml) and extracted with DCM (2 x 5 ml). The combined extracts were dried (MgSO_4), filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (ISCO, 4 g silica gel column, eluting with first with 0→10 % MeOH/DCM and then with 0→100 % EtOAc/hexanes). The fractions corresponding to

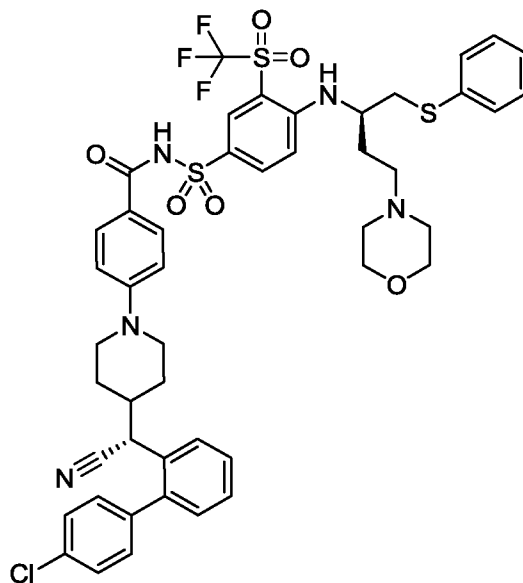
product were collected and evaporated to dryness to give a gummy residue. The material was dissolved in a trace of DCM and diethyl ether was added, resulting in a precipitate. The slurry was evaporated under reduced pressure to provide the title product (60.4 mg, yield: 44 %) as a mixture of diastereomers.

[000949] ^1H NMR (400 MHz, $\text{DICHLOROMETHANE-}d_2$) δ ppm 1.05 (qd, 1 H), 1.30 - 1.45 (m, 2 H), 1.60 - 1.71 (m, 1 H), 1.81 - 1.93 (m, 1 H), 1.95 - 2.12 (m, 2 H), 2.19 - 2.45 (m, 6 H), 2.62 (td, 1 H), 2.75 (td, 1 H), 3.05 - 3.16 (m, 2 H), 3.53 - 3.65 (m, 4 H), 3.67 - 3.75 (m, 1 H), 3.78 (d, 1 H), 3.83 - 3.91 (m, 1 H), 3.93 - 4.03 (m, 1 H), 6.67 - 6.74 (m, 1 H), 6.78 (d, 2 H), 7.04 (d, 1 H), 7.20 - 7.34 (m, 6 H), 7.34 - 7.40 (m, 2 H), 7.40 - 7.51 (m, 4 H), 7.55 - 7.60 (m, 1 H), 7.62 (d, 2 H), 8.03 (dd, 1 H), 8.33 (d, 1 H).

[000950] LCMS: (ESI) m/z 966 $[\text{M}+\text{H}]^+$.

EXAMPLE 18

[000951] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(cyano)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide



[000952] The title product (19.8 mg, yield: 20 %) was prepared using a procedure similar to the one described for the synthesis of EXAMPLE 14. (*R*)-4-(4-((4'-Chlorobiphenyl-2-yl)(cyano)methyl)piperidin-1-yl)benzoic acid, hydrochloride salt (INTERMEDIATE 84, 44.9 mg, 0.1 mmol) and (*R*)-4-(4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl) benzenesulfonamide (INTERMEDIATE 69, 54.4 mg, 0.1 mmol) were used as starting materials. The resulting product was purified by column chromatography (ISCO, 4 g silica gel column, eluting with 0→5% MeOH/DCM) followed by further purification by

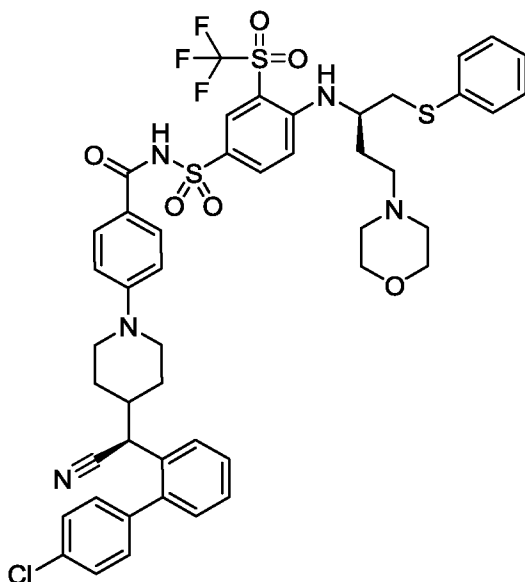
column chromatography (ISCO, 4 g silica gel column, eluting first with 0→100% EtOAc/hexanes and then with 0→5 % MeOH/DCM), providing the title product.

[000953] ^1H NMR (400 MHz, $\text{DICHLOROMETHANE-}d_2$) δ ppm 0.98 - 1.11 (m, 1 H), 1.29 - 1.45 (m, 3 H), 1.61 (br. s., 1 H), 1.81 - 2.05 (m, 3 H), 2.21 - 2.37 (m, 1 H), 2.49 - 2.87 (m, 6 H), 3.14 (d, 2 H), 3.66 - 3.98 (m, 7 H), 4.07 (br. s., 1 H), 6.73 - 6.84 (m, 3 H), 7.02 (d, 1 H), 7.20 - 7.33 (m, 6 H), 7.35 - 7.51 (m, 6 H), 7.57 (dd, 1 H), 7.62 (d, 2 H), 8.06 (dd, 1 H), 8.36 (d, 1 H).

[000954] LCMS: (ESI) m/z 966 $[\text{M}+\text{H}]^+$.

EXAMPLE 19

[000955] 4-(4-((*S*)-(4'-chlorobiphenyl-2-yl)(cyano)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide



[000956] The title product (10.7 mg, yield: 11 %) was prepared using a procedure similar to the one described for the synthesis of EXAMPLE 14. (*S*)-4-(4-((4'-Chlorobiphenyl-2-yl)(cyano)methyl)piperidin-1-yl)benzoic acid, HCl salt (INTERMEDIATE 85, 49.5 mg 0.11 mmol) and (*R*)-4-(4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide (INTERMEDIATE 69, 58.6 mg 0.11 mmol) were used as starting materials. The resulting product was purified by column chromatography (ISCO, 4 g silica gel column, eluting with 0→5% MeOH/DCM) followed by further purification by column chromatography (ISCO, 4 g silica gel column, eluting first with 0→100% EtOAc/hexanes and then with 0→3.5 % MeOH/DCM), providing the title product.

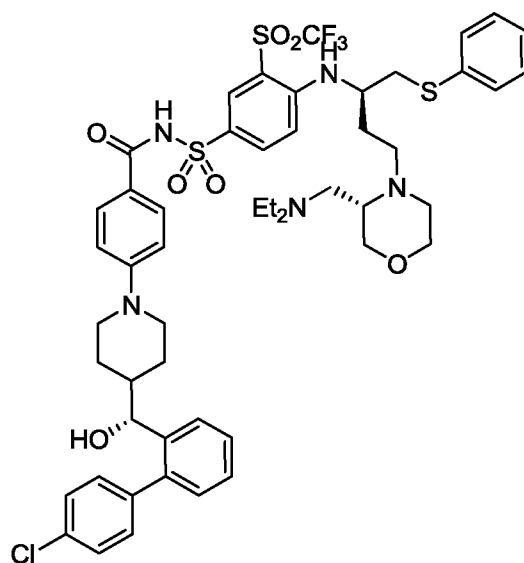
[000957] ^1H NMR (400 MHz, $\text{DICHLOROMETHANE-}d_2$) δ ppm 1.04 (qd, 1 H), 1.30 - 1.45 (m, 3 H), 1.61 - 1.72 (m, 1 H), 1.82 - 1.94 (m, 1 H), 2.21 - 2.47 (m, 6 H), 2.63 (td, 1 H), 2.76 (td,

1 H), 3.11 (d, 2 H), 3.53 - 3.66 (m, 4 H), 3.68 - 3.76 (m, 1 H), 3.78 (d, 1 H), 3.84 - 3.92 (m, 1 H), 3.94 - 4.05 (m, 1 H), 6.72 (d, 1 H), 6.78 (d, 2 H), 7.06 (d, 1 H), 7.20 - 7.34 (m, 6 H), 7.34 - 7.52 (m, 6 H), 7.55 - 7.65 (m, 3 H), 8.03 (dd, 1 H), 8.34 (d, 1 H).

[000958] LCMS: (ESI) m/z 966 $[M+H]^+$.

EXAMPLE 20

[000959] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-((*S*)-3-((diethylamino)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide



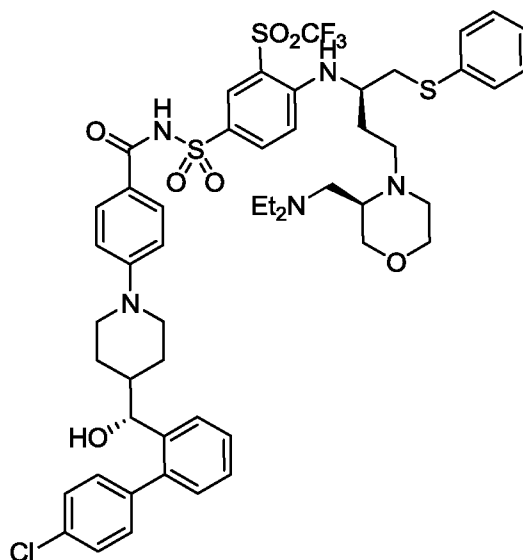
[000960] A solution of 4-(4-((*R*)-(tert-butyldimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-((*S*)-3-((diethylamino)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide, (INTERMEDIATE 89, 100 mg, 0.09 mmol) and TBAF (3.5 ml 3.46 mmol, 1 M in THF) was stirred for 45 minutes at room temperature. The solvent was removed under reduced pressure and the residue was taken up in DCM (50 ml). The organic layer was washed successively with 50 ml of water (50 ml) and saturated aqueous sodium bicarbonate (50 ml). The organic phase was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The concentrate was purified by column chromatography (ISCO, eluting with 0→100% DCM/[10% 2N ammonia in MeOH in DCM] over 19 minutes and then eluting with 0→20% MeOH/DCM) to give the title product (43.0 mg, yield: 48 %).

[000961] ^1H NMR (400 MHz, DICHLOROMETHANE- d_2) δ ppm 0.68 - 1.28 (m, 11 H) 1.43 - 1.77 (m, 2 H) 1.79 - 2.04 (m, 2 H) 2.04 - 2.74 (m, 13 H) 2.86 - 3.07 (m, 2 H) 3.18 - 3.32 (m, 1 H) 3.35 - 3.89 (m, 6 H) 4.39 (d, 1 H) 6.60 (d, 4 H) 7.03 - 7.39 (m, 12 H) 7.50 (d, 1 H) 7.66 (d, 2 H) 7.86 - 8.03 (m, 1 H) 8.16 (br. s., 1 H).

[000962] LCMS: (ESI) m/z 1042 $[M+H]^+$.

EXAMPLE 21

[000963] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-((*R*)-3-((diethylamino)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide



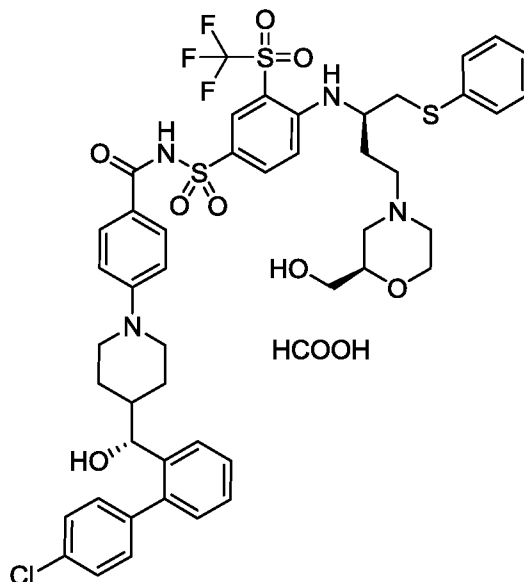
[000964] The title product (50 mg, yield: 55 %) was prepared using a procedure similar to the one described for the synthesis of EXAMPLE 16. 4-(4-((*R*)-(tert-butyldimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-((*R*)-3-((diethylamino)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide (INTERMEDIATE 93, 100 mg, 0.09 mmol) was used as starting material. The resulting product was purified by column chromatography (ISCO, eluting with 0→100% DCM/ [10% 2N ammonia in MeOH in DCM] over 19 minutes and then eluting with 0→20% MeOH/DCM), providing the title product.

[000965] ^1H NMR (400 MHz, DICHLOROMETHANE- d_2) δ ppm 0.85 - 1.30 (m, 10 H) 1.46 - 1.76 (m, 2 H) 1.78 - 2.02 (m, 2 H) 2.07 - 2.78 (m, 14 H) 2.86 - 3.11 (m, 2 H) 3.28 - 3.57 (m, 5 H) 3.68 (d, 1 H) 3.84 (br. s., 1 H) 4.38 (d, 1 H) 6.35 - 6.77 (m, 4 H) 6.97 - 7.40 (m, 12 H) 7.50 (dd, 1 H) 7.66 (d, 2 H) 7.91 (d, 1 H) 8.13 (br. s., 1 H).

[000966] LCMS: (ESI) m/z 1042 $[M+H]^+$.

EXAMPLE 22

[000967] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-((*R*)-2-(hydroxymethyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide, formic acid salt



[000968] A solution of TBAF (115 μ l, 0.11 mmol, 1M in THF) was added dropwise to a solution of 4-(4-((*R*)-(tert-butyl)dimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-((*R*)-2-((tert-butyl)diphenylsilyloxy)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide INTERMEDIATE 100, 77 mg, 0.06 mmol) in THF (420 μ l) and the resulting mixture was stirred at room temperature overnight. HCl (4 M in dioxane, 39.9 μ l, 1.15 mmol) was then added and the mixture was stirred at room temperature for 1 hr. The reaction mixture was diluted with EtOAc and the organic phase washed with H₂O (2x), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The concentrate was purified by reverse phase HPLC (Gilson column, eluting with 15→70% H₂O/MeCN with 1% formic acid for 14 minutes) to provide the title product (31.0 mg, yield: 52 %).

[000969] ¹H NMR (300 MHz, METHANOL-*d*₄) δ ppm 0.88 - 1.09 (m, 2 H) 1.10 - 1.35 (m, 3 H) 1.73 - 1.87 (m, 2 H) 1.91 - 2.20 (m, 5 H) 2.43 - 2.64 (m, 3 H) 2.68 - 2.85 (m, 3 H) 3.24 (dd, 2 H) 3.44 - 3.65 (m, 5 H) 3.70 (d, 1 H) 3.88 (d, 2 H) 4.06 (br. s., 1 H) 4.44 (d, 1 H) 6.81 - 6.90 (m, 3 H) 7.14 - 7.28 (m, 4 H) 7.28 - 7.48 (m, 9 H) 7.62 (d, 1 H) 7.73 (d, 2 H) 8.03 (d, 1 H) 8.29 (s, 1 H).

[000970] LCMS: (ESI) *m/z* 987.3 [M+H]⁺.

[000971] Optical rotation:

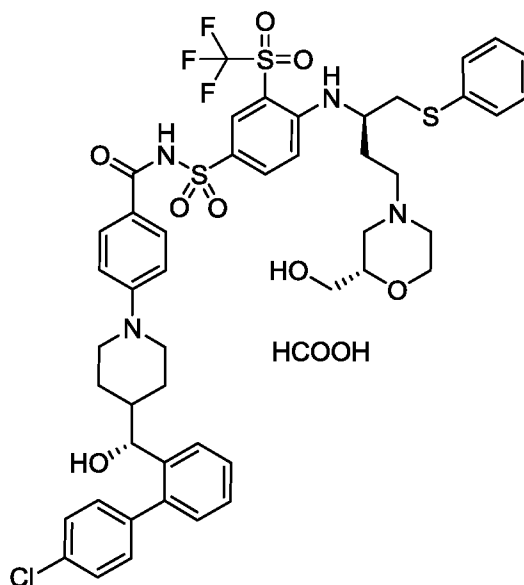
Concentration:	0.1 g/dL
Lamp:	Sodium
Wavelength:	589 nm
Temperature:	20° C
Path length:	10 cm
Cell volume:	1 ml

Solvent: Methanol

[α]= +4

EXAMPLE 23

[000972] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxymethyl)piperidin-1-yl)-*N*-(4-((*R*)-4-((*S*)-2-(hydroxymethyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide, formic acid salt



[000973] The title product (37 mg, yield: 62%) was prepared using a procedure similar to the one described for the synthesis of EXAMPLE 22. 4-(4-((*R*)-(tert-butyldimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-((*S*)-2-((tert-butyldiphenylsilyloxy)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide (INTERMEDIATE 101, 77 mg, 0.06 mmol) was used as starting material. The resulting product was purified by reverse phase HPLC (Gilson, eluting with 15→70% H₂O/MeCN with 1% formic acid for 14 minutes), providing the title product.

[000974] ¹H NMR (300 MHz, METHANOL-*d*₄) δ ppm 0.87 - 1.05 (m, 1 H) 1.08 - 1.33 (m, 2 H) 1.81 (dd, 2 H) 1.90 - 2.16 (m, 3 H) 2.16 - 2.28 (m, 1 H) 2.42 - 2.66 (m, 4 H) 2.69 - 2.81 (m, 1 H) 2.93 (d, 1 H) 3.14 - 3.29 (m, 2 H) 3.47 - 3.65 (m, 4 H) 3.71 (d, 1 H) 3.79 - 3.93 (m, 2 H) 4.08 (dd, 1 H) 4.44 (d, 1 H) 6.82 - 6.89 (m, 3 H) 7.14 - 7.28 (m, 4 H) 7.29 - 7.47 (m, 8 H) 7.60 - 7.64 (m, 1 H) 7.72 (d, 2 H) 8.02 (dd, 1 H) 8.29 (d, 1 H).

[000975] LCMS: (ESI) *m/z* 987 [M+H]⁺.

[000976] Optical rotation:

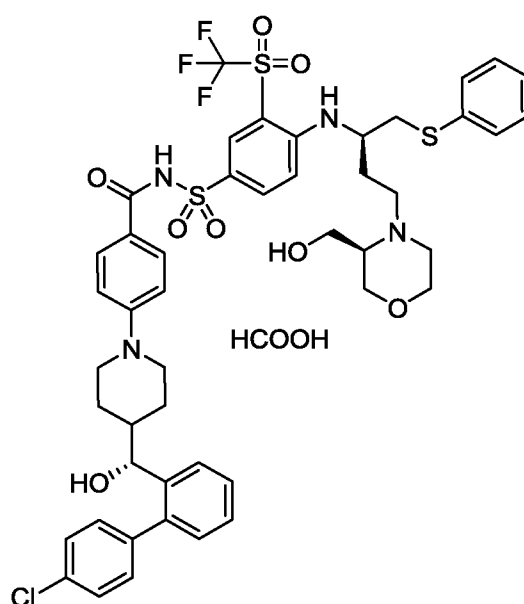
Concentration: 0.1 g/dL

Lamp: Sodium

Wavelength: 589 nm
 Temperature: 20° C
 Path length: 10 cm
 Cell volume: 1 ml
 Solvent: Methanol
 $[\alpha]_D^{20} = +10$

EXAMPLE 24

[000977] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxymethyl)piperidin-1-yl)-*N*-(4-((*R*)-4-((*R*)-3-(hydroxymethyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide, formic acid salt



[000978] Step 1: To a solution of (*R*)-4-(4-((*tert*-butyldimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)benzoic acid (INTERMEDIATE 13, 183 mg, 0.34mmol) in DCM (3 ml) were added sequentially DMAP (125 mg, 1.02mmol), 4-((*R*)-4-((*S*)-3-((*tert*-butyldiphenylsilyloxy)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide (INTERMEDIATE 105, 280 mg, 0.34 mmol) and EDC (131 mg, 0.68mmol). The resulting solution was stirred at room temperature overnight. Evaporation of the volatiles under reduced pressure gave a residue which was purified by column chromatography (ISCO, 27 g silica gel column, eluting with 0→20 % EtOAc/hexanes) to give 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-((*S*)-3-((*tert*-butyldiphenylsilyloxy)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide (EXAMPLE 24, STEP 1, 153 mg) which was used in the preparation of EXAMPLE 24, STEP 2 without further purification.

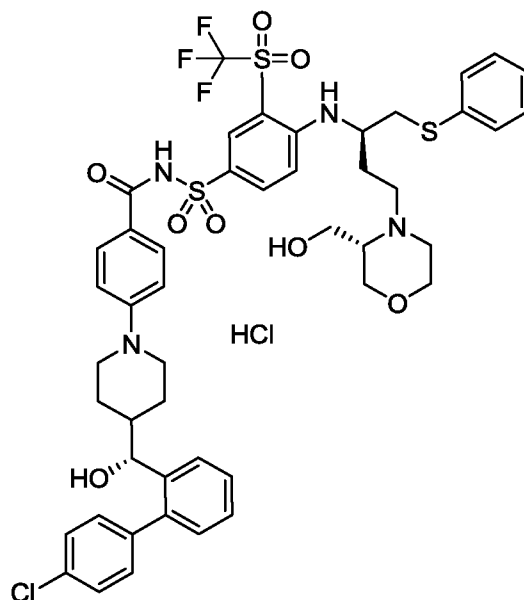
[000979] Step 2: To a solution of 4-(4-((*R*)-(tert-butyldimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-((*S*)-3-((tert-butyldiphenylsilyloxy)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide (EXAMPLE 24, STEP 1, 135 mg) in THF (2 ml) was added TBAF (0.54 ml, 0.54 mmol, 1M in THF). The resulting mixture was stirred at room temperature overnight whereupon HCl (2 ml, 4N in dioxane) was added and the mixture stirred for 30 minutes at ambient temperature. The volatiles were evaporated under reduced pressure to give a residue which was purified by reverse phase HPLC (Gilson column, eluting with 10→70% MeCN with 0.1% formic acid /water), to give the title product (92 mg, yield: 27%).

[000980] ¹H NMR (DMSO-*d*₆, 300Mz) 8.18 (s, 1H) 8.01 (d, 1H) 7.68 (d, 2 H) 7.58 (d, 1H) 7.49 (d, 2H) 7.43 (t, 1H) 7.27-7.37 (m, 5H) 7.20-7.26 (m, 2H) 7.12-7.18 (m, 2H) 6.99 (d, 1H) 6.84 (d, 2H) 4.30 (d, 1H) 4.12-4.23 (m, 2H) 3.80-4.06 (m, 9H) 3.62-3.75 (m, 2H) 3.55-3.61 (m, 1H) 3.44-3.64 (m, 2H) 3.25-3.42 (m, 2H) 1.83-1.93 (m, 1H) 1.64-1.74 (m, 1H) 0.99-1.36 (m, 3H) 0.83-0.92 (m, 2H).

[000981] LCMS: (ESI) *m/z* 987 [M+H]⁺.

EXAMPLE 25

[000982] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-((*S*)-3-(hydroxymethyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide, hydrochloride salt



[000983] To a solution of 4-(4-((*R*)-(tert-butyldimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-((*R*)-3-((tert-butyldiphenylsilyloxy)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide

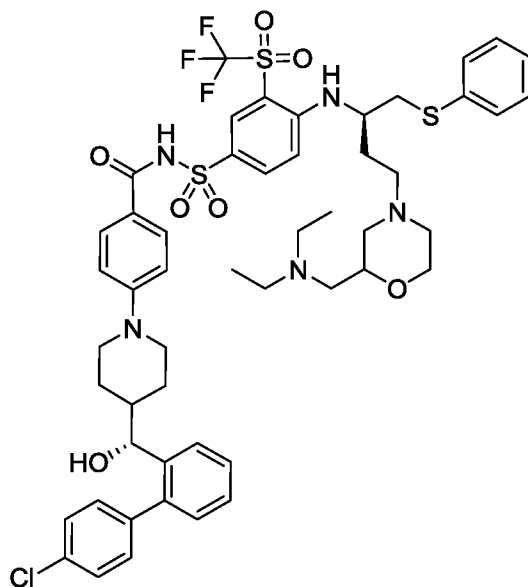
(INTERMEDIATE 110, 134 mg, 0.10 mmol) in THF (2 ml) was added TBAF (0.2 ml, 0.2 mmol, 1M in THF). The resulting mixture was heated at 60 °C for 2 hours. The volatiles were evaporated under reduced pressure to give a residue which was purified by reverse phase HPLC (Gilson column, eluting with 5→70% MeCN with 0.1% TFA /water) to give the trifluoroacetate salt of 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxymethyl)piperidin-1-yl)-*N*-(4-((*R*)-4-((*S*)-3-(hydroxymethyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide. The trifluoroacetate salt was dissolved in dioxane and treated with HCl in dioxane (4N in dioxane) and the resulting solution was stirred for 10 minutes at room temperature. Evaporation of the volatiles under reduced pressure gave the title product (72 mg, yield: 70 %).

[000984] ¹H NMR (DMSO-*d*₆, 300Mz) 8.17 (d, 1H) 8.01 (d, 1H) 7.68 (d, 2 H) 7.59 (d, 1H) 7.49 (d, 2H) 7.43 (t, 1 H) 7.28-7.37 (m, 5 H) 7.19-7.26 (m, 2 H) 7.13-7.18 (m, 2H) 6.98 (d, 1H) 6.84 (d, 2 H) 4.30 (d, 1 H) 4.09-4.22(m, 2 H) 3.52-4.08(m, 12 H) 3.07-3.44 (m, 4 H) 1.81-1.93 (m, 1H) 1.64-1.74 (m, 1H) 0.98-1.36 (m, 3H) 0.79-0.92 (m, 2H).

[000985] LCMS: *m/z* 987 [M+H]⁺.

EXAMPLE 26

[000986] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxymethyl)piperidin-1-yl)-*N*-(4-((2*R*)-4-(2-((diethylamino)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide, single diastereomer



[000987] To a solution of 4-(4-((*R*)-(tert-butyldimethylsilyloxy)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-*N*-(4-((2*R*)-4-(2-((diethylamino)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide, single

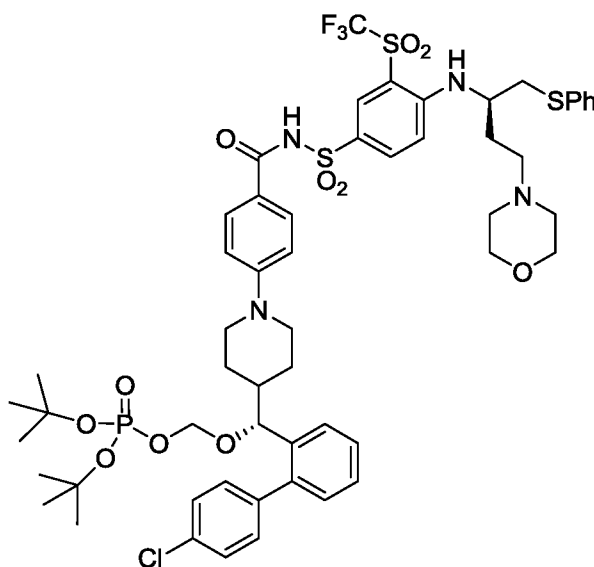
diastereomer (INTERMEDIATE 117, 199 mg, 0.17 mmol) in dioxane (2.027 ml) was added drop wise HCl (4M in dioxane, 0.430 ml, 1.72 mmol) and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was neutralized with Et₃N (2 ml), diluted with DCM and filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography (ISCO, eluting with 0→100 % DCM to 10% MeOH/0.1% NH₃ in DCM) to provide the title product as a substantially separated diastereomer (0.06 g, 30 %).

[000988] ¹H NMR (400 MHz, DICHLOROMETHANE-*d*₂) δ ppm 8.06 (d, 1 H), 8.02 (d, 1 H), 7.90 (d, 2H), 7.61 (m, 1H), 7.40 – 7.21 (m, 12 H), 6.82 – 6.76 (m, 3H), 6.46 (d, 1H), 4.49 (d, *J* = 8.1 Hz, 1H), 4.02 (m, 1H), 3.82 (d, 1H), 3.66 (m, 2H), 3.48 (m, 1H), 3.33 (m, 1 H), 3.17 (m, 1H), 3.09 (m, 4H), 2.83 (d, 1H), 2.73 (m, 2H), 2.55 (m, 2H), 2.32 (m, 1H), 2.20 – 2.01 (m, 3H), 1.86 – 1.69 (m, 4H), 1.50 (m, 1H), 1.40 – 1.28 (m, 4H), 1.12 (t, 6H).

[000989] LCMS: (ESI) *m/z* 1042 [M+H]⁺.

EXAMPLE 27

[000990] Di-*tert*-butyl ((*R*)-(4'-chlorobiphenyl-2-yl)(1-(4-(4-((*R*)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonylcarbamoyl)-phenyl)piperidin-4-yl)methoxy)methyl phosphate



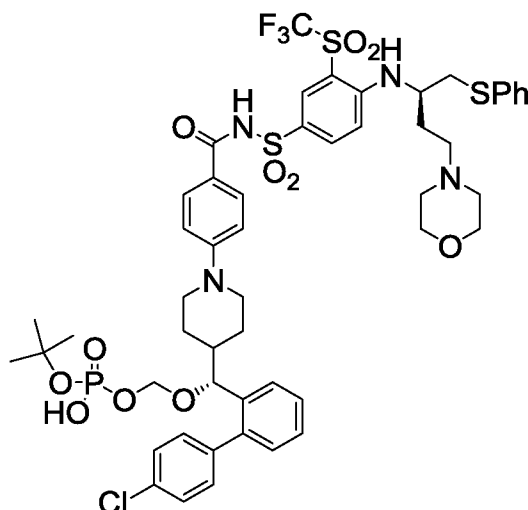
[000991] To a solution of (*R*)-4-(4-((4'-chlorobiphenyl-2-yl)(di-*tert*-butoxyphosphonooxymethoxy)methyl)piperidin-1-yl)benzoic acid (INTERMEDIATE 118, 73 mg, 0.11 mmol), EDC (43 mg, 0.23 mmol), and DMAP (28 mg, 0.23 mmol) in 3 ml of DCM was added (*R*)-4-(4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide (INTERMEDIATE 69, 69 mg, 0.12 mmol). The mixture was allowed to stir overnight at room temperature. The reaction mixture was diluted with DCM (20 ml) and washed with brine (5 ml). The collected organic layer was dried over Na₂SO₄

and concentrated *in vacuo*. The residue was purified by column chromatography (ISCO, eluting with 0→10% MeOH/EtOAc for 14 minutes) to provide the title product (58 mg, yield: 43%).

[000992] LCMS: m/z 1179 $[M + H]^+$.

EXAMPLE 28

[000993] *tert*-Butyl ((*R*)-(4'-chlorobiphenyl-2-yl)(1-(4-(4-((*R*)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonylcarbamoyl)-phenyl)piperidin-4-yl)methoxy)methyl hydrogen phosphate



[000994] Nitrolotrimethanol (5.27 mg, 0.05 mmol) was added to a solution of di-*tert*-butyl ((*R*)-(4'-chlorobiphenyl-2-yl)(1-(4-(4-((*R*)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonylcarbamoyl)phenyl)piperidin-4-yl)methoxy)methyl phosphate (EXAMPLE 27, 58.0 mg, 0.05 mmol) in acetone (1.8 ml) and 0.6 ml of pH7.2 buffer (Gibco, Dulbecco's Phosphate Buffered saline 1X). The resulting reaction mixture was stirred at 65 °C for 16 hours. Evaporation of the volatiles under reduced pressure gave a residue which was purified by reverse phase HPLC (Gilson column, eluting with 30→50% H₂O with 10 mM NH₄OAc/MeCN for 5 minutes) to provide the title product (0.017 g, yield: 19%).

[000995] ¹H NMR (300 MHz, METHANOL-*d*₄) δ ppm 0.97 - 1.08 (m, 3 H) 1.14 - 1.21 (m, 3 H) 1.34 (s, 12 H) 1.51 - 1.65 (m, 1 H) 1.73 - 1.90 (m, 2 H) 1.95 - 2.15 (m, 1 H) 2.42 - 2.72 (m, 9 H) 3.57 - 3.66 (m, 5 H) 3.71 - 3.82 (m, 1 H) 3.90 - 4.01 (m, 1 H) 4.93 - 5.03 (m, 1 H) 6.66 - 6.75 (m, 2 H) 6.76 - 6.83 (m, 1 H) 7.00 - 7.16 (m, 3 H) 7.18 - 7.35 (m, 9 H) 7.39 - 7.46 (m, 1 H) 7.51 - 7.62 (m, 2 H) 7.85 - 7.97 (m, 1 H) 8.11 - 8.24 (m, 1 H).

[000996] LCMS: (ESI) m/z 1124 $[M+H]^+$.

EXAMPLE 29

[000997] (*R*)-(4'-chlorobiphenyl-2-yl)(1-(4-(4-((*R*)-4-morpholino-1-(phenylthio)butan-2-

CCOP(=O)(OCC)C1CCN(CC1Cc2ccc(Cl)cc2)C(=O)c3ccc(NC(=O)S(=O)(=O)c4ccc(NC[C@H](c5ccccc5)CCN6CCOCC6)c4)c3

HCl

Column:	Atlantis T3, OBD
Column dimensions:	30 x 100mm, 5μ
Mobile phase A	water with 0.1% TFA, pH 2
Mobile phase B	100% Acetonitrile
Flow rate (ml/min):	60 ml/min
Gradient:	From A→B (60 to 80% in 10 minutes)

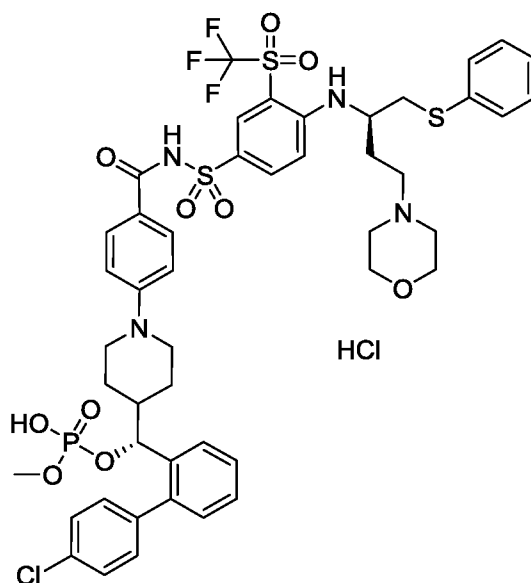
[000999] ¹H NMR (400 MHz, DICHLOROMETHANE-*d*₂) δ ppm 0.60 - 0.85 (m, 2 H) 0.90 - 1.14 (m, 9 H) 1.32 - 1.44 (m, 1 H) 1.59 (br. s., 1 H) 1.70 - 2.46 (m, 4 H) 2.65 - 3.20 (m, 7 H) 3.21 - 3.48 (m, 4 H) 3.50 - 3.73 (m, 1 H) 3.75 - 4.33 (m, 8 H) 6.81 - 7.02 (m, 1 H) 7.04 - 7.67 (m, 15 H) 7.90 (br. s., 3 H) 8.28 (br. s., 1 H).

[0001000] ^{31}P NMR (121 MHz, DICHLOROMETHANE- d_2) δ ppm -2.73 (s, 1 P).

[0001001] LCMS: (ESI) m/z 1092 $[\text{M-H}]^+$.

EXAMPLE 30

[0001002] (*R*)-(4'-chlorobiphenyl-2-yl)(1-(4-(4-((*R*)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonylcarbamoyl)phenyl)piperidin-4-yl)methyl methyl hydrogen phosphate, hydrochloride salt



[0001003] A mixture of (*R*)-4-(4-((4'-chlorobiphenyl-2-yl)(dimethoxyphosphoryloxy)methyl)piperidin-1-yl)benzoic acid (INTERMEDIATE 122, 57.4 mg, 0.11 mmol), (*R*)-4-(4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide (INTERMEDIATE 69, 60 mg, 0.11 mmol), EDC (41.6 mg, 0.22 mmol), TEA (0.03 ml, 0.22 mmol), and DCE (2 ml) were stirred at r.t. for 4 days. The volatiles were removed under reduced pressure and the concentrate was purified by reverse phase HPLC according to the following conditions:

Column: Xbridge Sunfire

Column dimensions: 19 x 100mm, 5 μ

Mobile phase A: water with 0.1% TFA, pH 2

Mobile phase B: 100% Acetonitrile

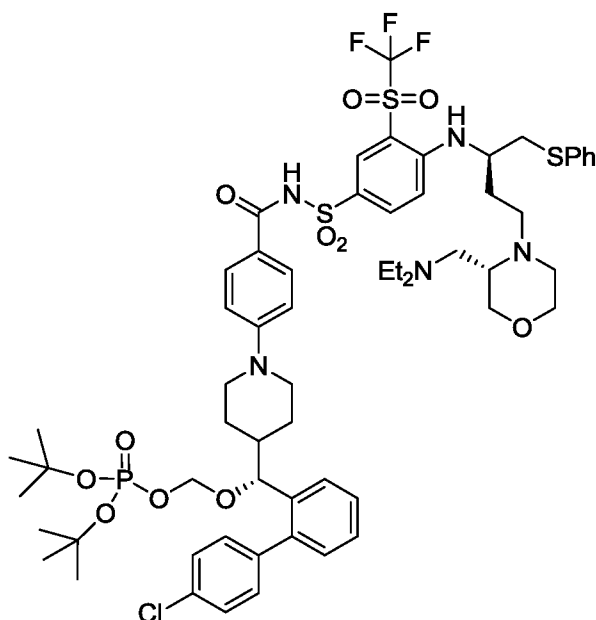
Flow rate (ml/min): 20 ml/min

Gradient: A $\rightarrow$ B (From 40 to 60% in 10 minutes)

The like fractions were combined and the volatiles were removed under reduced pressure. The residue left was treated with HCl in dioxane (4N, 0.5 ml) and diluted with MeOH and the volatiles were subsequently removed under reduced pressure to give the title compound (34.0 mg, yield: 30 %).

EXAMPLE 31

[10001006] Di-*tert*-butyl ((*R*)-(4'-chlorobiphenyl-2-yl)(1-(4-(4-((*R*)-4-((*S*)-3-((diethylamino)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonylcarbamoyl)phenyl)piperidin-4-yl)methoxy)methyl phosphate



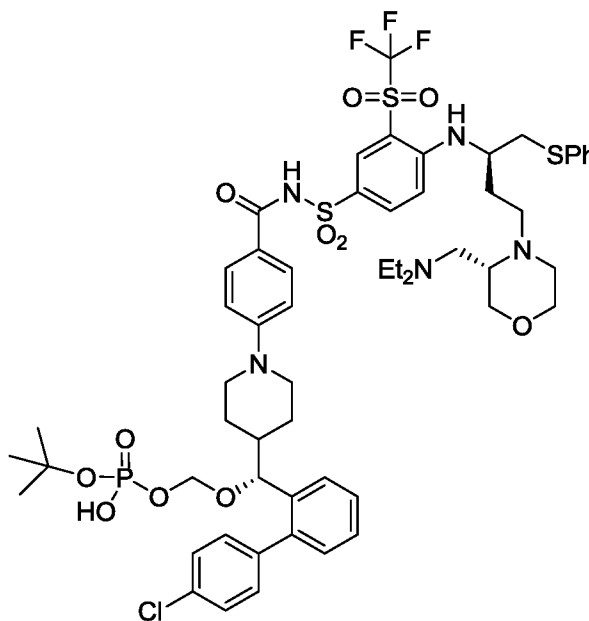
[0001007] To a solution of (R)-4-(4-((4'-chlorobiphenyl-2-yl)(di-tert-butoxyphosphonooxymethoxy)methyl)piperidin-1-yl)benzoic acid (INTERMEDIATE 118, 55.5 mg, 0.09 mmol), EDC (33 mg, 0.17 mmol), and DMAP (21 mg, 0.17 mmol) in DCM (3 ml) was added 4-((R)-4-((S)-3-((diethylamino)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide (INTERMEDIATE 88, 55 mg, 0.09 mmol). The resulting mixture was stirred overnight at room temperature. The reaction mixture was diluted with DCM (20 ml) and washed with brine (5 ml). The collected organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (ISCO, eluting with 0→10% MeOH/EtOAc for 14 minutes) to provide the title product (30 mg, 27%).

[0001008] LCMS: (ESI) *m/z* 1263 [M - H]⁺.

EXAMPLE 32

[0001009] *tert*-Butyl((*R*)-(4'-chlorobiphenyl-2-yl)(1-(4-(4-((*R*)-4-((*S*)-3-

((diethylamino)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-

(trifluoromethylsulfonyl)phenylsulfonylcarbamoyl)phenyl)piperidin-4-yl)methoxy)methyl
hydrogen phosphate

[0001010] A similar procedure to that described for EXAMPLE 28 utilizing di-*tert*-butyl (*R*)-(4'-chlorobiphenyl-2-yl)(1-(4-(4-((*R*)-4-((*S*)-3-((diethylamino)methyl)morpholino)-1-(phenylthio)butan-2-ylamino)-3-

(trifluoromethylsulfonyl)phenylsulfonylcarbamoyl)phenyl)piperidin-4-yl)methoxy)methyl

phosphate (EXAMPLE 31, 110 mg, 0.09 mmol) as starting material was followed, with subsequent purification by reverse phase HPLC (Gilson column, eluting with 15→50% H₂O with 10 mM NH₄OAc/MeCN for 4 minutes) to provide the title product (0.027 g, yield: 27%).

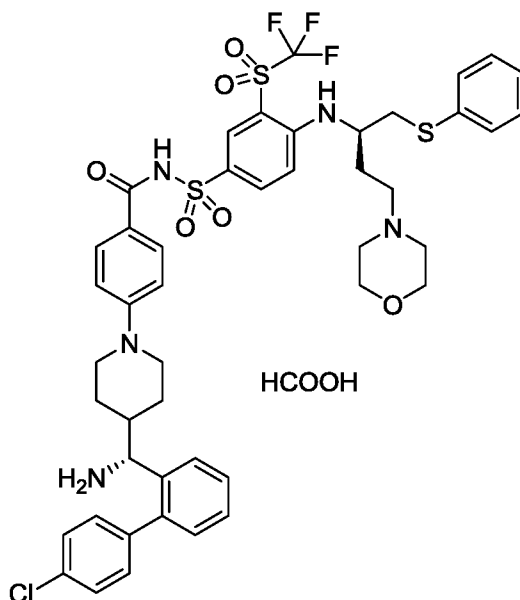
[0001011] ¹H NMR (300 MHz, METHANOL-*d*₄) δ ppm 0.80 - 0.92 (m, 6 H) 0.95 - 1.06 (m, 5 H) 1.25 (s, 9 H) 1.52 - 1.87 (m, 4 H) 1.98 - 2.13 (m, 1 H) 2.20 - 2.34 (m, 1 H) 2.41 - 2.83 (m, 12 H) 2.85 - 2.99 (m, 2 H) 3.24 - 3.38 (m, 2 H) 3.50 - 3.65 (m, 2 H) 3.68 - 3.79 (m, 2 H) 3.85 - 4.00 (m, 1 H) 4.90 - 5.04 (m, 2 H) 6.57 - 6.75 (m, 3 H) 6.99 - 7.48 (m, 14 H) 7.59 - 7.71 (m, 2 H) 7.86 - 7.99 (m, 1 H) 8.13 - 8.25 (m, 1 H).

[0001012] LCMS: (ESI) *m/z* 1208 [M-H]⁺.

EXAMPLE 33

[0001013] 4-(4-((*R*)-amino(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-

(trifluoromethylsulfonyl)phenylsulfonyl)benzamide, formic acid salt



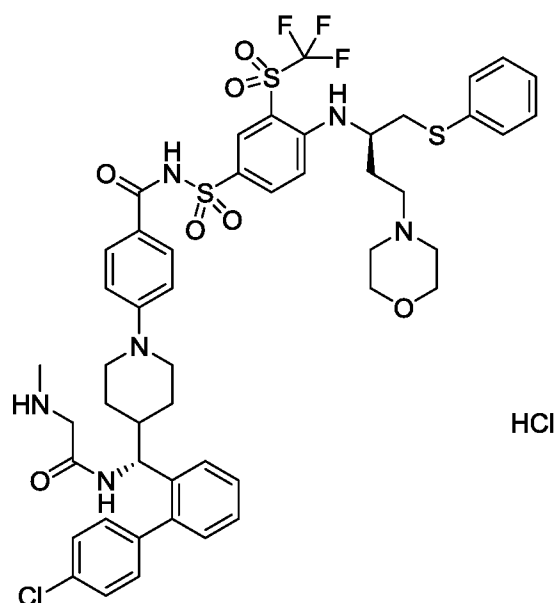
[0001014] A solution of HCl (0.80 ml, 3.21 mmol, 4 M in dioxane) was added to a solution of 4-((*R*)-(4'-chlorobiphenyl-2-yl)((*S*)-1,1-dimethylethylsulfinamido)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide (INTERMEDIATE 131, 0.17 g, 0.16 mmol) in MeOH (1.5 ml) and the reaction mixture was stirred at r.t for 2 hours. The reaction mixture was concentrated under reduced pressure to provide a residue which was purified by reverse phase HPLC (Gilson column, eluting with 20→50% H₂O/ACN with 0.1% formic acid for 10 minutes) to provide the title compound (0.10 g, yield: 60%).

[0001015] ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.05 (d, 1 H), 7.90 (dd, 1 H), 7.70 – 7.67 (m, 3H), 7.59 – 7.53 (m, 3H), 7.50 – 7.46 (m, 1H), 7.40 - 7.25 (m, 8 H), 7.22 - 7.18 (m, 1 H), 6.81 (d, 1 H), 6.73 (d, 2 H), 6.68 (d, 1 H), 4.00 (m, 1H), 3.87 – 3.85 (m, 1H), 3.79 – 3.76 (m, 1H), 3.59 – 3.45 (m, 6H), 3.33– 3.20 (m, 2H), 2.61 – 2.55 (m, 1H), 2.33 – 2.25 (m, 4H), 2.19 – 2.15 (m, 2H), 2.01 – 1.88 (m, 2 H), 1.84 – 1.81 (m, 1H), 1.73 – 1.66 (m, 1H), 1.17 – 1.08 (m, 2H), 0.83 – 0.75 (m, 1H).

[0001016] LCMS: (ESI) *m/z* 956 [M+H]⁺.

EXAMPLE 34

[0001017] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(2-(methylamino)acetamido)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide, hydrochloride salt



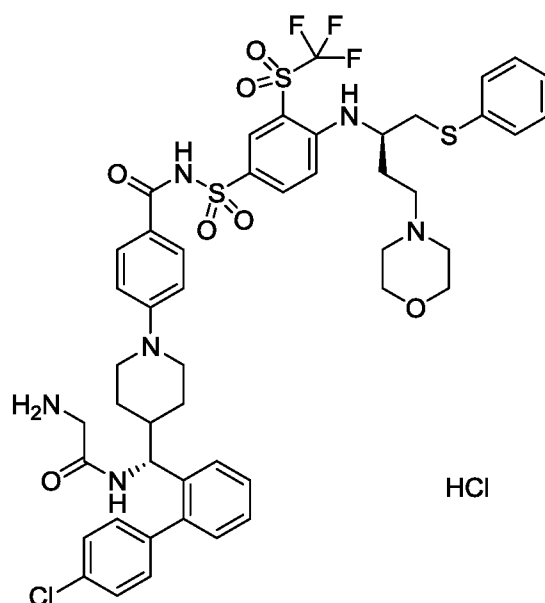
[0001018] A solution of HCl (0.42 ml, 1.67 mmol, 4 M in dioxane) was added to a solution of *tert*-butyl 2-((*R*)-(4'-chlorobiphenyl-2-yl)(1-(4-(4-((*R*)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonylcarbamoyl)phenyl)piperidin-4-yl)methylamino)-2-oxoethyl(methyl)carbamate (INTERMEDIATE 132, 94 mg, 0.08 mmol) in MeOH (1.3 ml) and the reaction mixture was stirred at r.t for 3 hours. The reaction mixture was concentrated under reduced pressure to provide a residue which was purified by reverse phase HPLC (Gilson column, eluting with 20→50% H₂O/ACN with 0.1% formic acid for 10 minutes) to give a solid. The solid was dissolved in MeOH and the mixture was treated with a solution of HCl (2 N) in diethylether. Evaporation of the volatiles under reduced pressure provided the title compound (56 mg, yield: 61%).

[0001019] ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.18 (d, 1 H), 7.98 (dd, 1 H), 7.70 – 7.68 (m, 2H), 7.55 – 7.51 (m, 3H), 7.48 – 7.43 (m, 3H), 7.36 - 7.29 (m, 3 H), 7.25 - 7.21 (m, 3 H), 7.17 – 7.13 (m, 2H), 6.98 (d, 1 H), 6.85 – 6.83 (m, 2H), 4.79 – 4.75 (m, 1H), 4.22 (m, 1H), 3.95 – 3.65 (m, 6H), 3.41 – 3.32 (m, 4H), 3.17 – 2.90 (m, 5H), 2.74 – 2.62 (m, 1H), 2.57 - 2.53 (m, 4 H), 2.25 – 2.13 (m, 2H), 1.84 – 1.75 (m, 2H), 1.12 – 1.00 (m, 2H), 0.74 – 0.71 (m, 1H).

[0001020] LCMS: (ESI) *m/z* 1027 [M+H]⁺.

EXAMPLE 35

[0001021] 4-(4-((*R*)-(2-aminoacetamido)(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide hydrochloride salt



[0001022] Step 1: DIPEA (0.08 ml, 0.46 mmol) was added to a solution of 4-(4-((*R*)-amino(4'-chlorobiphenyl-2-yl)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide, formic acid salt (EXAMPLE 33, 0.11 g, 0.11 mmol), 2-(*tert*-butoxycarbonylamino)acetic acid (20 mg, 0.11 mmol) and HATU (52 mg, 0.14 mmol) in DMF (2.2 ml) and the reaction mixture was stirred at r.t for 1 hour. The reaction mixture was concentrated under reduced pressure, diluted with DCM and washed with H₂O, 1N aq. NaHSO₄ and saturated aq. NaHCO₃. The organic layer was dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure to provide *tert*-butyl 2-((*R*)-(4'-chlorobiphenyl-2-yl)(1-(4-(4-((*R*)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonylcarbamoyl)phenyl)piperidin-4-yl)methylamino)-2-oxoethylcarbamate (EXAMPLE 35, STEP 1, 0.13 g) which was used in the preparation of EXAMPLE 35, STEP 2 without further purification.

[0001023] LCMS: (ESI) m/z 1113[M+H]⁺.

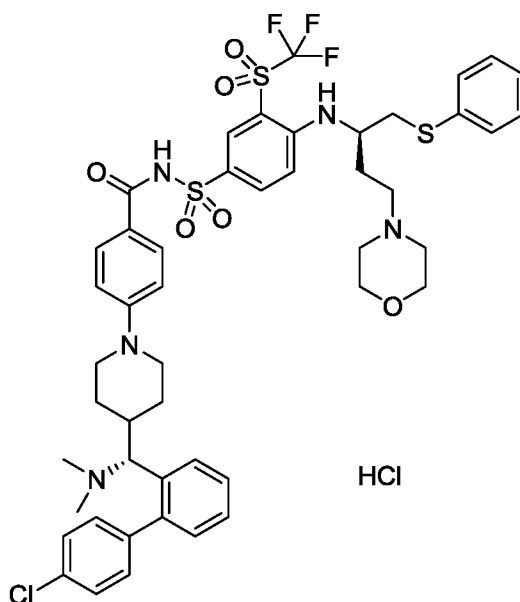
[0001024] Step 2: A solution of HCl (0.6 ml, 2.20 mmol, 4.0M in dioxane) was added to a solution of *tert*-butyl 2-((*R*)-(4'-chlorobiphenyl-2-yl)(1-(4-(4-((*R*)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonylcarbamoyl)phenyl)piperidin-4-yl)methylamino)-2-oxoethylcarbamate (EXAMPLE 35, STEP 1, 0.123 g, 0.11 mmol) in MeOH (1.7 ml) and the reaction mixture was stirred at r.t for 3 hours. The reaction mixture was concentrated under reduced pressure to provide a residue which was purified by reverse phase HPLC (Gilson column, eluting with 20→50% H₂O/ACN with 0.1% formic acid for 10 minutes) provided a solid. The solid was dissolved in MeOH and the mixture treated with 2N HCl in diethyl ether. Evaporation of the volatiles under reduced pressure provided the title compound (64 mg, yield: 54% for 2 steps).

[0001025] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.18 (d, 1 H), 7.98 (dd, 1 H), 7.70 – 7.68 (m, 2H), 7.56 – 7.53 (m, 3H), 7.48 – 7.43 (m, 3H), 7.36 – 7.29 (m, 3 H), 7.25 – 7.21 (m, 3 H), 7.17 – 7.13 (m, 2H), 6.98 (d, 1 H), 6.85 – 6.83 (m, 2H), 4.79 – 4.75 (m, 1H), 4.22 (m, 1H), 3.95 – 3.76 (m, 6H), 3.70 – 3.56 (m, 4H), 3.19 – 3.17 (m, 1H), 3.10 – 2.92 (m, 4H), 2.73 – 2.66 (m, 1H), 2.59 – 2.54 (m, 1 H), 2.23 – 2.15 (m, 2H), 1.86 – 1.83 (m, 1H), 1.75 – 1.73 (m, 1H), 1.12 – 1.00 (m, 2H), 0.74 – 0.71 (m, 1H).

[0001026] LCMS: (ESI) m/z 1013 $[\text{M}+\text{H}]^+$.

EXAMPLE 36

[0001027] 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(dimethylamino)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide, hydrochloride salt



[0001028] Step 1: To a solution of (*R*)-ethyl 4-(4-((4'-chlorobiphenyl-2-yl)(dimethylamino)methyl)piperidin-1-yl)benzoate (INTERMEDIATE 133, 0.11 g, 0.23 mmol) in THF (1.4 ml) was added MeOH (0.5 ml) and a solution of LiOH (28 mg, 1.15 mmol) in water (0.5 ml) and the reaction mixture was stirred at 40 °C overnight. The reaction mixture was cooled to r.t, concentrated under reduced pressure, and the residue dried in a vacuum oven overnight to provide (*R*)-4-(4-((4'-chlorobiphenyl-2-yl)(dimethylamino)methyl)piperidin-1-yl)benzoate, lithium salt (EXAMPLE 36 STEP 1, 0.12 g), which was used in the preparation of EXAMPLE 36, STEP 2 without further purification.

[0001029] LCMS: (ESI) m/z 449 $[\text{M}+\text{H}]^+$.

[0001030] Step 2: (*R*)-4-(4-((4'-chlorobiphenyl-2-yl)(dimethylamino)methyl)piperidin-1-yl)benzoate, lithium salt (EXAMPLE 36, STEP 1, 0.105 g, 0.23 mmol), DMAP (56 mg, 0.46 mmol), and EDC (0.176 g, 0.92 mmol) were placed in a 40 ml vial and flushed with nitrogen.

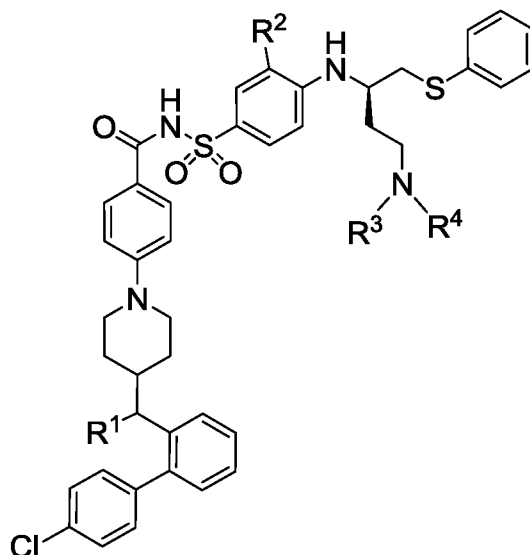
DCM (4.5 ml) and DIPEA (0.08 ml, 0.46 mmol) were added, and the solution was stirred at r.t for 15 minutes. (*R*)-4-(4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide (INTERMEDIATE 69, 0.127 g, 0.23 mmol) was added to the solution and the reaction mixture was stirred at r.t overnight. The reaction mixture was diluted with DCM and washed with 1N sodium bisulfate (aq.) followed by saturated aq. sodium bicarbonate. The organic layer was dried (Na₂SO₄), filtered, and evaporated under reduced pressure to give a residue which was purified by reverse phase HPLC (Gilson column, eluting with 30→50% H₂O/ACN with 0.1% formic acid for 10 minutes) to provide a solid. The solid was dissolved in MeOH and the mixture was treated with 2N HCl in diethylether. Evapoartion of the volatiles under reduced pressure provided the title compound (85 mg, yield: 35% for 2 steps).

[0001031] ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.18 (d, 1 H), 7.99 (dd, 1 H), 7.89 – 7.87 (m, 2H), 7.73 – 7.70 (m, 2H), 7.57 – 7.50 (m, 4H), 7.31 – 7.29 (m, 5H), 7.25 - 7.22 (m, 3 H), 7.17 – 7.14 (m, 1H), 6.98 (d, 1 H), 6.92 – 6.89 (m, 2H), 4.23 (m, 1H), 3.95 – 3.90 (m, 5H), 3.81 – 3.75 (m, 2H), 3.42 – 3.32 (m, 4H), 3.19 – 3.16 (m, 1H), 3.10 – 2.92 (m, 4H), 2.80 – 2.72 (m, 2H), 2.67 (m, 3H), 2.57 (m, 3 H), 2.23 – 2.15 (m, 2H), 1.80 – 1.76 (m, 1H), 1.57 – 1.54 (m, 1H), 1.25 – 1.17 (m, 1H), 1.02 – 0.94 (m, 1H).

[0001032] LCMS: (ESI) *m/z* 984 [M+H]⁺.

What is claimed is:

1. A compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof, wherein:

R¹ is selected from -CN, -OR^{1a}, and -N(R^{1a})₂;

R^{1a} in each occurrence is independently selected from H, C₁₋₄alkyl, -C(O)CH₂NH₂, -C(O)CH₂NHCH₃, and when **R¹** is -OR^{1a}, then **R^{1a}** is additionally selected from -P(=O)(OH)(OCH₃), -P(=O)(OCH₂CH₃)₂, -CH₂OP(=O)(OH)[OC(CH₃)₃] and -CH₂OP(=O)[OC(CH₃)₃]₂;

R² is selected from -N(O)₂ and -S(O)₂CF₃;

R³ is selected from H and C₁₋₄alkyl, wherein said C₁₋₄alkyl is optionally substituted with one or more R⁴⁰;

R⁴ is selected from H and C₁₋₄alkyl, wherein said C₁₋₄alkyl is optionally substituted with one or more R⁴⁰;

or **R³** and **R⁴** together with the nitrogen to which they are attached form a 5- or 6-membered heterocyclic ring, wherein

- i) said 5- or 6-membered heterocyclic ring is optionally substituted on carbon with one or more R⁴⁰; and
- ii) if said 5- or 6-membered heterocyclic ring contains a nitrogen, that nitrogen is

optionally substituted with R^{40*} to form a tertiary amine;

R^{40*} is selected from C_{1-4} alkyl and $-(CH_2)_2OP(=O)(OH)_2$, wherein said C_{1-4} alkyl is optionally substituted with one or more R^a ;

R^{40} in each occurrence is selected from $-OR^{40a}$, $-N(R^{40a})_2$, $-CH_2OR^{5a}$, $-CH_2N(R^{5a})_2$, $-OP(=O)(OH)_2$, and $-OP(=O)[OC(CH_3)_3]_2$;

R^{5a} in each occurrence is selected from H and C_{1-3} alkyl;

R^{40a} in each occurrence is independently selected from H and C_{1-4} alkyl; and

R^a is selected from halo, $-OR^m$, and $-N(R^m)_2$; and

R^m in each occurrence is independently selected from H and C_{1-4} alkyl.

2. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in claim 1, wherein,

R^1 is $-OH$;

R^2 is $-S(O)_2CF_3$;

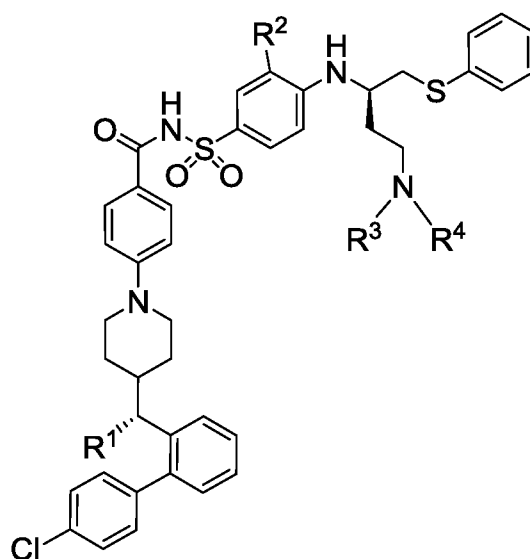
R^3 is C_{1-2} alkyl, wherein said C_{1-2} alkyl is optionally substituted with one or more R^{40} ;

R^4 is C_{1-2} alkyl, wherein said C_{1-2} alkyl is optionally substituted with one or more R^{40} ;

R^{40} in each occurrence is selected from $-OR^{40a}$ and $-OP(=O)(OH)_2$; and

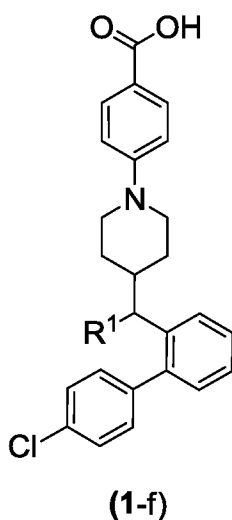
R^{40a} is H.

3. The compound of claim 1 or 2 wherein the compound has the following stereochemistry:

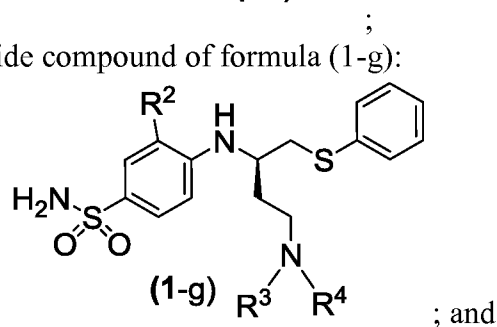


4. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in claim 3, wherein the compound is 4-(4-((R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-N-(4-((R)-4-((2-hydroxyethyl)(methyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide.
5. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in claim 3, wherein the compound is 2-(((R)-3-(4-(N-(4-(4-((R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-(phenylthio)butyl)(methyl)amino)ethyl dihydrogen phosphate.
6. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in claim 3, wherein the compound is 4-(4-((R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-N-(4-((R)-4-(ethyl(2-hydroxyethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide.
7. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in claim 3, wherein the compound is 2-(((R)-3-(4-(N-(4-(4-((R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-(phenylthio)butyl)(ethyl)amino)ethyl dihydrogen phosphate.
8. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 7, for use as a medicament.
9. The use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 7, in the manufacture of a medicament for use in the production of an anti-proliferation and/or pro-apoptotic effect in a warm-blooded animal.
10. The use according to claim 9 for use in the treatment of bladder cancer, breast cancer, colon cancer, ovarian cancer, AML, diffuse large B-cell lymphoma (DLBCL), CLL; small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), including the non-squamous and squamous subtypes, pancreatic cancer, prostate cancer, non-Hodgkin's lymphomas, Follicular Lymphoma (FL), Mantle Cell Lymphoma (MCL), Mantle Zone Lymphoma (MZL), Hairy Cell Leukemia (HCL), and Peripheral T-cell Lymphoma (PTCL).

11. A method for producing an anti-proliferation and/or pro-apoptotic effect in a warm-blooded animal, said method comprising administering to said animal an effective amount of a compound of Formula (I), as claimed in any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof.
12. The method according to claim 11 for treating bladder cancer, breast cancer, colon cancer, ovarian cancer, AML, diffuse large B-cell lymphoma (DLBCL), CLL; small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), including the non-squamous and squamous subtypes, pancreatic cancer, prostate cancer, non-Hodgkin's lymphomas, Follicular Lymphoma (FL), Mantle Cell Lymphoma (MCL), Mantle Zone Lymphoma (MZL), Hairy Cell Leukemia (HCL), and Peripheral T-cell Lymphoma (PTCL), in a warm-blooded animal, said method comprising administering to said animal an effective amount of a compound of Formula (I), as claimed in any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof.
13. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 7, for use in producing an anti-proliferation and/or pro-apoptotic effect in a warm-blooded animal.
14. The compound of Formula (I) according to claim 13, for use in treating bladder cancer, breast cancer, colon cancer, ovarian cancer, AML, diffuse large B-cell lymphoma (DLBCL), CLL; small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), including the non-squamous and squamous subtypes, pancreatic cancer, prostate cancer, non-Hodgkin's lymphomas, Follicular Lymphoma (FL), Mantle Cell Lymphoma (MCL), Mantle Zone Lymphoma (MZL), Hairy Cell Leukemia (HCL), and Peripheral T-cell Lymphoma (PTCL), in a warm-blooded animal.
15. A pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 7, and at least one pharmaceutically acceptable carrier, diluent, or excipient.
16. A process for preparing a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 7, said process comprising:
- (i) providing a carboxylic acid compound of formula (1-f):

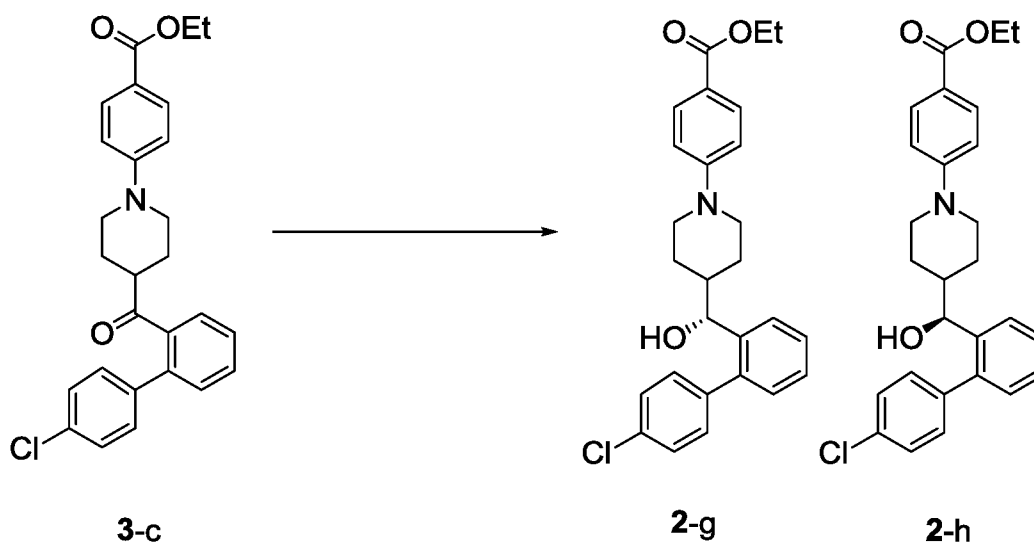


- (ii) providing a sulfonamide compound of formula (1-g):



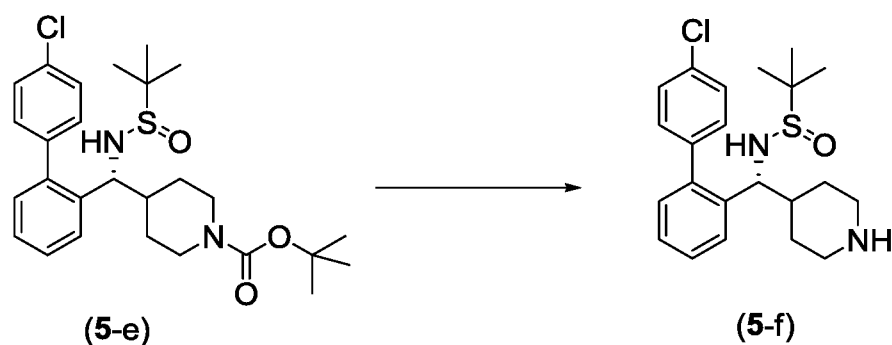
- (iii) coupling the carboxylic acid compound of formula (1-f) with the sulfonamide compound of formula (1-g).

17. A process for preparing a compound of formula (2-g) and (2-h), said process comprising:



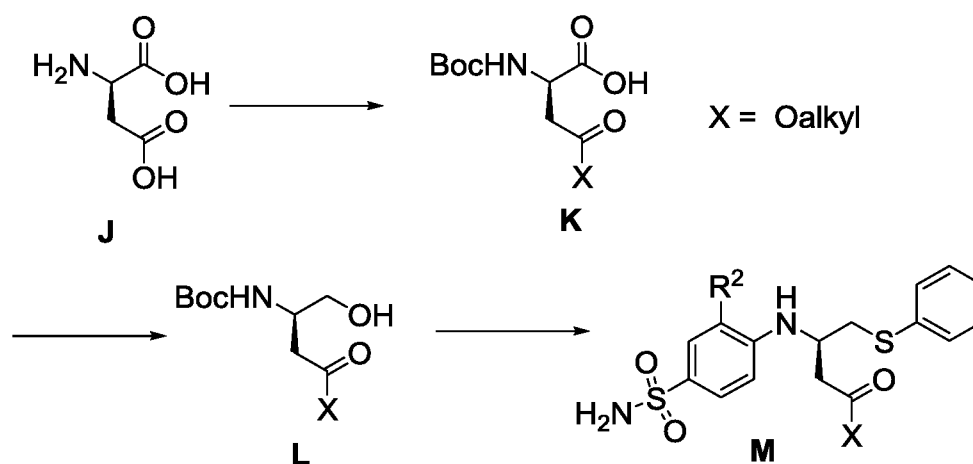
performing enantioselective reduction to a compound of formula (3-c).

18. A process for preparing a compound of formula (5-f), said process comprising:



selectively deprotecting a compound of formula (5-e).

19. A process for preparing a compound of formula (M), said process comprising:



- (i) converting a compound of formula (J) to a compound of formula (K);
- (ii) reducing a compound of formula (K) to form a compound of formula (L);
- (iii) performing a substitution reaction on a compound of formula (L) to form a corresponding thioether;
- (iv) performing a deprotection on the thioether to form a corresponding amine; and
- (v) performing an aromatic substitution reaction on the corresponding amine to form a compound of formula (M).

INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2011/051484

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D211/22 A61K31/445 A61P35/00 A61P35/02
ADD.

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, EMBASE, BIOSIS, BEILSTEIN 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.
Y	WO 2005/049594 A1 (ABBOTT LAB [US]; BRUNCKO MILAN [US]; DING HONG [US]; ELMORE STEVEN [US] 2 June 2005 (2005-06-02) page 116, lines 13-20; claims -----	1-17
Y	WO 2007/040650 A2 (ABBOTT LAB [US]; BRUNCKO MILAN [US]; DING HONG [US]; ELMORE STEVEN W [] 12 April 2007 (2007-04-12) abstract; claims -----	1-17
Y	WO 2009/036035 A1 (CURIS INC [US]; ZHAI HAIXIAO [US]; CAI XIONG [US]) 19 March 2009 (2009-03-19) abstract; claims; examples 8-10 ----- -/-	1-17



Further documents are listed in the continuation of Box C.



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 docu-
ments, 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

5 December 2011

Date of mailing of the international search report

16/12/2011

Name and mailing address of the ISA/

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Authorized officer

Frelon, Didier

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2011/051484

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1-17, 19
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-17

compounds of formula (I)

2. claim: 18

compound of formula (5-f)

3. claim: 19

compounds of formula M

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2011/051484

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BRUNCKO, MILAN ET AL: "Studies Leading to Potent, Dual Inhibitors of Bcl-2 and Bcl-xL", JOURNAL OF MEDICINAL CHEMISTRY, vol. 50, no. 4, 2007, pages 641-662, XP002661692, Figure 2, compound ABT-737 -----	1-17
X	WO 2010/065865 A2 (ABBOTT LAB [US]; BRUNCKO MILAN [US]; DING HONG [US]; DOHERTY GEORGE A) 10 June 2010 (2010-06-10) examples 81A-81D -----	19
X	WO 2008/061208 A2 (GENENTECH INC [US]; INST MEDICAL W & E HALL [AU]; BAELL JONATHAN BAYLD) 22 May 2008 (2008-05-22) examples 2 and 3, steps a-b, f-j; example 5, steps a-c; example 13, steps A-H -----	19
X	WENDT, MICHAEL D. ET AL: "Discovery and Structure-Activity Relationship of Antagonists of B-Cell Lymphoma 2 Family Proteins with Chemopotential Activity in Vitro and in Vivo", JOURNAL OF MEDICINAL CHEMISTRY, vol. 49, no. 3, 2006, pages 1165-1181, XP002665083, scheme 6, step d; scheme 87, step a -----	19
X	US 2002/086887 A1 (AUGERI DAVID J [US] ET AL) 4 July 2002 (2002-07-04) examples 122A-122E -----	19
X	WO 02/24636 A2 (ABBOTT LAB [US]) 28 March 2002 (2002-03-28) examples 112A-122E -----	19

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2011/051484

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2011/051484

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		WO 0224636 A2	28-03-2002

COMPUESTOS QUÍMICOS

SOLICITUDES RELACIONADAS

[0001] Esta solicitud reivindica la prioridad de la solicitud de patente provisional de EE. UU. con número de serie 61/371648, presentada el 6 de agosto de 2010, y de la solicitud de patente provisional de EE. UU. con número de serie 61/384170 presentada el 17 de septiembre de 2010; el contenido completo de cada una de ellas se incorpora a la presente por referencia.

CAMPO DE LA INVENCIÓN

[0002] La presente invención se refiere a compuestos nuevos, sus composiciones farmacéuticas y sus métodos de empleo. Además, la presente invención se refiere a métodos terapéuticos para tratar y prevenir cánceres y al uso de estos compuestos en la fabricación de medicamentos para emplear en el tratamiento y la prevención de cánceres.

ANTECEDENTES DE LA INVENCIÓN

[0003] La apoptosis es el proceso mediante el cual una célula sufre una muerte celular programada en respuesta a la privación de nutrientes, señales de estrés, señalización de receptores de muerte celular, lesiones del ADN, tratamiento con agentes citotóxicos o con blanco de acción localizado nuevos, u otros ataques del entorno externo. Se han identificado dos formas de apoptosis: la vía intrínseca o mitocondrial en la que participan miembros de la familia BCL2 de proteínas y proteínas BH3-*only*, y la vía extrínseca en la que señales del dominio de muerte celular que contiene receptores estimula la activación de la cascada de caspasas mediante la regulación de miembros de la familia de proteínas inhibidoras de la apoptosis (IAP).

[0004] La familia BCL2 de proteínas que contienen BH-3, que comprende Bcl-2, Bcl-X_L, Mcl-1, Bcl-w y Bcl-A1 (también conocida como Bfl-1), es una familia de moléculas adaptadoras que participan en la regulación del control de la apoptosis mitocondrial en varios tipos de células diferentes (discutido en (1)). Los miembros de la familia BCL2 generalmente se considera que son antiapoptóticos porque se unen y contrarrestan la actividad de miembros proapoptóticos de la familia BH3-*only*, incluidas Bim, tBid y Puma, y las proteínas efectoras multidominio Bak y Bax. Bim y tBid a su vez facilitan la oligomerización y activación de Bak y Bax para formar un poro en la membrana mitocondrial exterior a través del cual se liberan Smac y citocromo c en el citosol. La liberación de citocromo c estimula la activación de la casada de caspasas mediante la formación de un complejo con Apaf-1, denominado apoptosoma, que, en última instancia, conduce a la muerte celular apoptótica. La expresión de “centinelas”, otro grupo de proteínas BH3-*only*, aumenta mediante varios mecanismos transcripcionales y postraduccionales en

respuesta a los estímulos proapoptóticos mencionados anteriormente. Estas proteínas, incluidas Noxa, Bmf, Bad, Bik y Hrk, se unen selectivamente a ciertos miembros de la familia BCL2 y alteran el equilibrio entre miembros proapoptóticos libres y ligados mediante un proceso de sensibilización (unión a miembros antiapoptóticos de la familia BCL2) y depresión (desplazamiento de Bim, tBid, Bak y Bax ligadas), lo cual permite que tenga lugar la permeabilización de la membrana mitocondrial exterior (MOMP). En células sanas, el equilibrio entre proteínas pro- y antiapoptóticas garantiza que se mantenga la apoptosis controlada hasta que se necesite.

[0005] Normalmente, se suele detectar un aumento de la expresión de los miembros antiapoptóticos de la familia BCL2 en cánceres y estos se han asociado tanto con el estadio de la enfermedad como con el pronóstico. La sobreexpresión de Bcl-2, Bcl-X_L y Mcl-1 se ha relacionado con la resistencia a agentes terapéuticos habituales y las estrategias que tengan como objetivo los miembros de la familia BCL2 puede restaurar la sensibilidad a agentes citotóxicos al restablecer la capacidad de la célula para sufrir apoptosis. Un translocación, t(14;18)(q32;q31) en la que participan Bcl2 y IGH produce la sobreexpresión de la proteína Bcl-2 y esta se suele detectar en tumores de origen hematológico incluidos los linfomas no hodgkinianos (2-4). Incluso en ausencia de una translocación, la expresión de la familia BCL2 suele disminuir (2,3,5-8). También se suelen observar amplificaciones de Bcl-X_L y Mcl-1 en muchos tipos de tumores (9-11), por ejemplo, por activación de NFκB o por supresión de ciertos microARN (12).

[0006] En varios tumores, incluidos la leucemia linfocítica crónica (LLC) (4,13-15), el carcinoma pulmonar microcítico (CPMC) (16) y el cáncer de próstata (17), la expresión de Bcl-2 es un indicador independiente de un pronóstico insatisfactorio. En otros tipos de tumores, tales como el cáncer colorrectal, la expresión de Bcl-X_L se relaciona con el grado y el estadio (18), y el cáncer hepatocelular la expresión de Bcl-X_L es un indicador independiente de una menor supervivencia global sin enfermedad (19). La expresión de Mcl-1 también se ha asociado con el estadio de LLC y el pronóstico, por ejemplo, del mieloma, melanoma, tumores de ovarios y gástricos (20-22).

[0007] También se ha detectado redundancia entre miembros de la familia BCL2 y se cree que es la responsable, al menos en parte, de la resistencia a los compuestos miméticos a BH3 cuyo blanco de acción es Bcl-2, Bcl-X_L, Bcl-w y Bcl-A1, pero no Mcl-1 (23-26). Por lo tanto, para muchos cánceres, puede ser deseable una combinación de un mimético selectivo de BH-3 con otro agente que tenga como blanco de acción el eje Bim/Noxa/Mcl-1 para asegurarse de que se induzca la apoptosis y la regresión del tumor. Los ejemplos de estos agentes incluyen, pero no se limitan a, quimioterápicos citotóxicos, inhibidores de proteosomas, inhibidores de EGFR e inhibidores de la vía MEK/ERK.

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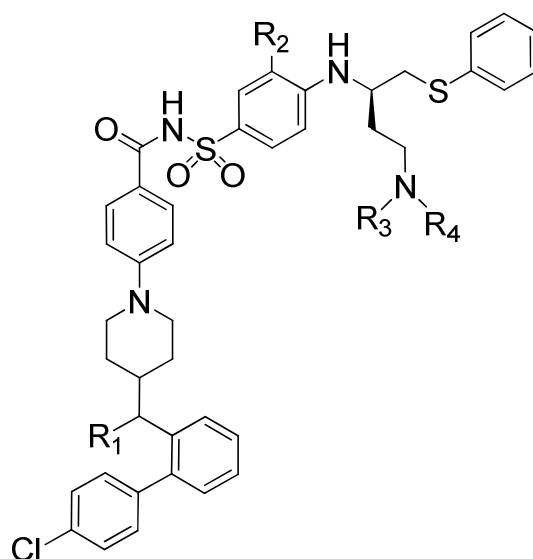
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RESUMEN DE LA INVENCION

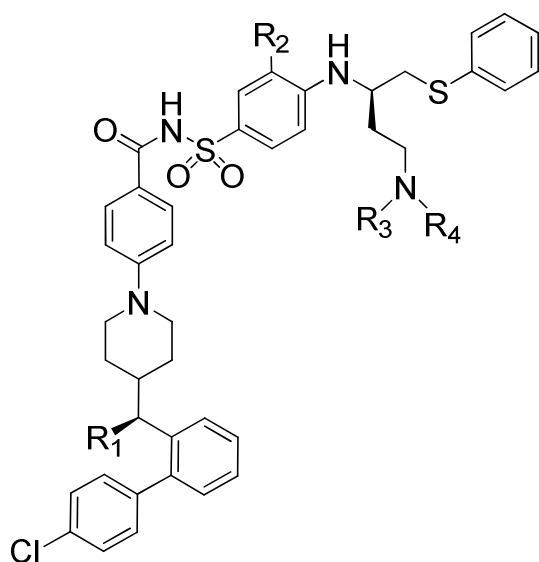
[0008] La presente invención se refiere a compuestos de Fórmula (I):



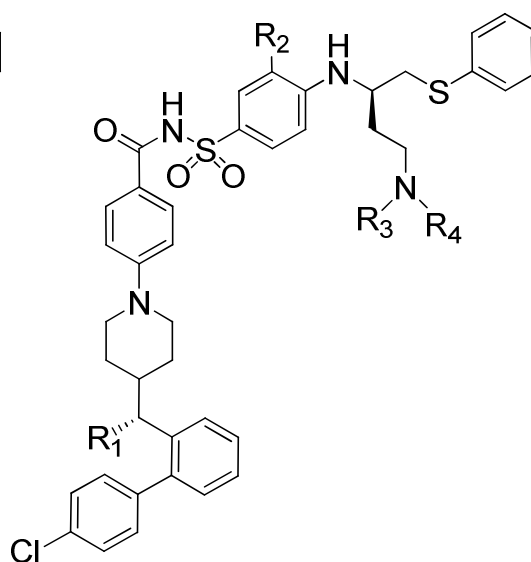
Fórmula (I)

y/o a sus sales farmacéuticamente aceptables.

[0009] En ciertas realizaciones, los compuestos que se proporcionan en la presente invención tienen la estructura que se expone en las Fórmulas (I-a) y/o (I-b):



(I-a)



(I-b)

y/o una de sus sales farmacéuticamente aceptables, donde R¹, R², R³ y R⁴ son cada uno como se definen para los compuestos de Fórmula (I) y en las clases y subclases descritas en la presente.

[00010] En algunas realizaciones, la presente invención proporciona un compuesto de fórmula (I-a), como el representado anteriormente, o una de sus sales farmacéuticamente aceptables, donde R¹, R², R³ y R⁴ son cada uno como se definen para los compuestos de Fórmula (I) y en las clases y subclases descritas en la presente.

[00011] En algunas realizaciones, la presente invención proporciona un compuesto de fórmula (I-b), como el representado anteriormente, o una de sus sales farmacéuticamente aceptables, donde R¹, R², R³ y R⁴ son cada uno como se definen para los compuestos de Fórmula (I) y en las clases y subclases descritas en la presente.

[00012] Los compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e) poseen propiedades metabólicas, farmacocinéticas y/o farmacodinámicas eficaces beneficiosas. Los compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e) son útiles por su capacidad para inhibir las actividades de Bcl-2 y Bcl-X_L y, por lo tanto, también son útiles para tratar enfermedades o afecciones médicas mediadas solo o en parte por la familia BCL2. Se ha descubierto que para ciertos enantiómeros de la presente invención pueden existir diferencias en una o más propiedades biológicas y/o fisiológicas que pueden resultar beneficiosas.

[00013] En particular, los compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e) se pueden utilizar para tratar el cáncer, incluidos los tumores sólidos tales como: cáncer de vejiga; cáncer de mama; cáncer de colon; cáncer de ovarios; LMA; linfoma difuso de linfocitos B grandes (DLBCL); LLC; carcinoma pulmonar microcítico (CPM), carcinoma pulmonar no microcítico (CPNM), incluidos los subtipos escamosos y no escamosos; carcinoma pulmonar microcítico; cáncer pancreático; linfoma folicular (LF) y cáncer de próstata.

[00014] La invención también se refiere a procesos para fabricar dichos compuestos a composiciones farmacéuticas que los contienen y a su uso en la fabricación de medicamentos para emplear en la producción de un efecto antiproliferativo y/o proapoptótico en animales de sangre caliente tales como el ser humano. Asimismo, de acuerdo con la presente invención, se proporcionan métodos de empleo de dichos compuestos o sus sales farmacéuticamente aceptables en el tratamiento del cáncer.

DESCRIPCIÓN DETALLADA DE LA INVENCION

I. DEFINICIONES

[00015] “ALQUILO”: Tal como se utiliza en la presente, el término “alquilo” se refiere a radicales hidrocarburo saturados tanto de cadena lineal como ramificada que contienen el número especificado de átomos de carbono. Las referencias a grupos alquilo individuales, tales como “propilo”, son específicas para la versión de cadena lineal solamente y las referencias a grupos alquilo individuales de cadena ramificada, tales como ‘isopropilo’, son específicas para la versión de cadena ramificada solamente. En un aspecto, “alquilo” puede ser “alquilo C₁₋₄”. En otro aspecto, “alquilo” y “alquilo C₁₋₄” pueden ser “alquilo C₁₋₃”. En otro aspecto, “alquilo,” “alquilo C₁₋₄” y “alquilo C₁₋₃” pueden ser metilo. En algunas realizaciones, el término “ALQUILO C₁” se refiere a un radical hidrocarburo saturado que contiene un átomo de carbono. En algunas realizaciones, el término “ALQUILO C₂” se refiere a radicales hidrocarburo saturados que contiene dos átomos de carbono. En algunas realizaciones, el término “ALQUILO C₃” se refiere tanto a radicales hidrocarburo saturados de cadena lineal o ramificada que contienen uno, dos o tres átomos de carbono. En algunas realizaciones, el término “ALQUILO C₄” se refiere tanto a radicales hidrocarburo saturados de cadena lineal o ramificada que contienen uno, dos, tres o cuatro átomos de carbono.

[00016] “ALQUILO C₁₋₄”: Tal como se utiliza en la presente el término “alquilo C₁₋₄” se refiere a radicales hidrocarburo saturados de cadena lineal o ramificada que contienen uno, dos, tres o cuatro átomos de carbono. En algunas realizaciones, “ALQUILO C₁₋₄” es “ALQUILO C₁”. En algunas realizaciones, “ALQUILO C₁₋₄” es “ALQUILO C₂”. En algunas realizaciones, “ALQUILO C₁₋₄” es “ALQUILO C₃”. En algunas realizaciones, “ALQUILO C₁₋₄” es “ALQUILO C₄”.

[00017] “ALQUILO C₁₋₃”: Tal como se utiliza en la presente el término “alquilo C₁₋₃” se refiere a radicales hidrocarburo saturados de cadena lineal o ramificada que contienen uno, dos o tres átomos de carbono. En algunas realizaciones, “ALQUILO C₁₋₃” es “ALQUILO C₁”. En

algunas realizaciones, “ALQUILO C₁₋₃” es “ALQUILO C₂”. En algunas realizaciones, “ALQUILO C₁₋₃” es “ALQUILO C₃”.

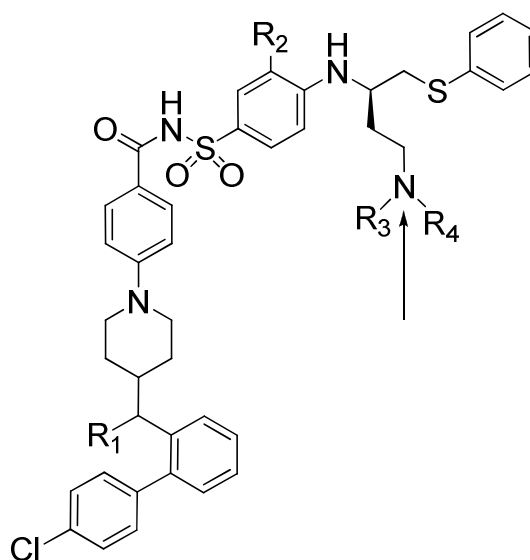
[00018] “ALQUILO C₁₋₂”: Tal como se utiliza en la presente el término “alquilo C₁₋₂” se refiere a radicales hidrocarburo saturados de cadena lineal o ramificada que contienen uno o dos átomos de carbono. En algunas realizaciones, “ALQUILO C₁₋₂” es “ALQUILO C₁”. En algunas realizaciones, “ALQUILO C₁₋₂” es “ALQUILO C₂”.

[00019] “CANTIDAD EFICAZ”: Tal como se utiliza en la presente, la expresión “cantidad eficaz” se refiere a una cantidad de un compuesto o composición que es suficiente para modificar de manera significativa y positiva los síntomas y/o afecciones que se han de tratar (p. ej., proporcionar una respuesta clínica positiva). La cantidad eficaz de un principio activo para emplear en una composición farmacéutica variará dependiendo de la afección particular que se está tratando, la gravedad de esta, la duración del tratamiento, la naturaleza de la terapia concurrente, los principios activos particulares que se utilicen, los excipientes/portadores farmacéuticamente aceptables particulares utilizados y factores similares con los cuales estará familiarizado el médico responsable.

