SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-132448- -00000-0000

Fecha: 2011-10-06 17:03:39 Dep 2020 DIR.NUEVASCR
Tra. 11 PATENTE!YII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 394

Industria y Comercio

SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIRECCIÓN DE NUEVAS CREACIONES

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: ANÁLOGOS DE ISOXAZOL-3(2H)-ONA COMO AGENTES TERAPÉUTICOS.

SOLICITANTE: ASTRAZENECA AB

DIRECCIÓN: S-SE-151 85 Södertälje, Suecia

APODERADO: CARLOS R. OLARTE

BOGOTÁ 06 de Octubre de 2011

P2011/000170

OLARTEMOURE

OLARTE MOURE & AS

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-132448- -00000-0000
Fecha: 2011-10-06 17:03:39 Dep: 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 394

PETITORIO - FORMULARIO UNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2011/000170**

SOLICITUD DE:

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

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**

Nombre: ASTRAZENECA AB
Dirección: S-151- 85 Sodertalje
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. [x] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual
Número 79.782.747
TP 74.295

INVENTOR (ES) (72)

Nombre: VER PAGINA ADJUNTA.
Dirección: VER PAGINA ADJUNTA.
Nacionalidad o Domicilio: VER PAGINA ADJUNTA.

(5) **PCT (86)**

Solicitud Internacional No. PCT/SE2010/050375 Fecha Abril 06, 2010

Publicación Internacional No. WO 2010/117323 Fecha Octubre 14, 2010

(6) **Título (54)** **ANÁLOGOS DE ISOXAZOL-3(2H)-ONA COMO AGENTES TERAPÉUTICOS.**

Clasificación Internacional (51) C07D 413/04; A61K 31/4523; A61P 7/04.

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

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Abril 07, 2009	61/167,224
US	Abril 23, 2009	61/171,956

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

ANEXOS

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Adjunto copia simple ver expediente No. 08-129.814.
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

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

LISTA DE INVENTORES

PCT/SE2010/050375

Jonas BOSTRÖM

AstraZeneca R&D Mölndal,

S-431 83, Mölndal.

Suecia

Nacionalidad: Sueco

Leifeng CHENG

AstraZeneca R&D China,

Building 7, No. 898 Halei Road

Zhangjiang Hi-Tech Park

Shanghai 201203

China

Nacionalidad: Sueco

Tomas FEX

AstraZeneca R&D Mölndal,

S-431 83, Mölndal.

Suecia

Nacionalidad: Sueco

Michael KARLE

AstraZeneca R&D Mölndal,

S-431 83, Mölndal.

Suecia

Nacionalidad: Alemana

Daniel PETTERSEN

AstraZeneca R&D Mölndal,

S-431 83, Mölndal.

Suecia

Nacionalidad: Sueco

Peter SCHELL

AstraZeneca R&D Mölndal,

S-431 83, Mölndal.

Suecia

Nacionalidad: Alemana

5

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 0093307

Bogotá D.C., Septiembre 22 de 2011 - 14:40:32

RECIBIDO DE : OLARTE MOURE & ASOCIADOS NI 830.122.870

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	408398605	21/09/2011	4.447.000.00

*** Conceptos Pagados ***

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

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

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-132448- -00000-0000
Fecha: 2011-10-06 17:03:39 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 394

X

Traducción oficial de un documento cuyo original está en inglés

No. 11426

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

En Estocolmo, este día 14 de Agosto de 2007.

(Firmado)

Hay un sello del Ministerio de Relaciones Exteriores de Suecia.

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

Firma de Agneta S...

Y sello de ...

Firma: Mohamed Hussein.

Fecha: 20 de Agosto de 2007.

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

Certificación Notarial

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

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

Ex oficio:

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

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

Apostilla adjunta:

APOSTILLE
(Convention du La Haye du 5 octobre 1961)

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

Certificación:

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

Fecha: 13 de Noviembre de 2007.

Traductor: Jorge Enrique Sierra Reyes.

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

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

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

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

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

7

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. **Country : Sweden**

   This public document

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

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

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

   Notary Public in Stockholm

Certified

5. **at** Stockholm

6. **the** 26.10.2007

7. **by** Björn Sandin

   Notary Public

8. **No** 4071

9. **Seal/stamp:**

NOTARIUS PUBLICUS I STOCKHOLM
BJÖRN SANDIN

10. **Signature:**

OLARTERAISBECK

OLARTE RAISBECK & FRIERI LTDA.

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

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

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

Power of Attorney

The undersigned, AstraZeneca AB

domiciled in Vastra Malarehamnen 9 S-151 85 Sodertalje, Sweden

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

Poder

El suscrito, AstraZeneca AB

domiciliado en Vastra Malarehamnen 9 S-151 85 Sodertalje, Sweden

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

Signature/Firma: Anders Burén
Authorized Signatory

Date/Fecha: 24 OCTOBER 2007

City,Country/Ciudad,País: SODERTALJE

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

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:- Crowns

Stockholm 2007-10-26
Ex officio:

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

Anders Burén
Authorised Signatory

OLARTERAISBECK
OLARTE RAISBECK & FRIERI LTDA.

MODEL OF NOTARIAL CERTIFICATION

Notarial Certification

On this date,

The undersigned Notary Public certifies:

1. That

of legal age and domiciled in

signed the foregoing document.

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

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

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

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

1. CERTIFICATE OF INCORPORATION OF ASTRAZENECA AB

2. AUTHORISATION IN FAVOUR OF SIGNATORY

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que

mayor de edad y domiciliado

suscribió el documento que antecede.

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

de

4. Que

con sede principal ubicada en

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

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

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

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

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

Traducción oficial de un documento cuyo original está en inglés

BOLAGSVERKET

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

Certificado de Existencia

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

AstraZeneca AB

Registro No. 556011-7482

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

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

(Firmado) Anna-Karin Östin.

Hay un sello de Bolagsverket

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

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

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

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

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

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

Certificación Notarial

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

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

Ex oficio:

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

Apostilla adjunta:

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

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:**



Bolagsverket

851 81 Sundsvall
Besökare: Badhusparken
Tel: 060-18 40 00 • Fax: 060-12 98 40
bolagsverket@bolagsverket.se • bolagsverket.se

Certificate of Good Standing

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

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

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

In testimony hereof, I have hereunto set my hand and the official seal of Bolagsverket at Sundsvall, this 8th day of August in the year of two thousand and seven.

Anna-Karin Östin

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

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

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

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:

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

...1142b
The Ministry for Foreign Affairs in Stockholm, Sweden certifies that
Mr./Ms. Anna-Karin Östh

Swedish Companies Registration Office, Sundsvall

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

For Stockholm this 14th day of August
Kr 00/- PAID

Agneta Ödelund

SIGNATURE OF Agneta Ödelund
SEAL STAMP OF Sc. MFA
SIGNATURE Mohammed Hussein
DATE 20-08-07

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

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

CORRECTED VERSION

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 October 2010 (14.10.2010)

PCT

(10) International Publication Number
WO 2010/117323 A8

(51) International Patent Classification:
C07D 413/04 (2006.01) *A61P 7/04* (2006.01)
A61K 31/4523 (2006.01)

(21) International Application Number:
PCT/SE2010/050375

(22) International Filing Date:
6 April 2010 (06.04.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

61/167,224	7 April 2009 (07.04.2009)	US
61/171,956	23 April 2009 (23.04.2009)	US

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

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BOSTRÖM, Jonas** [SE/SE]; AstraZeneca R&D Mölndal, S-431 83 Mölndal (SE). **CHENG, Leifeng** [GB/SE]; AstraZeneca R&D Mölndal, S-431 83 Mölndal (SE). **FEX, Tomas** [SE/SE]; AstraZeneca R&D Mölndal, S-431 83 Mölndal (SE). **KARLE, Michael** [DE/SE]; AstraZeneca R&D Mölndal, S-431 83 Mölndal (SE). **PETTERSEN, Daniel** [SE/SE]; AstraZeneca R&D Mölndal, S-431 83 Mölndal (SE). **SCHELL, Peter** [DE/SE]; AstraZeneca R&D Mölndal, S-431 83 Mölndal (SE).

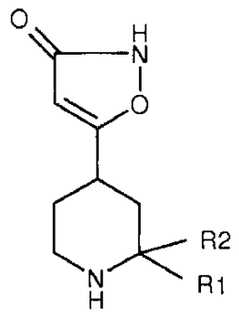
(74) Agent: **ASTRAZENECA INTELLECTUAL PROPERTY**; AstraZeneca AB, S-151 85 Södertälje (SE).

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

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[Continued on next page]

(54) Title: ISOXAZOL-3(2H)-ONE ANALOGS AS THERAPEUTIC AGENTS



(I)

(57) Abstract: Formula I or a pharmaceutically suitable salt thereof, wherein, R1 and R2 independently are hydrogen, deuterium, aryl, hetero aryl, C1-C8 alkyl, optionally being substituted with one or more substituents independently being R3, R3 is an aryl, hetero aryl, fluorine(s), a C1-C6 alkyl containing one or more fluorine, a C1-C6 alkyl containing one or more deuterium, a C1-C6 alkyl containing hydroxy, the aryl and heteroaryl optionally being substituted with one or more halogen, a fluorinated alkoxy, a fluorinated alkyl, a sulfonyl, one or more deuterium, a C1-6 alkyl, a C1-6 alkoxy, a nitrile, or R3 is a C1-6 alkyl optionally substituted with one or more of the following groups: COOR4, OCOR4, CONR5R6, NR5COR6, OR4; wherein, R4 is a C1-10 alkyl optionally substituted with one or more fluorine, deuterium, alkoxy, arylcarboxylate, alkyl carboxylate; R5 and R6 are independently selected from hydrogen, alkyl or they may together form a 4-8 membered carbon ring; or R1 and R2 form a 3-10 membered carbon ring optionally comprising O or N and optionally substituted with a C1-10 alkyl or aryl, hetero aryl optionally substituted with R3.

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

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BOSTRÖM, Jonas** [SE/SE]; AstraZeneca R&D Mölndal, S-431 83 Mölndal (SE). **CHENG, Leifeng** [GB/SE]; AstraZeneca R&D Mölndal, S-431 83 Mölndal (SE). **FEX, Tomas** [SE/SE]; AstraZeneca R&D Mölndal, S-431 83 Mölndal (SE). **KARLE, Michael** [DE/SE]; AstraZeneca R&D Mölndal, S-431 83 Mölndal (SE). **PETTERSEN, Daniel** [SE/SE]; AstraZeneca R&D Mölndal, S-431 83 Mölndal (SE). **SCHELL, Peter** [DE/SE]; AstraZeneca R&D Mölndal, S-431 83 Mölndal (SE).

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

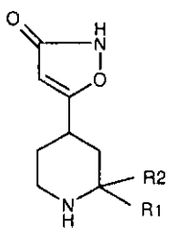
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(54) Title: METHOD AND APPARATUS FOR PRODUCING HEAT ENERGY AND CARBON DIOXIDE



(I)

(57) Abstract: Formula I or a pharmaceutically suitable salt thereof, wherein, R1 and R2 independently are hydrogen, deuterium, aryl, hetero aryl, C1-C8 alkyl, optionally being substituted with one or more substituents independently being R3, R3 is an aryl, hetero aryl, fluorine(s), a C1-C6 alkyl containing one or more fluorine, a C1-C6 alkyl containing one or more deuterium, a C1-C6 alkyl containing hydroxy, the aryl and heteroaryl optionally being substituted with one or more halogen, a fluorinated alkoxy, a fluorinated alkyl, a sulfonyl, one or more deuterium, a C1-6 alkyl, a C1-6 alkoxy, a nitrile, or R3 is a C1-6 alkyl optionally substituted with one or more of the following groups: COOR4, OCOR4, CONR5R6, NR5COR6, OR4; wherein, R4 is a C1-10 alkyl optionally substituted with one or more fluorine, deuterium, alkoxy, arylcarboxylate, alkyl carboxylate; R5 and R6 are independently selected from hydrogen, alkyl or they may together form a 4-8 membered carbon ring; or R1 and R2 form a 3-10 membered carbon ring optionally comprising O or N and optionally substituted with a C1-10 alkyl or aryl, hetero aryl optionally substituted with R3.

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Isoxazol-3(2H)-one analogs as therapeutic agents

Field of invention

The present invention relates to compounds of formula I, to a pharmaceutical composition comprising them, and to their use in treating fibrinolysis related diseases or conditions, for example inherited bleeding disorders, stroke, menorrhagia and liver diseases and for the treatment of hereditary angioedema.

Background

Bleeding is a common clinical problem in trauma, surgery, bleeding disorders, stroke, menorrhagia and liver diseases. Treatment of bleeding includes agents in primary and secondary haemostasis as well as fibrinolysis inhibition.

The fibrinolytic system comprises an inactive zymogen, plasminogen (PLG), that can be activated to the active enzyme plasmin (PLN). PLN degrades insoluble fibrin into soluble fibrin fragments. The result of this activity is the dissolution of the fibrin clot. The activation of plasminogen to plasmin occurs on the clot surface after binding to fibrin. Mediators of the activation are urokinase plasminogen activator (u-PA) or tissue-type plasminogen activator (t-PA).

Activation of the fibrinolytic process can be used to treat thrombotic conditions. Conversely, inhibition of fibrinolysis can be, and is, used for treatment of bleeding conditions. There are several possible targets for the inhibition of fibrinolysis. Activation of plasminogen activator inhibitor 1 (PAI-1), inhibition of u-PA and/or t-PA activity, inhibition of PLN activity and activation of antiplasmin are examples. Specific inhibition of proteolytic sites in tPA, uPA and PLN is difficult. However, bleeding control via inhibition of plasmin(ogen) fibrin binding by lysine analogues has been proven in humans as a safe and effective mechanism of action.

Inhibition of fibrinolysis via a lysine mimetic is a validated concept for reducing blood-loss, without increased risk for thrombotic complications, for instance following surgery, in menorrhagia, haemophilia and von Willebrands disease.

Potential uses of the compounds are to block plasmin-induced proteolysis as a universal pathomechanism propagating cancer, and cardiovascular, inflammatory, and many other diseases.

Antifibrinolytics have also been successfully used to treat hereditary angioedema. In this disease the skin or mucosa around the mouth, throat and tongue rapidly swell up. Swelling can occur at other places like limbs or genitals. For reasons that are not well-understood antifibrinolytics can be used as a prophylaxis or acute treatment of hereditary angioedema.

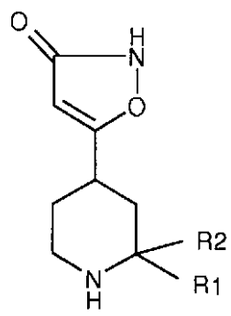
Tranexamic acid, currently the compound on the market to treat menorrhagia, requires very high and multiple doses and has gastrointestinal side effects. Its use has been described in "Tranexamic acid. A review of its use in surgery and other indications"; Dunn, C.J.; Goa K.L.; Drugs 1999, June 57(6): 1005-1032.

Object of the invention

An object of the invention is to provide for a pharmaceutical compound to prevent or treat excess bleeding, the treatment or prevention therapy having one or more improvements such as enhanced efficacy, selectivity, permeability, duration, less side effects and improved bio availability.

Description of the invention

The present invention provides for a compound of formula I:



I

or a pharmaceutically suitable salt thereof, wherein,

R1 and R2 independently are hydrogen, deuterium, aryl, hetero aryl, C1-C8 alkyl, optionally being substituted with one or more substituents independently being R3,

R3 is an aryl, hetero aryl, fluorine(s), a C1-C6 alkyl containing one or more fluorine, a C1-C6 alkyl containing one or more deuterium, a C1-C6 alkyl containing hydroxy, the aryl and heteroaryl optionally being substituted with one or more halogen, a fluorinated alkoxy, a fluorinated alkyl, a sulfonyl, one or more deuterium, a C1-6 alkyl, a C1-6 alkoxy, a nitrile,

or R3 is a C1-6 alkyl optionally substituted with one or more of the following groups: COOR4, OCOR4, CONR5R6, NR5COR6, OR4;

wherein, R4 is a C1-10 alkyl optionally substituted with one or more fluorine, deuterium, alkoxy, arylcarboxylate, alkyl carboxylate ;

R5 and R6 are independently selected from hydrogen, alkyl or they may together form a 4-8 membered carbon ring;

or R1 and R2 form a 3-10 membered carbon ring optionally comprising O or N and optionally substituted with a C1-10 alkyl or aryl, hetero aryl optionally substituted with R3.

According to an embodiment of the invention R1 and R2 can be independently hydrogen, deuterium, hetero aryl, C1-C8 alkyl, optionally being substituted with one or more substituents independently being R3,

R3 is an aryl, hetero aryl, fluorine(s), a C1-C6 alkyl containing one or more fluorine, a C1-C6 alkyl containing one or more deuterium, a C1-C6 alkyl containing hydroxy, the aryl and heteroaryl optionally being substituted with one or more halogen, a fluorinated alkoxy, a fluorinated alkyl, a sulfonyl, one or more deuterium, a C1-6 alkyl, a C1-6 alkoxy, a nitrile,

or R3 is a C1-6 alkyl optionally substituted with one or more of the following groups: COOR4, OCOR4, CONR5R6, NR5COR6, OR4;

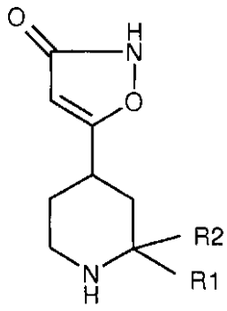
wherein, R4 is a C1-10 alkyl optionally substituted with one or more fluorine, deuterium, alkoxy, arylcarboxylate, alkyl carboxylate ;

R5 and R6 are independently selected from hydrogen, alkyl or they may together form a 4-8 membered carbon ring;

or R1 and R2 form a 3-10 membered carbon ring optionally comprising O or N and optionally substituted with a C1-10 alkyl or aryl, hetero aryl optionally substituted with R3.

The word alkyl includes straight alkyls, branched alkyls and 3-8 membered ring-formed alkyls. The word hetero aryl is a variant of a five or six membered ring system with one or more heteroatoms, i.e. not C, selected from N,O, or S.

According to another aspect of the invention there is provided for a compound of formula Ia:



Ia

or a pharmaceutically suitable salt thereof, wherein,

R1 and R2 independently are hydrogen, C1-C8 alkyl, optionally being substituted with R3,
R3 is an aryl, the aryl optionally being substituted with one or more fluorine, or OR4,
R4 is a C1-C6 alkyl.

According to another aspect of the invention it is provided for a compound selected from one or more of the following compounds:

5-((2S,4S)-2-Benzylpiperidin-4-yl)isoxazol-3(2H)-one;
5-((2R,4R)-2-Benzylpiperidin-4-yl)isoxazol-3(2H)-one;
5-((2R,4S)-2-Benzylpiperidin-4-yl)isoxazol-3(2H)-one;
5-((2S,4R)-2-Benzylpiperidin-4-yl)isoxazol-3(2H)-one;
5-((2R,4S)-2-Isobutylpiperidin-4-yl)isoxazol-3(2H)-one;
5-((2S,4R)-2-Isobutylpiperidin-4-yl)isoxazol-3(2H)-one;
5-((2S,4S)-2-Isobutylpiperidin-4-yl)isoxazol-3(2H)-one;
5-((2R,4S)-2-Phenethylpiperidin-4-yl)isoxazol-3(2H)-one;
5-((2S,4R)-2-Phenethylpiperidin-4-yl)isoxazol-3(2H)-one;
5-((2S,4S)-2-Phenethylpiperidin-4-yl)isoxazol-3(2H)-one;
5-((2S,4S)-2-(4-tert-Butylbenzyl)piperidin-4-yl)isoxazol-3(2H)-one;
5-((2R,4S)-2-(4-tert-Butylbenzyl)piperidin-4-yl)isoxazol-3(2H)-one;
5-((2S,4S)-2-Neopentylpiperidin-4-yl)isoxazol-3(2H)-one;
5-((2R,4S)-2-Neopentylpiperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-Methylpiperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-Methylpiperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4S)-2-Methylpiperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4S)-2-(2-Methyl-2-phenylpropyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(2-Methyl-2-phenylpropyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(Cyclohexylmethyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4R)-2-(Cyclohexylmethyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4S)-2-(Cyclohexylmethyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(3,4-Difluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(3,4-difluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(4-Fluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(4-fluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(4-Chlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(4-Chlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(4-chlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(3-(Trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(3-(Trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(3-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(4-(Trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(4-(Trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(3-tert-Butylphenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(4-tert-butylphenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(4-(Methylsulfonyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((Trans-2-(4-(methylsulfonyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(6-(Trifluoromethyl)pyridin-3-yl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(6-(trifluoromethyl)pyridin-3-yl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(5-tert-Butylthiophen-2-yl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(5-tert-Butylthiophen-2-yl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(2,4-Difluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(4-Chloro-2-fluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(4-chloro-2-fluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(2-Chloro-4-fluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(2-chloro-4-fluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(4-Chloro-3-fluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(4-chloro-3-fluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(2,4-Dichlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(2,4-Dichlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4S)-2-(2,4-Dichlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4R)-2-(2,4-Dichlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(3,5-Dichlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(3,5-Dichlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(3,5-dichlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(2-Fluoro-4-(trifluoromethoxy)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(2-fluoro-4-(trifluoromethoxy)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(3,4,5-Trifluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(3,4,5-Trifluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(3,4,5-trifluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(2,4,5-Trifluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4S)-2-(2,4,5-Trifluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(4-Chloro-3,5-difluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(4-chloro-3,5-difluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(3-Methyl-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(3-Methyl-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(3-methyl-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(3,5-Difluoro-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(3,5-difluoro-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(2-Methyl-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(2-Fluoro-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(2-fluoro-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(3-fluoro-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(3-Fluoro-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-Phenylpiperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4S)-2-Phenylpiperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-Cyclohexylpiperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4S)-2-Cyclohexylpiperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(2-Methyl-2H-tetrazol-5-yl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(2-methyl-2H-tetrazol-5-yl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(1-Methyl-1H-tetrazol-5-yl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(Cyclohexyloxymethyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(Cyclohexyloxymethyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(cyclohexyloxymethyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(Difluoromethyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(difluoromethyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4S)-2-((4,4-Difluorocyclohexyl)methyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4R)-2-((4,4-Difluorocyclohexyl)methyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-((4,4-difluorocyclohexyl)methyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4S)-2-(4-Fluorophenethyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4R)-2-(4-Fluorophenethyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(4-fluorophenethyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4S)-2-(3,3-Dimethylbutyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(3,3-Dimethylbutyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(4-Fluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4S)-2-(4-Fluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(3-Fluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4S)-2-(3-Fluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(2-Fluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4S)-2-(2-Fluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4R)-2-(2-Fluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(4-(Trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4S)-2-(4-(Trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4R)-2-(4-(Trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(3-(Trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(3-(Trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(3-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(2-(Trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(2-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(2-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(4-(Trifluoromethoxy)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(4-Chlorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(4-chlorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(4-(Methylsulfonyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(4-(Methylsulfonyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(4-(methylsulfonyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(3,4-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(3,4-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4S)-2-(3,4-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4R)-2-(3,4-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(2,5-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(2,5-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(2,5-difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(2,6-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(2,6-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(2,6-difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(3,5-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(3,5-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4S)-2-(3,5-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4R)-2-(3,5-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(2,4-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(2,4-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(2,4-difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(3-Fluoro-5-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(3-Fluoro-5-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(3-fluoro-5-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(3-Fluoro-4-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(3-Fluoro-4-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(3-fluoro-4-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(3,4,5-Trifluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(3,4,5-Trifluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(3,4,5-trifluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(3,5-Di-tert-butylbenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(3,5-Di-tert-butylbenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(3,5-di-tert-butylbenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-Benzyl-2,3,4,5,6-d_5-piperidin-4-yl)isoxazol-3(2H)-one;

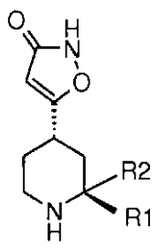
5-((2S,4R)-2-Benzyl-2,3,4,5,6-d_5-piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-benzyl-2,3,4,5,6-d_5-piperidin-4-yl)isoxazol-3(2H)-one.

The compounds of formula I may exist in stereoisomeric and/or tautomeric forms. It is to be understood that all enantiomers, diastereomers, racemates, tautomers and mixtures thereof are included within the scope of the invention.

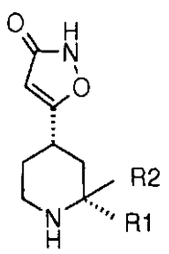
Different isomers may have different biological activity. It may be the case that different compounds of the general formula I may show the highest biological activity with different configuration. For instance for one compound the (2R,4S) configuration may have the highest biological activity, but for another compound the (2S,4S) may have the highest activity.

According to one aspect of the invention it is provided for a compound of formula II with the following configuration:



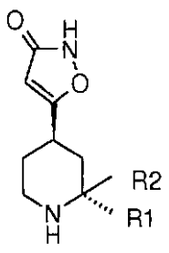
II

According to one aspect of the invention it is provided for a compound of formula III with the following configuration:



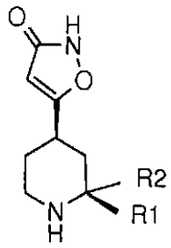
III

According to one aspect of the invention it is provided for a compound of formula IV with the following configuration:



IV

According to one aspect of the invention it is provided for a compound of formula V with the following configuration:



V

According to another aspect of the invention it is provided for a pharmaceutical composition comprising at least one compound and a pharmaceutically acceptable carrier or diluent.

According to another aspect of the invention it is provided for a method for treatment or prophylaxis of a disease or condition, such as heavy bleeding, inherited or acquired bleeding disorders, stroke, menorrhagia and liver diseases, in which modulation of fibrinolysis is beneficial, and for the treatment of hereditary angioedema, comprising administering to a warm-blooded animal in need of such treatment a therapeutically effective amount of at least one compound of formula I. Other areas of use for the compound according to formula I would be in wound healing, reduce blood loss in connection with surgery including dental surgery and for treating patients who are treated with anti-coagulation, for instance in preparation for surgery. The compound may also be used to reduce the blood transfusion needed in different situations. The compound may additionally be used in prophylactic treatment of von Willebrand's disease, haemophilia or in the case of anti-coagulating patients.

According to another aspect of the invention it is provided for a method wherein said disease or condition is selected from inherited bleeding disorders, stroke, menorrhagia and liver diseases.

According to another aspect of the invention it is provided for the treatment or prophylaxis of a disease or condition in which modulation of fibrinolysis is beneficial.

According to another aspect of the invention it is provided for wherein said disease or condition is selected from inherited bleeding disorders, stroke, menorrhagia and liver diseases.

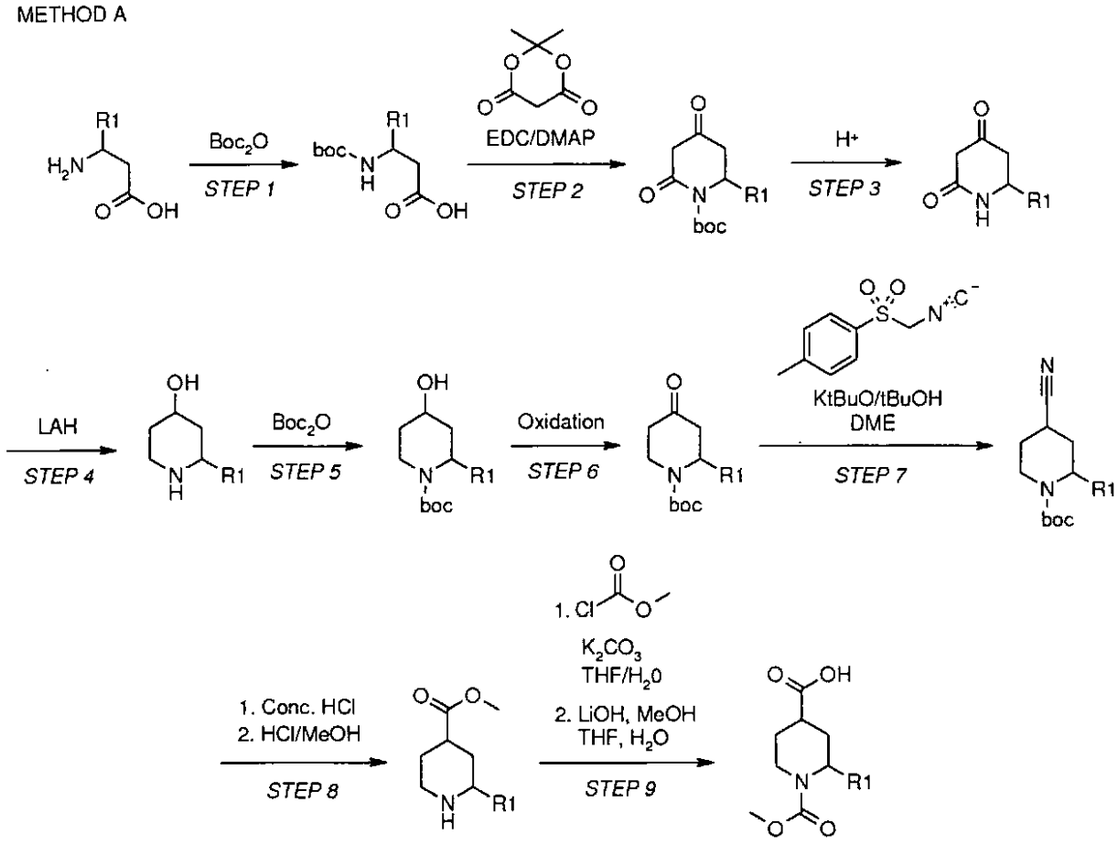
According to another aspect of the invention it is provided for the use of a compound according to the invention in the manufacture of a medicament for the treatment or prophylaxis of a disease or condition in which modulation of fibrinolysis is beneficial.

According to another aspect of the invention it is provided for treatment or prophylaxis wherein said disease is selected from inherited bleeding disorders, stroke, menorrhagia and liver diseases.

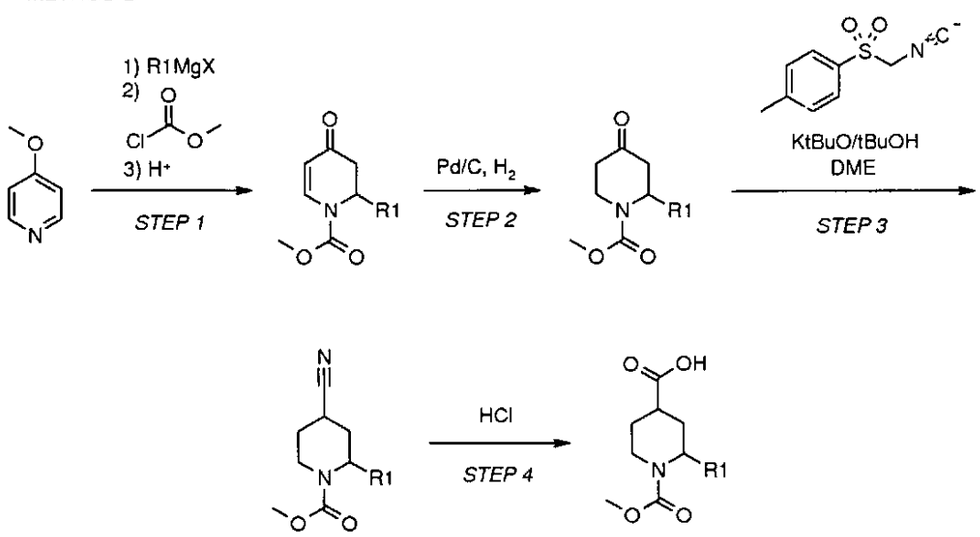
Compounds of formula I-V may be prepared by the following route:

Scheme A. Preparation of intermediates

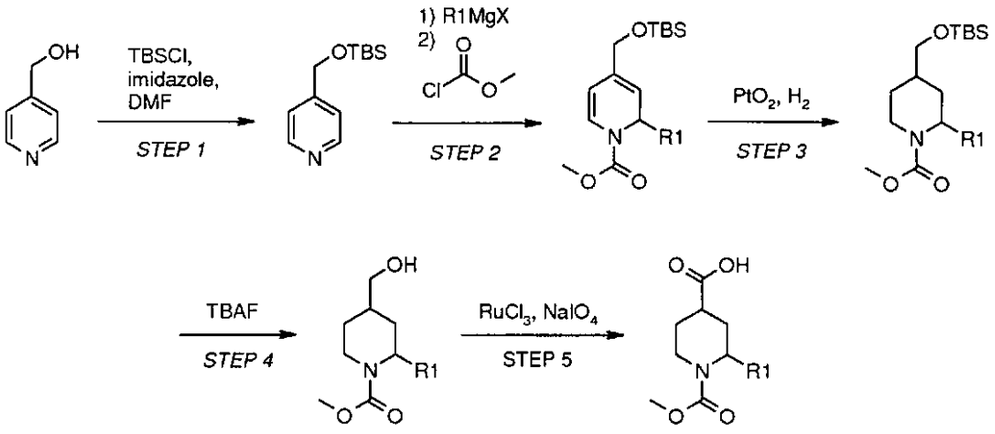
METHOD A



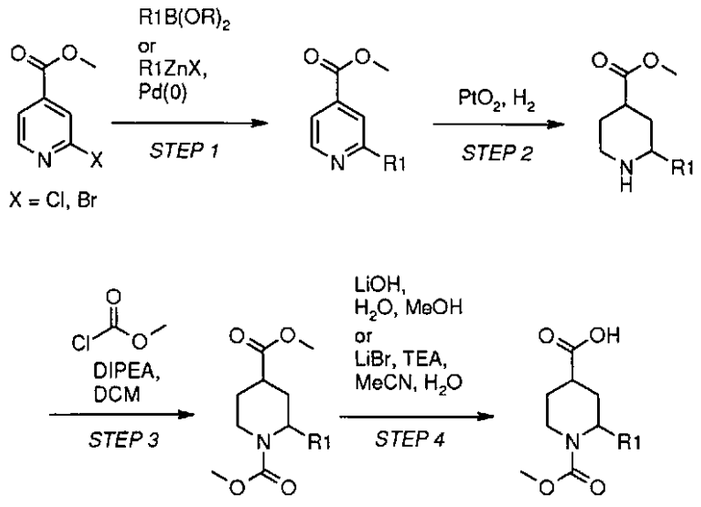
METHOD B



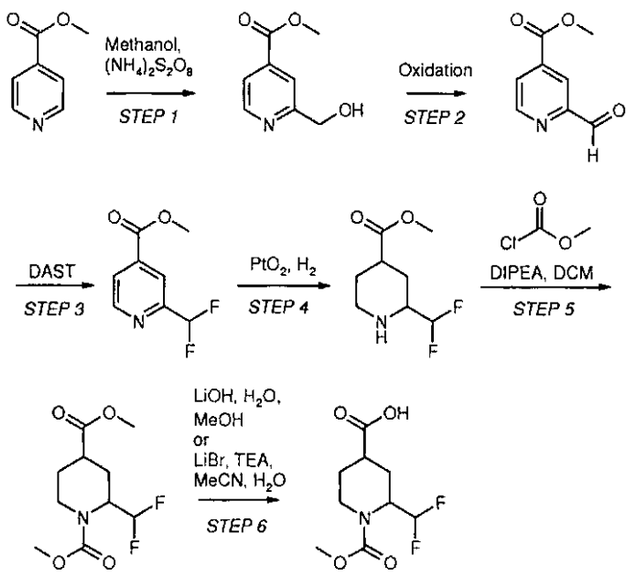
METHOD C



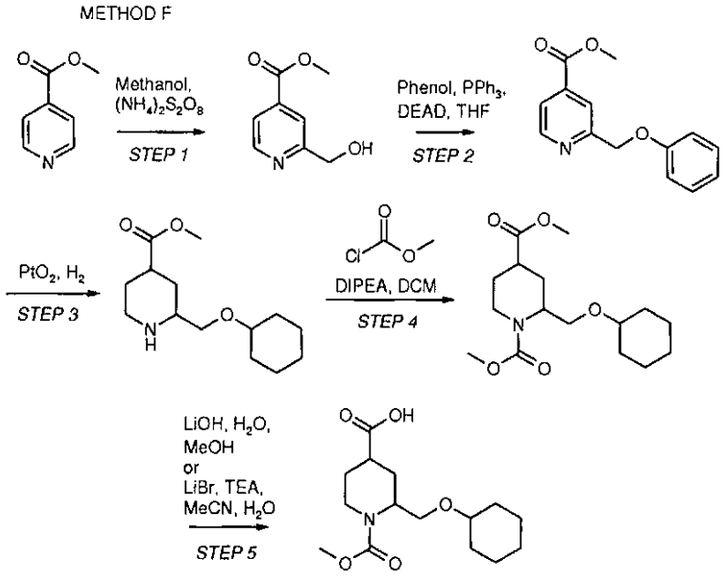
METHOD D



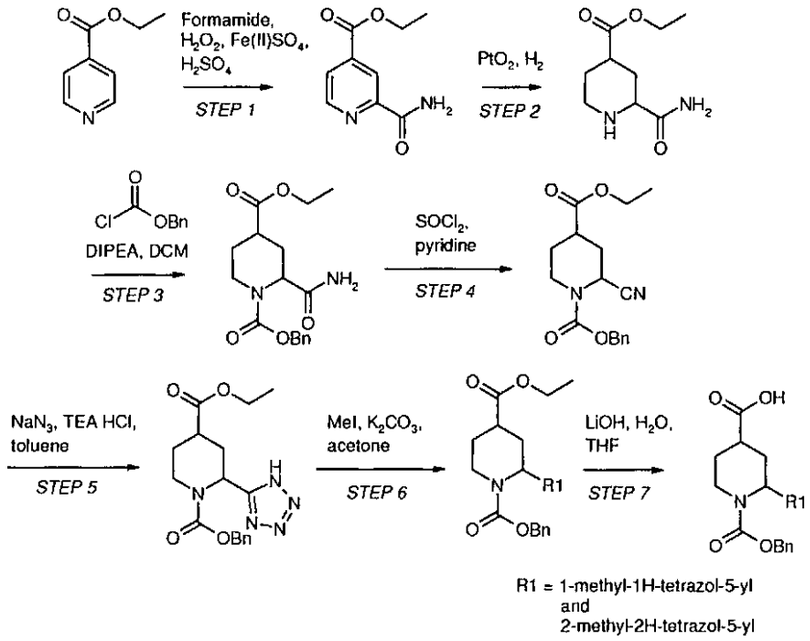
METHOD E



METHOD F

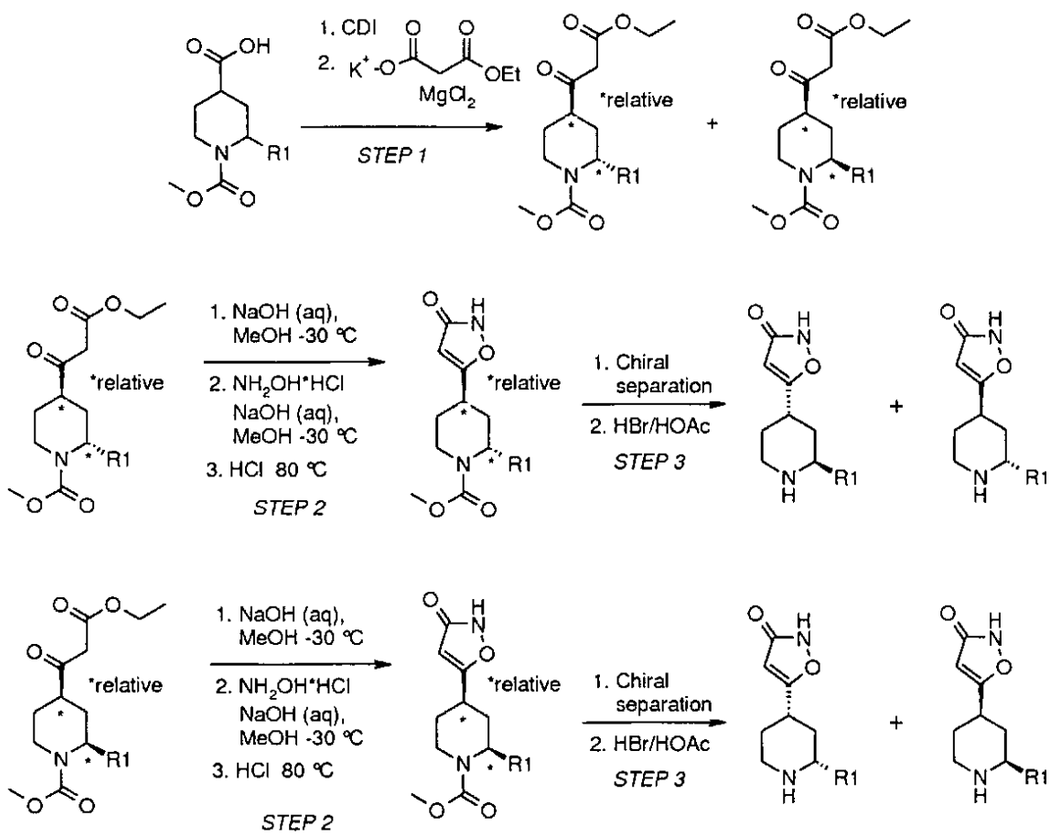


METHOD G



R1 = 1-methyl-1H-tetrazol-5-yl
and
2-methyl-2H-tetrazol-5-yl

Scheme B. Formation of 5-isoxazol-3-ones



NOTE: Stereochemical assignments marked with asterisks shall be taken to be definitive of the relative configurations of the carbon atoms marked, but not their absolute configurations, unless expressly stated otherwise

It will be apparent to the person skilled in the art that the above described processes are not the only way of producing the compounds according to the invention, but that a person skilled in the art may change order of sequences, reaction conditions and other parameters accordingly. Examples of parameters to be varied are using different solvents, acids and bases and temperature and furthermore to protect an amine, hydroxyl or other potentially reactive group. Suitable protecting groups and details of processes for adding and removing such groups are, in general, well known in the art. See, for example, "Protective groups on Organic Synthesis", 3rd edition (1999) by Greene and Wuts.

Resolution of the enantiomers could be done at any stage, by using for instance column separation, by recrystalization using a chiral acid or a base. Resolution could be also carried

out by enzymatically selective reaction. Alternatively, the enantiomers could be stereospecifically synthesized.

For the uses, methods, medicaments and compositions mentioned herein the amount of formula I-V compound, or pharmaceutically acceptable salts thereof, or mixtures thereof used and the dosage administered may vary with the formula I-V compound, or pharmaceutically acceptable salts, or mixtures thereof employed; and/or the desired mode of administration and/or treatment. However, in general, satisfactory results are obtained when a compound in accordance with formula I-V, or pharmaceutically acceptable salts, or mixtures thereof is administered at a daily dosage of about 0.1 mg to about 400 mg/kg of animal body weight. Such doses may be given in divided doses 1 to 4 times a day or in a sustained release form. For man, the total daily dose may, for example, range of from about 5 mg to about 7,000 mg, and more particularly from about 10 mg to about 1500 mg. Unit dosage forms suitable for oral administration generally comprise, for example, from about 2 mg to about 1,400 mg of at least one compound in accordance with formula I-V, or pharmaceutically acceptable salts, or mixtures thereof admixed with at least one solid and/or liquid pharmaceutical carrier, lubricant, and/or diluent.

The specific dose level and frequency of dosage for any particular subject, however, may vary and generally depends on a variety of factors, including, but not limited to, for example, the bioavailability of the specific formula I-V compound(s), or pharmaceutically acceptable salts, or mixtures thereof in the administered form; metabolic stability and length of action of the specific formula I-V compound(s), or pharmaceutically acceptable salts, or mixtures thereof; species, age, body weight, general health, sex, and diet of the subject; mode and time of administration; rate of excretion; drug combination; and severity of the particular condition.

Compound(s) in accordance with formula I-V, or pharmaceutically acceptable salts, or mixtures thereof may be administered by any means suitable for the condition to be treated and the quantity of formula I-V, or pharmaceutically acceptable salts, or mixtures thereof to be delivered.

Compound(s) in accordance with formula I-V, or pharmaceutically acceptable salts, or mixtures thereof may be administered in the form of a conventional pharmaceutical composition by any route including, but not limited to, for example, orally, intramuscularly, subcutaneously, topically, intranasally, epidurally, intraperitoneally, intrathoracially,

intravenously, intrathecally, intracerebroventricularly, through intra uterine device, and by injecting into the joints, by applied in a device such as a patch or a plug for topical treatment such as nose-bleeding.

In one embodiment, the route of administration is orally, intravenously, through intra uterine device or intramuscularly.

A compound of formula I-V, or pharmaceutically acceptable salts, or mixtures thereof may be used on their own or in the form of appropriate medicinal preparations for enteral or parenteral administration.

Acceptable solid pharmaceutical compositions include, but are not limited to, for example, powders, tablets, dispersible granules, capsules, cachets, and suppositories.

In a solid pharmaceutical composition, pharmaceutically acceptable carriers include, but are not limited to, for example, at least one solid, at least one liquid, and mixtures thereof. The solid carrier can also be a diluent, flavouring agent, solubilizer, lubricant, suspending agent, binder, encapsulating material, and/or tablet disintegrating agent. Suitable carriers, include, but are not limited to, for example, magnesium carbonate; magnesium stearate; talc; lactose; sugar; pectin; dextrin; starch; tragacanth; methyl cellulose; sodium carboxymethyl cellulose; a low-melting wax; cocoa butter; and mixtures thereof.

A powder can be prepared by, for example, mixing a finely divided solid with at least one finely divided compound of formula I-V, or pharmaceutically acceptable salts, or mixtures thereof.

A tablet can be prepared by, for example, mixing at least one compound in accordance with formula I-V, or pharmaceutically acceptable salts, or mixtures thereof in suitable proportions with a pharmaceutically acceptable carrier having the necessary binding properties and compacted into the desired shape and size.

A suppository can be prepared by, for example, mixing at least one compound of formula I-V, or pharmaceutically acceptable salts, or mixtures thereof with at least one suitable non-irritating excipient that is liquid at rectal temperature but solid at a temperature below rectal temperature, wherein the non-irritating excipient is first melted and the formula I compound dispersed therein. The molten homogeneous mixture is then poured into convenient sized moulds and allowed to cool and solidify. Exemplary non-irritating excipients include, but are not limited to, for example, cocoa butter; glycerinated gelatine; hydrogenated vegetable oils; mixtures of polyethylene glycols of various molecular weights; and fatty acid esters of polyethylene glycol.

Acceptable liquid pharmaceutical compositions include, but are not limited to, for example, solutions, suspensions, and emulsions.

Exemplary liquid pharmaceutical compositions suitable for parenteral administration include, but are not limited to, for example, sterile water or water propylene glycol solutions of at least one compound in accordance with formula I-V, or pharmaceutically acceptable salts, or mixtures thereof; and aqueous polyethylene glycol solutions of at least one compound in accordance with formula I-V, or pharmaceutically acceptable salts, or mixtures thereof.

Aqueous solutions for oral administration can be prepared by dissolving at least one compound in accordance with formula I-V, or pharmaceutically acceptable salts, or mixtures thereof in water and adding suitable colorants, flavouring agents, stabilizers, and/or thickening agents as desired.

Aqueous suspensions for oral administration can be prepared by dispersing at least one finely divided compound of formula I-V, or pharmaceutically acceptable salts, or mixtures thereof in water together with a viscous material, such as, for example, a natural synthetic gum, resin, methyl cellulose, and sodium carboxymethyl cellulose.

In one embodiment, the pharmaceutical composition contains from about 0.05% to about 99%w (percent by weight) of at least one compound in accordance with formula I-V, or pharmaceutically acceptable salts, or mixtures thereof. All percentages by weight being based on total composition.

In another embodiment, the pharmaceutical composition contains from about 0.10% to about 50%wt (percent by weight) of at least one compound in accordance with formula I-V, or pharmaceutically acceptable salts, or mixtures thereof. All percentages by weight being based on total composition.

Also provided herein is a process for preparing a pharmaceutical composition comprising mixing or compounding the ingredients together and forming the mixed ingredients into tablets or suppositories; encapsulating the ingredients in capsules; or dissolving the ingredients to form injectable solutions.

A compound according to the present invention may be used in combination with other agents to treat the conditions disclosed above. Examples of that are non-steroid anti-inflammatory agents, such as NSAID inhibitors and hormonal treatment, such as progesterone and/or oestrogen, antiplatelet or anti-coagulant agents to prevent side effects, coagulation factors such as factor VII and factor VIII, von Willebrand's factor.

25

Assay Method

The assay method used for evaluating biological activity of the compounds according to the invention was Clot-lysis buffer assay.

Measurement of inhibition of plasminogen were performed in a 200 µL reaction mixture containing 15 mM HEPES, pH 7.4, 100 mM NaCl, 0.008 % Tween-80, 13 µg/mL human Glu-plasminogen (Chromogenix, Italy), 1.7 mg/mL human fibrinogen (Aniara, USA), 0.02 nM human single-chain tissue type plasminogen activator (Biopool, Sweden), 1% DMSO and 0.05 NIH U/mL human thrombin (Sigma, USA).

Tested substance were added to the reaction mixture in 10% DMSO. Reaction was started by the addition of thrombin.

Fibrin formation and degradation were followed in a spectrophotometer at 405 nm for 15 hrs at 37° C.

Biological activity

Measured according to the Clot-lysis buffer assay described above.

Example 1 showed an IC_{50} value of 2.85 µM. Example 2 showed an IC_{50} value of 169 µM. Example 3 showed an IC_{50} value of 1.16 µM. Example 4 showed an IC_{50} value of 150 µM. Example 5 showed an IC_{50} value of 2.86 µM. Example 6 showed an IC_{50} value of 47.5 µM. Example 7 showed an IC_{50} value of 2.62 µM. Example 8 showed an IC_{50} value of 2.36 µM. Example 9 showed an IC_{50} value of 16.5 µM. Example 10 showed an IC_{50} value of 1.46 µM. Example 11 showed an IC_{50} value of 4.3 µM. Example 12 showed an IC_{50} value of 2.25 µM. Example 13 showed an IC_{50} value of 1.28 µM. Example 14 showed an IC_{50} value of 1.15 µM. Example 15 showed an IC_{50} value of 5.2 µM. Example 16 showed an IC_{50} value of 56.2 µM. Example 17 showed an IC_{50} value of 4.65 µM. Example 18 showed an IC_{50} value of 1.6 µM. Example 19 showed an IC_{50} value of 1.6 µM. Example 20 showed an IC_{50} value of 5.1 µM. Example 21 showed an IC_{50} value of 107 µM. Example 22 showed an IC_{50} value of 1.2 µM. Example 23 showed an IC_{50} value of 1 µM. Example 24 showed an IC_{50} value of 42.8 µM. Example 25 showed an IC_{50} value of 2.5 µM. Example 26 showed an IC_{50} value of 73.8 µM. Example 27 showed an IC_{50} value of 1.5 µM. Example 28 showed an

IC_{50} value of 283 μM. Example 29 showed an IC_{50} value of 24 μM. Example 30 showed an IC_{50} value of 0.7 μM. Example 31 showed an IC_{50} value of 33.1 μM. Example 32 showed an IC_{50} value of 23.6 μM. Example 33 showed an IC_{50} value of 1.43 μM. Example 34 showed an IC_{50} value of 150 μM. Example 35 showed an IC_{50} value of 14.4 μM. Example 36 showed an IC_{50} value of 1.9 μM. Example 37 showed an IC_{50} value of 228 μM. Example 38 showed an IC_{50} value of 1.5 μM. Example 39 showed an IC_{50} value of 97.3 μM. Example 40 showed an IC_{50} value of 1.5 μM. Example 41 showed an IC_{50} value of 40.9 μM. Example 42 showed an IC_{50} value of 34.9 μM. Example 43 showed an IC_{50} value of 77.5 μM. Example 44 showed an IC_{50} value of 2.3 μM. Example 45 showed an IC_{50} value of 2.35 μM. Example 46 showed an IC_{50} value of 90.7 μM. Example 47 showed an IC_{50} value of 1.4 μM. Example 48 showed an IC_{50} value of 44.3 μM. Example 49 showed an IC_{50} value of 2 μM. Example 50 showed an IC_{50} value of 5.3 μM. Example 51 showed an IC_{50} value of 0.9 μM. Example 52 showed an IC_{50} value of 1940 μM. Example 53 showed an IC_{50} value of 72.9 μM. Example 54 showed an IC_{50} value of 372 μM. Example 55 showed an IC_{50} value of 0.6 μM. Example 56 showed an IC_{50} value of 43.8 μM. Example 57 showed an IC_{50} value of 40 μM. Example 58 showed an IC_{50} value of 2.1 μM. Example 59 showed an IC_{50} value of 70.7 μM. Example 60 showed an IC_{50} value of 1.9 μM. Example 61 showed an IC_{50} value of 858 μM. Example 62 showed an IC_{50} value of 7.1 μM. Example 63 showed an IC_{50} value of 3.22 μM. Example 64 showed an IC_{50} value of 31.4 μM. Example 65 showed an IC_{50} value of 2.2 μM. Example 66 showed an IC_{50} value of 7.5 μM. Example 67 showed an IC_{50} value of 1.3 μM. Example 68 showed an IC_{50} value of 81.1 μM. Example 69 showed an IC_{50} value of 92.5 μM. Example 70 showed an IC_{50} value of 2.5 μM. Example 71 showed an IC_{50} value of 11.6 μM. Example 72 showed an IC_{50} value of 0.6 μM. Example 73 showed an IC_{50} value of 1.54 μM. Example 74 showed an IC_{50} value of 52.2 μM. Example 75 showed an IC_{50} value of 3.1 μM. Example 76 showed an IC_{50} value of 190 μM. Example 77 showed an IC_{50} value of 8 μM. Example 78 showed an IC_{50} value of 64.2 μM. Example 79 showed an IC_{50} value of 3.3 μM. Example 80 showed an IC_{50} value of 44 μM. Example 81 showed an IC_{50} value of 1.6 μM. Example 82 showed an IC_{50} value of 20.3 μM. Example 83 showed an IC_{50} value of 42 μM. Example 84 showed an IC_{50} value of 1.7 μM. Example 85 showed an IC_{50} value of 173 μM. Example 86 showed an IC_{50} value of 15.6 μM. Example 87 showed an IC_{50} value of 10.7 μM. Example 88 showed an IC_{50} value of 31.2 μM. Example 89 showed an IC_{50} value of 1.5 μM. Example 90 showed an IC_{50} value of 102 μM. Example 91 showed an IC_{50} value of 5.9 μM. Example 92 showed an IC_{50}

value of 1.1 μM. Example 93 showed an IC_{50} value of 69.8 μM. Example 94 showed an IC_{50} value of 4.6 μM. Example 95 showed an IC_{50} value of 1.04 μM. Example 96 showed an IC_{50} value of 7.3 μM. Example 97 showed an IC_{50} value of 0.7 μM. Example 98 showed an IC_{50} value of 2.51 μM. Example 99 showed an IC_{50} value of 0.81 μM. Example 100 showed an IC_{50} value of 1.93 μM. Example 101 showed an IC_{50} value of 4.7 μM. Example 102 showed an IC_{50} value of 2.18 μM. Example 103 showed an IC_{50} value of 94 μM. Example 104 showed an IC_{50} value of 1.5 μM. Example 105 showed an IC_{50} value of 7.2 μM. Example 106 showed an IC_{50} value of 88.8 μM. Example 107 showed an IC_{50} value of 1.7 μM. Example 108 showed an IC_{50} value of 70.5 μM. Example 109 showed an IC_{50} value of 5 μM. Example 110 showed an IC_{50} value of 1.2 μM. Example 111 showed an IC_{50} value of 31.3 μM. Example 112 showed an IC_{50} value of 5.5 μM. Example 113 showed an IC_{50} value of 1.1 μM. Example 114 showed an IC_{50} value of 6.5 μM. Example 115 showed an IC_{50} value of 0.8 μM. Example 116 showed an IC_{50} value of 5.6 μM. Example 117 showed an IC_{50} value of 0.8 μM. Example 118 showed an IC_{50} value of 225 μM. Example 119 showed an IC_{50} value of 10.7 μM. Example 120 showed an IC_{50} value of 0.89 μM. Example 121 showed an IC_{50} value of 120 μM. Example 122 showed an IC_{50} value of 4.4 μM. Example 123 showed an IC_{50} value of 147 μM. Example 124 showed an IC_{50} value of 1.2 μM. Example 125 showed an IC_{50} value of 92.9 μM. Example 126 showed an IC_{50} value of 3.6 μM. Example 127 showed an IC_{50} value of 1.4 μM. Example 128 showed an IC_{50} value of 31.4 μM. Example 129 showed an IC_{50} value of 10.2 μM. Example 130 showed an IC_{50} value of 1.1 μM. Example 131 showed an IC_{50} value of 128 μM. Example 132 showed an IC_{50} value of 2.2 μM. Example 133 showed an IC_{50} value of 120 μM. Example 134 showed an IC_{50} value of 0.85 μM. Example 135 showed an IC_{50} value of 69.1 μM. Example 136 showed an IC_{50} value of 4.94 μM. Example 137 showed an IC_{50} value of 1 μM. Example 138 showed an IC_{50} value of 123 μM. Example 139 showed an IC_{50} value of 2.9 μM. Example 140 showed an IC_{50} value of 0.6 μM. Example 141 showed an IC_{50} value of 69.5 μM. Example 142 showed an IC_{50} value of 1.8 μM. Example 143 showed an IC_{50} value of 0.9 μM. Example 144 showed an IC_{50} value of 88.2 μM. Example 145 showed an IC_{50} value of 4.3 μM. Example 146 showed an IC_{50} value of 6.6 μM. Example 147 showed an IC_{50} value of 44.6 μM. Example 148 showed an IC_{50} value of 2.7 μM. Example 149 showed an IC_{50} value of 0.9 μM. Example 150 showed an IC_{50} value of 87 μM. Example 151 showed an IC_{50} value of 7.7 μM.

X-ray powder diffraction

The X-ray powder diffraction (referred to herein as XRPD or XRD) pattern was determined by mounting a sample on a zero background holder, single silicon crystal, and spreading out the sample into a thin layer. Using a Bruker D8 Advance theta-2 theta diffractometer with a VÅNTEC-1 detector, the sample was spun (to improve counting statistics) and irradiated with X-rays generated by a copper tube operated at 30kV and 50mA. Automatic variable divergence slits were used.

The X-ray diffraction analysis was performed according to standard methods, which can be found in e.g. Kitaigorodsky, A.I. (1973), Molecular Crystals and Molecules, Academic Press, New York; Bunn, C.W. (1948), Chemical Crystallography, Clarendon Press, London; or Klug, H.P. & Alexander, L.E. (1974), X-ray Diffraction Procedures, John Wiley & Sons, New York. X-ray powder diffraction data were not corrected by using an internal reference. Measurements were performed with variable slits.

It will be understood that the 2-theta values of the X-ray powder diffraction pattern may vary slightly from one machine to another and also depending on variations in sample preparation and batch to batch variation, and so the values quoted are not to be construed as absolute. It will also be understood that the relative intensities of peaks may vary depending on orientation effects so that the intensities shown in the XRD trace included herein are illustrative and not intended to be used for absolute comparison.

The compounds may crystallize as ansolvates or solvates (including hydrates and mixed solvates). Solvent molecules may be more or less strongly bound in the structure. Transformations may appear between ansolvates and solvates or between stoicheiometric and non stoicheiometric solvates. Transformations may be either reversible or irreversible. The relative humidity or presence of other solvents is something that may affect the x-ray powder diffraction pattern more or less depending on the amount of solvent present in the structure.

The X-ray powder diffraction pattern of a typical sample of examples 10, 14, 18, 55, 65, 104, 115 and 143 are shown in Figures 1-13.

Examples

List of abbreviations used in the examples:

AcOH – ACETIC ACID

CV – COLUMN VOLUME

DME - 1,2-DIMETHOXYETHANE

DEE - DIETHYL ETHER

DMF - N,N-DIMETHYLFORMAMIDE

DIPEA - N,N-DIISOPROPYLETHYLAMINE

DCM - DICHLOROMETHANE

dppf - 1,1'-BIS(DIPHENYLPHOSPHINO)FERROCENE

DMAP - 4-DIMETHYLAMINOPYRIDINE

EDC - 1-ETHYL-3-(3-DIMETHYLAMINOPROPYL)CARBODIIMIDE

EtOH – ETHANOL

FA – FORMIC ACID

h – HOUR(S)

min – MINUTE(S)

MTBE – Methyl tert-butylether

IPA – ISOPROPYL ALCOHOL

LAH - LITHIUM ALUMINUM HYDRIDE

TEA - TRIETHYLAMINE

THF - TETRAHYDROFURAN

TBDMSCl - TERT-BUTYLDIMETHYLCHLOROSILANE

TBAF - TETRABUTYLAMMONIUM FLUORIDE

MeOH - METHANOL

EtOAc – ETHYL ACETATE

Ph – PHENYL

satd - SATURATED

Preparation of Reference Compounds

Reference compound 1

2-Benzyl-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: tert-Butyl 2-benzyl-4-cyanopiperidine-1-carboxylate

To a solution of 2-benzyl-4-oxo-piperidine-1-carboxylic acid tert-butyl ester (15 g, 51.8 mmol) (from SYNTECH) in DME (250 mL) under nitrogen atmosphere was simultaneously added toluene-4-sulfonylmethyl isocyanide (15.2 g, 77.7 mmol, in 250 mL DME) and potassium tert-butoxide (156 mL, 1 M in tert-butanol) over 1 h so that the temperature was kept below -10°C. The solution was stirred at -10°C for 2 h and then allowed to reach room temperature over 16 h. To the reaction mixture was added H_2O (400 mL) and the solution was stirred for 20 min and then extracted with DEE (x 3) and EtOAc (x 3). The combined organic phases were dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography using EtOAc/heptane (10-60 % gradient EtOAc) to yield tert-butyl 2-benzyl-4-cyanopiperidine-1-carboxylate (11.85 g, 76 %). ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.38 – 1.46 (m, 9H), 1.63 – 2.14 (m, 4H), 2.62 – 3.33 (m, 4H), 4.17 (m, 1H), 4.48 (m, 1H), 7.11 – 7.41 (m, 5H); MS m/z 301 $(M+H)^+$.

Step 2: Methyl 2-benzylpiperidine-4-carboxylate

To tert-butyl 2-benzyl-4-cyanopiperidine-1-carboxylate (11.85 g, 39.5 mmol) was added conc. HCl (43 mL). After 20 min of stirring the solution was transferred to microwave reaction vials and heated to 140°C for 30 min in single node microwave reactor. The solvents were evaporated. The residue was dissolved in HCl (1.25 M in MeOH, 50 mL) and the suspension was heated under reflux for 1 h. Removal of the solvents resulted in an oil that was taken up in satd $NaHCO_3$ (ca. 80 mL) and further neutralized with solid $NaHCO_3$. The aqueous phase was extracted with DCM (x3) which was dried using a phase separator and evaporated to yield methyl 2-benzylpiperidine-4-carboxylate (7.36 g, 80%) as an oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.18 – 2.40 (m, 5H), 2.47 – 3.15 (m, 5H), 3.66-2.69 (2 s, tot integral, 3H), 7.15 – 7.35 (m, 5H); MS m/z 234 $(M+H)^+$.

Step 3: 2-Benzyl-1-(methoxycarbonyl)piperidine-4-carboxylic acid

To a solution of methyl 2-benzylpiperidine-4-carboxylate (7.36 g, 31.55 mmol) and DIPEA (11.02 mL, 63.09 mmol) in DCM (200 mL) was added methyl chloroformate (3.18 mL, 41.01 mmol) in 100 mL DCM over 1 h. The reaction mixture was stirred for 40 min, then washed with satd $NaHCO_3$, dried using a phase separator and evaporated. The residue was dissolved in THF (80 mL) followed by addition of LiOH (1.0 g, 42.0 mmol), MeOH (60 mL) and water (60 mL). The reaction mixture was stirred at room temperature under nitrogen atmosphere for 72 h. After evaporation of solvents, the residue was taken up in water. The pH was adjusted to < 2 by addition of HCl (10 %). The aqueous phase was then extracted with DCM (x5). The combined organic layers were dried by using a phase separator and evaporated to give 2-benzyl-1-(methoxycarbonyl)piperidine-4-carboxylic acid as an oil. MS m/z 276 $(M-H)^-$.

Reference Compound 2

2-Isobutyl-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: 3-(tert-Butoxycarbonylamino)-5-methylhexanoic acid

To a solution of DL-β-homo leucine (45 g, 0.31 mol) in 1N NaOH (1 L) at 0°C, a solution of $(Boc)_2O$ (87.8 g, 0.403 mol) in 1,4-dioxane (500 mL) was added dropwise. The reaction mixture was stirred at room temperature overnight, cooled to 0°C and neutralized with 1 N HCl (ca. 1000 mL). The solid was filtered off and dried under vacuum to yield 3-(tert-butoxycarbonylamino)-5-methylhexanoic acid (48.0 g, 63 %) as a solid.

Step 2: tert-Butyl 2-isobutyl-4,6-dioxopiperidine-1-carboxylate

To a stirred solution of 3-(tert-butoxycarbonylamino)-5-methylhexanoic acid (44.0 g, 0.179 mol) in DCM (800 mL) at 0°C, EDC hydrochloride (51.56 g, 0.269 mol), DMAP (32.8 g, 0.269 mol) and Meldrum's acid (25.8 g, 0.179 mol) were added. The reaction mixture was stirred at room temperature for 3 h, washed with 1 N $KHSO_4$ (500 mL), dried over Na_2SO_4 and concentrated. The residue was dissolved in dry ethyl acetate (1.5 L) and heated under reflux overnight. The reaction mixture was washed with 1 N $KHSO_4$ (500 mL), brine (500 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography using petroleum ether and EtOAc (65:35) as eluent to yield 3-(tert-butoxycarbonylamino)-5-methylhexanoic acid as a solid (35 g, 72 %).

Step 3: 6-Isobutyl-piperidine-2,4-dione

To a solution of tert-butyl 2-isobutyl-4,6-dioxopiperidine-1-carboxylate (30 g, 0.114 mol) in dry 1,4 dioxane (300 mL), HCl (3 M in 1,4 dioxane, 100 mL) was added and stirred at room temperature for 3 h. The reaction mixture was concentrated and purified by crystallization using diethyl ether to yield 6-isobutyl-piperidine-2,4-dione (14 g, 74 %) as a white solid.

Step 4: 2-Isobutyl-piperidin-4-ol

To a stirred ice cooled suspension of LAH (16.1 g, 0.414 mol) in THF (100 mL), a solution of 6-isobutyl-piperidine-2,4-dione (14.0 g, 0.083 mol) in THF (100 mL) was added dropwise under N_2. The reaction mixture was warmed to room temperature and stirred under N_2 for 48 h. The reaction mixture was cooled to 0°C and quenched with water (16.1 mL), 1 N NaOH (16.1 mL) and water (16.1 mL). The reaction mixture was filtered and the solid was washed with hot THF (100 mL). The filtrate was concentrated to yield 2-isobutyl-piperidin-4-ol as a solid (9 g, crude).

Step 5: tert-Butyl-4-hydroxy-2-isobutylpiperidine-1-carboxylate

2-Isobutyl-piperidin-4-ol (9.0 g, 0.057 mol) was taken up in a 50:50 solution of THF and satd $NaHCO_3$ (100 mL) and the mixture was cooled to 0°C. A solution of $(Boc)_2O$ (13.7 g, 0.063 mol) in THF (50 mL) was added dropwise. The resulting solution was stirred at room temperature overnight. The reaction mixture was concentrated and extracted with EtOAc (100 mL). The organic phase was washed with water (100 mL), brine (100 mL), dried over Na_2SO_4 and concentrated. The concentrated product was purified by column chromatography using 20% of EtOAc in petroleum ether to yield a mixture of two compounds. The mixture was further purified by preparative HPLC to yield tert-butyl-4-hydroxy-2-isobutylpiperidine-1-carboxylate as a pale yellow liquid (4.5 g, 39.5 %).

Step 6: 2-Isobutyl-4-oxo-piperidine-1-carboxylic acid tert-butyl ester

To a stirred solution of tert-butyl-4-hydroxy-2-isobutylpiperidine-1-carboxylate (4.6 g, 0.018 mol) in DCM (50 mL) at 0°C, 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (9.1 g, 0.02146 mol) was added portionwise and the resulting solution was warmed to room temperature and stirred under N_2 overnight. The reaction mixture was quenched with satd $NaHCO_3$ solution (50 mL) and was filtered through a Celite® pad. The filtrate was extracted

several times with DCM (50 mL), the combined organic phases were washed with water (50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated. The concentrated product was purified by column chromatography using 10 % EtOAc in petroleum ether to yield the product with HPLC purity 90%. The impure product was further purified by preparative HPLC to yield 2-isobutyl-4-oxo-piperidine-1-carboxylic acid tert-butyl ester as a liquid (2.1 g, 46 %).

Step 7: tert-Butyl 4-cyano-2-isobutylpiperidine-1-carboxylate

The compound was prepared as described in Reference Compound 1, Step 1 from 2-Isobutyl-4-oxo-piperidine-1-carboxylic acid tert-butyl ester (4.55 g, 17.8 mmol), toluene-4-sulfonylmethyl isocyanide (5.2 g, 26.7 mmol) and potassium tert-butoxide (53.4 mL, 1 M in tert-butanol) which yielded crude tert-butyl 4-cyano-2-isobutylpiperidine-1-carboxylate. MS m/z 267 $(M+H)^+$.

Step 8: 2-Isobutyl-piperidine-4-carboxylic acid methyl ester

The compound was prepared as described in Reference Compound 1, Step 2 from crude tert-butyl-4-cyano-2-isobutylpiperidine-1-carboxylate (6.43 g, ca 24.2 mmol) which yielded crude 2-isobutyl-piperidine-4-carboxylic acid methyl ester. MS m/z 200 $(M+H)^+$.

Step 9: 2-Isobutyl-1-(methoxycarbonyl)piperidine-4-carboxylic acid

The compound was prepared as described in Reference Compound 1, Step 3 from crude 2-isobutyl-piperidine-4-carboxylic acid methyl ester (2.6 g, 13.0 mmol), DIPEA (4.55 mL, 26.1 mmol) and methyl chloroformate (1.31 mL, 17.0 mmol) and subsequently LiOH (1.3 equivalents) which yielded crude 2-isobutyl-1-(methoxycarbonyl)piperidine-4-carboxylic acid. MS m/z 242 $(M-H)^-$.

Reference Compound 3

1-(Methoxycarbonyl)-2-phenethylpiperidine-4-carboxylic acid

Step 1: Methyl 4-oxo-2-phenethyl-3,4-dihydropyridine-1(2H)-carboxylate

4-Methoxypyridine (9.30 mL, 91.64 mmol) was dissolved in THF (150 mL) under nitrogen atmosphere and cooled to -15°C. Phenethylmagnesium chloride (93 mL, 93.47 mmol, 1 M in

THF) was added dropwise and a suspension was formed. After stirring at –20°C for 30 minutes methyl chloroformate (9.23 mL, 119.13 mmol) was added over 1 minute. Stirring was continued at -10°C for 1 h and then HCl (10%) was added. The mixture was stirred for 20 minutes and then concentrated. The aqueous phase was extracted with ether (x2) and the organic phase was dried ($MgSO_4$) and evaporated to yield methyl 4-oxo-2-phenethyl-3,4-dihydropyridine-1(2H)-carboxylate (21.7 g, 82 %) as an oil. ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.98 (m, 2H), 2.54 (m, 2H), 2.69 (m, 1H), 2.81 (m, 1H), 3.83 (s, 3H), 4.62 (m, 1H), 5.33 (m, 1H), 7.12 – 7.38 (m, 5H), 7.72 (m, 1H); MS m/z 260 $(M+H)^+$.

Step 2: Methyl 4-oxo-2-phenethylpiperidine-1-carboxylate

Methyl 4-oxo-2-phenethyl-3,4-dihydropyridine-1(2H)-carboxylate (21.7 g, ca 75 mmol) was hydrogenated over Pd/C (5%) in EtOAc at 5 bar for 20 h. The mixture was filtered through a silica plug and then evaporated to give the product as an oil (19.8 g). ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.69 (m, 1H), 1.80 (m, 1H), 2.26 (m, 2H), 2.41 (m, 1H), 2.47 – 2.70 (m, 3H), 3.16 (m, 1H), 3.69 (m, 3H), 4.15-4,48 (br m, 2H), 7.14-7.30 (m, 5H). MS 262 m/z $(M+H)^+$.

Step 3: Methyl 4-cyano-2-phenethylpiperidine-1-carboxylate

To a solution of methyl 4-oxo-2-phenethylpiperidine-1-carboxylate (19.8 g, 75.7 mmol) in DME (250 mL) under nitrogen atmosphere was simultaneously added toluene-4-sulfonylmethyl isocyanide (16.6 g, 85.0 mmol, in 250 mL DME) and potassium tert-butoxide (197 mL, 1 M in tert-butanol) over 1 h so that the temperature was kept below -10°C. The mixture was then stirred at -10°C for 2 h and allowed to reach ambient temperature over 16 h. To the orange reaction mixture was added H_2O (400 mL), it was stirred for 20 minutes and then extracted with ether (x 3) and EtOAc (x 3). The organic phases were combined, dried over Na_2SO_4 and evaporated to give 24.8 g of residue. Flash chromatography using EtOAc/heptane (30-80% gradient EtOAc) gave the product (13.2 g, 64%) as a mixture of diastereomers (major cis isomer). MS m/z 273 $(M+H)^+$. Trans isomer: ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.71 (m, 2H), 1.84 – 2.09 (m, 4H), 2.47 – 2.68 (m, 2H), 2.71 – 2.92 (m, 2H), 3.70 (s, 3H), 4.12 (br m, 1H), 4.45 (br m, 1H), 7.01 – 7.40 (m, 5H). Cis isomer: ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.76 (m, 1H), 1.88 (m, 1H), 1.92 – 2.07 (m, 2H), 2.07 – 2.15 (m, 1H), 2.24 – 2.38 (m, 1H), 2.55 – 2.72 (m, 2H), 2.96 (m, 1H), 3.16 – 3.29 (m, 1H), 3.69 (s, 3H), 4.10 (m, 1H), 4.35 (m, 1H), 7.15 – 7.35 (m, 5H).

Step 4: 1-(Methoxycarbonyl)-2-phenethylpiperidine-4-carboxylic acid

To methyl 4-cyano-2-phenethylpiperidine-1-carboxylate (13.2 g, 48.5 mmol) in a microwave reaction vial was added 6 M HCl. The mixture was heated to 100°C for 30 min in a single node microwave reactor. The aqueous phase was extracted with EtOAc and the resulting organic phase was washed once with 10% HCl, dried over $MgSO_4$ and evaporated to give crude product 3.47 g. MS m/z 290 $(M-H)^-$.

Reference Compound 4

2-(4-tert-Butylbenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: 4-((tert-Butyldimethylsilyloxy)methyl)pyridine

To a solution of pyridin-4-ylmethanol (25.7 g, 0.24 mol) and imidazole (19.8 g, 0.29 mol) in dry DMF (300 mL) and dry DCM (33 mL) under nitrogen atmosphere was added TBDMSCl (42.6 g, 0.29 mol). The solution was stirred for 18 h under which time a precipitate formed. The reaction mixture was concentrated by removal of volatiles (about 100 mL) followed by addition of water (500 mL). The resulting mixture was extracted with 1:1 heptane:EtOAc (200 mL x3). The combined organic phases were washed with brine (x2), dried ($MgSO_4$), filtered and evaporated to yield 4-((tert-butyldimethylsilyloxy)-methyl)pyridine (51.70 g, 98%) as an oil. ^1H NMR (600 MHz, $cdcl_3$) δ -0.01 (s, 6H), 0.82 (s, 9H), 4.63 (s, 2H), 7.14 (m, 2H), 8.43 (m, 2H).

Step 2: Methyl 2-(4-tert-butylbenzyl)-4-((tert-butyldimethylsilyloxy)methyl)pyridine-1(2H)-carboxylate

To a suspension of 4-(tert-butyldimethylsilyloxy)methyl)pyridine (5.33 g, 23.86 mmol) in THF (50 mL) cooled to –30°C was added (4-tert-butylbenzyl)magnesium bromide (105 mL, 26.25 mmol, 0.25 M in THF) over 10 minutes. Methyl carbonochloridate (2.443 mL, 31.02 mmol) was added dropwise over 10 minutes. The reaction mixture was allowed to reach 0°C over 2 h. The organic solvents were evaporated, the reaction mixture was diluted with ethyl acetate, then washed with 1 N HCl and brine. The organic layer was dried over $MgSO_4$ and evaporated to give 9 g crude residue, which was purified in 2 equal portions by automated

column chromatography (Biotage, 340g KP-SIL), eluent: heptane/EtOAc gradient 0-50%, which yielded (6.5 g, 64 %) of the product as a clear oil. ^{1}H NMR (400 MHz, cdcl$_3$) (complex) δ -0.07 – 0.21 (m, 6H), 0.9 – 1.30 (m, 18H), 2.0 – 7.4 (m, 15H). MS m/z 431 $(M+H)^+$.

Step 3: Methyl 2-(4-tert-butylbenzyl)-4-((tert-butyldimethylsilyloxy)methyl)piperidine-1-carboxylate

To a solution of methyl 2-(4-tert-butylbenzyl)-4-((tert-butyldimethylsilyloxy)methyl)-pyridine-1(2H)-carboxylate (6.5 g, 15.13 mmol) in ethyl acetate (50 mL) was added platinum(IV) oxide (0.07 g, 0.31 mmol). The suspension was hydrogenated at 6 bar H_2 atmosphere for 20 h. The mixture was filtered through Celite and the solvents were evaporated to give the product (6.27 g, 96 %) as an oil. ^{1}H NMR (400 MHz, cdcl$_3$) δ -0.07 – 0.18 (m, 6H), 0.77 – 1.01 (m, 9H), 1.28 – 1.37 (m, 9H), 1.36 – 1.87 (m, 4H), 2.58 – 2.74 (m, 1H), 2.88 – 3.06 (m, 2H), 3.40 - 3.55 (m, 3H), 3.60 – 3.72 (m, 3H), 3.78 – 4.10 (m, 2H), 7.14 – 7.32 (m, 4H). MS m/z 434 $(M+H)^+$.

Step 4: Methyl 2-(4-tert-butylbenzyl)-4-(hydroxymethyl)piperidine-1-carboxylate

To a suspension of methyl 2-(4-tert-butylbenzyl)-4-((tert-butyldimethylsilyloxy)methyl)-piperidine-1-carboxylate (6.27 g, 14.46 mmol) in tetrahydrofuran (15 mL) was added tetrabutylammonium fluoride (18.79 mL, 18.79 mmol, 1 M in THF) and the reaction mixture was stirred at room temperature for 90 minutes. The solvents were evaporated, the residue dissolved in ethyl acetate and washed with satd $NaHCO_3$ (x 1), then brine (x 2). The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by automated column chromatography (Biotage, (340 g KP-SIL) eluent EtOAc/heptane, gradient 20-90% EtOAc) to yield the product (3.21 g, 70 %) as an oil. ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.30 (s, 9H), 1.42 – 1.50 (m, 2H), 1.65 – 1.91 (m, 2H), 2.68 (m, 1H), 2.89 – 3.07 (m, 2H), 3.39 – 3.62 (m, 3H), 3.67 (m, 3H), 3.87 (m 1H), 4.07 (m, 1H), 7.11 (m, 2H), 7.30 (m, 2H). MS m/z 320 $(M+H)^+$.

Step 5: 2-(4-tert-Butylbenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

To a solution of methyl 2-(4-tert-butylbenzyl)-4-(hydroxymethyl)piperidine-1-carboxylate (2.9 g, 9.08 mmol) in carbon tetrachloride (18 mL) was added sodium periodate (5.83 g, 27.24 mmol) and water (27 mL). Acetonitrile (18 mL) was added to this mixture, followed by ruthenium(III) chloride (0.041 g, 0.20 mmol). The resulting biphasic mixture was stirred

vigorously at room temperature for 2 h. The reaction mixture was diluted with water and DCM, the aqueous layer was extracted with DCM (x 3). The combined organic layers were dried over $MgSO_4$ and evaporated to give the product as an oil (3.0 g, 98 %) MS m/z 332 $(M-H)^-$.

Reference Compound 5

1-(Methoxycarbonyl)-2-neopentylpiperidine-4-carboxylic acid

Step 1: Methyl 4-((tert-butyldimethylsilyloxy)methyl)-2-neopentylpyridine-1(2H)-carboxylate

The compound was prepared as described in Reference Compound 4, Step 2 starting from 4-(tert-butyldimethylsilyloxy)methyl)pyridine, prepared as described in Reference Compound 4, Step 1, neopentylmagnesium chloride (40.5 mL, 40.5 mmol, 1 M in THF) and methyl carbonochloridate (3.77 mL, 47.9 mmol). The residue was purified by automated flash column chromatography on a Biotage® KP-SIL 340g column. A gradient of 15:1 to 10:1 heptane:EtOAc was used as mobile phase to give the title compound (9.3 g, 71 %): ^1H NMR (400 MHz, $cdcl_3$) δ -0.00 (s, 3H), 0.09 (s, 3H), 0.87 (s, 18H), 1.09 – 1.81 (m, 2H), 1.94 – 2.44 (m, 1H), 3.70 (s, 3H), 4.22 – 4.90 (m, 2H), 5.12 – 5.61 (m, 1H), 5.69 – 5.97 (m, 1H), 6.25 – 6.79 (m, 1H). MS m/z 354 $(M+H)^+$.

Step 2: Methyl 4-((tert-butyldimethylsilyloxy)methyl)-2-neopentylpiperidine-1-carboxylate

The compound was prepared as described in Reference Compound 4, Step 3 starting from methyl 4-((tert-butyldimethylsilyloxy)methyl)-2-neopentylpyridine-1(2H)-carboxylate which resulted in the title compound. MS m/z 358 $(M+H)^+$.

Step 3: Methyl 4-(hydroxymethyl)-2-neopentylpiperidine-1-carboxylate

The compound was prepared as described in Reference Compound 4, Step 4 starting from methyl 4-((tert-butyldimethylsilyloxy)methyl)-2-neopentylpiperidine-1-carboxylate and TBAF (34.2 mL, 34.2 mmol, 1 M in THF). The residue was purified by automated flash column chromatography on a Biotage® KP-SIL 340g column. A gradient from 30% to 100% EtOAc in heptane was used as eluent, which resulted in the title compound.

Step 5: 1-(Methoxycarbonyl)-2-neopentylpiperidine-4-carboxylic acid

The compound was prepared as described in Reference Compound 4, Step 5 starting from methyl 4-(hydroxymethyl)-2-neopentylpiperidine-1-carboxylate, sodium periodate (15.0 g, 70.3 mmol) and ruthenium(III) chloride (0.11 g, 0.52 mmol), which resulted in the title compound. MS m/z 256 $(M-H)^-$.

Reference Compound 6

1-(Methoxycarbonyl)-2-methylpiperidine-4-carboxylic acid

Step 1: Methyl 4-((tert-butyldimethylsilyloxy)methyl)-2-methylpyridine-1(2H)-carboxylate

The compound was prepared as described in Reference Compound 4, Step 2 starting from 4-(tert-butyldimethylsilyloxy)methyl)pyridine, prepared as described in Reference Compound 4, Step 1, methylmagnesium chloride (3 M in THF) (13.1 mL, 39.4 mmol, 1 M in THF) and methyl carbonochloridate (3.61 mL, 46.7 mmol). The residue was purified by column chromatography (Biotage heptane:EtOAc using a gradient 0-15% EtOAc; snap 360 column) which gave the title compound as a slightly yellow oil (2.48 g, 23 %): ^{1}H NMR (400 MHz, $cdcl_3$) δ -0.03 (d, 6H), 0.66 – 1.04 (m, 12H), 1.84 (m, 1H), 2.20 – 2.70 (m, 1H), 3.62 (s, 3H), 4.31 (m, 1H), 5.63 (m, 1H), 5.83 (m, 1H), 6.50 (m, 1H). MS m/z 298 $(M+H)^+$.

Step 2: Methyl 4-((tert-butyldimethylsilyloxy)methyl)-2-methylpiperidine-1-carboxylate

The compound was prepared as described in Reference Compound 4, Step 3 starting from methyl 4-((tert-butyldimethylsilyloxy)methyl)-2-methylpyridine-1(2H)-carboxylate which resulted in the title compound. MS m/z 302 $(M+H)^+$.

Step 3: Methyl 4-(hydroxymethyl)-2-methylpiperidine-1-carboxylate

The compound was prepared as described in Reference Compound 4, Step 4 starting from methyl 4-((tert-butyldimethylsilyloxy)methyl)-2-methylpiperidine-1-carboxylate and TBAF (10.65 mL, 10.65 mmol, 1 M in THF). The residue was purified by column chromatography (Biotage 40%-90% gradient EtOAc in heptane, 340 snap column), which resulted in the title compound. ^{1}H NMR (400 MHz, $cdcl_3$) δ 0.95 – 1.42 (m, 3H), 1.68 – 1.95 (m, 3H), 3.08 (m, 1H), 3.39 – 3.53 (m, 2H), 3.61 (m, 1H), 3.68 (s, 3H), 3.71 – 3.87 (m, 1H), 3.87 – 4.08 (m, 1H), 4.30 – 4.62 (m, 1H).

Step 5: 1-(Methoxycarbonyl)-2-methylpiperidine-4-carboxylic acid

The compound was prepared as described in Reference Compound 4, Step 5 starting from methyl 4-(hydroxymethyl)-2-methylpiperidine-1-carboxylate, sodium periodate (3.53 g, 16.5 mmol) and ruthenium(III) chloride (0.025 g, 0.12 mmol), which resulted in the title compound. MS m/z 200 $(M-H)^-$.

Reference Compound 7

1-(Methoxycarbonyl)-2-(2-methyl-2-phenylpropyl)piperidine-4-carboxylic acid

Step 1: Methyl 4-((tert-butyldimethylsilyloxy)methyl)-2-(2-methyl-2-phenylpropyl)pyridine-1(2H)-carboxylate

The compound was prepared as described in Reference Compound 4, Step 2 starting from 4-(tert-butyldimethylsilyloxy)methyl)pyridine, prepared as described in Reference Compound 4, Step 1, (2-methyl-2-phenylpropyl)magnesium chloride (0.5 M in THF, 93 mL, 46.6 mmol) and methyl carbonochloridate (3.61 mL, 46.7 mmol) to give the product (17.5 g). MS m/z 416 $(M+H)^+$.

Step 2: Methyl 4-((tert-butyldimethylsilyloxy)methyl)-2-(2-methyl-2-phenylpropyl)-piperidine-1-carboxylate

The compound was prepared as described in Reference Compound 4, Step 3 starting from crude methyl 4-((tert-butyldimethylsilyloxy)methyl)-2-(2-methyl-2-phenylpropyl)pyridine-1(2H)-carboxylate (17.5 g) which resulted in the titled compound (16.5 g). MS m/z 420 $(M+H)^+$.

Step 3: Methyl 4-(hydroxymethyl)-2-(2-methyl-2-phenylpropyl)piperidine-1-carboxylate

The compound was prepared as described in Reference Compound 4, Step 4 starting from crude methyl 4-((tert-butyldimethylsilyloxy)methyl)-2-(2-methyl-2-phenylpropyl)piperidine-1-carboxylate (16.5 g) and TBAF (46.5 mL, 46.6 mmol, 1 M in THF). The residue was purified by column chromatography (Biotage 40-65% gradient EtOAc in heptane, 340 snap column, 2 runs), which resulted in the titled compound. MS m/z 306 $(M+H)^+$.

Step 4: 1-(Methoxycarbonyl)-2-(2-methyl-2-phenylpropyl)piperidine-4-carboxylic acid

The compound was prepared as described in Reference Compound 4, Step 5 starting from methyl 4-(hydroxymethyl)-2-(2-methyl-2-phenylpropyl)piperidine-1-carboxylate (8.0 g, 26.2 mmol), sodium periodate (16.8 g, 78.6 mmol) and ruthenium(III) chloride (0.12 g, 0.58 mmol), which resulted in the title compound (7.24 g, 87 %). MS m/z 318 $(M-H)^-$.

Reference Compound 8

2-(Cyclohexylmethyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: Methyl 2-benzylisonicotinate

Methyl 2-chloroisonicotinate (4.29 g, 25 mmol) and $Pd(PPh_3)_4$ (1.156 g, 1.00 mmol) were dissolved in THF (60 mL) to give a yellow solution. Then benzylzinc(II) bromide (0.5 M in THF) (75 mL, 37.50 mmol) was added. The resulting brown mixture was warmed to 60°C in an oil-bath for 18 h. The reaction mixture was quenched by addition of methanol, then diluted with ethyl acetate and washed with satd NH_4Cl and water. The combined organic layers were dried over $MgSO_4$ and evaporated. The residue was purified via Biotage, Thompsson 160 g Silica, eluent isocratic heptanes/ethyl acetate 9:1 over 1 CV, then linear gradient 9:1-75:25 over 6 CV. Product containing fractions were evaporated to give methyl 2-benzylisonicotinate as an orange liquid. ^1H NMR (400 MHz, $cdcl_3$) δ 3.91 (s, 3H), 4.22 (s, 2H), 7.19 – 7.34 (m, 5H), 7.66 (dd, 1H), 7.69 (d, 1H), 8.70 (d, 1H).

Step 2: Methyl 2-(cyclohexylmethyl)piperidine-4-carboxylate

Methyl 2-benzylisonicotinate (1.29 g, 5.67 mmol) and PtO_2 (0.13 g, 0.57 mmol) were added to acetic acid (50 mL). The reaction mixture was hydrogenated in a Büchi hydrogentor at 8 bar at room temperature for 3 days. Methanol (100 mL) was added and the catalyst filtered off. The solvent was evaporated. The crude product was partitioned between Na_2CO_3 (aq) and ethyl acetate. The organic phase was isolated, dried over Na_2SO_4, filtered through Celite® and the solvent was evaporated. ^1H NMR (600 MHz, $cdcl_3$) δ 0.78 – 0.91 (m, 2H), 1.04 – 1.27 (m, 5H), 1.27 – 1.38 (m, 1H), 1.48 (ddd, 2H), 1.63 (dd, 5H), 1.80 – 1.93 (m, 2H), 2.36 (tt, 1H), 2.51 – 2.57 (m, 1H), 2.61 (td, 1H), 3.11 (ddd, 1H), 3.64 (s, 3H).

Step 3: Dimethyl 2-(cyclohexylmethyl)piperidine-1,4-dicarboxylate

Methyl 2-(cyclohexylmethyl)piperidine-4-carboxylate (1.79 g, 7.48 mmol), methyl carbonochloridate (1.06 g, 11.2 mmol) and DIPEA (1.93 g, 15.0 mmol) were added to dichloromethane (60 mL) at room temperature and stirred for 2 h. The reaction mixture was diluted with diethylether and washed with water. The organic phase was dried over $MgSO_4$, filtered through Celite® and the solvent was evaporated. Crude product 2.2 g. ^{1}H NMR (400 MHz, cdcl$_3$) δ 0.71 – 0.97 (m, 2H), 1.02 – 1.28 (m, 5H), 1.38 (dt, 1H), 1.69 (ddd, 6H), 1.98 (ddd, 3H), 2.52 – 2.61 (m, 1H), 3.01 – 3.16 (m, 1H), 3.67 (s, 3H), 3.69 (s, 3H), 3.81 – 3.94 (m, 1H), 4.13 – 4.31 (m, 1H).