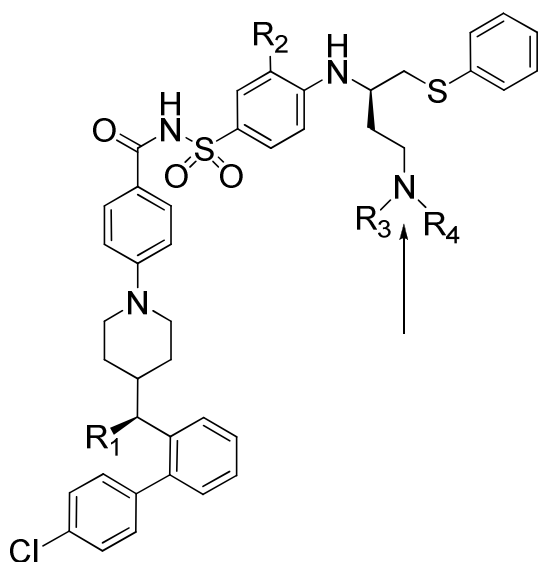
[00020] En particular, una cantidad eficaz de un compuesto de Fórmula (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e) para utilizar en el tratamiento del cáncer es una cantidad suficiente para aliviar sintomáticamente los síntomas del cáncer, en un animal de sangre caliente, tal como el ser humano, para retrasar la evolución del cáncer o para reducir el riesgo de empeoramiento que corren los pacientes con síntomas de cáncer.

[00021] “HALO”: Los términos “halo” o “halógeno”, tal como se utilizan en la presente, se refieren a fluoro, cloro, bromo y yodo. En ciertas realizaciones, el término “halo” se puede referir a fluoro, cloro y bromo. En ciertas realizaciones, el término “halo” puede referirse a fluoro y cloro. En ciertas realizaciones, el término “halo” puede referirse a fluoro. En ciertas realizaciones, el término “halo” puede referirse a cloro. En ciertas realizaciones, el término “halo” puede referirse a bromo.

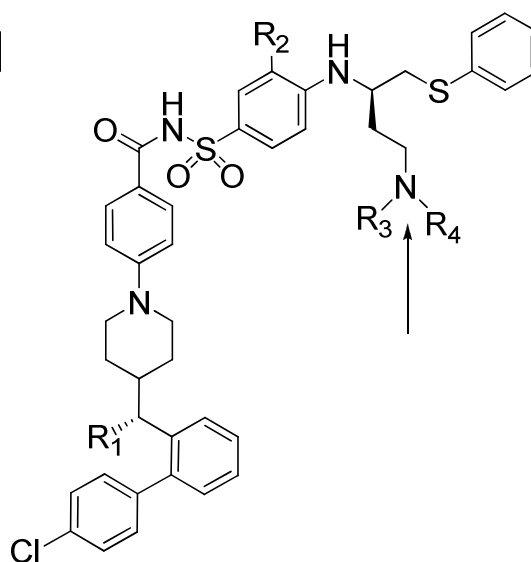
[00022] “ANILLO HETEROCÍCLICO DE 5 Ó 6 MIEMBROS” El término “anillo heterocíclico de 5 ó 6 miembros” se refiere a un anillo monocíclico saturado o parcialmente saturado que contiene 5 ó 6 átomos en el anillo, de los cuales un átomo del anillo es el nitrógeno marcado con la flecha en las siguientes Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e):



Fórmula (I)



Fórmula (I-a)



Fórmula (I-b)

[00023] El anillo puede incluir, además del nitrógeno indicado, uno o más heteroátomos seleccionados entre nitrógeno, azufre y oxígeno. Se pueden reemplazar opcionalmente uno o más grupos $-CH_2-$ por un número correspondiente de grupos $-C(O)-$. Los átomos de azufre del anillo pueden oxidarse opcionalmente para formar S-óxidos. Los ejemplos ilustrativos de “anillo heterocíclico de 5 ó 6 miembros” incluyen azetidino, imidazolin-1-ilo, imidazolidin-1-ilo, pirazolidin-1-ilo, piperazin-1-ilo, piperidin-1-ilo, pirrolidin-1-ilo, morfolino y tiomorfolino.

[00024] A menos que se especifique lo contrario, el átomo enlazante de un grupo puede ser cualquier átomo adecuado de dicho grupo; por ejemplo, propilo incluye prop-1-ilo y prop-2-ilo.

[00025] “GRUPO SALIENTE”: Tal como se utiliza en la presente, la expresión “grupo saliente” se refiere a grupos fácilmente desplazables por un nucleófilo tal como una amina nucleófila y un alcohol nucleófilo o un tiol nucleófilo. Los ejemplos de grupos salientes adecuados incluyen halo tales como cloro, fluoro, yodo y bromo; y grupos sulfonilo tales como

metanosulfoniloxi y tolueno-4-sulfoniloxi.

[00026] “OPCIONALMENTE SUSTITUIDO”: Tal como se utiliza en la presente, la frase “opcionalmente sustituido” indica que la sustitución es opcional y, por lo tanto, es posible que el grupo designado esté sustituido o no. En el caso de que se desee una sustitución, puede reemplazarse un número cualquiera de hidrógenos del grupo designado por una selección entre los sustituyentes indicados, siempre que no se exceda la valencia normal de los átomos de un sustituyente particular y que la sustitución dé como resultado un compuesto estable.

[00027] En un aspecto, cuando se designa un grupo particular como opcionalmente sustituido con “uno o más” sustituyentes, ese grupo particular puede que no esté sustituido. En otro aspecto, ese grupo en particular puede tener un sustituyente. En otro aspecto, ese sustituyente en particular puede tener dos sustituyentes. En otro aspecto más, ese grupo en particular puede tener tres sustituyentes. En otro aspecto más, ese grupo en particular puede tener cuatro sustituyentes. En otro aspecto, ese grupo en particular puede tener uno o dos sustituyentes. En otro aspecto más, ese grupo en particular puede que no esté sustituido o puede tener uno o dos sustituyentes.

[00028] “FARMACÉUTICAMENTE ACEPTABLE”: Tal como se utiliza en la presente, la expresión “farmacéuticamente aceptable” se refiere a los compuestos, materiales, composiciones y/o formas farmacéuticas que son, a criterio médico, adecuados para emplear en contacto con los tejidos de seres humanos y animales sin provocar excesiva toxicidad, irritación, respuesta alérgica u otro problema o complicación, con una relación riesgo/beneficio razonable.

[00029] Los ejemplos de sales de adición de ácido farmacéuticamente aceptables incluyen acetato, adipato, ascorbato, benzoato, bencenosulfonato, bicarbonato, bisulfato, butirato, camforato, camforsulfonato, colina, citrato, ciclohexilsulfamato, dietilendiamina, etanosulfonato, formiato, fumarato, glutamato, glicolato, hemisulfato, 2-hidroxietilsulfonato, heptanoato, hexanoato, clorhidrato, bromhidrato, yodhidrato, hidroximaleato, lactato, malato, maleato, metanosulfonato, meglumina, 2-naftalensulfonato, nitrato, oxalato, pamoato, persulfato, fenilacetato, fosfato, difosfato, picrato, pivalato, propionato, quinato, salicilato, estearato, succinato, sulfamato, sulfanilato, sulfato, tartrato, tosilato (*p*-toluenosulfonato), trifluoroacetato y undecanoato.

[00030] Los ejemplos de sales de adición de base farmacéuticamente aceptables incluyen sales de amonio; sales de metales alcalinos tales como sales de sodio, litio y potasio; sales de metales alcalinotérreos tales como sales de aluminio, calcio y magnesio; sales con bases orgánicas tales como sales de dicitclohexilamina y *N*-metil-D-glucamina; y sales con aminoácidos tales como arginina, lisina, ornitina, etc. También se pueden cuaternizar grupos básicos que contienen nitrógeno con agentes tales como: haluros de alquilo inferior tales como haluros de

metilo, etilo, propilo y butilo; sulfatos de dialquilo tales como dimetilo, dietilo y dibutilo; sulfatos de diamilo; haluros de cadena larga tales como haluros de decilo, laurilo, miristilo y estearilo; haluros de arilalquilo tales como bromuro de bencilo y otros. Se prefieren las sales fisiológicamente aceptables atóxicas, aunque otras sales también pueden ser útiles, como por ejemplo, en el aislamiento o la purificación del producto.

[00031] “GRUPO PROTECTOR”: Tal como se utiliza en la presente, el término “grupo protector” se refiere a aquellos grupos utilizados para evitar que los grupos reactivos seleccionados (tales como grupos carboxi, amino, hidroxilo y mercapto) sufran reacciones no deseadas.

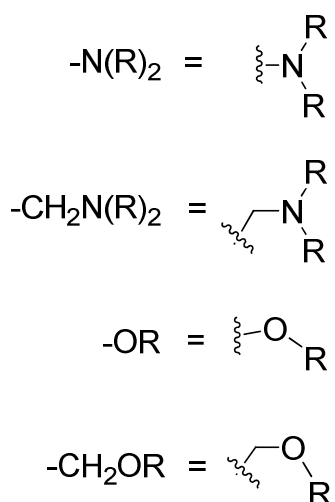
[00032] Los ejemplos ilustrativos de grupos protectores adecuados para un grupo hidroxilo incluyen, pero no se limitan a, un grupo acilo; grupos alcanóilo tales como acetilo; grupos aroílo tales como benzoílo; grupos sililo tales como trimetilsililo; y grupos arilmetilo tales como bencilo. Las condiciones de desprotección para los grupos protectores de hidroxilo anteriores variarán necesariamente dependiendo del grupo protector elegido. Así pues, por ejemplo, un grupo acilo tal como un grupo alcanóilo o un grupo aroílo puede eliminarse, por ejemplo, mediante hidrólisis con una base adecuada tal como un hidróxido de un metal alcalino, por ejemplo, hidróxido de sodio o litio. Como alternativa, se puede eliminar un grupo sililo, tal como trimetilsililo, por ejemplo, con fluoruro o con ácido acuoso; o se puede eliminar un grupo arilmetilo, tal como un grupo bencilo, por ejemplo, mediante hidrogenación en presencia de un catalizador tal como paladio sobre carbón.

[00033] Los ejemplos ilustrativos de grupos protectores adecuados para un grupo amino incluyen, pero no se limitan a, grupos acilo; grupos alcanóilo, tales como acetilo; grupos alcóxicarbonilo, tales como metóxicarbonilo, etóxicarbonilo y *t*-butoxicarbonilo; grupos arilmetóxicarbonilo, tales como bencilóxicarbonilo; y grupos aroílo, tales como benzoílo. Las condiciones de desprotección para los grupos protectores de amino anteriores varían necesariamente con el grupo protector elegido. Así pues, por ejemplo, un grupo acilo, tal como un grupo alcanóilo o alcóxicarbonilo, o un grupo aroílo puede eliminarse, por ejemplo, por hidrólisis con una base adecuada tal como un hidróxido de un metal alcalino, por ejemplo, hidróxido de sodio o litio. Como alternativa, un grupo acilo, tal como un grupo *t*-butoxicarbonilo, se puede eliminar, por ejemplo, por tratamiento con un ácido adecuado como el ácido clorhídrico, sulfúrico o fosfórico, o el ácido trifluoroacético, y un grupo arilmetóxicarbonilo, tal como un grupo bencilóxicarbonilo, se puede eliminar, por ejemplo, mediante hidrogenación con un catalizador, tal como paladio sobre carbón, o por tratamiento con un ácido de Lewis, por ejemplo, tricloruro de boro. Un grupo protector alternativo adecuado para un grupo amino primario es, por ejemplo, un grupo ftaloílo que se puede eliminar por tratamiento

con una alquilamina, por ejemplo, dimetilaminopropilamina o 2-hidroxiethylamina, o con hidrazina. Otro grupo protector adecuado para una amina es, por ejemplo, un éter cíclico, tal como tetrahydrofurano, que se puede eliminar por tratamiento con un ácido adecuado tal como el ácido trifluoroacético.

[00034] Los grupos protectores se pueden eliminar en cualquier etapa conveniente de la síntesis empleando técnicas convencionales de uso común en el campo de la química o se pueden eliminar durante una etapa de reacción o tratamiento posterior.

[00035] En lo que respecta al sustituyente “R”: a efectos ilustrativos, las siguientes definiciones de sustituyentes se refieren a la estructura indicada:



[00036] “SUSTANCIALMENTE AISLADO”: Tal como se utiliza en la presente, el término “sustancialmente aislado” quiere decir que se proporciona un estereoisómero específico (ya sea obtenido mediante separación, síntesis quiral u otros métodos), se proporciona de forma favorable sustancialmente aislado de otros estereoisómeros del mismo compuesto. En un aspecto, una mezcla que contiene un estereoisómero particular de un compuesto de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e) puede contener menos de un 30%, particularmente menos de un 20% y más particularmente menos de un 10% en peso de otro(s) estereoisómero(s) del mismo compuesto. En otro aspecto, la mezcla que contiene un estereoisómero particular de un compuesto de Formulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e) puede contener menos de un 6%, particularmente menos de un 3% y más particularmente menos de un 2% en peso de otro(s) estereoisómero(s) del compuesto. En otro aspecto, una mezcla que contiene un estereoisómero particular de un compuesto de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e) puede contener menos de un 1%, particularmente menos de un 0.5%, más particularmente menos de un 0.3% y aún más particularmente menos de un 0.1% en peso de otro(s) estereoisómero(s) del compuesto.

[00037] “TRATAR”, “QUE TRATA” O “TRATAMIENTO”: Los términos “tratar”, “que trata” o “tratamiento” incluyen administrar una cantidad terapéuticamente eficaz de un

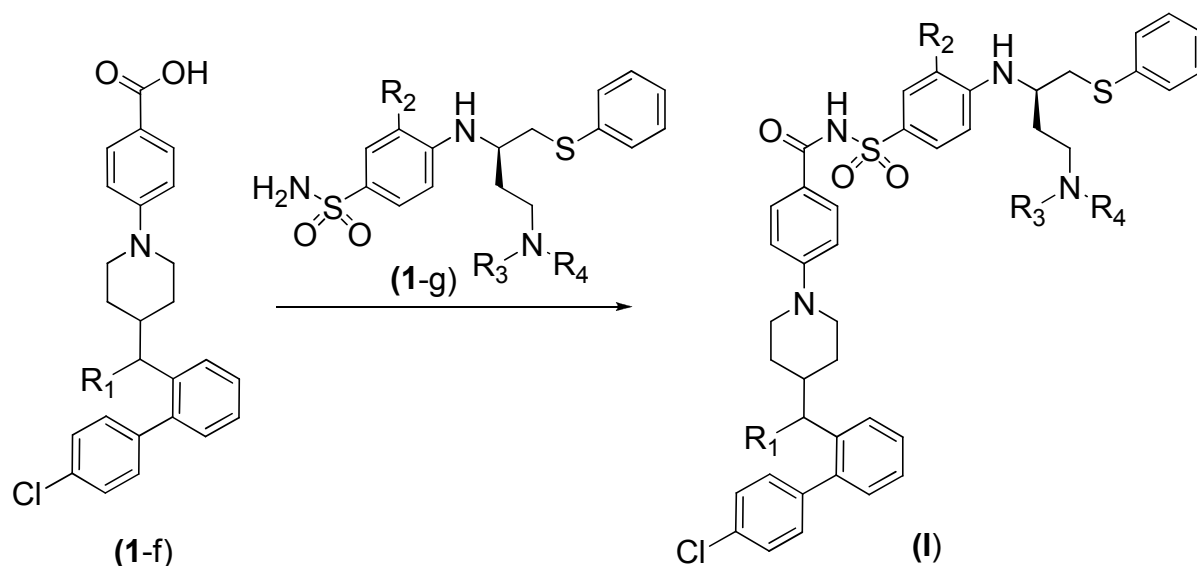
compuesto suficiente para reducir o eliminar al menos un síntoma de la afección, la enfermedad o el trastorno, p. ej., afecciones y enfermedades relacionadas con Bcl-2, p. ej., el cáncer.

II. MÉTODOS GENERALES DE PREPARACIÓN

[00038] La presente invención proporciona métodos sintéticos para preparar compuestos de Fórmulas (I), (I-a) y/o (I-b) que comprenden acoplar un ácido carboxílico de fórmula (1-f) con una sulfonamida de fórmula (1-g) en presencia de un reactivo de acoplamiento y una base adecuados. En ciertas realizaciones, los compuestos de Fórmulas (I), (I-a) y/o (I-b) se purifican posteriormente.

[00039] En ciertas realizaciones, los compuestos de Fórmulas (I), (I-a) y/o (I-b), en general, se preparan de acuerdo con los pasos representados en el ESQUEMA 1 que se expone a continuación.

ESQUEMA 1

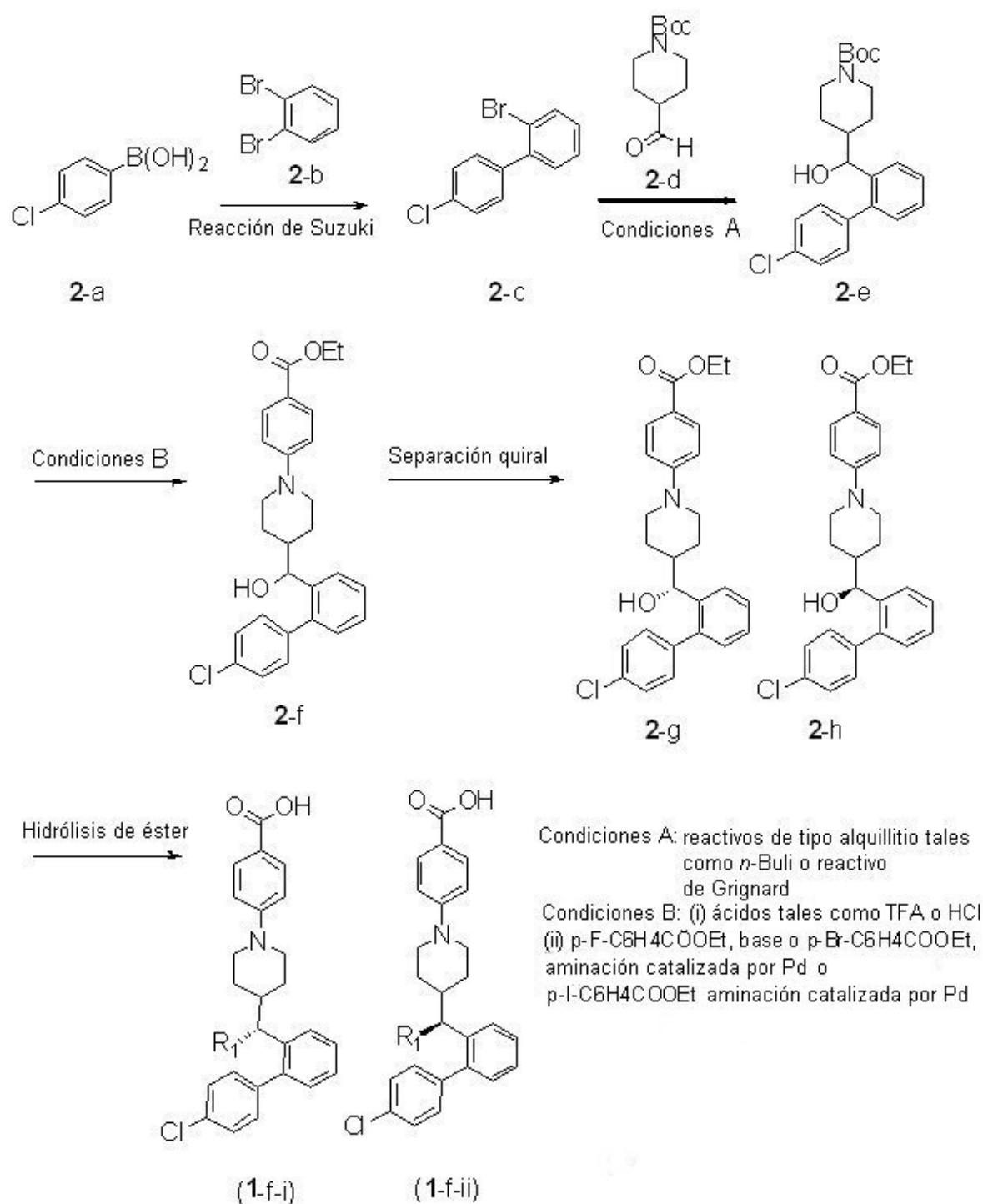


[00040] En el ESQUEMA 1 anterior, R¹, R², R³ y R⁴ son como los definidos en las clases y subclases descritas en la presente.

[00041] Un ácido carboxílico (1-f) y una sulfonamida (1-g) se pueden hacer reaccionar juntos en presencia de un solvente adecuado, los ejemplos de este incluyen, pero no se limitan a, diclorometano, 1,2-dicloroetano, N,N-dimetilformamida. La reacción se lleva a cabo en presencia de un agente de acoplamiento adecuado tal como EDC. La reacción se puede llevar a cabo preferentemente en presencia de una base adecuada, los ejemplos de esta incluyen DMAP, DIPEA y TEA o combinaciones de estas. La reacción se puede llevar a cabo a temperatura ambiente o calentando. En algunas realizaciones, la reacción se lleva a cabo a temperatura ambiente. En algunas realizaciones, la reacción se lleva a cabo a 40 °C.

[00042] Un ácido carboxílico de fórmula (1-f-i) y fórmula (1-f-ii) se puede preparar de acuerdo con el ESQUEMA 2 representado a continuación:

ESQUEMA 2



[00043] En el ESQUEMA 2 anterior, R¹ es como se define en las clases y subclases descritas en la presente.

[00044] Tal como se representa ESQUEMA 2 anterior, un ácido borónico de fórmula (2-a) se hace reaccionar con un benceno dihalogenado de fórmula (2-b) en las condiciones de la

reacción de Suzuki, con las cuales estará familiarizado un experto en la técnica, para formar un bifenilo de fórmula (2-c).

[00045] Un bifenilo de fórmula (2-c) se convierte en un arillitio correspondiente utilizando un alquillitio adecuado como reactivo. En algunas realizaciones, el alquillitio utilizado como reactivo es *n*-BuLi. En algunas realizaciones, el alquillitio utilizado como reactivo es *t*-BuLi. Como alternativa, un bifenilo de fórmula (2-c) se puede convertir en un reactivo de Grignard organomagnesiano correspondiente (remítase a Grignard reagent, *Angew. Chem. Int. Ed.*, **2004**, 43, 3333), utilizando un complejo de bromuro de alquilmagnesio y cloruro litio adecuado. En algunas realizaciones, el complejo de bromuro de alquilmagnesio y cloruro de litio adecuado es el complejo *i*-Pr-MgBr LiCl.

[00046] Un compuesto de fórmula (2-e) se prepara como una mezcla de enantiómeros por reacción *in situ* de un arillitio o un reactivo de Grignard organomagnesiano correspondiente con un carboxilato *N*-protegido de fórmula (2-d). Además, se puede desproteger un compuesto de fórmula (2-d) utilizando un ácido adecuado. En algunas realizaciones, el ácido es TFA. En algunas realizaciones, el ácido es HCl.

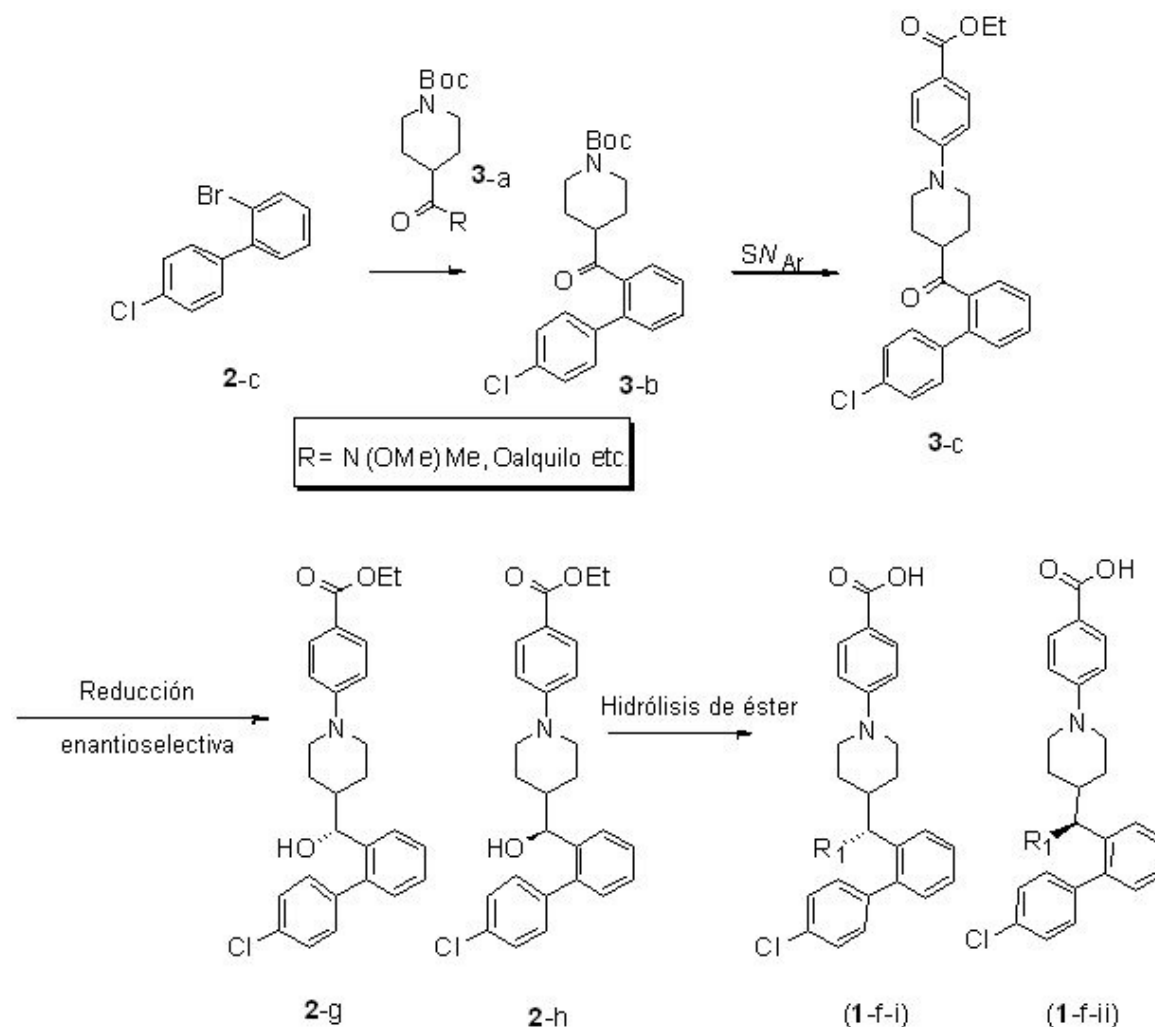
[00047] Un compuesto de fórmula (2-f) se prepara como una mezcla de enantiómeros llevando a cabo una reacción de sustitución entre un compuesto de fórmula (2-e) y un benzoato sustituido en *para* en presencia de un solvente y una base adecuados. En algunas realizaciones, la base adecuada es la trietilamina. En algunas realizaciones, la base adecuada es la DIPEA. En algunas realizaciones, la base adecuada es el K₂CO₃. En algunas realizaciones, la base adecuada es el Cs₂CO₃. En algunas realizaciones, el benzoato sustituido en *para* adecuado es un benzoato halogenado. En algunas realizaciones, el benzoato halogenado adecuado es el *p*-F-C₆H₄COOEt.

[00048] Como alternativa, un compuesto de fórmula (2-f) se prepara utilizando aminación catalizada por Pd (remítase a *Chem. Sci.* **2011**, 2, 27 y las referencias citadas en este) utilizando un benzoato sustituido en *para* y separando posteriormente los dos enantiómeros (antípodos) utilizando condiciones similares a las descritas en los EJEMPLOS, *infra*, para formar compuestos de fórmulas (2-g) y (2-h).

[00049] Un ácido carboxílico de fórmula (1-f-i) y/o (1-f-ii) se prepara como una mezcla de enantiómeros o como un único enantiómero llevando a cabo la hidrólisis de éster en los compuestos de fórmulas (2-g) y/o (2-h) utilizando condiciones estándares con las cuales estará familiarizado un experto en la técnica.

[00050] En una realización alternativa, un ácido carboxílico de fórmula (1-f-i) y/o (1-f-ii) se puede preparar de acuerdo con el ESQUEMA 3 representado a continuación:

ESQUEMA 3



[00051] En el ESQUEMA 3 anterior, R1 es como se define en las clases y subclases descritas en la presente.

[00052] Como alternativa, el *arillitio* o un reactivo de Grignard organomagnesiano correspondiente descrito en el ESQUEMA 2 anterior se puede hacer reaccionar con un compuesto N-protégido de fórmula (3-a) para obtener un compuesto de fórmula (3-b). Se lleva a cabo otra reacción de sustitución utilizando un compuesto de fórmula (3-b) y un benzoato sustituido en *para* en presencia de un solvente adecuado y una base adecuada utilizando condiciones similares a las descritas anteriormente para la formación de un compuesto de fórmula (3-c).

[00053] Llevar a cabo la reducción enantioselectiva para obtener un compuesto de fórmula (3-c): (a) en las condiciones de CBS (*Angew. Chem. Int. Ed.* **1998**, 37, 1986); o (b) condiciones de la hidrogenación asimétrica de Noyori (*Asymmetric Catalysis in Organic Synthesis*; John

Wiley & Sons: Nueva York, 1993, 56–82.) proporcionará mezclas con un contenido enantiomérico elevado de un compuesto de fórmula (2-g) o un compuesto de fórmula (2-h). La pureza enantiomérica se puede mejorar después de recrystalizar en uno o más solventes adecuados.

[00054] Para la reducción enantioselectiva, la conversión de un compuesto de fórmula (3-c) en un compuesto de fórmula (2-g) o (2-g) se puede llevar a cabo utilizando un catalizador adecuado en presencia de un borano adecuado y un solvente adecuado a temperaturas de aproximadamente -30 °C a aproximadamente 60 °C. En algunas realizaciones, el catalizador adecuado es la (*R*)-(+)-2-metil-CBS-oxazaborolidina. En algunas realizaciones, el catalizador adecuado es la (*S*)-(-)-2-metil-CBS-oxazaborolidina. En algunas realizaciones, el borano adecuado es el complejo de borano-tetrahidrofurano. En algunas realizaciones, el borano adecuado es el complejo de borano-sulfóxido de dimetilo. En algunas realizaciones, el solvente adecuado es el THF.

[00055] Como alternativa, la conversión de un compuesto de fórmula (3-c) en un compuesto de fórmula (2-g) o (2-g) se puede llevar a cabo utilizando la hidrogenación asimétrica de Noyori. La hidrogenación asimétrica se puede llevar a cabo utilizando un catalizador y una base adecuados en presencia de una mezcla de solventes adecuada en un atmósfera de hidrógeno. En algunas realizaciones, la base adecuada es el *t*-BuOK. En algunas realizaciones, la mezcla de solventes adecuada es *i*-PrOH y DMF.

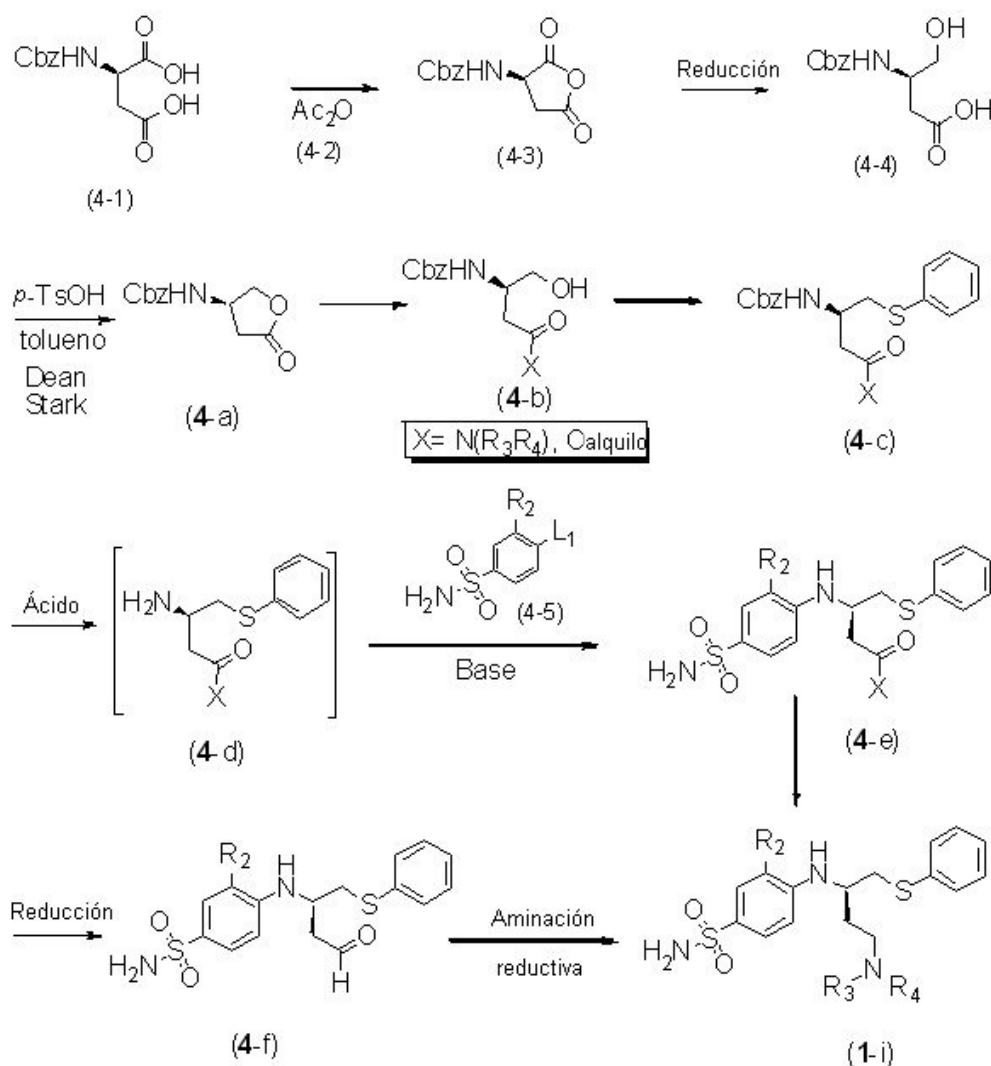
[00056] En algunas realizaciones, el catalizador adecuado es Ru(difosfina quiral)(amina quiral)Cl₂ donde la porción de la difosfina quiral del catalizador se puede seleccionar entre, pero no se limita a, *S*-ClMeOBIPHEP, *R*-ClMeOBIPHEP, *S*-Segphos, *R*-Segphos, *R*-CTH-Pphos, *S*-CTH-Pphos, *S*-BINAP y *R*-BINAP; y donde la porción de la amina quiral del catalizador se puede seleccionar entre, pero no se limita a, *S*-Daipen, *R*-Daipen, *S,S*-DACH y *R,R*-DACH. En algunas realizaciones, la porción de la difosfina quiral del catalizador es *S*-ClMeOBIPHEP. En algunas realizaciones, la porción de la difosfina quiral del catalizador es *R*-ClMeOBIPHEP. En algunas realizaciones, la porción de la difosfina quiral del catalizador es *S*-Segphos. En algunas realizaciones, la porción de la difosfina quiral del catalizador es *R*-Segphos. En algunas realizaciones, la porción de la difosfina quiral del catalizador es *S*-CTH-Pphos. En algunas realizaciones, la porción de la difosfina quiral del catalizador es *R*-CTH-Pphos. En algunas realizaciones, la porción de la difosfina quiral del catalizador es *S*-BINAP. En algunas realizaciones, la porción de la difosfina quiral del catalizador es *R*-BINAP. En algunas realizaciones, la porción de la amina quiral del catalizador es *S*-Daipen. En algunas realizaciones, la porción de la amina quiral del catalizador es *R*-Daipen. En algunas realizaciones, la porción de la amina quiral del catalizador es *S,S*-DACH. En algunas

realizaciones, la porción de la amina quiral del catalizador es *R,R*-DACH.

[00057] Un ácido carboxílico de fórmula (1-f-i) y/o (1-f-ii) se prepara como una mezcla de enantiómeros o como un único enantiómero llevando a cabo la hidrólisis de ésteres de fórmulas (2-g) y/o (2-h) utilizando condiciones estándares con las cuales estará familiarizado un experto en la técnica.

[00058] Una sulfonamida (1-i) se puede preparar mediante un método descrito en la presente, por ejemplo, de acuerdo con el siguiente ESQUEMA 4.

ESQUEMA 4



[00059] Tal como se representa en el ESQUEMA 4 anterior, X , L^1 , R^2 , R^3 y R^4 son como se definen en las clases y subclases descritas en la presente.

[00060] Un compuesto de fórmula (4-3) se puede preparar ciclando un ácido succínico N-prottegido adquirido de un proveedor comercial, por ejemplo, un compuesto de fórmula (4-1), y un anhídrido de ácido adecuado, por ejemplo, un compuesto de fórmula (4-2), utilizando condiciones con las cuales estará familiarizado un experto en la técnica. La reducción quimiosselectiva de un compuesto de fórmula (4-3) utilizando métodos con los que estará

familiarizado un experto en la técnica proporcionará un ácido *N*-protegido correspondiente de fórmula (4-4). Una lactona de fórmula (4-a) se prepara tratando el ácido *N*-protegido correspondiente de fórmula (4-4) con un ácido orgánico adecuado en un solvente adecuado en condiciones adecuadas. En algunas realizaciones, el ácido orgánico es *p*-TsOH. En algunas realizaciones, el ácido orgánico es el ácido camforsulfónico. En algunas realizaciones, el solvente adecuado es el tolueno. En algunas realizaciones, se lleva a cabo una destilación utilizando las condiciones de Dean-Stark.

[00061] La apertura del ciclo se lleva a cabo haciendo reaccionar una lactona de fórmula (4-a) en presencia de un alcohol adecuado para obtener un éster correspondiente (por ejemplo, cuando X = OMe) utilizando condiciones con las cuales estará familiarizado un experto en la técnica. En algunas realizaciones, el alcohol adecuado es el metanol. Como alternativa, la apertura del anillo se puede llevar a cabo en presencia de una amina adecuada (por ejemplo, HN(R₃R₄)) para formar una amida correspondiente representada como un compuesto de fórmula (4-b) en el ESQUEMA 4.

[00062] Un compuesto de fórmula (4-c) se puede preparar haciendo reaccionar un compuesto de fórmula (4-b) en las condiciones de la reacción de Mitsunobu en presencia de un tiofenol, una fosfina adecuada, un reactivo azodicarbonílico, un solvente adecuado, a una temperatura de aproximadamente 0 a aproximadamente 23 °C. En algunas realizaciones, la fosfina adecuada es una triarilfosfina o una triarilfosfina. Los ejemplos de triarilfosfina incluyen, pero no se limitan a, tributilfosfina. Los ejemplos de triarilfosfina incluyen, pero no se limitan a, trifenilfosfina. En algunas realizaciones, el reactivo azodicarbonílico adecuado incluye, pero no se limita a, azodicarboxilato de diisopropilo. En algunas realizaciones, el solvente adecuado es la *N,N*-dimetilformamida. En algunas realizaciones, el solvente adecuado es el diclorometano.

[00063] Un compuesto de fórmula (4-c) se desprotege utilizando un ácido adecuado para formar un compuesto de fórmula (4-d). En algunas realizaciones, el ácido adecuado es el TFA. En algunas realizaciones, el ácido adecuado es el HBr en ácido acético.

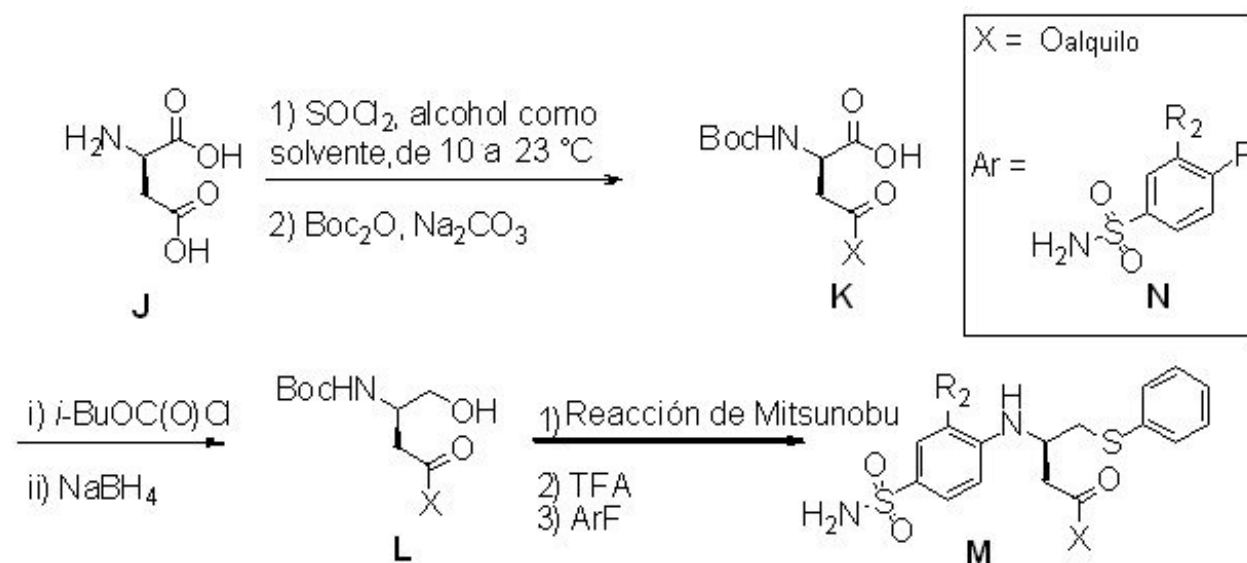
[00064] Un compuesto de fórmula (4-d) se acopla posteriormente con una amina de fórmula (4-5) en presencia de una base adecuada y un solvente adecuado para formar una sulfonamida de fórmula (4-e), por ejemplo, donde X = -OAlk, a una temperatura de aproximadamente 50 °C a aproximadamente 70 °C. En algunas realizaciones, la reacción se lleva a cabo a una temperatura de aproximadamente 50 °C. Una base adecuada incluye, pero no se limita a, DIPEA, trietilamina, *N*-metilmorfolina o carbonato de potasio. En algunas realizaciones, la base adecuada es la trietilamina. En algunas realizaciones, la base adecuada es el carbonato de potasio. El solvente adecuado incluye, pero no se limita a, *N,N*-dimetilformamida.

[00065] Cuando $X = N(R_3R_4)$ en un compuesto de fórmula (4-e), se lleva a cabo una reducción del grupo amida utilizando un agente reductor adecuado en condiciones con las cuales estará familiarizado un experto en la técnica, para formar un compuesto de fórmula (1-i). En algunas realizaciones, el agente reductor adecuado es el complejo de borano-tetrahidrofurano.

[00066] Cuando $X = -Oalk$ en un compuesto de fórmula (4-e), se lleva a cabo una reacción de reducción para formar un aldehído correspondiente (4-f) en condiciones con las cuales estará familiarizado un experto en la técnica. La aminación reductiva de un compuesto de fórmula (4-f) en presencia de una amina HNR_3R_4 utilizando un agente reductor adecuado se lleva a cabo en condiciones, con las cuales estará familiarizado un experto en la técnica, para formar una amina de fórmula (1-i). Los agentes reductores adecuados incluyen, pero no se limitan a, acetoxiborohidruro sódico.

ESQUEMA 4A

[00067] Un método alternativo para preparar un compuesto de fórmula (4-e) como el representado en el ESQUEMA 4 anterior es preparar un compuesto de fórmula M mediante un método descrito en la presente, por ejemplo, de acuerdo con el siguiente ESQUEMA 4A.



[00068] Tal como se describe en el ESQUEMA 4A, el ácido D-aspartico (J) se convierte en un éster metílico *N*-protegido con Boc de fórmula (K) mediante la esterificación catalizada por un ácido en presencia de un alcohol adecuado como solvente, seguida de la protección con *t*-butilcarboxi del NH_2 libre. En algunas realizaciones, el alcohol adecuado es el metanol. El paso 1) se lleva a cabo en presencia de un reactivo ácido adecuado a una temperatura de aproximadamente -10 °C a aproximadamente 23 °C. En algunas realizaciones, el reactivo ácido adecuado es el cloruro de tionilo. En algunas realizaciones, el catalizador ácido adecuado es el HCl anhidro. En algunas realizaciones, el catalizador ácido adecuado es el ácido sulfúrico

anhidro. La protección del *N* con Boc se lleva a cabo en presencia de dicarbonato de di-*tert*-butilo (Boc_2O) en presencia de una base adecuada tal como carbonato de potasio y en presencia de una mezcla de solventes adecuada. Los ejemplos de mezclas de solventes incluyen, pero no se limitan a, acetato de etilo/agua, dioxano/agua o tetrahidrofurano/agua. En algunas realizaciones, la temperatura de la reacción de protección del *N* con Boc es de aproximadamente 0 °C a aproximadamente 23 °C. En algunas realizaciones, la base adecuada es el bicarbonato de sodio. En algunas realizaciones, la base adecuada es el carbonato de sodio.

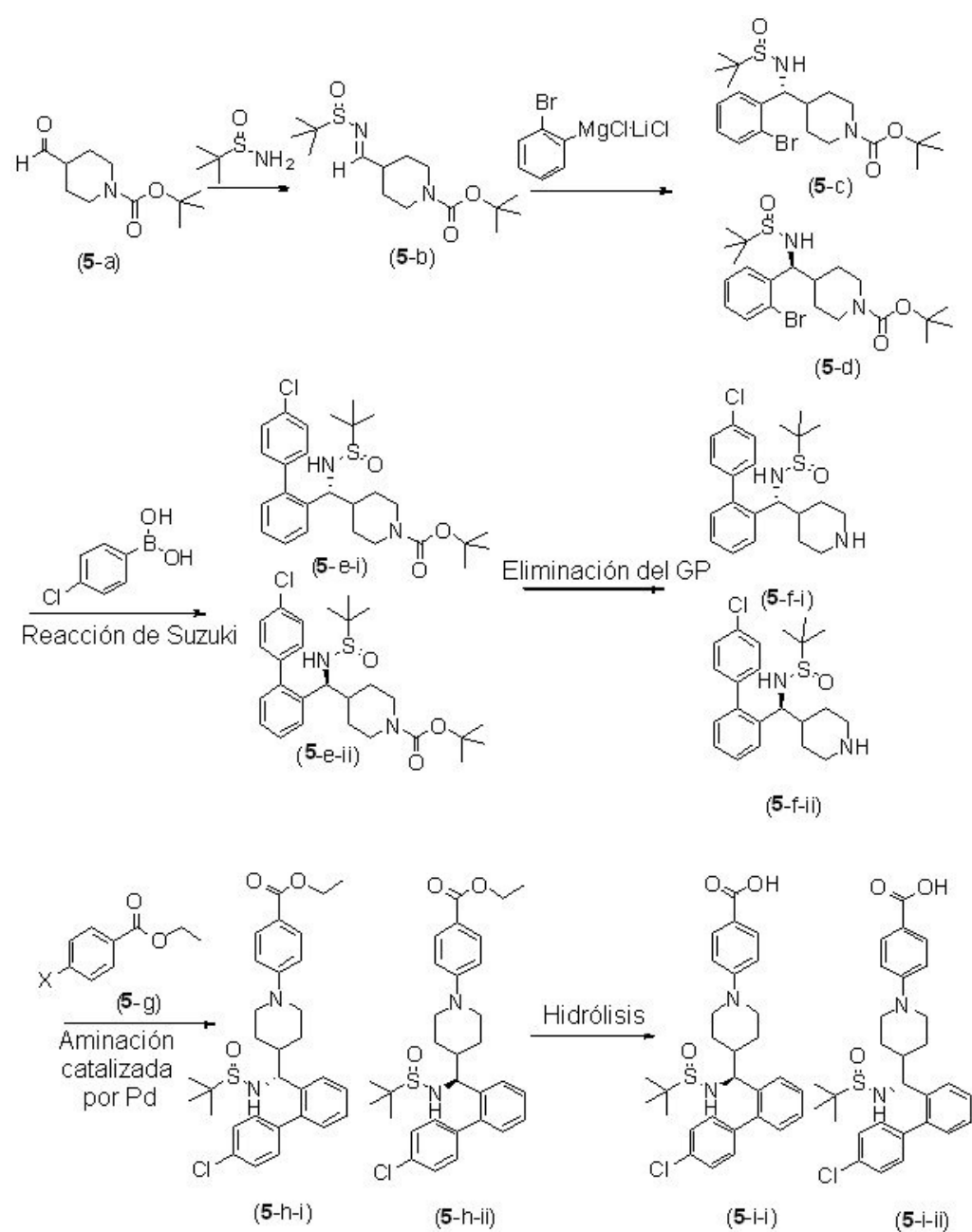
[00069] El éster alquílico *N*-protegido con Boc (K) se convierte en un alcohol primario (L) por conversión del resto ácido de (K) en un anhídrido mixto y la reducción posterior al alcohol correspondiente. La conversión de (K) en un anhídrido mixto se lleva a cabo en presencia de una base adecuada. En algunas realizaciones, la base adecuada es la *N*-metilmorfolina. En algunas realizaciones, el cloroformiato de alquilo adecuado es el cloroformiato de isobutilo. En algunas realizaciones, la temperatura adecuada es de aproximadamente -20 °C a aproximadamente 0 °C. En algunas realizaciones, el solvente adecuado es el tetrahidrofurano. En algunas realizaciones, el solvente adecuado es el 1,2-dimetoxietano o éter dietílico. En algunas realizaciones, se utiliza una base adecuada tal como trietilamina o *N,N*-diisopropiletilamina. En algunas realizaciones, el cloroformiato de alquilo adecuado es el cloroformiato de etilo. En algunas realizaciones, el cloruro de acilo adecuado es el cloruro de pivaloílo. La reducción del anhídrido mixto se lleva a cabo añadiendo un agente reductor adecuado, tal como borohidruro sódico, utilizando un cosolvente adecuado, tal como metanol, a una temperatura de aproximadamente -10 a aproximadamente 0 °C. En algunas realizaciones, el cosolvente adecuado es agua. En algunas realizaciones, el cosolvente adecuado es el etanol. En algunas realizaciones, el ácido se convierte directamente en un alcohol utilizando un reactivo adecuado, tal como el complejo de borano-tetrahidrofurano, en tetrahidrofurano a una temperatura tal como de 0 a 23 °C.

[00070] El alcohol (L) se convierte en sulfonamida (M) utilizando las condiciones de reacción de Mitsunobu, a continuación se elimina el grupo protector Boc en condiciones ácidas y posteriormente se añade a fluoruro de arilo (N). La reacción de Mitsunobu se lleva a cabo en presencia de tiofenol, una trialquil- o triarilfosfina adecuada, tal como tributilfosfina, y un reactivo azodicarbonílico adecuado, tal como azodicarbonildipiperidina, a una temperatura de aproximadamente 0 a aproximadamente 23 °C utilizando un solvente adecuado tal como tetrahidrofurano. En algunas realizaciones, la triarilfosfina adecuada es la trifenilfosfina. En algunas realizaciones, el reactivo azodicarbonílico adecuado es el azodicarboxilato de diisopropilo. En algunas realizaciones, el solvente adecuado es éter, *N,N*-dimetilformamida o diclorometano. La eliminación del grupo protector Boc se lleva a cabo utilizando un ácido adecuado, tal como el ácido trifluoroacético, ácido sulfúrico o ácido clorhídrico, en un solvente

adecuado, tal como diclorometano, dioxano o agua, a 23 °C. En algunas realizaciones, la reacción de desprotección se lleva a cabo a una temperatura de 0 a 23 °C. El material desprotegido crudo se añade posteriormente directamente a fluoruro de arilo (N) en presencia de un solvente adecuado, tal como *N,N*-diisopropilamina, en presencia de una base adecuada, tal como *N,N*-dimetilformamida, a una temperatura tal como 50 °C. En algunas realizaciones, la base adecuada es la trietilamina o el carbonato de potasio. En algunas realizaciones, la temperatura adecuada es de 50 a 70 °C.

[00071] Un ácido carboxílico de fórmulas (5-i-i) y/o (5-i-ii) se puede preparar mediante un método descrito en la presente, por ejemplo, de acuerdo con el siguiente ESQUEMA 5.

ESQUEMA 5



[00072] El aldehído (5-a) se convierte en una sulfinilimina (5-b) utilizando una 2-metilpropano-2-sulfinamida racémica auxiliar y un catalizador ácido adecuado en un solvente adecuado (*Acc. Chem. Res.* **2002**, 35, 984). En algunas realizaciones, el grupo auxiliar es la (*S*)-2-metilpropano-2-sulfinamida. En algunas realizaciones, el grupo auxiliar es la (*R*)-2-metilpropano-2-sulfinamida. En algunas realizaciones, el catalizador ácido adecuado es el sulfato de cobre (II) anhidro. En algunas realizaciones, el catalizador ácido adecuado es el etóxido de titanio (IV). La transformación se lleva a cabo a una temperatura de aproximadamente 0 a aproximadamente 60 °C utilizando un solvente adecuado. En algunas realizaciones, el solvente adecuado es el diclorometano. En algunas realizaciones, el solvente adecuado es el tetrahidrofurano.

[00073] La sulfinilimina (5-b) se hace reaccionar un reactivo de Grignard generado de acuerdo con el procedimiento descrito en *Angew. Chem. Int. Ed.*, 2004, 43, 3333, a una temperatura de aproximadamente -20 °C a aproximadamente 0 °C, en un solvente adecuado (p. ej., tetrahidrofurano) para obtener una sulfinamida de fórmulas (5-c) y/o (5-d).

[00074] Un compuesto de fórmulas (5-e-i) y/o (5-e-ii) se prepara llevando a cabo una reacción de Suzuki sobre compuestos de fórmulas (5-c) y/o (5-d) en condiciones con las que estará familiarizado un experto en la técnica (remítase a *J. Am. Chem. Soc.* 2005, 127, 4685; y *Nature Protocols* 2007, 2, 3115. *Aldrichimica Acta* **2006**, 39, 17). En algunas realizaciones, el ligando adecuado para la reacción es el dicitclohexilfosfino-2',6'-dimetoxibifenilo. En algunas realizaciones, una fuente de paladio adecuada es el tris(dibencilidenoacetona)dipaladio (0). En algunas realizaciones, la base adecuada es el fosfato de tripotasio.

[00075] Un compuesto de fórmulas (5-f-i) y/o (5-f-ii) se prepara mediante la eliminación quimioselectiva del grupo Boc de fórmulas (5-e-i) y/o (5-e-ii) en presencia de un grupo *t*-butil sulfinamida lábil a ácidos. En algunas realizaciones, la transformación se lleva a cabo en presencia de un ácido adecuado, tal como TFA, en un solvente adecuado, tal como diclorometano, a una temperatura comprendida entre aproximadamente 0 y aproximadamente 23 °C.

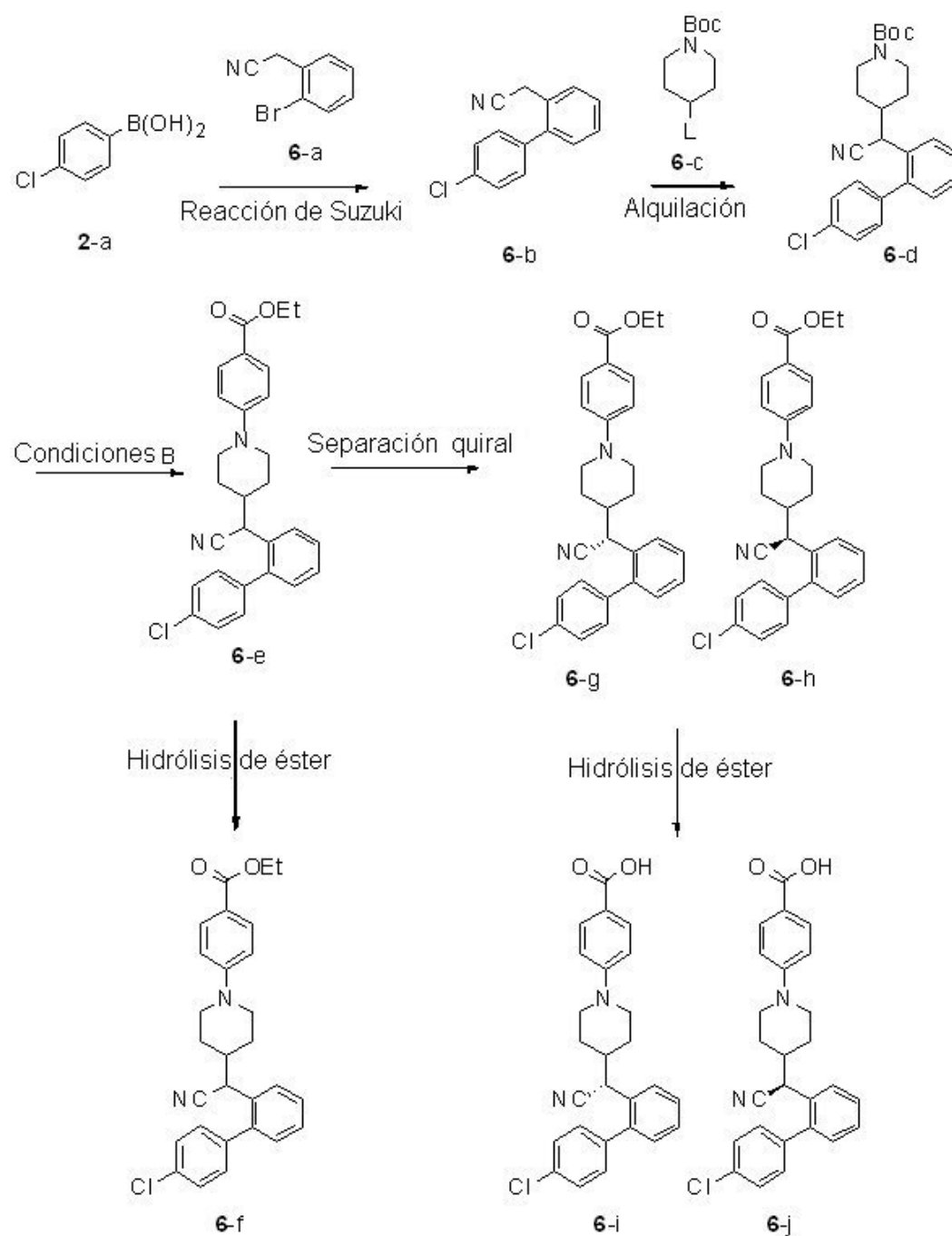
[00076] Un compuesto de fórmulas (5-h-i) y/o (5-h-ii) se prepara llevando a cabo una reacción de aminación catalizada por Pd en un compuesto de fórmulas (5-f-i) y/o (5-f-ii) en presencia de un compuesto de fórmula (5-g) en condiciones con las cuales estará familiarizado un experto en la técnica (remítase a *Chem. Sci.* **2011**, 2, 27, y las referencias citadas en este). En algunas realizaciones, se utiliza un aducto de catalizador:ligando preformado adecuado tal como el aducto metilbútilico de cloro(2-dicitclofosfino-2',6'-diisopropoxi-1,1'-bifenil)[2-(2-aminoetilfenil)]Pd(II). En algunas realizaciones, se añade más dicitclohexil(2'6'-diisopropoxibifenil-2-il)fosfina. En algunas realizaciones, se utiliza una base adecuada incluido,

pero sin limitarse a, carbonato de cesio. La transformación se lleva a cabo a temperaturas comprendidas entre aproximadamente 80 y aproximadamente 120 °C.

[00077] Un compuesto de fórmulas (5-i-i) y/o (5-i-ii) se prepara como una mezcla de diastereómeros o como un único diastereómero llevando a cabo la hidrólisis del éster de un compuesto de fórmulas (5-h-i) y/o (5-h-ii) utilizando condiciones estándares con las cuales estará familiarizado un experto en la técnica.

[00078] En ciertas realizaciones, los ácidos carboxílicos (6-f), (6-i) y (6-j) se preparan de acuerdo con el ESQUEMA 6.

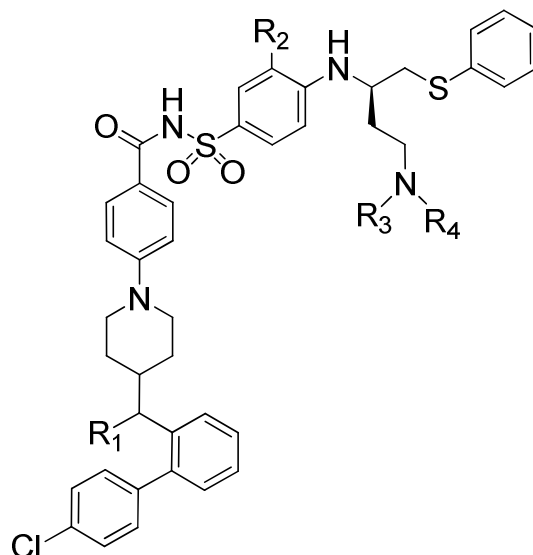
ESQUEMA 6



III. COMPUESTOS DE LA PRESENTE INVENCION

[00079] Los compuestos proporcionados por la presente invención incluyen aquellos descritos de forma general anteriormente y son ilustrados además por todas las clases, subclases y especies de cada uno de estos compuestos que se describen en la presente.

[00080] La presente invención se refiere a compuestos de Fórmula (I):



Fórmula (I)

y/o una de sus sales farmacéuticamente aceptables, donde:

R¹ se selecciona entre -CN, -OR^{1a} y -N(R^{1a})₂;

R^{1a} en cada caso se selecciona entre H, alquilo C₁₋₄, -C(O)CH₂NH₂,

-C(O)CH₂NHCH₃ y, cuando **R¹** es -OR^{1a}, entonces **R^{1a}** se selecciona adicionalmente entre

-P(=O)(OH)(OCH₃), -P(=O)(OCH₂CH₃)₂, -CH₂OP(=O)(OH)[OC(CH₃)₃] y

-CH₂OP(=O)[OC(CH₃)₃]₂;

R² se selecciona entre -N(O)₂ y -S(O)₂CF₃;

R³ se selecciona entre H y alquilo C₁₋₄, donde dicho alquilo C₁₋₄ está opcionalmente sustituido con uno o más R⁴⁰;

R⁴ se selecciona entre H y alquilo C₁₋₄, donde dicho alquilo C₁₋₄ está opcionalmente sustituido con uno o más R⁴⁰;

o **R³** y **R⁴** junto con el nitrógeno al cual están enlazados forman un anillo heterocíclico de 5 ó 6 miembros, donde:

- i) dicho anillo heterocíclico de 5 ó 6 miembros está opcionalmente sustituido en carbono con uno o más R⁴⁰; y
- ii) si dicho anillo heterocíclico de 5 ó 6 miembros contiene un nitrógeno, ese nitrógeno está

opcionalmente sustituido con R^{40*} para formar una amina terciaria;

R^{40*} es alquilo C_{1-4} y $-(CH_2)_2OP(=O)(OH)_2$, donde dicho alquilo C_{1-4} está opcionalmente sustituido con uno o más R^a ;

R^{40} en cada caso se selecciona entre $-OR^{40a}$, $-N(R^{40a})_2$, $-CH_2OR^{5a}$, $-CH_2N(R^{5a})_2$, $-OP(=O)(OH)_2$ y $-OP(=O)[OC(CH_3)_3]_2$;

R^{5a} en cada caso se selecciona entre H y alquilo C_{1-3} ;

R^{40a} en cada caso se selecciona independientemente entre H y alquilo C_{1-4} ; y

R^a se selecciona entre halo, $-OR^m$ y $-N(R^m)_2$; y

R^m en cada caso se selecciona independientemente entre H y alquilo C_{1-4} .

[00081] A continuación se presentan realizaciones adicionales de la invención. Estas realizaciones adicionales se refieren a compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e) y a sus sales farmacéuticamente aceptables. Tales sustituyentes específicos pueden utilizarse, cuando proceda, con cualquiera de las definiciones, reivindicaciones o realizaciones definidas anterior o posteriormente en la presente.

[00082] En algunas realizaciones, la presente invención se refiere a compuestos de Fórmula (I), y/o una de sus sales farmacéuticamente aceptables, donde:

R^1 se selecciona entre $-CN$, $-OR^{1a}$ y $-N(R^{1a})_2$;

R^{1a} en cada caso se selecciona independientemente entre H, alquilo C_{1-4} , $-C(O)CH_2NH_2$ y $-C(O)CH_2NHCH_3$;

R^2 se selecciona entre $-N(O)_2$ y $-S(O)_2CF_3$;

R^3 se selecciona entre H y alquilo C_{1-4} , donde dicho alquilo C_{1-4} está opcionalmente sustituido con uno o más R^{40} ;

R^4 se selecciona entre H y alquilo C_{1-4} , donde dicho alquilo C_{1-4} está opcionalmente sustituido con uno o más R^{40} ;

o R^3 y R^4 junto con el nitrógeno al cual están enlazados forman un anillo heterocíclico de 5 ó 6 miembros, donde:

- i) dicho anillo heterocíclico de 5 ó 6 miembros está opcionalmente sustituido en carbono con uno o más R^{40} ; y
- ii) si dicho anillo heterocíclico de 5 ó 6 miembros contiene un nitrógeno, ese nitrógeno está opcionalmente sustituido con R^{40*} para formar una amina terciaria;

R^{40*} es alquilo C₁₋₄, donde dicho alquilo C₁₋₄ está opcionalmente sustituido con uno o más R^a;

R⁴⁰ en cada caso se selecciona entre -OR^{40a}, -N(R^{40a})₂, -CH₂OR^{5a}, -CH₂N(R^{5a})₂,

R^{5a} en cada caso se selecciona entre H y alquilo C₁₋₃;

R^{40a} en cada caso se selecciona independientemente entre H y alquilo C₁₋₄; y

R^a se selecciona entre halo, -OR^m y -N(R^m)₂; y

R^m en cada caso se selecciona independientemente entre H y alquilo C₁₋₄.

[00083] En algunas realizaciones, la presente invención se refiere a compuestos de Fórmula (I), y/o una de sus sales farmacéuticamente aceptables, donde:

R¹ se selecciona entre -CN, -OR^{1a} y -N(R^{1a})₂;

R^{1a} en cada caso se selecciona independientemente entre H, alquilo C₁₋₄, -C(O)CH₂NH₂,

-C(O)CH₂NHCH₃ y, cuando **R¹** es -OR^{1a}, entonces **R^{1a}** se selecciona adicionalmente entre

-P(=O)(OH)(OCH₃), -P(=O)(OCH₂CH₃)₂, -CH₂OP(=O)(OH)[OC(CH₃)₃] y

-CH₂OP(=O)[OC(CH₃)₃]₂;

R² se selecciona entre -N(O)₂ y -S(O)₂CF₃;

R³ se selecciona entre H y alquilo C₁₋₄, donde dicho alquilo C₁₋₄ está opcionalmente sustituido con uno o más R⁴⁰;

R⁴ se selecciona entre H y alquilo C₁₋₄, donde dicho alquilo C₁₋₄ está opcionalmente sustituido con uno o más R⁴⁰;

o **R³** y **R⁴** junto con el nitrógeno al cual están enlazados forman un anillo heterocíclico de 5 ó 6 miembros, donde:

- i) dicho anillo heterocíclico de 5 ó 6 miembros está opcionalmente sustituido en carbono con uno o más R⁴⁰; y
- ii) si dicho anillo heterocíclico de 5 ó 6 miembros contiene un nitrógeno, ese nitrógeno está opcionalmente sustituido con R^{40*} para formar una amina terciaria;

R^{40*} se selecciona entre alquilo C₁₋₄ y -(CH₂)₂OP(=O)(OH)₂, donde dicho alquilo C₁₋₄ está opcionalmente sustituido con uno o más R^a;

R⁴⁰ en cada caso se selecciona entre -OR^{40a}, -N(R^{40a})₂, -CH₂OR^{5a}, -CH₂N(R^{5a})₂,

-OP(=O)(OH)₂ y -OP(=O)[OC(CH₃)₃]₂;

R^{5a} en cada caso se selecciona entre H y alquilo C₁₋₃;

R^{40a} en cada caso se selecciona independientemente entre H y alquilo C₁₋₄; y

R^a se selecciona entre halo, -OR^m y -N(R^m)₂; y

R^m en cada caso se selecciona independientemente entre H y alquilo C₁₋₄;

y donde al menos uno de **R¹**, **R³** o **R⁴** contiene un grupo -P(=O)-.

[00084] En algunas realizaciones, la presente invención se refiere a compuestos de Fórmula (I), y/o una de sus sales farmacéuticamente aceptables, donde:

R¹ se selecciona entre -CN, -OR^{1a} y -N(R^{1a})₂;

R^{1a} en cada caso se selecciona independientemente entre H, alquilo C₁, -C(O)CH₂NH₂ y -C(O)CH₂NHCH₃;

R² se selecciona entre -N(O)₂ y -S(O)₂CF₃;

R³ se selecciona entre alquilo C₁₋₂, donde dicho alquilo C₁₋₂ está opcionalmente sustituido con uno o más R⁴⁰;

R⁴ se selecciona entre alquilo C₁₋₂, donde dicho alquilo C₁₋₂ está opcionalmente sustituido con uno o más R⁴⁰;

o **R³** y **R⁴** junto con el nitrógeno al cual están enlazados forman un anillo heterocíclico de 5 ó 6 miembros, donde

- i) dicho anillo heterocíclico de 5 ó 6 miembros está opcionalmente sustituido en carbono con uno o más R⁴⁰; y
- ii) si dicho anillo heterocíclico de 5 ó 6 miembros contiene un nitrógeno, ese nitrógeno está opcionalmente sustituido con R^{40*} para formar una amina terciaria;

R^{40*} se selecciona entre alquilo C₂₋₃ donde dicho alquilo C₂₋₃ está opcionalmente sustituido con uno o más R^a;

R⁴⁰ en cada caso se selecciona entre -OR^{40a}, -CH₂OR^{5a} y -CH₂N(R^{5a})₂;

R^{5a} en cada caso se selecciona entre H y alquilo C₂;

R^{40a} en cada caso es independientemente H; y

R^a se selecciona entre halo y -OR^m; y

R^m en cada caso es independientemente H.

[00085] En algunas realizaciones, la presente invención se refiere a compuestos de Fórmula (I), y/o una de sus sales farmacéuticamente aceptables, donde:

R¹ es -OR^{1a};

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R^{1a} en cada caso se selecciona independientemente entre H, -P(=O)(OH)(OCH₃), -P(=O)(OCH₂CH₃)₂, -CH₂OP(=O)(OH)[OC(CH₃)₃] y -CH₂OP(=O)[OC(CH₃)₃]₂;

R² es -S(O)₂CF₃;

R³ es alquilo C₁₋₂, donde dicho alquilo C₁₋₂ está opcionalmente sustituido con uno o más R⁴⁰;

R⁴ es alquilo C₁₋₂, donde dicho alquilo C₁₋₂ está opcionalmente sustituido con uno o más R⁴⁰;

o **R³** y **R⁴** junto con el nitrógeno al cual están enlazados forman un anillo heterocíclico de 5 ó 6 miembros, donde

- i) dicho anillo heterocíclico de 5 ó 6 miembros está opcionalmente sustituido en carbono con uno o más R⁴⁰; y
- ii) si dicho anillo heterocíclico de 5 ó 6 miembros contiene un nitrógeno, ese nitrógeno está opcionalmente sustituido con R^{40*} para formar una amina terciaria;

R^{40*} es -(CH₂)₂OP(=O)(OH)₂;

R⁴⁰ en cada caso se selecciona entre -OP(=O)(OH)₂ y -CH₂N(R^{5a})₂;

R^{5a} en cada caso se selecciona entre H y alquilo C₂;

R^a se selecciona entre halo, -OR^m y -N(R^m)₂; y

R^m en cada caso se selecciona independientemente entre H y alquilo C₁₋₄.

[00086] En algunas realizaciones, la presente invención se refiere a compuestos de Fórmula (I), y/o una de sus sales farmacéuticamente aceptables, donde:

R¹ es -OH;

R² es -S(O)₂CF₃;

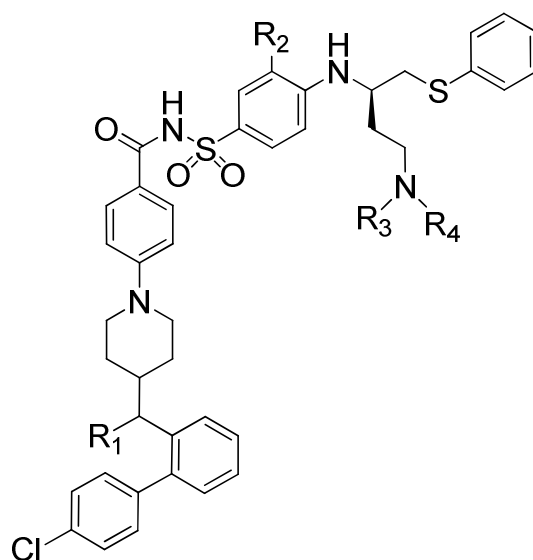
R³ es alquilo C₁₋₂, donde dicho alquilo C₁₋₂ está opcionalmente sustituido con uno o más R⁴⁰;

R⁴ es alquilo C₁₋₂, donde dicho alquilo C₁₋₂ está opcionalmente sustituido con uno o más R⁴⁰;

R⁴⁰ en cada caso se selecciona entre -OR^{40a} y -OP(=O)(OH)₂; y

R^{40a} es H.

[00087] En ciertas realizaciones, la presente invención proporciona un compuesto de Fórmula (I):



Fórmula (I)

y/o a sus sales farmacéuticamente aceptables, donde:

R¹ se selecciona entre -CN , -OR^{1a} y -N(R^{1a})₂;

R^{1a} en cada caso se selecciona independientemente entre H y alquilo C₁₋₄;

R² se selecciona entre -N(O)₂ y -S(O)₂CF₃;

R³ se selecciona entre H y alquilo C₁₋₄, donde dicho alquilo C₁₋₄ está opcionalmente sustituido con uno o más R⁴⁰;

R⁴ se selecciona entre H y alquilo C₁₋₄, donde dicho alquilo C₁₋₄ está opcionalmente sustituido con uno o más R⁴⁰;

o **R³** y **R⁴** junto con el nitrógeno al cual están enlazados forman un anillo heterocíclico de 5 ó 6 miembros, donde:

- i) dicho anillo de 5 ó 6 miembros no es morfolino;
- ii) dicho anillo heterocíclico de 5 ó 6 miembros está opcionalmente sustituido en carbono con uno o más R⁴⁰; y
- iii) si dicho anillo heterocíclico de 5 a 6 miembros contiene un resto NH-, ese nitrógeno está opcionalmente sustituido con R^{40*};

R^{40*} es alquilo C₁₋₄, donde dicho alquilo C₁₋₄ está opcionalmente sustituido con uno o más R^a;

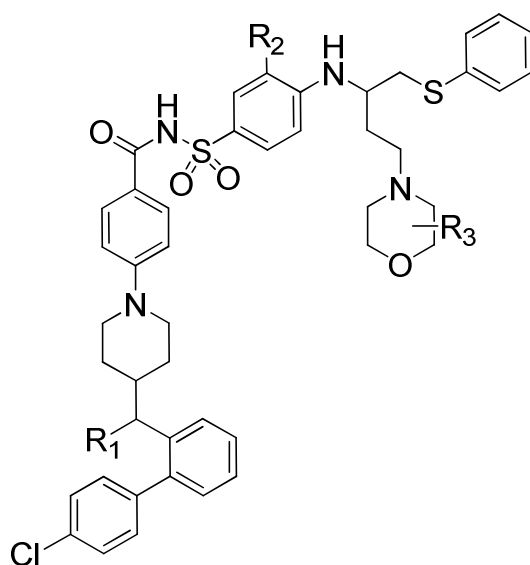
R⁴⁰ se selecciona entre -OR^{40a} y -N(R^{40a})₂;

R^{40a} en cada caso se selecciona entre H y alquilo C₁₋₄; y

R^a se selecciona entre halo, -OR^m y -N(R^m)₂; y

R^m en cada caso se selecciona independientemente entre H y alquilo C₁₋₄.

[00088] En ciertas realizaciones, la presente invención proporciona un compuesto de Fórmula (I-c):



Fórmula (I-c)

y/o sus sales farmacéuticamente aceptables, donde:

R¹ se selecciona entre -CN , -OR^{1a} y -N(R^{1a})₂;

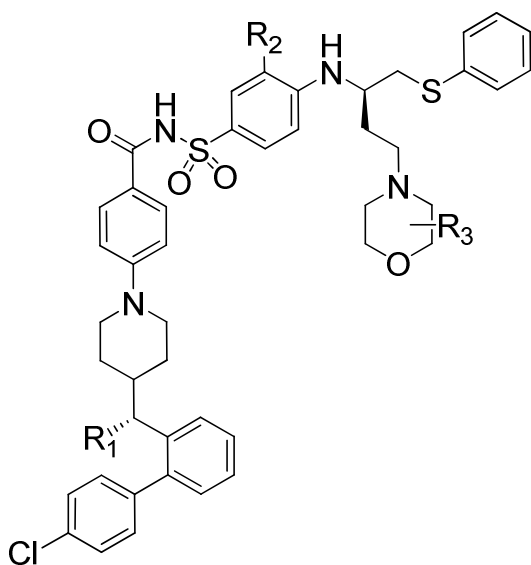
R^{1a} en cada caso se selecciona independientemente entre H y alquilo C₁₋₃;

R² se selecciona entre -N(O)₂ y -S(O)₂CF₃;

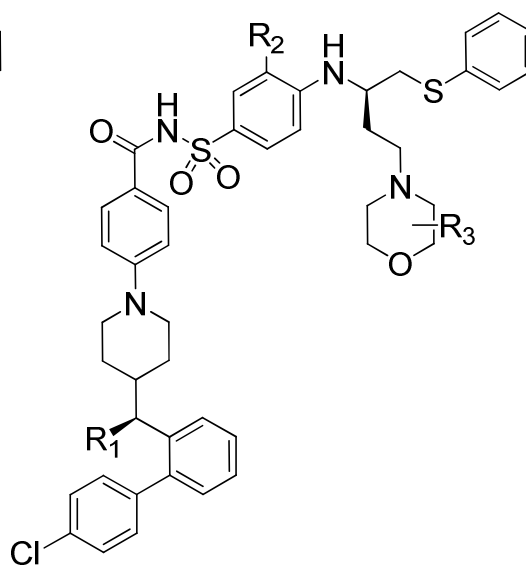
R³ se selecciona entre -CH₂OR^{3a} y -CH₂N(R^{3a})₂; y

R^{3a} se selecciona entre H y alquilo C₁₋₃.

[00089] En ciertas realizaciones, los compuestos que se proporcionan en la presente invención tienen la estructura que se expone en las Fórmulas (I-d) y/o (I-e):



Fórmula (I-d)



Fórmula (I-e)

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y/o una de sus sales farmacéuticamente aceptables, donde R^1 , R^2 y R^3 son cada uno como se definen y describen en las clases y subclases de la presente.

[00090] VALORES DE R^1

[00091] Tal como se definió de forma general en la presente, R^1 se selecciona entre -CN, -OR^{1a} y -N(R^{1a})₂.

[00092] En un aspecto, R^1 se selecciona entre -OH y -CN.

[00093] En algunas realizaciones, R^1 es -OH. En algunas realizaciones, R^1 es -CN. En algunas realizaciones R^1 es -NH₂. En algunas realizaciones, R^1 es -CH₂OP(=O)[OC(CH₃)₃]₂. En algunas realizaciones, R^1 es -CH₂OP(=O)(OH)[OC(CH₃)₃]. En algunas realizaciones, R^1 es -P(=O)(OCH₂CH₃)₂. En algunas realizaciones, R^1 es -P(=O)(OH)(OCH₃). En algunas realizaciones, R^1 es -NHC(O)CH₂NHCH₃. En algunas realizaciones, R^1 es -NHC(O)CH₂NH₂. En algunas realizaciones, R^1 es -N(CH₃)₂.

[00094] VALORES DE R^2

[00095] Tal como se definió de forma general anteriormente, R^2 se selecciona entre -NO₂ y -SO₂CF₃.

[00096] En algunas realizaciones, R^2 es -N(O)₂. En algunas realizaciones, R^2 es -S(O)₂CF₃.

[00097] VALORES DE R^3

[00098] Tal como se definió de forma general anteriormente, R^3 se selecciona entre H y alquilo C₁₋₄, donde dicho alquilo C₁₋₄ está opcionalmente sustituido con uno o más R⁴⁰.

[00099] En un aspecto, R^3 se selecciona entre -CH₂OR^{3a} y -CH₂N(R^{3a})₂.

[000100] En algunas realizaciones, R^3 se selecciona entre -CH₂OH y -CH₂N(R^{3a})₂. En algunas realizaciones, R^3 es metilo. En algunas realizaciones, R^3 es metilo opcionalmente sustituido con uno o más R⁴⁰. En algunas realizaciones, R^3 es etilo opcionalmente sustituido con uno o más R⁴⁰. En algunas realizaciones, R^3 es etilo. En algunas realizaciones, R^3 es -CH₂CH₂OH. En algunas realizaciones, R^3 es -CH₂CH₂OP(=O)(OH)₂.

[000101] VALORES DE R^{3a}

En un aspecto, R^{3a} en cada caso se selecciona independientemente entre H y alquilo C₁₋₃. En algunas realizaciones, R^{3a} es etilo.

[000102] VALORES DE R^4

[000103] Tal como se definió de forma general anteriormente, R^4 se selecciona entre H y alquilo C_{1-4} , donde dicho alquilo C_{1-4} está opcionalmente sustituido con uno o más R^{40} .

[000104] En algunas realizaciones, R^4 es H. En algunas realizaciones, R^4 es metilo. En algunas realizaciones, R^4 es metilo opcionalmente sustituido con uno o más R^{40} . En algunas realizaciones, R^4 es etilo opcionalmente sustituido con uno o más R^{40} . En algunas realizaciones, R^4 es etilo. En algunas realizaciones, R^4 es $-CH_2CH_2OH$. En algunas realizaciones, R^4 es $-CH_2CH_2OP(=O)(OH)_2$.

[000105] VALORES DE R^3 y R^4

[000106] En un aspecto, R^3 es alquilo C_{1-4} , donde dicho alquilo C_{1-4} está opcionalmente sustituido con uno o más R^{40} ; R^4 es alquilo C_{1-4} , donde dicho alquilo C_{1-4} está opcionalmente sustituido con R^{40} ; y R^{40} es $-OH$.

[000107] En otro aspecto, R^3 se selecciona entre metilo y etilo, donde dicho metilo y etilo están opcionalmente sustituidos con uno o más R^{40} ; R^4 es etilo, donde dicho etilo está opcionalmente sustituido con uno o más R^{40} ; y R^{40} es $-OH$.

[000108] En otro aspecto, R^3 se selecciona entre metilo, etilo y 2-hidroxietilo; y R^4 se selecciona entre metilo y 2-hidroxietilo.

[000109] En otro aspecto, R^3 y R^4 junto con el nitrógeno al cual están enlazados forman un anillo heterocíclico de 5 ó 6 miembros, donde:

- i) dicho anillo de 5 ó 6 miembros no es morfolino;
- ii) si dicho anillo heterocíclico de 5 ó 6 miembros contiene un resto $-NH-$, ese nitrógeno está opcionalmente sustituido con R^{40*} ; R^{40*} es alquilo C_{1-4} , donde dicho alquilo C_{1-4} está opcionalmente sustituido con uno o más R^a ; y R^a en cada caso se selecciona independientemente entre halo y $-OH$.

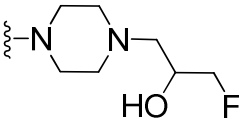
[000110] En otro aspecto, R^3 y R^4 junto con el nitrógeno al cual están enlazados forman un anillo piperazin-1-ilo, donde dicho anillo piperazin-1-ilo está opcionalmente sustituido en nitrógeno con R^{40*} ; R^{40*} es alquilo C_{1-4} , donde dicho alquilo C_{1-4} está opcionalmente sustituido con uno o más R^a ; y R^a en cada caso se selecciona independientemente entre halo y $-OH$.

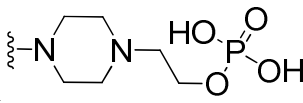
[000111] En otro aspecto, R^3 y R^4 junto con el nitrógeno al cual están enlazados forman un anillo piperazin-1-ilo, donde dicho anillo piperazin-1-ilo está opcionalmente sustituido en nitrógeno con R^{40*} ; R^{40*} se selecciona entre etilo y propilo, donde dicho etilo y propilo están

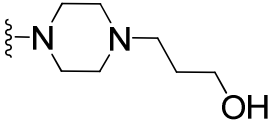
opcionalmente sustituidos con uno o más R^a ; y R^a en cada caso se selecciona independientemente entre fluoro y -OH.

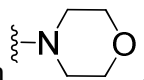
[000112] En otro aspecto, R^3 y R^4 junto con el nitrógeno al cual están enlazados forman un miembro seleccionado entre 4-(3-fluoro-2-hidroxipropil)piperazin-1-ilo y 4-(2-hidroxietil)piperazin-1-ilo.

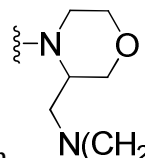
[000113] En algunas realizaciones, R^3 y R^4 junto con el nitrógeno al cual están enlazados forman el 4-(3-fluoro-2-hidroxipropil)piperazin-1-ilo. En algunas realizaciones, R^3 y R^4 junto

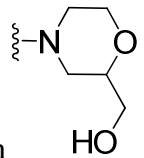
con el nitrógeno al cual están enlazados forman . En algunas realizaciones,

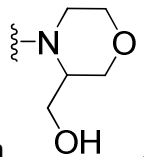
R^3 y R^4 junto con el nitrógeno al cual están enlazados forman . En algunas realizaciones, R^3 y R^4 junto con el nitrógeno al cual están enlazados

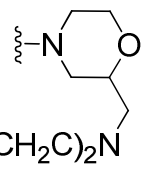
forman . En algunas realizaciones, R^3 y R^4 junto con el nitrógeno al cual

están enlazados forman . En algunas realizaciones, R^3 y R^4 junto con el nitrógeno al

cual están enlazados forman . En algunas realizaciones, R^3 y R^4 junto con el

nitrógeno al cual están enlazados forman . En algunas realizaciones, R^3 y R^4 junto

con el nitrógeno al cual están enlazados forman . En algunas realizaciones, R^3 y R^4

junto con el nitrógeno al cual están enlazados forman .

[000114] VALORES DE R^1 , R^2 y R^3

[000115] En un aspecto, R^1 se selecciona entre -OH y -CN; R^2 se selecciona entre -NO₂ y -SO₂CF₃; R^3 se selecciona entre -CH₂OR^{3a} y -CH₂N(R^{3a})₂; y R^{3a} en cada caso se selecciona

entre H y alquilo C₁₋₃.

[000116] En otro aspecto, **R¹** se selecciona entre -OH y -CN; **R²** se selecciona entre -NO₂ y -SO₂CF₃; **R³** se selecciona entre -CH₂OH y -CH₂N(R^{3a})₂; y **R^{3a}** es etilo.

[000117] VALORES DE **R¹**, **R²**, **R³** y **R⁴**

[000118] En un aspecto, **R¹** es -OH; **R²** se selecciona entre -N(O)₂ y -S(O)₂CF₃; **R³** es alquilo C₁₋₄, donde dicho alquilo C₁₋₄ está opcionalmente sustituido con **R⁴⁰**; **R⁴** es alquilo C₁₋₄, donde dicho alquilo C₁₋₄ está opcionalmente sustituido con uno o más **R⁴⁰**; o **R³** y **R⁴** junto con el átomo de nitrógeno al cual están enlazados forman un anillo heterocíclico de 5 ó 6 miembros, donde:

- i) dicho anillo de 5 ó 6 miembros no es morfolino;
- ii) si dicho anillo heterocíclico de 5 a 6 miembros contiene un resto NH-, ese nitrógeno está opcionalmente sustituido con **R^{40*}**;

R^{40*} es alquilo C₁₋₄, donde dicho alquilo C₁₋₄ está opcionalmente sustituido con uno o más **R^a**; **R⁴⁰** es -OH; y **R^a** en cada caso se selecciona independientemente entre halo y -OH.

[000119] En otro aspecto, **R¹** es -OH; **R²** se selecciona entre -N(O)₂ y -S(O)₂CF₃; **R³** se selecciona entre metilo, etilo y 2-hidroxietilo; **R⁴** se selecciona entre metilo y 2-hidroxietilo; o **R³** y **R⁴** junto con el nitrógeno al cual están enlazados forman un anillo piperazin-1-ilo, donde dicho anillo piperazin-1-ilo está opcionalmente sustituido en nitrógeno con **R^{40*}**; **R^{40*}** se selecciona entre etilo y propilo, donde dicho etilo y propilo están opcionalmente sustituidos con uno o más **R^a**; y **R^a** en cada caso se selecciona independientemente entre fluoro y -OH.

[000120] En algunas realizaciones, **R¹** es -OH; **R²** es -S(O)₂CF₃; **R³** es metilo; y **R⁴** es -CH₂CH₂OH.

[000121] En algunas realizaciones, **R¹** es -OH; **R²** es -S(O)₂CF₃; **R³** es etilo; y **R⁴** es -CH₂CH₂OH.

[000122] En algunas realizaciones, **R¹** es -OH; **R²** es -S(O)₂CF₃; **R³** es -CH₂CH₂OP(=O)(OH)₂; y **R⁴** es etilo.

[000123] En algunas realizaciones, **R¹** es -OH; **R²** es -S(O)₂CF₃; **R³** es -CH₂CH₂OP(=O)(OH)₂; y **R⁴** es metilo.

[000124] En un aspecto, se proporciona un compuesto seleccionado entre:

[000125] 4-(4-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-N-(4-((R)-4-(4-(2-

hidroxietil)piperazin-1-il)-1-(feniltio)butan-2-ilamino)-3-

(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000126] 4-(4-((4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-(dimetilamino)-1-(feniltio)butan-2-ilamino)-3-nitrofenilsulfonil)benzamida;

[000127] 4-(4-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-((2-hidroxietil)(metil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000128] 4-(4-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-(etil(2-hidroxietil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000129] *N*-(4-4-(bis(2-hidroxietil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)-4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzamida; y

[000130] 4-(4-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((2*R*)-4-(4-(3-fluoro-2-hidroxipropil)piperazin-1-il)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;

y/o una de sus sales farmacéuticamente aceptables.

[000131] En otro aspecto, se proporciona un compuesto seleccionado entre:

[000132] 4-{4-[(*S*)-(4'-clorobifenil-2-il)(hidroxi)metil]piperidin-1-il}-*N*-[(4-{[(2*R*)-4-(morfolin-4-il)-1-(fenilsulfanil)butan-2-il]amino}-3-[(trifluorometil)sulfonil]fenil)sulfonil]benzamida;

[000133] 4-{4-[(*R*)-(4'-clorobifenil-2-il)(hidroxi)metil]piperidin-1-il}-*N*-[(4-{[(2*R*)-4-(morfolin-4-il)-1-(fenilsulfanil)butan-2-il]amino}-3-[(trifluorometil)sulfonil]fenil)sulfonil]benzamida;

[000134] 4-{4-[(*S*)-(4'-clorobifenil-2-il)(hidroxi)metil]piperidin-1-il}-*N*-[(4-{[(2*R*)-4-(morfolin-4-il)-1-(fenilsulfanil)butan-2-il]amino}-3-nitrofenil)sulfonil]benzamida;

[000135] 4-{4-[(*R*)-(4'-clorobifenil-2-il)(hidroxi)metil]piperidin-1-il}-*N*-[(4-{[(2*R*)-4-(morfolin-4-il)-1-(fenilsulfanil)butan-2-il]amino}-3-nitrofenil)sulfonil]benzamida;

[000136] 4-{4-[(4'-clorobifenil-2-il)(ciano)metil]piperidin-1-il}-*N*-[(4-{[(2*R*)-4-(morfolin-4-il)-1-(fenilsulfanil)butan-2-il]amino}-3-[(trifluorometil)sulfonil]fenil)sulfonil]benzamida;

[000137] 4-{4-[(*S*)-(4'-clorobifenil-2-il)(ciano)metil]piperidin-1-il}-*N*-[(4-{[(2*R*)-4-(morfolin-4-il)-1-(fenilsulfanil)butan-2-il]amino}-3-[(trifluorometil)sulfonil]fenil)sulfonil]benzamida;

[000138] 4-{4-[(*R*)-(4'-clorobifenil-2-il)(ciano)metil]piperidin-1-il}-*N*-[(4-{[(2*R*)-4-(morfolin-4-il)-1-(fenilsulfanil)butan-2-il]amino}-3-[(trifluorometil)sulfonil]fenil)sulfonil]benzamida;

- [000139]** 4-{4-[(*S*)-(4'-clorobifenil-2-il)(hidroxi)metil]piperidin-1-il}-*N*-[(4-{[(2*R*)-4-[(3*S*)-3-{[dietilamino]metil}morfolin-4-il]-1-(fenilsulfanil)butan-2-il]amino}-3-[(trifluorometil)sulfonil]fenil)sulfonil]benzamida;
- [000140]** 4-{4-[(*R*)-(4'-clorobifenil-2-il)(hidroxi)metil]piperidin-1-il}-*N*-[(4-{[(2*R*)-4-[(3*S*)-3-{[dietilamino]metil}morfolin-4-il]-1-(fenilsulfanil)butan-2-il]amino}-3-[(trifluorometil)sulfonil]fenil)sulfonil]benzamida;
- [000141]** 4-{4-[(*S*)-(4'-clorobifenil-2-il)(hidroxi)metil]piperidin-1-il}-*N*-[(4-{[(2*R*)-4-[(3*R*)-3-{[dietilamino]metil}morfolin-4-il]-1-(fenilsulfanil)butan-2-il]amino}-3-[(trifluorometil)sulfonil]fenil)sulfonil]benzamida;
- [000142]** 4-{4-[(*R*)-(4'-clorobifenil-2-il)(hidroxi)metil]piperidin-1-il}-*N*-[(4-{[(2*R*)-4-[(3*R*)-3-{[dietilamino]metil}morfolin-4-il]-1-(fenilsulfanil)butan-2-il]amino}-3-[(trifluorometil)sulfonil]fenil)sulfonil]benzamida;
- [000143]** 4-{4-[(*S*)-(4'-clorobifenil-2-il)(hidroxi)metil]piperidin-1-il}-*N*-[(4-{[(2*R*)-4-[(2*R*)-2-(hidroximetil)morfolin-4-il]-1-(fenilsulfanil)butan-2-il]amino}-3-[(trifluorometil)sulfonil]fenil)sulfonil]benzamida;
- [000144]** 4-{4-[(*R*)-(4'-clorobifenil-2-il)(hidroxi)metil]piperidin-1-il}-*N*-[(4-{[(2*R*)-4-[(2*R*)-2-(hidroximetil)morfolin-4-il]-1-(fenilsulfanil)butan-2-il]amino}-3-[(trifluorometil)sulfonil]fenil)sulfonil]benzamida;
- [000145]** 4-{4-[(*S*)-(4'-clorobifenil-2-il)(hidroxi)metil]piperidin-1-il}-*N*-[(4-{[(2*R*)-4-[(2*S*)-2-(hidroximetil)morfolin-4-il]-1-(fenilsulfanil)butan-2-il]amino}-3-[(trifluorometil)sulfonil]fenil)sulfonil]benzamida;
- [000146]** 4-{4-[(*R*)-(4'-clorobifenil-2-il)(hidroxi)metil]piperidin-1-il}-*N*-[(4-{[(2*R*)-4-[(2*S*)-2-(hidroximetil)morfolin-4-il]-1-(fenilsulfanil)butan-2-il]amino}-3-[(trifluorometil)sulfonil]fenil)sulfonil]benzamida;
- [000147]** 4-{4-[(*S*)-(4'-clorobifenil-2-il)(hidroxi)metil]piperidin-1-il}-*N*-[(4-{[(2*R*)-4-[(3*R*)-3-(hidroximetil)morfolin-4-il]-1-(fenilsulfanil)butan-2-il]amino}-3-[(trifluorometil)sulfonil]fenil)sulfonil]benzamida;
- [000148]** 4-{4-[(*R*)-(4'-clorobifenil-2-il)(hidroxi)metil]piperidin-1-il}-*N*-[(4-{[(2*R*)-4-[(3*R*)-3-(hidroximetil)morfolin-4-il]-1-(fenilsulfanil)butan-2-il]amino}-3-[(trifluorometil)sulfonil]fenil)sulfonil]benzamida;
- [000149]** 4-{4-[(*S*)-(4'-clorobifenil-2-il)(hidroxi)metil]piperidin-1-il}-*N*-[(4-{[(2*R*)-4-[(3*S*)-3-(hidroximetil)morfolin-4-il]-1-(fenilsulfanil)butan-2-il]amino}-3-[(trifluorometil)sulfonil]fenil)sulfonil]benzamida;
- [000150]** 4-{4-[(*R*)-(4'-clorobifenil-2-il)(hidroxi)metil]piperidin-1-il}-*N*-[(4-{[(2*R*)-4-[(3*S*)-3-(hidroximetil)morfolin-4-il]-1-(fenilsulfanil)butan-2-il]amino}-3-[(trifluorometil)sulfonil]fenil)sulfonil]benzamida;

[(trifluorometil)sulfonil]fenil)sulfonil]benzamida;

[000151] 4-{4-[(*S*)-(4'-clorobifenil-2-il)(hidroxi)metil]piperidin-1-il}-*N*-[(4-{[(*2R*)-4-{(*2S*)-2-[(dietilamino)metil]morfolin-4-il}-1-(fenilsulfanil)butan-2-il]amino}-3-

[(trifluorometil)sulfonil]fenil)sulfonil]benzamida;

[000152] 4-{4-[(*R*)-(4'-clorobifenil-2-il)(hidroxi)metil]piperidin-1-il}-*N*-[(4-{[(*2R*)-4-{(*2S*)-2-[(dietilamino)metil]morfolin-4-il}-1-(fenilsulfanil)butan-2-il]amino}-3-

[(trifluorometil)sulfonil]fenil)sulfonil]benzamida;

[000153] 4-{4-[(*S*)-(4'-clorobifenil-2-il)(hidroxi)metil]piperidin-1-il}-*N*-[(4-{[(*2R*)-4-{(*2R*)-2-[(dietilamino)metil]morfolin-4-il}-1-(fenilsulfanil)butan-2-il]amino}-3-

[(trifluorometil)sulfonil]fenil)sulfonil]benzamida; y

[000154] 4-{4-[(*R*)-(4'-clorobifenil-2-il)(hidroxi)metil]piperidin-1-il}-*N*-[(4-{[(*2R*)-4-{(*2R*)-2-[(dietilamino)metil]morfolin-4-il}-1-(fenilsulfanil)butan-2-il]amino}-3-

[(trifluorometil)sulfonil]fenil)sulfonil]benzamida,

y/o una de sus sales farmacéuticamente aceptables.

[000155] En otro aspecto, se proporciona un compuesto seleccionado entre:

[000156] 4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-(4-(2-hidroxietil)piperazin-1-il)-1-(feniltio)butan-2-ilamino)-3-

(trifluorometilsulfonil)fenilsulfonil]benzamida;

[000157] 4-(4-((*S*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*S*)-4-(2-hidroxietil)(metil)amino)-1-(feniltio)butan-2-ilamino)-3-

(trifluorometilsulfonil)fenilsulfonil]benzamida;

[000158] 4-(4-((*S*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-(2-hidroxietil)(metil)amino)-1-(feniltio)butan-2-ilamino)-3-

(trifluorometilsulfonil)fenilsulfonil]benzamida;

[000159] 4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*S*)-4-(2-hidroxietil)(metil)amino)-1-(feniltio)butan-2-ilamino)-3-

(trifluorometilsulfonil)fenilsulfonil]benzamida;

[000160] 4-(4-((*S*)-4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*S*)-4-(etil(2-hidroxietil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil]benzamida;

[000161] 4-(4-((*S*)-4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-(etil(2-hidroxietil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil]benzamida;

[000162] 4-(4-((*R*)-4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*S*)-4-(etil(2-hidroxietil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil]benzamida;

[000163] *N*-(4-((*R*)-4-(bis(2-hidroxietil)amino)-1-(feniltio)butan-2-ilamino)-3-

(trifluorometilsulfonil)fenilsulfonil)-4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-

il)benzamida;

[000164] 4-(4-((R)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-N-(4-((R)-4-(4-((R)-3-fluoro-2-hidroxipropil)piperazin-1-il)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000165] 4-(4-((R)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-N-(4-((R)-4-(4-((S)-3-fluoro-2-hidroxipropil)piperazin-1-il)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000166] bis(dihidrogenofosfato) de 2,2'-((R)-3-(4-(N-(4-(4-((R)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)-4-(feniltio)butilazanodiil)bis(etano-2,1-diilo);

[000167] dihidrogenofosfato de 2-(((R)-3-(4-(N-(4-(4-((R)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)-4-(feniltio)butil)(etil)amino)etilo;

[000168] dihidrogenofosfato de 2-(((S)-3-(4-(N-(4-(4-((S)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)-4-(feniltio)butil)(etil)amino)etilo;

[000169] dihidrogenofosfato de 2-(((R)-3-(4-(N-(4-(4-((S)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)-4-(feniltio)butil)(etil)amino)etilo;

[000170] dihidrogenofosfato de 2-(((S)-3-(4-(N-(4-(4-((R)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)-4-(feniltio)butil)(etil)amino)etilo;

[000171] dihidrogenofosfato de 2-(((R)-3-(4-(N-(4-(4-((R)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)-4-(feniltio)butil)(metil)amino)etilo;

[000172] dihidrogenofosfato de 2-(((S)-3-(4-(N-(4-(4-((S)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)-4-(feniltio)butil)(metil)amino)etilo;

[000173] dihidrogenofosfato de 2-(((R)-3-(4-(N-(4-(4-((S)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)-4-(feniltio)butil)(metil)amino)etilo;

[000174] dihidrogenofosfato de 2-(((S)-3-(4-(N-(4-(4-((R)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)-4-(feniltio)butil)(metil)amino)etilo;

[000175] 4-(4-((R)-amino(4'-clorobifenil-2-il)metil)piperidin-1-il)-N-(4-((R)-4-((2-

hidroxietil)(metil)amino)-1-(feniltio)butan-2-ilamino)-3-

(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000176] 4-(4-((*R*)-amino(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((*R*)-4-(etil(2-hidroxietil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000177] 4-(4-((*R*)-amino(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((*R*)-4-(4-(2-hidroxietil)piperazin-1-il)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000178] 4-(4-((*R*)-(4'-clorobifenil-2-il)(ciano)metil)piperidin-1-il)-*N*-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000179] 4-(4-((*S*)-(4'-clorobifenil-2-il)(ciano)metil)piperidin-1-il)-*N*-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000180] 4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-((*R*)-2-(hidroximetil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000181] 4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-((*S*)-2-(hidroximetil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000182] 4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-((*R*)-3-(hidroximetil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000183] 4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-((*S*)-3-(hidroximetil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000184] (*R*)-(4'-clorobifenil-2-il)(1-(4-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonilcarbamoil)fenil)piperidin-4-il)metilfosfato de dietilo;

[000185] (*R*)-(4'-clorobifenil-2-il)(1-(4-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonilcarbamoil)fenil)piperidin-4-il)metilhidrogenofosfato de metilo;

[000186] 4-(4-((*R*)-amino(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000187] 4-(4-((*R*)-(4'-clorobifenil-2-il)(2-(metilamino)acetamido)metil)piperidin-1-il)-*N*-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000188] 4-(4-((*R*)-(2-aminoacetamido)(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000189] 4-(4-((*R*)-(4'-clorobifenil-2-il)(dimetilamino)metil)piperidin-1-il)-*N*-(4-((*R*)-4-

morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;
y/o una de sus sales farmacéuticamente aceptables.

[000190] Los ejemplos de compuestos de la presente invención incluyen:

[000191] sal de 4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-(2-hidroxi)etil)piperazin-1-il)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida y el ácido fórmico;

[000192] 4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-(dimetilamino)-1-(feniltio)butan-2-ilamino)-3-nitrofenilsulfonil)benzamida;

[000193] 4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-(2-hidroxi)etil)(metil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000194] 4-(4-((*S*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*S*)-4-(2-hidroxi)etil)(metil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000195] 4-(4-((*S*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-(2-hidroxi)etil)(metil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000196] 4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*S*)-4-(2-hidroxi)etil)(metil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000197] sal de 4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-(2-hidroxi)etil)(metil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida y el ácido fórmico;

[000198] sal de 4-(4-((*S*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*S*)-4-(2-hidroxi)etil)(metil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida y el ácido fórmico;

[000199] sal de 4-(4-((*S*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-(2-hidroxi)etil)(metil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida y el ácido fórmico;

[000200] sal de 4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*S*)-4-(2-hidroxi)etil)(metil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida y el ácido fórmico;

[000201] 4-(4-((*R*)-4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-(etil(2-hidroxi)etil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000202] 4-(4-((*S*)-4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*S*)-4-(etil(2-

hidroxietil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000203] 4-(4-((*S*)-4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-(etil(2-hidroxietil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000204] 4-(4-((*R*)-4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*S*)-4-(etil(2-hidroxietil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000205] sal de 4-(4-((*R*)-4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-(etil(2-hidroxietil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida y el ácido fórmico;

[000206] sal de 4-(4-((*S*)-4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*S*)-4-(etil(2-hidroxietil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida y el ácido fórmico;

[000207] sal de 4-(4-((*S*)-4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-(etil(2-hidroxietil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida y el ácido fórmico;

[000208] sal de 4-(4-((*R*)-4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*S*)-4-(etil(2-hidroxietil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida y el ácido fórmico;

[000209] sal de *N*-(4-((*R*)-4-(bis(2-hidroxietil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)-4-(4-((*R*)-4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzamida y el ácido fórmico;

[000210] sal de 4-(4-((*R*)-4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-(4-((*R*)-3-fluoro-2-hidroxipropil)piperazin-1-il)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida y el ácido fórmico;

[000211] sal de 4-(4-((*R*)-4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-(4-((*R*)-3-fluoro-2-hidroxipropil)piperazin-1-il)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida y el ácido fórmico;

[000212] sal de 4-(4-((*R*)-4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-(4-((*S*)-3-fluoro-2-hidroxipropil)piperazin-1-il)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida y el ácido fórmico, mezcla de diastereómeros;

[000213] 4-(4-((*R*)-4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-(4-((*S*)-3-fluoro-2-hidroxipropil)piperazin-1-il)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000214] sal de 4-(4-((*R*)-amino(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((*R*)-4-(2-hidroxietil)(metil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida y el ácido fórmico;

[000215] sal de 4-(4-((*R*)-amino(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((*R*)-4-(etil(2-hidroxietil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida y el ácido fórmico;

[000216] sal de 4-(4-((*R*)-amino(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((*R*)-4-(4-(2-hidroxietil)piperazin-1-il)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida y el ácido fórmico;

[000217] 4-(4-((*S*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000218] 4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000219] 4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-nitrofenilsulfonil)benzamida;

[000220] 4-(4-((*R*)-(4'-clorobifenil-2-il)(ciano)metil)piperidin-1-il)-*N*-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000221] 4-(4-((*S*)-(4'-clorobifenil-2-il)(ciano)metil)piperidin-1-il)-*N*-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000222] 4-(4-((*R*)-(4'-clorobifenil-2-il)(ciano)metil)piperidin-1-il)-*N*-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000223] 4-(4-((*S*)-(4'-clorobifenil-2-il)(ciano)metil)piperidin-1-il)-*N*-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000224] 4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-((*S*)-3-((dietilamino)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000225] 4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-((*R*)-3-((dietilamino)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000226] sal de 4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-((*R*)-2-(hidroximetil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida y el ácido fórmico;

[000227] sal de 4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-((*S*)-2-(hidroximetil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida y el ácido fórmico;

[000228] sal de 4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-((*R*)-3-(hidroximetil)morfolino)-1-(feniltio)butan-2-ilamino)-3-

(trifluorometilsulfonil)fenilsulfonil)benzamida y el ácido fórmico;

[000229] sal clorhídrica de 4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-((*S*)-3-(hidroximetil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000230] 4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((2*R*)-4-(2*S*)-((dietilamino)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000231] 4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((2*R*)-4-(2*R*)-((dietilamino)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000232] sal de 4-(4-((*R*)-amino(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida y el ácido fórmico;

[000233] sal clorhídrica de 4-(4-((*R*)-(4'-clorobifenil-2-il)(2-(metilamino)acetamido)metil)piperidin-1-il)-*N*-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000234] sal clorhídrica de 4-(4-((*R*)-(2-aminoacetamido)(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida; y

[000235] sal clorhídrica de 4-(4-((*R*)-(4'-clorobifenil-2-il)(dimetilamino)metil)piperidin-1-il)-*N*-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida.

[000236] Los ejemplos de compuestos de la presente invención incluyen:

[000237] sal clorhídrica de bis(dihidrogenofosfato) de 2,2'-((*R*)-3-(4-(*N*-(4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)-4-(feniltio)butilazanodiil)bis(etano-2,1-diilo);

[000238] sal clorhídrica de dihidrogenofosfato de 2-(((*R*)-3-(4-(*N*-(4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)-4-(feniltio)butil)(etil)amino)etilo;

[000239] sal clorhídrica de dihidrogenofosfato de 2-(((*S*)-3-(4-(*N*-(4-(4-((*S*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)-4-(feniltio)butil)(etil)amino)etilo;

[000240] sal clorhídrica de dihidrogenofosfato de 2-(((*R*)-3-(4-(*N*-(4-(4-((*S*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)-4-(feniltio)butil)(etil)amino)etilo;

[000241] sal clorhídrica de dihidrogenofosfato de 2-(((*R*)-3-(4-(*N*-(4-(4-((*S*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)-4-(feniltio)butil)(etil)amino)etilo;

[000242] dihidrogenofosfato de 2-(((*R*)-3-(4-(*N*-(4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)-4-(feniltio)butil)(etil)amino)etilo;

[000243] dihidrogenofosfato de 2-(((*S*)-3-(4-(*N*-(4-(4-((*S*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)-4-(feniltio)butil)(etil)amino)etilo;

[000244] dihidrogenofosfato de 2-(((*R*)-3-(4-(*N*-(4-(4-((*S*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)-4-(feniltio)butil)(etil)amino)etilo;

[000245] dihidrogenofosfato de 2-(((*S*)-3-(4-(*N*-(4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)-4-(feniltio)butil)(etil)amino)etilo;

[000246] sal clorhídrica de dihidrogenofosfato de 2-(((*R*)-3-(4-(*N*-(4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)-4-(feniltio)butil)(metil)amino)etilo;

[000247] sal clorhídrica de dihidrogenofosfato de 2-(((*S*)-3-(4-(*N*-(4-(4-((*S*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)-4-(feniltio)butil)(metil)amino)etilo;

[000248] sal clorhídrica de dihidrogenofosfato de 2-(((*R*)-3-(4-(*N*-(4-(4-((*S*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)-4-(feniltio)butil)(metil)amino)etilo;

[000249] sal clorhídrica de dihidrogenofosfato de 2-(((*S*)-3-(4-(*N*-(4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)-4-(feniltio)butil)(metil)amino)etilo;

[000250] dihidrogenofosfato de 2-(((*R*)-3-(4-(*N*-(4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)-4-(feniltio)butil)(metil)amino)etilo;

[000251] dihidrogenofosfato de 2-(((*S*)-3-(4-(*N*-(4-(4-((*S*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)-4-(feniltio)butil)(metil)amino)etilo;

[000252] dihidrogenofosfato de 2-(((*R*)-3-(4-(*N*-(4-(4-((*S*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)-4-

(feniltio)butil)(metil)amino)etilo;

[000253] dihidrogenofosfato de 2-(((S)-3-(4-(N-(4-(4-((R)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)-4-(feniltio)butil)(metil)amino)etilo;

[000254] dihidrogenofosfato de 2-(4-((R)-3-(4-(N-(4-(4-((R)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)-4-(feniltio)butil)piperazin-1-il)etilo;

[000255] ((R)-(4'-clorobifenil-2-il)(1-(4-(4-((R)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonilcarbamoil)fenil)piperidin-4-il)metoxi)metilfosfato de di-*tert*-butilo;

[000256] ((R)-(4'-clorobifenil-2-il)(1-(4-(4-((R)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonilcarbamoil)fenil)piperidin-4-il)metoxi)metilhidrogenofosfato de *tert*-butilo;

[000257] sal clorhídrica de (R)-(4'-clorobifenil-2-il)(1-(4-(4-((R)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonilcarbamoil)fenil)piperidin-4-il)metilfosfato de dietilo;

[000258] sal clorhídrica de (R)-(4'-clorobifenil-2-il)(1-(4-(4-((R)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonilcarbamoil)fenil)piperidin-4-il)metilhidrogenofosfato de metilo;

[000259] ((R)-(4'-clorobifenil-2-il)(1-(4-(4-((R)-4-((S)-3-((dietilamino)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonilcarbamoil)fenil)piperidin-4-il)metoxi)metilfosfato de di-*tert*-butilo; y

[000260] ((R)-(4'-clorobifenil-2-il)(1-(4-(4-((R)-4-((S)-3-((dietilamino)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonilcarbamoil)fenil)piperidin-4-il)metoxi)metilhidrogenofosfato de *tert*-butilo.

[000261] En otro aspecto, se proporciona un compuesto seleccionado entre:

[000262] 4-(4-((R)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-N-(4-((R)-4-((2-hidroxi)etil)(metil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000263] 4-(4-((R)-4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-N-(4-((R)-4-(etil(2-hidroxi)etil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida;

[000264] dihidrogenofosfato de 2-(((R)-3-(4-(N-(4-(4-((R)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)-4-(feniltio)butil)(etil)amino)etilo; y

[000265] dihidrogenofosfato de 2-(((R)-3-(4-(N-(4-(4-((R)-(4'-clorobifenil-2-

il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)-4-(feniltio)butil)(metil)amino)etilo.

y/o una de sus sales farmacéuticamente aceptables.

[000266] A continuación se exponen ejemplos de compuestos específicos que se describen en la presente en los siguientes EJEMPLOS. Los expertos en la técnica se darán cuenta de que los compuestos descritos en la presente, incluidos los expuesto en los EJEMPLOS, se pueden presentar como una forma libre no salina o como sales.

[000267] Se sobreentenderá que cualquier realización descrita en la presente se puede combinar con otras realizaciones descritas en la presente para proporcionar realizaciones adicionales. Por ejemplo, se pueden combinar valores diferentes del sustituyente R^1 con valores diferentes de los sustituyentes R^2 y R^3 ; se pueden combinar valores diferentes del sustituyente R^2 con valores diferentes de los sustituyentes R^1 y R^3 ; y se pueden combinar valores diferentes del sustituyente R^3 con valores diferentes de los sustituyentes R^1 y R^2 . Como podrá apreciar un experto en la técnica, toda combinación o grupo de sustituyentes se considera incluida en el alcance de la presente invención.

[000268] Los compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e) pueden formar sales de adición de ácido o base, o zwitteriones estables farmacéuticamente aceptables y, en tales casos, la administración de un compuesto en forma de sal o zwitterón puede ser adecuada. Se pueden preparar sales o bases de compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e) durante el aislamiento o después de la purificación de los compuestos. Los compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e) tienen al menos un átomo de nitrógeno protonable y, por lo tanto, pueden formar sales de adición de ácido o base, por ejemplo, de 1 a aproximadamente 3, de aproximadamente 1.1 a aproximadamente 3, de aproximadamente 1.2 a aproximadamente 3, de aproximadamente 1.3 a aproximadamente 3, de aproximadamente 1.4 a aproximadamente 3, de aproximadamente 1.5 a aproximadamente 3, de aproximadamente 1.6 a aproximadamente 3, de aproximadamente 1.7 a aproximadamente 3, de aproximadamente 1.8 a aproximadamente 3, de aproximadamente 1.9 a aproximadamente 3, de aproximadamente 2.0 a aproximadamente 3, de aproximadamente 2.1 a aproximadamente 3, de aproximadamente 2.2 a aproximadamente 3, de aproximadamente 2.3 a aproximadamente 3, de aproximadamente 2.4 a aproximadamente 3, de aproximadamente 2.5 a aproximadamente 3, de aproximadamente 2.6 a aproximadamente 3, de aproximadamente 2.7 a aproximadamente 3, de aproximadamente 2.8 a aproximadamente 3 o de aproximadamente 2.9 a aproximadamente 3 equivalentes de ácido o base por equivalente de compuesto.

[000269] Las sales pueden formarse por medios convencionales, como por ejemplo, haciendo

reaccionar la forma de base libre del producto con uno o más equivalentes del ácido apropiado en un solvente o medio en el que la sal es insoluble o en un solvente, tal como el agua, que se elimina al vacío o mediante liofilización; o intercambiando los aniones de una sal existente por otro anión en una resina adecuada de intercambio iónico.

[000270] Los compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e) son útiles por su capacidad para inhibir la actividad de Bcl-2 y Bcl-X_L. Los compuestos también son útiles para tratar cánceres de todo tipo, como por ejemplo, neuroblastoma, carcinoma intestinal tal como el carcinoma de recto, carcinoma de colon, carcinoma debido a la poliposis adenomatosa familiar y cáncer colorrectal hereditario no relacionado con la poliposis, carcinoma esofágico, carcinoma labial, carcinoma laríngeo, carcinoma hipofaríngeo, carcinoma de lengua, carcinoma de las glándulas salivares, carcinoma gástrico, adenocarcinoma, carcinoma medular tiroideo, carcinoma papilar tiroideo, carcinoma renal, carcinoma del parénquima renal, carcinoma ovárico, carcinoma del cuello uterino, carcinoma del cuerpo uterino, carcinoma del endometrio, carcinoma del corion, carcinoma pancreático, carcinoma de próstata, carcinoma testicular, carcinoma de mama, carcinoma urinario, melanoma, tumores cerebrales tales como el glioblastoma, astrocitoma, meningioma, meduloblastoma y tumores neuroectodérmicos periféricos, linfoma de Hodgkin, linfoma no hodgkiniano, linfoma difuso de linfocitos B grandes (LDLBG), linfoma folicular (LF), linfoma de células del manto (LCM), linfoma de la zona marginal (LZM), leucemia de células peludas (LCP), linfoma periférico de linfocitos T (LPLT), linfoma de Burkitt, leucemia linfática aguda (LLA), leucemia linfocítica crónica (LLC/LLP), leucemia mieloide aguda (AML), leucemia mieloide crónica (LMC), linfoma/leucemia de linfocitos T del adulto, carcinoma hepatocelular, carcinoma de la vesícula biliar, carcinoma bronquial, carcinoma pulmonar microcítico, carcinoma pulmonar no microcítico, mieloma múltiple, basalioma, teratoma, retinoblastoma, melanoma coroideo, seminoma, rabdomiosarcoma, craneofaringeoma, osteosarcoma, condrosarcoma, miosarcoma, liposarcoma, fibrosarcoma, sarcoma de Ewing y plasmocitoma.

[000271] En algunas realizaciones, uno o más compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e) son útiles para tratar el linfoma no hodgkiano. En algunas realizaciones, uno o más compuestos de Fórmula (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e) son útiles para tratar la LLC. En algunas realizaciones, uno o más compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e) son útiles para tratar el carcinoma pulmonar no microcítico (CPNM). En algunas realizaciones, uno o más compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e) son útiles para tratar el linfoma difuso de linfocitos B grandes (LDLBG). En algunas realizaciones, uno o más compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e) son útiles para tratar el cáncer de próstata. (Lista de enfermedades actuales seleccionadas).

[000272] Los compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e) también deberían ser útiles como estándares y reactivos en la determinación de la capacidad de un fármaco potencial para inhibir proteínas que contienen BH-3, particularmente la familia BCL2. Estos se proporcionarían en kits comerciales que comprenderían un compuesto de esta invención.

[000273] Se ha demostrado que los compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e) inhiben las actividades de Bcl-2 y Bcl-X_L en un ensayo basado en la siguiente descripción. Aunque las propiedades farmacológicas de los compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e) pueden variar con cambios estructurales, los compuestos típicos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e) presentan actividades inhibitorias de Bcl-2 y Bcl-X_L en concentraciones CI₅₀ (concentraciones para conseguir un 50% de inhibición) o dosis inferiores a 10 µM.

[000274] Los siguientes ensayos celulares y de unión *in vitro* se pueden utilizar para determinar la actividad y la especificidad de compuestos de la presente invención respecto a la unión a Bcl-2 e inhibición de la función de Bcl-2 en una célula.

A. Ensayos de unión a Bcl-2

[000275] La afinidad por la unión FP de uno o más compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e) a Bcl-x_L y Bcl-2 se puede determinar utilizando varios métodos conocidos. Un tipo de ensayo es un ensayo de unión *in vitro* sensitivo y cuantitativo utilizando polarización de fluorescencia ("FP", por sus siglas en inglés) descrito por Wang, J.-L.; Zhang, Z.-J.; Choksi, S.; Sjam, S.; Lu, Z.; Croce, C. M.; Alnemri, E. S.; Komgold, R.; Huang, Z. Cell permeable Bcl-2 binding peptides: a chemical approach to apoptosis induction in tumor cells. Cancer Res. 2000, 60, 1498-1502).

[000276] Además, la afinidad por la unión de uno o más compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e) a la proteína Bcl-2 *in vitro* se determinó mediante un ensayo de unión competitivo basado en polarización de fluorescencia. Por ejemplo, se pueden llevar a cabo los ensayos de polarización de fluorescencia ("FP") utilizando Bcl-2 marcada en el C terminal con 6XHIS (aa 1-204) y Bcl-X_L marcada en el C terminal con 6XHIS (aa 1-209). El marcador puede ser un péptido sintético BH-3 del péptido Bim conjugado con isotiocianato de fluoresceína (FITC- DLRPEIRIAQELRRIGDEFNETYTRR). Se pueden añadir diluciones de Bcl-2 (1.3 nM) o Bcl-X_L (0.8 nM) a diluciones en serie de antagonista y se pueden incubar durante una hora antes de añadir 2 nM del marcador peptídico fluorescente (Anaspec, Fremont, CA) en el tampón de ensayo. Las condiciones finales del tampón de ensayo pueden ser HEPES 20 mM, pH 7.5, DTT 1 mM, Tween-20 al 0.005% y NaCl 50 mM. Las muestras se pueden leer después de una incubación de 20 minutos. Los valores de la polarización de fluorescencia se puede representar gráficamente como una función de la concentración de antagonista.

[000277] Cuando se analizaron en un ensayo FP en función del ensayo FP descrito anteriormente, la actividad inhibitoria de los siguientes ejemplos se midió para las CI_{50} (μM) que se muestran en la Tabla 1.

TABLA 1

Ejemplo	Ensayo FP de Bcl-X _L CI_{50} (μM)	Ensayo FP de Bcl-2 CI_{50} (μM)
1	0.001	<0.001
2	0.001	0.0003
3	0.001	<0.0003
4	0.0008	0.0005
5	0.001	0.0008
6	0.002	0.001
7	0.001	0.002
8	0.001	0.0009
9	0.001	0.0009
10	0.001	0.0007
11	0.003	0.004
12	0.003	0.003
13	0.015	0.016
14	0.078	0.253
15	0.001	0.003
16	0.001	0.0008
17	0.001	0.002
18	0.002	0.007
19	0.008	1.195
20	0.001	0.0003
21	0.0005	0.0003
22	0.003	0.0006
23	0.001	0.001
24	0.002	0.0004
25	0.002	0.0004
26	0.0005	0.0004

27	SE	SE
28	0.002	0.004
29	0.012	0.03
30	0.001	0.001
31	SE	SE
32	SE	SE
33	0.033	0.03
34	0.019	0.027
35	0.022	0.038
36	0.018	0.024

B. Ensayos basados en células

[000278] Ciertos compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e) se pueden estudiar en ensayos basados en células utilizando líneas celulares dependientes de Bcl-2 y Bcl-X_L para determinar si se induce la apoptosis al tratar las líneas celulares con estos compuestos. Los ejemplos de líneas celulares incluyen la línea celular FDCP-1 transfectada con y que sobreexpresa Bcl-2, y la línea celular FDCP-1 transfectada con y que sobreexpresa Bcl-X_L.

[000279] En esta descripción, el sufijo C_{x-y} tal como se utiliza en los términos alquilo C_{x-y} y similares (en los que x e y son números enteros) indica el rango numérico de átomos de carbono que están presentes en el grupo; por ejemplo, alquilo C₁₋₄ incluye alquilo C₁ (metilo), alquilo C₂ (etilo), alquilo C₃ (propilo e isopropilo) y alquilo C₄ (butilo, 1-metilpropilo, 2-metilpropilo y *t*-butilo).

[000280] Los compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e) tienen centros quirales y, por lo tanto, existen como estereoisómeros. Se sobreentenderá que la invención contempla todos estos estereoisómeros, incluidos los enantiómeros y diastereoisómeros, así como también las mezclas de estos enantiómeros y/o las mezclas de estos diastereoisómeros. Debido a que los compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e) pueden existir como formas racémicas u ópticamente activas, la invención incluye en su definición todas estas formas racémicas u ópticamente activas que poseen la actividad mencionada anteriormente. La presente invención abarca todos estos estereoisómeros que presentan la actividad definida en la presente. En toda esta solicitud, se pretende que, cuando no se indique la configuración absoluta de un centro asimétrico, el nombre del producto de esta invención contemple los estereoisómeros individuales así como también las mezclas de estereoisómeros.

[000281] La síntesis de formas ópticamente activas puede llevarse a cabo mediante técnicas estándares de la química orgánica muy conocidas en la técnica, por ejemplo, mediante síntesis a

partir de materiales de partida ópticamente activos o mediante resolución de una forma racémica. Los racematos se pueden separar en enantiómeros individuales utilizando procedimientos conocidos (remítase, por ejemplo, a *Advanced Organic Chemistry*: 3.^a Edición: autor J. March, p.104-107). Un procedimiento adecuado implica la formación de derivados diastereoméricos por reacción del material racémico con un auxiliar quiral, seguida de la separación, por ejemplo, mediante cromatografía, de los diastereómeros y la eliminación posterior de las especies auxiliares. De forma análoga, la actividad mencionada anteriormente se puede evaluar utilizando las técnicas de laboratorio estándares a las que se hace referencia más adelante en la presente.

[000282] Así pues, en toda la descripción, cuando se hace referencia a compuestos de Fórmulas (I), (I-a) (I-b), (I-c), (I-d) y/o (I-e), se sobreentenderá que el término compuesto incluye estereoisómeros, mezclas de estereoisómeros y polimorfos que inhiben la actividad de Bcl-2 en un ser humano o animal.

[000283] Los estereoisómeros se pueden separar utilizando técnicas convencionales, por ejemplo, cromatografía o cristalización fraccionada. Los enantiómeros se pueden aislar por separación de un racemato, por ejemplo, mediante cristalización fraccionada, resolución o HPLC. Los diastereoisómeros se pueden aislar por separación en virtud de las diferentes propiedades físicas de los diastereoisómeros, por ejemplo, mediante cristalización fraccionada, HPLC o cromatografía flash. Como alternativa, se pueden sintetizar estereoisómeros particulares por síntesis quiral a partir de materiales de partida quirales en condiciones que no provoquen la racemización ni epimerización, o por derivatización con un reactivo quiral.

[000284] Cuando se proporcione un estereoisómero específico (ya sea obtenido mediante separación, síntesis quiral u otros métodos), se proporciona de forma favorable sustancialmente aislado de otros estereoisómeros del mismo compuesto. En un aspecto, una mezcla que contiene un estereoisómero particular de un compuesto de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e) puede contener menos de un 30%, particularmente menos de un 20% y más particularmente menos de un 10% en peso de otro(s) estereoisómero(s) del mismo compuesto. En otro aspecto, la mezcla que contiene un estereoisómero particular de un compuesto de Formulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e) puede contener menos de un 6%, particularmente menos de un 3% y más particularmente menos de un 2% en peso de otro(s) estereoisómero(s) del compuesto. En otro aspecto, una mezcla que contiene un estereoisómero particular de un compuesto de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e) puede contener menos de un 1%, particularmente menos de un 0.5%, más particularmente menos de un 0.3% y aún más particularmente menos de un 0.1% en peso de otro(s) estereoisómero(s) del compuesto.

[000285] Se sobreentenderá que, debido a que ciertos compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e) definidos anteriormente pueden existir en formas tautoméricas, la

invención incluye en su definición cualquiera de estas formas tautoméricas que posea la actividad o actividades mencionadas anteriormente. Por lo tanto, la invención se refiere a todas las formas tautoméricas de compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e) que inhiben las actividades de Bcl-2 y/o Bcl-X_L en un ser humano o animal.

[000286] También se debe sobreentender que ciertos compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e) pueden existir tanto como formas solvatadas como no solvatadas tales como, por ejemplo, formas hidratadas. Se sobreentenderá que la invención abarca todas estas formas solvatadas.

[000287] Además, a menos que se establezca lo contrario, se pretende que las estructuras representadas en la presente incluyan compuestos que difieren únicamente en la presencia de uno o más átomos enriquecidos isotópicamente. Por ejemplo, los compuestos que tienen las presentes estructuras, incluidos el reemplazo de hidrógeno por deuterio o tritio, o el reemplazo de un carbono por un carbono enriquecido en ¹³C o ¹⁴C, quedan incluidos en el alcance de esta invención. Tales compuestos son útiles, por ejemplo, como herramientas analíticas, como sondas en ensayos biológicos o como agentes terapéuticos de acuerdo con la presente invención. En algunas realizaciones, a modo de ejemplo, el grupo R¹ de las Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e) puede comprender uno o más átomos de deuterio. Las mezclas de formas isoméricas se pueden separar y/o purificar mediante técnicas con las que estará familiarizado un experto en este campo incluida, pero sin limitarse a, cromatografía en columna.

[000288] Ciertos compuestos de la presente invención que contienen fosfato se pueden transformar de forma metabólica (tal como por hidrólisis, por ejemplo, con fosfatasas alcalinas) en un compuesto originario correspondiente. Tales compuestos que contienen fosfato están diseñados para mejorar las propiedades con base farmacéutica y/o farmacocinética asociadas con la molécula farmacéutica de partida. Los ejemplos de ventajas de un compuestos que contiene fosfato se centran en sus propiedades físicas, tales como una mejor solubilidad en agua para diversos tipos de administración (p. ej., intravenosa, parenteral, subcutánea, intramuscular, etc.) a pH fisiológico en comparación con el fármaco de partida, o mejora la absorción en el aparato digestivo, o puede mejorar la estabilidad del fármaco durante un almacenamiento prolongado.

V. MÉTODOS

[000289] En un aspecto, se proporciona uno o más compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e), o una de sus sales farmacéuticamente aceptables, para emplear como medicamento.

[000290] En otro aspecto, se proporciona el uso de uno o más compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e), o una de sus sales farmacéuticamente aceptables, en la fabricación

de un medicamento para el tratamiento o la profilaxis de al menos uno de los siguientes: carcinoma, tumores hematopoyéticos de linaje linfoide, tumores hematopoyéticos de linaje mieloide, tumores de origen mesenquimático, melanoma, seminoma, tetratocarcinoma, neuroblastoma y glioma.

[000291] En otro aspecto, se proporciona el uso de uno o más compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e), o una de sus sales farmacéuticamente aceptables, en la fabricación de un medicamento para el tratamiento de al menos uno de los siguientes: cáncer de vejiga, cáncer de mama, cáncer de colon, cáncer ovárico, LMA, linfoma difuso de linfocitos B grandes (LDLBG), LLC; carcinoma pulmonar microcítico (CPM), carcinoma pulmonar no microcítico (CPNM), incluidos los subtipos escamosos y no escamosos, cáncer pancreático, cáncer de próstata, linfoma no hodgkiniano, linfoma folicular (LF), linfoma de células del manto (LCM), linfoma de la zona marginal (LZM), leucemia de células peludas (LCP) y linfoma periférico de linfocitos T (LPLT).

[000292] En algunas realizaciones, uno o más compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e) son útiles para fabricar un medicamento para tratar al menos uno de los siguientes: linfoma no hodgkiniano, LLC, carcinoma pulmonar no microcítico (CPNM), linfoma difuso de linfocitos B grandes (LDLBG) y cáncer de próstata.

[000293] En otro aspecto, se proporciona el uso de uno o más compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e), o una de sus sales farmacéuticamente aceptables, en la fabricación de un medicamento para tratar el cáncer.

[000294] En otro aspecto, se proporciona el uso de uno o más compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e), o una de sus sales farmacéuticamente aceptables, en la fabricación de un medicamento para producir un efecto antiproliferativo y/o proapóptico en un animal de sangre caliente tal como un ser humano.

[000295] En otro aspecto, se proporciona el uso de uno o más compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e), o una de sus sales farmacéuticamente aceptables, en la fabricación de un medicamento para producir un efecto inhibitorio de Bcl-2 y/o Bcl-X_L en un animal de sangre caliente tal como el ser humano.

[000296] En otro aspecto, se proporciona un método para el tratamiento o la profilaxis de al menos uno de los siguientes: carcinoma, tumores hematopoyéticos de linaje linfoide, tumores hematopoyéticos de linaje mieloide, tumores de origen mesenquimático, melanoma, seminoma, tetratocarcinoma, neuroblastoma y glioma, en un animal de sangre caliente tal como el ser humano, comprendiendo dicho método administrar a dicho animal una cantidad eficaz de uno o más compuesto de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e), o una de sus sales farmacéuticamente aceptables.

[000297] En otro aspecto, se proporciona un método para tratar al menos uno de los siguientes: cáncer de vejiga, cáncer de mama, cáncer de colon, cáncer ovárico, LMA, linfoma difuso de linfocitos B grandes (LDLBG), LLC; carcinoma pulmonar microcítico (CPM), carcinoma pulmonar no microcítico (CPNM), incluidos los subtipos escamosos y no escamosos, cáncer pancreático, cáncer de próstata, linfoma no hodgkiniano, linfoma folicular (LF), linfoma de células del manto (LCM), linfoma de la zona marginal (LZM), leucemia de células peludas (LCP) y linfoma periférico de linfocitos T (LPLT) en un animal de sangre caliente tal como el ser humano, comprendiendo dicho método administrar a dicho animal una cantidad eficaz de uno o más compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e), o una de sus sales farmacéuticamente aceptables.

[000298] En algunas realizaciones, uno o más compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e) son útiles para tratar al menos uno de los siguientes: linfoma no hodgkiniano, LLC, carcinoma pulmonar no microcítico (CPNM), linfoma difuso de linfocitos B grandes (LDLBG) y cáncer de próstata.

[000299] En otro aspecto, se proporciona un método para producir un efecto antiproliferativo y/o proapoptótico en un animal de sangre caliente, tal como un ser humano, comprendiendo dicho método administrar a dicho animal una cantidad eficaz de uno o más compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e), o una de sus sales farmacéuticamente aceptables.

[000300] En algunas realizaciones, el efecto antiproliferativo y/o proapoptótico es para tratar el cáncer de vejiga, cáncer de mama, cáncer de colon, cáncer ovárico, LMA, linfoma difuso de linfocitos B grandes (LDLBG), LLC; carcinoma pulmonar microcítico (CPM), carcinoma pulmonar no microcítico (CPNM), incluidos los subtipos escamosos y no escamosos, cáncer pancreático, cáncer de próstata, linfoma no hodgkiniano, linfoma folicular (LF), linfoma de células del manto (LCM), linfoma de la zona marginal (LZM), leucemia de células peludas (LCP) y linfoma periférico de linfocitos T (LPLT).

[000301] En algunas realizaciones, uno o más compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e) presentan un efecto antiproliferativo y/o proapoptótico que es útil para tratar al menos uno de los siguientes: linfoma no hodgkiniano, LLC, carcinoma pulmonar no microcítico (CPNM), linfoma difuso de linfocitos B grandes (LDLBG) y cáncer de próstata.

[000302] En otro aspecto, se proporciona un método para producir un efecto inhibitorio de Bcl-2 y/o Bcl-X_L en un animal de sangre caliente, tal como un ser humano, comprendiendo dicho método administrar a dicho animal una cantidad eficaz de uno o más compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e), o una de sus sales farmacéuticamente aceptables.

[000303] En otro aspecto, se proporciona un método para tratar el cáncer en un animal de sangre caliente, tal como un ser humano, comprendiendo dicho método administrar a dicho

animal una cantidad eficaz de uno o más compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e), o una de sus sales farmacéuticamente aceptables.

[000304] En otro aspecto, se proporciona uno o más compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e), o una de sus sales farmacéuticamente aceptables, para emplear en el tratamiento de al menos uno de los siguientes: carcinoma, tumores hematopoyéticos de linaje linfoide, tumores hematopoyéticos de linaje mieloide, tumores de origen mesenquimático, melanoma, seminoma, tetratocarcinoma, neuroblastoma y glioma.

[000305] En otro aspecto, se proporciona uno o más compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e), o una de sus sales farmacéuticamente aceptables, para emplear en el tratamiento de al menos uno de los siguientes: cáncer de vejiga, cáncer de mama, cáncer de colon, cáncer ovárico, LMA, linfoma difuso de linfocitos B grandes (LDLBG), LLC; carcinoma pulmonar microcítico (CPM), carcinoma pulmonar no microcítico (CPNM), incluidos los subtipos escamosos y no escamosos, cáncer pancreático, cáncer de próstata, linfoma no hodgkiniano, linfoma folicular (LF), linfoma de células del manto (LCM), linfoma de la zona marginal (LZM), leucemia de células peludas (LCP) y linfoma periférico de linfocitos T (LPLT).

[000306] En algunas realizaciones, uno o más compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e) son útiles para tratar al menos uno de los siguientes: linfoma no hodgkiniano, LLC, carcinoma pulmonar no microcítico (CPNM), linfoma difuso de linfocitos B grandes (LDLBG) y cáncer de próstata.

[000307] En otro aspecto más, se proporciona uno o más compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e), o una de sus sales farmacéuticamente aceptables, para emplear en la producción de un efecto antiproliferativo y/o proapoptótico en un animal de sangre caliente tal como un ser humano.

[000308] En algunas realizaciones, el efecto antiproliferativo y/o proapoptótico es para tratar el cáncer de vejiga, cáncer de mama, cáncer de colon, cáncer ovárico, LMA, linfoma difuso de linfocitos B grandes (LDLBG), LLC; carcinoma pulmonar microcítico (CPM), carcinoma pulmonar no microcítico (CPNM), incluidos los subtipos escamosos y no escamosos, cáncer pancreático, cáncer de próstata, linfoma no hodgkiniano, linfoma folicular (LF), linfoma de células del manto (LCM), linfoma de la zona marginal (LZM), leucemia de células peludas (LCP) y linfoma periférico de linfocitos T (LPLT).

[000309] En algunas realizaciones, uno o más compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e) son útiles para producir un efecto antiproliferativo y/o proapoptótico para tratar al menos uno de los siguientes: linfoma no hodgkiniano, LLC, carcinoma pulmonar no microcítico (CPNM), linfoma difuso de linfocitos B grandes (LDLBG) y cáncer de próstata.

[000310] En otro aspecto, se proporciona uno o más compuestos de Fórmulas (I), (I-a), (I-b), (I-

c), (I-d) y/o (I-e), o una de sus sales farmacéuticamente aceptables, para emplear en la producción de un efecto inhibitorio de Bcl-2 y/o Bcl-X_L en un animal de sangre caliente tal como el ser humano.

[000311] En otro aspecto, se proporciona uno o más compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e), o una de sus sales farmacéuticamente aceptables, para emplear en el tratamiento del cáncer en un animal de sangre caliente tal como un ser humano.

VI. COMPOSICIONES Y COMPOSICIONES FARMACÉUTICAS

[000312] En otro aspecto, se proporciona una composición farmacéutica que comprende un compuesto de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e), o una de sus sales farmacéuticamente aceptables, y al menos un portador, diluyente o excipiente farmacéuticamente aceptable.

[000313] Las composiciones de la invención pueden estar en una forma adecuada para uso oral (por ejemplo, en forma de comprimidos, grageas, cápsulas duras o blandas, suspensiones acuosas u oleosas, emulsiones, polvos o gránulos dispersables, jarabes o elixires), para uso tópico (por ejemplo, en forma de cremas, pomadas, geles, o soluciones o suspensiones acuosas u oleosas), para administración por inhalación (por ejemplo, en forma de un polvo finamente dividido o un aerosol líquido), para administración por insuflación (por ejemplo, en forma de un polvo finamente dividido) o para administración parenteral (por ejemplo, en forma de una solución acuosa u oleosa estéril para la dosificación intravenosa, subcutánea, intramuscular o en forma de un supositorio para dosificación rectal). En algunas realizaciones, los compuestos y/o las composiciones de la presente invención se administran por vía intravenosa (I.V.).

[000314] Las composiciones de la presente invención se pueden obtener mediante procedimientos convencionales, utilizando excipientes farmacéuticos convencionales de uso común en la técnica. Así pues, las composiciones destinadas al uso oral pueden contener, por ejemplo, uno o varios agentes colorantes, edulcorantes, saborizantes y/o conservantes.

[000315] Los excipientes farmacéuticamente aceptables apropiados para una formulación en comprimidos incluyen, por ejemplo, diluyentes inertes como lactosa, carbonato de sodio, fosfato de calcio o carbonato de calcio; agentes granulantes y desintegrantes como almidón de maíz o ácido algénico; agentes aglutinantes como almidón; agentes lubricantes como estearato de magnesio, ácido esteárico o talco; agentes conservantes como *p*-hidroxibenzoato de etilo o propilo; y antioxidantes como ácido ascórbico. Las formulaciones en comprimidos pueden estar recubiertas o no, ya sea para modificar su desintegración y la subsiguiente absorción del principio activo dentro del tracto gastrointestinal, o para mejorar su estabilidad y/o apariencia utilizando en ambos casos agentes y procedimientos de recubrimiento convencionales de uso común en la técnica.

[000316] Las composiciones para uso oral pueden presentarse en forma de cápsulas de gelatina dura en las que el principio activo se mezcla con un diluyente inerte sólido, por ejemplo, carbonato de calcio, fosfato de calcio o caolín, o como cápsulas de gelatina blanda en las que el principio activo se mezcla con agua o un aceite, como aceite de maní, parafina líquida o aceite de oliva.

[000317] Las suspensiones acuosas generalmente contienen el principio activo en forma de polvo finamente dividido o en forma de partículas nano- o micronizadas junto con uno o más agentes de suspensión, tales como carboximetilcelulosa de sodio, metilcelulosa, hidroxipropilmetilcelulosa, alginato de sodio, polivinilpirrolidona, goma tragacanto y goma acacia; agentes dispersantes o humectantes tales como lecitina o productos de la condensación de óxido de alquileo con ácidos grasos (por ejemplo, estearato de polioxietileno) o productos de la condensación de óxido de etileno con alcoholes alifáticos de cadena larga, por ejemplo, heptadecaetilenooxicetanol, o productos de la condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y un hexitol tales como monooleato de sorbitol polioxietilenado o productos de la condensación de óxido de etileno con alcoholes alifáticos de cadena larga, por ejemplo, heptadecaetilenooxicetanol, o productos de la condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y un hexitol tales como monooleato de sorbitol polioxietilenado o productos de la condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y anhídridos de hexitol, por ejemplo, monooleato de sorbitán polietilenado. Las suspensiones acuosas también pueden contener uno o más conservantes como *p*-hidroxibenzoato de propilo o etilo; antioxidantes tales como ácido ascórbico; agentes colorantes; agentes saborizantes y/o agentes edulcorantes como sacarosa, sacarina o aspartamo.

[000318] Las suspensiones oleosas pueden formularse por suspensión del principio activo en un aceite vegetal, como aceite de maní, aceite de oliva, aceite de sésamo o aceite de coco, o en un aceite mineral como parafina líquida. Las suspensiones oleosas también pueden contener un agente espesante como cera de abeja, parafina dura o alcohol cetílico. Se pueden agregar agentes edulcorantes, como los mencionados anteriormente, y agentes saborizantes para obtener un preparado oral agradable al paladar. Estas composiciones pueden conservarse agregando un antioxidante como el ácido ascórbico.

[000319] Los polvos y gránulos dispersables adecuados para preparar una suspensión acuosa por adición de agua contienen generalmente el principio activo junto con un agente dispersante o humectante, un agente de suspensión y uno o más conservantes. Los agentes dispersantes o humectantes y agentes de suspensión adecuados quedan ejemplificados por los mencionados anteriormente. También pueden estar presentes excipientes adicionales como agentes edulcorantes, saborizantes y colorantes.

[000320] Las composiciones farmacéuticas de la invención también pueden estar en forma de emulsiones de aceite en agua. La fase oleosa puede ser un aceite vegetal, como aceite de oliva o aceite de maní, o un aceite mineral, como por ejemplo, parafina líquida, o una mezcla de cualquiera de estos. Los agentes emulsionantes adecuados son, por ejemplo, gomas naturales como goma arábiga o goma de tragacanto, fosfátidos naturales como soja, lecitina, ésteres o ésteres parciales derivados de ácidos grasos y anhídridos de hexitol (por ejemplo, monooleato de sorbitán), y productos de la condensación de dichos ésteres parciales con un óxido de etileno como monooleato de sorbitán polioxietilenado. Las emulsiones también pueden contener agentes edulcorantes, saborizantes y conservantes.

[000321] Los jarabes y elixires pueden formularse con edulcorantes como glicerol, propilenglicol, sorbitol, aspartamo o sacarosa, y también pueden contener un demulcente, conservante, saborizante y/o colorante.

[000322] Las composiciones farmacéuticas también pueden estar en forma de una suspensión oleosa o acuosa inyectable estéril, que puede formularse de acuerdo con los procedimientos conocidos, utilizando uno o más de los agentes dispersantes o humectantes y agentes de suspensión adecuados mencionados anteriormente. Una preparación inyectable estéril también puede ser una solución o suspensión inyectable estéril en un solvente o diluyente atóxico parenteralmente aceptable, por ejemplo, una solución en 1,3-butanodiol.

[000323] Las composiciones para la administración por inhalación pueden presentarse en forma de un aerosol presurizado convencional diseñado para dispensar el principio activo, ya sea como un aerosol que contiene un sólido finamente dividido o como microgotas líquidas. Se pueden emplear propelentes para aerosoles convencionales como hidrocarburos fluorados o hidrocarburos volátiles y el dispositivo de aerosol puede diseñarse convenientemente para dispensar una cantidad controlada de principio activo.

[000324] Para obtener más información sobre la formulación, se remite al lector al Capítulo 25.2 del Volumen 5 de Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

[000325] La cantidad de principio activo que se combina con uno o más excipientes para producir una única forma farmacéutica variará necesariamente según el huésped tratado y la vía de administración particular. Por ejemplo, una formulación preparada para la administración a humanos por vía oral contendrá generalmente, por ejemplo, de 0.5 mg a 4 g de principio activo y estará compuesta por una cantidad apropiada y conveniente de excipientes que puede variar desde aproximadamente un 5 hasta aproximadamente un 98 por ciento en peso de la composición total. Las formas de dosificación unitaria generalmente contendrán aproximadamente de 1 mg a aproximadamente 500 mg de un principio activo. Para consultar información adicional sobre las

vías de administración y regímenes de dosificación, se remite al lector al Capítulo 25.3 del Volumen 5 de Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

[000326] Como se indicó anteriormente, el tamaño de dosis requerido para el tratamiento terapéutico o profiláctico de una patología particular variará necesariamente según el huésped tratado, la vía de administración y la gravedad de la enfermedad objeto de tratamiento. Se puede emplear una dosis diaria en el intervalo de 0.1-50 mg/kg. Por lo tanto, el médico que esté tratando a un paciente particular podrá determinar la dosis óptima.

VII. COMBINACIONES

[000327] El tratamiento contra el cáncer definido precedentemente se puede aplicar como una monoterapia o puede incluir, además del compuesto de la invención, cirugía convencional, radioterapia o quimioterapia. Dicha quimioterapia puede incluir una o más de las siguientes categorías de agentes antitumorales:

(i) otros fármacos antiproliferativos/antineoplásticos y sus combinaciones, tal como se emplean en la oncología médica, tales como agentes alquilantes (por ejemplo, cisplatino, oxaliplatino, carboplatino, ciclofosfamida, mostaza nitrogenada, melfalán, clorambucil, bendamustina, busulfán, temozolamida y nitrosoureas); antimetabolitos (por ejemplo, gemcitabina, capecitabina y antifolatos tales como fluoropirimidinas como 5-fluorouracilo y tegafur, raltitrexed, metotrexato, arabinósido de citosina e hidroxiaurea); antibióticos antitumorales (por ejemplo, antraciclinas tales como adriamicina, bleomicina, doxorubicina, daunomicina, epirubicina, idarubicina, mitomicina-C, dactinomicina y mitramicina); agentes antimitóticos (por ejemplo, alcaloides de la vinca como vincristina, vinblastina, vindesina y vinorelbina; y taxoides como taxol y taxotere; e inhibidores de polo cinasas o proteínas cinesinas motoras); e inhibidores de topoisomerasas (por ejemplo, epipodofilotoxinas como etopósido y tenipósido, amsacrina, topotecán, camptotecina, pixantrona e irinotecán); inhibidores de mecanismo de reparación del ADN tales como, pero sin limitarse a, CHK cinasa, inhibidores de proteínas cinasas dependientes del ADN e inhibidores de poli (ADP-ribosa) polimerasa (inhibidores de PARP), ATM o ATR; e inhibidores de Hsp90 tales como tanespamicina y retaspimicina. Compuestos que inhiben el avance del ciclo celular tales como agentes antimitóticos (por ejemplo, y sin limitarse a, alcaloides de la vinca como vincristina, vinblastina, vindesina y vinorelbina; epotilonas tales como ixabepilona; y taxoides como taxol y taxotere; inhibidores de cinasas semejantes a polo; e inhibidores de proteínas cinesinas motoras como los inhibidores de la proteína Eg5); inhibidores de aurora cinasas (por ejemplo, pero sin limitarse a, AZD1152, PH739358, VX-680, MLN8054, R763, MP235, MP529, VX-528 y AX39459) e

inhibidores de cinasas dependientes de ciclina tales como inhibidores de CDK2 y/o CDK4 (por ejemplo, flavopiridol/Alvocidib, roscovitina, seliciclib); inhibidores de la función de las proteínas centroméricas tales como inhibidores de CENP-E.

(ii) agentes citostáticos como antiestrógenos (por ejemplo, tamoxifeno, fulvestrant, toremifeno, raloxifeno, droloxifeno e iodoxifeno), antiandrógenos (por ejemplo, bicalutamida, flutamida, nilutamida y acetato de ciproterona), antagonistas de LHRH o agonistas de LHRH (por ejemplo, goserelina, leuprorelina y buserelina), progestágenos (por ejemplo, acetato de megestrol), inhibidores de la aromatasas (por ejemplo, como anastrozol, letrozol, vorazol y exemestano); inhibidores de la 5*-reductasa tales como finasteride; e inhibidores de CYP17A1 tales como acetato de abiraterona;

(iii) agentes antiinvasión [por ejemplo, inhibidores de la familia de cinasas c-Src como 4-(6-cloro-2,3-metilenodioxianilino)-7-[2-(4-metilpiperazin-1-il)etoxi]-5-tetrahidropiran-4-iloxiquinazolina (AZD0530; Solicitud de Patente Internacional WO 01/94341), *N*-(2-cloro-6-metilfenil)-2-{6-[4-(2-hidroxietyl)piperazin-1-il]-2-metilpirimidin-4-ilamino}tiazol-5-carboxamida (dasatinib, BMS-354825; J. Med. Chem., 2004, 47, 6658-6661) y bosutinib (SKI-606), e inhibidores de metaloproteinasas como marimastat, inhibidores de la función del receptor activador del plasminógeno tipo uroquinasa o anticuerpos de heparanasa, inhibidores de FAK o cinasas de adhesión focal, inhibidores o anticuerpos del receptor cinasa MET o el factor de crecimiento hepatocítico del ligando de MET;

(iv) inhibidores de la función del factor de crecimiento: por ejemplo, tales inhibidores incluyen anticuerpos del factor de crecimiento, anticuerpos del receptor del factor de crecimiento (por ejemplo, el anticuerpo anti-erbB2 trastuzumab [Herceptin™], el anticuerpo anti-EGFR panitumumab, el anticuerpo anti-erbB1 cetuximab [Erbix, C225] y cualquiera de los anticuerpos del factor de crecimiento o del receptor del factor de crecimiento descritos por Stern *et al.* en Critical reviews in oncology/haematology, 2005, Vol. 54, págs. 11-29); dichos inhibidores también incluyen los inhibidores de tirosina cinasas, por ejemplo, inhibidores de la familia del factor de crecimiento epidérmico (por ejemplo, inhibidores de la familia de tirosina cinasas EGFR como *N*-(3-cloro-4-fluorofenil)-7-metoxi-6-(3-morfolinopropoxi)quinazolin-4-amina (gefitinib, ZD1839), *N*-(3-etinilfenil)-6,7-bis(2-metoxietoxi)quinazolin-4-amina (erlotinib, OSI 774) y 6-acrilamido-*N*-(3-cloro-4-fluorofenil)-7-(3-morfolinopropoxi)quinazolin-4-amina (CI 1033), inhibidores de la tirosina cinasa erbB2 como lapatinib); inhibidores de la familia del factor de crecimiento hepatocítico; inhibidores de la familia del factor de crecimiento insulinoide; inhibidores de la familia del factor de crecimiento derivado de plaquetas tales como imatinib y/o nilotinib (AMN107); inhibidores de tirosina cinasas del bazo (SYK) tales como fostamatinib disódico (R788/R406), PRT062607; inhibidores de serina/treonina cinasas (por ejemplo,

inhibidores de la señalización Ras/Raf como inhibidores de la farnesil transferasa, por ejemplo, sorafenib (BAY 43-9006), tipifarnib (R75777) y lonafarnib (SCH66336)), inhibidores de la señalización celular a través de cinasas MEK y/o AKT, inhibidores de c-kit, inhibidores de la cinasa abl, inhibidores de la cinasa PI3, inhibidores de la cinasa Flt3, inhibidores de la cinasa CSF-1R, inhibidores del receptor cinasa IGF (factor de crecimiento insulinoide); inhibidores de aurora cinasas (por ejemplo, AZD1152, PH739358, VX-680, MLN8054, R763, MP235, MP529, VX-528 y AX39459) e inhibidores de las cinasas dependientes de ciclina tales como inhibidores de CDK2 y/o de CDK4; e inhibidores de la señalización de JAK/STAT tales como inhibidores de Pim cinasas e inhibidores de Jak 1 y 2 cinasas (por ejemplo, pero sin limitarse a, AZD1480, Ruxolitinib);

(v) agentes antiangiogénicos tales como los que inhiben los efectos del factor de crecimiento endotelial vascular [por ejemplo, el anticuerpo del factor del crecimiento celular endotelial antivascular bevacizumab [Avastin™], por ejemplo, un inhibidor del receptor tirosina quinasa del VEGF tal como vandetanib (ZD6474), vatalanib (PTK787), sunitinib (SU11248), axitinib (AG-013736), pazopanib (GW 786034) y 4-(4-fluoro-2-metilindol-5-iloxi)-6-metoxi-7-(3-pirrolidin-1-ilpropoxi)quinazolina (AZD2171; Ejemplo 240 en WO 00/47212), compuestos tales como los descritos en las Solicitudes de Patente Internacional WO97/22596, WO 97/30035, WO 97/32856 y WO 98/13354 y compuestos que trabajan mediante otros mecanismos (por ejemplo linomida, inhibidores de la función integrina $\alpha v \beta 3$ y angiostatina)];

(vi) agentes perjudiciales vasculares como combretastatina A4 y compuestos divulgados en las Solicitudes Internacionales de Patente WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 y WO 02/08213; e inhibidores de angiopoyetinas o sus receptores (Tie-1 y Tie-2);

(vii) un antagonista del receptor de endotelina, por ejemplo zibotentán (ZD4054) o atrasentán;

(viii) terapias antisentido, por ejemplo, las que tienen como blanco de acción los indicados anteriormente, tales como ISIS 2503, un agente antisentido anti-ras; o oblimersen sódico, un agente antisentido anti-Bcl-2;

(ix) tratamientos genotéricos incluidos, por ejemplo, los tratamientos para remplazar genes aberrantes, tales como p53 aberrante o BRCA1 o BRCA2 aberrantes, tratamientos GDEPT (terapia con profármacos activados enzimáticamente dirigida por genes) como los que emplean citosina desaminasa, timidina cinasa o una enzima nitroreductasa bacteriana, y tratamientos que aumentan la tolerabilidad del paciente a la quimioterapia o la radioterapia como la genoterapia de multirresistencia;

- (x) tratamientos inmunoterápicos incluidos, por ejemplo, tratamientos *ex- vivo* e *in- vivo* para aumentar la inmunogenicidad de las células tumorales del paciente, como la transfección con citocinas tales como la interleucina 2, interleucina 4 o el factor de estimulación de colonias de granulocitos y macrófagos, tratamientos para disminuir la anergia de los linfocitos T, tratamientos que emplean células inmunitarias transfectadas tales como células dendríticas transfectadas con citocinas, tratamientos que emplean líneas celulares tumorales transfectadas con citocinas, tratamientos que emplean anticuerpos anti-idiotípicos, tratamientos para aumentar el número de linfocitos T incluidos anticuerpos CTLA4 y anticuerpos contra CD137, PD-1 o B7-H1, agonistas de receptores toll; anticuerpos agonistas de CD40 tales como SGN-40 (Dacetuzumab) o del receptor de Tweak tales como PDL-192; anticuerpos agonistas de FAS; tratamientos que utilizan anticuerpos de antígenos asociados con tumores y anticuerpos que provocan la depleción de tipos de células diana (p. ej., anticuerpos anti-CD20 no conjugados como Rituximab, ofatumumab, Obinutuzumab, anticuerpos anti-CD19 como MEDI-551, anticuerpos anti-CD52 como Alemtuzumab, anticuerpos anti-CD37 como TRU-016, anticuerpos anti-CD22 como Inotuzumab, anticuerpos anti-CD20 radiomarcados Bexxar y Zevalin, y el anticuerpo anti-CD54 Campath; inmunotoxinas tales como moxetumumab pasudotox), tratamientos que utilizan anticuerpos anti-idiotípicos, tratamientos que aumentan la función de los linfocitos citolíticos y tratamientos que utilizan conjugados de anticuerpo-toxina (p. ej., el anticuerpo anti-CD33 Mylotarg). Modificadores inmunitarios como Revlimid (Lenalidomida);
- (xi) tratamientos proapoptóticos incluidos anticuerpos del receptor de muerte celular 4 o del receptor de muerte celular 5, anticuerpos que se unen tanto al receptor de muerte celular 4 como al receptor de muerte celular 5; miméticos de SMAC o compuestos que inhiben las interacciones proteína-proteína del inhibidor de proteínas de la apoptosis tales como cIAP-1, cIAP-2 y XIAP; moléculas de ARN antisentido o pequeño interferente de cIAP-1, cIAP-2, XIAP o supervivientes;
- (xii) tratamiento con citocinas incluidos el factor de necrosis tumoral alfa y la proteína Trail recombinante o miméticos proteicos o de molécula pequeña de la proteína Trail; ligandos FAS o Tweak, o miméticos de estos ligandos;
- (xiii) potenciadores de la eficacia tales como leucovorina;
- (xiv) radiación; dicha radioterapia puede incluir una o más de las siguientes categorías o radiaciones:
- (a) radioterapia externa con radiación electromagnética y radioterapia intraoperativa con radiación electromagnética;
 - (b) radioterapia interna o braquiterapia; incluidas la radioterapia intersticial o la radioterapia intraluminal; y/o

- (c) radioterapia sistémica incluidos, pero sin limitarse a, yodo 131 y estroncio 89;
- (xv) inhibidores de la señalización de los receptores de antígeno incluidos los inhibidores de tirosina cinasas del bazo (Syk) como fostamatinib (R788/R406), PRT062607, inhibidores de la tirosina cinasa de Bruton (Btk) tales como PCI-32765, AVL-292, inhibidores de proteína cinasa C tales como sotrastaurina, inhibidores de IKK/NFkB, inhibidores de la PI3 cinasa como CAL-101 (GS 1101), Enzastaurina, AZD8186, inhibidores de la PI3 cinasa como CAL-101 (GS 1101), Enzastaurina, AZD8186, inhibidores de BCL6; y
- (xvi) reguladores del tráfico/la migración de células hematopoyéticas incluidos agentes que tienen como blanco de acción CXCR4 tales como Plerixafor (rINN y USAN, también conocido como MOZOBIL, JM 3100 y AMD3100), BKT140, inhibidores de Syk tales como fostamatinib, agentes que tienen como blanco de acción VLA-4 y agentes que tienen como blanco de acción CD44; y
- (xvii) inhibidores de la degradación proteica mediada por proteasomas incluidos, pero sin limitarse a, inhibidores de proteasomas tales como VelcadeTM (bortezomib), carfilzomib, inhibidores de ubiquitina ligasas e inhibidores de ubiquitina proteasas, inhibidores de la modificación proteica por Nedd-8, inhibidores de la sumolización proteica.

[000328] Dicho tratamiento conjunto se puede conseguir con dosis simultáneas, secuenciales o separadas de los componentes individuales del tratamiento. Tales productos de combinación emplean compuestos de esta invención, o sus sales farmacéuticamente aceptables, dentro del intervalo de dosis descrito anteriormente en la presente y el otro agente farmacéuticamente activo dentro de su intervalo de dosis autorizado.

[000329] Además de su uso en medicina terapéutica, los compuestos de Fórmulas (I), (I-a), (I-b), (I-c), (I-d) y/o (I-e) y sus sales farmacéuticamente aceptables también son útiles como herramientas farmacológicas en el desarrollo y la normalización de sistemas de prueba *in vitro* e *in vivo* para evaluar los efectos de los inhibidores de Bcl-2 y/o Bcl-X_L en animales de laboratorio, tales como gatos, perros, conejos, monos, ratas y ratones, como parte de la búsqueda de nuevos agentes terapéuticos.

[000330] En cualquiera de las composiciones farmacéuticas, procesos, métodos, usos, medicamentos y peculiaridades de fabricación de la presente invención anteriormente mencionados, también se aplican cualquiera de las realizaciones alternativas de compuestos de la presente invención descritas en la presente.

EJEMPLOS

[000331] A continuación, la invención se describirá además mediante los siguientes ejemplos ilustrativos, en los que, a menos que se indique lo contrario:

- (i) las temperaturas se presentan en grados Celsius (°C); las operaciones se llevaron a cabo a temperatura ambiente, es decir, en el rango de 18-25 °C;
- (ii) las soluciones orgánicas se secaron con sulfato de magnesio anhidro, a menos que se indique lo contrario; la evaporación de solvente orgánico se llevó a cabo usando un evaporador rotatorio a presión reducida (4.5 – 30 mmHg) con una temperatura del baño de hasta 60 °C;
- (iii) cromatografía en columna quiere decir cromatografía flash en gel de sílice; la cromatografía en capa fina (TLC) se llevó a cabo en placas de gel de sílice;
- (iv) en general, las reacciones se monitorizaron por TLC o cromatografía líquida/espectroscopía de masas (LC/MS) y los tiempos de reacción se proporcionan a modo meramente ilustrativo;
- (v) los productos finales presentan resultados satisfactorios para los espectros de resonancia magnética nuclear protónica (RMN) y/o espectros de masas;
- (vi) los rendimientos se dan a título meramente ilustrativo y no son necesariamente los que se pueden obtener mediante el desarrollo de procesos diligentes; las preparaciones se repitieron si se requería más material;
- (vii) los datos de RMN, si se presentan, se presentan en forma de valores delta para los protones diagnósticos principales, dados en partes por millón (ppm) respecto a un patrón interno de tetrametilsilano (TMS);
- (viii) los símbolos químicos gozan de su significado habitual;
- (ix) en el caso en que la nomenclatura asignada a un compuesto determinado no se corresponda con la estructura representada para el compuesto en la presente, la estructura gozará de prioridad;
- (x) las proporciones de solventes se proporcionan en términos de volumen:volumen (v/v);
- (xi) “ISCO” se refiere a la cromatografía flash en columna en fase normal utilizando cartuchos de gel de sílice preempaquetada (12 g, 40 g, etc.) empleados de acuerdo con las instrucciones del fabricante y adquiridos de ISCO, Inc, 4700 Superior Street Lincoln, NE, EE. UU.;
- (xii) una “columna Gilson” se refiere a una columna de HPLC YMC-AQC18 de fase inversa con las siguientes dimensiones: 20 mm/100 y 50 mm/250, en H₂O/MeCN con un 0.1% de TFA como fase móvil, a menos que se establezca lo contrario, empleada de acuerdo con las instrucciones del fabricante y adquirida de Gilson, Inc. 3000 Parmenter Street, Middleton, WI 53562-0027, EE. UU.; o una columna de HPLC Atlantis T3 de fase inversa (Waters Corp., 34 Maple St., Milford, MA 01757, EE. UU.) con las siguientes dimensiones: 20 mm/100 y 50 mm/250, en H₂O/MeCN con un 0.1% de TFA como fase

móvil a menos que se establezca lo contrario. Ambas columnas se utilizaron con un equipo de HPLC preparativa (cromatografía líquida de alta resolución) adquirido de Gilson, Inc. 3000 Parmenter Street, Middleton, WI 53562-0027, EE. UU., de acuerdo con las instrucciones del fabricante;

- (xiii) “SFC (cromatografía de fluidos supercríticos)” se refiere a un sistema de SFC analítica (sistema de SFC analítica ASC-1000 con un detector de haz de diodos o sistema de SFC analítica/MS AMS-1000 con detección de haz de diodos y espectrómetro de masas) y/o SFC preparativa (APS-1000 SFC preparativa AutoPrep o SFC MultiGram III), utilizado con dióxido de carbono, de acuerdo con las instrucciones del fabricante, adquirido de Waters Corp., 34 Maple Street, Milford, MA 01757, EE. UU.;
- (xiv) se utilizan columnas Chiralpak® (p. ej., del tipo “IA”, “IB” y/o “IC”), de acuerdo con las instrucciones del fabricante, adquiridas de Chiral Technologies, Inc. 800 North Five Points Road West Chester, PA19380, EE. UU.;
- (xv) exceso enantiomérico para cada enantiómero individual (e.e.): > % calculado utilizando el porcentaje de área a 220 nm o 254 nm a menos que se establezca lo contrario;
- (xvi) exceso diastereomérico para cada enantiómero individual (e.d.): > % calculado utilizando el porcentaje de área a 220 nm o 254 nm a menos que se establezca lo contrario;
- (xvii) la rotación o las rotaciones $[\alpha]$ específicas se calcularon sobre la base de la siguiente ecuación: $[\alpha] = (100 \cdot \alpha) / (l \cdot c)$, α es la rotación observada, l es el paso óptico y c es la concentración del compuesto;
- (xviii) las rotaciones ópticas observadas se midieron utilizando un polarímetro PerkinElmer, modelo 341, adquirido de PerkinElmer, 940 Winter Street, Waltham, MA 02451, EE. UU.;
- (xix) los espectros de FT-IR (espectroscopía infrarroja por transformada de Fourier) se midieron utilizando un FTIR Nicolet Magna 560 (Thermo Fisher Scientific 81 Wyman Street, Waltham, MA 02454, EE. UU.) dotado de un montaje de ATR Harrick SplitPea™ de 32 barridos, $4000\text{--}600\text{ cm}^{-1}$; la muestra se aplicó directamente sobre la superficie del ATR, el valor del ruido de fondo se registró antes de empezar a analizar la muestra y posteriormente se sustrajo el valor del ruido de fondo del valor de la muestra;
- (xx) los espectros de masas se adquirieron cuando las muestras se separaron utilizando cromatografía líquida en fase inversa (LC) y se detectaron mediante espectrometría de masas (MS) con ionización por electronebulización (ESI) en modo de ión positivo y negativo; se presentan los valores de m/z ; generalmente, solo se presentan los iones

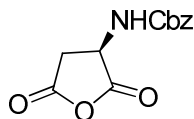
correspondientes a la masa original; y a menos que se establezca lo contrario, la masa iónica presentada es $(M+H)^+$ o $(M-H)^+$; y

(xxi) Se han empleado las siguientes abreviaturas:

Cbz	benciloxycarbonilo;
DCM	diclorometano;
DCE	1,2-dicloroetano;
HPLC	cromatografía líquida de alta resolución;
DIPEA	<i>N, N</i> -diisopropiletilamina;
DMF	<i>N,N</i> -dimetilformamida;
EDC	clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida;
HOBt	1-hidroxibenzotriazol hidratado;
THF	tetrahidrofurano;
DMAP	4-dimetilaminopiridina;
DMSO	sulfóxido de dimetilo;
EtOAc	acetato de etilo;
Et ₂ O	éter dietílico;
TA	temperatura ambiente;
d/n	durante toda la noche;
h	hora(s);
min	minuto(s);
DMA	<i>N,N</i> -dimetilacetamida;
TEA	triethylamina;
TASF	difluorotrimetilsilicato de tris(dimetilamino)sulfonio; y
HATU	hexafluorofosfato de 2-(7-aza-1 <i>H</i> -benzotriazol-1-il)-1,1,3,3-tetrametiluronio

INTERMEDIO 1

[000332] (*R*)-2,5-dioxotetrahidrofuran-3-ilcarbamato de bencilo



[000333] Una mezcla del ácido (*R*)-2-(benciloxycarbonilamino)succínico (Aldrich, 30 g, 112.26 mmol) y anhídrido acético (65.7 ml, 696.02 mmol) se agitó durante la noche a temperatura ambiente; durante este tiempo la mezcla de reacción se volvió transparente. Los componentes volátiles se eliminaron a presión reducida (temperatura del baño de agua 65 °C), se añadió

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tolueno (3 x 50 ml) al concentrado para formar un azeótropo y se obtuvo el producto del título después de secar ~48 horas a 60 °C al alto vacío (28.0 g, rendimiento: casi cuantitativo).

[000334] ^1H RMN (400 MHz, DMSO- d_6) δ ppm 2.94 (dd, 1 H) 3.28 (dd, 1 H) 4.61 - 4.82 (m, 1 H) 5.08 (s, 2 H) 7.21 - 7.51 (m, 5 H) 8.16 (d, 1 H)

[000335] Rotación óptica:

Concentración: 0.14 g/dl

Lámpara: Sodio

Longitud de onda: 589 nm

Temperatura: 20 °C

Paso óptico: 10 cm

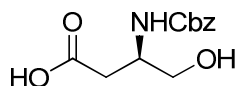
Volumen de la celda: 1 ml

Solvente: CH_2Cl_2

$[\alpha] = +13$

INTERMEDIO 2

[000336] Ácido (*R*)-3-(benciloxycarbonilamino)-4-hidroxibutanoico



[000337] Una solución de (*R*)-2,5-dioxotetrahydrofuran-3-ilcarbamato de bencilo (INTERMEDIO 1, 53.28 g, 213.79 mmol) en THF (330 ml) se añadió en un periodo de 4 horas utilizando un embudo de adición a una mezcla de borohidruro sódico (8.09 g, 213.79 mmol) en THF (330 ml) a 0 °C. Una vez finalizada la adición, la mezcla se calentó hasta temperatura ambiente y se agitó durante 2 horas. La solución se concentró posteriormente a presión reducida hasta 1/4 del volumen original, se enfrió hasta 0 °C y se detuvo cuidadosamente añadiendo agua (400 ml) lentamente. La mezcla se acidificó hasta pH 4 con ácido clorhídrico acuoso 1N y se extrajo con Et_2O (5 x 300 ml). Las capas orgánicas combinadas se secaron (Na_2SO_4) y se concentraron al vacío para proporcionar el producto del título (45.9 g, rendimiento: 85%).

[000338] ^1H RMN (300 MHz, METANOL- d_4) δ ppm 2.41 - 2.54 (m, 1 H) 2.56 - 2.70 (m, 1 H) 3.33 (dt, 2 H) 3.42 - 3.65 (m, 2 H) 3.95 - 4.12 (m, 1 H) 5.01 - 5.22 (m, 2 H) 7.14 - 7.46 (m, 5 H).

[000339] LCMS: (ESI) m/z 254.1 $[\text{M}+\text{H}]^+$.

[000340] Rotación óptica:

Concentración: 0.14 g/dl

Lámpara: Sodio

Longitud de onda: 589 nm

Temperatura: 20 °C

104020-1 US/O

Paso óptico: 10 cm

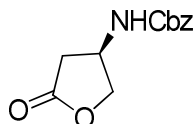
Volumen de la celda: 1 ml

Solvente: CH₂Cl₂

[α]= +13

INTERMEDIO 3

[000341] (*R*)-5-oxotetrahidrofuran-3-ilcarbamato de bencilo



[000342] Se disolvió el ácido (*R*)-3-(benciloxycarbonilamino)-4-hidroxi-butanoico (INTERMEDIO 2, 27.7 g, 109.38 mmol) en tolueno (648 ml). Se añadió el ácido *p*-toluenosulfónico (367 mg, 2.13 mmol) a la solución y la mezcla resultante se calentó a reflujo en las condiciones de Dean-Stark durante 3 horas. La mezcla de reacción se enfrió hasta temperatura ambiente y se concentró al vacío. Se añadió éter dietílico (200 ml) y se observó formación de cristales en reposo. Los cristales se filtraron al vacío. Las aguas madres se concentraron al vacío y se añadió más éter dietílico (40 ml). Se formaron más cristales que se filtraron al vacío. Ambos lotes de cristales se combinaron para proporcionar el producto del título (22.8 g, rendimiento: 83%).

[000343] ¹H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 2.49 (dd, 1 H) 2.76 - 2.94 (m, 1 H) 4.24 (d, 1 H) 4.42 - 4.61 (m, 2 H) 5.03 - 5.24 (m, 3 H) 7.27 - 7.46 (m, 5 H).

[000344] LCMS: (ESI) *m/z* 234 [M-H]⁺.

[000345] Rotación óptica:

Concentración: 0.155 g/dl

Lámpara: Sodio

Longitud de onda: 589 nm

Temperatura: 20 °C

Paso óptico: 10 cm

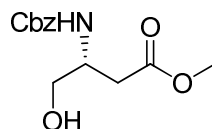
Volumen de la celda: 1 ml

Solvente: CH₂Cl₂

[α]= +46

INTERMEDIO 4

[000346] (*R*)-3-(Benciloxycarbonilamino)-4-hidroxi-butanoato de metilo

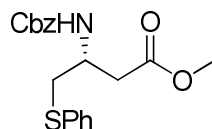


[000347] Se disolvió (*R*)-5-oxotetrahidrofuran-3-ilcarbamato de bencilo (INTERMEDIO 3, 27.0 g, 114.78 mmol) en metanol (75 ml) y se añadió trietilamina (75 ml) a temperatura ambiente. La mezcla resultante se dejó agitar durante toda la noche a esta temperatura. La mezcla se concentró al vacío para proporcionar el producto del título. Este material se utilizó para preparar el INTERMEDIO 5 sin purificación posterior.

[000348] ^1H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 2.67 (d, 2 H) 3.60 - 3.72 (m, 3 H) 3.70 - 3.78 (m, 1 H) 4.00 - 4.15 (m, 2 H) 5.03 - 5.18 (m, 2 H) 5.52 (s a, 1 H) 7.28 - 7.42 (m, 5 H).

INTERMEDIO 5

[000349] (*R*)-3-(Benciloxycarbonilamino)-4-(feniltio)butanoato de metilo

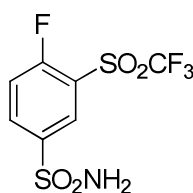


[000350] A una solución de bencenotiol (11.16 ml, 108.65 mmol) se añadieron (*R*)-3-(benciloxycarbonilamino)-4-hidroxibutanoato de metilo (INTERMEDIO 4, 26.4 g, 98.77 mmol) y tributilfosfina (34.5 ml, 138.28 mmol) en THF anhidro (350 ml) en atmósfera de nitrógeno. Se añadió una solución de (*E*)-diazeno-1,2-diilbis(piperidin-1-ilmetanona) (34.9 g, 138.22 mmol) en THF anhidro (350 ml) gota a gota en un periodo de 30 minutos. Durante la adición se formó un precipitado blanco y se continuó agitando durante 2 horas una vez finalizada la adición. El precipitado blanco se filtró y la evaporación de los componentes volátiles a presión reducida proporcionó un residuo, que se purificó mediante cromatografía en columna (ISCO, eluyendo con un 0→100% de EtOAc/hexanos) para proporcionar el producto del título (25.0 g, rendimiento: 70%).

[000351] ^1H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 2.59 - 2.73 (m, 1 H) 2.75 - 2.88 (m, 1 H) 3.04 - 3.19 (m, 1 H) 3.21 - 3.37 (m, 1 H) 3.57 - 3.69 (m, 3 H) 4.08 - 4.24 (m, 1 H) 5.00 - 5.14 (m, 2 H) 5.46 (s a, 1 H) 7.14 - 7.48 (m, 10 H).