Step 4: 2-(Cyclohexylmethyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Dimethyl 2-(cyclohexylmethyl)piperidine-1,4-dicarboxylate (2.20 g, 7.40 mmol) was dissolved in THF (25 mL) and water (25 mL). LiOH (0.266 g, 11.1 mmol) was added and the resulting mixture was stirred at room temperature overnight and heated under reflux for 30 min. The reaction mixture was partitioned between 1 M $KHSO_4$ and diethyl ether. The organic phase was dried (Na_2SO_4), filtered through Celite® and the solvent was evaporated. The crude product was dissolved again in THF (25 mL) and water (25 mL). LiOH (0.23 g) was added to the reaction flask. The reaction mixture was stirred overnight. The reaction was worked up as above to give the product. ^{1}H NMR (600 MHz, cdcl$_3$) δ 0.85 (ddd, 2H), 1.19 (dddd, 5H), 1.38 – 1.48 (m, 1H), 1.61 (d, 4H), 1.72 (tt, 2H), 1.97 (qd, 3H), 2.56 – 2.65 (m, 1H), 3.02 – 3.14 (m, 1H), 3.67 (d, 3H), 3.88 (d, 1H), 4.22 (s, 1H).

Reference compound 9

2-(3,4-Difluorophenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: Methyl 2-(3,4-difluorophenyl)isonicotinate

A mixture of methyl 2-chloroisonicotinate (5 g, 29.14 mmol), 3,4-difluorophenylboronic acid (5.06 g, 32.05 mmol), potassium carbonate (2.416 g, 17.48 mmol) and $PdCl_2$(dppf) (1.066 g, 1.46 mmol) was stirred in methanol (30 mL) and heated in a single-node microwave reactor at 100°C for 30 min. The solvent was evaporated in vacuo. DCM (400 mL) and 8 % $NaHCO_3$ (aq) (400 mL) were added, shaken and the phases separated. The aqueous phase was extracted with DCM (400 mL). The combined organic phases were dried with a phase separator and evaporated in vacuo. The residue was purified by automated flash chromatography on three

Biotage® KP-SIL 100g columns. A gradient from 5 % EtOAc in heptane over 2 CV followed by 5 % to 20 % of EtOAc in heptane over 9 CV was used as mobile phase. Methyl 2-(3,4-difluorophenyl)isonicotinate (5.82 g, 80 %) was isolated as a white solid. ^{1}H NMR (400 MHz, $cdcl_3$) δ 4.00 (s, 3H), 7.23 – 7.33 (m, 1H), 7.76 – 7.84 (m, 2H), 7.90 – 8.00 (m, 1H), 8.21 – 8.27 (m, 1H), 8.82 (dd, 1H).

Step 2: Methyl 2-(3,4-difluorophenyl)piperidine-4-carboxylate hydrochloride

Methyl 2-(3,4-difluorophenyl)isonicotinate (5.821 g, 23.36 mmol) was dissolved in hydrogen chloride (1.25 M in MeOH) (37.4 mL, 46.72 mmol) and stirred at room temperature for 30 min. The solvent was evaporated in vacuo. The remaining HCl salt was redissolved in MeOH (20 mL), platinum(IV) oxide (0.159 g, 0.70 mmol) was added and the reaction mixture hydrogenated in a Büchi hydrogenator at 5 bar and room temperature for 6 h. The catalyst was filtered off, washed with MeOH and the filtrate evaporated in vacuo to yield methyl 2-(3,4-difluorophenyl)piperidine-4-carboxylate hydrochloride (6.10 g, 90 %) as a pale solid. MS m/z 256 $(M+H)^+$.

Step 3: Dimethyl 2-(3,4-difluorophenyl)piperidine-1,4-dicarboxylate

Methyl 2-(3,4-difluorophenyl)piperidine-4-carboxylate hydrochloride (6.1 g, 20.91 mmol) and DIPEA (9.13 mL, 52.28 mmol) were dissolved in DCM (30 mL). Methyl chloroformate (1.944 mL, 25.09 mmol) was added and the reaction stirred at room temperature for 1.5 h. DCM (170 mL) was added. The organic phase was washed with 0.1 M HCl (2 x 200 mL), satd $NaHCO_3$ (200 mL), dried with a phase separator and evaporated in vacuo yielding dimethyl 2-(3,4-difluorophenyl)piperidine-1,4-dicarboxylate (6.58 g, 100 %) as a dark oil. MS m/z 314 $(M+H)^+$.

Step 4: 2-(3,4-Difluorophenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Dimethyl 2-(3,4-difluorophenyl)piperidine-1,4-dicarboxylate (6.578 g, 21.00 mmol) was dissolved in THF (40 mL) and water (0.800 mL). Lithium bromide (14.59 g, 167.97 mmol) and TEA (11.71 mL, 83.98 mmol) were added and the reaction was stirred at 80°C for 3 h. The reaction mixture was cooled to room temperature and some solvent evaporated in vacuo. EtOAc (150 mL) and water (150 mL) were added, shaken and the phases separated. The organic phase was extracted with water (150 mL). The combined aqueous phases were

acidified with 3 M HCl to pH 1 and extracted with EtOAc (2x300 mL). The combined organic phases were dried with Na_2SO_4, filtered and evaporated in vacuo to yield 2-(3,4-difluorophenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (5.66 g, 90 %) as a light brown oil. MS m/z 298 $(M+H)^+$.

Reference compound 10

2-(4-Fluorophenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: Methyl 2-(4-fluorophenyl)isonicotinate hydrochloride

Methyl 2-chloroisonicotinate (4.5 g, 26.23 mmol), 4-fluorophenylboronic acid (4.51 g, 32.26 mmol), potassium carbonate (2.247 g, 16.26 mmol) and $PdCl_2$(dppf) (0.380 g, 0.52 mmol) were mixed in methanol (30 mL) in two 20 mL microwave vials. The vials were capped and heated at 100°C for 10 min in a single node microwave reactor. The solids were removed by filtration and the filtrate evaporated to yield a darkred slurry. To the residue was added HCl (1.25 M in methanol, 100 mL). The mixture was stirred at 45°C for 4 h, then concentrated. Satd $NaHCO_3$ (100 mL) was added under ice cooling and extracted with DCM (3 x 100 mL) The combined organic phases were washed with brine, passed through a phase separator and evaporated to yield a brown solid. The crude was dissolved in MTBE (180 mL) and some solids were filtered off. Cooled with ice-water, hydrogen chloride (4 M in dioxane, 10 mL, 40 mmol) was added dropwise during stirring and a suspension was formed. The suspension was stirred at 0°C for 10 min. The solid was collected by filtration and washed with MTBE to yield methyl 2-(4-fluorophenyl)isonicotinate hydrochloride (6.4 g, 91 %) as a beige solid. ^1H NMR (400 MHz, cd3od) d 4.07 (s, 3H), 7.37 - 7.51 (m, 2H), 8.02 - 8.13 (m, 2H), 8.37 (dd, 1H), 8.71 (d, 1H), 8.97 (dd, 1H). MS m/z 232 $(M+H)^+$

Step 2: Methyl 2-(4-fluorophenyl)piperidine-4-carboxylate

Methyl 2-(4-fluorophenyl)isonicotinate hydrochloride (6.4 g, 23.91 mmol) was dissolved in methanol (100 mL) and platinum(IV) oxide (0.271 g, 1.20 mmol) added. The resulting mixture was hydrogenated in a Büchi hydrogenator at room temperature and 5 bar for 21 h. The catalyst was filtered off, washed with MeOH and the filtrate evaporated. DCM and satd $NaHCO_3$ were added and the phases separated. The organic layer was washed with brine, passed through a phase separator and evaporated to yield a brown oil. The residue was

purified by automated flash chromatography on a Biotage® KP-SIL 100g column. A gradient from 0 % to 5% of MeOH in DCM (containing 1 % Et_3N) over 10 CV was used as mobile phase and then isocratically eluted with 5% of MeOH in DCM (containing 1% Et_3N). Methyl 2-(4-fluorophenyl)piperidine-4-carboxylate (4.2 g, 74 %) was isolated. MS m/z 238 $(M+H)^+$

Step 3: Dimethyl 2-(4-fluorophenyl)piperidine-1,4-dicarboxylate

Methyl 2-(4-fluorophenyl)piperidine-4-carboxylate (7.4 g, 31.19 mmol) was dissolved in DCM (100 mL) and DIPEA (6.52 mL, 37.43 mmol) added followed by methyl chloroformate (2.95 mL, 37.43 mmol) at 0°C. The solution was stirred at room temperature for 1 h. The reaction mixture washed with 0.1 M HCl and satd $NaHCO_3$. The organic phase was passed through a phase separator and evaporated to yield dimethyl 2-(4-fluorophenyl)piperidine-1,4-dicarboxylate (8.07 g, 97 %) as a brown oil. MS m/z 296 $(M+H)^+$

Step 4: 2-(4-Fluorophenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Dimethyl 2-(4-fluorophenyl)piperidine-1,4-dicarboxylate (8.97 g, 30.38 mmol) was dissolved in acetonitrile (60 mL) and water (1.200 mL), then lithium bromide (21.10 g, 243.00 mmol) was added. Triethylamine (16.84 mL, 121.50 mmol) was added and the resulting brown suspension was heated under reflux for 1 h. Water (120 mL) and MTBE (120 mL) were added. The organic phase was extracted with water (2 x 25 mL). The pooled aqueous layer was acidified to pH 1 with 6 M HCl and extracted with MTBE (2 x 150 mL). The combined organic layer was washed with water (25 mL), dried over anhydrous Na_2SO_4 and evaporated. 2-(4-Fluorophenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (8.4 g, 98 %) was isolated as a brown oil.

Reference compound 11

2-(4-Chlorophenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: Methyl 2-(4-chlorophenyl)isonicotinate hydrochloride

Methyl 2-bromoisonicotinate (3.39 g, 15.69 mmol), 4-chlorophenylboronic acid (3.68 g, 23.54 mmol), potassium carbonate (3.25 g, 23.54 mmol) and $PdCl_2(dppf)$ (0.341 g, 0.47 mmol) were mixed in methanol (30 mL) in two separate 20 mL microwave vials. The vials were capped and heated at 100°C for 10 min in a single node microwave reactor. Water and DCM were

added and the phases were separated. The water phase (pH 9) was extracted with DCM and the combined organic phase washed with brine, passed through a phase separator and evaporated to yield an orange solid. The solid was dissolved in MTBE, then HCl (4 M in dioxane) was added to give crude methyl 2-(4-chlorophenyl)isonicotinate hydrochloride (4.3 g). MS m/z 248 $(M+H)^+$

Step 2: Methyl 2-(4-chlorophenyl)piperidine-4-carboxylate

Methyl 2-(4-chlorophenyl)isonicotinate hydrochloride (4.46 g, 15.69 mmol) was dissolved in MeOH (40 mL) and platinum(IV) oxide (0.356 g, 1.57 mmol) added. The resulting mixture was hydrogenated in a Büchi hydrogenator at room temperature and 5 bar for 1 h. The catalyst was filtered off and washed with MeOH and the eluate evaporated leaving a brown solid. The solid was dissolved in DCM and washed with 1 M K_2CO_3 and brine. The organic layer was dried through a phase-separator and evaporated. The residue was dissolved in DCM and added onto SCX-2 cation exchange columns (4*10 g columns. Each column was washed with DCM, MeOH and then eluted with NH_3/MeOH (1 CV each). The NH_3/MeOH layer was evaporated yielding methyl 2-(4-chlorophenyl)piperidine-4-carboxylate (3.13 g, 79 %). MS m/z 254 $(M+H)^+$

Step 3: Dimethyl 2-(4-chlorophenyl)piperidine-1,4-dicarboxylate

Methyl 2-(4-chlorophenyl)piperidine-4-carboxylate (3.13 g, 12.34 mmol) was dissolved in DCM (50 mL), then DIPEA (5.39 mL, 30.84 mmol) was added. Methyl carbonochloridate (1.360 mL, 17.27 mmol) was added dropwise to the solution. The mixture was stirred at room temperature for 3 h. The mixture was washed with 0.1 M HCl (2*100 mL) and satd $NaHCO_3$ (100 mL), then dried through a phase-separator and evaporated yielding dimethyl 2-(4-chlorophenyl)piperidine-1,4-dicarboxylate (3.97 g, quant.) as an orange oil. MS m/z 312 $(M+H)^+$

Step 4: 2-(4-Chlorophenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Dimethyl 2-(4-chlorophenyl)piperidine-1,4-dicarboxylate (3.97 g, 12.73 mmol) was dissolved into acetonitrile (55 mL) and water (1.1 mL), then lithium bromide (8.85 g, 101.87 mmol) was added. Et_3N (7.10 mL, 50.94 mmol) was added and the resulting yellow suspension was heated at reflux for 2 h. Water (100 mL) and MTBE (150 mL) were added. The phases were separated and the organic layer was extracted with water (2 x). The pooled water layers were

acidified to pH 1 with 3.8 M HCl and extracted with MTBE (2 x). The combined organic layer was dried over Na_2SO_4, filtered and evaporated leaving 2-(4-chlorophenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (3.49 g, 92 %) as a yellow semi-solid. MS m/z 298 $(M+H)^+$

Reference compound 12

1-(Methoxycarbonyl)-2-(3-(trifluoromethyl)phenyl)piperidine-4-carboxylic acid

Step 1: Methyl 2-(3-(trifluoromethyl)phenyl)isonicotinate

Methyl 2-bromoisonicotinate (2.71 g, 12.57 mmol), 3-(trifluoromethyl)phenylboronic acid (3.58 g, 18.85 mmol), potassium carbonate (2.61 g, 18.85 mmol) and $PdCl_2$(dppf) (0.162 g, 0.25 mmol) were mixed in methanol (30 mL) in two 20 mL microwave vials. The vials were capped and heated at 100°C for 10 min in a single node microwave reactor. DCM and water were added and the phases separated. The water phase (pH 9) was extracted with DCM and the combined organic phase washed with brine, passed through a phase separator and evaporated to yield a brown solid. The residue was dissolved in DCM and added onto an SCX-2 cation exchange column. The column was washed with DCM, MeOH and then eluted with NH_3/MeOH (1 CV each). The NH_3/MeOH layer was evaporated yielding methyl 2-(3-(trifluoromethyl)phenyl)isonicotinate (2.6 g, 73 %). MS m/z 282 $(M+H)^+$

Step 2: Methyl 2-(3-(trifluoromethyl)phenyl)piperidine-4-carboxylate

Methyl 2-(3-(trifluoromethyl)phenyl)isonicotinate (2.6 g, 9.25 mmol) was dissolved in acetic acid (40 mL) and platinum(IV) oxide (0.210 g, 0.92 mmol) added. The resulting mixture was hydrogenated in a Büchi hydrogenator at room temperature and 5 bar for 3 h. The catalyst was filtered off, washed with MeOH and the eluate evaporated. DCM and 1 M K_2CO_3 were added and the phases separated. The organic layer was washed with brine, passed through a phase separator and evaporated to yield methyl 2-(3-(trifluoromethyl)phenyl)piperidine-4-carboxylate (1.4 g, 52 %) as a slightly brown oil. MS m/z 288 $(M+H)^+$

Step 3: Dimethyl 2-(3-(trifluoromethyl)phenyl)piperidine-1,4-dicarboxylate

Methyl 2-(3-(trifluoromethyl)phenyl)piperidine-4-carboxylate (1.4 g, 4.87 mmol) was dissolved in DCM (50 mL), then DIPEA (2.128 mL, 12.18 mmol) was added. Methyl

chloroformate (0.537 mL, 6.82 mmol) was added dropwise to the solution. The reaction mixture was stirred at room temperature for 4 h, washed with 0.1 M HCl (100 mL) and satd NaHCO3 (100 mL), dried through a phase separator and evaporated yielding dimethyl 2-(3-(trifluoromethyl)phenyl)piperidine-1,4-dicarboxylate (1.7 g, quant.) as an orange oil. MS m/z 346 $(M+H)^+$

Step 4: 1-(Methoxycarbonyl)-2-(3-(trifluoromethyl)phenyl)piperidine-4-carboxylic acid

Dimethyl 2-(3-(trifluoromethyl)phenyl)piperidine-1,4-dicarboxylate (1.7 g, 4.92 mmol) was dissolved into acetonitrile (22 mL) and water (0.440 mL), then lithium bromide (3.42 g, 39.38 mmol) was added. Et_3N (2.74 mL, 19.69 mmol) was added and the resulting yellow suspension was heated under reflux for 2 h. Water (50 mL) and MTBE (150 mL) were added. The phases were separated and the organic layer was extracted with water (2 times). The pooled water layers were acidified to pH 1 with 3.8 M HCl and extracted with MTBE (2 times). The combined organic layer was dried over Na_2SO_4, filtered and evaporated yielding 1-(methoxycarbonyl)-2-(3-(trifluoromethyl)phenyl)piperidine-4-carboxylic acid (1.48 g, 91 %) as a slightly yellow semi-solid. MS m/z 332 $(M+H)^+$

Reference compound 13

1-(Methoxycarbonyl)-2-(4-(trifluoromethyl)phenyl)piperidine-4-carboxylic acid

Step 1: Methyl 2-(4-(trifluoromethyl)phenyl)isonicotinate

Methyl 2-chloroisonicotinate (5 g, 29.14 mmol), 4-(trifluoromethyl)phenylboronic acid (8.30 g, 43.71 mmol), potassium carbonate (6.04 g, 43.71 mmol) and $PdCl_2$(dppf) (0.633 g, 0.87 mmol) were mixed in methanol (30 mL) in two 20 mL microwave vials. Two drops of water were added to one of the vials and the vials were capped and heated at 100°C for 10 min in a single node microwave reactor. The solids were removed by filtration and the filtrate evaporated to yield a darkred slurry. DCM and water were added and the phases separated. The water phase (pH 9) was extracted with DCM and the combined organic phase washed with brine, passed through a phase separator and evaporated to yield a brown solid. The crude was dissolved in MTBE (180 mL) and solids filtered off. Hydrogen chloride (4 M in dioxane, (7.29 mL, 29.14 mmol) was added dropwise during stirring and a suspension was formed. The suspension was stirred at room temperature for 2.5 h. The solid was collected by filtration and

washed with MTBE. MTBE and satd $NaHCO_3$ was added to the solid, the organic phase dried (Na_2SO_4), filtered and evaporated to yield methyl 2-(4-(trifluoromethyl)phenyl)isonicotinate (5.75 g, 70 %) as a beige solid. ^1H NMR (400 MHz, cdcl$_3$) δ 4.00 (s, 3H), 7.75 (d, 2H), 7.84 (dd, 1H), 8.18 (d, 2H), 8.33 (s, 1H), 8.87 (dd, 1H). MS m/z 282 $(M+H)^+$

Step 2: Methyl 2-(4-(trifluoromethyl)phenyl)piperidine-4-carboxylate

Methyl 2-(4-(trifluoromethyl)phenyl)isonicotinate (4.985 g, 17.73 mmol) was dissolved in acetic acid (45 mL) and platinum(IV) oxide (0.232 g, 1.02 mmol) added. The resulting mixture was hydrogenated in a Büchi hydrogenator at room temperature and 5 bar for 5 h. More platinum(IV) oxide (0.116 g, 0.51 mmol) was added and the hydrogenation continued at 5 bar for 1 h. The catalyst was filtered off and washed with MeOH and the eluate evaporated. DCM and 10 % K_2CO_3 were added and the phases separated. The organic layer was washed with brine, passed through a phase separator and evaporated to yield methyl 2-(4-(trifluoromethyl)phenyl)piperidine-4-carboxylate (5.04 g, 99 %) as a brown oil. MS m/z 288 $(M+H)^+$

Step 3: Dimethyl 2-(4-(trifluoromethyl)phenyl)piperidine-1,4-dicarboxylate

Methyl 2-(4-(trifluoromethyl)phenyl)piperidine-4-carboxylate (4.973 g, 17.31 mmol) was dissolved in DCM (100 mL) and DIPEA (3.62 mL, 20.77 mmol) added followed by methyl carbonochloridate (1.636 mL, 20.77 mmol). The solution was stirred at room temperature for 1 h 45 min. The reaction mixture was washed with 0.1 M HCl and satd $NaHCO_3$. The organic phase was passed through a phase separator and evaporated to yield crude dimethyl 2-(4-(trifluoromethyl)phenyl)piperidine-1,4-dicarboxylate (6.05 g, 101 %) as a brown oil. MS m/z 346 $(M+H)^+$

Step 4: 1-(Methoxycarbonyl)-2-(4-(trifluoromethyl)phenyl)piperidine-4-carboxylic acid

Dimethyl 2-(4-(trifluoromethyl)phenyl)piperidine-1,4-dicarboxylate (5.996 g, 17.36 mmol) was dissolved in acetonitrile (60 mL) and water (1.200 mL), then lithium bromide (12.06 g, 138.91 mmol) was added. Triethylamine (9.63 mL, 69.46 mmol) was added and the resulting brown suspension was heated under reflux for 1 h. Water and MTBE were added. The organic phase was extracted with water (x2). The combined aqueous layer was acidified to pH 1 with 3.8 M aq HCl and then extracted with MTBE (x2). The combined organic layer was washed with water and evaporated. Trace of water was azeotropically removed by MeCN. 1-

(Methoxycarbonyl)-2-(4-(trifluoromethyl)phenyl)piperidine-4-carboxylic acid (5.71 g, 99 %) was isolated as a brown oil. MS m/z 332 $(M+H)^+$

Reference compound 14

2-(3-tert-Butylphenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: 2-(3-tert-Butylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

1-Bromo-3-tert-butylbenzene (4.48 g, 21 mmol) was dissolved in DMSO (150 mL) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (5.87 g, 23.10 mmol), potassium acetate (6.18 g, 63.00 mmol) and $Pd(PPh_3)_4$ (1.213 g, 1.05 mmol) added. The resulting brown suspension was heated to 80°C under nitrogen. After 9 h water and diethyl ether were added and the phases separated. The organic phase was evaporated and water azeotropically removed by MeCN. The residue was purified via Biotage in two runs (0 => 20 % EtOAc in heptane, 5 CV; Biotage® KP-SIL 340 g column) to yield a yellow oil. Purified again via Biotage (0 => 20 % EtOAc in heptane, 8 CV; Biotage® KP-SIL 340 g column). 2-(3-tert-Butylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.39 g, 62 %) was isolated as a yellow oil. ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.32 (s, 9H), 1.33 (s, 12H), 7.29 (t, 1H), 7.47 – 7.50 (m, 1H), 7.61 (d, 1H), 7.81 (s, 1H).

Step 2: Methyl 2-(3-tert-butylphenyl)isonicotinate hydrochloride

Methyl 2-chloroisonicotinate (1.7 g, 9.91 mmol), 2-(3-tert-butylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.393 g, 13.04 mmol), potassium carbonate (2.054 g, 14.86 mmol) and $PdCl_2$(dppf) (0.215 g, 0.30 mmol) were mixed in methanol (14 mL) in a 20 mL microwave vial. The vial was capped and heated at 100°C for 10 min in a single node microwave reactor. The reaction mixture was suspended in methanol, the solids removed by filtration and the filtrate evaporated to yield a darkred slurry. DCM and water were added and the phases separated. The water phase (pH 9) was extracted with DCM and the combined organic phase washed with brine, passed through a phase separator and evaporated to a brown solid. The solid was dissolved in MTBE (100 mL) and the solids were filtered off. Hydrogen chloride(4 M in dioxane, 3.50 mL, 13.99 mmol) was added dropwise during stirring and a suspension was formed. The suspension was stirred at room temperature for 3 days. The solid was collected by filtration and washed with MTBE to yield methyl 2-(3-tert-

butylphenyl)isonicotinate hydrochloride (2.14 g, 70 %) as a slightly brown solid. ^{1}H NMR (600 MHz, cd_3od) δ 1.41 (s, 9H), 4.07 (s, 3H), 7.62 (t, 1H), 7.77 – 7.80 (m, 2H), 8.00 – 8.02 (m, 1H), 8.37 – 8.40 (m, 1H), 8.69 – 8.71 (m, 1H), 8.94 – 8.97 (m, 1H).

Step 3: Methyl 2-(3-tert-butylphenyl)piperidine-4-carboxylate

Methyl 2-(3-tert-butylphenyl)isonicotinate hydrochloride (3 g, 9.81 mmol) was dissolved in methanol (100 mL) and platinum(IV) oxide (0.111 g, 0.49 mmol) added. The resulting mixture was hydrogenated in a Büchi hydrogenator at room temperature and 5 bar for 13 h. To the mixture was added platinum(IV) oxide (40 mg), and the mixture was hydrogenated in a Büchi hydrogenator at room temperature and 5 bar for 1 h. The catalyst was filtered off and washed with MeOH and the eluate evaporated. DCM and satd $NaHCO_3$ were added and the phases separated. Washed with brine, passed through a phase separator and evaporated to yield methyl 2-(3-tert-butylphenyl)piperidine-4-carboxylate (2.56 g, 95 %) as a brown oil

Step 4: Dimethyl 2-(3-tert-butylphenyl)piperidine-1,4-dicarboxylate

Methyl 2-(3-tert-butylphenyl)piperidine-4-carboxylate (2.56 g, 9.30 mmol) was dissolved in DCM (100 mL) and DIPEA (2.429 mL, 13.94 mmol) added followed by methyl carbonochloridate (0.9 mL, 11.43 mmol) at 0°C. The solution was stirred at room temperature for 1 h. The reaction mixture was washed with 1 M aq HCl (pH 4) followed by brine, satd $NaHCO_3$. The organic phase was passed through a phase separator and evaporated to yield dimethyl 2-(3-tert-butylphenyl)piperidine-1,4-dicarboxylate (3.17 g, quant.) as a brown oil.

Step 5: 2-(3-tert-Butylphenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Dimethyl 2-(3-tert-butylphenyl)piperidine-1,4-dicarboxylate (3.17 g, 9.51 mmol) was dissolved in acetonitrile (60 mL) and water (1.200 mL), then lithium bromide (6.61 g, 76.06 mmol) was added in one portion. Triethylamine (5.27 mL, 38.03 mmol) was added and the resulting brown suspension was heated under reflux for 1.5 h. Water (120 mL) and MTBE (120 mL) were added. The organic phase was extracted with water (2 x 25 mL). The pooled aqueous layer was acidified to pH 1 with 0.5 M HCl (30 mL) and extracted with MTBE (2 x 150 mL). The combined organic layer was washed with water (25 mL), dried over Na_2SO_4 and evaporated. 2-(3-tert-Butylphenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (2.73 g, 90 %) was isolated as a foam.

Reference compound 15

2-(4-tert-Butylphenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: Methyl 2-(4-tert-butylphenyl)isonicotinate hydrochloride

Methyl 2-chloroisonicotinate (7 g, 40.80 mmol), 4-tert-butylphenylboronic acid (10 g, 56.17 mmol), potassium carbonate (3.5 g, 25.32 mmol) and $PdCl_2$(dppf) (0.9 g, 1.24 mmol) were mixed in methanol (30 mL) in two equal portions in 20 mL microwave vials. The vials were capped and heated at 100°C for 10 min in a single node microwave reactor. The solids were removed by filtration and the filtrate evaporated to yield a dark red slurry. DCM and brine were added and the phases separated. The water phase (pH 9) was extracted with DCM and the combined organic phases dried over $MgSO_4$ and evaporated. The crude was dissolved in MTBE (180 mL) and the solids filtered off. Hydrogen chloride (4 M in dioxane, 10.20 mL, 40.80 mmol) was added dropwise during stirring and a suspension was formed. The suspension was stirred at room temperature for 1 h. The solid was collected by filtration and washed with MTBE. Methyl 2-(4-tert-butylphenyl)isonicotinate hydrochloride (9.6 g, 77 %) was isolated as a dark brown solid. ^{1}H NMR (400 MHz, dmso) δ 1.30 (s, 9H), 3.92 (s, 3H), 7.53 (d, 2H), 7.80 (dd, 1H), 8.04 (d, 2H), 8.29 (s, 1H), 8.85 (d, 1H), 9.86 (br, 1H). MS m/z 270 $(M+H)^+$

Step 2: Methyl 2-(4-tert-butylphenyl)piperidine-4-carboxylate hydrochloride

To a solution of methyl 2-(4-tert-butylphenyl)isonicotinate hydrochloride (9.6 g, 31.39 mmol) in MeOH (100 mL) was added platinum(IV) oxide (0.713 g, 3.14 mmol). The resulting mixture was hydrogenated in a Büchi hydrogenator at 5 bar. After 8 h the reaction mixture was filtered through a diatomeous earth filter carton, the residue washed with methanol, and the filtrate evaporated. Methyl 2-(4-tert-butylphenyl)piperidine-4-carboxylate hydrochloride (9.66 g, 99 %) was isolated as a brown solid. ^{1}H NMR (400 MHz, dmso) δ 1.26 (s, 9H), 1.88 – 2.15 (m, 4H), 2.82 – 2.92 (m, 1H), 3.03 – 3.16 (m, 1H), 3.27 – 3.38 (m, 1H), 3.61 (s, 3H), 4.22 – 4.29 (m, 1H), 7.42 – 7.53 (m, 4H), 9.43 (br, 2H). MS m/z 276 $(M+H)^+$

Step 3: Dimethyl 2-(4-tert-butylphenyl)piperidine-1,4-dicarboxylate

To a suspension of methyl 2-(4-tert-butylphenyl)piperidine-4-carboxylate hydrochloride (9.66 g, 30.98 mmol) in dichloromethane (100 mL) was added DIPEA (12 mL, 68.89 mmol). The

reaction mixture was cooled in an ice-bath and methyl carbonochloridate (2.8 mL, 35.56 mmol) was added dropwise over 5 min. The reaction mixture was stirred for 18 h at room temperature and washed with 3.8 N HCl. The aqueous layer was extracted with DCM. The combined organic layers were dried over $MgSO_4$ and evaporated. Dimethyl 2-(4-tert-butylphenyl)piperidine-1,4-dicarboxylate (10.6 g, quant.) was isolated as a dark brown oil. MS m/z 334 $(M+H)^+$

Step 4: 2-(4-tert-Butylphenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

To a solution of dimethyl 2-(4-tert-butylphenyl)piperidine-1,4-dicarboxylate (10.937 g, 32.80 mmol) in MeCN (100 mL) was added lithium bromide (6.58 mL, 262.42 mmol), triethylamine (18.19 mL, 131.21 mmol) and water (2 mL). The resulting mixture was heated under reflux for 3 h, then cooled to room temperature. The solvents were evaporated and the residue dissolved in water. The aqueous layer was washed with MTBE, then acidified by the addition of 3.8 N HCl. The aqueous layer was extracted three times with DCM. The combined organic layers were dried over $MgSO_4$ and evaporated. 2-(4-tert-Butylphenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (9.5 g, 91%) was isolated as a light brown foam. MS m/z 320 $(M+H)^+$

Reference compound 16

1-(Methoxycarbonyl)-2-(4-(methylsulfonyl)phenyl)piperidine-4-carboxylic acid

Step 1: Methyl 2-(4-(methylsulfonyl)phenyl)isonicotinate

Methyl 2-chloroisonicotinate (5 g, 29.14 mmol), 4-(methylsulfonyl)phenylboronic acid (7.58 g, 37.88 mmol), potassium carbonate (2.416 g, 17.48 mmol) and $PdCl_2$(dppf) (0.633 g, 0.87 mmol) were dissolved in methanol (30 mL) and divided up in two microwave vials. Each vial was heated to 100°C in a single node microwave raector for 35 min. DCM (250 mL) and water (250 mL) were added, shaken and the phases separated. The aqueous phase was extracted with DCM (250 mL). The combined organic phases were washed with brine (500 mL), dried with a phase separator and evaporated in vacuo. The residue was purified by automated flash chromatography on two Biotage® KP-SIL 340g columns. A gradient of 20 - 70 % EtOAc in heptane over 10 CV and then 70 % EtOAc in heptane over 5 CV was used as mobile phase. The product was collected using the wavelength 253 nm. The product fractions

were collected and evaporated in vacuo yielding methyl 2-(4-(methylsulfonyl)phenyl)-isonicotinate (5.66 g, 66.7 %) as a white solid. ^{1}H NMR (600 MHz, CDCl3) δ 3.09 (s, 3H), 3.98 (s, 3H), 7.85 (dd, 1H), 8.05 (d, 2H), 8.25 (d, 2H), 8.34 (s, 1H), 8.86 (t, 1H).

Step 2: Methyl 2-(4-(methylsulfonyl)phenyl)piperidine-4-carboxylate hydrochloride

Methyl 2-(4-(methylsulfonyl)phenyl)isonicotinate (5.663 g, 19.44 mmol) was suspended in MeOH (20 mL) and hydrogen chloride (1.25 M in MeOH, 40 mL, 50.00 mmol) was added. The mixture was stirred at room temperature for 20 min and then evaporated in vacuo. The HCl salt was suspended in MeOH (100 mL) and platinum(IV) oxide (0.221 g, 0.97 mmol) added. The mixture was hydrogenated in a Büchi hydrogenator at room temperature and 5 bar for 2 h. The catalyst was filtered off and washed with MeOH. The filtrate was evaporated in vacuo yielding methyl 2-(4-(methylsulfonyl)phenyl)piperidine-4-carboxylate hydrochloride (5.84 g, 90 %) as a white solid. MS m/z 298 $(M+H)^+$

Step 3: Dimethyl 2-(4-(methylsulfonyl)phenyl)piperidine-1,4-dicarboxylate

Methyl 2-(4-(methylsulfonyl)phenyl)piperidine-4-carboxylate hydrochloride (5.2 g, 15.58 mmol) and DIPEA (6.78 mL, 38.94 mmol) were dissolved in DCM (40 mL) and methyl carbonochloridate (1.472 mL, 18.69 mmol) added. The reaction was stirred at room temperature for 50 min. DCM (160 mL) was added. The organic phase was washed with 0.1 M HCl (2x200 mL), satd $NaHCO_3$ (200 mL), dried with a phase separator and evaporated in vacuo yielding crude dimethyl 2-(4-(methylsulfonyl)phenyl)piperidine-1,4-dicarboxylate (5.95 g, 108 %). MS m/z 356 $(M+H)^+$

Step 4: 1-(Methoxycarbonyl)-2-(4-(methylsulfonyl)phenyl)piperidine-4-carboxylic acid

Dimethyl 2-(4-(methylsulfonyl)phenyl)piperidine-1,4-dicarboxylate (5.952 g, 16.75 mmol) was dissolved in acetonitrile (50 mL) and water (1.000 mL), then lithium bromide (11.64 g, 133.98 mmol) added. Triethylamine (9.29 mL, 66.99 mmol) was added and the reaction mixture heated under reflux for 1.5 h. MTBE (150 mL) and water (150 mL) were added, shaken and the phases separated. The organic phase was extracted with water (2x200 mL). The combined aqueous phases were acidified to pH 1 with 3 M HCl and extracted with MTBE (2x500 mL). The combined organic phases were dried with Na_2SO_4, filtered and evaporated in vacuo yielding 1-(methoxycarbonyl)-2-(4-(methylsulfonyl)phenyl)piperidine-4-carboxylic acid (4.76 g, 83 %). MS m/z 342 $(M+H)^+$

Reference compound 17

1-(Methoxycarbonyl)-2-(6-(trifluoromethyl)pyridin-3-yl)piperidine-4-carboxylic acid

Step 1: Methyl 6'-(trifluoromethyl)-2,3'-bipyridine-4-carboxylate hydrochloride

Methyl 2-chloroisonicotinate (3 g, 17.48 mmol), 6-(trifluoromethyl)pyridin-3-yl boronic acid (5.01 g, 26.23 mmol), potassium carbonate (1.450 g, 10.49 mmol) and $PdCl_2$(dppf) (0.380 g, 0.52 mmol) were mixed in methanol (30 mL) in two separate 20 mL microwave vials. The vials were capped and heated at 100°C for 10 min in a single node microwave reactor. Water and DCM were added and the phases were separated. The water phase (pH 9) was extracted with DCM and the combined organic phase washed with brine, passed through a phase separator and evaporated to yield an orange solid. The solid was diluted with MTBE, then HCl (4 M in dioxane) was added to give a suspension. The solids were collected by filtration to yield methyl 6'-(trifluoromethyl)-2,3'-bipyridine-4-carboxylate hydrochloride (3.2 g, 57 %). MS m/z 283 $(M+H)^+$

Step 2: Methyl 2-(6-(trifluoromethyl)pyridin-3-yl)piperidine-4-carboxylate hydrochloride

Methyl 6'-(trifluoromethyl)-2,3'-bipyridine-4-carboxylate hydrochloride (2.5 g, 7.86 mmol) was dissolved in MeOH (20 mL) and platinum(IV) oxide (0.036 g, 0.16 mmol) added. The resulting mixture was hydrogenated in a Büchi hydrogenator at room temperatute and 5 bar for 1 h. Additional catalyst was added and the hydrogenation was continued for 1 h. The catalyst was filtered off, washed with MeOH and the eluate evaporated yielding methyl 2-(6-(trifluoromethyl)pyridin-3-yl)piperidine-4-carboxylate hydrochloride (2.2 g, 86 %) as a brown solid. MS m/z 289 $(M+H)^+$

Step 3: Dimethyl 2-(6-(trifluoromethyl)pyridin-3-yl)piperidine-1,4-dicarboxylate

Methyl 2-(6-(trifluoromethyl)pyridin-3-yl)piperidine-4-carboxylate hydrochloride (3 g, 9.24 mmol) was dissolved in DCM (50 mL) and DIPEA (4.03 mL, 23.10 mmol). Methyl carbonochloridate (1.019 mL, 12.93 mmol) was added dropwise to the solution. The mixture was stirred at room temperature for 10 minutes. The mixture was washed with 0.1 M HCl (2x100 mL) and satd $NaHCO_3$ (100 mL), then dried through a phase-separator and evaporated

yielding crude dimethyl 2-(6-(trifluoromethyl)pyridin-3-yl)piperidine-1,4-dicarboxylate (3 g, 94 %) as a darkbrown oil. MS m/z 347 $(M+H)^+$

Step 4: 1-(Methoxycarbonyl)-2-(6-(trifluoromethyl)pyridin-3-yl)piperidine-4-carboxylic acid

Crude dimethyl 2-(6-(trifluoromethyl)pyridin-3-yl)piperidine-1,4-dicarboxylate (2.9 g, 8.38 mmol) was dissolved in acetonitrile (35 mL) and water (0.700 mL), then lithium bromide (2.91 g, 33.50 mmol) was added. Et_3N (2.334 mL, 16.75 mmol) was added and the resulting yellow suspension was heated under reflux for 1 h. Water (100 mL) and MTBE (150 mL) were added. The phases were separated and the organic layer was extracted with water (2 times). The pooled water layers were acidified to pH 1 with 3.8 M HCl and extracted into MTBE (2 times). The combined organic layer was dried over Na_2SO_4, filtered and evaporated yielding crude 1-(methoxycarbonyl)-2-(6-(trifluoromethyl)pyridin-3-yl)piperidine-4-carboxylic acid (2.5 g, 90 %) as a slightly yellow solid. MS m/z 333 $(M+H)^+$

Reference compound 18

2-(5-tert-Butylthiophen-2-yl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: Methyl 2-(5-tert-butylthiophen-2-yl)isonicotinate

Methyl 2-chloroisonicotinate (175 mg, 1.02 mmol), 2-(5-tert-butylthiophen-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (300 mg, 1.13 mmol), K_2CO_3 (85 mg, 0.61 mmol) and $PdCl_2$(dppf) (37.3 mg, 0.05 mmol) was stirred in methanol (2 mL) and heated in a single node microwave reactor to 100°C for 30 min. DCM (50 mL) and water (50mL) were added, shaken and the phases separated. The aqueous phase was extracted with DCM (50 mL). The combined organic phases were dried with a phase separator and evaporated in vacuo. The residue was purified by automated flash chromatography on a Biotage® KP-SIL 50g column. A gradient from 5 % EtOAc in heptane over 2 CV followed by 5 % to 20 % of EtOAc in heptane over 9 CV was used as mobile phase. The product was collected using the wavelength 295 nm. The product fractions were collected and evaporated in vacuo yielding methyl 2-(5-tert-butylthiophen-2-yl)isonicotinate (213 mg, 76 %). ^1H NMR (600 MHz, cdcl$_3$) δ 1.41 (s, 9H), 3.96 (s, 3H), 6.85 (d, 1H), 7.50 (s, 1H), 7.61 (d, 1H), 8.13 (s, 1H), 8.64 (d, 1H). MS m/z 276 $(M+H)^+$

Step 2: Methyl 2-(5-tert-butylthiophen-2-yl)piperidine-4-carboxylate hydrochloride

Methyl 2-(5-tert-butylthiophen-2-yl)isonicotinate (2.02 g, 7.34 mmol) was dissolved in hydrogen chloride (1.25 M in MeOH, 11.74 mL, 14.67 mmol) and stirred at room temperature for 30 min. The solvent was evaporated in vacuo. The residue was dissolved in MeOH (20 mL), platinum(IV) oxide (0.050 g, 0.22 mmol) added and the reaction mixture hydrogenated in a Büchi hydrogenator at 5 bar and room temperature for 3 h. Additional platinum(IV) oxide (0.050 g, 0.22 mmol) was added and the hydrogenation continued for 3 h. The reaction mixture was filtered through celite, washed with MeOH and the filtrate evaporated in vacuo. The residue was redissolved in MeOH (15 mL) and platinum(IV) oxide (0.167 g, 0.73 mmol) added. Hydrogenation was continued for 3 h. Additional platinum(IV) oxide (0.167 g, 0.73 mmol) was added and the hydrogenation continued for 2 h. The reaction mixture was filtered through celite, washed with MeOH and the filtrate evaporated in vacuo to yield methyl 2-(5-tert-butylthiophen-2-yl)piperidine-4-carboxylate hydrochloride (2.360 g, 101 %) as a black oil. MS m/z 282 $(M+H)^+$

Step 3: Dimethyl 2-(5-tert-butylthiophen-2-yl)piperidine-1,4-dicarboxylate

Methyl 2-(5-tert-butylthiophen-2-yl)piperidine-4-carboxylate hydrochloride (2.36 g, 7.42 mmol) and DIPEA (3.24 mL, 18.56 mmol) were dissolved in DCM (30 mL). Methyl chloroformate (0.690 mL, 8.91 mmol) was added and the reaction mixture stirred at room temperature for 1 h. DCM (170 mL) was added. The organic phase was washed with 0.1 M HCl (2 x 200 mL), satd $NaHCO_3$ (200 mL), dried with a phase separator and evaporated in vacuo yielding dimethyl 2-(5-tert-butylthiophen-2-yl)piperidine-1,4-dicarboxylate (2.490 g, 99 %) as a dark oil. MS m/z 340 $(M+H)^+$

Step 4: 2-(5-tert-Butylthiophen-2-yl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Dimethyl 2-(5-tert-butylthiophen-2-yl)piperidine-1,4-dicarboxylate (2.49 g, 7.34 mmol) was dissolved in acetonitrile (20 mL). Water (0.400 mL) and lithium bromide (5.10 g, 58.68 mmol) were added. After 5 min, TEA (4.09 mL, 29.34 mmol) was added and the reaction heated at reflux for 1 h. MTBE (150 mL) and water (150 mL) were added, shaken and the phases separated. The organic phase was extracted with water (150 mL). The combined aqueous phases were acidified with 3 M HCl to pH 1 and extracted with MTBE (2 x 300 mL). The combined organic phases were dried with Na_2SO_4, filtered and evaporated in vacuo

yielding 2-(5-tert-butylthiophen-2-yl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (1.125 g, 47.1 %) as a white foam. MS m/z 326 $(M+H)^+$

Reference compound 19

2-(2,4-Difluorophenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: Methyl 2-(2,4-difluorophenyl)isonicotinate hydrochloride

Methyl 2-chloroisonicotinate (3 g, 17.48 mmol), 2,4-difluorophenylboronic acid (4.14 g, 26.23 mmol), potassium carbonate (1.812 g, 13.11 mmol) and $PdCl_2$(dppf) (0.380 g, 0.52 mmol) were mixed in methanol (30 mL) in two separate 20 mL microwave vials. The vials were capped and heated at 100°C for 10 min in a single node microwave reactor. Water and DCM were added and the phases were separated. The water phase (pH 9) was extracted with DCM and the combined organic phase washed with brine, passed through a phase separator and evaporated to yield a brown solid. The solid was dissolved in MTBE and stirred for 15 minutes, then filtered. The orange MTBE layer was treated with hydrogen chloride (4 M in dioxane, 4.37 mL, 17.48 mmol) and stirred for 1 h at room temperature. The formed solid was collected by filtration. Methyl 2-(2,4-difluorophenyl)isonicotinate hydrochloride (4.0 g, 80 %) was isolated as a slightly orange solid. MS m/z 250 $(M+H)^+$

Step 2: Methyl 2-(2,4-difluorophenyl)piperidine-4-carboxylate hydrochloride

Methyl 2-(2,4-difluorophenyl)isonicotinate hydrochloride (3.93 g, 13.76 mmol) was dissolved in MeOH (40 mL) and platinum(IV) oxide (0.312 g, 1.38 mmol) added. The resulting mixture was hydrogenated in a Büchi hydrogenator at room temperature and 5 bar for 2 h. The catalyst was filtered off, washed with MeOH and the eluate evaporated leaving methyl 2-(2,4-difluorophenyl)piperidine-4-carboxylate hydrochloride (2.34 g, 58 %) as a slightly yellow solid. MS m/z 256 $(M+H)^+$

Step 3: Dimethyl 2-(2,4-difluorophenyl)piperidine-1,4-dicarboxylate

Methyl 2-(2,4-difluorophenyl)piperidine-4-carboxylate hydrochloride (2.34 g, 8.02 mmol) was dissolved in DCM (50 mL), then DIPEA (3.50 mL, 20.05 mmol) was added. Methyl carbonochloridate (0.884 mL, 11.23 mmol) was added dropwise to the solution. The mixture was stirred at room temperature for 4 h, washed with 0.1 M HCl (100 mL) and satd $NaHCO_3$

(100 mL), then dried through a phase-separator and evaporated yielding dimethyl 2-(2,4-difluorophenyl)piperidine-1,4-dicarboxylate (2.38 g, 95 %) as an orange oil.

Step 4: 2-(2,4-Difluorophenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Dimethyl 2-(2,4-difluorophenyl)piperidine-1,4-dicarboxylate (2.38 g, 7.60 mmol) was dissolved into acetonitrile (35 mL) and water (0.700 mL), then lithium bromide (5.28 g, 60.77 mmol) was added. Et_3N (4.24 mL, 30.39 mmol) was added and the resulting yellow suspension was heated under reflux for 2 h. Water (50 mL) and MTBE (150 mL) were added. The phases were separated and the organic layer was extracted with water (2 times). The pooled water layers were acidified to pH 1 with 3.8 M HCl and extracted with MTBE (2 times). The combined organic layer was dried over Na_2SO_4, filtered and evaporated yielding 2-(2,4-difluorophenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (2.27, quant.) as a slightly yellow semi-solid. MS m/z 300 $(M+H)^+$

Reference compound 20

2-(4-Chloro-2-fluorophenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: Methyl 2-(4-chloro-2-fluorophenyl)isonicotinate hydrochloride

Methyl 2-chloroisonicotinate (4 g, 23.31 mmol), 4-chloro-2-fluorophenylboronic acid (6.10 g, 34.97 mmol), potassium carbonate (2.416 g, 17.48 mmol) and $PdCl_2$(dppf) (0.506 g, 0.70 mmol) were mixed in methanol (30 mL) in two separate 20 mL microwave vials. The vials were capped and heated at 100°C for 10 min in a single node microwave reactor. Water and DCM were added and the phases were separated. The water phase (pH 9) was extracted with DCM and the combined organic phase washed with brine, passed through a phase separator and evaporated to yield a dark-orange solid. The solid was dissolved in MTBE and stirred for 15 minutes, then filtered. The orange MTBE layer was treated with hydrogen chloride (4 M in dioxane, 5.83 mL, 23.31 mmol) and stirred for 1 h at room temperature. The precipitate was collected by filtration to yield methyl 2-(4-chloro-2-fluorophenyl)isonicotinate hydrochloride (7.22 g, quant.) as a slightly orange solid. MS m/z 266 $(M+H)^+$

Step 2: Methyl 2-(4-chloro-2-fluorophenyl)piperidine-4-carboxylate

Methyl 2-(4-chloro-2-fluorophenyl)isonicotinate hydrochloride (7.26 g, 24.03 mmol) was

dissolved in MeOH (100 mL) and platinum(IV) oxide (0.546 g, 2.40 mmol) added. The resulting mixture was hydrogenated in a Büchi hydrogenator at room temperature and 5 bar for 1 h. The catalyst was filtered off and washed with MeOH and the eluate evaporated yielding methyl 2-(4-chloro-2-fluorophenyl)piperidine-4-carboxylate hydrochloride (7.45 g, quant.) as a brown solid. MS m/z 272 $(M+H)^+$

Step 3: Dimethyl 2-(4-chloro-2-fluorophenyl)piperidine-1,4-dicarboxylate

Methyl 2-(4-chloro-2-fluorophenyl)piperidine-4-carboxylate (7.45 g, 27.42 mmol) was dissolved into DCM (120 mL) then DIPEA (11.97 mL, 68.55 mmol) was added. Methyl carbonochloridate (3.02 mL, 38.39 mmol) was added dropwise to the solution. The mixture was stirred at room temperature for 3 h. The mixture was washed with 0.1 M HCl (2x100 mL) and satd $NaHCO_3$ (100 mL), then dried through a phase-separator and evaporated leaving dimethyl 2-(4-chloro-2-fluorophenyl)piperidine-1,4-dicarboxylate (7.77 g, 86 %) as an orange oil. MS m/z 330 $(M+H)^+$

Step 4: 2-(4-Chloro-2-fluorophenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Dimethyl 2-(4-chloro-2-fluorophenyl)piperidine-1,4-dicarboxylate (7.77 g, 23.56 mmol) was dissolved into acetonitrile (100 mL) and water (2.000 mL), then lithium bromide (16.37 g, 188.51 mmol) was added. Et_3N (13.14 mL, 94.25 mmol) was added and the resulting yellow suspension was heated under reflux for 2 h. Water (200 mL) and MTBE (300 mL) were added. The phases were separated and the organic layer was extracted with water (2 times). The pooled water layers were acidified to pH 1 with 3.8 M HCl and extracted with MTBE (2 times). The combined organic layer was dried over $MgSO_4$, filtered and evaporated yielding 2-(4-chloro-2-fluorophenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (7.28 g, 98 %) as a yellow semi-solid. MS m/z 316 $(M+H)^+$

Reference compound 21

2-(2-Chloro-4-fluorophenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: Methyl 2-(2-chloro-4-fluorophenyl)isonicotinate hydrochloride

Methyl 2-chloroisonicotinate (3.5 g, 20.40 mmol), 2-chloro-4-fluorophenylboronic acid (3.91 g, 22.44 mmol), potassium carbonate (2.114 g, 15.30 mmol) and $PdCl_2$(dppf) (0.443 g, 0.61

mmol) were mixed in methanol (30 mL) in two separate 20 mL microwave vials. The vials were capped and heated at 100°C for 10 min in a single node microwave reactor. Water and DCM were added and the phases were separated. The water phase (pH 9) was extracted with DCM and the combined organic phase washed with brine, passed through a phase separator and evaporated to yield a dark-brown solid. The solid was dissolved in MTBE and stirred for 15 minutes, then filtered. The MTBE layer was treated with hydrogen chloride (4 M in dioxane, 5.10 mL, 20.40 mmol) and stirred for 1 h at room temperature. The precipitate was collected by filtration. Methyl 2-(2-chloro-4-fluorophenyl)isonicotinate (2.350 g, 38.1 %) was obtained as a light yellow solid. ^{1}H NMR (400 MHz, cdcl$_3$) δ 4.13 (s, 3H), 7.24 – 7.33 (m, 1H), 7.36 (d, 1H), 7.82 – 8.03 (m, 1H), 8.34 (s, br., 1H), 8.56 (s, br., 1H), 9.08 (s, br., 1H). MS m/z 266 $(M+H)^+$

Step 2: Methyl 2-(2-chloro-4-fluorophenyl)piperidine-4-carboxylate hydrochloride

Methyl 2-(2-chloro-4-fluorophenyl)isonicotinate hydrochloride (2.35 g, 7.78 mmol) was dissolved in methanol (50 mL) and platinum(IV) oxide (0.177 g, 0.78 mmol) was added. The reaction mixture was hydrogenated in a Büchi hydrogenator at 5 bar and room temperature for 9 h. The catalyst was removed by filtration and the solvent was evaporated. The residue was dissolved in methanol (50.0 mL) and platinum(IV) oxide (144 mg, 0.63 mmol) was added. Hydrogenation was continued at 5 bar and room temperature for 4 h. The catalyst was removed by filtration and the solvent was evaporated. Crude methyl 2-(2-chloro-4-fluorophenyl)piperidine-4-carboxylate hydrochloride (2.4 g, 100 %) was obtained as a yellow solid. MS m/z 272 $(M+H)^+$

Step 3: Dimethyl 2-(2-chloro-4-fluorophenyl)piperidine-1,4-dicarboxylate

Methyl 2-(2-chloro-4-fluorophenyl)piperidine-4-carboxylate hydrochloride (2.4 g, 7.79 mmol) was dissolved in dichloromethane (50 mL) to give a colorless solution. DIPEA (3.39 mL, 19.47 mmol) and methyl carbonochloridate (0.736 mL, 9.35 mmol) were added and the mixture was stirred at room temperatute for 14 h. 0.1 M HCl was added and the aqueous phase was extracted with DCM. The combined organic layers were filtered through a phase separator and evaporated. Crude 2-(2-chloro-4-fluorophenyl)piperidine-1,4-dicarboxylate (2.5 g, 97 %) was obtained as a yellow oil. MS m/z 330 $(M+H)^+$

Step 4: 2-(2-Chloro-4-fluorophenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Dimethyl 2-(2-chloro-4-fluorophenyl)piperidine-1,4-dicarboxylate (2.5 g, 7.58 mmol) was dissolved in acetonitrile (50 mL) and water (1 mL), then lithium bromide (5.27 g, 60.65 mmol) was added. Triethylamine (4.20 mL, 30.33 mmol) was added and the resulting suspension was heated under reflux for 7 h. MTBE (170 mL) and water (90 mL) were added, the phases separated and the organic layer was extracted with water. The combined aqueous layers were acidified with 3.8 M HCl and extracted with EtOAc. The combined organic layers were dried with Na_2SO_4 and evaporated. 2-(2-Chloro-4-fluorophenyl)-1-(methoxycarbonyl)-piperidine-4-carboxylic acid (2.130 g, 89 %) was isolated as a brown solid. MS m/z 316 $(M+H)^+$

Reference compound 22

2-(4-Chloro-3-fluorophenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: 2-(4-Chloro-3-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

4-bromo-1-chloro-2-fluorobenzene (4 g, 19.10 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (5.63 g, 22.15 mmol), $PdCl_2$(dppf) (0.691 g, 0.95 mmol) and potassium acetate (3.75 g, 38.20 mmol) were suspended in DMSO (40 mL) and heated to 80°C for 4 h. The reaction mixture was allowed to cool to room temperature. Diluted with EtOAc (400 mL) and filtered over celite. The organic phase was washed with water (3x500 mL), brine (500 mL), dried with a phase separator and evaporated in vacuo. The residue was purified by automated flash chromatography on 2 Biotage® KP-SIL 100g columns. A gradient from 0 % to 30 % of EtOAc in heptane over 15 CV was used as mobile phase. The product was collected using the wavelength 258 nm. 2-(4-Chloro-3-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.100 g, 42.9 %) was isolated as a colorless oil. ^{1}H NMR (600 MHz, $cdcl_3$) δ 1.32 (s, 12H), 7.37 (t, 1H), 7.48 (d, 1H), 7.52 (d, 1H).

Step 2: Methyl 2-(4-chloro-3-fluorophenyl)isonicotinate

Methyl 2-chloroisonicotinate (1.2 g, 6.99 mmol), potassium carbonate (0.580 g, 4.20 mmol) and $PdCl_2$(dppf) (0.122 g, 0.17 mmol) were combined in a microwave vial. 2-(4-Chloro-3-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.1 g, 8.19 mmol) dissolved in MeOH (15 mL) was added. The reaction mixture was heated in a single node microwave reactor at 100°C for 15 min. DCM (125 mL) and water (125 mL) were added, shaken and the phases

separated. The aqueous phase was extracted with DCM (125 mL). The combined organic phases were washed with brine (250 mL), dried with a phase separator and evaporated in vacuo. The residue was purified by automated flash chromatography on a Biotage® KP-SIL 100g column. A gradient of 10 % EtOAc in heptane over 3 CV and then 10 to 50 % EtOAc in heptane over 12 CV was used as mobile phase. The product was collected using the wavelength 253 nm. Methyl 2-(4-chloro-3-fluorophenyl)isonicotinate (1.473 g, 79 %) was isolated as a white solid. ^{1}H NMR (400 MHz, cdcl$_3$) δ 4.00 (s, 3H), 7.48 – 7.54 (m, 1H), 7.76 – 7.83 (m, 2H), 7.88 – 7.94 (m, 1H), 8.24 – 8.27 (m, 1H), 8.83 (dd, 1H).

Step 3: Methyl 2-(4-chloro-3-fluorophenyl)piperidine-4-carboxylate hydrochloride

Methyl 2-(4-chloro-3-fluorophenyl)isonicotinate (1.473 g, 5.54 mmol) was suspended in MeOH (30 mL) and hydrogen chloride (1.25 M in MeOH, 9.86 mL, 11.09 mmol) was added dropwise during stirring. The solvent was evaporated after 15 min and the HCl salt redissolved in MeOH (10 mL) and platinum(IV) oxide (0.063 g, 0.28 mmol) added. The resulting mixture was hydrogenated in a Büchi hydrogenator at room temperature and 5 bar for 1.5 h. Platinum(IV) oxide (0.038 g, 0.17 mmol) was added and the hydrogenation continued for 1 h. The catalyst was filtered off and washed with MeOH. The solvent was evaporated in vacuo yielding methyl 2-(4-chloro-3-fluorophenyl)piperidine-4-carboxylate hydrochloride (1.639 g, 96 %) as a white solid. MS m/z 272 $(M+H)^+$

Step 4: Dimethyl 2-(4-chloro-3-fluorophenyl)piperidine-1,4-dicarboxylate

Methyl 2-(4-chloro-3-fluorophenyl)piperidine-4-carboxylate hydrochloride (1.639 g, 5.32 mmol) and DIPEA (2.316 mL, 13.30 mmol) were dissolved in DCM (10 mL). Methyl carbonochloridate (0.503 mL, 6.38 mmol) was added dropwise and the reaction stirred at room temperature for 2 h. The reaction mixture was diluted with DCM (100 mL) and washed with 0.1 M HCl (2 x 75 mL), sat. $NaHCO_3$ (100 mL), dried through a phase separator and evaporated in vacuo yielding dimethyl 2-(4-chloro-3-fluorophenyl)piperidine-1,4-dicarboxylate (1.625 g, 93 %) as a colorless oil. MS m/z 330 $(M+H)^+$

Step 5: 2-(4-Chloro-3-fluorophenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Dimethyl 2-(4-chloro-3-fluorophenyl)piperidine-1,4-dicarboxylate (1.625 g, 4.93 mmol) was dissolved in acetonitrile (20 mL) and water (0.400 mL). lithium bromide (3.42 g, 39.42 mmol) was added. Triethylamine (2.73 mL, 19.71 mmol) was then added and the reaction heated

under reflux for 1.5 h. Water (200 mL) and MTBE (150 mL) were added, shaken and the phases separated. The organic phase was extracted with water (2x200 mL). The combined aqueous phases were acidified with 3 M HCl to pH 1 and then extracted with MTBE (2x500 mL). The combined organic phases were dried with Na_2SO_4, filtered and evaporated in vacuo yielding 2-(4-chloro-3-fluorophenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (1.430 g, 92 %). MS m/z 314 $(M-H)^-$

Reference compound 23

2-(2,4-Dichlorophenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: Methyl 2-(2,4-dichlorophenyl)isonicotinate

Potassium carbonate (1.812 g, 13.11 mmol), methyl 2-chloroisonicotinate (3 g, 17.48 mmol), 2,4-dichlorophenylboronic acid (5.00 g, 26.23 mmol), $PdCl_2$(dppf) (0.380 g, 0.52 mmol), and MeOH (30.6 mL) were split in two 20 mL microwave vials and heated to 100°C for 35 min in a single node microwave reactor. The reaction mixture was diluted with water and DCM, extracted with DCM and evaporated. Purified by automated flash chromatography using 5% EtOAc in heptane -> 30% EtOAc over 15 CV at 280 nm. Methyl 2-(2,4-dichlorophenyl)isonicotinate (2.3 g, 47 %) was isolated as a white solid. ^{1}H NMR (400 MHz, $cdcl_3$) δ 3.98 (s, 3H), 7.37 (dd, 1H), 7.53 (d, 1H), 7.57 (d, 1H), 7.86 (dd, 1H), 8.20 (s, 1H), 8.87 (d, 1H). MS m/z 282 $(M+H)^+$

Step 2: Methyl 2-(2,4-dichlorophenyl)piperidine-4-carboxylate hydrochloride

Methyl 2-(2,4-dichlorophenyl)isonicotinate hydrochloride (2.60 g, 8.15 mmol) was dissolved in MeOH (50 mL), added platinum(IV) oxide (0.019 g, 0.08 mmol) and hydrogenated in a Büchi hydrogenator at 5 bar for 90 min. The reaction mixture was filtered and evaporated to give crude methyl 2-(2,4-dichlorophenyl)piperidine-4-carboxylate hydrochloride (2.8 g) as a white solid. MS m/z 288 $(M+H)^+$

Step 3: Dimethyl 2-(2,4-dichlorophenyl)piperidine-1,4-dicarboxylate

Methyl 2-(2,4-dichlorophenyl)piperidine-4-carboxylate hydrochloride (2.8 g, 8.63 mmol) was diluted with DCM (24.18 mL). DIPEA (3.76 mL, 21.56 mmol) and methyl carbonochloridate (0.815 mL, 10.35 mmol) were added. The reaction mixture was stirred at room temperature

for 30 min, then washed with 3 x 0.1 M HCl and brine. Filtered through a phase separator. Evaporated to yield dimethyl 2-(2,4-dichlorophenyl)piperidine-1,4-dicarboxylate (2.78 g, 93 %) as an oil. MS m/z 346 $(M+H)^+$

Step 4: 2-(2,4-dichlorophenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Dimethyl 2-(2,4-dichlorophenyl)piperidine-1,4-dicarboxylate (2.78 g, 8.03 mmol) was dissolved in acetonitrile (27.1 mL) and water (0.542 mL). Lithium bromide (5.58 g, 64.24 mmol) and triethylamine (4.48 mL, 32.12 mmol) were added and the resulting mixture heated under reflux for 4 h, diluted with Water and MTBE and the organic layer extracted with water. The combined aqueous layers were acidified with 3 M HCl, extracted with MTBE, dried over $MgSO_4$, filtered and evaporated to give 2-(2,4-dichlorophenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (2.440 g, 91 %) as a foam. MS m/z 332 $(M+H)^+$

Reference compound 24

2-(3,5-Dichlorophenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: Methyl 2-(3,5-dichlorophenyl)isonicotinate

Potassium carbonate (2.416 g, 17.48 mmol), methyl 2-chloroisonicotinate (5 g, 29.14 mmol), 2-(3,5-dichlorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (10.34 g, 37.88 mmol), $PdCl_2$(dppf) (0.633 g, 0.87 mmol), and MeOH (45.7 mL) were split in three 20 mL microwave-vials and heated to 100°C in a single node microwave reactor for 20 min. The reaction mixture was diluted with water and DCM, the aqueous layer extracted with DCM and the combined organic layers were evaporated. Purified by automated flash chromatography using 5% EtOAc in heptane -> 30% EtOAc over 15 CV at 280 nm. Methyl 2-(3,5-dichlorophenyl)isonicotinate (6.1 g, 74 %) was isolated as a white powder. ^1H NMR (400 MHz, $cdcl_3$) δ 4.01 (s, 3H), 7.44 (t, 1H), 7.84 (dd, 1H), 7.96 (d, 2H), 8.23 – 8.28 (m, 1H), 8.85 (dd, 1H).

Step 2: Methyl 2-(3,5-dichlorophenyl)piperidine-4-carboxylate hydrochloride

Methyl 2-(3,5-dichlorophenyl)isonicotinate hydrochloride (6.88 g, 21.6 mmol) was dissolved in MeOH (50 mL), added platinum(IV) oxide (0.049 g, 0.22 mmol) and hydrogenated in a Büchi hydrogenator at 5 bar for 4 h. Reaction mixture filtered, washed with MeOH until all

product had dissolved and evaporated. Methyl 2-(3,5-dichlorophenyl)piperidine-4-carboxylate hydrochloride (4.8 g, 69 %) was isolated as a yellowish solid. MS m/z 288 $(M+H)^+$

Step 3: Dimethyl 2-(3,5-dichlorophenyl)piperidine-1,4-dicarboxylate

Methyl 2-(3,5-dichlorophenyl)piperidine-4-carboxylate hydrochloride (4.8 g, 14.79 mmol) was dissolved in DCM (41.5 mL) and DIPEA (6.46 mL, 36.97 mmol). Methyl chloroformate (1.374 mL, 17.74 mmol) was added and the reaction mixture was stirred at room temperature for 1 h, then diluted with DCM and washed with 0.3 M HCl and brine. The organic layer was filtered through a phase separator and evaporated to give dimethyl 2-(3,5-dichlorophenyl)-piperidine-1,4-dicarboxylate (5.3 g) as an oil. MS m/z 346 $(M+H)^+$

Step 4: 2-(3,5-Dichlorophenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Dimethyl 2-(3,5-dichlorophenyl)piperidine-1,4-dicarboxylate (5.3 g, 15.31 mmol) was dissolved in acetonitrile (51.7 mL). Water (1.033 mL), lithium bromide (10.64 g, 122.47 mmol) and triethylamine (8.53 mL, 61.24 mmol) were added and the resulting mixture was heated under reflux for 2.5 h. It was diluted with water and MTBE. The aqueous layer was extracted with water. The combined aqueous layers were acidified with 3 M HCl, extracted with MTBE, dried over $MgSO_4$, filtered and evaporated to give 2-(3,5-dichlorophenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (4.60 g, 90 %) as a greenish foam. MS m/z 330 $(M-H)^-$

Reference compound 25

2-(2-Fluoro-4-(trifluoromethoxy)phenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: 2-(2-Fluoro-4-(trifluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

1-Bromo-2-fluoro-4-(trifluoromethoxy)benzene (7.41 g, 28.61 mmol) was dissolved in DMSO (50 mL). 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (8.43 g, 33.19 mmol), $PdCl_2$(dppf) (1.035 g, 1.43 mmol) and potassium acetate (5.62 g, 57.22 mmol) were added and the mixture was heated in an oil bath at 80°C for 15 h. The reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by automated flash chromatography on a Biotage® KP-SIL 340g column. A gradient from 0 % to 25 % of EtOAc in heptane over 10 CV was

used as mobile phase. 2-(2-Fluoro-4-(trifluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5.38 g, 61.4 %) was obtained as colorless solid.

Step 2: Methyl 2-(2-fluoro-4-(trifluoromethoxy)phenyl)isonicotinate

Methyl 2-chloroisonicotinate (3 g, 17.48 mmol), 2-(2-fluoro-4-(trifluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5.37 g, 17.55 mmol), potassium carbonate (1.812 g, 13.11 mmol) and $PdCl_2$(dppf) (0.380 g, 0.52 mmol) were mixed in methanol (30 mL) in two separate 20 mL microwave vials. The vials were capped and heated at 100°C for 10 min in a single node microwave reactor. Water and DCM were added and the phases were separated. The aqueous phase was extracted with DCM and the combined organic layers were filtered through a phase separator and evaporated to yield a dark-brown solid. The residue was purified by automated flash chromatography on a Biotage® KP-SIL 340g column. A gradient from 8:1 to 3:1 of EtOAc in heptane over 10 CV was used as mobile phase. Methyl 2-(2-fluoro-4-(trifluoromethoxy)phenyl)isonicotinate (4.48 g, 81 %) was yielded as a colorless solid. ^{1}H NMR (600 MHz, cdcl$_3$) δ 3.96 (s, 3H), 7.07 (d, 1H), 7.14 (d, 1H), 7.79 – 7.84 (m, 1H), 8.03 – 8.09 (m, 1H), 8.31 (s, 1H), 8.82 – 8.88 (m, 1H). MS m/z 316 $(M+H)^+$

Step 3: Methyl 2-(2-fluoro-4-(trifluoromethoxy)phenyl)piperidine-4-carboxylate hydrochloride

Methyl 2-(2-fluoro-4-(trifluoromethoxy)phenyl)isonicotinate (4.47 g, 14.18 mmol) was disssolved in methanol and hydrogen chloride (1.25 M in methanol, 17.02 mL, 21.27 mmol) was added. The solvent was evaporated and the residue redissolved in methanol (50 mL). Platinum(IV) oxide (0.322 g, 1.42 mmol) was added and the mixture hydrogenated at 5 bar at room temperature for 5 h. The catalyst was filtered off and the solvent was evaporated. Crude methyl 2-(2-fluoro-4-(trifluoromethoxy)phenyl)piperidine-4-carboxylate hydrochloride (4.97 g, 98 %) was obtained as a colorless solid. MS m/z 322 $(M+H)^+$

Step 4 : Dimethyl 2-(2-fluoro-4-(trifluoromethoxy)phenyl)piperidine-1,4-dicarboxylate

Methyl 2-(2-fluoro-4-(trifluoromethoxy)phenyl)piperidine-4-carboxylate hydrochloride (4.97 g, 13.89 mmol) was dissolved in dichloromethane (50 mL) and DIPEA (6.05 mL, 34.73 mmol). Methyl carbonochloridate (1.313 mL, 16.67 mmol) was added and the reaction mixture was stirred at room temperature for 4 h. 0.1 M HCl was added and the aqueous layer extracted with DCM. The combined organic layers were filtered through a phase separator and

evaporated. Crude dimethyl 2-(2-fluoro-4-(trifluoromethoxy)phenyl)piperidine-1,4-dicarboxylate (5.39 g, 102 %) was obtained as a yellow oil. MS m/z 380 $(M+H)^+$

Step 5: 2-(2-Fluoro-4-(trifluoromethoxy)phenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Dimethyl 2-(2-fluoro-4-(trifluoromethoxy)phenyl)piperidine-1,4-dicarboxylate (5.35 g, 14.10 mmol) was dissolved in acetonitrile (100 mL) and water (2.000 mL), then lithium bromide (9.80 g, 112.84 mmol) was added. Triethylamine (7.82 mL, 56.42 mmol) was added and the resulting suspension was heated under reflux for 7 h. MTBE (350 mL) and water (180 mL) were added, the phases separated and the organic layer was extracted with water. The combined aqueous layers were acidified with 3.8 M HCl and extracted with EtOAc. The combined organic layers were dried with Na_2SO_4 and evaporated. 2-(2-Fluoro-4-(trifluoromethoxy)phenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (5.09 g, 99 %) was yielded as a colorless solid. MS m/z 364 $(M-H)^-$

Reference compound 26

1-(Methoxycarbonyl)-2-(3,4,5-trifluorophenyl)piperidine-4-carboxylic acid

Step 1: Methyl 2-(3,4,5-trifluorophenyl)isonicotinate

Methyl 2-bromoisonicotinate (4 g, 18.52 mmol), 3,4,5-trifluorophenylboronic acid (4.89 g, 27.77 mmol), potassium carbonate (3.84 g, 27.77 mmol) and $PdCl_2$(dppf) (0.402 g, 0.56 mmol) were mixed in methanol (30 mL) in two separate 20 mL microwave vials. The vials were capped and heated at 100°C for 10 min in a single node microwave reactor. Water and DCM were added and the phases were separated. The water phase (pH 9) was extracted with DCM and the combined organic phase washed with brine, passed through a phase separator and evaporated to yield a brown solid. The residue was dissolved in DCM and purified by SCX-2 cation exchange chromatography. Methyl 2-(3,4,5-trifluorophenyl)isonicotinate (2.62 g, 52 %) was isolated as a slightly yellow solid. MS m/z 268 $(M+H)^+$

Step 2: Methyl 2-(3,4,5-trifluorophenyl)piperidine-4-carboxylate hydrochloride

Methyl 2-(3,4,5-trifluorophenyl)isonicotinate (2.62 g,) was dissolved in MTBE, then HCl (4 M in dioxane, 15 mL) was added. The solvents were evaporated to give methyl 2-(3,4,5-

trifluorophenyl)isonicotinate hydrochloride (2.94 g, 9.68 mmol), which was dissolved in MeOH (40 mL) and platinum(IV) oxide (0.220 g, 0.97 mmol) added. The resulting mixture was hydrogenated in a Büchi hydrogenator at room temperatute and 5 bar for 1 h. The catalyst was filtered off, washed with MeOH and the eluate evaporated yielding methyl 2-(3,4,5-trifluorophenyl)piperidine-4-carboxylate hydrochloride (2.75 g, 92 %) as a brown solid. MS m/z 274 $(M+H)^+$

Step 3: Dimethyl 2-(3,4,5-trifluorophenyl)piperidine-1,4-dicarboxylate

Methyl 2-(3,4,5-trifluorophenyl)piperidine-4-carboxylate hydrochloride (2.75 g, 8.88 mmol) was dissolved into DCM (50 mL), then DIPEA (3.88 mL, 22.20 mmol) was added. Methyl carbonochloridate (0.979 mL, 12.43 mmol) was added dropwise to the solution. The mixture was stirred at room temperature for 4 h. The mixture was washed with HCl (0.1 M, 100 mL) and satd $NaHCO_3$ (100 mL), then dried through a phase-separator and evaporated yielding dimethyl 2-(3,4,5-trifluorophenyl)piperidine-1,4-dicarboxylate (2.77 g, 94 %) as an orange oil.

Step 4: 1-(Methoxycarbonyl)-2-(3,4,5-trifluorophenyl)piperidine-4-carboxylic acid

Dimethyl 2-(3,4,5-trifluorophenyl)piperidine-1,4-dicarboxylate (2.77 g, 8.36 mmol) was dissolved in acetonitrile (35 mL) and water (0.700 mL), then lithium bromide (5.81 g, 66.89 mmol) was added. Et_3N (4.66 mL, 33.45 mmol) was added and the resulting yellow suspension was heated under reflux for 2 h. Water (50 mL) and MTBE (150 mL) were added. The phases were separated and the organic layer was extracted with water (2 times). The pooled aqueous layers were acidified to pH 1 with 3.8 M HCl and with MTBE (2 times). The combined organic layer was dried over Na_2SO_4, filtered and evaporated yielding 1-(methoxycarbonyl)-2-(3,4,5-trifluorophenyl)piperidine-4-carboxylic acid (2.23 g, 84 %) as a slightly yellow semi-solid. MS m/z 316 $(M-H)^-$

Reference compound 27

1-(Methoxycarbonyl)-2-(2,4,5-trifluorophenyl)piperidine-4-carboxylic acid

Step 1: Methyl 2-(2,4,5-trifluorophenyl)isonicotinate

Methyl 2-chloroisonicotinate (3.25 g, 18.94 mmol), 2,4,5-trifluorophenylboronic acid (5.00 g, 28.41 mmol), potassium carbonate (3.93 g, 28.41 mmol) and $PdCl_2$(dppf) (0.411 g, 0.57

mmol) were mixed in methanol (20 mL) in two 20 mL microwave vials. The vials were capped and heated at 100°C for 10 min in a single node microwave reactor. The reaction mixture was suspended in methanol, filtered and the filtrate evaporated to yield a darkred slurry. DCM and water were added and the phases separated. The water phase (pH 9) was extracted with DCM and the combined organic phase washed with brine, passed through a phase separator and evaporated to yield a brown solid. The crude brown solid was dissolved in MTBE (120 mL) and solids filtered off. Hydrogen chloride (4 M in dioxane, 4.74 mL, 18.94 mmol) was added dropwise and a suspension was formed. The suspension was stirred at room temperature for 45 min. The solid was collected by filtration and washed with MTBE. MTBE and satd $NaHCO_3$ were added. The organic phase was dried over Na_2SO_4, filtered and evaporated to yield methyl 2-(2,4,5-trifluorophenyl)isonicotinate (1.676 g, 33 %) as a beige solid. The MTBE-filtrate was washed with satd $NaHCO_3$, dried over Na_2SO_4, filtered and evaporated to yield a brown solid. The residue was purified via Biotage (0 => 20 % EtOAc in heptane, 6 CV; Biotage® KP-SIL 100g column) to yield methyl 2-(2,4,5-trifluorophenyl)-isonicotinate (0.86 g, 17 %) as a white solid. ^{1}H NMR (600 MHz, cdcl$_3$) δ 3.97 (s, 3H), 7.00 – 7.07 (m, 1H), 7.81 (dd, 1H), 7.90 – 7.97 (m, 1H), 8.32 – 8.33 (m, 1H), 8.83 (dd, 1H). MS m/z 268 $(M+H)^+$

Step 2: Methyl 2-(2,4,5-trifluorophenyl)piperidine-4-carboxylate

Methyl 2-(2,4,5-trifluorophenyl)isonicotinate (2.509 g, 9.39 mmol) was dissolved in acetic acid (25 mL) and platinum(IV) oxide (0.107 g, 0.47 mmol) added. The resulting mixture was hydrogenated in a Büchi hydrogenator at room temperature and 5 bar for 6 h. The catalyst was filtered off, washed with MeOH and the eluate evaporated. DCM and 10 % K_2CO_3 were added and the phases separated. The organic layer was washed with brine, passed through a phase separator and evaporated to yield methyl 2-(2,4,5-trifluorophenyl)piperidine-4-carboxylate (2.434 g, 95 %) as a brown oil. MS m/z 274 $(M+H)^+$

Step 3: Dimethyl 2-(2,4,5-trifluorophenyl)piperidine-1,4-dicarboxylate

Methyl 2-(2,4,5-trifluorophenyl)piperidine-4-carboxylate (2.232 g, 8.17 mmol) was dissolved in DCM (50 mL) and DIPEA (1.707 mL, 9.80 mmol) , then methyl carbonochloridate (0.965 mL, 12.25 mmol) was added. The solution was stirred at room temperature for 1 h. The reaction mixture was washed with 0.1 M HCl and satd $NaHCO_3$, passed through a phase separator and evaporated to yield crude dimethyl 2-(2,4,5-trifluorophenyl)piperidine-1,4-

dicarboxylate (2.971 g, quant.) as a brown oil. MS m/z 332 $(M+H)^+$

Step 4: 1-(Methoxycarbonyl)-2-(2,4,5-trifluorophenyl)piperidine-4-carboxylic acid

Dimethyl 2-(2,4,5-trifluorophenyl)piperidine-1,4-dicarboxylate (2.971 g, 8.97 mmol) was dissolved in acetonitrile (30 mL) and water (0.600 mL), then lithium bromide (6.23 g, 71.74 mmol) was added. Triethylamine (4.97 mL, 35.87 mmol) was added and the resulting brown suspension was heated under reflux. Water and MTBE were added. The organic phase was extracted with water (x2). The pooled aqueous layer was acidified to pH 1 with 3.8 M HCl and then extracted with MTBE (x2). The combined organic layer was washed with water and evaporated. Traces of water were azeotropically removed by MeCN. 1-(Methoxycarbonyl)-2-(2,4,5-trifluorophenyl)piperidine-4-carboxylic acid (2.388 g, 84 %) was isolated as a yellow oil. MS m/z 318 $(M+H)^+$

Reference compound 28

2-(4-Chloro-3,5-difluorophenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: 2-(4-Chloro-3,5-difluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

To 5-Bromo-2-chloro-1,3-difluorobenzene (4.8 g, 21.11 mmol) dissolved in DMSO (40 mL) was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (6.22 g, 24.48 mmol), $PdCl_2$(dppf) (0.764 g, 1.06 mmol) and potassium acetate (4.14 g, 42.21 mmol). The reaction mixture was heated in an oil bath at 80°C for 10 h, then was diluted with ethyl acetate and washed with water. The organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by automated flash chromatography on a Biotage® KP-SIL 340g column. A gradient from 0 % to 30 % of EtOAc in heptane over 10 CV was used as mobile phase. 2-(4-Chloro-3,5-difluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.01 g, 69 %) was isolated.

Step 2: Methyl 2-(4-chloro-3,5-difluorophenyl)isonicotinate hydrochloride

Methyl 2-chloroisonicotinate (3.01 g, 17.53 mmol), $PdCl_2$(dppf) (0.317 g, 0.44 mmol) and potassium carbonate (1.322 mL, 21.91 mmol) were distributed equally over 3 microwave reaction vials. 2-(4-Chloro-3,5-difluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.01 g, 14.61 mmol) was dissolved in methanol (45 mL) to give a colorless solution. The solution was split into 3 equal portions and added to the vials. The vials were capped and heated in a

single node microwave reactor at 100°C for 10 min each. The content of the vials was combined and the solvent evaporated. The residue was dissolved in DCM and washed with water. The organic phase was filtered through a phase separator and evaporated. The residue was dissolved in MTBE and solids were filtered off. Hydrogen chloride (4 M in dioxane, 3.65 mL, 14.61 mmol) was added and the precipitate collected to yield methyl 2-(4-chloro-3,5-difluorophenyl)isonicotinate hydrochloride (1.72 g, 42 %) as a solid. ^{1}H NMR (400 MHz, $cdcl_3$) δ 4.06 (s, 3H), 7.86 (d, 2H), 8.09 (d, 1H), 8.39 (s, 1H), 8.96 (d, 1H). MS m/z 284 $(M+H)^+$

Step 3: Methyl 2-(4-chloro-3,5-difluorophenyl)piperidine-4-carboxylate

Methyl 2-(4-chloro-3,5-difluorophenyl)isonicotinate hydrochloride (1.94 g, 6.06 mmol) was dissolved in methanol. Platinum(IV) oxide (0.138 g, 0.61 mmol) was added and the mixture was hydrogenated at 5 bar at room temperature in a Büchi hydrogenator for 7 h. The catalyst was removed by filtration and the solvent evaporated. Methyl 2-(4-chloro-3,5-difluorophenyl)piperidine-4-carboxylate hydrochloride (1.820 g, 92 %) was yielded as a colorless oil. MS m/z 290 $(M+H)^+$

Step 4: Dimethyl 2-(4-chloro-3,5-difluorophenyl)piperidine-1,4-dicarboxylate

Methyl 2-(4-chloro-3,5-difluorophenyl)piperidine-4-carboxylate hydrochloride (1.82 g, 5.58 mmol) was dissolved in dichloromethane (50 mL). DIPEA (2.430 mL, 13.95 mmol) and methyl carbonochloridate (0.527 mL, 6.70 mmol) were added and the mixture was stirred at room temperature for 3 h. 0.1 M HCl was added and the aqueoaus layer was extracted with DCM. The combined organic layers were filtered through a phase separator and evaporated to yield dimethyl 2-(4-chloro-3,5-difluorophenyl)piperidine-1,4-dicarboxylate (1.83 g, 94 %). MS m/z 348 $(M+H)^+$

Step 5: 2-(4-Chloro-3,5-difluorophenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Dimethyl 2-(4-chloro-3,5-difluorophenyl)piperidine-1,4-dicarboxylate (1.83 g, 5.26 mmol) was dissolved in acetonitrile (30 mL) and water (0.600 mL), then lithium bromide (3.66 g, 42.10 mmol) was added. Triethylamine (2.92 mL, 21.05 mmol) was added and the resulting suspension was heated under reflux for 4 h. MTBE (100 mL) and water (50 mL) were added, the phases separated and the organic layer was extracted with water. The combined aqueous layers were acidified to pH 1 with 3.8 M HCl and extracted with MTBE. The combined

organic layers were dried over Na_2SO_4 and evaporated to yield 2-(4-chloro-3,5-difluoro-phenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (1.600 g, 91 %) as a light yellow solid. MS m/z 332 $(M-H)^-$

Reference compound 29

1-(Methoxycarbonyl)-2-(3-methyl-4-(trifluoromethyl)phenyl)piperidine-4-carboxylic acid

Step 1: 4,4,5,5-Tetramethyl-2-(3-methyl-4-(trifluoromethyl)phenyl)-1,3,2-dioxaborolane

4-Bromo-2-methyl-1-(trifluoromethyl)benzene (3.3 g, 13.8 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (4.07 g, 16.01 mmol), potassium acetate (2.71 g, 27.61 mmol) and $PdCl_2$(dppf) (0.5 g, 0.69 mmol) were combined in DMF (60 mL) and divided into three microwave vials. The reaction mixtures were heated in a single node microwave reactor to 100°C for 10 min. The reaction mixtures were diluted with ethyl acetate and filtered through celite. The filtrate was washed with water (3 x) and brine. The organic layer was isolated, dried over Na_2SO_4, filtered through celite and the solvent evaporated. Auto mated column chromatography using the Biotage apparatus. Gradient eluation using heptane - ethyl acetate, started 0% ethyl acetate up to 30%. 4,4,5,5-Tetramethyl-2-(3-methyl-4-(trifluoromethyl)phenyl)-1,3,2-dioxaborolane (1.66 g, 42%) was isolated. ^{1}H NMR (600 MHz, $cdcl_3$) δ 1.33 (s, 12H), 2.47 (s, 3H), 7.57 (d, 1H), 7.66 – 7.70 (m, 2H).

Step 2: Methyl 2-(3-methyl-4-(trifluoromethyl)phenyl)isonicotinate

Methyl 2-chloroisonicotinate (0.996 g, 5.80 mmol), potassium carbonate (1.042 g, 7.54 mmol), 4,4,5,5-tetramethyl-2-(3-methyl-4-(trifluoromethyl)phenyl)-1,3,2-dioxaborolane (1.66 g, 5.80 mmol) and $PdCl_2$(dppf) (0.105 g, 0.15 mmol) were mixed in methanol (20 mL) in two microwave vials. The vials were capped and heated at 100°C for 10 min in a single node microwave reactor. The solution was partitioned between water and ethyl acetate. The organic layer was isolated, dried over Na_2SO_4, filtered through celite and the solvent was evaporated. Automated column chromatography using the Biotage equipment. Gradient eluation using heptane - ethyl acetate, 0% to 50%. Methyl 2-(3-methyl-4-(trifluoromethyl)phenyl)-isonicotinate (1.22 g, 71 %) was isolated. ^{1}H NMR (600 MHz, $cdcl_3$) δ 2.57 (s, 3H), 3.99 (s, 3H), 7.70 (d, 1H), 7.81 (dd, 1H), 7.91 (d, 1H), 7.98 (s, 1H), 8.29 (s, 1H), 8.84 (d, 1H).

Step 3: Methyl 2-(3-methyl-4-(trifluoromethyl)phenyl)piperidine-4-carboxylate

Methyl 2-(3-methyl-4-(trifluoromethyl)phenyl)isonicotinate (2.32 g, 7.86 mmol) was dissolved in acetic acid (150 mL) and platinum(IV) oxide (36 mg, 0.16 mmol) was added. Hydrogenation in a Büchi hydrogenator at room temperature and 6 bar for 2 h. The catalyst was filtered off. More platinum(IV) oxide was added and hydrogenation continued until starting material was consumed. Catalyst was filtered off and the solvent was evaporated to yield crude methyl 2-(3-methyl-4-(trifluoromethyl)phenyl)piperidine-4-carboxylate (2.60 g, 110 %).

Step 4: Dimethyl 2-(3-methyl-4-(trifluoromethyl)phenyl)piperidine-1,4-dicarboxylate

Methyl 2-(4-(trifluoromethyl)benzyl)piperidine-4-carboxylate (2.9 g, 9.62 mmol) was dissolved in DIPEA (1.866 g, 14.44 mmol) and dichloromethane (50 mL). Methyl carbonochloridate (1.091 g, 11.55 mmol) was added dropwise and the resulting mixture was stirred at room temperature overnight. 1 M $KHSO_4$ and diethyl ether were added and the phases separated. The organic layer was washed with Na_2CO_3, dried over $MgSO_4$, filtered through celite and evaporated to yield dimethyl 2-(3-methyl-4-(trifluoromethyl)phenyl)-piperidine-1,4-dicarboxylate (3.09 g, 89 %).

Step 5: 1-(Methoxycarbonyl)-2-(3-methyl-4-(trifluoromethyl)phenyl)piperidine-4-carboxylic acid

Dimethyl 2-(3-methyl-4-(trifluoromethyl)phenyl)piperidine-1,4-dicarboxylate (3.09 g, 8.60 mmol) was dissolved in acetonitrile (30 mL) and water (0.6 mL), lithium bromide (5.97 g, 68.79 mmol) was added. Triethylamine (3.48 g, 34.40 mmol) was added and the resulting suspension was heated under reflux for 1 h. Water (60 mL) and MTBE were added. The organic phase was extracted with water (x 2). To the pooled aqueous layer was added MTBE and the solution was acidified to pH 1 with HCl and then extracted with MTBE (x 2). The organic layer was dried over Na_2SO_4, filtered through celite and the solvent evaporated to yield 1-(methoxycarbonyl)-2-(3-methyl-4-(trifluoromethyl)phenyl)piperidine-4-carboxylic acid (2.65 g, 7.67 mmol).

Reference compound 30

2-(3,5-Difluoro-4-(trifluoromethyl)phenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: 2-(3,5-Difluoro-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

5-Bromo-1,3-difluoro-2-(trifluoromethyl)benzene (4.7 g, 18.01 mmol), $PdCl_2$(dppf) (0.652 g, 0.90 mmol) and potassium acetate (3.53 g, 36.02 mmol) were suspended in MeOH (20 mL), divided in two microwave vials and heated to 120°C in a single node microwave reactor for 20 min. The reaction mixture was diluted with EtOAc (400 mL), washed with water (400 mL), brine (400 mL), dried with Na_2SO_4, filtered and evaporated in vacuo. The residue was purified by automated flash chromatography on 2 Biotage® KP-SIL 100g columns. A gradient from 0 % to 30 % of EtOAc in heptane over 12 CV was used as mobile phase. The product was collected using the wavelength 265 nm. 2-(3,5-Difluoro-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.30 g, 59.5 %) was isolated as a white solid. ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.32 (s, 12H), 7.37 (d, 2H).

Step 2: Methyl 2-(3,5-difluoro-4-(trifluoromethyl)phenyl)isonicotinate

Methyl 2-chloroisonicotinate (1,838 g, 10,71 mmol), potassium carbonate (0.888 g, 6.43 mmol) and $PdCl_2$(dppf) (0.233 g, 0.32 mmol) were added to a microwave vial. 2-(3,5-difluoro-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.3 g, 10.71 mmol) dissolved in MeOH (15 mL) was added and the reaction heated in a single node microwave reactor at 100°C for a total of 40 min. DCM (100 mL) and water (100 mL) were added, shaken and the phases separated. The aqueous phase was extracted with DCM (100 mL). The combined organic phases were washed with brine (200 mL), dried with a phase separator and evaporated in vacuo. The residue was purified by automated flash chromatography on a Biotage® KP-SIL 100g column. A gradient from 5 % EtOAc in heptane over 3 CV followed by 5 % to 30 % of EtOAc in heptane over 9 CV was used as mobile phase. The product was collected using the wavelength 250 nm. Methyl 2-(3,5-difluoro-4-(trifluoromethyl)phenyl)isonicotinate (1.810 g, 53 %) was isolated as a white solid. ^{1}H NMR (600 MHz, cdcl$_3$) δ 3.99 (s, 3H), 7.74 (d, 2H), 7.86 – 7.89 (m, 1H), 8.27 (s, 1H), 8.86 (d, 1H).

Step 3: Methyl 2-(3,5-difluoro-4-(trifluoromethyl)phenyl)piperidine-4-carboxylate hydrochloride

Methyl 2-(3,5-difluoro-4-(trifluoromethyl)phenyl)isonicotinate (3.147 g, 9.92 mmol) was dissolved in MeOH (20 mL) and hydrogen chloride (1.25 M in MeOH, 23.81 mL, 29.76 mmol) was added. The reaction was stirred at room temperature for 2 h and evaporated.

Methanol (20 mL) and platinum(IV) oxide (0.113 g, 0.50 mmol) was added and the solution hydrogenated in a Büchi hydrogenator at 5 bar and room temperature for 4.5 h. Platinum(IV) oxide (0.113 g, 0.50 mmol) was added and hydrogenation continued for 4 h. The catalyst was filtered off and washed with MeOH. The filtrate was evaporated in vacuo to yield methyl 2-(3,5-difluoro-4-(trifluoromethyl)phenyl)piperidine-4-carboxylate hydrochloride (3.12 g, 87 %) as a white solid. MS m/z 324 $(M+H)^+$

Step 4: Dimethyl 2-(3,5-difluoro-4-(trifluoromethyl)phenyl)piperidine-1,4-dicarboxylate

Methyl 2-(3,5-difluoro-4-(trifluoromethyl)phenyl)piperidine-4-carboxylate hydrochloride (3.118 g, 8.67 mmol) and DIPEA (3.02 mL, 17.34 mmol) were dissolved in DCM (30 mL). Methyl carbonochloridate (1.024 mL, 13.00 mmol) was added and the reaction stirred at room temperature for 1.5 h. Additional methyl carbonochloridate (0.341 mL, 4.33 mmol) was added and stirring continued for 0.5 h. DCM (170 mL) was added. The organic phase was washed with 0.1 M HCl (2x200 mL), satd $NaHCO_3$ (200 mL), dried with a phase separator and evaporated in vacuo to yield dimethyl 2-(3,5-difluoro-4-(trifluoromethyl)phenyl)-piperidine-1,4-dicarboxylate (2.85 g, 86 %) as a colorless oil. MS m/z 382 $(M+H)^+$

Step 5: 2-(3,5-Difluoro-4-(trifluoromethyl)phenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Dimethyl 2-(3,5-difluoro-4-(trifluoromethyl)phenyl)piperidine-1,4-dicarboxylate (2.851 g, 7.48 mmol) was dissolved in acetonitrile (25 mL) and water (2.5 mL), then lithium bromide (5.19 g, 59.82 mmol) was added followed by triethylamine (4.15 mL, 29.91 mmol). The reaction mixture was heated under reflux for 1 h. MTBE (150 mL) and water (150 mL) were added, shaken and the phases separated. The organic phase was extracted with water (2x150 mL). The combined aqueous phases were acidified with 3 M HCl to pH 1 and extracted with MTBE (2x450 mL). The combined organic phases were dried over Na_2SO_4, filtered and evaporated in vacuo yielding 2-(3,5-difluoro-4-(trifluoromethyl)phenyl)-1-(methoxy-carbonyl)piperidine-4-carboxylic acid (2.363 g, 86 %). MS m/z 368 $(M+H)^+$

Reference compound 31

1-(Methoxycarbonyl)-2-(2-methyl-4-(trifluoromethyl)phenyl)piperidine-4-carboxylic acid

Step 1: Methyl 2-(2-methyl-4-(trifluoromethyl)phenyl)isonicotinate hydrochloride

Potassium carbonate (2.66 g, 19.23 mmol), methyl 2-chloroisonicotinate (5.5 g, 32.05 mmol), 2-methyl-4-(trifluoromethyl)phenylboronic acid (8.50 g, 41.67 mmol), $PdCl_2$(dppf) (0.696 g, 0.96 mmol), and MeOH (50.3 mL) were split into three microwave vials and heated in a single node microwave reactor to 100°C for 20 min. Diluted with DCM, filtered and evaporated. Purified by flash chromatography using 5% EtOAc in heptane -> 20% EtOAc over 10 CV at 280 nm. The residue was dissolved in ether and hydrogen chloride (4 M in dioxane, 8.01 mL, 32.05 mmol) was added and the solvents evaporated to yield methyl 2-(2-methyl-4-(trifluoromethyl)phenyl)isonicotinate hydrochloride (9.15 g, 86 %) as a white solid. ^{1}H NMR (400 MHz, cd_3od) δ 2.41 (s, 3H), 4.03 (s, 3H), 7.63 – 7.76 (m, 3H), 8.27 (dd, 1H), 8.33 (dd, 1H), 8.99 (dd, 1H). MS m/z 296 $(M+H)^+$

Step 2: Methyl 2-(2-methyl-4-(trifluoromethyl)phenyl)piperidine-4-carboxylate hydrochloride

Methyl 2-(2-methyl-4-(trifluoromethyl)phenyl)isonicotinate hydrochloride (9 g, 27.13 mmol) was dissolved in MeOH (50 mL), platinum(IV) oxide (0.185 g, 0.81 mmol) was added and the resulting mixture hydrogenated in a Büchi hydrogenator at 5 bar for 5 h. The catalyst was filtered off and the filtrate evaporated to give methyl 2-(2-methyl-4-(trifluoromethyl)phenyl)-piperidine-4-carboxylate hydrochloride (8 g, 87 %) as a yellowish solid. MS m/z 302 $(M+H)^+$

Step 3: Dimethyl 2-(2-methyl-4-(trifluoromethyl)phenyl)piperidine-1,4-dicarboxylate

Methyl 2-(2-methyl-4-(trifluoromethyl)phenyl)piperidine-4-carboxylate hydrochloride (8.2 g, 24.28 mmol) and DIPEA (10.60 mL, 60.69 mmol) were dissolved in dichloromethane (100 mL). Methyl carbonochloridate (2.257 mL, 29.13 mmol) was added and the reaction stirred at room temperature for 1 h. DCM (100 mL) was added. The organic phase was washed twice with 1 M HCl and water, dried over Na_2SO_4 and evaporated to yield dimethyl 2-(2-methyl-4-(trifluoromethyl)phenyl)piperidine-1,4-dicarboxylate (8.9 g, quant.). MS m/z 360 $(M+H)^+$

Step 4: 1-(Methoxycarbonyl)-2-(2-methyl-4-(trifluoromethyl)phenyl)piperidine-4-carboxylic acid

Dimethyl 2-(2-methyl-4-(trifluoromethyl)phenyl)piperidine-1,4-dicarboxylate (8.9 g, 24.77 mmol) was dissolved in acetonitrile (80 mL). Water (1.6 mL), lithium bromide (17.21 g, 198.14 mmol), and triethylamine (13.73 mL, 99.07 mmol) were added. The mixture was heated at reflux for 2.5 h. After cooling it was diluted with water and extracted with EtOAc

twice and the combined organic layer washed with water. The combined aqueous layer was acidified with 2 M HCl and extracted three times with EtOAc. The combined organic layer was dried over Na_2SO_4, filtered and evaporated to give crude 1-(methoxycarbonyl)-2-(2-methyl-4-(trifluoromethyl)phenyl)piperidine-4-carboxylic acid (7.79 g, 91 %). MS m/z 344 $(M-H)^-$

Reference compound 32

2-(2-Fluoro-4-(trifluoromethyl)phenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: Methyl 2-(2-fluoro-4-(trifluoromethyl)phenyl)isonicotinate hydrochloride

Methyl 2-chloroisonicotinate (2.8 g, 16.32 mmol), 2-fluoro-4-(trifluoromethyl)phenylboronic acid (5.09 g, 24.48 mmol), potassium carbonate (1.692 g, 12.24 mmol) and $PdCl_2$(dppf) (0.354 g, 0.49 mmol) were mixed in methanol (30 mL) in two separate 20 mL microwave vials. The vials were capped and heated at 100°C for 10 min in a single node microwave reactor. Water and DCM were added and the phases were separated. The water phase (pH 9) was extracted with DCM and the combined organic phase washed with brine, passed through a phase separator and evaporated to yield a dark-orange solid. The solid was dissolved in MTBE and stirred for 15 minutes, then filtered. The orange MTBE layer was treated with hydrogen chloride (4 M in dioxane, 4.08 mL, 16.32 mmol) and stirred for 1 h at room temperature. The precipitate was collected by filtration. Methyl 2-(2-fluoro-4-(trifluoromethyl)phenyl)isonicotinate hydrochloride (5.4 g, 99 %) was isolated as a slightly orange solid. MS m/z 300 $(M+H)^+$

Step 2: Methyl 2-(2-fluoro-4-(trifluoromethyl)phenyl)piperidine-4-carboxylate hydrochloride

Methyl 2-(2-fluoro-4-(trifluoromethyl)phenyl)isonicotinate hydrochloride (5.4 g, 16.09 mmol) was dissolved in MeOH (40 mL) and platinum(IV) oxide (0.365 g, 1.61 mmol) added. The resulting mixture was hydrogenated in a Büchi hydrogenator at room temperature and 5 bar for 2 h. The catalyst was filtered off and washed with MeOH and the eluate evaporated yielding methyl 2-(2-fluoro-4-(trifluoromethyl)phenyl)piperidine-4-carboxylate hydrochloride (5.1 g, 93 %) as a slightly brown solid. MS m/z 306 $(M+H)^+$

Step 3: Dimethyl 2-(2-fluoro-4-(trifluoromethyl)phenyl)piperidine-1,4-dicarboxylate

Methyl 2-(2-fluoro-4-(trifluoromethyl)phenyl)piperidine-4-carboxylate hydrochloride (5.50 g, 16.09 mmol) was dissolved in DCM (100 mL), then DIPEA (7.03 mL, 40.23 mmol) was added. Methyl carbonochloridate (1.774 mL, 22.53 mmol) was added dropwise to the solution. The mixture was stirred at room temperature for 4 h. The mixture was washed with 0.1 M HCl (100 mL) and satd $NaHCO_3$ (100 mL), then dried through a phase-separator and evaporated yielding dimethyl 2-(2-fluoro-4-(trifluoromethyl)phenyl)piperidine-1,4-dicarboxylate (5.33 g, 91 %) as a brown oil.

Step 4: 2-(2-Fluoro-4-(trifluoromethyl)phenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Dimethyl 2-(2-fluoro-4-(trifluoromethyl)phenyl)piperidine-1,4-dicarboxylate (5.33 g, 14.67 mmol) was dissolved in acetonitrile (35 mL) and water (0.700 mL), then lithium bromide (10.19 g, 117.37 mmol) was added. Et_3N (8.18 mL, 58.68 mmol) was added and the resulting yellow suspension was heated under reflux for 1 h. Water (50 mL) and MTBE (150 mL) were added. The phases were separated and the organic layer was extracted with water (2 times). The pooled water layers were acidified to pH 1 with 3.8 M HCl and extracted with MTBE (2 times). The combined organic layer was dried over Na_2SO_4, filtered and evaporated yielding 2-(2-fluoro-4-(trifluoromethyl)phenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (4.82 g, 94 %) as a slightly yellow solid. MS m/z 348 $(M-H)^-$

Reference compound 33

2-(3-Fluoro-4-(trifluoromethyl)phenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: 2-(3-Fluoro-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

4-Bromo-2-fluoro-1-(trifluoromethyl)benzene (5.08 g, 20.91 mmol) was dissolved in DMSO (40 mL), then 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (6.16 g, 24.25 mmol), $PdCl_2$(dppf) (0.756 g, 1.05 mmol) and potassium acetate (4.10 g, 41.81 mmol) were added and the mixture was heated in an oil bath at 80°C for 10 h. The reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was dried with Na_2SO_4 and evaporated. The residue was purified by automated flash chromatography on a Biotage® KP-SIL 340g column. A gradient from 0 % to 20 % of EtOAc in heptane over 10 CV was used as mobile phase. 2-(3-Fluoro-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxa-

borolane (3.72 g, 61 %) was isolated.

Step 2: Methyl 2-(3-fluoro-4-(trifluoromethyl)phenyl)isonicotinate

Methyl 2-chloroisonicotinate (2.86 g, 16.67 mmol), $PdCl_2$(dppf) (0.278 g, 0.38 mmol) and potassium carbonate (1.161 mL, 19.24 mmol) were distributed equally over 3 microwave reaction vials. 2-(3-Fluoro-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.72 g, 12.82 mmol) dissolved in methanol (45 mL) was split into 3 equal portions and added to the vials. The vials were capped and heated in a single node microwave reactor at 100°C for 10 min each. The contents of the vials was combined and the solvent evaporated. The residue was dissolved in DCM and washed with water. The organic phase was filtered through a phase separator and evaporated. The residue was purified by automated flash chromatography on a Biotage® KP-SIL 340g column. 7:1 of heptane:EtOAc over 10 CV was used as mobile phase. Crude methyl 2-(3-fluoro-4-(trifluoromethyl)phenyl)isonicotinate (2.92 g, 76 %) was isolated. MS m/z 300 $(M+H)^+$

Step 3: Methyl 2-(3-fluoro-4-(trifluoromethyl)phenyl)piperidine-4-carboxylate

Methyl 2-(3-fluoro-4-(trifluoromethyl)phenyl)isonicotinate (2.9 g, 9.69 mmol) was dissolved in methanol and hydrogen chloride (1.25 M in methanol, 11.63 mL, 14.54 mmol) was added. The solvent was evaporated and the residue redissolved in methanol (50 mL), platinum(IV) oxide (0.220 g, 0.97 mmol) was added and the reaction mixture was hydrogenated at 5 bar and room temperature in a Büchi hydrogenator for 2 h. The catalyst was removed by filtration and the solvent was evaporated to yield methyl 2-(3-fluoro-4-(trifluoromethyl)phenyl)-piperidine-4-carboxylate hydrochloride (3.12 g, 94 %). MS m/z 306 $(M+H)^+$

Step 4: Dimethyl 2-(3-fluoro-4-(trifluoromethyl)phenyl)piperidine-1,4-dicarboxylate

2-(3-Fluoro-4-(trifluoromethyl)phenyl)piperidine-4-carboxylate hydrochloride (3.12 g, 10.22 mmol) was dissolved in dichloromethane (50 mL), then DIPEA (4.45 mL, 25.55 mmol) and methyl carbonochloridate (0.966 mL, 12.26 mmol) were added and the mixture was stirred at room temperature for 3 h. 0.1 M HCl was added and the aqueous layer was extracted with DCM. The combined organic layers were filtered through a phase separator and evaporated to yield dimethyl 2-(3-fluoro-4-(trifluoromethyl)phenyl)piperidine-1,4-dicarboxylate (3.2 g, 86 %). MS m/z 364 $(M+H)^+$

Step 5: 2-(3-Fluoro-4-(trifluoromethyl)phenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Dimethyl 2-(3-fluoro-4-(trifluoromethyl)phenyl)piperidine-1,4-dicarboxylate (3.2 g, 8.81 mmol) was dissolved in acetonitrile (40 mL) and water (0.800 mL), then lithium bromide (6.12 g, 70.46 mmol) was added. Triethylamine (4.88 mL, 35.23 mmol) was added and the resulting solution was heated under reflux for 5 h. MTBE (110 mL) and water (60 mL) were added, the phases separated and the organic layer was extracted with water. The combined aqueous layers were acidified to pH 1 with 3.8 M HCl and extracted with MTBE. The combined organic layers were dried with Na_2SO_4 and evaporated to yield 2-(3-fluoro-4-(trifluoromethyl)phenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (3.07 g, quant.). MS m/z 348 $(M-H)^-$

Reference compound 34

1-(Methoxycarbonyl)-2-phenylpiperidine-4-carboxylic acid

Step 1: Methyl 2-phenylisonicotinate

Methyl 2-chloroisonicotinate (2.5 g, 14.57 mmol), phenylboronic acid (2.66 g, 21.86 mmol), potassium carbonate (3.02 g, 21.86 mmol) and $PdCl_2$(dppf) (0.316 g, 0.44 mmol) were mixed in methanol (15 mL) in a 20 mL microwave vial. Two drops of water were added and the vial was capped and heated at 100°C for 10 min in a single node microwave reactor. The solids were removed by filtration and the filtrate partly evaporated to yield a darkred slurry. DCM and water were added and the phases separated. The water phase (pH 9) was extracted with DCM and the combined organic phase washed with brine, passed through a phase separator and evaporated to yield a darkred oil. The compound was purified via Biotage, SNAP 340g KP-SIL, eluent isocratic heptane/ethyl acetate 9:1 for 2 CV, then linear gradient heptane/ethyl acetate 9:1 to 6:4 over 5 CV to give methyl 2-phenylisonicotinate (1.83 g, 58 %) as a colourless oil. ^1H NMR (400 MHz, $cdcl_3$) δ 3.98 (s, 3H), 7.39 – 7.54 (m, 3H), 7.76 (dd, 1H), 8.01 – 8.09 (m, 2H), 8.29 (s, 1H), 8.82 (d, 1H). MS m/z 214 $(M+H)^+$

Step 2: Methyl 2-phenylpiperidine-4-carboxylate

Methyl 2-phenylisonicotinate (1.83 g, 8.58 mmol) was dissolved in acetic acid (20 mL) and platinum(IV) oxide (0.097 g, 0.43 mmol) added. The resulting mixture was hydrogenated in a

Büchi hydrogenator at room temperature and 5 bar for 2.5 h. The catalyst was filtered off and washed with MeOH and the eluate evaporated. DCM and 10 % K_2CO_3 were added and the phases separated. The water phase was extracted with DCM and the combined organic phase washed with brine, passed through a phase separator and evaporated to yield crude methyl 2-phenylpiperidine-4-carboxylate (2.131 g) as a yellow oil. MS m/z 220 $(M+H)^+$

Step 3: Dimethyl 2-phenylpiperidine-1,4-dicarboxylate

Methyl 2-phenylpiperidine-4-carboxylate (4.33 g, 19.75 mmol) was dissolved in DCM (150 mL) and DIPEA (3.78 mL, 21.72 mmol), then methyl carbonochloridate (1.710 mL, 21.72 mmol) was added. The solution was stirred at room temperature for 1 h 45 min. More DIPEA (1.720 mL, 9.87 mmol) and methyl carbonochloridate (0.777 mL, 9.87 mmol) were added and the reaction continued at room temperature for another 30 min. The reaction mixture was washed with 0.1 M HCl and satd $NaHCO_3$. The organic phase was passed through a phase separator and evaporated to yield dimethyl 2-phenylpiperidine-1,4-dicarboxylate (5.88 g, quant.) as a yellow oil. MS m/z 278 $(M+H)^+$

Step 4: 1-(Methoxycarbonyl)-2-phenylpiperidine-4-carboxylic acid

Dimethyl 2-phenylpiperidine-1,4-dicarboxylate (5.88 g, 21.20 mmol) was dissolved in acetonitrile (60 mL) and water (1.2 mL), then lithium bromide (4.25 mL, 169.63 mmol) was added . Triethylamine (11.76 mL, 84.81 mmol) was added and the resulting yellow suspension was heated at reflux for 1 h. Water (60 mL) and MTBE were added. The organic phase was extracted with water (x2). To the pooled aqueous layer was added MTBE and the solution was acidified to pH 1 with 3.8 M aq HCl and then extracted with MTBE (x2). The combined organic layer was washed with water and evaporated. Traces of water were azeotropically removed by MeCN. 1-(Methoxycarbonyl)-2-phenylpiperidine-4-carboxylic acid (5.25 g, 94 %) was isolated as a slightly yellow semisolid. MS m/z 264 $(M+H)^+$

Reference compound 35

2-Cyclohexyl-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: Methyl 2-cyclohexylpiperidine-4-carboxylate hydrochloride

Methyl 2-phenylisonicotinate (3.182 g, 14.92 mmol) (from reference compound 34, step 1)

was dissolved in MeOH (30 mL) and hydrogen chloride (1.25 M in MeOH, 14.33 mL, 17.91 mmol) was added. The solvents were evaporated to give a slightly yellow solid. The residue was dissolved in MeOH (60 mL) and platinum(IV) oxide (0.102 g, 0.45 mmol) was added. The resulting mixture was then hydrogenated in a Büchi hydrogenator at 8 bar for 5 h. More platinum(IV) oxide (121 mg) was added and the hydrogenation continued overnight at 8 bar (15 h). Platinum(IV) oxide (120 mg) was added and the hydrogenation continued at 60 C for 5 hours. Platinum(IV) oxide (120 mg) was added and the hydrogenation was continued at 60C overnight (15 h). The reaction mixture was filtered through diatomic earth containing filter carton and washed with methanol. The solvents were evaporated and the residue dried in vacuum to give a white solid. The residue was redissolved in MeOH (60 mL). Platinum(IV) oxide (340 mg) was added and the hydrogenation continued at 8 bar, 60 C overnight (22 h). The reaction mixture was filtered through diatomic earth containing filter carton and washed with methanol. The solvents were evaporated and the residue dried in vacuum to give methyl 2-cyclohexylpiperidine-4-carboxylate hydrochloride (3.50 g, 89 %) as a white solid. MS m/z 226 (M+H)+

Step 2: Dimethyl 2-cyclohexylpiperidine-1,4-dicarboxylate

Methyl chloroformate (1.344 mL, 17.36 mmol) in DCM (50 mL) was added to a solution of methyl 2-cyclohexylpiperidine-4-carboxylate hydrochloride (3.50 g, 13.35 mmol) and DIPEA (1.88 mL, 10.76 mmol) in DCM (100 mL). The reaction solution was stirred for 3 h. 1.88 mL DIPEA and 1.345 mL methyl chloroformate was added and the reaction continued overnight (16 h). The organic phase was washed with satd $NaHCO_3$. The phases were separated and the organic phase dried using a phase separator to give crude dimethyl 2-cyclohexylpiperidine-1,4-dicarboxylate (4.90 g). MS m/z 284 (M+H)+

Step 3: 2-Cyclohexyl-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Dimethyl 2-cyclohexylpiperidine-1,4-dicarboxylate (4.90 g, crude) was dissolved in acetonitrile (30 mL) and water (0.600 mL). lithium bromide (9.28 g, 106.80 mmol) and triethylamine (7.40 mL, 53.40 mmol) were added and the mixture was heated under reflux for 2h. Water (60 mL) and MTBE were added. The organic phase was extracted with water (x2). MTBE was added to the pooled aqueous layer and the solution was acidified to pH 1 with 2 M HCl and then extracted with MTBE (x2). The combined organic layer was dried over Na_2SO_4

and evaporated to give 2-cyclohexyl-1-(methoxycarbonyl)piperidine-4-carboxylic acid (3.28 g, 91 % (over 2 steps)) as a slightly yellow semisolid. MS m/z 270 (M+H)+

Reference compound 36

1-(Benzyloxycarbonyl)-2-(2-methyl-2H-tetrazol-5-yl)piperidine-4-carboxylic acid

Step 1: Ethyl 2-carbamoylisonicotinate

To a solution of ethyl isonicotinate (10 g, 66.15 mmol) and concentrated sulfuric acid (3.53 mL, 66.15 mmol) in formamide (80 mL, 2012.41 mmol), 30% hydrogen peroxide (2.399 mL, 99.23 mmol) and powdered iron(II) sulfate heptahydrate (27.6 g, 99.23 mmol) were separately and simultaneously added over 15 min with efficient stirring and cooling in an ice-bath. After complete addition the ice bath was removed and stirring was continued for 2 h. Sodium 2-hydroxypropane-1,2,3-tricarboxylate (132 mL, 132.31 mmol) (trisodium citrate) was added and the mixture was brought to pH 8 by addition of satd $NaHCO_3$ The resultant mixture was extracted with DCM three times and the combined organic extracts were washed with cold water, dried over Na_2SO_4 and evaporated. The solid residue contained a minority of product. The crude product was subjected to the same treatment as above twice more before there was a majority of the desired product in the crude product which was recrystallised from EtOH. Yield: 4.3 g. The mother liquor was purified on Biotage using heptane/EtOAc 80/20 - 10/90 and gave another 0.8 g of product. Ethyl 2-carbamoylisonicotinate (5.1 g, 40 %) was isolated. ^{1}H NMR (400 MHz, dmso) δ 1.34 (t, 3H), 4.37 (q, 2H), 7.79 (s, 1H), 8.00 (d, 1H), 8.22 (s, 1H), 8.40 (s, 1H), 8.83 (d, 1H). MS m/z 195 $(M+H)^+$

Step 2: Ethyl 2-carbamoylpiperidine-4-carboxylate hydrochloride

Ethyl 2-carbamoylisonicotinate (4.24 g, 21.83 mmol) was slurried in MeOH (50 mL) and HCl in MeOH (17.47 mL, 21.83 mmol) and platinum(IV) oxide (0.248 g, 1.09 mmol) were added. The mixture was hydrogenated at 5 bar in a Büchi hydrogenation apparatus. After 3 h there were still starting material left. platinum(IV) oxide (0.14 g, 0.62 mmol) was added and the reaction continued for 2 h when platinum(IV) oxide (0.387 g, 1.70 mmol) was added and the reaction was stirred overnight. The reaction mixture was filtered and evaporated to give ethyl 2-carbamoylpiperidine-4-carboxylate hydrochloride (3.93 g, 90 %). ^{1}H NMR (400 MHz,

dmso) δ 1.16 (t, 3H), 1.31 – 1.63 (m, 2H), 1.86 (d, 1H), 2.26 (d, 1H), 2.54 – 2.66 (m, 1H), 2.74 – 2.88 (m, 1H), 3.10 – 3.19 (m, 1H), 3.47 – 3.56 (m, 1H), 4.06 (q, 2H), 7.38 (s, 1H), 7.71 (s, 1H). MS m/z 201 $(M+H)^+$

Step 3: 1-Benzyl 4-ethyl 2-carbamoylpiperidine-1,4-dicarboxylate

Ethyl 2-carbamoylpiperidine-4-carboxylate hydrochloride (2 g, 7.86 mmol) was slurried in dichloromethane (25 mL) and DIPEA (3.43 mL, 19.65 mmol) was added followed by benzyl carbonochloridate (1.161 mL, 8.25 mmol) dropwise. The reaction was stirred for 1 h then washed with 25 mL of 2 M HCl and water, dried over Na_2SO_4 and evaporated. The crude product was purified on a 100 g Biotage column with heptane/EtOAc over 4 CV followed by 100% EtOAc over 10 CV. 1-Benzyl 4-ethyl 2-carbamoylpiperidine-1,4-dicarboxylate (1.99 g, 76 %) was isolated. ^{1}H NMR (400 MHz, dmso) δ 1.16 (t, 3H), 1.57 – 1.69 (m, 1H), 1.81 – 1.92 (m, 1H), 1.95 – 2.07 (m, 1H), 2.21 – 2.32 (m, 1H), 2.58 – 2.67 (m, 1H), 3.29 – 3.45 (m, 1H), 3.69 – 3.77 (m, 1H), 3.92 – 4.06 (m, 2H), 4.34 (t, 1H), 4.99 – 5.08 (m, 2H), 6.95 (s, 1H), 7.25 – 7.38 (m, 6H). MS m/z 335 $(M+H)^+$

Step 4: 1-Benzyl 4-ethyl 2-cyanopiperidine-1,4-dicarboxylate

1-Benzyl 4-ethyl 2-carbamoylpiperidine-1,4-dicarboxylate (2.4 g, 7.18 mmol) was dissolved in pyridine (50 mL, 618.21 mmol). The mixture was cooled on an ice bath and $SOCl_2$ (3.14 mL, 43.07 mmol) was added dropwise and left overnight at room temperature. The reaction mixture was evaporated and partitioned between diluted HCl and DCM. The aqueous layer was extracted with DCM and the combined organic layer was washed with water, dried over Na_2SO_4 and evaporated. Crude 1-benzyl 4-ethyl 2-cyanopiperidine-1,4-dicarboxylate (2.25 g, 99 %) was isolated. ^{1}H NMR (400 MHz, dmso) δ 1.21 (t, 3H), 1.54 – 1.66 (m, 1H), 1.98 – 2.12 (m, 2H), 2.29 – 2.37 (m, 1H), 2.83 – 2.91 (m, 1H), 3.04 – 3.16 (m, 1H), 3.83 – 3.91 (m, 1H), 4.02 – 4.18 (m, 2H), 5.13 (s, 2H), 5.25 – 5.31 (m, 1H), 7.28 – 7.40 (m, 5H).

Step 5: 1-Benzyl 4-ethyl 2-(1H-tetrazol-5-yl)piperidine-1,4-dicarboxylate

1-Benzyl 4-ethyl 2-cyanopiperidine-1,4-dicarboxylate (2.5 g, 7.90 mmol) was dissolved in toluene (50 mL) and sodium azide (0.822 g, 12.64 mmol) and triethylamine hydrochloride (1.740 g, 12.64 mmol) were added and the mixture was heated at 95°C overnight. The rection mixture was allowed to cool to room temperature and was washed with 2 M HCl. The aqueous phase was extracted with EtOAc and the combined organic phase was dried over

Na_2SO_4 and evaporated to yield 1-benzyl 4-ethyl 2-(1H-tetrazol-5-yl)piperidine-1,4-dicarboxylate (2.8 g, 99 %). MS m/z 360 $(M+H)^+$

Step 6: 1-Benzyl 4-ethyl 2-(2-methyl-2H-tetrazol-5-yl)piperidine-1,4-dicarboxylate and 1-benzyl 4-ethyl 2-(1-methyl-1H-tetrazol-5-yl)piperidine-1,4-dicarboxylate

1-Benzyl 4-ethyl 2-(1H-tetrazol-5-yl)piperidine-1,4-dicarboxylate (3.45 g, 9.60 mmol) was dissolved in acetone (20 mL) and iodomethane (2.99 mL, 48.00 mmol) and K_2CO_3 (3.98 g, 28.80 mmol) were added. The mixture was stirred at room temperature for 3 h. The reaction mixture was partitioned between water and EtOAc. The aqueous layer was extracted twice with EtOAc and the combined organic phase was washed with water and evaporated. The crude product was purified on a 100 g Biotage column with heptane/EtOAc 88/12 - 0/100 over 12 column volumes (CV). 1-Benzyl 4-ethyl 2-(2-methyl-2H-tetrazol-5-yl)piperidine-1,4-dicarboxylate (1.84 g, 51 %) and 1-benzyl 4-ethyl 2-(1-methyl-1H-tetrazol-5-yl)piperidine-1,4-dicarboxylate (1.14 g, 32 %) were isolated. 2-Methyl-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.15 (t, 3H), 1.75 – 1.87 (m, 1H), 2.02 – 2.11 (m, 1H), 2.27 – 2.37 (m, 1H), 2.66 – 2.78 (m, 2H), 3.55 – 3.65 (m, 1H), 3.75 – 3.86 (m, 1H), 3.90 – 3.99 (m, 1H), 4.01 – 4.09 (m, 1H), 4.25 (s, 3H), 5.13 (q, 2H), 5.55 – 5.62 (m, 1H), 7.25 – 7.38 (m, 5H). MS m/z 374 $(M+H)^+$. 3-Methyl-isomer: MS m/z 374 $(M+H)^+$

Step 7: 1-(Benzyloxycarbonyl)-2-(2-methyl-2H-tetrazol-5-yl)piperidine-4-carboxylic acid

1-Benzyl 4-ethyl 2-(2-methyl-2H-tetrazol-5-yl)piperidine-1,4-dicarboxylate (0.92 g, 2.36 mmol) was dissolved in THF (10 mL) and water (10 mL) and LiOH (0.239 g, 9.98 mmol) was added. The mixture was stirred at room temperature for 1 h 10 min and then diluted with water and acidified with 2 M HCl. The aqueous phase was extracted 3 times with EtOAc, the combined organic phase dried over Na_2SO_4 and evaporated to yield 1-(benzyloxycarbonyl)-2-(2-methyl-2H-tetrazol-5-yl)piperidine-4-carboxylic acid (828 mg, quant.). ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.80 – 1.91 (m, 1H), 2.01 – 2.11 (m, 1H), 2.34 (dt, 1H), 2.63 – 2.79 (m, 2H), 3.55 – 3.65 (m, 1H), 4.01 – 4.09 (m, 1H), 4.24 (s, 3H), 5.13 (d, 2H), 5.60 (dd, 1H), 7.27 – 7.39 (m, 5H). MS m/z 346 $(M+H)^+$

Reference compound 37

1-(Benzyloxycarbonyl)-2-(1-methyl-1H-tetrazol-5-yl)piperidine-4-carboxylic acid

1-Benzyl 4-ethyl 2-(1-methyl-1H-tetrazol-5-yl)piperidine-1,4-dicarboxylate (1.14 g, 2.93 mmol) (from reference compound 36, step 6) was dissolved in THF (10 mL) and water (10 mL) and LiOH (0.280 g, 11.69 mmol) was added. The mixture was stirred at room temperature for 30 min and then diluted with water and acidified with 2 M HCl. The aqeous phase was extracted 3 times with EtOAc, the combined organic phase dried over Na_2SO_4 and evaporated to yield 1-(Benzyloxycarbonyl)-2-(1-methyl-1H-tetrazol-5-yl)piperidine-4-carboxylic acid (990 mg, 98 %). ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.89 – 2.01 (m, 1H), 2.15 – 2.24 (m, 1H), 2.27 – 2.36 (m, 1H), 2.50 – 2.61 (m, 1H), 2.78 (p, 1H), 3.68 – 3.80 (m, 1H), 3.91 – 4.09 (m, 4H), 5.08 (q, 2H), 5.44 (t, 1H), 7.23 – 7.39 (m, 5H). MS m/z 346 $(M+H)^+$

Reference compound 38

2-(Cyclohexyloxymethyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: Methyl 2-(hydroxymethyl)isonicotinate

The reaction was performed in 2 separate 1000 mL round-bottomed flasks. To a solution of methyl isonicotinate (70 g, 510.44 mmol) and sulfuric acid (2.340 mL, 43.90 mmol) in MeOH (700 mL) under reflux, was added a solution of ammonium peroxydisulfate (210 g, 918.80 mmol) in water (350 mL) over 20 min. The reaction was refluxed for 20 min and was then allowed to cool to room temperature. The solid was filtered off and washed with MeOH. MeOH was removed from the filtrate under reduced pressure and then was neutralised by cautious stepwise addition of solid Na_2CO_3 under ice-cooling. The aqueous solution was extracted with ethyl acetate and the combined organic layers were dried with Na_2SO_4 and evaporated. The dark-brown residue was treated with cyclohexane (3 x 300 mL) and the cyclohexane phase was decanted. The remaining dark-brown residue was purified by automated flash chromatography on 2 Biotage® KP-SIL 340g columns. A gradient from 25 % to 100 % of EtOAc in heptane over 10 CV was used as mobile phase. Methyl 2-(hydroxymethyl)isonicotinate (27.5 g, 32 %) was isolated. ^{1}H NMR (400 MHz, cdcl$_3$) δ 3.90 (s, 3H), 4.78 (s, 2H), 7.57 – 7.90 (m, 2H), 8.64 (s, 1H). MS m/z 168 $(M+H)^+$

Step 2: Methyl 2-(phenoxymethyl)isonicotinate

Methyl 2-(hydroxymethyl)isonicotinate (2.232 g, 13.35 mmol) dissolved in THF (15 mL) and

phenol (1.426 mL, 16.02 mmol) and triphenylphosphine (3.71 mL, 16.02 mmol) were added. The mixture was cooled to 0°C. (E)-diisopropyl diazene-1,2-dicarboxylate (3.24 g, 16.02 mmol) was added dropwise, the ice-bath removed and the reaction stirred at room temperature for 2 h. The solvent was evaporated and the residue was purified by automated flash chromatography on a Biotage® KP-SIL 340g column. 4:1 of EtOAc in heptane over 10 CV was used as mobile phase. Methyl 2-(phenoxymethyl)isonicotinate (2.65 g, 82 %) was isolated .^{1}H NMR (400 MHz, cdcl$_3$) δ 3.96 (s, 3H), 5.26 (s, 2H), 6.95 – 7.04 (m, 3H), 7.27 – 7.34 (m, 2H), 7.76 – 7.80 (m, 1H), 8.10 (s, 1H), 8.75 (d, 1H). MS m/z 244 $(M+H)^+$

Step 3 Methyl 2-(cyclohexyloxymethyl)piperidine-4-carboxylate

Methyl 2-(phenoxymethyl)isonicotinate (2.6 g, 10.69 mmol) was dissolved in acetic acid (50 mL), then platinum(IV) oxide (0.243 g, 1.07 mmol) was added and the mixture hydrogenated in a Büchi hydrogenator at 5 bar and room temperature for 6 h. The catalyst was removed by filtration and the solvent evaporated. The residue was taken up in DCM and the organic phase was washed with satd $NaHCO_3$. The aqueous phase was extracted with DCM and the combined organic phases were filtered through a phase separator and evaporated. Methyl 2-(cyclohexyloxymethyl)piperidine-4-carboxylate (2 g, 73 %) was isolated.

Step 4: Dimethyl 2-(cyclohexyloxymethyl)piperidine-1,4-dicarboxylate

Methyl 2-(cyclohexyloxymethyl)piperidine-4-carboxylate (2.13 g, 8.34 mmol) was dissolved in dichloromethane (50 mL). DIPEA (2.034 mL, 11.68 mmol) and methyl carbonochloridate (0.788 mL, 10.01 mmol) were added and the mixture was stirred at room temperature for 3 h. 0.1 M NH_4Cl was added and the aqueous layer was extracted with DCM. The combined organic layers were filtered through a phase separator and evaporated. Dimethyl 2-(cyclohexyloxymethyl)piperidine-1,4-dicarboxylate (2.54 g, 97 %) was isolated. MS m/z 314 $(M+H)^+$

Step 5: 2-(Cyclohexyloxymethyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Dimethyl 2-(cyclohexyloxymethyl)piperidine-1,4-dicarboxylate (2.54 g, 8.1 mmol) was dissolved in acetonitrile (35 mL) and water (0.7 mL), then lithium bromide (5.63 g, 64.80 mmol) was added. Triethylamine (4.49 mL, 32.40 mmol) was added and the resulting suspension was heated under reflux for 4 h. MTBE (100 mL) and water (50 mL) were added, the phases separated and the organic layer was extracted with water. The combined aqueous

layers were acidified to pH 1 with 3.8 M HCl and extracted with MTBE. The combined organic layers were dried with Na_2SO_4 and evaporated. 2-(Cyclohexyloxymethyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (2.43 g, quant.) was isolated. MS m/z 300 $(M+H)^+$

Reference compound 39

2-(Difluoromethyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: Methyl 2-formylisonicotinate

Methyl 2-(hydroxymethyl)isonicotinate (8.36 g, 50 mmol) (from reference compound 38, step 1) was dissolved in dichloromethane (150 mL). Dess-Martin periodinane (25 g, 58.94 mmol) was added and the mixture stirred at room temperature for 2 h 30 min. Sodium sulfothioate (59.3 g, 375.00 mmol) was dissolved in satd $NaHCO_3$ and added to the reaction mixture. The suspension was vigorously stirred at room temperature for 15 min, DCM was added and the phases were separated. The aqueous phase was extracted with DCM twice and the combined organic layers were dried over $MgSO_4$ and evaporated. The residue was purified by automated flash chromatography on a Biotage® KP-SIL 340g column. Gradient heptanes / EtOAc 80:20 to 65:35 over 5 CV was used as mobile phase. Methyl 2-formylisonicotinate (7 g, 85 %) was isolated as an off-white solid. ^1H NMR (400 MHz, cdcl$_3$) δ 4.00 (s, 3H), 8.09 (dd, 1H), 8.49 (s, 1H), 8.95 (d, 1H), 10.15 (s, 1H). MS m/z 165 $(M)^+$

Step 2: Methyl 2-(difluoromethyl)isonicotinate

Methyl 2-formylisonicotinate (2.51 g, 15.20 mmol) was dissolved in dichloromethane (50 mL) and cooled to 0°C. Diethylaminosulfur trifluoride (DAST) (2.61 mL, 19.76 mmol) was added dropwise. The cooling was removed and the mixture was stirred at room temperature for 2 h. Satd $NaHCO_3$ was added at 0°C and the phases were separated. The aqueous phase was extracted with DCM. The combined organic phases were filtered through a phase separator and evaporated. The residue was purified by automated flash chromatography on a Biotage® KP-SIL 50g column. 5:1 of EtOAc in heptane over 10 CV was used as mobile phase. Methyl 2-(difluoromethyl)isonicotinate (2.4 g, 84 %) was isolated. ^1H NMR (400 MHz, cdcl$_3$) δ 4.00 (s, 3H), 6.70 (t, 1H), 7.97 (d, 1H), 8.19 (s, 1H), 8.82 (d, 1H).

Step 3: Methyl 2-(difluoromethyl)piperidine-4-carboxylate

Methyl 2-(difluoromethyl)isonicotinate (2.4 g, 12.82 mmol) was dissolved in acetic acid (40 mL). Platinum(IV) oxide (0.291 g, 1.28 mmol) was added and the mixture was hydrogenated at 5 bar and room temperature for 7 h in a Büchi hydrogenation apparatus. The catalyst was removed by filtration, fresh platinum(IV) oxide (210 mg, 0.92 mmol) was added and the hydrogenation was continued at 5 bar and room temperature for 6 h. The catalyst was removed by filtration and the solvent evaporated. The residue was taken up in DCM and the organic phase was washed with satd $NaHCO_3$. The aqueous phase was extracted with DCM and the combined organic phases were filtered through a phase separator and evaporated. Methyl 2-(difluoromethyl)piperidine-4-carboxylate (1.85 g, 75 %) was isolated. MS m/z 194 (M+H)+

Step 4: Dimethyl 2-(difluoromethyl)piperidine-1,4-dicarboxylate

Methyl 2-(difluoromethyl)piperidine-4-carboxylate (1.85 g, 9.58 mmol) was dissolved in dichloromethane (50 mL), DIPEA (2.335 mL, 13.41 mmol) and methyl carbonochloridate (0.905 mL, 11.49 mmol) were added and the mixture was stirred at room temperature for 3 h. 0.1 M NH_4Cl was added and the aqueous layer was extracted with DCM. The combined organic layers were filtered through a phase separator and evaporated. Crude dimethyl 2-(difluoromethyl)piperidine-1,4-dicarboxylate (2.35 g, 98 %) was isolated.

Step 5: 2-(Difluoromethyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Dimethyl 2-(difluoromethyl)piperidine-1,4-dicarboxylate (2.35 g, 9.35 mmol) was dissolved in THF (35 mL) and 1 M lithium hydroxide (12.16 mL, 12.16 mmol) in water was added. The mixture was stirred at room temperature for 3 h, then 1 M HCl and DCM were added and the phases were separated. The aqueous phase was extracted with DCM and the combined organic layers were dried by filtration through a phase separator and evaporated. 2-(Difluoromethyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (2.2 g, 99 %) was isolated. MS m/z 275 (M-H)-

Reference compound 40

2-((4,4-Difluorocyclohexyl)methyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: (4,4-Difluorocyclohexyl)methanol

Ethyl 4,4-difluorocyclohexanecarboxylate (10 g, 52.03 mmol) was dissolved in THF (100 mL) and cooled to 1°C under nitrogen atmosphere. LAH (57.2 mL, 57.23 mmol) was added dropwise to the solution at a rate to keep the temperature below 10°C. The resulting mixture was allowed to reach 20°C and stirred at that temperature for approximately 1 h. The reaction mixture was then cooled to 10°C and quenched carefully by the sequential slow addition of 2.2 mL of water, 2.2 mL of 15 w/v% aqueous NaOH and 6.6 mL of water and stirred for 30 minutes at 20°C. The solids were removed by filtration and washed with THF. The reaction solution was dried over $MgSO_4$ and evaporated in vacuo to give crude (4,4-difluoro-cyclohexyl)methanol (7.22 g, 92 %). ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.21 – 1.38 (m, 2H), 1.44 (s, 1H), 1.51 – 1.90 (m, 5H), 2.04 – 2.18 (m, 2H), 3.52 (d, 2H).

Step 2: 4-(Bromomethyl)-1,1-difluorocyclohexane

(4,4-Difluorocyclohexyl)methanol (7.22 g, 48.08 mmol) and triphenylphosphine (25.2 g, 96.16 mmol) were dissolved in DCM (75 mL) and cooled to 0°C under nitrogen athmosphere. Carbon tetrabromide (31.9 g, 96.16 mmol) was dissolved in DCM (75 mL) and added to the reaction mixture. The mixture was stirred at room temperature overnight. The solvent was evaporated. Pentane (250 mL) was added to the orange residue, which caused triphenylphosphineoxide to precipitate. The off-white solids were filtered off. The filtrate was evaporated and purified on a ISOLUTE Silica Flash column (50 g). Pentane followed by EtOAc:pentane (1% EtOAc) was used as eluent. 4-(Bromomethyl)-1,1-difluorocyclohexane (5.48 g, 54 %) was isolated. ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.32 – 1.46 (m, 2H), 1.64 – 1.84 (m, 3H), 1.90 – 1.99 (m, 2H), 2.05 – 2.18 (m, 2H), 3.31 (d, 2H).

Step 3: ((4,4-Difluorocyclohexyl)methyl)zinc(II) bromide

Zinc powder (1.43 g, 21.87 mmol) was added to a dried flask and was heated at 70°C under vacuum for 30 minutes. Dry DMA (29 mL) and iodine (0.092 g, 0.37 mmol) were added and the mixture was heated at 70°C until the red-brown colour had disappeared (approx. 5 minutes). 4-(Bromomethyl)-1,1-difluorocyclohexane (3.1 g, 14.55 mmol) was added and heating was continued for ca. 42 h. The resulting solution was used in the next transformation.

Step 4: Methyl 2-((4,4-difluorocyclohexyl)methyl)isonicotinate

To methyl-2-chloroisonicotinate (1.664 g, 9.7 mmol) and bis(tri-tert-butylphosphine)palladium(0) (198 mg, 0.38 mmol) under nitrogen was added tetrahydrofuran (10 mL). To the resulting solution was added freshly prepared ((4,4-difluorocyclohexyl)methyl)zinc(II) bromide (14.55 mmol, 0.5 M in 29 mL DMA) and the resulting brown mixture heated to 60°C for 4 h. The reaction mixture was diluted with ethyl acetate and washed with satd $NaHCO_3$ (2 times), satd NH_4Cl and brine. The organic layer was dried over $MgSO_4$, filtered and evaporated. The residue was dissolved in DCM and added onto an SCX-2 cation exchange column. The column was washed with DCM, MeOH and then eluted with NH_3/MeOH. The NH_3/MeOH layer was evaporated leaving methyl 2-((4,4-difluorocyclohexyl)methyl)isonicotinate (2 g, 67%) as a yellow oil. ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.30 – 1.46 (m, 2H), 1.58 – 1.79 (m, 4H), 1.87 – 2.14 (m, 3H), 2.82 (d, 2H), 3.96 (s, 3H), 7.65 – 7.73 (m, 2H), 8.70 (d, 1H). MS m/z 270 $(M+H)^+$

Step 5: Methyl 2-((4,4-difluorocyclohexyl)methyl)piperidine-4-carboxylate hydrochloride

Methyl 2-((4,4-difluorocyclohexyl)methyl)isonicotinate (5 g, 18.6 mmol) was treated with HCl (4 M in dioxane) and evaporated to give methyl 2-((4,4-difluorocyclohexyl)methyl)-isonicotinate hydrochloride (5.6 g, 18.32 mmol) which was dissolved in MeOH (100 mL), then platinum(IV) oxide (0.416 g, 1.83 mmol) was added. The mixture was hydrogenated in a Büchi hydrogenator at 5 bar overnight. The catalyst was filtered off and solvents were evaporated yielding methyl 2-((4,4-difluorocyclohexyl)methyl)piperidine-4-carboxylate hydrochloride (5.1 g, 89 %). MS m/z 276 $(M+H)^+$

Step 6: Dimethyl 2-((4,4-difluorocyclohexyl)methyl)piperidine-1,4-dicarboxylate

Methyl 2-((4,4-difluorocyclohexyl)methyl)piperidine-4-carboxylate hydrochloride (5.1 g, 16.36 mmol) was dissolved in DCM (150 mL), then DIPEA (7.14 mL, 40.89 mmol) was added. Methyl carbonochloridate (1.803 mL, 22.90 mmol) was added dropwise to the solution. The mixture was stirred at room temperature for 2 h. The mixture was washed with 0.1 M HCl (100 mL) and satd $NaHCO_3$ (100 mL), then dried through a phase separator and evaporated yielding crude dimethyl 2-((4,4-difluorocyclohexyl)methyl)piperidine-1,4-dicarboxylate (5.7 g, 105 %)

Step 7: 2-((4,4-Difluorocyclohexyl)methyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Dimethyl 2-((4,4-difluorocyclohexyl)methyl)piperidine-1,4-dicarboxylate (5.7 g, 17.10 mmol)

was dissolved in acetonitrile (75 mL) and water (1.5 mL), then lithium bromide (11.88 g, 136.78 mmol) was added. Et_3N (9.53 mL, 68.39 mmol) was added to the solution. The resulting yellow suspension was heated at reflux for 2 h. Water (100 mL) and MTBE (300 mL) were added. The phases were separated and the organic layer was extracted with water (2 times). The pooled water layers were acidified to pH 1 with 3.8 M HCl and extracted with MTBE (2 times). The combined organic layer was dried over Na_2SO_4, filtered and evaporated to yield 2-((4,4-difluorocyclohexyl)methyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (4.82 g, 88 %) as a white solid.

Reference compound 41

2-(4-Fluorophenethyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: (E)-Methyl 2-(4-fluorostyryl)isonicotinate

Methyl 2-chloroisonicotinate (5.5 g, 32.05 mmol), (E)-4-fluorostyrylboronic acid (7.98 g, 48.08 mmol), potassium phosphate (3.93 mL, 48.08 mmol) and $PdCl_2(dppf)$ (0.464 g, 0.64 mmol) were split into 5 equal portions and each portion was placed in a microwave reaction vessel. The vessels were evacuated and backfilled with nitrogen. Methanol (15 mL) was added to each vessel, the vessels were sealed and heated in a single node microwave reactor at 100°C for 10 min each. The contents of the vessels was pooled and water and DCM were added, the phases separated and the aqueous layer was extracted with DCM. The combined organic layers were filtered through a phase separator and evaporated. The residue was purified by automated flash chromatography on a Biotage® KP-SIL 340g column. A gradient from 6:1 to 4:1 of EtOAc in heptane over 15 CV was used as mobile phase. (E)-Methyl 2-(4-fluorostyryl)isonicotinate (3.88 g, 47 %) was isolated. ^{1}H NMR (400 MHz, cdcl$_3$) δ 3.98 (s, 3H), 7.04 – 7.18 (m, 3H), 7.52 – 7.62 (m, 2H), 7.63 – 7.71 (m, 2H), 7.93 (s, 1H), 8.74 (d, 1H). MS m/z 258 $(M+H)^+$

Step 2: Methyl 2-(4-fluorophenethyl)isonicotinate

(E)-methyl 2-(4-fluorostyryl)isonicotinate (3.6 g, 13.99 mmol) was dissolved in methanol (200 mL). Palladium on charcoal (0.149 g, 1.40 mmol) was added and the mixture was hydrogenated at atmospheric pressure and room temperature for 18 h. The catalyst was filtered

off and the filtrate was evaporated. Methyl 2-(4-fluorophenethyl)isonicotinate (3.63 g, 99 %) was isolated. MS m/z 260 $(M+H)^+$

Step 3: Methyl 2-(4-fluorophenethyl)piperidine-4-carboxylate

Methyl 2-(4-fluorophenethyl)isonicotinate (3.8 g, 14.66 mmol) dissolved in acetic acid (150 mL) and platinum(IV) oxide (0.25 g, 1.10 mmol) was added. The mixture was hydrogenated in a Büchi hydrogenation apparatus at 5 bar and room temperature for 5 h. The catalyst was removed by filtration and the solvent was evaporated. The residue was taken up in DCM and washed with satd $NaHCO_3$. The organic phase was filtered through a phase separator and evaporated. Methyl 2-(4-fluorophenethyl)piperidine-4-carboxylate (3.89 g, quant.) was isolated. MS m/z 266 $(M+H)^+$

Step 4: Dimethyl 2-(4-fluorophenethyl)piperidine-1,4-dicarboxylate

Methyl 2-(4-fluorophenethyl)piperidine-4-carboxylate (3.89 g, 14.65 mmol) was dissolved in dichloromethane (150 mL). DIPEA (3.06 mL, 17.58 mmol) was added, followed by methyl carbonochloridate (1.615 mL, 20.51 mmol). The mixture was stirred at room temperature for 2 h. 0.1 HCl and DCM were added. The phases were separated and the aqueous phase was extracted with DCM. The combined organic layers were washed with satd $NaHCO_3$, filtered through a phase separator and evaporated. Dimethyl 2-(4-fluorophenethyl)piperidine-1,4-dicarboxylate (3.19 g, 67 %) was isolated. MS m/z 324 $(M+H)^+$

Step 5: 2-(4-Fluorophenethyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Dimethyl 2-(4-fluorophenethyl)piperidine-1,4-dicarboxylate (3.18 g, 9.83 mmol) was dissolved in acetonitrile (35 mL) and water (0.7 mL) and lithium bromide (6.83 g, 78.67 mmol) was added. Triethylamine (5.45 mL, 39.34 mmol) was added and the resulting suspension was heated under reflux for 5 h. MTBE and water were added, the phases separated and the organic layer was extracted with water. The combined aqueous layers were acidified to pH 1 with 3.8 M HCl and extracted with MTBE. The combined organic layers were washed with water, dried with Na_2SO_4 and evaporated. Crude 2-(4-fluorophenethyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (4.37 g) was isolated. MS m/z 310 $(M+H)^+$

Reference compound 42

2-(3,3-Dimethylbutyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: Methyl 4-((tert-butyldimethylsilyloxy)methyl)-2-(3,3-dimethylbutyl)pyridine-1(2H)-carboxylate

4-((tert-Butyldimethylsilyloxy)methyl)pyridine (5.58 g, 25 mmol) (from reference compound 4, step 1) was dissolved in dry THF (50 mL) under nitrogen and the mixture cooled to -15°C. (3,3-Dimethylbutyl)magnesium chloride (0.5 M in THF) (50 mL, 25 mmol) was added dropwise during 20 min to yield a yellow solution which was stirred at -15°C for 30 min. Then, methyl carbonochloridate (2.5 mL, 32 mmol) was added during 1 min. The reaction was continued at -15°C for 30 min and then the mixture was cooled to -60°C. After 2 h the temperature had reached room temperature. Water (20 mL) was added and the solvent evaporated. The aqueous phase was extracted with DCM (x2) and the combined organic phase passed through a phase separator. The solvent was evaporated to yield a yellow oil. The residue was purified via Biotage (0 => 10 % EtOAc in heptane) to yield methyl 4-((tert-butyldimethylsilyloxy)methyl)-2-(3,3-dimethylbutyl)pyridine-1(2H)-carboxylate (3.67 g, 44 %) as a colourless oil. MS m/z 368 $(M+H)^+$

Step 2: Methyl 4-((tert-butyldimethylsilyloxy)methyl)-2-(3,3-dimethylbutyl)piperidine-1-carboxylate

To a solution of methyl 4-((tert-butyldimethylsilyloxy)methyl)-2-(3,3-dimethylbutyl)-pyridine-1(2H)-carboxylate (3.63 g, 9.87 mmol) in ethyl acetate (60 mL) was platinum (IV) oxide (224 mg, 1 mmol) added. Hydrogenated at 6 bar in a Büchi hydrogenator for 3.5 h. The catalyst was filtered off and the filtrate evaporated to yield methyl 4-((tert-butyl-dimethylsilyloxy)methyl)-2-(3,3-dimethylbutyl)piperidine-1-carboxylate (3.62 g, 99 %) as a colourless oil. MS m/z 372 $(M+H)^+$

Step 3: Methyl 2-(3,3-dimethylbutyl)-4-(hydroxymethyl)piperidine-1-carboxylate

Methyl 4-((tert-butyldimethylsilyloxy)methyl)-2-(3,3-dimethylbutyl)piperidine-1-carboxylate (3.606 g, 9.7 mmol) was dissolved in THF (50 mL) and TBAF (1M in THF) (13 mL, 13 mmol) added. Stirred at room temperature for 3.5 h. The solvent was evaporated. Redissolved in DCM and washed with satd $NaHCO_3$. The organic phase was passed through a phase separator and evaporated to yield an oil. The residue was purified via Biotage (eluent 30-70% EtOAc in heptane) to yield methyl 2-(3,3-dimethylbutyl)-4-(hydroxymethyl)piperidine-1-

carboxylate (2.45 g, 98 %) as a colourless oil. MS m/z 258 $(M+H)^+$

Step 4: 2-(3,3-Dimethylbutyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Methyl 2-(3,3-dimethylbutyl)-4-(hydroxymethyl)piperidine-1-carboxylate (2.44 g, 9.49 mmol) was dissolved in CCl_4 (20 mL) and acetonitrile (20 mL). Sodium periodiate (6.09 g, 28.5 mmol) was added followed by water (30 mL) and ruthenium (III) chloride (43 mg, 0.21 mmol). The resulting suspension was stirred at room temperature for 3 h 50 min. The reaction mixture was diluted with DCM (100 mL) and water (100 mL). The aqueous layer was extracted with DCM (x3) and the combined organic phase passed through a phase separator and evaporated to yield crude 2-(3,3-dimethylbutyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (2.42 g, 94 %) as a black solid. MS m/z 272 $(M+H)^+$

Reference compound 43

2-(4-Fluorobenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: Methyl 2-(4-fluorobenzyl)isonicotinate

Methyl 2-chloroisonicotinate (5.6 g, 32.64 mmol) and $Pd(PPh_3)_4$(0.754 g, 0.65 mmol) were dissolved under nitrogen in THF (100 mL) and (4-fluorobenzyl)zinc(II) chloride (0.5 M in THF) (100 mL, 50.00 mmol) was added. The brown solution was stirred at 60°C for 19 h. The reaction was quenched by addition of methanol (50.0 mL). The solution was diluted with EtOAc and washed with NH_4Cl (aq) and water. The organic layer was evaporated, dissolved in DCM and washed with NH4Cl (aq) and then dried by passage through a phase separator. The solvent was evaporated to yield a brown oil. The compound was purified in 2 runs via Biotage, SNAP 340g KP-SIL, eluent isocratic heptane/ethyl acetate 8:2 for 2 CV, then linear gradient heptane/ethyl acetate 8:2 to 5:5 over 5 CV to yield methyl 2-(4-fluorobenzyl)isonicotinate 7.08 g (88%) as a yellow oil. ^1H NMR (400 MHz, $cdcl_3$) δ 3.92 (s, 3H), 4.18 (s, 2H), 6.94 – 7.02 (m, 2H), 7.19 – 7.27 (m, 2H), 7.65 – 7.69 (m, 2H), 8.68 – 8.71 (m, 1H). MS m/z 246 $(M+H)^+$

Step 2: Methyl 2-(4-fluorobenzyl)piperidine-4-carboxylate

Methyl 2-(4-fluorobenzyl)isonicotinate (5.06 g, 20.63 mmol) was dissolved in acetic acid (50 mL) and platinum(IV) oxide (0.234 g, 1.03 mmol) added. The resulting mixture was

hydrogenated in a Büchi hydrogenator overnight at room temperature and 5 bar. The catalyst was filtered off and washed with MeOH and the eluate evaporated. DCM and 10 % K_2CO_3 were added and the phases separated. The aqueous phase was extracted with DCM and the combined organic phase washed with brine, passed through a phase separator and evaporated to yield methyl 2-(4-fluorobenzyl)piperidine-4-carboxylate (3.816 g, 73.6 %) as a yellow oil. MS m/z 252 $(M+H)^+$

Step 3: Dimethyl 2-(4-fluorobenzyl)piperidine-1,4-dicarboxylate

Methyl 2-(4-fluorobenzyl)piperidine-4-carboxylate (4.981 g, 19.82 mmol) was dissolved in DCM (150 mL) and DIPEA (4.14 mL, 23.79 mmol), then methyl carbonochloridate (1.873 mL, 23.79 mmol) was added. The solution was stirred at room temperature for 50 min. More methyl carbonochloridate (a few drops) were added and the reaction continued at room temperature for 1 h. The reaction mixture was washed with 0.1 M HCl and satd $NaHCO_3$. The organic phase was passed through a phase separator and evaporated to yield dimethyl 2-(4-fluorobenzyl)piperidine-1,4-dicarboxylate (5.82 g, 95 %) as a yellow oil. MS m/z 310 $(M+H)^+$

Step 4: 2-(4-Fluorobenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Dimethyl 2-(4-fluorobenzyl)piperidine-1,4-dicarboxylate (5.797 g, 18.74 mmol) was dissolved in acetonitrile (60 mL) and water (1.2 mL), then lithium bromide (13.02 g, 149.92 mmol) was added. Triethylamine (10.39 mL, 74.96 mmol) was added and the resulting yellow suspension was heated at reflux for 1.5 h. water (60 mL) and MTBE (120 mL) were added. The organic phase was extracted with water (x2). The pooled aqueous layer was acidified to pH 1 with 3.8 M HCl and then extracted with MTBE (x2). The combined organic layer was washed with water and evaporated. Traces of water were azeotropically removed by MeCN. 2-(4-Fluorobenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (4.43 g, 80 %) was isolated as a beige solid. MS m/z 296 $(M+H)^+$

Reference compound 44

2-(3-Fluorobenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: Methyl 2-(3-fluorobenzyl)isonicotinate

Methyl 2-chloroisonicotinate (5.6 g, 32.64 mmol) and $Pd(PPh_3)_4$ (0.754 g, 0.65 mmol) were

dissolved in THF (100 mL) under nitrogen and (3-fluorobenzyl)zinc(II) chloride (0.5 M in THF) (100 mL, 50.00 mmol) was added. The brown solution was stirred at 60°C for 4 h. The reaction was quenched by addition of methanol (50 mL), diluted with EtOAc and washed with NH_4Cl. The organic layer was dried over Na_2SO_4, filtered and evaporated to yield a yellow oil. The compound was purified in 2 runs via Biotage, SNAP 340g KP-SIL, eluent isocratic heptane/ethyl acetate 8:2 for 2 CV, then linear gradient heptane/ethyl acetate 8:2 to 5:5 over 5 CV to yield methyl 2-(3-fluorobenzyl)isonicotinate (6.766 g, 85%) as a yellow oil. ^1H NMR (400 MHz, cdcl$_3$) δ 3.93 (s, 3H), 4.21 (s, 2H), 6.88 – 7.00 (m, 2H), 7.02 – 7.07 (m, 1H), 7.22 – 7.30 (m, 1H), 7.66 – 7.73 (m, 2H), 8.68 – 8.73 (m, 1H). MS m/z 246 $(M+H)^+$

Step 2: Methyl 2-(3-fluorobenzyl)piperidine-4-carboxylate

Methyl 2-(3-fluorobenzyl)isonicotinate (6.766 g, 27.59 mmol) was dissolved in acetic acid (70 mL) and platinum(IV) oxide (0.313 g, 1.38 mmol) added. The resulting mixture was hydrogenated in a Büchi hydrogenator at room temperature and 5 bar for 4.5 h. More platinum(IV) oxide (0.313 g, 1.38 mmol) was added and the hydrogenation continued at 5 bar for 2 h 40 min. The catalyst was filtered off, washed with MeOH and the eluate evaporated. DCM and 10 % K_2CO_3 were added and the phases separated. The water phase was extracted with DCM and the combined organic phase washed with brine, passed through a phase separator and evaporated to yield crude methyl 2-(3-fluorobenzyl)piperidine-4-carboxylate (7.6 g, 110%) as a brown oil. MS m/z 252 $(M+H)^+$

Step 3: Dimethyl 2-(3-fluorobenzyl)piperidine-1,4-dicarboxylate

Methyl 2-(3-fluorobenzyl)piperidine-4-carboxylate (7.6 g, 30.24 mmol) was dissolved in DCM (200 mL) and DIPEA (6.32 mL, 36.29 mmol), then methyl carbonochloridate (3.3 mL, 41.91 mmol) was added. The solution was stirred at room temperature for 2 h. The reaction mixture was washed with 0.1 M HCl and satd $NaHCO_3$. The organic phase was passed through a phase separator and evaporated to yield dimethyl 2-(3-fluorobenzyl)piperidine-1,4-dicarboxylate (9.30 g, 99%) as a brown oil. MS m/z 310 $(M+H)^+$

Step 4: 2-(3-Fluorobenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Dimethyl 2-(3-fluorobenzyl)piperidine-1,4-dicarboxylate (9.153 g, 29.59 mmol) was dissolved in acetonitrile (100 mL) and water (2 mL), then lithium bromide (20.56 g, 236.72 mmol) was added. Triethylamine (16.41 mL, 118.36 mmol) was added and the resulting

brown suspension was heated at reflux for 2 h. Water (100 mL) and MTBE (300 mL) were added. The organic phase was extracted with water (x2). The pooled aqueous layer was acidified to pH 1 with 3.8 M HCl and then extracted with MTBE (x2). The combined organic layer was washed with water, dried over Na_2SO_4, filtered through a Celite containing filter and evaporated. 2-(3-Fluorobenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (7.07 g, 81%) was isolated as a yellow solid. MS m/z 296 $(M+H)^+$

Reference compound 45

2-(2-Fluorobenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: Methyl 2-(2-fluorobenzyl)isonicotinate

Methyl 2-chloroisonicotinate (5.2 g, 30.31 mmol) and $Pd(PPh_3)_4$ (0.700 g, 0.61 mmol) were dissolved under nitrogen in THF (100 mL) and (2-fluorobenzyl)zinc(II) chloride (0.5 M in THF) (90 mL, 45.00 mmol) was added and the brown solution was stirred at 60°C for 18 h. The reaction was quenched by addition of methanol (50.0 mL). The solution was diluted with EtOAc, washed with NH_4Cl (aq) and dried over Na_2SO_4, then evaporated. The compound was purified in 2 runs via Biotage, SNAP 340g KP-SIL, eluent isocratic heptane/ethyl acetate 8:2 for 2 CV, then linear gradient heptane/ethyl acetate 8:2 to 5:5 over 5 CV to give methyl 2-(2-fluorobenzyl)isonicotinate (5.42 g, 73%) as a yellow oil. ^1H NMR (400 MHz, $cdcl_3$) 3.92 (s, 3H), 4.25 (s, 2H), 7.00 – 7.13 (m, 2H), 7.18 – 7.30 (m, 2H), 7.64 – 7.74 (m, 2H), 8.69 (d, 1H). MS m/z 246 (M+H)+

Step 2: Methyl 2-(2-fluorobenzyl)piperidine-4-carboxylate

Methyl 2-(2-fluorobenzyl)isonicotinate (5.42 g, 22.08 mmol) was dissolved in acetic acid (50 mL) and platinum(IV) oxide (0.251 g, 1.10 mmol) added. The resulting mixture was hydrogenated in a Büchi hydrogenator for 4 h at room temperature and 5 bar. The catalyst was filtered off and washed with MeOH and the eluate evaporated. DCM and 10 % K_2CO_3 were added and the phases separated. The water phase was extracted with DCM and the combined organic phase washed with water, passed through a phase separator and evaporated to yield methyl 2-(2-fluorobenzyl)piperidine-4-carboxylate (4.49 g, 81 %) MS m/z 252 (M+H)+

Step 3: Dimethyl 2-(2-fluorobenzyl)piperidine-1,4-dicarboxylate

To a solution of methyl 2-(2-fluorobenzyl)piperidine-4-carboxylate (4.49 g, 17.85 mmol) and DIPEA (9.35 mL, 53.55 mmol) in DCM (100 mL) was added methyl chloroformate (1.798 mL, 23.21 mmol) in DCM (50 mL). The reaction mixture was stirred for 1.5 h. The organic phase was washed with satd $NaHCO_3$. The phases were separated and the organic phase dried using a phase separator to yield crude dimethyl 2-(2-fluorobenzyl)piperidine-1,4-dicarboxylate (6.16 g, 112 %). MS m/z 310 $(M+H)^+$

Step 4: 2-(2-Fluorobenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Dimethyl 2-(2-fluorobenzyl)piperidine-1,4-dicarboxylate (6.16 g, crude) was dissolved in acetonitrile (45 mL) and water (0.9 mL). Lithium bromide (13.84 g, 159.39 mmol) and triethylamine (11.05 mL, 79.69 mmol) were added and the mixture was heated at reflux overnight. Water (90 mL) and MTBE were added. The organic phase was extracted with water (x2). To the pooled aqueous layer was added MTBE and the solution was acidified to pH 1 with 2 M HCl and then extracted with MTBE (x2). The combined organic layer was dried over Na_2SO_4 and evaporated to give 2-(2-fluorobenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (4.48 g, 76 %) as a slightly yellow semisolid. MS m/z 296 $(M+H)^+$

Reference compound 46

Cis-1-(methoxycarbonyl)-2-(4-(trifluoromethyl)benzyl)piperidine-4-carboxylic acid

Step 1: Methyl 2-(4-(trifluoromethyl)benzyl)isonicotinate

Methyl 2-chloroisonicotinate (18 g, 104.91 mmol) and $Pd(PPh_3)_4$ (2.43 g, 2.10 mmol) were dissolved in THF (300 mL). (4-Trifluoromethyl)benzyl)zinc(II) chloride (0.5 M in THF) (273 mL, 137 mmol) was added to the yellow solution and the flask was warmed to 60°C overnight. The reaction mixture was quenched by adding methanol. The solution was diluted with ethyl acetate and washed with NH_4Cl (aq) and water. The organic layer was dried with Na_2SO_4, filtered through celite, and the solvent was evaporated. The crude was chromatographed using the Biotage equipment. Eluent ethyl acetate-heptane, started 0-100 and linear gradient until 100-0. Methyl 2-(4-(trifluoromethyl)benzyl)isonicotinate (11.5 g, 37.1%) was isolated. ^1H NMR (600 MHz, $cdcl_3$) δ 3.91 (s, 3H), 4.25 (s, 2H), 7.36 (d, 2H),

7.54 (d, 2H), 7.66 – 7.70 (m, 2H), 8.68 (d, 1H).

Step 2: Methyl 2-(4-(trifluoromethyl)benzyl)piperidine-4-carboxylate

Methyl 2-(4-(trifluoromethyl)benzyl)isonicotinate (11.5 g, 38.95 mmol) was dissolved in acetic acid (200 mL) and methanol (100 mL). Platinum(IV) oxide (0.177 g, 0.78 mmol) was added and the mixture hydrogenated in a Büchi hydrogenator at room temperature and 7 bar for 6 h. The catalyst was filtered off. Fresh platinum(IV) oxide (0.18 g, 0.78 mmol) was added and hydrogenation continued at 9 bar for 7 h. The catalyst was filtered off, the solvent was evaporated and the residue partitioned between ethyl acetate and Na_2CO_3 (aq). The organic layer was dried over $MgSO_4$, filtered through celite and the solvent evaporated. Methyl 2-(4-(trifluoromethyl)benzyl)piperidine-4-carboxylate (9.5 g, 81 %) was isolated.

Step 3: Dimethyl 2-(4-(trifluoromethyl)benzyl)piperidine-1,4-dicarboxylate

Methyl 2-(4-(trifluoromethyl)benzyl)piperidine-4-carboxylate (9.5 g, 31.53 mmol) was dissolved in DIPEA (8.24mL, 47.29 mmol) and dichloromethane (150 mL). Methyl carbonochloridate (3.58 g, 37.50 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 1 h, diluted with ether and washed with 1 M HCl. The organic layer was washed with Na_2CO_3 (aq), dried $MgSO_4$, filtered through celite and the solvent was evaporated to yield dimethyl 2-(4-(trifluoromethyl)benzyl)piperidine-1,4-dicarboxylate (10.9 g , 96 %).

Step 4: 1-(Methoxycarbonyl)-2-(4-(trifluoromethyl)benzyl)piperidine-4-carboxylic acid

Dimethyl 2-(4-(trifluoromethyl)benzyl)piperidine-1,4-dicarboxylate (10.9 g, 30.33 mmol) was dissolved in acetonitrile (80 mL) and water (1.6 mL), then lithium bromide (21.07 g, 242.67 mmol) and triethylamine (16.82 mL, 121.33 mmol) were added and the resulting yellow suspension was heated at reflux. Water (60 mL) and MTBE were added. The organic phase was extracted with water (x2). To the pooled aqueous layer was added MTBE and the solution was acidified to pH 1 with HCl and then extracted with MTBE (x2). The organic layer was dried Na_2SO_4, filtered through celite and the solvent evaporated to yield 1-(methoxycarbonyl)-2-(4-(trifluoromethyl)benzyl)piperidine-4-carboxylic acid (9.14 g, 87 %).

Step 5: Cis-1-(methoxycarbonyl)-2-(4-(trifluoromethyl)benzyl)piperidine-4-carboxylic acid

1-(Methoxycarbonyl)-2-(4-(trifluoromethyl)benzyl)piperidine-4-carboxylic acid (14.65 g,

42.43 mmol) was suspended in MTBE (150 mL) and heated under reflux for 1 min, then stirred at room temperature for 3 days. The solids were isolated and dried under vacuum. Cis-1-(methoxycarbonyl)-2-(4-(trifluoromethyl)benzyl)piperidine-4-carboxylic acid (9.3 g, 63.5 %) was isolated. ^{1}H NMR (600 MHz, cd_3od) δ 1.68 – 1.77 (m, 1H), 1.90 – 1.97 (m, 1H), 1.99 – 2.10 (m, 2H), 2.58 – 2.64 (m, 1H), 2.83 – 2.89 (m, 1H), 2.93 – 3.00 (m, 1H), 3.16 – 3.31 (m, 1H), 3.43 (s, 3H), 3.86 – 3.92 (m, 1H), 4.31 – 4.36 (m, 1H), 7.36 (d, 2H), 7.53 (d, 2H).

Reference compound 47

1-(Methoxycarbonyl)-2-(4-(trifluoromethyl)benzyl)piperidine-4-carboxylic acid

Step 1: Methyl 4-cyano-2-(4-(trifluoromethyl)benzyl)piperidine-1-carboxylate

To a solution of methyl 4-oxo-2-(4-(trifluoromethyl)benzyl)piperidine-1-carboxylate (8.75 g, 27.75 mmol) (Syngene) in DME (100 mL) under nitrogen was added simultaneously 1-(isocyanomethylsulfonyl)-4-methylbenzene (8.13 g, 41.63 mmol) in 100 mL DME and potassium tert-butoxide (83 mL, 83.26 mmol) (1 M) over 30 min at -20 to -10°C. The solution was stirred at -20°C for 2 h and then allowed to warm to room temperature overnight. To the orange reaction mixture was added water (200 mL), the solution was stirred for 20 min and then extracted with diethyl ether (3x) and EtOAc (3x). The combined organic phases were washed once with brine and then dried over Na_2SO_4 and evaporated to yield a brown oil. The oil was purified by flash chromatography on silica gel using a gradient of 20-60 % EtOAc in heptane as eluent. Methyl 4-cyano-2-(4-(trifluoromethyl)benzyl)piperidine-1-carboxylate (7.96 g, 87.9 %) was isolated as a yellow oil.

Step 2: 1-(Methoxycarbonyl)-2-(4-(trifluoromethyl)benzyl)piperidine-4-carboxylic acid

Methyl 4-cyano-2-(4-(trifluoromethyl)benzyl)piperidine-1-carboxylate (2.1 g, 6.44 mmol), hydrogen peroxide (5 mL, 206.78 mmol) and potassium hydroxide (3.61 g, 54.36 mmol) in water (50 mL) were heated to 80°C overnight. 1 M HCl and EtOAc was added to the reaction mixture. The organic phase was isolated, dried with Na_2SO_4, filtered through Celite and the solvent was evaporated to yield 1-(methoxycarbonyl)-2-(4-(trifluoromethyl)benzyl)-piperidine-4-carboxylic acid (1.67 g, 75 %).

Reference compound 48

1-(Methoxycarbonyl)-2-(3-(trifluoromethyl)benzyl)piperidine-4-carboxylic acid

Step 1: Methyl 2-(3-(trifluoromethyl)benzyl)isonicotinate

Methyl 2-chloroisonicotinate (8.1 g, 47.21 mmol) and $Pd(PPh_3)_4$ (1.091 g, 0.94 mmol) were dissolved in THF (150 mL) under nitrogen. (3-Trifluoromethyl)benzyl)zinc(II) chloride (0.5 M in THF) (142 mL, 71 mmol) was added to the orange solution and the flask was warmed to 60°C overnight. The reaction mixture was quenched by adding methanol (50 mL) and most of the solvent was removed by evaporation. The residue was diluted with ethyl acetate and washed with NH_4Cl (aq) and water. The organic layer was dried with Na_2SO_4, filtered through celite, and the solvent was evaporated. The crude was chromatographed using the Biotage equipment. Eluent ethyl acetate-heptane, started 20-80 and linear gradient until 40-60. Methyl 2-(3-(trifluoromethyl)benzyl)isonicotinate (12.83 g, 92 %) was isolated. ^1H NMR (400 MHz, $cdcl_3$) δ 3.93 (s, 3H), 4.27 (s, 2H), 7.37 – 7.56 (m, 4H), 7.66 – 7.75 (m, 2H), 8.67 – 8.76 (m, 1H).

Step 2: Methyl 2-(3-(trifluoromethyl)benzyl)piperidine-4-carboxylate

Methyl 2-(3-(trifluoromethyl)benzyl)isonicotinate (12.83 g, 43.45 mmol) and platinum(IV) oxide (0.197 g, 0.87 mmol) were added to acetic acid (150 mL). The reaction mixture was hydrogenated in a Büchi hydrogenator for 6 h at room temperature and 5 bar. The catalyst was filtered off and fresh platinum(IV) oxide (0.26 g) was added. Hydrogenation was continued overnight at 6 bar. The catalyst was filtered off and the solvent was evaporated. The residue was dissolved in ethyl acetate and washed with Na_2CO_3 (aq). The organic layer was isolated, dried over $MgSO_4$, filtered through celite and the solvent evaporated. Crude methyl 2-(3-(trifluoromethyl)benzyl)piperidine-4-carboxylate (14. 4 g, 110%) was isolated.

Step 3: Dimethyl 2-(3-(trifluoromethyl)benzyl)piperidine-1,4-dicarboxylate

Methyl 2-(3(trifluoromethyl)benzyl)piperidine-4-carboxylate (6.0 g, 19.91 mmol) was dissolved in DIPEA (6.94 mL, 39.83 mmol) and dichloromethane (150 mL). Methyl carbonochloridate (2.258 g, 23.90 mmol) was added dropwise. Ether was added and the reaction mixture was washed with 1 M HCl and Na_2CO_3 (aq). The organic layer was dried over $MgSO_4$, filtered through celite and the solvent was evaporated to yield dimethyl 2-(3-(trifluoromethyl)benzyl)piperidine-1,4-dicarboxylate (6.1 g, 85 %).

Step 4: 1-(Methoxycarbonyl)-2-(3-(trifluoromethyl)benzyl)piperidine-4-carboxylic acid

Dimethyl 2-(3-(trifluoromethyl)benzyl)piperidine-1,4-dicarboxylate (6.1 g, 16.98 mmol) and LiBr (11.79 g, 135.8 mmol) were dissolved in acetonitrile (60 mL) and water (1.2 mL). Triethylamine (9.41 mL, 67.90 mmol) was added and the resulting suspension was heated at reflux for 1h, then cooled to room temperature and stirred overnight. Dissolved between ethyl acetate and 3 M HCl. The water layer was extracted once with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered through celite and the solvent was evaporated to yield 1-(methoxycarbonyl)-2-(3-(trifluoromethyl)benzyl)piperidine-4-carboxylic acid (5.8 g, 99%).

Reference compound 49

1-(Methoxycarbonyl)-2-(2-(trifluoromethyl)benzyl)piperidine-4-carboxylic acid

Step 1: (2-(Trifluoromethyl)benzyl)zinc(II) bromide

In a dried flask zinc powder (2.489 g, 38.07 mmol) was suspended in anhydrous tetrahydrofuran (50 mL) under nitrogen. The resulting suspension was warmed to 60°C, then 1,2-dibromoethane (0.126 mL, 1.46 mmol) was added and stirred at that temperature for 15 min. It was cooled to room temperature, then chlorotrimethylsilane (0.149 mL, 1.17 mmol) was added and stirred for 20 min. 1-(Bromomethyl)-2-(trifluoromethyl)benzene (4.46 mL, 29.28 mmol) in THF (2 mL) was added dropwise and stirring was continued at room temperature for 4 h. Stirring was switched off to let the precipitates settle. The supernatant was used in the next transformation.

Step 2: Methyl 2-(2-(trifluoromethyl)benzyl)isonicotinate

Freshly made (2-(trifluoromethyl)benzyl)zinc(II) bromide (8.91 g, 29.28 mmol) in tetrahydrofuran (50 mL) was added to a solution of methyl 2-chloroisonicotinate (3.35 g, 19.52 mmol) and bis(tri-tert-butylphosphine)Pd(0) (0.399 g, 0.78 mmol) in tetrahydrofuran (50 mL) under nitrogen in a dried flask. The resulting red mixture was heated to 60°C overnight (16 h). After cooling to room temperature, the reaction was quenched by the addition of 10 % aq NH_4Cl and diluted with ethyl acetate. After phase separation, the organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The residue was dissolved in

100 mL MTBE. Insolubles were filtered off and the filtrate was evaporated. Purification via Biotage, SNAP 340g KP-SIL, eluent isocratic heptane/ethyl acetate 8:2 for 1 CV, then linear gradient heptane/ethyl acetate 8:2 to 5:5 over 6 CV to yield methyl 2-(2-(trifluoromethyl)benzyl)isonicotinate (4.61 g, 80 %) as a yellow oil. ^{1}H NMR (400 MHz, cdcl$_3$) δ 3.91 (s, 3H), 4.43 (s, 2H), 7.28 – 7.40 (m, 2H), 7.47 (t, 1H), 7.54 – 7.65 (m, 1H), 7.65 – 7.72 (m, 2H), 8.71 (d, 1H). MS m/z 296 (M+H)+

Step 3: Methyl 2-(2-(trifluoromethyl)benzyl)piperidine-4-carboxylate

Methyl 2-(2-(trifluoromethyl)benzyl)isonicotinate (4.613 g, 15.62 mmol) was dissolved in acetic acid (40 mL) and platinum(IV) oxide (0.26 g, 1.14 mmol) added. The resulting mixture was hydrogenated in a Büchi hydrogenator for 3 h at room temperature and 5 bar. More platinum(IV) oxide (160 mg) was added and the hydrogenation continued at room temperature at 5 bar for 2 h. The catalyst was filtered off and washed with MeOH and the eluate evaporated. DCM and 10 % K_2CO_3 were added and the phases separated. The water phase was extracted with DCM and the combined organic phase washed with water, passed through a phase separator and evaporated to yield methyl 2-(2-(trifluoromethyl)benzyl)-piperidine-4-carboxylate (4.20 g, 89%) as a yellow oil. MS m/z 302 (M+H)+

Step 4: Dimethyl 2-(2-(trifluoromethyl)benzyl)piperidine-1,4-dicarboxylate

Methyl chloroformate (1.399 mL, 18.07 mmol) in DCM (40 mL) was added to a solution of methyl 2-(2-(trifluoromethyl)benzyl)piperidine-4-carboxylate (4.19 g, 13.9 mmol) and DIPEA (7.28 mL, 41.69 mmol) in DCM (60 mL). The reaction mixture was stirred for 1.5 h at room temperature, then washed with satd $NaHCO_3$. The phases were separated and the organic phase dried using a phase separator to give crude dimethyl 2-(2-(trifluoromethyl)-benzyl)piperidine-1,4-dicarboxylate (5.42 g, 109%). MS m/z 360 (M+H)+

Step 5: 1-(Methoxycarbonyl)-2-(2-(trifluoromethyl)benzyl)piperidine-4-carboxylic acid

Crude dimethyl 2-(2-(trifluoromethyl)benzyl)piperidine-1,4-dicarboxylate (5.42 g, 15.15 mmol) was dissolved in acetonitrile (40 mL) and water (0.800 mL). lithium bromide (9.66 g, 111.20 mmol) and triethylamine (7.71 mL, 55.60 mmol) were added and the mixture was heated at reflux for 1 h 45min. Water (90 mL) and MTBE were added. The organic phase was extracted with water. To the pooled aqueous layer was added MTBE and the solution was acidified to pH 1 with 2 M HCl and then extracted with MTBE (x2). The combined organic

layer was dried over Na_2SO_4 and evaporated to give 1-(methoxycarbonyl)-2-(2-(trifluoromethyl)benzyl)piperidine-4-carboxylic acid (4.72 g, 98%) as a slightly yellow semisolid. MS m/z 346 $(M+H)^+$

Reference compound 50

1-(Methoxycarbonyl)-2-(4-(trifluoromethoxy)benzyl)piperidine-4-carboxylic acid

Step 1: (4-(Trifluoromethoxy)benzyl)zinc(II) bromide

In a dried flask was zinc powder (0.769 g, 11.76 mmol) suspended in anhydrous tetrahydrofuran (20 mL) under nitrogen. The resulting suspension was warmed to 60°C, then 1,2-dibromoethane (0.042 mL, 0.49 mmol) was added and stirred at that temperature for 15 min. It was cooled to room temperature, then chlorotrimethylsilane (0.050 mL, 0.39 mmol) was added and stirred at room temperature for 1 h. Then, 1-(bromomethyl)-4-(trifluoromethoxy)benzene (2.5 g, 9.80 mmol) in tetrahydrofuran (5 mL) was added over 2 min, then stirring continued at room temperature for 22 h. The stirring was switched off to let the solids settle. The supernatant was used in next transformation

Step 2: Methyl 2-(4-(trifluoromethoxy)benzyl)isonicotinate

To a solution of methyl 2-chloroisonicotinate (4.80 g, 28 mmol) and $Pd(PPh_3)_4$ (0.647 g, 0.56 mmol) in tetrahydrofuran (50 mL) under nitrogen in a dried flask was added a freshly prepared solution of (4-(trifluoromethoxy)benzyl)zinc(II) bromide (12.56 g, 39.20 mmol) in tetrahydrofuran (90 mL). The resulting bright yellow mixture was heated to 60°C for 2 h 30 min, then cooled to room temperature. The reaction was quenched by the addition of 10 % aqueous NH_4Cl. It was diluted with ethyl acetate. After phase separation, the organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The residue was suspended in 50 mL MTBE and sonicated, then the yellow insolubles were filtered off and washed with MTBE. The volume of the filtrate was increased to ca. 150 mL, then 5 mL MeOH was added, followed by hydrogen chloride (4 M in dioxane) (7.00 mL, 28.00 mmol). A colorless precipitate formed, which then dissolved again. The solvents were evaporated. The residue was dissolved in ca. 15 mL DCM and then MTBE and heptanes were added. An oil had formed that was triturated and after a few minutes a solid started to form. It was sonicated and

then stirred at room temperature for 20 min. The formed solid was collected and washed with MTBE and dried. The solid was dissolved in DCM and washed with 10% K_2CO_3. After phase separation, the aqueous layer was extracted with DCM. The combined organic layers were dried over $MgSO_4$ and evaporated. Methyl 2-(4-(trifluoromethoxy)benzyl)isonicotinate (8.04 g, 92 %) was isolated as a pale yellow oil. ^1H NMR (400 MHz, cdcl$_3$) δ 3.93 (s, 3H), 4.22 (s, 2H), 7.11 – 7.17 (m, 2H), 7.24 – 7.31 (m, 2H), 7.67 – 7.72 (m, 2H), 8.68 – 8.72 (m, 1H). MS m/z 312 $(M+H)^+$

Step 3: Methyl 2-(4-(trifluoromethoxy)benzyl)piperidine-4-carboxylate

To a solution of methyl 2-(4-(trifluoromethoxy)benzyl)isonicotinate (8.04 g, 25.83 mmol) in acetic acid (40 mL) was added platinum(IV) oxide (0.343 g, 1.51 mmol) and the resulting mixture hydrogenated at 5 bar in a Büchi hydrogenator for 5h. The reaction mixture was filtered through a diatomeous earth filter carton and the catalyst washed with methanol. The solvents were evaporated, the residue dissolved in DCM and washed with 10% Na_2CO_3. After phase separation the aqueous layer was extracted with DCM. The combined organic layers were dried over $MgSO_4$ and evaporated. Methyl 2-(4-(trifluoromethoxy)benzyl)piperidine-4-carboxylate (8.19 g, 100%) was isolated as a dark brown oil. MS m/z 318 $(M+H)^+$

Step 4: Dimethyl 2-(4-(trifluoromethoxy)benzyl)piperidine-1,4-dicarboxylate

To a solution of methyl 2-(4-(trifluoromethoxy)benzyl)piperidine-4-carboxylate (8.19 g, 25.81 mmol) in DCM (100 mL) was added DIPEA (5.40 mL, 30.97 mmol) followed by methyl carbonochloridate (2.236 mL, 28.39 mmol). The reaction mixture was stirred at room temperature for 30 min. The solvents were evaporated and the residue partitioned between ethyl acetate and 3.8 M HCl. After phase separation the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and evaporated to give a yellow oil. Dimethyl 2-(4-(trifluoromethoxy)benzyl)piperidine-1,4-dicarboxylate (9.72 g, 100 %) was isolated. MS m/z 376 $(M+H)^+$

Step 5: 1-(Methoxycarbonyl)-2-(4-(trifluoromethoxy)benzyl)piperidine-4-carboxylic acid

To a solution of dimethyl 2-(4-(trifluoromethoxy)benzyl)piperidine-1,4-dicarboxylate (9.72 g, 25.90 mmol) in MeCN (80 mL) and water (1.6 mL) was added lithium bromide (18.2 g, 209.57 mmol) and triethylamine (15 mL, 108.21 mmol). The resulting mixture was heated under reflux for 3 h, then cooled to room temperature. Water and MTBE were added. The

organic phase was extracted with water twice. The pooled aqueous layers were adjusted to pH 1 with 3.8 M HCl and then extracted with DCM (3 x). The mixture was filtered through a diatomeous earth filter carton. The combined organic layers were dried over $MgSO_4$ and evaporated. 1-(Methoxycarbonyl)-2-(4-(trifluoromethoxy)benzyl)piperidine-4-carboxylic acid (8.75 g, 94 %) was isolated as a pale yellow solid. MS m/z 360 $(M-H)^-$

Reference compound 51

2-(4-Chlorobenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: tert-Butyl 2-(4-chlorobenzyl)-4-cyanopiperidine-1-carboxylate

To a solution of tert-butyl 2-(4-chlorobenzyl)-4-oxopiperidine-1-carboxylate (8.737 g, 26.98 mmol) in DME (200 mL) under nitrogen was added simultaneously 1-(isocyanomethyl-sulfonyl)-4-methylbenzene (7.90 g, 40.47 mmol) in 200 mL DME and potassium tert-butoxide (81 mL, 80.94 mmol) over 1 hour so that the temperature never rose above 0°C. The solution was stirred at -20°C for 2 h and then let to warm to room temperature overnight. Water (200 mL) was added to the orange reaction mixture and the solution was stirred for 20 min and then extracted with 3x diethyl ether and 3x EtOAc. The organic phases were combined and dried over Na_2SO_4 and evaporated to give a brown residue. Further purification was done on Biotage (340 g column, 3 runs, heptane/EtOAc, gradient 20-60% EtOAc) to give tert-butyl 2-(4-chlorobenzyl)-4-cyanopiperidine-1-carboxylate (5.54 g, 61 %). ^1H NMR (400 MHz, cdcl$_3$) δ, 1.21 – 1.50 (m, 9H), 1.58 – 2.14 (m, 4H), 2.55 – 3.27 (m, 4H), 4.06 – 4.25 (m, 1H), 4.34-4.60 (m, 1H), 7.02 – 7.34 (m, 4H). MS m/z 235, 237 (M-C5H8O2+H)+

Step 2: 2-(4-Chlorobenzyl)piperidine-4-carboxylic acid hydrochloride

Conc. HCl (20 mL, 651.11 mmol) was added to tert-butyl 2-(4-chlorobenzyl)-4-cyanopiperidine-1-carboxylate (5.54 g, 16.55 mmol) and the mixture stirred for 20 minutes. The mixture was transferred to a 20 mL microwave vial. The vial was capped and heated at 140°C for 30 min in a single node microwave reactor. Concentration of the reaction solution yielded crude 2-(4-chlorobenzyl)piperidine-4-carboxylic acid hydrochloride (5.34 g, 111 %). MS m/z 254, 256 (M+H)+

Step 3: Methyl 2-(4-chlorobenzyl)piperidine-4-carboxylate

To crude 2-(4-chlorobenzyl)piperidine-4-carboxylic acid hydrochloride (5.34 g, 20.9 mmol) was added HCl (1.25 M in MeOH, 60 mL). The resulting suspension was refluxed for 2 h and then concentrated to give a slightly yellow solid. The residue was taken up in satd $NaHCO_3$ (100 mL). The aqueous phase was extracted with DCM (x3), the combined organic layers dried with a phase separator and evaporated to yield methyl 2-(4-chlorobenzyl)piperidine-4-carboxylate (3.85 g, 87 %) as a brown oil. MS m/z 268, 270 (M+H)+

Step 4: Dimethyl 2-(4-chlorobenzyl)piperidine-1,4-dicarboxylate

To a solution of methyl 2-(4-chlorobenzyl)piperidine-4-carboxylate (3.72 g, 13.2 mmol) and DIPEA (4.85 mL, 27.78 mmol) in DCM (100 mL) was added methyl chloroformate (1.431 mL, 18.48 mmol) in DCM (50 mL) over 30 minutes. The reaction solution was stirred overnight (16h). The organic phase was washed with satd $NaHCO_3$, dried using a phase separator and evaporated to yield dimethyl 2-(4-chlorobenzyl)piperidine-1,4-dicarboxylate (4.74 g, 110 %) as a yellow oil. MS m/z 326, 328 (M+H)+

Step 5: 2-(4-Chlorobenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Dimethyl 2-(4-chlorobenzyl)piperidine-1,4-dicarboxylate (4.74 g, 14.55 mmol) was dissolved in tetrahydrofuran (15 mL) followed by addition of LiOH (0.430 g, 17.97 mmol), MeOH (10 mL) and water (10 mL). The reaction mixture was stirred at room temperature overnight. The solvents were evaporated and the residue was taken up in water. The pH was adjusted to < 2 by addition of 2 M HCl. The product was poorly soluble and attempts to extract the aqueous phase with DCM and ethyl acetate failed. Instead the mixture was concentrated and then filtered, washed with water and dried to give a yellow solid material. The water phase did contain some product and was extracted with DCM (x3) and dried with a phase separator to give about 500 mg. Crude 2-(4-chlorobenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (4.27 g, quant.) was isolated. MS m/z 312, 314 (M+H)+

Reference compound 52

1-(Methoxycarbonyl)-2-(4-(methylsulfonyl)benzyl)piperidine-4-carboxylic acid

Step 1: (4-(Methylsulfonyl)benzyl)zinc(II) bromide

Zink powder (2.81 g, 42.97 mmol) was suspended in THF (50 mL) under nitrogen and heated to 60°C. 1,2-dibromoethane (0.336 g, 1.79 mmol) was added and stirred for 15 min at 60°C. It was cooled to ambient temperature, TMSCl (0.156 g, 1.43 mmol) was added and stirred for 15 min at ambient temperature. 1-(Bromomethyl)-4-(methylsulfonyl)benzene (8.92 g, 35.81 mmol) dissolved in THF (50mL) was added over 15 min and the resulting mixture was stirred at ambient temperature overnight. Stirring was stopped and the supernatant used in the next reaction.