INTERMEDIO 6

[000352] 4-Fluoro-3-(trifluorometilsulfonyl)bencenosulfonamida



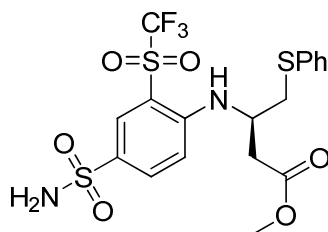
[000353] Una mezcla del ácido clorosulfónico (49.3 ml, 736.31 mmol) y 1-fluoro-2-(trifluorometilsulfonyl)benceno (60.0 g, 262.9 mg) se calentó a 125 °C durante 18 horas. La mezcla de reacción se dejó enfriar hasta temperatura ambiente y a continuación se vertió cuidadosamente sobre 500 ml de hielo picado. La mezcla se extrajo con acetato de etilo (3 x 300 ml) y las capas orgánicas combinadas se lavaron con agua (300 ml) y salmuera (300 ml), se secaron con sulfato de sodio y se concentraron a presión reducida. El concentrado se disolvió en alcohol isopropílico (1200 ml) y se enfrió hasta -65 °C. Se añadió una solución de hidróxido de amonio (280 ml) a una velocidad tal que la temperatura interna no superara -60 °C. Una vez finalizada la adición, la mezcla de reacción se dejó calentar hasta 0 °C durante ~1.5 horas. La solución se enfrió de nuevo posteriormente hasta aproximadamente -50 °C y se acidificó añadiendo HCl concentrado (240 ml) gota a gota, lo cual produjo la formación de un precipitado blanco. El sólido se separó por filtración y el filtrado se concentró a presión reducida para eliminar los componentes volátiles. La mezcla resultante se filtró y el sólido recogido combinado se lavó con agua (~200 ml). El filtrado se extrajo posteriormente con EtOAc (2 x 250 ml) y los extractos orgánicos combinados se lavaron con agua y salmuera, se secaron con sulfato de sodio y se filtraron. Tras concentrar los componentes volátiles a presión reducida, se obtuvo un aceite, que se cristalizó en acetato de etilo/hexano para proporcionar el producto del título (45.0 g, rendimiento: 56%).

[000354] ^1H RMN (400 MHz, DMSO- d_6) δ ppm 7.70 - 7.90 (m, 2 H) 7.98 (dd, 1 H) 8.32 - 8.60 (m, 2 H).

[000355] LCMS: (ESI) m/z 306 $[\text{M}-\text{H}]^+$.

INTERMEDIO 7

[000356] (*R*)-4-(Feniltio)-3-(4-sulfamoil-2-(trifluorometilsulfonyl)fenilamino)-butanoato de metilo



[000357] Paso 1: Una solución de (*R*)-3-(benciloxycarbonilamino)-4-(feniltio)butanoato de metilo (INTERMEDIO 5, 25.6 g, 71.22 mmol), y TFA (200 ml) se calentó a reflujo durante 1 hora. El exceso de reactivo se eliminó a presión reducida y se añadieron al concentrado 50 ml de DCM para formar un azeótropo que se eliminó al vacío para proporcionar (*R*)-3-amino-4-(feniltio)butanoato de metilo, sal trifluoroacética, que se utilizó en la preparación del

INTERMEDIO 7, PASO 2 sin purificación posterior.

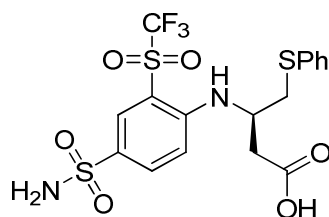
Paso 2: Se añadieron 4-fluoro-3-(trifluorometilsulfonyl)benzenosulfonamida (INTERMEDIO 6, 21.67 g, 71.22 mmol) y DIPEA (129 ml, 738 mmol) a una solución de (*R*)-3-amino-4-(feniltio)butanoato de metilo, sal trifluoroacética, (INTERMEDIO 7, PASO 2) en DMF (20 ml). La mezcla de reacción resultante se calentó a 50 °C durante 1.5 horas, se dejó enfriar hasta temperatura ambiente, se diluyó con acetato de etilo (500 ml), y se lavó con agua (250 ml) y salmuera (250 ml). La capa orgánica se secó con sulfato de sodio, se filtró y se concentró a presión reducida. El concentrado se purificó mediante cromatografía en columna (ISCO, eluyendo con 0→30% de EtOAc/DCM durante 54 minutos) para proporcionar el producto del título (20.5 g, rendimiento: 56%).

[000358] ^1H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 2.75 - 2.88 (m, 2 H) 3.06 - 3.20 (m, 2 H) 3.63 - 3.76 (m, 3 H) 4.04 - 4.21 (m, 1 H) 4.84 (s, 1 H) 6.55 (d, 1 H) 7.19 - 7.49 (m, 5 H) 7.85 (dd, 1 H) 8.28 (d, 1 H).

[000359] LCMS: (ESI) m/z 511 $[\text{M}-\text{H}]^+$.

INTERMEDIO 8

[000360] Ácido (*R*)-4-(feniltio)-3-(4-sulfamoil-2-(trifluorometilsulfonyl)fenilamino)butanoico



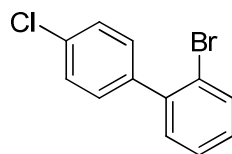
[000361] En un matraz de 100 ml se introdujo (*R*)-4-(feniltio)-3-(4-sulfamoil-2-(trifluorometilsulfonyl)fenilamino)butanoato de metilo (INTERMEDIO 7, 7.5 g, 14.63 mmol) y se añadieron THF (117 ml), MeOH (39 ml) y agua (39 ml) secuencialmente. Se añadió LiOH (1.05 g, 43.9 mmol) a la solución y la mezcla de reacción se agitó a temperatura ambiente durante 3 horas. La mezcla de reacción se concentró a presión reducida para eliminar los componentes volátiles y se enfrió hasta 0 °C. Se añadió una solución acuosa de HCl (1N) gota a gota a la solución y la mezcla resultante se filtró. La masa retenida en el filtro se secó al vacío a 60 °C para proporcionar el producto del título (6.8 g, rendimiento: 93%).

[000362] ^1H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 2.70 - 3.02 (m, 2 H) 3.04 - 3.26 (m, 2 H) 4.01 - 4.20 (m, 1 H) 4.95 (s, 2 H) 6.54 (d, 1 H) 7.29 - 7.49 (m, 5 H) 7.85 (dd, 1 H) 8.26 (d, 1 H).

[000363] LCMS: (ESI) m/z 497 $[\text{M}-\text{H}]^+$.

INTERMEDIO 9

[000364] 2-Bromo-4'-clorobifenilo



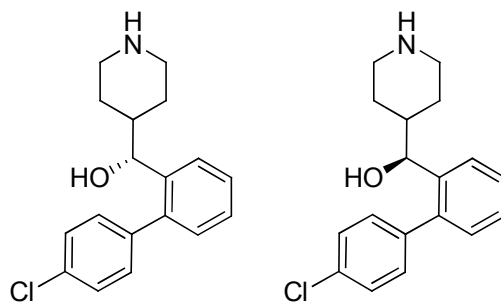
[000365] Se añadieron carbonato de sodio (19.8 g, 186.81 mmol) y tetrakis(trifenilfosfina)paladio (0) (1.05 g, 0.90 mmol) a una solución de 1,2-dibromobenceno (12.8 ml, 105.98 mmol) y ácido 4-clorofenilborónico (14.1 g, 90.08 mmol) en tolueno (170 ml) y agua (80 ml). La mezcla se purgó con nitrógeno y se calentó a reflujo toda la noche. La mezcla de reacción se dejó enfriar hasta temperatura ambiente y se repartió entre NH_4Cl acuoso saturado y acetato de etilo (500 ml). La capa orgánica se secó con MgSO_4 , se filtró y los componentes volátiles se evaporaron a presión reducida para proporcionar un residuo. El residuo se purificó mediante cromatografía en columna (ISCO, columna de 330 g de gel de sílice, eluyendo con 100% de hexanos) para proporcionar el producto del título (17.0 g, rendimiento: 71 %).

[000366] ^1H RMN (400 MHz, DMSO-d_6) δ ppm 7.34 (td, 1 H) 7.37 - 7.45 (m, 3 H) 7.45 - 7.50 (m, 1 H) 7.50 - 7.56 (m, 2 H) 7.75 (d, 1 H).

[000367] GC-MS: 268 [M]

INTERMEDIO 10

[000368] (*R*)-(4'-Clorobifenil-2-il)(piperidin-4-il)metanol y (*S*)-(4'-clorobifenil-2-il)(piperidin-4-il)metanol, mezcla de enantiómeros

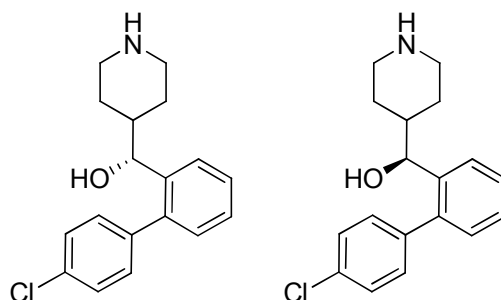


[000369] Se añadió *n*-butillitio (29.4 ml, 47.09 mmol) gota a gota a una solución de 2-bromo-4'-clorobifenil (INTERMEDIO 9, 12 g, 44.85 mmol) en THF (220 ml) en atmósfera de nitrógeno a -78°C . La mezcla coloreada resultante se agitó a -78°C durante 30 minutos y se añadió una solución de 4-formilpiperidin-1-carboxilato de *tert*-butilo (10.04 g, 47.09 mmol) en THF (15 ml). La mezcla de reacción se dejó calentar hasta 0°C durante 3 horas y después se detuvo con una solución acuosa saturada de NH_4Cl . La capa acuosa se extrajo (3 x) con acetato de etilo y los extractos orgánicos combinados se secaron con MgSO_4 . La mezcla se filtró y la evaporación de los componentes volátiles a presión reducida proporcionó un residuo, que se purificó mediante

cromatografía en columna (ISCO, columna de 330 g de gel de sílice, eluyendo con 0→40% de EtOAc/hexanos) para proporcionar 4-[(4'-clorobifenil-2-il)(hidroxi)metil]piperidin-1-carboxilato de *tert*-butilo como una mezcla de enantiómeros.

INTERMEDIO 10A

[000370] (*R*)-(4'-Clorobifenil-2-il)(piperidin-4-il)metanol y (*S*)-(4'-clorobifenil-2-il)(piperidin-4-il)metanol, mezcla de enantiómeros



[000371] Como procedimiento alternativo a las preparaciones del INTERMEDIO 10, se preparó (*R*)-(4'-clorobifenil-2-il)(piperidin-4-il)metanol y (*S*)-(4'-clorobifenil-2-il)(piperidin-4-il)metanol, mezclas de enantiómeros, de acuerdo con los Pasos 1 y 2 como se indica a continuación.

[000372] Paso 1: En un matraz de fondo redondo de 50 ml secado con calor se introdujo el complejo de *i*-PrMgCl/LiCl (1.3 M en THF, 12.0 ml, 15.6 mmol) en atmósfera de nitrógeno. El matraz se enfrió hasta aproximadamente -15 °C) y se añadió 2-bromo-4'-clorobifenilo (INTERMEDIO 9, 4.01 g, 14.99 mmol). La mezcla resultante se agitó a -15 °C durante 1 hora, después a 0 °C durante 2.5 horas y posteriormente se dejó calentar hasta temperatura ambiente durante toda la noche. La mezcla de reacción se enfrió hasta 0 °C y se añadió 4-formilpiperidin-1-carboxilato de *tert*-butilo (3.53 g, 16.35 mmol) en THF (5.0 ml) gota a gota en aproximadamente 5 minutos y la mezcla resultante se dejó agitar durante 90 minutos a esta temperatura. La mezcla de reacción se detuvo añadiendo NH₄Cl acuoso saturado (30 ml) y se extrajo con EtOAc (4 x 60 ml). La capa orgánica se secó (MgSO₄), se filtró y se evaporó a presión reducida. El concentrado se purificó mediante cromatografía en columna (ISCO, columna de 120 g de gel de sílice, eluyendo con 100% de hexanos →50% de EtOAc/hexanos y posteriormente con 0→ 3% de MeOH/DCM) para proporcionar (*R*)-4-((4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-carboxilato de *tert*-butilo y (*S*)-4-((4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-carboxilato de *tert*-butilo, mezcla de enantiómeros, (2.04 g, rendimiento: 43%).

[000373] ¹H RMN (400 MHz, DMSO-*d*₆) δ ppm 0.61 (cd, 1 H) 0.81 - 0.96 (m, 2 H) 1.33 (s, 9 H) 1.50 - 1.63 (m, 1 H) 1.74 - 1.85 (m, 1 H) 3.63 - 3.78 (m, 1 H) 3.81 - 3.93 (m, 1 H) 4.28 (dd, 1

H) 5.21 (d, 1 H) 7.12 (d, 1 H) 7.26 - 7.38 (m, 3 H) 7.41 (t, 1 H) 7.50 (d, 2 H) 7.56 (d, 1 H).

[000374] LCMS: (ESI) m/z 424 $[M+Na]^+$

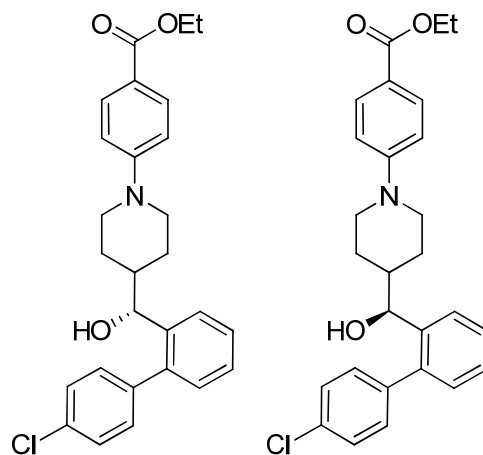
[000375] Paso 2: (*R*)-4-((4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-carboxilato de *tert*-butilo y (*S*)-4-((4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-carboxilato de *tert*-butilo, mezcla de enantiómeros (INTERMEDIO 10, PASO 1, 1.0 g, 2.49 mmol) se disolvieron en DCM (10.0 ml) y MeOH (0.4 ml), y se trataron con TFA (10.0 ml) a temperatura ambiente. La mezcla resultante se agitó a esta temperatura durante 40 minutos y los componentes volátiles se evaporaron a presión reducida. El residuo se disolvió en EtOAc (50 ml), se lavó con bicarbonato de sodio acuoso saturado (100 ml) y agua (50 ml), se secaron ($MgSO_4$), se filtraron y se evaporaron al vacío para proporcionar el producto del título (701 mg, rendimiento: 92%) como una goma transparente, que cristalizó en reposo.

[000376] ^1H RMN (400 MHz, $DMSO-d_6$) δ ppm 0.59 (cd, 1 H) 0.75 - 0.94 (m, 2 H) 1.40 - 1.53 (m, 1 H) 1.71 - 1.83 (m, 1 H) 2.15 (td, 1 H) 2.22 - 2.35 (m, 1 H) 2.61 - 2.71 (m, 1 H) 2.77 - 2.87 (m, 1 H) 4.25 (dd, 1 H) 5.08 (d, 1 H) 7.11 (d, 1 H) 7.25 - 7.31 (m, 1 H) 7.31 - 7.37 (m, 2 H) 7.40 (t, 1 H) 7.47 - 7.52 (m, 2 H) 7.54 (d, 1 H).

[000377] LCMS: (ESI) m/z 302 $[M+H]^+$.

INTERMEDIO 11

[000378] (*R*)-4-(4-((4'-Clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoato de etilo y (*S*)-4-(4-((4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoato de etilo



[000379] Se añadió DIPEA (11 ml, 63 mmol) a una solución de (4'-clorobifenil-2-il)(piperidin-4-il)metanol (INTERMEDIO 10, 6.41 g, 21.24 mmol) y 4-fluorobenzoato de etilo (6.25 ml, 42.59 mmol) en DMSO seco (25 ml). La solución resultante se calentó a 120 °C durante 20 horas y se añadió más trietilamina (12.2 ml, 87.67 mmol). La solución se calentó a 120 °C durante 24 horas más y después se repartió entre acetato de etilo (500 ml) y solución acuosa saturada de NH_4Cl (250 ml). La fase orgánica se lavó con agua, se secó con Na_2SO_4 , se filtró y

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se concentró a presión reducida para proporcionar un residuo. Este residuo se purificó mediante cromatografía en columna (ISCO, columna de 120 g de sílice, eluyendo con 0→65% de EtOAc/hexanos) para proporcionar el producto del título (5.12 g, rendimiento: 54%) como una mezcla de enantiómeros.

[000380] Los enantiómeros R y S del producto del título se separaron utilizando Chiral SFC (columna Chiralpak IA).

Dimensiones de la columna: 21 x 250 mm, 5□□

Modificador: 35% de isopropanol

Velocidad de flujo (ml/min): 60

Presión de salida (bar): 100

Detección (nm): 220

INTERMEDIO 11A (primer compuesto eluido)

[000381] (*R*)-4-(4-((4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoato de etilo

[000382] El primer compuesto eluido tuvo un tiempo de retención de 4.97 minutos.

[000383] ¹H RMN (400 MHz, DMSO-d₆) δ ppm 0.84 (cd, 1 H) 0.98 - 1.17 (m, 2 H) 1.27 (t, 3 H) 1.60 - 1.73 (m, 1 H) 1.85 - 1.95 (m, 1 H) 2.52 - 2.61 (m, 1 H) 2.63 - 2.74 (m, 1 H) 3.64 - 3.73 (m, 1 H) 3.80 - 3.90 (m, 1 H) 4.21 (c, 2 H) 4.31 (dd, 1 H) 5.23 (d, 1 H) 6.85 (d, 2 H) 7.14 (dd, 1 H) 7.28 - 7.38 (m, 3 H) 7.43 (td, 1 H) 7.46 - 7.52 (m, 2 H) 7.56 - 7.62 (m, 1 H) 7.71 (d, 2 H).

[000384] LCMS: (ESI) *m/z* 450 [M+H]⁺.

[000385] Rotación óptica:

Concentración: 0.1 g/dl

Lámpara: Sodio

Longitud de onda: 589 nm

Temperatura: 20 °C

Paso óptico: 10 cm

Volumen de la celda: 1 ml

Solvente: DCM

[α]_D = +107

INTERMEDIO 11B (segundo compuesto eluido)

[000386] (*S*)-4-(4-((4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoato de etilo

[000387] El segundo compuesto eluido tuvo un tiempo de retención de 6.72 minutos.

[000388] ¹H RMN (400 MHz, DMSO-d₆) δ ppm 0.84 (cd, 1 H) 0.98 - 1.17 (m, 2 H) 1.27 (t, 3 H) 1.61 - 1.73 (m, 1 H) 1.85 - 1.94 (m, 1 H) 2.52 - 2.61 (m, 1 H) 2.63 - 2.74 (m, 1 H) 3.65 - 3.73

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(m, 1 H) 3.80 - 3.89 (m, 1 H) 4.21 (c, 2 H) 4.31 (dd, 1 H) 5.23 (d, 1 H) 6.85 (d, 2 H) 7.14 (dd, 1 H) 7.28 - 7.38 (m, 3 H) 7.43 (td, 1 H) 7.46 - 7.52 (m, 2 H) 7.56 - 7.62 (m, 1 H) 7.71 (d, 2 H).

[000389] LCMS: (ESI) m/z 450 $[M+H]^+$.

[000390] Rotación óptica:

Concentración: 0.1 g/dl

Lámpara: Sodio

Longitud de onda: 589 nm

Temperatura: 20 °C

Paso óptico: 10 cm

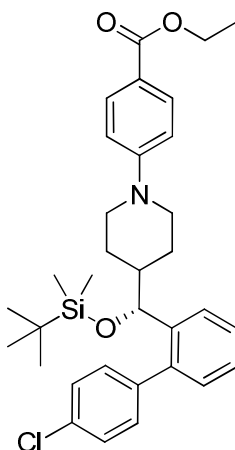
Volumen de la celda: 1 ml

Solvente: DCM

$[\alpha] = -116$

INTERMEDIO 12

[000391] (*R*)-4-(4-((*tert*-butildimetilsililoxi)(4'-clorobifenil-2-il)metil)piperidin-1-il)benzoato de etilo



[000392] Se añadió 2,6-lutidina (1.128 ml, 9.68 mmol) a una solución de (*R*)-4-(4-((4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoato de etilo (INTERMEDIO 11A (primer compuesto eluido), 1.74 g, 3.87 mmol) en DCM (10 ml) a 0 °C. Se añadió trifluorometanosulfonato de *tert*-butildimetilsililo (1.3 ml, 5.81 mmol) gota a gota a través de una jeringa a 0 °C y la mezcla resultante se dejó calentar hasta temperatura ambiente durante 10 minutos. La evaporación de los componentes volátiles a presión reducida proporcionó un residuo, el cual se purificó mediante cromatografía en columna (ISCO, columna de 80 g de gel de sílice, eluyendo con 0→10% de EtOAc/hexanos) para proporcionar el producto del título (2.1 g, rendimiento: casi cuantitativo).

[000393] ^1H RMN (400 MHz, CLOROFORMO- d) δ ppm -0.23 (s, 3 H) -0.06 (s, 3 H) 0.86 (s,

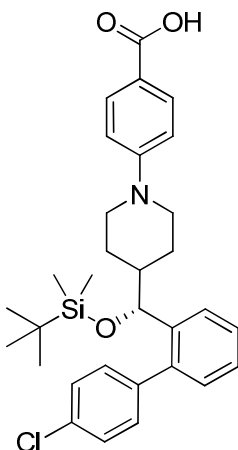
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9 H) 1.22 - 1.48 (m, 6 H) 1.73 - 1.83 (m, 1 H) 2.53 - 2.70 (m, 2 H) 3.70 - 3.78 (m, 1 H) 3.80 - 3.89 (m, 1 H) 4.32 (c, 2 H) 4.56 - 4.65 (m, 1 H) 6.82 (d, 2 H) 7.10 - 7.15 (m, 1 H) 7.22 (d, 2 H) 7.28 - 7.33 (m, 1 H) 7.36 - 7.43 (m, 3 H) 7.59 (d, 1 H) 7.89 (d, 2 H).

[000394] LCMS: (ESI) m/z 564 $[M+H]^+$.

INTERMEDIO 13

[000395] Ácido (R)-4-(4-((*tert*-butildimetilsililoxi)(4'-clorobifenil-2-il)metil)piperidin-1-il)benzoico



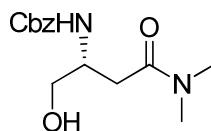
[000396] Se añadió hidróxido de litio (1.42 g, 59.29 mmol) a una mezcla de (R)-4-(4-((*tert*-butildimetilsililoxi)(4'-clorobifenil-2-il)metil)piperidin-1-il)benzoato de etilo (INTERMEDIO 12, 3.83 g, 6.78 mmol) en THF (27 ml), MeOH (9 ml) y agua (1 ml). La mezcla resultante se agitó a temperatura ambiente durante toda la noche y a continuación los componentes volátiles se eliminaron a presión reducida. El concentrado se purificó mediante cromatografía en columna (ISCO, columna de 80 g de sílice, eluyendo con 0→80% de EtOAc/hexanos) para proporcionar el producto del título (3.24 g, rendimiento: 89%).

[000397] ^1H RMN (400 MHz, DICLOROMETANO- d_2) δ ppm -0.23 (s, 3 H) -0.06 (s, 3 H) 0.85 (s, 9 H) 1.19 - 1.49 (m, 3 H) 1.52 - 1.64 (m, 1 H) 1.70 - 1.80 (m, 1 H) 2.57 - 2.73 (m, 2 H) 3.75 - 3.84 (m, 1 H) 3.85 - 3.94 (m, 1 H) 4.61 (d, $J=4.80$ Hz, 1 H) 6.82 (d, $J=9.09$ Hz, 2 H) 7.13 (dd, $J=7.58$, 1.26 Hz, 1 H) 7.24 (d, $J=8.34$ Hz, 2 H) 7.30 (td, $J=7.45$, 1.52 Hz, 1 H) 7.35 - 7.45 (m, 3 H) 7.60 (d, $J=7.83$ Hz, 1 H) 7.85 - 7.92 (m, 2 H).

[000398] LCMS: m/z 536 $[M+H]^+$.

INTERMEDIO 14

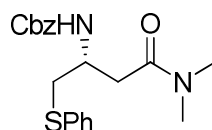
[000399] (R)-4-(Dimetilamino)-1-hidroxi-4-oxobutan-2-ilcarbamato de bencilo



[000400] Una solución de (*R*)-5-oxotetrahidrofuran-3-ilcarbamato de bencilo (INTERMEDIO 3, 18.4 g, 7.8 mmol) en THF (100 ml) se purgó a temperatura ambiente con dimetilamina gaseosa durante 5 minutos. Tras agitar a temperatura ambiente durante 14 horas, la mezcla de reacción se concentró a sequedad y se purificó mediante cromatografía en columna (gel de sílice, eluyendo primero con 50% de acetato de etilo/hexanos y a continuación 100% de acetona) para proporcionar el producto del título (20 g, rendimiento: 91.5 %).

INTERMEDIO 15

[000401] (*R*)-4-(Dimetilamino)-4-oxo-1-(feniltio)butan-2-ilcarbamato de bencilo



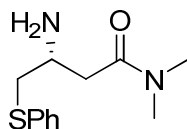
[000402] Se añadieron disulfuro de difenilo (55.8 g, 0.3 mol) y Bu₃P (75 ml, 0.3 mol) secuencialmente a una solución de (*R*)-4-(dimetilamino)-1-hidroxi-4-oxobutan-2-ilcarbamato de bencilo (INTERMEDIO 14, 48 g, 0.17 mol) en tolueno (100 ml). La mezcla resultante se calentó a 80 °C durante 8 horas. La mezcla de reacción se dejó enfriar hasta temperatura ambiente y los componentes volátiles se eliminaron al vacío. El residuo se purificó mediante cromatografía en columna (gel de sílice, 7 cm de altura x 14 cm de ancho, eluyendo con hexanos y a continuación 10:1, 2:1 y después 1:1 de hexanos/acetato de etilo) para proporcionar el producto del título (40 g, rendimiento: 63%).

[000403] ¹H-RMN (300 MHz, DMSO-d₆) δ 2.59 (m, 2 H), 2.79 (s, 3 H), 2.89 (s, 3 H), 3.12 (m, 2 H), 4.71 (m, 1 H), 4.02 (m, 1 H), 5.01 (s, 2 H), 7.18 (t, 1 H), 7.26-7.41 (m, 10 H).

[000404] LCMS (ESI) *m/z* 373 (M+H)⁺.

INTERMEDIO 16

[000405] (*R*)-3-Amino-*N,N*-dimetil-4-(feniltio)butanamida



[000406] Se agitó una suspensión de (*R*)-4-(dimetilamino)-4-oxo-1-(feniltio)butan-2-ilcarbamato de bencilo (INTERMEDIO 15, 40 g, 0.10 mol) en HBr al 40% en ácido acético (100 ml) a temperatura ambiente durante 16 h y la mezcla de reacción se volvió homogénea durante este periodo de tiempo. La mezcla se concentró a sequedad, se diluyó con agua (200 ml) y AcOH (200 ml), y se lavó con éter dietílico (3x 50 ml). Se ajustó el pH de la fase acuosa a aproximadamente pH 8-9 con Na₂CO₃ sólido y se extrajo con CH₂Cl₂ (5x). Las fases orgánicas

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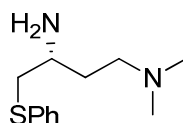
combinadas se secaron (MgSO_4) y se concentraron a presión reducida para proporcionar el producto del título (15 g, 59%) que se utilizó en la preparación del INTERMEDIO 17 sin purificación posterior.

[000407] ^1H -RMN (300 MHz, $\text{DMSO}-d_6$) δ 2.37 (dd, 1 H), 2.51 (dd, 1 H), 2.79 (s, 3 H), 2.89 (dd, 1 H), 2.91 (s, 3 H), 3.05-3.20 (m, 2 H), 3.32 (m, 2 H), 7.16 (t, 1 H), 7.30 (dd, 2 H), 7.35 (d, 2 H).

[000408] LCMS (ESI) m/z 239 ($\text{M}+\text{H}$) $^+$.

INTERMEDIO 17

[000409] (3*R*)-4-*N*^{*l*},*N*^{*l*}-Dimetilamino-1-(feniltio)butan-2-amina



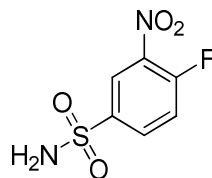
[000410] Una solución de (*R*)-3-amino-*N,N*-dimetil-4-(feniltio)butanamida (INTERMEDIO 16, 1.0 g, 4.2 mmol) en THF (30 ml) se trató gota a gota con una solución del complejo de $\text{BH}_3 \cdot \text{THF}$ (16 ml, solución 1 M en THF, 16 mmol) añadida a través de un embudo de adición. La solución oscura resultante se agitó a temperatura ambiente durante toda la noche. La mezcla se enfrió hasta 0 °C y se trató gota a gota con 5 ml de MeOH, lo cual produjo un desprendimiento de gas vigoroso. Una vez que dejó de desprenderse gas, la mezcla de reacción se concentró a sequedad, se reconstituyó con MeOH (35 ml) y HCl concentrado (5 ml), y se calentó a reflujo durante 4 horas. La mezcla de reacción se dejó enfriar hasta temperatura ambiente, se concentró a sequedad y se repartió entre NaHCO_3 acuoso saturado y CH_2Cl_2 . La fase acuosa se extrajo con CH_2Cl_2 (3x) y las fases orgánicas combinadas se lavaron con salmuera y NaHCO_3 acuosa saturada, se secaron (MgSO_4) y se concentraron a presión reducida. La concentración de los componentes volátiles a presión reducida proporcionó un residuo que se purificó mediante cromatografía en columna (gel de sílice, eluyendo con un gradiente en pasos de CH_2Cl_2 saturado con $\text{NH}_3(\text{g})$, desde 5% de MeOH en CH_2Cl_2 saturado con $\text{NH}_3(\text{g})$, 10% de MeOH/ CH_2Cl_2 saturado con $\text{NH}_3(\text{g})$ hasta 13% de MeOH/ CH_2Cl_2 saturado con $\text{NH}_3(\text{g})$) para proporcionar el producto del título (0.3 g, rendimiento: 32%).

[000411] ^1H -RMN (300 MHz, $\text{DMSO}-d_6$) δ 1.31 (m, 1 H), 1.64 (m, 1 H), 2.08 (m, 6 H), 2.25 (m, 2 H), 2.78 (m, 1 H), 2.98 (m, 1 H), 7.17 (m, 1 H), 7.35 (m, 4 H).

[000412] LCMS (ESI) m/z 225 ($\text{M}+\text{H}$) $^+$.

INTERMEDIO 18

[000413] 4-Fluoro-3-nitrobenzenosulfonamida



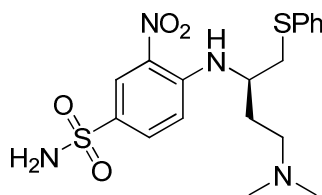
[000414] Una solución de 2-fluoronitrobenzeno (14.1 g, 0.10 mol) en el ácido clorosulfónico (30 ml) se calentó a 80 °C durante 10 horas. Después de enfriar la mezcla de reacción hasta temperatura ambiente, se vertió cuidadosamente sobre hielo (aproximadamente 100 g) en un Erlenmeyer de 500 ml enfriado de forma eficaz con hielo. La mezcla resultante se extrajo con éter dietílico (2 x 200 ml) y los extractos orgánicos combinados se concentraron a presión reducida. El residuo se disolvió en 70 ml de THF/CH₂Cl₂ 1:1 (v/v) enfriados a -78 °C y se trató cuidadosamente con hidróxido de amonio concentrado (7.5 ml). La mezcla fría se vertió sobre HCl ac. 5 M (50 ml), las capas se separaron, la fase acuosa se extrajo con acetato de etilo (2 x 200 ml) y las fases orgánicas combinadas se lavaron con HCl ac. 4 M y salmuera, y se secaron (MgSO₄). Tras evaporar los componentes volátiles a presión reducida, se obtuvo un sólido. El sólido resultante se recrystalizó en acetato de etilo y hexanos para proporcionar el compuesto del título (15 g, 70%).

[000415] ¹H RMN (300 MHz, DMSO-*d*₆) 8.53 (dd, 1 H), 8.20 (ddd, 1 H), 7.87 (dd, 1 H), 7.72 (s, 2 H).

[000416] LCMS (ESI) *m/z* 219 (M-H)⁻.

INTERMEDIO 19

[000417] (*R*)-4-(4-(Dimetilamino)-1-(feniltio)butan-2-ilamino)-3-nitrobenzenosulfonamida



[000418] Una solución de (*R*)-*N*¹, *N*¹-dimetilamino-4-(feniltio)butano-1,3-diamina (INTERMEDIO 17, 25 mg, 0.11 mmol) en DMF (5 ml) y DIPEA (0.01 ml) se trató con 4-fluoro-3-nitrobenzenosulfonamida (INTERMEDIO 18, 24.9 mg, 0.11 mmol) en una porción y la mezcla resultante se agitó a temperatura ambiente durante toda la noche. La mezcla de reacción se vertió sobre agua y se extrajo con EtOAc (2x 50 ml). Las capas orgánicas combinadas se lavaron con salmuera, se secaron con Na₂SO₄ y se concentraron al vacío. El residuo se purificó mediante cromatografía en columna (gel de sílice, eluyendo con un gradiente en pasos de CH₂Cl₂ saturado con NH₃(g), desde 5% de MeOH en CH₂Cl₂ saturado con NH₃(g), 10% de MeOH/CH₂Cl₂ saturado con NH₃(g) hasta 13% de MeOH/CH₂Cl₂ saturado con NH₃(g)) para proporcionar el

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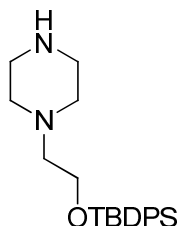
producto del título (31 mg, rendimiento: 66%) después de recrystalizar en EtOAc.

[000419] ^1H -RMN (300 MHz, DMSO- d_6) δ 1.83 (m, 1 H), 1.95 (m, 1 H), 2.11 (s, 6 H), 2.21 (m, 1 H), 2.43 (m, 1 H), 3.30 (m a, 2 H), 3.39 (m, 2 H), 4.10 (m, 1 H), 7.06 (d, 1 H), 7.17 (t, 2H), 7.25 (dd, 2 H), 7.30 (d, 2 H), 7.70 (dd, 1 H), 8.38 (d, 1 H), 8.62 (d, 1 H).

[000420] LCMS (ESI) m/z 425 (M+H) $^+$.

INTERMEDIO 20

[000421] 1-(2-(*tert*-Butildifenilsililoxi)etil)piperazina

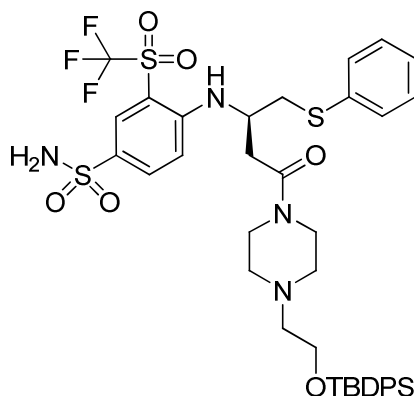


[000422] Se disolvió 2-(piperazin-1-il)etanol (1.000 g, 7.68 mmol) en DCM (35.1 ml) y se añadió piridina (0.932 ml, 11.52 mmol) seguida de DMAP (0.094 g, 0.77 mmol). Se añadió *tert*-butilclorodifenilsilano (2.368 ml, 9.22 mmol) a la solución y la mezcla de reacción se agitó durante toda la noche a temperatura ambiente. La mezcla de reacción se concentró a presión reducida y el concentrado se purificó mediante cromatografía en columna (ISCO, eluyendo con 10% de MeOH/DCM) para proporcionar el producto del título (2.73 g, rendimiento: 96%).

[000423] LCMS: (ESI) m/z 369 [M+H] $^+$.

INTERMEDIO 21

[000424] (*R*)-4-(4-(4-(2-(*tert*-butildifenilsililoxi)etil)piperazin-1-il)-4-oxo-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)benzenosulfonamida



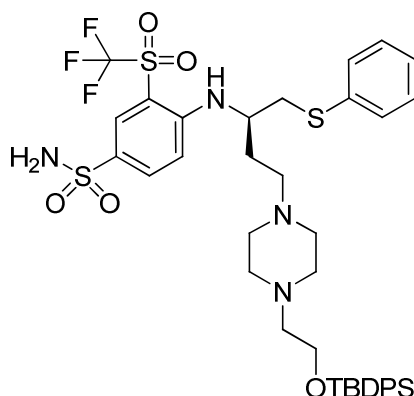
[000425] HATU (0.915 g, 2.41 mmol) y DIPEA (0.701 ml, 4.01 mmol) se añadieron secuencialmente a una solución del ácido (*R*)-4-(feniltio)-3-(4-sulfamoyl-2-(trifluorometilsulfonyl)fenilamino)butanoico (INTERMEDIO 8, 1.0 g, 2.01 mmol) y 1-(2-(*tert*-butildifenilsililoxi)etil)piperazina (INTERMEDIO 20, 0.894 g, 2.21 mmol) en DMA (2.0 ml). Se

añadió más DMA (1.7 ml) y la mezcla resultante se agitó a temperatura ambiente durante 2 h. La mezcla se diluyó con EtOAc y la capa orgánica se lavó con H₂O (2x), NaHSO₄ 1 N (ac.) y NaHCO₃ saturado acuoso. La capa orgánica se secó (Na₂SO₄) y se concentró a presión reducida para proporcionar el producto del título (2.0 g, rendimiento: cuantitativo), que se utilizó en la preparación del INTERMEDIO 22 sin purificación posterior.

[000426] LCMS: (ESI) m/z 849 [M+H]⁺.

INTERMEDIO 22

[000427] (*R*)-4-(4-(4-(2-(*tert*-Butildifenilsililo)etil)piperazin-1-il)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida

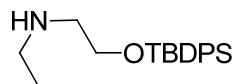


[000428] Se disolvió (*R*)-4-(4-(4-(2-(*tert*-butildifenilsililo)etil)piperazin-1-il)-4-oxo-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida (INTERMEDIO 21, 0.98 g, 1.15 mmol) en THF (4.6 ml), en atmósfera de nitrógeno y se añadió una solución del complejo de borano-THF (1 M en THF; 6.93 ml, 6.93 mmol). La mezcla se diluyó con NH₃ en MeOH (7 N, 20 ml) y se agitó a temperatura ambiente durante toda la noche. La mezcla de reacción se concentró a presión reducida, se diluyó con EtOAc (75 ml), se lavó con agua (40 ml) y se secó (Na₂SO₄). La evaporación de los componentes volátiles a presión reducida proporcionó un concentrado, el cual se purificó mediante cromatografía en columna (ISCO, columna de 40 g de gel de sílice, eluyendo con 0→100% de EtOAc/ hexanos) para proporcionar el compuesto del título (245 mg, rendimiento: 25%).

[000429] LCMS: (ESI) m/z 835 [M+H]⁺.

INTERMEDIO 23

[000430] 2-(*tert*-Butildifenilsililo)-*N*-etiletanamina



[000431] Se añadieron secuencialmente imidazol (1.53 g, 22.44 mmol) y una solución de *tert*-butilclorodifenilsilano (4.63 g, 16.83 mmol) en DCM (10 ml) a una solución de 2-

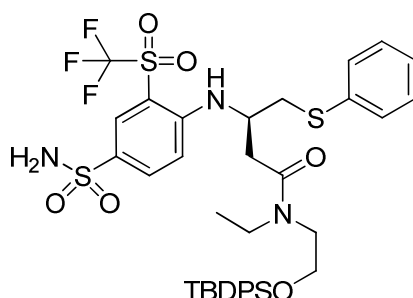
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(etilamino)etanol (1.099 ml, 11.22 mmol) en DCM (30 ml) y la mezcla de reacción resultante se agitó a temperatura ambiente durante toda la noche. La mezcla fue diluida con DCM y lavada con NaHSO₄ 1 N acuoso y NaHCO₃ saturado acuoso. La capa orgánica se secó (Na₂SO₄), se concentró a presión reducida para proporcionar un residuo que se purificó mediante cromatografía en columna (ISCO, columna de 40 g de gel de sílice, eluyendo con 0→100% de EtOAc/hexanos) para proporcionar el compuesto del título (2.95 g, rendimiento: 80%).

[000432] LCMS: (ESI) m/z 328 [M+H]⁺.

INTERMEDIO 24

[000433] (*R*)-*N*-(2-(*tert*-butildifenilsililo)etil)-*N*-etil-4-(feniltio)-3-(4-sulfamoyl-2-(trifluorometilsulfonyl)fenilamino)butanamida

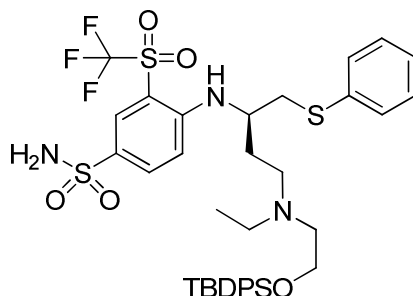


[000434] 2-(*tert*-Butildifenilsililo)-*N*-etiletanamina (INTERMEDIO 23, 0.263 g, 0.80 mmol) en THF (2.5 ml), 4-oxobenzo[*d*][1,2,3]triazin-3(4*H*)-ilfosfato de dietilo (0.480 g, 1.60 mmol) y DIPEA (0.280 ml, 1.60 mmol) se añadieron secuencialmente a una solución del ácido (*R*)-4-(feniltio)-3-(4-sulfamoyl-2-(trifluorometilsulfonyl)fenilamino)butanoico (INTERMEDIO 8, 0.4 g, 0.80 mmol) en THF (5.0 ml) y la mezcla se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se concentró posteriormente a presión reducida, se diluyó con EtOAc y la capa orgánica se lavó con NaHSO₄ ac. 1 N y NaHCO₃ saturado acuoso. La capa orgánica se secó (Na₂SO₄), se concentró a presión reducida para proporcionar un residuo que se purificó mediante cromatografía en columna (ISCO, columna de 40 g de gel de sílice, eluyendo con 0→100% de EtOAc/hexanos) para proporcionar el producto del título (590 mg, rendimiento: 91%).

[000435] LCMS: (ESI) m/z 808 [M+H]⁺.

INTERMEDIO 25

[000436] (*R*)-4-(4-((2-(*tert*-butildifenilsililo)etil)(etil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)benzenosulfonamida

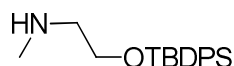


[000437] Se disolvió (*R*)-*N*-(2-(*tert*-butildifenilsililoxy)etil)-*N*-etil-4-(feniltio)-3-(4-sulfamoil-2-(trifluorometilsulfonyl)fenilamino)butanamida (INTERMEDIO 24, 0.59 g, 0.73 mmol) en THF (4.6 ml), en atmósfera de nitrógeno, se añadió una solución del complejo de borano-THF (1 M en THF; 2.2 ml, 2.2 mmol) y la solución resultante se agitó a temperatura ambiente durante toda la noche. Se añadió más solución del complejo de borano-THF (1 M en THF; 2.2 ml, 2.2 mmol). La mezcla resultante se agitó a temperatura ambiente durante 6 h más. La mezcla se diluyó con NH₃ en MeOH (7 N, 20 ml) y se agitó a temperatura ambiente durante toda la noche. La mezcla de reacción se concentró a presión reducida, se diluyó con EtOAc (75 ml), se lavó con agua (40 ml) y se secó (Na₂SO₄). La evaporación de los componentes volátiles a presión reducida proporcionó un concentrado, el cual se purificó mediante cromatografía en columna (ISCO, columna de 40 g de gel de sílice, eluyendo con 0→100% de EtOAc/ hexanos) para proporcionar el compuesto del título (280 mg, rendimiento: 48%).

[000438] LCMS: (ESI) m/z 796 [M+H]⁺.

INTERMEDIO 26

[000439] 2-(*tert*-Butildifenilsililoxy)-*N*-metiletanamina

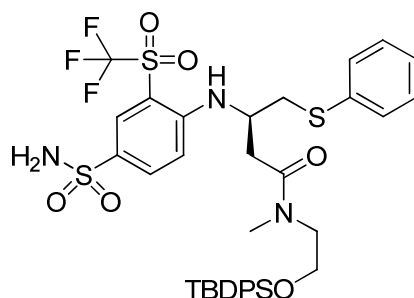


[000440] El compuesto del título (4.1 g, rendimiento: 49%) se preparó utilizando un procedimiento similar al descrito para la síntesis del INTERMEDIO 23 utilizando 2-(metilamino)etanol (2.0 g, 26.6 mmol) como material de partida. El producto del título se purificó mediante cromatografía en columna (ISCO, columna de 40 g de gel de sílice, eluyendo con 0→100 % de DCM/10% de MeOH en DCM con 1% de NH₄OH).

[000441] LCMS: (ESI) m/z 314 [M+H]⁺.

INTERMEDIO 27

[000442] (*R*)-*N*-(2-(*tert*-Butildifenilsililoxy)etil)-*N*-metil-4-(feniltio)-3-(4-sulfamoil-2-(trifluorometilsulfonyl)fenilamino)butanamida

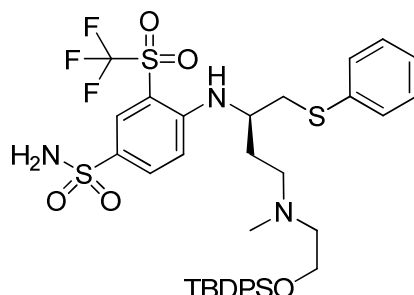


[000443] El producto del título (590 mg, rendimiento: 93%) se preparó utilizando un procedimiento similar al descrito para la síntesis del INTERMEDIO 24 utilizando el ácido (*R*)-4-(feniltio)-3-(4-sulfamoil-2-(trifluorometilsulfonil)fenilamino)butanoico (INTERMEDIO 8, 400 mg, 0.8 mmol) y 2-(*tert*-butildifenilsililoxi)-*N*-metiletanamina (INTERMEDIO 26, 251 mg, 0.8 mmol) como materiales de partida. El producto del título se purificó mediante cromatografía en columna (ISCO, columna de 12 g de gel de sílice, eluyendo con 0→100 % de EtOAc/hexanos).

[000444] LCMS: (ESI) m/z 794[M+H]⁺.

INTERMEDIO 28

[000445] (*R*)-4-(4-((2-(*tert*-Butildifenilsililoxi)etil)(metil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)bencenosulfonamida

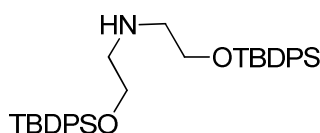


[000446] El compuesto del título (230 mg, rendimiento: 40%) se preparó utilizando un procedimiento similar al descrito para la síntesis del INTERMEDIO 25 utilizando (*R*)-*N*-(2-(*tert*-butildifenilsililoxi)etil)-*N*-metil-4-(feniltio)-3-(4-sulfamoil-2-(trifluorometilsulfonil)fenilamino)butanamida (INTERMEDIO 27, 590 mg, 0.74 mmol) como material de partida. El compuesto del título se purificó mediante cromatografía en columna (ISCO, columna de 12 g de gel de sílice, eluyendo con 0→100 % de EtOAc/hexanos).

[000447] LCMS: (ESI) m/z 780[M+H]⁺.

INTERMEDIO 29

[000448] Bis(2-(*tert*-butildifenilsililoxi)etil)amina

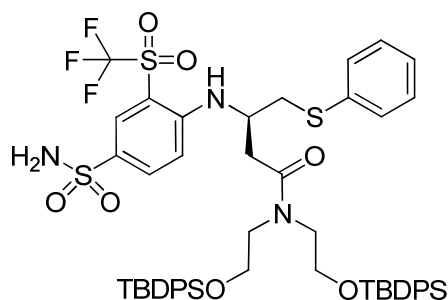


[000449] El compuesto del título (4.8 g, rendimiento: 87%) se preparó utilizando un procedimiento similar al descrito para la síntesis del INTERMEDIO 23 utilizando 2,2'-azanodiildietanol (1.0 g, 9.51 mmol) como material de partida. El producto del título se purificó mediante cromatografía en columna (ISCO, columna de 40 g de gel de sílice, eluyendo con 0→50 % de EtOAc/hexanos).

[000450] LCMS: (ESI) m/z 582 $[M+H]^+$.

INTERMEDIO 30

[000451] (*R*)-*N,N*-Bis(2-(*tert*-butildifenilsililoxi)etil)-4-(feniltio)-3-(4-sulfamoil-2-(trifluorometilsulfonyl)fenilamino)butanamida

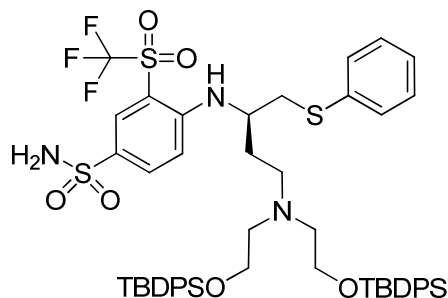


[000452] El producto del título (1.06 g, rendimiento: 83%) se preparó utilizando un procedimiento similar al descrito para la síntesis del INTERMEDIO 24 utilizando el ácido (*R*)-4-(feniltio)-3-(4-sulfamoil-2-(trifluorometilsulfonyl)fenilamino)butanoico (INTERMEDIO 8, 600 mg, 1.2 mmol) y bis(2-(*tert*-butildifenilsililoxi)etil)amina (INTERMEDIO 29, 0.700 g, 1.20 mmol) como materiales de partida. El producto del título se purificó mediante cromatografía en columna (ISCO, columna de 40 g de gel de sílice, eluyendo con 0→100% de EtOAc/hexanos).

[000453] LCMS: (ESI) m/z 1062 $[M+H]^+$.

INTERMEDIO 31

[000454] (*R*)-4-(4-(Bis(2-(*tert*-butildifenilsililoxi)etil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida



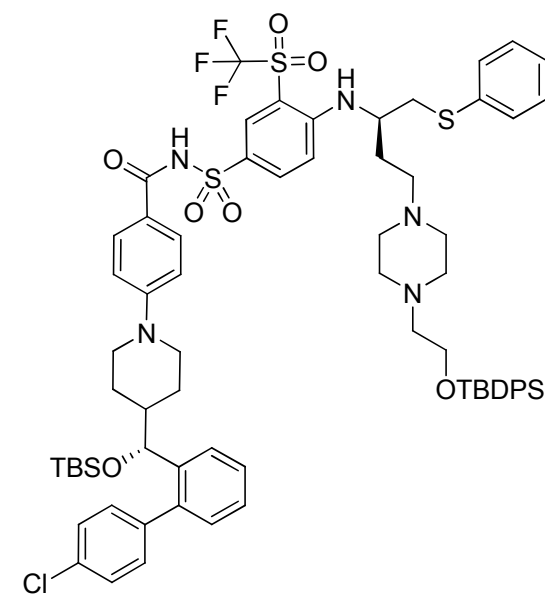
[000455] El producto del título (800 mg, rendimiento: 77%) se preparó utilizando un procedimiento similar al descrito para la síntesis del INTERMEDIO 25 utilizando (*R*)-*N,N*-bis(2-

(*tert*-butildifenilsililoxi)etil)-4-(feniltio)-3-(4-sulfamoil-2-(trifluorometilsulfonyl)fenilamino)butanamida (INTERMEDIO 30, 1.05 g, 0.99 mmol) como material de partida. El producto del título se purificó mediante cromatografía en columna (ISCO, columna de 40 g de gel de sílice, eluyendo con 0→50 % de EtOAc/hexanos).

[000456] LCMS: (ESI) m/z 1048[M+H]⁺.

INTERMEDIO 32

[000457] 4-(4-((*R*)-(tert-Butildimetilsililoxi)(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((*R*)-4-(4-(2-(*tert*-butildifenilsililoxi)etil)piperazin-1-il)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)fenilsulfonyl)benzamida

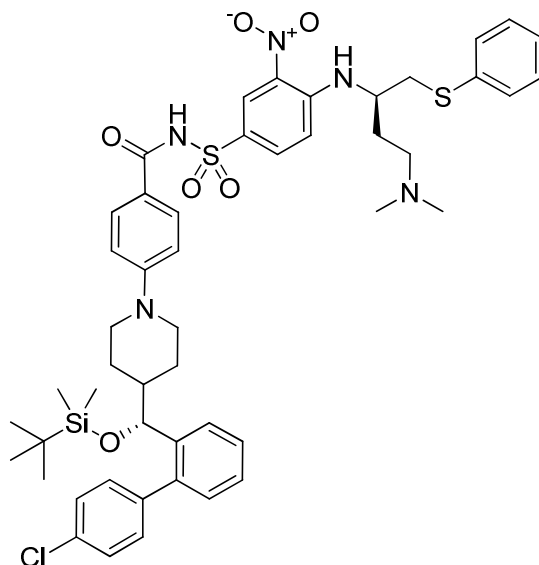


[000458] Se introdujeron el ácido (*R*)-4-(4-((*tert*-butildimetilsililoxi)(4'-clorobifenil-2-il)metil)piperidin-1-il)benzoico (INTERMEDIO 13, 56.5 mg, 0.11 mmol), (*R*)-4-(4-(4-(2-(*tert*-butildifenilsililoxi)etil)piperazin-1-il)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida (INTERMEDIO 22, 80 mg, 0.1 mmol), DMAP (35.1 mg, 0.29 mmol) y EDC (36.7 mg, 0.19 mmol) en un matraz de 50 ml y se purgó con nitrógeno. Se añadió DCM (0.96 ml) y la solución se agitó a temperatura ambiente durante toda la noche. La mezcla de reacción se diluyó con DCM (40 ml) y se lavó con bisulfato de sodio 1 N (35 ml) y a continuación con bicarbonato de sodio saturado acuoso (40 ml). La capa orgánica se secó (Na₂SO₄), se filtró y se evaporó a presión reducida para proporcionar el producto del título (147 mg, rendimiento: cuantitativo), que se utilizó en la preparación del EJEMPLO 1 sin purificación posterior.

[000459] LCMS: (ESI) m/z 1354 [M+H]⁺.

INTERMEDIO 33

[000460] 4-(4-((*R*)-(tert-butildimetilsililoxi)(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((*R*)-4-(dimetilamino)-1-(feniltio)butan-2-ilamino)-3-nitrofenilsulfonil)benzamida



[000461] El producto del título (162.8 mg, rendimiento: 32%) se preparó utilizando un procedimiento similar al descrito para la síntesis del INTERMEDIO 32 utilizando el ácido (*R*)-4-(4-((tert-butildimetilsililoxi)(4'-clorobifenil-2-il)metil)piperidin-1-il)benzoico (INTERMEDIO 13, 249.6 mg, 0.47 mmol) y (*R*)-4-(4-(dimetilamino)-1-(feniltio)butan-2-ilamino)-3-nitrobenzenosulfonamida (INTERMEDIO 19, 208.8 mg, 0.49 mmol). El producto del título se purificó mediante cromatografía en columna (ISCO, columna de 12 g de gel de sílice, eluyendo con 0→10 % de MeOH/DCM).

[000462] ^1H RMN (300 MHz, DICLOROMETANO- d_2) δ ppm -0.24 (s, 3 H) -0.07 (s, 3 H) 0.86 (s, 9 H) 1.47 - 1.62 (m, 1 H) 1.68 - 1.81 (m, 1 H) 2.04 - 2.18 (m, 1 H) 2.43 (s, 6 H) 2.50 - 2.77 (m, 4 H) 3.15 (d, $J=5.84$ Hz, 2 H) 3.65 - 3.87 (m, 2 H) 4.07 (s, 1 H) 4.60 (d, 1 H) 6.68 - 6.82 (m, 3 H) 7.08 - 7.45 (m, 12 H) 7.54 - 7.63 (m, 1 H) 7.70 (d, 2 H) 7.75 - 7.84 (m, 1 H) 8.64 (s, 2 H).

[000463] LCMS: m/z 942 $[\text{M}+\text{H}]^+$.

[000464] Rotación óptica:

Concentración: 0.1 g/dl

Lámpara: Sodio

Longitud de onda: 589 nm

Temperatura: 20 °C

Paso óptico: 10 cm

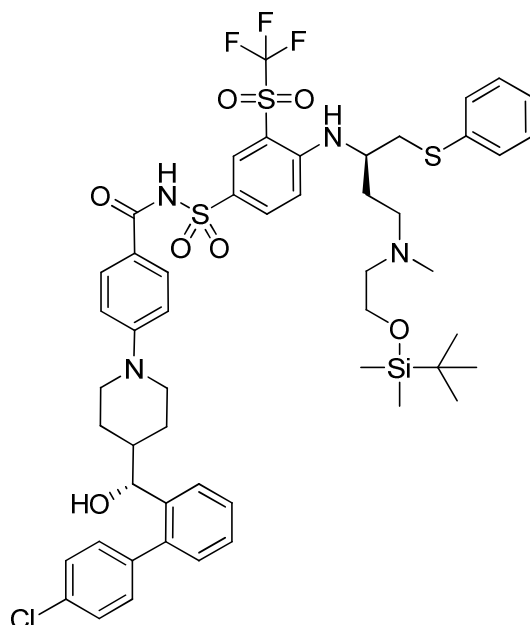
Volumen de la celda: 1 ml

Solvente: CH_2Cl_2

[α]= -13°

INTERMEDIO 34

[000465] *N*-(4-((*R*)-4-((2-(*tert*-Butildimetilsililoxi)etil)(metil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)-4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzamida



[000466] A una solución amarilla del ácido (*R*)-4-(4-((4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoico (INTERMEDIO 40, 1.64 g, 3.89 mmol), (*R*)-4-(4-((2-(*tert*-butildimetilsililoxi)etil)(metil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)bencenosulfonamida (INTERMEDIO 67, 2.68 g, 4.09 mmol), DMAP (0.95 g, 7.78 mmol) y diclorometano (41 ml) se añadió EDC (1.492 g, 7.78 mmol). Tras agitar durante 16 horas, la mezcla se diluyó con bicarbonato sódico saturado acuoso. Las capas se separaron y la capa acuosa se extrajo con diclorometano (x2). Las capas orgánicas combinadas se lavaron con cloruro sódico saturado acuoso, se secaron con sulfato de sodio, se filtraron y se concentraron a presión reducida. El concentrado se purificó mediante cromatografía en columna (ISCO, 330 g SiO₂, gradiente isocrático de 50% de acetato de etilo en hexanos durante 50 minutos, a continuación 50→65% de acetato de etilo en hexanos durante 30 minutos seguido de 65→100% de acetato de etilo en hexanos durante 20 min y posteriormente 0→10% de metanol en acetato de etilo durante 20 minutos) para proporcionar el producto del título (3.25 g, rendimiento: 79%).

[000467] ¹H RMN (300 MHz, DMSO-d₆, a 27 °C) δ 10.09 (s a, 0.4H), 8.11 (d, 1H), 7.90 - 8.00 (m, 1H), 7.68 (d, 2H), 7.59 (d, 1H), 7.10 - 7.54 (m, 12H), 6.89 (d, 2H), 6.75 (d, 2H), 5.21 (d, 1H), 4.24 - 4.39 (m, 1H), 4.04 (d, 1H), 3.73 (s a, 3H), 3.52 - 3.66 (m, 1H), 3.19 - 3.38 (m, 2H), 2.67 -

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3.01 (m, 4H), 2.39 - 2.66 (m, 5H), 2.00 (s, 3H), 1.53 - 1.71 (m, 1H), 0.96 - 1.15 (m, 2H), 0.83 - 0.93 (m, 1H), 0.81 (s, 9H), 0.00 (s, 6H).

[000468] ^{19}F RMN (282 MHz, DMSO- d_6) δ -78.91 (3F).

LCMS: (ESI) m/z 1059.4, 1061.4 $[\text{M}+\text{H}]^+$.

[000469] Rotación óptica:

Concentración: 0.14 g/dl

Lámpara: Sodio

Longitud de onda: 589 nm

Temperatura: 20 °C

Paso óptico: 10 cm

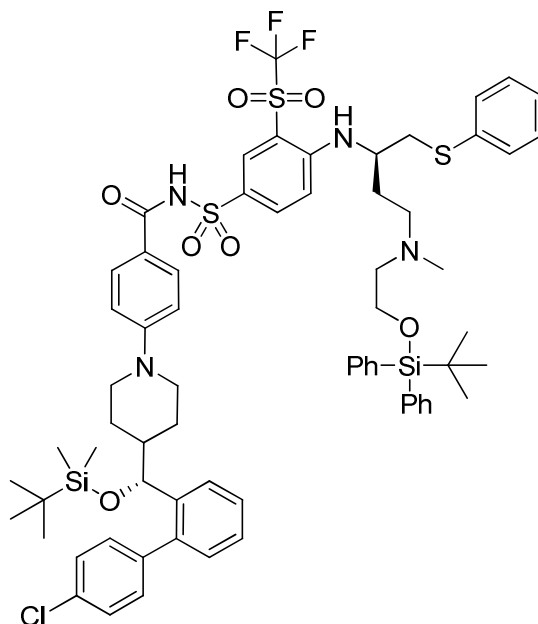
Volumen de la celda: 1 ml

Solvente: CH_2Cl_2

$[\alpha] = -2$

INTERMEDIO 34A

[000470] 4-(4-((*R*)-(tert-Butildimetilsililoxi)(4'-clorobifenil-2-il)metil)piperidin-1-il)-N-(4-((*R*)-4-((2-(tert-butildifenilsililoxi)etil)(metil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)fenilsulfonyl)benzamida

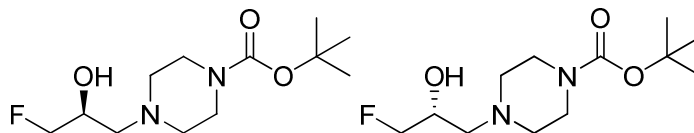


[000471] El producto del título (110 mg, rendimiento: 88%) se preparó utilizando un procedimiento similar al descrito para la síntesis del INTERMEDIO 32 utilizando el ácido 4-(4-((tert-butildimetilsililoxi)(4'-clorobifenil-2-il)metil)piperidin-1-il)benzoico (INTERMEDIO 13, 56.7 mg, 0.11 mmol) y (*R*)-4-(4-((2-(tert-butildifenilsililoxi)etil)(metil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida (INTERMEDIO 28, 75 mg, 0.10 mmol)

como materiales de partida. El producto del título se purificó mediante cromatografía en columna (ISCO, columna de 12 g de gel de sílice, eluyendo con 0→30 % de EtOAc/hexanos).

INTERMEDIO 35

[000472] (*S*)-4-(3-Fluoro-2-hidroxipropil)piperazin-1-carboxilato de *tert*-butilo y (*R*)-4-(3-fluoro-2-hidroxipropil)piperazin-1-carboxilato de *tert*-butilo, mezcla de enantiómeros



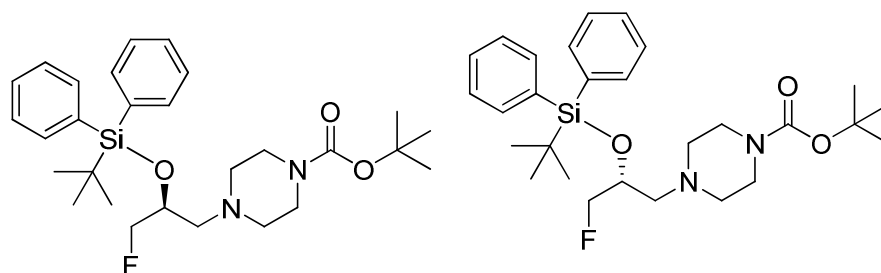
[000473] Se disolvió piperazin-1-carboxilato de *tert*-butilo (2.448 g, 13.15 mmol) en etanol (44.0 ml), se añadió epifluorohidrina (1.00 g, 13.15 mmol) a la solución y la mezcla de reacción resultante se agitó a 50 °C durante toda la noche. La mezcla de reacción se enfrió hasta temperatura ambiente, se concentró a presión reducida y se secó al alto vacío durante toda la noche para proporcionar los productos del título (0.345 g, rendimiento: cuantitativo) como una mezcla de enantiómeros.

[000474] ¹H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 4.59 – 4.46 (m, 1 H), 4.45 – 4.32 (m, 1 H), 3.98 (m, 1 H), 3.52 – 3.46 (m, 4 H), 2.66 – 2.55 (m, 3 H), 2.47 – 2.38 (m, 3 H), 1.47 (s, 9 H).

[000475] LCMS:(ESI) *m/z* 263[M+H]⁺.

INTERMEDIO 36

[000476] (*S*)-4-(2-(*tert*-Butildifenilsililoxi)-3-fluoropropil)piperazin-1-carboxilato de *tert*-butilo y (*R*)-4-(2-(*tert*-butildifenilsililoxi)-3-fluoropropil)piperazin-1-carboxilato de *tert*-butilo, mezcla de enantiómeros



[000477] (*S*)-4-(3-Fluoro-2-hidroxipropil)piperazin-1-carboxilato de *tert*-butilo y (*R*)-4-(3-fluoro-2-hidroxipropil)piperazin-1-carboxilato de *tert*-butilo, mezcla de enantiómeros (INTERMEDIO 35, 3.45 g, 13.15 mmol) se disolvieron en DMF (39.0 ml) y se añadió imidazol (1.790 g, 26.30 mmol). Se añadió *tert*-butildifenilclorosilano (5.06 ml, 19.73 mmol) a la solución y la mezcla de reacción se agitó durante toda la noche a temperatura ambiente. La mezcla de reacción se diluyó con EtOAc y se lavó con H₂O (2x). La capa orgánica se secó

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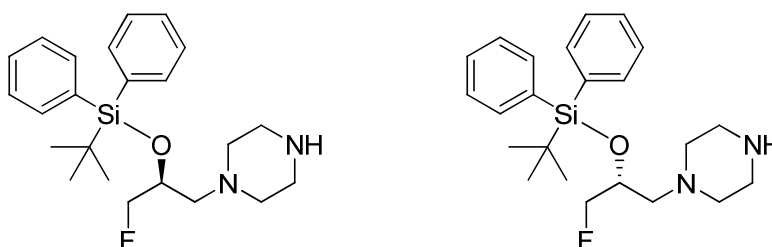
(Na₂SO₄) y se purificó mediante cromatografía SFC eluyendo con 90% de CO₂/10% de MeOH para proporcionar los productos del título como una mezcla de enantiómeros (3.77 g, rendimiento: 57%).

[000478] ¹H RMN (400 MHz, CLOROFORMO-d) δ ppm 7.73 – 7.70 (m, 4H), 7.46 – 7.40 (m, 6H), 4.49 – 4.37 (m, 2 H), 3.92 (m, 1 H), 3.50 (m, 1H), 3.30 – 3.20 (m, 4 H), 2.45 – 2.32 (m, 2 H), 2.22 – 2.14 (m, 3 H), 1.44 (s, 9 H), 1.07 (s, 9H).

[000479] LCMS: (ESI) *m/z* 501[M+H]⁺.

INTERMEDIO 37

[000480] (S)-1-(2-(*tert*-Butildifenilsililoxy)-3-fluoropropil)piperazina y (R)-1-(2-(*tert*-butildifenilsililoxy)-3-fluoropropil)piperazina, mezcla de enantiómeros



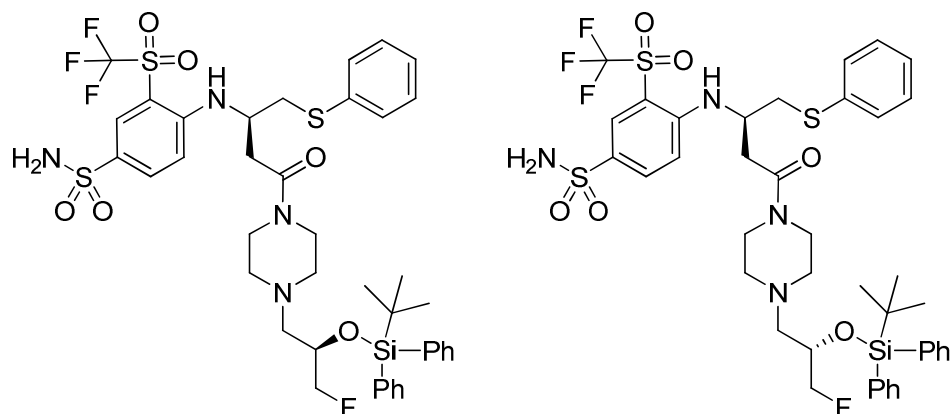
[000481] (S)-4-(2-(*tert*-Butildifenilsililoxy)-3-fluoropropil)piperazin-1-carboxilato de *tert*-butilo y (R)-4-(2-(*tert*-butildifenilsililoxy)-3-fluoropropil)piperazina-1-carboxilato de *tert*-butilo, mezcla de enantiómeros (INTERMEDIO 36, 3.7 g, 7.39 mmol) se disolvieron en DCM (31.0 ml) y se añadió TFA (5.69 ml, 73.89 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se concentró a presión reducida, se diluyó con DCM y se lavó con NaHCO₃ saturado acuoso. La capa orgánica se secó (Na₂SO₄), se concentró a presión reducida y se secó al alto vacío durante toda la noche para proporcionar los productos del título (3.12 g, rendimiento: 82%).

[000482] ¹H RMN (400 MHz, DMSO-d₆) δ ppm 7.68 - 7.63 (m, 4 H), 7.50 – 7.41 (m, 6H), 4.48 (m, 1H), 4.36 (m, 1H), 3.97 (m, 1H), 2.72 (m, 4H), 2.40 – 2.27 (m, 2H), 2.24 – 2.20 (m, 4H), 1.00 (s, 9H).

[000483] LCMS: (ESI) *m/z* 401[M+H]⁺.

INTERMEDIO 38

[000484] 4-((R)-4-(4-((R)-2-(*tert*-Butildifenilsililoxy)-3-fluoropropil)piperazin-1-il)-4-oxo-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida y 4-((R)-4-(4-((S)-2-(*tert*-butildifenilsililoxy)-3-fluoropropil)piperazin-1-il)-4-oxo-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida, mezcla de diastereómeros



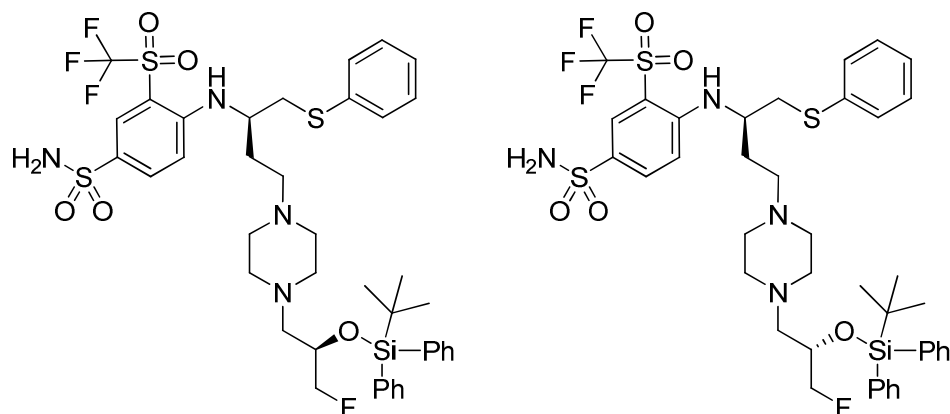
[000485] (*S*)-1-(2-(*tert*-Butildifenilsililoxy)-3-fluoropropil)piperazina y (*R*)-1-(2-(*tert*-butildifenilsililoxy)-3-fluoropropil)piperazina, mezcla de enantiómeros (INTERMEDIO 37, 0.194 g, 0.48 mmol) en THF (1.5 ml), 4-oxobenzo[*d*][1,2,3]triazin-3(4*H*)-ilfosfato de dietilo (0.276 g, 0.92 mmol) y DIPEA (0.161 ml, 0.92 mmol) se añadieron secuencialmente a una solución del ácido (*R*)-4-(feniltio)-3-(4-sulfamoil-2-(trifluorometilsulfonyl)fenilamino)butanoico (INTERMEDIO 8, 0.23 g, 0.46 mmol) en THF (3.0 ml) y la mezcla se agitó a temperatura ambiente durante toda la noche. La mezcla de reacción se concentró a presión reducida, se diluyó con EtOAc y la capa orgánica se lavó con NaHSO₄ ac. 1 N y NaHCO₃ saturado acuoso. La capa orgánica se secó (Na₂SO₄), se concentró a presión reducida para proporcionar un residuo que se purificó mediante cromatografía en columna (ISCO, columna de 40 g de gel de sílice, eluyendo con 0→100% de EtOAc/hexanos) para proporcionar los productos del título (280 mg, rendimiento: 69%).

[000486] ¹H RMN (400 MHz, DICLOROMETANO-*d*₂) δ ppm 8.18 (d, 1H), 7.83 - 7.79 (m, 2 H), 7.73 - 7.68 (m, 4 H), 7.48 - 7.23 (m, 11H), 6.62 (d, 1 H), 4.51 - 4.44 (m, 1H), 4.39 - 4.32 (m, 1H), 4.19 - 4.09 (m, 1H), 3.98 - 3.88 (m, 1H), 3.37 - 3.22 (m, 4H), 3.15 - 3.10 (m, 2H), 2.78 (dd, 1H), 2.56 (dd, 1H), 2.42 - 2.32 (m, 2H), 2.20 - 2.08 (m, 4H), 1.05 (s, 9H).

[000487] LCMS: (ESI) *m/z* 881[M+H]⁺.

INTERMEDIO 39

[000488] 4-((*R*)-4-(4-((*R*)-2-(*tert*-Butildifenilsililoxy)-3-fluoropropil)piperazin-1-il)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida y 4-((*R*)-4-(4-((*S*)-2-(*tert*-butildifenilsililoxy)-3-fluoropropil)piperazin-1-il)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida, mezcla de diastereómeros

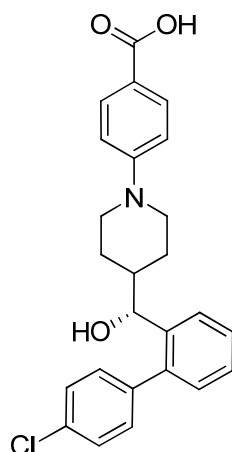


[000489] El producto del título (130 mg, rendimiento: 55%) se preparó utilizando un procedimiento similar al descrito para la síntesis del INTERMEDIO 25 utilizando 4-((*R*)-4-(4-((*R*)-2-(*tert*-butildifenilsililoxy)-3-fluoropropil)piperazin-1-il)-4-oxo-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)bencenosulfonamida y 4-((*R*)-4-(4-((*S*)-2-(*tert*-butildifenilsililoxy)-3-fluoropropil)piperazin-1-il)-4-oxo-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)bencenosulfonamida, mezcla de diastereómeros (INTERMEDIO 38, 0.24 g, 0.27 mmol) como materiales de partida. Los productos del título se purificaron mediante cromatografía en columna (ISCO, columna de 12 g de gel de sílice, eluyendo con 0→50 % de DCM/MeOH/NH₃ (10:1:0.1).

[000490] LCMS: (ESI) m/z 867[M+H]⁺.

INTERMEDIO 40

[000491] Ácido (*R*)-4-(4-((4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoico



[000492] Una solución de (*R*)-4-(4-((4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoato de etilo (INTERMEDIO 11A (primer compuesto eluido), 5.37 g, 11.93 mmol) en THF (160 ml), agua (40 ml) y metanol (40 ml) se agitó a 50 °C durante toda la noche. Los componentes volátiles se eliminaron a presión reducida y el sólido resultante se diluyó con agua (100 ml). El pH de la solución se ajustó a ~5 con HCl ac. 1 N (35 ml), esto provocó la formación de un precipitado. El sólido blanco se recogió por filtración y se lavó con agua (~150 ml). La masa

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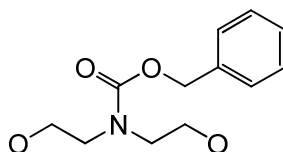
retenida en el filtro se secó al vacío durante toda la noche a 50 °C para proporcionar el producto del título (4.0 g, rendimiento: 79%).

[000493] ^1H RMN (400 MHz, DMSO- d_6) δ ppm 0.63 (cd, 3.79 Hz, 1 H) 0.72 - 1.00 (m, 2 H) 1.35 - 1.49 (m, 1 H) 1.67 (d, 1 H) 2.28 - 2.39 (m, 1 H) 2.46 (t, 1 H) 3.43 (d, 1 H) 3.59 (d, 1 H) 4.09 (d, 1 H) 6.63 (d, 2 H) 6.91 (dd, 1 H) 7.05 - 7.23 (m, 4 H) 7.23 - 7.29 (m, 2 H) 7.36 (d, 1 H) 7.47 (d, 2 H).

[000494] LCMS: (ESI) m/z 422[M+H] $^+$.

INTERMEDIO 41

[000495] Bis(2-hidroxietil)carbamato de bencilo



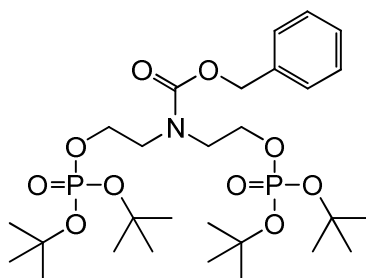
[000496] Una suspensión de 2,2'-azanodiildietanol (7.3 ml, 76.09 mmol), carbonato de sodio (18.33 g, 172.94 mmol), acetona (125 ml) y agua (125 ml) a 0 °C se trató gota a gota en un periodo de 15 minutos con Cbz-Cl (10.25 ml, 69.17 mmol). La suspensión se agitó durante 3 horas más a 0 °C. La suspensión se diluyó con agua (500 ml) y se extrajo con CHCl_3 (2 x 250 ml). Los extractos orgánicos combinados se secaron sobre sulfato de sodio, se filtraron y se concentraron a presión reducida. El concentrado se purificó mediante cromatografía en columna (ISCO, eluyendo con 0→10 % de MeOH/DCM durante 40 minutos) para proporcionar el producto del título (12.5 g, rendimiento: 76%).

[000497] ^1H RMN (400 MHz, DICLOROMETANO- d_2) δ ppm 3.04 - 3.22 (m, 1 H) 3.28 - 3.43 (m, 1 H) 3.51 (s a, 4 H) 3.80 (d, 4 H) 5.16 (s, 2 H) 7.24 - 7.60 (m, 5 H).

[000498] LCMS: (ESI) m/z 262 [M+Na] $^+$.

INTERMEDIO 42

[000499] Bis(2-(di-*tert*-butoxifosforilo)etil)carbamato de bencilo



[000500] Una solución de bis(2-hidroxietil)carbamato de bencilo (INTERMEDIO 41, 1.8 g, 7.52 mmol), dietilfosforamidito de di-*tert*-butilo (5.6 ml, 18.81 mmol) y THF (80 ml) se trató con

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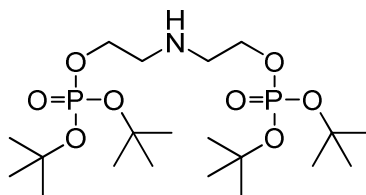
1*H*-tetrazol (1.58 g, 22.57 mmol). La mezcla se agitó durante 30 min a temperatura ambiente, posteriormente se enfrió hasta -78 °C y se añadió *m*-CPBA (7.42 g, 30.09 mmol) en porciones en un periodo de 2 minutos. La mezcla se agitó durante 20 minutos a -78 °C y se dejó calentar hasta temperatura ambiente. Los componentes volátiles se redujeron hasta 2/3 del volumen total a presión reducida mientras se mantenía el baño de agua a 30 °C. El concentrado se diluyó con acetato de etilo (300 ml), se lavó con bisulfito sódico ac. al 10% (100 ml) y NaHCO₃ saturado ac. (4x 100 ml), y se secó con sulfato de sodio. La evaporación de los componentes volátiles a presión reducida proporcionó un residuo, el cual se purificó mediante cromatografía en columna (ISCO, columna de 330g de gel de sílice, eluyendo con 0→20% de MeOH en DCM durante 53 minutos) para proporcionar el compuesto del título (2.5 g, rendimiento: 53%).

[000501] ¹H RMN (400 MHz, DICLOROMETANO-*d*₂) δ ppm 1.42 - 1.51 (m, 36 H) 3.58 - 3.66 (m, 4 H) 3.99 - 4.12 (m, 4 H) 5.16 (s, 2 H) 7.39 (d, 5 H).

[000502] LCMS: (ESI) *m/z* 624 [M+H]⁺.

INTERMEDIO 43

[000503] 2,2'-Azanodiilbis(etano-2,1-diil)difosfato de di-*tert*-butilo



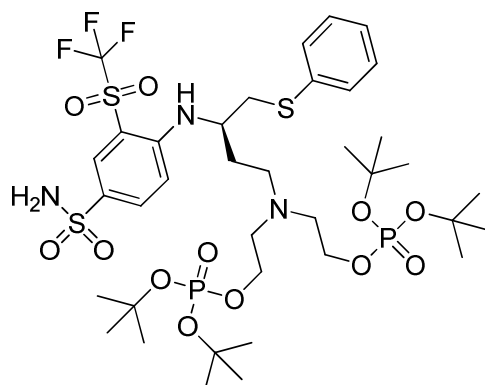
[000504] Una mezcla de Pd sobre carbón (5%, 0.64 g, 0.30 mmol), bis(2-(di-*tert*-butoxifosforiloxi)etil)carbamato de bencilo (INTERMEDIO 42, 2.500 g, 4.01 mmol) y MeOH (50 ml) se agitó en una atmósfera de hidrógeno durante 2 horas. El catalizador se filtró a través de un lecho de Celite® y el filtrado se concentró a presión reducida para proporcionar el compuesto del título (1.65 g, 84 %), que se utilizó en la preparación del INTERMEDIO 44 sin purificación posterior.

[000505] ¹H RMN (400 MHz, METANOL-*d*₄) δ ppm 1.48 - 1.58 (m, 36 H) 2.93 (s, 4 H) 3.99 - 4.22 (m, 4 H)

[000506] LCMS: *m/z* 490 [M+H]⁺.

INTERMEDIO 44

[000507] (*R*)-2,2'-(4-(Feniltio)-3-(4-sulfamoil-2-(trifluorometilsulfonil)fenilamino)butilazanodiil)bis(etano-2,1-diil)difosfato de di-*tert*-butilo



[000508] 2,2'-Azanodiilbis(etano-2,1-diil)difosfato de di-*tert*-butilo

Una solución de 2,2'-azanodiilbis(etano-2,1-diil)difosfato de di-*tert*-butilo (INTERMEDIO 43, 336 mg, 0.69 mmol), (*R*)-4-(4-oxo-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida (INTERMEDIO 45, 276 mg, 0.57 mmol) y DCM (10 ml) se trató con triacetoxiborohidruro de sodio (242 mg, 1.14 mmol). La mezcla resultante se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se diluyó con DCM (20 ml) y se lavó con bicarbonato sódico (saturado, 30 ml). La fase orgánica se secó con sulfato de sodio, se filtró y se concentró a presión reducida. El concentrado se purificó mediante cromatografía en columna (ISCO, eluyendo con 0→10% de MeOH en DCM durante 19 minutos) para proporcionar el compuesto del título (311 mg, rendimiento: 57 %).

[000509] ^1H RMN (300 MHz, DICLOROMETANO- d_2) δ ppm 1.36 - 1.52 (m, 36 H) 1.65 (s, 1 H) 2.04 (s, 1 H) 2.45 - 2.94 (m, 6 H) 3.21 (d, 2 H) 3.83 (q, 4 H) 4.05 - 4.31 (m, 1 H) 5.76 (s, 2 H) 6.95 (d, 2 H) 7.19 - 7.49 (m, 5 H) 7.96 - 8.09 (m, 1 H) 8.19 (d, 1 H).

[000510] LCMS: (ESI) m/z 956 $[\text{M}+\text{H}]^+$.

[000511] Rotación óptica:

Concentración: 0.1 g/dl

Lámpara: Sodio

Longitud de onda: 589 nm

Temperatura: 20 °C

Paso óptico: 10 cm

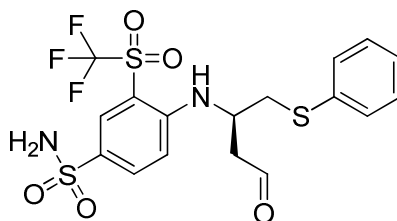
Volumen de la celda: 1 ml

Solvente: diclorometano

$[\alpha] = +12$

INTERMEDIO 45

[000512] (*R*)-4-(4-Oxo-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida



[000513] Una mezcla de (*R*)-4-(feniltio)-3-(4-sulfamoil-2-(trifluorometilsulfonyl)fenilamino)butanoato de metilo (INTERMEDIO 7, 3.1 g, 6.05 mmol) en DCM (155 ml) se enfrió hasta -78 °C y se añadió DIBAL-H en heptano (18.1 ml, 18.1 mmol) gota a gota. Una vez finalizada la adición, la mezcla se agitó durante 3 horas a -78 °C. Se añadieron metanol (8 ml) y solución acuosa de la sal de Rochelle (15.0 ml) secuencialmente y la mezcla de reacción se calentó hasta TA. Se agregó agua (150 ml) a la reacción y se separaron las capas. La capa orgánica se lavó con agua, se secó (Na₂SO₄) y se concentró al vacío para proporcionar el compuesto del título (2.9 g, rendimiento: casi cuantitativo).

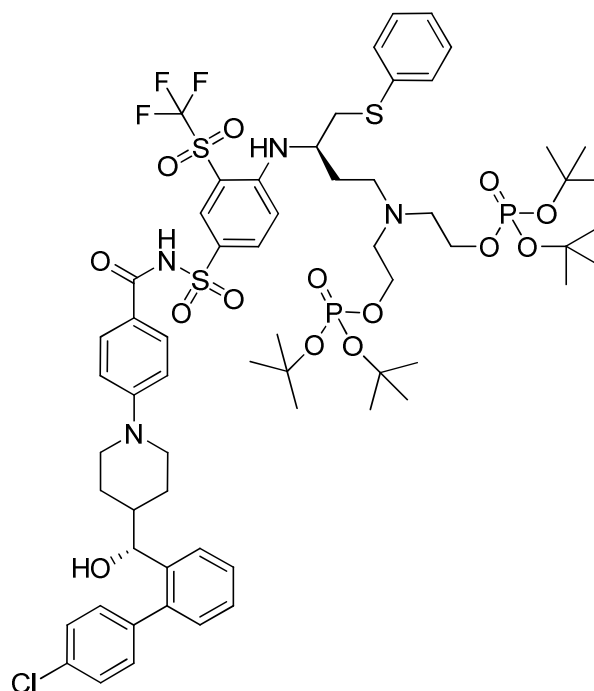
[000514] ¹H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 2.99 (dd2 H) 3.09 - 3.23 (m, 2 H) 4.22 (s a, 1 H) 4.78 (s, 1 H) 6.59 (d, 1 H) 7.19 (d, 1 H) 7.30 - 7.50 (m, 3 H) 7.88 (dd, 1 H) 8.28 (d, 1 H) 9.77 (s, 1 H).

[000515] LCMS: (ESI) *m/z* 481 [M-H]⁺.

[000516] A escalas superiores a 3.1 g, el INTERMEDIO 7 precipitó en solución en diclorometano a -78 °C. Por lo tanto, para reducciones con cantidades > 3.1 g de INTERMEDIO 7, el orden de adición se invirtió de forma que la solución del INTERMEDIO 7 en tetrahydrofurano se añadió a la solución de DIBAL-H a -78 °C mientras se mantenía la temperatura de reacción interna ≤ -70 °C. Una vez finalizada la adición del INTERMEDIO 7, la reacción se agitó y se trató de forma idéntica a la que se describió anteriormente.

INTERMEDIO 46

[000517] 2,2'-((*R*)-3-(4-(*N*-(4-(4-((*R*)-(4'-Clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonyl)fenilamino)-4-(feniltio)butilazanodiil)bis(etano-2,1-diil)difosfato de di-*tert*-butilo



[000518] Una solución de (*R*)-2,2'-(4-(feniltio)-3-(4-sulfamoil-2-(trifluorometilsulfonyl)fenilamino)butilazanodiil)bis(etano-2,1-diil)difosfato de di-*tert*-butilo (INTERMEDIO 44, 311 mg, 0.33 mmol), ácido (*R*)-4-(4-((4'-clorobifenil-2-il)(hidroxi)metil)piperidín-1-il)benzoico (INTERMEDIO 40, 137 mg, 0.33 mmol), EDC (125 mg, 0.65 mmol), DMAP (79 mg, 0.65 mmol), trietilamina (0.1 ml, 0.65 mmol) y DCM (10 ml) se agitó a temperatura ambiente durante 72 horas. Los componentes volátiles se eliminaron a presión reducida y el concentrado se purificó mediante cromatografía en columna (ISCO, columna de 80 g de gel de sílice, eluyendo con 0→10% de MeOH en DCM durante 19 minutos) para proporcionar el compuesto del título (258 mg, rendimiento: 58%).

[000519] ^1H RMN (400 MHz, DICLOROMETANO- d_2) δ ppm 0.92 - 1.37 (m, 3 H) 1.37 - 1.55 (m, 37 H) 1.56 - 1.89 (m, 3 H) 2.04 (s, 2 H) 2.54 - 2.89 (m, 8 H) 3.20 (dd, 2 H) 3.68 - 3.80 (m, 1 H) 3.85 - 4.00 (m, 5 H) 4.02 - 4.10 (m, 1 H) 4.40 - 4.60 (m, 1 H) 6.67 - 6.92 (m, 3 H) 7.09 - 7.55 (m, 13 H) 7.56 - 7.73 (m, 3 H) 8.07 - 8.21 (m, 1 H) 8.40 (d, 1 H).