Step 2: Methyl 2-(4-(methylsulfonyl)benzyl)isonicotinate

Methyl 2-chloroisonicotinate (5.12 g, 29.84 mmol) and $Pd(PPh_3)_4$ (1.379 g, 1.19 mmol) were dissolved in THF (50 mL) under nitrogen. Freshly prepared 4-(methylsulfonyl)benzyl)zinc(II) bromide (11.26 g, 35.81 mmol) in THF (100 mL) was added and the reaction mixture heated to 60°C for 3 h. Water (20 mL) was added. It was diluted with $NaHCO_3$ (aq) and extracted with diethylether. The organic layer was washed with NaCl (aq), dried over Na_2SO_4, filtered and evaporated. Purified using the Biotage equipment. Ethyl acetate and hexane used as eluent. Gradient 0% to 100% of ethyl acetate. Methyl 2-(4-(methylsulfonyl)benzyl)-isonicotinate (8.0 g, 88 %) was isolated. ^1H NMR (600 MHz, cdcl$_3$) δ 3.00 (s, 3H), 3.92 (s, 3H), 4.28 (s, 2H), 7.45 (d, 2H), 7.68 – 7.72 (m, 2H), 7.85 (d, 2H), 8.69 (d, 1H). MS m/z 306 $(M+H)^+$

Step 3: Methyl 2-(4-(methylsulfonyl)benzyl)piperidine-4-carboxylate

Methyl 2-(4-(methylsulfonyl)benzyl)isonicotinate (8.0 g, 26.2 mmol) was dissolved in acetic acid (250 mL). Activated carbon was added and stirred for 30 min. The activated carbon was filtered off. To the solution was added PtO_2 (0.119 g, 0.52 mmol) and the reaction mixture hydrogenated in a Büchi hydrogenator overnight at room temperature and 9 bar. The catalyst was filtered off. The solvent was evaporated. The crude was partitioned between Na_2CO_3 (aq) and ethyl acetate. The organic layer was dried over Na_2SO_4, filtered through celite and evaporated to yield methyl 2-(4-(methylsulfonyl)benzyl)piperidine-4-carboxylate (5.38 g, 65.9%).

Step 4: Dimethyl 2-(4-(methylsulfonyl)benzyl)piperidine-1,4-dicarboxylate

Methyl 2-(4-(methylsulfonyl)benzyl)piperidine-4-carboxylate (5.88 g, 18.88 mmol) was dissolved in DIPEA (4.93 mL, 28.32 mmol) and dichloromethane (150 mL). Methyl

carbonochloridate (2.141 g, 22.66 mmol) was added dropwise and the reaction mixture stirred at room temperature overnight. The solvent was evaporated and the residue partitioned between 1 M $KHSO_4$ and diethyl ether. The organic layer was dried over Na_2SO_4, filtered through celite and evaporated to yield dimethyl 2-(4-(methylsulfonyl)benzyl)piperidine-1,4-dicarboxylate (5.5 g, 79 %).

Step 5: 1-(Methoxycarbonyl)-2-(4-(methylsulfonyl)benzyl)piperidine-4-carboxylic acid

Dimethyl 2-(4-(methylsulfonyl)benzyl)piperidine-1,4-dicarboxylate (5.5 g, 14.89 mmol) was dissolved in acetonitrile (50 mL) and water (1 mL), then lithium bromide (10.34 g, 119.10 mmol) and triethylamine (8.25 mL, 59.55 mmol) were added and the resulting suspension was heated at reflux for 2 h. Water and MTBE were added. The organic phase was extracted with water (x2). To the pooled aqueous layer was added ethyl acetate and the solution was acidified to pH 1 with HCl and then extracted with ethyl acetate twice. The organic layer was dried (Na_2SO_4), filtered through celite and evaporated to yield 1-(methoxycarbonyl)-2-(4-(methylsulfonyl)benzyl)piperidine-4-carboxylic acid (4.2 g, 79 %). MS m/z 354 $(M-H)^-$

Reference compound 53

2-(3,4-Difluorobenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: Methyl 2-(3,4-difluorobenzyl)isonicotinate

Methyl 2-chloroisonicotinate (5.6 g, 32.64 mmol) and $Pd(PPh_3)_4$ (0.754 g, 0.65 mmol) were dissolved in THF (100 mL) under nitrogen. (3,4-Difluorobenzyl)zinc(II) bromide (0.5 M in THF) (100 mL, 50.00 mmol) was added and the brown solution was stirred at 60°C overnight. The reaction was quenched by addition of methanol (50 mL). The solution was diluted with EtOAc and washed with NH_4Cl (aq). The organic layer was dried over $MgSO_4$, filtered and evaporated to yield a yellow oil. The compound was purified via Biotage, SNAP 340g KP-SIL, eluent isocratic heptane/ethyl acetate 8:2 for 2 CV, then linear gradient heptane/ethyl acetate 8:2 to 5:5 over 6 CV to yield methyl 2-(3,4-difluorobenzyl)isonicotinate (7.7 g, 90%) as a yellow oil. ^1H NMR (400 MHz, $cdcl_3$) δ 3.93 (s, 3H), 4.16 (s, 2H), 6.94 – 7.01 (m, 1H), 7.02 – 7.12 (m, 2H), 7.66 – 7.71 (m, 2H), 8.70 (dd, 1H). MS m/z 264 $(M+H)^+$

Step 2: Methyl 2-(3,4-difluorobenzyl)piperidine-4-carboxylate

Methyl 2-(3,4-difluorobenzyl)isonicotinate (7.7 g, 29.25 mmol) was dissolved in acetic acid (75 mL) and platinum(IV) oxide (0.332 g, 1.46 mmol) added. The resulting mixture was hydrogenated in a Büchi hydrogenator at room temperature and 5 bar for 4 h 45 min. More platinum(IV) oxide (0.166 g, 0.73 mmol) was added and the hydrogenation continued at 5 bar for 2 h. More platinum(IV) oxide (0.166 g, 0.73 mmol) was added and the hydrogenation continued at 5 bar for 1 h 20 min. The catalyst was filtered off and washed with MeOH and the eluate evaporated. DCM and 10 % K_2CO_3 were added and the phases separated. The organic layer was washed with brine, passed through a phase separator and evaporated to yield crude methyl 2-(3,4-difluorobenzyl)piperidine-4-carboxylate (8.133 g, 103 %) as a brown oil. MS m/z 270 $(M+H)^+$

Step 3: Dimethyl 2-(3,4-difluorobenzyl)piperidine-1,4-dicarboxylate

Methyl 2-(3,4-difluorobenzyl)piperidine-4-carboxylate (8.115 g, 30.14 mmol) was dissolved in DCM (200 mL) and DIPEA (6.30 mL, 36.16 mmol), then methyl carbonochloridate (3.3 mL, 41.91 mmol) was added. The solution was stirred at room temperature for 2 h. The reaction mixture was washed with 0.1 M HCl satd $NaHCO_3$. The organic phase was passed through a phase separator and evaporated. The residue was redissolved in ether/pentane, 80/20, the solution washed with 1 M HCl 5 times, then with satd $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and evaporated to yield dimethyl 2-(3,4-difluorobenzyl)piperidine-1,4-dicarboxylate (7.05 g, 71 %). MS m/z 328 $(M+H)^+$

Step 4: 2-(3,4-Difluorobenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Dimethyl 2-(3,4-difluorobenzyl)piperidine-1,4-dicarboxylate (7.010 g, 21.42 mmol) was dissolved in acetonitrile (75 mL) and water (1.5 mL). Lithium bromide (14.88 g, 171.33 mmol) and triethylamine (11.87 mL, 85.66 mmol) were added and the resulting yellow suspension was heated at reflux for 3 h. Water (100 mL) and MTBE (300 mL) were added. The organic phase was extracted with water (x2). The pooled aqueous layer was acidified to pH 1 with 3.8 M HCl and then extracted with MTBE (x2). The combined organic layer was washed with water, dried over Na_2SO_4, filtered and evaporated to yield 2-(3,4-difluorobenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (6.62 g, 99 %) as a yellow solid. MS m/z 314 $(M+H)^+$

Reference compound 54

2-(2,5-Difluorobenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: Methyl 2-(2,5-difluorobenzyl)isonicotinate

To a solution of methyl 2-chloroisonicotinate (5.6 g, 32.64 mmol) and $Pd(PPh_3)_4$ (0.754 g, 0.65 mmol) in anhydrous THF (100 mL) was added (2,5-difluorobenzyl)zinc(II) bromide (0.5 M in THF) (100 mL, 50.00 mmol) dropwise under nitrogen. The reaction mixture was heated at 60°C for 15 h. The reaction mixture was quenched by addition of methanol (50 mL) and then filtered. The solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate and washed with satd NH_4Cl solution and brine, then dried. The solvent was evaporated under reduced pressure. The residue was suspended in ethanol, filtered and the solid washed with ethanol. The filtrate was concentrated. The residue was dissolved in MTBE (150 mL), then HCl (4 M in dioxane, (8.15 mL) and MeOH (7.5 mL) were added.The resulting suspension was stirred for 20 min, the solid collected, washed with MTBE (x2) and air dried. The solid was dissolved in DCM (200 mL) and washed with satd $NaHCO_3$. The organic phase was dried using a phase separator and evaporated to yield methyl 2-(2,5-difluorobenzyl)isonicotinate (6.8 g, 79 %). MS m/z 264 $(M+H)^+$

Step 2: Methyl 2-(2,5-difluorobenzyl)piperidine-4-carboxylate

A mixture of methyl 2-(2,5-difluorobenzyl)isonicotinate (6.8 g, 25.83 mmol) and platinum(IV) oxide (0.293 g, 1.29 mmol) in acetic acid (68 mL) was hydrogenated in a Büchi hydrogenator at room temperature and 5 bar for 5 h. More PtO_2 (190 mg) was added and the hydrogenation continued at room temperature and 5 bar for additional 80 min. The reaction mixture was filtered through Celite and the catalyst was washed with methanol. The filtrate was concentrated, the residue was dissolved in DCM, washed with satd $NaHCO_3$ and the organic layer was dried using a phase separator. The solvent was evaporated under reduced pressure. The residue was dissolved in iso-hexane/ether and filtered. The solvents were evaporated in vacuo to yield methyl 2-(2,5-difluorobenzyl)piperidine-4-carboxylate (6.65 g, 96%). MS m/z 270 $(M+H)^+$

Step 3: Dimethyl 2-(2,5-difluorobenzyl)piperidine-1,4-dicarboxylate

To a solution of methyl 2-(2,5-difluorobenzyl)piperidine-4-carboxylate (6.65 g, 24.69 mmol) in DCM (100 mL) and DIPEA (5.16 mL, 29.63 mmol) was added methyl carbonochloridate

(2.53 mL, 32.10 mmol) dropwise at room temperature under nitrogen. The reaction mixture was stirred at room temperature for 1 h. The reaction was quenched with 0.15 M HCl (250 mL). The organic phase was separated, washed with satd $NaHCO_3$, dried using a phase separator and evaporated to yield dimethyl 2-(2,5-difluorobenzyl)piperidine-1,4-dicarboxylate (8.1 g, 100%). MS m/z 328 $(M+H)^+$

Step 4: 2-(2,5-Difluorobenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

To a solution of dimethyl 2-(2,5-difluorobenzyl)piperidine-1,4-dicarboxylate (8.08 g, 24.69 mmol) in acetonitrile (85 mL) and water (1.7 mL) was added lithium bromide (4.95 mL, 197.48 mmol) and triethylamine (13.69 mL, 98.74 mmol). The reaction mixture was heated to reflux for 2.5 h, then allowed to cool to room temperature. Water (150 mL) and MTBE (300 mL) was added. The aqueous phase was separated and the organic phase was extracted twice with water. The water phases were combined and 4.0 M HCl was added until a pH of 1 was obtained. The aqueous was extracted with MTBE (300 mL x2). The organic phases were combined, washed with brine, dried with Na_2SO_4 and evaporated under reduced pressure to give 2-(2,5-difluorobenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (7.4 g, 96%). MS m/z 314 $(M+H)^+$

Reference compound 55

2-(2,6-Difluorobenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: Methyl 2-(2,6-difluorobenzyl)isonicotinate

Methyl 2-chloroisonicotinate (5.600 g, 32.64 mmol) and $Pd(PPh_3)_4$ (0.754 g, 0.65 mmol) were dissolved in THF (100 mL) under nitrogen and (2,6-difluorobenzyl)zinc(II) bromide (0.5 M in THF, 100 mL, 50.00 mmol) was added and the resulting solution was stirred at 60°C for 4 h before it was cooled to room temperature and quenched with methanol (50.0 mL). The mixture was diluted with EtOAc and washed with satd NH_4Cl. The organic phase was dried with $MgSO_4$, filtered and evaporated. The crude product was dissolved in MTBE (200 mL), solids were filtered off, and HCl (4 M in dioxane, 8.16 mL, 32.64 mmol) was added dropwise. The mixture was stirred for 10 minutes before the precipitate was filtered off, washed with MTBE and dissolved in MTBE / satd $NaHCO_3$. The organic layer was dried with $MgSO_4$, filtered and evaporated to give methyl 2-(2,6-difluorobenzyl)isonicotinate (5.03 g, 58.6 %) as

a white solid. ^{1}H NMR (400 MHz, cdcl$_3$) δ 3.92 (s, 3H), 4.29 (s, 2H), 6.87 – 6.97 (m, 2H), 7.18 – 7.29 (m, 1H), 7.61 – 7.73 (m, 2H), 8.63 – 8.70 (m, 1H). MS m/z 264 $(M+H)^+$

Step 2: Methyl 2-(2,6-difluorobenzyl)piperidine-4-carboxylate

Methyl 2-(2,6-difluorobenzyl)isonicotinate (5.031 g, 19.11 mmol) was dissolved in acetic acid (49 mL) and platinum(IV) oxide (0.217 g, 0.96 mmol) was added. The mixture was hydrogenated in a Büchi hydrogenator at room temperature and 5 bar for 5 h. More platinum(IV) oxide (0.108 g, 0.48 mmol) was added and hydrogenation was continued for 1 h. Additional platinum(IV) oxide (0.108 g, 0.48 mmol) was added and the mixture was again hydrogenated for 1.5 h. More platinum(IV) oxide (0.108 g, 0.48 mmol) was added. After a total of 8.5 h the reaction mixture was filtered through celite and the catalyst was washed with MeOH. The eluate was concentrated and DCM and 1 M K_2CO_3were added. The phases were separated and the organic phase was washed with brine before it was dried and concentrated to yield methyl 2-(2,6-difluorobenzyl)piperidine-4-carboxylate (5.01 g, 97 %). MS m/z 270 $(M+H)^+$

Step 3: Dimethyl 2-(2,6-difluorobenzyl)piperidine-1,4-dicarboxylate

Methyl 2-(2,6-difluorobenzyl)piperidine-4-carboxylate (5.008 g, 18.60 mmol) was dissolved in DCM (121 mL) and DIPEA (3.89 mL, 22.32 mmol) followed by methyl carbonochloridate (2.050 mL, 26.04 mmol) were added. After 3.5 h at room temperature the solution was washed with 0.1 M HCl and satd $NaHCO_3$. The organic phase was dried and concentrated to yield dimethyl 2-(2,6-difluorobenzyl)piperidine-1,4-dicarboxylate (5.98 g, 98 %). MS m/z 328 $(M+H)^+$

Step 4: 2-(2,6-Difluorobenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Dimethyl 2-(2,6-difluorobenzyl)piperidine-1,4-dicarboxylate (5.98 g, 18.27 mmol) was dissolved in acetonitrile (50 mL) and water (1 mL), then lithium bromide (12.69 g, 146.16 mmol) and triethylamine (10.13 mL, 73.08 mmol) were added. The suspension was heated to reflux for 3.5 h, then water (60 mL) and MTBE (180 mL) were added. The organic phase was extracted with water (x2). The combined water phases were acidified to pH 1 with 3.8 M HCl and extracted with MTBE (x2). The combined organic phases were washed with water, dried with $MgSO_4$, filtered through celite and concentrated to give 2-(2,6-difluorobenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (4.72 g, 82 %) as a light yellow solid. MS m/z

314 $(M+H)^+$

Reference compound 56

2-(3,5-Difluorobenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: Methyl 2-(3,5-difluorobenzyl)isonicotinate

Methyl 2-chloroisonicotinate (5.600 g, 32.64 mmol) and $Pd(PPh_3)_4$ (0.754 g, 0.65 mmol) were dissolved in THF (100 mL) under nitrogen, then (3,5-difluorobenzyl)zinc(II) chloride (0.5 M in THF, 100 mL, 50.00 mmol) was added and the resulting solution was stirred at 60°C for 3 h before it was cooled to room temperature and quenched with methanol (50.0 mL). The mixture was diluted with EtOAc and washed with satd NH_4Cl. The organic phase was dried and concentrated. The residue was purified by automated flash chromatography on a Biotage® KP-SIL 340g column, eluent isocratic heptane/EtOAc 8:2 for 2 CV, then a gradient from 20 % to 50 % of EtOAc in heptane over 6 CV was used as mobile phase. Methyl 2-(3,5-difluorobenzyl)isonicotinate (7.42 g, 86 %) was isolated as an oil. ^1H NMR (400 MHz, $cdcl_3$) δ 3.94 (s, 3H), 4.18 (s, 2H), 6.66 (tt, 1H), 6.74 – 6.82 (m, 2H), 7.67 – 7.75 (m, 2H), 8.67 – 8.75 (m, 1H). MS m/z 264 $(M+H)^+$

Step 2: Methyl 2-(3,5-difluorobenzyl)piperidine-4-carboxylate

Methyl 2-(3,5-difluorobenzyl)isonicotinate (7.417 g, 28.18 mmol) was dissolved in acetic acid (72 mL) and platinum(IV) oxide (0.320 g, 1.41 mmol) was added. The mixture was hydrogenated in a Büchi hydrogenator at room temperature and 5 bar for 5 h. The reaction mixture was filtered through celite and the catalyst was washed with MeOH. The eluate was concentrated and DCM and 1 M K_2CO_3 were added. The phases were separated and the organic phase was washed with brine before it was dried and concentrated to yield methyl 2-(3,5-difluorobenzyl)piperidine-4-carboxylate (7.08 g, 93 %). MS m/z 270 $(M+H)^+$

Step 3: Dimethyl 2-(3,5-difluorobenzyl)piperidine-1,4-dicarboxylate

Methyl 2-(3,5-difluorobenzyl)piperidine-4-carboxylate (7.082 g, 26.30 mmol) was dissolved in DCM (170 mL) and DIPEA (5.50 mL, 31.56 mmol), then methyl carbonochloridate (2.88 mL, 36.58 mmol) was added. The reaction mixture was stirred at room temperature for 3 h, then additional methyl carbonochloridate (0.7 mL, 8.89 mmol) was added. The solution was

stirred for 30 min then washed with 0.1 M HCl and satd $NaHCO_3$. The organic phase was dried and concentrated to give dimethyl 2-(3,5-difluorobenzyl)piperidine-1,4-dicarboxylate (8.55 g, 99 %). MS m/z 328 $(M+H)^+$

Step 4: 2-(3,5-Difluorobenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Dimethyl 2-(3,5-difluorobenzyl)piperidine-1,4-dicarboxylate (8.459 g, 25.84 mmol) was dissolved in acetonitrile (85 mL) and water (1.7 mL). Lithium bromide (17.95 g, 206.74 mmol) and triethylamine (14.33 mL, 103.37 mmol) were added. The suspension was heated to reflux 1.5 h before water (100 mL) and MTBE (300 mL) were added. The organic phase was extracted with water (x2). The combined water phases were acidified to pH 1 with 3.8 M HCl and extracted with MTBE (x2). The combined organic phases were washed with water, dried with $MgSO_4$, filtered through celite and concentrated. The crude product was redissolved in MTBE and washed with 0.1 M HCl (x2) and water. The organic phase was dried with $MgSO_4$ and concentrated to give 2-(3,5-difluorobenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (6.88 g, 85 %). MS m/z 314 $(M+H)^+$

Reference compound 57

2-(2,4-Difluorobenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: Methyl 2-(2,4-difluorobenzyl)isonicotinate

Methyl 2-chloroisonicotinate (5.2 g, 30.31 mmol) and $Pd(PPh_3)_4$ (0.700 g, 0.61 mmol) were dissolved in THF (100 mL) under nitrogen and (2,4-difluorobenzyl)zinc(II) chloride (0.5 M in THF, 90 mL, 45.00 mmol) was added and the brown solution was stirred at 60°C overnight (18 h). The reaction was quenced by addition of methanol (50.0 mL). The solution was diluted with EtOAc and washed with NH_4Cl (aq) and brine and dried over Na_2SO_4 to give a red oil. The crude was redissolved in MTBE (200 mL) and solids were filtered off. Hydrogen chloride (4 M in dioxane, 7.58 mL, 30.31 mmol) was added dropwise during stirring and a suspension was formed. The suspension was stirred at room temperature for 15 min. The solid was collected by filtration and washed with MTBE. The solid was dissolved in MTBE / satd $NaHCO_3$. The phases were separated, the organic phase dried over Na_2SO_4, filtered and evaporated to yield methyl 2-(2,4-difluorobenzyl)isonicotinate (7.011 g, 88 %) as a red oil. ^1H NMR (400 MHz, $cdcl_3$) δ 3.93 (s, 3H), 4.20 (s, 2H), 6.77 – 6.88 (m, 2H), 7.18 – 7.25 (m, 1H),

7.62 – 7.73 (m, 2H), 8.69 (dd, 1H). MS m/z 264 $(M+H)^+$

Step 2: Methyl 2-(2,4-difluorobenzyl)piperidine-4-carboxylate

Methyl 2-(2,4-difluorobenzyl)isonicotinate (7.011 g, 26.63 mmol) was dissolved in acetic acid (50 mL) and platinum(IV) oxide (0.302 g, 1.33 mmol) added. The resulting mixture was hydrogenated in a Büchi hydrogenator for 4.5 h at room temperature and 5 bar. platinum(IV) oxide (174 mg) was added and the hydrogenation continued at room temperature at 5 bar for 2 h. Additional platinum(IV) oxide (185 mg) was added and the hydrogenation contuinued at room temperature at 5 bar for 2 h. The catalyst was filtered off and washed with MeOH and the eluate evaporated. DCM and 10 % K_2CO_3 were added and the phases separated. The water phase was extracted with DCM and the combined organic phase washed with water, passed through a phase separator and evaporated to yield methyl 2-(2,4-difluorobenzyl)-piperidine-4-carboxylate (7.103 g, 99%) as a yellow oil. MS m/z 270 $(M+H)^+$

Step 3: Dimethyl 2-(2,4-difluorobenzyl)piperidine-1,4-dicarboxylate

To a solution of methyl 2-(2,4-difluorobenzyl)piperidine-4-carboxylate (7.1 g, 26.37 mmol) in DCM (100 mL) was added DIPEA (6.5 mL, 37.32 mmol) followed by methyl carbonochloridate (2.3 mL, 29.21 mmol) dropwise. After completed addition the reaction mixture was stirred at room temperature for 4 h, then 2 M HCl was added. The organic layer was diluted with MTBE, the biphasic mixture was filtered to remove insolubles and after phase separation the organic layer was washed with brine and satd $NaHCO_3$, dried over $MgSO_4$ and evaporated to give dimethyl 2-(2,4-difluorobenzyl)piperidine-1,4-dicarboxylate (8.51 g, 99 %) as a dark oil. MS m/z 328 $(M+H)^+$

Step 4: 2-(2,4-Difluorobenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

To a suspension of lithium bromide (18.06 g, 207.99 mmol) in acetonitrile (80 mL) and water (1.6 mL) was added triethylamine (14.42 mL, 104.00 mmol) followed by dimethyl 2-(2,4-difluorobenzyl)piperidine-1,4-dicarboxylate (8.51 g, 26.00 mmol) in acetonitrile (40 mL). The resulting mixture was heated under reflux for 2 h 30 min, then cooled to room temperature and water and MTBE were added. The organic phase was extracted with water twice. The pooled aqueous layers were adjusted to pH 1 with 3.8 M HCl and then extracted with DCM (3 x). The combined organic layers were dried over $MgSO_4$ and evaporated to yield 2-(2,4-

difluorobenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (7.48 g, 92%) as an orange solid. MS m/z 314 $(M+H)^+$

Reference compound 58

2-(3-Fluoro-5-(trifluoromethyl)benzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: (3-Fluoro-5-(trifluoromethyl)benzyl)zinc(II) bromide

In a dried flask was zinc powder (1.526 g, 23.34 mmol) suspended in anhydrous THF (12.5 mL) under nitrogen. The resulting suspension was warmed to 60°C, then 1,2-dibromoethane (0.084 mL, 0.97 mmol) was added and stirred at that temperature for 15 min. It was cooled to room temperature, then chlorotrimethylsilane (0.099 mL, 0.78 mmol) was added and stirred at room temperature for 20 min. Then, 1-(bromomethyl)-3-fluoro-5-(trifluoromethyl)benzene (5 g, 19.45 mmol) dissolved in anhydrous THF (12.5 mL) was added over 7 min and stirring continued at room temperature for 1 h, then stirring was switched off to let the solids settle. The supernatant was used in the next transformation.

Step 2: Methyl 2-(3-fluoro-5-(trifluoromethyl)benzyl)isonicotinate

Methyl 2-chloroisonicotinate (3.0 g, 17.48 mmol) and $Pd(PPh_3)_4$ (0.606 g, 0.52 mmol) were dissolved in THF (50 mL) under nitrogen. Freshly prepared (3-fluoro-5-(trifluoromethyl)benzyl)zinc(II) bromide (5.41 g, 19.45 mmol) in THF (25 mL) was added to the yellow solution and the flask was warmed to 60°C overnight. The reaction mixture was quenched by adding methanol. The solution was diluted with ethyl acetate and washed with NH_4Cl and water. The organic layer was dried with Na_2SO_4, filtered through celite, and the solvent was evaporated. The residue was chromatographed using the Biotage equipment. Eluent ethyl acetate-heptane, started 20-80 and linear gradient until 60-40. Methyl 2-(3-fluoro-5-(trifluoromethyl)benzyl)isonicotinate (4.1 g, 75 % yield) was isolated. ^1H NMR (400 MHz, $cdcl_3$) δ 3.94 (s, 3H), 4.25 (s, 2H), 7.13 – 7.22 (m, 2H), 7.33 (s, 1H), 7.69 – 7.75 (m, 2H), 8.70 – 8.74 (m, 1 H). MS m/z 314 $(M+H)^+$

Step 3: Methyl 2-(3-fluoro-5-(trifluoromethyl)benzyl)piperidine-4-carboxylate

To a solution of methyl 2-(3-fluoro-5-(trifluoromethyl)benzyl)isonicotinate (4.5 g, 14.37 mmol) in acetic acid (50 mL) was added platinum(IV) oxide (0.36 g, 1.59 mmol) and the

resulting mixture hydrogenated at 5 bar in a Büchi hydrogenator for 3 h 45 min. The reaction mixture was filtered through a diatomeous earth filter carton and the catalyst washed with methanol. The solvents were evaporated, the residue dissolved in DCM and washed with 10% Na_2CO_3. After phase separation the aqueous layer was extracted with DCM. The combined organic layers were dried over $MgSO_4$ and evaporated. Methyl 2-(3-fluoro-5-(trifluoromethyl)benzyl)piperidine-4-carboxylate (4.11 g, 90 %) was isolated as a pale yellow oil that partially solidified upon standing. MS m/z 320 $(M+H)^+$

Step 4: Dimethyl 2-(3-fluoro-5-(trifluoromethyl)benzyl)piperidine-1,4-dicarboxylate

To a solution of methyl 2-(3-fluoro-5-(trifluoromethyl)benzyl)piperidine-4-carboxylate (4.10 g, 12.84 mmol) in DCM (50 mL) cooled in an ice-bath was added DIPEA (3.5 mL, 20.09 mmol) followed by methyl carbonochloridate (1.112 mL, 14.12 mmol). After completed addition the reaction mixture was stirred at room temperature for 2 h. The solvents were evaporated and the residue partitioned between ethyl acetate and 3.8 M HCl. After phase separation the organic layer was washed with brine, then dried over $MgSO_4$ and evaporated to yield crude dimethyl 2-(3-fluoro-5-(trifluoromethyl)benzyl)piperidine-1,4-dicarboxylate (4.94 g, 102 %) as a pale yellow oil. MS m/z 378 $(M+H)^+$

Step 5: 2-(3-Fluoro-5-(trifluoromethyl)benzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

To a solution of dimethyl 2-(3-fluoro-5-(trifluoromethyl)benzyl)piperidine-1,4-dicarboxylate (4.94 g, 13.09 mmol) in acetonitrile (60 mL) and water (1.2 mL) was added lithium bromide (9.10 g, 104.74 mmol) and triethylamine (7.26 mL, 52.37 mmol). The resulting mixture was heated under reflux for 2 h, then cooled to room temperature. Water was added and acetonitrile removed by evaporation. The aqueous layer was further diluted with water, then washed with MTBE. The organic layer was extracted with water. The combined aqueous layers were acidified with 3.8 M HCl, a colorless precipitate formed. The aqueous layer was extracted with DCM three times. The combined organic layers were dried over $MgSO_4$ and evaporated. 2-(3-Fluoro-5-(trifluoromethyl)benzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (4.58 g, 96 %) was isolated as a pale yellow viscous oil. MS m/z 364 $(M+H)^+$

Reference compound 59

2-(3-Fluoro-4-(trifluoromethyl)benzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: (3-Fluoro-4-(trifluoromethyl)benzyl)zinc(II) bromide

In a dried flask was zinc powder (3.05 g, 46.69 mmol) suspended in anhydrous tetrahydrofuran (25 mL) under nitrogen. The resulting suspension was warmed to 60°C, then 1,2-dibromoethane (0.168 mL, 1.95 mmol) was added and stirred at that temperature for 15 min. It was cooled to room temperature, then chlorotrimethylsilane (0.2 mL, 1.58 mmol) was added and stirred at room temperature for 1 h 15 min. Then, 4-(bromomethyl)-2-fluoro-1-(trifluoromethyl)benzene (10 g, 38.91 mmol) in tetrahydrofuran (5 mL) was added in 6 equal portions every 10 minutes under ice-cooling. After complete addition the ice-bath was removed and the reaction mixture stirred at room temperature for 18 h. Then was stirring switched off to let the solids settle. The supernatant was used in next transformation.

Step 2: Methyl 2-(3-fluoro-4-(trifluoromethyl)benzyl)isonicotinate

To a solution of methyl 2-chloroisonicotinate (5.15 g, 30 mmol) and $Pd(PPh_3)_4$ (0.693 g, 0.60 mmol) in tetrahydrofuran (40 mL) under nitrogen in a dried flask was added freshly prepared (3-fluoro-4-(trifluoromethyl)benzyl)zinc(II) bromide (12.55 g, 38.91 mmol) in tetrahydrofuran (50 mL). The resulting bright yellow mixture was heated to 60°C for 2 h 20 min, then cooled to room temperature. The reaction was quenched by the addition of 10 % NH_4Cl. It was diluted with ethyl acetate. After phase separation, the organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The residue was suspended in 150 mL MTBE and sonicated, then the yellow insolubles were filtered off and washed with MTBE. The volume of the filtrate was increased to ca. 200 mL, then hydrogen chloride (7.50 mL, 30.00 mmol) (4M in dioxane) was added dropwise. A colorless precipitate formed. The resulting suspension was stirred for ca. 1 h, then sonicated for 2 min. The formed solid was collected and washed with MTBE and dried. The solid was dissolved in DCM and washed with 10% K_2CO_3. After phase separation, the aqueous layer was extracted with DCM. The combined organic layers were dried over $MgSO_4$ and evaporated. Methyl 2-(3-fluoro-4-(trifluoromethyl)benzyl)isonicotinate (8.26 g, 88 %) was isolated as a pale orange oil. ^1H NMR (400 MHz, $cdcl_3$) δ 3.94 (s, 3H), 4.24 (s, 2H), 7.06 – 7.18 (m, 2H), 7.52 (t, 1H), 7.69 – 7.75 (m, 2H), 8.68 – 8.75 (m, 1H). MS m/z 314 $(M+H)^+$

Step 3: Methyl 2-(3-fluoro-4-(trifluoromethyl)benzyl)piperidine-4-carboxylate

To a solution of methyl 2-(3-fluoro-4-(trifluoromethyl)benzyl)isonicotinate (8.26 g, 26.37 mmol) in acetic acid (50 mL) was added platinum(IV) oxide (0.44 g, 1.94 mmol) and the resulting mixture hydrogenated at 5 bar in a Büchi hydrogenator for 8 h. The reaction mixture was filtered through a diatomeous earth filter carton and the catalyst washed with methanol. The solvents were evaporated, the residue dissolved in DCM and washed with 10% Na_2CO_3. After phase separation the aqueous layer was extracted with DCM. The combined organic layers were dried over MgSO4 and evaporated. Methyl 2-(3-fluoro-4-(trifluoromethyl)-benzyl)piperidine-4-carboxylate (8.4 g, 100 %) was isolated as a pale yellow oil that partially solidified upon standing. MS m/z 320 $(M+H)^+$

Step 4: Dimethyl 2-(3-fluoro-4-(trifluoromethyl)benzyl)piperidine-1,4-dicarboxylate

To a solution of methyl 2-(3-fluoro-4-(trifluoromethyl)benzyl)piperidine-4-carboxylate (5.96 g, 18.67 mmol) in DCM (100 mL) cooled in an ice-bath was added DIPEA (4 mL, 22.96 mmol) followed by methyl carbonochloridate (1.617 mL, 20.53 mmol). After completed addition the reaction mixture was stirred at room temperature for 2 h. The solvents were evaporated and the residue partitioned between ethyl acetate and 3.8 M HCl. After phase separation the organic layer was washed with brine, then dried over $MgSO_4$ and evaporated. Dimethyl 2-(3-fluoro-4-(trifluoromethyl)benzyl)piperidine-1,4-dicarboxylate (7.17 g, 102 %) was isolated as a pale yellow oil.

Step 5: 2-(3-Fluoro-4-(trifluoromethyl)benzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

To a solution of dimethyl 2-(3-fluoro-4-(trifluoromethyl)benzyl)piperidine-1,4-dicarboxylate (7.17 g, 19.00 mmol) in acetonitrile (60 mL) and water (1.2 mL) was added lithium bromide (13.20 g, 152.02 mmol) and triethylamine (10.54 mL, 76.01 mmol). The resulting mixture was heated under reflux for 2 h, then cooled to room temperature. Water was added and acetonitrile removed by evaporation. The aqueous layer was further diluted with water, then washed with MTBE. The organic layer was extracted with water. The combined aqueous layers were acidified with 3.8 M HCl, a colorless precipitate formed. The solids were extracted with DCM 6 times. The aqueous layer was extracted twice again with DCM. The combined organic layers were dried over $MgSO_4$ and evaporated. 2-(3-Fluoro-4-(trifluoromethyl)benzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (6.56 g, 95 %) was isolated as an off-white solid. MS m/z 364 $(M+H)^+$

Reference compound 60

1-(Methoxycarbonyl)-2-(3,4,5-trifluorobenzyl)piperidine-4-carboxylic acid

Step 1: (3,4,5-Trifluorobenzyl)zinc(II) bromide

Zinc powder (2.62 g, 40.00 mmol) and lithium chloride (1.696 g, 40.00 mmol) were added to a dried flask and heated to 150°C under vacuum for 30 min. The flask was allowed to reach room temperature. THF (20 mL) and 1,2-dibromoethane (0.115 mL, 1.33 mmol) were added. The mixture was heated until boiling occured and the flask was then allowed to reach room temperature. Chlorotrimethylsilane (0.034 mL, 0.27 mmol) was added and the mixture was again heated until boiling occured. The flask was cooled with an ice-bath and 5-(bromomethyl)-1,2,3-trifluorobenzene (6 g, 26.67 mmol) dissolved in THF (5 mL) was then added dropwise. The ice-bath was removed and the reaction stirred at room temperature for 20 h. Solids were allowed to settle and the supernatant used in the next transformation.

Step 2: Methyl 2-(3,4,5-trifluorobenzyl)isonicotinate hydrochloride

Methyl 2-chloroisonicotinate (3.5 g, 20.40 mmol) was dissolved in THF (30 mL) under a nitrogen atmosphere. Bis(tri-tert-butylphosphine)Pd(0) (0.208 g, 0.41 mmol) was added. Freshly made (3,4,5-trifluorobenzyl)zinc(II) bromide (1.06 M in THF) (25.1 mL, 26.65 mmol) was then added and the reaction mixture stirred at 60°C for 3 h. Water (15 mL) was added and THF was evaporated. The reaction mixture was diluted with satd $NaHCO_3$ and extracted with EtOAc (3x). The combined organic phases were washed with satd $NaHCO_3$, water, NH_4Cl and brine, and dried with Na_2SO_4, filtered and evaporated in vacuo yielding a red oil (5 g). MTBE (70 mL) was added, insolubles filtered off and washed with MTBE (10 mL). To the filtrate was added hydrogen chloride (4 M in dioxane, 5.10 mL, 20.40 mmol) dropwise, an orange precipitate formed. The mixture was cooled with an ice-bath. The precipitate was filtered off, washed with cold MTBE and dried in vacuo yielding methyl 2-(3,4,5-trifluorobenzyl)isonicotinate hydrochloride (4.00 g, 61.7 %) as an orange solid. ^{1}H NMR (600 MHz, CD_3OD) δ 4.02 (s, 3H), 4.45 (s, 2H), 7.13 - 7.22 (m, 2H), 8.24 - 8.32 (m, 2H), 8.87 - 8.93 (m, 1H). MS m/z 282 $(M+H)^+$

Step 3: Methyl 2-(3,4,5-trifluorobenzyl)piperidine-4-carboxylate hydrochloride

Methyl 2-(3,4,5-trifluorobenzyl)isonicotinate hydrochloride (4 g, 12.59 mmol) was dissolved in MeOH (45 mL) and platinum(IV) oxide (0.143 g, 0.63 mmol) added. The resulting mixture was hydrogenated in a Büchi hydrogenator at room temperature and 5 bar for 3 h. Additional platinum(IV) oxide (0.029 g, 0.13 mmol) was added and the hydrogenation continued for 20 min. The catalyst was filtered off and washed with MeOH. The filtrate was evaporated in vacuo to yield methyl 2-(3,4,5-trifluorobenzyl)piperidine-4-carboxylate hydrochloride (3.96 g, 97 %) as a brown solid. MS m/z 288 $(M+H)^+$

Step 4: Dimethyl 2-(3,4,5-trifluorobenzyl)piperidine-1,4-dicarboxylate

Methyl 2-(3,4,5-trifluorobenzyl)piperidine-4-carboxylate hydrochloride (3.957 g, 12.22 mmol) and DIPEA (4.68 mL, 26.89 mmol) were dissolved in DCM (20 mL) and methyl carbonochloridate (1.059 mL, 13.45 mmol) was added. The reaction was stirred at room temperature for 18 h, diluted with DCM (200 mL), washed with 0.1 M HCl (2 x 200 mL), satd NaHCO3 (200 mL), dried through a phase separator and evaporated in vacuo to yield dimethyl 2-(3,4,5-trifluorobenzyl)piperidine-1,4-dicarboxylate (4.01 g, 95 %) as a brown oil. MS m/z 346 $(M+H)^+$

Step 5: 1-(Methoxycarbonyl)-2-(3,4,5-trifluorobenzyl)piperidine-4-carboxylic acid

Dimethyl 2-(3,4,5-trifluorobenzyl)piperidine-1,4-dicarboxylate (4.01 g, 11.61 mmol) was dissolved in acetonitrile (40 mL) and water (0.8 mL). Lithium bromide (2.329 mL, 92.90 mmol) was added followed by triethylamine (6.44 mL, 46.45 mmol). The reaction was refluxed for 2 h. The reaction was cooled to room temperature. Water (200 mL) and MTBE (150 mL) were added, shaken and the phases separated. The organic phase was extracted with water (2x150 mL). The combined aqueous phases were acidified with 3 M HCl to pH 1 and then extracted with MTBE (2x400 mL). The combined organic phases were dried with Na_2SO_4, filtered and evaporated in vacuo to yield 1-(methoxycarbonyl)-2-(3,4,5-trifluoro-benzyl)piperidine-4-carboxylic acid (3.42 g, 89 %) as a light brown foam. MS m/z 330 $(M-H)^-$

Reference compound 61

2-(3,5-Di-tert-butylbenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: (3,5-Di-tert-butylbenzyl)zinc(II) bromide

In a dried flask was zinc powder (2.493 g, 38.13 mmol) suspended in anhydrous tetrahydrofuran (23 mL) under nitrogen. The resulting suspension was warmed to 60°C, then 1,2-dibromoethane (0.137 mL, 1.59 mmol) was added and stirred at that temperature for 15 min. It was cooled to room temperature, then chlorotrimethylsilane (0.161 mL, 1.27 mmol) was added and stirred at room temperature for 45 min. Then, 1-(bromomethyl)-3,5-di-tert-butylbenzene (9 g, 31.77 mmol) dissolved in anhydrous tetrahydrofuran (23.00 mL) was added over 10 min. Stirring continued at room temperature for 16 h, then stirring was switched off to let the solids settle. The supernatant was used in the next transformation.

Step 2: Methyl 2-(3,5-di-tert-butylbenzyl)isonicotinate

To a solution of methyl 2-chloroisonicotinate (4 g, 23.31 mmol) and $Pd(PPh_3)_4$ (0.539 g, 0.47 mmol) in tetrahydrofuran (120 mL) under nitrogen in a dried flask was added a freshly prepared solution of (3,5-di-tert-butylbenzyl)zinc(II) bromide (11.08 g, 31.78 mmol) in tetrahydrofuran (46 mL). The resulting bright yellow solution was heated to 60°C for 35 min, then stirred at room temperature for 1 h. The reaction was quenced by addition of methanol (50 mL). The solution was diluted with EtOAc and washed with NH_4Cl. The organic layer was dried over $MgSO_4$, filtered and evaporated to yield a brown oil. The crude was redissolved in MTBE (180 mL) and solids were filtered off. Hydrogen chloride (4 M in dioxane, 6.42 mL, 25.66 mmol) was added dropwise during stirring and a suspension was formed. The suspension was stirred at room temperature for 10 min. The solid was collected by filtration and washed with MTBE. Redissolved in MTBE / satd $NaHCO_3$. The phases were separated, the organic phase dried over Na_2SO_4, filtered and evaporated to yield methyl 2-(3,5-di-tert-butylbenzyl)isonicotinate (7.132 g, 90 %) as a brown oil. ^1H NMR (600 MHz, cdcl$_3$) δ 1.28 (s, 18H), 3.89 (s, 3H), 4.19 (s, 2H), 7.11 (d, 2H), 7.27 (t, 1H), 7.64 (dd, 1H), 7.71 (s, 1H), 8.68 (d, 1H). MS m/z 340 $(M+H)^+$

Step 3: Methyl 2-(3,5-di-tert-butylbenzyl)piperidine-4-carboxylate

Methyl 2-(3,5-di-tert-butylbenzyl)isonicotinate (3.538 g, 10.42 mmol) was dissolved in acetic acid (30 mL) and platinum(IV) oxide (0.118 g, 0.52 mmol) added. The resulting mixture was hydrogenated in a Büchi hydrogenator at room temperature and 5 bar for 5 h 45 min. The catalyst was filtered off and washed with MeOH and the eluate evaporated. DCM and 10 % K_2CO_3 were added and the phases separated. The organic layer was washed with brine, passed through a phase separator and evaporated to yield crude methyl 2-(3,5-di-tert-

butylbenzyl)piperidine-4-carboxylate (3.80 g, 106%) as a beige oil. MS m/z 346 $(M+H)^+$

Step 4: Dimethyl 2-(3,5-di-tert-butylbenzyl)piperidine-1,4-dicarboxylate

Methyl 2-(3,5-di-tert-butylbenzyl)piperidine-4-carboxylate (3.691 g, 10.68 mmol) was dissolved in DCM (80 mL) and DIPEA (2.233 mL, 12.82 mmol) added followed by methyl carbonochloridate (1.262 mL, 16.02 mmol). The solution was stirred at room temperature for 1.5 h. The reaction mixture was washed with 0.1 M HCl and satd $NaHCO_3$. The organic phase was passed through a phase separator and evaporated to yield dimethyl 2-(3,5-di-tert-butylbenzyl)piperidine-1,4-dicarboxylate (3.91 g, 91 %) as a yellow oil. MS m/z 404 $(M+H)^+$

Step 5: 2-(3,5-Di-tert-butylbenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Dimethyl 2-(3,5-di-tert-butylbenzyl)piperidine-1,4-dicarboxylate (3.886 g, 9.63 mmol) was dissolved in acetonitrile (40 mL) and water (0.8 mL), then lithium bromide (6.69 g, 77.04 mmol) and triethylamine (5.34 mL, 38.52 mmol) were added and the resulting yellow suspension was heated at reflux. After 5 h water (100 mL) and MTBE (250 mL) were added. The organic phase was extracted with water (x2). The pooled aqueous layer was acidified to pH 1 with 3.8 M HCl and then extracted with MTBE (x3). The combined organic layer was washed with water, dried Na_2SO_4, filtered and evaporated to yield 2-(3,5-di-tert-butylbenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (3.723 g, 99%) as a yellow gum. MS m/z 390 $(M+H)^+$

Reference compound 62

2-Benzyl-2,3,4,5,6-d_5-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Step 1: Benzyl-2,3,4,5,6-d_5 zinc(II) bromide

In a dried flask was zinc powder (2.4 g, 36.70 mmol) suspended in anhydrous tetrahydrofuran (40 mL) under nitrogen. The resulting suspension was warmed to 60°C, then 1,2-dibromoethane (0.125 mL, 1.45 mmol) was added and stirred at that temperature for 20 min. It was cooled to room temperature, then chlorotrimethylsilane (0.15 mL, 1.18 mmol) was added and stirred at room temperature for 30 min. Then, benzyl-2,3,4,5,6-d_5 bromide (5 g, 28.40 mmol) (99.2 % deuterated) was added in portions over 30 min, then stirring was continued at room temperature for 18h. Stirring was switched off to let the precipitate settle.

The supernatant was used in the next transformation.

Step 2: Methyl 2-benzyl-2,3,4,5,6-d_5 isonicotinate

To a solution of methyl 2-chloroisonicotinate (3.95 g, 23 mmol) and $Pd(PPh_3)_4$ (0.532 g, 0.46 mmol) in tetrahydrofuran (40 mL) under nitrogen in a dried flask was added freshly prepared benzyl-2,3,4,5,6-d_5 zinc(II) bromide (6.86 g, 28.4 mmol) in tetrahydrofuran (50 mL). The resulting bright yellow mixture was heated to 60°C for 2 h. After cooling to room temperature, the reaction was quenched by the addition of 10 % NH_4Cl. It was diluted with ethyl acetate. After phase separation, the organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The residue was suspended in MTBE (50 mL) and sonicated, the yellow insolubles were filtered off and washed with MTBE. The volume of the filtrate was increased to ca. 150 mL, then 5 mL MeOH was added, followed by hydrogen chloride (5.75 mL, 23.00 mmol) (4M in dioxane). A colorless precipitate formed. The mixture was stirred for 10 min, sonicated for 5 min, then the solids were collected and washed with MTBE. The solid was tranferred with MeOH into a separation funnel and was diluted with MTBE. Then 10% Na_2CO_3 was added and vigorously shaken. After phase separation, the organic layer was washed with brine, dried over $MgSO_4$ and evaporated. Methyl 2-benzyl-2,3,4,5,6-d_5 isonicotinate (4.78 g, 89 %) was isolated as a pale yellow oil. ^1H NMR (400 MHz, cdcl$_3$) δ 3.92 (s, 3H), 4.23 (s, 2H), 7.65 – 7.71 (m, 2H), 8.66 – 8.74 (m, 1H). MS m/z 233 $(M+H)^+$

Step 3: Methyl 2-benzyl-2,3,4,5,6-d_5 piperidine-4-carboxylate

Methyl 2-benzyl-2,3,4,5,6-d_5 isonicotinate (4.69 g, 20.19 mmol) was dissolved in acetic acid (3 mL) and platinum(IV) oxide (0.364 g, 1.60 mmol) was added. The resulting mixture was hydrogenated in a Büchi hydrogenator at 4 bar for 4 h. The reaction mixture was filtered through a diatomous earth filter carton, washed with methanol and the solvents evaporated. The residue was dissolved in MTBE and washed with satd $NaHCO_3$. Before phase separation, the aqueous phase was adjusted to pH 9 by addition of 10 % K_2CO_3. The organic phase was dried over $MgSO_4$ and evaporated to yield methyl 2-benzyl-2,3,4,5,6-d_5 piperidine-4-carboxylate (4.6 g, 96 %) as a yellow oil. MS m/z 239 $(M+H)^+$

Step 4: Dimethyl 2-benzyl-2,3,4,5,6-d_5 piperidine-1,4-dicarboxylate

To a solution of methyl 2-benzyl-2,3,4,5,6-d_5 piperidine-4-carboxylate (4.6 g, 19.30 mmol) and DIPEA (5 mL, 28.71 mmol) in DCM (75 mL) was added methyl carbonochloridate (1.8

mL, 22.86 mmol) dropwise. Stirring continued at room temperature for 45 min, then solvents evaporated. Residue partitioned between MTBE and 1 N HCl. Organic layer washed with brine and satd $NaHCO_3$, then dried over $MgSO_4$ and evaporated to yield dimethyl 2-benzyl-2,3,4,5,6-d_5 piperidine-1,4-dicarboxylate (5.55 g, 97 %) as a pale yellow oil. MS m/z 297 $(M+H)^+$

Step 5: 2-Benzyl-2,3,4,5,6-d_5-1-(methoxycarbonyl)piperidine-4-carboxylic acid

Dimethyl 2-benzyl-2,3,4,5,6-d_5 piperidine-1,4-dicarboxylate (5.55 g, 18.73 mmol) was dissolved in acetonitrile (60 mL) and water (1.2 mL), then lithium bromide (13.01 g, 149.81 mmol) and triethylamine (10.38 mL, 74.91 mmol) were added. The resulting yellow suspension was heated under reflux. After 2 h 10 min the reaction mixture was cooled to room temperature, then water and MTBE were added. The organic phase was extracted with water twice. The pooled aqueous layers were adjusted to pH 1 with 3.8 M HCl and then extracted with DCM (3 x). The combined organic layers were dried over $MgSO_4$ and evaporated to yield 2-benzyl-2,3,4,5,6-d_5-1-(methoxycarbonyl)piperidine-4-carboxylic acid (5.16 g, 98 %) as an off-white solid. MS m/z 283 $(M+H)^+$

Preparation of Compound Examples. Formation of 5-isoxazol-3-ones

Example 1

5-((2S,4S)-2-Benzylpiperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-benzyl-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate and cis-methyl 2-benzyl-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate

A suspension of magnesium chloride (3.11 g, 32.66 mmol) and ethyl potassium malonate (8.34 g, 48.99 mmol) in dry THF (70 mL) was stirred under nitrogen atmosphere at 50°C for 4 h (flask 1). In another flask was added carbonyldiimidazole (6.35 g, 39.19 mmol) portionwise to a suspension of 2-benzyl-1-(methoxycarbonyl)piperidine-4-carboxylic acid (9.057 g, 32.66 mmol) (reference compound 1) in dry THF (70 mL) at 5°C under nitrogen atmosphere. This reaction mixture was stirred for 1 h at 5°C (flask 2). The contents of flask 2 was then added dropwise to flask 1 and the resulting mixture was stirred for 24 h. The reaction mixture was concentrated and the residue was partitioned between EtOAc and H_2O. The aqueous phase was extracted once with EtOAc and the combined organic phases were washed with H_2O, satd Na_2CO_3 and then dried over Na_2SO_4 and evaporated to give 11.02 g oil. Purification using automated column chromatography (Biotage) (2 runs - 340 g column, grad 10-60% EtOAc/heptane) yielded trans-methyl 2-benzyl-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (6.35 g): ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.27 (m, 3H), 1.41 – 1.66 (m, 3H), 1.70 – 2.11 (m, 2H), 2.53 – 3.10 (m, 4H), 3.55 (d, 4H), 4.19 (dd, 3H), 4.42 – 4.99 (m, 1H), 7.08 – 7.37 (m, 5H); MS m/z 348 $(M+H)^+$ and cis-methyl 2-benzyl-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (2.15 g): ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.25 (m, 3H), 1.61 – 1.96 (m, 4H), 2.64 – 2.79 (m, 2H), 2.80 – 3.10 (m, 2H), 3.44 (s, 2H), 3.63 (s, 3H), 3.84 – 4.00 (m, 1H), 4.03 – 4.25 (m, 3H), 7.15 – 7.42 (m, 5H); MS m/z 348 $(M+H)^+$.

Step 2: Trans-methyl 2-benzyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

A solution of trans-methyl 2-benzyl-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (6.35 g, 18.3 mmol) in MeOH (2 mL) was added to a solution of NaOH (0.77 g, 19.4 mmol) in MeOH/H_2O (15 mL/0.9 mL) at –30°C. After 10 minutes was added a solution of hydroxylamine hydrochloride (2.54 g, 36.6 mmol) and NaOH (1.46 g, 36.6 mmol) in MeOH

(18 mL) and H_2O (18 mL). Stirring was continued at -30°C for 30 minutes. The reaction mixture was then poured into concentrated HCl (20 mL) held at 80°C. The solution was stirred for 30 minutes. The organic solvent was evaporated and the aqueous phase extracted with DEE (x3). The organic phase was dried over Na_2SO_4 and evaporated to give a solid, 3.68 g, which was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x20 ID mm) using a gradient of 20-70% acetonitrile in H_2O/MeCN/FA 95/5/0.2 buffer, over 18 minutes with a flow of 19 mL/minutes. Trans-methyl-2-benzyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (2.54 g, 54.6 %) was isolated as a solid. ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.50 – 2.21 (m, 4H), 2.91 (m, 2H), 3.10 (m, 2H), 3.58 (d, 3H), 4.04 – 4.41 (m, 1H), 4.43 – 4.82 (m, 1H), 5.55 – 5.84 (m, 1H), 7.15 – 7.30 (m, 5H); MS m/z 317 $(M+H)^+$.

Step 3: (2S,4S)-Methyl 2-benzyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Racemic trans-methyl 2-benzyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (2.54 g, 8.04 mmol) was subjected to chiral separation using Chiralcel IA, mobile phase heptane/EtOH/FA 80/20/0.4/0.1, which resulted in (2S,4S)-methyl 2-benzyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.99 g).

Step 4: 5-((2S,4S)-2-Benzylpiperidin-4-yl)isoxazol-3(2H)-one

To (2S,4S)-methyl 2-benzyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.99 g) was added HBr (33 % in HOAc, 20 mL) and the solution was stirred for 8 h. The volatiles were concentrated and the residues purified by preparative HPLC on a XBridge C18 column (10 µm 250x50 ID mm) using a gradient of 0-40 % acetonitrile in H_2O/MeCN/NH_3 95/5/0.2 buffer over 15 minutes with a flow of 100 mL/minutes. The title compound was isolated (0.62 g, 30%). ^{1}H NMR (600 MHz, dmso) δ 1.47 (m, 1H), 1.67 – 1.83 (m, 3H), 2.51 – 2.67 (m, 3H), 2.74 – 2.89 (m, 2H), 3.04 – 3.15 (m, 1H), 5.67 (s, 1H), 7.21 (m, 5H); $[\alpha]^{20}_D$ +47.0 (MeOH/H_2O 1:1, c = 1); HRMS Calculated for $[C_{15}H_{19}N_2O_2]$+: 259.1447; Found: 259.1449.

Example 2

5-((2R,4R)-2-Benzylpiperidin-4-yl)isoxazol-3(2H)-one

Step 1: (2R,4R)-Methyl 2-benzyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

The title compound was obtained in the preparation of Example 1, Step 3 (0.93 g).

Step 2: 5-((2R,4R)-2-Benzylpiperidin-4-yl)isoxazol-3(2H)-one

Following the same procedure as described in Example 1, Step 4 using ((2R,4R)-methyl 2-benzyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate the title compound (0.55 g, 27%) was obtained. $[\alpha]^{20}_{D}$ -43.0 (MeOH/H_2O 1:1, c = 1); HRMS Calculated for $[C_{15}H_{19}N_2O_2]$+: 259.1447; found: 259.1449.

Example 3

5-((2R,4S)-2-Benzylpiperidin-4-yl)isoxazol-3(2H)-one

Step 1: Cis-methyl 2-benzyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

A solution of cis-methyl 2-benzyl-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (2,15 g, 6.18 mmol) (from Example 1, Step 1) in MeOH (0.75 mL) was added to a solution of NaOH (0.26 g, 6.55 mmol) in MeOH/H_2O (5 mL/0.3 mL) at –30°C. After 10 minutes was added a solution of hydroxylamine hydrochloride (0.86 g, 12.4 mmol) and NaOH (0.49 g, 12.4 mmol) in MeOH (6.1 mL) and H_2O (6.1 mL). Stirring was continued at -30°C for 30 minutes. The reaction mixture was then poured into concentrated HCl (7 mL) held at 80°C. The solution was stirred for 30 minutes. The organic solvent was evaporated and the aqueous phase extracted with ether (x3). The combined organic phases were dried over Na_2SO_4, and evaporated to yield a solid, 2.2 g. The compound was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x20 ID mm) using a gradient of 20-70% acetonitrile in H_2O/MeCN/FA 95/5/0.2 buffer, over 18 minutes with a flow of 19 mL/minutes. The title compound was isolated (1.1 g, 57%). ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.76 – 2.15 (m, 4H), 2.63 (m, 1H), 2.82 (m, 1H), 2.87 – 3.03 (m, 1H), 3.03 – 3.22 (m, 1H), 3.61 (s, 3H), 3.99 (m, 1H), 4.19 – 4.33 (m, 1H), 5.71 (s, 1H), 7.01 – 7.37 (m, 5H). MS m/z 317 $(M+H)^+$.

Step 2: (2R,4S)-Methyl 2-benzyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Racemic cis-methyl 2-benzyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.1 g) was subjected to chiral separation using Chiralcel OD, mobile phase heptane/EtOH/FA

90/10/0.1 at 40°C which resulted in (2R,4S)-methyl 2-benzyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.47 g).

Step 3: 5-((2R,4S)-2-Benzylpiperidin-4-yl)isoxazol-3(2H)-one

To (2R,4S)-methyl 2-benzyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.47 g) was added HBr (33% in HOAc, 10 mL) and the solution was stirred for 16 h. The volatiles were concentrated and the residue purified by preparative HPLC on a XBridge C18 column (10 μm 250x50 ID mm) using a gradient of 0-40% acetonitrile in H_2O/MeCN/NH_3 95/5/0.2 buffer over 15 minutes with a flow of 100 mL/minutes. The title compound was isolated (0.26 g, 29 %): ^{1}H NMR (600 MHz, dmso) δ 1.07 (m, 1H), 1.26 – 1.45 (m, 1H), 1.75 (m, 2H), 2.53 (m, 2H), 2.58 – 2.67 (m, 2H), 2.69 (m, 1H), 2.97 (m, 1H), 5.66 (s, 1H), 7.08 – 7.34 (m, 5H); $[\alpha]^{20}_D$ +67.8 (MeOH/H_2O 1:1, c = 1); HRMS Calculated for $[C_{15}H_{19}N_2O_2]$+: 259.1447; found: 259.1442.

Example 4

5-((2S,4R)-2-Benzylpiperidin-4-yl)isoxazol-3(2H)-one

Step 1: (2S,4R)-Methyl 2-benzyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

The title compound was obtained in Example 3, Step 2 (0.47 g).

Step 2: 5-((2S,4R)-2-Benzylpiperidin-4-yl)isoxazol-3(2H)-one

Following the same procedure as described in Example 3, Step 3 using (2S,4R)-methyl 2-benzyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate yielded the title compound (0.23 g, 26%); HRMS Calculated for $[C_{15}H_{19}N_2O_2]$+: 259.1447; found: 259.1433.

Example 5

5-((2R,4S)-2-Isobutylpiperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-isobutyl-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate and cis-methyl 2-isobutyl-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate

The compounds were prepared as described in Example 1, Step 1 starting from crude 2-isobutyl-1-(methoxycarbonyl)piperidine-4-carboxylic acid (2.28 g, 9.4 mmol) (Reference Compound 2), magnesium chloride (0.95 g, 9.95 mmol), ethyl potassium malonate (2.5 g, 14.9 mmol) and carbonyldiimidazole (1.98 g, 12.2 mmol) which resulted in trans-methyl 2-isobutyl-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (1.60 g, 54 %). Trans isomer: ^{1}H NMR (500 MHz, cdcl$_3$) δ 0.91 (m, 6H), 1.29 (t, 3H), 1.42 – 1.98 (m, 6H), 2.48 - 2.84 (m, 3H), 3.48 (s, 2H), 3.70 (s, 3H), 3.98 – 4.28 (m, 3H), 4.30-4-60 (m, 1H); MS m/z 314 $(M+H)^+$ and cis-methyl 2-isobutyl-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (0.59 g, 20 %). Cis isomer: ^{1}H NMR (500 MHz, cdcl$_3$) δ 0.80 (d, 3H), 0.83 (d, 3H), 1.09 (m, 1H), 1.20 (t, 3H), 1.31 – 1.54 (m, 2H), 1.60 (m, 1H), 1.69 – 1.86 (m, 2H), 1.98 (m, 1H), 2.56 – 2.68 (m, 1H), 2.91 – 3.04 (m, 1H), 3.44 (s, 2H), 3.60 (s, 3H), 3.78 (m, 1H), 4.00 – 4.17 (m, 3H); MS m/z 314 $(M+H)^+$.

Step 2: Trans-methyl 2-isobutyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

The compound was prepared as described in Example 1, Step 2 starting from trans-methyl 2-isobutyl-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (1.60 g, 5.0 mmol) which yielded the product (1.02 g, 71 %): ^{1}H NMR (500 MHz, cdcl$_3$) δ 0.95 (m, 6H), 1.32 (m, 1H), 1.54 (s, 2H), 1.71 (m, 2H), 1.84 – 2.05 (m, 2H), 3.04 (m, 2H), 3.72 (s, 3H), 4.23 (s, 1H), 4.44 (s, 1H), 5.65 (s, 1H); MS m/z 283 $(M+H)^+$.

Step 3: Trans-5-(2-isobutylpiperidin-4-yl)isoxazol-3(2H)-one

Racemic trans-methyl 2-isobutyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.39 g, 1.3 mmol) was stirred in HBr (33% in HOAc) for 16 h. The volatiles were concentrated and the residue purified by preparative HPLC on a XBridge C18 column (10 µm 250x50 ID mm) using a gradient of 0-25% acetonitrile in H_2O/MeCN/NH_3 95/5/0.2 buffer over 10 minutes with a flow of 100 mL/minutes. The title compound (0.26 g) was isolated. ^{1}H NMR (600 MHz, d_2o) δ 0.76 (d, 3H), 0.79 (d, 3H), 1.14 (m, 1H), 1.33 – 1.41 (m, 1H), 1.45 (m, 1H), 1.59 (m, 1H), 1.76 (m, 1H), 1.98 (m, 1H), 2.06 (m, 1H), 2.21 (m, 1H), 3.04 (m, 2H), 3.14 – 3.31 (m, 4H), 5.67 (s, 1H).

Step 4: 5-((2R,4S)-2-Isobutylpiperidin-4-yl)isoxazol-3(2H)-one

A racemic mixture of trans-5-(2-isobutylpiperidin-4-yl)isoxazol-3(2H)-one was subjected to chiral separation using Chiralcel IC, mobile phase heptane/EtOH/FA/TEA 60/40/0.4/0.2

which resulted in the title compound (117 mg, 40%). $[\alpha]^{20}_{D}$ +21.1(H_2O, c = 1); HRMS Calculated for $[C_{12}H_{21}N_2O_2]$+: 225.1603; found: 225.1599.

Example 6

5-((2S,4R)-2-Isobutylpiperidin-4-yl)isoxazol-3(2H)-one

The titled compound was obtained from Example 5, Step 4 (113 mg, 39%). HRMS Calculated for $[C_{12}H_{21}N_2O_2]$+: 225.1603; found: 225.1596.

Example 7

5-((2S,4S)-2-Isobutylpiperidin-4-yl)isoxazol-3(2H)-one

Step 1: Cis-methyl 2-isobutyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate
The compound was prepared as described in Example 5, Step 2 starting from cis-methyl 2-isobutyl-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate obtained in Example 5, Step 1 (0.59 g, 1.9 mmol) which resulted in the title compound (0.29 g, 51%). ^{1}H NMR (600 MHz, cdcl$_3$) δ 0.85 (2 d, 6H), 1.15 (m, 1H), 1.29 – 1.40 (m, 1H), 1.50 (m, 1H), 1.82 – 1.93 (m, 2H), 2.04 (m, 2H), 2.91 – 3.05 (m, 1H), 3.06 – 3.20 (m, 1H), 3.69 (s, 3H), 3.93 (m, 1H), 4.17 (m, 1H), 5.70 (s, 1H). MS m/z 283 $(M+H)^+$.

Step 2: Cis-5-(2-isobutylpiperidin-4-yl)isoxazol-3(2H)-one
Racemic cis-methyl 2-isobutyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.29 g, 1.03 mmol) was stirred in HBr (12 mL, 33% in HOAc) for 24 h. The volatiles were concentrated and the residue purified by preparative HPLC on a XBridge C18 column (10 µm 250x50 ID mm) using a gradient of 0-25% acetonitrile in H_2O/MeCN/NH_3 95/5/0.2 buffer over 10 minutes with a flow of 100 mL/min. The title compound (160 mg) was isolated. ^{1}H NMR (600 MHz, d_2o) δ 0.79 (2 d, 6H), 1.34 – 1.51 (m, 3H), 1.54 – 1.72 (m, 2H), 2.13 (m, 1H), 2.25 (m, 1H), 2.99 (m, 2H), 3.21 (m, 1H), 3.38 (m, 1H), 5.61 (s, 1H).

Step 3: 5-((2S,4S)-2-Isobutylpiperidin-4-yl)isoxazol-3(2H)-one

A racemic mixture of cis-5-(2-isobutylpiperidin-4-yl)isoxazol-3(2H)-one was subjected to chiral separation using Chiralpak IC, mobile phase heptane/EtOH/FA/TEA 60/40/0.4/0.2 which resulted in the title compound (85 mg, 37%). $[\alpha]^{20}_{D}$ +19.5 (H_2O, c = 1); HRMS Calculated for $[C_{12}H_{21}N_2O_2]$+: 225.1603; found: 225.1593

Example 8

5-((2R,4S)-2-Phenethylpiperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-phenethylpiperidine-1-carboxylate and cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-phenethylpiperidine-1-carboxylate

The compounds were prepared as described in Example 1, Step 1 starting from crude 1-(methoxycarbonyl)-2-phenethylpiperidine-4-carboxylic acid (5.7 g, 19.6 mmol) (Reference Compound 3), magnesium chloride (1.86 g, 19.6 mmol), ethyl potassium malonate (4.99 g, 29.3 mmol) and carbonyldiimidazole (3.81 g, 23.5 mmol) which resulted in trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-phenethylpiperidine-1-carboxylate (2.56 g, 36 %) and cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-phenethylpiperidine-1-carboxylate (0.29 g, 4 %). Trans isomer: ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.28 (m, 3H), 1.49 (m, 1H), 1.60 – 1.93 (m, 4H), 2.01 (m, 1H), 2.57 (m, 2H), 2.84 (m, 2H), 3.42 (m, 2H), 3.69 (s, 3H), 4.00 – 4.63 (m, 4H), 7.08 – 7.41 (m, 5H). MS m/z 362 $(M+H)^+$. Cis isomer: ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.25 (t, 3H), 1.63 – 1.82 (m, 3H), 1.91 (m, 3H), 2.00 – 2.12 (m, 1H), 2.53 – 2.66 (m, 2H), 2.71 (m, 1H), 3.09 (m, 1H), 3.49 (s, 2H), 3.69 (s, 3H), 3.89 (m, 1H), 4.08 (m, 1H), 4.17 (q, 2H), 7.15 – 7.31 (m, 5H). MS m/z 362 $(M+H)^+$.

Step 2: Trans-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-phenethylpiperidine-1-carboxylate

The compounds were prepared as described in Example 1, Step 2 starting from trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-phenethylpiperidine-1-carboxylate (2.53 g, 7.0 mmol) which resulted in the title compound (1.35 g, 58%). ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.55 (m, 1H), 1.79 (m, 2H), 2.03 (m, 3H), 2.58 (m, 2H), 3.01 (m, 2H), 3.70 (s, 3H), 4.01 – 4.60 (m 2H), 5.62 (s, 1H), 7.05 – 7.40 (m, 5H). MS m/z 331 $(M+H)^+$.

Step 3: (2R,4S)-Methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-phenethylpiperidine-1-carboxylate

As described in Example 1, Step 3, racemic trans-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-phenethylpiperidine-1-carboxylate (1.35 g, 4.09 mmol) was subjected to chiral separation using Chiralpak AD, mobile phase heptane/EtOH/TEA 80/20 at 30°C which resulted in (2R,4S)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-phenethylpiperidine-1-carboxylate (0.53 g, 1.6 mmol)

Step 4: 5-((2R,4S)-2-Phenethylpiperidin-4-yl)isoxazol-3(2H)-one

Starting from (2R,4S)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-phenethylpiperidine-1-carboxylate (0.53 g) and following the procedure in Example 1, Step 4 the title compound was obtained (0.30 g, 28%). ^{1}H NMR (600 MHz, dmso) δ 1.47 (m, 1H), 1.55 (m, 1H), 1.62 (m, 1H), 1.70 (m, 2H), 1.86 (m, 1H), 2.58 (m, 4H), 2.76 (m, 1H), 3.06 (m, 1H), 5.70 (s, 1H), 7.15 – 7.32 (m, 5H). $[\alpha]^{20}_D$ +24.6 (MeOH/H_2O 1:1, c = 1); HRMS calculated for $[C_{16}H_{21}N_2O_2]$+: 273.1603; found: 273.1598.

Example 9

5-((2S,4R)-2-Phenethylpiperidin-4-yl)isoxazol-3(2H)-one

Step 1: (2S,4R)-Methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-phenethylpiperidine-1-carboxylate

The title compound was obtained from the preparation in Example 8, Step 3 (0.62 g, 1.87 mmol).

Step 2: 5-((2S,4R)-2-Phenethylpiperidin-4-yl)isoxazol-3(2H)-one

Following the same procedure as described in Example 8, step 4 and starting from (2S,4R)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-phenethylpiperidine-1-carboxylate yielded the title compound (0.62 g, 24%): $[\alpha]^{20}_D$ –23.0 (MeOH/H_2O 1:1, c = 1); HRMS calculated for $[C_{16}H_{21}N_2O_2]$+: 273.1603; found: 273.1592.

Example 10

5-((2S,4S)-2-Phenethylpiperidin-4-yl)isoxazol-3(2H)-one

Step 1: Cis-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-phenethylpiperidine-1-carboxylate

The compound was prepared as described in Example 1, Step 2 starting from cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-phenethylpiperidine-1-carboxylate from Example 8, Step 1 (0.29 g, 0.82 mmol) resulting in the title compound (0.07 g, 26%). ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.65 (m, 1H), 1.79 – 2.14 (m, 5H), 2.60 (m, 2H), 3.00 (m, 1H), 3.20 (m, 1H), 3.70 (s, 3H), 3.92 (m, 1H), 4.10 (m, 1H), 5.71 (s, 1H), 7.10 – 7.29 (m, 5H); MS m/z 331 $(M+H)^+$.

Step 2: (2S,4S)-Methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-phenethylpiperidine-1-carboxylate

Following the procedure described in Example 1, Step 3, racemic cis-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-phenethylpiperidine-1-carboxylate (0.07 g, 0.22 mmol) was subjected to chiral separation using Chiralcel IC, mobile phase heptane/IPA 80/20 at 40°C which resulted in (2S,4S)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-phenethylpiperidine-1-carboxylate (0.032 g, 0.1 mmol) and (2R,4R)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-phenethylpiperidine-1-carboxylate (0.03 g, 0.09 mmol).

Step 3: 5-((2S,4S)-2-Phenethylpiperidin-4-yl)isoxazol-3(2H)-one

Starting from (2S,4S)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-phenethylpiperidine-1-carboxylate (0.032 g) and following the procedure described in Example 1, Step 4 could the title compound be obtained (12.6 mg, 21%): ^{1}H NMR (400 MHz, dmso) δ 1.15 (m, 1H), 1.38 (m, 1H), 1.60 (m, 2H), 1.79 (m, 1H), 1.95 (m, 1H), 2.45 – 2.75 (m, 5H), 3.05 (m, 1H), 5.77 (s, 1H), 7.15 – 7.30 (m, 5H). $[\alpha]^{20}_D$ +54.1 (MeOH/H_2O 1:1, c = 1); HRMS calculated for $[C_{16}H_{21}N_2O_2]$+: 273.1603; found: 273.1601.

Example 11

5-((2S,4S)-2-(4-tert-Butylbenzyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(4-tert-butylbenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate and cis-methyl 2-(4-tert-butylbenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate

The compounds were prepared as described in Example 1, Step 1 starting from crude 2-(4-tert-butylbenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (3.07 g, 9.2 mmol) (Reference Compound 4), magnesium chloride (0.88 g, 9.2 mmol) and ethyl potassium malonate (2.35 g, 13.8 mmol) and subsequently carbonyldiimidazole (1.98 g, 12.2 mmol) which resulted in trans-methyl 2-(4-tert-butylbenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (0.55 g, 15 %) and cis-methyl 2-(4-tert-butylbenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (1.65 g, 44%). Trans isomer: ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.08 – 1.32 (m, 12H), 1.32 –1.78 (m, 4H), 2.53 – 3.06 (m, 4H), 3.30 – 3.62 (m, 5H), 3.93 – 4.61 (m, 4H), 7.03 – 7.36 (m, 4H); MS m/z 404 $(M+H)^+$. Cis isomer: ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.21 – 1.35 (m, 12H), 1.59 – 1.79 (m, 1H), 1.79 – 1.99 (m, 3H), 2.69 (m, 2H), 2.84 – 2.94 (m, 1H), 2.94 – 3.07 (m, 1H), 3.45 (s, 2H), 3.61 (m, 3H), 3.92 (m, 1H), 4.08 – 4.22 (m, 3H), 7.09 (m, 2H), 7.25 – 7.32 (m, 2H); MS m/z 404 $(M+H)^+$.

Step 2: Trans-methyl 2-(4-tert-butylbenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

The compound was prepared as described in Example 1, Step 2 starting from trans-methyl 2-(4-tert-butylbenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (0.54 g, 1.34 mmol) which resulted in trans-methyl 2-(4-tert-butylbenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.24 g, 48 %); ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.29 (s, 9H), 1.41 – 1.60 (m, 2H), 1.89 – 2.09 (m, 2H), 2.87 (m, 2H), 3.03 – 3.20 (m, 2H), 3.42 - 3.73 (m, 3H), 4.06 – 4.32 (m, 1H), 4.45 – 4.77 (m, 1H), 5.63 (s, 1H), 7.02 – 7.17 (m, 2H), 7.31 (m, 2H); MS m/z 373 $(M+H)^+$.

Step 3: (2S,4S)-Methyl 2-(4-tert-butylbenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Following the procedure described in Example 1, Step 3, racemic trans-methyl 2-(4-tert-butylbenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.24 g, 0.64 mmol) was subjected to chiral separation using Chiralcel AD, mobile phase heptane/EtOH/FA 80/20/0.1 which resulted in (2S,4S)-methyl 2-(4-tert-butylbenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.106 g, 0.28 mmol).

Step 4: 5-((2S,4S)-2-(4-tert-Butylbenzyl)piperidin-4-yl)isoxazol-3(2H)-one

Starting from (2S,4S)-methyl 2-(4-tert-butylbenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.106 g, 0.28 mmol) and following the procedure described in Example 1, Step 4 the title compound (50.3 mg, 25 %) was obtained: ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.29 (s, 9H), 1.43 – 1.74 (m, 1H), 1.81 – 2.07 (m, 3H), 2.60 (m, 3H), 2.82 (m, 2H), 3.11 (m, 1H), 5.71 (s, 1H), 7.08 (d, 2H), 7.27 (d, 2H); $[\alpha]^{20}_D$ +56.7 (MeOH/H_2O 1:1, c = 1); HRMS calculated for $[C_{19}H_{27}N_2O_2]$+: 315.2072; found: 315.2069.

Example 12

5-((2R,4S)-2-(4-tert-Butylbenzyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Cis-methyl 2-(4-tert-butylbenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

The compounds were prepared as described in Example 1, Step 2 by starting from cis-methyl 2-(4-tert-butylbenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (1.64 g, 4.06 mmol) that resulted in cis-methyl 2-(4-tert-butylbenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate (0.69 g, 47 %). ^{1}H NMR (500 MHz, cdcl$_3$) δ 1.31 (s, 9H), 1.84 – 1.93 (m, 2H), 1.96 (m, 1H), 2.10 (m, 1H), 2.62 (m, 1H), 2.82 (m, 2H), 2.97 (m, 1H), 3.08 – 3.24 (m, 1H), 3.62 (s, 3H), 4.02 (m, 1H), 4.18 – 4.34 (m, 1H), 5.73 (s, 1H), 7.06 (m, 2H), 7.23 – 7.38 (m, 2H). MS m/z 373 $(M+H)^+$.

Step 2: (2R,4S)-Methyl 2-(4-tert-butylbenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Following the procedure described in Example 1, Step 3, racemic cis-methyl 2-(4-tert-butylbenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.69 g, 1.85 mmol) was subjected to chiral separation using Chiralcel AD, mobile phase heptane/EtOH/FA 80/20/0.1 which resulted in (2R,4S)-methyl 2-(4-tert-butylbenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.32 g, 0.86 mmol).

Step 3: 5-((2R,4S)-2-(4-tert-Butylbenzyl)piperidin-4-yl)isoxazol-3(2H)-one

Using (2R,4S)-methyl 2-(4-tert-butylbenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.32 g, 0.86 mmol) and following the procedure described in Example 1, Step 4 the title compound could be obtained (0.125 g, 22 %). ^{1}H NMR (600 MHz, dmso) δ 1.05 (m, 1H), 1.23 (m, 9H), 1.34 (m, 1H), 1.74 (m, 2H), 2.50 – 2.80 (m, 5H), 2.96 (m, 1H), 5.63 (s, 1H), 7.08 (m, 2H), 7.27 (m, 2H). $[\alpha]^{20}_D$ –7.5 ($CHCl_3$ c = 0.2). HRMS calculated for $[C_{19}H_{27}N_2O_2]$+: 315.2072; found: 315.2058.

Example 13

5-((2S,4S)-2-Neopentylpiperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-neopentylpiperidine-1-carboxylate

The compound was prepared as described in Example 1, Step 1 starting from crude 1-(methoxycarbonyl)-2-neopentylpiperidine-4-carboxylic acid (4.95 g, 19.2 mmol) (Reference Compound 5), magnesium chloride (2.381 g, 25.01 mmol), ethyl potassium malonate (5.57 g, 32.70 mmol) and carbonyldiimidazole (3.74 g, 23.08 mmol) which resulted in cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-neopentylpiperidine-1-carboxylate (2.40 g, 38 %) and trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-neopentylpiperidine-1-carboxylate (1.2 g, 19 %). Cis-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 0.93 (m, 9H), 1.18 (m, 1H), 1.28 (t, 3H), 1.52 – 1.65 (m, 1H), 1.65 – 1.83 (m, 2H), 1.89 (m, 1H), 2.12 (m, 1H), 2.69 (m, 1H), 3.11 (m, 1H), 3.52 (s, 2H), 3.69 (s, 3H), 3.87 (m, 1H), 4.15 – 4.24 (m, 2H), 4.27 (m, 1H); MS m/z 328 $(M+H)^+$.

Step 2: Trans-methyl 2-neopentyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

The compounds were prepared as described in Example 1, Step 2 starting from trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-neopentylpiperidine-1-carboxylate (4.49 g, 13.7 mmol) that resulted in trans-methyl 2-neopentyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.26 g, 31 %). ^{1}H NMR (600 MHz, cdcl$_3$) δ 0.94 (s, 9H), 1.34 (m, 1H), 1.40 – 1.62 (m, 1H), 1.71 (m, 2H), 1.83 (m, 1H), 1.97 (m, 1H), 3.05 (m, 2H), 3.70 (s, 3H), 4.01 – 4.31 (m, 1H), 4.44 – 4.74 (m, 1H), 5.62 (s, 1H). MS m/z 297 $(M+H)^+$.

Step 3: (2S,4S)-Methyl 2-neopentyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Following the procedure described in Example 1, Step 3, racemic trans-methyl 2-neopentyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.26 g, 4.26 mmol) was subjected to chiral separation using Chiralcel OD, mobile phase heptane/IPA/FA 80/20/0.1 which resulted in (2S,4S)-methyl 2-neopentyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.64 g, 2.16 mmol)

Step-4: (2S,4S)-5-(2-Neopentylpiperidin-4-yl)isoxazol-3(2H)-one

Starting from (2S,4S)-methyl 2-neopentyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.64 g, 2.16 mmol) and following the procedure described in Example 1, Step 4 the title compound (0.44 g, 85 %) was obtained: ^{1}H NMR (600 MHz, dmso) δ 0.86 (s, 9H), 1.17 (dd, 1H), 1.27 (dd, 1H), 1.45 (m, 1H), 1.68 (m, 2H), 1.81 (m, 1H), 2.59 (m, 1H), 2.67 (m, 1H), 2.73 (m, 1H), 3.04 (m, 2H), 5.71 (s, 1H); $[\alpha]^{20}_D$ +18.4 (MeOH/H_2O 1:1, c = 1); HRMS calculated for $[C_{13}H_{23}N_2O_2]$+: 239.1759; found: 239.1742.

Example 14

5-((2R,4S)-2-Neopentylpiperidin-4-yl)isoxazol-3(2H)-one

Step 1: Cis-methyl 2-neopentyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

The compound was prepared as described in Example 1, Step 2 starting from cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-neopentylpiperidine-1-carboxylate (2.68 g, 8.19 mmol) which resulted in cis-methyl 2-neopentyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.60 g, 66 %) : 1H NMR (400 MHz, cdcl3) δ 0.89 (s, 9H), 1.18 (dd, 1H), 1.45 (dd, 1H), 1.80 - 1.92 (m, 2H), 1.97 - 2.17 (m, 2H), 2.94 - 3.02 (m, 1H), 3.11 - 3.23 (m, 1H), 3.71 (s, 3H), 3.88 - 3.99 (m, 1H), 4.22 - 4.32 (m, 1H), 5.72 (s, 1H); m/z (MH^+) 297.

Step 2: (2R,4S)-Methyl 2-neopentyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Following the procedure described in Example 1, Step 3, racemic cis-methyl 2-neopentyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.60 g, 5.4 mmol) was subjected to chiral separation using Chiralcel IC mobile phase heptane/IPA/FA 60/40/0.1 which resulted in

(2R,4S)-methyl 2-neopentyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.8 g, 2.7 mmol).

Step 3: 5-((2R,4S)-2-Neopentylpiperidin-4-yl)isoxazol-3(2H)-one

Starting from (2R,4S)-methyl 2-neopentyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.8 g, 2.7 mmol) and following the procedure described in Example 1, Step 4 the title compound was obtained (0.44 g, 69 %): ^{1}H NMR (600 MHz, DMSO-d6) δ 0.89 (s, 9H), 1.18 (m, 2H), 1.50 (m, 2H), 1.82-1.90 (m, 2H), 2.70-2.85 (m, 3H), 3.08 (m, 1H), 5.71 (s, 1H). $[\alpha]^{20}_D$ +43.8 (MeOH/H_2O 1:1, c = 1); HRMS calculated for $[C_{13}H_{23}N_2O_2]$+: 239.1759; found: 239.1753.

Example 15

5-((2R,4S)-2-Methylpiperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-methylpiperidine-1-carboxylate and cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-methylpiperidine-1-carboxylate

The compounds were prepared as described in Example 1, Step 1 starting from crude 1-(methoxycarbonyl)-2-methylpiperidine-4-carboxylic acid (0.90 g, 4.47 mmol) (Reference Compound 6), magnesium chloride (0.42 g, 4.47 mmol) and ethyl potassium malonate (1.14 g, 6.71 mmol) and subsequently carbonyldiimidazole (0.87 g, 5.47 mmol) which resulted in trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-methylpiperidine-1-carboxylate (0.31 g, 26 %) and cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-methylpiperidine-1-carboxylate (0.50 g, 41 %). Trans isomer: ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.18 (dd, 3H), 1.23 – 1.31 (m, 3H), 1.47 (m, 1H), 1.65 – 1.78 (m, 2H), 1.85 (m, 1H), 2.82 (m, 1H), 2.91 (m, 1H), 3.48 (s, 2H), 3.68 (s, 3H), 3.99 – 4.14 (m, 1H), 4.15 – 4.23 (m, 2H), 4.57 (m, 1H). Cis isomer: ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.13 (d, 3H), 1.22 – 1.32 (m, 3H), 1.63 – 1.73 (m, 1H), 1.78 – 1.94 (m, 2H), 1.95 – 2.07 (m, 1H), 2.67 – 2.76 (m, 1H), 3.04 – 3.16 (m, 1H), 3.50 (s, 2H), 3.68 (s, 3H), 3.79 – 3.91 (m, 1H), 4.12 (m, 1H), 4.15 (m, 2H).

Step 2: Trans-methyl 2-methyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

The compound was prepared as described in Example 1, Step 2 starting from trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-methylpiperidine-1-carboxylate (0.31 g, 1.15 mmol) which resulted in trans methyl 2-methyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.149 g, 54 %); ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.21 (m, 3H), 1.49 – 1.59 (m, 1H), 1.76 (m, 1H), 1.86 (m, 1H), 1.99 (m, 1H), 3.02 (m, 2H), 3.69 (m, 3H), 4.13 (m, 1H), 4.59 (m, 1H), 5.64 (s, 1H). MS m/z 241 $(M+H)^+$.

Step 3: (2R,4S)-Methyl 2-methyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Following the procedure described in Example 1, Step 3, racemic trans methyl 2-methyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.149 g, 0.62 mmol) was subjected to chiral separation using Chiralcel OJ, mobile phase heptane/EtOH 80/20 at 22°C which resulted in (2R,4S)-methyl 2-methyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.051 g, 0.21 mmol).

Step 4: 5-((2R,4S)-2-Methylpiperidin-4-yl)isoxazol-3(2H)-one

Starting from (2R,4S)-methyl 2-methyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.051 g, 0.21 mmol) and following the procedure described in Example 1, Step 4 the title compound was obtained (32 mg, 84 %). ^{1}H NMR (600 MHz, cd3od) δ 1.31 (d, 3H), 1.79 - 1.89 (m, 1H), 2.02 - 2.25 (m, 3H), 3.04 - 3.13 (m, 1H), 3.26 (d, 2H), 3.38 (m, 1H), 5.66 (s, 1H); $[\alpha]^{20}_D$ +8.4 (MeOH/H_2O 1:1, c = 1)

Example 16

5-((2S,4R)-2-Methylpiperidin-4-yl)isoxazol-3(2H)-one

Step-1: (2S,4R)-Methyl 2-methyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

The title compound was obtained from Example 15, Step 3 (62 mg, 0.26 mmol).

Step 2: 5-((2S,4R)-2-Methylpiperidin-4-yl)isoxazol-3(2H)-one

Using the same procedure as described in Example 1, Step 4 and starting from (2S,4R)-methyl 2-methyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (62 mg , 0.26 mmol) the title compound was obtained (30 mg, 64 %).

Example 17

5-((2S,4S)-2-Methylpiperidin-4-yl)isoxazol-3(2H)-one

Step 1: Cis-methyl 2-methyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

The compound was prepared as described in Example 1, Step 2 starting from cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-methylpiperidine-1-carboxylate (0.49 g, 1.83 mmol), which resulted in cis-methyl 2-methyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.23 g, 52%); ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.08 (d, 3H), 1.86 (m, 2H), 2.05 (m, 2H), 2.96 – 3.02 (m, 1H), 3.12 – 3.30 (m, 1H), 3.69 (s, 3H), 3.83 – 3.99 (m, 1H), 4.19 (m, 1H), 5.70 (s, 1H); MS m/z 241 $(M+H)^+$.

Step 2: (2S,4S)-Methyl 2-methyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Following the procedure described in Example 1, Step 3, racemic cis-methyl 2-methyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.23 g, 0.96 mmol) was subjected to chiral separation using Chiralcel IC, mobile phase heptane/IPA 70/30 which resulted in (2S,4S)-methyl 2-methyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.101 g, 0.42 mmol).

Step 3: 5-((2S,4S)-2-Methylpiperidin-4-yl)isoxazol-3(2H)-one

Starting from (2S,4S)-methyl 2-methyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.101 g, 0.42 mmol) and following the procedure described in Example 1, Step 4 the title compound was obtained (0.046 g, 60 %) ^{1}H NMR (600 MHz, cd3od) δ 1.32 - 1.44 (d, 3H), 1.65 (m, 1H), 1.84 (m, 1H), 2.24 (m, 2H), 3.08 - 3.23 (m, 2H), 3.34 - 3.52 (m, 2H), 5.82 (s, 1H).; $[\alpha]^{20}_D$ +0 (MeOH/H_2O 1:1, c = 1).

Example 18

5-((2S,4S)-2-(2-Methyl-2-phenylpropyl)piperidin-4-yl)isoxazol-3(2H)-one

Step1: Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(2-methyl-2-phenylpropyl)piperidine-1-carboxylate and cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(2-methyl-2-phenylpropyl)-piperidine-1-carboxylate

The compounds were prepared as described in Example 1, Step 1 starting from crude 1-(methoxycarbonyl)-2-(2-methyl-2-phenylpropyl)piperidine-4-carboxylic acid (7.24 g, 22.7 mmol) (Reference compound 7), magnesium chloride (2.16 g, 22.7 mmol) and ethyl potassium malonate (5.79 g, 34 mmol) and subsequently carbonyldiimidazole (4.41 g, 27.2 mmol) which gave trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(2-methyl-2-phenylpropyl)piperidine-1-carboxylate (1.59 g, 18 %) and cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(2-methyl-2-phenylpropyl)piperidine-1-carboxylate (2.38 g, 27 %). Trans isomer: ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.20 – 1.50 (m, 10H), 1.59 – 1.84 (m, 2H), 1.90 (m, 2H), 2.50 – 2.89 (m, 2H), 3.16 (m, 2H), 3.58 (m, 4H), 4.17 (m, 4H), 7.06 – 7.51 (m, 5H). Cis isomer: ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.20 – 1.41 (m, 10H), 1.57 – 1.74 (m, 3H), 1.79 (d, 1H), 2.03 (m, 1H), 2.53 (m, 1H), 2.83 – 3.02 (m, 1H), 3.40 (m, 2H), 3.48 – 3.68 (m, 4H), 4.03 (m, 1H), 4.12 – 4.22 (m, 2H), 7.18 – 7.44 (m, 5H).

Step 2: Trans-methyl 2-(2-methyl-2-phenylpropyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate

The compound was prepared as described in Example 1, Step 2 starting from trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(2-methyl-2-phenylpropyl)piperidine-1-carboxylate (1.58 g, 4.06 mmol) which resulted in trans-methyl 2-(2-methyl-2-phenylpropyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.82 g, 56 %); ^{1}H NMR (600 MHz, cdcl3) δ 1.29 - 1.65 (m, 6H), 1.67 - 1.98 (m, 4H), 2.10 (m, 2H), 2.88 (m, 2H), 3.57 (s, 3H), 3.70 - 4.18 (m, 1H), 4.18 - 4.67 (m, 1H), 5.45 (s, 1H), 7.17-7.31 (m, 5H); MS m/z 359 $(M+H)^+$.

Step 3: (2S,4S)-methyl 2-(2-methyl-2-phenylpropyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate

Racemic trans-methyl 2-(2-methyl-2-phenylpropyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate (0.82 g, 2.28 mmol) was subjected to chiral separation using Chiralcel IC, mobile phase heptane/IPA 80/20 at 40°C which resulted in (2S,4S)-methyl 2-(2-methyl-2-phenylpropyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.361 g, 1.01 mmol).

Step 4: 5-((2S,4S)-2-(2-methyl-2-phenylpropyl)piperidin-4-yl)isoxazol-3(2H)-one

Starting from (2S,4S)-methyl 2-(2-methyl-2-phenylpropyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.361 g, 1.01 mmol) and following the procedure described in Example 1, Step 4 the title compound was obtained (0.21 g, 69 %) ^{1}H NMR (600 MHz, dmso) δ 1.24 (m, 7H), 1.45 (m, 1H), 1.59 (m, 2H), 1.69 (m, 2H), 2.42 (m, 1H), 2.59 (m, 2H), 2.87 (m, 1H), 5.36 (s, 1H), 7.12 (m, 1H), 7.21 - 7.36 (m, 4H).; $[\alpha]^{20}_D$ +66.7 (MeOH/H_2O 1:1, c = 1); HRMS Calculated for $[C_{18}H_{25}N_2O_2]$+: 301.1916; found: 301.1888.

Example 19

5-((2R,4S)-2-(2-Methyl-2-phenylpropyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Cis-methyl 2-(2-methyl-2-phenylpropyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate

The compound was prepared as described in Example 1, Step 2 starting from cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(2-methyl-2-phenylpropyl)piperidine-1-carboxylate (2.38 g, 6.11 mmol) which resulted in cis-methyl 2-(2-methyl-2-phenylpropyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.93 g, 42 %); ^{1}H NMR (500 MHz, cdcl3) δ 1.31 (s, 3H), 1.37 (s, 3H), 1.53 - 1.67 (m, 2H), 1.77 (m, 2H), 1.90 - 2.01 (m, 2H), 2.80 - 2.91 (m, 1H), 2.95 - 3.06 (m, 1H), 3.60 (s, 3H), 3.69 (m, 1H), 4.01 - 4.15 (m, 1H), 5.63 (s, 1H), 7.17 (m, 1H), 7.30 (m, 4H); MS m/z 359 $(M+H)^+$.

Step 2: (2R,4S)-Methyl 2-(2-methyl-2-phenylpropyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Racemic cis-methyl 2-(2-methyl-2-phenylpropyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate (0.93 g, 2.59 mmol) was subjected to chiral separation using Chiralcel IC, mobile phase heptane/IPA 80/20 at the temperature 40°C which resulted in (2R,4S)-methyl 2-(2-methyl-2-phenylpropyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.432 g, 1.21 mmol).

Step 3: 5-((2R,4S)-2-(2-Methyl-2-phenylpropyl)piperidin-4-yl)isoxazol-3(2H)-one

Starting from (2R,4S)-methyl 2-(2-methyl-2-phenylpropyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.432 g, 1.21 mmol) and following the procedure described in Example 1, Step 4 the title compound was obtained (0.16 g, 43 %); ^{1}H NMR (600 MHz, dmso) δ 1.08 (m, 1H), 1.28 (s, 3H), 1.34 (m, 4H), 1.46 (m, 1H), 1.76 - 1.83 (m, 1H), 1.83 - 1.97 (m, 2H), 2.73 (m, 1H), 2.86 (m, 1H), 2.97 (m, 1H), 3.17 (m, 1H), 5.46 (s, 1H), 7.16 (m, 1H), 7.28 (m, 2H), 7.35 (m, 2H); $[\alpha]^{20}_D$ +57.9 (MeOH/H_2O 1:1, c = 1); HRMS Calculated for $[C_{18}H_{25}N_2O_2]$+: 301.1916; found: 301.1892.

Example 20

5-((2R,4S)-2-(Cyclohexylmethyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Methyl 2-(cyclohexylmethyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate

Ethyl potassium malonate (1.75 g, 10.3 mmol) and $MgCl_2$ (0.665 g, 6.88 mmol) were added to dry THF (50 mL). The reaction flask was stirred vigorously 4 h at 50°C (flask 1). 2-(Cyclohexylmethyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (1.95 g, 6.88 mmol) (Reference Compound 8) and carbonyldiimidazole (1.34 g, 8.26 mmol) were added to dry THF (50 mL) at 5°C (flask 2). The contents of flask 2 was added to flask 1 at room temperature. The reaction mixture was evaporated to remove most of the THF. The crude was partitioned between water and diethyl ether. The organic phase was isolated, dried with $MgSO_4$, filtered through Celite® and the solvent was evaporated. The residue was purified by automated column chromatography using the Biotage equipment. Gradient eluation using ethylacetate-heptane, started 15-85 and ended 40-60 which gave trans-methyl 2-(cyclohexylmethyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (0.38 g, 16 %) and cis-methyl 2-(cyclohexylmethyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (1.28 g, 53 %). Trans-isomer: ^{1}H NMR (600 MHz, cdcl$_3$) δ 0.88 (d, 2H), 0.99 – 1.32 (m, 8H), 1.38 – 1.56 (m, 2H), 1.68 (dd, 8H), 2.80 (t, 2H), 3.45 (s, 2H), 3.66 (s, 3H), 3.93 – 4.21 (m, 3H), 4.47 (d, 1H). Cis-isomer ^{1}H NMR (600 MHz, cdcl$_3$) δ 0.72 – 0.95 (m, 2H), 1.04 – 1.31 (m, 8H), 1.38 – 1.49 (m, 1H), 1.53 – 1.69 (m, 6H), 1.70 – 1.92 (m, 3H), 2.02 (dt, 1H), 2.61 – 2.71 (m, 1H), 2.95 – 3.07 (m, 1H), 3.48 (s, 2H), 3.66 (s, 3H), 3.85 (dd, 1H), 4.09 – 4.21 (m, 3H).

Step 2: (2R,4S)-Methyl 2-(cyclohexylmethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

A solution of methyl 2-(cyclohexylmethyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (1.5 g, 4.2 mmol) in MeOH (4 mL) was added to a solution of NaOH (221 mg, 5.5 mmol) in MeOH/H_2O (4 mL/ 0.25 mL) at -30°C. After 10 minutes was added hydroxylamine-HCl (0.59 g, 8.5 mmol) and NaOH (0.339 g, 8.5 mmol) in MeOH (5 mL) and H_2O (5 mL). Stirring was continued at -30°C for 30 minutes. The reaction solution was poured into 6M HCl (6 mL) at 80°C and heated for 30 minutes. The reaction mixture was partitioned between water and ethyl acetate. The organic phase was isolated, dried with Na_2SO_4, filtered through Celite® and the solvent was evaporated. Crude 1.7 g. Purification using reversed phase chromatography, which gave 0.3 g, yield 22%. Chiral separation using Chiralcel OJ, mobile phase heptane/ethanol 80/20 at 40°C gave of (2R,4S)-methyl 2-(cyclohexylmethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.11 g). ^{1}H NMR (600 MHz, cdcl$_3$) δ 0.91 (d, 2H), 1.06 – 1.39 (m, 5H), 1.68 (dt, 7H), 1.85 (s, 2H), 1.94 (s, 1H), 2.99 (t, 2H), 3.68 (s, 3H), 4.11 (d, 1H), 4.50 (d, 1H), 5.60 (s, 1H). $[\alpha]^{20}_D$ +3.2 (MeCN, c = 1).

Step 3: 5-((2R,4S)-2-(Cyclohexylmethyl)piperidin-4-yl)isoxazol-3(2H)-one

HBr (33 % in acetic acid) (7 mL) was added to a reaction flask containing (2R,4S)-methyl 2-(cyclohexylmethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.11 g, 0.34 mmol). The reaction was stirred vigorously overnight. The solvent was evaporated. Purification using preparative HPLC (pH=11, small column, sample dissolved in methanol/ water (50/50), gradient 0-40, 20 minutes) gave the title compound (62 mg, yield 69 %). ^{1}H NMR (600 MHz, cd$_3$od) δ 0.94 (s, 2H), 1.18 (s, 1H), 1.27 (s, 2H), 1.35 – 1.55 (m, 3H), 1.57 – 1.80 (m, 6H), 2.01 (s, 1H), 2.13 (s, 1H), 2.24 (s, 1H), 3.09 (s, 1H), 3.22 (s, 3H), 5.53 (s, 1H).

Example 21

5-((2R,4R)-2-(Cyclohexylmethyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: (2R,4R)-Methyl 2-(cyclohexylmethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate and (2S,4S)-Methyl 2-(cyclohexylmethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate

A solution of cis-methyl 2-(cyclohexylmethyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate, from a preparation of Example 20, Step 1 (1.28 g, 3.62 mmol) in MeOH (3 mL) was added dropwise to a solution of NaOH (0.159 g) in MeOH/H_2O (3 mL/0.2 mL) at -30°C. After stirring for 10 minutes a solution of hydroxylamine hydrochloride (0.50 g, 7.24 mmol) and NaOH (0.29 g, 7.24 mmol) in methanol/water (5 mL/5 mL) was added at -30°C. Stirring was continued for 30 minutes at -30°C. The solution was added dropwise to HCl (6M) at 80°C. Stirred 30 minutes at 80°C. The reaction mixture was partitioned between water and ethyl acetate. The organic phase was isolated, dried with Na_2SO_4, filtered through Celite® and the solvent was evaporated. Acidic reversed phase chromatography, gradient 35% to 75% acetonitrile gave cis-methyl 2-(cyclohexylmethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.62 g, 53.1 %). Chiral separation using Chiralpac IC, mobile phase heptane/isopropyl alcohol 80/20 at the temperature 40°C gave (2R,4R)-methyl 2-(cyclohexylmethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.28g), e.e. 98.5% and (2S,4S)-methyl 2-(cyclohexylmethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.27 g), e.e 98.5%. ^{1}H NMR (600 MHz, cdcl$_3$, RR) δ 0.67 – 0.88 (m, 2H), 0.98 – 1.20 (m, 5H), 1.28 (dd, 1H), 1.56 (dd, 5H), 1.75 – 1.86 (m, 2H), 1.92 – 2.06 (m, 2H), 2.87 – 2.99 (m, 1H), 3.02 – 3.15 (m, 1H), 3.65 (s, 3H), 3.88 (dd, 1H), 4.15 (p, 1H), 5.65 (d, 1H). $[\alpha]^{20}_D$ -30.7 (MeCN, c = 1); ^{1}H NMR (600 MHz, cdcl$_3$, SS) δ 0.70 – 0.87 (m, 2H), 0.97 – 1.20 (m, 5H), 1.28 (dd, 1H), 1.51 – 1.65 (m, 5H), 1.77 – 1.85 (m, 2H), 1.96 – 2.05 (m, 2H), 2.87 – 2.96 (m, 1H), 3.03 – 3.14 (m, 1H), 3.65 (s, 3H), 3.88 (dd, 1H), 4.15 (p, 1H), 5.65 (d, 1H) $[\alpha]^{20}_D$ +29.9 (MeCN, c = 1).

Step 2: 5-((2R,4R)-2-(Cyclohexylmethyl)piperidin-4-yl)isoxazol-3(2H)-one

HBr (33 % in acetic acid) (5 mL) was added to (2R,4R)-methyl 2-(cyclohexylmethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.28g, 0.87mmol). The reaction was stirred vigorously overnight. The solvent was evaporated. Purification using PrepLC (pH=11, small column, no sandwitching, sample dissolved in methanol/water (50/50), gradient 15-55, 20 minutes). The title compound (57 mg, 25 %) was obtained. ^{1}H NMR (400 MHz, cd$_3$od) δ

0.78 – 0.95 (m, 2H), 1.17 (dd, 3H), 1.28 – 1.48 (m, 4H), 1.63 (dd, 6H), 2.04 (d, 1H), 2.12 (d, 1H), 2.85 (t, 1H), 2.96 (dd, 1H), 3.13 (s, 1H), 3.31 (d, 1H), 5.40 (s, 1H).

Example 22

5-((2S,4S)-2-(Cyclohexylmethyl)piperidin-4-yl)isoxazol-3(2H)-one

HBr (33 % in acetic acid) (5 mL) was added to (2S,4S)-methyl 2-(cyclohexylmethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate, from a preparation of example 21, step 1 (0.27g, 0.85 mmol). The reaction was stirred vigorously overnight. The solvent was evaporated. Purification using PrepLC (pH=11, small column, sample dissolved in acetonitrile/water (40/60), gradient 15-55, 20 minutes) gave the title compound (75 mg, 33 %). ^{1}H NMR (600 MHz, cd_3od) δ 0.80 – 0.95 (m, 2H), 1.03 – 1.27 (m, 3H), 1.29 – 1.47 (m, 4H), 1.53 – 1.72 (m, 6H), 2.05 (d, 1H), 2.13 (d, 1H), 2.82 – 2.90 (m, 1H), 2.97 (td, 1H), 3.13 (s, 1H), 3.31 (d, 1H), 5.40 (s, 1H).

Example 23

5-((2R,4S)-2-(3,4-Difluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(3,4-difluorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate and cis-methyl 2-(3,4-difluorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate

2-(3,4-Difluorophenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (5.655 g, 18.90 mmol) (reference compound 9) was dissolved in THF (60 mL) and di(1H-imidazol-1-yl)methanone (4.60 g, 28.34 mmol) added. The suspension was stirred at room temperature under nitrogen for 5 h (flask 1). In a separate flask 3-ethoxy-3-oxopropanoic acid, potassium salt (6.47 g, 37.79 mmol) and magnesium chloride (3.60 g, 37.79 mmol) were suspended in THF (60 mL) and stirred with an oversized stirring bar at 50°C under nitrogen for 5 h. The white suspension in flask 2 was then added to flask 1. The thick white suspension was stirred at room temperature for 18 h. The reaction mixture was acidified by addition of 3 M HCl to pH 1. The solvent was evaporated in vacuo. EtOAc (250 mL) and water were added, shaken and the phases separated. The organic phase was washed with water (200 mL), satd $NaHCO_3$

(200 mL), brine (200 mL), dried with a phase separator and evaporated in vacuo. The residue was purified by automated flash chromatography on a Biotage® KP-SIL 100g column. A gradient from 10 % EtOAc in heptane over 2 CV followed by 10 % to 40 % of EtOAc in heptane over 9 CV was used as mobile phase. Cis-methyl 2-(3,4-difluorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (5.23 g, 74.9 %) and trans-methyl 2-(3,4-difluorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (0.502 g, 7.19 %) were obtained. Cis-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.23 – 1.30 (m, 3H), 1.74 – 2.18 (m, 3H), 2.22 – 2.30 (m, 1H), 2.82 – 2.91 (m, 1H), 3.24 – 3.37 (m, 1H), 3.44 (d, 2H), 3.65 (s, 3H), 4.05 – 4.22 (m, 1H), 4.18 (q, 2H), 4.85 – 4.98 (m, 1H), 6.90 – 6.97 (m, 1H), 6.98 – 7.05 (m, 1H), 7.05 – 7.14 (m, 1H). MS m/z 370 $(M+H)^+$. Trans-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.23 – 1.32 (m, 3H), 1.51 – 2.02 (m, 3H), 2.42 – 2.53 (m, 1H), 2.59 – 2.71 (m, 1H), 2.77 – 2.88 (m, 1H), 3.47 (d, 2H), 3.76 (s, 3H), 4.19 (q, 2H), 4.14 – 4.33 (m, 1H), 5.47 – 5.66 (m, 1H), 6.90 – 6.97 (m, 1H), 6.99 – 7.07 (m, 1H), 7.11 – 7.20 (m, 1H). MS m/z 370 $(M+H)^+$

Step 2: Cis-methyl 2-(3,4-difluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 2-(3,4-difluorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (5.23 g, 14.16 mmol) was dissolved in MeOH (50 mL) and cooled to - 40°C. Sodium hydroxide (3.73 mL, 14.16 mmol) dissolved in water (5.00 mL) was added and the reaction stirred at - 40°C for 40 min. Hydroxylamine (0.868 mL, 14.16 mmol) was added and stirring continued for 3.5 h at - 40°C. The reaction mixture was then added to a prewarmed 80°C solution of 6 M hydrogen chloride (73.2 mL, 438.95 mmol) and stirred for 20 min. The solvent was concentrated in vacuo. DCM (200 mL) and water (150 mL) were added, shaken and the phases separated. The aqueous phase was extracted with DCM (150 mL). The combined organic phases were dried with a phase separator and evaporated in vacuo. The compound was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x50 ID mm) using a gradient of 20-60% Acetonitrile in H2O/MeCN/AcOH 95/5/0.2 buffer over 25 minutes with a flow of 100 mL/min. Cis-methyl 2-(3,4-difluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (3.41 g, 71.2 %) was isolated as a white solid. ^{1}H NMR (600 MHz, CDCl3) δ 1.81 – 1.88 (m, 1H), 2.08 – 2.18 (m, 1H), 2.19 – 2.28 (m, 1H), 2.30 – 2.38 (m, 1H), 3.02 – 3.11 (m, 1H), 3.32 – 3.40 (m, 1H), 3.67 (s, 3H), 4.09 – 4.18 (m, 1H), 5.02 – 5.08 (m, 1H), 5.56 (s, 1H), 6.86 – 6.92 (m, 1H), 6.95 – 7.01 (m, 1H), 7.03 – 7.10 (m, 1H). MS m/z 339 $(M+H)^+$.

Step 3: (2R,4S)-Methyl 2-(3,4-difluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 2-(3,4-difluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (3.41 g, 10 mmol) was subjected to chiral preparative HPLC (Column: Lux Cell2 (250x30), 5 µm particle size, mobile phase: 15% MeOH in CO_2 (175 bar), flow rate 130 mL/min, temperature 40°C) to yield (2R,4S)-Methyl 2-(3,4-difluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.70 g, 50 %), Chiral purity 99.0 %ee, Optical rotation $[\alpha]_D^{20} = +49.9$ (acetonitrile, c=1). ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.81 – 1.87 (m, 1H), 2.09 – 2.17 (m, 1H), 2.20 – 2.28 (m, 1H), 2.31 – 2.37 (m, 1H), 3.02 – 3.09 (m, 1H), 3.32 – 3.41 (m, 1H), 3.67 (s, 3H), 4.10 – 4.16 (m, 1H), 5.03 – 5.08 (m, 1H), 5.56 (s, 1H), 6.87 – 6.92 (m, 1H), 6.95 – 7.01 (m, 1H), 7.03 – 7.09 (m, 1H).

Step 4: 5-((2R,4S)-2-(3,4-Difluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-methyl 2-(3,4-difluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.7 g, 5.03 mmol) was dissolved in hydrobromic acid (33 % in AcOH, 25 mL, 151.92 mmol) and stirred at room temperature for 20 h. The solvent was evaporated in vacuo. The compound was purified by preparative HPLC on a XBridge C18 column (10 µm 250x50 ID mm) using a gradient of 5-30% Acetonitrile in H2O/MeCN/NH3 95/5/0.2 buffer over 25 minutes with a flow of 100 mL/min. The compound was repurified by preparative HPLC on a XBridge C18 column (10 µm 250x50 ID mm) using a gradient of 0-30% Acetonitrile in H2O/MeCN/NH3 95/5/0.2 buffer over 25 minutes with a flow of 100 mL/min. 5-((2R,4S)-2-(3,4-difluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one (0.923 g, 65.5 %) was isolated as a white solid. ^{1}H NMR (600 MHz, cd$_3$od) δ 1.66 – 1.76 (m, 2H), 2.09 (d, 1H), 2.19 (d, 1H), 2.96 – 3.07 (m, 2H), 3.28 – 3.35 (omitted signals), 3.90 – 3.95 (m, 1H), 5.65 (s, 1H), 7.20 – 7.29 (m, 2H), 7.34 – 7.39 (m, 1H). HRMS Calcd for $[C_{14}H_{14}F_2N_2O_2+H]^+$: 281.1101. Found: 281.1106.

Example 24

5-(Trans-2-(3,4-difluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(3,4-difluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Trans-methyl 2-(3,4-difluorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (502 mg, 1.36 mmol) (from example 23, step 1) was dissolved in MeOH (5 mL) and cooled to - 40°C. Sodium hydroxide (0.358 mL, 1.36 mmol) dissolved in water (0.500 mL) was added and the reaction stirred at - 40°C for 20 min. Hydroxylamine (0.083 mL, 1.36 mmol) was added and stirring continued for 3.5 h at - 40°C. The reaction mixture was then added to a prewarmed 80°C solution of hydrogen chloride (7.02 mL, 42.13 mmol) and stirred for 20 min. The solvent was evaporated in vacuo. DCM (50 mL) and water (50 mL) were added, shaken and the phases separated. The aqueous phase was extracted with DCM (50 mL). The combined organic phase were dried with a phase separator and evaporated in vacuo. The compound was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x50 ID mm) using a gradient of 20-60% Acetonitrile in H2O/MeCN/AcOH 95/5/0.2 buffer over 25 minutes with a flow of 100 mL/min. Trans-methyl 2-(3,4-difluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (242 mg, 52.6 %) was isolated as a white solid. ^{1}H NMR (600 MHz, CDCl3) δ 1.60 – 1.72 (m, 1H), 1.94 (d, 1H), 1.98 – 2.07 (m, 1H), 2.60 (d, 1H), 2.78 – 2.94 (m, 2H), 3.77 (s, 3H), 4.25 (s, 1H), 5.51 – 5.71 (m, 2H), 6.94 – 6.99 (m, 1H), 7.02 – 7.09 (m, 1H), 7.17 (dd, 1H). MS m/z 337 $(M-H)^-$.

Step 2: 5-(Trans-2-(3,4-difluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

Trans-methyl 2-(3,4-difluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (242 mg, 0.72 mmol) was dissolved in hydrobromic acid (33 % in AcOH, 4 mL, 24.31 mmol) and stirred at room temperature for 20 h. The solvent was evaporated in vacuo. The residue was purified by preparative HPLC (Instrument: Agilent, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-(trans-2-(3,4-difluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one (137 mg, 68 %). ^{1}H NMR (600 MHz, dmso) δ 1.74 – 1.81 (m, 2H), 1.84 – 1.89 (m, 1H), 1.98 – 2.03 (m, 1H), 2.65 – 2.71 (m, 1H), 2.81 (dt, 1H), 3.09 – 3.13 (m, 1H), 3.70 (dd, 1H), 5.96 (s, 1H), 7.18 – 7.22 (m, 1H), 7.30 – 7.36 (m, 1H), 7.39 – 7.44 (m, 1H). HRMS Calcd for $[C_{14}H_{14}F_2N_2O_2+H]^+$: 281.1101. Found: 281.1114.

Example 25

5-((2R,4S)-2-(4-Fluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-fluorophenyl)piperidine-1-carboxylate and cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-fluorophenyl)piperidine-1-carboxylate

2-(4-fluorophenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (8.4 g, 29.86 mmol) (reference compound 10) was dissolved in methyl THF (120 mL) and di(1H-imidazol-1-yl)methanone (7.26 g, 44.80 mmol) added. The suspension was stirred at room temperature under nitrogen for 2 h (flask 1). In a separate flask potassium 3-ethoxy-3-oxopropanoate (9.15 g, 53.75 mmol) was suspended in methyl THF (120 mL) and magnesium chloride (5.12 g, 53.75 mmol) added. The suspension was stirred at 50°C under nitrogen for 3 h using an oversized stirring bar (flask 2). The beige suspension in flask 1 was now added to the white suspension in flask 2. The resulting beige suspension was stirred under nitrogen at room temperature for 23 h. The mixture was acidified to pH 1 with 3 M HCl (50 mL) and MTBE (200 mL) and water (70 mL) were added. The phases were separated and the organic phase extracted with water (30 mL), satd $NaHCO_3$ (30 mL) and water (30mL), dried over anhydrous Na_2SO_4 and evaporated. The diastereoisomers were separated on Biotage (20 % => 55 % EtOAc in heptane, 8 CV; Biotage® KP-SIL 340g column) to yield trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-fluorophenyl)piperidine-1-carboxylate (1.26 g, 12 %) and cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-fluorophenyl)piperidine-1-carboxylate (6.58 g, 62 %) as colorless oils. Cis-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.27 (t, 3H), 1.83 – 2.14 (m, 3H), 2.27 (ddd, 1H), 2.80 – 2.93 (m, 1H), 3.26 – 3.50 (m, 3H), 3.64 (s, 3H), 4.10 – 4.22 (m, 3H), 4.93 – 5.01 (m, 1H), 6.95 – 7.05 (m, 2H), 7.14 – 7.22 (m, 2H). MS m/z 352 $(M+H)^+$. Trans-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.18 – 1.33 (m, 3H), 1.50 – 1.89 (m, 2H), 1.90 – 2.02 (m, 1H), 2.47 – 2.59 (m, 1H), 2.59 – 2.72 (m, 1H), 2.79 – 2.91 (m, 1H), 3.47 (s, 2H), 3.76 (s, 3H), 4.08 – 4.30 (m, 3H), 5.50 – 5.69 (s, br., 1H), 6.98 – 7.10 (m, 2H), 7.10 – 7.23 (m, 2H). MS m/z 350 $(M-H)^-$

Step 2: Cis-methyl 2-(4-fluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-fluorophenyl)piperidine-1-carboxylate (6.58 g, 18.7 mmol) was dissolved in MeOH (50 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (0.749 g, 18.73 mmol) dissolved in water (5.00 mL) was added during 10 min and

the colourless solution continued to stir at -40°C for 20 min. Hydroxylamine (50 % by weight in water, 1.148 mL, 18.73 mmol) was added during 8 min. The resulting solution was stirred at -40°C for 3 h 20 min. The mixture was transferred into a prewarmed (80°C) solution of 6 M hydrogen chloride (94 mL, 561.80 mmol) and the mixture continued to stir at 80°C for 20 min. The solvent was evaporated and DCM/water added. The phases were separated and the organic phase passed through a phase separator and evaporated to yield 5.8 g of a yellow solid. 2.9 g of this solid was purified by preparative HPLC in 3 injections on a XBridge C18 column (10 µm 250x50 ID mm) using a gradient of 30-75 % Acetonitrile in H2O/MeCN/HOAc 95/5/0.2 buffer over 15 minutes with a flow of 100 mL/min. Cis-methyl 2-(4-fluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.7 g, 28 %) was obtained. ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.79 – 1.90 (m, 1H), 2.08 – 2.40 (m, 3H), 3.01 – 3.12 (m, 1H), 3.32 – 3.44 (m, 1H), 3.67 (s, 3H), 4.15 (ddd, 1H), 5.05 – 5.14 (m, 1H), 5.54 (s, 1H), 6.92 – 7.02 (m, 2H), 7.10 – 7.18 (m, 2H). MS m/z 321 $(M+H)^+$.

Step 3: <u>(2R,4S)-Methyl 2-(4-fluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate</u>

Cis-methyl 2-(4-fluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.7 g, 5.3 mmol) was subjected to chiral preparative HPLC (Column: Chiralcel OJ (250x50), 20 µm particle size, mobile phase: EtOH, flow rate 118 mL/min) to yield (2R,4S)-methyl 2-(4-fluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (860 mg, 50 %), Chiral purity 99.9 %ee, Optical rotation $[\alpha]_D^{20} = +57.0$ (acetonitrile, c=1).

Step 4: <u>5-((2R,4S)-2-(4-Fluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one</u>

(2R,4S)-Methyl 2-(4-fluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.86 g, 2.68 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 15.52 mL, 88.60 mmol) and the solution stirred at room temperature overnight. The solvent was evaporated and the residue was purified by preparative HPLC (Instrument: Agilent, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) and on a XBridge C18 column (10 µm 250x19 ID mm) using a gradient of 0 - 30 % Acetonitrile in H2O/MeCN/NH3 95/5/0.2 buffer over 20 minutes with a flow of 19 mL/min. 5-((2R,4S)-2-(4-Fluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one (167 mg, 23 %) was isolated. ^{1}H NMR (400 MHz, dmso) δ 1.27 – 1.53 (m, 2H), 1.81 – 1.98 (m, 2H), 2.67 –

2.77 (m, 1H), 2.78 – 2.91 (m, 1H), 3.10 (d, 1H), 3.63 (d, 1H), 5.67 – 5.77 (m, 1H), 7.04 –7.16 (m, 2H), 7.34 – 7.45 (m, 2H). HRMS Calculated for $[C_{14}H_{15}FN_2O_2+H]^+$: 263.1196. Found: 263.1201

Example 26

5-(Trans-2-(4-fluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(4-fluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-fluorophenyl)piperidine-1-carboxylate (1.26 g, 3.59 mmol) (from example 25, step 1) was dissolved in MeOH (50 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (0.143 g, 3.59 mmol) dissolved in water (5.00 mL) was added during 5 min and the colourless solution continued to stir at -40°C for 20 min. Hydroxylamine (50 % by weight in water, 0.220 mL, 3.59 mmol) was added during 8 min. The resulting solution was stirred at -40°C for 3 h 20 min. The mixture was transferred into a prewarmed (80°C) solution of 6 M hydrogen chloride (17.93 mL, 107.58 mmol) and the mixture continued to stir at 80°C for 20 min. The solvent was evaporated and DCM/water added. The phases were separated and the organic phase passed through a phase separator and evaporated to yield trans-methyl 2-(4-fluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.1 g, 95 %) as a brown solid, 1.1 g. MS m/z 321 $(M+H)^+$.

Step 2: 5-(Trans-2-(4-fluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

Trans-methyl 2-(4-fluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.3 g, 0.94 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 6 mL, 34.26 mmol) and the solution stirred at room temperature overnight. The solvent was evaporated and the residue was purified by preparative HPLC (Instrument: Agilent, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH10, Column: Xbridge Prep C18 5µm OBD 19*150 mm). 5-(Trans-2-(4-fluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one (54 mg, 22 %) was isolated. ^1H NMR (400 MHz, dmso) δ 1.75 – 2.10 (m, 4H), 2.67 – 2.77 (m, 1H), 2.80 – 2.89 (m, 1H), 3.11 – 3.18 (m, 1H), 3.70 (d, 1H), 5.94 (s, 1H), 7.07 – 7.15 (m, 2H), 7.36 – 7.43 (m, 2H). HRMS Calculated for $[C_{14}H_{15}FN_2O_2+H]^+$: 263.1196. Found: 263.1201

Example 27

5-((2R,4S)-2-(4-Chlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(4-chlorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate and cis-methyl 2-(4-chlorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate

2-(4-Chlorophenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (3.49 g, 11.72 mmol) (reference compound 11) was dissolved in methyl THF (120 mL), then di(1H-imidazol-1-yl)methanone (2.85 g, 17.58 mmol) was added. The mixture was stirred at room temperature under nitrogen for 3 h (flask 1). In a separate flask potassium 3-ethoxy-3-oxopropanoate (3.59 g, 21.10 mmol) was suspended in methyl THF (120 mL), then magnesium chloride (2.009 g, 21.10 mmol) was added. The suspension was stirred at 50°C under nitrogen for 3 h using a large magnetic stirring bar (flask 2). The contents of flask 1 was transferred to flask 2. The resulting white suspension was stirred under nitrogen at room temperature overnight. The mixture was acidified to pH 1 with 3.8 M HCl, then MTBE (50 mL) and water (50 mL) was added. The phases were separated and the organic layer was washed with water, satd $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and evaporated giving a slightly yellow oil. The residue was purified by automated column chromatography on Biotage (340 g) with a gradient of 20-60% EtOAc in n-heptane (8 CV) to yield trans-methyl 2-(4-chlorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (205 mg, 5 %) and cis-methyl 2-(4-chlorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (2.27 g, 53 %). Cis-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.21 – 1.32 (m, 3H), 1.82 – 2.15 (m, 3H), 2.22 – 2.31 (m, 1H), 2.81 – 2.92 (m, 1H), 3.26 – 3.49 (m, 3H), 3.63 (s, 3H), 4.06 – 4.22 (m, 3H), 4.91 – 4.99 (m, 1H), 7.11 – 7.18 (m, 2H), 7.24 – 7.31 (m, 2H). MS m/z 366 $(M-H)^-$. Trans-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.16 – 1.33 (m, 3H), 1.47 – 2.02 (m, 3H), 2.43 – 2.70 (m, 2H), 2.75 – 2.91 (m, 1H), 3.42 – 3.48 (m, 2H), 3.74 (s, 3H), 4.00 – 4.39 (m, 3H), 5.45 – 5.71 (s, br., 1H), 7.14 (d, 2H), 7.29 – 7.35 (m, 2H). MS m/z 368 $(M+H)^+$.

Step 2: Cis-methyl 2-(4-chlorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 2-(4-chlorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (2.11 g, 5.74 mmol) was dissolved in MeOH (24 mL) and cooled to -40°C under nitrogen. Sodium

hydroxide (1.687 mL, 5.74 mmol) was added during 10 min and the yellow solution continued to stir at -40°C for 20 min. Hydroxylamine (50 % by weight in water, 0.352 mL, 5.74 mmol) was added during 8 min. The resulting solution was stirred at -40°C for 3 h. The mixture was then rapidly poured into a prewarmed (80°C) solution of 6 M hydrogen chloride (29.5 mL, 177.26 mmol) and the mixture continued to stir at 80°C for 20 min. The solvent was evaporated and DCM/water added. The phases were separated and the organic phase passed through a phase separator and evaporated to yield a white solid. The compound was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x50 ID mm) using a gradient of 10-60% Acetonitrile in H2O/MeCN/AcOH 95/5/0.2 buffer over 30 minutes with a flow of 100 mL/min. Cis-methyl 2-(4-chlorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (923 mg, 47 %) was isolated. MS m/z 337 $(M+H)^+$

Step 3: (2R,4S)-Methyl 2-(4-chlorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate and (2S,4R)-methyl 2-(4-chlorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate

Cis-methyl 2-(4-chlorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (923 mg, 2.75 mmol) was subjected to chiral preparative HPLC (Column: ReproSil (250x50), 8 µm particle size, mobile phase: EtOH, flow rate 100 mL/min) to yield (2R,4S)-methyl 2-(4-chlorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (447 mg, 48 %), Chiral purity 99.9 %ee, Optical rotation $[\alpha]_D^{20} = +67.7$ (acetonitrile, c=1), ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.79 – 1.89 (m, 1H), 2.07 – 2.40 (m, 3H), 3.01 – 3.11 (m, 1H), 3.33 – 3.43 (m, 1H), 3.66 (s, 3H), 4.10 – 4.19 (m, 1H), 5.07 (dd, 1H), 5.55 (s, 1H), 7.08 – 7.14 (m, 2H), 7.23 – 7.28 (m, 2H) and (2S,4R)-methyl 2-(4-chlorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate (458 mg, 49 %), Chiral purity 99.6 %ee, Optical rotation $[\alpha]_D^{20} = -67.6$ (acetonitrile, c=1), ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.79 – 1.88 (m, 1H), 2.07 – 2.38 (m, 3H), 3.02 – 3.10 (m, 1H), 3.33 – 3.43 (m, 1H), 3.66 (s, 3H), 4.11 – 4.18 (m, 1H), 5.04 – 5.09 (m, 1H), 5.54 (s, 1H), 7.09 – 7.13 (m, 2H), 7.23 – 7.28 (m, 2H).

Step 4: 5-((2R,4S)-2-(4-Chlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-Methyl 2-(4-chlorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.447 g, 1.33 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 10.46 mL, 59.73 mmol) and the mixture was stirred at room temperature overnight. The

solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4S)-2-(4-chlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one (233 mg, 63 %). ^{1}H NMR (600 MHz, dmso) δ 1.32 (q, 1H), 1.44 (dq, 1H), 1.82 – 1.88 (m, 1H), 1.90 – 1.97 (m, 1H), 2.71 (dt, 1H), 2.80 – 2.88 (m, 1H), 3.06 – 3.12 (m, 1H), 3.63 (dd, 1H), 5.70 (s, 1H), 7.31 – 7.35 (m, 2H), 7.35 – 7.40 (m, 2H). HRMS Calculated for $[C_{14}H_{15}ClN_2O_2+H]^+$: 279.0900. Found: 279.0905

Example 28

5-((2S,4R)-2-(4-Chlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

(2S,4R)-Methyl 2-(4-chlorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.458 g, 1.36 mmol) (from example 27, step 3) was dissolved in hydrogen bromide (33 % in acetic acid, 10.72 mL, 61.20 mmol) and the mixture was stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2S,4R)-2-(4-chlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one (198 mg, 52 %). ^{1}H NMR (600 MHz, dmso) δ 1.32 (q, 1H), 1.44 (dq, 1H), 1.83 – 1.88 (m, 1H), 1.91 – 1.96 (m, 1H), 2.71 (dt, 1H), 2.84 (tt, 1H), 3.07 – 3.11 (m, 1H), 3.63 (dd, 1H), 5.70 (s, 1H), 7.31 – 7.40 (m, 4H). HRMS Calculated for $[C_{14}H_{15}ClN_2O_2+H]^+$: 279.0900. Found: 279.0887

Example 29

5-(Trans-2-(4-chlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(4-chlorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Trans-methyl 2-(4-chlorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (184 mg, 0.50 mmol) (from example 27, step 1) was dissolved in MeOH (2 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (0.147 mL, 0.50 mmol) was added during 10 min and the yellow solution continued to stir at -40°C for 20 min. Hydroxylamine (50 % by weight in

water, 0.031 mL, 0.50 mmol) was added during 8 min. The resulting solution was stirred at -40°C for 3 h. The mixture was then rapidly poured into a prewarmed (80°C) solution of 6 M hydrogen chloride (2.58 mL, 15.46 mmol) and the mixture continued to stir at 80°C for 20 min. The solvent was evaporated and DCM/water added. The phases were separated and the organic phase passed through a phase separator and evaporated to yield crude trans-methyl 2-(4-chlorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (155 mg, 92 %) as a slightly yellow oil. MS m/z 337 $(M+H)^+$

Step 2: 5-(Trans-2-(4-chlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

Trans-methyl 2-(4-chlorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (155 mg, 0.46 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 3.63 mL, 20.71 mmol) and the mixture was stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-(trans-2-(4-chlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one (23.5 mg, 18 %). ^{1}H NMR (600 MHz, dmso) δ 1.74 – 1.83 (m, 2H), 1.84 – 1.91 (m, 1H), 1.96 – 2.03 (m, 1H), 2.70 (dt, 1H), 2.79 – 2.86 (m, 1H), 3.09 – 3.15 (m, 1H), 3.69 (dd, 1H), 5.89 – 5.98 (m, 1H), 7.32 – 7.36 (m, 2H), 7.36 – 7.41 (m, 2H). HRMS Calculated for $[C_{14}H_{15}ClN_2O_2+H]^+$: 279.0900. Found: 279.0889

Example 30

5-((2R,4S)-2-(3-(Trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3-(trifluoromethyl)phenyl)piperidine-1-carboxylate and cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3-(trifluoromethyl)phenyl)-piperidine-1-carboxylate

1-(Methoxycarbonyl)-2-(3-(trifluoromethyl)phenyl)piperidine-4-carboxylic acid (1.479 g, 4.46 mmol) (reference compound 12) was dissolved into methyl THF (50 mL), then di(1H-imidazol-1-yl)methanone (1.086 g, 6.70 mmol) was added. The mixture was stirred at room temperature under nitrogen for 3 h (flask 1). In a separate flask potassium 3-ethoxy-3-oxopropanoate (1.368 g, 8.04 mmol) was suspended in methyl THF (50.0 mL), then magnesium chloride (0.765 g, 8.04 mmol) was added. The suspension was stirred at 50°C

under nitrogen for 3 h using a large magnetic stirring bar (flask 2). The contents of flask 1 was transferred to flask 2. The resulting white suspension was stirred under nitrogen at room temperature overnight. The mixture was acidified to pH 1 with 3.8 M HCl, then MTBE (50 mL) and water (50 mL) were added. The phases were separated and the organic layer was washed with water, satd $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and evaporated leaving a slightly yellow oil. The residue was purified by automated column chromatography on Biotage (340g) with a gradient of 20-55% EtOAc in n-heptane (8 CV) to yield trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3-(trifluoromethyl)phenyl)-piperidine-1-carboxylate (157 mg, 9 %) and cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3-(trifluoromethyl)phenyl)piperidine-1-carboxylate (679 mg, 38 %). Cis-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.19 – 1.27 (m, 3H), 1.75 – 2.20 (m, 3H), 2.23 – 2.32 (m, 1H), 2.82 – 2.94 (m, 1H), 3.26 – 3.48 (m, 3H), 3.61 (s, 3H), 4.05 – 4.21 (m, 3H), 4.91 – 5.04 (m, 1H), 7.35 – 7.50 (m, 4H). MS m/z 402 $(M+H)^+$. Trans-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.16 – 1.32 (m, 3H), 1.46 – 2.09 (m, 4H), 2.48 – 2.90 (m, 2H), 3.40 – 3.50 (m, 2H), 3.75 (s, 3H), 4.02 – 4.42 (m, 3H), 5.65 (s, br., 1H), 7.36 – 7.56 (m, 4H). MS m/z 402 $(M+H)^+$

Step 2: Cis-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3-(trifluoromethyl)phenyl)-piperidine-1-carboxylate

Cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3-(trifluoromethyl)phenyl)piperidine-1-carboxylate (679 mg, 1.69 mmol) was dissolved in MeOH (8 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (0.498 mL, 1.69 mmol) dissolved in water (0.800 mL) was added during 10 min and the yellow solution continued to stir at -40°C for 20 min. Hydroxylamine (50 % by weight in water, 0.104 mL, 1.69 mmol) was added during 8 min. The resulting solution was stirred at -40°C for 3 h. The mixture was then rapidly poured into a prewarmed (80°C) solution of 6 M hydrogen chloride (8.71 mL, 52.27 mmol) and the mixture continued to stir at 80°C for 20 min. The solvent was evaporated and DCM/water added. The phases were separated and the organic phase passed through a phase separator and evaporated to yield a white solid. The compound was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x50 ID mm) using a gradient of 10-60% Acetonitrile in H2O/MeCN/AcOH 95/5/0.2 buffer over 30 minutes with a flow of 100 mL/min. Cis-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3-(trifluoromethyl)phenyl)piperidine-1-carboxylate (311 mg, 50 %) was isolated. MS m/z 371 $(M+H)^+$

Step 3: (2R,4S)-Methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3-(trifluoromethyl)phenyl)-piperidine-1-carboxylate and (2S,4R)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3-(trifluoromethyl)phenyl)piperidine-1-carboxylate

Cis-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3-(trifluoromethyl)phenyl)piperidine-1-carboxylate (311 mg, 0.84 mmol) was subjected to chiral preparative HPLC (Column: Chiralpak IC (250x20), 5 µm particle size, mobile phase: Heptane/IPA 40/60, flow rate 12 mL/min) to yield (2R,4S)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3-(trifluoromethyl)-phenyl)piperidine-1-carboxylate (155 mg, 50 %), Chiral purity 99.9 %ee, Optical rotation $[\alpha]_D^{20}$ = +54.4 (acetonitrile, c=1), ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.78 – 1.90 (m, 1H), 2.08 – 2.42 (m, 3H), 3.01 – 3.13 (m, 1H), 3.34 – 3.48 (m, 1H), 3.65 (s, 3H), 4.09 – 4.22 (m, 1H), 5.08 – 5.19 (m, 1H), 5.53 (s, 1H), 7.31 – 7.50 (m, 4H) and (2S,4R)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3-(trifluoromethyl)phenyl)piperidine-1-carboxylate (152 mg, 49 %), Chiral purity 99.9 %ee. Optical rotation $[\alpha]_D^{20}$ = –55.7 (acetonitrile, c=1), ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.80 – 1.90 (m, 1H), 2.11 – 2.32 (m, 2H), 2.33 – 2.42 (m, 1H), 3.02 – 3.12 (m, 1H), 3.36 – 3.47 (m, 1H), 3.66 (s, 3H), 4.12 – 4.21 (m, 1H), 5.11 – 5.17 (m, 1H), 5.53 (s, 1H), 7.33 – 7.48 (m, 4H).

Step 4: 5-((2R,4S)-2-(3-(Trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-Methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3-(trifluoromethyl)phenyl)piperidine-1-carboxylate (0.155 g, 0.42 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 3.30 mL, 18.83 mmol) and the mixture was stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4S)-2-(3-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one (43 mg, 33 %). ^{1}H NMR (600 MHz, dmso) δ 1.35 (q, 1H), 1.47 (dq, 1H), 1.87 (d, 1H), 2.00 (d, 1H), 2.69 – 2.77 (m, 1H), 2.83 – 2.91 (m, 1H), 3.08 – 3.14 (m, 1H), 3.75 (d, 1H), 5.74 (s, 1H), 7.50 – 7.55 (m, 1H), 7.55 – 7.59 (m, 1H), 7.64 – 7.68 (m, 1H), 7.71 (s, 1H). HRMS Calculated for $[C_{15}H_{15}F_3N_2O_2+H]^+$: 313.1164. Found: 313.1144

Example 31

5-((2S,4R)-2-(3-(Trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one

(2S,4R)-Methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3-(trifluoromethyl)phenyl)piperidine-1-carboxylate (0.152 g, 0.42 mmol) (from example 30, step 3) was dissolved in hydrogen bromide (33 % in acetic acid, 3.30 mL, 18.83 mmol) and the mixture was stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2S,4R)-2-(3-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one (28 mg, 22 %). ^{1}H NMR (600 MHz, dmso) δ 1.35 (q, 1H), 1.47 (qd, 1H), 1.87 (d, 1H), 2.00 (d, 1H), 2.73 (dt, 1H), 2.84 – 2.91 (m, 1H), 3.09 – 3.14 (m, 1H), 3.75 (d, 1H), 5.74 (s, 1H), 7.50 – 7.54 (m, 1H), 7.55 – 7.58 (m, 1H), 7.66 (d, 1H), 7.71 (s, 1H). HRMS Calculated for $[C_{15}H_{15}F_3N_2O_2+H]^+$: 313.1164. Found: 313.1158

Example 32

5-(Trans-2-(3-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3-(trifluoromethyl)phenyl)-piperidine-1-carboxylate

Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3-(trifluoromethyl)phenyl)piperidine-1-carboxylate (157 mg, 0.39 mmol) (from example 30, step 1) was dissolved in MeOH (2 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (0.115 mL, 0.39 mmol) dissolved in water (0.200 mL) was added during 10 min and the yellow solution continued to stir at -40°C for 20 min. Hydroxylamine (50 % by weight in water, 0.024 mL, 0.39 mmol) was added during 8 min. The resulting solution was stirred at -40°C for 3 h 15 min. The mixture was then rapidly poured into a prewarmed (80°C) solution of 6 M hydrogen chloride (2.014 mL, 12.09 mmol) and the mixture continued to stir at 80°C for 20 min. The solvent was evaporated and DCM/water added. The phases were separated and the organic phase passed through a phase separator and evaporated to yield crude trans-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3-(trifluoromethyl)phenyl)piperidine-1-carboxylate (128 mg, 88 %) as a white solid. MS m/z 371 $(M+H)^+$

Step 2: 5-(Trans-2-(3-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one

Trans-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3-(trifluoromethyl)phenyl)piperidine-1-carboxylate (0.128 g, 0.35 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 2.72 mL, 15.55 mmol) and the mixture was stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-(trans-2-(3-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one (31 mg, 28 %). ^{1}H NMR (600 MHz, dmso) δ 1.77 – 1.86 (m, 2H), 1.86 – 1.93 (m, 1H), 2.01 – 2.08 (m, 1H), 2.71 (dt, 1H), 2.81 – 2.87 (m, 1H), 3.11 – 3.16 (m, 1H), 3.76 – 3.83 (m, 1H), 5.99 (s, 1H), 7.50 – 7.55 (m, 1H), 7.55 – 7.59 (m, 1H), 7.64 – 7.68 (m, 1H), 7.72 (s, 1H). HRMS Calculated for $[C_{15}H_{15}F_3N_2O_2+H]^+$: 313.1164. Found: 313.1153

Example 33

5-((2R,4S)-2-(4-(Trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate and cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-(trifluoromethyl)phenyl)-piperidine-1-carboxylate

1-(Methoxycarbonyl)-2-(4-(trifluoromethyl)phenyl)piperidine-4-carboxylic acid (5.629 g, 16.99 mmol) (reference compound 13) was dissolved in methyl THF (120 mL) and di(1H-imidazol-1-yl)methanone (4.13 g, 25.49 mmol) added. The suspension was stirred at room temperature under nitrogen for 3 h 45 min (flask 1). In a separate flask potassium 3-ethoxy-3-oxopropanoate (5.21 g, 30.58 mmol) was suspended in methyl THF (120 mL) and magnesium chloride (2.91 g, 30.58 mmol) added. The suspension was stirred at 50°C under nitrogen for 3.5 h using an oversized stirring bar (flask 2). The beige suspension in flask 1 was now added to the white suspension in flask 2. The resulting beige suspension was stirred under nitrogen at room temperature for 23 h. The mixture was acidified to pH 1 with 3.8 M HCl and MTBE and water added. The phases were separated and the organic phase extracted with water, satd $NaHCO_3$ and water. The organic layer was evaporated and traces of water were azeotropically removed by MeCN to yield a brown oil. The diastereoisomers were separated in 2 runs on Biotage (20 % => 55 % EtOAc in heptane, 8 CV; Biotage® KP-SIL 340g column). Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (0.474 g, 7 %) and cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-(trifluoromethyl)phenyl)-

piperidine-1-carboxylate (3.532 g, 52 %) were isolated as colorless oils. Cis-isomer:^{1}H NMR (400 MHz, cdcl$_3$) δ 1.26 (t, 3H), 1.72 – 2.22 (m, 3H), 2.29 (ddd, 1H), 2.83 – 2.96 (m, 1H), 3.29 – 3.49 (m, 3H), 3.64 (s, 3H), 4.07 – 4.23 (m, 3H), 4.92 – 5.06 (m, 1H), 7.32 (d, 2H), 7.58 (d, 2H). MS m/z 402 $(M+H)^+$. Trans-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.13 – 1.26 (m, 3H), 1.43 – 1.60 (m, 1H), 1.64 – 1.85 (m, 1H), 1.95 (dt, 1H), 2.44 – 2.61 (m, 2H), 2.73 – 2.85 (m, 1H), 3.39 (s, 2H), 3.70 (s, 3H), 3.99 – 4.36 (m, 3H), 5.59 (br. s, 1H), 7.28 (d, 2H), 7.56 (d, 2H). MS m/z 402 $(M+H)^+$

Step 2: Cis-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(4-(trifluoromethyl)phenyl)-piperidine-1-carboxylate

Cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (2.307 g, 5.75 mmol) was dissolved in MeOH (20 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (0.230 g, 5.75 mmol) dissolved in water (2 mL) was added during 10 min and the colourless solution continued to stir at -40°C for 20 min. Hydroxylamine (50 % by weight in water, 0.352 mL, 5.75 mmol) was added during 8 min. The resulting solution was stirred at -40°C for 3 h 20 min. The mixture was then transferred into a prewarmed (80°C) solution of 6 M hydrogen chloride (30 mL, 180.00 mmol) and the mixture continued to stir at 80°C for 20 min. The solvent was evaporated and DCM/water added. The phases were separated and the organic phase passed through a phase separator and evaporated to yield a yellow solid. The compound was purified by preparative HPLC in 3 injections on a XBridge C18 column (10 µm 250x50 ID mm) using a gradient of 0-25 % Acetonitrile in H2O/MeCN/NH3 95/5/0.2 buffer over 20 minutes with a flow of 100 mL/min. Cis-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (1.682 g, 79 %) was isolated as a white solid. ^{1}H NMR (400 MHz, cd$_3$od) δ 1.83 – 1.94 (m, 1H), 2.16 – 2.29 (m, 2H), 2.34 – 2.43 (m, 1H), 3.06 – 3.18 (m, 1H), 3.51 (ddd, 1H), 3.64 (s, 3H), 4.12 (ddd, 1H), 5.10 – 5.22 (m, 1H), 5.57 (s, 1H), 7.40 (d, 2H), 7.58 (d, 2H). MS m/z 371 $(M+H)^+$

Step 3: (2R,4S)-Methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(4-(trifluoromethyl)phenyl)-piperidine-1-carboxylate and (2R,4S)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate

Cis-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (1.682 g, 4.54 mmol) was subjected to chiral preparative HPLC (Column:

Chiralpak IA (250x30), 5 μm particle size, mobile phase: 15% MeOH in CO_2 (175 bar), flow rate 130 mL/min, temperature 40 °C) to yield (2R,4S)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (580 mg, 34 %), Chiral purity 99.9 %ee, Optical rotation $[\alpha]_D^{20} = +53.3$ (acetonitrile, c=1) and (2S,4R)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (591 mg, 35 %), Chiral purity 98.8 %ee, Optical rotation $[\alpha]_D^{20} = -74.2$ (acetonitrile, c=1)

Step 4: 5-((2R,4S)-2-(4-(Trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-Methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (580 mg, 1.57 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 12 mL, 68.52 mmol) and the mixture stirred at room temperature for 17 h. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5μm OBD 19*150 mm) to yield 5-((2R,4S)-2-(4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one (341 mg, 70 %). ^{1}H NMR (600 MHz, cd_3od) δ 1.68 – 1.79 (m, 2H), 2.10 (d, 1H), 2.21 (d, 1H), 2.98 – 3.10 (m, 2H), 3.35 (d, 1H), 3.99 – 4.07 (m, 1H), 5.64 (s, 1H), 7.60 (d, 2H), 7.66 (d, 2H). HRMS Calculated for $[C_{15}H_{15}F_3N_2O_2+H]^+$: 313.1164. Found: 313.1150

Example 34

5-((2S,4R)-2-(4-(Trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one

(2S,4R)-Methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (591 mg, 1.60 mmol) (from example 33, step 3) was dissolved in hydrogen bromide (33 % in acetic acid, 12 mL, 68.52 mmol) and the mixture stirred at room temperature. After 24 h more hydrogen bromide (33 % in acetic acid, 5 mL, 28.55 mmol) was added and the reaction continued at room temperature for a total of 1.5 days. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx III, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH10, Column: Xbridge Prep C18 5μm OBD 19*150 mm) to yield 5-((2S,4R)-2-(4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one (337 mg, 67 %). ^{1}H NMR (600 MHz, cd_3od) δ 1.69 – 1.78 (m, 2H), 2.09 (d, 1H),

2.21 (d, 1H), 2.99 – 3.09 (m, 2H), 3.32 – 3.38 (m, 1H), 4.01 – 4.04 (m, 1H), 5.63 (s, 1H), 7.59 (d, 2H), 7.66 (d, 2H). HRMS Calculated for $[C_{15}H_{15}F_3N_2O_2+H]^+$: 313.1164. Found: 313.1156

Example 35

5-(Trans-2-(4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(4-(trifluoromethyl)phenyl)-piperidine-1-carboxylate

Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (0.467 g, 1.16 mmol) (from example 33, step 1) was dissolved in MeOH (4 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (0.047 g, 1.16 mmol) dissolved in water (0.4 mL) was added during 10 min and the colourless solution continued to stir at -40°C for 20 min. Hydroxylamine (50 % by weight in water, 0.071 mL, 1.16 mmol) was added during 8 min. The resulting solution was stirred at -40°C for 3.5 h. The mixture was then transferred into a prewarmed (80°C) solution of 6 M hydrogen chloride (6 mL, 36.00 mmol) and the mixture continued to stir at 80°C for 20 min. The solvent was evaporated and DCM/water added. The phases were separated and the organic phase passed through a phase separator and evaporated to yield crude trans-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (0.432 g, quant.) as a yellow oil. MS m/z 371 $(M+H)^+$

Step 2: 5-(Trans-2-(4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one

Trans-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (148 mg, 0.40 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 3 mL, 17.13 mmol) and the solution stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-(trans-2-(4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one (50 mg, 40 %). ^{1}H NMR (600 MHz, dmso) δ 1.75 – 1.83 (m, 2H), 1.84 – 1.92 (m, 1H), 2.00 – 2.06 (m, 1H), 2.70 (dt, 1H), 2.79 – 2.86 (m, 1H), 3.09 – 3.15 (m, 1H), 3.77 (d, 1H), 5.95 (s, 1H), 7.59 (d, 2H), 7.64 (d, 2H). HRMS Calculated for $[C_{15}H_{15}F_3N_2O_2+H]^+$: 313.1164. Found: 313.1166

Example 36

5-((2R,4S)-2-(3-tert-Butylphenyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Methyl 2-(3-tert-butylphenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate

2-(3-tert-Butylphenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (2.73 g, 8.55 mmol) (reference compound 14) was dissolved in methyl THF (40 mL) and di(1H-imidazol-1-yl)methanone (2.079 g, 12.82 mmol) added. The suspension was stirred at room temperature under nitrogen for 2 h (flask 1). In a separate flask potassium 3-ethoxy-3-oxopropanoate (2.62 g, 15.39 mmol) was suspended in methyl THF (60 mL) and magnesium chloride (1.465 g, 15.39 mmol) added. The suspension was stirred at 50°C under nitrogen for 3 h using an oversized stirring bar (flask 2). The beige suspension in flask 1 was now added to the white suspension in flask 2. The resulting beige suspension was stirred under nitrogen at room temperature for 23 h. The mixture was acidified to pH 1 with 0.5 M HCl (100 mL) and MTBE (200 mL) was added. The phases were separated and the organic phase extracted with water (30 mL), satd $NaHCO_3$ (30 mL) and water (30 mL), dried over anhydrous Na_2SO_4, and evaporated to yield crude methyl 2-(3-tert-butylphenyl)-4-(3-ethoxy-3-oxopropanoyl)-piperidine-1-carboxylate (3.14 g, 95 %) as a brown oil.

Step 2: Cis-methyl 2-(3-tert-butylphenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Methyl 2-(3-tert-butylphenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (3.14 g, 8.06 mmol) was dissolved in MeOH (50 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (0.322 g, 8.06 mmol) dissolved in water (5.00 mL) was added during 5 min and the colourless mixture continued to stir at -40°C for 20 min. Hydroxylamine (50 % by weight in water, 0.494 mL, 8.06 mmol) was added during 8 min. The resulting solution was stirred at -55°C for 6 h 30 min. The mixture was then transferred into a prewarmed (80°C) solution of 6 M hydrogen chloride (60 mL, 360.00 mmol) and the mixture continued to stir at 80°C for 20 min. The solvent was evaporated and DCM/water added. The phases were separated and the organic phase passed through a phase separator and evaporated to yield a brown oil. The crude was purified by preparative HPLC in 3 injections on a XBridge C18 column (10 µm 250x50 ID mm) using a gradient of 40-85 % Acetonitrile in H2O/MeCN/HOAc 95/5/0.2 buffer over

25 minutes with a flow of 100 mL/min. Cis-methyl 2-(3-tert-butylphenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (690 mg, 24 %) was isolated.^{1}H NMR (600 MHz, cdcl$_3$) δ 1.29 (s, 9H), 1.81 – 1.88 (m, 1H), 2.14 – 2.21 (m, 1H), 2.22 – 2.31 (m, 1H), 2.35 – 2.42 (m, 1H), 3.03 – 3.10 (m, 1H), 3.37 – 3.44 (m, 1H), 3.66 (s, 3H), 4.16 – 4.22 (m, 1H), 5.12 – 5.16 (m, 1H), 5.48 (s, 1H), 6.97 – 7.01 (m, 1H), 7.17 (s, 1H), 7.21 – 7.25 (m, 2H). MS m/z 359 $(M+H)^+$

Step 3: (2R,4S)-Methyl 2-(3-tert-butylphenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 2-(3-tert-butylphenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (690 mg, 1.93 mmol) was subjected to chiral preparative HPLC (Column: ReproSil (250x50), 8 µm particle size, mobile phase: Heptane/EtOH 40/60, flow rate 118 mL/min) to yield (2R,4S)-methyl 2-(3-tert-butylphenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate (340 mg, 49 %), Chiral purity 99.9 %ee, Optical rotation $[\alpha]_D^{20} = +55.8$ (acetonitrile, c=1).

Step 4: 5-((2R,4S)-2-(3-tert-Butylphenyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-Methyl 2-(3-tert-butylphenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.340 g, 0.95 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 5.49 mL, 31.35 mmol) and the solution stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4S)-2-(3-tert-butylphenyl)piperidin-4-yl)isoxazol-3(2H)-one (107 mg, 37 %). ^{1}H NMR (400 MHz, dmso) δ 1.26 (s, 9H), 1.32 – 1.43 (m, 1H), 1.43 – 1.54 (m, 1H), 1.81 – 1.90 (m, 1H), 1.90 – 1.99 (m, 1H), 2.68 – 2.78 (m, 1H), 2.80 – 2.91 (m, 1H), 3.08 – 3.16 (m, 1H), 3.59 – 3.66 (m, 1H), 5.72 (s, 1H), 7.13 – 7.29 (m, 3H), 7.37 (s, 1H). HRMS Calcd for $[C_{18}H_{24}N_2O_2+H]+$: 301.1916. Found: 301.1909.

Example 37

5-(Trans-2-(4-tert-butylphenyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(4-tert-butylphenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate

Magnesium chloride (5.38 g, 56.51 mmol) and potassium 3-ethoxy-3-oxopropanoate (9.62 g, 56.51 mmol) were suspended in methyl THF (100 mL) and heated to 50°C under nitrogen for 18 h using an oversized stirring bar, then cooled to room temperature (flask 1). In a separate flask was to a suspension of 2-(4-tert-butylphenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (9.5 g, 29.74 mmol) (reference compound 15) in methyl THF (100 mL) added di(1H-imidazol-1-yl)methanone (7.23 g, 44.62 mmol) under nitrogen. The resulting mixture was stirred at room temperature for 4 h (flask 2). Then, the contents of flask 2 is transferred into flask 1 by transfer needle. Wash with methyl THF (30 mL). Resulting suspension stirred at room temperature for 18 h. 3.8 M HCl was added (ca. 150 mL) and the resulting biphasic mixture stirred vigorously for 2 h. The phases were separated. The organic phase was washed with water, satd $NaHCO_3$ and brine, then dried over MgSO4 and evaporated. The residue was purified via Biotage in two equal portions (Biotage® KP-SIL 340g column, 1 CV 20% EtOAc in heptanes, then 20% => 60% over 7 CV). Trans-methyl 2-(4-tert-butylphenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (1.09 g, 9.4 %) was isolated as a pale yellow oil. ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.22 – 1.31 (m, 3H), 1.31 (s, 9H), 1.50 – 1.99 (m, 4H), 2.50 – 2.96 (m, 2H), 3.47 (s, 2H), 3.74 (s, 3H), 4.08 – 4.23 (m, 3H), 5.46 – 5.71 (m, 1H), 7.09 – 7.16 (m, 2H), 7.34 – 7.40 (m, 2H).

Step 2: Trans-methyl 2-(4-tert-butylphenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Trans-methyl 2-(4-tert-butylphenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (1.09 g, 2.80 mmol) was dissolved in MeOH (10 mL) and cooled to -40°C. Sodium hydroxide (0.112 g, 2.80 mmol) dissolved in water (1.2 mL) was added over 1 min and the resulting solution was stirred at -40°C for 20 min. Then, hydroxylamine (50 % in water, 0.178 mL, 2.91 mmol) was added over 1 min and stirring continued at -40°C for 3h. The reaction mixture was then transferred into a prewarmed (80°C) solution of 6M hydrogen chloride (30 mL, 180.00 mmol) and the mixture was continued to be stirred at 80°C for 1h. Then cooled to room temperature. Methanol was evaporated, then water was added. Extracted three times with DCM. Combined organic layers dried over $MgSO_4$ and evaporated. Crude trans-methyl 2-(4-tert-butylphenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (910 mg, 90 %) was isolated as off-white foam. ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.32 (s, 9H), 1.46 – 2.23 (m,

3H), 2.46 – 3.05 (m, 3H), 3.74 (s, 3H), 3.98 – 4.43 (m, 1H), 5.48 – 5.72 (m, 2H), 7.10 – 7.22 (m, 2H), 7.35 – 7.45 (m, 2H). MS m/z 359 $(M+H)^+$

Step 3: 5-(Trans-2-(4-tert-butylphenyl)piperidin-4-yl)isoxazol-3(2H)-one

Trans-methyl 2-(4-tert-butylphenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.26 g, 0.73 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 5 mL, 71.37 mmol) and stirred at room temperature for 18 h. Solvents were evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-(trans-2-(4-tert-butylphenyl)piperidin-4-yl)isoxazol-3(2H)-one (182 mg, 84 %). ^{1}H NMR (600 MHz, dmso) δ 1.23 (s, 9H), 1.76 – 1.85 (m, 2H), 1.86 – 1.93 (m, 1H), 1.96 – 2.03 (m, 1H), 2.71 (td, 1H), 2.81 – 2.88 (m, 1H), 3.10 – 3.15 (m, 1H), 3.65 (dd, 1H), 5.90 (s, 1H), 7.24 – 7.33 (m, 4H). HRMS Calculated for $[C_{18}H_{24}N_2O_2+H]^+$: 301.1916. Found: 301.1919

Example 38

5-((2R,4S)-2-(4-(Methylsulfonyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-(methylsulfonyl)phenyl)piperidine-1-carboxylate and cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-(methylsulfonyl)phenyl)-piperidine-1-carboxylate

1-(Methoxycarbonyl)-2-(4-(methylsulfonyl)phenyl)piperidine-4-carboxylic acid (4.756 g, 13.93 mmol) was dissolved in methyl THF (70 mL) and di(1H-imidazol-1-yl)methanone (3.39 g, 20.90 mmol) added. A thick white precipitate was formed. methyl THF (70.0 mL) was added and the suspension stirred under nitrogen at room temperature for 6 h (flask 1). In a separate flask potassium 3-ethoxy-3-oxopropanoate (4.74 g, 27.86 mmol) was suspended in methyl THF (70.0 mL) and magnesium chloride (2.65 g, 27.86 mmol) added. Heated at 50°C under nitrogen for 6 h (flask 2). The white suspension in flask 2 was then added to the thick white suspension in flask 1. The suspension was stirred at room temperature for 16 h. The temperature was increased to 50°C for 6 h. More of potassium 3-ethoxy-3-oxopropanoate (4.74 g, 27.86 mmol) and magnesium chloride (2.65 g, 27.86 mmol) in MeTHF (15 mL) was added along with dioxane (60 mL). The reaction was stirred at 50°C for 18 h. The reaction mixture was acidified to pH 1 with 3 M HCl. The organic phase was washed with water

(2x400 mL), satd $NaHCO_3$ (400 mL), brine (400 mL), dried with Na_2SO_4, filtered and evaporated in vacuo. The residue was purified by automated flash chromatography on a Biotage® KP-SIL 100g column. A gradient from 50 % EtOAc in heptane over 2 CV followed by 50 % to 80 % of EtOAc in heptane over 10 CV was used as mobile phase. Cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-(methylsulfonyl)phenyl)piperidine-1-carboxylate (2.70 g, 47.1 %) and trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-(methylsulfonyl)phenyl)-piperidine-1-carboxylate (0.505 g, 8.81 %) were isolated. Cis-isomer: NMR: ^{1}H NMR (600 MHz, CDCl3) δ 1.25 (t, 3H), 1.80 – 1.95 (m, 2H), 2.04 – 2.16 (m, 1H), 2.23 – 2.32 (m, 1H), 2.84 – 2.95 (m, 1H), 3.02 (s, 3H), 3.29 – 3.38 (m, 1H), 3.38 – 3.48 (m, 2H), 3.63 (s, 3H), 4.10 – 4.21 (m, 3H), 4.95 – 5.04 (m, 1H), 7.40 (d, 2H), 7.88 (d, 2H). MS m/z 410 $(M-H)^-$. Trans-isomer: ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.23 (t, 3H), 1.12 – 2.26 (m, 3H), 2.51 – 2.62 (m, 2H), 2.83 (td, 1H), 3.04 (s, 3H), 3.40 – 3.48 (s, 2H), 3.75 (s, 3H), 4.07 – 4.38 (m, 1H), 4.15 (q, 2H), 5.49 – 5.77 (m, 1H), 7.41 (d, 2H), 7.93 (d, 2H). MS m/z 412 $(M+H)^+$

Step 2: Cis-methyl 2-(4-(methylsulfonyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-(methylsulfonyl)phenyl)piperidine-1-carboxylate (2.6 g, 6.32 mmol) was suspended in MeOH (100 mL). DCM (40 mL) was added and the reaction cooled to - 40°C. 3.8 M sodium hydroxide (1.663 mL, 6.32 mmol) in water (10.00 mL) was added and the reaction stirred at - 40°C for 20 min. Hydroxylamine (50 % in water, 0.387 mL, 6.32 mmol) was added and the reaction stirred at - 40°C for 3 h. The reaction mixture was then added to a prewarmed 80°C solution of 6 M hydrogen chloride (63.2 mL, 379.13 mmol) and the reaction stirred for 30 min. The solvent was evaporated in vacuo. DCM (250 mL) and water (250 mL) were added, shaken and the phases separated. The organic phase was dried with a phase separator and evaporated in vacuo. The compound was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x50 ID mm) using a gradient of 15-45% Acetonitrile in H2O/MeCN/AcOH 95/5/0.2 buffer over 30 minutes with a flow of 100 mL/min. Cis-methyl 2-(4-(methylsulfonyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.200 g, 49.9 %) was isolated as a white solid. ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.85 – 1.91 (m, 1H), 2.18 – 2.29 (m, 2H), 2.35 – 2.41 (m, 1H), 2.98 (s, 3H), 3.00 – 3.13 (m, 1H), 3.38 – 3.44 (m, 1H), 3.67 (s, 3H), 4.13 – 4.19 (m, 1H), 5.20 (t, 1H), 5.47 (s, 1H), 7.34 (d, 2H), 7.83 (d, 2H). MS m/z 381 $(M+H)^+$

Step 3: (2R,4S)-Methyl 2-(4-(methylsulfonyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 2-(4-(methylsulfonyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.200 g, 3.16 mmol) was subjected to chiral preparative HPLC (Column: ReproSil (250x50), 8 µm particle size, mobile phase: EtOH, flow rate 120 mL/min) to yield (2R,4S)-methyl 2-(4-(methylsulfonyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (536 mg, 45%), Chiral purity 99.9 %ee, Optical rotation $[\alpha]_D^{20} = +59.5$ (acetonitrile, c=1), ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.78 – 1.85 (m, 1H), 2.12 – 2.23 (m, 2H), 2.29 – 2.37 (m, 1H), 2.93 (s, 3H), 3.02 – 3.08 (m, 1H), 3.33 – 3.41 (m, 1H), 3.61 (s, 3H), 4.07 – 4.13 (m, 1H), 5.14 (t, 1H), 5.44 (s, 1H), 7.31 (d, 2H), 7.77 (d, 2H).

Step 4: 5-((2R,4S)-2-(4-(Methylsulfonyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-Methyl 2-(4-(methylsulfonyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (536 mg, 1.41 mmol) was dissolved in hydrogen bromide (33 % in AcOH, 5 mL, 71.37 mmol) and stirred at room temperature for 20 h. The reaction mixture was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx III, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4S)-2-(4-(methylsulfonyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one (309 mg, 68 %),^{1}H NMR (600 MHz, dmso) δ 1.39 (q, 1H), 1.49 (dq, 1H), 1.87 – 1.93 (m, 1H), 2.01 (d, 1H), 2.76 (t, 1H), 2.87 – 2.94 (m, 1H), 3.11 – 3.19 (m, 1H), 3.17 (s, 3H), 3.80 (d, 1H), 5.74 (s, 1H), 7.64 (d, 2H), 7.85 (d, 2H). HRMS Calcd for $[C_{15}H_{18}N_2O_4S+H]+$: 323.1065. Found: 323.1042.

Example 39

5-((Trans-2-(4-(methylsulfonyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(4-(methylsulfonyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate

Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-(methylsulfonyl)phenyl)piperidine-1-carboxylate (505 mg, 1.23 mmol) (from example 38, step 1) was suspended in MeOH (5 mL)

and cooled to - 40°C. 3.8 M sodium hydroxide (0.323 mL, 1.23 mmol) in water was added. After 20 min, hydroxylamine (50 % in water, 0.075 mL, 1.23 mmol) was added and stirring continued at - 40°C for 3 h. The reaction mixture was then added to a prewarmed 80°C solution of 6 M hydrogen chloride (6.14 mL, 36.82 mmol) and stirred for 20 min. The solvent was evaporated in vacuo. DCM (50 mL) and water (50 mL) were added, shaken and the phases separated. The organic phase was dried with a phase separator and evaporated in vacuo. The residue was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x20 ID mm) using a gradient of 15-40% Acetonitrile in H2O/MeCN/AcOH 95/5/0.2 buffer, over 25 minutes with a flow of 19 mL/min. Trans-methyl 2-(4-(methylsulfonyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (301 mg, 64.5 %) was isolated. ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.61 – 1.73 (m, 1H), 1.91 – 1.99 (m, 1H), 2.05 – 2.14 (m, 1H), 2.66 – 2.82 (m, 2H), 2.91 (t, 1H), 3.05 (s, 3H), 3.77 (s, 3H), 4.12 – 4.46 (m, 1H), 5.60 – 5.80 (m, 2H), 7.44 (d, 2H), 7.95 (d, 2H). MS m/z 381 $(M+H)^+$

Step 2: 5-(Trans-2-(4-(methylsulfonyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one

Trans-methyl 2-(4-(methylsulfonyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (301 mg, 0.79 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 2 mL, 28.55 mmol) and stirred at room temperature for 20 h. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-(trans-2-(4-(methylsulfonyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one (119 mg, 47 %), HRMS Calcd for $[C_{15}H_{18}N_2O_4S+H]+$: 323.1065. Found: 323.1054.

Example 40

5-((2R,4S)-2-(6-(Trifluoromethyl)pyridin-3-yl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(6-(trifluoromethyl)pyridin-3-yl)piperidine-1-carboxylate and cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(6-(trifluoromethyl)pyridin-3-yl)piperidine-1-carboxylate

1-(Methoxycarbonyl)-2-(6-(trifluoromethyl)pyridin-3-yl)piperidine-4-carboxylic acid (2.5 g, 3.76 mmol) (reference compound 17) was dissolved in methyl THF (80 mL) then di(1H-imidazol-1-yl)methanone (1.098 g, 6.77 mmol) was added. The mixture was stirred at room

temperature under nitrogen for 3 h (flask 1). In a separate flask potassium 3-ethoxy-3-oxopropanoate (1.153 g, 6.77 mmol) was suspended in methyl THF (80 mL), then magnesium chloride (0.645 g, 6.77 mmol) was added. The suspension was stirred at 50°C under nitrogen for 3 h using a large magnetic stirring bar (flask 2). After 3 h, the contents of flask 1 was transferred into flask 2. The resulting white suspension was stirred under nitrogen at room temperature overnight. The mixture was acidified to pH 1 with 3.8 M HCl, then MTBE (50 mL) and water (50 mL) was added. The phases were separated and the organic layer was washed with water, satd $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and evaporated leaving a slightly yellow oil. The product was flashed on Biotage (340g) with 1 CV at 20 % followed by a gradient of 20-60% EtOAc in n-heptane (8 CV). Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(6-(trifluoromethyl)pyridin-3-yl)piperidine-1-carboxylate (70 mg, 5 %) and cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(6-(trifluoro-methyl)pyridin-3-yl)piperidine-1-carboxylate (1.085 g, 72 %) were isolated. Cis-isomer: MS m/z 403 $(M+H)^+$. Trans-isomer: ^1H NMR (400 MHz, cdcl$_3$) δ 1.18 – 1.31 (m, 3H), 1.53 – 1.72 (m, 1H), 1.82 – 1.93 (m, 1H), 2.00 – 2.13 (m, 1H), 2.49 – 2.69 (m, 2H), 2.82 (dt, 1H), 3.46 (d, 2H), 3.76 (s, 3H), 4.10 – 4.40 (m, 3H), 5.72 (s, br., 1H), 7.64 – 7.77 (m, 2H), 8.63 (s, 1H). MS m/z 403 $(M+H)^+$

Step 2: Cis-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(6-(trifluoromethyl)pyridin-3-yl)-piperidine-1-carboxylate

Cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(6-(trifluoromethyl)pyridin-3-yl)piperidine-1-carboxylate (1.085 g, 2.70 mmol) was dissolved in MeOH (12 mL) and cooled to -45°C under nitrogen. Sodium hydroxide (0.793 mL, 2.70 mmol) was added during 10 min and the yellow solution continued to stir at -45°C for 20 min. Hydroxylamine (50 % by weight in water, 0.165 mL, 2.70 mmol) was added during 8 min. The resulting solution was stirred at -45°C for 3 h. The mixture was then rapidly poured into a prewarmed (80°C) solution of 6 M hydrogen chloride (13.89 mL, 83.32 mmol) and the mixture continued to stir at 80°C for 20 min. The solvent was evaporated and DCM/water added. The phases were separated and the organic phase passed through a phase separator and evaporated to yield a white solid. The compound was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x50 ID mm) using a gradient of 10-60% Acetonitrile in H2O/MeCN/AcOH 95/5/0.2 buffer over 30 minutes with a flow of 100 mL/min. Cis-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(6-

(trifluoromethyl)pyridin-3-yl)piperidine-1-carboxylate (160 mg, 16 %) was isolated. MS m/z 372 $(M+H)^+$

Step 3: (2R,4S)-Methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(6-(trifluoromethyl)pyridin-3-yl)piperidine-1-carboxylate

Cis-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(6-(trifluoromethyl)pyridin-3-yl)piperidine-1-carboxylate (160 mg, 0.43 mmol) was subjected to chiral preparative HPLC (Column: CelluCoat (250x50 mm), 10 µm particle size, mobile phase: Heptane/EtOH 50/50, flow rate 120 mL/min) to yield (2R,4S)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(6-(trifluoromethyl)pyridin-3-yl)piperidine-1-carboxylate (74.5 mg, 47 %), Chiral purity 99.9 %ee, Optical rotation $[\alpha]_D^{20} = +32.0$ (acetonitrile, c=0.1)

Step 4: 5-((2R,4S)-2-(6-(Trifluoromethyl)pyridin-3-yl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-Methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(6-(trifluoromethyl)pyridin-3-yl)-piperidine-1-carboxylate (74.5 mg, 0.20 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 1.58 mL, 9.03 mmol) and the mixture was stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4S)-2-(6-(trifluoromethyl)pyridin-3-yl)piperidin-4-yl)isoxazol-3(2H)-one (43 mg, 68 %), ^{1}H NMR (600 MHz, dmso) δ 1.36 – 1.53 (m, 2H), 1.89 (d, 1H), 2.04 (d, 1H), 2.70 – 2.78 (m, 1H), 2.90 (tt, 1H), 3.09 – 3.16 (m, 1H), 3.83 (d, 1H), 5.75 (s, 1H), 7.84 (d, 1H), 8.04 (dd, 1H), 8.75 (d, 1H). HRMS Calculated for $[C_{14}H_{14}F_3N_3O_2+H]^+$: 314.1116. Found: 314.1134

Example 41

5-(Trans-2-(6-(trifluoromethyl)pyridin-3-yl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(6-(trifluoromethyl)pyridin-3-yl)piperidine-1-carboxylate

Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(6-(trifluoromethyl)pyridin-3-yl)piperidine-1-carboxylate (70 mg, 0.17 mmol) (from example 40, step 1) was dissolved in MeOH (1 mL)

and cooled to -45°C under nitrogen. Sodium hydroxide (0.051 mL, 0.17 mmol) was added during 10 min and the yellow solution continued to stir at -45°C for 20 min. Hydroxylamine (50 % by weight in water, 10.66 µL, 0.17 mmol) was added during 8 min. The resulting solution was stirred at -45°C for 3 h. The mixture was then rapidly poured into a prewarmed (80°C) solution of 6 M hydrogen chloride (0.896 mL, 5.38 mmol) and the mixture continued to stir at 80°C for 20 min. The solvent was evaporated and DCM/water added. The phases were separated and the organic phase passed through a phase separator and evaporated to yield crude trans-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(6-(trifluoromethyl)pyridin-3-yl)piperidine-1-carboxylate (60 mg, quant.) as a slightly yellow oil. MS m/z 372 $(M+H)^+$

Step 2: 5-(Trans-2-(6-(trifluoromethyl)pyridin-3-yl)piperidin-4-yl)isoxazol-3(2H)-one

Trans-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(6-(trifluoromethyl)pyridin-3-yl)-piperidine-1-carboxylate (60 mg, 0.16 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 1.27 mL, 7.27 mmol) and the mixture was stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-(trans-2-(6-(trifluoromethyl)pyridin-3-yl)piperidin-4-yl)isoxazol-3(2H)-one (11.4 mg, 23 %), ^{1}H NMR (400 MHz, dmso) δ 1.77 – 1.99 (m, 3H), 2.06 – 2.16 (m, 1H), 2.69 – 2.80 (m, 1H), 2.83 – 2.94 (m, 1H), 3.07 – 3.59 (m, 1H), 3.94 (d, 1H), 6.03 (s, 1H), 7.86 (d, 1H), 8.08 (d, 1H), 8.78 (s, 1H). HRMS Calculated for $[C_{14}H_{14}F_3N_3O_2+H]^+$: 314.1116. Found: 314.1122

Example 42

5-((2R,4S)-2-(5-tert-Butylthiophen-2-yl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Cis-methyl 2-(5-tert-butylthiophen-2-yl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate

2-(5-tert-Butylthiophen-2-yl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (1.125 g, 3.46 mmol) (reference compound 18) was dissolved in THF (30 mL) and di(1H-imidazol-1-yl)methanone (0.911 g, 5.62 mmol) added. The suspension was stirred at room temperature under nitrogen for 6 h (flask 1). In a separate flask 3-ethoxy-3-oxopropanoic acid, potassium salt (1.509 g, 8.82 mmol) and magnesium chloride (0.84 g, 8.82 mmol) were suspended in

THF (30 mL) and stirred with an oversized stirring bar at 50°C under nitrogen for 20 h (flask 2). The white suspension in flask 2 was then added to flask 1. The thick white suspension was stirred at room temperature for 18 h. The reaction mixture was acidified by addition of 3 M HCl to pH 1. The solvent was evaporated in vacuo. MTBE (250 mL) and water were added, shaken and the phases separated. The organic phase was washed with water (200 mL), satd $NaHCO_3$ (200 mL), brine (200 mL), dried with a phase separator and evaporated in vacuo. The residue was purified by automated flash chromatography on a Biotage® KP-SIL 100g column. A gradient from 10 % EtOAc in heptane over 2 CV followed by 10 % to 40 % of EtOAc in heptane over 9 CV was used as mobile phase. Cis-methyl 2-(5-tert-butylthiophen-2-yl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (0.963 g, 70.4 %) was isolated. Cis-isomer: MS m/z 396 $(M+H)^+$

Step 2: Cis-methyl 2-(5-tert-butylthiophen-2-yl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate

Cis-methyl 2-(5-tert-butylthiophen-2-yl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (963 mg, 2.43 mmol) was dissolved in methanol (15 mL) and cooled to - 40°C. NaOH (0.641 mL, 2.43 mmol) dissolved in water (1 mL) was added and stirred for 20 min. Hydroxylamine (50 % by weight in water, 0.149 mL, 2.43 mmol) was added and the reaction stirred at - 40°C for 3 h. The reaction mixture was then added to a prewarmed 80°C solution of 6 M HCl (12.58 mL, 75.48 mmol) and stirred for 20 min. The solvent was evaporated in vacuo. DCM (150 mL) and water (150 mL) were added, shaken and the phases separated. The aqueous phase was extracted with DCM (150 mL). The combined organic phase were dried with a phase separator and evaporated in vacuo. The compound was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x50 ID mm) using a gradient of 35-75% Acetonitrile in H2O/MeCN/AcOH 95/5/0.2 buffer over 25 minutes with a flow of 100 mL/min. Cis-methyl 2-(5-tert-butylthiophen-2-yl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (436 mg, 49.1 %) was isolated as a white solid. MS m/z 363 $(M-H)^-$

Step 3: (2R,4S)-Methyl 2-(5-tert-butylthiophen-2-yl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate and (2S,4R)-methyl 2-(5-tert-butylthiophen-2-yl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 2-(5-tert-butylthiophen-2-yl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-

carboxylate (436 mg, 1.2 mmol) was subjected to chiral preparative HPLC (Column: CelluCoat (250x20 mm), 5 µm particle size, mobile phase: Heptane/EtOH 80/20, flow rate 18 mL/min) to yield (2R,4S)-methyl 2-(5-tert-butylthiophen-2-yl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (212 mg, 49 %), Chiral purity 98.7 %ee, Optical rotation $[\alpha]_D^{20} = +3.0$ (acetonitrile, c=1.0), ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.34 (s, 9H), 1.55 – 1.68 (m, 1H), 1.90 – 2.04 (m, 2H), 2.49 (d, 1H), 3.12 (s, br., 2H), 3.76 (s, 3H), 4.19 (d, br., 1H), 5.60 – 5.87 (m, 2H), 6.59 – 6.69 (m, 2H) and (2S,4R)-methyl 2-(5-tert-butylthiophen-2-yl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (210 mg, 48 %), Chiral purity 99.3 %ee, Optical rotation $[\alpha]_D^{20} = -1.1$ (acetonitrile, c=1.0), ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.33 (s, 9H), 1.54 – 1.66 (m, 1H), 1.88 – 2.03 (m, 2H), 2.48 (d, 1H), 3.11 (s, br., 2H), 3.74 (s, 3H), 4.17 (d, br., 1H), 5.58 – 5.85 (m, 2H), 6.58 – 6.67 (m, 2H).