[000520] LCMS: (ESI) m/z 1359 $[\text{M}+\text{H}]^+$.

[000521] Rotación óptica:

Concentración: 0.1 g/dl

Lámpara: Sodio

Longitud de onda: 589 nm

Temperatura: 20 °C

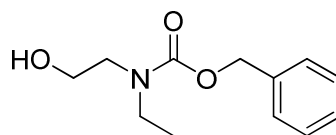
Paso óptico: 10 cm

Volumen de la celda: 1 ml

Solvente: diclorometano

[α]= +14

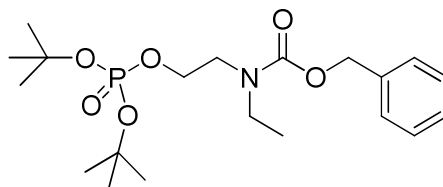
INTERMEDIO 47

[000522] Etil(2-hidroxietil)carbamato de bencilo

[000523] Se añadieron cloroformiato de bencilo (5.91 g, 34.67 mmol) y trietilamina (5.2 ml) secuencialmente a una solución de 2-(etilamino)etanol (3.0 g, 33.66 mmol) en DCM (180 ml) a 0 °C. El baño de hielo se eliminó y la mezcla de reacción se dejó agitar durante toda la noche a temperatura ambiente. La solución se lavó con ácido cítrico al 10% (100 ml) y H₂O (2 x 100 ml), y se concentró al vacío. La fase orgánica se secó (MgSO₄), se concentró a presión reducida y el concentrado se purificó mediante cromatografía en columna (ISCO, columna de gel de sílice, eluyendo con 60→100% de EtOAc/hexanos durante 14 minutos) para proporcionar el compuesto del título (7.29 g, rendimiento: 97%).

[000524] ¹H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1.16 (t, 3 H) 3.29 - 3.53 (m, 4 H) 3.79 (s a, 2 H) 5.17 (s, 2 H) 7.27 - 7.45 (m, 5 H).

INTERMEDIO 48

[000525] 2-(di-*tert*-Butoxifosforiloxi)etil(etil)carbamato de bencilo

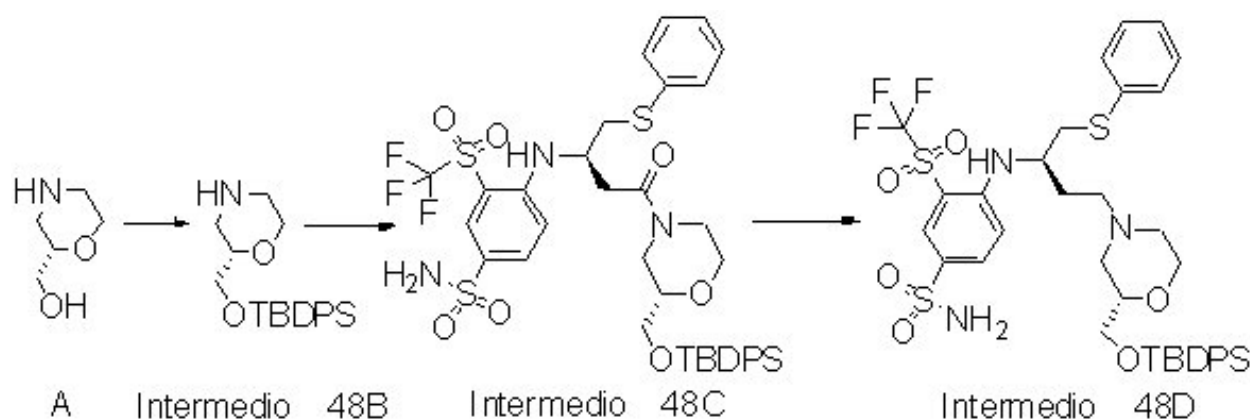
[000526] Una solución de etil(2-hidroxietil)carbamato de bencilo (INTERMEDIO 47, 1.0 g, 4.48 mmol) y dietilfosforamidito de di-*tert*-butilo (4.47 ml, 16.1 mmol) en THF (146 ml) se trató con tetrazol (1.57 g, 22.39 mmol) en una porción. La mezcla resultante se agitó a TA durante 50 minutos y la solución transparente se volvió turbia. La mezcla se filtró utilizando un baño de acetona/hielo seco (~ -77 °C) y se añadió *m*-CPBA (6.96 g) en el transcurso de ~1 minuto. La mezcla se agitó en estas condiciones durante 20 minutos y posteriormente se dejó calentar hasta TA durante 10 minutos. Se añadió bisulfito sódico (ac., al 10% p/v, 3.41 ml) y la mezcla se agitó durante 10 minutos, se concentró al vacío, se diluyó con EtOAc (200 ml), y se lavó con bisulfito sódico (ac., 100 ml) y NaHCO₃ (ac., 5% p/v, 100 ml). La capa orgánica se secó (Na₂SO₄), se filtró y se evaporó a presión reducida. El concentrado se purificó mediante cromatografía en columna (ISCO, columna de gel de sílice, eluyendo con 0→100% de EtOAc en hexanos) para

proporcionar el compuesto del título (1.1 g, rendimiento: 60%).

[000527] ^1H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1.28 (t, 3 H) 1.40 - 1.53 (s, 18 H) 2.97 - 3.08 (m, 2 H) 3.56 (d, 2 H) 3.97 - 4.17 (m, 2 H) 5.15 (s, 2 H) 7.29 - 7.42 (m, 5 H).

INTERMEDIO 48A

[000528] La estereoquímica del INTERMEDIO 48 se asignó en función del procedimiento que se describe a continuación:



[000529] Paso 1: Se añadieron piridina (0.207 ml, 2.56 mmol) y DMAP (0.021 g, 0.17 mmol) a una solución de (*S*)-morfolin-2-ilmetanol (A, Tyger Scientific Inc, 0.2 g, 1.71 mmol) en DCM (5.0 ml) y a continuación *tert*-butilclorodifenilsilano (0.526 ml, 2.05 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 48 horas. La mezcla de reacción se concentró a presión reducida y el concentrado se purificó mediante cromatografía en columna (ISCO, eluyendo con 10% de MeOH/DCM) para proporcionar (*S*)-2-((*tert*-butildifenilsililoxy)methyl)morfolina B (INTERMEDIO 48B, 0.26 g, rendimiento: 43%).

[000530] LCMS: m/z 356 $[\text{M}+\text{H}]^+$.

[000531] Paso 2: El ácido (*R*)-4-(feniltio)-3-(4-sulfamoil-2-(trifluorometilsulfonyl)fenilamino)butanoico (INTERMEDIO 8, 1.51 g, 3.03 mmol) se añadió a una solución de (*S*)-2-((*tert*-butildifenilsililoxy)methyl)morfolina (INTERMEDIO 48B, 1.185 g, 3.33 mmol) en DMF (9.04 ml) y a continuación se añadió secuencialmente DIPEA (1.058 ml, 6.06 mmol), EDC (0.871 g, 4.54 mmol) y HOBt (0.696 g, 4.54 mmol). La mezcla de reacción resultante se agitó a temperatura ambiente durante toda la noche y a continuación se diluyó con EtOAc. La fase orgánica se lavó con H_2O (2x), NaHSO_4 , ac. 1 N, NaHCO_3 saturado ac. y salmuera. La capa orgánica se secó (Na_2SO_4) y se concentró a presión reducida para proporcionar un residuo que se purificó mediante cromatografía en columna (ISCO, eluyendo con 50% de EtOAc/hexanos) para proporcionar 4-((2*R*)-4-(2-((*tert*-butildifenilsililoxy)methyl)morfolino)-4-oxo-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)

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bencenosulfonamida (INTERMEDIO 48C, 2.380 g, rendimiento: 94%).

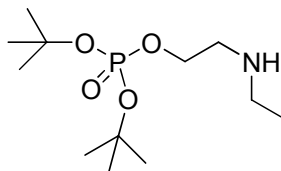
[000532] LCMS: m/z 837 $[M+H]^+$.

[000533] Paso 3: Una solución del complejo de $BH_3 \cdot THF$ (0.6 ml, 0.6 mmol) se añadió lentamente a una solución de 4-((2*R*)-4-(2-((*tert*-butildifenilsililo)metil)morfolino)-4-oxo-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida (INTERMEDIO 48C, 0.083 g, 0.10 mmol) y THF (0.4 ml), y la mezcla de reacción resultante se agitó a temperatura ambiente durante toda la noche. La mezcla se diluyó con una solución de NH_3 en MeOH (7 N, 20 ml) y se agitó a temperatura ambiente durante toda la noche. Tras evaporar los componentes volátiles a presión reducida, se obtuvo un residuo que se diluyó con EtOAc. La fase orgánica se lavó con H_2O (2x), se secó (Na_2SO_4), se filtró y se concentró a presión reducida para proporcionar 4-((*R*)-4-((*S*)-3-((*tert*-butildifenilsililo)metil)morfolino-1-il)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida (INTERMEDIO 48D, 0.030 g, 37%), que coincidía con el INTERMEDIO 48 al examinar las condiciones de HPLC quiral evaluadas previamente.

[000534] LCMS: m/z 822 $[M+H]^+$.

INTERMEDIO 49

[000535] 2-(Etilamino)etilfosfato de di-*tert*-butilo

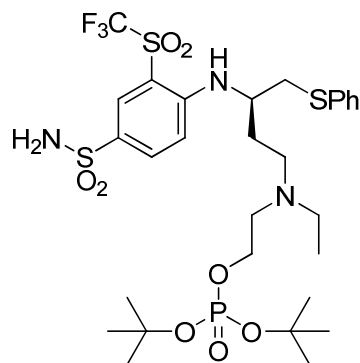


[000536] Se disolvió 2-(di-*tert*-butoxifosforiloxi)etil(etil)carbamato de bencilo (INTERMEDIO 48, 0.9 g, 2.17 mmol) en metanol (5 ml) y se añadió Pd al 5% sobre carbón (0.10 g). La mezcla de reacción se agitó a TA en una atmósfera de hidrógeno durante toda la noche. La mezcla de reacción se filtró y se concentró al vacío para proporcionar el compuesto del título (0.57 g, rendimiento: 94%).

[000537] ^1H RMN (300 MHz, $CDCl_3$) δ ppm 1.15 (t, 3 H) 1.42 - 1.55 (m, 18 H) 2.72 (d, 2 H) 2.84 - 2.96 (m, 2 H) 4.04 - 4.14 (m, 2 H).

INTERMEDIO 50

[000538] (*R*)-2-(Etil(4-(feniltio)-3-(4-sulfamoyl-2-(trifluorometilsulfonyl)fenilamino)butil)amino)etilfosfato de di-*tert*-butilo



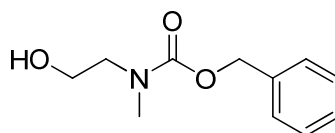
[000539] Se añadió una solución de 2-(etilamino)etilfosfato de di-*tert*-butilo (INTERMEDIO 49, 455 mg, 1.62 mmol) en 1,2-dicloroetano (0.5 ml) a TA a una solución de (*R*)-4-(4-oxo-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida (INTERMEDIO 45, 0.78 g, 1.62 mmol) y 1,2-dicloroetano (10.0 ml). La reacción resultante se agitó durante 15 minutos a TA y se añadió triacetoxiborohidruro de sodio sólido (0.514 g, 2.42 mmol). La mezcla resultante se agitó a TA durante 4 horas. Una solución de NaOH (ac., 0.5 N, 40 ml) y DCM (20 ml) se añadió a la mezcla de reacción. Tras agitar durante 15 min a TA, las capas se separaron. Después de la separación, la capa orgánica se lavó con NaHCO₃ saturado y salmuera, se secó (Na₂SO₄) y se concentró al vacío. El concentrado se purificó mediante cromatografía en columna (ISCO, gel de sílice, eluyendo con 0→100% de EtOAc/hexanos) para proporcionar el compuesto del título (610 mg, rendimiento: 50%).

[000540] ¹H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 0.96 (t, 3 H) 1.32 - 1.53 (m, 18 H) 1.58 (s, 3 H) 2.37 - 2.60 (m, 4 H) 3.10 (d, 2 H) 3.71 (d, 2 H) 3.91 - 4.08 (m, 1 H) 5.43 (s, 2 H) 6.75 (d, 1 H) 6.98 (d, 1 H) 7.27 - 7.44 (m, 4 H) 7.93 (dd, 1 H) 8.26 (d, 1 H).

[000541] LCMS: (ESI) *m/z* 746 [M-H]⁺.

INTERMEDIO 51

[000542] 2-Hidroxietil(metil)carbamato de bencilo



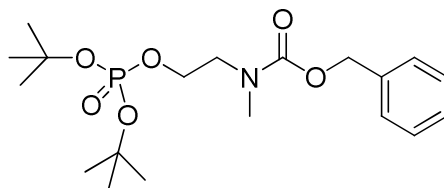
[000543] Se siguió un procedimiento similar al descrito para el INTERMEDIO 47 utilizando 2-(metilamino)etanol (2.3 g, 30.62 mmol) como material de partida, y a continuación se purificó posteriormente mediante cromatografía en columna (ISCO, columna de gel de sílice, eluyendo con 60→100% de EtOAc/hexanos durante 14 minutos) para proporcionar el producto del título (5.96 g, rendimiento: 93%).

[000544] ¹H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 2.25 (s, 1 H) 3.02 (s, 3 H) 3.48 (t, 2

H) 3.78 (s a, 2 H) 5.15 (s, 2 H) 7.21 - 7.44 (m, 5 H).

INTERMEDIO 52

[000545] 2-(Di-*tert*-Butoxifosforiloxi)etil(metil)carbamato de bencilo

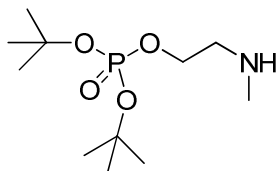


[000546] Se siguió un procedimiento similar al descrito para el INTERMEDIO 48 utilizando 2-hidroxi-etil(metil)carbamato de bencilo (INTERMEDIO 51, 0.46 g, 2.20 mmol) como material de partida y a continuación se purificó mediante cromatografía en columna (ISCO, columna de 12 g de gel de sílice, eluyendo con 0→100% de EtOAc/hexanos) para proporcionar el producto del título (590 mg, rendimiento: 67%).

[000547] ^1H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1.39 - 1.53 (m, 18 H) 2.95 - 3.09 (m, 3 H) 3.56 (d, 2 H) 4.07 (dd, 2 H) 5.15 (s, 2 H) 7.25 - 7.43 (m, 5 H).

INTERMEDIO 53

[000548] 2-(Metilamino)etilfosfato de di-*tert*-butilo

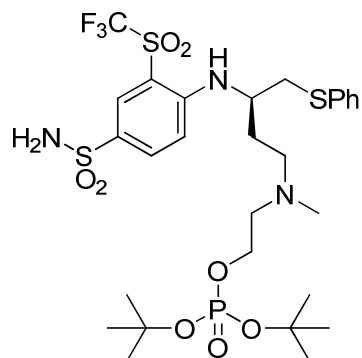


[000549] Se siguió un procedimiento similar al descrito para el INTERMEDIO 49 utilizando 2-(di-*tert*-butoxifosforiloxi)etil(metil)carbamato de bencilo (INTERMEDIO 52, 0.59 g, 1.47 mmol) como material de partida para proporcionar el producto del título (370 mg, rendimiento: 95%).

[000550] ^1H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1.48 - 1.55 (m, 18 H) 2.67 (s, 3 H) 3.11 - 3.22 (m, 2 H) 4.21 - 4.36 (m, 2 H).

INTERMEDIO 54

[000551] (*R*)-2-(Metil(4-(feniltio)-3-(4-sulfamoil-2-(trifluorometilsulfonil)fenilamino)butil)amino)etilfosfato de di-*tert*-butilo



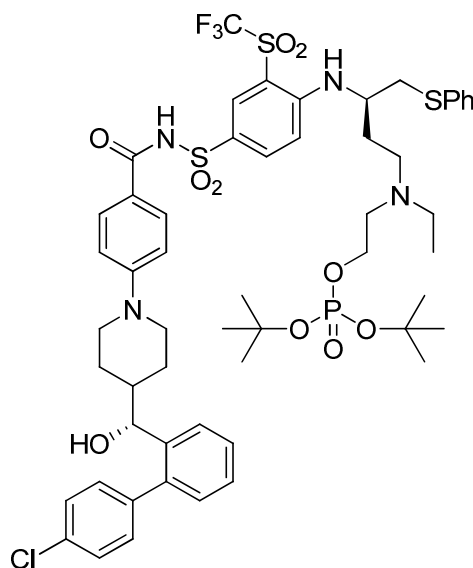
[000552] Se siguió un procedimiento similar al descrito para el INTERMEDIO 50 utilizando (*R*)-4-(4-oxo-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida (INTERMEDIO 45, 0.68 g, 1.4 mmol) y 2-(metilamino)etilfosfato de di-*tert*-butilo (INTERMEDIO 53 0.37 mg, 1.4 mmol) como materiales de partida y a continuación se purificó mediante cromatografía en columna (ISCO, columna de 12 g de gel de sílice, eluyendo con 0→100% de EtOAc/hexanos) para proporcionar el producto del título (640 mg, rendimiento: 62%).

[000553] ^1H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1.35 - 1.52 (m, 18 H) 2.21 (s, 3 H) 2.54 (s a, 2 H) 3.10 (t, 2 H) 3.80 (s a, 3 H) 3.96 - 4.11 (m, 2 H) 5.45 (s a, 2 H) 6.84 (d, 1 H) 7.04 (s, 1 H) 7.27 - 7.44 (m, 4 H) 7.98 (dd, 1 H) 8.25 (d, 1 H).

[000554] LCMS: (ESI) m/z 732 $[\text{M}-\text{H}]^+$.

INTERMEDIO 55

[000555] 2-(((*R*)-3-(4-(*N*-(4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonyl)fenilamino)-4-(feniltio)butil)(etil)amino)etilfosfato de di-*tert*-butilo



[000556] A una solución del ácido (*R*)-4-(4-((4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-

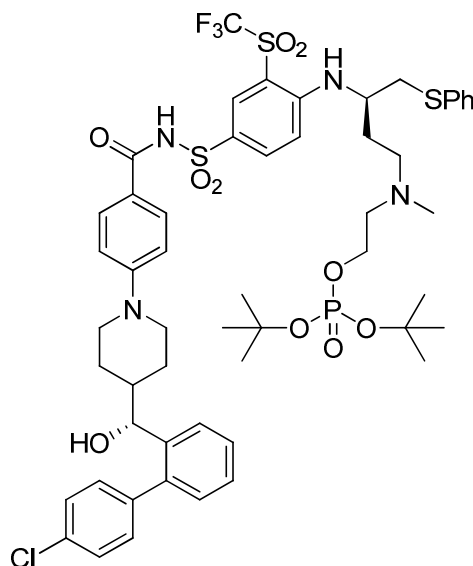
il)benzoico (INTERMEDIO 40, 88 mg, 0.20 mmol), EDC (77 mg, 0.40 mmol), DMAP (49 mg, 0.40 mmol) y trietilamina (28 μ l, 0.20 mmol) en 5 ml de DCM se añadió (R)-2-(etil(4-(feniltio)-3-(4-sulfamoil-2-(trifluorometilsulfonil)fenilamino)butil)amino)etilfosfato de di-*tert*-butilo (INTERMEDIO 50, 150 mg, 0.20 mmol). La mezcla se agitó a TA durante toda la noche. La solución de reacción se diluyó con DCM (20 ml) y se lavó con agua (30 ml). La capa acuosa se extrajo con DCM (30 ml) y las capas orgánicas combinadas se secaron con sulfato de sodio y se concentraron al vacío para obtener un aceite. Este material se purificó mediante cromatografía en columna (ISCO, 0→100% de EtOAc/hexano, seguido de 0→10% de MeOH/EtOAc) para proporcionar el compuesto del título (137 mg, rendimiento: 59%).

[000557] ^1H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 0.85 - 1.10 (m, 4 H) 1.16 - 1.35 (m, 1 H) 1.48 (d, 18 H) 1.81 (s a, 3 H) 2.40 - 2.88 (m, 8 H) 3.11 (d, 2 H) 3.62 - 3.76 (m, 1 H) 3.93 (d, 4 H) 4.50 (d, 1 H) 6.58 - 6.70 (m, 1 H) 6.77 (d, 2 H) 7.11 - 7.51 (m, 12 H) 7.54 - 7.70 (m, 3 H) 8.12 (s a, 1 H) 8.38 (s, 1 H).

[000558] LCMS: (ESI) m/z 1150 $[\text{M}-\text{H}]^+$.

INTERMEDIO 56

[000559] 2-(((R)-3-(4-(N-(4-(4-((R)-(4'-Clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)-4-(feniltio)butil)(metil)amino)etilfosfato de di-*tert*-butilo



[000560] Se siguió un procedimiento similar al descrito para el INTERMEDIO 55 utilizando el ácido (R)-4-(4-((4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoico (INTERMEDIO 40, 63 mg, 0.14 mmol) y (R)-2-(metil(4-(feniltio)-3-(4-sulfamoil-2-(trifluorometilsulfonil)fenilamino)butil)amino)etilfosfato de di-*tert*-butilo (INTERMEDIO 54, 105 mg, 0.14 mmol) como materiales de partida y posteriormente se purificó mediante

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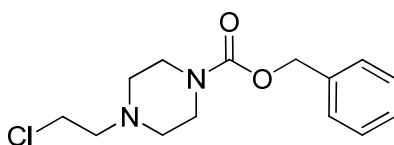
cromatografía en columna (ISCO, 0→100% de EtOAc/hexano seguido de 0→10% de MeOH/EtOAc) para proporcionar el producto del título (98 mg, rendimiento: 60%).

[000561] ^1H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 0.97 - 1.12 (m, 2 H) 1.48 (d, 21 H) 1.79 (s a, 4 H) 2.27 (s a, 3 H) 2.68 (s a, 7 H) 3.10 (s a, 2 H) 3.69 (s a, 1 H) 3.81 - 4.09 (m, 4 H) 4.50 (d, 1 H) 6.55 - 6.68 (m, 1 H) 6.78 (d, 2 H) 7.12 - 7.52 (m, 12 H) 7.53 - 7.67 (m, 3 H) 8.13 (d, 1 H) 8.39 (d, 1 H).

[000562] LCMS: (ESI) m/z 1138[M+H] $^+$.

INTERMEDIO 57

[000563] 4-(2-Cloroetil)piperazin-1-carboxilato de bencilo



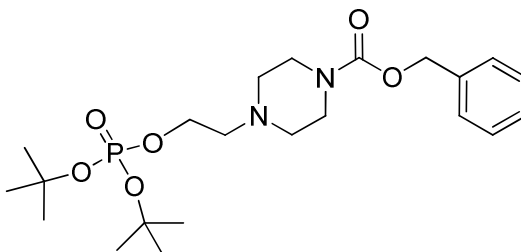
[000564] Se disolvieron piperazin-1-carboxilato de bencilo (1.00 g, 4.54 mmol) y K_2CO_3 (1.255 g, 9.08 mmol) en acetonitrilo (12.87 ml) para formar una suspensión. Se añadió 1-bromo-2-cloroetano (2.3 ml, 27.24 mmol) a la mezcla de reacción a TA y la mezcla resultante se agitó a esta temperatura durante 96 horas. Se filtró la mezcla de reacción y se concentró el filtrado a presión reducida. La purificación mediante cromatografía en columna (ISCO, columna de gel de sílice, eluyendo con 0→100% de EtOAc en hexanos) proporcionó el compuesto del título (0.64 g, rendimiento: 50 %).

[000565] ^1H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 7.28 - 7.43 (m, 5 H) 5.15 (s, 2 H) 3.48 - 3.65 (m, 6 H) 2.76 (t, 2 H) 2.42 - 2.57 (m, 4 H).

[000566] LCMS: (ESI) m/z 283[M+H] $^+$.

INTERMEDIO 58

[000567] 4-(2-(Di-*tert*-butoxifosforilo)etil)piperazin-1-carboxilato de bencilo



[000568] Se trató una solución de 4-(2-cloroetil)piperazin-1-carboxilato de bencilo (INTERMEDIO 57 0.12 g, 0.42 mmol) en tolueno (1.415 ml) con di-*tert*-butilfosfato de plata (INTERMEDIO 59, 0.148 g, 0.47 mmol). La mezcla de reacción se agitó a 100 °C durante 100 min. Se filtró la mezcla de reacción y se concentró el filtrado a presión reducida para

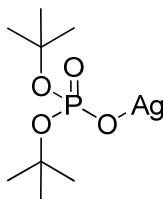
proporcionar el compuesto del título (0.14 g, rendimiento: 73%), el cual se utilizó en la preparación del INTERMEDIO 60, sin purificación adicional.

[000569] ^1H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 7.31 - 7.43 (m, 5 H) 5.15 (s, 2 H) 4.01 - 4.14 (m, 2 H) 3.47 - 3.60 (m, 4 H) 2.69 (t, 2 H) 2.44 - 2.57 (m, 4 H) 1.50 (s, 18 H).

[000570] LCMS: (ESI) m/z 457[M+H] $^+$.

INTERMEDIO 59

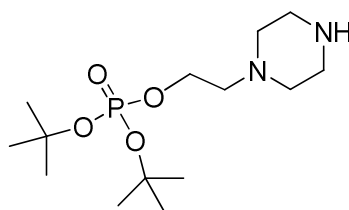
[000571] Di-*tert*-butilfosfato de plata



[000572] Se disolvió di-*tert*-butilfosfato de potasio (18.94 g, 76.28 mmol) en agua (140 ml) y se enfrió en un baño de hielo. La solución se removió a mano y se trató con HCl concentrado gota a gota (~28 ml), lo que provocó la formación de un precipitado blanco. El precipitado se recogió en un embudo Büchner, se lavó con agua (70 ml) y se secó al aire durante varios minutos. El polvo crudo resultante (15.09 g) se disolvió en un vaso de 2 l en una mezcla de hidróxido de bario octahidratado (24.12 g, 76.45 mmol) en agua (400 ml). Se burbujó dióxido de carbono (g) en la solución, lo que provocó la formación copiosa de precipitado blanco. La mezcla se filtró con un embudo Büchner y el filtrado turbio se evaporó para proporcionar un sólido blanco (~21 g). Se disolvió la mayor parte del material en MeOH (~250 ml). La suspensión blanca de polvo se eliminó mediante filtración a través de Celite® y el filtrado transparente se evaporó para proporcionar un sólido blanco crudo (~20 g). El material se disolvió en MeOH (25-30 ml) y se añadió acetona (900 ml) para que precipitara. El precipitado blanco se recogió en un embudo Büchner y se lavó con acetona para proporcionar di-*tert*-butilfosfato de bario como un sólido blanco (14.60 g, 26.27 mmol). El di-*tert*-butilfosfato de bario se disolvió en agua (100 ml) y se añadió a una solución de sulfato de plata (8.19 g, 26.27 mmol) en agua (1100 ml), lo que provocó la formación de un precipitado blanco. La mezcla se filtró a través de Celite® y el filtrado transparente se evaporó para proporcionar un sólido blanco. Se disolvió la mayor parte del material en MeOH (~600 ml) y se eliminó la suspensión blanca de polvo mediante filtración a través de Celite®. El filtrado se concentró, se trató con tolueno (~200 ml) y se evaporó a sequedad para proporcionar el compuesto del título (15.1 g, rendimiento: 62%).

[000573] LCMS: (ESI) m/z 209 [M-Ag].

INTERMEDIO 60

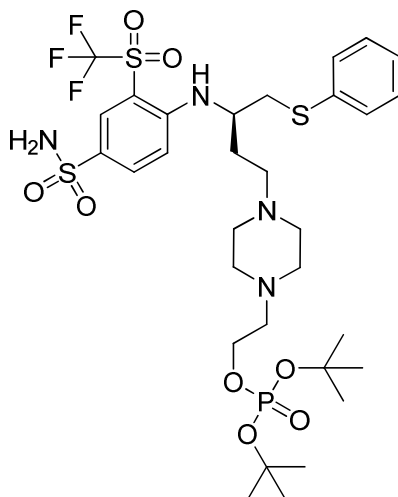
[000574] 2-(Piperazin-1-il)etilfosfato de di-*tert*-butilo

[000575] En un matraz de 100 ml, se introdujeron 4-(2-(di-*tert*-butoxifosforiloxi)etil)piperazin-1-carboxilato de bencilo (INTERMEDIO 58, 0.90 g, 1.97 mmol) en MeOH (19.7 ml) paladio sobre carbón al 10% (0.042 g, 0.04 mmol). La mezcla de reacción se agitó en una atmósfera de hidrógeno durante toda la noche. Se filtró la mezcla de reacción y se concentró el filtrado al vacío para proporcionar el compuesto del título (0.63 g, rendimiento: 99 %), el cual se utilizó en la preparación del INTERMEDIO 61 sin purificación adicional.

[000576] ^1H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 4.08 (d, 2 H) 3.50 (s, 3 H) 2.89 - 2.99 (m, 4 H) 2.67 (t, 2 H) 2.51 - 2.61 (m, 4 H) 1.50 (s, 18 H). LCMS: (ESI) m/z 323[M+H] $^+$.

INTERMEDIO 61

[000577] (*R*)-2-(4-(4-(Feniltio)-3-(4-sulfamoil-2-(trifluorometilsulfonyl)fenilamino)butil)piperazin-1-il)etilfosfato de di-*tert*-butilo



[000578] Se añadió una solución de 2-(piperazin-1-il)etilfosfato de di-*tert*-butilo (INTERMEDIO 60, 0.31 g, 0.95 mmol) en 1,2-dicloroetano (4 ml) a una solución de (*R*)-4-(4-oxo-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida (INTERMEDIO 45, 0.46 g, 0.95 mmol) en dicloroetano (5.0 ml) a temperatura ambiente. La mezcla de reacción se agitó durante 15 minutos a TA y se añadió triacetoxiborohidruro de sodio sólido (0.30 g, 1.43 mmol). La mezcla se agitó durante 1 hora a temperatura ambiente. Se añadieron NaOH 0.5 N (10 ml) y DCM (20 ml) a la mezcla de reacción. Después de agitar durante 15 min a TA, las

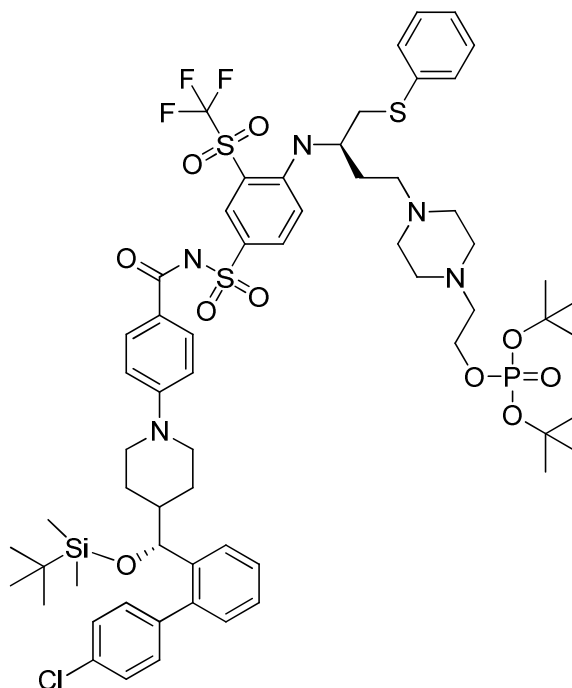
fases se separaron y la fase orgánica se lavó con NaHCO_3 (saturado acuoso) y salmuera, y se secó (Na_2SO_4). Los componentes volátiles se eliminaron a presión reducida. La purificación mediante cromatografía en columna (ISCO, columna de gel de sílice, eluyendo con 0→100% de EtOAc en hexanos) proporcionó el compuesto del título (0.71 g, rendimiento: 94 %).

[000579] ^1H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 8.26 (d, 1 H) 7.91 (dd, 1 H) 7.29 - 7.44 (m, 6 H) 5.24 (s a, 2 H) 4.07 (s a, 2 H) 3.94 (s a, 1 H) 3.10 (d, 2 H) 2.74 (s a, 3 H) 2.57 (s a, 4 H) 2.41 (s a, 5 H) 2.07 (s a, 1 H) 1.51 (d, 18 H).

[000580] LCMS: (ESI) m/z 790 $[\text{M}+\text{H}]^+$.

INTERMEDIO 62

[000581] 2-(4-((*R*)-3-(4-(*N*-(4-(4-((*R*)-(tert-butildimetilsililoxi)(4'-clorobifenil-2-il)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)-4-(feniltio)butil)piperazin-1-il)etilfosfato de di-*tert*-butilo

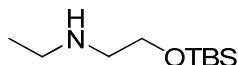


[000582] Se disolvieron el ácido (*R*)-4-(4-((*tert*-butildimetilsililoxi)(4'-clorobifenil-2-il)metil)piperidin-1-il)benzoico (INTERMEDIO 13, 170 mg, 0.32 mmol), (*R*)-2-(4-(4-(feniltio)-3-(4-sulfamoil-2-(trifluorometilsulfonil)fenilamino)butil)piperazin-1-il)etilfosfato de di-*tert*-butilo (INTERMEDIO 61, 275 mg, 0.35 mmol), DMAP (116 mg, 0.95 mmol) y EDC (122 mg, 0.63 mmol) en DCM (3.2 ml). La mezcla de reacción se agitó a TA durante 72 horas. La mezcla se diluyó con DCM (10 ml) y se lavó con una solución de NaHCO_3 (saturada, acuosa, 5 ml) y salmuera (5 ml). La fase orgánica recogida se secó con Na_2SO_4 y se concentró para proporcionar el compuesto del título (446 mg, rendimiento: casi cuantitativo). El compuesto del título se utilizó en la preparación del EJEMPLO 10 sin purificación adicional.

[000583] LCMS: (ESI) 1307 [M+H]⁺.

INTERMEDIO 63

[000584] 2-(*tert*-butildimetilsililoxi)-*N*-etiletanamina



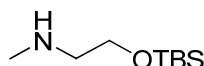
[000585] Se añadieron DIPEA (5.48 ml, 31.38 mmol) y *tert*-butilclorodimetilsilano (6.76 g, 22.42 mmol) a una solución de 2-(etilamino)etanol (1.998 g, 22.42 mmol) en DCM (39.3 ml) a temperatura ambiente. La mezcla se agitó a temperatura ambiente durante 20 horas y se repartió entre H₂O/Et₂O (50 ml/50 ml). La fase acuosa se extrajo con éter (3 x 30 ml). Las fases orgánicas combinadas se concentraron a presión reducida para proporcionar un residuo, el cual se volvió a disolver en DCM (50 ml), se secó (Na₂SO₄), se filtró y se concentró al vacío para proporcionar el compuesto del título (3.9 g, rendimiento: 85%).

[000586] ¹H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 3.66 (t, 2 H) 2.55 - 2.69 (m, 4 H) 1.43 (s a, 1 H) 1.05 (t, 3 H) 0.80 - 0.86 (m, 9 H) -0.03 - 0.05 (m, 6 H).

[000587] LCMS: *m/z* 204 [M+H]⁺.

INTERMEDIO 64

[000588] 2-(*tert*-butildimetilsililoxi)-*N*-metiletanamina



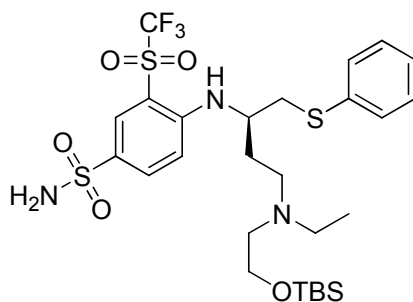
[000589] Se siguió un procedimiento similar al descrito para el INTERMEDIO 63 utilizando 2-(metilamino)etanol (2.0 g, 26.68 mmol) como material de partida, para proporcionar el producto del título (4.17 g, rendimiento: 83%).

[000590] LCMS: *m/z* 190 [M+H]⁺.

[000591] ¹H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 3.61 - 3.69 (m, 2 H) 2.57 - 2.65 (m, 2 H) 2.39 (s, 3 H) 1.47 (s a, 1 H) 0.80 - 0.87 (m, 9 H) -0.04 -0.01 (m, 6 H).

INTERMEDIO 65

[000592] (*R*)-4-(4-((2-(*tert*-butildimetilsililoxi)etil)(etil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)bencenosulfonamida

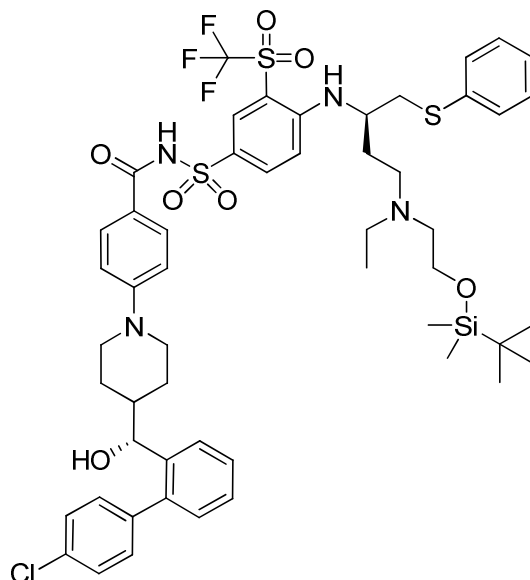


[000593] Se añadió triacetoxiborohidruro de sodio (2.62 g, 12.37 mmol) a una solución de (*R*)-4-(4-oxo-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida (INTERMEDIO 45, 3.98 g, 8.25 mmol) y 2-(*tert*-butildimetilsililoxi)-*N*-etiletanamina (INTERMEDIO 63, 1.68 g, 8.25 mmol) en 1,2-dicloroetano (27.5 ml). La mezcla resultante se agitó en la oscuridad durante 11.5 h y a continuación se detuvo con hidróxido de sodio acuoso 0.5 M (50 ml). Después de agitar enérgicamente durante 10 min, la mezcla opaca se volvió transparente. Las fases se diluyeron con acetato de etilo y a continuación se separaron. La fase orgánica se lavó con bicarbonato de sodio acuoso saturado y con cloruro de sodio acuoso saturado, antes de secarla con sulfato de sodio, filtrarla y concentrarla a presión reducida. El residuo resultante se purificó mediante cromatografía en columna (ISCO, 330 g de SiO₂, 50→100% de acetato de etilo en hexanos durante 20 min, a continuación 0→20% de metanol en acetato de etilo durante 20 min, a continuación 0→20% de metanol en acetato de etilo en 20 min) para proporcionar el producto del título (3.41 g, rendimiento: 62%).

[000594] LCMS: (ESI) m/z 670 [M+H]⁺.

INTERMEDIO 66

[000595] *N*-(4-((*R*)-4-((2-(*tert*-butildimetilsililoxi)etil)(etil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)fenilsulfonyl)-4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzamida



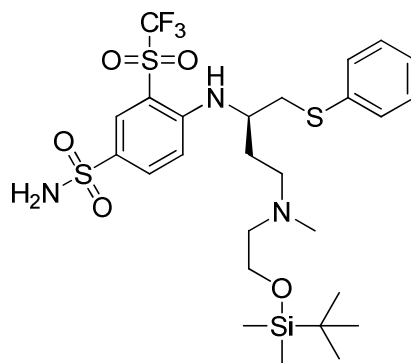
[000596] Se disolvieron el ácido (*R*)-4-(4-((4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoico (INTERMEDIO 40, 2.15 g, 5.10 mmol), (*R*)-4-(4-((2-(*tert*-butildimetilsililoxy)etil)(etil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)bencenosulfonamida (INTERMEDIO 65, 3.41 g, 5.10 mmol), DMAP (1.87 g, 15.29 mmol) y EDC (1.954 g, 10.19 mmol) en DCM (17 ml). La mezcla de reacción se agitó a TA durante toda la noche, se diluyó con DCM (50 ml) y se lavó con una solución de NH₄Cl (saturada, acuosa, 20 ml), NaHCO₃ saturado acuoso (20 ml) y salmuera (20 ml). La fase orgánica recogida se secó con Na₂SO₄ y se concentró a presión reducida. El concentrado se purificó mediante cromatografía en columna (ISCO, 12 g de gel de sílice, se eluyó con 0→20% de MeOH en EtOAc) para proporcionar el compuesto del título (3.41 g, rendimiento: 62%).

[000597] ¹H RMN (300 MHz, DICLOROMETANO-*d*₂) δ ppm 8.27 (s, 1 H) 7.92 (d, 1 H) 7.63 (d, 2 H) 7.55 - 7.59 (m, 1 H) 7.30 - 7.45 (m, 5 H) 7.15 - 7.30 (m, 6 H) 7.06 (d, 1 H) 6.74 (d, 2 H) 6.63 (d, 1 H) 4.46 (d, 1 H) 3.94 (d, 1 H) 3.83 (d, 1 H) 3.62 - 3.72 (m, 3 H) 3.08 (d, 2 H) 2.55 - 2.78 (m, 9 H) 2.00 (s a, 2H) 1.88 (s a, 1 H) 1.69 - 1.83 (m, 2 H) 1.20 - 1.35 (m, 1 H) 1.15 (s a, 1 H) 0.94 - 1.06 (m, 4 H) 0.80 - 0.87 (m, 9 H) 0.00 (s, 6 H).

[000598] LCMS: (ESI) *m/z* 1074[M+H]⁺.

INTERMEDIO 67

[000599] (*R*)-4-(4-((2-(*tert*-butildimetilsililoxy)etil)(metil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)bencenosulfonamida



[000600] Se añadió triacetoxiborohidruro de sodio (2.62 g, 12.37 mmol) a una solución de (*R*)-4-(4-oxo-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida (INTERMEDIO 45, 3.98 g, 8.25 mmol) y 2-(*tert*-butildimetilsililo)-*N*-metiletanamina (INTERMEDIO 64, 1.56 g, 8.25 mmol) en 1,2-diclorometano (27.5 ml). La mezcla resultante se agitó en la oscuridad durante 11.5 h y a continuación se añadió hidróxido de sodio (0.5 M, acuoso, 50 ml). La mezcla se diluyó con diclorometano (70 ml) y se agitó enérgicamente durante 10 min. Se separaron las fases y la fase orgánica se lavó con bicarbonato de sodio acuoso saturado. A continuación, la fase orgánica se diluyó mucho con acetato de etilo y se lavó con cloruro de sodio acuoso saturado (x2), antes de secarla con sulfato de sodio, filtrarla y concentrarla a presión reducida. El residuo resultante se purificó mediante cromatografía en columna (ISCO, 330 g de SiO₂, 0→50% de acetato de etilo en hexanos durante 30 min, a continuación se mantuvo un gradiente isocrático durante 30 min, a continuación 50→100% de acetato de etilo en hexanos en 20 min) para proporcionar el producto del título (2.68 g, rendimiento: 49.5 %). También se obtuvo producto del título adicional impuro (1.65 g), el cual se purificó mediante HPLC de fase reversa (Columna: Xbridge Phenyl OBD 19 mm x 100 mm, 5 µm; eluyendo con 65→80% de acetonitrilo en agua (NH₄OAc 10 mM, pH 8) durante 15 min). Las fracciones del producto se combinaron, se diluyeron con bicarbonato de sodio acuoso saturado y se extrajeron con acetato de etilo (x3). Las fases orgánicas combinadas se secaron con sulfato de sodio, se filtraron y se concentraron a presión reducida para proporcionar el producto del título (1.05 g, rendimiento: 19%).

[000601] ¹H RMN (300 MHz, CLOROFORMO-*d*) δ 8.21 (d, 1H), 7.75 (dd, 1H), 7.33 - 7.47 (m, 3H), 7.20 - 7.32 (m, 3H), 6.56 (d, 1H), 4.74 (s a, 2H), 3.80 - 3.97 (m, 1H), 3.52 - 3.71 (m, 2H), 3.04 (d, 2H), 2.31 - 2.65 (m, 4H), 2.21 (s a, 3H), 2.01 (s, 1H), 1.61 - 1.80 (m, 1H), 0.79 - 0.88 (m, 9H), 0.00 (s, 6H).

[000602] LCMS: (ESI) *m/z* 654 [M-H]⁺.

[000603] Rotación óptica:

Concentración: 0.15 g/dl

Lámpara: Sodio

104020-1 US/O

Longitud de onda: 589 nm

Temperatura: 20° C

Paso óptico: 10 cm

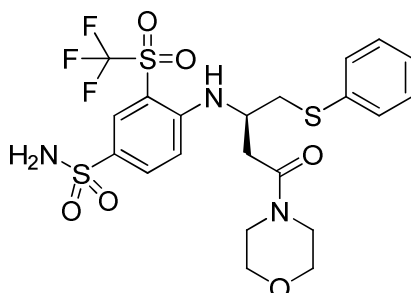
Volumen de la celda: 1 ml

Solvente: CH₂Cl₂

[α] = -111

INTERMEDIO 68

[000604] (R)-4-(4-morfolino-4-oxo-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)benzenosulfonamida



[000605] Una solución del ácido (R)-4-(feniltio)-3-(4-sulfamoil-2-(trifluorometilsulfonyl)fenilamino) butanoico (INTERMEDIO 8, 1.99 g, 4.01 mmol) y HATU (1.83 g, 4.82 mmol) en DMA (18.0 ml) se trató con morfolina (0.35 ml, 4.02 mmol) y DIPEA (1.40 ml, 8.02 mmol). La mezcla de reacción resultante se agitó a temperatura ambiente durante 1 hora y a continuación se diluyó con EtOAc (250 ml). La fase orgánica se lavó con agua (3 x 250 ml), NaHSO₄ 1M acuoso (200 ml) y NaHCO₃ saturado acuoso (200 ml). La fase orgánica se secó (Na₂SO₄), se filtró y se evaporó a presión reducida para proporcionar una espuma pegajosa. La espuma se disolvió en EtOAc (40 ml) y se lavó con agua (2 x 250 ml). Durante el segundo lavado, se observó la precipitación de material. Se añadió EtOAc (80 ml) y se agitó la mezcla resultante, lo que provocó la redisolución del precipitado. La mezcla se secó adicionalmente (Na₂SO₄), se filtró y se evaporó a presión reducida. El residuo se disolvió en unos ml de DCM, lo que provocó la formación de un precipitado. Finalmente, la evaporación de los componentes volátiles a presión reducida proporcionó el producto del título (2.02 g, rendimiento: 89%).

[000606] LCMS: (ESI) *m/z* 568[M+H]⁺.

[000607] Rotación óptica:

Concentración: 0.1 g/dl

Lámpara: Sodio

Longitud de onda: 589 nm

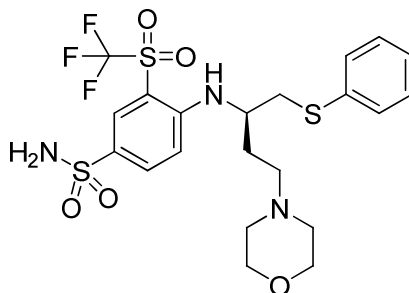
Temperatura: 20° C

104020-1 US/O

Paso óptico: 10 cm
Volumen de la celda: 1 ml
Solvente: CH₂Cl₂
[α]= -122

INTERMEDIO 69

[000608] (*R*)-4-(4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida



[000609] Se disolvió (*R*)-4-(4-morfolino-4-oxo-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida (INTERMEDIO 68, 2.01 g, 3.5 mmol) en una solución del complejo borano-THF (1M en THF, 8.0 ml, 8.0 mmol) y la solución resultante se agitó a temperatura ambiente durante toda la noche. El recipiente se abrió, poniéndolo en contacto con la atmósfera, y se trató cuidadosamente con MeOH (4.0 ml) y a continuación con HCl concentrado (1.55 ml). La mezcla resultante se calentó a reflujo durante 3 horas y a continuación se dejó enfriar hasta temperatura ambiente. El pH de la mezcla se ajustó hasta aproximadamente 10 mediante la adición de solución acuosa de Na₂CO₃ (2 M), lo que provocó la aparición de un precipitado. La mezcla se disolvió en EtOAc (250 ml), se lavó con agua (125ml) y salmuera (125 ml) y se secó (Na₂SO₄). La evaporación de los componentes volátiles a presión reducida proporcionó un concentrado, el cual se purificó mediante cromatografía en columna (ISCO, columna de 80 g de gel de sílice, eluyendo con 0→100% de EtOAc/ hexanos) para proporcionar el producto del título (1.33 g, rendimiento: 68%).

[000610] ¹H RMN (300 MHz, DMSO-*d*₆) δ ppm 1.65 - 1.81 (m, 1 H) 1.87 - 2.02 (m, 1 H) 2.09 - 2.40 (m, 6 H) 3.43 - 3.57 (m, 4 H) 4.02 - 4.18 (m, 1 H) 6.91 (d, 1 H) 7.06 (d, 1 H) 7.16 - 7.42 (m, 7 H) 7.85 (dd, 1 H) 7.98 (d, 1 H).

[000611] LCMS: (ESI) *m/z* : 554 [M+H]⁺.

[000612] Rotación óptica:

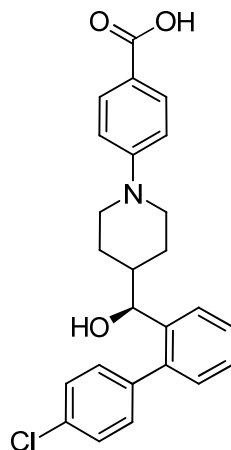
Concentración: 0.1 g/dl
Lámpara: Sodio
Longitud de onda: 589 nm

104020-1 US/O

Temperatura:	20° C
Paso óptico:	10 cm
Volumen de la celda:	1 ml
Solvente:	CH ₂ Cl ₂
[α]=	-147

INTERMEDIO 70

[000613] ácido (S)-4-(4-((4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoico



[000614] Se disolvió (S)-4-(4-((4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoato de etilo (INTERMEDIO 11B, 150.0 mg, 0.33 mmol) en THF (6.0 ml) y metanol (1.4 ml). Se añadió una solución de LiOH (40.6 mg) en agua (1.4 ml). La solución se calentó a 50 °C durante toda la noche. La mezcla de reacción se dejó enfriar hasta temperatura ambiente y a continuación se concentró a presión reducida. El residuo se diluyó con agua (5 ml), se acidificó con HCl 1 N acuoso (2.0 ml) y se extrajo con DCM (2 x 5 ml). El extracto se secó (MgSO₄), se filtró a través de algodón y se evaporó al vacío para proporcionar el producto del título como un enantiómero sustancialmente separado (155 mg, rendimiento: casi cuantitativo) ¹H RMN (400 MHz, DICLOROMETANO-*d*₂) δ ppm 0.79 - 0.94 (m, 1 H) 0.98 - 1.12 (m, 1 H) 1.14 - 1.40 (m, 4 H) 2.04 (m, 1 H) 2.67 (td, *J*=12.51, 2.78 Hz, 1 H) 2.78 (td, 1 H) 3.74 (d, 1 H) 3.91 (m, 1 H) 4.48 (d, 1 H) 6.81 (d, 2 H) 7.17 - 7.29 (m, 3 H) 7.31 - 7.49 (m, 4 H) 7.61 (dd, 1 H) 7.84 - 7.93 (m, 2 H).

[000615] LCMS: (ESI) *m/z* 420 [M-H]⁺.

[000616] Rotación óptica:

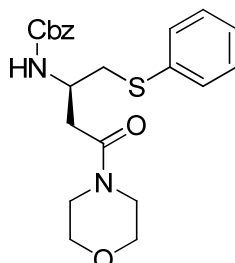
Concentración:	0.1 g/dl
Lámpara:	Sodio
Longitud de onda:	589 nm
Temperatura:	20 °C
Paso óptico:	10 cm

104020-1 US/O

Volumen de la celda: 1 ml
Solvente: CH₂Cl₂
[α]= -107

INTERMEDIO 71

[000617] (*R*)-4-morfolino-4-oxo-1-(feniltio)butan-2-ilcarbamato de bencilo

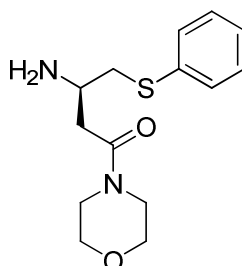


[000618] Se añadió morfolina (130 g, 1.49 mol) a una solución de (*R*)-5-oxotetrahidrofuran-3-ilcarbamato de bencilo (INTERMEDIO 3, 34.46 g, 0.147 mmol) en THF y la mezcla resultante se agitó a temperatura ambiente durante toda la noche. La mezcla de reacción se concentró a sequedad a presión reducida y el concentrado se volvió a disolver en EtOAc. La fase orgánica se lavó con HCl diluido, se secó con Na₂SO₄ y se concentró a presión reducida para proporcionar un aceite denso incoloro (24.2 g). Se trató una solución del aceite resultante (27.2 g, 84 mmol) en tolueno (250 ml) con sulfuro de difenilo (20.3 g, 109.2 mmol) y a continuación con Bu₃P (27.2 ml, 109.2 mmol). La mezcla de reacción se calentó a 80 °C durante toda la noche en una atmósfera de nitrógeno. La evaporación de los componentes volátiles a presión reducida proporcionó un residuo, el cual se purificó mediante cromatografía en columna (gel de sílice, 7 cm de altura x 14 cm de ancho, eluyendo con hexanos y a continuación 10:1, 2:1 y después 1:1 v/v de hexanos/EtOAc) para proporcionar el producto del título (25 g, rendimiento: 71.5 %).

[000619] LCMS: (ESI) *m/z* 413 [M-H]⁺.

INTERMEDIO 72

[000620] (*R*)-3-amino-1-morfolino-4-(feniltio)butan-1-ona



[000621] Se agitó una suspensión de (*R*)-4-morfolino-4-oxo-1-(feniltio)butan-2-ilcarbamato de bencilo (INTERMEDIO 71, 25 g, 60 mmol) en HBr al 40% en ácido acético (500 ml) a

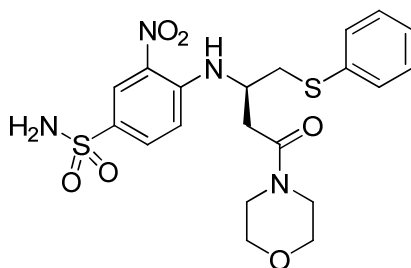
temperatura ambiente durante 50 h. La mezcla de reacción se volvió homogénea durante este periodo de tiempo. La mezcla de reacción se concentró a sequedad, se diluyó con agua (400 ml) y HCl acuoso al 5 % (200 ml) y se lavó con éter dietílico (3 x 100 ml). Se ajustó el pH de la fase acuosa a pH ~8-9 con Na₂CO₃ sólido y se extrajo enérgicamente con CH₂Cl₂ (5x). Las fases orgánicas combinadas se secaron (MgSO₄) y se concentraron a presión reducida para proporcionar el producto del título (16.9 g, rendimiento: casi cuantitativo), el cual se utilizó en la preparación del INTERMEDIO 73 sin purificación adicional.

[000622] ¹H-RMN (300 MHz, DMSO-*d*₆) δ 2.42 (dd, 1 H), 2.57 (dd, 1 H), 2.77 (m, 3 H), 2.97-3.02 (m, 1 H), 3.06-3.14 (m, 1 H), 3.37 (m, 2 H), 3.59 (m, 6 H), 7.18 (t, 1 H), 7.27 (d, 2 H), 7.37 (d, 2 H).

[000623] LCMS: (ESI) *m/z* 281 (M+H)⁺.

INTERMEDIO 73

[000624] (*R*)-4-(4-morfolino-4-oxo-1-(feniltio)butan-2-ilamino)-3-nitrobenzenosulfonamida



[000625] A una solución de (*R*)-3-amino-1-morfolino-4-(feniltio)butan-1-ona (INTERMEDIO 72, 375.5 mg, 1.34 mmol) en DMF (2.5 ml) y DIPEA (1.20 ml, 6.87 mmol), se añadió 4-fluoro-3-nitrobenzenosulfonamida (INTERMEDIO 18, 325.8 mg, 1.48 mmol) y la solución oscura resultante se agitó a 50 °C durante toda la noche en una atmósfera de nitrógeno. La mezcla se diluyó con EtOAc (50 ml), se lavó con agua y salmuera (30 ml cada lavado), se secó (Na₂SO₄), se filtró y se evaporó a presión reducida. El concentrado se purificó mediante cromatografía en columna (ISCO, columna de 40 g de gel de sílice, eluyendo con 0→100% de EtOAc/DCM) para proporcionar el producto del título (532.5 mg, rendimiento: 83%).

[000626] ¹H RMN (400 MHz, DICLOROMETANO-*d*₂) δ ppm 2.72 (dd, 1 H) 2.85 - 2.97 (m, 1 H) 3.25 - 3.44 (m, 4 H) 3.48 - 3.68 (m, 6 H) 4.26 - 4.39 (m, 1 H) 4.96 (s, 2 H) 6.76 (d, 1 H) 7.23 - 7.37 (m, 3 H) 7.37 - 7.46 (m, 2 H) 7.74 (dd, 1 H) 8.61 (d, 1 H) 9.08 (d, 1 H).

[000627] LCMS:(ESI) *m/z* 481 [M+H]⁺.

[000628] Rotación óptica:

Concentración: 0.1 g/dl

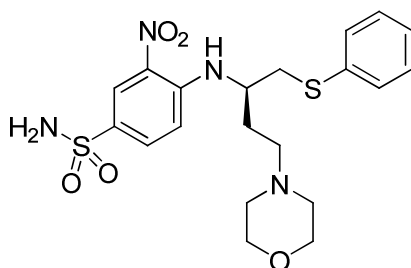
Lámpara: Sodio

104020-1 US/O

Longitud de onda: 589 nm
Temperatura: 20° C
Paso óptico: 10 cm
Volumen de la celda: 1 ml
Solvente: CH₂Cl₂
[α]= -212

INTERMEDIO 74

[000629] (*R*)-4-(4-morfolino-1-(feniltio)butan-2-ilamino)-3-nitrobenzenosulfonamida



[000630] En una atmósfera de nitrógeno, se disolvió (*R*)-4-(4-morfolino-4-oxo-1-(feniltio)butan-2-ilamino)-3-nitrobenzenosulfonamida (INTERMEDIO 73, 523.6 mg, 1.09 mmol) en una solución del complejo borano-THF (1M en THF; 2.4 ml, 2.4 mmol) y la solución resultante se agitó a temperatura ambiente durante toda la noche. El recipiente se abrió, poniéndolo en contacto con la atmósfera, y se trató cuidadosamente con MeOH (1.20 ml) y a continuación con HCl concentrado (0.48 ml). La mezcla resultante se calentó a reflujo durante 3 horas y a continuación se dejó enfriar hasta temperatura ambiente. El pH de la mezcla se ajustó hasta aproximadamente 10 mediante la adición de solución acuosa de Na₂CO₃ (4 M), lo que provocó la aparición de un precipitado. La mezcla se disolvió en EtOAc (75 ml), se lavó con agua (40 ml) y salmuera (40 ml) y se secó (Na₂SO₄). La evaporación de los componentes volátiles a presión reducida proporcionó un concentrado, el cual se purificó mediante cromatografía en columna (ISCO, columna de 40 g de gel de sílice, eluyendo con 0→100% de EtOAc/ hexanos) para proporcionar el producto del título (406.6 mg, rendimiento: 80 %).

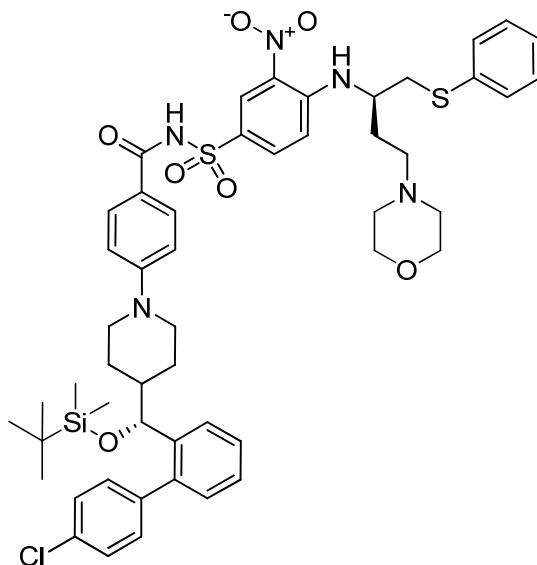
[000631] ¹H RMN (400 MHz, DMSO-*d*₆) δ ppm 1.75 - 1.87 (m, 1 H) 1.93 - 2.06 (m, 1 H) 2.14 - 2.43 (m, 6 H) 3.37 (m, 2 H) 3.45 - 3.59 (m, 4 H) 4.16 (m, 1 H) 7.12 (d, 1 H) 7.16 - 7.22 (m, 1 H) 7.23 - 7.29 (m, 2 H) 7.29 - 7.35 (m, 4 H) 7.71 (dd, 1 H) 8.36 - 8.45 (m, 2 H).

[000632] LCMS: (ESI) *m/z* 467 [M+H]⁺.

INTERMEDIO 75

[000633] 4-(4-((*R*)-(tert-butildimetilsililoxi)(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((*R*)-

4-morfolino-1-(feniltio)butan-2-ilamino)-3-nitrofenilsulfonil)benzamida



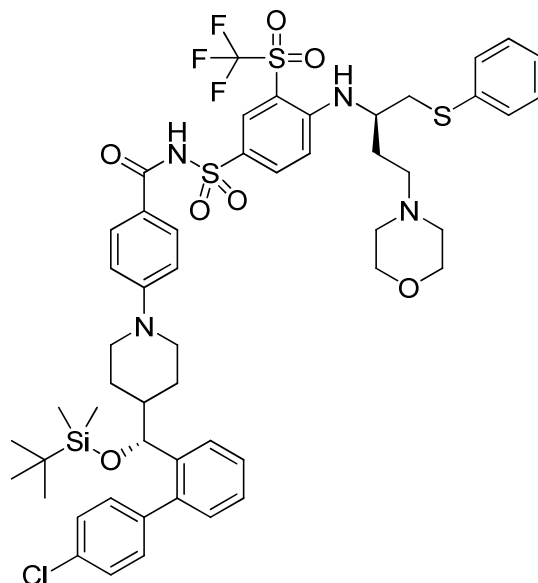
[000634] El producto del título (346.6 mg, rendimiento: 75%) se preparó utilizando un procedimiento similar al descrito para la síntesis del INTERMEDIO 33. Se utilizaron como materiales de partida el ácido (*R*)-4-(4-((*tert*-butildimetilsililoxy)(4'-clorobifenil-2-il)metil)piperidin-1-il)benzoico (INTERMEDIO 13, 250.7 mg, 0.47 mmol) y (*R*)-4-(4-morfolino-1-(feniltio)butan-2-ilamino)-3-nitrobenzenosulfonamida (INTERMEDIO 74, 229.0 mg, 0.49 mmol). El producto resultante se purificó mediante cromatografía en columna (ISCO, columna de 12 g de gel de sílice, eluyendo con 0→10 % de MeOH/DCM) para proporcionar el producto del título.

[000635] ^1H RMN (400 MHz, DICLOROMETANO- d_2) δ ppm -0.24 (s, 3 H) -0.07 (s, 3 H) 0.84 (s, 9 H) 1.50 - 1.62 (m, 1 H) 1.68 - 1.84 (m, 2 H) 2.04 - 2.15 (m, 1 H) 2.23 - 2.49 (m, 6 H) 2.56 - 2.72 (m, 2 H) 3.18 (d, 2 H) 3.55 - 3.69 (m, 4 H) 3.72 - 3.80 (m, 1 H) 3.81 - 3.90 (m, 1 H) 4.55 - 4.63 (m, 1 H) 6.78 (d, 2 H) 6.84 (d, 1 H) 7.12 (dd, 1 H) 7.17 - 7.44 (m, 11 H) 7.59 (d, 3 H) 7.93 (dd, 1 H) 8.55 - 8.63 (m, 1 H) 8.77 (d, 1 H).

[000636] LCMS:(ESI) m/z 984 $[\text{M}+\text{H}]^+$.

INTERMEDIO 76

[000637] 4-(4-((*R*)-(*tert*-butildimetilsililoxy)(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida



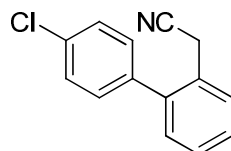
[000638] El producto del título (71.4 mg, rendimiento: 33%) se preparó utilizando un procedimiento similar al descrito para la síntesis del INTERMEDIO 33. Se utilizaron como materiales de partida el ácido (*R*)-4-(4-((*tert*-butildimetilsililoxi)(4'-clorobifenil-2-il)metil)piperidin-1-il)benzoico (INTERMEDIO 13, 106.7 mg, 0.2 mmol) y (*R*)-4-(4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)bencenosulfonamida (INTERMEDIO 69, 117 mg, 0.21 mmol). El producto resultante se purificó mediante cromatografía en columna (ISCO, columna de 4 g de gel de sílice, eluyendo con 0→100 % de EtOAc/hexanos) para proporcionar el producto del título.

[000639] ^1H RMN (400 MHz, CLOROFORMO-*d*) δ ppm -0.24 (s, 3 H) -0.07 (s, 3 H) 0.85 (s, 9 H) 1.38 (nonete, 2 H) 1.47 - 1.80 (m, 5 H) 2.08 - 2.19 (m, 1 H) 2.25 - 2.51 (m, 6 H) 2.57 - 2.73 (m, 2 H) 2.99 - 3.15 (m, 2 H) 3.60 - 3.72 (m, 4 H) 3.72 - 3.80 (m, 1 H) 3.81 - 3.89 (m, 1 H) 3.89 - 3.98 (m, 1 H) 4.56 - 4.63 (m, 1 H) 6.59 - 6.66 (m, 1 H) 6.78 (d, 2 H) 7.06 - 7.15 (m, 2 H) 7.20 (d, 2 H) 7.35 - 7.43 (m, 5 H) 7.53 - 7.65 (m, 3 H) 8.10 - 8.16 (m, 1 H) 8.35 - 8.40 (m, 1 H).

[000640] LCMS: (ESI) m/z 1071[M+H] $^+$.

INTERMEDIO 77

[000641] 2-(4'-clorobifenil-2-il)acetonitrilo



[000642] En un matraz de 3 bocas de 250 ml, se mezclaron 2-(2-bromofenil)acetonitrilo (5.00 g, 25.5 mmol), ácido 4-clorofenilborónico (4.30 g, 27.5 mmol) y tetrakis(trifenilfosfina)paladio(0) (0.48 g 0.42 mmol) con tolueno (57 ml). Se acopló un condensador de reflujo y el matraz se purgó con nitrógeno. Se añadió una solución acuosa de

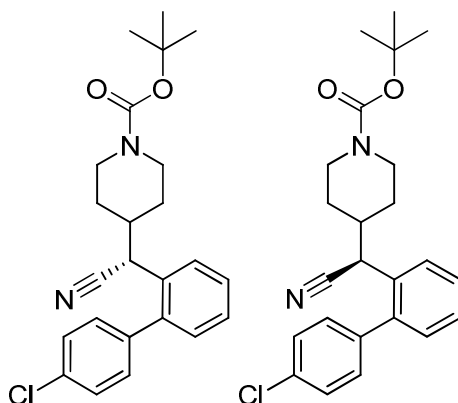
Na_2CO_3 (2 M, 29 ml, 58 mmol) con una jeringa, se hizo el vacío y a continuación se introdujo una atmósfera de nitrógeno. La mezcla de reacción se calentó a reflujo durante toda la noche y a continuación se dejó enfriar hasta temperatura ambiente. La mezcla se repartió entre NH_4Cl saturado acuoso y EtOAc (200 ml de cada uno). La fase orgánica se separó, se secó (MgSO_4), se filtró a través de tierra de diatomeas y el filtrado se evaporó a presión reducida. El residuo se purificó mediante cromatografía en columna (ISCO, columna de 120 g de gel de sílice, 0→20% de EtOAc/hexanos) para proporcionar el compuesto del título (5.44 g, rendimiento: 94%).

[000643] ^1H RMN (400 MHz, $\text{DMSO}-d_6$) δ ppm 3.91 (s, 2 H), 7.26 - 7.33 (m, 1 H), 7.36 - 7.49 (m, 4 H), 7.50 - 7.59 (m, 3 H).

[000644] LCMS: (ESI) m/z 228 $[\text{M}+\text{H}]^+$.

INTERMEDIO 78

[000645] (*R*)-4-((4'-clorobifenil-2-il)(ciano)metil)piperidin-1-carboxilato de *tert*-butilo y (*S*)-*tert*-4-((4'-clorobifenil-2-il)(ciano)metil)piperidin-1-carboxilato de *tert*-butilo, mezcla de enantiómeros



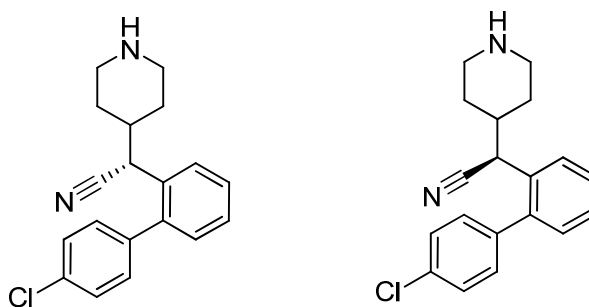
[000646] Se suspendió NaH (0.84 g, dispersión en aceite al 60%, 21 mmol) en DMF (5.0 ml) y la suspensión se trató con 2-(4'-clorobifenil-2-il)acetonitrilo (INTERMEDIO 77, 4.1 g, 17.9 mmol), lo que provocó que la mezcla se volviera de color rojo. La mezcla de reacción se agitó a temperatura ambiente durante 1 hora y durante este tiempo se observó la formación de más precipitado. La mezcla se enfrió hasta 0 °C y se añadió 4-iodopiperidin-1-carboxilato de *tert*-butilo (5.59 g, 17.97 mmol) junto con DMF adicional (5.0 ml) para facilitar la agitación. La mezcla se agitó a 0 °C durante 2 horas y a continuación se dejó calentar hasta alcanzar la temperatura ambiente durante 36 horas. La mezcla se diluyó con NH_4Cl saturado acuoso (50 ml) y agua (50 ml) y se extrajo con DCM (3 x 50 ml). Los extractos se lavaron con agua (150 ml), se secaron (MgSO_4), se filtraron y se evaporaron a presión reducida. El concentrado se purificó mediante cromatografía en columna (ISCO, columna de 330 g de gel de sílice, 0→25% de EtOAc/hexanos) para proporcionar los productos del título como una mezcla de enantiómeros.

[000647] ^1H RMN (400 MHz, DMSO- d_6) δ ppm 0.73 (cd, 1 H), 1.06 - 1.20 (m, 2 H), 1.35 (s, 9 H), 1.65 - 1.73 (m, 1 H), 1.83 - 1.95 (m, 1 H), 2.54 - 2.69 (m, 1 H), 3.72 - 3.82 (m, 1 H), 3.85 (d, 1 H), 3.88 - 3.97 (m, 1 H), 7.27 (dd, 1 H), 7.30 - 7.37 (m, 2 H), 7.42 - 7.48 (m, 1 H), 7.48 - 7.61 (m, 4 H).

[000648] LCMS: (ESI) m/z 433 $[\text{M}+\text{Na}]^+$

INTERMEDIO 79

[000649] (*R*)-2-(4'-clorobifenil-2-il)-2-(piperidin-4-il)acetonitrilo y (*S*)-2-(4'-clorobifenil-2-il)-2-(piperidin-4-il)acetonitrilo, mezcla de enantiómeros



[000650] Se mezclaron (*R*)-4-((4'-clorobifenil-2-il)(ciano)metil)piperidin-1-carboxilato de *tert*-butilo y (*S*)-4-((4'-clorobifenil-2-il)(ciano)metil)piperidin-1-carboxilato de *tert*-butilo, mezcla de enantiómeros (INTERMEDIO 78, 501 mg, 1.22 mmol), con DCM (3.0 ml) y MeOH (0.12 ml) y se trataron con TFA (3.0 ml). La mezcla de reacción se agitó a temperatura ambiente durante 15 minutos y a continuación los componentes volátiles se eliminaron a presión reducida. La mezcla resultante se mezcló con agua (~15 ml) y se basificó (pH ~11) mediante la adición de pequeñas porciones de K_2CO_3 sólido, removiendo con precaución (a la vez que enérgicamente). La mezcla turbia resultante se extrajo con DCM (3 x 15 ml) y los extractos combinados se lavaron con agua (20 ml), se secaron (MgSO_4), se filtraron y se evaporaron a presión reducida para proporcionar los productos del título (397 mg, rendimiento: cuantitativo) como una mezcla de enantiómeros.

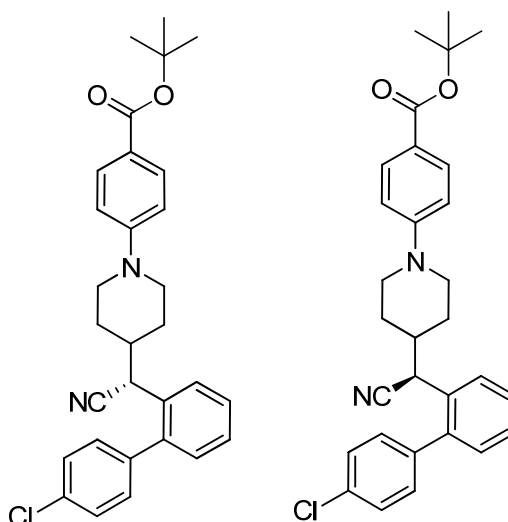
[000651] ^1H RMN (400 MHz, DMSO- d_6) δ ppm 0.75 (cd, 1 H), 1.02 - 1.15 (m, 2 H), 1.57 - 1.66 (m, 1 H), 1.67 - 1.78 (m, 1 H), 2.18 (td, 1 H), 2.32 (td, 2 H), 2.69 - 2.78 (m, 1 H), 2.83 - 2.91 (m, 1 H), 3.80 (d, 1 H), 7.26 (d, 1 H), 7.33 (d, 2 H), 7.44 (t, 1 H), 7.50 (t, 1 H), 7.53 - 7.59 (m, 3 H).

[000652] El espectro de FTIR presentó una banda de nitrilo a 2238 $/\text{cm}$.

INTERMEDIO 80

[000653] (*R*)-4-(4-((4'-clorobifenil-2-il)(ciano)metil)piperidin-1-il)benzoato de *tert*-butilo y (*S*)-4-(4-((4'-clorobifenil-2-il)(ciano)metil)piperidin-1-il)benzoato de *tert*-butilo, mezcla de

enantiómeros



[000654] Se añadieron (*R*)-2-(4'-clorobifenil-2-il)-2-(piperidin-4-il)acetonitrilo y (*S*)-2-(4'-clorobifenil-2-il)-2-(piperidin-4-il)acetonitrilo, mezcla de enantiómeros (INTERMEDIO 79, 196.4 mg, 0.63 mmol), a una mezcla de *tert*-butilo 4-fluorobenzoato de (152.2 mg, 1.39 mmol) en DMSO (0.6 ml) y DIPEA (0.132 ml, 1.49 mmol). La mezcla resultante se calentó a 120 °C durante 8 horas, a continuación se añadió *tert*-butilo 4-fluorobenzoato de (121.0 mg) y se continuó calentando durante 24 horas más. Se añadió DIPEA adicional (0.13 ml) y se continuó calentando durante 48 horas más. La mezcla se diluyó con EtOAc (20 ml), se lavó con agua (3 x 20 ml) y salmuera (20 ml), se secó (MgSO₄), se filtró y se evaporó a presión reducida. El concentrado se purificó mediante cromatografía en columna (ISCO, columna de 4 g de gel de sílice, eluyendo con 0→20% de EtOAc/hexanos) para proporcionar los productos del título (62.6 mg, rendimiento: 20%) como una mezcla de enantiómeros.

[000655] ¹H RMN (400 MHz, DMSO-*d*₆) δ ppm 0.90 - 1.02 (m, 1 H), 1.21 - 1.39 (m, 2 H), 1.49 (s, 9 H), 1.72 - 1.81 (m, 1 H), 2.53 - 2.63 (m, 1 H), 2.65 - 2.77 (m, 1 H), 3.74 (d, 1 H), 3.89 (d, 2 H), 6.86 (d, 2 H), 7.26 - 7.31 (m, 1 H), 7.32 - 7.38 (m, 2 H), 7.46 (td, 1 H), 7.50 - 7.57 (m, 3 H), 7.58 - 7.63 (m, 1 H), 7.67 (d, 2 H).

[000656] LCMS: (ESI) *m/z* 487[M+H]⁺.

[000657] Los enantiómeros *R* y *S* del producto del título se separaron utilizando SFC quiral, (columna Chiralpak IA), para proporcionar el INTERMEDIO 81 y el INTERMEDIO 82 como enantiómeros sustancialmente separados.

Dimensiones de la columna: 21 x 250 mm, 5 μ

Modificador: 25 % de metanol/ 0.1 % de dimetiletilamina

Velocidad de flujo (ml/min): 60

Presión de salida (bar): 100

Detección (nm): 210

INTERMEDIO 81 (Primer compuesto eluido)

[000658] (*R*)-4-(4-((4'-clorobifenil-2-il)(ciano)metil)piperidin-1-il)benzoato de *tert*-butilo

El primer compuesto eluido tuvo un tiempo de retención de 9.62 minutos.

[000659] ^1H RMN (400 MHz, DMSO- d_6) δ ppm 0.89 - 1.02 (m, 1 H), 1.21 - 1.39 (m, 2 H), 1.49 (s, 9 H), 1.72 - 1.81 (m, 1 H), 1.91 - 2.03 (m, 1 H), 2.53 - 2.63 (m, 1 H), 2.65 - 2.77 (m, 1 H), 3.74 (d, 1 H), 3.84 - 3.94 (m, 2 H), 6.86 (d, 2 H), 7.25 - 7.31 (m, 1 H), 7.32 - 7.38 (m, 2 H), 7.43 - 7.49 (m, 1 H), 7.50 - 7.57 (m, 3 H), 7.58 - 7.63 (m, 1 H), 7.64 - 7.70 (m, 2 H).

[000660] LCMS: (ESI) m/z 487[M+H] $^+$.

INTERMEDIO 82 (Segundo compuesto eluido)

[000661] (*S*)-4-(4-((4'-clorobifenil-2-il)(ciano)metil)piperidin-1-il)benzoato de *tert*-butilo

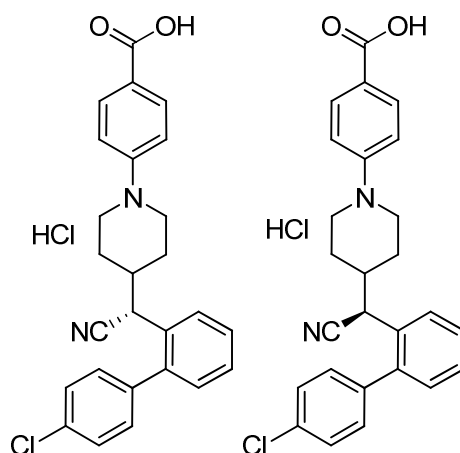
[000662] El segundo compuesto eluido tuvo un tiempo de retención de 12.95 minutos.

[000663] ^1H RMN (400 MHz, DMSO- d_6) δ ppm 0.96 (cd, 1 H), 1.21 - 1.39 (m, 2 H), 1.49 (s, 9 H), 1.72 - 1.81 (m, 1 H), 1.91 - 2.03 (m, 1 H), 2.58 (td, 1 H), 2.65 - 2.77 (m, 1 H), 3.70 - 3.78 (m, 1 H), 3.84 - 3.94 (m, 2 H), 6.87 (d, 2 H), 7.28 (dd, 1 H), 7.32 - 7.38 (m, 2 H), 7.46 (td, 1 H), 7.50 - 7.57 (m, 3 H), 7.58 - 7.63 (m, 1 H), 7.67 (d, 2 H).

[000664] LCMS: (ESI) m/z 487[M+H] $^+$.

INTERMEDIO 83

[000665] sales clorhídricas del ácido (*R*)-4-(4-((4'-clorobifenil-2-il)(ciano)metil)piperidin-1-il)benzoico y del ácido (*S*)-4-(4-((4'-clorobifenil-2-il)(ciano)metil)piperidin-1-il)benzoico, mezcla de enantiómeros



[000666] Se disolvieron (*R*)-4-(4-((4'-clorobifenil-2-il)(ciano)metil)piperidin-1-il)benzoato de *tert*-butilo y (*S*)-4-(4-((4'-clorobifenil-2-il)(ciano)metil)piperidin-1-il)benzoato de *tert*-butilo, mezcla de enantiómeros (INTERMEDIO 80, 213.5 mg, 0.44 mmol), en DCM (2.0 ml) y MeOH

104020-1 US/O

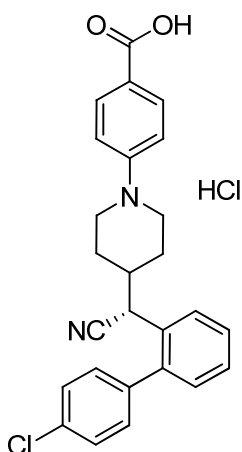
(0.1 ml) y se trataron con TFA (2.0 ml, 25.96 mmol). La mezcla se agitó a temperatura ambiente durante 30 minutos y se evaporó el solvente a presión reducida. El residuo se disolvió secuencialmente y se evaporó a sequedad con tolueno y DCM, para proporcionar las correspondientes sales de tipo trifluoroacetato (251.3 mg). El material se disolvió en MeOH (6 ml) y se añadió HCl 2 M en éter (2 ml). Después de agitar la solución durante 10 minutos, los componentes volátiles se eliminaron a presión reducida, para proporcionar los productos del título (182 mg, rendimiento: 89 %) como una mezcla de enantiómeros.

[000667] ^1H RMN (300 MHz, DMSO- d_6) δ ppm 0.89 - 1.08 (m, 1 H), 1.19 - 1.45 (m, 2 H), 1.71 - 1.85 (m, 1 H), 1.89 - 2.07 (m, 1 H), 2.55 - 2.68 (m, 1 H) 2.69 - 2.82 (m, 1 H), 3.66 - 3.80 (m, 1 H), 3.82 - 3.94 (m, 2 H), 6.91 (d, 2 H), 7.28 (d, 1 H), 7.35 (d, 2 H), 7.40 - 7.50 (m, 1 H), 7.49 - 7.57 (m, 3 H), 7.57 - 7.64 (m, 1 H), 7.73 (d, 2 H).

[000668] LCMS: (ESI) m/z 431[M+H] $^+$.

INTERMEDIO 84

[000669] sal clorhídrica del ácido (*R*)-4-(4-((4'-clorobifenil-2-il)(ciano)metil)piperidin-1-il)benzoico



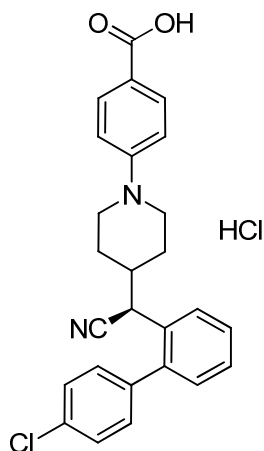
[000670] El producto del título (215 mg, rendimiento: cuantitativo) se obtuvo utilizando un procedimiento similar al descrito para la síntesis del INTERMEDIO 83. Se utilizó como material de partida (*R*)-4-(4-((4'-clorobifenil-2-il)(ciano)metil)piperidin-1-il)benzoato de *tert*-butilo (INTERMEDIO 81, 103.8 mg, 0.21 mmol).

[000671] ^1H RMN (400 MHz, DMSO- d_6) δ ppm 0.97 (cd, 1 H), 1.21 - 1.42 (m, 2 H), 1.73 - 1.83 (m, 1 H), 1.91 - 2.03 (m, 1 H), 2.56 - 2.65 (m, 1 H), 2.69 - 2.80 (m, 1 H), 3.68 - 3.79 (m, 1 H), 3.83 - 3.93 (m, 2 H), 7.27 (d, 1 H), 7.34 (d, 2 H), 7.42 - 7.48 (m, 1 H), 7.49 - 7.56 (m, 3 H), 7.57 - 7.62 (m, 1 H), 7.72 (d, 2 H).

[000672] LCMS: (ESI) m/z 431[M+H] $^+$.

INTERMEDIO 85

[000673] sal clorhídrica del ácido (*S*)-4-(4-((4'-clorobifenil-2-il)(ciano)metil)piperidin-1-il)benzoico



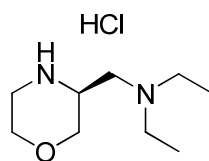
[000674] El producto del título (215 mg, rendimiento: cuantitativo) se obtuvo utilizando un procedimiento similar al descrito para la síntesis del INTERMEDIO 83. Se utilizó como material de partida (*S*)-4-(4-((4'-clorobifenil-2-il)(ciano)metil)piperidin-1-il)benzoato de *tert*-butilo (INTERMEDIO 82, 101.8 mg, 0.21 mmol).

[000675] ^1H RMN (400 MHz, DMSO- d_6) δ ppm 0.90 - 1.03 (m, 1 H), 1.21 - 1.40 (m, 3 H), 1.73 - 1.82 (m, 1 H), 1.91 - 2.03 (m, 1 H), 2.55 - 2.65 (m, 1 H), 2.69 - 2.80 (m, 1 H), 3.68 - 3.80 (m, 1 H), 3.84 - 3.95 (m, 2 H), 6.89 (d, 2 H), 7.27 (dd, 1 H), 7.31 - 7.39 (m, 2 H), 7.45 (td, 1 H), 7.49 - 7.57 (m, 3 H), 7.58 - 7.63 (m, 1 H), 7.69 - 7.79 (m, 2 H).

[000676] LCMS: (ESI) m/z 431 $[\text{M}+\text{H}]^+$.

INTERMEDIO 86

[000677] sal clorhídrica de (*S*)-*N*-etil-*N*-(morfolin-3-ilmetil)etanamina



[000678] Paso 1: Se trató una solución de (*S*)-3-(aminometil)morfolin-4-carboxilato de *tert*-butilo (1.0 g, 4.62 mmol) en MeOH (15 ml) con acetaldehído (0.204 g, 4.62 mmol). La mezcla de reacción se agitó a 0 °C durante 15 minutos y se añadió triacetoxiborohidruro de sodio (2.450 g, 11.56 mmol) de una vez. La mezcla resultante se agitó durante 24 h, la mezcla se diluyó con DCM (15 ml) y se lavó con bicarbonato de sodio acuoso saturado (15 ml). La fase orgánica se secó con sulfato de sodio, se filtró y se concentró a presión reducida para proporcionar un residuo, el cual se purificó mediante cromatografía en columna (ISCO, columna de 12 g de gel de sílice, eluyendo con 0→20 % de MeOH en DCM) para proporcionar (*S*)-3-

((dietilamino)metil)morfolin-4-carboxilato de *tert*-butilo (INTERMEDIO 86, PASO 1).

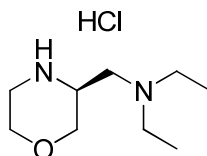
[000679] LCMS: (ESI) m/z 273[M+H]⁺.

[000680] Paso 2: Se disolvió (*S*)-3-((dietilamino)metil)morfolin-4-carboxilato de *tert*-butilo (INTERMEDIO 86, PASO 1) en TFA/DCM (10 ml, 1:1 v/v) y la mezcla resultante se agitó durante 1 hora a temperatura ambiente. Los componentes volátiles se eliminaron a presión reducida y el concentrado se trató con HCl 4N en dioxano (5 ml), se agitó durante 10 minutos y se eliminaron los componentes volátiles a presión reducida. El semisólido resultante se lavó con éter dietílico (2x 30 ml), se filtró y se secó para proporcionar el producto del título (0.65 g, rendimiento: 67%).

[000681] LCMS: (ESI) m/z 173[M+H]⁺.

[000682] INTERMEDIO 86A

[000683] El INTERMEDIO 86 también se preparó según el siguiente procedimiento:



[000684] Paso 1: A una solución de (*S*)-3-(aminometil)morfolin-4-carboxilato de *tert*-butilo (disponible de proveedores comerciales, 0.62 g, 2.87 mmol) en diclorometano (28.0 ml), se añadieron secuencialmente piridina (0.5 ml, 5.73 mmol) y cloruro de acetilo (0.25 ml, 3.44 mmol). Después de 30 min, la reacción se diluyó con bicarbonato de sodio acuoso saturado y con cloruro de sodio acuoso saturado. La mezcla resultante se extrajo con acetato de etilo (x3) y a continuación las fases orgánicas combinadas se secaron con sulfato de sodio, se filtraron y se concentraron a presión reducida. El aceite resultante de color amarillo claro se purificó mediante cromatografía flash en columna (ISCO, SiO₂, 0-10% de metanol en acetato de etilo durante 10 min) para proporcionar (*S*)-3-(acetamidometil)morfolin-4-carboxilato de *tert*-butilo (0.741 g, rendimiento: casi cuantitativo, INTERMEDIO 86A PASO 1).