Step 4: 5-((2R,4S)-2-(5-tert-butylthiophen-2-yl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-Methyl 2-(5-tert-butylthiophen-2-yl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (50 mg, 0.14 mmol) was dissolved in hydrobromic acid (33 % in acetic acid, 1 mL, 6.08 mmol) and stirred at room temperature for 24 h. The solvent was evaporated in vacuo and the residue was purified by preparative HPLC on a XBridge C18 column (10 µm 250x19 ID mm) using a gradient of 10-50% Acetonitrile in H2O/MeCN/NH3 95/5/0.2 buffer over 25 minutes with a flow of 19 mL/min. 5-((2R,4S)-2-(5-tert-Butylthiophen-2-yl)piperidin-4-yl)isoxazol-3(2H)-one (4.00 mg, 9.52 %) was isolated as a white solid. ^{1}H NMR (400 MHz, cd$_3$od) δ 1.36 (s, 9H), 1.99 – 2.17 (m, 2H), 2.20 – 2.31 (m, 1H), 2.36 – 2.44 (m, 1H), 3.05 – 3.21 (m, 2H), 3.28 – 3.37 (m, 1H), 4.37 (dd, 1H), 5.70 (d, 1H), 6.77 (d, 1H), 6.93 (d, 1H). HRMS Calculated for $[C_{16}H_{22}N_2O_2S+H]^+$: 307.1480. Found: 307.1502

Example 43

5-((2S,4R)-2-(5-tert-Butylthiophen-2-yl)piperidin-4-yl)isoxazol-3(2H)-one

(2S,4R)-Methyl 2-(5-tert-butylthiophen-2-yl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (50 mg, 0.14 mmol) (from example 42, step 3) was dissolved in hydrobromic acid (33 % in AcOH, 1 mL, 6.08 mmol) and stirred at room temperature for 20 h. The solvent was evaporated in vacuo. The compound was purified by preparative HPLC on a XBridge C18

column (10 µm 250x19 ID mm) using a gradient of 10-50% Acetonitrile in H2O/MeCN/NH3 95/5/0.2 buffer over 25 minutes with a flow of 19 mL/min. 5-((2S,4R)-2-(5-tert-Butylthiophen-2-yl)piperidin-4-yl)isoxazol-3(2H)-one (7.00 mg, 16.65 %) was isolated as a white solid. ^{1}H NMR (600 MHz, cd_3od) δ 1.36 (s, 9H), 2.03 – 2.12 (m, 1H), 2.12 – 2.19 (m, 1H), 2.26 – 2.33 (m, 1H), 2.40 – 2.46 (m, 1H), 3.09 – 3.17 (m, 1H), 3.18 – 3.24 (m, 1H), 3.34 – 3.40 (m, 1H), 4.38 – 4.44 (m, 1H), 5.75 (s, 1H), 6.78 (d, 1H), 6.96 (d, 1H).

Example 44

5-((2R,4S)-2-(2,4-Difluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Cis-methyl 2-(2,4-difluorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate

2-(2,4-Difluorophenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (2.20 g, 7.35 mmol) (reference compound 19) was dissolved in methyl THF (70 mL), then di(1H-imidazol-1-yl)methanone (2.146 g, 13.23 mmol) was added. The mixture was stirred at room temperature under nitrogen for 5 h (flask 1). In a separate flask potassium 3-ethoxy-3-oxopropanoate (2.252 g, 13.23 mmol) was suspended in methyl THF (70.0 mL), then magnesium chloride (1.260 g, 13.23 mmol) was added. The suspension was stirred at 50°C under nitrogen for 5 h using a large magnetic stirring bar (flask 2). After the 3 h, the contents of flask 1 was transferred into flask 2. The resulting white suspension was stirred under nitrogen at room temperature overnight. The mixture was acidified to pH 1 with 3.8 M HCl, then MTBE (50 mL) and water (50 mL) was added. The phases were separated and the organic layer was washed with water, satd $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and evaporated leaving a slightly yellow oil. The product was flashed on Biotage (340g) with 1 CV EtOAc in heptane (20%) followed by a gradient of 20-60% EtOAc in n-heptane (8 CV). The column was conditioned at 20% EtOAc in -n-heptane (1 CV). Cis-methyl 2-(2,4-difluorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (870 mg, 32 %) was isolated. MS m/z 370 $(M+H)^+$

Step 2: Cis-methyl 2-(2,4-difluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 2-(2,4-difluorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (870

mg, 2.36 mmol) was dissolved in MeOH (9 mL) and cooled to -45°C under nitrogen. Sodium hydroxide (0.693 mL, 2.36 mmol) was added during 10 min and the yellow solution continued to stir at -45°C for 20 min. Hydroxylamine (50 % by weight in water, 0.144 mL, 2.36 mmol) was added during 8 min. The resulting solution was stirred at -45°C for 3 h. The mixture was then rapidly poured into a prewarmed (80°C) solution of 6 M hydrogen chloride (12.13 mL, 72.78 mmol) and the mixture continued to stir at 80°C for 20 min. The solvent was evaporated and DCM/water added. The phases were separated and the organic phase passed through a phase separator and evaporated to yield a white solid. The compound was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x50 ID mm) using a gradient of 10-60% Acetonitrile in H2O/MeCN/AcOH 95/5/0.2 buffer over 30 minutes with a flow of 100 mL/min. Cis-methyl 2-(2,4-difluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (397 mg, 49 %) was isolated . MS m/z 339 $(M+H)^+$

Step 3: (2R,4S)-Methyl 2-(2,4-difluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 2-(2,4-difluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (397 mg, 1.17 mmol) was subjected to chiral preparative HPLC (Column: CelluCoat (250x50 mm), 10 µm particle size, mobile phase: Heptane/EtOH 60/40, flow rate 120 mL/min) to yield (2R,4S)-methyl 2-(2,4-difluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (187 mg, 47 %), Chiral purity 99.1 %ee, Optical rotation $[\alpha]_D^{20} = +65.0$ (acetonitrile, c=0.5), ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.82 – 1.92 (m, 1H), 2.02 – 2.14 (m, 1H), 2.23 – 2.40 (m, 2H), 3.01 – 3.13 (m, 1H), 3.44 – 3.55 (m, 1H), 3.63 (s, 3H), 4.11 – 4.21 (m, 1H), 5.16 (dd, 1H), 5.61 (s, 1H), 6.74 – 6.83 (m, 2H), 7.06 – 7.15 (m, 1H).

Step 4: 5-((2R,4S)-2-(2,4-difluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-methyl 2-(2,4-difluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (187 mg, 0.55 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 4.36 mL, 24.87 mmol) and the mixture was stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4S)-2-(2,4-difluorophenyl)piperidin-4-yl)isoxazol-3(2H)-

one (93 mg, 60 %). ^{1}H NMR (600 MHz, dmso) δ 1.36 (q, 1H), 1.46 (dq, 1H), 1.83 – 1.89 (m, 1H), 1.90 – 1.95 (m, 1H), 2.72 (dt, 1H), 2.89 (tt, 1H), 3.06 – 3.12 (m, 1H), 3.89 (dd, 1H), 5.73 (s, 1H), 7.03 (dt, 1H), 7.11 – 7.17 (m, 1H), 7.52 – 7.59 (m, 1H). HRMS Calculated for $[C_{14}H_{14}F_2N_2O_2+H]^+$: 281.1101. Found: 281.1106

Example 45

5-((2R,4S)-2-(4-Chloro-2-fluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(4-chloro-2-fluorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate and cis-methyl 2-(4-chloro-2-fluorophenyl)-4-(3-ethoxy-3-oxopropanoyl)-piperidine-1-carboxylate

2-(4-Chloro-2-fluorophenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (6.49 g, 20.56 mmol) (reference compound 20) was dissolved in methyl THF (250 mL), then di(1H-imidazol-1-yl)methanone (5.00 g, 30.83 mmol) was added. The mixture was stirred at room temperature under nitrogen for 3 h (flask 1). In a separate flask potassium 3-ethoxy-3-oxopropanoate (6.30 g, 37.00 mmol) was suspended in methyl THF (250 mL), then magnesium chloride (3.52 g, 37.00 mmol) was added. The suspension was stirred at 50°C under nitrogen for 3 h using a large magnetic stirring bar (flask 2). After the 3 h, the contents of flask 1 was transferred into flask 2. The resulting white suspension was stirred under nitrogen at room temperature overnight. The mixture was acidified to pH 1 with 3.8 M HCl, then MTBE (50 mL) and water (50 mL) was added. The phases were separated and the organic layer was washed with water, satd $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and evaporated leaving a slightly yellow oil. The product was flashed on Biotage (340g) with 1 CV 20 % EtOAc in heptane followed by a gradient of 20-60% EtOAc in n-heptane (8 CV). The column was conditioned at 20% EtOAc in -n-heptane (1 CV). Trans-methyl 2-(4-chloro-2-fluorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (0.5 g, 6 %) and cis-methyl 2-(4-chloro-2-fluorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (2.31 g, 29 %) were isolated. Cis-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.27 (t, 3H), 1.79 – 1.99 (m, 2H), 2.03 – 2.21 (m, 1H), 2.23 – 2.32 (m, 1H), 2.84 – 2.95 (m, 1H), 3.33 – 3.51 (m, 3H), 3.62 (s, 3H), 4.12 – 4.23 (m, 3H), 4.98 – 5.21 (m, 1H), 6.98 – 7.24 (m, 3H). MS m/z 386 $(M+H)^+$. Trans-isomer:^{1}H NMR (400 MHz, cdcl$_3$) δ 1.22 (t, 3H), 1.57 – 1.69 (m, 1H), 1.86 – 2.01 (m, 2H), 2.36 – 2.62 (m, 2H), 3.07 – 3.18 (m,

1H), 3.44 (s, 2H), 3.70 (s, 3H), 4.10 – 4.21 (m, 2H), 4.32 (br, 1H), 5.67 (br, 1H), 7.02 – 7.14 (m, 3H). MS m/z 386 $(M+H)^+$

Step 2: Cis-methyl 2-(4-chloro-2-fluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate

Cis-methyl 2-(4-chloro-2-fluorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (2.31 g, 5.99 mmol) was dissolved in MeOH (24 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (1.761 mL, 5.99 mmol) was added during 10 min and the yellow solution continued to stir at -40°C for 20 min. Hydroxylamine (50 % by weight in water, 0.367 mL, 5.99 mmol) was added during 8 min. The resulting solution was stirred at -40°C for 3 h. The mixture was then rapidly poured into a prewarmed (80°C) solution of 6 M hydrogen chloride (30.8 mL, 185.01 mmol) and the mixture continued to stir at 80°C for 20 min. The solvent was evaporated and DCM/water added. The phases were separated and the organic phase passed through a phase separator and evaporated to yield a slightly yellow solid. The compound was purified by preparative HPLC on a XBridge C18 column (10 µm 250x50 ID mm) using a gradient of 10-55% Acetonitrile in H2O/MeCN/NH3 95/5/0.2 buffer over 30 minutes with a flow of 100 mL/min. Cis-methyl 2-(4-chloro-2-fluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1 g, 47 %) was isolated after. MS m/z 355 $(M+H)^+$

Step 3: (2R,4S)-methyl 2-(4-chloro-2-fluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate

Cis-methyl 2-(4-chloro-2-fluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1g, 2.82 mmol) was subjected to chiral preparative HPLC (Column: CelluCoat (250x50), 10 µm particle size, mobile phase: Heptane/IPA 50/50, flow rate 120 mL/min) to yield (2R,4S)-methyl 2-(4-chloro-2-fluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate (504 mg, 50 %), Chiral purity 99.7 %ee. Optical rotation $[\alpha]_D^{20} = +65.5$ (acetonitrile, c=1)

Step 4: 5-((2R,4S)-2-(4-chloro-2-fluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-Methyl 2-(4-chloro-2-fluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.504 g, 1.42 mmol) was dissolved in hydrogen bromide (33 % in acetic acid,

11.20 mL, 63.93 mmol) and the mixture was stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4S)-2-(4-chloro-2-fluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one (313 mg, 74 %). ^{1}H NMR (600 MHz, dmso) δ 1.35 (q, 1H), 1.46 (dq, 1H), 1.86 (d, 1H), 1.94 (d, 1H), 2.73 (dt, 1H), 2.90 (tt, 1H), 3.10 (td, 1H), 3.91 (d, 1H), 5.73 (s, 1H), 7.25 (dd, 1H), 7.34 (dd, 1H), 7.55 (t, 1H). HRMS Calcd for $[C_{14}H_{14}ClFN_2O_2+H]+$: 297.0806. Found: 297.0786.

Example 46

5-(Trans-2-(4-chloro-2-fluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(4-chloro-2-fluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate

Trans-methyl 2-(4-chloro-2-fluorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (500 mg, 1.30 mmol) (from example 45, step 1) was dissolved in MeOH (6 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (0.381 mL, 1.30 mmol) was added during 10 min and the yellow solution continued to stir at -40°C for 20 min. Hydroxylamine (50 % by weight in water, 0.079 mL, 1.30 mmol) was added during 8 min. The resulting solution was stirred at -40°C for 3 h. The mixture was then rapidly poured into a prewarmed (80°C) solution of 6 M hydrogen chloride (6.67 mL, 40.05 mmol) and the mixture continued to stir at 80°C for 20 min. The solvent was evaporated and DCM/water added. The phases were separated and the organic phase passed through a phase separator and evaporated to yield crude trans-methyl 2-(4-chloro-2-fluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.45 g, 98 %) as a slightly yellow dry film. MS m/z 355 $(M+H)^+$

Step 2: 5-(Trans-2-(4-chloro-2-fluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

(2S,4S)-methyl 2-(4-chloro-2-fluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.45 g, 1.27 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 10.00 mL, 57.08 mmol) and the mixture was stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge

Prep C18 5µm OBD 19*150 mm) to yield 5-(trans-2-(4-chloro-2-fluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one (82 mg, 22 %). ^{1}H NMR (400 MHz, dmso) δ 1.66 – 1.77 (m, 1H), 1.77 – 1.90 (m, 1H), 1.92 – 2.00 (m, 1H), 2.02 – 2.10 (m, 1H), 2.63 – 2.79 (m, 1H), 2.88 – 2.97 (m, 1H), 3.03 – 3.86 (omitted signals), 3.95 (d, 1H), 5.88 (s, 1H), 7.27 (dd, 1H), 7.35 (dd, 1H), 7.56 (t, 1H). HRMS Calcd for $[C_{14}H_{14}ClFN_2O_2+H]+$: 297.0806. Found: 297.0806.

Example 47

5-((2R,4S)-2-(2-Chloro-4-fluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Methyl 2-(2-chloro-4-fluorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate

2-(2-Chloro-4-fluorophenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (2.13 g, 6.75 mmol) (reference compound 21) was dissolved in methyl THF (50 mL) under nitrogen atmosphere and di(1H-imidazol-1-yl)methanone (1.641 g, 10.12 mmol) was added. The suspension was stirred at room temperature for 3 h (flask 1). In a separate flask was potassium 3-ethoxy-3-oxopropanoate (2.067 g, 12.14 mmol) suspended in methyl THF (25 mL) and magnesium chloride (1.156 g, 12.14 mmol) was added. The suspension was stirred at 50°C under nitrogen for 15 h using an oversized stirring bar. The contents of flask 1 was added to flask 2 and the resulting white suspension was stirred at room temperature for 20 h. In a separate flask was potassium 3-ethoxy-3-oxopropanoate (1.033 g, 6.07 mmol) suspended in methyl THF (25 mL) and magnesium chloride (0.578 g, 6.07 mmol) was added. The suspension was stirred at 50°C for 15 h and then added to the reaction mixture. The mixture was stirred at room temperature for 15 h. 0.1 M HCl and DCM were added and the phases separated. The aqueous phase was extracted with DCM, the combined organic layers filtered through a phase separator and evaporated. The residue was purified via Biotage (gradient 2:1->1:1 heptane:EtOAc, Biotage® KP-SIL 340g column, 10 CV). Methyl 2-(2-chloro-4-fluorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (1.655 g, 63.6 %) was isolated as a colorless oil. MS m/z 386 $(M+H)^+$

Step 2: Methyl 2-(2-chloro-4-fluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Methyl 2-(2-chloro-4-fluorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (1.655 g, 4.29 mmol) was dissolved in MeOH (22 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (0.180 g, 4.50 mmol) dissolved in water (2.200 mL) was added and the mixture was stirred at -40°C for 15 min. Hydroxylamine (50 % by weight in water, 0.276 mL, 4.50 mmol) was added. The resulting solution was stirred at -40°C for 1h. The mixture was then transferred with a pipette into a prewarmed (80°C) solution of 6 M hydrogen chloride (22.16 mL, 132.98 mmol) and the mixture was stirred at 80°C for 15 min. Water and DCM were added and the phases separated. The aqueous phase was extracted with DCM and the combined organic layers were filtered through a phase separator and evaporated. The compound was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x50 ID mm) using a gradient of 15-55% Acetonitrile in H2O/MeCN/FA 95/5/0.2 buffer over 25 minutes with a flow of 100 mL/min (3 runs). Methyl 2-(2-chloro-4-fluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.995 g, 65.4 %) was yielded as a white solid. MS m/z 355 $(M+H)^+$

Step 3: (2R,4S)-Methyl 2-(2-chloro-4-fluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate and trans-methyl 2-(2-chloro-4-fluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Methyl 2-(2-chloro-4-fluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.995 g, 2.81 mmol) was subjected to chiral chromatography: Separation 1: Chiral preparative HPLC (Column: Chiralpak IA (250x50 mm), 20 µm particle size, mobile phase: Heptane/EtOH 70/30, flow rate 120 mL/min). Separation 2: Chiral preparative HPLC (Column: CelluCoat (250x50 mm), 10 µm particle size, mobile phase: Heptane/EtOH 90/10, flow rate 120 mL/min). (2R,4S)-Methyl 2-(2-chloro-4-fluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate was isolated (382 mg, 38 %), Chiral purity: 98.9 %ee. Optical rotation $[\alpha]_D^{20} = +71.2$ (acetonitrile, c=0.5). Trans-methyl 2-(2-chloro-4-fluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate was isolated (130 mg, 13 %).

Step 4: 5-((2R,4S)-2-(2-Chloro-4-fluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-methyl 2-(2-chloro-4-fluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (382 mg, 1.08 mmol) was dissolved in hydrogen bromide (33 % in acetic acid

(8.5 mL, 48.46 mmol) and stirred at room temperature for 16 h. The solvent was removed in vacuo and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4S)-2-(2-chloro-4-fluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one (304 mg, 95 %). ^{1}H NMR (600 MHz, dmso) δ 1.24 (q, 1H), 1.47 (dq, 1H), 1.85 – 1.91 (m, 1H), 1.97 – 2.02 (m, 1H), 2.75 (dt, 1H), 2.87 (tt, 1H), 3.09 – 3.14 (m, 1H), 3.97 (d, 1H), 5.73 (d, 1H), 7.19 (dt, 1H), 7.37 (dd, 1H), 7.66 (dd, 1H). HRMS Calculated for $[C_{14}H_{14}ClFN_2O_2+H]^+$: 297.0806. Found: 297.0834

Example 48

5-(Trans-2-(2-chloro-4-fluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

Trans-methyl 2-(2-chloro-4-fluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (130 mg, 0.37 mmol) (from example 47, step 3) was dissolved in hydrogen bromide (33 % in acetic acid, 2.9 mL, 16.49 mmol) and stirred at room temperature for 16 h. The solvent was removed and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-(Trans-2-(2-chloro-4-fluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one (94 mg, 86 %). ^{1}H NMR (600 MHz, dmso) δ 1.50 – 1.60 (m, 1H), 1.79 – 1.88 (m, 1H), 1.95 – 2.01 (m, 1H), 2.06 – 2.12 (m, 1H), 2.70 (t, 1H), 2.88 – 2.96 (m, 1H), 3.20 – 3.24 (m, 1H), 4.01 (d, 1H), 5.95 (d, 1H), 7.21 (dt, 1H), 7.37 (dd, 1H), 7.68 (dd, 1H). HRMS Calculated for $[C_{14}H_{14}ClFN_2O_2+H]^+$: 297.0806. Found: 297.0823

Example 49

5-((2R,4S)-2-(4-Chloro-3-fluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(4-chloro-3-fluorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate and cis-methyl 2-(4-chloro-3-fluorophenyl)-4-(3-ethoxy-3-oxopropanoyl)-piperidine-1-carboxylate

2-(4-Chloro-3-fluorophenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (1.430 g, 4.53 mmol) (reference compound 22) was dissolved in methyl THF (20 mL) and di(1H-imidazol-1-

yl)methanone (1.102 g, 6.79 mmol) added. The reaction was stirred at room temperature for 6 h (flask 1). In a separate flask potassium 3-ethoxy-3-oxopropanoate (1.388 g, 8.15 mmol) was suspended in methyl THF (20.00 mL) and magnesium chloride (0.776 g, 8.15 mmol) added. The suspension was stirred at 50°C for 6 h (flask 2). The white suspension from flask 2 was added to flask 1. A white suspension was formed. The suspension was stirred at room temperature for 18 h. The suspension was acidified to pH 1 with 3 M HCl. MTBE (100 mL) and water (150 mL) were added, shaken and the phases separated. The organic phase was washed with water (150 mL), satd $NaHCO_3$ (150 mL) and brine (150 mL), dried with Na_2SO_4, filtered and evaporated in vacuo. The residue was purified by automated flash chromatography on a Biotage® KP-SIL 100g column. A gradient of 20% EtOAc in heptane over 2 CV followed by 20-60 % of EtOAc in heptane over 10 CV was used as mobile phase. Cis-methyl 2-(4-chloro-3-fluorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (1.153 g, 66.0 %) and trans-methyl 2-(4-chloro-3-fluorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (0.107 g, 6.12 %) were isolated as colorless oils. Cis-isomer: ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.19 – 1.30 (m, 3H), 1.73 – 1.97 (m, 2H), 2.00 – 2.16 (m, 1H), 2.20 – 2.27 (m, 1H), 2.81 – 2.89 (m, 1H), 3.24 – 3.48 (m, 3H), 3.60 – 3.65 (m, 3H), 4.04 – 4.20 (m, 3H), 4.84 – 4.98 (m, 1H), 6.86 – 7.01 (m, 2H), 7.28 – 7.34 (m, 1H). MS m/z 386 $(M+H)^+$.Trans-isomer: ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.19 – 1.29 (m, 3H), 1.38 – 2.98 (m, 6H), 3.39 – 3.49 (m, 2H), 3.63 – 3.82 (m, 3H), 4.00 – 4.37 (m, 3H), 5.56 (s, br., 1H), 6.86 – 7.02 (m, 2H), 7.33 – 7.39 (m, 1H). MS m/z 386 $(M+H)^+$

Step 2: Cis-methyl 2-(4-chloro-3-fluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 2-(4-chloro-3-fluorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (1.731 g, 4.49 mmol) was dissolved in MeOH (20 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (1.181 mL, 4.49 mmol) dissolved in water (2 mL) was added and the reaction stirred at -40°C for 20 min. Hydroxylamine (50 % by weight in water, 0.247 mL, 4.49 mmol) was added dropwise and stirring continued for 3 h. The mixture was then transferred to a prewarmed 80°C solution of 6 M hydrogen chloride (23.18 mL, 139.09 mmol) and stirring was continued at 80°C for 20 min. The solvent was evaporated and DCM (200 mL) and water (200 mL) were added. The phases were shaken, separated and the organic phase dried with a phase separator and evaporated in vacuo. The compound was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x50 ID mm) using a gradient of 10-60% Acetonitrile in

H2O/MeCN/AcOH 95/5/0.2 buffer over 30 minutes with a flow of 100 mL/min. Cis-methyl 2-(4-chloro-3-fluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate (0.921 g, 57.9 %) was isolated as a white solid. ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.79 – 1.87 (m, 1H), 2.06 – 2.15 (m, 1H), 2.19 – 2.28 (m, 1H), 2.30 – 2.37 (m, 1H), 3.00 – 3.09 (m, 1H), 3.31 – 3.40 (m, 1H), 3.66 (s, 3H), 4.07 – 4.16 (m, 1H), 5.00 – 5.07 (m, 1H), 5.56 (s, 1H), 6.87 – 6.91 (m, 1H), 6.95 (dd, 1H), 7.29 (t, 1H). MS m/z 355 $(M+H)^+$

Step 3: (2R,4S)-Methyl 2-(4-chloro-3-fluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 2-(4-chloro-3-fluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.921 g, 2.6 mmol) was subjected to chiral preparative HPLC (Column: CelluCoat (250x50 mm), 10 µm particle size, mobile phase: Heptane/EtOH 1/1, flow rate 120 mL/min) to yield (2R,4S)-methyl 2-(4-chloro-3-fluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (446 mg, 48 %), Chiral purity 99.9 %ee, Optical rotation $[\alpha]_D^{20} = +61.8$ (acetonitrile, c=0.5)

Step 4: 5-((2R,4S)-2-(4-chloro-3-fluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-Methyl 2-(4-chloro-3-fluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (446 mg, 1.26 mmol) was dissolved in hydrogen bromide (33 % in AcOH, 6.8 mL, 38.97 mmol) and stirred at room temperature for 20 h. The solvent was then evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4S)-2-(4-chloro-3-fluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one (266 mg, 71 %). ^{1}H NMR (600 MHz, dmso) δ 1.31 (q, 1H), 1.44 (dq, 1H), 1.82 – 1.89 (m, 1H), 1.94 – 2.00 (m, 1H), 2.70 (dt, 1H), 2.84 (tt, 1H), 3.06 – 3.12 (m, 1H), 3.66 (dd, 1H), 5.72 (s, 1H), 7.23 (dd, 1H), 7.38 (dd, 1H), 7.49 (t, 1H). HRMS Calculated for $[C_{14}H_{14}ClFN_2O_2+H]^+$: 297.0806. Found: 297.0795

Example 50

5-(Trans-2-(4-chloro-3-fluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(4-chloro-3-fluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Trans-methyl 2-(4-chloro-3-fluorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (171 mg, 0.44 mmol) (from example 49, step 1) was dissolved in MeOH (2 mL) and cooled to -40°C. Sodium hydroxide (0.117 mL, 0.44 mmol) dissolved in water (0.200 mL) was added dropwise and the solution stirred for 20 min. Hydroxylamine (50 % by weight in water, 0.024 mL, 0.44 mmol) was then added and stirring was continued for 3.5 h. The mixture was then transferred to a prewarmed 80°C solution of 6 M hydrogen chloride (2.290 mL, 13.74 mmol) and stirring was continued at 80°C for 20 min. The solvent was evaporated in vacuo and DCM (50 mL) and water (50 mL) were added. The phases were shaken, separated and the organic phase dried with a phase separator and evaporated in vacuo. The compound was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x20 ID mm) using a gradient of 10-60% Acetonitrile in H2O/MeCN/AcOH 95/5/0.2 buffer over 30 minutes with a flow of 19 mL/min. (2S,4S)-Methyl 2-(4-chloro-3-fluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (49.0 mg, 31.2 %) was isolated as a white solid. ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.58 – 1.70 (m, 1H), 1.85 – 2.06 (m, 2H), 2.60 (d, 1H), 2.73 – 2.96 (m, 2H), 3.73 (s, 3H), 4.04 – 4.44 (m, 1H), 5.42 – 5.78 (m, 2H), 6.92 – 7.05 (m, 2H), 7.38 (t, 1H). MS m/z 355 $(M+H)^+$

Step 2: 5-(Trans-2-(4-chloro-3-fluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

Trans-methyl 2-(4-chloro-3-fluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (49 mg, 0.14 mmol) was dissolved in hydrogen bromide (33 % in AcOH, 2 mL, 11.42 mmol) and stirred at room temperature for 5 h. The reaction was heated to 50°C for 3 h. The reaction mixture was evaporated in vacuo and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-(trans-2-(4-chloro-3-fluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one (23 mg, 56 %). ^{1}H NMR (600 MHz, dmso) δ 1.72 – 1.81 (m, 2H), 1.82 – 1.89 (m, 1H), 1.97 – 2.04 (m, 1H), 2.64 – 2.71 (m, 1H), 2.77 – 2.83 (m, 1H), 3.06 – 3.12 (m, 1H), 3.72 (dd, 1H), 5.96 (s, 1H), 7.23 (dd, 1H), 7.40 (dd, 1H), 7.49 (t, 1H). HRMS Calculated for $[C_{14}H_{14}ClFN_2O_2+H]^+$: 297.0806. Found: 297.0807

Example 51

5-((2R,4S)-2-(2,4-Dichlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Methyl 2-(2,4-dichlorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate

2-(2,4-Dichlorophenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (2.44 g, 7.35 mmol) (reference compound 23) was dissolved in methyl THF (36.7 mL) and di(1H-imidazol-1-yl)methanone (1.787 g, 11.02 mmol) added. The suspension was stirred at room temperature under nitrogen for 6 h (flask 1). In a separate flask potassium 3-ethoxy-3-oxopropanoate (2.250 g, 13.22 mmol) was suspended in methyl THF (36.7 mL) and magnesium chloride (1.259 g, 13.22 mmol) added. The suspension was stirred under nitrogen for 6 h (flask 2). The white suspension in flask 2 was then added to the brown suspension in flask 1. The resulting suspension was stirred at room temperature for 40 h. The mixture was acidified to pH 1 with 3 M HCl. Water and methyl THF were added, the phases separated. The organic layer was washed with water, satd $NaHCO_3$, brine, dried over $MgSO_4$, filtered and evaporated. Purified by flash chromatography using 20% EtOAc in heptane -> 50% EtOAc over 10 CV, 3CV at 50%. Repurified by flash chromatography using 20% EtOAc in EtOAc -> 30% EtOAc over 12 CV. Methyl 2-(2,4-dichlorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (1.55g, 52 %) was isolated.

Step 2: Methyl 2-(2,4-dichlorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Methyl 2-(2,4-dichlorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (1.55 g, 3.85 mmol) was dissolved in MeOH (15.79 mL) and cooled to - 40°C under nitrogen. Sodium hydroxide (1.014 mL, 3.85 mmol) in water (1.579 mL) was added and the mixture stirred at - 40°C for 20 min. Hydroxylamine (50 % by weight in water, 0.236 mL, 3.85 mmol) was added and stirring continued at - 40°C for 3.5 h. The reaction mixture was then transferred to a preheated 80°C solution of 6 M hydrogen chloride (19.91 mL, 119.45 mmol) and heating was continued for 20 min. The solvent was then evaporated. DCM and water were added, shaken and the phases separated. The organic phase was dried with a phase separator and evaporated in vacuo. The compound was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x50 ID mm) using a gradient of 25-65% Acetonitrile in H2O/MeCN/AcOH 95/5/0.2 buffer over 30 minutes with a flow of 100 mL/min. Methyl 2-(2,4-dichlorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.870 g, 60.8 %) was isolated as a white solid. MS m/z 371 $(M+H)^+$

Step 3: (2R,4S)-Methyl 2-(2,4-dichlorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate, (2S,4R)-methyl 2-(2,4-dichlorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate, (2S,4S)-methyl 2-(2,4-dichlorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate and (2R,4R)-methyl 2-(2,4-dichlorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Methyl 2-(2,4-dichlorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.870 g, 2.34 mmol) was subjected to chiral preparative HPLC: Separation 1: The enantiomers were separated using chiral preparative HPLC (Column: ReproSil (250x50 mm), 8 µm particle size, mobile phase: Heptane/EtOH/FA 60/40/0.1, flow rate 120 mL/min) to yield a mixture of one cis- and one trans-enantiomer. Separation 2: The enantiomers were separated using chiral preparative HPLC (Column: CelluCoat (250x20 mm), 5 µm particle size, mobile phase: Heptane/IPA/FA 80/20/0.1, flow rate 18 mL/min). (2R,4S)-Methyl 2-(2,4-dichlorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (334 mg, 38 %) was isolated. Chiral purity 99.7 %de, Optical rotation $[\alpha]_D^{20} = +64.0$ (acetonitrile, c=1.0), ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.79 – 1.92 (m, 2H), 2.25 – 2.48 (m, 2H), 3.02 – 3.13 (m, 1H), 3.53 – 3.64 (m, 4H), 4.12 – 4.21 (m, 1H), 5.16 (dd, 1H), 5.64 (s, 1H), 7.12 – 7.22 (m, 2H), 7.36 (d, 1H). (2S,4R)-methyl 2-(2,4-dichlorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (340 mg, 39 %) was isolated. Chiral purity 99.9 %de, Optical rotation $[\alpha]_D^{20} = -65.1$ (acetonitrile, c=1.0), ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.79 – 1.92 (m, 2H), 2.26 – 2.38 (m, 1H), 2.39 – 2.48 (m, 1H), 3.03 – 3.13 (m, 1H), 3.53 – 3.64 (m, 4H), 4.12 – 4.22 (m, 1H), 5.16 (dd, 1H), 5.64 (s, 1H), 7.13 – 7.22 (m, 2H), 7.36 (d, 1H). (2S,4S)-Methyl 2-(2,4-dichlorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (67 mg, 8%) was isolated. Chiral purity 98.7 %de, Optical rotation $[\alpha]_D^{20} = +11.5$ (acetonitrile, c=1.0), ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.72 (dq, 1H), 2.01 – 2.19 (m, 2H), 2.40 – 2.49 (m, 1H), 2.74 (tt, 1H), 3.43 (dt, 1H), 3.66 (s, 3H), 4.40 (d, br., 1H), 5.61 – 5.71 (m, 2H), 7.14 – 7.24 (m, 2H), 7.40 (d, 1H). (2R,4R)-Methyl 2-(2,4-dichlorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (75 mg, 9 %) was isolated. Chiral purity 98.5 %de, Optical rotation $[\alpha]_D^{20} = -10.9$ (acetonitrile, c=1.0), ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.72 (dq, 1H), 2.01 – 2.19 (m, 2H), 2.40 – 2.49 (m, 1H), 2.74 (tt, 1H), 3.43 (dt, 1H), 3.68 (s, 3H), 4.40 (d, br., 1H), 5.61 – 5.71 (m, 2H), 7.14 – 7.24 (m, 2H), 7.41 (d, 1H).

Step 4: 5-((2R,4S)-2-(2,4-Dichlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-Methyl 2-(2,4-dichlorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (334mg, 0.90 mmol) was diluted with hydrogen bromide (33% in AcOH, 4.7 mL, 26.99 mmol) and stirred at ambient temperature for 24 h. Evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4S)-2-(2,4-dichlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one (173 mg, 61 %). ^{1}H NMR (600 MHz, dmso) δ 1.22 (q, 1H), 1.47 (dq, 1H), 1.85 – 1.90 (m, 1H), 1.97 – 2.02 (m, 1H), 2.74 (dt, 1H), 2.87 (tt, 1H), 3.09 – 3.14 (m, 1H), 3.96 (dd, 1H), 5.73 (d, 1H), 7.40 (dd, 1H), 7.54 (d, 1H), 7.64 (d, 1H). HRMS Calculated for $[C_{14}H_{14}Cl_2N_2O_2+H]^+$: 313.0511. Found: 313.0493

Example 52

5-((2S,4R)-2-(2,4-Dichlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

(2S,4R)-Methyl 2-(2,4-dichlorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (340mg, 0.92 mmol) (from example 51, step 3) was diluted with hydrogen bromide (33% in AcOH, 4812 µl, 27.48 mmol) and stirred at ambient temperature for 24h. Evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2S,4R)-2-(2,4-dichlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one (). ^{1}H NMR (600 MHz, dmso) δ 1.22 (q, 1H), 1.47 (dq, 1H), 1.84 – 1.90 (m, 1H), 1.96 – 2.03 (m, 1H), 2.74 (dt, 1H), 2.87 (tt, 1H), 3.07 – 3.15 (m, 1H), 3.96 (dd, 1H), 5.73 (s, 1H), 7.40 (dd, 1H), 7.54 (d, 1H), 7.64 (d, 1H). HRMS Calculated for $[C_{14}H_{14}Cl_2N_2O_2+H]^+$: 313.0511. Found: 313.0490

Example 53

5-((2S,4S)-2-(2,4-Dichlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

(2S,4S)-Methyl 2-(2,4-dichlorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (67 mg, 0.18 mmol) (from example 51, step 3) was diluted with hydrogen bromide (33% in AcOH, 948 µl, 5.41 mmol) and stirred at ambient temperature for 24h.

Evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2S,4S)-2-(2,4-dichlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one (36 mg, 64 %). ^{1}H NMR (600 MHz, dmso) δ 1.46 – 1.54 (m, 1H), 1.77 – 1.85 (m, 1H), 1.93 – 1.99 (m, 1H), 2.05 – 2.11 (m, 1H), 2.67 (dt, 1H), 2.86 – 2.92 (m, 1H), 3.18 – 3.22 (m, 1H), 3.98 (dd, 1H), 5.93 (d, 1H), 7.40 (dd, 1H), 7.53 (d, 1H), 7.66 (d, 1H). HRMS Calculated for $[C_{14}H_{14}Cl_2N_2O_2+H]^+$: 313.0511. Found: 313.0499

Example 54

5-((2R,4R)-2-(2,4-Dichlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4R)-Methyl 2-(2,4-dichlorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (75mg, 0.20 mmol) (from example 51, step 3) was diluted with hydrogen bromide (33% in AcOH, 1062 µl, 6.06 mmol) and stirred at ambient temperature for 24 h. Evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4R)-2-(2,4-dichlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one (38 mg, 60 %). ^{1}H NMR (600 MHz, dmso) δ 1.47 – 1.54 (m, 1H), 1.78 – 1.85 (m, 1H), 1.93 – 1.99 (m, 1H), 2.05 – 2.11 (m, 1H), 2.67 (dt, 1H), 2.86 – 2.92 (m, 1H), 3.18 – 3.22 (m, 1H), 3.98 (dd, 1H), 5.93 (d, 1H), 7.41 (dd, 1H), 7.53 (d, 1H), 7.66 (d, 1H). HRMS Calculated for $[C_{14}H_{14}Cl_2N_2O_2+H]^+$: 313.0511. Found: 313.0494

Example 55

5-((2R,4S)-2-(3,5-Dichlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(3,5-dichlorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate and cis-methyl 2-(3,5-dichlorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate

2-(3,5-Dichlorophenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (4.6 g, 13.85 mmol) (reference compound 24) was dissolved in methyl THF (69.2 mL) and di(1H-imidazol-1-yl)methanone (3.37 g, 20.77 mmol) added. The suspension was stirred at room temperature

overnight under nitrogen (flask 1). In a separate flask potassium 3-ethoxy-3-oxopropanoate (4.24 g, 24.93 mmol) was suspended in methyl THF (69.2 mL) and magnesium chloride (2.373 g, 24.93 mmol) added. The suspension was stirred at 50°C overnight under nitrogen (flask 2). The white suspension in flask 2 was then added to the brown suspension in flask 1. The resulting suspension was stirred at room temperature for 40 h. The mixture was acidified to pH 1 with 3 M HCl. Water and methyl THF were added. The phases were separated, the organic layer washed with water, satd $NaHCO_3$, brine, dried over MgSO4, filtered and evaporated. Purified by flash chromatography using 20% EtOAc in heptane -> 50% EtOAc over 10 CV, 3 CV at 50%. Trans-methyl 2-(3,5-dichlorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (0.6 g, 11 %) and cis-methyl 2-(3,5-dichlorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (3.57 g, 64 %) were isolated. Cis-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.22 – 1.32 (m, 3H), 1.79 – 1.94 (m, 2H), 2.03 – 2.17 (m, 1H), 2.20 – 2.29 (m, 1H), 2.82 – 2.93 (m, 1H), 3.24 – 3.34 (m, 1H), 3.46 (d, 2H), 3.64 – 3.68 (m, 3H), 4.10 – 4.23 (m, 3H), 4.83 – 4.92 (m, 1H), 7.06 – 7.09 (m, 2H), 7.22 – 7.25 (m, 1H). MS m/z 402 $(M+H)^+$. Trans-isomer: MS m/z 402 $(M+H)^+$

Step 2: Cis-methyl 2-(3,5-dichlorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 2-(3,5-dichlorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (3.57 g, 8.87 mmol) was dissolved in MeOH (36.4 mL) and cooled to - 40°C under nitrogen. Sodium hydroxide (2.335 mL, 8.87 mmol) in water (3.64 mL) was added and the mixture stirred at - 40°C for 20 min. Hydroxylamine (50 % by weight in water, 0.544 mL, 8.87 mmol) was added and stirring continued at - 40°C for 3.5 h. The reaction mixture was then transferred to a preheated 80°C solution of 6 M hydrogen chloride (45.9 mL, 275.11 mmol) and heating was continued for 20 min. The solvent was then evaporated. DCM and water were added, shaken and the phases separated. The organic phase was dried with a phase separator and evaporated in vacuo. The compound was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x50 ID mm) using a gradient of 25-65% Acetonitrile in H2O/MeCN/AcOH 95/5/0.2 buffer over 30 minutes with a flow of 100 mL/min. Cis-methyl 2-(3,5-dichlorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (2.000 g, 60.7 %) was isolated as a white solid. ^{1}H NMR (400 MHz, cd$_3$od) δ 1.82 – 1.93 (m, 1H), 2.13 – 2.27 (m, 2H), 2.30 – 2.39 (m, 1H), 3.06 – 3.16 (m, 1H), 3.42 – 3.53 (m, 1H), 3.66 (s, 3H), 4.04 – 4.12 (m, 1H), 5.06 (dd, 1H), 5.64 (d, 1H), 7.14 – 7.18 (m, 2H), 7.27 (t, 1H). MS m/z

371 $(M+H)^+$

Step 3: (2R,4S)-Methyl 2-(3,5-dichlorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate and (2S,4R)-Methyl 2-(3,5-dichlorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 2-(3,5-dichlorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (2.000 g, 5.4 mmol) was subjected to chiral preparative HPLC (Column: CelluCoat (250x50 mm), 10 µm particle size, mobile phase: Heptane/EtOH 70/30, flow rate 120 mL/min) to yield (2R,4S)-methyl 2-(3,5-dichlorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.05 g, 50 %), Chiral purity 99.6 %ee, Optical rotation $[\alpha]_D^{20} = +67.1$ (acetonitrile, c=1.0), and (2S,4R)-methyl 2-(3,5-dichlorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.06 g, 50 %), Chiral purity 97.6 %ee, Optical rotation $[\alpha]_D^{20} = -58.4$ (acetonitrile, c=1.0).

Step 4: 5-((2R,4S)-2-(3,5-Dichlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-Methyl 2-(3,5-dichlorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1 g, 2.69 mmol) was dissolved in hydrogen bromide (33 % in AcOH, 4.67 mL, 80.82 mmol). Stirred overnight and evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4S)-2-(3,5-dichlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one (607 mg, 72 %). ^{1}H NMR (600 MHz, dmso) δ 1.32 (q, 1H), 1.44 (dq, 1H), 1.84 – 1.89 (m, 1H), 1.97 – 2.03 (m, 1H), 2.70 (dt, 1H), 2.80 – 2.87 (m, 1H), 3.06 – 3.12 (m, 1H), 3.67 (dd, 1H), 5.75 (s, 1H), 7.42 (d, 2H), 7.44 (t, 1H). HRMS Calculated for $[C_{14}H_{14}Cl_2N_2O_2+H]^+$: 313.0511. Found: 313.0513

Example 56

5-((2S,4R)-2-(3,5-Dichlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

(2S,4R)-Methyl 2-(3,5-dichlorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1 g, 2.69 mmol) (from example 55, step 3) was dissolved in hydrogen bromide (33 % in AcOH, 4.67 mL, 80.82 mmol) and stirred overnight. Evaporated and the residue

purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2S,4R)-2-(3,5-dichlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one (509 mg, 60 %). ^{1}H NMR (600 MHz, dmso) δ 1.32 (q, 1H), 1.44 (dq, 1H), 1.84 – 1.89 (m, 1H), 1.97 – 2.02 (m, 1H), 2.70 (dt, 1H), 2.84 (tt, 1H), 3.07 – 3.12 (m, 1H), 3.67 (dd, 1H), 5.75 (s, 1H), 7.42 (d, 2H), 7.44 (t, 1H). HRMS Calculated for $[C_{14}H_{14}Cl_2N_2O_2+H]^+$: 313.0511. Found: 313.0516

Example 57

5-(Trans-2-(3,5-dichlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(3,5-dichlorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Trans-methyl 2-(3,5-dichlorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (0.6 g, 1.49 mmol) (from example 55, step 1) was dissolved in MeOH (6.11 mL) and cooled to - 40°C under nitrogen. Sodium hydroxide (0.393 mL, 1.49 mmol) in water (0.611 mL) was added and the mixture stirred at - 40°C for 20 min. Hydroxylamine (50 % by weight in water, 0.091 mL, 1.49 mmol) was added and stirring continued at - 40°C for 3.5 h. The reaction mixture was then transferred to a preheated 80°C solution of 6 M hydrogen chloride (7.71 mL, 46.24 mmol) and heating was continued for 20 min. The solvent was then evaporated. DCM and water were added, shaken and the phases separated. The organic phase was dried with a phase separator and evaporated to yield crude trans-methyl 2-(3,5-dichlorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (300 mg, 54 %). MS m/z 371 $(M+H)^+$

5-(Trans-2-(3,5-dichlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

Trans-methyl 2-(3,5-dichlorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (300mg, 0.81 mmol) was diluted with hydrogen bromide (33 % in AcOH, 4.3 mL, 24.24 mmol) and stirred at ambient temperature for 48 h. Evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-(trans-2-(3,5-dichlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one (162 mg, 64 %). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.77 – 2.17 (m, 4H), 2.66 – 2.74 (m, 1H), 2.82 – 2.89 (m, 1H), 3.12 – 3.18 (m, 1H), 3.79 (d, 1H), 6.06 (s, 1H), 7.44 – 7.51 (m, 3H). HRMS Calculated for $[C_{14}H_{14}Cl_2N_2O_2+H]^+$:

313.0511. Found: 313.0513

Example 58

5-((2R,4S)-2-(2-Fluoro-4-(trifluoromethoxy)phenyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(2-fluoro-4-(trifluoromethoxy)phenyl)-piperidine-1-carboxylate and cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(2-fluoro-4-(trifluoromethoxy)phenyl)piperidine-1-carboxylate

2-(2-Fluoro-4-(trifluoromethoxy)phenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (4.07 g, 11.14 mmol) (reference compound 25) was dissolved in methyl THF (100 mL) under nitrogen atmosphere and di(1H-imidazol-1-yl)methanone (2.71 g, 16.71 mmol) was added. The suspension was stirred at room temperature for 5 h (flask 1). In a separate flask was potassium 3-ethoxy-3-oxopropanoate (3.41 g, 20.06 mmol) suspended in methyl THF (50 mL) and magnesium chloride (1.910 g, 20.06 mmol) was added. The suspension was stirred at 50°C under nitrogen for 15 h using an oversized stirring bar (flask 2). The contents of flask 1 was added to flask 2 and the resulting white suspension was stirred at room temperature for 20 h. 0.1 M HCl and DCM were added and the phases separated. The aqueous phase was extracted with DCM, the combined organic layers filtered through a phase separator and evaporated. The residue was purified via Biotage (gradient 3:1->1:1 heptane:EtOAc, Biotage® KP-SIL 340g column, 10 CV). Cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(2-fluoro-4-(trifluoromethoxy)phenyl)piperidine-1-carboxylate (3.44 g, 70.9 %) and trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(2-fluoro-4-(trifluoromethoxy)phenyl)piperidine-1-carboxylate (0.420 g, 8.66 %) were isolated as colorless oils. Cis-isomer: ^{1}H NMR (600 MHz, $cdcl_3$) δ 1.23 – 1.28 (m, 3H), 1.77 – 1.96 (m, 2H), 2.03 – 2.14 (m, 1H), 2.24 – 2.31 (m, 1H), 2.84 – 2.93 (m, 1H), 3.32 – 3.48 (m, 3H), 3.57 – 3.65 (m, 3H), 4.08 – 4.20 (m, 3H), 5.03 – 5.12 (m, 1H), 6.89 – 6.98 (m, 2H), 7.13 – 7.21 (m, 1H). MS m/z 436 $(M+H)^+$. Trans-isomer: ^{1}H NMR (600 MHz, $cdcl_3$) δ 1.16 – 1.28 (m, 3H), 1.62 (dq, 1H), 1.85 – 2.00 (m, 2H), 2.37 – 2.60 (m, 2H), 3.12 (dt, 1H), 3.43 (s, 2H), 3.68 (s, br., 3H), 4.08 – 4.20 (m, 2H), 4.25 (s, br., 1H), 5.68 (s, br., 1H), 6.92 – 7.01 (m, 2H), 7.13 (t, 1H). MS m/z 436 $(M+H)^+$

Step 2: Cis-methyl 2-(2-fluoro-4-(trifluoromethoxy)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(2-fluoro-4-(trifluoromethoxy)phenyl)piperidine-1-carboxylate (3.22 g, 7.40 mmol) was dissolved in MeOH (30 mL) and cooled to - 40°C under nitrogen. Sodium hydroxide (0.311 g, 7.77 mmol) dissolved in water (3.00 mL) was added and the mixture was stirred at - 40°C for 15 min. Hydroxylamine (50 % by weight in water, 0.476 mL, 7.77 mmol) was added. The resulting solution was stirred at - 40°C for 1 h. The mixture was then transferred into a prewarmed (80°C) solution of 6 M hydrogen chloride (38.2 mL, 229.28 mmol) and the mixture was stirred at 80°C for 15 min. Water and DCM were added and the phases separated. The aqueous phase was extracted with DCM and the combined organic layers were filtered through a phase separator and evaporated. The compound was purified by preparative HPLC on a Kromasil C8 column (4 runs) (10 µm 250x50 ID mm) using a gradient of 25-65% Acetonitrile in H2O/MeCN/HOAc 95/5/0.2 buffer over 25 minutes with a flow of 100 mL/min. Cis-methyl 2-(2-fluoro-4-(trifluoromethoxy)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.82 g, 61 %) was isolated. ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.82 – 1.91 (m, 1H), 2.03 – 2.13 (m, 1H), 2.22 – 2.41 (m, 2H), 3.01 – 3.10 (m, 1H), 3.43 – 3.53 (m, 1H), 3.63 (s, 3H), 4.11 – 4.21 (m, 1H), 5.19 (dd, 1H), 5.59 (s, 1H), 6.89 – 6.95 (m, 2H), 7.14 (t, 1H). MS m/z 405 $(M+H)^+$

Step 3: <u>(2R,4S)-Methyl 2-(2-fluoro-4-(trifluoromethoxy)phenyl)-4-(3-oxo-2,3-dihydro-isoxazol-5-yl)piperidine-1-carboxylate</u>

Cis-methyl 2-(2-fluoro-4-(trifluoromethoxy)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate (1.82 g, 4.5 mmol) was subjected to chiral preparative HPLC (Column: CelluCoat (250x50 mm), 10 µm particle size, mobile phase: Heptane/EtOH 1/1, flow rate 120 mL/min) to yield (2R,4S)-methyl 2-(2-fluoro-4-(trifluoromethoxy)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (917 mg, 50 %), Chiral purity 99.9 %ee, Optical rotation $[\alpha]_D^{20} = +49.7$ (acetonitrile, c=1.0)

Step 4: <u>5-((2R,4S)-2-(2-Fluoro-4-(trifluoromethoxy)phenyl)piperidin-4-yl)isoxazol-3(2H)-one</u>

(2R,4S)-Methyl 2-(2-fluoro-4-(trifluoromethoxy)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate (458 mg, 1.13 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 8.93 mL, 50.98 mmol) and stirred at room temperature for 16 h. The solvent was removed in vacuo and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm

OBD 19*150 mm) to yield 5-((2R,4S)-2-(2-fluoro-4-(trifluoromethoxy)phenyl)piperidin-4-yl)isoxazol-3(2H)-one (246 mg, 63 %). ^{1}H NMR (600 MHz, dmso) δ 1.37 (q, 1H), 1.47 (dq, 1H), 1.84 – 1.90 (m, 1H), 1.93 – 1.99 (m, 1H), 2.74 (dt, 1H), 2.87 – 2.94 (m, 1H), 3.07 – 3.13 (m, 1H), 3.94 (dd, 1H), 5.74 (s, 1H), 7.18 – 7.22 (m, 1H), 7.28 – 7.33 (m, 1H), 7.66 (t, 1H); HRMS Calculated for $[C_{15}H_{14}F_4N_2O_3+H]^+$: 347.1019. Found: 347.0995

Example 59

5-(Trans-2-(2-fluoro-4-(trifluoromethoxy)phenyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(2-fluoro-4-(trifluoromethoxy)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(2-fluoro-4-(trifluoromethoxy)phenyl)-piperidine-1-carboxylate (420 mg, 0.96 mmol) (from example 58, step 1) was dissolved in MeOH (4 mL) and cooled to - 40°C under nitrogen. Sodium hydroxide (40.5 mg, 1.01 mmol) dissolved in water (0.400 mL) was added and the mixture was stirred at - 40°C for 15 min. Hydroxylamine (50 % by weight in water, 62 µL, 1.01 mmol) was added. The resulting solution was stirred at - 40°C for 1 h. The mixture was then transferred into a prewarmed (80°C) solution of 6 M hydrogen chloride (4.98 mL, 29.91 mmol) and the mixture was stirred at 80°C for 15 min. Water and DCM were added and the phases separated. The aqueous phase was extracted with DCM and the combined organic layers were filtered through a phase separator and evaporated. Crude trans-methyl 2-(2-fluoro-4-(trifluoromethoxy)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (365 mg, 94 %) was yielded as a colorless oil. MS m/z 405 $(M+H)^+$

Step 2: 5-(Trans-2-(2-fluoro-4-(trifluoromethoxy)phenyl)piperidin-4-yl)isoxazol-3(2H)-one

Trans-methyl 2-(2-fluoro-4-(trifluoromethoxy)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (365 mg, 0.90 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 7.115 mL, 40.62 mmol) and stirred at room temperature for 16 h. The solvent was removed in vacuo and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-(trans-2-(2-fluoro-4-(trifluoromethoxy)phenyl)-piperidin-4-

yl)isoxazol-3(2H)-one (185 mg, 59 %). ^{1}H NMR (600 MHz, dmso) δ 1.64 – 1.72 (m, 1H), 1.77 – 1.85 (m, 1H), 1.91 – 1.97 (m, 1H), 2.02 – 2.08 (m, 1H), 2.69 (dt, 1H), 2.86 – 2.92 (m, 1H), 3.17 – 3.22 (m, 1H), 3.95 (dd, 1H), 5.87 (d, 1H), 7.19 – 7.23 (m, 1H), 7.28 – 7.32 (m, 1H), 7.66 (t, 1H); HRMS Calculated for $[C_{15}H_{14}F_4N_2O_3+H]^+$: 347.1019. Found: 347.1002

Example 60

5-((2R,4S)-2-(3,4,5-Trifluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3,4,5-trifluorophenyl)piperidine-1-carboxylate and cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3,4,5-trifluorophenyl)piperidine-1-carboxylate

1-(Methoxycarbonyl)-2-(3,4,5-trifluorophenyl)piperidine-4-carboxylic acid (1.94 g, 6.11 mmol) (reference compound 26) was dissolved in methyl THF (70 mL), then di(1H-imidazol-1-yl)methanone (1.487 g, 9.17 mmol) was added. The mixture was stirred at room temperature under nitrogen for 3 h (flask 1). In a separate flask potassium 3-ethoxy-3-oxopropanoate (1.873 g, 11.01 mmol) was suspended in methyl THF (70.0 mL), then magnesium chloride (1.048 g, 11.01 mmol) was added. The suspension was stirred at 50°C under nitrogen for 3 h using a large magnetic stirring bar (flask 2). Then the contents of flask 1 was transferred into flask 2. The resulting white suspension was stirred under nitrogen at room temperature overnight. The mixture was acidified to pH 1 with 3.8 M HCl, then MTBE (50 mL) and water (50 mL) was added. The phases were separated and the organic layer was washed with water, satd $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and evaporated leaving a slightly yellow oil. The product was flashed on Biotage (340g) with a gradient of 20-60% EtOAc in n-heptane (8 CV). The column was conditioned at 20% EtOAc in n-heptane (1 CV). Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3,4,5-trifluorophenyl)piperidine-1-carboxylate (59 mg, 2.5 %) and cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3,4,5-trifluorophenyl)piperidine-1-carboxylate (810 mg, 34 %) were isolated. Cis-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.07 – 1.18 (m, 3H), 1.60 – 2.43 (m, 4H), 2.71 – 2.83 (m, 1H), 3.12 – 3.27 (m, 1H), 3.36 (s, 2H), 3.52 (s, 3H), 3.91 – 4.09 (m, 3H), 4.72 – 4.83 (m, 1H), 6.71 – 6.81 (m, 2H). MS m/z 388 $(M+H)^+$. Trans-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.20 – 1.30 (m, 3H), 1.47 – 2.01 (m, 3H), 2.35 – 2.47 (m, 1H), 2.55 – 2.68 (m, 1H), 2.79 (dt, 1H), 3.42 – 3.49 (m, 2H), 3.75 (s, 3H), 4.09 – 4.37 (m, 3H), 5.52 (s, br., 1H),

6.78 – 6.89 (m, 2H). MS m/z 388 $(M+H)^+$

Step 2: Cis-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3,4,5-trifluorophenyl)piperidine-1-carboxylate

Cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3,4,5-trifluorophenyl)piperidine-1-carboxylate (810 mg, 2.09 mmol) was dissolved in MeOH (8 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (0.615 mL, 2.09 mmol) was added during 10 min and the yellow solution continued to stir at -40°C for 20 min. Hydroxylamine (50 % by weight in water, 0.128 mL, 2.09 mmol) was added during 8 min. The resulting solution was stirred at -40°C for 3 h. The mixture was then rapidly poured into a prewarmed (80°C) solution of 6 M hydrogen chloride (10.77 mL, 64.62 mmol) and the mixture continued to stir at 80°C for 20 min. The solvent was evaporated and DCM/water added. The phases were separated and the organic phase passed through a phase separator and evaporated to yield a white solid. The compound was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x50 ID mm) using a gradient of 10-60% Acetonitrile in H2O/MeCN/AcOH 95/5/0.2 buffer over 30 minutes with a flow of 100 mL/min. Cis-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3,4,5-trifluorophenyl)piperidine-1-carboxylate (355 mg, 48 %) was isolated. MS m/z 357 $(M+H)^+$

Step 3: (2R,4S)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3,4,5-trifluorophenyl)-piperidine-1-carboxylate and (2S,4R)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3,4,5-trifluorophenyl)piperidine-1-carboxylate

Cis-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3,4,5-trifluorophenyl)piperidine-1-carboxylate (355 mg, 1 mmol) was subjected to chiral preparative HPLC (Column: CelluCoat (250x20), 5 µm particle size, mobile phase: Heptane/EtOH 60/40, flow rate 18 mL/min) to yield (2R,4S)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3,4,5-trifluorophenyl)piperidine-1-carboxylate (164 mg, 46 %), Chiral purity 98.7 %ee, Optical rotation $[\alpha]_D^{20} = +60.6$ (acetonitrile, c=0.5), ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.80 – 1.90 (m, 1H), 1.99 – 2.40 (m, 3H), 3.00 – 3.13 (m, 1H), 3.29 – 3.42 (m, 1H), 3.69 (s, 3H), 4.07 – 4.19 (m, 1H), 4.97 – 5.07 (m, 1H), 5.60 (s, 1H), 6.75 – 6.85 (m, 2H), and (2S,4R)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3,4,5-trifluorophenyl)piperidine-1-carboxylate (160 mg, 45 %), Chiral purity 99.9 %ee, Optical rotation $[\alpha]_D^{20} = -52.9$ (acetonitrile, c=1), ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.81 – 1.90 (m, 1H), 2.05 – 2.15 (m, 1H), 2.19 – 2.38 (m, 2H), 3.02 – 3.11 (m, 1H), 3.30 – 3.40 (m, 1H), 3.69

(s, 3H), 4.09 – 4.18 (m, 1H), 4.99 – 5.05 (m, 1H), 5.60 (s, 1H), 6.76 – 6.84 (m, 2H).

Step 4: 5-((2R,4S)-2-(3,4,5-Trifluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-Methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3,4,5-trifluorophenyl)piperidine-1-carboxylate (164 mg, 0.46 mmol) was dissolved in hydrogen bromide (33 % in acetic acid (3.63 mL, 20.71 mmol) and the mixture was stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4S)-2-(3,4,5-trifluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one (93 mg, 67 %). ^{1}H NMR (600 MHz, dmso) δ 1.29 (q, 1H), 1.43 (dq, 1H), 1.82 – 1.89 (m, 1H), 1.96 – 2.02 (m, 1H), 2.70 (dt, 1H), 2.79 – 2.87 (m, 1H), 3.05 – 3.12 (m, 1H), 3.64 (dd, 1H), 5.72 (s, 1H), 7.26 – 7.34 (m, 2H). HRMS Calculated for $[C_{14}H_{13}F_3N_2O_2+H]^+$: 299.1007. Found: 299.1002

Example 61

5-((2S,4R)-2-(3,4,5-Trifluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

(2S,4R)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3,4,5-trifluorophenyl)piperidine-1-carboxylate (160 mg, 0.45 mmol) (from example 60, step 3) was dissolved in hydrogen bromide (33 % in acetic acid, 3.54 mL, 20.21 mmol) and the mixture was stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2S,4R)-2-(3,4,5-trifluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one (85 mg, 63 %) ^{1}H NMR (600 MHz, dmso) δ 1.29 (q, 1H), 1.43 (qd, 1H), 1.83 – 1.88 (m, 1H), 1.97 – 2.02 (m, 1H), 2.70 (td, 1H), 2.80 – 2.87 (m, 1H), 3.06 – 3.12 (m, 1H), 3.64 (dd, 1H), 5.73 (s, 1H), 7.27 – 7.34 (m, 2H). HRMS Calculated for $[C_{14}H_{13}F_3N_2O_2+H]^+$: 299.1007. Found: 299.1037

Example 62

5-(Trans-2-(3,4,5-trifluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3,4,5-trifluorophenyl)piperidine-1-carboxylate

Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3,4,5-trifluorophenyl)piperidine-1-carboxylate (59 mg, 0.15 mmol) (from example 60, step 1) was dissolved in MeOH (1 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (0.045 mL, 0.15 mmol) was added during 10 min and the yellow solution continued to stir at - 40°C for 20 min. Hydroxylamine (50 % by weight in water, 9.33 µL, 0.15 mmol) was added during 8 min. The resulting solution was stirred at -40°C for 3 h 15 min. The mixture was then rapidly poured into a prewarmed (80°C) solution of 6 M hydrogen chloride (0.784 mL, 4.71 mmol) and the mixture continued to stir at 80°C for 20 min. The solvent was evaporated and DCM/water added. The phases were separated, the organic phase passed through a phase separator and evaporated to yield crude trans-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3,4,5-trifluorophenyl)piperidine-1-carboxylate (53 mg, quant.) as a slightly yellow oil. MS m/z 357 $(M+H)^+$

Step 2: 5-(Trans-2-(3,4,5-trifluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

Trans-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3,4,5-trifluorophenyl)piperidine-1-carboxylate (53.4 mg, 0.15 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 1.18 mL, 6.75 mmol) and the mixture was stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-(trans-2-(3,4,5-trifluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one (11 mg, 25 %). ^1H NMR (600 MHz, dmso) δ 1.72 – 1.88 (m, 3H), 1.97 – 2.04 (m, 1H), 2.61 – 2.69 (m, 1H), 2.76 – 2.83 (m, 1H), 3.06 – 3.11 (m, 1H), 3.69 – 3.75 (m, 1H), 5.98 (s, 1H), 7.28 – 7.36 (m, 2H). HRMS Calculated for $[C_{14}H_{13}F_3N_2O_2+H]^+$: 299.1007. Found: 299.1031

Example 63

5-((2R,4S)-2-(2,4,5-Trifluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(2,4,5-trifluorophenyl)piperidine-1-carboxylate

1-(Methoxycarbonyl)-2-(2,4,5-trifluorophenyl)piperidine-4-carboxylic acid (2.388 g, 7.53

mmol) (reference compound 27) was dissolved in methyl THF (50 mL) and di(1H-imidazol-1-yl)methanone (1.831 g, 11.29 mmol) added. The suspension was stirred at room temperature under nitrogen for 6 h (flask 1). In a separate flask potassium 3-ethoxy-3-oxopropanoate (2.306 g, 13.55 mmol) was suspended in methyl THF (50.0 mL) and magnesium chloride (1.290 g, 13.55 mmol) added. The suspension was stirred at 50°C under nitrogen for 5.5 h using an oversized stirring bar (flask 2). The suspension in flask 1 was now added to the white suspension in flask 2. The resulting beige suspension was stirred under nitrogen at room temperature overnight. The mixture was acidified to pH 1 with 3.8 M HCl and MTBE and water added. The phases were separated and the organic phase washed with water, satd $NaHCO_3$ and water and was evaporated. Traces of water were azeotropically removed by MeCN to yield a yellow oil. The residue was purified on Biotage (20 % => 50 % EtOAc in heptane, 8 CV; Biotage® KP-SIL 340g column). Cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(2,4,5-trifluorophenyl)piperidine-1-carboxylate (1.877 g, 64 %) was isolated as colorless oil. ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.19 – 1.29 (m, 3H), 1.49 – 2.19 (m, 3H), 2.22 – 2.29 (m, 1H), 2.82 – 2.91 (m, 1H), 3.34 (ddd, 1H), 3.39 – 3.48 (m, 2H), 3.62 (s, 3H), 4.05 – 4.20 (m, 3H), 5.00 – 5.06 (m, 1H), 6.85 – 7.00 (m, 2H). MS m/z 388 $(M+H)^+$.

Step 2: Cis-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(2,4,5-trifluorophenyl)piperidine-1-carboxylate and trans-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(2,4,5-trifluorophenyl)-piperidine-1-carboxylate

Cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(2,4,5-trifluorophenyl)piperidine-1-carboxylate (1.888 g, 4.87 mmol) was dissolved in MeOH (18 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (0.195 g, 4.87 mmol) dissolved in water (1.800 mL) was added during 10 min and the colourless solution continued to stir at -40°C for 20 min. Hydroxylamine (50 % by weight in water, 0.299 mL, 4.87 mmol) was added during 8 min. The resulting solution was stirred at -40°C for 3 h 20 min. The mixture was then transferred into a prewarmed (80°C) solution of 6 M hydrogen chloride (24 mL, 144.00 mmol) and the mixture continued to stir at 80°C for 20 min. The solvent was evaporated and DCM/water added. The phases were separated and the organic phase passed through a phase separator and evaporated to yield a yellow oil. The compound was purified by preparative HPLC in 3 injections on a XBridge C18 column (10 µm 250x50 ID mm) using a gradient of 5-30 % Acetonitrile in H2O/MeCN/NH3 95/5/0.2 buffer over 20 minutes with a flow of 100 mL/min. A mixture of cis-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(2,4,5-trifluorophenyl)piperidine-1-

carboxylate and trans-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(2,4,5-trifluorophenyl)-piperidine-1-carboxylate (1.027 g, 59 %) was obtained as white solid after freeze drying. MS m/z 357 $(M+H)^+$

Step 3: (2R,4S)-Methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(2,4,5-trifluorophenyl)-piperidine-1-carboxylate and (2S,4S)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(2,4,5-trifluorophenyl)piperidine-1-carboxylate

The mixture of cis-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(2,4,5-trifluorophenyl)-piperidine-1-carboxylate and trans-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(2,4,5-trifluorophenyl)piperidine-1-carboxylate (1.027 g, 2.88 mmol) was subjected to chiral preparative HPLC (Column: CelluCoat (250x20), 5 µm particle size, mobile phase: Heptane/IPA 80/20, flow rate 18 mL/min) to yield (2R,4S)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(2,4,5-trifluorophenyl)piperidine-1-carboxylate (259 mg, 25 %), Chiral purity A% 99.9, Optical rotation $[\alpha]_D^{20} = +50.3$ (acetonitrile, c=1), and (2S,4S)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(2,4,5-trifluorophenyl)piperidine-1-carboxylate (203 mg, 20 %), Chiral purity A%: 99.9, Optical rotation $[\alpha]_D^{20} = +4.5$ (acetonitrile, c=1)

Step 4: 5-((2R,4S)-2-(2,4,5-Trifluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(2,4,5-trifluorophenyl)piperidine-1-carboxylate (259 mg, 0.73 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 4 mL, 22.84 mmol) and the mixture stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4S)-2-(2,4,5-trifluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one (161 mg, 74 %). ^{1}H NMR (600 MHz, dmso) δ 1.36 (q, 1H), 1.45 (dq, 1H), 1.83 – 1.90 (m, 1H), 1.91 – 1.97 (m, 1H), 2.74 (dt, 1H), 2.90 (tt, 1H), 3.06 – 3.13 (m, 1H), 3.91 (d, 1H), 5.74 (d, 1H), 7.44 – 7.57 (m, 2H). HRMS Calculated for $[C_{14}H_{13}F_3N_2O_2+H]^+$: 299.1007. Found: 299.1021

Example 64

5-((2S,4S)-2-(2,4,5-Trifluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

(2S,4S)-Methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(2,4,5-trifluorophenyl)piperidine-1-carboxylate (203 mg, 0.57 mmol) (from example 63, step 4) was dissolved in hydrogen bromide (33 % in acetic acid, 4 mL, 22.84 mmol) and the mixture stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2S,4S)-2-(2,4,5-trifluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one (138 mg, 81 %). ^{1}H NMR (600 MHz, dmso) δ 1.62 – 1.70 (m, 1H), 1.80 (tt, 1H), 1.90 – 1.96 (m, 1H), 2.00 – 2.06 (m, 1H), 2.68 (dt, 1H), 2.85 – 2.91 (m, 1H), 3.20 (s, br., 1H), 3.90 (d, 1H), 5.86 (d, 1H), 7.43 – 7.56 (m, 2H). HRMS Calculated for $[C_{14}H_{13}F_3N_2O_2+H]^+$: 299.1007. Found: 299.1023

Example 65

5-((2R,4S)-2-(4-Chloro-3,5-difluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(4-chloro-3,5-difluorophenyl)-4-(3-ethoxy-3-oxopropanoyl)-piperidine-1-carboxylate and cis-methyl 2-(4-chloro-3,5-difluorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate

2-(4-Chloro-3,5-difluorophenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (1.6 g, 4.79 mmol) (reference compound 28) was dissolved in methyl THF (30 mL) under nitrogen atmosphere and di(1H-imidazol-1-yl)methanone (1.166 g, 7.19 mmol) was added. The suspension was stirred at room temperature for 3 h (flask 1). In a separate flask was potassium 3-ethoxy-3-oxopropanoate (1.469 g, 8.63 mmol) suspended in methyl THF (15 mL) and magnesium chloride (0.822 g, 8.63 mmol) was added. The suspension was stirred at 50°C under nitrogen for 7 h using an oversized stirring bar (flask 2). To flask 2 the contents of flask 1 was added and the resulting white suspension was stirred at room temperature for 20 h. In a separate flask was potassium 3-ethoxy-3-oxopropanoate (0.734 g, 4.32 mmol) suspended in methyl THF (15 mL) and magnesium chloride (0.411 g, 4.32 mmol) was added. The suspension was stirred at 50°C for 5 h and then added to the reaction mixture. The mixture was stirred at room temperature for 15 h. 0.1 M HCl and DCM were added and the phases separated. The aqueous phase was extracted with DCM, the combined organic layers filtered through a phase separator and evaporated. The residue was purified by column

chromatography on silica (2:1 heptane:EtOAc, Biotage® KP-SIL 340g column, 10 CV). Cis-methyl 2-(4-chloro-3,5-difluorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (1.448 g, 74.8 %) and trans-methyl 2-(4-chloro-3,5-difluorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (0.178 g, 9.19 %) were isolated as colorless oils. Cis-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.23 – 1.32 (m, 3H), 1.74 – 2.19 (m, 3H), 2.20 – 2.30 (m, 1H), 2.82 – 2.92 (m, 1H), 3.23 – 3.34 (m, 1H), 3.46 (s, 2H), 3.63 – 3.69 (m, 3H), 4.04 – 4.23 (m, 3H), 4.84 – 4.95 (m, 1H), 6.81 – 6.90 (m, 2H). MS m/z 404 $(M+H)^+$. Trans-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.20 – 1.33 (m, 3H), 1.48 – 1.92 (m, 2H), 1.92 – 2.04 (m, 1H), 2.36 – 2.51 (m, 1H), 2.54 – 2.70 (m, 1H), 2.82 (dt, 1H), 3.47 (d, 2H), 3.73 (s, 3H), 4.08 – 4.45 (m, 3H), 5.56 (s, br., 1H), 6.86 (d, 2H). MS m/z 404 $(M+H)^+$

Step 2: Cis-methyl 2-(4-chloro-3,5-difluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 2-(4-chloro-3,5-difluorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (1.445 g, 3.58 mmol) was dissolved in MeOH (14 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (0.150 g, 3.76 mmol) dissolved in water (1.4 mL) was added and the mixture was stirred at -40°C for 15 min. Hydroxylamine (50 % by weight in water, 0.230 mL, 3.76 mmol) was added. The resulting solution was stirred at -40°C for 1 h. The mixture was then transferred into a prewarmed (80°C) solution of 6 M hydrogen chloride (18.49 mL, 110.93 mmol) and the mixture was stirred at 80°C for 20 min. Water and DCM were added and the phases separated. The aqueous phase was extracted with DCM and the combined organic layers were filtered through a phase separator and evaporated. The compound was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x50 ID mm) using a gradient of 15-55% Acetonitrile in H2O/MeCN/FA 95/5/0.2 buffer over 30 minutes with a flow of 100 mL/min. The compounds were detected by UV at 220 nm. Cis-methyl 2-(4-chloro-3,5-difluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.831 g, 62.3 %) was yielded as colorless solid. ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.80 – 1.87 (m, 1H), 2.04 – 2.15 (m, 1H), 2.19 – 2.28 (m, 1H), 2.30 – 2.36 (m, 1H), 3.00 – 3.09 (m, 1H), 3.30 – 3.39 (m, 1H), 3.66 (s, 3H), 4.07 – 4.16 (m, 1H), 4.98 – 5.05 (m, 1H), 5.59 (s, br., 1H), 6.80 (d, 2H). MS m/z 273 $(M+H)^+$

Step 3: (2R,4S)-Methyl 2-(4-chloro-3,5-difluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 2-(4-chloro-3,5-difluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (830 mg, 2.23 mmol) was subjected to chiral preparative HPLC (Column: CelluCoat (250x50 mm), 10 µm particle size, mobile phase: Heptane/EtOH 1/1, flow rate 120 mL/min) to yield (2R,4S)-methyl 2-(4-chloro-3,5-difluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (390 mg, 47 %), Chiral purity 99.7 %ee, Optical rotation $[\alpha]_D^{20}$ = +55.9 (acetonitrile, c=1.0)

Step 4: 5-((2R,4S)-2-(4-Chloro-3,5-difluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-Methyl 2-(4-chloro-3,5-difluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.39 g, 1.05 mmol) was dissolved in hydrogen bromide (33% in acetic acid, 10 mL, 142.75 mmol) and stirred at room temperature for 18 h. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4S)-2-(4-chloro-3,5-difluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one (272 mg, 83 %). ^{1}H NMR (600 MHz, dmso) δ 1.29 (q, 1H), 1.43 (dq, 1H), 1.82 – 1.89 (m, 1H), 1.97 – 2.04 (m, 1H), 2.70 (dt, 1H), 2.84 (tt, 1H), 3.06 – 3.12 (m, 1H), 3.68 (dd, 1H), 5.73 (s, 1H), 7.31 (d, 2H). HRMS Calculated for $[C_{14}H_{13}ClF_2N_2O_2+H]^+$: 315.0712. Found: 315.0707

Example 66

5-(Trans-2-(4-chloro-3,5-difluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(4-chloro-3,5-difluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate

Trans-methyl 2-(4-chloro-3,5-difluorophenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (178 mg, 0.44 mmol) (from example 65, step 1) was dissolved in MeOH (2 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (18.51 mg, 0.46 mmol) dissolved in water (0.200 mL) was added and the mixture was stirred at -40°C for 15 min. Hydroxylamine (50 % by weight in water, 0.028 mL, 0.46 mmol) was added. The resulting solution was stirred at -40°C for 1 h. The mixture was transferred into a prewarmed (80°C) solution of 6 M hydrogen chloride (2.278 mL, 13.67 mmol) and the mixture was stirred at 80°C for 20 min.

Water and DCM were added and the phases separated. The aqueous phase was extracted with DCM and the combined organic layers were filtered through a phase separator and evaporated. Crude trans-methyl 2-(4-chloro-3,5-difluorophenyl)-4-(3-oxo-2,3-dihydro-isoxazol-5-yl)piperidine-1-carboxylate (158 mg, 96 %) was isolated as a light yellow oil. MS m/z 273 $(M+H)^+$

Step 2: 5-(Trans-2-(4-chloro-3,5-difluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one

Trans-methyl 2-(4-chloro-3,5-difluorophenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (157 mg, 0.42 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 3.32 mL, 18.95 mmol) and stirred at room temperature for 16 h. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-(trans-2-(4-chloro-3,5-difluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one (26 mg, 19 %). ^{1}H NMR (600 MHz, dmso) δ 1.75 – 2.11 (m, 4H), 2.66 – 2.77 (m, 1H), 2.81 – 2.95 (m, 1H), 3.14 (s, br., 1H), 3.86 (s, br., 1H), 6.03 (s, 1H), 7.32 – 7.42 (m, 2H). HRMS Calculated for $[C_{14}H_{13}ClF_2N_2O_2+H]^+$: 315.0712. Found: 315.0715

Example 67

5-((2R,4S)-2-(3-Methyl-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3-methyl-4-(trifluoromethyl)phenyl)-piperidine-1-carboxylate and cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3-methyl-4-(trifluoromethyl)phenyl)piperidine-1-carboxylate

Ethyl potassium malonate (1.567 g, 9.21 mmol) and $MgCl_2$ (0.731 g, 7.67 mmol) were added to dry THF (50 mL). The reaction flask was stirred vigorously for 4 h at 50°C (flask 1). 1-(Methoxycarbonyl)-2-(3-methyl-4-(trifluoromethyl)phenyl)piperidine-4-carboxylic acid (2.65 g, 7.67 mmol) (reference compound 29) and carbonyldiimidazole (1.867 g, 11.51 mmol) were added to dry THF (50 mL) at room temperature (flask 2). The contents of flask 2 was added to flask 1 and the resulting mixture stirred at room temperature overnight. The reaction mixture was dissolved between water and diethyl ether. The organic phase was isolated, dried with Na_2SO_4, filtered through celite and the solvent was evaporated. Chromatography using the Biotage equipment. Gradient eluation using ethylacetate-heptane, started 0-100 and ended

100-0. Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3-methyl-4-(trifluoromethyl)phenyl)-piperidine-1-carboxylate (0.69 g, 22 %) and cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3-methyl-4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (1.40 g, 44 %) were isolated. Cis-isomer: ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.25 (t, 3H), 1.00 – 2.29 (m, 4H), 2.44 (s, 3H), 2.47 – 2.95 (m, 1H), 3.27 – 3.34 (m, 1H), 3.37 – 3.48 (m, 2H), 3.62 (s, 3H), 3.66 – 4.20 (m, 3H), 4.88 – 4.96 (m, 1H), 7.05 – 7.11 (m, 2H), 7.50 – 7.54 (m, 1H). Trans-isomer: ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.22 (t, 3H), 1.47 – 2.03 (m, 4H), 2.47 (s, 3H), 2.49 – 2.89 (m, 2H), 3.40 – 3.47 (m, 2H), 3.74 (s, 3H), 4.15 (q, 2H), 4.11 – 4.36 (m, 1H), 5.37 – 5.75 (m, 1H), 7.06 – 7.13 (m, 2H), 7.57 (d, 1H).

Step 2: Cis-methyl 2-(3-methyl-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3-methyl-4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (1.4 g, 3.37 mmol) was dissolved in MeOH (20 mL) and cooled to -40°C. NaOH (0.135 g, 3.37 mmol) dissolved in water (2 mL) was added during 10 min and the resulting colourless solution continued to stir at -40°C for 20 min. Hydroxylamine (50 % by weight in water, 0.223 g, 3.37 mmol) was added dropwise. The resulting solution was stirred at -40°C for 30 min. The mixture was then transferred into a prewarmed (80°C) solution of 6 M HCl and the mixture continued to stir at 80°C for 20 min. The mixture was dissolved between diethyl ether and water. The phases were separated and the organic phase was dried over Na_2SO_4, filtered through celite and the solvent removed. Purified by preparative HPLC. Gradient eluation using acetonitrile - acidic buffer, started 40-60 and ended 55-45. Cis-methyl 2-(3-methyl-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.37 g, 29 %) was isolated. ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.80 – 1.87 (m, 1H), 2.07 – 2.28 (m, 2H), 2.31 – 2.38 (m, 1H), 2.41 (s, 3H), 3.03 – 3.10 (m, 1H), 3.35 – 3.43 (m, 1H), 3.66 (s, 3H), 4.13 – 4.19 (m, 1H), 5.09 (t, 1H), 5.52 (s, 1H), 7.02 – 7.06 (m, 2H), 7.49 (d, 1H). MS m/z 385 $(M+H)^+$

Step 3: (2R,4S)-Methyl 2-(3-methyl-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydro-isoxazol-5-yl)piperidine-1-carboxylate and (2S,4R)-methyl 2-(3-methyl-4-(trifluoromethyl)-phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 2-(3-methyl-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate (0.37 g, 0.96 mmol) was subjected to chiral preparative HPLC

(Column: CelluCoat OJ (250x50), 10 μm particle size, mobile phase: Heptane/EtOH 50/50, flow rate 120 mL/min) to yield (2R,4S)-methyl 2-(3-methyl-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (177 mg, 48 %), Chiral purity 99.2 %ee, Optical rotation $[\alpha]_D^{20} = +57.1$ (acetonitrile, c=1), ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.78 – 1.85 (m, 1H), 2.08 – 2.16 (m, 1H), 2.17 – 2.26 (m, 1H), 2.29 – 2.36 (m, 1H), 2.39 (s, 3H), 3.01 – 3.09 (m, 1H), 3.34 – 3.42 (m, 1H), 3.64 (s, 3H), 4.09 – 4.17 (m, 1H), 5.07 (t, 1H), 5.50 (s, 1H), 7.01 – 7.07 (m, 2H), 7.47 (d, 1H), 10.63 (br, 1H), and (2S,4R)-methyl 2-(3-methyl-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (168 mg, 45 %), Chiral purity 99.9 %ee, Optical rotation $[\alpha]_D^{20} = -57.1$ (acetonitrile, c=1), ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.79 – 1.86 (m, 1H), 2.10 – 2.18 (m, 1H), 2.19 – 2.27 (m, 1H), 2.31 – 2.37 (m, 1H), 2.41 (s, 3H), 3.02 – 3.09 (m, 1H), 3.35 – 3.42 (m, 1H), 3.65 (s, 3H), 4.11 – 4.18 (m, 1H), 5.08 (t, 1H), 5.51 (s, 1H), 7.02 – 7.07 (m, 2H), 7.48 (d, 1H).

Step 4: 5-((2R,4S)-2-(3-Methyl-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-Methyl 2-(3-methyl-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate (0.177 g, 0.46 mmol) was dissolved in HBr (33 % in acetic acid, 5.6 g, 22.84 mmol) and the mixture was stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5μm OBD 19*150 mm) to yield 5-((2R,4S)-2-(3-methyl-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one (0.082 g, 55 %). ^{1}H NMR (600 MHz, dmso) δ 1.31 – 1.39 (m, 1H), 1.41 – 1.50 (m, 1H), 1.84 – 1.90 (m, 1H), 1.95 – 2.00 (m, 1H), 2.40 (d, 3H), 2.57 – 2.59 (m, 1H), 2.83 – 2.90 (m, 1H), 3.08 – 3.13 (m, 1H), 3.68 (d, 1H), 5.72 (s, 1H), 7.35 (d, 1H), 7.43 (s, 1H), 7.57 (d, 1H). HRMS Calcd for $[C_{16}H_{17}F_3N_2O_2+H]^+$: 327.1320. Found: 327.1311.

Example 68

5-((2S,4R)-2-(3-Methyl-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one

(2S,4R)-Methyl 2-(3-methyl-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate (0.168 g, 0.44 mmol) (from example 67, step 3) was dissolved in HBr (33 % in acetic acid, 5.6g, 22.84 mmol) and the mixture was stirred at room temperature

overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2S,4R)-2-(3-methyl-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one (0.068g, 48%). ^{1}H NMR (600 MHz, dmso) δ 1.31 – 1.40 (m, 1H), 1.41 – 1.50 (m, 1H), 1.85 – 1.90 (m, 1H), 1.95 – 2.00 (m, 1H), 2.40 (s, 3H), 2.69 – 2.76 (m, 1H), 2.83 – 2.90 (m, 1H), 3.08 – 3.13 (m, 1H), 3.68 (d, 1H), 5.73 (s, 1H), 7.36 (d, 1H), 7.43 (s, 1H), 7.57 (d, 1H). HRMS Calcd for $[C_{16}H_{17}F_3N_2O_2+H]^+$: 327.1320. Found: 327.1318.

Example 69

5-(Trans-2-(3-methyl-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(3-methyl-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3-methyl-4-(trifluoromethyl)phenyl)-piperidine-1-carboxylate (0.69 g, 1.66 mmol) (from example 67, step 1) was dissolved in MeOH (8mL) and cooled to -40°C under nitrogen. NaOH (0.066 g, 1.66 mmol) dissolved in water (0.7 mL) was added during 10 min and the resulting colourless solution continued to stir at -40°C for 20 min. Hydroxylamine (50 % by weight in water, 0.110 g, 1.66 mmol) was added dropwise. The resulting solution was stirred at -40°C for 30 min. The mixture was then transferred into a prewarmed (80°C) solution of 6 M HCl and the mixture continued to stir at 80°C for 20 min. The mixture was dissolved between diethyl ether and water. The phases were separated and the organic phase was dried over Na_2SO_4, filtered through celite and evaporated to yield crude trans-methyl 2-(3-methyl-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.54 g, 85 %). ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.60 – 1.72 (m, 1H), 1.89 – 1.97 (m, 1H), 1.99 – 2.07 (m, 1H), 2.48 (s, 3H), 2.58 – 2.71 (m, 1H), 2.80 (s, 1H), 2.93 (t, 1H), 3.73 (s, 3H), 4.23 (s, 1H), 5.49 – 5.73 (m, 2H), 7.06 – 7.16 (m, 2H), 7.60 (d, 1H).

Step 2: 5-(Trans-2-(3-methyl-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one

Trans-methyl 2-(3-methyl-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.139 g, 0.36 mmol) was dissolved in HBr (33 % in acetic acid,

5.60 g, 22.84 mmol) and the mixture was stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-(trans-2-(3-methyl-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one (0.075 g, 64 %). ^{1}H NMR (600 MHz, dmso) δ 1.76 – 1.85 (m, 2H), 1.85 – 1.93 (m, 1H), 1.99 – 2.07 (m, 1H), 2.40 (d, 2H), 2.67 – 2.75 (m, 1H), 2.80 – 2.89 (m, 1H), 3.10 – 3.17 (m, 1H), 3.68 – 3.78 (m, 1H), 5.96 (s, 1H), 7.36 (d, 1H), 7.43 (s, 1H), 7.57 (d, 1H). HRMS Calcd for $[C_{16}H_{17}F_3N_2O_2+H]^+$: 327.1320. Found: 327.1298.

Example 70

5-((2R,4S)-2-(3,5-Difluoro-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(3,5-difluoro-4-(trifluoromethyl)phenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate and cis-methyl 2-(3,5-difluoro-4-(trifluoromethyl)-phenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate

2-(3,5-Difluoro-4-(trifluoromethyl)phenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (2.363 g, 6.43 mmol) (reference compound 30) was dissolved in methyl THF (30 mL) and di(1H-imidazol-1-yl)methanone (1.565 g, 9.65 mmol) added. The suspension was stirred at room temperature under nitrogen for 20 h (flask 1). In a separate flask potassium 3-ethoxy-3-oxopropanoate (2.190 g, 12.87 mmol) and magnesium chloride (1.225 g, 12.87 mmol) were suspended in methyl THF (30.0 mL) and stirred with an oversized stirring bar at 50°C under nitrogen for 20 h (flask 2). The white suspension in flask 2 was then added to flask 1. The thick white suspension was stirred at room temperature for 24 h. The reaction mixture was acidified by addition of 3 M HCl to pH 1. MTBE (250 mL) and water were added, shaken and the phases separated. The organic phase was washed with water (200 mL), satd $NaHCO_3$ (200 mL), brine (200 mL), dried with a phase separator and evaporated in vacuo. The residue was purified by automated flash chromatography on a Biotage® KP-SIL 100g column. A gradient from 40 % EtOAc in heptane over 2 CV followed by 40 % to 80 % of EtOAc in heptane over 10 CV was used as mobile phase. Cis-methyl 2-(3,5-difluoro-4-(trifluoromethyl)phenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (1.489 g, 52.9 %) and trans-methyl 2-(3,5-difluoro-4-(trifluoromethyl)phenyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (0.110 g, 3.91 %) were isolated. Cis-isomer: ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.25 (t, 3H), 1.49 –

2.28 (m, 4H), 2.80 – 2.91 (m, 1H), 3.23 – 3.31 (m, 1H), 3.44 (s, 2H), 3.65 (s, 3H), 4.07 – 4.14 (m, 1H), 4.17 (q, 2H), 4.86 – 4.95 (m, 1H), 6.83 (d, 2H). Trans-isomer: ^{1}H NMR (600 MHz, $cdcl_3$) δ 1.24 (t, 3H), 1.54 – 1.60 (m, 1H), 1.73 – 1.89 (m, 1H), 1.96 – 2.03 (m, 1H), 2.38 – 2.47 (m, 1H), 2.53 – 2.62 (m, 1H), 2.76 – 2.84 (m, 1H), 3.40 – 3.49 (m, 2H), 3.75 (s, 3H), 4.17 (q, 2H), 4.15 – 4.42 (m, 1H), 5.40 – 5.71 (m, 1H), 6.87 (d, 2H).

Step 2: Cis-methyl 2-(3,5-difluoro-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 2-(3,5-difluoro-4-(trifluoromethyl)phenyl)-4-(3-ethoxy-3-oxopropanoyl)-piperidine-1-carboxylate (1.489 g, 3.40 mmol) was dissolved in MeOH (15 mL) and cooled to - 40°C. Sodium hydroxide (0.896 mL, 3.40 mmol) dissolved in water (1.500 mL) was added and the reaction stirred at - 40°C for 20 min. Hydroxylamine (50 % by weight in water, 0.209 mL, 3.40 mmol) was added and stirring continued for 3.5 h at - 40°C. The reaction mixture was then added to a prewarmed 80°C solution of hydrogen chloride (17.59 mL, 105.54 mmol) and stirred for 20 min. The solvent was evaporated in vacuo. DCM (100 mL) and water (100 mL) were added, shaken and the phases separated. The organic phase was dried with a phase separator and evaporated in vacuo. The compound was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x50 ID mm) using a gradient of 20-65% Acetonitrile in H2O/MeCN/AcOH 95/5/0.2 buffer over 30 minutes with a flow of 100 mL/min. Cis-methyl 2-(3,5-difluoro-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.594 g, 42.9 %) was isoalted as a white solid. ^{1}H NMR (600 MHz, $cdcl_3$) δ 1.82 – 1.89 (m, 1H), 2.08 – 2.16 (m, 1H), 2.19 – 2.27 (m, 1H), 2.32 – 2.38 (m, 1H), 3.04 – 3.11 (m, 1H), 3.34 – 3.41 (m, 1H), 3.68 (s, 3H), 4.09 – 4.15 (m, 1H), 5.04 – 5.08 (m, 1H), 5.57 (s, 1H), 6.80 (d, 2H).

Step 3: (2R,4S)-methyl 2-(3,5-difluoro-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydro-isoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 2-(3,5-difluoro-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate (465 mg, 1.14 mmol) was subjected to chiral preparative HPLC (Column: CelluCoat (250x50), 10 µm particle size, mobile phase: Heptane/EtOH 60/40, flow rate 120 mL/min) to yield (2R,4S)-methyl 2-(3,5-difluoro-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (226 mg, 48 %), Chiral purity 99.8

%ee, Optical rotation $[\alpha]_D^{20} = +48.2$ (acetonitrile, c=1), ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.82 – 1.88 (m, 1H), 2.07 – 2.14 (m, 1H), 2.19 – 2.27 (m, 1H), 2.32 – 2.38 (m, 1H), 3.04 – 3.10 (m, 1H), 3.34 – 3.41 (m, 1H), 3.68 (s, 3H), 4.09 – 4.15 (m, 1H), 5.04 – 5.08 (m, 1H), 5.58 (s, 1H), 6.80 (d, 2H).

Step 4: 5-((2R,4S)-2-(3,5-Difluoro-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-Methyl 2-(3,5-difluoro-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (226 mg, 0.56 mmol) was dissolved in hydrobromic acid (33 % in AcOH, 5 mL, 30.38 mmol) and stirred at room temperature for 20 h. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4S)-2-(3,5-difluoro-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one (133 mg, 68 %). ^{1}H NMR (600 MHz, dmso) δ 1.30 (q, 1H), 1.43 (dq, 1H), 1.84 – 1.89 (m, 1H), 2.02 – 2.07 (m, 1H), 2.70 (dt, 1H), 2.86 (tt, 1H), 3.07 – 3.13 (m, 1H), 3.75 (dd, 1H), 5.73 (s, 1H), 7.37 (d, 2H). HRMS Calcd for $[C_{15}H_{13}F_5N_2O_2+H]^+$: 349.0975. Found: 349.0972.

Example 71

5-(Trans-2-(3,5-difluoro-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(3,5-difluoro-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydro-isoxazol-5-yl)piperidine-1-carboxylate

Trans-methyl 2-(3,5-difluoro-4-(trifluoromethyl)phenyl)-4-(3-ethoxy-3-oxopropanoyl)-piperidine-1-carboxylate (110 mg, 0.25 mmol) (from example 70, step 1) was dissolved in MeOH (5 mL) and cooled to -40°C. Sodium hydroxide (0.066 mL, 0.25 mmol) dissolved in water (0.500 mL) was added. After 20 min at - 40°C, hydroxylamine (50 % by weight in water, 7.71 µL, 0.25 mmol) was added and stirring continued for 4 h. The reaction mixture was then added to a prewarmed 80°C solution of 6 M hydrogen chloride (1.299 mL, 7.80 mmol) and stirred for 1 h. The solvent was evaporated in vacuo. DCM (50 mL) and water (50 mL) were added, shaken and the phases separated. The organic phase was dried with a phase

separator and evaporated in vacuo. The compound was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x20 ID mm) using a gradient of 20-65% Acetonitrile in H2O/MeCN/AcOH 95/5/0.2 buffer, over 30 minutes with a flow of 19 mL/min. Trans-methyl 2-(3,5-difluoro-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (7.00 mg, 6.85 %) was isolated as a white solid. ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.61 – 1.73 (m, 1H), 1.90 – 2.01 (m, 1H), 2.06 (dt, 1H), 2.56 (d, 1H), 2.76 (t, 1H), 2.89 (t, 1H), 3.78 (s, 3H), 4.13 – 4.47 (m, 1H), 5.46 – 5.74 (m, 1H), 5.68 (s, 1H), 6.89 (d, 2H). MS m/z 407 $(M+H)^+$

Step 2: 5-(Trans-2-(3,5-difluoro-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one

Trans-methyl 2-(3,5-difluoro-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (26 mg, 0.06 mmol) was dissolved in hydrogen bromide (33 % in AcOH, 2 mL, 0.06 mmol) and stirred at room temperature for 20 h. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-(trans-2-(3,5-difluoro-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one (7.00 mg, 31 %). ^{1}H NMR (600 MHz, dmso) δ 1.73 – 1.88 (m, 3H), 2.02 – 2.08 (m, 1H), 2.64 – 2.70 (m, 1H), 2.77 – 2.83 (m, 1H), 3.06 – 3.11 (m, 1H), 3.83 – 3.86 (m, 1H), 6.02 (s, 1H), 7.42 (d, 2H). HRMS Calcd for $[C_{15}H_{13}F_5N_2O_2+H]^+$: 349.0975. Found: 349.0983.

Example 72

5-((2R,4S)-2-(2-Methyl-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(2-methyl-4-(trifluoromethyl)phenyl) piperidine-1-carboxylate

1-(Methoxycarbonyl)-2-(2-methyl-4-(trifluoromethyl)phenyl)piperidine-4-carboxylic acid (7.79 g, 22.56 mmol) (reference compound 31) was dissolved in THF (60 mL) and then di(1H-imidazol-1-yl)methanone (5.49 g, 33.84 mmol) was added. The reaction was stirred overnight at room temperature (flask 1). In a separate flask potassium 3-ethoxy-3-oxopropanoate (7.68 g, 45.12 mmol) and anhydrous magnesium chloride (4.30 g, 45.12 mmol) were suspended in THF (60.0 mL) and stirred at 50°C under nitrogen overnight and

then allowed to cool to room temperature (flask 2). The content of flask 1 was added to flask 2 and stirred under nitrogen for 48 h. The reaction was quenched by addition of 2 M HCl. The mixture was extracted three times with EtOAc, the combined organic phases were evaporated and purified by column chromatography on silica (100 g Biotage column with heptane/EtOAc 88/12 - 33/67 over 9 column volumes) to give cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(2-methyl-4-(trifluoromethyl)phenyl) piperidine-1-carboxylate (6.28 g, 67 %). ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.23 – 1.33 (m, 3H), 1.68 – 1.97 (m, 2H), 2.08 – 2.21 (m, 2H), 2.44 (s, 3H), 2.87 – 2.98 (m, 1H), 3.46 (s, 2H), 3.44 – 3.66 (m, 1H), 3.58 (s, 3H), 4.15 – 4.29 (m, 3H), 4.91 – 5.01 (m, 1H), 7.24 – 7.32 (m, 1H), 7.36 – 7.43 (m, 2H). MS m/z 416 $(M+H)^+$

Step 2: Cis-methyl 2-(2-methyl-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(2-methyl-4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (6.28 g, 15.12 mmol) was dissolved in MeOH (60 mL) and cooled to - 40°C. 3.8 M NaOH (3.98 mL, 15.12 mmol) was dissolved in water (6 mL) and added to the mixture and the reaction stirred at - 40°C for 40 min. Hydroxylamine (50 % by weight in water, 0.926 mL, 15.12 mmol) was added and stirring continued for 3.5 h at - 40°C. The reaction mixture was then added to a preheated 80°C warm solution of 6 M HCl (76 mL, 453.53 mmol) and stirred for 20 min. The reaction mixture was partitioned between water and DCM. The aqueous phase was extracted twice with DCM and the combined organic phase was dried and evaporated. The compound was purified in two runs by preparative HPLC on a Kromasil C8 column (10 µm 250x50 ID mm) using a gradient of 35-75% acetonitrile in H2O/MeCN/AcOH 95/5/0.2 buffer over 30 minutes with a flow of 100 mL/min. Cis-methyl 2-(2-methyl-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (3.2 g, 55 %) was isolated. ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.81 – 1.93 (m, 2H), 2.21 – 2.42 (m, 2H), 2.44 (s, 3H), 3.03 – 3.13 (m, 1H), 3.59 (s, 3H), 3.63 – 3.75 (m, 1H), 4.12 – 4.20 (m, 1H), 5.02 (dd, 1H), 5.65 (s, 1H), 7.30 (d, 1H), 7.37 – 7.44 (m, 2H). MS m/z 383 $(M-H)^-$

Step 3: (2R,4S)-Methyl 2-(2-methyl-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 2-(2-methyl-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate (3.2 g, 8.33 mmol) was subjected to chiral preparative HPLC (Column: CelluCoat (250x50), 10 µm particle size, mobile phase: Heptane/EtOH 75/25, flow

rate 120 mL/min) to yield (2R,4S)-Methyl 2-(2-methyl-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.45 g, 45 %), Chiral purity 99.3 %ee, Optical rotation $[\alpha]_D^{20}$ = +49.0 (acetonitrile, c=1), ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.79 – 1.95 (m, 2H), 2.20 – 2.40 (m, 2H), 2.44 (s, 3H), 3.02 – 3.15 (m, 1H), 3.59 (s, 3H), 3.63 – 3.76 (m, 1H), 4.11 – 4.22 (m, 1H), 5.02 (dd, 1H), 5.65 (s, 1H), 7.24 – 7.32 (m, 1H), 7.36 – 7.43 (m, 2H).

Step 4: 5-((2R,4S)-2-(2-Methyl-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-Methyl 2-(2-methyl-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate (1.45 g, 3.77 mmol) was dissolved in hydrogen bromide (33 % in HOAc, 19.82 mL, 113.18 mmol) and stirred overnight. The mixture was evaporated and purified on a Kromasil C8 column (10 µm 250x50 ID mm) using a gradient of 15-55% acetonitrile in H_2O/MeCN/NH_3 95/5/0.2 buffer over 20 minutes with a flow of 100 mL/min. 5-((2R,4S)-2-(2-Methyl-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one (810 mg, 65 %) was isolated as a white powder. ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.35 (q, 1H), 1.52 (dq, 1H), 1.88 – 2.01 (m, 2H), 2.42 (s, 3H), 2.75 – 2.85 (m, 1H), 2.89 – 3.00 (m, 1H), 3.12 – 3.18 (m, 1H), 3.93 (d, 1H), 5.76 (s, 1H), 7.49 – 7.54 (m, 2H), 7.73 (d, 1H). HRMS Calculated for $[C_{16}H_{17}F_3N_2O_2+H]^+$: 327.1320. Found: 327.1312.

Example 73

5-((2R,4S)-2-(2-Fluoro-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(2-fluoro-4-(trifluoromethyl)phenyl) piperidine-1-carboxylate and cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(2-fluoro-4-(trifluoromethyl)phenyl) piperidine-1-carboxylate

2-(2-fluoro-4-(trifluoromethyl)phenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (4.82 g, 13.80 mmol) was dissolved in methyl THF (120 mL), then di(1H-imidazol-1-yl)methanone (4.03 g, 24.84 mmol) was added. The mixture was stirred at room temperature under nitrogen for 5 h (flask 1). In a separate flask potassium 3-ethoxy-3-oxopropanoate (4.23 g, 24.84 mmol) was suspended in methyl THF (120 mL), then magnesium chloride (2.365 g, 24.84 mmol) was added. The suspension was stirred at 50°C under nitrogen for 5 h using a large magnetic stirring bar (flask 2). The contents of flask 1 was transferred into flask 2. The

resulting white suspension was stirred under nitrogen at room temperature overnight. The mixture was acidified to pH 1 with 3.8 M HCl, then MTBE (50 mL) and water (50 mL) was added. The phases were separated and the organic layer was washed with water, satd $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and evaporated leaving a slightly yellow oil. The residue was purified by chromatography on silica (Biotage (340g) with a 1 CV EtOAc in heptane (20%) followed by a gradient of 20-60% EtOAc in n-heptane (8 CV). The column was conditioned at 20% EtOAc in -n-heptane (1 CV)). Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(2-fluoro-4-(trifluoromethyl)phenyl) piperidine-1-carboxylate (413 mg, 7 %) and cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(2-fluoro-4-(trifluoromethyl)-phenyl)piperidine-1-carboxylate (2.83 g, 49 %) were isolated. Cis-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.22 – 1.32 (m, 3H), 1.81 – 1.96 (m, 2H), 2.06 – 2.18 (m, 1H), 2.27 – 2.36 (m, 1H), 2.87 – 2.97 (m, 1H), 3.34 – 3.51 (m, 3H), 3.58 – 3.66 (m, 3H), 4.14 – 4.23 (m, 3H), 5.15 (dd, 1H), 7.25 – 7.40 (m, 3H). MS m/z 420 $(M+H)^+$. Trans-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.18 – 1.31 (m, 3H), 1.58 – 1.72 (m, 1H), 1.87 – 2.06 (m, 2H), 2.40 – 2.60 (m, 2H), 3.17 (dt, 1H), 3.45 (s, 2H), 3.73 (s, br., 3H), 4.08 – 4.23 (m, 2H), 4.34 (s, br., 1H), 5.75 (s, br., 1H), 7.22 – 7.43 (m, 3H). MS m/z 420 $(M+H)^+$

Step 2: Cis-methyl 2-(2-fluoro-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(2-fluoro-4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (3 g, 7.15 mmol) was dissolved in MeOH (25 mL) and cooled to -45°C under nitrogen. Sodium hydroxide (2.104 mL, 7.15 mmol) was added during 10 min and the yellow solution continued to stir at -45°C for 20 min. Hydroxylamine (50 % by weight in water, 0.438 mL, 7.15 mmol) was added during 8 min. The resulting solution was stirred at -45°C for 3 h. The mixture was then rapidly poured into a prewarmed (80°C) solution of 6 M hydrogen chloride (36.8 mL, 221.05 mmol) and the mixture continued to stir at 80°C for 20 min. The solvent was evaporated and DCM/water added. The phases were separated and the organic phase passed through a phase separator and evaporated to yield a slightly yellow solid. The compound was purified by preparative HPLC on a XBridge C18 column (10 µm 250x50 ID mm) using a gradient of 10-60% Acetonitrile in H2O/MeCN/NH3 95/5/0.2 buffer over 20 minutes with a flow of 100 mL/min. Cis-methyl 2-(2-fluoro-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (2.12 g, 76 %) was isolated as a colourless oil. MS m/z 389 $(M+H)^+$

Step 3: (2R,4S)-Methyl 2-(2-fluoro-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 2-(2-fluoro-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl) piperidine-1-carboxylate (2.12 g, 5.46 mmol) was subjected to chiral preparative HPLC (Column: CelluCoat (250x50 mm), 10 µm particle size, mobile phase: Heptane/EtOH 50/50, flow rate 120 mL/min) to yield (2R,4S)-methyl 2-(2-fluoro-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (958 mg, 45 %), Chiral purity 99.9 %ee, Optical rotation $[\alpha]_D^{20} = +48.0$ (acetonitrile, c=1.0), ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.84 – 1.95 (m, 1H), 2.04 – 2.15 (m, 1H), 2.24 – 2.45 (m, 2H), 3.04 – 3.15 (m, 1H), 3.47 – 3.58 (m, 1H), 3.65 (s, 3H), 4.14 – 4.23 (m, 1H), 5.25 (dd, 1H), 5.61 (s, 1H), 7.23 – 7.37 (m, 3H).

Step 4: 5-((2R,4S)-2-(2-Fluoro-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-Methyl 2-(2-fluoro-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl) piperidine-1-carboxylate (0.96 g, 2.47 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 19.48 mL, 111.25 mmol) and the mixture was stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4S)-2-(2-fluoro-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one (687 mg, 84 %). ^{1}H NMR (600 MHz, dmso) δ 1.36 (q, 1H), 1.48 (dq, 1H), 1.84 – 1.92 (m, 1H), 1.94 – 2.02 (m, 1H), 2.75 (dt, 1H), 2.92 (tt, 1H), 3.08 – 3.15 (m, 1H), 4.00 (d, 1H), 5.73 (s, 1H), 7.53 – 7.62 (m, 2H), 7.78 (t, 1H). HRMS Calculated for $[C_{15}H_{14}F_4N_2O_2+H]^+$: 331.1070. Found: 331.1086

Example 74

5-(Trans-2-(2-fluoro-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(2-fluoro-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(2-fluoro-4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (430 mg, 1.03 mmol) (from example 73, step 1) was dissolved in MeOH (3 mL)

and cooled to -45°C under nitrogen. Sodium hydroxide (0.302 mL, 1.03 mmol) was added during 10 min and the yellow solution continued to stir at -45°C for 20 min. Hydroxylamine (50 % by weight in water, 0.063 mL, 1.03 mmol) was added during 8 min. The resulting solution was stirred at -45°C for 3 h. The mixture was then rapidly poured into a prewarmed (80°C) solution of 6 M hydrogen chloride (5.28 mL, 31.68 mmol) and the mixture continued to stir at 80°C for 20 min. The solvent was evaporated and DCM/water added. The phases were separated and the organic phase passed through a phase separator and evaporated to yield a slightly yellow oil. Crude trans-methyl 2-(2-fluoro-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (398 mg, quant.) was isolated. MS m/z 387 $(M-H)^-$

Step 2: 5-(Trans-2-(2-fluoro-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one

Trans-methyl 2-(2-fluoro-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate (400 mg, 1.03 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 8.12 mL, 46.35 mmol) and the mixture was stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-(trans-2-(2-fluoro-4-(trifluoromethyl)phenyl)-piperidin-4-yl)isoxazol-3(2H)-one (146 mg, 43 %). ^{1}H NMR (600 MHz, dmso) δ 1.63 – 1.71 (m, 1H), 1.78 – 1.86 (m, 1H), 1.91 – 1.99 (m, 1H), 2.04 – 2.11 (m, 1H), 2.69 (dt, 1H), 2.87 – 2.93 (m, 1H), 3.19 – 3.23 (m, 1H), 4.00 (d, 1H), 5.88 (d, 1H), 7.53 – 7.61 (m, 2H), 7.77 (t, 1H). HRMS Calculated for $[C_{15}H_{14}F_4N_2O_2+H]^+$: 331.1070. Found: 331.1074

Example 75

5-((2R,4S)-2-(3-Fluoro-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3-fluoro-4-(trifluoromethyl)phenyl) piperidine-1-carboxylate

2-(3-Fluoro-4-(trifluoromethyl)phenyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (3.07 g, 8.8 mmol) (reference compound 33) was dissolved in methyl THF (60 mL) under nitrogen atmosphere and di(1H-imidazol-1-yl)methanone (2.140 g, 13.20 mmol) was added. The suspension was stirred at room temperature for 3 h (flask 1). In a separate flask was

potassium 3-ethoxy-3-oxopropanoate (2.70 g, 15.84 mmol) suspended in methyl THF (30 mL) and magnesium chloride (1.508 g, 15.84 mmol) was added. The suspension was stirred at 50°C under nitrogen for 22 h using an oversized stirring bar (flask 2). The contents of flask 1 was transferred into flask 2 and the resulting white suspension was stirred at room temperature for 20 h. In a separate flask was potassium 3-ethoxy-3-oxopropanoate (1.348 g, 7.92 mmol) suspended in methyl THF (30 mL) and magnesium chloride (0.754 g, 7.92 mmol) was added. The suspension was stirred at 50°C for 5 h and then added to the reaction mixture. The mixture was stirred at room temperature for 15 h. 0.1 M HCl and DCM were added and the phases separated. The aqueous phase was extracted with DCM, the combined organic layers filtered through a phase separator and evaporated. The residue was purified via Biotage (5:1 heptane:EtOAc, Biotage® KP-SIL 340g column, 10 CV). The product methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3-fluoro-4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (2.190 g, 59.3 %) was isolated as a colorless oil. MS m/z 420 $(M+H)^+$

Step 2: Methyl 2-(3-fluoro-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3-fluoro-4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (2.19 g, 5.22 mmol) was dissolved in MeOH (20 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (0.219 g, 5.48 mmol) dissolved in water (2.000 mL) was added and the mixture was stirred at -40°C for 15 min. Hydroxylamine (50 % by weight in water, 0.336 mL, 5.48 mmol) was added. The resulting solution was stirred at -40°C for 1 h. The mixture was then transferred into a prewarmed (80°C) solution of 6 M hydrogen chloride (27.0 mL, 161.89 mmol) and the mixture was stirred at 80°C for 20 min. Water and DCM were added and the phases separated. The aqueous phase was extracted with DCM and the combined organic layers were filtered through a phase separator and evaporated. The compound was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x50 ID mm) using a gradient of 15-55% Acetonitrile in H2O/MeCN/FA 95/5/0.2 buffer over 25 minutes with a flow of 100 mL/min. Methyl 2-(3-fluoro-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.670 g, 33.0 %) was yielded as a colorless solid. ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.82 – 1.93 (m, 1H), 2.12 – 2.44 (m, 3H), 3.04 – 3.16 (m, 1H), 3.35 – 3.46 (m, 1H), 3.69 (s, 3H), 4.11 – 4.21 (m, 1H), 5.09 – 5.18 (m, 1H), 5.56 (s, 1H), 6.97 – 7.09 (m, 2H), 7.52 (t, 1H). MS m/z 387 $(M-H)^-$

Step 3: (2R,4S)-Methyl 2-(3-fluoro-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate and (2S,4R)-methyl 2-(3-fluoro-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Methyl 2-(3-fluoro-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (670 mg, 1.73 mmol) was subjected to chiral preparative HPLC (Column: CelluCoat (250x50), 10 µm particle size, mobile phase: Heptane/EtOH 50/50, flow rate 120 mL/min) to yield (2R,4S)-methyl 2-(3-fluoro-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (319 mg, 47 %), Chiral purity 99.9 %ee, optical rotation $[\alpha]_D^{20} = +53.4$ (acetonitrile, c=0.5) and (2S,4R)-methyl 2-(3-fluoro-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (332 mg, 49 %), Chiral purity 99.3 %ee, Optical rotation $[\alpha]_D^{20} = -47.6$ (acetonitrile, c=0.5).

Step 4: 5-((2R,4S)-2-(3-Fluoro-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-Methyl 2-(3-fluoro-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (319 mg, 0.82 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 6.5 mL, 36.97 mmol) and stirred at room temperature for 16 h. The solvent was removed in vacuo and the residue was purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4S)-2-(3-fluoro-4-(trifluoromethyl)phenyl)-piperidin-4-yl)isoxazol-3(2H)-one (150 mg, 55 %). ^{1}H NMR (600 MHz, dmso) δ 1.33 (q, 1H), 1.45 (dq, 1H), 1.84 – 1.90 (m, 1H), 1.99 – 2.05 (m, 1H), 2.72 (dt, 1H), 2.83 – 2.91 (m, 1H), 3.07 – 3.14 (m, 1H), 3.72 – 3.79 (m, 1H), 5.73 (s, 1H), 7.41 (d, 1H), 7.48 (d, 1H), 7.70 (t, 1H). HRMS Calculated for $[C_{15}H_{14}F_4N_2O_2+H]^+$: 331.1070. Found: 331.1058.

Example 76

5-((2S,4R)-2-(3-Fluoro-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one

(2S,4R)-Methyl 2-(3-fluoro-4-(trifluoromethyl)phenyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (332 mg, 0.85 mmol) was dissolved in hydrogen bromide (33 % in acetic acid (6.74 mL, 38.47 mmol) and stirred at room temperature for 16 h. The solvent was removed in vacuo and the residue was purified by preparative HPLC (Instrument:

FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2S,4R)-2-(3-fluoro-4-(trifluoromethyl)phenyl)-piperidin-4-yl)isoxazol-3(2H)-one (174 mg, 62 %). ^{1}H NMR (600 MHz, dmso) δ 1.32 (q, 1H), 1.45 (dq, 1H), 1.85 – 1.90 (m, 1H), 2.00 – 2.04 (m, 1H), 2.72 (dt, 1H), 2.87 (tt, 1H), 3.08 – 3.13 (m, 1H), 3.73 – 3.77 (m, 1H), 5.73 (s, 1H), 7.41 (d, 1H), 7.48 (d, 1H), 7.70 (t, 1H). HRMS Calculated for $[C_{15}H_{14}F_4N_2O_2+H]^+$: 331.1070. Found: 331.1067.

Example 77

5-((2R,4S)-2-Phenylpiperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-phenylpiperidine-1-carboxylate and cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-phenylpiperidine-1-carboxylate

1-(Methoxycarbonyl)-2-phenylpiperidine-4-carboxylic acid (5.133 g, 19.50 mmol) (reference compound 34) was dissolved in methyl THF (90 mL) and di(1H-imidazol-1-yl)methanone (4.74 g, 29.24 mmol) was added. The suspension was stirred at room temperature under nitrogen overnight (flask 1). In a separate flask potassium 3-ethoxy-3-oxopropanoate (5.97 g, 35.09 mmol) was suspended in methyl THF (90 mL) and magnesium chloride (3.34 g, 35.09 mmol) was added. The suspension was stirred at room temperature under nitrogen overnight (flask 2). Then, the slightly yellow suspension in flask 1 was added to the white suspension in flask 2. The resulting white suspension was stirred under nitrogen at room temperature for 6 h 30 min. In the meantime, potassium 3-ethoxy-3-oxopropanoate (5.97 g, 35.09 mmol) was suspended in methyl THF (90 mL) and magnesium chloride (3.34 g, 35.09 mmol) was added. The suspension was stirred at 50°C under nitrogen for 2 h and then added to the reaction mixture. The resulting white suspension was stirred at room temperature under nitrogen for 3 days. The mixture was acidified to pH 1 with 1 M HCl and MTBE was added. The phases were separated and the organic phase washed with water, satd $NaHCO_3$ and water. The solvents were evaporated to yield a yellow oil. The diastereoisomers were separated by column chromatography on silica (Biotage, gradient 0% => 50 % EtOAc in heptane; Biotage® KP-SIL 340g column) to yield trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-phenylpiperidine-1-carboxylate (1.14 g, 19 %) and cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-phenylpiperidine-1-carboxylate (3.77 g, 62 %). Cis-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.22

– 1.31 (m, 3H), 1.84 – 2.11 (m, 3H), 2.26 – 2.35 (m, 1H), 2.82 – 2.92 (m, 1H), 3.28 – 3.48 (m, 3H), 3.63 (s, 3H), 4.12 – 4.21 (m, 3H), 4.96 – 5.04 (m, 1H), 7.17 – 7.35 (m, 5H). MS m/z 334 $(M+H)^+$. Trans-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.13 – 1.25 (m, 3H), 1.44 – 1.95 (m, 3H), 2.45 – 2.66 (m, 2H), 2.78 – 2.88 (m, 1H), 3.39 (s, 2H), 3.68 (s, 3H), 3.98 – 4.34 (m, 3H), 5.55 (s, br., 1H), 7.10 – 7.23 (m, 3H), 7.26 – 7.34 (m, 2H). MS m/z 334 $(M+H)^+$.

Step 2: Cis-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-phenylpiperidine-1-carboxylate

Cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-phenylpiperidine-1-carboxylate (1.913 g, 5.74 mmol) was dissolved in MeOH (15 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (0.230 g, 5.74 mmol) dissolved in water (1.500 mL) was added during 5 min and the colourless solution continued to stir at -40°C for 20 min. Hydroxylamine (50 % by weight in water, 0.352 mL, 5.74 mmol) was added during 8 min. The resulting solution was stirred at -40°C for 2 h 15 min. The mixture was then rapidly poured into a prewarmed (80°C) solution of 6 M hydrogen chloride (24 mL, 144.00 mmol) and the mixture continued to stir at 80°C for 20 min. The solvent was evaporated and MTBE/water added. The phases were separated and the organic phase evaporated to yield a slightly yellow oil. The compound was purified by preparative HPLC in 2 injections on a XBridge C18 column (10 µm 250x50 ID mm) using a gradient of 0-30 % Acetonitrile in H2O/MeCN/NH3 95/5/0.2 buffer over 20 minutes with a flow of 100 mL/min. Cis-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-phenylpiperidine-1-carboxylate (1.344 g, 77 %) was isolated as a white solid. ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.77 – 1.85 (m, 1H), 2.10 – 2.18 (m, 1H), 2.19 – 2.28 (m, 1H), 2.32 – 2.39 (m, 1H), 3.01 – 3.08 (m, 1H), 3.37 (ddd, 1H), 3.64 (s, 3H), 4.15 (ddd, 1H), 5.08 – 5.13 (m, 1H), 5.48 (s, 1H), 7.13 – 7.20 (m, 3H), 7.27 (t, 2H). MS m/z 303 $(M+H)^+$

Step 3: (2R,4S)-Methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-phenylpiperidine-1-carboxylate

Racemic cis-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-phenylpiperidine-1-carboxylate (1.34 g, 4.42 mmol) was subjected to chiral preparative HPLC (Column: ReproSil (250x20), 8 µm particle size, mobile phase: EtOH, flow rate 100 mL/min) to yield (2R,4S)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-phenylpiperidine-1-carboxylate (621 mg, 46 %). Chiral purity 99.9 % ee. Optical rotation $[\alpha]_D^{20}$ = +65.8 (acetonitrile, c=1).

Step 4: 5-((2R,4S)-2-phenylpiperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-phenylpiperidine-1-carboxylate (621 mg, 2.05 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 7 mL, 99.92 mmol) and the mixture stirred at room temperature for 24 h. The solvent was evaporated and the residue was purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4S)-2-phenylpiperidin-4-yl)isoxazol-3(2H)-one (306 mg, 61 %) (the isolated sample contained DMSO). ^{1}H NMR (400 MHz, cd_3od) δ 1.76 – 2.02 (m, 2H), 2.11 – 2.30 (m, 2H), 3.05 – 3.21 (m, 2H), 3.41 – 3.49 (m, 1H), 4.14 (dd, 1H), 5.56 (s, 1H), 7.27 – 7.48 (m, 5H). HRMS Calculated for $[C_{14}H_{16}N_2O_2+H]^+$: 245.1290. Found: 245.1270

Example 78

5-((2S,4S)-2-Phenylpiperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-phenylpiperidine-1-carboxylate
Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-phenylpiperidine-1-carboxylate (1.104 g, 3.31 mmol) (from example 77, step 1) was dissolved in MeOH (10 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (0.132 g, 3.31 mmol) dissolved in water (1.000 mL) was added during 10 min and the colourless solution continued to stir at -40°C for 30 min. Hydroxylamine (50 % by weight in water, 0.203 mL, 3.31 mmol) was added during 6 min. The resulting solution was stirred at -40°C for 2 h 30 min. The mixture was then rapidly poured into a prewarmed (80°C) solution of 6 M hydrogen chloride (14 mL, 84.00 mmol) and the mixture continued to stir at 80°C for 20 min. The solvent was evaporated and MTBE/water was added. The phases were separated and the organic phase evaporated to yield a brown oil. The residue was purified by preparative HPLC on a XBridge C18 column (10 µm 250x50 ID mm) using a gradient of 0-30 % Acetonitrile in H_2O/MeCN/NH_3 95/5/0.2 buffer over 20 minutes with a flow of 100 mL/min. Trans-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-phenylpiperidine-1-carboxylate (722 mg, 72 %) was isolated. ^{1}H NMR (400 MHz, $cdcl_3$) δ 1.66 (dq, 1H), 1.86 – 2.09 (m, 2H), 2.72 (d, 1H), 2.79 – 3.03 (m, 2H), 3.78 (s, 3H), 4.26 (br. s, 1H), 5.68 (br. s, 2H), 7.20 – 7.32 (m, 3H), 7.34 – 7.43 (m, 2H). MS m/z 303 $(M+H)^+$

Step 2: (2S,4S)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-phenylpiperidine-1-carboxylate
Racemic trans-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-phenylpiperidine-1-carboxylate

(772 mg, 2.55 mmol) was subjected to chiral preparative HPLC (Column: Chiralpak AD (250x20), 5 μm particle size, mobile phase: Heptane/EtOH 75/25, flow rate 15 mL/min) to yield (2S,4S)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-phenylpiperidine-1-carboxylate (249 mg, 32 %). Optical rotation $[\alpha]_D^{20} = +23.0$ (acetonitrile, c=1), Chiral purity 99.7 %ee.

Step 3: 5-((2S,4S)-2-phenylpiperidin-4-yl)isoxazol-3(2H)-one

(2S,4S)-Methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-phenylpiperidine-1-carboxylate (249 mg, 0.82 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 3 mL, 42.82 mmol) and the mixture was stirred at room temperature for 16 h. The solvent was evaporated and the residue was purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5μm OBD 19*150 mm) to yield 5-((2S,4S)-2-phenylpiperidin-4-yl)isoxazol-3(2H)-one (255 mg, 127 %) (the isolated sample contained DMSO). ^{1}H NMR (400 MHz, cdcl$_3$) δ 2.10 – 2.43 (m, 4H), 3.21 (dt, 1H), 3.26 – 3.35 (m, 1H), 3.35 – 3.43 (m, 1H), 4.17 (dd, 1H), 5.73 (s, 1H), 7.34 – 7.48 (m, 5H). HRMS Calculated for $[C_{14}H_{16}N_2O_2+H]^+$: 245.1290. Found: 245.1271.

Example 79

5-((2R,4S)-2-Cyclohexylpiperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-cyclohexyl-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate and cis-methyl 2-cyclohexyl-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate

A suspension of magnesium chloride (2.085 g, 21.89 mmol) and ethyl potassium malonate (3.73 g, 21.89 mmol) in dry THF (80 mL) was stirred under nitrogen atmosphere at 50°C for 2.5 h (flask 1). In another flask di(1H-imidazol-1-yl)methanone (2.96 g, 18.24 mmol) was added portionwise to a solution of 2-cyclohexyl-1-(methoxycarbonyl)piperidine-4-carboxylic acid (3.28 g, 12.16 mmol) (reference compound 35) in dry THF (20 mL) at 0°C and put under nitrogen atmosphere. The ice bath was removed and the solution was stirred for 2 h at room temperature (flask 2). Then the contents of flask 1 was added to flask 2 and the resulting mixture was stirred overnight (20 h). The reaction mixture was concentrated and the residue was taken up in EtOAc and H_2O. The aqueous phase was extracted once with EtOAc and the

combined organic phase was washed with water, 10 % Na_2CO_3 and then dried over Na_2SO_4. The organic phase was washed with 0.1 M NaOH and dried again and evaporated to give a yellow oil. The compound was purified further via Biotage, 2 runs, SNAP 340g KP-SIL, linear gradient heptanes/ethyl acetate 9:1 to 1:1 over 7CV. Trans-methyl 2-cyclohexyl-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (349 mg, 6.9%) and cis-methyl 2-cyclohexyl-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (2.501, 49%) were isolated. Cis-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 0.90 – 1.29 (m, 5H), 1.26 (t, 3H), 1.37 – 2.05 (m, 10H), 2.57 – 2.70 (m, 1H), 2.85-3.02 (m, 1H), 3.48 (s, 2H), 3.67 (s, 3H), 3.71-3.84 (m, 1H), 3.86-3.99 (m, 1H), 4.18 (q, 2H). MS m/z 340 (M+H)+. Trans-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 0.80 – 1.30 (m, 5H), 1.26 (t, 3H), 1.33 – 1.90 (m, 9H), 1,96-2.12 (m, 1H), 2.69 – 2.86 (m, 2H), 3.46 (s, 2H), 3.67 (s, 3H), 3.84-4.33 (m, 2H), 4.21 (q, 2H). MS m/z 340 (M+H)+

Step 2: Cis-methyl 2-cyclohexyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 2-cyclohexyl-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (1.644 g, 4.84 mmol) was dissolved in MeOH (15 mL) and cooled to -40°C. Sodium hydroxide (0.194 g, 4.84 mmol) dissolved in water (1.500 mL) was added dropwise and the colourless solution continued to stir at -40°C for 30 min. Hydroxylamine (50 % by weight in water, 0.297 mL, 4.84 mmol) was added dropwise. The resulting solution was stirred at -40°C for 3 h. The mixture was then rapidly poured into a prewarmed (80°C) solution of 6 M hydrogen chloride (21 mL, 126.00 mmol) and the mixture continued to stir at 80°C for 20 min. The solvent was evaporated and MTBE/water added. The phases were separated and the organic phase dried over Na_2SO_4 and evaporated to yield a slightly yellow foam. The compound was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x50 ID mm) using two injections with a gradient of 15-75% Acetonitrile in H2O/MeCN/AcOH 95/5/0.2 buffer over 30 minutes with a flow of 100 mL/min. Cis-methyl 2-cyclohexyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (814 mg, 55%) was isolated. ^{1}H NMR (400 MHz, cdcl$_3$) δ 0.83-0.98 (m, 2H), 1.01-1.16 (m, 3H), 1.25-1.40 (m, 1H), 1.50 – 1.88 (m, 6H), 1.95 – 2.13 (m, 3H), 2.88-3.07 (m, 2H), 3.70 (s, 3H), 3.79 – 3.89 (m, 1H), 3.95-4.07 (m, 1H), 5.70 (s, 1H). MS m/z 309 (M+H)+

Step 3: (2R,4S)-Methyl 2-cyclohexyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 2-cyclohexyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (814 mg, 2.66 mmol) was subjected to chiral preparative HPLC (Column: Chiralpak IC (250x20), 5 µm particle size, mobile phase: Heptane/IPA 60/40, flow rate 15 mL/min) to yield (2R,4S)-methyl 2-cyclohexyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (427 mg, 50 %), Chiral purity 99.9 %ee. Optical rotation $[\alpha]_D^{20} = +38.5$ (acetonitrile, c=1)

Step 4: 5-((2R,4S)-2-Cyclohexylpiperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-Methyl 2-cyclohexyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.427 g, 1.38 mmol) was stirred in HBr (33% in AcOH) overnight (19 hours). Evaporation of solvents and the residue purified by preparative HPLC (Instrument: FractionLynx I, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4S)-2-cyclohexylpiperidin-4-yl)isoxazol-3(2H)-one (228 mg, 66%). ^{1}H NMR (400 MHz, cd_3od) δ 1.05-1.42 (m, 5H), 1.49-1.66 (m, 2H), 1.67 – 1.91 (m, 6H), 2.17-2.26 (m, 1H), 2.26-2.35 (m, 1H), 2.97 – 3.19 (m, 3H), 3.43-3.52 (m, 1H), 5.70 (s, 1H), 8.51 (s, 1H). HRMS Calcd for $[C_{14}H_{22}N_2O_2+H]+$: 251.1760. Found: 251.1750.

Example 80

5-((2S,4S)-2-Cyclohexylpiperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-cyclohexyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Trans-methyl 2-cyclohexyl-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (349 mg, 1.03 mmol) (from example 79, step 1) was dissolved in MeOH (5 mL) and cooled to -40°C. Sodium hydroxide (41.1 mg, 1.03 mmol) dissolved in water (0.500 mL) was added dropwise and the colourless solution continued to stir at -40°C for 30 min. Hydroxylamine (50 % by weight in water, 0.063 mL, 1.03 mmol) was added dropwise. The resulting solution was stirred at -40°C for 2 h 20 min. The mixture was then rapidly poured into a prewarmed (80°C) solution of 6 M hydrogen chloride (5 mL, 30.00 mmol) and the mixture continued to stir at 80°C for 20 min. The solvent was evaporated and MTBE/water added. The phases were separated and the organic phase was dried over Na_2SO_4 and evaporated to yield a yellow oil. The compound was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x50

ID mm) using a gradient of 15-75% Acetonitrile in H2O/MeCN/AcOH 95/5/0.2 buffer over 30 minutes with a flow of 100 mL/min. Trans-methyl 2-cyclohexyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (170 mg, 53%) was isolated. ^{1}H NMR (400 MHz, cdcl$_3$) δ 0.82-1.08 (m, 2H), 1.08-1.32 (m, 3H), 1.45-1.83 (m, 8H), 1.89-2.02 (m, 1H), 2.12-2.23 (m, 1H), 2.79-3.04 (m, 2H), 3.70 (s, 3H), 3.87-4.83 (m, 2H), 5.64 (s, 1H). MS m/z 309 (M+H)+

Step 2: (2S,4S)-Methyl 2-cyclohexyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Trans-methyl 2-cyclohexyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (212 mg, 0.69 mmol) was subjected to chiral preparative HPLC (Column: Chiralcel OJ (250x20), 5 µm particle size, mobile phase: EtOH, flow rate 12 mL/min) to yield (2S,4S)-methyl 2-cyclohexyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (79 mg, 37 %), Chiral purity 99.3 %ee. Optical rotation $[\alpha]_D^{20} = +5.1$ (acetonitrile, c=1)

Step 3: 5-((2S,4S)-2-Cyclohexylpiperidin-4-yl)isoxazol-3(2H)-one

(2S,4S)-Methyl 2-cyclohexyl-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (79 mg, 0.26 mmol) was stirred in HBr (33% in AcOH) overnight. Evaporation of solvents and the residue purified by preparative HPLC (Instrument:FractionLynx I,Mobilphase:gradient 5-95% MeCN in 0.2% NH3, pH10,Column:Xbridge Prep C18 5µm OBD 19*150 mm.) to yield 5-((2S,4S)-2-cyclohexylpiperidin-4-yl)isoxazol-3(2H)-one 22 mg (35%). ^{1}H NMR (400 MHz, cd$_3$od) δ 1.00-1.39 (m, 5H), 1.51-1.64 (m, 1H), 1.64 – 1.93 (m, 6H), 1.96-2.11 (m, 1H), 2.15-2.25 (m, 1H), 2.26-2.35 (m, 1H), 2.92 – 3.02 (m, 1H), 3.03-3.16 (m, 1H), 3.22-3.33 (m, 2H), 5.57 (s, 1H). HRMS Calcd for [$C_{14}H_{22}N_2O_2$+H]+: 251.1760. Found: 251.1754.

Example 81

5-((2R,4S)-2-(2-Methyl-2H-tetrazol-5-yl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Benzyl 4-(3-ethoxy-3-oxopropanoyl)-2-(2-methyl-2H-tetrazol-5-yl)piperidine-1-carboxylate

1-(Benzyloxycarbonyl)-2-(2-methyl-2H-tetrazol-5-yl)piperidine-4-carboxylic acid (0.828 g,

2.40 mmol) (reference compound 36) was dissolved in THF (7 mL) and then di(1H-imidazol-1-yl)methanone (0.583 g, 3.60 mmol) was added. The reaction was stirred overnight at room temperature (flask 1). In a separate flask potassium 3-ethoxy-3-oxopropanoate (0.816 g, 4.80 mmol) and anhydrous magnesium chloride (0.457 g, 4.80 mmol) were suspended in THF (7.00 mL) and stirred at 50°C under nitrogen overnight and then allowed to cool to room temperature (flask 2). The content of flask 1 was added to flask 2 and stirred under nitrogen over the weekend (72 h). The reaction was quenched by addition of 2 M HCl. The mixture was extracted three times with EtOAc, the combined organic phase was evaporated and purified on a 50 g Biotage column with heptane/EtOAc 88/12 - 100/0 over 12 CV. Benzyl 4-(3-ethoxy-3-oxopropanoyl)-2-(2-methyl-2H-tetrazol-5-yl)piperidine-1-carboxylate (499 mg, 59 %) was isolated. ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.22 – 1.31 (m, 3H), 1.72 – 1.83 (m, 1H), 2.00 – 2.08 (m, 1H), 2.41 (dt, 1H), 2.70 – 2.78 (m, 1H), 2.88 – 2.95 (m, 1H), 3.35 – 3.63 (m, 3H), 3.99 – 4.07 (m, 1H), 4.12 – 4.20 (m, 2H), 4.28 (s, 3H), 5.11 – 5.21 (m, 2H), 5.59 (t, 1H), 7.27 – 7.40 (m, 5H). MS m/z 416 $(M+H)^+$

Step 2: Benzyl 2-(2-methyl-2H-tetrazol-5-yl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Benzyl 4-(3-ethoxy-3-oxopropanoyl)-2-(2-methyl-2H-tetrazol-5-yl)piperidine-1-carboxylate (0.499 g, 1.20 mmol) was dissolved in MeOH (6 mL) and cooled to - 40°C. 3.8 M NaOH (0.316 mL, 1.20 mmol) dissolved in water (0.6 mL) was added and the reaction stirred at - 40°C for 40 min. Hydroxylamine (50 % by weight in water, 0.074 mL, 1.20 mmol) was added and stirring continued for 3.5 h at - 40°C. The reaction mixture was then added to a preheated 80°C solution of 6 M HCl (6.01 mL, 36.03 mmol) and stirred for 20 min. The reaction mixture was partitioned between water and DCM. The aqueous phase was extracted twice with DCM and the combined organic phase was dried and evaporated. The compound was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x50 ID mm) using a gradient of 15-55% Acetonitrile in H_2O/MeCN/NH_3 95/5/0.2 buffer over 20 minutes with a flow of 100 mL/min. Benzyl 2-(2-methyl-2H-tetrazol-5-yl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (327 mg, 71 %) was isolated. ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.96 – 2.15 (m, 2H), 2.41 (dt, 1H), 2.64 – 2.74 (m, 1H), 3.12 – 3.19 (m, 1H), 3.61 – 3.72 (m, 1H), 4.07 – 4.20 (m, 4H), 5.13 (s, 2H), 5.43 (s, 1H), 5.58 – 5.64 (m, 1H), 7.25 – 7.41 (m, 5H). MS m/z 385 $(M+H)^+$

Step 3: (2R,4S)-Benzyl 2-(2-methyl-2H-tetrazol-5-yl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate and trans-benzyl 2-(2-methyl-2H-tetrazol-5-yl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Benzyl 2-(2-methyl-2H-tetrazol-5-yl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (866 mg, 2.25 mmol) was subjected to chiral preparative HPLC: The cis isomers were separated from the trans isomers using preparative HPLC (Column: Chiralcel OJ (250x20), 5 µm particle size, mobile phase: Heptane/EtOH/DEA 65/45/0.1, flow rate 18 mL/min). The cis-enatiomers were separated using chiral preparative HPLC (Column: Chiralpak AD (250x20), 5 µm particle size, mobile phase: Heptane/IPA/DEA 50/50/0.1, flow rate 15 mL/min) to yield (2R,4S)-benzyl 2-(2-methyl-2H-tetrazol-5-yl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (301 mg, 35 %), chiral purity 99.1%ee, Optical rotation $[\alpha]_D^{20} = +28.9$ (acetonitrile, c=1), ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.96 – 2.13 (m, 2H), 2.39 (dt, 1H), 2.61 – 2.71 (m, 1H), 3.10 (p, 1H), 3.62 – 3.72 (m, 1H), 4.09 (dt, 1H), 4.18 (s, 3H), 5.12 (d, 2H), 5.33 (s, 1H), 5.56 (t, 1H), 7.21 – 7.36 (m, 5H). and trans-benzyl 2-(2-methyl-2H-tetrazol-5-yl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (99 mg, 11 %) were isolated.

Step 4: 5-((2R,4S)-2-(2-Methyl-2H-tetrazol-5-yl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-Benzyl 2-(2-methyl-2H-tetrazol-5-yl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (301 mg, 0.78 mmol) was dissolved in hydrogen bromide (33 % in AcOH) (4.1 mL, 23.49 mmol) and reacted for 1 h. The mixture was evaporated and the residue was partitioned between water and EtOAc. The aqueous phase was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x50 ID mm) using a gradient of 0-15% Acetonitrile in H2O/MeCN/NH3 95/5/0.2 buffer over 20 minutes with a flow of 100 mL/min. 5-((2R,4S)-2-(2-Methyl-2H-tetrazol-5-yl)piperidin-4-yl)isoxazol-3(2H)-one (143 mg, 73 %) was isolated. ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.70 (qd, 1H), 1.85 (q, 1H), 2.04 – 2.12 (m, 1H), 2.43 – 2.50 (m, 1H), 2.91 – 3.02 (m, 2H), 3.33 – 3.41 (m, 1H), 4.18 (dd, 1H), 4.32 (s, 3H), 5.68 (s, 1H). HRMS Calcd for $[C_{10}H_{14}N_6O_2+H]^+$: 251.1256. Found: 251.1233.

Example 82

5-(Trans-2-(2-methyl-2H-tetrazol-5-yl)piperidin-4-yl)isoxazol-3(2H)-one

Trans-benzyl 2-(2-methyl-2H-tetrazol-5-yl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (99 mg, 0.26 mmol) (from example 81, step 3) was dissolved in hydrogen bromide (33 % in HOAc, 1.35 mL, 7.73 mmol) and reacted for 1 h. The mixture was evaporated and the residue was partitioned between water and EtOAc. The aqueous phase was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x50 ID mm) using a gradient of 0-15% Acetonitrile in H2O/MeCN/NH3 95/5/0.2 buffer over 20 minutes with a flow of 100 mL/min. 5-(Trans-2-(2-methyl-2H-tetrazol-5-yl)piperidin-4-yl)isoxazol-3(2H)-one (45 mg, 70 %). ^{1}H NMR (400 MHz, cd_3od) δ 1.83 – 2.05 (m, 2H), 2.21 – 2.31 (m, 1H), 2.36 – 2.44 (m, 1H), 2.93 – 3.06 (m, 2H), 3.17 – 3.25 (m, 1H), 4.37 (s, 3H), 4.49 (t, 1H), 5.77 (s, 1H). HRMS Calcd for $[C_{10}H_{14}N_6O_2+H]^+$: 251.1256. Found: 251.1262.

Example 83

5-((2R,4S)-2-(1-Methyl-1H-tetrazol-5-yl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Cis-benzyl 4-(3-ethoxy-3-oxopropanoyl)-2-(1-methyl-1H-tetrazol-5-yl)piperidine-1-carboxylate

1-(Benzyloxycarbonyl)-2-(1-methyl-1H-tetrazol-5-yl)piperidine-4-carboxylic acid (0.495 g, 1.43 mmol) (reference compound 37) was dissolved in THF (4 mL) and then di(1H-imidazol-1-yl)methanone (0.349 g, 2.15 mmol) was added. The reaction was stirred overnight at room temperature (flask 1). In a separate flask potassium 3-ethoxy-3-oxopropanoate (0.488 g, 2.87 mmol) and anhydrous magnesium chloride (0.273 g, 2.87 mmol) were suspended in THF (4.00 mL) and stirred at 50°C under nitrogen overnight and then allowed to cool to room temperature (flask 2). The contents of flask 1 was added to flask 2 and stirred under nitrogen over the weekend (72 h). The reaction was quenched by addition of 2 M HCl. The mixture was extracted three times with EtOAc, the combined organic phase was evaporated and purified on a 50 g Biotage column with heptane/EtOAc 88/12 - 100/0 over 12 CV. Cis-benzyl 4-(3-ethoxy-3-oxopropanoyl)-2-(1-methyl-1H-tetrazol-5-yl)piperidine-1-carboxylate (482 mg, 81 %) was isolated. ^{1}H NMR (600 MHz, $cdcl_3$) δ 1.25 (t, 3H), 1.89 – 1.97 (m, 1H), 2.05 – 2.12 (m, 1H), 2.28 – 2.34 (m, 1H), 2.59 – 2.66 (m, 1H), 2.93 (p, 1H), 3.35 – 3.41 (m, 1H), 3.62 (dd, 2H), 3.85 – 3.98 (m, 4H), 4.16 (q, 2H), 5.09 (q, 2H), 5.36 – 5.42 (m, 1H), 7.21 – 7.37 (m, 5H). MS m/z 416 $(M+H)^+$

Step 2: Benzyl 2-(1-methyl-1H-tetrazol-5-yl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Benzyl 4-(3-ethoxy-3-oxopropanoyl)-2-(1-methyl-1H-tetrazol-5-yl)piperidine-1-carboxylate (0.947 g, 2.28 mmol) was dissolved in MeOH (10 mL) and cooled to - 40°C. 3.8 M NaOH (0.600 mL, 2.28 mmol) dissolved in water water (1 mL) was added and the reaction stirred at - 40°C for 40 min. Hydroxylamine (50 % by weight in water, 0.140 mL, 2.28 mmol) was added and stirring continued for 3.5 h at - 40°C. The reaction mixture was then added to a preheated 80°C warm solution of 6 M HCl (11.40 mL, 68.38 mmol) and stirred for 20 min. The reaction mixture was partitioned between water and DCM. The aqueous phase was extracted twice with DCM and the combined organic phase was dried and evaporated. The compound was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x50 ID mm) using a gradient of 15-55% Acetonitrile in H2O/MeCN/NH3 95/5/0.2 buffer over 20 minutes with a flow of 100 mL/min. Benzyl 2-(1-methyl-1H-tetrazol-5-yl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (488 mg, 56 %) was isolated. ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.86 – 1.99 (m, 1H), 2.18 – 2.30 (m, 1H), 2.33 – 2.54 (m, 2H), 3.01 – 3.12 (m, 1H), 3.78 – 4.09 (m, 5H), 5.05 (s, 2H), 5.20 – 5.30 (m, 1H), 5.67 (s, 1H), 7.20 – 7.27 (m, 2H), 7.27 – 7.39 (m, 3H). MS m/z 385 $(M+H)^+$

Step 3: (2R,4S)-Benzyl 2-(1-methyl-1H-tetrazol-5-yl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Benzyl 2-(1-methyl-1H-tetrazol-5-yl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (488 mg, 1.27 mmol) was subjected to chiral preparative HPLC (Column: Chiralpak AS (250x20), 5 µm particle size, mobile phase: Heptane/EtOH/DEA 60/40/0.1, flow rate 18 mL/min) to yield (2R,4S)-benzyl 2-(1-methyl-1H-tetrazol-5-yl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (231 mg, 47 %), chiral purity 98%ee, Optical rotation $[\alpha]_D^{20} = +14.5$ (acetonitrile, c=1)

Step 4: 5-((2R,4S)-2-(1-Methyl-1H-tetrazol-5-yl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-Benzyl 2-(1-methyl-1H-tetrazol-5-yl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.231 g, 0.60 mmol) was dissolved in hydrogen bromide (33 % in HOAc, 5.26 mL, 30.05 mmol) and allowed to react for 1 h. The mixture was evaporated and the residue

was partitioned between water and EtOAc. The aqueous phase was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x50 ID mm) using a gradient of 0-10% Acetonitrile in H_2O/MeCN/NH_3 95/5/0.2 buffer over 20 minutes with a flow of 100 mL/min. The compounds were detected by UV at 220nm. Product fractions (which contained DMSO) were collected and the acetonitrile was evaporated. The aqueous phase was freeze dried. Most of the DMSO was left so the residue was dissolved in 2 mL of MeOH and loaded onto a 2 g SCX-2 column and the column washed with MeOH. The amine was liberated by running 10 mL of 10 % triethylamine in MeOH through it. The solvent was evaporated and the residue was freeze dried from water to yield 5-((2R,4S)-2-(1-methyl-1H-tetrazol-5-yl)piperidin-4-yl)isoxazol-3(2H)-one (100 mg, 67 %). ^{1}H NMR (400 MHz, dmso) δ 1.47 (dq, 1H), 1.70 – 1.81 (m, 1H), 1.87 (d, 1H), 2.12 (d, 1H), 2.74 (dt, 1H), 2.92 – 3.02 (m, 1H), 3.04 – 3.13 (m, 1H), 4.09 (s, 3H), 4.18 (dd, 1H), 5.78 (s, 1H). HRMS Calcd for [(2 x $C_{10}H_{14}N_6O_2$)+H]$^+$: 501.2435. Found: 501.2418.

Example 84

5-((2R,4S)-2-(Cyclohexyloxymethyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(cyclohexyloxymethyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate and cis-methyl 2-(cyclohexyloxymethyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate

2-(Cyclohexyloxymethyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (2.425 g, 8.1 mmol) (reference compound 38) was dissolved in methyl THF (60 mL) under nitrogen atmosphere and di(1H-imidazol-1-yl)methanone (1.970 g, 12.15 mmol) was added. The suspension was stirred at room temperature for 3h (flask 1). In a separate flask was potassium 3-ethoxy-3-oxopropanoate (2.482 g, 14.58 mmol) suspended in methyl THF (30 mL) and magnesium chloride (1.388 g, 14.58 mmol) was added. The suspension was stirred at 50°C under nitrogen for 22 h using an oversized stirring bar (flask 2). The contents of flask 1 was added to flask 2 and the resulting white suspension was stirred at room temperature for 20 h. In a separate flask was potassium 3-ethoxy-3-oxopropanoate (1.241 g, 7.29 mmol) suspended in methyl THF (30 mL) and magnesium chloride (0.694 g, 7.29 mmol) was added. The suspension was stirred at 50°C for 5 h and then added to the reaction mixture. The mixture was stirred at room temperature for 15 h. 0.1 M HCl and DCM were added and the phases

separated. The aqueous phase was extracted with DCM, the combined organic layers filtered through a phase separator and evaporated. The residue was purified via Biotage (5:1 heptane:EtOAc, Biotage® KP-SIL 340g column, 10 CV). Trans-methyl 2-(cyclohexyloxymethyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (210 mg, 7 %) and cis-methyl 2-(cyclohexyloxymethyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (1.13 g, 38 %) were isolated. Cis-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.14 – 2.14 (m, 17H), 2.70 – 2.79 (m, 1H), 3.11 – 3.30 (m, 2H), 3.34 – 3.62 (m, 4H), 3.69 (s, 3H), 3.82 – 3.91 (m, 1H), 4.07 – 4.24 (m, 3H). MS m/z 370 $(M+H)^+$. Trans-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.16 – 2.19 (m, 17H), 2.80 – 3.10 (m, 2H), 3.16 – 3.32 (m, 1H), 3.44 – 3.64 (m, 4H), 3.66 – 3.74 (m, 3H), 3.97 – 4.27 (m, 3H), 4.33 – 4.57 (m, 1H). MS m/z 370 $(M+H)^+$

Step 2: Cis-methyl 2-(cyclohexyloxymethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 2-(cyclohexyloxymethyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (1.13 g, 3.06 mmol) was dissolved in MeOH (14 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (0.128 g, 3.21 mmol) dissolved in water (1.400 mL) was added and the mixture was stirred at -40°C for 15 min. Hydroxylamine(50 % by weight in water, 0.197 mL, 3.21 mmol) was added. The resulting solution was stirred at -40°C for 1 h. The mixture was transferred into a prewarmed (80°C) solution of 6 M hydrogen chloride (15.80 mL, 94.82 mmol) and the mixture was stirred at 80°C for 20 min. Water and DCM were added and the phases separated. The aqueous phase was extracted with DCM and the combined organic layers were filtered through a phase separator and evaporated. The compound was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x50 ID mm) using a gradient of 15-55% Acetonitrile in H2O/MeCN/AcOH 95/5/0.2 buffer over 25 minutes with a flow of 100 mL/min. Cis-methyl 2-(cyclohexyloxymethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (423 mg, 41 %) was isolated. ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.12 – 2.15 (m, 14H), 2.93 – 3.04 (m, 1H), 3.10 – 3.31 (m, 2H), 3.35 – 3.50 (m, 2H), 3.70 (s, 3H), 3.83 – 3.94 (m, 1H), 4.05 – 4.15 (m, 1H), 5.75 (s, 1H). MS m/z 339 $(M+H)^+$

Step 3: (2R,4S)-Methyl 2-(cyclohexyloxymethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate and (2S,4R)-methyl 2-(cyclohexyloxymethyl)-4-(3-oxo-2,3-dihydro-isoxazol-5-yl)piperidine-1-carboxylate

Cis-Methyl 2-(cyclohexyloxymethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-

carboxylate (423 mg, 1.25 mmol) was subjected to chiral preparative HPLC (Column: Chiralpak IC (250x20), 5 µm particle size, mobile phase: Heptane/EtOH 70/30, flow rate 18 mL/min) to yield (2R,4S)-methyl 2-(cyclohexyloxymethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (190 mg, 45 %), Chiral purity 98.3 %ee, Optical rotation $[\alpha]_D^{20} = +55.9$ (acetonitrile, c=1) and (2S,4R)-methyl 2-(cyclohexyloxymethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (194 mg, 46 %), Chiral purity 98.6 %ee, Optical rotation $[\alpha]_D^{20} = -55.4$ (acetonitrile, c=1)

Step 4: 5-((2R,4S)-2-(Cyclohexyloxymethyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-Methyl 2-(cyclohexyloxymethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (190 mg, 0.56 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 4.43 mL, 25.27 mmol) and stirred at room temperature for 16 h. The solvent was removed in vacuo and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4S)-2-(cyclohexyloxymethyl)piperidin-4-yl)isoxazol-3(2H)-one (5 mg, 3 %). ^{1}H NMR (600 MHz, dmso) δ 1.03 – 1.25 (m, 6H), 1.32 – 1.48 (m, 2H), 1.55 – 1.68 (m, 2H), 1.70 – 1.90 (m, 4H), 2.56 – 2.66 (m, 1H), 2.68 – 2.79 (m, 2H), 2.99 – 3.06 (m, 1H), 3.06 – 3.83 (m, 3H), 5.70 (s, 1H). HRMS Calculated for $[C_{15}H_{24}N_2O_3+H]^+$: 281.1865. Found: 281.1860

Example 85

5-((2S,4R)-2-(Cyclohexyloxymethyl)piperidin-4-yl)isoxazol-3(2H)-one

(2S,4R)-Methyl 2-(cyclohexyloxymethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (194 mg, 0.57 mmol) (from example 84, step 3) was dissolved in hydrogen bromide (33 % in acetic acid, 4.52 mL, 25.80 mmol) and stirred at room temperature for 16 h. The solvent was removed in vacuo and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2S,4R)-2-(Cyclohexyloxymethyl)piperidin-4-yl)isoxazol-3(2H)-one (4.5 mg, 3 %). ^{1}H NMR (600 MHz, dmso) δ 1.04 – 1.24 (m, 6H), 1.33 – 1.46 (m, 2H), 1.57 – 1.66 (m, 2H), 1.73 – 1.88 (m, 4H), 2.56 – 2.67 (m, 1H), 2.68 – 2.80 (m,

2H), 2.99 – 3.06 (m, 1H), 3.07 – 3.84 (m, 3H), 5.70 (s, 1H). HRMS Calculated for $[C_{15}H_{24}N_2O_3+H]^+$: 281.1865. Found: 281.1893

Example 86

5-(Trans-2-(cyclohexyloxymethyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(cyclohexyloxymethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Trans-methyl 2-(cyclohexyloxymethyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (210 mg, 0.57 mmol) (from example 84, step 1) was dissolved in MeOH (3 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (23.87 mg, 0.60 mmol) dissolved in water (0.300 mL) was added and the mixture was stirred at -40°C for 15 min. Hydroxylamine (50 % by weight in water, 0.037 mL, 0.60 mmol) was added. The resulting solution was stirred at -40°C for 1 h. The mixture was transferred into a prewarmed (80°C) solution of 6 M hydrogen chloride (2.94 mL, 17.62 mmol) and the mixture was stirred at 80°C for 20 min. Water and DCM were added and the phases separated. The aqueous phase was extracted with DCM and the combined organic layers were filtered through a phase separator and evaporated. The compound was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x50 ID mm) using a gradient of 15-55% Acetonitrile in H2O/MeCN/AcOH 95/5/0.2 buffer over 20 minutes with a flow of 100 mL/min. Trans-methyl 2-(cyclohexyloxymethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (121 mg, 63 %) was isolated. MS m/z 339 $(M+H)^+$

Step 2: 5-(Trans-2-(cyclohexyloxymethyl)piperidin-4-yl)isoxazol-3(2H)-one

Trans-methyl 2-(cyclohexyloxymethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (121 mg, 0.36 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, (2.75 mL, 15.69 mmol) and stirred at room temperature for 16 h. The solvent was removed in vacuo and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-(trans-2-(cyclohexyloxymethyl)piperidin-4-yl)isoxazol-3(2H)-one (15 mg, 15 %). ^{1}H NMR (600 MHz, dmso) δ 1.09 – 1.25 (m, 5H), 1.38 – 1.53 (m, 2H), 1.55 – 1.65 (m, 2H), 1.65 – 1.83 (m, 5H), 2.55 – 2.63 (m, 1H), 2.69 – 2.80 (m, 2H), 3.02 –

3.88 (m, 4H), 5.76 (s, 1H). HRMS Calculated for $[C_{15}H_{24}N_2O_3+H]^+$: 281.1865. Found: 281.1879

Example 87

5-((2R,4S)-2-(Difluoromethyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(difluoromethyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate and cis-methyl 2-(difluoromethyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate

2-(Difluoromethyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (2.2 g, 9.27 mmol) (reference compound 39) was dissolved in methyl THF (60 mL) under nitrogen atmosphere and di(1H-imidazol-1-yl)methanone (2.256 g, 13.91 mmol) was added. The suspension was stirred at room temperature for 3 h (flask 1). In a separate flask was potassium 3-ethoxy-3-oxopropanoate (2.84 g, 16.69 mmol) suspended in methyl THF (60 mL) and magnesium chloride (1.590 g, 16.69 mmol) was added. The suspension was stirred at 50°C under nitrogen for 22 h using an oversized stirring bar (flask 2). The contents of flask 1 was added to flask 2 and the resulting white suspension was stirred at room temperature for 20 h. In a separate flask potassium 3-ethoxy-3-oxopropanoate (0.71 g, 4.17 mmol) was suspended in methyl THF (30 mL) under nitrogen atmosphere and magnesium chloride (0.41 g, 4.31 mmol) was added. The suspension was stirred vigorously at 50°C for 6 h. The suspension was added to the reaction mixture and stirring was continued at room temperature for 17 h. Satd NH_4Cl and DCM were added and the phases were separated. The aqueous phase was extracted with DCM and the combined organic layers were filtered through a phase separator and evaporated. The residue was purified by automated flash chromatography on a Biotage® KP-SIL 340g column. A gradient of 5:1 to 1:1 of EtOAc in heptane over 15 CV was used as mobile phase. Trans-methyl 2-(difluoromethyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (203 mg, 7 %) and cis-methyl 2-(difluoromethyl)-4-(3-ethoxy-3-oxopropanoyl)-piperidine-1-carboxylate (1.38 g, 48 %) were isolated. Cis-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.29 (t, 3H), 1.47 – 2.09 (m, 4H), 2.70 – 2.83 (m, 1H), 3.05 – 3.18 (m, 1H), 3.51 (d, 2H), 3.73 (s, 3H), 3.91 – 4.02 (m, 1H), 4.20 (q, 2H), 4.11 – 4.30 (m, 1H), 5.91 (dt, 1H). MS m/z 308 (M+H)+. Trans-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.28 (t, 3H), 1.39 – 2.32 (m, 4H), 2.88 – 3.23 (m, 2H),

3.51 (s, 2H), 3.73 (s, 3H), 4.20 (q, 2H), 4.11 – 4.70 (m, 2H), 5.88 (t, 1H). MS m/z 308 (M+H)+

Step 2: Cis-methyl 2-(difluoromethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 2-(difluoromethyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (1.38 g, 4.49 mmol) was dissolved in MeOH (20 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (0.180 g, 4.49 mmol) dissolved in water (2.000 mL) was added and the mixture was stirred at -40°C for 15 min. Hydroxylamine (50 % by weight in water, 0.275 mL, 4.49 mmol) was added. The resulting solution was stirred at -40°C for 1 h. The mixture was then transferred into a prewarmed (80°C) solution of 6 M hydrogen chloride (23.20 mL, 139.22 mmol) and the mixture was stirred at 80°C for 20 min. Water and DCM were added and the phases separated. The aqueous phase was extracted with DCM and the combined organic layers were filtered through a phase separator and evaporated. The compound was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x50 ID mm) using a gradient of 5-55% Acetonitrile in H2O/MeCN/AcOH 95/5/0.2 buffer over 20 minutes with a flow of 100 mL/min. Cis-methyl 2-(difluoromethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (650 mg, 52 %) was isolated. ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.77 – 1.88 (m, 1H), 2.03 – 2.24 (m, 3H), 2.93 – 3.03 (m, 1H), 3.22 – 3.33 (m, 1H), 3.75 (s, 3H), 3.92 – 4.02 (m, 1H), 4.21 – 4.34 (m, 1H), 5.73 (s, 1H), 5.92 (dt, 1H). MS m/z 275 $(M-H)^-$

Step 3: (2R,4S)-Methyl 2-(difluoromethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 2-(difluoromethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (650 mg, 2.35 mmol) was subjected to chiral preparative HPLC (Column: Chiralpak AD (250x20), 5 µm particle size, mobile phase: Heptane/EtOH 70/30, flow rate 18 mL/min) to yield (2R,4S)-methyl 2-(difluoromethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (278 mg, 43 %), Chiral purity 99.5%ee, Optical rotation $[\alpha]_D^{20} = +73.7$ (acetonitrile, c=1), ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.75 – 1.86 (m, 1H), 2.01 – 2.21 (m, 3H), 2.91 – 3.01 (m, 1H), 3.20 – 3.30 (m, 1H), 3.72 (s, 3H), 3.89 – 4.01 (m, 1H), 4.18 – 4.33 (m, 1H), 5.72 (s, 1H), 5.88 (dt, 1H), 9.00 (br, 1H).

Step 4: 5-((2R,4S)-2-(Difluoromethyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-Methyl 2-(difluoromethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (278 mg, 1.01 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 7.93 mL, 45.29 mmol) and stirred at room temperature for 16 h. The solvent was removed in vacuo and the compound was purified by preparative HPLC on a XBridge C18 column (10 µm 250x19 ID mm) using a gradient of 0-10% Acetonitrile in H2O/MeCN/NH3 95/5/0.2 buffer over 20 minutes with a flow of 19 mL/min. 5-((2R,4S)-2-(Difluoromethyl)piperidin-4-yl)isoxazol-3(2H)-one (224 mg) was isolated. ^{1}H NMR (400 MHz, cd_3od) δ 1.66 – 1.77 (m, 1H), 1.77 – 1.89 (m, 1H), 2.24 – 2.31 (m, 1H), 2.36 – 2.43 (m, 1H), 3.12 – 3.27 (m, 2H), 3.51 – 3.58 (m, 1H), 3.73 – 3.86 (m, 1H), 5.84 (s, 1H), 6.14 (dt, 1H). HRMS Calcd for $[C_9H_{12}F_2N_2O_2+H]+$: 219.0945. Found: 219.0950.

Example 88

5-(Trans-2-(difluoromethyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(difluoromethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Trans-methyl 2-(difluoromethyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (203 mg, 0.66 mmol) (from example 87, step 1) was dissolved in MeOH (3 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (26.4 mg, 0.66 mmol) dissolved in water (0.300 mL) was added and the mixture was stirred at -40°C for 15 min. Hydroxylamine (50 % by weight in water, 0.040 mL, 0.66 mmol) was added. The resulting solution was stirred at -40°C for 2 h. The mixture was then transferred into a prewarmed (80°C) solution of 6 M hydrogen chloride (3.41 mL, 20.48 mmol) and the mixture was stirred at 80°C for 20 min. Water and DCM were added and the phases separated. The aqueous phase was extracted with DCM and the combined organic layers were filtered through a phase separator and evaporated. The compound was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x20 ID mm) using a gradient of 5-55% Acetonitrile in H2O/MeCN/AcOH 95/5/0.2 buffer, over 15 minutes with a flow of 19 mL/min. Trans-methyl 2-(difluoromethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (122 mg, 67 %) was isolated. ^{1}H NMR (400 MHz, $cdcl_3$) δ 1.35 – 1.65 (m, 1H), 1.68 – 1.82 (m, 1H), 1.87 – 2.12 (m, 1H), 2.30 – 2.45 (m, 1H), 2.70 – 3.22 (m, 2H), 3.74 (s, 3H), 4.10 – 4.74 (m, 2H), 5.69 (s, 1H), 5.75 – 6.09 (m, 1H).

MS m/z 275 $(M-H)^-$

Step 2: 5-(Trans-2-(difluoromethyl)piperidin-4-yl)isoxazol-3(2H)-one

Trans-methyl 2-(difluoromethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (122 mg, 0.44 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 8.21 mL, 46.87 mmol) and stirred at room temperature for 16 h. The solvent was removed in vacuo and the compound was purified by preparative HPLC on a XBridge C18 column (10 µm 250x19 ID mm) using a gradient of 0-10% Acetonitrile in H2O/MeCN/NH3 95/5/0.2 buffer over 20 minutes with a flow of 19 mL/min. 5-(Trans-2-(difluoromethyl)piperidin-4-yl)isoxazol-3(2H)-one (86 mg, 89 %) was isolated.^{1}H NMR (400 MHz, cd_3od) δ 1.80 – 2.00 (m, 3H), 2.03 – 2.12 (m, 1H), 2.76 – 2.86 (m, 1H), 2.93 – 3.13 (m, 2H), 3.22 – 3.28 (m, 1H), 5.78 (s, 1H), 5.81 (dt, 1H). MS m/z 219 $(M+H)^+$

Example 89

5-((2S,4S)-2-((4,4-Difluorocyclohexyl)methyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-((4,4-difluorocyclohexyl)methyl)-4-(3-ethoxy-3-oxopropanoyl)-piperidine-1-carboxylate and cis-methyl 2-((4,4-difluorocyclohexyl)methyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate

2-((4,4-Difluorocyclohexyl)methyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (4.82 g, 15.09 mmol) (reference compound 40) was dissolved in methyl THF (150 mL), then di(1H-imidazol-1-yl)methanone (3.67 g, 22.64 mmol) was added. The mixture was stirred at room temperature under nitrogen for 3 h (flask 1). In a separate flask potassium 3-ethoxy-3-oxopropanoate (4.62 g, 27.17 mmol) was suspended in methyl THF (150 mL), then magnesium chloride (2.59 g, 27.17 mmol) was added. The suspension was stirred at 50°C under nitrogen for 3 h using a large magnetic stirring bar (flask 2). The contents of flask 1 was transferred into flask 2. The resulting yellow suspension was stirred under nitrogen at room temperature overnight. The mixture was acidified to pH 1 with 3.8 M HCl, then MTBE (100 mL) and water (100 mL) was added. The phases were separated and the organic layer was washed with water, satd $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and evaporated leaving a colourless oil. The residue was purified by automated flash

chromatography on Biotage (340g) with a gradient of 20-50% (8 CV). The column was conditioned at 20% (1 CV). Trans-methyl 2-((4,4-difluorocyclohexyl)methyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (300 mg, 5 %) and cis-methyl 2-((4,4-difluorocyclohexyl)methyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (2.66 g, 45 %) were isolated. Cis-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.15 – 2.11 (m, 18H), 2.66 – 2.76 (m, 1H), 2.98 – 3.09 (m, 1H), 3.50 (s, 2H), 3.70 (s, 3H), 3.83 – 3.93 (m, 1H), 4.11 – 4.24 (m, 3H). MS m/z 390 $(M+H)^+$. Trans-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.15 – 2.13 (m, 18H), 2.77 – 2.94 (m, 2H), 3.49 (s, 2H), 3.70 (s, 3H), 3.97 – 4.33 (m, 3H), 4.34 – 4.65 (m, 1H).

Step 2: Cis-methyl 2-((4,4-difluorocyclohexyl)methyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 2-((4,4-difluorocyclohexyl)methyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (2.66 g, 6.83 mmol) was dissolved in MeOH (20 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (2.009 mL, 6.83 mmol) dissolved in water (2.000 mL) was added during 10 min and the yellow solution continued to stir at -40°C for 20 min. Hydroxylamine (50 % by weight in water, 0.419 mL, 6.83 mmol) was added during 8 min. The resulting solution was stirred at -40°C for 3 h. The mixture was then rapidly poured into a prewarmed (80°C) solution of 6 M hydrogen chloride (30 mL, 180.00 mmol) and the mixture continued to stir at 80°C for 20 min. The solvent was evaporated and DCM/water added. The phases were separated and the organic phase passed through a phase separator and evaporated to yield a white solid. The compound was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x50 ID mm) using a gradient of 5-55% Acetonitrile in H2O/MeCN/FA 95/5/0.2 buffer over 30 minutes with a flow of 100 mL/min. Cis-methyl 2-((4,4-difluorocyclohexyl)methyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.6 g, 65 %) was isolated. ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.10 – 2.12 (m, 15H), 2.96 – 3.05 (m, 1H), 3.08 – 3.19 (m, 1H), 3.71 (s, 3H), 3.87 – 4.00 (m, 1H), 4.14 – 4.24 (m, 1H), 5.72 (s, 1H). MS m/z 357 $(M-H)^-$

Step 3: (2S,4S)-Methyl 2-((4,4-difluorocyclohexyl)methyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate and (2R,4R)-methyl 2-((4,4-difluorocyclohexyl)methyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 2-((4,4-difluorocyclohexyl)methyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.6 g, 4.46 mmol) was subjected to chiral preparative HPLC (Column: CelluCoat (250x20), 5 µm particle size, mobile phase: Heptane/IPA 80/20, flow rate 18

mL/min) to yield (2S,4S)-methyl 2-((4,4-difluorocyclohexyl)methyl)-4-(3-oxo-2,3-dihydro-isoxazol-5-yl)piperidine-1-carboxylate (787 mg, 49 %), Chiral purity 99.8 %ee, Optical rotation $[\alpha]_D^{20}$ = +28.8 (acetonitrile, c=1) and (2R,4R)-methyl 2-((4,4-difluorocyclohexyl)-methyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (752 mg, 47 %) Chiral purity 99.9 %ee, Optical rotation $[\alpha]_D^{20}$ = –30.2 (acetonitrile, c=1).