[000685] ¹H RMN (300 MHz, CLOROFORMO-*d*) δ 5.85 (s a, 1H), 3.92 - 4.26 (m, 2H), 3.67 - 3.91 (m, 3H), 3.56 - 3.64 (m, 1H), 3.46 (dt, 1H), 3.09 - 3.32 (m, 2H), 1.96 (s, 3H), 1.49 (s, 9H).

[000686] LCMS: (ESI) m/z 259 [M+H]⁺.

[000687] Paso 2: A una solución desgasificada de (*S*)-3-(acetamidometil)morfolin-4-carboxilato de *tert*-butilo (INTERMEDIO 86A, Paso 1, 0.69 g, 2.68 mmol) y DMF (20 ml), se añadió secuencialmente yodoetano (1.297 ml, 16.05 mmol) e hidruro de sodio al 60% en aceite mineral (0.118 g, 2.94 mmol) en una porción. Después de 15 min, la reacción se diluyó con acetato de etilo y se lavó con agua (x2). La fase acuosa se extrajo con acetato de etilo y a

continuación las fases orgánicas combinadas se lavaron con cloruro de sodio acuoso saturado. Las fases orgánicas se secaron con sulfato de sodio, se filtraron y se concentraron a presión reducida. El aceite resultante de color amarillo claro se purificó mediante cromatografía flash en columna (SiO_2 , ISCO, 0-100% de acetato de etilo en hexanos durante 10 min, a continuación 10% de metanol en acetato de etilo durante 5 min) para proporcionar (*S*)-3-((*N*-etilacetamido)metil)morfolin-4-carboxilato de *tert*-butilo (0.586 g, rendimiento: 76 %, INTERMEDIO 86A, Paso 2).

[000688] ^1H RMN (300 MHz, $\text{DMSO}-d_6$, 87 °C) δ 4.07 (s a, 1H), 3.80 (d, 1H), 3.05 - 3.74 (m, 9H), 2.00 (s, 3H), 1.38 - 1.46 (m, 9H), 1.10 (t, 3H).

[000689] LCMS: (ESI) m/z 287 $[\text{M}+\text{H}]^+$.

[000690] Paso 3: Se añadió hidruro de carboniltris(trifenilfosfina)rodio(I) (6.42 mg, 6.98 μmol) a una solución de (*S*)-3-((*N*-etilacetamido)metil)morfolin-4-carboxilato de *tert*-butilo (INTERMEDIO 86A, Paso 2, 0.04 g, 0.14 mmol) y difenilsilano (0.052 ml, 0.28 mmol) en tetrahidrofurano (1.345 ml) a TA. Después de un breve aumento repentino de la formación de gas, se agitó la reacción, que en este punto era de color amarillo, durante 30 min y a continuación se detuvo con cloruro de hidrógeno acuoso 1 N. La mezcla se extrajo con éter y la fase acuosa se basificó con hidróxido de sodio acuoso al 50%. La fase acuosa se extrajo con acetato de etilo (x4) y las fases orgánicas combinadas se secaron con sulfato de sodio, se filtraron y se concentraron a presión reducida para proporcionar (*S*)-3-((dietilamino)metil)morfolin-4-carboxilato de *tert*-butilo (0.038 g, rendimiento: casi cuantitativo) (INTERMEDIO 86A, Paso 3).

[000691] ^1H RMN (300 MHz, $\text{CLOROFORMO}-d$) δ 3.98 (d, 1H), 3.58 - 3.82 (m, 3H), 3.29 - 3.46 (m, 2H), 2.90 - 3.04 (m, 1H), 2.71 - 2.86 (m, 1H), 2.36 - 2.63 (m, 4H), 2.21 (d, 1H), 1.36 - 1.42 (m, 9H), 0.87 - 1.01 (m, 6H).

[000692] LCMS: (ESI) m/z 273 $[\text{M}+\text{H}]^+$.

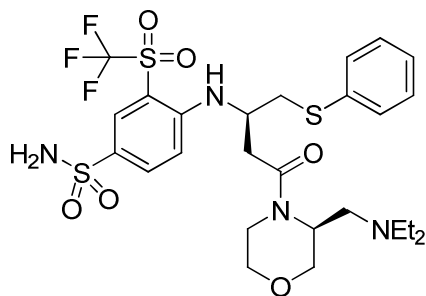
[000693] Paso 4: Se añadió ácido clorhídrico al 32% en peso en agua (1.5 ml, 15.80 mmol) a (*S*)-3-((dietilamino)metil)morfolin-4-carboxilato de *tert*-butilo (0.348 g, 1.28 mmol, INTERMEDIO 86A, Paso 3). Cuando la formación de gas finalizó, la mezcla se concentró a presión reducida. El residuo amarillo resultante se trató con metanol al 5% en diclorometano y se volvió a concentrar (x3) para proporcionar la sal clorhídrica de (*S*)-*N*-etil-*N*-(morfolin-3-ilmetil)etanamina (INTERMEDIO 86, rendimiento: casi cuantitativo).

[000694] ^1H RMN (300 MHz, $\text{METANOL}-d_4$) δ 4.20 (dd, 1H), 3.99 - 4.13 (m, 2H), 3.79 - 3.96 (m, 2H), 3.60 - 3.70 (m, 1H), 3.27 - 3.54 (m, 6H), 1.43 (t, 6H).

[000695] LCMS: (ESI) m/z 173 $[\text{M}+\text{H}]^+$.

INTERMEDIO 87

[000696] 4-((*R*)-4-((*S*)-3-((dietilamino)metil)morfolino)-4-oxo-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida

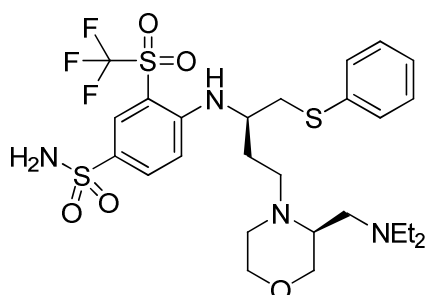


[000697] Se añadió HATU (458 mg, 1.20 mmol) a una solución del ácido (*R*)-4-(feniltio)-3-(4-sulfamoyl-2-(trifluorometilsulfonyl)fenilamino)butanoico (INTERMEDIO 8, 500 mg, 1.00 mmol), la sal clorhídrica de (*S*)-*N*-etil-*N*-(morfolin-3-ilmetil)etanamina (INTERMEDIO 86, 50 mg, 1.2 mmol) y DIPEA (0.526 ml, 3.01 mmol), en DMA (5 ml). La mezcla se agitó durante 1 hora a temperatura ambiente y se diluyó con acetato de etilo (200 ml). La mezcla se lavó sucesivamente con bisulfato de sodio acuoso 1 M, bicarbonato de sodio saturado y salmuera. La fase orgánica se secó con sulfato de sodio, se filtró y se concentró a presión reducida. El concentrado se purificó mediante cromatografía en columna (ISCO, eluyendo con 0→100 % de DCM/10% de amoniaco 2 M en MeOH en DCM durante 24 minutos) para proporcionar el producto del título (380 mg, rendimiento: 58 %).

[000698] LCMS: (ESI) m/z 653 $[M+H]^+$.

INTERMEDIO 88

[000699] 4-((*R*)-4-((*S*)-3-((dietilamino)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida



[000700] Se agitó una mezcla de 4-((*R*)-4-((*S*)-3-((dietilamino)metil)morfolino)-4-oxo-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida (INTERMEDIO 87, 360 mg, 0.55 mmol) y el complejo borano-tetrahidrofurano 1 M en THF (1191 μ l, 1.19 mmol) a temperatura ambiente durante 16 horas. La mezcla de reacción se trató cuidadosamente con MeOH (5 ml) y HCl concentrado (1 ml). La mezcla se calentó a 80 °C durante 3 horas, se enfrió

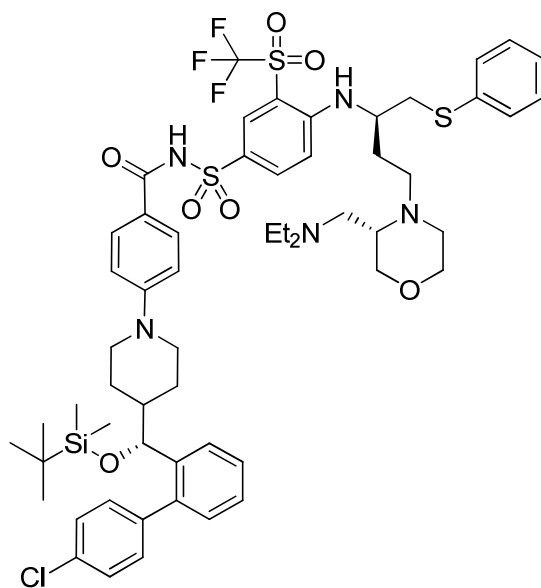
hasta temperatura ambiente y el pH se ajustó a un pH de 10 con carbonato de sodio acuoso 4 N. La mezcla se diluyó con acetato de etilo (300 ml), se lavó sucesivamente con agua (150 ml) y salmuera (150 ml), se secó con sulfato de sodio, se filtró y se concentró a presión reducida. El concentrado se purificó mediante cromatografía en columna (ISCO, eluyendo con 0→20% de MeOH/DCM durante 15 minutos) para proporcionar el producto del título (130 mg, rendimiento: 37 %).

[000701] ^1H RMN (400 MHz, METANOL- d_4) δ ppm 0.79 (t, 6 H) 1.53 - 1.69 (m, 1 H) 1.91 - 2.45 (m, 11 H) 2.63 - 2.87 (m, 2 H) 2.98 - 3.24 (m, 5 H) 3.43 (ddd, 1 H) 3.60 (dt, 1 H) 3.68 (dd, 1 H) 3.87 - 4.05 (m, 1 H) 6.68 (d, 1 H) 7.07 - 7.26 (m, 3 H) 7.26 - 7.39 (m, 2 H) 7.75 (dd, 1 H) 8.04 (d, 1 H).

[000702] LCMS: (ESI) m/z 639[M+H] $^+$.

INTERMEDIO 89

[000703] 4-(4-((*R*)-(tert-butildimetilsililoxi)(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((*R*)-4-((*S*)-3-((dietilamino)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida



[000704] Se agitó una solución del ácido (*R*)-4-(4-((tert-butildimetilsililoxi)(4'-clorobifenil-2-il)metil)piperidin-1-il)benzoico, (INTERMEDIO 13, 109 mg, 0.20 mmol), 4-((*R*)-4-((*S*)-3-((dietilamino)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)benzenosulfonamida (INTERMEDIO 88, 130 mg, 0.20 mmol), EDC (78 mg, 0.41 mmol), DMAP (49.7 mg, 0.41 mmol), TEA (0.028 ml, 0.20 mmol) y DCM (5 ml) durante toda la noche a temperatura ambiente. La mezcla de reacción se diluyó con DCM (50 ml) y se lavó sucesivamente con agua (2 x 50 ml) y salmuera (50 ml). La fase orgánica se secó con

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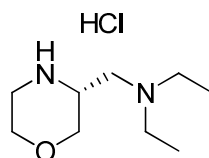
sulfato de sodio, se filtró y se concentró a presión reducida. El concentrado se purificó mediante cromatografía en columna (ISCO, eluyendo con 0→20% de MeOH/DCM durante 19 minutos) para proporcionar el producto del título (100 mg, rendimiento: 42.5 %).

[000705] ^1H RMN (400 MHz, DICLOROMETANO- d_2) δ ppm 0.00 (s, 3 H) 0.17 (s, 3 H) 1.09 (s, 9 H) 1.19 (t, 6 H) 1.51 (s a, 5 H) 1.69 - 1.93 (m, 2 H) 1.92 - 2.05 (m, 1 H) 2.24 - 2.38 (m, 1 H) 2.41 - 2.53 (m, 1 H) 2.59 - 3.05 (m, 11 H) 3.30 (t, 2 H) 3.54 - 3.65 (m, 1 H) 3.71 - 3.80 (m, 1 H) 3.92 (d, 3 H) 3.99 - 4.09 (m, 1 H) 4.10 - 4.24 (m, 1 H) 4.84 (s a, 1 H) 6.86 (d, 1 H) 7.00 (d, $J=8.84$ Hz, 2 H) 7.13 (d, 1 H) 7.36 (dd, 1 H) 7.40 - 7.72 (m, 11 H) 7.76 - 7.88 (m, 1 H) 7.95 (d, 2 H) 8.24 (s, 1 H) 8.53 (d, 1 H).

[000706] LCMS: (ESI) m/z 1156 $[\text{M}+\text{H}]^+$.

INTERMEDIO 90

[000707] sal clorhídrica de (*R*)-*N*-etil-*N*-(morfolin-3-ilmetil)etanamina



[000708] Paso 1: Se trató una solución de (*R*)-3-(aminometil)morfolin-4-carboxilato de *tert*-butilo (disponible de proveedores comerciales, 250 mg, 1.16 mmol) y DCM (7 ml) a 0 °C con acetaldehído (0.162 ml, 2.89 mmol). La mezcla de reacción se agitó a 0 °C durante 15 minutos y se añadió triacetoxiborohidruro de sodio (612 mg, 2.89 mmol) de una vez. La mezcla resultante se agitó durante 24 h, la mezcla se diluyó con 20 ml de DCM (20 ml) y se lavó con bicarbonato de sodio acuoso saturado (20 ml). La fase orgánica se secó con sulfato de sodio, se filtró y se concentró a presión para proporcionar (*R*)-3-((dietilamino)metil)morfolin-4-carboxilato de *tert*-butilo (INTERMEDIO 90, PASO 1).

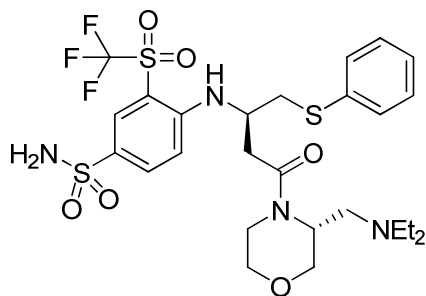
[000709] LCMS: (ESI) m/z 273 $[\text{M}+\text{H}]^+$.

[000710] Paso 2: Se disolvió (*R*)-3-((dietilamino)metil)morfolin-4-carboxilato de *tert*-butilo (INTERMEDIO 90, PASO 1) en TFA/DCM (6 ml, 1:1 v/v) y la mezcla resultante se agitó durante 1 h a temperatura ambiente. Los componentes volátiles se eliminaron a presión reducida y el concentrado se trató con HCl 4N en dioxano (3 ml), se agitó durante 10 minutos y se eliminaron los componentes volátiles a presión reducida. El semisólido resultante se lavó con éter dietílico (2x 30 ml) y se secó para proporcionar el producto del título (140 mg, rendimiento: 58 %).

[000711] LCMS: (ESI) m/z 173 $[\text{M}+\text{H}]^+$.

INTERMEDIO 91

[000712] 4-((*R*)-4-((*R*)-3-((dietilamino)metil)morfolino)-4-oxo-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida



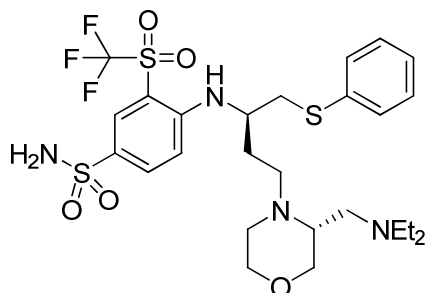
[000713] Se añadió HATU (458 mg, 1.20 mmol) a una solución del ácido (*R*)-4-(feniltio)-3-(4-sulfamoyl-2-(trifluorometilsulfonyl)fenilamino)butanoico (INTERMEDIO 8, 500 mg, 1.00 mmol), la sal clorhídrica de (*R*)-*N*-etil-*N*-(morfolin-3-ilmetil)etanamina (INTERMEDIO 90, 209 mg, 1.00 mmol) y DIPEA (0.701 ml, 4.01 mmol), en DMA (5 ml). La mezcla se agitó durante 1 h a temperatura ambiente y se diluyó con acetato de etilo (200 ml). La mezcla se lavó sucesivamente con bisulfato de sodio acuoso 1 M, bicarbonato de sodio saturado y salmuera. La fase orgánica se secó con sulfato de sodio, se filtró y se concentró a presión reducida. El concentrado se purificó mediante cromatografía en columna (ISCO, eluyendo con 0→100 % de DCM/10% de amoníaco 2 M en MeOH en DCM durante 24 minutos) para proporcionar el producto del título (200 mg, rendimiento: 30.5 %).

[000714] ^1H RMN (400 MHz, METANOL- d_4) δ ppm 0.75 - 1.06 (m, 6 H) 2.32 - 2.67 (m, 6 H) 2.69 - 2.89 (m, 3 H) 3.11 - 3.42 (m, 7 H) 3.45 - 3.57 (m, 1 H) 3.67 - 3.92 (m, 3 H) 4.26 (d, 2 H) 6.73 (d, 1 H) 7.08 - 7.26 (m, 3 H) 7.27 - 7.37 (m, 2 H) 7.65 - 7.83 (m, 1 H) 7.96 - 8.12 (m, 1 H).

[000715] LCMS: (ESI) m/z 653[M+H] $^+$.

INTERMEDIO 92

[000716] 4-((*R*)-4-((*R*)-3-((dietilamino)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida



[000717] Se agitó una mezcla de 4-((*R*)-4-((*R*)-3-((dietilamino)metil)morfolino)-4-oxo-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida (INTERMEDIO 91, 200

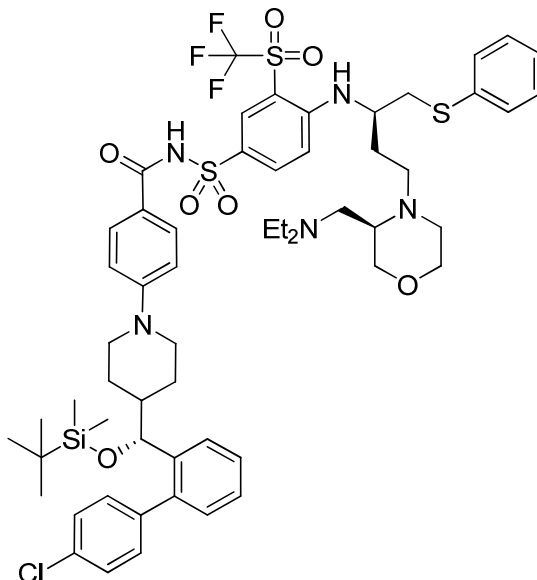
mg, 0.31 mmol) y el complejo borano-tetrahidrofurano 1 M (662 μ l, 0.66 mmol) a temperatura ambiente durante 16 horas. La mezcla de reacción se trató cuidadosamente con MeOH (5 ml) y HCl concentrado (1 ml). La mezcla se calentó a 80 °C durante 3 horas, se enfrió hasta TA y el pH se ajustó a un pH de 10 con carbonato de sodio acuoso 4 N. La mezcla se diluyó con acetato de etilo (300 ml), se lavó sucesivamente con agua (150 ml) y salmuera (150 ml), se secó con sulfato de sodio, se filtró y se concentró a presión reducida. El concentrado se purificó mediante cromatografía en columna (ISCO, eluyendo con 0→20% de MeOH/DCM durante 15 minutos) para proporcionar el producto del título (109 mg, rendimiento: 56 %).

[000718] ^1H RMN (400 MHz, METANOL- d_4) δ ppm 0.79 - 0.91 (m, 6 H) 1.54 - 1.74 (m, 1 H) 1.89 - 2.07 (m, 1 H) 2.13 - 2.48 (m, 10 H) 2.58 (ddd, 1 H) 2.75 (ddd, 1 H) 3.02 - 3.24 (m, 3 H) 3.36 (dd, 1 H) 3.46 - 3.65 (m, 3 H) 3.95 (dd, 1 H) 6.74 (d, 1 H) 7.08 - 7.26 (m, 3 H) 7.26 - 7.38 (m, 2 H) 7.78 (dd, 1 H) 8.04 (d, 1 H).

[000719] LCMS: (ESI) m/z 639[M+H] $^+$.

INTERMEDIO 93

[000720] 4-(4-((*R*)-(tert-butildimetilsililoxi)(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((*R*)-4-((*R*)-3-((dietilamino)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida



[000721] El producto del título (100 mg, rendimiento: 55 %) se preparó utilizando un procedimiento similar al descrito para la síntesis del INTERMEDIO 89. Se utilizaron como materiales de partida el ácido (*R*)-4-(4-((tert-butildimetilsililoxi)(4'-clorobifenil-2-il)metil)piperidin-1-il)benzoico, (INTERMEDIO 13, 84 mg, 0.16 mmol) y 4-((*R*)-4-((*R*)-3-((dietilamino)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)bencenosulfonamida (INTERMEDIO 92, 100 mg, 0.16 mmol). El

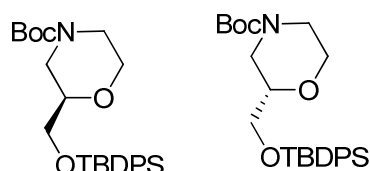
producto resultante se purificó mediante cromatografía en columna (ISCO, eluyendo con 0→20% de MeOH/DCM durante 19 minutos) para proporcionar el producto del título.

[000722] ^1H RMN (400 MHz, DICLOROMETANO- d_2) δ ppm 0.00 (s, 3 H) 0.17 (s, 3 H) 1.09 (s, 9 H) 1.29 (t, 6 H) 1.40 - 1.69 (m, 4 H) 1.71 - 1.92 (m, 2 H) 1.92 - 2.06 (m, 1 H) 2.24 (s, 1 H) 2.58 (s a, 3 H) 2.71 - 3.09 (m, 10 H) 3.35 (dd, 2 H) 3.71 (s a, 3 H) 3.84 (s a, 1 H) 3.90 - 3.99 (m, 1 H) 3.99 - 4.09 (m, 1 H) 4.16 - 4.30 (m, 1 H) 4.76 - 4.96 (m, 1 H) 6.76 - 7.11 (m, 5 H) 7.36 (dd, 1 H) 7.41 - 7.70 (m, 13 H) 7.74 - 7.87 (m, 1 H) 7.91 (d, 2 H) 8.19 (s, 1 H) 8.53 (d, 1 H).

[000723] LCMS: (ESI) m/z 1158[M+H] $^+$.

INTERMEDIO 94

[000724] (*R*)-2-((*tert*-butildifenilsililoxi)metil)morfolin-4-carboxilato de *tert*-butilo y (*S*)-2-((*tert*-butildifenilsililoxi)metil)morfolin-4-carboxilato de *tert*-butilo, mezcla de enantiómeros

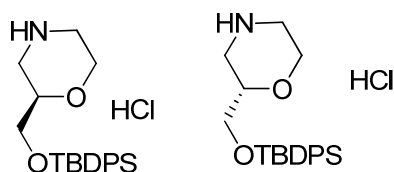


[000725] Se añadieron piridina (0.313 ml, 3.87 mmol) y DMAP (0.031 g, 0.26 mmol) a una solución de (*R*)-2-(hidroximetil)morfolin-4-carboxilato de *tert*-butilo y (*S*)-2-(hidroximetil)morfolin-4-carboxilato de *tert*-butilo, mezcla de enantiómeros (disponible de proveedores comerciales, 0.560 g, 2.58 mmol), en DCM (7.48 ml) a temperatura ambiente. Se añadió *tert*-butilclorodifenilsilano (0.795 ml, 3.09 mmol) y la mezcla de reacción se agitó durante toda la noche a temperatura ambiente. La mezcla se concentró a presión reducida y el concentrado se purificó mediante cromatografía en columna (ISCO, eluyendo con 0→100% de EtOAc/hexanos) para proporcionar los productos del título como una mezcla de enantiómeros (0.853 g, rendimiento: 73 %).

[000726] LCMS: (ESI) m/z 456[M+H] $^+$.

INTERMEDIO 95

[000727] sales clorhídricas de (*R*)-2-((*tert*-butildifenilsililoxi)metil)morfolina y (*S*)-2-((*tert*-butildifenilsililoxi)metil)morfolina, mezcla de enantiómeros



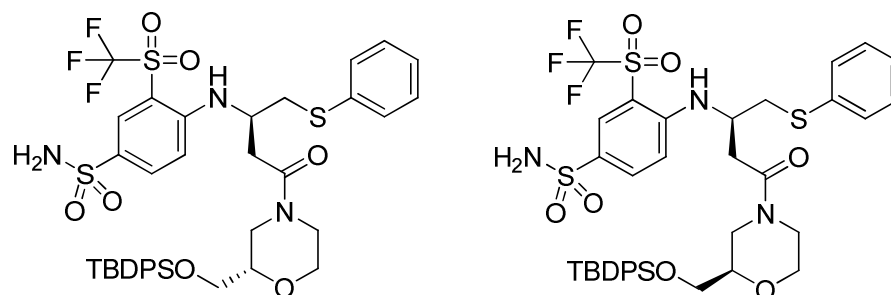
[000728] Se añadió HCl (4M en dioxano, 3.24 ml, 93.27 mmol) gota a gota a una solución de

(*R*)-2-((*tert*-butildifenilsililoxi)metil)morfolin-4-carboxilato de *tert*-butilo y (*S*)-2-((*tert*-butildifenilsililoxi)metil)morfolin-4-carboxilato de *tert*-butilo, mezcla de enantiómeros (INTERMEDIO 94, 0.85 g, 1.87 mmol), en DCM (2.98 ml) y la mezcla de reacción resultante se agitó a temperatura ambiente durante 30 minutos. Los componentes volátiles se eliminaron a presión reducida para proporcionar el producto del título como una mezcla de enantiómeros (0.73 g, rendimiento: cuantitativo).

[000729] LCMS: (ESI) m/z 356[M+H]⁺.

INTERMEDIO 96

[000730] 4-((*R*)-4-((*R*)-2-((*tert*-butildifenilsililoxi)metil)morfolino)-4-oxo-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)benzenosulfonamida y 4-((*R*)-4-((*S*)-2-((*tert*-butildifenilsililoxi)metil)morfolino)-4-oxo-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)benzenosulfonamida



[000731] Se añadió ácido (*R*)-4-(feniltio)-3-(4-sulfamoyl-2-(trifluorometilsulfonyl)fenilamino)butanoico (INTERMEDIO 8, 0.850 g, 1.71 mmol) a una solución de

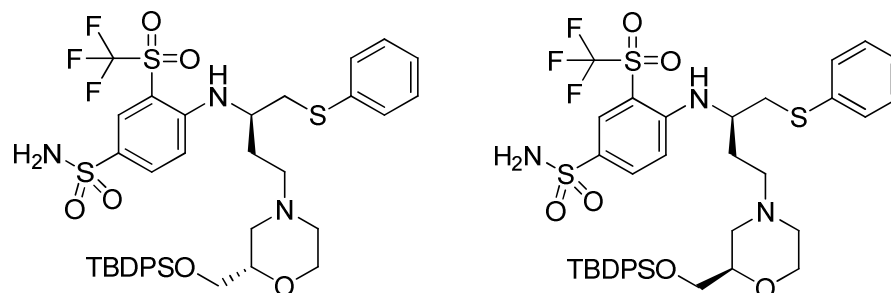
las sales clorhídricas de (*R*)-2-((*tert*-butildifenilsililoxi)metil)morfolina y de (*S*)-2-((*tert*-butildifenilsililoxi)metil)morfolina, mezcla de enantiómeros

(INTERMEDIO 95, 0.735 g, 1.88 mmol), en DMF (5.09 ml) y a continuación se añadieron secuencialmente DIPEA (0.596 ml, 3.41 mmol), EDC (0.490 g, 2.56 mmol) y HOBT (0.392 g, 2.56 mmol). La mezcla de reacción resultante se agitó a temperatura ambiente durante toda la noche. La mezcla se diluyó con EtOAc y se lavó con H₂O (2x), NaHSO₄ 1 N acuoso, NaHCO₃ acuoso saturado y salmuera. La fase orgánica se secó (Na₂SO₄) y se concentró a presión reducida. El concentrado se purificó mediante cromatografía en columna (ISCO, eluyendo con 50% de EtOAc/hexanos) para proporcionar los productos del título como una mezcla de enantiómeros (1.6 g, rendimiento: cuantitativo).

[000732] LCMS: (ESI) m/z 836[M+H]⁺.

INTERMEDIO 97

[000733] 4-((*R*)-4-((*R*)-2-((*tert*-butildifenilsililoxi)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida y 4-((*R*)-4-((*S*)-2-((*tert*-butildifenilsililoxi)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida



[000734] Se añadió lentamente una solución del complejo $\text{BH}_3 \cdot \text{THF}$ en THF (10.23 ml, 10.23 mmol) a una solución de 4-((*R*)-4-((*R*)-2-((*tert*-butildifenilsililoxi)metil)morfolino)-4-oxo-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida y 4-((*R*)-4-((*S*)-2-((*tert*-butildifenilsililoxi)metil)morfolino)-4-oxo-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida (INTERMEDIO 96, 1.43 g, 1.71 mmol) y THF (4 ml) y la mezcla de reacción resultante se agitó a temperatura ambiente durante toda la noche. La mezcla se diluyó con una solución de NH_3 en MeOH (7 N, 20 ml) y se agitó a temperatura ambiente durante toda la noche. La evaporación de los componentes volátiles a presión reducida proporcionó un residuo, que se diluyó con EtOAc. La fase orgánica se lavó con H_2O (2x), se secó (Na_2SO_4), se filtró y se concentró a presión reducida para proporcionar los productos del título (0.52 g, 37%) como una mezcla de diastereómeros.

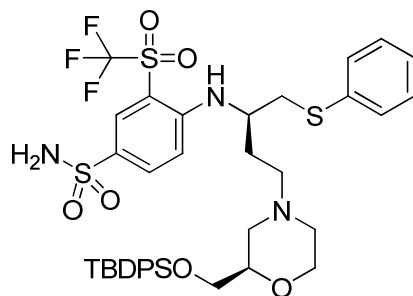
[000735] LCMS: (ESI) m/z 822 $[\text{M}+\text{H}]^+$.

[000736] Los dos diastereómeros resultantes del producto del título se separaron utilizando HPLC quiral, para proporcionar el INTERMEDIO 98 y el INTERMEDIO 99 como diastereómeros sustancialmente separados.

Columna:	columna Chiralpak IC
Dimensiones de la columna:	4.6 x 100 mm, 5 μ
Fase móvil:	80% de hexanos, 20% de isopropanol
Velocidad de flujo (ml/min):	1.0 ml/min
Detección (nm):	220 nm

INTERMEDIO 98

[000737] 4-((*R*)-4-((*R*)-2-((*tert*-butildifenilsililoxi)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida



[000738] El primer compuesto eluido tuvo un tiempo de retención de 5.84 minutos, 86% de e.d. (294 mg, rendimiento: 21%).

[000739] ^1H RMN (300 MHz, METANOL- d_4) δ ppm 1.07 (s, 5 H) 1.02 (s, 5 H) 1.73 - 1.91 (m, 2 H) 2.04 - 2.16 (m, 2 H) 2.36 - 2.45 (m, 2 H) 2.53 (d, 1 H) 2.73 (d, 1 H) 2.92 (d, 1 H) 3.12 - 3.29 (m, 2 H) 3.50 - 3.64 (m, 4 H) 3.71 (dd, 1 H) 3.81 (t, 1 H) 4.06 (d, 1 H) 6.86 (d, 1 H) 7.22 - 7.33 (m, 3 H) 7.35 - 7.48 (m, 9 H) 7.62 - 7.73 (m, 4 H) 7.87 (dt, 1 H) 8.15 (s, 1 H).

[000740] LCMS: (ESI) m/z 822[M+H] $^+$.

[000741] Rotación óptica:

Concentración: 0.1 g/dl

Lámpara: Sodio

Longitud de onda: 589 nm

Temperatura: 20 °C

Paso óptico: 10 cm

Volumen de la celda: 1 ml

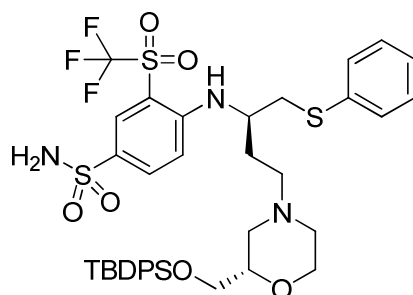
Solvente: Metanol

$[\alpha]_D = -88$

INTERMEDIO 99

[000742]

4-((R)-4-((S)-2-((*tert*-butildifenilsililoxy)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida



[000743] El segundo compuesto eluido tuvo un tiempo de retención de 6.86 minutos, 92% de e.d. (223 mg, rendimiento: 16%).

[000744] ^1H RMN (300 MHz, METANOL- d_4) δ ppm 1.07 (s, 5 H) 1.02 (s, 5 H) 1.73 - 1.91 (m, 2 H) 2.04 - 2.16 (m, 2 H) 2.36 - 2.45 (m, 2 H) 2.53 (d, 1 H) 2.73 (d, 1 H) 2.92 (d, 1 H) 3.12 - 3.29 (m, 2 H) 3.50 - 3.64 (m, 4 H) 3.71 (dd, 1 H) 3.81 (t, 1 H) 4.06 (d, 1 H) 6.86 (d, 1 H) 7.22 - 7.33 (m, 3 H) 7.35 - 7.48 (m, 9 H) 7.62 - 7.73 (m, 4 H) 7.87 (dt, 1 H) 8.15 (s, 1 H).

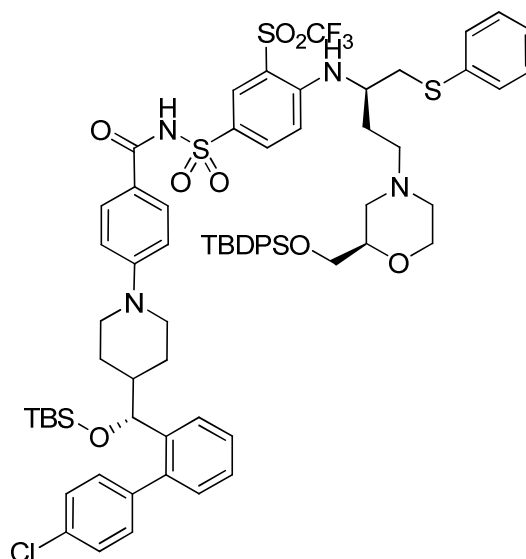
[000745] LCMS: (ESI) m/z 822 $[\text{M}+\text{H}]^+$.

[000746] Rotación óptica:

Concentración:	0.1 g/dl
Lámpara:	Sodio
Longitud de onda:	589 nm
Temperatura:	20 °C
Paso óptico:	10 cm
Volumen de la celda:	1 ml
Solvente:	Metanol
$[\alpha]_D$	-65

INTERMEDIO 100

[000747] 4-(4-((*R*)-(tert-butildimetilsililoxi)(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((*R*)-4-((*R*)-2-((tert-butildifenilsililoxi)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)fenilsulfonyl)benzamida



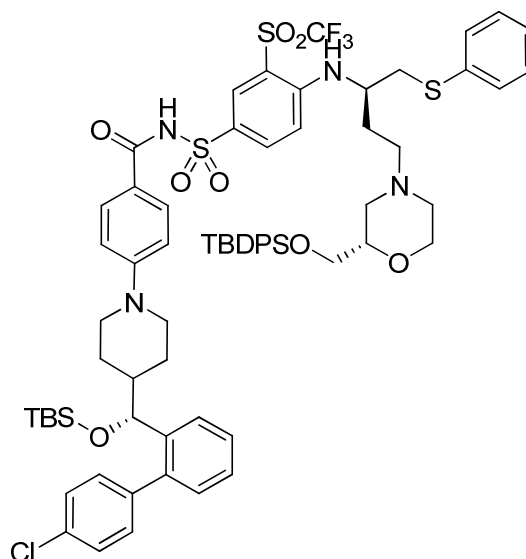
[000748] El producto del título (77 mg, 66%) se preparó utilizando un procedimiento similar al descrito para la síntesis del INTERMEDIO 33. Se utilizaron como materiales de partida el ácido (*R*)-4-(4-((*R*)-(tert-butildimetilsililoxi)(4'-clorobifenil-2-il)metil)piperidin-1-il)benzoico (INTERMEDIO 13, 51.7 mg, 0.10 mmol) y 4-((*R*)-4-((*R*)-2-((tert-butildifenilsililoxi)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-

(trifluorometilsulfonyl)bencenosulfonamida (INTERMEDIO 98, 72 mg, 0.09 mmol). El producto del título se utilizó en la preparación del EJEMPLO 22 sin purificación adicional.

[000749] LCMS:(ESI) m/z 1340 $[M+H]^+$.

INTERMEDIO 101

[000750] 4-(4-((*R*)-(tert-butildimetilsililoxi)(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((*R*)-4-((*S*)-2-((tert-butildifenilsililoxi)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)fenilsulfonyl)benzamida

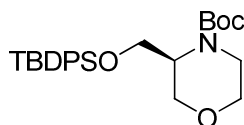


[000751] El producto del título (99 mg, rendimiento: casi cuantitativo) se preparó utilizando un procedimiento similar al descrito para la síntesis del INTERMEDIO 33. Se utilizaron como materiales de partida el ácido (*R*)-4-(4-((tert-butildimetilsililoxi)(4'-clorobifenil-2-il)metil)piperidin-1-il)benzoico (INTERMEDIO 13, 43.6 mg, 0.08 mmol) y 4-((*R*)-4-((*S*)-2-((tert-butildifenilsililoxi)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida (INTERMEDIO 99, 61 mg, 0.07 mmol). El producto del título se utilizó en la preparación del EJEMPLO 23 sin purificación adicional.

[000752] LCMS: (ESI) m/z 1340 $[M+H]^+$.

INTERMEDIO 102

[000753] (*S*)-3-((tert-butildifenilsililoxi)metil)morfolin-4-carboxilato de *tert*-butilo



[000754] A una solución de (*S*)-3-(hidroximetil)morfolin-4-carboxilato de *tert*-butilo (1.00 g, 4.60 mmol) en DCM (10 ml), se añadieron secuencialmente trietilamina (1.3 ml, 9.21 mmol), *tert*-butilclorodifenilsilano (1.414 ml, 5.52 mmol) y DMAP (0.56 g, 4.60 mmol) y la mezcla

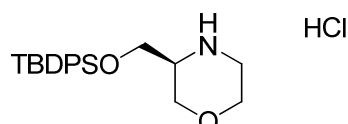
104020-1 US/O

resultante se agitó a temperatura ambiente durante toda la noche. La mezcla se diluyó con agua y la fase acuosa se extrajo con DCM. La fase orgánica se separó y se concentró a presión reducida. El concentrado se purificó mediante cromatografía en columna (ISCO, eluyendo con 0→50% de EtOAc/hexanos) para proporcionar el producto del título (1.0 g, rendimiento: 48 %).

[000755] LCMS:(ESI) m/z 478 $[M+Na]^+$.

Intermedio 103

[000756] sal clorhídrica de (*S*)-3-((*tert*-butildifenilsililo)metil)morfolina

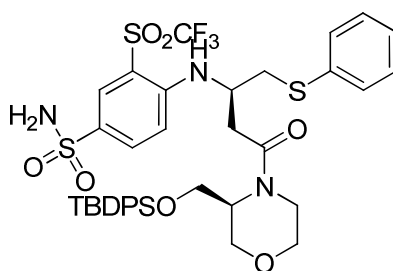


[000757] Se trató (*S*)-3-((*tert*-butildifenilsililo)metil)morfolin-4-carboxilato de *tert*-butilo (INTERMEDIO 102, 1.0 g, 2.19 mmol) en 1,4-dioxano (10 ml) con HCl (4 M en dioxano, 0.76 ml, 21.95 mmol) y la mezcla resultante se agitó a temperatura ambiente durante toda la noche. La evaporación de los componentes volátiles a presión reducida proporcionó el producto del título (0.8 g, rendimiento: 93 %).

[000758] LCMS: (ESI) m/z 356 $[M+H]^+$.

INTERMEDIO 104

[000759] 4-((*R*)-4-((*S*)-3-((*tert*-butildifenilsililo)metil)morfolino)-4-oxo-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)benzenosulfonamida

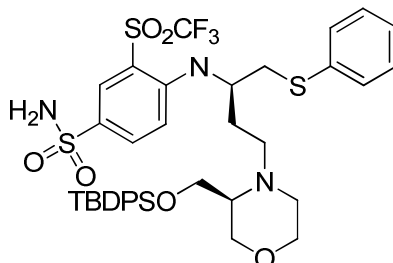


[000760] Se añadió ácido (*R*)-4-(feniltio)-3-(4-sulfamoyl-2-(trifluorometilsulfonyl)fenilamino)butanoico (INTERMEDIO 8, 0.8 g, 1.60 mmol) a una solución de la sal clorhídrica de (*S*)-3-((*tert*-butildifenilsililo)metil)morfolina (INTERMEDIO 103, 0.57 g, 1.60 mmol), DIPEA (0.84 ml, 4.81 mmol) y HATU (0.92 g, 2.41 mmol) en DCM (10 ml) y la mezcla resultante se agitó a temperatura ambiente durante 2 horas. La mezcla se diluyó con DCM y se lavó con H₂O (2x), NaHSO₄ 1 N acuoso y NaHCO₃ saturado acuoso. La fase orgánica se secó (Na₂SO₄), se concentró a presión reducida y se purificó mediante cromatografía en columna (ISCO, eluyendo con 0→100% de DCM/ 10% de MeOH en DCM) para proporcionar el producto del título (0.5 g, rendimiento: 37 %).

[000761] LCMS: (ESI) m/z 834 $[M-H]^+$.

INTERMEDIO 105

[000762] 4-((*R*)-4-((*S*)-3-((*tert*-butildifenilsililoxi)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)bencenosulfonamida

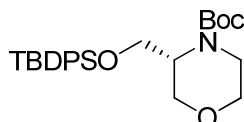


[000763] El producto del título (0.1 g, rendimiento: 51 %) se preparó utilizando un procedimiento similar al descrito para la síntesis del INTERMEDIO 97. Se utilizó como material de partida 4-((*R*)-4-((*S*)-3-((*tert*-butildifenilsililoxi)metil)morfolino)-4-oxo-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)bencenosulfonamida (INTERMEDIO 104, 0.2 g, 0.24 mmol). El producto del título se purificó mediante cromatografía en columna (ISCO, eluyendo con 0→50 % de EtOAc/hexanos).

[000764] LCMS: (ESI) m/z 822 $[M+H]^+$.

INTERMEDIO 106

[000765] (*R*)-3-((*tert*-butildifenilsililoxi)metil)morfolin-4-carboxilato de *tert*-butilo

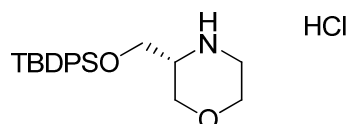


[000766] El producto del título (2.0 g, rendimiento: 95%) se preparó utilizando un procedimiento similar al descrito para la síntesis del INTERMEDIO 102. Se utilizaron como materiales de partida (*R*)-3-(hidroximetil)morfolin-4-carboxilato de *tert*-butilo (disponible de proveedores comerciales, 1.0 g, 4.60 mmol) y *tert*-butilclorodifenilsilano (1.4 ml, 5.52 mmol). El producto del título se purificó mediante cromatografía en columna (ISCO, eluyendo con 0→50 % de EtOAc/hexanos).

[000767] LCMS: (ESI) m/z 478 $[M+Na]^+$.

INTERMEDIO 107

[000768] sal clorhídrica de (*R*)-3-((*tert*-butildifenilsililoxi)metil)morfolina

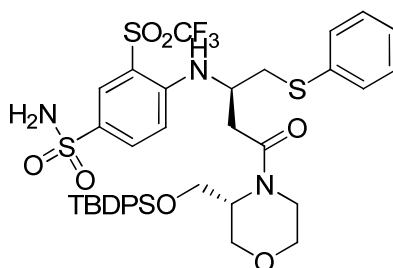


[000769] El producto del título (1.2 g, rendimiento: 77%) se preparó utilizando un procedimiento similar al descrito para la síntesis del INTERMEDIO 103. Se utilizó como material de partida (*R*)-3-((*tert*-butildifenilsililoxy)metil)morfolin-4-carboxilato de *tert*-butilo (INTERMEDIO 106, 2.0 g, 4.39 mmol). El producto del título se obtuvo como una sal clorhídrica después de evaporar los componentes volátiles a presión reducida.

[000770] LCMS: (ESI) m/z 356[M+H]⁺.

INTERMEDIO 108

[000771] 4-((*R*)-4-((*R*)-3-((*tert*-butildifenilsililoxy)metil)morfolino)-4-oxo-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida

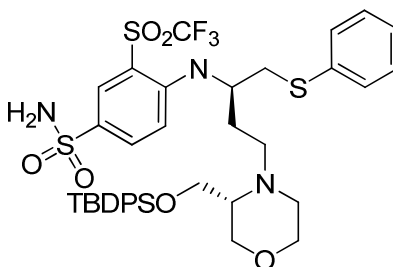


[000772] El producto del título (0.2 g, rendimiento: 24 %) se preparó utilizando un procedimiento similar al descrito para la síntesis del INTERMEDIO 104. Se utilizaron como materiales de partida la sal clorhídrica de (*R*)-3-((*tert*-butildifenilsililoxy)metil)morfolina (INTERMEDIO 107, 0.200 g, 0.24 mmol) y el ácido (*R*)-4-(feniltio)-3-(4-sulfamoyl-2-(trifluorometilsulfonyl)fenilamino)butanoico (INTERMEDIO 8, 0.500 g, 1.00 mmol). El producto del título se purificó mediante cromatografía en columna (ISCO, eluyendo con 0→100 % de DCM/ 10% de MeOH en DCM).

[000773] LCMS:(ESI) m/z 834 [M-H]⁺.

INTERMEDIO 109

[000774] 4-((*R*)-4-((*R*)-3-((*tert*-butildifenilsililoxy)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida

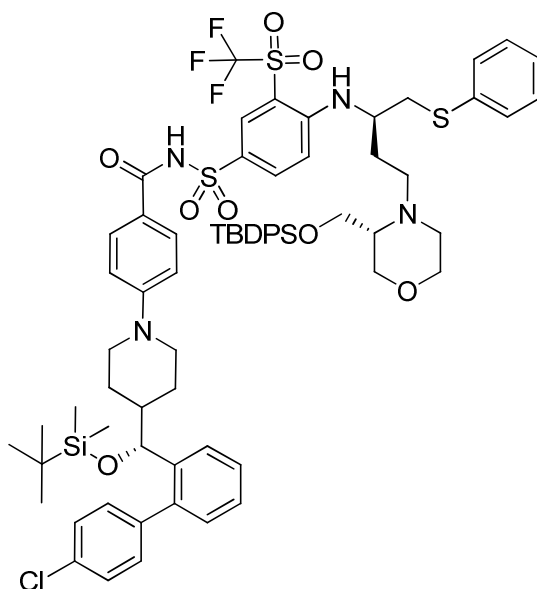


[000775] El producto del título (0.082 g, rendimiento: 75 %) se preparó utilizando un procedimiento similar al descrito para la síntesis del INTERMEDIO 97. Se utilizó como material de partida 4-((*R*)-4-((*R*)-3-((*tert*-butildifenilsililo)metil)morfolino)-4-oxo-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)benzenosulfonamida (INTERMEDIO 108, 0.120 g, 0.14 mmol). El producto del título se purificó mediante cromatografía en columna (ISCO, eluyendo con 0→50 % de EtOAc/hexanos).

[000776] LCMS: (ESI) m/z 822[M+H]⁺.

INTERMEDIO 110

[000777] 4-(4-((*R*)-(*tert*-butildimetilsililo)(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((*R*)-4-((*R*)-3-((*tert*-butildifenilsililo)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)fenilsulfonyl)benzamida

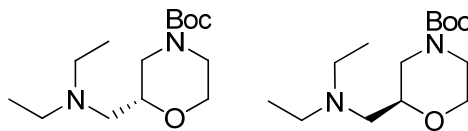


[000778] El producto del título (134 mg, rendimiento: 77%) se preparó utilizando un procedimiento similar al descrito para la síntesis del INTERMEDIO 33. Se utilizaron como materiales de partida el ácido (*R*)-4-(4-((*tert*-butildimetilsililo)(4'-clorobifenil-2-il)metil)piperidin-1-il)benzoico (INTERMEDIO 13, 67.7 mg, 0.13 mmol) y 4-((*R*)-4-((*R*)-3-((*tert*-butildifenilsililo)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)benzenosulfonamida (INTERMEDIO 109, 94.4 mg, 0.11 mmol). El producto resultante se purificó mediante cromatografía en columna (ISCO, columna de 12 g de gel de sílice, eluyendo con 0→30 % de EtOAc/hexanos) para proporcionar el compuesto del título.

INTERMEDIO 111

[000779] (*R*)-2-((dietilamino)metil)morfolin-4-carboxilato de *tert*-butilo y (*S*)-*tert*-2-

((dietilamino)metil)morfolin-4-carboxilato de *tert*-butilo, mezcla de enantiómeros



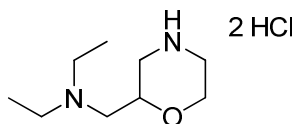
[000780] Se añadieron secuencialmente carbonato de potasio (3.20 g, 23.12 mmol) y yodoetano (1.9 ml, 23.12 mmol) a una solución de (*R*)-*tert*-2-(aminometil)morfolin-4-carboxilato de *tert*-butilo y (*S*)-2-(aminometil)morfolin-4-carboxilato de *tert*-butilo, mezcla de enantiómeros (disponible de proveedores comerciales, 1.0 g, 4.62 mmol), en EtOH (21.25 ml) y la mezcla resultante se calentó a 80 °C durante 3 horas. La mezcla de reacción se enfrió hasta TA, se diluyó con EtOAc, se filtró a través de un lecho de Celite® y se lavó varias veces (EtOAc). El filtrado se concentró a presión reducida y el concentrado se purificó mediante cromatografía en columna (ISCO, eluyendo con 100% de DCM → 100 % de DCM/MeOH/NH₃ (10:1:0.1 v/v/v)) para proporcionar el producto del título como una mezcla de enantiómeros (1.1 g, rendimiento: 85%).

[000781] ¹H RMN (400 MHz, DICLOROMETANO-*d*₂) δ ppm 4.0 – 3.75 (m, 4H), 3.56 (m, 1H), 3.00 – 2.55 (m, 8H), 1.48 (s, 9H), 1.26 (m, 6H).

[000782] LCMS: (ESI) *m/z* 273[M+H]⁺.

INTERMEDIO 112

[000783] (*R*)-*N*-etil-*N*-(morfolin-2-ilmetil)etanamina y (*S*)-*N*-etil-*N*-(morfolin-2-ilmetil)etanamina, mezcla de enantiómeros

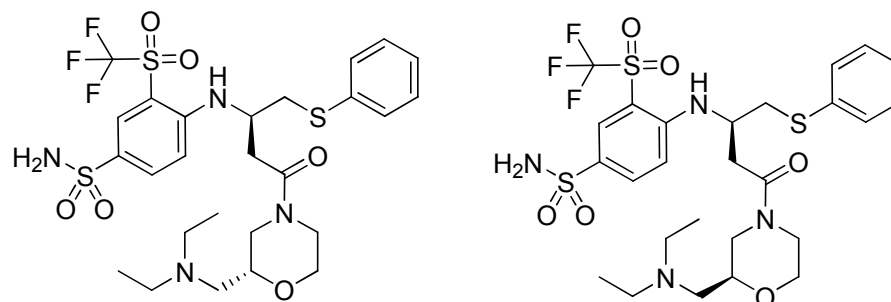


[000784] A una solución de (*R*)-2-((dietilamino)metil)morfolin-4-carboxilato de *tert*-butilo y (*S*)-2-((dietilamino)metil)morfolin-4-carboxilato de *tert*-butilo, mezcla de enantiómeros (INTERMEDIO 111, 1.03 g, 3.78 mmol), en MeOH (15.8 ml) se añadió HCl (4 M en dioxano, 9.45 ml, 37.81 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se concentró a presión reducida y se secó al vacío durante toda la noche para proporcionar el producto del título como una mezcla de enantiómeros en forma de sal clorhídrica (0.92 g, rendimiento: 99 %).

[000785] ¹H RMN (400 MHz, DMSO-*d*₆) δ ppm 4.34 (m, 1H), 3.99 (m, 1H), 3.88– 3.82 (m, 3H), 3.27 (d, 2H), 3.20 – 3.10 (m, 4H), 2.94 (m, 1H), 2.82 (m, 1H), 1.21 (m, 6H).

INTERMEDIO 113

[000786] sales clorhídricas de 4-((*R*)-4-((*R*)-2-((dietilamino)metil)morfolino)-4-oxo-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida y 4-((*R*)-4-((*S*)-2-((dietilamino)metil)morfolino)-4-oxo-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida, mezcla de diastereómeros



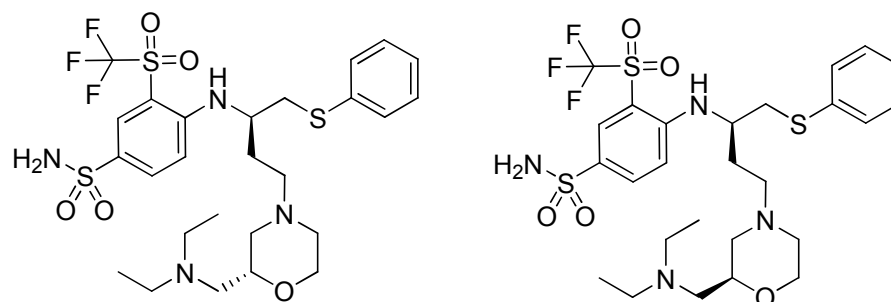
[000787] El producto del título (1.05 g, rendimiento: 43 %) se preparó utilizando un procedimiento similar al descrito para la síntesis del INTERMEDIO 104. Se utilizaron como materiales de partida las sales clorhídricas de (*R*)-*N*-etil-*N*-(morfolin-2-ilmetil)etanamina y (*S*)-*N*-etil-*N*-(morfolin-2-ilmetil)etanamina, mezcla de enantiómeros (INTERMEDIO 112, 0.91 g, 3.71 mmol), y el ácido (*R*)-4-(feniltio)-3-(4-sulfamoyl-2-(trifluorometilsulfonyl)fenilamino)butanoico (INTERMEDIO 8, 1.850 g, 3.71 mmol). El producto del título se purificó mediante cromatografía en columna (ISCO, eluyendo con 0→100 % de DCM hasta el 10% de MeOH/0.1% de NH₃ en DCM) como una mezcla de diastereómeros.

[000788] ¹H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 8.15 (s, 1 H), 7.85 – 7.70 (m, 2 H), 7.43 (m, 2 H), 7.35 – 7.27 (m, 2 H), 6.58 (m, 1 H), 4.40 (m, 1 H), 4.16 (m, 1 H), 3.91 (m, 1 H), 3.55 – 3.40 (m, 2 H), 3.35 – 3.05 (m, 3 H), 3.00 – 2.37 (m, 10 H), 1.04 (m, 6 H).

[000789] LCMS: (ESI) *m/z* 653[M+H]⁺.

INTERMEDIO 114

[000790] 4-((*R*)-4-((*R*)-2-((dietilamino)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida y 4-((*R*)-4-((*S*)-2-((dietilamino)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida, mezcla de diastereómeros



[000791] El producto del título (0.75 g, rendimiento: 83 %) se preparó utilizando un

procedimiento similar al descrito para la síntesis del INTERMEDIO 97. Se utilizaron como materiales de partida 4-((*R*)-4-((*R*)-2-((dietilamino)metil)morfolino)-4-oxo-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida y 4-((*R*)-4-((*S*)-2-((dietilamino)metil)morfolino)-4-oxo-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida, mezcla de diastereómeros (INTERMEDIO 113, 0.92 g, 1.41 mmol). El producto del título se obtuvo como una mezcla de enantiómeros después de evaporar los componentes volátiles a presión reducida.

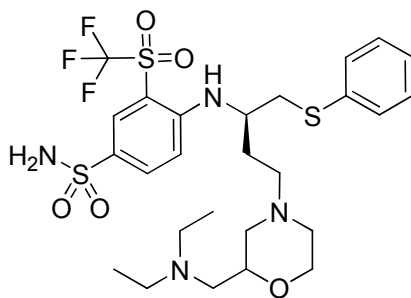
[000792] LCMS: (ESI) m/z 639[M+H]⁺.

[000793] Los dos diastereómeros resultantes del producto del título se separaron utilizando SFC quiral, para proporcionar los INTERMEDIOS 115 y 116 como diastereómeros sustancialmente separados.

Columna:	columna Chiralpak IB
Dimensiones de la columna:	21 x 250 mm, 5 μ
Modificador:	15 % de metanol, 0.1% de dimetiletilamina
Velocidad de flujo (ml/min):	60
Presión de salida (bar):	100
Detección (nm):	220

INTERMEDIO 115

[000794] 4-((2*R*)-4-(2-((dietilamino)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida, primer compuesto eluido

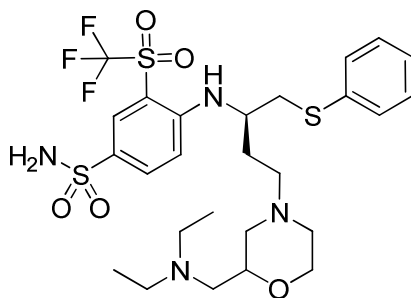


[000795] El primer compuesto eluido tuvo un tiempo de retención de 17.41 minutos.

[000796] LCMS: (ESI) m/z 639[M+H]⁺.

INTERMEDIO 116

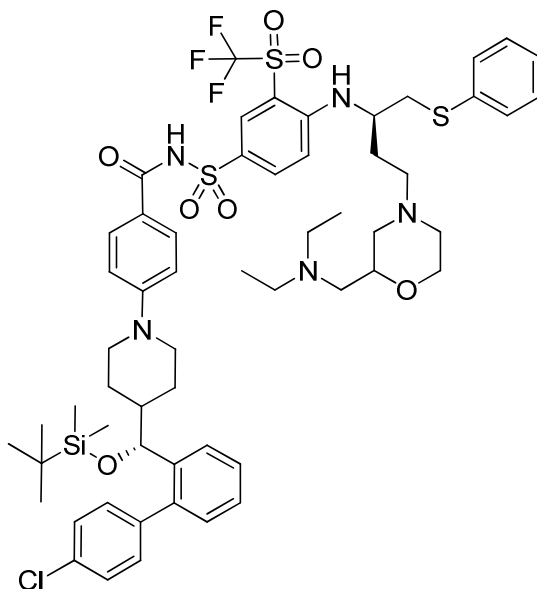
[000797] 4-((2*R*)-4-(2-((dietilamino)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida, segundo compuesto eluido



[000798] El segundo compuesto eluido tuvo un tiempo de retención de 19.18 minutos.

INTERMEDIO 117

[000799] 4-(4-((*R*)-(tert-butildimetilsililoxi)(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((2*R*)-4-(2-((dietilamino)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)fenilsulfonyl)benzamida, diastereómero único

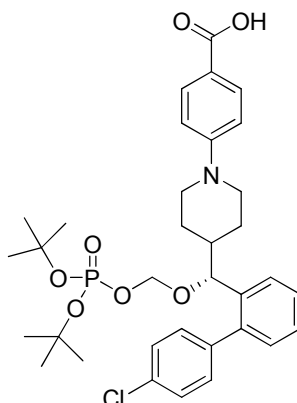


[000800] El producto del título (199 mg, rendimiento: 74 %) se preparó utilizando un procedimiento similar al descrito para la síntesis del INTERMEDIO 33. Se utilizaron como materiales de partida el ácido (*R*)-4-(4-((tert-butildimetilsililoxi)(4'-clorobifenil-2-il)metil)piperidin-1-il)benzoico (INTERMEDIO 13, 125 mg, 0.23 mmol) y 4-((2*R*)-4-(2-((dietilamino)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida (INTERMEDIO 115, primer compuesto eluido, 149 mg, 0.23 mmol). Tras evaporar los componentes volátiles a presión reducida, se obtuvo el producto del título, el cual se utilizó en la preparación del EJEMPLO 26 sin purificación adicional.

[000801] LCMS: (ESI) m/z 1156[M+H]⁺.

INTERMEDIO 118

[000802] ácido (*R*)-4-(4-((4'-clorobifenil-2-il)(di-*tert*-butoxifosfonooximetoxi)metil)piperidin-1-il)benzoico



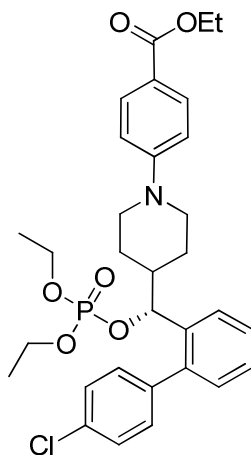
[000803] Se trató una solución del ácido (*R*)-4-(4-((4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoico (INTERMEDIO 40, 360 mg, 0.85 mmol) en tolueno (4.0 ml) con paraformaldehído (128 mg, 4.27 mmol) y la mezcla resultante se enfrió a 0 °C. Se burbujeó lentamente HCl (g) en la solución con una pipeta. La mezcla se agitó durante 1 hora y a continuación se secó con pelets de CaCl₂, lo que provocó efervescencia. Se extrajo la solución con una pipeta y a continuación se hizo rotar a presión reducida (40 mbar) durante unos minutos para eliminar el exceso de HCl. La solución de color amarillo claro se agitó y se trató con di-*tert*-butilfosfato de plata (INTERMEDIO 59, 0.90 g). Después de 0.25 horas, la reacción se filtró a través de Celite® utilizando un embudo Büchner y el sólido retenido en el filtro se lavó con varias porciones de tolueno. La evaporación del filtrado a presión reducida proporcionó un residuo, que se purificó mediante cromatografía en columna (ISCO, eluyendo con 0→50% de EtOAc/CH₂Cl₂ durante 14 minutos) para proporcionar el producto del título (150 mg, rendimiento: 25%).

[000804] ¹H RMN (300 MHz, DMSO-*d*₆) δ ppm 0.93 - 1.43 (m, 21 H) 1.68 - 1.93 (m, 2 H) 2.52 - 2.75 (m, 2 H) 3.66 - 3.78 (m, 1 H) 3.78 - 3.90 (m, 1 H) 4.53 (d, 1 H) 4.71 - 4.83 (m, 1 H) 5.04 - 5.15 (m, 1 H) 6.86 (d, 2 H) 7.20 (d, 1 H) 7.26 - 7.53 (m, 7 H) 7.71 (d, 2 H) 12.17 (s, 1 H).

[000805] LCMS: *m/z* 644 [M + H]⁺.

INTERMEDIO 119

[000806] (*R*)-4-(4-((4'-clorobifenil-2-il)(dietoxifosforiloxi)metil)piperidin-1-il)benzoato de etilo



[000807] Se trató una solución de (*R*)-4-(4-((4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoato de etilo (INTERMEDIO 11A, 600 mg, 1.33 mmol), CBr₄ (575 mg, 1.73 mmol) y piridina (2 ml) a 0 °C con fosfito de trietilo (0.56 ml, 3.33 mmol) gota a gota durante un periodo de 10 minutos. La solución se agitó a 0 °C durante aproximadamente 10 minutos y a continuación se retiró el baño de hielo. La reacción se agitó durante toda la noche a TA, a continuación se eliminó el exceso de piridina a presión reducida y el concentrado se disolvió en 50 ml de DCM. La fase orgánica se lavó sucesivamente con 50 ml de cada una de las siguientes soluciones: HCl 0.5 N acuoso, bicarbonato de sodio saturado acuoso y agua. Las fases orgánicas se secaron con sulfato de sodio, se filtraron y se adsorbieron en gel de sílice. La purificación mediante cromatografía en columna (ISCO, columna de 80 g de gel de sílice, eluyendo con 0→100 % de EtOAc/hexanos durante 24 minutos) proporcionó el compuesto del título (500 mg, rendimiento: 64 %).

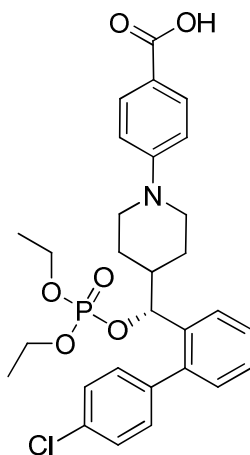
[000808] ¹H RMN (400 MHz, DICLOROMETANO-*d*₂) δ ppm 1.00 - 1.16 (m, 1 H) 1.18 - 1.29 (m, 7 H) 1.28 - 1.46 (m, 4 H) 1.74 - 1.92 (m, 1 H) 2.01 (dt, 1 H) 2.61 (td, 1 H) 2.73 (td, 1 H) 3.71 (d, 1 H) 3.79 - 3.91 (m, 1 H) 3.91 - 4.00 (m, 3 H) 4.07 (dt, 1 H) 4.31 (c, 2 H) 5.25 (t, 1 H) 6.82 (d, 2 H) 7.24 (dd, 1 H) 7.34 - 7.54 (m, 6 H) 7.63 (dd, 1 H) 7.79 - 7.97 (m, 2 H).

[000809] ³¹P RMN (121 MHz, DICLOROMETANO-*d*₂) δ ppm -1.76 (s, 2 P).

[000810] LCMS: (ESI) *m/z* 586, [M+H]⁺.

INTERMEDIO 120

[000811] ácido (*R*)-4-(4-((4'-clorobifenil-2-il)(dietoxifosforiloxi)metil)piperidin-1-il)benzoico



[000812] Se trató una solución de (*R*)-4-(4-((4'-clorobifenil-2-il)(dietoxifosforiloxi)metil)piperidin-1-il)benzoato de etilo (INTERMEDIO 119, 500 mg, 0.85 mmol) en THF (10 ml) y MeOH (2.5 ml), a temperatura ambiente, con una solución de hidróxido de litio (102 mg, 4.27 mmol) en agua (2.5 ml). La reacción se calentó hasta 30 °C durante toda la noche y posteriormente se calentó hasta 40 °C durante aproximadamente 5 horas. Se dejó enfriar la mezcla hasta temperatura ambiente y a continuación se eliminaron los componentes volátiles a presión reducida. El concentrado se diluyó con 30 ml de agua y se acidificó con unas gotas de HCl 6 N para proporcionar un precipitado blanco. El precipitado se aisló mediante filtración al vacío, para proporcionar el compuesto del título (410 mg, rendimiento: 86%).

[000813] ^1H RMN (400 MHz, DICLOROMETANO- d_2) δ ppm 1.01 - 1.15 (m, 1 H) 1.21 (tdd, 7 H) 1.28 - 1.44 (m, 1 H) 1.81 - 1.94 (m, 1 H) 1.94 - 2.07 (m, 1 H) 2.64 (d, 1 H) 2.76 (m, 1 H) 3.68 - 3.81 (m, 1 H) 3.85 - 4.01 (m, 4 H) 4.01 - 4.15 (m, 1 H) 5.24 (t, 1 H) 6.83 (d, 2 H) 7.23 (dd, 1 H) 7.37 - 7.54 (m, 6 H) 7.58 - 7.68 (m, 1 H) 7.86 - 7.95 (m, 2 H).

[000814] ^{31}P RMN (121 MHz, DICLOROMETANO- d_2) δ ppm -1.45 (s, 2 P).

[000815] LCMS: (ESI) m/z 558[M+H] $^+$.

[000816] Rotación óptica:

Concentración: 0.1 g/dl

Lámpara: Sodio

Longitud de onda: 589 nm

Temperatura: 20 °C

Paso óptico: 10 cm

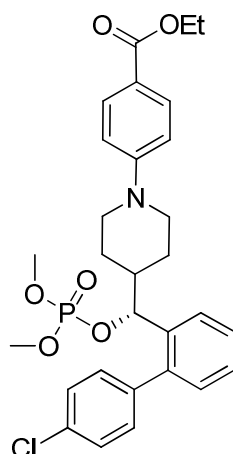
Volumen de la celda: 1 ml

Solvente: diclorometano

$[\alpha] = +76$

INTERMEDIO 121

[000817] (*R*)-4-(4-((4'-clorobifenil-2-il)(dimetoxifosforiloxi)metil)piperidin-1-il)benzoato de etilo



[000818] Se siguió un procedimiento similar al descrito para el INTERMEDIO 119 , utilizando (*R*)-4-(4-((4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoato de etilo (INTERMEDIO 11A, 600 mg, 1.33 mmol) y fosfito de trimetilo (0.473 ml, 4.0 mmol) como materiales de partida, con la purificación posterior mediante cromatografía en columna (ISCO, 0→100% de EtOAc/hexano durante 24 minutos) para proporcionar el compuesto del título (500 mg, rendimiento: 67%). El compuesto del título se utilizó en la preparación del INTERMEDIO 122 sin purificación adicional.

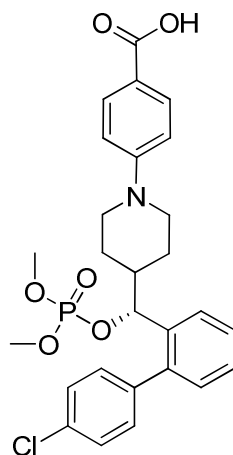
[000819] ^1H RMN (400 MHz, DICLOROMETANO- d_2) δ ppm 0.88 - 1.02 (m, 1 H) 1.06 - 1.12 (m, 1 H) 1.17 - 1.31 (m, 5 H) 1.63 - 1.79 (m, 1 H) 1.80 - 1.89 (m, 1 H) 2.48 (td, 1 H) 2.60 (td, 1 H) 3.42 - 3.56 (m, 7 H) 3.58 (d, 1 H) 3.65 - 3.80 (m, 1 H) 4.17 (c, 2 H) 5.11 (t, 1 H) 6.58 - 6.75 (m, 2 H) 7.11 (dd, 1 H) 7.25 - 7.40 (m, 6 H) 7.51 (dd, 1 H) 7.68 - 7.85 (m, 2 H).

[000820] ^{31}P RMN (121 MHz, DICLOROMETANO- d_2) δ ppm 0.68 (s, 1 P).

[000821] LCMS: (ESI) m/z 558, $[\text{M}+\text{H}]^+$.

INTERMEDIO 122

[000822] ácido (*R*)-4-(4-((4'-clorobifenil-2-il)(dimetoxifosforiloxi)metil)piperidin-1-il)benzoico



[000823] Se calentó una mezcla de hidróxido de litio (107 mg, 4.48 mmol), (*R*)-4-(4-((4'-clorobifenil-2-il)(dimetoxifosforiloxi)metil)piperidin-1-il)benzoato de etilo (INTERMEDIO 121, 500 mg, 0.9 mmol), THF (10 ml), agua (2.5 ml) y MeOH (2.5 ml) a 35 °C durante toda la noche. La mezcla de reacción se concentró a presión reducida, se diluyó con agua (10 ml) y se acidificó con una solución acuosa de HCl 6 N, lo que provocó la formación de un precipitado. El sólido se aisló mediante filtración, para proporcionar el compuesto del título (270 mg, rendimiento: 57%). El compuesto del título se utilizó en la preparación del EJEMPLO 30 sin purificación adicional.

[000824] ¹H RMN (400 MHz, DICLOROMETANO-*d*₂) δ ppm 0.91 - 1.40 (m, 4 H) 1.70 - 2.05 (m, 2 H) 2.48 - 2.62 (m, 1 H) 2.70 (m, 1 H) 3.19 - 3.63 (m, 7 H) 3.69 - 3.83 (m, 1 H) 5.16 (t, 1 H) 6.77 (m, 1 H) 7.12 (m, 1 H) 7.21 - 7.46 (m, 7 H) 7.52 (m, 1 H) 7.79 (m, 2 H).

[000825] LCMS: (ESI) *m/z* 530[M+H]⁺.

[000826] Rotación óptica:

Concentración: 0.2 g/dl

Lámpara: Sodio

Longitud de onda: 589 nm

Temperatura: 20 °C

Paso óptico: 10 cm

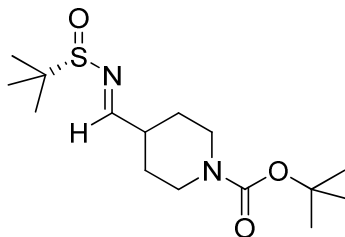
Volumen de la celda: 1 ml

Solvente: Diclorometano

[α]= +51

INTERMEDIO 123

[000827] (*S,E*)-4-((*tert*-butilsulfinilimino)metil)piperidin-1-carboxilato de *tert*-butilo

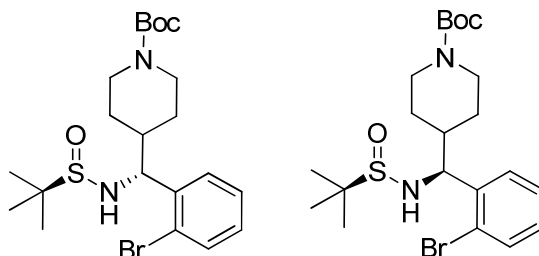


[000828] Se añadieron secuencialmente una solución de (*S*)-2-metilpropan-2-sulfinamida (2.0 g, 16.50 mmol) en THF (8.0 ml) y etóxido de titanio (IV) (17.3 ml, 82.51 mmol) a una solución de 4-formilpiperidin-1-carboxilato de *tert*-butilo (3.70 g, 17.33 mmol) en THF (8.0 ml). La mezcla resultante se agitó a TA durante 2 horas. La mezcla de reacción se vertió sobre agua/hielo y se filtró la suspensión. El filtrado se extrajo con EtOAc, la fase orgánica se secó con MgSO₄ y se filtró y el filtrado se concentró a presión reducida. El residuo se secó al vacío para proporcionar el compuesto del título (4.45 g, rendimiento: 85%).

[000829] LCMS: (ESI) m/z 317[M+H]⁺.

INTERMEDIO 124

[000830] 4-((*R*)-(2-bromofenil)((*S*)-1,1-dimetiletilsulfinamido)metil)piperidin-1-carboxilato de *tert*-butilo y 4-((*S*)-(2-bromofenil)((*S*)-1,1-dimetiletilsulfinamido)metil)piperidin-1-carboxilato de *tert*-butilo, mezcla de diastereómeros

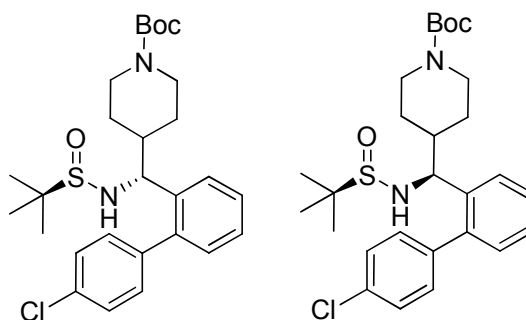


[000831] Se enfrió una solución del complejo cloruro de isopropilmagnesio - cloruro de litio (24.9 ml, 32.39 mmol, 1.3 M en THF) hasta -15 °C. Se añadió 1,2-dibromobenceno (3.80 ml, 31.60 mmol) y la mezcla se agitó a -15 °C durante 2 horas. Se añadió gota a gota una solución de (*S,E*)-4-((*tert*-butilsulfinilimino)metil)piperidin-1-carboxilato de *tert*-butilo (INTERMEDIO 123, 2.50 g, 3.90 mmol) en THF (10.8 ml) a la primera mezcla y la mezcla de reacción resultante se agitó a -15 °C durante toda la noche. La mezcla de reacción se dejó calentar hasta 0 °C y se detuvo con NH₄Cl saturado acuoso. La mezcla se diluyó con EtOAc y se lavó con H₂O. La fase orgánica se secó con Na₂SO₄, se filtró y el filtrado se concentró a presión reducida para proporcionar un residuo, el cual se purificó mediante cromatografía en columna (ISCO, columna de gel de sílice, eluyendo con 0→100% de EtOAc/ hexanos) para proporcionar los compuestos del título (3.0 g, rendimiento: 80%) como una mezcla de diastereómeros (con una proporción de 2:1 a favor del 4-((*R*)-(2-bromofenil)((*S*)-1,1-dimetiletilsulfinamido)metil)piperidin-1-carboxilato de *tert*-butilo).

[000832] LCMS: (ESI) m/z 474[M+H]⁺.

Intermedio 125

[000833] 4-((*R*)-(4'-clorobifenil-2-il)((*S*)-1,1-dimetiletilsulfinamido)metil)piperidin-1-carboxilato de *tert*-butilo y 4-((*S*)-(4'-clorobifenil-2-il)((*S*)-1,1-dimetiletilsulfinamido)metil)piperidin-1-carboxilato de *tert*-butilo, mezcla de diastereómeros

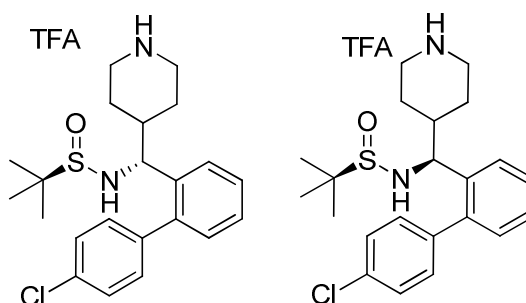


[000834] Una suspensión de la mezcla diastereomérica de 4-((*R*)-(2-bromofenil)((*S*)-1,1-dimetiletilsulfinamido)metil)piperidin-1-carboxilato de *tert*-butilo y 4-((*S*)-(2-bromofenil)((*S*)-1,1-dimetiletilsulfinamido)metil)piperidin-1-carboxilato de *tert*-butilo (INTERMEDIO 124, 2.98 g, 6.29 mmol), ácido 4-clorofenilborónico (1.48 g, 9.44 mmol), 2-diciclohexilfosfino-2',6'-dimetoxibifenilo (0.258 g, 0.63 mmol), tris(dibencilidenoacetona)dipaladio(0) (0.231 g, 0.25 mmol) y fosfato de tripotasio (4.01 g, 18.88 mmol) en tolueno (15.0 ml) y H₂O (6.0 ml) desgasificados se agitó a 100 °C durante 5 horas. La mezcla de reacción se enfrió hasta TA, se diluyó con EtOAc y se filtró a través de un lecho de Celite®. La fase orgánica se separó y se secó con Na₂SO₄, se filtró y se concentró el filtrado para proporcionar un residuo, el cual se purificó mediante cromatografía en columna (ISCO, columna de gel de sílice, eluyendo con 0→100% de EtOAc/ hexanos) para proporcionar los compuestos del título (2.42 g, rendimiento: 76%) como una mezcla de diastereómeros.

[000835] LCMS: (ESI) m/z 505[M+H]⁺.

INTERMEDIO 126

[000836] sal trifluoroacética de (*S*)-*N*-((*R*)-(4'-clorobifenil-2-il)(piperidin-4-il)metil)-2-metilpropan-2-sulfinamida y (*S*)-*N*-((*S*)-(4'-clorobifenil-2-il)(piperidin-4-il)metil)-2-metilpropan-2-sulfinamida, mezcla de diastereómeros



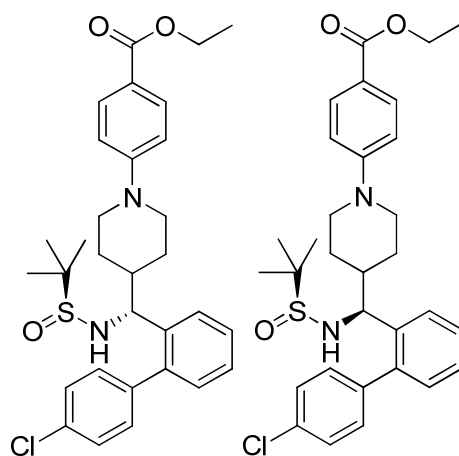
[000837] Se añadió TFA (3.55 ml, 46.13 mmol) a una solución de 4-((*R*)-(4'-clorobifenil-2-il)((*S*)-1,1-dimetiletilsulfinamido)metil)piperidin-1-carboxilato de *tert*-butilo y 4-((*S*)-(4'-clorobifenil-2-il)((*S*)-1,1-dimetiletilsulfinamido)metil)piperidin-1-carboxilato de *tert*-butilo, mezcla de diastereómeros (INTERMEDIO 125, 2.33 g, 4.61 mmol), en DCM (43 ml) y la mezcla de reacción se agitó a TA durante 1 hora. La mezcla de reacción se concentró a presión reducida,

se diluyó con EtOAc y se lavó con NaHCO₃ saturado acuoso (2x). La fase orgánica se secó con Na₂SO₄, se filtró y se concentró el filtrado a presión reducida. El residuo obtenido se secó al vacío para proporcionar los compuestos del título (2.44 g, rendimiento: casi cuantitativo) como una mezcla de diastereómeros.

[000838] LCMS: (ESI) m/z 405[M+H]⁺.

INTERMEDIO 127

[000839] 4-(4-((*R*)-(4'-clorobifenil-2-il)((*S*)-1,1-dimetiletilsulfonamido)metil)piperidin-1-il)benzoato de etilo y 4-(4-((*S*)-(4'-clorobifenil-2-il)((*S*)-1,1-dimetiletilsulfonamido)metil)piperidin-1-il)benzoato de etilo, mezcla de diastereómeros



[000840] Una suspensión de la sal trifluoroacética de (*S*)-*N*-((*R*)-(4'-clorobifenil-2-il)(piperidin-4-il)metil)-2-metilpropan-2-sulfonamida y (*S*)-*N*-((*S*)-(4'-clorobifenil-2-il)(piperidin-4-il)metil)-2-metilpropan-2-sulfonamida, mezcla de diastereómeros (INTERMEDIO 126, 2.39 g, 4.61 mmol), aducto éter butil metílico de cloro(2-diciclohexilfosfino-2',6'-diisopropoxi-1,1'-bifenil)[2-(2-aminoetilfenil)]Pd(II) (0.168 g, 0.23 mmol), diciclohexil(2',6'-diisopropoxibifenil-2-il)fosfina (0.108 g, 0.23 mmol), 4-yodobenzoato de etilo (0.77 ml, 4.61 mmol) y carbonato de cesio (5.26 g, 16.14 mmol) en tolueno desgasificado (22.3 ml) se agitó a 110 °C durante 1.5 horas. La mezcla de reacción se enfrió hasta TA, se diluyó con EtOAc y se filtró a través de un lecho de Celite®. El filtrado se concentró a presión reducida para proporcionar un residuo, el cual se purificó mediante cromatografía en columna (ISCO, columna de gel de sílice, eluyendo con 0→100% de EtOAc/ hexanos) para proporcionar el compuesto del título (2.10 g, rendimiento: 82%) como una mezcla de diastereómeros.

[000841] LCMS: (ESI) m/z 553[M+H]⁺.

[000842] Los dos diastereómeros se separaron utilizando SFC quiral, para proporcionar

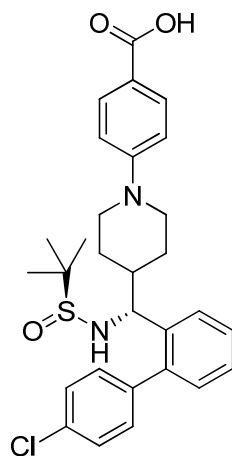
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4-(4-((*R*)-(4'-clorobifenil-2-il)((*S*)-1,1-dimetiletilsulfonamido)metil)piperidin-1-il)benzoato de etilo (INTERMEDIO 128), como el diastereómero principal (1.23 g), y 4-(4-((*S*)-(4'-clorobifenil-2-il)((*S*)-1,1-dimetiletilsulfonamido)metil)piperidin-1-il)benzoato de etilo (INTERMEDIO 129), como el diastereómero minoritario (0.59 g).

Columna:	columna Chiralpak AD
Dimensiones de la columna:	30 x 250 mm, 5 μ
Fase móvil:	75% de CO ₂ y 25% de EtOH
Velocidad de flujo (ml/min):	120 ml/min
Detección (nm):	220 nm

INTERMEDIO 130

[000843] ácido 4-(4-((*R*)-(4'-clorobifenil-2-il)((*S*)-1,1-dimetiletilsulfonamido)metil)piperidin-1-il)benzoico



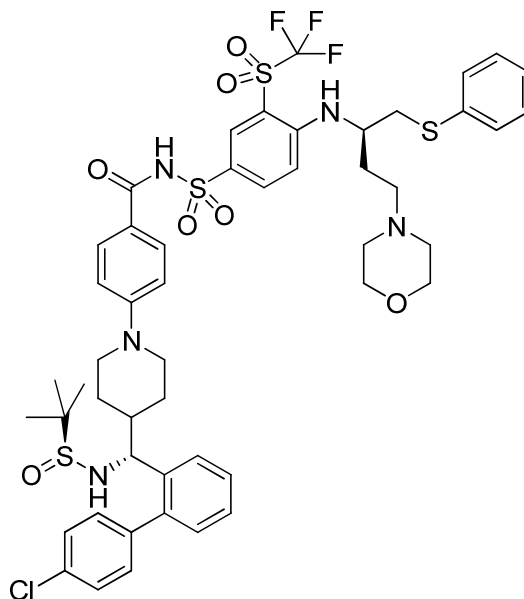
[000844] A una solución de 4-(4-((*R*)-(4'-clorobifenil-2-il)((*S*)-1,1-dimetiletilsulfonamido)metil)piperidin-1-il)benzoato de etilo (INTERMEDIO 128, 0.40 g, 0.62 mmol) en THF (4.3 ml), se añadió MeOH (1.4 ml) y una solución de LiOH (0.09 g, 4.44 mmol) en agua (1.4 ml). La mezcla de reacción se agitó a 40 °C durante toda la noche. La mezcla de reacción se enfrió hasta TA, se concentró a presión reducida y el residuo se suspendió en agua. La suspensión se enfrió hasta 0 °C, se acidificó hasta pH ~2 utilizando HCl 1 N acuoso, se filtró y el sólido retenido en el filtro se secó en un horno de vacío para proporcionar el compuesto del título (0.38 g, rendimiento: casi cuantitativo).

[000845] LCMS: (ESI) m/z 525[M+H]⁺.

INTERMEDIO 131

[000846] 4-(4-((*R*)-(4'-clorobifenil-2-il)((*S*)-1,1-dimetiletilsulfonamido)metil)piperidin-1-il)-*N*-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-

(trifluorometilsulfonil)fenilsulfonil)benzamida



[000847] En un vial de 40 ml, se introdujeron el ácido 4-(4-((*R*)-(4'-clorobifenil-2-il)((*S*)-1,1-dimetiletilsulfonamido)metil)piperidin-1-il)benzoico (INTERMEDIO 130, 0.150 g, 0.29 mmol), DMAP (70 mg, 0.57 mmol) y EDC (0.110 g, 0.57 mmol) y se purgaron con nitrógeno. Se añadieron DCM (4.0 ml) y DIPEA (0.10 ml, 0.57 mmol) y la solución se agitó a TA durante 10 minutos. Se añadió una solución de (*R*)-4-(4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)bencenosulfonamida (INTERMEDIO 69, 0.158 g, 0.29 mmol) en DCM (1.6 ml) a la solución y la mezcla de reacción se agitó a TA durante toda la noche. La mezcla se diluyó con DCM y se lavó con bisulfato de sodio 1 N (acuoso) y a continuación con bicarbonato de sodio saturado acuoso. La fase orgánica se secó (Na₂SO₄), se filtró y se evaporó a presión reducida para proporcionar un residuo, el cual se purificó mediante cromatografía en columna (ISCO, columna de gel de sílice, eluyendo con 0→100 % de DCM/MeOH/NH₃ (10:1:0.1 v/v/v)) para proporcionar el compuesto del título (0.21 g, rendimiento: 69%).

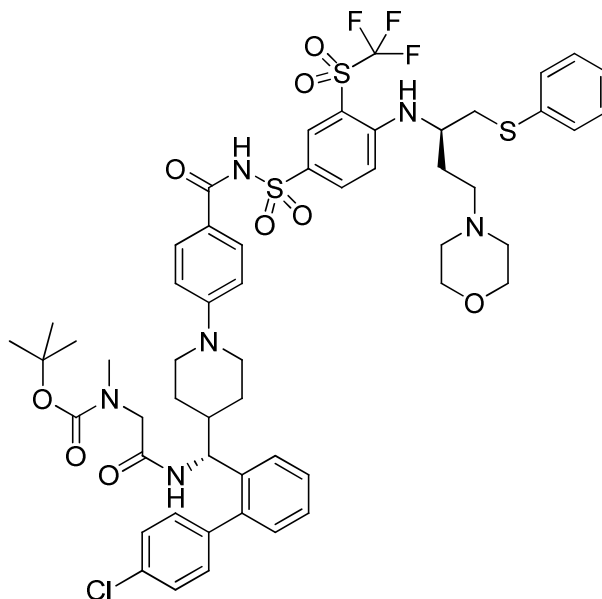
[000848] ¹H RMN (400 MHz, DICLOROMETANO-*d*₂) δ ppm 8.30 (d, 1H), 8.01 (dd, 1H), 7.70 – 7.67 (m, 2H), 7.45 – 7.18 (m, 14H), 6.96 – 6.93 (m, 1H), 6.70 – 6.65 (m, 3H), 4.29 (m, 1H), 3.96 (m, 1H), 3.76 – 3.73 (m, 1H), 3.62 – 3.55 (m, 6H), 3.11 – 3.06 (m, 2H), 2.65 – 2.48 (m, 2H), 2.38 – 2.25 (m, 6H), 2.06 (m, 2H), 1.81 (m, 1H), 1.69 – 1.62 (m, 2H), 1.17 (s, 9H), 1.11 – 0.95 (m, 3H).

[000849] LCMS: (ESI) *m/z* 1060[M+H]⁺.

INTERMEDIO 132

[000850] 2-((*R*)-(4'-clorobifenil-2-il)(1-(4-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonilcarbamoil)fenil)piperidin-4-il)metilamino)-2-

oxoetil(metil)carbamato de *tert*-butilo

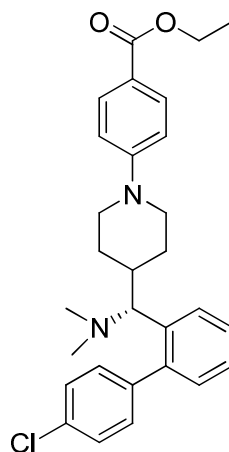


[000851] Se añadió DIPEA (0.08 ml, 0.46 mmol) a una solución de la sal del ácido fórmico y 4-(4-((*R*)-amino(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)fenilsulfonyl)benzamida (EJEMPLO 33, 0.11 g, 0.11 mmol), ácido 2-(*tert*-butoxicarbonil(metil)amino)acético (22 mg, 0.11 mmol) y HATU (52 mg, 0.14 mmol) en DMF (2.2 ml) y la solución resultante se agitó a TA durante 1 hora. La mezcla de reacción se concentró a presión reducida, se diluyó con DCM y se lavó con H₂O, NaHSO₄ 1 N (acuoso) y NaHCO₃ saturado acuoso. La fase orgánica se secó con Na₂SO₄, se filtró y se concentró el filtrado a presión reducida para proporcionar un residuo, el cual se purificó mediante cromatografía en columna (ISCO, columna de gel de sílice, eluyendo con 0→100% de DCM/MeOH/NH₃ (10:1:0.1)) para proporcionar el compuesto del título (94 mg, rendimiento: 73%).

[000852] LCMS: (ESI) m/z 1127[M+H]⁺.

INTERMEDIO 133

[000853] (*R*)-4-(4-((4'-clorobifenil-2-il)(dimetilamino)metil)piperidin-1-il)benzoato de etilo



[000854] Paso 1: Se añadió HCl (1.16 ml, 4.63 mmol, 4.0 M en dioxano) a una solución de 4-((*R*)-(4'-clorobifenil-2-il)((*S*)-1,1-dimetiletilsulfinamido)metil)piperidin-1-il)benzoato de etilo (INTERMEDIO 128, 0.128 g, 0.23 mmol) en MeOH (3.5 ml) y la mezcla de reacción se agitó a TA durante 3 horas. La mezcla de reacción se concentró a presión reducida y se secó al vacío para proporcionar la sal clorhídrica de (*R*)-4-(4-(amino(4'-clorobifenil-2-il)metil)piperidin-1-il)benzoato de etilo (INTERMEDIO 133, PASO 1, 0.12 g), la cual se utilizó en la preparación del INTERMEDIO 133, PASO 2 sin purificación adicional.

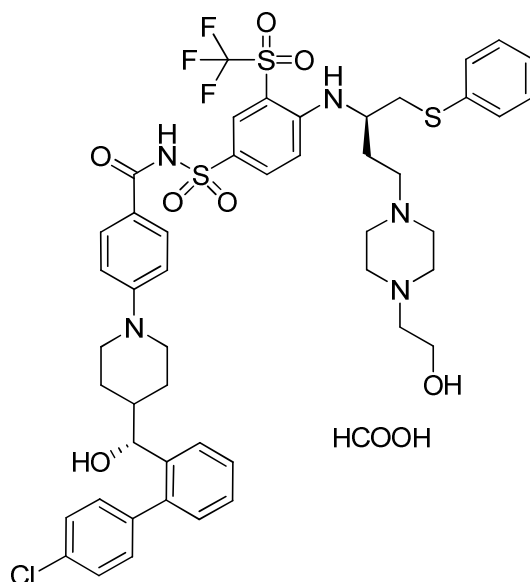
[000855] LCMS: (ESI) m/z 449 $[M+H]^+$.

[000856] Paso 2: Se añadieron secuencialmente formaldehído (0.17 ml, 2.3 mmol, al 37% en peso en MeOH) y triacetoxiborohidruro de sodio (0.49 g, 2.30 mmol) a una solución de la sal clorhídrica de (*R*)-4-(4-(amino(4'-clorobifenil-2-il)metil)piperidin-1-il)benzoato de etilo (INTERMEDIO 133, PASO 1, 0.12 g, 0.23 mmol) en DCM (2.1 ml) y la mezcla de reacción se agitó durante 2 horas. La mezcla de reacción se diluyó con DCM y se lavó con NaHCO₃ saturado acuoso. La fase orgánica se secó (Na₂SO₄), se filtró y se concentró el filtrado a presión reducida para proporcionar el compuesto del título (0.11 g, rendimiento: casi cuantitativo) después de secar al vacío.

[000857] LCMS: (ESI) m/z 477 $[M+H]^+$.

EJEMPLO 1

[000858] sal de 4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-(4-(2-hidroxietil)piperazin-1-il)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)fenilsulfonyl)benzamida y el ácido fórmico



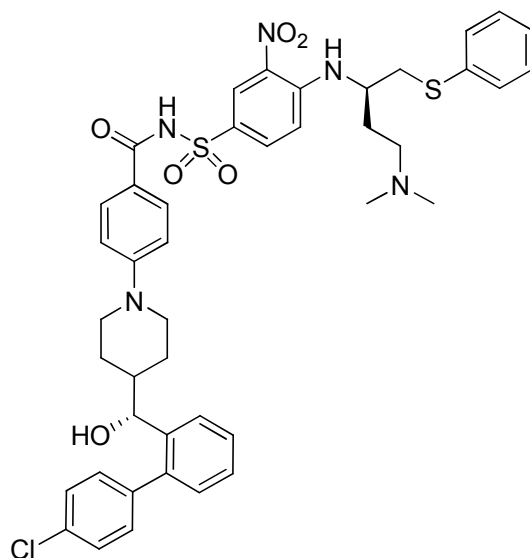
[000859] Se añadió gota a gota TBAF (solución 1 M en THF, 192 μ l, 0.19 mmol) a una solución de 4-(4-((*R*)-(tert-butildimetilsililoxi)(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((*R*)-4-(4-(2-(tert-butildifenilsililoxi)etil)piperazin-1-il)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida (INTERMEDIO 32, 130 mg, 0.10 mmol) en THF (702 μ l) y la mezcla de reacción resultante se agitó a temperatura ambiente durante toda la noche. Se añadió HCl (1 ml, 4 M en dioxano) a la mezcla y se agitó durante 1 hora más a temperatura ambiente. La mezcla de reacción se diluyó con EtOAc y la fase orgánica se lavó con H₂O (2x) y se secó (Na₂SO₄). La evaporación de los componentes volátiles a presión reducida proporcionó un residuo, el cual se purificó mediante HPLC de fase inversa (columna Gilson, eluyendo con 15→70% de H₂O/MeCN con el 0.1% de fórmico durante 14 minutos) para proporcionar el producto del título (78 mg, rendimiento: 78 %).

[000860] ¹H RMN (300 MHz, DMSO-*d*₆) δ ppm 8.07 (d, 1 H) 7.95 (dd, 1 H) 7.67 (d, 2 H) 7.59 (d, 1 H) 7.49 (d, 2 H) 7.43 (t, 1 H) 7.25 - 7.38 (m, 7 H) 7.07 - 7.23 (m, 3 H) 6.90 (d, 1 H) 6.73 (d, 3 H) 5.21 (s a, 1 H) 4.25 - 4.36 (m, 2 H) 4.02 (d, 1 H) 3.73 (d, 1 H) 3.61 - 3.68 (m, 3 H) 3.22 - 3.33 (m, 4 H) 2.83 - 3.03 (m, 6 H) 2.69 - 2.82 (m, 2 H) 2.61 (dd, 4 H) 2.43 (d, 3 H) 1.90 (d, 2 H) 1.74 (d, 1 H) 1.60 (d, 1 H) 1.14 - 1.22 (m, 2 H) 0.95 - 1.08 (m, 2 H) 0.86 (d, 1 H).

[000861] LCMS: (ESI) *m/z* 1001 [M+H]⁺.

EJEMPLO 2

[000862] 4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-(dimetilamino)-1-(feniltio)butan-2-ilamino)-3-nitrofenilsulfonil)benzamida



[000863] El compuesto del título (77.2 mg, rendimiento: 59%) se preparó utilizando un procedimiento similar al descrito en el EJEMPLO 1, utilizando como material de partida 4-(4-((*R*)-(tert-butildimetilsililo)(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((*R*)-4-(dimetilamino)-1-(feniltio)butan-2-ilamino)-3-nitrofenilsulfonil)benzamida (INTERMEDIO 33, 147.5 mg, 0.16 mmol). El producto del título se purificó mediante cromatografía en columna (ISCO, columna de 4 g de gel de sílice, eluyendo con 0→4.5% de MeOH/DCM) y a continuación [ISCO, columna de 12 g de gel de sílice, eluyendo con 0→8% de MeOH/DCM y 0→100% de (10% de NH₃ 2 M en MeOH/90% de DCM)].

[000864] ¹H RMN (400 MHz, DMSO-*d*₆) δ ppm 0.85 (m, 1 H) 0.96 - 1.05 (m, 1 H) 1.05 - 1.17 (m, 1 H) 1.53 - 1.66 (m, 1 H) 1.84 - 2.13 (m, 3 H) 2.73 - 2.96 (m, 2 H) 3.55 (d, 1 H) 3.71 (m, 1 H) 4.06 (m, 1 H) 4.31 (dd, 1 H) 5.20 (d, 1 H) 6.71 (d, 2 H) 6.89 (d, 1 H) 7.09 - 7.20 (m, 2 H) 7.24 (t, 2 H) 7.28 - 7.39 (m, 5 H) 7.42 (t, 1 H) 7.49 (d, 2 H) 7.58 (d, 1 H) 7.67 (d, 2 H) 7.79 (dd, 1 H) 8.24 (d, 1 H) 8.44 (d, 1 H).

[000865] LCMS: (ESI) *m/z* 828[M+H]⁺.

[000866] Rotación óptica:

Concentración: 0.1 g/dl

Lámpara: Sodio

Longitud de onda: 589 nm

Temperatura: 20 °C

Paso óptico: 10 cm

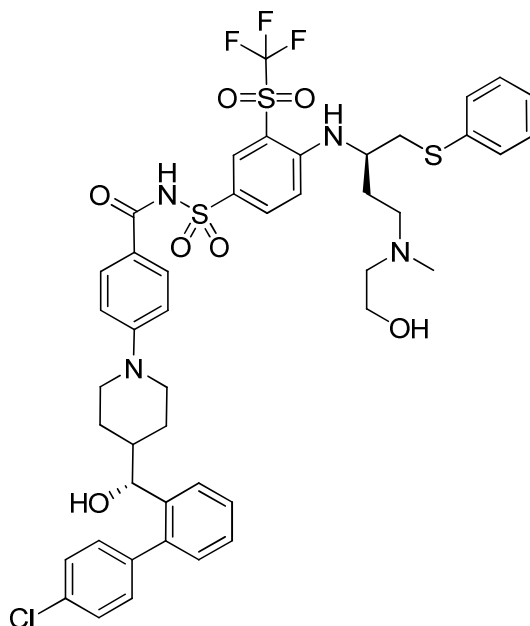
Volumen de la celda: 1 ml

Solvente: CH₂Cl₂

[α]_D = -16°

EJEMPLO 3

[000867] 4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-((2-hidroxi)etil)(metil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)fenilsulfonyl)benzamida



[000868] Se añadió lentamente HCl (4 M en dioxano, 15.08 ml, 60.33 mmol) a una solución de *N*-(4-((*R*)-4-((2-(*tert*-butildimetilsililo)etil)(metil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)fenilsulfonyl)-4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzamida (INTERMEDIO 34, 2.96 g, 2.51 mmol) en dioxano (5.03 ml) y metanol (5.03 ml). Aproximadamente en la mitad de la adición, se detectó un ligero calentamiento y la reacción se enfrió hasta 0 °C. Se continuó añadiendo el ácido clorhídrico en dioxano (4 M) y, una vez completada la adición, se retiró el baño de hielo. La solución amarilla resultante se dejó calentar hasta TA y se agitó durante 3 min, antes de concentrarla a presión reducida hasta obtener la mitad del volumen y diluirla con acetato de etilo. La mezcla resultante se lavó con bicarbonato de sodio (saturado, acuoso) y cloruro de sodio (saturado, acuoso), antes de secarla con sulfato de sodio, filtrarla y concentrarla. Durante el proceso de concentración, precipitó un residuo oleoso denso a partir de la solución y este material se volvió a disolver en acetona, antes de volverlo a concentrar para obtener una película de color beige. Esta película se disolvió en metanol al 10% en acetato de etilo y se purificó mediante cromatografía en columna (ISCO, 330 g de SiO₂, gradiente isocrático de metanol al 15% en acetato de etilo durante 30 min) para proporcionar el compuesto del título (1.90 g, rendimiento: 80%).

[000869] ¹H RMN (300 MHz, METANOL-d₄) δ 8.27 (s, 1H), 8.04 (dd, 1H), 7.82 (d, 2H), 7.62 (d, 1H), 7.09 - 7.50 (m, 12H), 6.66 - 6.86 (m, 3H), 4.44 (d, 1H), 3.99 (s a, 1H), 3.69 - 3.85 (m, 3H), 3.62 (d, 1H), 3.12 - 3.29 (m, 2H), 2.86 - 3.05 (m, 4H), 2.60 - 2.75 (m, 4H), 2.46 - 2.58 (m,

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¹H), 2.11 - 2.28 (m, 1H), 1.88 - 2.12 (m, 2H), 1.65 - 1.84 (m, 1H), 1.08 - 1.35 (m, 2H), 0.88 - 1.07 (m, 1H).

[000870] ¹⁹F RMN (282 MHz, METANOL-d₄) δ -80.88 (3F).

[000871] LCMS: (ESI) *m/z* 945.4, 947.4 [M+H]⁺.

[000872] Rotación óptica:

Concentración: 0.305 g/dl

Lámpara: Sodio

Longitud de onda: 589 nm

Temperatura: 20 °C

Paso óptico: 10 cm

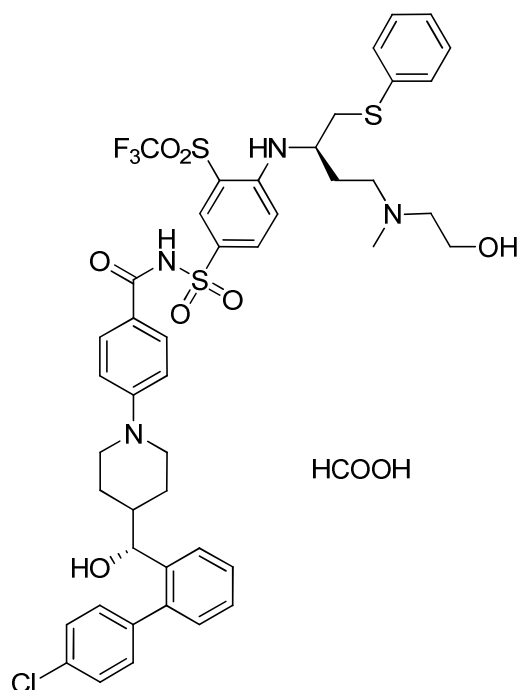
Volumen de la celda: 1 ml

Solvente: CH₂Cl₂

[α] = +28

EJEMPLO 3A

[000873] sal de 4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-((2-hidroxi)etil)(metil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida y el ácido fórmico



[000874] Como un procedimiento alternativo al EJEMPLO 3, se trató una solución de 4-(4-((*R*)-(tert-butildimetilsililoxi)(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((*R*)-4-((2-(tert-butildifenilsililoxi)etil)(metil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida (INTERMEDIO 34A, 110 mg, 0.08 mmol) en

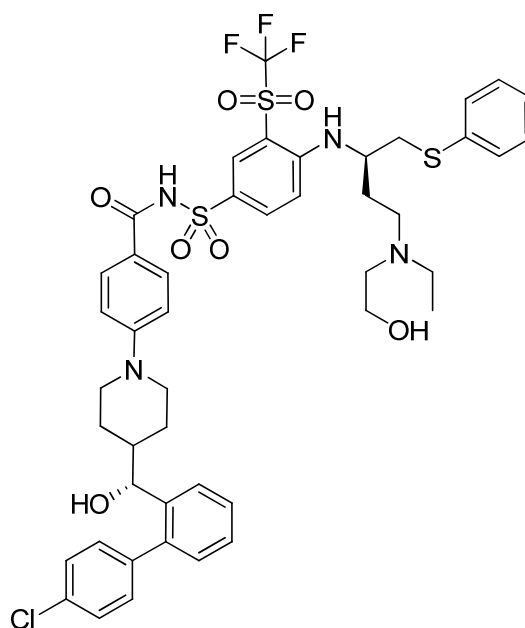
THF con una solución de TBAF (0.169 ml, 0.17 mmol, 1 M en THF) y la solución resultante se agitó a temperatura ambiente durante toda la noche. Se añadió HCl (2 ml, 4 N en dioxano) a la solución y la mezcla se agitó durante 30 minutos a temperatura ambiente. La evaporación de los componentes volátiles a presión reducida proporcionó un residuo, el cual se purificó mediante HPLC de fase inversa (columna Gilson, eluyendo con 10→70% de H₂O/MeCN con el 0.1% de fórmico durante 14 minutos) para proporcionar el producto del título (53.3 mg, rendimiento: 66 %).

[000875] ¹H RMN (DMSO-d₆, 300Mz) δ 8.14 (s, 1H) 8.10 (s, 1H) 7.97 (d, 1H) 7.67 (d, 2H) 7.59 (d, 1H) 7.49 (d, 2H) 7.43 (t, 1H) 7.26-7.37 (m, 7H) 7.21 (d, 1H) 7.14 (d, 1H) 6.93 (d, 1H) 6.74 (d, 2H) 5.20 (d, 1H) 4.28-4.33 (m, 1H) 3.99-4.09 (m, 1H) 3.71-3.79 (m, 1H) 3.55-3.66 (m, 3H) 2.93-3.14 (m, 4H) 2.65 (s, 3H) 2.40-2.61 (m, 3H) 1.99-2.14 (m, 2H) 1.88-1.95 (m, 1H) 1.56-1.68 (m, 1H) 0.96-1.26 (m, 2H) 0.79-0.93 (m, 1H).

[000876] LCMS: (ESI) *m/z* 946 [M+H]⁺.

EJEMPLO 4

[000877] 4-(4-((*R*)-4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-(etil(2-hidroxi)etil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida



[000878] Se añadió lentamente una solución de HCl en dioxano (4 M, 11.18 ml, 44.70 mmol) a una solución de color amarillo claro de *N*-(4-((*R*)-4-((2-(*tert*-butildimetilsililo)etil)(etil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)-4-(4-((*R*)-4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzamida (INTERMEDIO 66, 2.4 g, 2.24 mmol) en DCM (11.2 ml) a 0 °C. Una vez completada la adición, se retiró el baño de hielo. La solución resultante se dejó calentar hasta TA y se agitó durante 1 hora, antes de concentrarla a presión reducida hasta

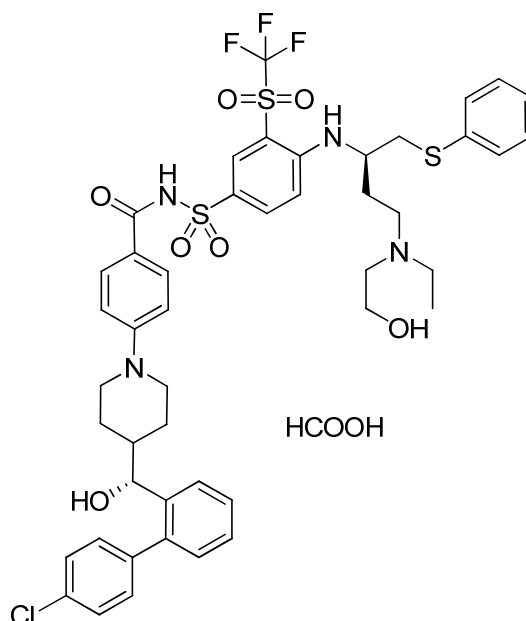
obtener la mitad del volumen y diluirla con acetato de etilo. La mezcla resultante se lavó con bicarbonato de sodio (saturado, acuoso) y cloruro de sodio (saturado, acuoso), antes de secarla con sulfato de sodio, filtrarla y concentrarla a presión reducida. El concentrado se purificó mediante cromatografía en columna (ISCO, gel de sílice, 0→20% de metanol en acetato de etilo durante 30 min) para proporcionar el compuesto del título (1.64 g, rendimiento: 76%).

[000879] ^1H RMN (300 MHz, DICLOROMETANO- d_2) δ ppm 8.25 (s, 1 H) 8.03 (d, 1 H) 7.77 (d, 2 H) 7.61 (d, 1 H) 7.39 - 7.48 (m, 2 H) 7.31 - 7.39 (m, 4 H) 7.17 - 7.30 (m, 6 H) 6.90 (d, 1 H) 6.69 (d, 3 H) 4.49 (d, 1 H) 3.91 (s a, 2 H) 3.55 - 3.81 (m, 5 H) 3.09 (d, 2 H) 2.76 - 2.96 (m, 6 H) 2.47 - 2.72 (m, 3 H) 2.04 - 2.15 (m, 1 H) 1.84 - 1.99 (m, 2 H) 1.76 (dd, 1 H) 1.23 - 1.36 (m, 2 H) 1.13 - 1.23 (m, 1 H) 1.01 - 1.13 (m, 4 H).

[000880] LCMS: (ESI) m/z 959[M+H] $^+$.

EJEMPLO 4A

[000881] sal de 4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-(etil(2-hidroxietil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida y el ácido fórmico



[000882] Paso 1: En un matraz de 50 ml, se introdujeron el ácido (*R*)-4-(4-((*tert*-butildimetilsililoxi)(4'-clorobifenil-2-il)metil)piperidin-1-il)benzoico (INTERMEDIO 13, 160 mg, 0.3 mmol), (*R*)-4-(4-((2-(*tert*-butildifenilsililoxi)etil)(etil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)bencenosulfonamida (INTERMEDIO 25, 216 mg, 0.27 mmol), DMAP (100 mg, 0.82 mmol) y EDC (104 mg, 0.54 mmol) y se purgaron con nitrógeno. Se añadió DCM (3 ml) y la solución se agitó a temperatura ambiente durante toda la noche. La mezcla de reacción se diluyó con DCM (40 ml) y se lavó con bisulfato de sodio 1 N acuoso y a

continuación con bicarbonato de sodio saturado acuoso (40 ml). La fase orgánica se secó (Na_2SO_4), se filtró y se evaporó a presión reducida para proporcionar un residuo, el cual se purificó mediante cromatografía en columna (ISCO, columna de 40 g de gel de sílice, eluyendo con 0→25 % de EtOAc/hexanos) para proporcionar 4-(4-((*R*)-(tert-butildimetilsililoxi)(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((*R*)-4-((2-(tert-butildifenilsililoxi)etil)(etil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida (EJEMPLO 4A, PASO 1, 140 mg), la cual se utilizó en la preparación del EJEMPLO 4A, PASO 2, sin purificación adicional.

[000883] Paso 2: Se añadió gota a gota TBAF (0.54 ml, 0.54 mmol, 1 M en THF) a una solución de

4-(4-((*R*)-(tert-butildimetilsililoxi)(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((*R*)-4-((2-(tert-butildifenilsililoxi)etil)(etil)amino)-1-(feniltio)butan-2-ilamino)-3-

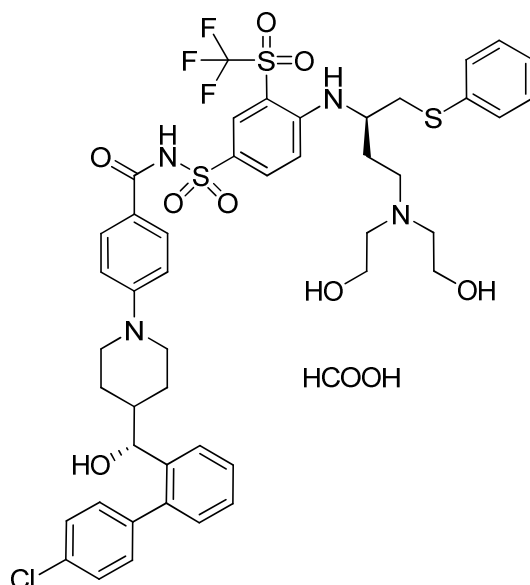
(trifluorometilsulfonil)fenilsulfonil)benzamida (EJEMPLO 4A, PASO 1, 140 mg) en THF (2 ml) y la mezcla de reacción resultante se agitó a temperatura ambiente durante toda la noche. Se añadió HCl (2 ml, 4 M en dioxano) a la mezcla y se agitó durante 30 minutos más a temperatura ambiente. La mezcla de reacción se diluyó con EtOAc y la fase orgánica se lavó con H_2O (2x) y se secó (Na_2SO_4). La evaporación de los componentes volátiles a presión reducida proporcionó un residuo, el cual se purificó mediante HPLC de fase inversa (columna Gilson, eluyendo con 10→70% de H_2O /MeCN con 0.1% de fórmico durante 14 minutos) para proporcionar el producto del título (60.4 mg, rendimiento: 23%).

[000884] ^1H RMN(DMSO-*d*₆, 300Mz) δ 8.09 (d, 1H) 7.97 (s, 1H) 7.67 (d, 2H) 7.59 (d, 1H) 7.49 (d, 2H) 7.43 (t, 1H) 7.26-7.36 (m, 7H) 7.20 (d, 1H) 7.14 (d, 1H) 6.90-6.96 (m, 1H) 6.73 (d, 1H) 5.28 (s a, 1 H) 5.19 (d, 1H) 4.31 (t, 1H) 4.05 (t, 1H) 3.53-3.76 (m, 4H) 2.96-3.21 (m, 4H) 2.38-2.69 (m, 5H) 2.0-2.14 (m, 2H) 1.90 (d, 1H) 1.53-1.68 (m, 1H) 0.98-1.23 (m, 6H) 0.81-0.91 (m, 1H).

[000885] LCMS: m/z 960 $[\text{M}+\text{H}]^+$.

EJEMPLO 5

[000886] sal de *N*-(4-((*R*)-4-(bis(2-hidroxietil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)-4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzamida y el ácido fórmico



[000887] Paso 1: En un matraz de 50 ml, se introdujeron el ácido (*R*)-4-(4-((*tert*-butidimetisililoxy)(4'-clorobifenil-2-il)metil)piperidin-1-il)benzoico (INTERMEDIO 13, 225 mg, 0.22 mmol), DMAP (140 mg, 1.14 mmol), (*R*)-4-(4-(bis(2-(*tert*-butildifenilsililoxy)etil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)bencenosulfonamida (INTERMEDIO 31, 400 mg, 0.38 mmol) y EDC (146 mg, 0.76 mmol) y se purgaron con nitrógeno. Se añadió DCM (3 ml) y la solución se agitó a temperatura ambiente durante toda la noche. La mezcla de reacción se diluyó con DCM (40 ml) y se lavó con bisulfato de sodio (1 N, 35 ml) y a continuación con bicarbonato de sodio (saturado, acuoso, 40 ml). La fase orgánica se secó (Na₂SO₄), se filtró y se evaporó a presión reducida para proporcionar un residuo, el cual se purificó mediante cromatografía en columna (ISCO, columna de 40 g de gel de sílice, eluyendo con 0→25 % de EtOAc/hexanos) para proporcionar 4-(4-((*R*)-4-((2-(*tert*-butildifenilsililoxy)etil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida (EJEMPLO 5, PASO 1, 252 mg), la cual se utilizó en la preparación del EJEMPLO 5, PASO 2 sin purificación adicional.

[000888] Paso 2: Se añadió gota a gota una solución de TBAF (0.76 ml 0.76 mmol, 1 M in THF) a una solución de 4-(4-((*R*)-4-((2-(*tert*-butildifenilsililoxy)etil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida (EJEMPLO 5, PASO 1, 252 mg) en THF (2 ml) y la mezcla de reacción resultante se agitó a temperatura ambiente durante toda la noche. Se añadió HCl (2 ml, 4 M en dioxano) a la mezcla y se agitó durante 30 minutos más a temperatura ambiente. La mezcla de reacción se diluyó con EtOAc y la fase orgánica se lavó con H₂O (2x) y se secó (Na₂SO₄). La evaporación de los componentes volátiles a presión reducida proporcionó un residuo, el cual se purificó mediante HPLC de fase inversa

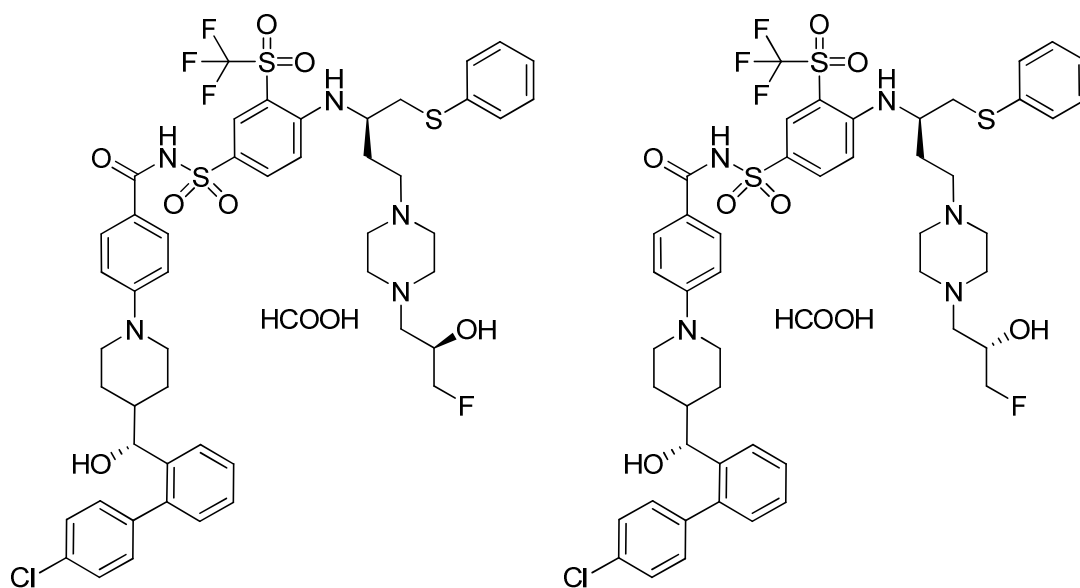
(columna Gilson, eluyendo con 10→70% de H₂O/MeCN con el 0.1% de fórmico durante 14 minutos) para proporcionar el producto del título (150.2 mg, rendimiento: 40%).

[000889] ¹H RMN (DMSO-d₆, 300Mz) δ 8.10 (s, 2H) 7.97 (d, 1H) 7.67 (d, 2H) 7.59 (d, 1H) 7.49 (d, 2H) 7.43 (t, 1H) 7.24-7.37 (m, 7H) 7.19 (d, 1H) 7.15 (d, 1H) 6.93-6.99 (m, 1H) 6.75 (d, 2H) 5.20 (d, 1H) 5.05 (s a, 1H) 4.28-4.33 (m, 1H) 4.02-4.12 (m, 1H) 3.72-3.79 (m, 1H) 3.54-3.69 (m, 5H) 2.98-3.18 (m, 5H) 2.40-2.68 (m, 4H) 1.84-2.16 (m, 3H) 1.56-1.68 (m, 1H) 0.98-1.18 (m, 2H) 0.78-0.93 (m, 1H).

[000890] LCMS: (ESI) *m/z* 975[M+H]⁺.

EJEMPLO 6

[000891] sal de 4-(4-((R)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-N-(4-((R)-4-(4-((R)-3-fluoro-2-hidroxipropil)piperazin-1-il)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida y 4-(4-((R)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-N-(4-((R)-4-(4-((S)-3-fluoro-2-hidroxipropil)piperazin-1-il)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida y el ácido fórmico, mezcla de diastereómeros



[000892] Paso 1: En un vial de 40 ml, se introdujeron el ácido (R)-4-(4-((4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoico (INTERMEDIO 40, 58 mg, 0.14 mmol), 4-((R)-4-(4-((R)-2-(*tert*-butildifenilsililoxi)-3-fluoropropil)piperazin-1-il)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)bencenosulfonamida y 4-((R)-4-(4-((S)-2-(*tert*-butildifenilsililoxi)-3-fluoropropil)piperazin-1-il)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)bencenosulfonamida, mezcla de diastereómeros (INTERMEDIO 39, 120 mg, 0.14 mmol), DMAP (34 mg, 0.28 mmol) y EDC (53 mg, 0.28 mmol) y se purgaron con nitrógeno. Se añadió DCM (2.8 ml) y la solución se agitó a temperatura ambiente durante toda la

noche. La mezcla de reacción se diluyó con DCM y se lavó con bisulfato de sodio 1 N acuoso y a continuación con bicarbonato de sodio saturado acuoso. La fase orgánica se secó (Na_2SO_4), se filtró y se evaporó a presión reducida para proporcionar *N*-(4-((2*R*)-4-(4-(2-(*tert*-butildifenilsililo)-3-fluoropropil)piperazin-1-il)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)-4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzamida (EJEMPLO 6, PASO 1, 180 mg), la cual se utilizó en la preparación del EJEMPLO 6, PASO 2, sin purificación adicional.

[000893] LCMS: m/z 1270 $[\text{M}+\text{H}]^+$.

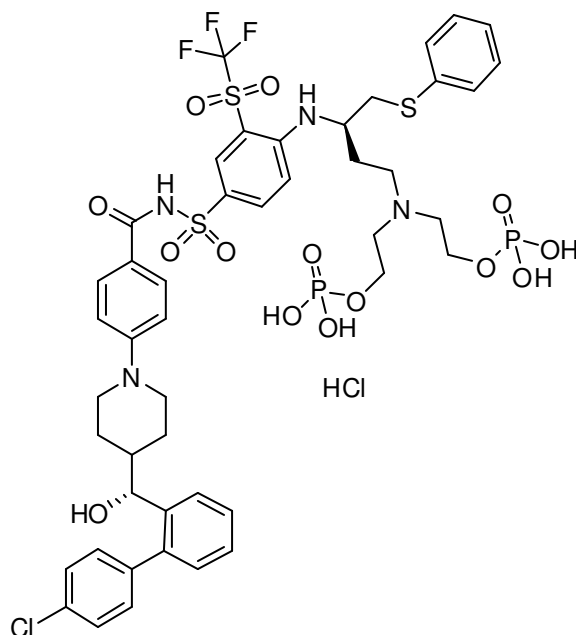
[000894] Paso 2: Se añadió gota a gota una solución de TASF (0.43 ml, 0.43 mmol, 1 M en DMF) a una solución de *N*-(4-((2*R*)-4-(4-(2-(*tert*-butildifenilsililo)-3-fluoropropil)piperazin-1-il)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)-4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzamida (EJEMPLO 6, PASO 1, 180 mg) en DMF (1 ml) y la mezcla de reacción resultante se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se diluyó con DCM/MeOH (10:1 v/v), se lavó con H_2O , se secó (Na_2SO_4), se filtró y la evaporación de los componentes volátiles a presión reducida proporcionó un residuo, el cual se purificó mediante HPLC de fase inversa (columna Gilson, eluyendo con 40→60 % de H_2O /MeCN con el 0.1% de fórmico durante 5 minutos) para proporcionar el producto del título (48.0 mg, rendimiento: 33 %).

[000895] ^1H RMN (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.08 (d, 1 H), 7.94 – 7.90 (m, 1 H), 7.66 (d, J = 8.80 Hz, 2 H), 7.60 – 7.55 (m, 1 H), 7.51 – 7.46 (m, 2H), 7.45 – 7.40 (m, 1 H), 7.37 – 7.26 (m, 8 H), 7.21 – 7.12 (m, 2 H), 6.93 – 6.88 (m, 1 H), 6.77 – 6.71 (m, 3 H), 5.21 (d, J = 4.3 Hz, 1 H), 4.41 – 4.20 (m, 4 H), 4.05 – 3.85 (m, 3 H), 3.77 – 3.70 (m, 1 H), 3.60 – 3.55 (m, 2 H), 2.66 – 2.53 (m, 8 H), 2.45 – 2.42 (m, 5 H), 2.00 – 1.85 (m, 2 H), 1.75 (m, 1 H), 1.15 – 0.99 (m, 3 H), 0.90 – 0.81 (m, 1 H).

[000896] LCMS: (ESI) m/z 1032 $[\text{M}+\text{H}]^+$.

EJEMPLO 7

[000897] sal clorhídrica de bis(dihidrogenofosfato) de 2,2'-((*R*)-3-(4-(*N*-(4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)-4-(feniltio)butilazanodiil)bis(etano-2,1-diilo)



[000898] Se trató una solución de 2,2'-((*R*)-3-(4-(*N*-(4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoyl)sulfamoil)-2-(trifluorometilsulfonyl)fenilamino)-4-(feniltio)butilazanodiil)bis(etano-2,1-diil)difosfato de di-*tert*-butilo (INTERMEDIO 46, 250 mg, 0.18 mmol) y DCM (5 ml) con una solución de HCl (4 M en dioxano, 0.92 ml, 3.68 mmol). Se observó la formación de un precipitado blanco y la mezcla se agitó enérgicamente durante 45 minutos. El compuesto del título se aisló mediante filtración (185 mg, rendimiento: 89%).

[000899] ^1H RMN (400 MHz, METANOL- d_4) δ ppm 1.41 (s a, 2 H) 1.54 - 1.71 (m, 1 H) 1.91 - 2.09 (m, 1 H) 2.31 (s a, 3 H) 3.29 (s a, 1 H) 3.36 - 3.51 (m, 4 H) 3.53 - 3.66 (m, 5 H) 3.70 - 3.83 (m, 1 H) 4.12 - 4.24 (m, 1 H) 4.35 (s a, 4 H) 4.56 (d, 1 H) 7.05 (d, 1 H) 7.13 - 7.28 (m, 4 H) 7.32 - 7.41 (m, 5 H) 7.42 - 7.52 (m, 3 H) 7.58 (d, 2 H) 7.68 (d, 1 H) 7.96 (d, 2 H) 8.11 (dd, 1 H) 8.35 (d, 1 H).

[000900] ^{31}P RMN (121 MHz, METANOL- d_4) δ ppm 0.05 (t, 2 P).

[000901] ^{31}P RMN (121 MHz, METANOL- d_4) δ ppm 0.05 (s, 2 P) (desacoplado)

[000902] Rotación óptica:

Concentración: 0.2 g/dl

Lámpara: Sodio

Longitud de onda: 589 nm

Temperatura: 20 °C

Paso óptico: 10 cm

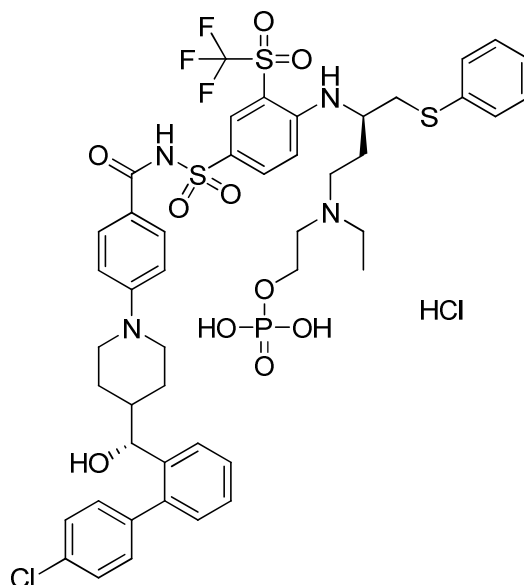
Volumen de la celda: 1 ml

Solvente: MeOH

$[\alpha] = +3$

EJEMPLO 8

[000903] sal clorhídrica de dihidrogenofosfato de 2-(((*R*)-3-(4-(*N*-(4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)-4-(feniltio)butil)(etil)amino)etilo



[000904] Se trató una solución de 2-(((*R*)-3-(4-(*N*-(4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)-4-(feniltio)butil)(etil)amino)etilfosfato de di-*tert*-butilo (INTERMEDIO 55, 147 mg, 0.14 mmol) en DCM (3.17 ml) con una solución de HCl (4 M en dioxano, 0.60 ml). Al finalizar la adición, se observó la formación de un precipitado blanco. La mezcla se diluyó con MeOH después de una hora y los componentes volátiles se evaporaron a presión reducida para proporcionar un residuo pegajoso. El material se disolvió en MeOH y se diluyó con ~20 ml de DCM, lo que provocó la formación de un precipitado blanco. La mezcla se concentró a presión reducida para proporcionar un sólido blanco. El material se lavó con 10-15 ml de CH₂Cl₂ y se secó a un vacío elevado para proporcionar el compuesto del título (108 mg, 95%).

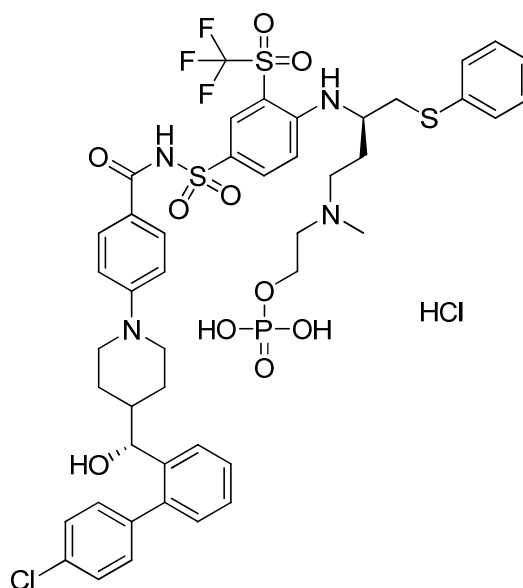
[000905] ¹H RMN (300 MHz, METANOL-*d*₄) δ ppm 1.34 (t, 5 H) 1.46 - 1.66 (m, 1 H) 1.87 - 2.05 (m, 1 H) 2.07 - 2.38 (m, 3 H) 3.12 - 3.40 (m, 8 H) 3.42 - 3.52 (m, 2 H) 3.52 - 3.65 (m, 1 H) 3.70 - 3.84 (m, 1 H) 4.04 - 4.21 (m, 1 H) 4.23 - 4.37 (m, 2 H) 4.46 - 4.59 (m, 1 H) 6.94 - 7.10 (m, 2 H) 7.21 (d, 4 H) 7.30 - 7.52 (m, 9 H) 7.58 - 7.73 (m, 1 H) 7.92 (d, 2 H) 8.04 - 8.16 (m, 1 H) 8.27 - 8.40 (m, 1 H).

[000906] LCMS: (ESI) *m/z* 1037 [M-H]⁺.

EJEMPLO 9

[000907] sal clorhídrica de dihidrogenofosfato de 2-(((*R*)-3-(4-(*N*-(4-(4-((*R*)-(4'-clorobifenil-2-

il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)-4-(feniltio)butil)(metil)amino)etilo



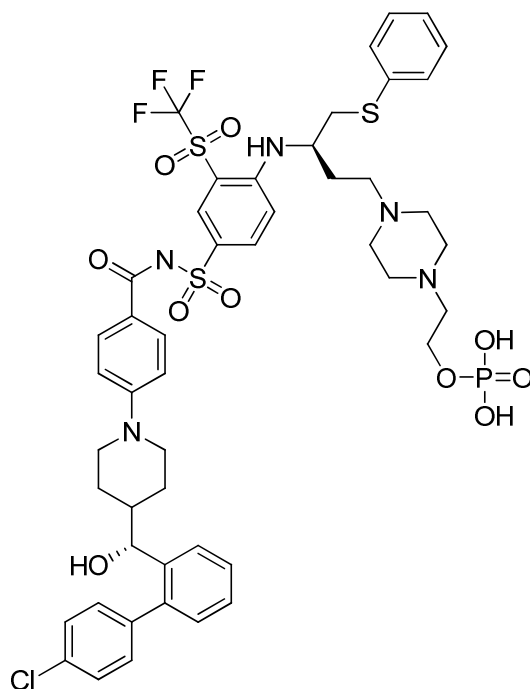
[000908] Se trató una solución de 2-(((*R*)-3-(4-(*N*-(4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)-4-(feniltio)butil)(metil)amino)etilfosfato de di-*tert*-butilo (INTERMEDIO 56, 140 mg, 0.13 mmol) en DCM (3 ml) con una solución de HCl (4 M en dioxano, 0.6 ml). Al finalizar la adición, se observó la formación de un precipitado blanco. La mezcla se diluyó con MeOH después de una hora y los componentes volátiles se evaporaron a presión reducida para proporcionar un residuo pegajoso. El material se disolvió en MeOH y se diluyó con ~20 ml de DCM, lo que provocó la formación de un precipitado blanco. La mezcla se concentró a presión reducida para proporcionar un sólido blanco. El material se lavó con 10-15 ml de CH₂Cl₂ y se secó a un vacío elevado para proporcionar el compuesto del título (120 mg, rendimiento: 95%).

[000909] ¹H RMN (300 MHz, METANOL-*d*₄) δ ppm 1.07 - 1.39 (m, 4 H) 1.83 - 2.00 (m, 1 H) 2.08 - 2.38 (m, 3 H) 2.99 - 3.38 (m, 8 H) 3.40 - 3.52 (m, 2 H) 3.57 - 3.69 (m, 1 H) 3.74 - 3.90 (m, 1 H) 4.03 - 4.19 (m, 1 H) 4.19 - 4.36 (m, 2 H) 4.45 - 4.58 (m, 1 H) 6.92 - 7.09 (m, 2 H) 7.10 - 7.52 (m, 13 H) 7.59 - 7.71 (m, 1 H) 7.77 - 7.94 (m, 2 H) 8.02 - 8.17 (m, 1 H) 8.28 - 8.41 (m, 1 H).

[000910] LCMS: (ESI) *m/z* 1023 [M-H]⁺.

EJEMPLO 10

[000911] dihidrogenofosfato de 2-(4-((*R*)-3-(4-(*N*-(4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)-4-(feniltio)butil)piperazin-1-il)etilo



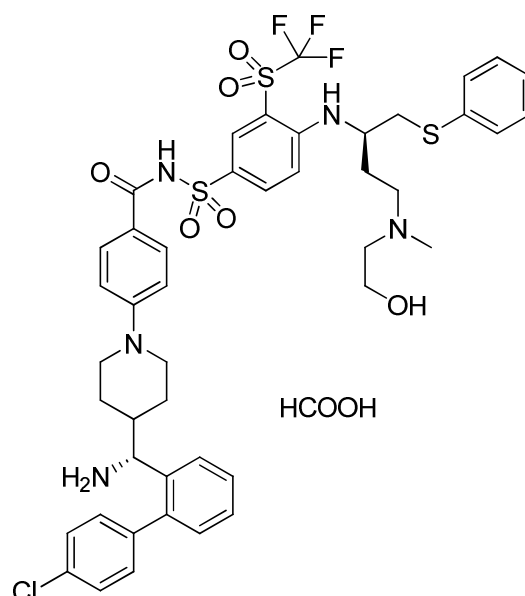
[000912] Se disolvió 2-(4-((*R*)-3-(4-(*N*-(4-(4-((*R*)-(tert-butildimetilsililo)xi)(4'-clorobifenil-2-il)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonyl)fenilamino)-4-(feniltio)butil)piperazin-1-il)etilfosfato de di-*tert*-butilo (INTERMEDIO 62, 414 mg, 0.32 mmol) en DCM (0.5 ml) y se trató con una solución de HCl (4 M en dioxano, 4.0 ml, 15.84 mmol) a TA para proporcionar una solución turbia. La mezcla de reacción se concentró a presión reducida para proporcionar un residuo oleoso, el cual se purificó mediante HPLC de fase inversa (columna Gilson, eluyendo con 20→95% de MeCN en NH₄OAc 10 mM con el 5% de MeCN durante 15 min). Las fracciones recogidas se concentraron y se lavaron con agua y se filtraron para eliminar el NH₄OAc y proporcionar el compuesto del título (120 mg, rendimiento: 35%).

[000913] ¹H RMN (300 MHz, METANOL-*d*₄) δ ppm 8.28 (d, 1 H) 8.04 (dd, 1 H) 7.78 (d, 2 H) 7.59 - 7.66 (m, 1 H) 7.34 - 7.47 (m, 5 H) 7.24 - 7.34 (m, 5 H) 7.16 - 7.23 (m, 2 H) 6.83 (d, 3 H) 4.44 (d, 1 H) 4.01 - 4.15 (m, 3 H) 3.83 (d, 1 H) 3.66 (d, 1 H) 3.08 - 3.26 (m, 7 H) 2.63 - 2.79 (m, 3 H) 2.41 - 2.63 (m, 5 H) 1.99 - 2.16 (m, 2 H) 1.69 - 1.85 (m, 2 H) 1.10 - 1.35 (m, 3 H) 0.98 (dd, 1 H).

[000914] LCMS: (ESI) *m/z* 1080 [M+H]⁺.

EJEMPLO 11

[000915] sal de 4-(4-((*R*)-amino(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((*R*)-4-((2-hidroxi)etil)(metil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)fenilsulfonyl)benzamida y el ácido fórmico



[000916] Paso 1: En un vial de 40 ml, se introdujeron el ácido 4-(4-((*R*)-(4'-clorobifenil-2-il))((*S*)-1,1-dimetiletilsulfinamido)metil)piperidin-1-il)benzoico (INTERMEDIO 130, 0.12 g, 0.23 mmol), DMAP (56 mg, 0.46 mmol) y EDC (88 mg, 0.46 mmol) y se purgaron con nitrógeno. Se añadieron DCM (3.0 ml) y DIPEA (0.08 ml, 0.46 mmol) y la solución se agitó a TA durante 15 min. Se añadió una solución de (*R*)-4-(4-((2-(*tert*-butildifenilsililoxi)etil)(metil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)benzenosulfonamida (INTERMEDIO 28, 0.178 g, 0.23 mmol) en DCM (1.5 ml) a la solución y la mezcla de reacción se agitó a TA durante toda la noche. La mezcla de reacción se diluyó con DCM y se lavó con bisulfato de sodio (1 N, acuoso) y a continuación con bicarbonato de sodio (saturado, acuoso). La fase orgánica se secó (Na₂SO₄), se filtró y se evaporó a presión reducida para proporcionar un residuo, el cual se secó al vacío para proporcionar *N*-(4-((*R*)-4-((2-(*tert*-butildifenilsililoxi)etil)(metil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)fenilsulfonyl)-4-(4-((*R*)-(4'-clorobifenil-2-il))((*S*)-1,1-dimetiletilsulfinamido)metil)piperidin-1-il)benzamida (EJEMPLO 11, PASO 1, 0.26 g), la cual se utilizó en la preparación del EJEMPLO 11, PASO 2 sin purificación adicional.

[000917] Paso 2: Se añadió una solución de TASF (0.40 ml, 0.40 mmol, 1.0 M en DMF) a una solución de *N*-(4-((*R*)-4-((2-(*tert*-butildifenilsililoxi)etil)(metil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)fenilsulfonyl)-4-(4-((*R*)-(4'-clorobifenil-2-il))((*S*)-1,1-dimetiletilsulfinamido)metil)piperidin-1-il)benzamida (EJEMPLO 11, PASO 1, 0.26 g, 0.20 mmol) en DMF (1.6 ml) y la mezcla de reacción se agitó a TA durante 1 hora. La mezcla de reacción se concentró a presión reducida, se diluyó con DCM y se lavó con H₂O. La fase orgánica se secó (Na₂SO₄), se concentró a presión reducida y se secó al vacío para proporcionar 4-(4-((*R*)-(4'-clorobifenil-2-il))((*S*)-1,1-dimetiletilsulfinamido)metil)piperidin-1-il)-*N*-(4-((*R*)-4-((2-hidroxietil)(metil)amino)-1-(feniltio)butan-2-ilamino)-3-

(trifluorometilsulfonyl)fenilsulfonyl)benzamida (EJEMPLO 11, PASO 2, 0.25 g), la cual se utilizó en la preparación del EJEMPLO 11, PASO 3, sin purificación adicional.

[000918] Paso 3: Se añadió una solución de HCl (1.00 ml, 4.00 mmol, 4.0 M en dioxano) a una solución de 4-(4-((*R*)-(4'-clorobifenil-2-il)((*S*)-1,1-dimetiletilsulfinamido)metil)piperidin-1-il)-*N*-(4-((*R*)-4-((2-hidroxietyl)(metil)amino)-1-(feniltio)butan-2-ilamino)-3-

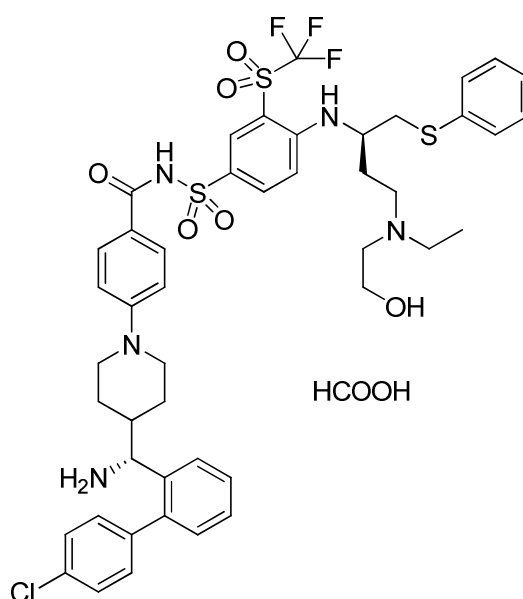
(trifluorometilsulfonyl)fenilsulfonyl)benzamida (EJEMPLO 11, PASO 2, 0.21 g, 0.20 mmol) en MeOH (1.0 ml) y la mezcla de reacción se agitó a TA durante 1 hora. La mezcla de reacción se concentró a presión reducida para proporcionar un residuo, el cual se purificó mediante HPLC de fase inversa (columna Gilson, eluyendo con 30→50% de H₂O/MeCN con el 0.1% de ácido fórmico durante 10 minutos) para proporcionar el compuesto del título (0.1 g, rendimiento: 51% para 3 pasos).

[000919] ¹H RMN (400 MHz, DMSO-*d*₆) δ ppm 8.05 (d, 1H), 7.92 (dd, 1H), 7.71 – 7.67 (m, 3H), 7.59 – 7.52 (m, 3H), 7.49 – 7.45 (m, 1H), 7.37 – 7.34 (m, 4H), 7.30 – 7.26 (m, 3H), 7.20 – 7.17 (m, 1H), 6.83 (d, 1H), 6.78 – 6.72 (m, 3H), 4.00 (m, 1H), 3.87 – 3.84 (m, 1H), 3.78 – 3.75 (m, 1H), 3.32 – 3.16 (m, 5H), 2.67 – 2.54 (m, 5H), 2.46 – 2.43 (m, 1H), 2.31 (s, 3H), 1.98 – 1.90 (m, 2H), 1.83 – 1.75 (m, 2H), 1.19 – 1.08 (m, 2H), 0.82 – 0.74 (m, 1H).

[000920] LCMS: (ESI) *m/z* 944[M+H]⁺.

EJEMPLO 12

[000921] sal de 4-(4-((*R*)-amino(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((*R*)-4-(etil(2-hidroxietyl)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)fenilsulfonyl)benzamida y el ácido fórmico



[000922] En un vial de 40 ml, se introdujeron el ácido 4-(4-((*R*)-(4'-clorobifenil-2-il)((*S*)-1,1-dimetiletilsulfinamido)metil)piperidin-1-il)benzoico (INTERMEDIO 130, 0.12 g, 0.23 mmol),

DMAP (56 mg, 0.46 mmol) y EDC (88 mg, 0.46 mmol) y se purgaron con nitrógeno. Se añadieron DCM (3.0 ml) y DIPEA (0.08 ml, 0.46 mmol) y la solución se agitó a TA durante 15 min. Se añadió una solución de (*R*)-4-(4-((2-(*tert*-butildifenilsililo)etil)(etil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)benzenosulfonamida (INTERMEDIO 25, 0.18 g, 0.23 mmol) en DCM (1.5 ml) a la solución y la mezcla de reacción se agitó a TA durante toda la noche. La mezcla de reacción se diluyó con DCM y se lavó con bisulfato de sodio (1 N, acuoso) y a continuación con bicarbonato de sodio (saturado, acuoso). La fase orgánica se secó (Na_2SO_4), se filtró y se evaporó a presión reducida para proporcionar un residuo, el cual se secó al vacío para proporcionar *N*-(4-((*R*)-4-((2-(*tert*-butildifenilsililo)etil)(etil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)-4-(4-((*R*)-(4'-clorobifenil-2-il)((*S*)-1,1-dimetiletilsulfinamido)metil)piperidin-1-il)benzamida (EJEMPLO 12, PASO 1, 0.31 g), la cual se utilizó en la preparación del EJEMPLO 12, PASO 2 sin purificación adicional.

[000923] Paso 2: Se añadió una solución de TASF (0.46 ml, 0.46 mmol, 1.0 M en DMF) a una solución de *N*-(4-((*R*)-4-((2-(*tert*-butildifenilsililo)etil)(etil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)-4-(4-((*R*)-(4'-clorobifenil-2-il)((*S*)-1,1-dimetiletilsulfinamido)metil)piperidin-1-il)benzamida (EJEMPLO 12, PASO 1, 0.30 g, 0.23 mmol) en DMF (1.9 ml) y la mezcla de reacción se agitó a TA durante 1 hora. La mezcla de reacción se concentró a presión reducida, se diluyó con DCM y se lavó con H_2O . La fase orgánica se secó (Na_2SO_4), se concentró a presión reducida y se secó al vacío para proporcionar 4-(4-((*R*)-(4'-clorobifenil-2-il)((*S*)-1,1-dimetiletilsulfinamido)metil)piperidin-1-il)-*N*-(4-((*R*)-4-(etil(2-hidroxietil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida (EJEMPLO 12, PASO 2, 0.28 g), la cual se utilizó en la preparación del EJEMPLO 12, PASO 3, sin purificación adicional.

[000924] Paso 3: Se añadió una solución de HCl (1.15 ml, 4.60 mmol, 4.0 M en dioxano) a una solución de 4-(4-((*R*)-(4'-clorobifenil-2-il)((*S*)-1,1-dimetiletilsulfinamido)metil)piperidin-1-il)-*N*-(4-((*R*)-4-(etil(2-hidroxietil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida (EJEMPLO 12, PASO 2, 0.244 g, 0.23 mmol) en MeOH (1.2 ml) y la mezcla de reacción se agitó a TA durante 1 hora. La mezcla de reacción se concentró a presión reducida para proporcionar un residuo, el cual se purificó mediante HPLC de fase inversa (columna Gilson, eluyendo con 30→50% de H_2O /MeCN con el 0.1% de fórmico durante 10 minutos) para proporcionar el compuesto del título (0.12 g, rendimiento: 52% para 3 pasos).

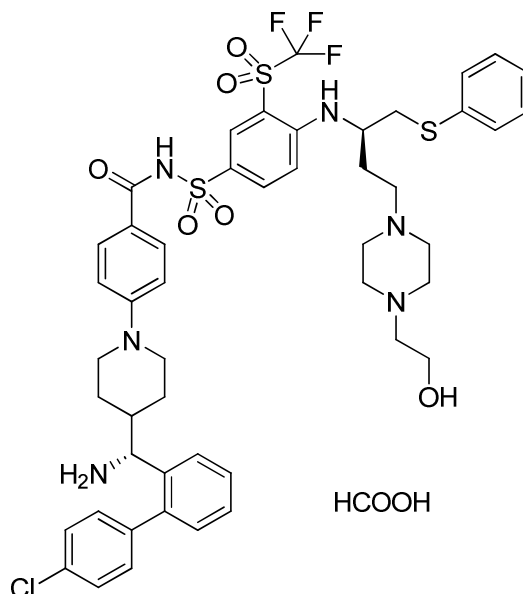
[000925] ^1H RMN (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.05 (d, 1H), 7.91 (dd, 1H), 7.71 – 7.67 (m, 3H), 7.59 – 7.53 (m, 3H), 7.49 – 7.45 (m, 1H), 7.37 – 7.34 (m, 4H), 7.30 – 7.26 (m, 3H), 7.21 – 7.17 (m, 1H), 6.82 (d, 1H), 6.74 – 6.68 (m, 3H), 4.00 (m, 1H), 3.87 – 3.84 (m, 1H), 3.78 – 3.75

(m, 1H) 3.58 – 3.55 (m, 1H), 3.32– 3.19 (m, 4H), 2.65 – 2.55 (m, 7H), 2.46 – 2.43 (m, 1H), 1.99 – 1.90 (m, 2H), 1.84 – 1.73 (m, 2H), 1.18 – 1.08 (m, 2H), 0.93 (t, 3 H), 0.82 – 0.73 (m, 1H).

[000926] LCMS: (ESI) m/z 958 $[M+H]^+$.

EJEMPLO 13

[000927] sal de 4-(4-((*R*)-amino(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((*R*)-4-(4-(2-hidroxietil)piperazin-1-il)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)fenilsulfonyl)benzamida y el ácido fórmico



[000928] Paso 1: En un vial de 40 ml, se introdujeron el ácido 4-(4-((*R*)-(4'-clorobifenil-2-il)((*S*)-1,1-dimetiletilsulfinamido)metil)piperidin-1-il)benzoico (INTERMEDIO 130, 0.150 g, 0.29 mmol), DMAP (70 mg, 0.57 mmol) y EDC (0.110 g, 0.57 mmol) y se purgaron con nitrógeno. Se añadieron DCM (4.0 ml) y DIPEA (0.10 ml, 0.57 mmol) y la solución se agitó a TA durante 15 min. Se añadió una solución de (*R*)-4-(4-(4-(2-(*tert*-butildifenilsililoxi)etil)piperazin-1-il)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)benzenosulfonamida (INTERMEDIO 22, 0.24 g, 0.29 mmol) en DCM (1.6 ml) a la solución y la mezcla de reacción se agitó a TA durante toda la noche. La mezcla de reacción se diluyó con DCM y se lavó con bisulfato de sodio (1 N, acuoso) y a continuación con bicarbonato de sodio (saturado, acuoso). La fase orgánica se secó (Na_2SO_4), se filtró y se evaporó a presión reducida para proporcionar un residuo, el cual se secó al vacío para proporcionar *N*-(4-((*R*)-4-(4-(2-(*tert*-butildifenilsililoxi)etil)piperazin-1-il)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)fenilsulfonyl)-4-(4-((*R*)-(4'-clorobifenil-2-il)((*S*)-1,1-dimetiletilsulfinamido)metil)piperidin-1-il)benzamida (EJEMPLO 13, PASO 1, 0.40 g), la cual se utilizó en la preparación del EJEMPLO 13, PASO 2 sin purificación adicional.

[000929] Paso 2: Se añadió una solución de TASF (0.58 ml, 0.58 mmol, 1.0 M en DMF) a una

solución de *N*-(4-((*R*)-4-((2-(*tert*-butildifenilsililo)etil)piperazin-1-il)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)fenilsulfonyl)-4-(4-((*R*)-(4'-clorobifenil-2-il)((*S*)-1,1-dimetiletilsulfinamido)metil)piperidin-1-il)benzamida (EJEMPLO 13, PASO 2, 0.39 g, 0.29 mmol) en DMF (2.3 ml) y la mezcla de reacción se agitó a TA durante 1 hora. La mezcla de reacción se concentró a presión reducida, se diluyó con DCM y se lavó con H₂O. La fase orgánica se secó (Na₂SO₄), se concentró a presión reducida y, después de filtrar, se secó al vacío para proporcionar 4-(4-((*R*)-(4'-clorobifenil-2-il)((*S*)-1,1-dimetiletilsulfinamido)metil)piperidin-1-il)-*N*-(4-((*R*)-4-(4-(2-hidroxietil)piperazin-1-il)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)fenilsulfonyl)benzamida (EJEMPLO 13, PASO 2, 0.41 g), la cual se utilizó en la preparación del EJEMPLO 13, PASO 3 sin purificación adicional.

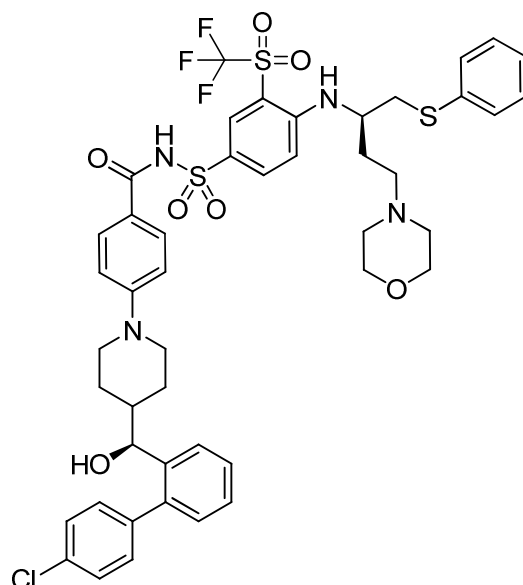
[000930] Paso 3: Se añadió una solución de HCl (1.45 ml, 5.80 mmol, 4.0 M en dioxano) a una solución de 4-(4-((*R*)-(4'-clorobifenil-2-il)((*S*)-1,1-dimetiletilsulfinamido)metil)piperidin-1-il)-*N*-(4-((*R*)-4-(4-(2-hidroxietil)piperazin-1-il)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)fenilsulfonyl)benzamida (EJEMPLO 13, PASO 2, 0.4 g, 0.29 mmol) en MeOH (1.5 ml) y la mezcla de reacción se agitó a TA durante 1 hora. La mezcla de reacción se concentró a presión reducida para proporcionar un residuo, el cual se purificó mediante HPLC de fase inversa (columna Gilson, eluyendo con 30→45% de H₂O/MeCN con el 0.1% de fórmico durante 10 minutos) para proporcionar el compuesto del título (0.16 g, rendimiento: 49% para 3 pasos).

[000931] ¹H RMN (400 MHz, DMSO-*d*₆) δ ppm 8.05 (d, 1H), 7.91 (dd, 1H), 7.72 – 7.68 (m, 3H), 7.60 – 7.53 (m, 3H), 7.50 – 7.46 (m, 1H), 7.38 – 7.34 (m, 4H), 7.31 – 7.27 (m, 3H), 7.21 – 7.18 (m, 1H), 6.84 (d, 1H), 6.74 (d, 2H), 6.67 (d, 1H), 4.00 (m, 1H), 3.88 – 3.86 (m, 1H), 3.79 – 3.76 (m, 1H), 3.34 – 3.21 (m, 4H), 2.69 – 2.54 (m, 7H), 2.47 – 2.44 (m, 2H), 2.40 – 2.29 (m, 5H), 1.99 – 1.91 (m, 2H), 1.84 – 1.81 (m, 1H), 1.73 – 1.66 (m, 1H), 1.20 – 1.08 (m, 3H), 0.83 – 0.74 (m, 1H).

[000932] LCMS: (ESI) *m/z* 999 [M+H]⁺.

EJEMPLO 14

[000933] 4-(4-((*S*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)fenilsulfonyl)benzamida



[000934] En un matraz de 50 ml, se introdujeron el ácido (*S*)-4-(4-((4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoico (INTERMEDIO 70, 137.4 mg, 0.33 mmol), (*R*)-4-(4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida (INTERMEDIO 69, 190.3 mg, 0.34 mmol), DMAP (81.0 mg, 0.66 mmol) y EDC (134.5 mg, 0.70 mmol) y se purgaron con nitrógeno. Se añadió DCM (6.5 ml) y la solución se agitó a temperatura ambiente durante toda la noche. La mezcla de reacción se diluyó con DCM (40 ml) y se lavó con bisulfato de sodio 1 N acuoso (35 ml) y a continuación con bicarbonato de sodio saturado acuoso (40 ml). La fase acuosa se secó (Na_2SO_4), se filtró y se evaporó a presión reducida. El concentrado se purificó mediante cromatografía en columna (ISCO, columna de 12 g de gel de sílice, eluyendo con 0→10 % de MeOH en DCM). Las fracciones limpias se combinaron, se evaporaron al vacío y se secaron durante toda la noche en un horno de vacío a 40 °C para proporcionar el producto del título como un isómero sustancialmente separado (129.3 mg, rendimiento: 41.5%).

[000935] ^1H RMN (400 MHz, DMSO- d_6) δ ppm 0.74 - 0.90 (m, 1 H) 0.95 - 1.15 (m, 2 H) 1.65 (m, 1 H) 1.88 (m, 2 H) 2.60 - 2.71 (m, 1 H) 3.45 - 3.61 (m, 4 H) 3.66 (m, 1 H) 3.82 (m, 1 H) 4.05 - 4.14 (m, 1 H) 4.30 (dd, 1 H) 5.21 (d, 1 H) 6.79 (d, 2 H) 6.91 (m, 1 H) 7.02 (d, 1 H) 7.11 - 7.21 (m, 2 H) 7.23 - 7.38 (m, 7 H) 7.42 (t, 1 H) 7.48 (d, 2 H) 7.58 (d, 1 H) 7.67 (d, 2 H) 7.94 (dd, 1 H) 8.13 (d, 1 H).

[000936] LCMS: (ESI) m/z 957 $[\text{M}+\text{H}]^+$.

[000937] Rotación óptica:

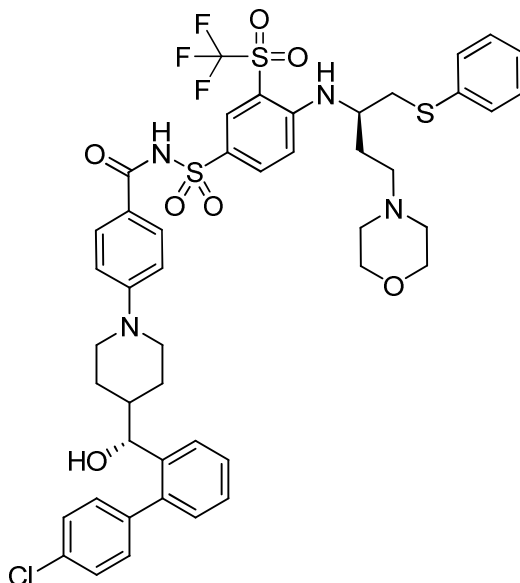
Concentración:	0.1 g/dl
Lámpara:	Sodio
Longitud de onda:	589 nm
Temperatura:	20 °C

104020-1 US/O

Paso óptico: 10 cm
Volumen de la celda: 1 ml
Solvente: CH₂Cl₂
[α]= -128

EJEMPLO 15

[000938] 4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida



[000939] El producto del título (34.1 mg, rendimiento: 59%) se preparó utilizando un procedimiento similar al descrito para la síntesis del EJEMPLO 16. Se utilizó como material de partida 4-(4-((*R*)-(tert-butildimetilsililo)(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida (INTERMEDIO 76, 64.7 mg, 0.06 mmol). El producto resultante se purificó mediante cromatografía en columna (ISCO, columna de 4 g de gel de sílice, eluyendo con 0→5% de MeOH/DCM) y a continuación se purificó adicionalmente mediante cromatografía en columna (ISCO, columna de 4 g de gel de sílice, eluyendo con 0→100% de DCM/ [10% de NH₃ 2 M en MeOH/90 % de DCM]), para proporcionar el producto del título.

[000940] ¹H RMN (400 MHz, DMSO-*d*₆) δ ppm 0.76 - 1.17 (m, 4 H) 1.57 - 1.69 (m, 1 H) 1.69 - 1.81 (m, 1 H) 1.84 - 2.02 (m, 2 H) 2.57 - 2.69 (m, 2 H) 3.44 - 3.57 (m, 5 H) 3.58 - 3.67 (m, 1 H) 3.74 - 3.83 (m, 1 H) 3.99 - 4.11 (m, 1 H) 4.27 - 4.33 (m, 1 H) 5.19 - 5.23 (m, 1 H) 6.72 - 6.80 (m, 2 H) 6.80 - 6.88 (m, 1 H) 6.90 - 6.99 (m, 1 H) 7.11 - 7.22 (m, 2 H) 7.23 - 7.38 (m, 8 H) 7.39 - 7.45 (m, 1 H) 7.48 (d, 2 H) 7.56 - 7.61 (m, 1 H) 7.66 (d, 2 H) 7.89 - 7.95 (m, 1 H) 8.08 - 8.13 (m, 1 H).

[000941] LCMS: m/z 957 $[M+H]^+$.

[000942] Rotación óptica:

Concentración: 0.1 g/dl

Lámpara: Sodio

Longitud de onda: 589 nm

Temperatura: 20 °C

Paso óptico: 10 cm

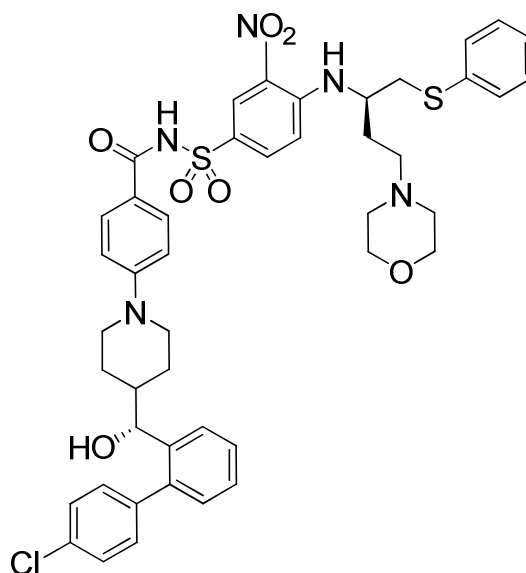
Volumen de la celda: 1 ml

Solvente: CH_2Cl_2

$[\alpha]_D = -9$

EJEMPLO 16

[000943] 4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-nitrofenilsulfonil)benzamida



[000944] En un matraz de 100 ml con atmósfera de nitrógeno, se introdujo 4-(4-((*R*)-(tert-butildimetilsililo)(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-nitrofenilsulfonil)benzamida (INTERMEDIO 75, 329.0 mg, 0.33 mmol) y se trató con TBAF (10.0 ml, 1.0 M en THF, 10 mmol). La solución resultante se agitó a temperatura ambiente durante 35 minutos y a continuación los componentes volátiles se eliminaron a presión reducida. El concentrado se diluyó con DCM (100 ml) y se lavó con $NaHSO_4$ 1 N acuoso (100 ml) y $NaHCO_3$ saturado acuoso (30 ml); a continuación se secó (Na_2SO_4), se filtró y se evaporó al vacío. El concentrado se purificó mediante cromatografía en columna (ISCO, columna de 12 g de gel de sílice, eluyendo con 0→5% de MeOH/DCM) y a continuación se purificó adicionalmente mediante cromatografía en columna (ISCO, columna de

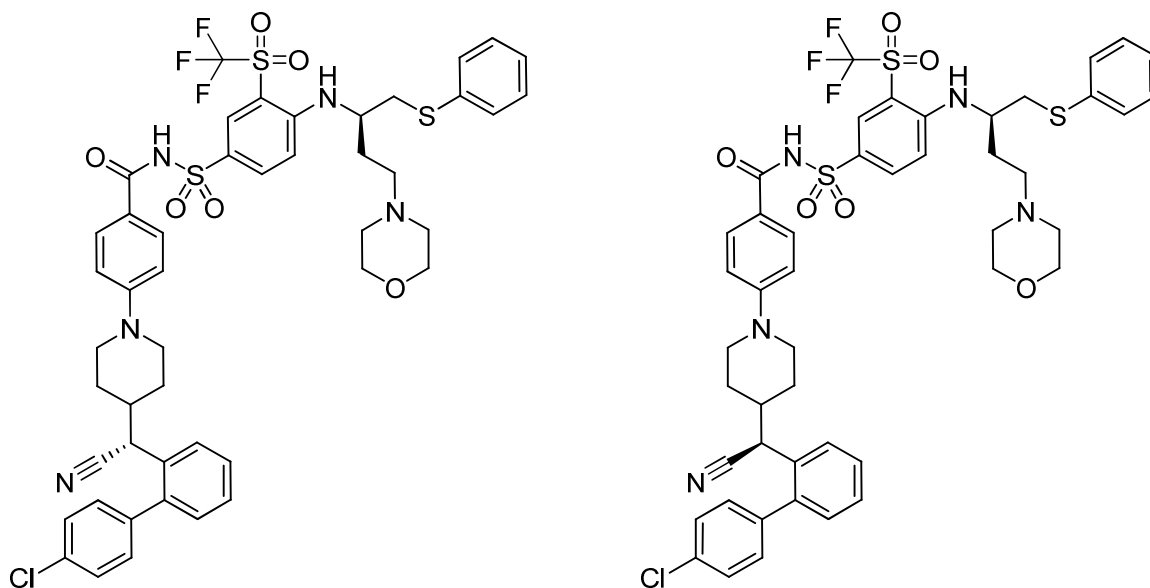
12 g de gel de sílice, eluyendo con 0→90% de DCM/ [10% de NH₃ 2 M en MeOH/90% de DCM]), para proporcionar el producto del título (228 mg, rendimiento: 78%).

[000945] ¹H RMN (300 MHz, DMSO-*d*₆) δ ppm 0.84 (s a, 1 H) 1.01 (d, 2 H) 1.56 - 1.72 (m, 1 H) 1.88 (m, 2 H) 1.94 - 2.09 (m, 1 H) 3.36 (d, 2 H) 3.45 - 3.59 (m, 4 H) 3.64 (m, 1 H) 3.75 - 3.87 (m, 1 H) 4.07 - 4.21 (m, 1 H) 4.30 (dd, 1 H) 5.20 (d, 1 H) 6.78 (d, 2 H) 7.05 (d, 1 H) 7.10 - 7.25 (m, 4 H) 7.25 - 7.38 (m, 5 H) 7.38 - 7.52 (m, 3 H) 7.58 (d, 1 H) 7.67 (d, Hz, 2 H) 7.75 - 7.84 (m, 1 H) 8.38 (d, 1 H) 8.50 (d, 1 H).

[000946] LCMS: (ESI) *m/z* 870[M+H]⁺.

EJEMPLO 17

[000947] 4-(4-((*R*)-(4'-clorobifenil-2-il)(ciano)metil)piperidin-1-il)-*N*-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida y 4-(4-((*S*)-(4'-clorobifenil-2-il)(ciano)metil)piperidin-1-il)-*N*-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida, mezcla de diastereómeros



[000948] Las sales clorhídricas del ácido (*R*)-4-(4-((4'-clorobifenil-2-il)(ciano)metil)piperidin-1-il)benzoico y del ácido (*S*)-4-(4-((4'-clorobifenil-2-il)(ciano)metil)piperidin-1-il)benzoico (INTERMEDIO 83, 67.8 mg, 0.15 mmol), (*R*)-4-(4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)bencenosulfonamida (INTERMEDIO 69, 81.4 mg, 0.15 mmol), DMAP (38.1 mg, 0.31 mmol) y EDC (59.0 mg, 0.31 mmol) se combinaron y se sellaron en un tubo de microondas. El tubo se purgó con nitrógeno y se añadieron DCM (3.0 ml) y DIPEA (0.05 ml, 0.29 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 4 días y a continuación se diluyó con agua (5 ml) y se extrajo con DCM (2 x 5 ml). Los extractos combinados se secaron (MgSO₄), se filtraron y se evaporaron a presión reducida. El residuo se purificó mediante cromatografía en columna (ISCO, columna de 4 g de gel de sílice, eluyendo en

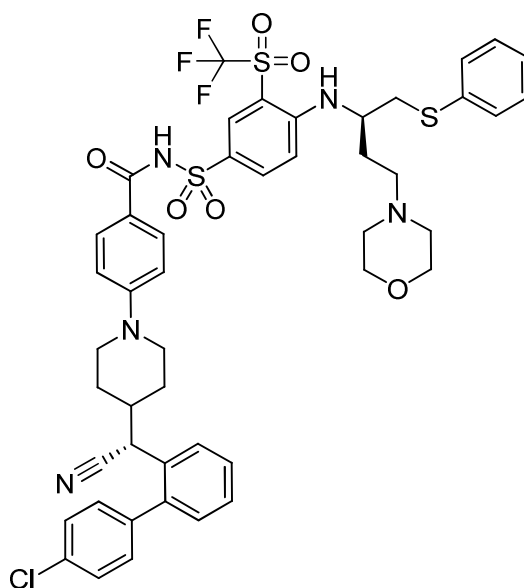
primer lugar con 0→10% de MeOH/DCM y a continuación con 0→100% de EtOAc/hexanos). Las fracciones que correspondían al producto se recogieron y se evaporaron a sequedad para proporcionar un residuo pegajoso. El material se disolvió en trazas de DCM y se añadió éter dietílico, lo que provocó la formación de un precipitado. La suspensión se evaporó a presión reducida para proporcionar el producto del título (60.4 mg, rendimiento: 44%) como una mezcla de diastereómeros.

[000949] ^1H RMN (400 MHz, DICLOROMETANO- d_2) δ ppm 1.05 (cd, 1 H), 1.30 - 1.45 (m, 2 H), 1.60 - 1.71 (m, 1 H), 1.81 - 1.93 (m, 1 H), 1.95 - 2.12 (m, 2 H), 2.19 - 2.45 (m, 6 H), 2.62 (td, 1 H), 2.75 (td, 1 H), 3.05 - 3.16 (m, 2 H), 3.53 - 3.65 (m, 4 H), 3.67 - 3.75 (m, 1 H), 3.78 (d, 1 H), 3.83 - 3.91 (m, 1 H), 3.93 - 4.03 (m, 1 H), 6.67 - 6.74 (m, 1 H), 6.78 (d, 2 H), 7.04 (d, 1 H), 7.20 - 7.34 (m, 6 H), 7.34 - 7.40 (m, 2 H), 7.40 - 7.51 (m, 4 H), 7.55 - 7.60 (m, 1 H), 7.62 (d, 2 H), 8.03 (dd, 1 H), 8.33 (d, 1 H).

[000950] LCMS: (ESI) m/z 966 $[\text{M}+\text{H}]^+$.

EJEMPLO 18

[000951] 4-(4-((*R*)-(4'-clorobifenil-2-il)(ciano)metil)piperidin-1-il)-*N*-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)fenilsulfonyl)benzamida



[000952] El producto del título (19.8 mg, rendimiento: 20%) se preparó utilizando un procedimiento similar al descrito para la síntesis del EJEMPLO 14. Se utilizaron como materiales de partida la sal clorhídrica del ácido (*R*)-4-(4-((4'-clorobifenil-2-il)(ciano)metil)piperidin-1-il)benzoico (INTERMEDIO 84, 44.9 mg, 0.1 mmol) y (*R*)-4-(4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida (INTERMEDIO 69, 54.4 mg, 0.1 mmol). El producto resultante se purificó mediante

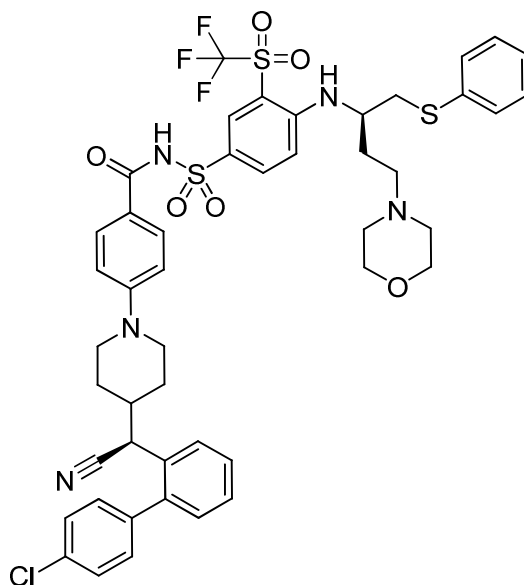
cromatografía en columna (ISCO, columna de 4 g de gel de sílice, eluyendo con 0→5% de MeOH/DCM) y a continuación se purificó adicionalmente mediante cromatografía en columna (ISCO, columna de 4 g de gel de sílice, eluyendo en primer lugar con 0→100% de EtOAc/hexanos y a continuación con 0→5% de MeOH/DCM), para proporcionar el producto del título.

[000953] ^1H RMN (400 MHz, DICLOROMETANO- d_2) δ ppm 0.98 - 1.11 (m, 1 H), 1.29 - 1.45 (m, 3 H), 1.61 (s a, 1 H), 1.81 - 2.05 (m, 3 H), 2.21 - 2.37 (m, 1 H), 2.49 - 2.87 (m, 6 H), 3.14 (d, 2 H), 3.66 - 3.98 (m, 7 H), 4.07 (s a, 1 H), 6.73 - 6.84 (m, 3 H), 7.02 (d, 1 H), 7.20 - 7.33 (m, 6 H), 7.35 - 7.51 (m, 6 H), 7.57 (dd, 1 H), 7.62 (d, 2 H), 8.06 (dd, 1 H), 8.36 (d, 1 H).

[000954] LCMS: (ESI) m/z 966 $[\text{M}+\text{H}]^+$.

EJEMPLO 19

[000955] 4-(4-((*S*)-(4'-clorobifenil-2-il)(ciano)metil)piperidin-1-il)-*N*-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)fenilsulfonyl)benzamida



[000956] El producto del título (10.7 mg, rendimiento: 11%) se preparó utilizando un procedimiento similar al descrito para la síntesis del EJEMPLO 14. Se utilizaron como materiales de partida la sal clorhídrica del ácido (*S*)-4-(4-((4'-clorobifenil-2-il)(ciano)metil)piperidin-1-il)benzoico (INTERMEDIO 85, 49.5 mg, 0.11 mmol) y (*R*)-4-(4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida (INTERMEDIO 69, 58.6 mg, 0.11 mmol). El producto resultante se purificó mediante cromatografía en columna (ISCO, columna de 4 g de gel de sílice, eluyendo con 0→5% de MeOH/DCM) y a continuación se purificó adicionalmente mediante cromatografía en columna (ISCO, columna de 4 g de gel de sílice, eluyendo en primer lugar con 0→100% de

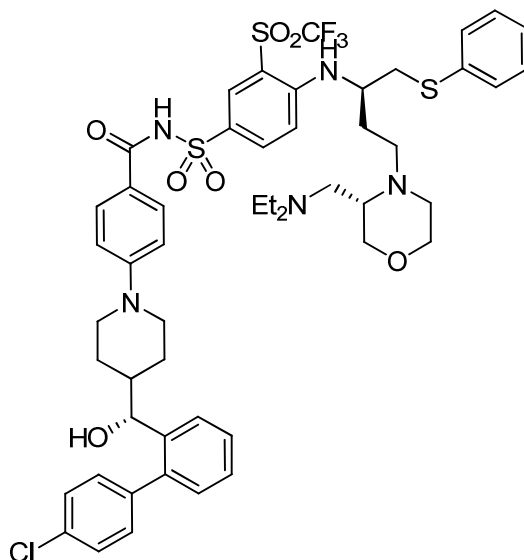
EtOAc/hexanos y a continuación con 0→3.5% de MeOH/DCM), para proporcionar el producto del título.

[000957] ^1H RMN (400 MHz, DICLOROMETANO- d_2) δ ppm 1.04 (cd, 1 H), 1.30 - 1.45 (m, 3 H), 1.61 - 1.72 (m, 1 H), 1.82 - 1.94 (m, 1 H), 2.21 - 2.47 (m, 6 H), 2.63 (td, 1 H), 2.76 (td, 1 H), 3.11 (d, 2 H), 3.53 - 3.66 (m, 4 H), 3.68 - 3.76 (m, 1 H), 3.78 (d, 1 H), 3.84 - 3.92 (m, 1 H), 3.94 - 4.05 (m, 1 H), 6.72 (d, 1 H), 6.78 (d, 2 H), 7.06 (d, 1 H), 7.20 - 7.34 (m, 6 H), 7.34 - 7.52 (m, 6 H), 7.55 - 7.65 (m, 3 H), 8.03 (dd, 1 H), 8.34 (d, 1 H).

[000958] LCMS: (ESI) m/z 966 $[\text{M}+\text{H}]^+$.

EJEMPLO 20

[000959] 4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-((*S*)-3-((dietilamino)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)fenilsulfonyl)benzamida



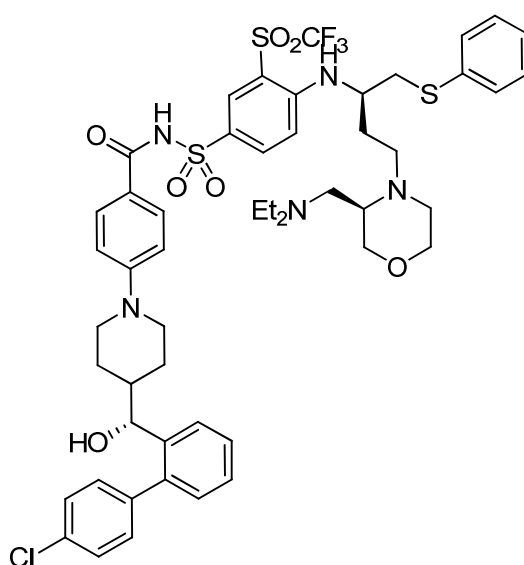
[000960] Se agitó una solución de 4-(4-((*R*)-(tert-butildimetilsililo)xi)(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((*R*)-4-((*S*)-3-((dietilamino)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)fenilsulfonyl)benzamida, (INTERMEDIO 89, 100 mg, 0.09 mmol) y TBAF (3.5 ml, 3.46 mmol, 1 M en THF) durante 45 minutos a temperatura ambiente. El solvente se eliminó a presión reducida y el residuo se disolvió en DCM (50 ml). La fase orgánica se lavó sucesivamente con 50 ml de agua (50 ml) y bicarbonato de sodio acuoso saturado (50 ml). La fase orgánica se secó con sulfato de sodio, se filtró y se concentró a presión reducida. El concentrado se purificó mediante cromatografía en columna (ISCO, eluyendo con 0→100% de DCM/[10% de amoníaco 2 N en MeOH en DCM] durante 19 minutos y a continuación eluyendo con 0→20% de MeOH/DCM) para proporcionar el producto del título (43.0 mg, rendimiento: 48%).

[000961] ^1H RMN (400 MHz, DICLOROMETANO- d_2) δ ppm 0.68 - 1.28 (m, 11 H) 1.43 - 1.77 (m, 2 H) 1.79 - 2.04 (m, 2 H) 2.04 - 2.74 (m, 13 H) 2.86 - 3.07 (m, 2 H) 3.18 - 3.32 (m, 1 H) 3.35 - 3.89 (m, 6 H) 4.39 (d, 1 H) 6.60 (d, 4 H) 7.03 - 7.39 (m, 12 H) 7.50 (d, 1 H) 7.66 (d, 2 H) 7.86 - 8.03 (m, 1 H) 8.16 (s a, 1 H).

[000962] LCMS: (ESI) m/z 1042 $[\text{M}+\text{H}]^+$.

EJEMPLO 21

[000963] 4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-((*R*)-3-((dietilamino)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida



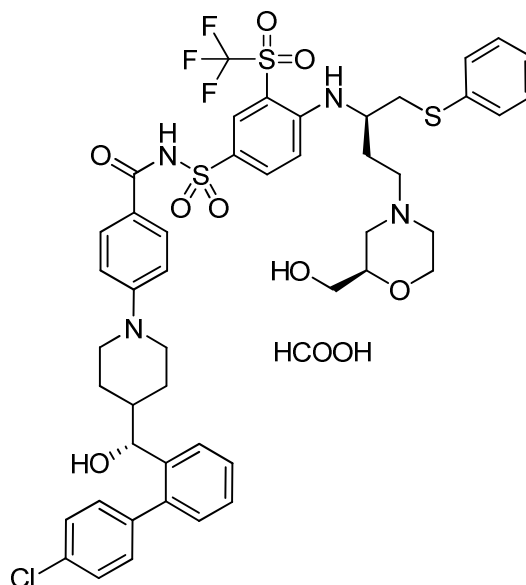
[000964] El producto del título (50 mg, rendimiento: 55%) se preparó utilizando un procedimiento similar al descrito para la síntesis del EJEMPLO 16. Se utilizó como material de partida 4-(4-((*R*)-(tert-butildimetilsililo)(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((*R*)-4-((*R*)-3-((dietilamino)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida (INTERMEDIO 93, 100 mg, 0.09 mmol). El producto resultante se purificó mediante cromatografía en columna (ISCO, eluyendo con 0→100% de DCM/[10% de amoníaco 2 N en MeOH en DCM] durante 19 minutos y a continuación eluyendo con 0→20% de MeOH/DCM) para proporcionar el producto del título.

[000965] ^1H RMN (400 MHz, DICLOROMETANO- d_2) δ ppm 0.85 - 1.30 (m, 10 H) 1.46 - 1.76 (m, 2 H) 1.78 - 2.02 (m, 2 H) 2.07 - 2.78 (m, 14 H) 2.86 - 3.11 (m, 2 H) 3.28 - 3.57 (m, 5 H) 3.68 (d, 1 H) 3.84 (s a, 1 H) 4.38 (d, 1 H) 6.35 - 6.77 (m, 4 H) 6.97 - 7.40 (m, 12 H) 7.50 (dd, 1 H) 7.66 (d, 2 H) 7.91 (d, 1 H) 8.13 (s a, 1 H).

[000966] LCMS: (ESI) m/z 1042 $[\text{M}+\text{H}]^+$.

EJEMPLO 22

[000967] sal de 4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-((*R*)-2-(hidroximetil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)fenilsulfonyl)benzamida y el ácido fórmico



[000968] Se añadió gota a gota una solución de TBAF (115 μ l, 0.11 mmol, 1 M en THF) a una solución de 4-(4-((*R*)-(tert-butildimetilsililo)(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((*R*)-4-((*R*)-2-((tert-butildifenilsililo)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)fenilsulfonyl)benzamida INTERMEDIO 100, 77 mg, 0.06 mmol) en THF (420 μ l) y la mezcla resultante se agitó a temperatura ambiente durante toda la noche. A continuación se añadió HCl (4 M en dioxano, 39.9 μ l, 1.15 mmol) y la mezcla se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se diluyó con EtOAc y la fase orgánica se lavó con H₂O (2x), se secó (Na₂SO₄), se filtró y se concentró a presión reducida. El concentrado se purificó mediante HPLC de fase inversa (columna Gilson, eluyendo con 15→70% de H₂O/MeCN con el 1% de ácido fórmico durante 14 minutos) para proporcionar el producto del título (31.0 mg, rendimiento: 52%).

[000969] ¹H RMN (300 MHz, METANOL-*d*₄) δ ppm 0.88 - 1.09 (m, 2 H) 1.10 - 1.35 (m, 3 H) 1.73 - 1.87 (m, 2 H) 1.91 - 2.20 (m, 5 H) 2.43 - 2.64 (m, 3 H) 2.68 - 2.85 (m, 3 H) 3.24 (dd, 2 H) 3.44 - 3.65 (m, 5 H) 3.70 (d, 1 H) 3.88 (d, 2 H) 4.06 (s, 1 H) 4.44 (d, 1 H) 6.81 - 6.90 (m, 3 H) 7.14 - 7.28 (m, 4 H) 7.28 - 7.48 (m, 9 H) 7.62 (d, 1 H) 7.73 (d, 2 H) 8.03 (d, 1 H) 8.29 (s, 1 H).

[000970] LCMS: (ESI) *m/z* 987.3 [M+H]⁺.

[000971] Rotación óptica:

Concentración: 0.1 g/dl

Lámpara: Sodio

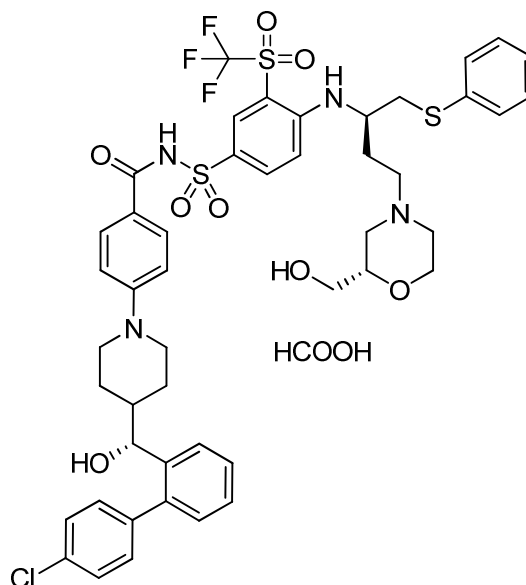
Longitud de onda: 589 nm

104020-1 US/O

Temperatura:	20 °C
Paso óptico:	10 cm
Volumen de la celda:	1 ml
Solvente:	Metanol
$[\alpha]_D$:	+4

EJEMPLO 23

[000972] sal de 4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-((*S*)-2-(hidroximetil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)fenilsulfonyl)benzamida y el ácido fórmico



[000973] El producto del título (37 mg, rendimiento: 62%) se preparó utilizando un procedimiento similar al descrito para la síntesis del EJEMPLO 22. Se utilizó como material de partida 4-(4-((*R*)-(tert-butildimetilsililo)(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((*R*)-4-((*S*)-2-((tert-butildifenilsililo)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)fenilsulfonyl)benzamida (INTERMEDIO 101, 77 mg, 0.06 mmol). El producto resultante se purificó mediante HPLC de fase inversa (Gilson, eluyendo con 15→70% de H₂O/MeCN con el 1% de ácido fórmico durante 14 minutos) para proporcionar el producto del título.

[000974] ¹H RMN (300 MHz, METANOL-*d*₄) δ ppm 0.87 - 1.05 (m, 1 H) 1.08 - 1.33 (m, 2 H) 1.81 (dd, 2 H) 1.90 - 2.16 (m, 3 H) 2.16 - 2.28 (m, 1 H) 2.42 - 2.66 (m, 4 H) 2.69 - 2.81 (m, 1 H) 2.93 (d, 1 H) 3.14 - 3.29 (m, 2 H) 3.47 - 3.65 (m, 4 H) 3.71 (d, 1 H) 3.79 - 3.93 (m, 2 H) 4.08 (dd, 1 H) 4.44 (d, 1 H) 6.82 - 6.89 (m, 3 H) 7.14 - 7.28 (m, 4 H) 7.29 - 7.47 (m, 8 H) 7.60 - 7.64 (m, 1 H) 7.72 (d, 2 H) 8.02 (dd, 1 H) 8.29 (d, 1 H).

[000975] LCMS: (ESI) *m/z* 987 [M+H]⁺.

[000976] Rotación óptica:

Concentración: 0.1 g/dl

Lámpara: Sodio

Longitud de onda: 589 nm

Temperatura: 20 °C

Paso óptico: 10 cm

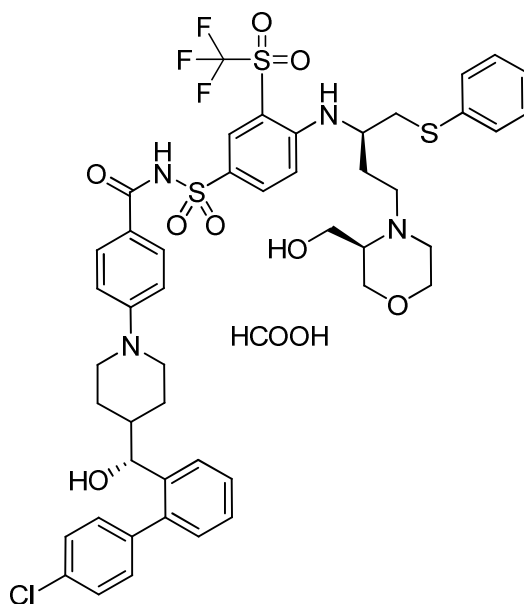
Volumen de la celda: 1 ml

Solvente: Metanol

[α]= +10

EJEMPLO 24

[000977] sal de 4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-((*R*)-3-(hidroximetil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)fenilsulfonyl)benzamida y el ácido fórmico



[000978] Paso 1: A una solución del ácido (*R*)-4-(4-((*tert*-butildimetilsililoxy)(4'-clorobifenil-2-il)metil)piperidin-1-il)benzoico (INTERMEDIO 13, 183 mg, 0.34 mmol) en DCM (3 ml) se añadieron secuencialmente DMAP (125 mg, 1.02 mmol),

4-((*R*)-4-((*S*)-3-((*tert*-butildifenilsililoxy)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida

(INTERMEDIO 105, 280 mg, 0.34 mmol) y EDC (131 mg, 0.68 mmol). La solución resultante se agitó a temperatura ambiente toda la noche. La evaporación de los componentes volátiles a presión reducida proporcionó un residuo, el cual se purificó mediante cromatografía en columna (ISCO, columna de 27 g de gel de sílice, eluyendo con 0→20% de EtOAc/hexanos) para proporcionar 4-(4-((*R*)-(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-

((*R*)-4-((*S*)-3-((*tert*-butildifenilsililoxi)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida (EJEMPLO 24, PASO 1, 153 mg), la cual se utilizó en la preparación del EJEMPLO 24, PASO 2 sin purificación adicional.

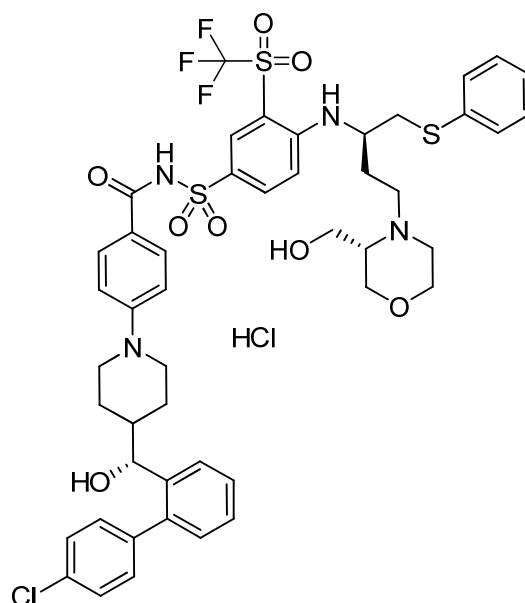
[000979] Paso 2: Se añadió TBAF (0.54 ml, 0.54 mmol, 1 M en THF) a una solución de 4-(4-((*R*)-(tert-butildimetilsililoxi)(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((*R*)-4-((*S*)-3-((*tert*-butildifenilsililoxi)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida (EJEMPLO 24, PASO 1, 135 mg) en THF (2 ml). La mezcla resultante se agitó a temperatura ambiente durante toda la noche y a continuación se añadió HCl (2 ml, 4 N en dioxano) y la mezcla se agitó durante 30 minutos a temperatura ambiente. Los componentes volátiles se evaporaron a presión reducida para proporcionar un residuo, el cual se purificó mediante HPLC de fase inversa (columna Gilson, eluyendo con 10→70% de MeCN con el 0.1% de ácido fórmico /agua), para proporcionar el producto del título (92 mg, rendimiento: 27%).

[000980] ¹H RMN (DMSO-*d*₆, 300Mz) 8.18 (s, 1H) 8.01 (d, 1H) 7.68 (d, 2H) 7.58 (d, 1H) 7.49 (d, 2H) 7.43 (t, 1H) 7.27-7.37 (m, 5H) 7.20-7.26 (m, 2H) 7.12-7.18 (m, 2H) 6.99 (d, 1H) 6.84 (d, 2H) 4.30 (d, 1H) 4.12-4.23 (m, 2H) 3.80-4.06 (m, 9H) 3.62-3.75 (m, 2H) 3.55-3.61 (m, 1H) 3.44-3.64 (m, 2H) 3.25-3.42 (m, 2H) 1.83-1.93 (m, 1H) 1.64-1.74 (m, 1H) 0.99-1.36 (m, 3H) 0.83-0.92 (m, 2H).

[000981] LCMS: (ESI) *m/z* 987 [M+H]⁺.

EJEMPLO 25

[000982] sal clorhídrica de 4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-((*S*)-3-(hidroximetil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida



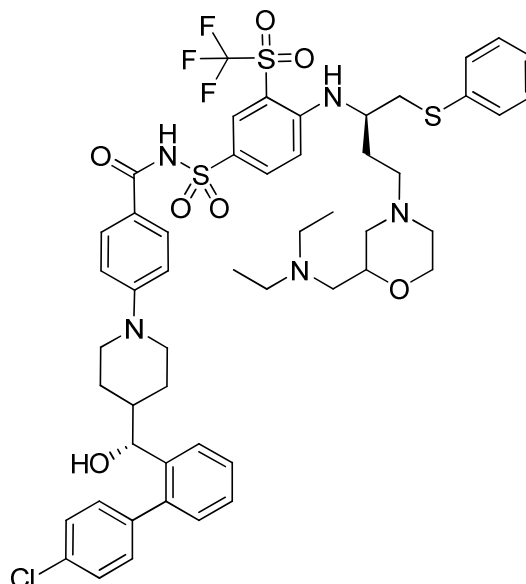
[000983] Se añadió TBAF (0.2 ml, 0.2 mmol, 1 M en THF) a una solución de 4-(4-((*R*)-(tert-butildimetilsililoxy)(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((*R*)-4-((*R*)-3-((tert-butildifenilsililoxy)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida (INTERMEDIO 110, 134 mg, 0.10 mmol) en THF (2 ml). La mezcla resultante se calentó a 60 °C durante 2 horas. Los componentes volátiles se evaporaron a presión reducida para proporcionar un residuo, el cual se purificó mediante HPLC de fase inversa (columna Gilson, eluyendo con 5→70% de MeCN con el 0.1% de TFA /agua) para proporcionar la sal de tipo trifluoroacetato de 4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-((*S*)-3-(hidroximetil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida. La sal de tipo trifluoroacetato se disolvió en dioxano y se trató con HCl en dioxano (4 N en dioxano) y la solución resultante se agitó durante 10 minutos a temperatura ambiente. La evaporación de los componentes volátiles a presión reducida proporcionó el producto del título (72 mg, rendimiento: 70%).

[000984] ¹H RMN (DMSO-*d*₆, 300Mz) 8.17 (d, 1H) 8.01 (d, 1H) 7.68 (d, 2H) 7.59 (d, 1H) 7.49 (d, 2H) 7.43 (t, 1H) 7.28-7.37 (m, 5H) 7.19-7.26 (m, 2H) 7.13-7.18 (m, 2H) 6.98 (d, 1H) 6.84 (d, 2H) 4.30 (d, 1H) 4.09-4.22 (m, 2H) 3.52-4.08 (m, 12H) 3.07-3.44 (m, 4H) 1.81-1.93 (m, 1H) 1.64-1.74 (m, 1H) 0.98-1.36 (m, 3H) 0.79-0.92 (m, 2H).

[000985] LCMS: *m/z* 987 [M+H]⁺.

EJEMPLO 26

[000986] 4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((2*R*)-4-(2-((dietilamino)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida, diastereómero único



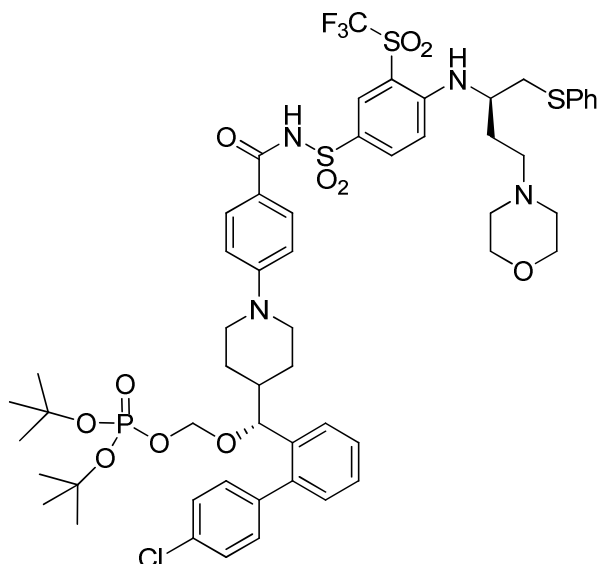
[000987] Se añadió gota a gota HCl (4 M en dioxano, 0.430 ml, 1.72 mmol) a una solución de 4-(4-((*R*)-(tert-butildimetilsililoxy)(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((2*R*)-4-(2-(diethylamino)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida, diastereómero único (INTERMEDIO 117, 199 mg, 0.17 mmol), en dioxano (2.027 ml) y la mezcla de reacción se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se neutralizó con Et₃N (2 ml), se diluyó con DCM y se filtró. El filtrado se concentró a presión reducida y se purificó mediante cromatografía en columna (ISCO, eluyendo con 0→100% de DCM hasta 10% de MeOH/0.1% de NH₃ en DCM) para proporcionar el producto del título como un diastereómero sustancialmente separado (0.06 g, 30%).

[000988] ¹H RMN (400 MHz, DICLOROMETANO-*d*₂) δ ppm 8.06 (d, 1H), 8.02 (d, 1H), 7.90 (d, 2H), 7.61 (m, 1H), 7.40 – 7.21 (m, 12H), 6.82 – 6.76 (m, 3H), 6.46 (d, 1H), 4.49 (d, *J* = 8.1 Hz, 1H), 4.02 (m, 1H), 3.82 (d, 1H), 3.66 (m, 2H), 3.48 (m, 1H), 3.33 (m, 1H), 3.17 (m, 1H), 3.09 (m, 4H), 2.83 (d, 1H), 2.73 (m, 2H), 2.55 (m, 2H), 2.32 (m, 1H), 2.20 – 2.01 (m, 3H), 1.86 – 1.69 (m, 4H), 1.50 (m, 1H), 1.40 – 1.28 (m, 4H), 1.12 (t, 6H).

[000989] LCMS: (ESI) *m/z* 1042 [M+H]⁺.

EJEMPLO 27

[000990] ((*R*)-(4'-clorobifenil-2-il)(1-(4-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)carbamoyl)fenil)piperidin-4-il)metoxi)metilfosfato de di-*tert*-butilo

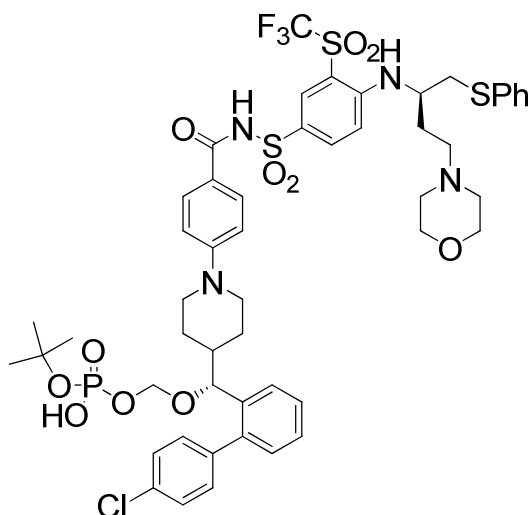


[000991] A una solución de ácido (*R*)-4-(4-((4'-clorobifenil-2-il)(di-*tert*-butoxifosfonooximetoxi)metil)piperidin-1-il)benzoico (INTERMEDIO 118, 73 mg, 0.11 mmol), EDC (43 mg, 0.23 mmol) y DMAP (28 mg, 0.23 mmol) en 3 ml de DCM se añadió (*R*)-4-(4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)bencenosulfonamida (INTERMEDIO 69, 69 mg, 0.12 mmol). La mezcla se agitó durante toda la noche a temperatura ambiente. La mezcla de reacción se diluyó con DCM (20 ml) y se lavó con salmuera (5 ml). La fase orgánica recogida se secó con Na₂SO₄ y se concentró al vacío. El residuo se purificó mediante cromatografía en columna (ISCO, eluyendo con 0→10% de MeOH/EtOAc durante 14 minutos) para proporcionar el producto del título (58 mg, rendimiento: 43%).

[000992] LCMS: m/z 1179 [M + H]⁺.

EJEMPLO 28

[000993] ((*R*)-(4'-clorobifenil-2-il)(1-(4-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonilcarbamoil)fenil)piperidin-4-il)metoxi)metilhidrogenofosfato de *tert*-butilo



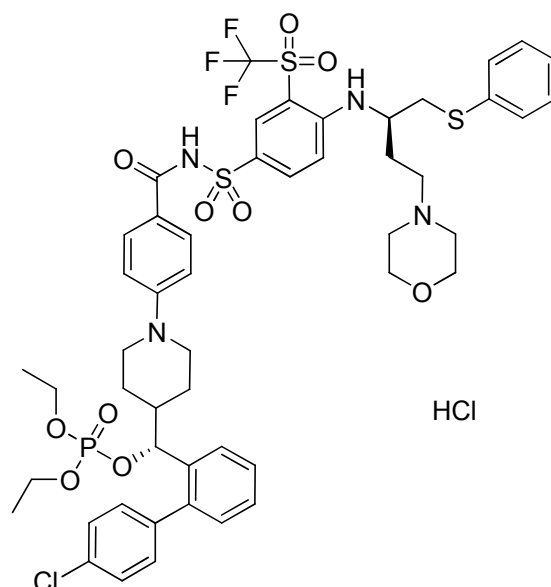
[000994] Se añadió nitrolotrimetanol (5.27 mg, 0.05 mmol) a una solución de ((*R*)-(4'-clorobifenil-2-il)(1-(4-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)fenilsulfonilcarbamoil)fenil)piperidin-4-il)metoxi)metilfosfato de di-*tert*-butilo (EJEMPLO 27, 58.0 mg, 0.05 mmol) en acetona (1.8 ml) y 0.6 ml de tampón de pH 7.2 (solución salina tamponada con fosfato 1X Gibco de Dulbecco). La mezcla de reacción resultante se agitó a 65 °C durante 16 horas. La evaporación de los componentes volátiles a presión reducida proporcionó un residuo, el cual se purificó mediante HPLC de fase inversa (columna Gilson, eluyendo con 30→50% de H₂O con NH₄OAc 10 mM/MeCN durante 5 minutos) para proporcionar el producto del título (0.017 g, rendimiento: 19%).

[000995] ¹H RMN (300 MHz, METANOL-*d*₄) δ ppm 0.97 - 1.08 (m, 3 H) 1.14 - 1.21 (m, 3 H) 1.34 (s, 12 H) 1.51 - 1.65 (m, 1 H) 1.73 - 1.90 (m, 2 H) 1.95 - 2.15 (m, 1 H) 2.42 - 2.72 (m, 9 H) 3.57 - 3.66 (m, 5 H) 3.71 - 3.82 (m, 1 H) 3.90 - 4.01 (m, 1 H) 4.93 - 5.03 (m, 1 H) 6.66 - 6.75 (m, 2 H) 6.76 - 6.83 (m, 1 H) 7.00 - 7.16 (m, 3 H) 7.18 - 7.35 (m, 9 H) 7.39 - 7.46 (m, 1 H) 7.51 - 7.62 (m, 2 H) 7.85 - 7.97 (m, 1 H) 8.11 - 8.24 (m, 1 H).

[000996] LCMS: (ESI) *m/z* 1124 [M+H]⁺.

EJEMPLO 29

[000997] sal clorhídrica de (*R*)-(4'-clorobifenil-2-il)(1-(4-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)fenilsulfonilcarbamoil)fenil)piperidin-4-il)metilfosfato de dietilo



[000998] Se agitó una mezcla del ácido (*R*)-4-(4-((4'-clorobifenil-2-il)(dietoxifosforiloxi)metil)piperidin-1-il)benzoico (INTERMEDIO 120, 371 mg, 0.66 mmol), (*R*)-4-(4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)bencenosulfonamida (INTERMEDIO 69, 368 mg, 0.66 mmol), EDC (255 mg, 1.33 mmol), TEA (0.185 ml, 1.33 mmol) y DCE (5 ml) a temperatura ambiente durante 2 horas. La mezcla se diluyó con DCM (15 ml) y se adsorbió en gel de sílice. La purificación mediante cromatografía en columna (ISCO, eluyendo con 0→10% de MeOH/DCM durante 19 minutos y a continuación eluyendo con 0→10% de NH₃ 2 M/MeOH/ DCM durante 24 minutos) proporcionó un residuo, el cual se purificó adicionalmente mediante HPLC de fase inversa, de acuerdo con las siguientes condiciones:

Columna:	Atlantis T3, OBD
Dimensiones de la columna:	30 x 100 mm, 5 μ
Fase móvil A	agua con el 0.1% de TFA, pH 2
Fase móvil B	100% de acetonitrilo
Velocidad de flujo (ml/min):	60 ml/min
Gradiente:	De A→B (de 60 a 80% en 10 minutos)

Las fracciones similares se concentraron a presión reducida. El concentrado se disolvió en DCM (5 ml) y se trató con HCl 4 N en dioxano (0.5 ml). La evaporación de los componentes volátiles proporcionó el compuesto del título (60 mg, rendimiento: 8%).

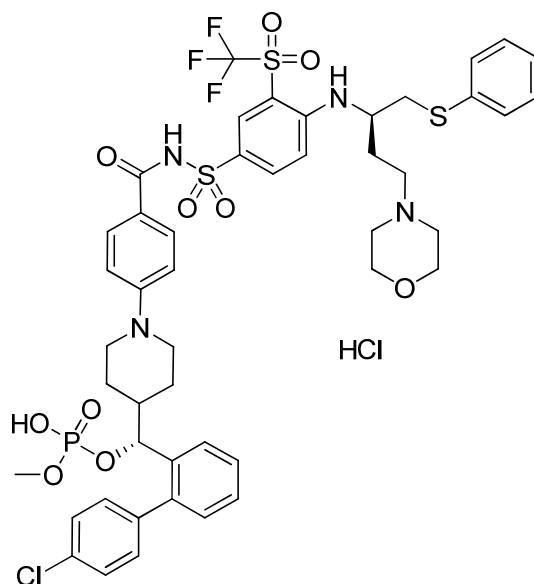
[000999] ¹H RMN (400 MHz, DICLOROMETANO-*d*₂) δ ppm 0.60 - 0.85 (m, 2 H) 0.90 - 1.14 (m, 9 H) 1.32 - 1.44 (m, 1 H) 1.59 (s a, 1 H) 1.70 - 2.46 (m, 4 H) 2.65 - 3.20 (m, 7 H) 3.21 - 3.48 (m, 4 H) 3.50 - 3.73 (m, 1 H) 3.75 - 4.33 (m, 8 H) 6.81 - 7.02 (m, 1 H) 7.04 - 7.67 (m, 15 H) 7.90 (s a, 3 H) 8.28 (s a, 1 H).

[0001000] ³¹P RMN (121 MHz, DICLOROMETANO-*d*₂) δ ppm -2.73 (s, 1 P).

[0001001] LCMS: (ESI) m/z 1092 $[M-H]^+$.

EJEMPLO 30

[0001002] sal clorhídrica de (*R*)-(4'-clorobifenil-2-il)(1-(4-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonilcarbamoil)fenil)piperidin-4-il)metilhidrogenofosfato de metilo



[0001003] Se agitó una mezcla del ácido (*R*)-4-(4-((4'-clorobifenil-2-il)(dimetoxifosforiloxi)metil)piperidin-1-il)benzoico (INTERMEDIO 122, 57.4 mg, 0.11 mmol), (*R*)-4-(4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)bencenosulfonamida (INTERMEDIO 69, 60 mg, 0.11 mmol), EDC (41.6 mg, 0.22 mmol), TEA (0.03 ml, 0.22 mmol) y DCE (2 ml) a TA durante 4 días. Los componentes volátiles se eliminaron a presión reducida y el concentrado se purificó mediante HPLC de fase inversa, de acuerdo con las siguientes condiciones:

Columna:	Xbridge Sunfire
Dimensiones de la columna:	19 x 100 mm, 5 μ
Fase móvil A:	agua con el 0.1% de TFA, pH 2
Fase móvil B:	100% de acetonitrilo
Velocidad de flujo (ml/min):	20 ml/min
Gradiente:	de A $\rightarrow$ B (de 40 a 60% en 10 minutos)

Las fracciones similares se combinaron y los componentes volátiles se eliminaron a presión reducida. El residuo obtenido se trató con HCl en dioxano (4 N, 0.5 ml) y se diluyó con MeOH y posteriormente se eliminaron los componentes volátiles a presión reducida para proporcionar el compuesto del título (34.0 mg, rendimiento: 30%).

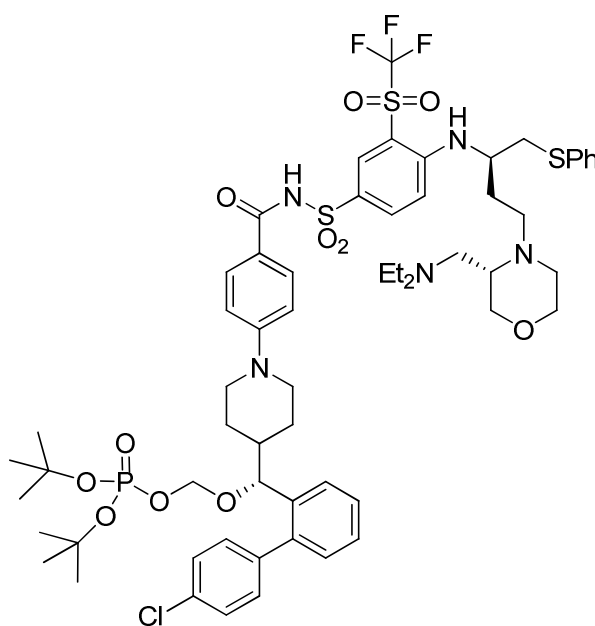
[0001004] ^1H RMN (400 MHz, METANOL- d_4) δ ppm 1.37 (s a, 2 H) 1.66 (s a, 1 H) 1.86 - 2.40

(m, 4 H) 1.86 - 2.40 (m, 4 H) 3.04 (s a, 5 H) 3.30 - 3.82 (m, 12 H) 3.87 - 4.25 (m, 3 H) 5.22 (s a, 1 H) 6.99 (s a, 1 H) 7.04 - 7.22 (m, 4 H) 7.23 - 7.71 (m, 11 H) 7.85 (s a, 2 H) 8.02 (s a, 1 H) 8.26 (s, 1 H). ^{31}P RMN (121 MHz, METANOL- d_4) δ ppm -0.37 (s, 1 P).

[0001005] LCMS: m/z 1052 $[\text{M}+\text{H}]^+$.

EJEMPLO 31

[0001006] ((*R*)-(4'-clorobifenil-2-il)(1-(4-(4-((*R*)-4-((*S*)-3-((dietilamino)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonilcarbamoil)fenil)piperidin-4-il)metoxi)metilfosfato de di-*tert*-butilo



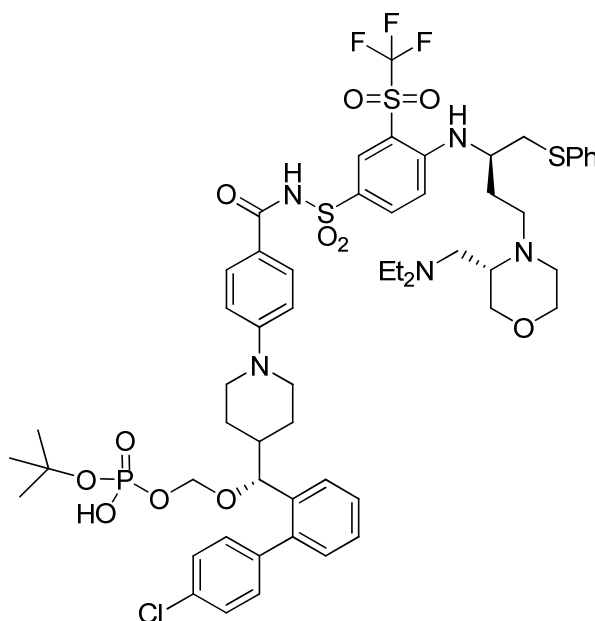
[0001007] A una solución del ácido (*R*)-4-(4-((4'-clorobifenil-2-il)(di-*tert*-butoxifosfonooximetoxi)metil)piperidin-1-il)benzoico (INTERMEDIO 118, 55.5 mg, 0.09 mmol), EDC (33 mg, 0.17 mmol) y DMAP (21 mg, 0.17 mmol) en DCM (3 ml), se añadió 4-((*R*)-4-((*S*)-3-((dietilamino)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)bencenosulfonamida (INTERMEDIO 88, 55 mg, 0.09 mmol). La mezcla resultante se agitó durante la noche a temperatura ambiente. La mezcla de reacción se diluyó con DCM (20 ml) y se lavó con salmuera (5 ml). La fase orgánica recogida se secó con Na_2SO_4 y se concentró al vacío. El residuo se purificó mediante cromatografía en columna (ISCO, eluyendo con 0→10% de MeOH/EtOAc durante 14 minutos) para proporcionar el producto del título (30 mg, 27%).

[0001008] LCMS: (ESI) m/z 1263 $[\text{M} - \text{H}]^+$.

EJEMPLO 32

[0001009] ((*R*)-(4'-clorobifenil-2-il)(1-(4-(4-((*R*)-4-((*S*)-3-((dietilamino)metil)morfolino)-1-

(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonilcarbamoil)fenil)piperidin-4-il)metoxi)metilhidrogenofosfato de *tert*-butilo



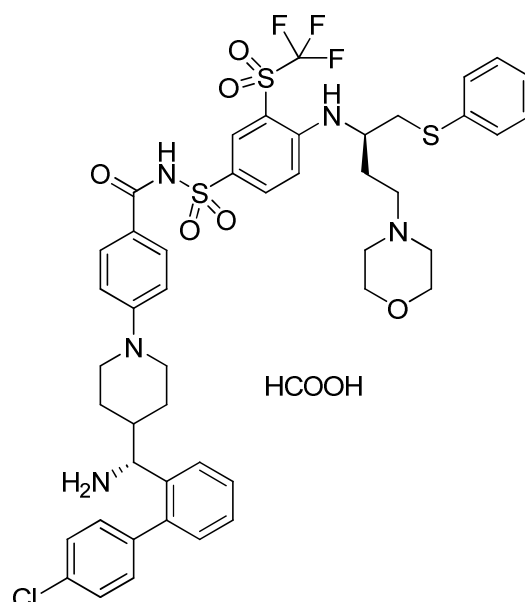
[0001010] Se siguió un procedimiento similar al descrito para el EJEMPLO 28 , utilizando como material de partida (*R*)-(4'-clorobifenil-2-il)(1-(4-(4-((*R*)-4-((*S*)-3-((dietilamino)metil)morfolino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonilcarbamoil)fenil)piperidin-4-il)metoxi)metilfosfato de di-*tert*-butilo (EJEMPLO 31, 110 mg, 0.09 mmol) y posteriormente se purificó mediante HPLC de fase inversa (columna Gilson, eluyendo con 15→50% de H₂O con NH₄OAc 10 mM/MeCN durante 4 minutos) para proporcionar el producto del título (0.027 g, rendimiento: 27%).

[0001011] ¹H RMN (300 MHz, METANOL-*d*₄) δ ppm 0.80 - 0.92 (m, 6 H) 0.95 - 1.06 (m, 5 H) 1.25 (s, 9 H) 1.52 - 1.87 (m, 4 H) 1.98 - 2.13 (m, 1 H) 2.20 - 2.34 (m, 1 H) 2.41 - 2.83 (m, 12 H) 2.85 - 2.99 (m, 2 H) 3.24 - 3.38 (m, 2 H) 3.50 - 3.65 (m, 2 H) 3.68 - 3.79 (m, 2 H) 3.85 - 4.00 (m, 1 H) 4.90 - 5.04 (m, 2 H) 6.57 - 6.75 (m, 3 H) 6.99 - 7.48 (m, 14 H) 7.59 - 7.71 (m, 2 H) 7.86 - 7.99 (m, 1 H) 8.13 - 8.25 (m, 1 H).

[0001012] LCMS: (ESI) *m/z* 1208 [M-H]⁺.

EJEMPLO 33

[0001013] sal de 4-(4-((*R*)-amino(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida y el ácido fórmico



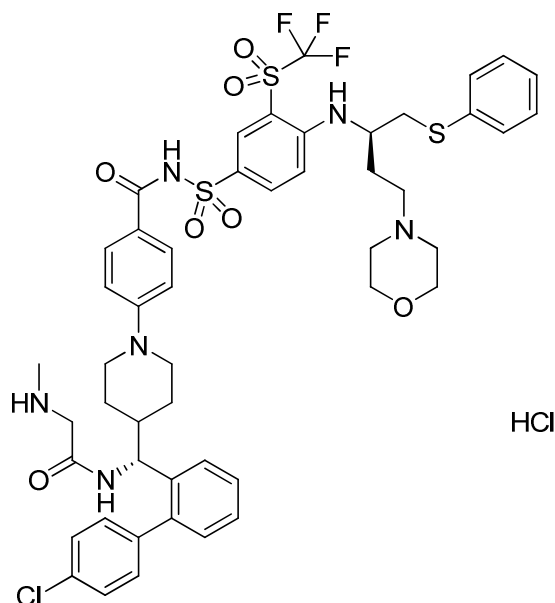
[0001014] Se añadió una solución de HCl (0.80 ml, 3.21 mmol, 4.0 M en dioxano) a una solución de 4-(4-((*R*)-(4'-clorobifenil-2-il)((*S*)-1,1-dimetiletilsulfinamido)metil)piperidin-1-il)-*N*-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)fenilsulfonyl)benzamida (INTERMEDIO 131, 0.17 g, 0.16 mmol) en MeOH (1.5 ml) y la mezcla de reacción se agitó a TA durante 2 horas. La mezcla de reacción se concentró a presión reducida para proporcionar un residuo, el cual se purificó mediante HPLC de fase inversa (columna Gilson, eluyendo con 20→50% de H₂O/ACN con el 0.1% de ácido fórmico durante 10 minutos) para proporcionar el compuesto del título (0.10 g, rendimiento: 60%).

[0001015] ¹H RMN (400 MHz, DMSO-*d*₆) δ ppm 8.05 (d, 1H), 7.90 (dd, 1H), 7.70 – 7.67 (m, 3H), 7.59 – 7.53 (m, 3H), 7.50 – 7.46 (m, 1H), 7.40 - 7.25 (m, 8H), 7.22 - 7.18 (m, 1H), 6.81 (d, 1H), 6.73 (d, 2H), 6.68 (d, 1H), 4.00 (m, 1H), 3.87 – 3.85 (m, 1H), 3.79 – 3.76 (m, 1H), 3.59 – 3.45 (m, 6H), 3.33– 3.20 (m, 2H), 2.61 – 2.55 (m, 1H), 2.33 – 2.25 (m, 4H), 2.19 – 2.15 (m, 2H), 2.01 – 1.88 (m, 2 H), 1.84 – 1.81 (m, 1H), 1.73 – 1.66 (m, 1H), 1.17 – 1.08 (m, 2H), 0.83 – 0.75 (m, 1H).

[0001016] LCMS: (ESI) *m/z* 956 [M+H]⁺.

EJEMPLO 34

[0001017] sal clorhídrica de 4-(4-((*R*)-(4'-clorobifenil-2-il)(2-(metilamino)acetamido)metil)piperidin-1-il)-*N*-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)fenilsulfonyl)benzamida



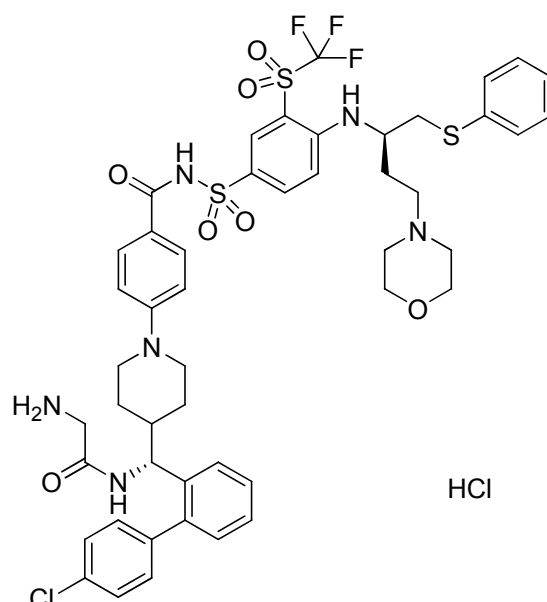
[0001018] Se añadió una solución de HCl (0.42 ml, 1.67 mmol, 4 M en dioxano) a una solución de 2-((*R*)-(4'-clorobifenil-2-il)(1-(4-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonilcarbamoil)fenil)piperidin-4-il)metilamino)-2-oxoetil(metil)carbamato de *tert*-butilo (INTERMEDIO 132, 94 mg, 0.08 mmol) en MeOH (1.3 ml) y la mezcla de reacción se agitó a TA durante 3 horas. La mezcla de reacción se concentró a presión reducida para proporcionar un residuo, el cual se purificó mediante HPLC de fase inversa (columna Gilson, eluyendo con 20→50% de H₂O/ACN con el 0.1% de ácido fórmico durante 10 minutos) para proporcionar un sólido. El sólido se disolvió en MeOH y la mezcla se trató con una solución de HCl (2 N) en éter dietílico. La evaporación de los componentes volátiles a presión reducida proporcionó el compuesto del título (56 mg, rendimiento: 61%).

[0001019] ¹H RMN (400 MHz, DMSO-*d*₆) δ ppm 8.18 (d, 1H), 7.98 (dd, 1H), 7.70 – 7.68 (m, 2H), 7.55 – 7.51 (m, 3H), 7.48 – 7.43 (m, 3H), 7.36 – 7.29 (m, 3H), 7.25 – 7.21 (m, 3H), 7.17 – 7.13 (m, 2H), 6.98 (d, 1H), 6.85 – 6.83 (m, 2H), 4.79 – 4.75 (m, 1H), 4.22 (m, 1H), 3.95 – 3.65 (m, 6H), 3.41 – 3.32 (m, 4H), 3.17 – 2.90 (m, 5H), 2.74 – 2.62 (m, 1H), 2.57 – 2.53 (m, 4H), 2.25 – 2.13 (m, 2H), 1.84 – 1.75 (m, 2H), 1.12 – 1.00 (m, 2H), 0.74 – 0.71 (m, 1H).

[0001020] LCMS: (ESI) *m/z* 1027 [M+H]⁺.

EJEMPLO 35

[0001021] sal clorhídrica de 4-(4-((*R*)-(2-aminoacetamido)(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida



[0001022] Paso 1: Se añadió DIPEA (0.08 ml, 0.46 mmol) a una solución de la sal del ácido fórmico y 4-(4-((*R*)-amino(4'-clorobifenil-2-il)metil)piperidin-1-il)-*N*-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida (EJEMPLO 33, 0.11 g, 0.11 mmol), ácido 2-(*tert*-butoxicarbonilamino)acético (20 mg, 0.11 mmol) y HATU (52 mg, 0.14 mmol) en DMF (2.2 ml) y la mezcla de reacción se agitó a TA durante 1 hora. La mezcla de reacción se concentró a presión reducida, se diluyó con DCM y se lavó con H₂O, NaHSO₄ 1 N acuoso y NaHCO₃ saturado acuoso. La fase orgánica se secó con Na₂SO₄, se filtró y se concentró el filtrado a presión reducida para proporcionar 2-((*R*)-(4'-clorobifenil-2-il)(1-(4-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonilcarbamoil)fenil)piperidin-4-il)metilamino)-2-oxoetilcarbamato de *tert*-butilo (EJEMPLO 35, PASO 1, 0.13 g), el cual se utilizó en la preparación del EJEMPLO 35, PASO 2 sin purificación adicional.

[0001023] LCMS: (ESI) m/z 1113[M+H]⁺.

[0001024] Paso 2: Se añadió una solución de HCl (0.6 ml, 2.20 mmol, 4 M en dioxano) a una solución de 2-((*R*)-(4'-clorobifenil-2-il)(1-(4-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonilcarbamoil)fenil)piperidin-4-il)metilamino)-2-oxoetilcarbamato de *tert*-butilo (EJEMPLO 35, PASO 1, 0.123 g, 0.11 mmol) en MeOH (1.7 ml) y la mezcla de reacción se agitó a TA durante 3 horas. La mezcla de reacción se concentró a presión reducida para proporcionar un residuo, el cual se purificó mediante HPLC de fase inversa (columna Gilson, eluyendo con 20→50% de H₂O/ACN con el 0.1% de ácido fórmico durante 10 minutos) para proporcionar un sólido. El sólido se disolvió en MeOH y la mezcla se trató con HCl 2 N en éter dietílico. La evaporación de los componentes volátiles a presión reducida proporcionó el compuesto del título (64 mg, rendimiento: 54% para 2 pasos).

[0001025] ¹H RMN (400 MHz, DMSO-*d*₆) δ ppm 8.18 (d, 1H), 7.98 (dd, 1H), 7.70 – 7.68 (m, 204

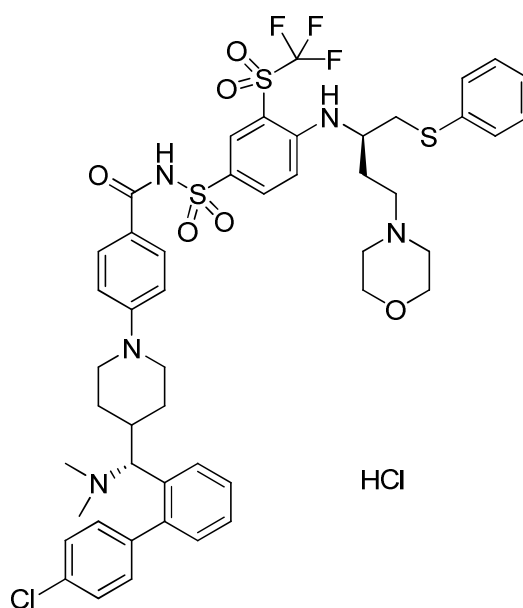
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2H), 7.56 – 7.53 (m, 3H), 7.48 – 7.43 (m, 3H), 7.36 – 7.29 (m, 3H), 7.25 – 7.21 (m, 3H), 7.17 – 7.13 (m, 2H), 6.98 (d, 1 H), 6.85 – 6.83 (m, 2H), 4.79 – 4.75 (m, 1H), 4.22 (m, 1H), 3.95 – 3.76 (m, 6H), 3.70 – 3.56 (m, 4H), 3.19 – 3.17 (m, 1H), 3.10 – 2.92 (m, 4H), 2.73 – 2.66 (m, 1H), 2.59 – 2.54 (m, 1H), 2.23 – 2.15 (m, 2H), 1.86 – 1.83 (m, 1H), 1.75 – 1.73 (m, 1H), 1.12 – 1.00 (m, 2H), 0.74 – 0.71 (m, 1H).

[0001026] LCMS: (ESI) m/z 1013 $[M+H]^+$.

EJEMPLO 36

[0001027] sal clorhídrica de 4-(4-((*R*)-(4'-clorobifenil-2-il)(dimetilamino)metil)piperidin-1-il)-*N*-(4-((*R*)-4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)fenilsulfonyl)benzamida



[0001028] Paso 1: A una solución de (*R*)-4-(4-((4'-clorobifenil-2-il)(dimetilamino)metil)piperidin-1-il)benzoato de etilo (INTERMEDIO 133, 0.11 g, 0.23 mmol) en THF (1.4 ml), se añadieron MeOH (0.5 ml) y una solución de LiOH (28 mg, 1.15 mmol) en agua (0.5 ml) y la mezcla de reacción se agitó a 40 °C durante toda la noche. La mezcla de reacción se enfrió hasta TA, se concentró a presión reducida y el residuo se secó en un horno de vacío durante toda la noche, para proporcionar la sal (*R*)-4-(4-((4'-clorobifenil-2-il)(dimetilamino)metil)piperidin-1-il)benzoato de litio (EJEMPLO 36, PASO 1, 0.12 g), la cual se utilizó en la preparación del EJEMPLO 36, PASO 2 sin purificación adicional.

[0001029] LCMS: (ESI) m/z 449 $[M+H]^+$.

[0001030] Paso 2: En un vial de 40 ml, se introdujeron la sal (*R*)-4-(4-((4'-clorobifenil-2-il)(dimetilamino)metil)piperidin-1-il)benzoato de litio (EJEMPLO 36, PASO 1, 0.105 g, 0.23 mmol), DMAP (56 mg, 0.46 mmol) y EDC (0.176 g, 0.92 mmol) y se purgaron con nitrógeno. Se añadieron DCM (4.5 ml) y DIPEA (0.08 ml, 0.46 mmol) y la solución se agitó a TA durante 15

minutos. Se añadió (*R*)-4-(4-morfolino-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida (INTERMEDIO 69, 0.127 g, 0.23 mmol) a la solución y la mezcla de reacción se agitó a TA durante toda la noche. La mezcla de reacción se diluyó con DCM y se lavó con bisulfato de sodio 1 N (acuoso) y a continuación con bicarbonato de sodio saturado acuoso. La fase orgánica se secó (Na₂SO₄), se filtró y se evaporó a presión reducida para proporcionar un residuo, el cual se purificó mediante HPLC de fase inversa (columna Gilson, eluyendo con 30→50% de H₂O/ACN con el 0.1% de ácido fórmico durante 10 minutos) para proporcionar un sólido. El sólido se disolvió en MeOH y la mezcla se trató con HCl 2 N en éter dietílico. La evaporación de los componentes volátiles a presión reducida proporcionó el compuesto del título (85 mg, rendimiento: 35% para 2 pasos).

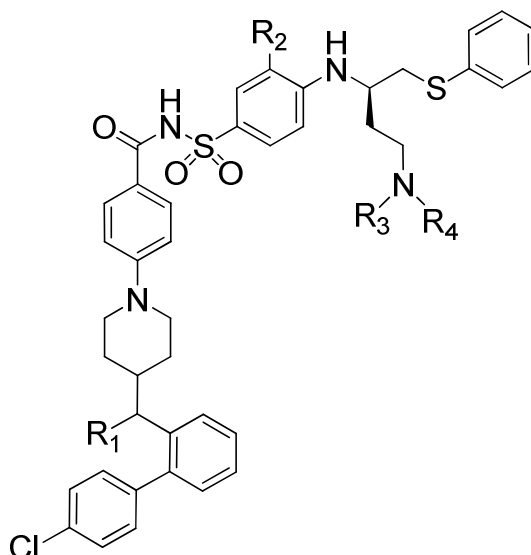
[0001031] ¹H RMN (400 MHz, DMSO-*d*₆) δ ppm 8.18 (d, 1H), 7.99 (dd, 1H), 7.89 – 7.87 (m, 2H), 7.73 – 7.70 (m, 2H), 7.57 – 7.50 (m, 4H), 7.31 – 7.29 (m, 5H), 7.25 – 7.22 (m, 3H), 7.17 – 7.14 (m, 1H), 6.98 (d, 1H), 6.92 – 6.89 (m, 2H), 4.23 (m, 1H), 3.95 – 3.90 (m, 5H), 3.81 – 3.75 (m, 2H), 3.42 – 3.32 (m, 4H), 3.19 – 3.16 (m, 1H), 3.10 – 2.92 (m, 4H), 2.80 – 2.72 (m, 2H), 2.67 (m, 3H), 2.57 (m, 3H), 2.23 – 2.15 (m, 2H), 1.80 – 1.76 (m, 1H), 1.57 – 1.54 (m, 1H), 1.25 – 1.17 (m, 1H), 1.02 – 0.94 (m, 1H).

[0001032] LCMS: (ESI) *m/z* 984 [M+H]⁺.

REIVINDICACIONES

Se reivindica:

1. Un compuesto de Fórmula (I):



Fórmula (I)

o una de sus sales farmacéuticamente aceptables, donde:

R¹ se selecciona entre -CN, -OR^{1a} y -N(R^{1a})₂;

R^{1a} en cada caso se selecciona independientemente entre H, alquilo C₁₋₄, -C(O)CH₂NH₂, -C(O)CH₂NHCH₃ y, cuando **R¹** es -OR^{1a}, entonces **R^{1a}** se selecciona adicionalmente entre -P(=O)(OH)(OCH₃), -P(=O)(OCH₂CH₃)₂, -CH₂OP(=O)(OH)[OC(CH₃)₃] y -CH₂OP(=O)[OC(CH₃)₃]₂;

R² se selecciona entre -N(O)₂ y -S(O)₂CF₃;

R³ se selecciona entre H y alquilo C₁₋₄, donde dicho alquilo C₁₋₄ está opcionalmente sustituido con uno o más R⁴⁰;

R⁴ se selecciona entre H y alquilo C₁₋₄, donde dicho alquilo C₁₋₄ está opcionalmente sustituido con uno o más R⁴⁰;

o **R³** y **R⁴** junto con el nitrógeno al cual están enlazados forman un anillo heterocíclico de 5 ó 6 miembros, donde

- i) dicho anillo heterocíclico de 5 ó 6 miembros está opcionalmente sustituido en carbono con uno o más R⁴⁰; y

- ii) si dicho anillo heterocíclico de 5 ó 6 miembros contiene un nitrógeno, ese nitrógeno está opcionalmente sustituido con R^{40*} para formar una amina terciaria;

R^{40*} se selecciona entre alquilo C_{1-4} y $-(CH_2)_2OP(=O)(OH)_2$, donde dicho alquilo C_{1-4} está opcionalmente sustituido con uno o más R^a ;

R^{40} en cada caso se selecciona entre $-OR^{40a}$, $-N(R^{40a})_2$, $-CH_2OR^{5a}$, $-CH_2N(R^{5a})_2$, $-OP(=O)(OH)_2$ y $-OP(=O)[OC(CH_3)_3]_2$;

R^{5a} en cada caso se selecciona entre H y alquilo C_{1-3} ;

R^{40a} en cada caso se selecciona independientemente entre H y alquilo C_{1-4} ; y

R^a se selecciona entre halo, $-OR^m$ y $-N(R^m)_2$; y

R^m en cada caso se selecciona independientemente entre H y alquilo C_{1-4} .

2. Un compuesto de Fórmula (I), o una de sus sales farmacéuticamente aceptables, como se reivindica en la reivindicación 1, donde

R^1 es $-OH$;

R^2 es $-S(O)_2CF_3$;

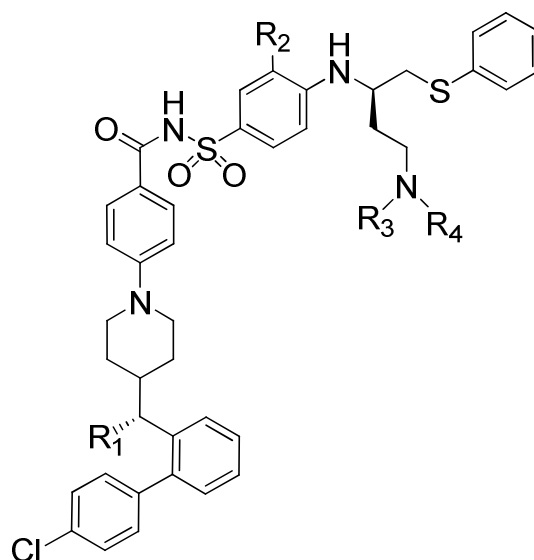
R^3 es alquilo C_{1-2} , donde dicho alquilo C_{1-2} está opcionalmente sustituido con uno o más R^{40} ;

R^4 es alquilo C_{1-2} , donde dicho alquilo C_{1-2} está opcionalmente sustituido con uno o más R^{40} ;

R^{40} en cada caso se selecciona entre $-OR^{40a}$ y $-OP(=O)(OH)_2$; y

R^{40a} es H.

3. El compuesto de la reivindicación 1 ó 2, donde el compuesto tiene la siguiente estereoquímica:



4. Un compuesto de Fórmula (I), o una de sus sales farmacéuticamente aceptables, como se reivindica en la reivindicación 3, donde el compuesto es 4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-((2-hidroxi)etil)(metil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida.

5. Un compuesto de Fórmula (I), o una de sus sales farmacéuticamente aceptables, como se reivindica en la reivindicación 3, donde el compuesto es dihidrogenofosfato de 2-(((*R*)-3-(4-(*N*-(4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)-4-(feniltio)butil)(metil)amino)etilo.

6. Un compuesto de Fórmula (I), o una de sus sales farmacéuticamente aceptables, como se reivindica en la reivindicación 3, donde el compuesto es 4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)-*N*-(4-((*R*)-4-(etil(2-hidroxi)etil)amino)-1-(feniltio)butan-2-ilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida.

7. Un compuesto de Fórmula (I), o una de sus sales farmacéuticamente aceptables, como se reivindica en la reivindicación 3, donde el compuesto es dihidrogenofosfato de 2-(((*R*)-3-(4-(*N*-(4-(4-((*R*)-(4'-clorobifenil-2-il)(hidroxi)metil)piperidin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)-4-(feniltio)butil)(etil)amino)etilo.

8. Un compuesto de fórmula (I), o una de sus sales farmacéuticamente aceptables, como se reivindica en cualquiera de las reivindicaciones 1 a 7, para emplear como un medicamento.

9. El uso de un compuesto de Fórmula (I), o una de sus sales farmacéuticamente aceptables, como se reivindica en cualquiera de las reivindicaciones 1 a 7, en la fabricación de un medicamento para emplear en la producción de un efecto antiproliferativo y/o proapoptótico en un animal de sangre caliente.

10. El uso de acuerdo con la reivindicación 9 para emplear en el tratamiento del cáncer de vejiga, cáncer de mama, cáncer de colon, cáncer ovárico, LMA, linfoma difuso de linfocitos B grandes (DLBCL), LLC; carcinoma pulmonar microcítico (CPM), carcinoma pulmonar no microcítico (CPNM), incluidos los subtipos escamosos y no escamosos, cáncer pancreático, cáncer de próstata, linfomas no hodgkinianos, linfoma folicular (LF), linfoma de células del manto (LCM), linfoma de la zona marginal (LZM), leucemia de células peludas (LCP) y linfoma periférico de linfocitos T (LPT).

11. Un método para producir un efecto antiproliferativo y/o proapoptótico en un animal de sangre caliente, comprendiendo dicho método administrar a dicho animal una cantidad eficaz de un compuesto de Fórmula (I), como se reivindica en cualquiera de las reivindicaciones 1 a 7, o una de sus sales farmacéuticamente aceptables.

12. El método de acuerdo con la reivindicación 11 para tratar el cáncer de vejiga, cáncer de mama, cáncer de colon, cáncer ovárico, LMA, linfoma difuso de linfocitos B grandes (DLBCL), LLC; carcinoma pulmonar microcítico (CPM), carcinoma pulmonar no microcítico (CPNM), incluidos los subtipos escamosos y no escamosos, cáncer pancreático, cáncer de próstata, linfomas no hodgkinianos, linfoma folicular (LF), linfoma de células del manto (LCM), linfoma de la zona marginal (LZM), leucemia de células peludas (LCP) y linfoma periférico de linfocitos T (LPT) en un animal de sangre de caliente, comprendiendo dicho método administrar a dicho animal una cantidad eficaz de un compuesto de Fórmula (I), como se reivindica en cualquiera de las reivindicaciones 1 a 7, o una de sus sales farmacéuticamente aceptables.

13. Un compuesto de Fórmula (I), o una de sus sales farmacéuticamente aceptables, como se reivindica en cualquiera de las reivindicaciones 1 a 7, para emplear en la producción de un efecto antiproliferativo y/o proapoptótico en un animal de sangre caliente.

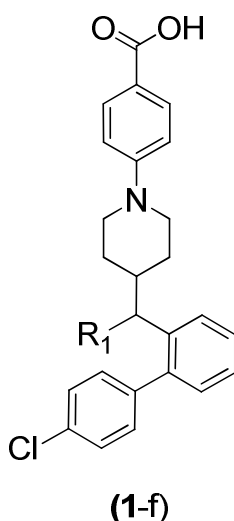
14. El compuesto de Fórmula (I) de acuerdo con la reivindicación 13 para emplear en el tratamiento del cáncer de vejiga, cáncer de mama, cáncer de colon, cáncer ovárico, LMA, linfoma difuso de linfocitos B grandes (DLBCL), LLC; carcinoma pulmonar microcítico (CPM),

carcinoma pulmonar no microcítico (CPNM), incluidos los subtipos escamosos y no escamosos, cáncer pancreático, cáncer de próstata, linfomas no hodgkinianos, linfoma folicular (LF), linfoma de células del manto (LCM), linfoma de la zona marginal (LZM), leucemia de células peludas (LCP) y linfoma periférico de linfocitos T (LPLT) en un animal de sangre caliente.

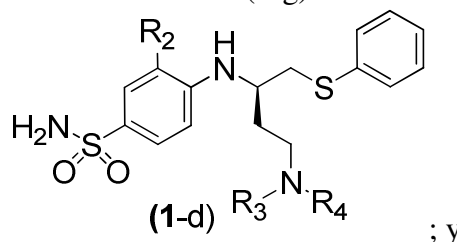
15. Una composición farmacéutica que comprende un compuesto de Fórmula (I) o una de sus sales farmacéuticamente aceptables, como se reivindica en cualquiera de las reivindicaciones 1-7, y al menos un portador, diluyente o excipiente farmacéuticamente aceptable.

16. Un proceso para preparar un compuesto de Fórmula (I), o una de sus sales farmacéuticamente aceptables, como se reivindica en cualquiera de las reivindicaciones 1 a 7, comprendiendo dicho proceso:

(i) proporcionar un ácido carboxílico de fórmula (1-f):

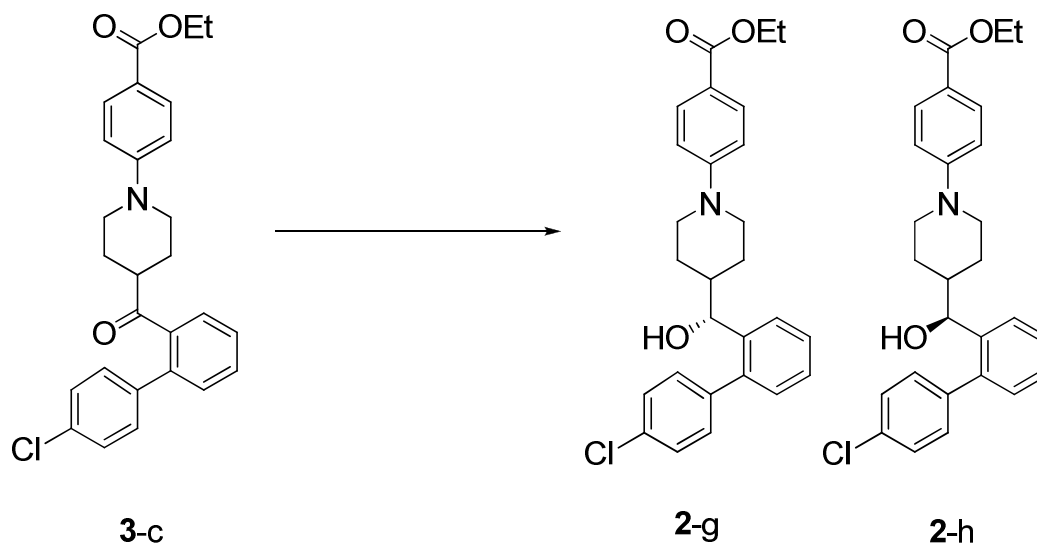


(ii) proporcionar una sulfonamida de fórmula (1-g):



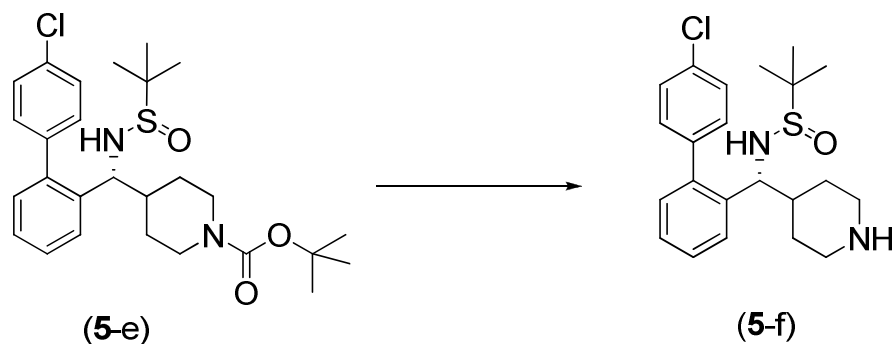
(iii) acoplar el ácido carboxílico de fórmula (1-f) con la sulfonamida de fórmula (1-g).

17. Un proceso para preparar un compuesto de fórmula (2-g) y (2-h), comprendiendo dicho proceso:



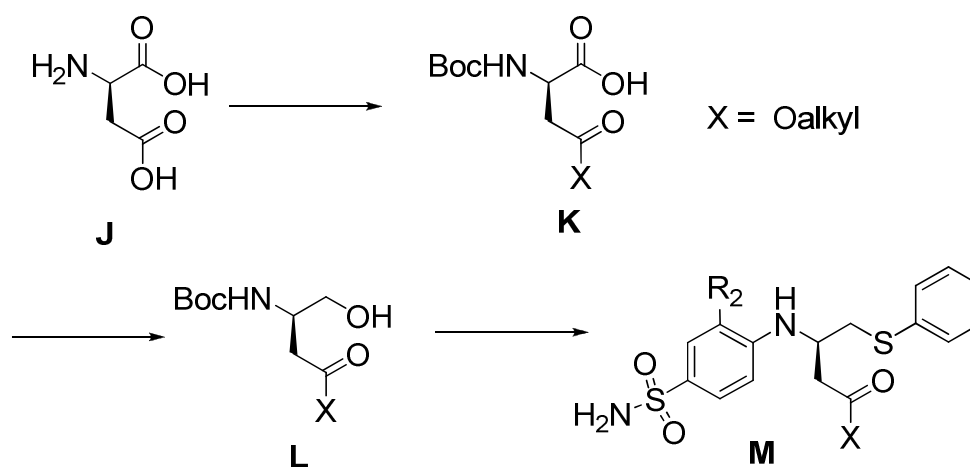
llevar a cabo la reducción enantioselectiva para obtener un compuesto de fórmula (3-c).

18. Un proceso para preparar un compuesto de fórmula (5-f), comprendiendo dicho proceso:



desproteger selectivamente un compuesto de fórmula (5-e).

19. Un proceso para preparar un compuesto de fórmula (M), comprendiendo dicho proceso:



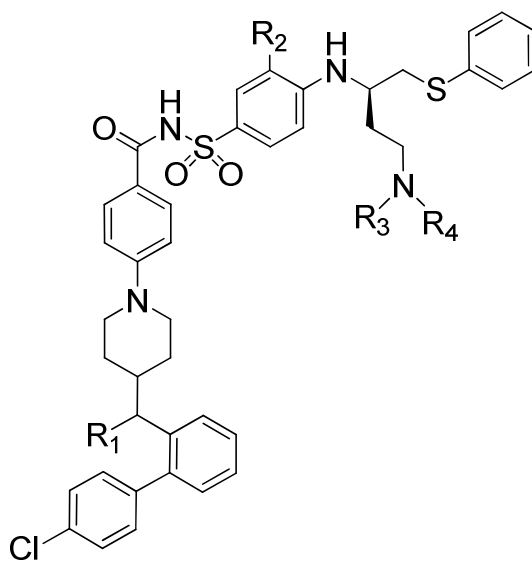
- convertir un compuesto de fórmula (J) en un compuesto de fórmula (K);
- reducir un compuesto de fórmula (K) para formar un compuesto de fórmula (L);

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- (iii) llevar a cabo una reacción de sustitución de un compuesto de fórmula (L) para formar un tioéter correspondiente;
- (iv) llevar a cabo la desprotección del tioéter para formar una amina correspondiente; y
- (v) llevar a cabo una reacción de sustitución aromática de la amina correspondiente para formar un compuesto de fórmula (M).

RESUMEN

La presente invención se refiere a compuestos de Fórmula (I):



Fórmula (I)

y a sus sales, composiciones farmacéuticas, métodos de empleo y métodos para su preparación. Estos compuestos inhiben las actividades de Bcl-2 y/o Bcl-X_L, y se pueden utilizar para el tratamiento del cáncer.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.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. PCT/GB2011/051484	International filing date (day/month/year) 05.08.2011	Priority date (day/month/year) 06.08.2010
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International Patent Classification (IPC) or both national classification and IPC
INV. C07D211/22 A61K31/445 A61P35/00 A61P35/02

Applicant
ASTRAZENECA AB

- 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 43bis.1(a)(i) with regard to novelty, inventive step and 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
- 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 notified the International Bureau under Rule 66.1bis(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.
- For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:  European Patent Office Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Frelon, Didier Telephone No. +49 30 25901-312 
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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:
 - a. (means)
 - ☐ on paper
 - ☐ in electronic form
 - b. (time)
 - ☐ in the international application as filed
 - ☐ together with the international application in electronic form
 - ☐ 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 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. 18

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. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☒ no international search report has been established for the whole application or for said claims Nos. 18

☐ 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).

☐ See Supplemental Box for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:
- ☒ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☐ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. 1-17, 19

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-17</u>
	No: Claims	<u>19</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-17, 19</u>
Industrial applicability (IA)	Yes: Claims	<u>1-17, 19</u>
	No: Claims	

2. Citations and explanations

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2011/051484

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re item IV.

1. The present set of claims comprises four independent claims: claims 1, 17, 18 and 19. Claims 2 to 15 are stressed dependent on claim 1. Claim 16 is a process for the direct preparation of compounds of formula (I) of claim 1 from compounds (1-f) and (1-g). Claims 1 to 16 can be therefore grouped together as related to the same invention since the subject-matter of each of these claims is linked to a same concept seen in the common structural parts of the final products.

Claim 17 is related to the preparation of intermediates (2-g) and (2-h) by enantiomeric reduction. It is apparent that compounds (2-g) and (2-h) represent particular cases of the intermediates (1-f) of the claim 16 process which are directly used in the preparation of the compounds of the invention. Claim 17 shares consequently the concept of claim 1 (at least by an essential structural part) and can be considered to be unitary with the group of claims 1 to 16.

Claim 18 is directed to the preparation of the compound (5-f). This compound is not directly involved in the preparation of the final compounds. As shown in scheme 5, page 21, the path to arrive to the compounds of the invention starting from compounds (5-f) needs further steps. Such a link is not directly apparent from the wording of the claims and the common structure between compound (5-f) and the final compound (*i.e.*, the 4'-chloro-biphenyl-2-yl-piperidine portion) does not represent a novel characteristic. In other words, a (shared) *special technical feature* as required for the unity of invention according to the PCT (Art. 3(4)(iii); Rule 13.2) is therefore absent and claim 18 should be considered as another invention. The unity could be restored by indicating clearly the synthetic link (*e.g.*, the connecting synthetic steps) which leads to the final compounds.

Claim 19 is directed to the preparation of compounds of formula M. The same remarks as for claim 18 apply to this claim.

It results that at least three inventions can be identified as following:

- **invention A** according to claims 1 to 17 characterized by compounds of formula (I),
- **invention B** according to claims 18 characterized by compound of formula (5-f),
- **invention C** according to claims 19 characterized by compounds of formula M.

2. The first novel invention A was the object of a first version of the WOISA. After receipt of the invitation to pay additional fees, the applicant paid and asked a further opinion on invention C as designated above.

Re item V.

Invention A

A1. Cited documents

- D1 WO 2005/049594
- D2 WO 2007/040650
- D3 WO 2009/036035
- D4 BRUNCKO, MILAN ET AL: JOURNAL OF MEDICINAL CHEMISTRY, vol. 50, no. 4, 2007, pages 641-662

A2. Novelty

The present invention differs essentially from D1 by the substituent R^1 which can represent CN, OR^{1a} or $N(R^{1a})_2$. The structurally closest compounds of D1 appear to be the two compounds listed on page 116, lines 13-20, wherein a hydrogen is in place of the corresponding rest R^1 in the presently claimed compounds.

Similarly the present invention differs essentially from D2 by the substituent R^1 which is CN, OR^{1a} or $N(R^{1a})_2$. There is no substituent in D2 corresponding to R^1 . A second minor difference is the isosteric replacement of N by C forming the present piperidine in place of the prior art piperazine.

The essential difference with the prior art D3 lies in the link $>W-W_1-CH<$. As W_1 can be absent, the group corresponding to the present R^1 can be seen in R_{28} which represents hydrogen, oxo, aryl or heteroaryl (both evt. substituted) whereas R_{27} can be a substituted aryl which, in the structurally close examples 8 to 10, is illustrated by a 4-chloro-biphenyl group like in the presently claimed compounds.

D4 discloses particularly the compound ABT-737 known for the same activities as the presently claimed compounds. The same essential differences are observed as with D2 whereas, in the compounds of D2, the rest corresponding to R^2 of the invention is a trifluoromethyl sulfonyl, it is a nitro group in D4.

The compounds of the present application are consequently considered to be novel.

A3. Inventive step - non unity *a posteriori*

A3.1 The problem underlying the present invention A is to provide N-acyl sulfonamide derivatives of formula (I) which are useful as anti-proliferative agents and/or apoptosis promoters in the treatment of cancer.

A3.2 All the compounds of the above cited prior art have the same therapeutical purposes. The closest prior art appears to be seen in the compounds of D1 which, at the corresponding position of the present rest R^1 which can be CN, OR^{1a} or $N(R^{1a})_2$, carry a hydrogen or the rest R^{31} which can represent F, Cl, Br or an alkyl group.

The prior art teaches to the skilled person the possibility of a relatively large variability of the substitution pattern on the position of R^1/R^{31} . It does not seem that a particular common concept covers the meanings regrouped in the R^1 definition such that it would appear clearly distinct from another concept covering the meanings regrouped in the R^{31} definition. Consequently the skilled person expects to maintain the activity in the presently claimed compounds. Furthermore, when considering additionally the IC_{50} values in the Bcl- X_L assays provided in both documents, no significant difference is straightforwardly in favor of the presently claimed compounds.

In order to support the presence of an inventive step under the PCT, an unexpected effect originated from the differentiating group R^1 is still to be evidenced. Where each meaning comprised by R^1 is not obviously equivalent, it should be shown that they are responsible of the same surprising effect, otherwise the requirement of unity is broken because structurally different elements would thus lead to different effects.

A3.3 The Applicant's attention is drawn to the fact that the protection which is sought should comply with a reasonable breadth for the claimed scope covering only compounds, their variants and equivalents which solve the problem underlying the invention, what is a prerequisite for the pertinence of the acknowledgement of an inventive step over the whole claimed scope (Art. 33(3) PCT).

Definitions covering a plurality of very different meanings and derivatives thereof may extend unrealistically the scope of the claims, *i.e.*, *far beyond* what has actually been investigated by the inventor(s) and/or verified in the worked examples on file and *far beyond* what the skilled person, also taking into account physico-chemical and biological considerations, can regard as the legitimate object of the invention. The *effect* (that is, *the contribution over the prior art*) of unspecific and not illustrated meanings may *not be foreseen* having regard to the problem underlying the present application.

As a rule, protection conferred by a patent should be commensurate with the range of compounds for which the effect has been properly demonstrated, including obvious variants thereof. The extent of a "reasonable generalisation" depends therefore on the extent of the illustration which should render credible that substantially all alternatives claimed are solutions to the problem. In principle, the application should not be regarded as satisfying the requirements for patentability unless the description gives a number of examples or describes alternative embodiments or variations extending over the whole area protected by the claims.

The given examples represent a **relatively narrow** illustration of the claimed scope. It should be credible that all potentially comprised embodiments, specially far remote ones embraced by the claimed scope, exhibit the same pharmacological effect(s) and as such solve the problem underlying the present application. In view of the regularly occurring structural elements and other limited variations of this illustration, a skilled person can consider that such constant features combine to form a characteristic which is necessary and **essential** to the invention and, consequently, should be included in the main claim.

A reasonable generalisation of tested examples appear to be acceptable if it is not in contradiction to the basic principles of pharmacology and drug design (cf. SAR studies) that a biological activity can *prima facie* be expected to be retained in compounds with a same chemical core when making small structural modifications or replacing groups by known equivalent or (bio)isosteric groups. Reasonable predictions based on the relations between chemical structures and biological activities are in principle possible, but **there is a limit** beyond which no such prediction can be validly done. It is therefore necessary to fix limits to the claimed scope.

It should be clear that a generalization is considered to be reasonable when it remains in a frame for which the benefit of the doubt is technically admissible. A proper balance must be found between, on the one hand, the *actual technical contribution* to the state of the art by the invention disclosed in the application, if any, and, on the other hand, the *manner of claiming* so that, if patent protection is granted, its scope is fair and adequate. The Applicant is entitled to claim all **obvious** modifications,

equivalents and/or (bio)isosteric values of what was concretely described and for which it can be reasonably predicted that all the variations covered have the properties or uses ascribed to them in the description, *i.e.*, all such forms would be suitable for solving the problem underlying the application and therefore likely to represent the very invention.

Invention C

C1. Cited documents

Reference is made to the following documents:

- D5 WO 2010/065865
- D6 WO 2008/061208
- D7 WENDT, MICHAEL D. ET AL: JOURNAL OF MEDICINAL CHEMISTRY,
 vol. 49, no. 3, 2006, pages 1165-1181
- D8 US 2002/086887
- D9 WO 02/24636

C2. Novelty

It is noticed that the omission of the definition of the rest R². This is necessary as part of in this independent claim. For the consistency of the procedure, the meanings of R² has been taken from claim 1.

D5 discloses a close process in examples 81A to 81D: the difference lies essentially in the protection group on the α -amino group. It is a Fmoc-rest in D5 whereas it is a Boc in the present application. The present invention further adds a first step starting from Asp.

D6 discloses a close process in examples 2 and 3, steps a to b and f to j, example 5, step 1+b to c and principally example 13, steps A to F. The essential difference is in the nitrogen protection by Fmoc. Additionally the present invention adds a first step starting from Asp. The present invention further adds a first step starting from Asp.

D7 describes the same process as above in scheme 6. The possibility of the N protection by Boc in the formation of the phenyl-sulfanyl substitution for the hydroxy group is indicated in scheme 7.

D8 and D9 disclose a close process in examples 122A to 122E similar to the precedent ones of D6 and D7. The first step starting from Asp is not explicitly described.

The novelty can therefore be formally acknowledged.

C3. Inventive step

C3.1 The problem underlying this sub-invention is to provide a process starting from Asp to produce the sulfonamide for formula (M).

C3.2 It is noted that R^2 is undefined and the various steps from J to M are also designated by their global concepts without further specification as to their *modus operandi*: conversion, reduction, substitution, deprotection and aromatic substitution. This means that any convenient analogous method can apply.

The teaching of the cited prior art reproduces the same step sequencing (except the first step J to K). Concerning this additional first step, it appears to merely consist of the protection of the α -amino group of Asp and the protection by alkyl-esterification of the β -carboxyl group. These protection steps are routine processes for skilled people in synthesis involving α -amino-acids as starting products.

The prior art teaching leads consequently unambiguously the skilled person to the present process for the preparation of compounds (M).

Re Item VIII.

1. Since examples are, by definition, illustrative of the invention, they normally should not serve any limiting purpose. It is the claims, when appropriately drafted, which define the scope, not the examples. If the invention is clearly defined and appropriately illustrated, it is superfluous to express precautionary measures on the limits of the scope as it finally prevents a proper definition of the invention and opens the way to speculations about the very inventive subject-matter.

Expressions and/or sentences which refer to an extent of protection beyond the actual invention like "the compounds of the invention (...) are further illustrated by all classes, subclasses and species of each of the compounds disclosed herein" appear to be essentially speculative. The insertion of such broadening expressions and/or sentences is therefore also objectionable because it would suggest that the subject-matter is not properly covered by the claimed scope for which a protection is sought. Any expression which can be interpreted as an unjustified extension of the claimed scope should be objected. The specification should be clear and sufficient by itself and the claims should find a clear support in the description. Unspecific expressions cannot serve as a support for the invention and are misleading since they cannot participate of a proper definition of the very invention and, particularly, do not help a skilled person looking for reproducing it.

Consequently any element against clarity has to be deleted.

2. References to methods of treatment or prevention (or diagnostic methods) as further objects of the invention must be avoided since they are considered by the ISA to be covered by the provisions of Rule 67.1(iv) PCT.
3. Some designations may appear confusing where compounds (1-g), page 12, seem to be the same as compounds (1-i), page 17 or where compounds (4-e), page 17, seem to be the same as compounds M, page 19.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 104020-1P WO	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/GB2011/051484	International filing date (<i>day/month/year</i>) 05/08/2011	(Earliest) Priority Date (<i>day/month/year</i>) 06/08/2010
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 7 sheets.

☒ 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:

- ☒ 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**,

- ☐ the text is approved as submitted by the applicant
- ☒ the text has been established by this Authority to read as follows:

N-ACYLSULFONAMIDE APOPTOSIS PROMOTERS

5. With regard to the **abstract**,

- ☒ 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. ☐ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2011/051484

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

1-17, 19
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2011/051484

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D211/22 A61K31/445 A61P35/00 A61P35/02
ADD.

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, EMBASE, BIOSIS, BEILSTEIN 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.
Y	WO 2005/049594 A1 (ABBOTT LAB [US]; BRUNCKO MILAN [US]; DING HONG [US]; ELMORE STEVEN [US] 2 June 2005 (2005-06-02) page 116, lines 13-20; claims -----	1-17
Y	WO 2007/040650 A2 (ABBOTT LAB [US]; BRUNCKO MILAN [US]; DING HONG [US]; ELMORE STEVEN W [] 12 April 2007 (2007-04-12) abstract; claims -----	1-17
Y	WO 2009/036035 A1 (CURIS INC [US]; ZHAI HAIXIAO [US]; CAI XIONG [US]) 19 March 2009 (2009-03-19) abstract; claims; examples 8-10 ----- -/-	1-17



Further documents are listed in the continuation of Box C.



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 docu-
ments, 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

5 December 2011

Date of mailing of the international search report

16/12/2011

Name and mailing address of the ISA/

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Frelon, Didier

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2011/051484

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BRUNCKO, MILAN ET AL: "Studies Leading to Potent, Dual Inhibitors of Bcl-2 and Bcl-xL", JOURNAL OF MEDICINAL CHEMISTRY, vol. 50, no. 4, 2007, pages 641-662, XP002661692, Figure 2, compound ABT-737 -----	1-17
X	WO 2010/065865 A2 (ABBOTT LAB [US]; BRUNCKO MILAN [US]; DING HONG [US]; DOHERTY GEORGE A) 10 June 2010 (2010-06-10) examples 81A-81D -----	19
X	WO 2008/061208 A2 (GENENTECH INC [US]; INST MEDICAL W & E HALL [AU]; BAELL JONATHAN BAYLD) 22 May 2008 (2008-05-22) examples 2 and 3, steps a-b, f-j; example 5, steps a-c; example 13, steps A-H -----	19
X	WENDT, MICHAEL D. ET AL: "Discovery and Structure-Activity Relationship of Antagonists of B-Cell Lymphoma 2 Family Proteins with Chemopotential Activity in Vitro and in Vivo", JOURNAL OF MEDICINAL CHEMISTRY, vol. 49, no. 3, 2006, pages 1165-1181, XP002665083, scheme 6, step d; scheme 87, step a -----	19
X	US 2002/086887 A1 (AUGERI DAVID J [US] ET AL) 4 July 2002 (2002-07-04) examples 122A-122E -----	19
X	WO 02/24636 A2 (ABBOTT LAB [US]) 28 March 2002 (2002-03-28) examples 112A-122E -----	19

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2011/051484

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005049594	A1	02-06-2005	AU 2004290666 A1 02-06-2005 BR PI0416602 A 30-01-2007 CA 2546101 A1 02-06-2005 CN 1906183 A 31-01-2007 EP 1685119 A1 02-08-2006 EP 2308812 A2 13-04-2011 JP 2007511530 A 10-05-2007 KR 20060114704 A 07-11-2006 NZ 547160 A 27-11-2009 US 2005159427 A1 21-07-2005 US 2010022773 A1 28-01-2010 WO 2005049593 A2 02-06-2005 WO 2005049594 A1 02-06-2005
WO 2007040650	A2	12-04-2007	AU 2006297853 A1 12-04-2007 AU 2010233055 A1 04-11-2010 BR PI0610108 A2 25-05-2010 CA 2606147 A1 12-04-2007 CN 101175738 A 07-05-2008 CN 101928264 A 29-12-2010 EP 1888550 A2 20-02-2008 JP 2008540577 A 20-11-2008 KR 20080011695 A 05-02-2008 NZ 561609 A 26-03-2010 NZ 583758 A 25-02-2011 US 2007027135 A1 01-02-2007 US 2008287419 A1 20-11-2008 US 2010249133 A1 30-09-2010 WO 2007040650 A2 12-04-2007
WO 2009036035	A1	19-03-2009	NONE
WO 2010065865	A2	10-06-2010	AR 074510 A1 19-01-2011 AU 2009322219 A1 10-06-2010 CA 2744711 A1 10-06-2010 CR 20110351 A 27-10-2011 DO P2011000152 A 31-10-2011 EP 2376480 A2 19-10-2011 KR 20110103406 A 20-09-2011 TW 201029992 A 16-08-2010 UY 32305 A 30-07-2010 UY 32680 A 28-02-2011 WO 2010065865 A2 10-06-2010
WO 2008061208	A2	22-05-2008	AU 2007319209 A1 22-05-2008 CA 2666837 A1 22-05-2008 CN 101535280 A 16-09-2009 EP 2094672 A2 02-09-2009 JP 2010510237 A 02-04-2010 US 2010056517 A1 04-03-2010 WO 2008061208 A2 22-05-2008
US 2002086887	A1	04-07-2002	US 2002086887 A1 04-07-2002 US 2004192681 A1 30-09-2004 US 2009137585 A1 28-05-2009
WO 0224636	A2	28-03-2002	AR 031130 A1 10-09-2003 AT 317382 T 15-02-2006

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2011/051484

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		AU 9115101 A	02-04-2002
		BR 0110101 A	07-06-2005
		CA 2423103 A1	28-03-2002
		DE 60117157 T2	21-09-2006
		DK 1318978 T3	06-06-2006
		EP 1318978 A2	18-06-2003
		ES 2258102 T3	16-08-2006
		HK 1058031 A1	12-01-2007
		JP 2004529852 A	30-09-2004
		MX PA03002477 A	10-09-2004
		PT 1318978 E	30-06-2006
		UY 26942 A1	26-04-2002
		WO 0224636 A2	28-03-2002

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-17

compounds of formula (I)

2. claim: 18

compound of formula (5-f)

3. claim: 19

compounds of formula M