Step 4: 5-((2S,4S)-2-((4,4-Difluorocyclohexyl)methyl)piperidin-4-yl)isoxazol-3(2H)-one

(2S,4S)-Methyl 2-((4,4-difluorocyclohexyl)methyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate (0.787 g, 2.20 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 17.31 mL, 98.82 mmol) and the mixture stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2S,4S)-2-((4,4-difluorocyclohexyl)methyl)-piperidin-4-yl)isoxazol-3(2H)-one (424 mg, 64 %). ^{1}H NMR (600 MHz, DMSO) δ 0.98 – 1.41 (m, 5H), 1.51 – 2.61 (m, 12H), 2.66 – 2.75 (m, 1H), 2.95 – 3.04 (m, 1H), 5.59 – 5.67 (m, 1H). HRMS Calculated for $[C_{15}H_{22}F_2N_2O_2+H]^+$: 301.1728. Found: 301.1713

Example 90

5-((2R,4R)-2-((4,4-Difluorocyclohexyl)methyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4R)-Methyl 2-((4,4-difluorocyclohexyl)methyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate (0.752 g, 2.10 mmol) (from example 89, step 3) was dissolved in hydrogen bromide (33 % in acetic acid, 16.54 mL, 94.42 mmol) and the mixture stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4R)-2-((4,4-difluorocyclohexyl)methyl)piperidin-4-yl)isoxazol-3(2H)-one (415 mg, 66 %). HRMS Calculated for $[C_{15}H_{22}F_2N_2O_2+H]^+$: 301.1728. Found: 301.1741

Example 91

5-(Trans-2-((4,4-difluorocyclohexyl)methyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-((4,4-difluorocyclohexyl)methyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate

Trans-methyl 2-((4,4-difluorocyclohexyl)methyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (300 mg, 0.77 mmol) (from example 89, step 1) was dissolved in MeOH (3 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (0.227 mL, 0.77 mmol) dissolved in water (0.300 mL) was added during 10 min and the yellow solution continued to stir at -40°C for 20 min. Hydroxylamine (50 % by weight in water, 0.047 mL, 0.77 mmol) was added during 8 min. The resulting solution was stirred at -40°C for 3 h 15 min. The mixture was then rapidly poured into a prewarmed (80°C) solution of 6 M hydrogen chloride (4 mL, 24.00 mmol) and the mixture continued to stir at 80°C for 20 min. The solvent was evaporated and DCM/water added. The phases were separated and the organic phase passed through a phase separator and evaporated to yield crude trans-methyl 2-((4,4-difluorocyclohexyl)methyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (267 mg, 97 %) as a slightly yellow solid. MS m/z 357 $(M-H)^-$

Step 2: 5-(Trans-2-((4,4-difluorocyclohexyl)methyl)piperidin-4-yl)isoxazol-3(2H)-one

Trans-methyl 2-((4,4-difluorocyclohexyl)methyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate (0.267 g, 0.75 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 5.87 mL, 33.53 mmol) and the mixture stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-(trans-2-((4,4-difluorocyclohexyl)methyl)-piperidin-4-yl)isoxazol-3(2H)-one (63 mg, 28 %). ^1H NMR (600 MHz, dmso) δ 0.99 – 1.19 (m, 3H), 1.27 – 1.35 (m, 1H), 1.38 – 1.46 (m, 1H), 1.46 – 1.55 (m, 1H), 1.61 – 1.87 (m, 7H), 1.87 – 1.98 (m, 2H), 2.54 – 2.61 (m, 1H), 2.61 – 2.70 (m, 1H), 2.72 – 2.79 (m, 1H), 3.03 – 3.09 (m, 1H), 5.75 (s, 1H). HRMS Calculated for $[C_{15}H_{22}F_2N_2O_2+H]^+$: 301.1728. Found: 301.1751

Example 92

5-((2S,4S)-2-(4-Fluorophenethyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-fluorophenethyl)piperidine-1-carboxylate and cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-fluorophenethyl)piperidine-1-carboxylate

2-(4-Fluorophenethyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (4.34 g, 14.03 mmol) (reference compound 41) was dissolved in methyl THF (100 mL) under nitrogen atmosphere and di(1H-imidazol-1-yl)methanone (3.41 g, 21.05 mmol) added. The suspension was stirred at room temperature for 4 h (flask 1). In a separate flask was potassium 3-ethoxy-3-oxopropanoate (4.30 g, 25.25 mmol) suspended in methyl THF (100 mL) and magnesium chloride (2.404 g, 25.25 mmol) was added. The suspension was stirred at 50°C under nitrogen for 4 h using an oversized stirring bar (flask 2). The contents of flask 1 was added to flask 2 and the mixture (white suspension) was stirred at room temperature for 19 h. In a new flask was potassium 3-ethoxy-3-oxopropanoate (4.30 g, 25.25 mmol) suspended in methyl THF (100 mL) and magnesium chloride (2.404 g, 25.25 mmol) was added. The suspension was stirred at 50°C under nitrogen for 4 h using an oversized stirring bar and subsequently added to the reaction mixture. The mixture was stirred at room temperature for another 16 h at room temperature. 0.1 M HCl and DCM was added, the phases separated and the aqueous phase was extracted with DCM. The combined organic layers were washed with satd $NaHCO_3$, filtered through a phase separator and evaporated. The residue was purified by automated flash chromatography on 2 Biotage® KP-SIL 340g columns. Mobile phase 2:1 heptane:EtOAc over 4 CV, then gradient from 2:1->1:1 heptane:EtOAc over 6 CV. Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-fluorophenethyl)piperidine-1-carboxylate (0.74 g, 14 %) and cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-fluorophenethyl)piperidine-1-carboxylate (3.17 g, 60 %) were isolated. Cis-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.24 (t, 3H), 1.50 – 2.11 (m, 6H), 2.48 – 2.65 (m, 2H), 2.67 – 7.77 (m, 1H), 3.03 – 3.14 (m, 1H), 3.50 (s, 2H), 3.69 (s, 3H), 3.84 – 3.93 (m, 1H), 4.07 (p, 1H), 4.12 – 4.22 (m, 2H), 6.95 (t, 2H), 7.08 – 7.16 (m, 2H). MS m/z 380 $(M+H)^+$. Trans-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.23 – 1.32 (m, 3H), 1.41 – 2.11 (m, 6H), 2.42 – 2.66 (m, 2H), 2.76 – 2.96 (m, 2H), 3.45 (s, 2H), 3.69 (s, 3H), 4.01 – 4.65 (m, 4H), 6.97 (t, 2H), 7.13 (s, br., 2H). MS m/z 380 $(M+H)^+$

Step 2: Cis-methyl 2-(4-fluorophenethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-fluorophenethyl)piperidine-1-carboxylate (3.15 g, 8.30 mmol) was dissolved in MeOH (30 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (0.332 g, 8.30 mmol) dissolved in water (3.00 mL) was added and the mixture was stirred at -40°C for 15 min. Hydroxylamine (50 % by weight in water, 0.509 mL, 8.30 mmol) was added. The resulting solution was stirred at -40°C for 3 h. The mixture was then transferred into a prewarmed (80°C) solution of 6 M hydrogen chloride (42.9 mL, 257.36 mmol) and the mixture was stirred at 80°C for 20 min. DCM and water were added. The phases were separated and the organic phase passed through a phase separator and evaporated. The compound (split into 4 runs) was purified by preparative HPLC on a XBridge C18 column (10 µm 250x50 ID mm) using a gradient of 0-25% Acetonitrile in H2O/MeCN/NH3 95/5/0.2 buffer over 20 minutes with a flow of 100 mL/min. Cis-methyl 2-(4-fluorophenethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.9 g, 66 %) was isolated. ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.53 – 2.14 (m, 6H), 2.46 – 2.64 (m, 2H), 2.98 – 3.07 (m, 1H), 3.12 – 3.24 (m, 1H), 3.70 (s, 3H), 3.87 – 3.99 (m, 1H), 4.05 – 4.16 (m, 1H), 5.72 (s, 1H), 6.85 – 6.94 (m, 2H), 7.04 – 7.11 (m, 2H). MS m/z 349 $(M+H)^+$

Step 3: (2S,4S)-Methyl 2-(4-fluorophenethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate and (2R,4R)-methyl 2-(4-fluorophenethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate

Cis-methyl 2-(4-fluorophenethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.4 g, 4 mmol) was subjected to chiral preparative HPLC (Column: Chiralpak AD (250x20), 5 µm particle size, mobile phase: Heptane/EtOH 80/20, flow rate 18 mL/min) to yield (2S,4S)-methyl 2-(4-fluorophenethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (582 mg, 42 %), Chiral purity 99.9 %ee, Optical rotation $[\alpha]_D^{20} = +51.6$ (acetonitrile, c=1) and (2R,4R)-methyl 2-(4-fluorophenethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (676 mg, 48 %), Chiral purity 99.4 %ee, Optical rotation $[\alpha]_D^{20} = -45.0$ (acetonitrile, c=1)

Step 4: 5-((2S,4S)-2-(4-Fluorophenethyl)piperidin-4-yl)isoxazol-3(2H)-one

(2S,4S)-Methyl 2-(4-fluorophenethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (435 mg, 1.25 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 9.84 mL, 56.19 mmol) to give a yellow solution. The mixture was stirred at room temperature

for 16 h, the solvent was removed and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2S,4S)-2-(4-fluorophenethyl)piperidin-4-yl)isoxazol-3(2H)-one (228 mg, 63 %). ^{1}H NMR (400 MHz, cd_3od) δ 1.48 (dd, 1H), 1.64 – 1.97 (m, 3H), 2.13 (d, 1H), 2.30 (d, 1H), 2.66 – 2.80 (m, 2H), 2.84 – 3.10 (m, 3H), 3.34 – 3.43 (m, 1H), 5.51 (s, 1H), 6.97 – 7.05 (m, 2H), 7.19 – 7.28 (m, 2H). HRMS Calculated for $[C_{16}H_{19}FN_2O_2+H]^+$: 291.1509. Found: 291.1497

Example 93

5-((2R,4R)-2-(4-Fluorophenethyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4R)-Methyl 2-(4-fluorophenethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (507 mg, 1.46 mmol) (from example 92, step 3) was dissolved in hydrogen bromide (33 % in acetic acid (11.5 mL, 65.49 mmol) to give a yellow solution. The mixture was stirred at room temperature for 16 h, the solvent was removed and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4R)-2-(4-fluorophenethyl)piperidin-4-yl)isoxazol-3(2H)-one (278 mg, 65%). ^{1}H NMR (400 MHz, cd_3od) δ 1.48 (q, 1H), 1.70 (dq, 1H), 1.78 – 1.96 (m, 2H), 2.09 – 2.17 (m, 1H), 2.26 – 2.34 (m, 1H), 2.66 – 2.80 (m, 2H), 2.86 – 3.09 (m, 3H), 3.35 – 3.43 (m, 1H), 5.52 (s, 1H), 6.98 – 7.05 (m, 2H), 7.21 – 7.26 (m, 2H). HRMS Calculated for $[C_{16}H_{19}FN_2O_2+H]^+$: 291.1509. Found: 291.1483

Example 94

5-(Trans-2-(4-fluorophenethyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(4-fluorophenethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-fluorophenethyl)piperidine-1-carboxylate (730 mg, 1.92 mmol) (from example 92, step 1) was dissolved in MeOH (7 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (77 mg, 1.92 mmol) dissolved in water (0.700 mL)

was added and the mixture was stirred at -40°C for 15 min. Hydroxylamine (50 % by weight in water, 0.118 mL, 1.92 mmol) was added. The resulting solution was stirred at -40°C for 3 h. The mixture was then transferred into a prewarmed (80°C) solution of 6 M hydrogen chloride (9.94 mL, 59.64 mmol) and the mixture was stirred at 80°C for 20 min. DCM and water were added. The phases were separated, the aqueous phase extracted with DCM and the combined organic layers passed through a phase separator and evaporated. The residue was purified by automated flash chromatography on a Biotage® KP-SIL 100g column. DCM:MeOH:HCOOH=50:1:0.1 over 10 CV was used as mobile phase. Trans-methyl 2-(4-fluorophenethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (550 mg, 82 %) was isolated. ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.01 – 2.13 (m, 6H), 2.48 – 2.70 (m, 2H), 2.88 – 3.08 (m, 2H), 3.70 (s, 3H), 3.98 – 4.69 (m, 2H), 5.64 (s, 1H), 6.91 – 7.02 (m, 2H), 7.06 – 7.21 (m, 2H). MS m/z 349 $(M+H)^+$

Step 2: 5-(Trans-2-(4-fluorophenethyl)piperidin-4-yl)isoxazol-3(2H)-one

Trans-methyl 2-(4-fluorophenethyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (137 mg, 0.39 mmol) dissolved in hydrogen bromide (33 % in acetic acid, 3.1 mL, 17.70 mmol) to give a yellow solution. The mixture was stirred at room temperature for 16 h, the solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-(trans-2-(4-fluorophenethyl)piperidin-4-yl)isoxazol-3(2H)-one (80 mg, 70 %). ^{1}H NMR (400 MHz, dmso) δ 1.42 – 1.78 (m, 5H), 1.82 – 1.95 (m, 1H), 2.52 – 2.68 (m, 4H), 2.74 – 2.84 (m, 1H), 3.05 – 3.13 (m, 1H), 5.73 (s, 1H), 7.01 – 7.10 (m, 2H), 7.15 – 7.25 (m, 2H). HRMS Calculated for $[C_{16}H_{19}FN_2O_2+H]^+$: 291.1509. Found: 291.1522

Example 95

5-((2S,4S)-2-(3,3-Dimethylbutyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(3,3-dimethylbutyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate and cis-methyl 2-(3,3-dimethylbutyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate

A suspension of magnesium chloride (0.852 g, 8.94 mmol) and ethyl potassium malonate

(2.283 g, 13.42 mmol) in dry THF (40 mL) was stirred under nitrogen atmosphere at 50°C for 3.5 h (flask 1). In another flask was added carbonyldiimidazole (1.740 g, 10.73 mmol) portionwise to a solution of 2-(3,3-dimethylbutyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (2.427 g, 8.94 mmol) (reference compound 42) in dry THF (40 mL) at 0°C under nitrogen atmosphere. This solution was stirred for 1.5 h (flask 2). The contents of flask 1 was added over 10 min to flask 2 and the resulting mixture was stirred at room temperature for 20 h. The reaction mixture was concentrated and the residue was taken up in EtOAc and H2O. The aqueous phase was extracted once with EtOAc and the combined organic phase was washed with H_2O, satd $NaHCO_3$ and then dried over Na_2SO_4, filtered and evaporated to give a black oil. Separation using Biotage (340g column, grad 20-30% EtOAc in heptane 7 CV) yielded trans-methyl 2-(3,3-dimethylbutyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (574 mg, 24 %) and cis-methyl 2-(3,3-dimethylbutyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (1.74 g, 72 %) as yellow oils. Cis-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 0.85 (s, 9H), 1.03 – 1.95 (m, 10H), 2.01 – 2.10 (m, 1H), 2.65 – 2.75 (m, 1H), 2.98 – 3.08 (m, 1H), 3.51 (s, 2H), 3.69 (s, 3H), 3.83 – 4.02 (m, 2H), 4.19 (q, 2H). MS m/z 342 $(M+H)^+$. Trans-isomer: MS m/z 342 $(M+H)^+$

Step 2: Cis-methyl 2-(3,3-dimethylbutyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

A solution of cis-methyl 2-(3,3-dimethylbutyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (1.78 g, 5.22 mmol) in MeOH (3.9 mL) was added to a solution of NaOH (288 mg, 7.2 mmol) in MeOH/H2O (4.4 mL / 0.3 mL) at -30°C. After 10 min was added hydroxylamine hydrochloride (726 mg, 10.45 mmol) and NaOH (418 mg, 10.45 mmol) in MeOH (5.2 mL) and H2O (5.2 mL). Stirring was continued at -30°C for 30 min. The reaction solution was poured into 6 M HCl (7.7 mL) at 80°C and heated at 80°C for 1 h. Concentration of the organic solvent and extraction with DCM (x2), drying using a phase separator and evaporation gave an orange oil. The compound was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x50 ID mm) using a gradient of 30-60% Acetonitrile in H2O/MeCN/FA 95/5/0.2 buffer over 30 minutes with a flow of 100 mL/min. Cis-methyl 2-(3,3-dimethylbutyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (717 mg, 44 %) was isolated. ^{1}H NMR (400 MHz, cdcl$_3$) δ 0.79 (s, 9H), 1.01 – 1.19 (m, 2H), 1.23 – 1.48 (m, 2H), 1.83 – 1.96 (m, 2H), 1.98 – 2.11 (m, 2H), 2.94 – 3.04 (m, 1H), 3.09 – 3.19 (m, 1H), 3.70 (s, 3H), 3.91 – 4.06 (m, 2H), 5.71 (d, 1H). MS m/z 311 $(M+H)^+$

Step 3: (2S,4S)-Methyl 2-(3,3-dimethylbutyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 2-(3,3-dimethylbutyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (717 mg, 2.31 mmol) was subjected to chiral preparative HPLC (Column: Chiralpak IC (250x20), 5 µm particle size, mobile phase: Heptane/IPA 80/20, flow rate 18 mL/min) to yield (2S,4S)-methyl 2-(3,3-dimethylbutyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate (341 mg, 48 %), Chiral purity 99.9 %ee, Optical rotation $[\alpha]_D^{20} = +36.5$ (acetonitrile, c=1)

Step 4: 5-((2S,4S)-2-(3,3-Dimethylbutyl)piperidin-4-yl)isoxazol-3(2H)-one

(2S,4S)-Methyl 2-(3,3-dimethylbutyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (341 mg, 1.1 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 20 mL) and the mixture was stirred at room temperature for 24 h. The solvent was evaporated and the compound was purified by preparative HPLC on a XBridge C18 clumn (10 µm 250x50 ID mm) using a gradient of 5-30% Acetonitrile in H2O/MeCN/NH3 95/5/0.2 buffer over 15 minutes with a flow of 100 mL/min. 5-((2S,4S)-2-(3,3-Dimethylbutyl)piperidin-4-yl)-isoxazol-3(2H)-one (235 mg, 85 %) was isolated. ^{1}H NMR (600 MHz, cd_3od) δ 0.90 (s, 9H), 1.22 – 1.34 (m, 2H), 1.43 – 1.78 (m, 4H), 2.10 (d, 1H), 2.22 (d, 1H), 2.85 – 2.94 (m, 1H), 2.98 – 3.07 (m, 2H), 3.40 (d, 1H), 5.46 (s, 1H). HRMS Calculated for $[C_{14}H_{24}N_2O_2+H]^+$: 253.1916. Found: 253.1898

Example 96

5-((2R,4S)-2-(3,3-Dimethylbutyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(3,3-dimethylbutyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

A solution of cis-methyl 2-(3,3-dimethylbutyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (549 mg, 1.61 mmol) (from example 95, step 1) in MeOH (1.2 mL) was added to a solution of NaOH (70 mg, 1.75 mmol) in MeOH/H2O (1.3 mL / 0.08 mL) at -30°C. After 10 min was added hydroxylaminehydrochloride (223 mg, 3.22 mmol) and NaOH (129 mg, 3.22

mmol) in MeOH (1.6 mL) and H_2O (1.6 mL). Stirring was continued at -30°C for 30 min. The reaction solution was poured into 6 M HCl (2.4 mL) at 80°C and heated at 80°C for 1 h. Concentration of the organic solvent and extraction with DCM (x2), drying using a phase separator and evaporation gave an orange oil. The compound was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x50 ID mm) using a gradient of 30-60% Acetonitrile in H2O/MeCN/FA 95/5/0.2 buffer over 30 minutes with a flow of 100 mL/min. Trans-methyl 2-(3,3-dimethylbutyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (194 mg, 39 %) was isolated as a white solid. ^{1}H NMR (400 MHz, cdcl$_3$) δ 0.89 (s, 9H), 1.02 – 1.78 (m, 6H), 1.89 – 2.03 (m, 2H), 2.83 – 3.09 (m, 2H), 3.71 (s, 3H), 3.99 – 4.51 (m, 2H), 5.65 (s, 1H). MS m/z 311 $(M+H)^+$

Step 2: (2R,4S)-Methyl 2-(3,3-dimethylbutyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Trans-methyl 2-(3,3-dimethylbutyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (194 mg, 0.63 mmol) was subjected to chiral preparative HPLC (Column: Chiralpak IC (250x20), 5 µm particle size, mobile phase: Heptane/IPA 85/15, flow rate 18 mL/min) to yield (2R,4S)-methyl 2-(3,3-dimethylbutyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate (83 mg, 43 %), Chiral purity 99.3 %ee, Optical rotation $[\alpha]_D^{20} = -12.3$ (acetonitrile, c=1)

Step 3: 5-((2R,4S)-2-(3,3-Dimethylbutyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-Methyl 2-(3,3-dimethylbutyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (62 mg, 0.2 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 4 mL) and the mixture was stirred at room temperature for 18 h. The solvent was evaported and the compound was purified by preparative HPLC on a XBridge C18 column (10 µm 250x19 ID mm) using a gradient of 5-30% Acetonitrile in H2O/MeCN/NH3 95/5/0.2 buffer over 15 minutes with a flow of 19 mL/min. 5-((2R,4S)-2-(3,3-Dimethylbutyl)piperidin-4-yl)isoxazol-3(2H)-one (39.8 mg, 79 %) was isolated as a white solid. ^{1}H NMR (600 MHz, cd$_3$od) δ 0.92 (s, 9H), 1.20 – 1.34 (m, 2H), 1.56 – 1.69 (m, 2H), 1.83 – 1.90 (m, 1H), 2.05 – 2.13 (m, 1H), 2.14 – 2.21 (m, 1H), 2.26 – 2.34 (m, 1H), 3.05 – 3.19 (m, 2H), 3.25 – 3.34 (m, 2H), 5.75 (s, 1H). HRMS Calculated for $[C_{14}H_{24}N_2O_2+H]^+$: 253.1916. Found: 253.1925

Example 97

5-((2R,4S)-2-(4-Fluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-fluorobenzyl)piperidine-1-carboxylate and cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-fluorobenzyl)piperidine-1-carboxylate

2-(4-Fluorobenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (4.428 g, 14.99 mmol) (reference compound 43) was dissolved in methyl THF (100 mL) and di(1H-imidazol-1-yl)methanone (3.65 g, 22.49 mmol) added. The suspension was stirred at room temperature overnight under nitrogen (flask 1). In a separate flask potassium 3-ethoxy-3-oxopropanoate (4.59 g, 26.99 mmol) was suspended in methyl THF (100 mL) and magnesium chloride (2.57 g, 26.99 mmol) added. The suspension was stirred at 50°C under nitrogen for 3 h (flask 2). The slightly yellow suspension in flask 1 was now added to the white suspension in flask 2. The resulting white suspension was stirred under nitrogen at room temperature overnight. The mixture was acidified to pH 1 with 3.8 M HCl and MTBE added. The phases were separated and the organic phase extracted with water, sat $NaHCO_3$ and water. Evaporated the solvents to yield a yellow oil. The diastereoisomers were separated on Biotage (0% => 70 % EtOAc in heptane, 7 CV; Biotage® KP-SIL 340g column). Mixed fractions were repurified on Biotage (30% => 65 % EtOAc in heptane, 10 CV; Biotage® KP-SIL 50g column). Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-fluorobenzyl)piperidine-1-carboxylate (0.458 g, 10.36 %) and cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-fluorobenzyl)piperidine-1-carboxylate (2.531 g, 57.3 %) were isolated. Cis-isomer: ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.20 – 1.25 (m, 3H), 1.61 – 1.68 (m, 1H), 1.77 – 1.91 (m, 3H), 2.64 – 2.73 (m, 2H), 2.82 – 2.87 (m, 1H), 2.94 – 3.00 (m, 1H), 3.43 (s, 2H), 3.60 (s, 3H), 3.90 (dd, 1H), 4.11 – 4.17 (m, 3H), 6.91 – 6.96 (m, 2H), 7.08 – 7.13 (m, 2H). MS m/z 366 $(M+H)^+$. Trans-isomer: ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.15 – 1.26 (m, 3H), 1.39 – 1.94 (m, 4H), 2.59 – 3.00 (m, 4H), 3.32 – 3.66 (m, 5H), 3.96 – 4.28 (m, 3H), 4.50 (d, br., 1H), 6.88 – 6.95 (m, 2H), 6.99 – 7.18 (m, 2H). MS m/z 366 $(M+H)^+$

Step 2: Cis-methyl 2-(4-fluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-fluorobenzyl)piperidine-1-carboxylate (2.53 g, 6.92 mmol) was dissolved in MeOH (20 mL) and cooled to -40°C under nitrogen. Sodium

hydroxide (0.277 g, 6.92 mmol) dissolved in water (2.000 mL) was added during 10 min and the colourless solution continued to stir at -40°C for 20 min. Hydroxylamine (50 % by weight in water, 0.424 mL, 6.92 mmol) was added during 8 min. The resulting solution was stirred at -40°C for 2 h. The mixture was then rapidly poured into a prewarmed (80°C) solution of 6 M hydrogen chloride (30 mL, 180.00 mmol) and the mixture continued to stir at 80°C for 20 min. The solvent was evaporated and DCM/water added. The phases were separated and the organic phase passed through a phase separator and evaporated to yield a yellow solid. The compound was purified by preparative HPLC in 3 injections on a XBridge C18 column (10 µm 250x50 ID mm) using a gradient of 0-35 % Acetonitrile in H2O/MeCN/NH3 95/5/0.2 buffer over 20 minutes with a flow of 100 mL/min. Cis-methyl 2-(4-fluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.516 g, 65.5%) was isolated as a white solid. ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.83 – 2.14 (m, 4H), 2.55 – 2.65 (m, 1H), 2.72 – 2.81 (m, 1H), 2.93 – 3.03 (m, 1H), 3.08 – 3.19 (m, 1H), 3.61 (s, 3H), 3.95 – 4.05 (m, 1H), 4.20 – 4.30 (m, 1H), 5.73 (s, 1H), 6.91 – 6.99 (m, 2H), 7.02 – 7.09 (m, 2H). MS m/z 335 $(M+H)^+$

Step 3: <u>(2R,4S)-Methyl 2-(4-fluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate</u>

Cis-methyl 2-(4-fluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.516 g, 4.53 mmol) was subjected to chiral preparative HPLC (Column: Chiralpak IC (250x20), 5 µm particle size, mobile phase: Heptane/(MTBE/MeOH 95/5) 50/50, flow rate 18 mL/min) to yield (2R,4S)-methyl 2-(4-fluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate 647 mg (43%), Chiral purity 99.9 %ee, Optical rotation $[\alpha]_D^{20} = +17.8$ (acetonitrile, c=1)

Step 4: <u>5-((2R,4S)-2-(4-Fluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one</u>

(2R,4S)-Methyl 2-(4-fluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (647 mg, 1.94 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 15 mL, 85.65 mmol) and the mixture stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4S)-2-(4-fluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one (360 mg, 67 %). ^{1}H NMR (600 MHz, DMSO) δ 1.08 (q, 1H), 1.37 (dq, 1H), 1.73 – 1.81 (m,

2H), 2.44 – 2.73 (m, 5H), 2.96 – 3.03 (m, 1H), 5.70 (s, 1H), 7.07 – 7.14 (m, 2H), 7.21 – 7.27 (m, 2H). HRMS Calculated for $[C_{15}H_{17}FN_2O_2+H]^+$: 277.1352. Found: 277.1333

Example 98

5-((2S,4S)-2-(4-Fluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(4-fluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-fluorobenzyl)piperidine-1-carboxylate (0.454 g, 1.24 mmol) (from example 97, step 1) was dissolved in MeOH (5 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (0.050 g, 1.24 mmol) dissolved in water (1 mL) was added during 10 min and the colourless solution continued to stir at -40°C for 20 min. Hydroxylamine (50 % by weight in water, 0.076 mL, 1.24 mmol) was added during 5 min. The resulting solution was stirred at -40°C for 2 h. The mixture was then rapidly poured into a prewarmed (80°C) solution of 6 M hydrogen chloride (6 mL, 36.00 mmol) and the mixture continued to stir at 80°C for 20 min. The solvent was evaporated and DCM/water added. The phases were separated and the organic phase passed through a phase separator and evaporated to yield a slightly yellow oil. The compound was purified by preparative HPLC on a XBridge C18 column (10 µm 250x50 ID mm) using a gradient of 0-30 % Acetonitrile in H2O/MeCN/NH3 95/5/0.2 buffer over 20 minutes with a flow of 100 mL/min. Trans-methyl 2-(4-fluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.268 g, 64.5 %) was isolated as a white solid. ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.47 – 1.75 (m, 2H), 1.85 – 2.14 (m, 2H), 2.71 – 3.00 (m, 2H), 3.02 – 3.16 (m, 2H), 3.40 – 3.76 (m, 3H), 4.22 (d, br., 1H), 4.59 (d, br., 1H), 5.64 (s, 1H), 6.95 – 7.03 (m, 2H), 7.15 (s, br., 2H). MS m/z 335 $(M+H)^+$

Step 2: (2S,4S)-Methyl 2-(4-fluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Trans-methyl 2-(4-fluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.268 g,0.8 mmol) was subjected to chiral preparative HPLC (Column: Chiralcel OJ (250x30), 5 µm particle size, mobile phase: 10% EtOH in CO2 (175 bar), flow rate 150 mL/min) to yield (2S,4S)-methyl 2-(4-fluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-

piperidine-1-carboxylate (81 mg, 30%), Chiral purity 99.8 %ee, Optical rotation $[\alpha]_D^{20} = +29.3$ (acetonitrile, c=1)

Step 3: 5-((2S,4S)-2-(4-Fluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

(2S,4S)-Methyl 2-(4-fluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (81 mg, 0.24 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 2 mL, 11.42 mmol) and the mixture stirred at room temperature for 24 h, then more hydrogen bromide (33 % in acetic acid, 0.5 mL) was added and stirring continued overnight, then more hydrogen bromide (33 % in acetic acid, 1 mL) was added and stirring continued overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: Agilent, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2S,4S)-2-(4-fluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one (46.9 g, 70 %). ^{1}H NMR (400 MHz, cd_3od) δ 1.73 – 1.83 (m, 1H), 1.98 – 2.17 (m, 3H), 2.81 – 3.10 (m, 3H), 3.20 – 3.28 (m, 2H), 3.32 – 3.41 (m, 1H), 5.48 (d, 1H), 7.01 – 7.09 (m, 2H), 7.20 – 7.27 (m, 2H). HRMS Calculated for $[C_{15}H_{17}FN_2O_2+H]^+$: 277.1352. Found: 277.1346

Example 99

5-((2R,4S)-2-(3-Fluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3-fluorobenzyl)piperidine-1-carboxylate and cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3-fluorobenzyl)piperidine-1-carboxylate

2-(3-Fluorobenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (7.112 g, 24.08 mmol) (reference compound 44) was dissolved in methyl THF (150 mL) and di(1H-imidazol-1-yl)methanone (5.86 g, 36.13 mmol) added. The suspension was stirred at room temperature under nitrogen for 3.5 h (flask 1). In a separate flask potassium 3-ethoxy-3-oxopropanoate (7.38 g, 43.35 mmol) was suspended in methyl THF (150 mL) and magnesium chloride (4.13 g, 43.35 mmol) added. The suspension was stirred at 50°C under nitrogen for 3 h (flask 2). The orange suspension in flask 1 was now added to the white suspension in flask 2. The resulting yellow suspension was stirred under nitrogen at room temperature for 3 days. The

mixture was acidified to pH 1 with 3.8 M HCl and MTBE added. The phases were separated and the organic phase extracted with water, satd $NaHCO_3$ and water. Evaporated the solvents to yield an orange oil. 42 % of the oil was purified on Biotage (20% => 50 % EtOAc in heptane, 6 CV + 50 %, 4 CV; Biotage® KP-SIL 340g column) to yield trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3-fluorobenzyl)piperidine-1-carboxylate (664 mg, 18 %) and cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3-fluorobenzyl)piperidine-1-carboxylate (1.8 g, 49 %). Cis-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.20 (t, 3H), 1.56 – 1.93 (m, 4H), 2.62 – 2.73 (m, 2H), 2.83 – 3.03 (m, 2H), 3.41 (s, 2H), 3.59 (s, 3H), 3.83 – 3.93 (m, 1H), 4.07 – 4.20 (m, 3H), 6.82 – 6.93 (m, 3H), 7.15 – 7.22 (m, 1H). MS m/z 366 $(M+H)^+$. Trans-isomer: MS m/z 366 $(M+H)^+$

Step 2: Cis-methyl 2-(3-fluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3-fluorobenzyl)piperidine-1-carboxylate (1.826 g, 5.00 mmol) was dissolved in MeOH (20 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (0.200 g, 5.00 mmol) dissolved in water (2.000 mL) was added during 20 min and the yellow solution continued to stir at -40°C for 20 min. Hydroxylamine (50 % by weight in water, 0.306 mL, 5.00 mmol) was added during 8 min. The resulting solution was stirred at -40°C for 3.5 h. The mixture was then rapidly poured into a prewarmed (80°C) solution of 6 M hydrogen chloride (25 mL, 150.00 mmol) and the mixture continued to stir at 80°C for 20 min. The solvent was evaporated and DCM/water added. The phases were separated and the organic phase passed through a phase separator and evaporated to yield a brown semi-solid. The compound was purified by preparative HPLC in 2 injections on a XBridge C18 column (10 µm 250x50 ID mm) using a gradient of 0-25 % Acetonitrile in H2O/MeCN/NH3 95/5/0.2 buffer over 20 minutes with a flow of 100 mL/min. Cis-methyl 2-(3-fluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.141 g, 68%) was isolated as a white solid. ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.83 – 2.15 (m, 4H), 2.58 – 2.67 (m, 1H), 2.77 – 2.86 (m, 1H), 2.93 – 3.03 (m, 1H), 3.10 – 3.21 (m, 1H), 3.63 (s, 3H), 3.96 – 4.05 (m, 1H), 4.22 – 4.32 (m, 1H), 5.73 (s, 1H), 6.81 – 6.95 (m, 3H), 7.18 – 7.27 (m, 1H). MS m/z 335 $(M+H)^+$

Step 3: (2R,4S)-Methyl 2-(3-fluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 2-(3-fluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

(1.141 g, 3.42 mmol) was subjected to chiral preparative HPLC (Column: Chiralpak IC (250x20), 5 µm particle size; mobile phase: Heptane/THF 80/20, flow rate 18 mL/min) to yield (2R,4S)-methyl 2-(3-fluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (545 mg, 48 %), Chiral purity 99.7 %ee, Optical rotation $[\alpha]_D^{20} = +17.8$ (acetonitrile, c=1)

Step 4: 5-((2R,4S)-2-(3-Fluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-Methyl 2-(3-fluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (545 mg, 1.63 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 10 mL, 57.10 mmol) and the mixture stirred at room temperature for 23 h. The solvent was evaporated and the residue purified by preparative HPLC (Instrument:FractionLynx I, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4S)-2-(3-fluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one (286 mg, 63.5%). ^{1}H NMR (400 MHz, dmso) δ 1.09 (q, 1H), 1.36 (dq, 1H), 1.71 – 1.81 (m, 2H), 2.50 – 2.79 (m, 5H), 2.95 – 3.03 (m, 1H), 5.66 (s, 1H), 6.95 – 7.07 (m, 3H), 7.26 – 7.34 (m, 1H). HRMS Calculated for $[C_{15}H_{17}FN_2O_2+H]^+$: 277.1352. Found: 277.1343

Example 100

5-((2S,4S)-2-(3-Fluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(3-fluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3-fluorobenzyl)piperidine-1-carboxylate (0.663 g, 1.81 mmol) (from example 99, step 1) was dissolved in MeOH (8 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (0.073 g, 1.81 mmol) dissolved in water (1 mL) was added during 20 min and the yellow solution continued to stir at -40°C for 20 min. Hydroxylamine (50 % by weight in water, 0.111 mL, 1.81 mmol) was added during 5 min. The resulting solution was stirred at -40°C for 4 h. The mixture was then rapidly poured into a prewarmed (80°C) solution of 6 M hydrogen chloride (9 mL, 54.00 mmol) and the mixture continued to stir at 80°C for 20 min. The solvent was evaporated and DCM/water added. The phases were separated and the organic phase passed through a phase separator and evaporated to yield a

brown semi-solid. The compound was purified by preparative HPLC on a XBridge C18 column (10 µm 250x50 ID mm) using a gradient of 0-25 % Acetonitrile in H2O/MeCN/NH3 95/5/0.2 buffer over 20 minutes with a flow of 100 mL/min. Trans-methyl 2-(3-fluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (214 mg, 35%) was isolated. ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.47 – 1.77 (m, 2H), 1.82 – 2.15 (m, 2H), 2.75 – 3.00 (m, 2H), 3.00 – 3.15 (m, 2H), 3.40 – 3.80 (m, 3H), 4.00 – 4.42 (m, 1H), 4.42 – 4.80 (m, 1H), 5.64 (s, 1H), 6.83 – 7.05 (m, 3H), 7.22 – 7.31 (m, 1H). MS m/z 335 $(M+H)^+$

Step 2: (2S,4S)-Methyl 2-(3-fluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Trans-methyl 2-(3-fluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (214 mg, 0.64 mmol) was subjected to chiral preparative HPLC (Column: Chiralcel OJ (250x30), 5 µm particle size, mobile phase: 10% EtOH in CO2 (175 bar), flow rate 150 mL/min) to yield (2S,4S)-methyl 2-(3-fluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate 77 mg (38.5%), Chiral purity 99.6 %ee, Optical rotation $[\alpha]_D^{20} = +64.9$ (acetonitrile, c=1)

Step 3: 5-((2S,4S)-2-(3-Fluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

(2S,4S)-methyl 2-(3-fluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (77 mg, 0.23 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 2 mL, 11.42 mmol) and the mixture stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: Agilent, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2S,4S)-2-(3-fluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one (51.4 mg, 81%). ^{1}H NMR (400 MHz, cd$_3$od) δ 1.74 – 1.84 (m, 1H), 1.98 – 2.16 (m, 3H), 2.84 – 3.10 (m, 3H), 3.19 – 3.29 (m, 2H), 3.35 – 3.44 (m, 1H), 5.50 (s, 1H), 6.96 – 7.07 (m, 3H), 7.29 – 7.37 (m, 1H). HRMS Calculated for $[C_{15}H_{17}FN_2O_2+H]^+$: 277.1352. Found: 277.1357

Example 101

5-((2R,4S)-2-(2-Fluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(2-fluorobenzyl)piperidine-1-carboxylate and cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(2-fluorobenzyl)piperidine-1-carboxylate

A suspension of magnesium chloride (2.60 g, 27.33 mmol) and ethyl potassium malonate (4.65 g, 27.33 mmol) in dry THF (80 mL) was stirred under nitrogen atmosphere at 50°C for 2.5 h (flask 1). In another flask di(1H-imidazol-1-yl)methanone (3.69 g, 22.77 mmol) was added portionwise to a solution of 2-(2-fluorobenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (4.483 g, 15.18 mmol) (reference compound 45) in dry THF (20 mL) at 0°C under nitrogen atmosphere. The ice bath was removed and the solution was stirred for 2 h at room temperature (flask 2). The contents of flask 1 was added slowly to flask 2 and the resulting mixture was stirred for 19 h under nitrogen. The reaction mixture was concentrated and the residue was taken up in EtOAc and H_2O. The aqueous phase was extracted once with EtOAc and the combined organic phases were washed with H_2O, 10 % Na_2CO_3 and then dried over Na_2SO_4. The compound was purified further via Biotage, 2 runs, SNAP 340g KP-SIL, first 8:2 for 2 CV then linear gradient heptanes/ethyl acetate 8:2 to 3:7 over 7CV. Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(2-fluorobenzyl)piperidine-1-carboxylate (1.145 g, 14%) and cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(2-fluorobenzyl)piperidine-1-carboxylate (3.19 g, 58 %) were isolated. Cis-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.20-1.30 (m, 3H), 1.63 – 1.99 (m, 4H), 2.63-2.76 (m, 1H), 2.77 – 3.13 (m, 3H), 3.46 (s, 2H), 3.53 (s, 3H), 3.85-3.99 (m, 1H), 4.17 (q, 2H), 4.22 – 4.32 (m, 1H), 6.93 – 7.08 (m, 2H), 7.09 – 7.22 (m, 2H). MS m/z 366 (M+H)+. Trans-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1:19 – 1.32 (m, 3H), 1.39-1.99 (m, 4H), 2.52 – 3.12 (m, 4H), 3.37 – 3.71 (m, 5H), 4.18 (q, 2H), 4.02 – 4.32 (m, 1H), 4.48-4.71 (m, 1H), 6.94 – 7.24 (m, 4H). MS m/z 366 (M+H)+

Step 2: Cis-methyl 2-(2-fluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(2-fluorobenzyl)piperidine-1-carboxylate (1.95 g, 5.34 mmol) was dissolved in MeOH (20 mL) and cooled to -40°C. Sodium hydroxide (0.213 g, 5.34 mmol) dissolved in water (2.000 mL) was added dropwise and the colourless solution continued to stir at -40°C for 30 min. Hydroxylamine (50 % by weight in water, 0.327 mL, 5.34 mmol) was added dropwise. The resulting solution was stirred at -40°C for 3 h. The mixture was then rapidly poured into a prewarmed (80°C) solution of 6 M hydrogen chloride

(25 mL, 150.00 mmol) and the mixture continued to stir at 80°C for 20 min. The solvent was evaporated and MTBE/water added. The phases were separated and the organic phase dried over Na_2SO_4 and evaporated to yield a slightly yellow foam. The compound was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x50 ID mm) using two injections with a gradient of 15-75% Acetonitrile in H2O/MeCN/AcOH 95/5/0.2 buffer over 30 minutes with a flow of 100 mL/min. Cis-methyl 2-(2-fluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.09 g, 61%) was isolated. ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.80 – 2.17 (m, 4H), 2.72-2.87 (m, 2H), 2.91-3.02 (m, 1H), 3.12-3.24 (m, 1H), 3.52 (s, 3H), 3.95-4.05 (m, 1H), 4.29 – 4.40 (m, 1H), 5.72 (s, 1H), 6.94 – 7.12 (m, 3H), 7.12 – 7.20 (m, 1H). MS m/z 335 (M+H)+

Step 3: (2R,4S)-Methyl 2-(2-fluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 2-(2-fluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.09 g, 3.26 mmol) was subjected to chiral preparative HPLC (Column: Chiralpak AS (250x20), 5 µm particle size, mobile phase: Heptane/EtOH 80/20, flow rate 18 mL/min) to yield (2R,4S)-methyl 2-(2-fluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (492 mg, 45 %), Chiral purity 98.2 %ee. Optical rotation $[\alpha]_D^{20} = -3$ (acetonitrile, c=1)

Step 4: 5-((2R,4S)-2-(2-Fluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-Methyl 2-(2-fluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (492 mg, 1.47 mmol) was stirred in hydrogen bromide (33 % in AcOH) overnight (19 h). Evaporation of solvents and purification by preparative HPLC (Instrument: FractionLynx I, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) yielded 5-((2R,4S)-2-(2-fluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one (504 mg, 124%). The sample contained DMSO and acetic acid. ^{1}H NMR (400 MHz, cd$_3$od) δ 1.50 – 1.65 (m, 1H), 1.69-1.84 (m, 1H), 2.08-2.22 (m, 2H), 2.89 – 3.18 (m, 4H), 3.38-3.51 (m, 2H), 5.66 (s, 1H), 7.11 – 7.23 (m, 2H), 7.28 – 7.41 (m, 2H). HRMS Calcd for [$C_{15}H_{17}FN_2O_2$+H]+: 277.1352. Found: 277.1344.

Example 102

5-((2S,4S)-2-(2-Fluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(2-fluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(2-fluorobenzyl)piperidine-1-carboxylate (1.145 g, 3.13 mmol) (from example 101, step 1) was dissolved in methanol (10 mL) and cooled to -40°C. Sodium hydroxide (0.194 g, 4.84 mmol) dissolved in water (1.000 mL) was added dropwise and continued to stir at -40°C for 30 min. Hydroxylamine (50 % by weight in water, 0.192 mL, 3.13 mmol) was added dropwise. The resulting solution was stirred at -40°C for 2 h. The mixture was then rapidly poured into a prewarmed (80°C) solution of 6 M hydrogen chloride (15 mL, 90.00 mmol) and the mixture continued to stir at 80°C for 55 min. The solvent was evaporated and MTBE/water added. The phases were separated and the organic phase dried over Na_2SO_4 and evaporated to a yellow foam. The compound was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x50 ID mm) with a gradient of 15-75% Acetonitrile in H2O/MeCN/AcOH 95/5/0.2 buffer over 30 minutes with a flow of 100 mL/min. Trans-methyl 2-(2-fluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate (468 mg, 45 %) was isolated. ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.46-1.77 (m, 2H), 1.80-2.13 (m, 2H), 2.28-3.23 (m, 4H), 3.38-3.80 (m, 3H), 4.04 – 4.34 (m, 1H), 4.50 – 4.80 (m, 1H), 5.65 (s, 1H), 6.99-7.12 (m, 2H), 7.12-7.30 (m, 2H). MS m/z 335 (M+H)+

Step 2: (2S,4S)-Methyl 2-(2-fluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate and (2R,4R)-methyl 2-(2-fluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Trans-methyl 2-(2-fluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (468 mg, 1.4 mmol) was subjected to chiral preparative HPLC (Column: Chiralcel OJ (250x30), 5 µm particle size, mobile phase: 20 % EtOH in CO_2 (175 bar), flow rate 130 mL/min, temperature 40°C) to yield (2S,4S)-methyl 2-(2-fluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (199 mg, 43 %), Chiral purity 98.5 %ee, Optical rotation $[\alpha]_D^{20} = +28.8$ (acetonitrile, c=1) and (2R,4R)-methyl 2-(2-fluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (185 mg, 40 %), Chiral purity 99.7 %ee, Optical rotation $[\alpha]_D^{20} = -28.9$ (acetonitrile, c=1)

Step 3: 5-((2S,4S)-2-(2-Fluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

(2S,4S)-Methyl 2-(2-fluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (199 mg, 0.60 mmol) was stirred in hydrogen bromide (33 % in AcOH) overnight (17 h). Evaporation of solvents and purification by preparative HPLC (Instrument: FractionLynx I, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) yielded 5-((2S,4S)-2-(2-fluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one (115 mg, 70 %). ^{1}H NMR (600 MHz, DMSO) δ 1.47-1.56 (m, 1H), 1.67-1.81 (m, 3H), 2.57-2.64 (m, 1H), 2.72 (d, 2H), 2.81-2.87 (m, 1H), 2.87 – 2.95 (m, 1H), 3.12-3.18 (m, 1H), 5.70 (s, 1H), 7.09 – 7.18 (m, 2H), 7.22-7.33 (m, 2H). HRMS Calcd for $[C_{15}H_{17}FN_2O_2+H]+$: 277.1352. Found: 277.1352.

Example 103

5-((2R,4R)-2-(2-Fluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4R)-Methyl 2-(2-fluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (185 mg, 0.55 mmol) (from example 102, step 2) was stirred in hydrogen bromide (33 % in AcOH) overnight (17 h).. Evaporation of solvents and purification by preparative HPLC (Instrument: FractionLynx I, Mobilphase: gradient 5-95% MeCN in 0.2% NH3, pH10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) yielded 5-((2R,4R)-2-(2-fluorobenzyl)-piperidin-4-yl)isoxazol-3(2H)-one (75 mg, 49 %). ^{1}H NMR (600 MHz, DMSO) δ 1.48 – 1.55 (m, 1H), 1.68 – 1.80 (m, 3H), 2.58 – 2.64 (m, 1H), 2.72 (d, 2H), 2.81 – 2.87 (m, 1H), 2.87 – 2.94 (m, 1H), 3.12 – 3.17 (m, 1H), 5.70 (s, 1H), 7.11 – 7.17 (m, 2H), 7.24 – 7.31 (m, 2H). HRMS Calcd for $[C_{15}H_{17}FN_2O_2+H]+$: 277.1352. Found: 277.1357.

Example 104

5-((2R,4S)-2-(4-(Trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-(trifluoromethyl)benzyl)piperidine-1-carboxylate

Magnesium chloride (7.39 g, 77.58 mmol) and potassium 3-ethoxy-3-oxopropanoate (13.20 g, 77.58 mmol) were suspended in methyl THF (100 mL) under nitrogen and the resulting

suspension heated to 50°C while stirring with an oversized stirring bar for 4 h, then cooled to room temperature (flask 1). In a separate flask was added to cis-1-(methoxycarbonyl)-2-(4-(trifluoromethyl)benzyl)piperidine-4-carboxylic acid (14.1 g, 40.83 mmol) (reference compound 46) in methyl THF (100 mL) di(1H-imidazol-1-yl)methanone (10 g, 61.67 mmol) under nitrogen. The resulting mixture was stirred at room temperature for 4 h 30 min (flask 2). Then, the contents of flask 2 is transferred into flask 1 by transfer needle, washed with methyl THF (40 mL). The resulting suspension was stirred at room temperature for 19 h 30 min. Additional magnesium chloride (3.7 g, 38.86 mmol) and potassium 3-ethoxy-3-oxopropanoate (6.6 g, 38.78 mmol) in methyl THF (50 mL) were sonicated at 50°C for 2 h 30 min, then added to the reaction mixture. Stirred at room temperature for 21 h. The reaction mixture was partitioned between 2 M HCl (ca. 150 mL) and MTBE. The phases were separated. The organic phase was washed with brine and satd $NaHCO_3$, then dried over $MgSO_4$ and evaporated. Crude cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-(trifluoromethyl)benzyl)piperidine-1-carboxylate (14.9 g, 88%) was isolated. ^1H NMR (400 MHz, cdcl$_3$) δ 1.21 – 1.30 (m, 3H), 1.63 – 2.04 (m, 4H), 2.67 – 2.86 (m, 2H), 2.93 – 3.09 (m, 2H), 3.46 (s, 2H), 3.60 (s, 3H), 3.85 – 3.98 (m, 1H), 4.11 – 4.26 (m, 3H), 7.30 (d, 2H), 7.53 (d, 2H). MS m/z 416 $(M+H)^+$

Step 2: Cis-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(4-(trifluoromethyl)benzyl)-piperidine-1-carboxylate

Cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-(trifluoromethyl)benzyl)piperidine-1-carboxylate (14.9 g, 35.87 mmol) was dissolved in MeOH (120 mL) and cooled to -40°C. Sodium hydroxide (1.495 g, 37.38 mmol) dissolved in water (14.4 mL) was added over 2 min and the resulting solution stirred at -40°C for 20 min. Then hydroxylamine (50 % by weight in water, 2.2 mL, 35.90 mmol) was added over 1 min and stirring continued between -40°C and -45°C for 80 min. The reaction mixture was then poured into a prewarmed (80°C) solution of 6 M hydrogen chloride (400 mL, 2400.00 mmol) and the mixture was continued to be stirred at 80°C for 1h. Then cooled to room temperature. Methanol was evaporated, then water was added. Extracted three times with DCM. Combined organic layers dried over Na_2SO_4 and evaporated. Crude cis-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(4-(trifluoromethyl)benzyl)piperidine-1-carboxylate (12.88 g, 94 %) was isolated. MS m/z 385 $(M+H)^+$

Step 3: (2R,4S)-Methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(4-(trifluoromethyl)benzyl)-piperidine-1-carboxylate

Crude cis-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(4-(trifluoromethyl)benzyl)-piperidine-1-carboxylate (12.88 g, 33.54 mmol) was purified by preparative HPLC (Column: Kromasil-C18 (250x20), 10 µm particle size, mobile phase: MeCN/H2O/FA 50/50/0.1, flow rate 120 mL/min) to yield pure cis-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(4-(trifluoromethyl)benzyl)piperidine-1-carboxylate (8.7 g) which was then separated using chiral preparative HPLC (Column: Chiralpak AD (250x20), 5 µm particle size, mobile phase: Heptane/EtOH/DEA 85/15, flow rate 18 mL/min) to yield (2R,4S)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(4-(trifluoromethyl)benzyl)piperidine-1-carboxylate (3.90 g, 30 %), chiral purity 98.5%ee, Optical rotation $[\alpha]_D^{20} = +11.9$ (acetonitrile, c=1), ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.86 – 2.01 (m, 3H), 2.03 – 2.15 (m, 1H), 2.67 (dd, 1H), 2.85 (dd, 1H), 2.96 – 3.05 (m, 1H), 3.12 – 3.22 (m, 1H), 3.59 (s, 3H), 3.97 – 4.07 (m, 1H), 4.26 – 4.34 (m, 1H), 5.75 (s, 1H), 7.22 (d, 2H), 7.52 (d, 2H).

Step 4: 5-((2R,4S)-2-(4-(Trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-Methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(4-(trifluoromethyl)benzyl)piperidine-1-carboxylate (4.889 g, 12.72 mmol) was dissolved in hydrogen bromide (33 % in AcOH, 30 mL, 428.24 mmol) and stirred at room temperature for 18 h. The compound was purified by preparative HPLC (2 equal injections) on a XBridge C18 column (10 µm 250x50 ID mm) using a gradient of 05-40% Acetonitrile in H2O/MeCN/NH3 95/5/0.2 buffer over 20 minutes with a flow of 100 mL/min. The product containing fractions were freeze dried and again treated with hydrogen bromide as described above. The compound was purified by preparative HPLC (3 equal injections) on a XBridge C18 column (10 µm 250x50 ID mm) using a gradient of 05-40% Acetonitrile in H2O/MeCN/NH3 95/5/0.2 buffer over 20 minutes with a flow of 100 mL/min. 5-((2R,4S)-2-(4-(Trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one (3.34 g, 80 %) was isolated as a colorless solid. ^{1}H NMR (400 MHz, dmso) δ 1.04 – 1.15 (m, 1H), 1.35 (qd, 1H), 1.72 – 1.80 (m, 2H), 2.49 – 2.58 (m, 1H), 2.61 – 2.81 (m, 4H), 2.94 – 3.02 (m, 1H), 5.66 (s, 1H), 7.42 (d, 2H), 7.62 (d, 2H). HRMS Calcd for $[C_{16}H_{17}F_3N_2O_2+H]^+$: 327.1320. Found: 327.1305.

Example 105

5-((2S,4S)-2-(4-(Trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-(trifluoromethyl)benzyl)piperidine-1-carboxylate

Ethyl potassium malonate (1.065 g, 6.26 mmol) and $MgCl_2$ (0.496 g, 5.21 mmol) were added to dry THF (50 mL). The reaction mixture was stirred vigorously for 4 h at 50°C (flask 1). 1-(Methoxycarbonyl)-2-(4-(trifluoromethyl)benzyl)piperidine-4-carboxylic acid (1.8 g, 5.21 mmol) (reference compound 47) and carbonyldiimidazole (1.268 g, 7.82 mmol) were added to dry THF (50ml) at 5°C (flask 2). The contents of flask 2 was added to flask 1 and the resulting suspension was stirred at room temperature overnight. THF was evaporated and the reaction mixture was partitioned between water and diethyl ether. The organic phase was isolated, dried with Na_2SO_4, filtered through celite and the solvent was evaporated. Chromatography using the Biotage equipment. Gradient eluation using ethylacetate-heptane, started 15-85 and ended 40-60. Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-(trifluoromethyl)benzyl)piperidine-1-carboxylate (0.93 g, 42.9 %) was isolated. ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.20 – 1.29 (m, 3H), 1.46 – 1.99 (m, 4H), 2.74 – 3.04 (m, 4H), 3.34 – 3.70 (m, 5H), 4.01 – 4.32 (m, 3H), 4.60 (d, 1H), 7.22 – 7.38 (m, 2H), 7.51 – 7.56 (m, 2H). MS m/z 416 $(M+H)^+$

Step 2: Trans-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(4-(trifluoromethyl)benzyl)-piperidine-1-carboxylate

A solution of trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-(trifluoromethyl)benzyl)-piperidine-1-carboxylate (0.4 g, 0.96 mmol) in methanol (3 mL) was added dropwise to a solution of NaOH (0.042g, 1.06 mmol) in methanol/water (3 mL / 0.2 mL) at -30°C. After stirring for 10 min a solution of hydroxylamine hydrochloride (0.134 g, 1.93 mmol) and NaOH (0.077 g, 1.93 mmol) in methanol/water (5 mL / 5 mL) was added at -30°C. Stirring was continued for 30 min at -30°C. The solution was added dropwise to 6 M HCl at 80°C. Stirred 30 min at 80°C. The reaction mixture was dissolved between water and ethyl acetate. The organic phase was isolated, dried with Na_2SO_4, filtered through celite and the solvent was evaporated. Acidic reversed phase chromatography, gradient 35% to 75% acetonitrile. Trans-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(4-(trifluoromethyl)benzyl)piperidine-1-carboxylate (205 mg, 55.4 %) was isolated. ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.63 (d, 2H), 1.98 (d,

2H), 2.81 – 3.14 (m, 4H), 3.55 (d, 3H), 4.21 (d, 1H), 4.63 (d, 1H), 5.63 (s, 1H), 7.22 – 7.37 (m, 2H), 7.54 (d, 2H). MS m/z 385 $(M+H)^+$

Step 3: (2S,4S)-Methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(4-(trifluoromethyl)benzyl)-piperidine-1-carboxylate and (2R,4R)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(4-(trifluoromethyl)benzyl)piperidine-1-carboxylate

Trans-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(4-(trifluoromethyl)benzyl)piperidine-1-carboxylate (205 mg, 0.53 mmol) was subjected to chiral preparative HPLC (Column: Chiralpak IC (250x20), 5 µm particle size, mobile phase: Heptane/EtOH/FA 90/10/0.1, flow rate 18 mL/min) to yield (2S,4S)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(4-(trifluoromethyl)benzyl)piperidine-1-carboxylate (77 mg, 38.5 %), chiral purity 99.3%ee, Optical rotation $[\alpha]_D^{20} = +34.6$ (acetonitrile, c=1) and (2R,4R)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(4-(trifluoromethyl)benzyl)piperidine-1-carboxylate (87 mg, 43.5%), chiral purity 99.9%ee, Optical rotation $[\alpha]_D^{20} -30.2$ (acetonitrile, c=1)

Step 4: 5-((2S,4S)-2-(4-(Trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one

Hydrogen bromide (33 % in acetic acid, 5 mL) was added to a reaction flask containing (2S,4S)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(4-(trifluoromethyl)benzyl)piperidine-1-carboxylate (77 mg, 0.20 mmol). The reaction was stirred vigorously overnight. The solvent was evaporated. Purification using PrepLC (pH=11, small column, sample dissolved in MeOH, gradient 5-45, 20 min) yielded 5-((2S,4S)-2-(4-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one (50 mg, 76%). ^{1}H NMR (600 MHz, cd_3od) δ 1.73 – 1.79 (m, 1H), 1.98 – 2.12 (m, 3H), 2.93 (dd, 1H), 2.97 – 3.04 (m, 2H), 3.17 – 3.25 (m, 2H), 3.35 – 3.41 (m, 1H), 5.48 (s, 1H), 7.41 (d, 2H), 7.61 (d, 2H). HRMS Calcd for $[C_{16}H_{17}F_3N_2O_2+H]^+$: 327.1320. Found: 327.1289.

Example 106

5-((2R,4R)-2-(4-(Trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one

Hydrogen bromide (33 % in acetic acid, 5 mL) was added to a reaction flask containing (2R,4R)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(4-(trifluoromethyl)benzyl)piperidine-

1-carboxylate (87 mg, 0.23 mmol). The reaction was stirred vigorously overnight. The solvent was evaporated. Purification using PrepLC (pH=11, small column, sample dissolved in MeOH, gradient 5-45, 20 min) yielded 5-((2R,4R)-2-(4-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one (48 mg, 65 %). ^{1}H NMR (600 MHz, cd_3od) δ 1.74 – 1.80 (m, 1H), 1.99 – 2.13 (m, 3H), 2.94 (dd, 1H), 2.98 – 3.05 (m, 2H), 3.19 – 3.26 (m, 2H), 3.36 – 3.42 (m, 1H), 5.50 (s, 1H), 7.42 (d, 2H), 7.62 (d, 2H). HRMS Calcd for $[C_{16}H_{17}F_3N_2O_2+H]^+$: 327.1320. Found: 327.1289.

Example 107

5-((2R,4S)-2-(3-(Trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3-(trifluoromethyl)benzyl)piperidine-1-carboxylate and cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3-(trifluoromethyl)benzyl)-piperidine-1-carboxylate

Ethyl potassium malonate (3.42g, 20.16 mmol) and $MgCl_2$ (1.599 g, 16.80 mmol) were added to dry THF (50ml). The reaction flask was stirred vigorously overnight at 50°C (flask 1). 1-(Methoxycarbonyl)-2-(3-(trifluoromethyl)benzyl)piperidine-4-carboxylic acid (5.8 g, 16.80 mmol) (reference compound 48) and carbonyldiimidazole (4.09 g, 25.19 mmol) were added to dry THF (50 mL) at 5°C and was stirred overnight at room temperature (flask 2). The contents of flask 2 was added to flask 1 at room temperature and stirred for 3 days. The reaction mixture was dissolved between water and diethyl ether. The organic phase was evaporated to remove most of the THF. Dissolved the crude between water and diethyl ether again. The organic phase was isolated, dried with Na_2SO_4, filtered through celite and the solvent was evaporated. Chromatography using the Biotage equipment. Gradient eluation using ethyl acetate-heptane, started 0-100 and ended 100-0. Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3-(trifluoromethyl)benzyl)piperidine-1-carboxylate (1.8 g, 26 %) and cis- methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3-(trifluoromethyl)benzyl)piperidine-1-carboxylate (2.45 g, 35 %) were isolated. Cis-isomer: ^{1}H NMR (400 MHz, $cdcl_3$) δ 1.20 – 1.32 (m, 3H), 1.63 – 1.99 (m, 4H), 2.67 – 2.86 (m, 2H), 2.92 – 3.12 (m, 2H), 3.47 (s, 2H), 3.59 (s, 3H), 3.89 – 4.00 (m, 1H), 4.09 – 4.29 (m, 3H), 7.32 – 7.51 (m, 4H). MS m/z 416 $(M+H)^+$. Trans-isomer: ^{1}H NMR (400 MHz, $cdcl_3$) δ 1.19 – 1.35 (m, 3H), 1.42 – 2.08 (m, 4H), 2.51 – 3.09 (m, 4H), 3.35 – 3.78 (m, 5H), 4.04 – 4.38 (m, 3H), 4.47 – 4.79 (m, 1H), 7.23 – 7.56 (m, 4H). MS m/z 416 $(M+H)^+$

Step 2: Cis-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3-(trifluoromethyl)benzyl)-piperidine-1-carboxylate

A solution of Cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3-(trifluoromethyl)benzyl)-piperidine-1-carboxylate (2.45 g, 5.90 mmol) in MeOH (7 mL) was added to a solution of NaOH (307 mg, 7.67 mmol) in MeOH/H2O (8ml/ 0.5 mL) at -30°C. After 10 min hydroxylamine hydrochloride (0.82 g, 11.80 mmol) and NaOH (472mg, 11.80 mmol) were added in MeOH (8 mL) and H_2O (8 mL). Stirring was continued at -30°C for 30 min. The reaction solution was poured into 6 M HCl 60 mL) at 80°C and heated for 30 min. The reaction mixture was dissolved between water and ethyl acetate. The organic phase was isolated, dried with Na_2SO_4, filtered through celite and the solvent was evaporated. Purification using prepLC (pH=3, large column 40-55% MeCN over 20 min). Cis-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3-(trifluoromethyl)benzyl)piperidine-1-carboxylate (1.27 g, 56 %) was isolated. ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.86 – 2.15 (m, 4H), 2.68 (dd, 1H), 2.86 (dd, 1H), 2.96 – 3.06 (m, 1H), 3.12 – 3.25 (m, 1H), 3.58 (s, 3H), 3.95 – 4.08 (m, 1H), 4.25 – 4.37 (m, 1H), 5.75 (s, 1H), 7.23 – 7.32 (m, 1H), 7.35 – 7.41 (m, 2H), 7.43 – 4.49 (m, 1H). MS m/z 385 $(M+H)^+$

Step 3: (2R,4S)-Methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3-(trifluoromethyl)benzyl)-piperidine-1-carboxylate and (2S,4R)-Methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3-(trifluoromethyl)benzyl)piperidine-1-carboxylate

Cis-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3-(trifluoromethyl)benzyl)piperidine-1-carboxylate (1.27 g, 3.31 mmol) was subjected to chiral preparative HPLC (Column: Chiralpak AD (250x20), 5 µm particle size, mobile phase: Heptane/IPA/FA 90/10/0.1, flow rate 18 mL/min) to yield (2R,4S)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3-(trifluoromethyl)benzyl)piperidine-1-carboxylate (620 mg, 49%), Chiral purity 99.7 %ee, Optical rotation $[\alpha]_D^{20} = +7.3$ (acetonitrile, c=1) and (2S,4R)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3-(trifluoromethyl)benzyl)piperidine-1-carboxylate (640 mg, 50%), Chiral purity 99.3 %ee, Optical rotation $[\alpha]_D^{20} = -6.3$ (acetonitrile, c=1)

Step 4: 5-((2R,4S)-2-(3-(Trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-Methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3-(trifluoromethyl)benzyl)piperidine-1-carboxylate (0.62 g, 1.61 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 5 mL, 71.37 mmol) and stirred at room temperature for 41 h. Reaction mixture was evaporated and restarted under the same conditions. After 28 h solvents evaporated and the residue purified by preparative HPLC. (Instrument: FractionLynx I, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4S)-2-(3-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one (366 mg, 69%). ^{1}H NMR (600 MHz, DMSO) δ 1.07 – 1.17 (m, 1H), 1.32 – 1.41 (m, 1H), 1.73 – 1.81 (m, 2H), 2.48 – 2.58 (m, 1H), 2.63 – 2.79 (m, 4H), 2.96 – 3.02 (m, 1H), 5.67 (s, 1H), 7.50 – 7.60 (m, 4H). HRMS Calculated for $[C_{16}H_{17}F_3N_2O_2+H]^+$: 327.1320. Found: 327.1328

Example 108

5-((2S,4R)-2-(3-(Trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one

(2S,4R)-Methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3-(trifluoromethyl)benzyl)piperidine-1-carboxylate (0.64 g, 1.67 mmol) (from example 107, step 3) was dissolved in hydrogen bromide (33 % in acetic acid, 5 mL, 71.37 mmol) and stirred at room temperature for 41 h. Reaction mixture was evaporated and restarted under the same conditions. After 28 h solvents evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx I, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2S,4R)-2-(3-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one (368 mg, 68%). ^{1}H NMR (600 MHz, DMSO) δ 1.07 – 1.15 (m, 1H), 1.36 (dq, 1H), 1.74 – 1.80 (m, 2H), 2.54 – 2.58 (m, 1H), 2.64 – 2.79 (m, 4H), 2.96 – 3.01 (m, 1H), 5.66 (s, 1H), 7.50 – 7.59 (m, 4H). HRMS Calculated for $[C_{16}H_{17}F_3N_2O_2+H]^+$: 327.1320. Found: 327.1333

Example 109

5-(Trans-2-(3-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3-(trifluoromethyl)benzyl)-piperidine-1-carboxylate

A solution of trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3-(trifluoromethyl)benzyl)-

piperidine-1-carboxylate (1.8 g, 4.33 mmol) (from example 107, step 1) in MeOH (7 mL) was added to a solution of NaOH (225 mg, 5.63 mmol) in MeOH/H2O (8 mL/ 0.5 mL) at -30°C. After 10 min hydroxylamine hydrochloride (0.602 g, 8.67 mmol) and NaOH (347mg, 8.67 mmol) were added in MeOH (7 mL) and H_2O (7 mL). Stirring was continued at -30°C for 30 min. The reaction solution was poured into 6 M HCl (60 mL) at 80°C and heated for 30 min. The reaction mixture was dissolved between water and ethyl acetate. The organic phase was isolated, dried with Na_2SO_4, filtered through celite and the solvent was evaporated. Purification using prepLC (pH=3, large column 25-55% MeCN over 20 min). Trans-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3-(trifluoromethyl)benzyl)piperidine-1-carboxylate (1.06 g, 63.6 %) was isolated. ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.49 – 2.17 (m, 4H), 2.80 – 3.22 (m, 4H), 3.34 – 3.76 (m, 3H), 4.07 – 4.40 (m, 1H), 4.52 – 4.84 (m, 1H), 5.65 (s, 1H), 7.28 – 7.54 (m, 4H). MS m/z 385 $(M+H)^+$

Step 2: 5-(Trans-2-(3-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one

Hydrogen bromide (33 % in acetic acid, 10 mL) was added to a reaction flask containing trans-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3-(trifluoromethyl)benzyl)piperidine-1-carboxylate (0.25 g, 0.65 mmol). The reaction was stirred vigorously overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-(trans-2-(3-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one (91 mg, 43%). ^{1}H NMR (600 MHz, cd$_3$od) δ 1.94 – 2.05 (m, 1H), 2.11 – 2.30 (m, 3H), 3.09 – 3.26 (m, 3H), 3.37 – 3.47 (m, 2H), 3.58 – 3.66 (m, 1H), 5.83 (s, 1H), 7.53 – 7.67 (m, 4H). HRMS Calculated for $[C_{16}H_{17}F_3N_2O_2+H]^+$: 327.1320. Found: 327.1322

Example 110

5-((2R,4S)-2-(2-(Trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(2-(trifluoromethyl)benzyl)piperidine-1-carboxylate and cis- methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(2-(trifluoromethyl)benzyl)-piperidine-1-carboxylate

1-(Methoxycarbonyl)-2-(2-(trifluoromethyl)benzyl)piperidine-4-carboxylic acid (4.718 g, 13.66 mmol) (reference compound 49) was dissolved in methyl THF (100 mL) and di(1H-

imidazol-1-yl)methanone (3.32 g, 20.49 mmol) added. The suspension was stirred at room temperature under nitrogen overnight (flask 1). In a separate flask potassium 3-ethoxy-3-oxopropanoate (4.19 g, 24.59 mmol) was suspended in methyl THF (100 mL) and magnesium chloride (2.342 g, 24.59 mmol) added. The suspension was stirred at 50°C under nitrogen overnight using an oversized stirring bar (flask 2). The yellow suspension in flask 1 was now added to the white suspension in flask 2. The resulting white suspension was stirred under nitrogen at room temperature for 3 days. The mixture was acidified to pH 1 with 3.8 M HCl and MTBE and water added. The phases were separated and the organic phase washed with water and satd $NaHCO_3$. Evaporated the solvents to yield a yellow oil. The diastereomers were separated in 2 runs on Biotage (20 % => 50 % EtOAc in heptane, 8 CV; Biotage® KP-SIL 340 g column). Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(2-(trifluoromethyl)-benzyl)piperidine-1-carboxylate (0.67 g, 12 %) and cis- methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(2-(trifluoromethyl)benzyl)piperidine-1-carboxylate (2.11 g, 37 %) were isolated as yellow oils. Cis-isomer: ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.22 (t, 3H), 1.65 – 1.99 (m, 4H), 2.65 – 2.73 (m, 1H), 2.85 – 2.91 (m, 1H), 2.95 – 3.02 (m, 1H), 3.15 (ddd, 1H), 3.35 (s, 3H), 3.46 (s, 2H), 4.01 (dd, 1H), 4.12 – 4.19 (m, 2H), 4.23 – 4.33 (m, 1H), 7.20 (d, 1H), 7.27 (t, 1H), 7.41 (t, 1H), 7.60 (d, 1H). MS m/z 416 $(M+H)^+$. Trans-isomer: ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.13 – 1.27 (m, 3H), 1.41 – 1.97 (m, 5H), 2.79 – 3.67 (m, 8H), 4.01 – 4.33 (m, 3H), 4.64 (br. d, 1H), 7.07 – 7.50 (m, 3H), 7.53 – 7.62 (m, 1H). MS m/z 416 $(M+H)^+$

Step 2: <u>Cis-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(2-(trifluoromethyl)benzyl)-piperidine-1-carboxylate</u>

Cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(2-(trifluoromethyl)benzyl)piperidine-1-carboxylate (2.062 g, 4.96 mmol) was dissolved in MeOH (16 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (0.199 g, 4.96 mmol) dissolved in water (1.600 mL) was added during 10 min and the colourless solution continued to stir at -40°C for 20 min. Hydroxylamine (50 % by weight in water, 0.304 mL, 4.96 mmol) was added during 8 min. The resulting solution was stirred at -40°C for 3.5 h. The mixture was then transferred into a prewarmed (80°C) solution of 6 M hydrogen chloride (25 mL, 150.00 mmol) and the mixture continued to stir at 80°C for 20 min. DCM and water were added. The phases were separated and the organic phase passed through a phase separator and evaporated to yield a yellow semi-solid. The compound was purified by preparative HPLC in 3 injections on a XBridge C18 column (10 µm 250x50 ID mm) using a gradient of 5-30 % Acetonitrile in H2O/MeCN/NH3

95/5/0.2 buffer over 20 minutes with a flow of 100 mL/min. Cis-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(2-(trifluoromethyl)benzyl)piperidine-1-carboxylate (1.30 g, 68%) was isolated as a white solid. ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.79 – 1.95 (m, 2H), 1.95 – 2.14 (m, 2H), 2.79 – 2.98 (m, 3H), 3.17 – 3.27 (m, 1H), 3.34 (s, 3H), 4.04 (dd, 1H), 4.30 – 4.41 (m, 1H), 5.68 (s, 1H), 7.14 (d, 1H), 7.19 – 7.28 (m, 1H), 7.39 (t, 1H), 7.57 (d, 1H). MS m/z 385 $(M+H)^+$

Step 3: (2R,4S)-Methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(2-(trifluoromethyl)benzyl)-piperidine-1-carboxylate and (2S,4R)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(2-(trifluoromethyl)benzyl)piperidine-1-carboxylate

Cis-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(2-(trifluoromethyl)benzyl)piperidine-1-carboxylate (1.30 g, 3.39 mmol) was subjected to chiral preparative HPLC (Column: Chiralcel OJ (250x20), 5 µm particle size, mobile phase: Heptane/EtOH/FA 80/20/0.1, flow rate 18 mL/min) to yield (2R,4S)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(2-(trifluoromethyl)benzyl)piperidine-1-carboxylate (597 mg, 46%), Chiral purity 99.6 %ee, Optical rotation $[\alpha]_D^{20} = -4.0$ (acetonitrile, c=1) and (2S,4R)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(2-(trifluoromethyl)benzyl)piperidine-1-carboxylate (624 mg, 48%), Chiral purity 99.8 %ee, Optical rotation $[\alpha]_D^{20} = +6.1$ (acetonitrile, c=1).

Step 4: 5-((2R,4S)-2-(2-(Trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-Methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(2-(trifluoromethyl)benzyl)piperidine-1-carboxylate (597 mg, 1.55 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 10 mL, 57.10 mmol) and the mixture stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx III, Mobilphase: gradient 5-95% MeCN in 0.2% NH3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4S)-2-(2-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one (358 mg, 71 %). ^{1}H NMR (600 MHz, cd$_3$od) δ 1.68 (q, 1H), 1.84 (qd, 1H), 2.11 (d, 1H), 2.22 (d, 1H), 3.02 – 3.20 (m, 3H), 3.21 – 3.32 (m, 1H), 3.51 (d, 1H), 3.57 – 3.67 (m, 1H), 5.74 (s, 1H), 7.44 – 7.56 (m, 2H), 7.64 (t, 1H), 7.74 (d, 1H). HRMS Calculated for $[C_{16}H_{17}F_3N_2O_2+H]^+$: 327.1320. Found: 327.1328

Example 111

5-((2S,4R)-2-(2-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one

(2S,4R)-Methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(2-(trifluoromethyl)benzyl)piperidine-1-carboxylate (624 mg, 1.62 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 10 mL, 57.10 mmol) and the mixture stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx III, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2S,4R)-2-(2-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one (359 mg, 68 %). ^{1}H NMR (600 MHz, cd_3od) δ 1.68 (q, 1H), 1.84 (dq, 1H), 2.11 (d, 1H), 2.22 (d, 1H), 3.04 – 3.19 (m, 3H), 3.23 – 3.30 (m, 4H), 3.49 – 3.54 (m, 1H), 3.59 – 3.66 (m, 1H), 5.74 (s, 1H), 7.48 (t, 1H), 7.52 (d, 1H), 7.64 (t, 1H), 7.74 (d, 1H). HRMS Calculated for $[C_{16}H_{17}F_3N_2O_2+H]^+$: 327.1320. Found: 327.1321

Example 112

5-(Trans-2-(2-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(2-(trifluoromethyl)benzyl)-piperidine-1-carboxylate

Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(2-(trifluoromethyl)benzyl)piperidine-1-carboxylate (0.661 g, 1.59 mmol) was dissolved in MeOH (5 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (0.064 g, 1.59 mmol) dissolved in water (0.500 mL) was added during 10 min and the colourless solution continued to stir at -40°C for 20 min. Hydroxylamine (50 % by weight in water, 0.098 mL, 1.59 mmol) was added during 8 min. The resulting solution was stirred at -40°C for 3.5 h. The mixture was then transferred into a prewarmed (80°C) solution of 6 M hydrogen chloride (8 mL, 48.00 mmol) and the mixture continued to stir at 80°C for 20 min. DCM and water were added. The phases were separated and the organic phase passed through a phase separator and evaporated to yield crude trans-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(2-(trifluoromethyl)benzyl)piperidine-1-carboxylate (0.748 g, 122%) as a yellow semi-solid. MS m/z 385 $(M+H)^+$

Step 2: 5-(Trans-2-(2-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one

Trans-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(2-(trifluoromethyl)benzyl)piperidine-1-carboxylate (157 mg, 0.41 mmol) was dissolved in hydrogen bromide (33 % in acetic acid (3 mL, 17.13 mmol) and the mixture stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx III, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-(trans-2-(2-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one (53 mg, 40 %). ^{1}H NMR (600 MHz, cd_3od) δ 1.95 (ddd, 1H), 2.08 – 2.19 (m, 2H), 2.19 – 2.28 (m, 1H), 3.07 – 3.18 (m, 2H), 3.18 – 3.25 (m, 1H), 3.33 – 3.43 (m, 2H), 3.51 – 3.62 (m, 1H), 5.75 (d, 1H), 7.43 – 7.51 (m, 2H), 7.63 (t, 1H), 7.73 (d, 1H). HRMS Calculated for $[C_{16}H_{17}F_3N_2O_2+H]^+$: 327.1320. Found: 327.1297

Example 113

5-((2R,4S)-2-(4-(Trifluoromethoxy)benzyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-(trifluoromethoxy)benzyl)piperidine-1-carboxylate and cis- methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-(trifluoromethoxy)benzyl)-piperidine-1-carboxylate

1-(Methoxycarbonyl)-2-(4-(trifluoromethoxy)benzyl)piperidine-4-carboxylic acid (4.7 g, 13.01 mmol) (reference compound 50) was dissolved into methyl THF (150 mL), then di(1H-imidazol-1-yl)methanone (3.16 g, 19.51 mmol) was added in one portion. The mixture was stirred at room temperature under nitrogen for 3 h (flask 1). In a separate flask potassium 3-ethoxy-3-oxopropanoate (3.99 g, 23.41 mmol) was suspended in methyl THF (150 mL) then magnesium chloride (2.229 g, 23.41 mmol) was added. The suspension was stirred at 50°C under nitrogen for 3 h using a large magnetic stirring bar (flask 2). After 3 h, the contents of flask 1 was transferred into flask 2. The resulting yellow suspension was stirred under nitrogen at room temperature overnight. The mixture was acidified to pH 1 with 3.8 M HCl, then MTBE (100 mL) and water (100 mL) was added. The phases were separated and the organic layer was washed with water, satd $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and evaporated leaving a slightly yellow oil. The product was flashed on Biotage (340g) with a gradient of 20-60% EtOAc in n-heptane (8 CV). The column was conditioned at 20% EtOAc in -n-heptane (1 CV). Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-(trifluoromethoxy)benzyl)piperidine-1-carboxylate (679 mg, 12.1%) and cis- methyl 4-

(3-ethoxy-3-oxopropanoyl)-2-(4-(trifluoromethoxy)benzyl)piperidine-1-carboxylate (2.457 g, 43.8 %) were isolated. Cis-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.19 – 1.32 (m, 3H), 1.64 – 1.98 (m, 4H), 2.67 – 2.78 (m, 2H), 2.86 – 3.11 (m, 2H), 3.47 (s, 2H), 3.59 (s, 3H), 3.87 – 3.98 (m, 1H), 4.07 – 4.23 (m, 3H), 7.09 – 7.16 (m, 2H), 7.16 – 7.23 (m, 2H). MS m/z 432 $(M+H)^+$. Trans-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.20 – 1.31 (m, 3H), 1.38 – 2.03 (m, 4H), 2.66 – 3.08 (m, 4H), 3.32 – 3.75 (m, 5H), 3.97 – 4.36 (m, 3H), 4.40 – 4.77 (m, 1H), 7.10 – 7.32 (m, 4H). MS m/z 432 $(M+H)^+$

Step 2: Cis-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(4-(trifluoromethoxy)benzyl)-piperidine-1-carboxylate

Cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-(trifluoromethoxy)benzyl)piperidine-1-carboxylate (2.475 g, 5.74 mmol) was dissolved in MeOH (20 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (1.687 mL, 5.74 mmol) dissolved in water (2.000 mL) was added during 10 min and the yellow solution continued to stir at -40°C for 20 min. Hydroxylamine (50 % by weight in water, 0.352 mL, 5.74 mmol) was added during 8 min. The resulting solution was stirred at -40°C for 3 h. The mixture was then rapidly poured into a prewarmed (80°C) solution of 6 M hydrogen chloride (29.5 mL, 177.28 mmol) and the mixture continued to stir at 80°C for 20 min. The solvent was evaporated and DCM/water added. The phases were separated and the organic phase passed through a phase separator and evaporated to yield a white solid. The compound was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x50 ID mm) using a gradient of 10-60% Acetonitrile in H2O/MeCN/AcOH 95/5/0.2 buffer over 30 minutes with a flow of 100 mL/min. Cis-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(4-(trifluoromethoxy)benzyl)piperidine-1-carboxylate (1.41 g, 61.4 %) was isolated. MS m/z 401 $(M+H)^+$

Step 3: (2R,4S)-Methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(4-(trifluoromethoxy)benzyl)-piperidine-1-carboxylate

Cis-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(4-(trifluoromethoxy)benzyl)piperidine-1-carboxylate (1.41 g, 3.53 mmol) was subjected to chiral preparative HPLC (Column: Chiralpak AD (250x20), 5 µm particle size, mobile phase: Heptane/EtOH 90/10, flow rate 18 mL/min) to yield (2R,4S)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(4-(trifluoro-methoxy)benzyl)piperidine-1-carboxylate (691 mg, 49 %), Chiral purity 99.0 %ee, Optical

rotation $[\alpha]_D^{20} = +9.4$ (acetonitrile, c=1), ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.84 – 2.14 (m, 4H), 2.56 – 2.66 (m, 1H), 2.72 – 2.82 (m, 1H), 2.94 – 3.04 (m, 1H), 3.09 – 3.21 (m, 1H), 3.57 (s, 3H), 3.96 – 4.06 (m, 1H), 4.21 – 4.32 (m, 1H), 5.74 (s, 1H), 7.06 – 7.15 (m, 4H).

Step 4: 5-((2R,4S)-2-(4-(Trifluoromethoxy)benzyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(4-(trifluoromethoxy)benzyl)-piperidine-1-carboxylate (0.690 g, 1.72 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 13.58 mL, 77.56 mmol) and the mixture stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx III, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4S)-2-(4-(trifluoromethoxy)benzyl)-piperidin-4-yl)isoxazol-3(2H)-one (55 mg, 9.4 %). ^{1}H NMR (600 MHz, dmso) δ 1.07 (q, 1H), 1.34 (dq, 1H), 1.69 – 1.78 (m, 2H), 2.45 – 2.74 (m, 5H), 2.93 – 2.99 (m, 1H), 5.64 (s, 1H), 7.20 – 7.25 (m, 2H), 7.26 – 7.32 (m, 2H). HRMS Calculated for $[C_{16}H_{17}F_3N_2O_3+H]^+$: 343.1270. Found: 343.1241

Example 114

5-(Trans-2-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(4-(trifluoromethoxy)benzyl)-piperidine-1-carboxylate

Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-(trifluoromethoxy)benzyl)piperidine-1-carboxylate (679 mg, 1.57 mmol) (from example 113, step 1) was dissolved in MeOH (10 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (0.463 mL, 1.57 mmol) dissolved in water (1.000 mL) was added during 10 min and the yellow solution continued to stir at -40°C for 20 min. Hydroxylamine (50 % by weight in water, 0.096 mL, 1.57 mmol) was added during 8 min. The resulting solution was stirred at -40°C for 3 h 15 min. The mixture was then rapidly poured into a prewarmed (80°C) solution of 6 M hydrogen chloride (8.11 mL, 48.63 mmol) and the mixture continued to stir at 80°C for 20 min. The solvent was evaporated and DCM/water added. The phases were separated and the organic phase passed through a phase separator and evaporated to yield a white solid. Crude trans-methyl 4-(3-oxo-

2,3-dihydroisoxazol-5-yl)-2-(4-(trifluoromethoxy)benzyl)piperidine-1-carboxylate (603 mg, 96%) was isolated. MS m/z 401 $(M+H)^+$

Step 2: 5-(Trans-2-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)isoxazol-3(2H)-one

Trans-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(4-(trifluoromethoxy)benzyl)piperidine-1-carboxylate (0.603 g, 1.51 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 11.87 mL, 67.78 mmol) and the mixture was stirred at room temperature overnight. The solvent was evaporated and the compound was purified by preparative HPLC on a XBridge C18 column (10 µm 250x50 ID mm) using a gradient of 10-50% Acetonitrile in H2O/AcN/NH3 95/5/0.2 buffer over 20 minutes with a flow of 100 mL/min. 5-(Trans-2-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)isoxazol-3(2H)-one (200 mg, 38.8 %)was isolated as a white solid. ^{1}H NMR (400 MHz, dmso) δ 1.47 – 1.60 (m, 1H), 1.68 – 1.87 (m, 3H), 2.43 – 4.01 (m, 6H), 5.73 (s, 1H), 7.20 – 7.40 (m, 4H). HRMS Calculated for $[C_{16}H_{17}F_3N_2O_3+H]^+$: 343.1270. Found: 343.1260

Example 115

5-((2R,4S)-2-(4-Chlorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Methyl 2-(4-chlorobenzyl)-4-((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)-(hydroxy)methyl)piperidine-1-carboxylate

Dichloromethane (200 mL) was added to 2-(4-chlorobenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (4.27 g, 13.7 mmol) (reference compound 51). The mixture was cooled with an ice bath. DMAP (2.008 g, 16.44 mmol), 2,2-dimethyl-1,3-dioxane-4,6-dione (2.96 g, 20.54 mmol) and DIPEA (5.25 mL, 30.13 mmol) were added and then N1-((ethylimino)methylene)-N3,N3-dimethylpropane-1,3-diamine hydrochloride (5.25 g, 27.39 mmol) was added. The mixture was stirred at 0°C for 15 min, then the mixture was warmed to room temperature and stirred overnight. The organic phase was washed with 1 M HCl and once with water. The organic layer was filtered through a phase separator and evaporated to yield crude methyl 2-(4-chlorobenzyl)-4-((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)(hydroxy)methyl)-piperidine-1-carboxylate (7.00 g, 117 %). MS m/z 438, 440 (M+H)+

Step 2: Trans-methyl 2-(4-chlorobenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate and cis-methyl 2-(4-chlorobenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate

Methyl 2-(4-chlorobenzyl)-4-((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)(hydroxy)-methyl)piperidine-1-carboxylate (7.00 g, 16 mmol) was dissolved in EtOH (100 mL) to give a yellow solution. The mixture was warmed up to almost reflux and stirred for 90 min. The solvent was evaporated and the residue was purified via Biotage (heptane:ethyl acetate, gradient 20%->70% ethyl acteate, 7 CV, 340 g column, two runs) to yield trans-methyl 2-(4-chlorobenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (780 mg, 13 %) and cis-methyl 2-(4-chlorobenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (1.45 g, 24 %). Cis-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.14 – 1.31 (m, 3H), 1.56 – 1.95 (m, 4H), 2.59 – 3.08 (m, 4H), 3.43 (d, 2H), 3.59 (d, 3H), 3.80-3.95 (m, 1H), 4.00 – 4.22 (m, 3H), 7.05 – 7.11 (m, 2H), 7.18-7.24 (m, 2H). MS m/z 382, 384 (M+H)+. Trans-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.26 (t, 3H), 1.39-1.99 (m, 4H), 2.46-3.06 (m, 4H), 3.35-3.72 (m, 5H), 3.95-4.32 (m, 3H), 4.40-4.72 (m, 1H), 6.99-7.37 (m, 4H). MS m/z 382, 384 (M+H)+

Step 3: Cis-methyl 2-(4-chlorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

A solution of cis-methyl 2-(4-chlorobenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (1.45 g, 3.80 mmol) in MeOH (10 mL) was added to a solution of sodium hydroxide (3.16 mL, 3.80 mmol) in MeOH/H2O (2.981 mL/ 0.179 mL) at -30°C. After 10 min a solution of hydroxylamine hydrochloride (0.528 g, 7.59 mmol) and sodium hydroxide (0.304 g, 7.59 mmol) in MeOH (10 mL) and H2O (10 mL) was added. Stirring was continued at -30°C for 30 min. The reaction solution was poured into 6 M HCl (6.33 mL, 37.97 mmol) at 80°C and heated at 80°C for 1 hour. Concentration of the organic solvent and extraction with diethyl ether (x3), drying over Na_2SO_4 and evaporation gave a yellow foam. Purification using prepLC (2 injections, pH=3, large column 20-80% MeCN over 30 min) yielded cis-methyl 2-(4-chlorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (557 mg, 41 %). ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.83-2.00 (m, 3H), 2.02-2.12 (m, 1H), 2.59 (dd, 1H), 2.77 (dd, 1H), 2.97 – 3.02 (m, 1H), 3.08-3.20 (m, 1H), 3.62 (s, 3H), 4.00 (dd, 1H), 4.21 – 4.29 (m, 1H), 5.73 (s, 1H), 7.04 (d, 2H), 7.21 – 7.25 (m, 2H). MS m/z 351, 353 (M+H)+

Step 4: (2R,4S)-Methyl 2-(4-chlorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 2-(4-chlorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (557 mg, 1.58 mmol) was subjected to chiral preparative HPLC (Column: Chiralpak IC (250x20), 5 µm particle size, mobile phase: Heptane/IPA/FA 50/50/0.1, flow rate 15 mL/min) to yield (2R,4S)-methyl 2-(4-chlorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (253 mg, 45 %), Chiral purity 99.3 %ee, Optical rotation $[\alpha]_D^{20} = +16.2$ (acetonitrile, c=1)

Step 5: 5-((2R,4S)-2-(4-Chlorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-Methyl 2-(4-chlorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (253 mg, 0.72 mmol) was stirred in HBr (33% in AcOH) overnight (24 hours). Evaporation of solvents and the residue was purified by preparative HPLC on a XBridge C18 column (10 µm 250x50 ID mm) using a gradient of 5% to 45% Acetonitrile in H2O/MeCN/NH3 95/5/0.2 buffer over 20 minutes with a flow of 100 mL/min. 5-((2R,4S)-2-(4-chlorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one (150 mg, 71%) was isolated. ^{1}H NMR (400 MHz, cd_3od) δ 1.37-1.50 (m, 1H), 1.61 – 1.77 (m, 1H), 2.01-2.13 (m, 2H), 2.78-2.98 (m, 4H), 3.18-3.28 (m, 1H), 3.28 – 3.36 (m, 1H), 5.51 (s, 1H), 7.24 (d, 2H), 7.34 (d, 2H). HRMS Calcd for $[C_{15}H_{17}ClN_2O_2+H]+$: 293.1057. Found: 293.1043.

Example 116

5-(Trans-2-(4-chlorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(4-chlorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

A solution of methyl 2-(4-chlorobenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (780 mg, 2.04 mmol) (from example 115, step 2) in MeOH (5 mL) was added to a solution of sodium hydroxide (1.705 mL, 2.05 mmol) in MeOH/H2O (1.608 mL/ 0.097 mL) at -30°C. After 10 min a solution of hydroxylamine hydrochloride (284 mg, 4.09 mmol) and sodium hydroxide (163 mg, 4.09 mmol) in MeOH (5 mL) and H2O (5 mL) was added. Stirring was continued at -30°C for 30 min. The reaction solution was poured into 6 M HCl

(3.40 mL, 20.43 mmol) at 80°C and heated at 80°C for 30 min. Concentration of the organic solvent and extraction with diethyl ether (x3), drying over Na_2SO_4 and evaporation gave a yellow foam. Purification using prepLC (pH=3, large column 20-80% MeCN over 30 min) yielded trans-methyl 2-(4-chlorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (272.5 mg, 38 %). ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.44 – 2.18 (m, 4H), 2.70 – 3.01 (m, 2H), 3.02-3.14 (m, 2H), 3.42 – 3.76 (m, 3H), 4.04 – 4.37 (m, 1H), 4.39 – 4.79 (m, 1H), 5.64 (s, 1H), 7.05 – 7.31 (m, 4H). MS m/z 351, 353 (M+H)+

Step 2: 5-(Trans-2-(4-chlorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

Methyl 2-(4-chlorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (347 mg, 0.99 mmol) was stirred in HBr (33% in AcOH) overnight (19 hours). Evaporation of solvents and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) yielded 5-(trans-2-(4-chlorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one (151 mg, 52 %). ^{1}H NMR (400 MHz, tfa) δ 2.25-2.60 (m, 4H), 3.06-3.20 (m, 2H), 3.35 – 3.52 (m, 1H), 3.55-3.75 (s, 2H), 3.77 – 3.96 (m, 1H), 6.59 (s, 1H), 7.15-7.22 (m, 2H), 7.22-7.41 (m, 2H). HRMS Calcd for $[C_{15}H_{17}ClN_2O_2+H]$+: 293.1057. Found: 293.1031.

Example 117

5-((2R,4S)-2-(4-(Methylsulfonyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-(methylsulfonyl)benzyl)piperidine-1-carboxylate

Ethyl potassium malonate (2.414 g, 14.18 mmol) and $MgCl_2$ (1.125 g, 11.82 mmol) were added to dry THF (75 mL). The reaction flask was stirred vigorously for 4 h at 50°C (flask 1). 1-(Methoxycarbonyl)-2-(4-(methylsulfonyl)benzyl)piperidine-4-carboxylic acid (4.2 g, 11.82 mmol) (reference compound 51) and carbonyldiimidazole (2.87 g, 17.73 mmol) were added to dry THF (75 mL) at room temperature (flask 2). More di(1H-imidazol-1-yl)methanone (0.5g) was added and after 2 h the contents of flask 2 was added to flask 1 at room temperature and stirred overnight. The reaction mixture was dissolved between water and diethyl ether. The organic phase was isolated, dried with Na_2SO_4, filtered through celite and the solvent was

evaporated. Chromatography using the Biotage equipment. Gradient eluation using ethylacetate-heptane, started 10-90 and ended 100-0. Methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-(methylsulfonyl)benzyl)piperidine-1-carboxylate (3.99 g, 79 %) was isolated.

Step 2: Methyl 2-(4-(methylsulfonyl)benzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(4-(methylsulfonyl)benzyl)piperidine-1-carboxylate (3.99 g, 9.38 mmol) was dissolved in MeOH (70 mL) and cooled to -30°C. NaOH (0.375 g, 9.38 mmol) dissolved in water (7 mL) was added during 10 min and the resulting colourless solution continued to stir at -30°C for 20 min. Hydroxylamine (50 % by weight in water, 0.575 mL, 9.38 mmol) was added dropwise. The resulting solution was stirred at -30°C for 30 min. The mixture was then transferred into a prewarmed (80°C) solution of 6 M HCl (30 mL, 180 mmol) and the mixture continued to stir at 80°C for 20 min. The mixture was dissolved between ethyl acetate and water. The aqueous layer was extracted three more times with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered through celite and the solvent was evaporated. The residue was purified using reversed phase chromatography, gradient acid buffer and acetonitril, started 35% and ended 40%. Methyl 2-(4-(methylsulfonyl)benzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.05 g, 28.4%) was isolated.

Step 3: (2R,4S)-Methyl 2-(4-(methylsulfonyl)benzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate, (2S,4R)-methyl 2-(4-(methylsulfonyl)benzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate and trans-methyl 2-(4-(methylsulfonyl)-benzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Methyl 2-(4-(methylsulfonyl)benzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1 g, 2.54 mmol) was subjected to chiral preparative HPLC in two steps (first using Column: Chiralcel OJ (250x50), 20 µm particle size, mobile phase: Heptane/IPA/FA 30/70/0.1, flow rate 120 mL/min and then using Column: Chiralpak AD (250x50), 20 µm particle size, mobile phase: Heptane/EtOH/FA 40/60/0.1, flow rate 120 mL/min) to yield (2R,4S)-Methyl 2-(4-(methylsulfonyl)benzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (231 mg, 23 %), Chiral purity 99.5 %ee, Optical rotation $[\alpha]_D^{20} = +10.1$ (acetonitrile, c=1), ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.87 – 1.97 (m, 3H), 2.02 – 2.11 (m, 1H),

2.68 (dd, 1H), 2.88 (dd, 1H), 2.96 – 3.06 (m, 4H), 3.12 – 3.22 (m, 1H), 3.60 (s, 3H), 3.96 – 4.02 (m, 1H), 4.27 – 4.35 (m, 1H), 5.74 (s, 1H), 7.30 (d, 2H), 7.82 (d, 2H); (2S,4R)-methyl 2-(4-(methylsulfonyl)benzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (225 mg, 22.5 %), Chiral purity 98.4 %ee, Optical rotation $[\alpha]_D^{20} = -11.4$ (acetonitrile, c=1), ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.86 – 1.97 (m, 3H), 2.02 – 2.10 (m, 1H), 2.67 (dd, 1H), 2.87 (dd, 1H), 2.96 – 3.05 (m, 4H), 3.12 – 3.20 (m, 1H), 3.59 (s, 3H), 3.95 – 4.02 (m, 1H), 4.27 – 4.34 (m, 1H), 5.74 (s, 1H), 7.29 (d, 2H), 7.81 (d, 2H) and trans-methyl 2-(4-(methylsulfonyl)benzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (185 mg, 18.5 %)

Step 4: 5-((2R,4S)-2-(4-(Methylsulfonyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-Methyl 2-(4-(methylsulfonyl)benzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (231 mg, 0.59 mmol) was dissolved in HBr (33 % in acetic acid, 5 mL, 28.55 mmol) and the mixture was stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4S)-2-(4-(methylsulfonyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one (171 mg, 87 %). ^{1}H NMR (600 MHz, dmso) δ 1.06 – 1.15 (m, 1H), 1.30 – 1.39 (m, 1H), 1.76 (d, 2H), 2.43 –2.56 (omitted signals), 2.62 – 2.81 (m, 4H), 2.95 – 3.00 (m, 1H), 3.16 (s, 3H), 5.68 (s, 1H), 7.46 (d, 2H), 7.80 (d, 2H). HRMS Calcd for $[C_{16}H_{20}N_2O_4S+H]^+$: 337.1222. Found: 337.1198

Example 118

5-((2S,4R)-2-(4-(Methylsulfonyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one

(2S,4R)-Methyl 2-(4-(methylsulfonyl)benzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (225 mg, 0.57mmol) was dissolved in HBr (33 % in acetic acid, 5 mL, 28.55 mmol) and the mixture was stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2S,4R)-2-(4-(methylsulfonyl)benzyl)piperidin-4-yl)isoxazol-

3(2H)-one (91 mg, 47.4%).^{1}H NMR (600 MHz, dmso) δ 1.05 – 1.14 (m, 1H), 1.30 – 1.38 (m, 1H), 1.72 – 1.79 (m, 2H), 2.39 – 2.56 (omitted signals), 2.62 – 2.80 (m, 4H), 2.94 – 3.00 (m, 1H), 3.16 (s, 3H), 5.68 (s, 1H), 7.46 (d, 2H), 7.80 (d, 2H). HRMS Calcd for $[C_{16}H_{20}N_2O_4S+H]+$: 337.1222. Found: 337.1198

Example 119

5-(Trans-2-(4-(methylsulfonyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one

Trans-methyl 2-(4-(methylsulfonyl)benzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (185 mg, 0.47 mmol) was dissolved in HBr (33 % in acetic acid, 4 mL, 22.84 mmol) and the mixture was stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-(trans-2-(4-(methylsulfonyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one (161 mg, 102%). ^{1}H NMR (600 MHz, dmso) δ 1.65 – 1.97 (m, 4H), 2.34 – 2.63 (omitted signals), 2.80 – 3.15 (m, 5H), 3.18 (s, 3H), 5.84 (s, 1H), 7.51 (d, 2H), 7.87 (d, 2H). HRMS Calcd for $[C_{16}H_{20}N_2O_4S+H]+$: 337.1222. Found: 337.1236

Example 120

5-((2R,4S)-2-(3,4-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(3,4-difluorobenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate and cis-methyl 2-(3,4-difluorobenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate

2-(3,4-Difluorobenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (6.62 g, 21.13 mmol) (reference compound 53) was dissolved in methyl THF (150 mL) and di(1H-imidazol-1-yl)methanone (5.14 g, 31.70 mmol) added. The suspension was stirred at room temperature under nitrogen for 3.5 h (flask 1). In a separate flask potassium 3-ethoxy-3-oxopropanoate (6.47 g, 38.03 mmol) was suspended in methyl THF (150 mL) and magnesium chloride (3.62 g, 38.03 mmol) added. The suspension was stirred at 50°C under nitrogen for 3 h using an oversized stirring bar (flask 2). The yellow suspension in flask 1 was now added to the white

suspension in flask 2. The resulting yellow suspension was stirred under nitrogen at room temperature for 4 h. The mixture was acidified to pH 1 with 3.8 M HCl and MTBE and water added. The phases were separated and the organic phase extracted with water, satd $NaHCO_3$ and water. Evaporated the solvents to yield an orange oil. The diastereomers were separated in 2 runs on Biotage (20 % => 50 % EtOAc in heptane, 8 CV; Biotage® KP-SIL 340g column). Trans-methyl 2-(3,4-difluorobenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (0.278 g, 3.4 %) and cis-methyl 2-(3,4-difluorobenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (2.233 g, 27.6 %) were isolated as yellow oils. Cis-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.21 – 1.29 (m, 3H), 1.61 – 1.98 (m, 4H), 2.63 – 2.78 (m, 2H), 2.82 – 3.11 (m, 2H), 3.47 (s, 2H), 3.64 (s, 3H), 3.86 – 3.97 (m, 1H), 4.12 – 4.23 (m, 3H), 6.85 – 6.92 (m, 1H), 6.95 – 7.13 (m, 2H). MS m/z 384 $(M+H)^+$. Trans-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.22 – 1.29 (m, 3H), 1.40 – 2.00 (m, 4H), 2.63 – 3.03 (m, 4H), 3.37 – 3.75 (m, 5H), 4.00 – 4.31 (m, 3H), 4.55 (d, br., 1H), 6.77 – 7.12 (m, 3H). MS m/z 384 $(M+H)^+$

Step 2: Cis-methyl 2-(3,4-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 2-(3,4-difluorobenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (2.233 g, 5.82 mmol) was dissolved in MeOH (20 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (0.233 g, 5.82 mmol) dissolved in water (2.000 mL) was added during 10 min and the yellow solution continued to stir at -40°C for 20 min. Hydroxylamine (50 % by weight in water, 0.357 mL, 5.82 mmol) was added during 8 min. The resulting solution was stirred at -40°C for 3 h. The mixture was then rapidly poured into a prewarmed (80°C) solution of 6 M hydrogen chloride (30 mL, 180.00 mmol) and the mixture continued to stir at 80°C for 20 min. The solvent was evaporated and DCM/water added. The phases were separated and the organic phase passed through a phase separator and evaporated to yield a yellow semi-solid. The compound was purified by preparative HPLC in 3 injections on a XBridge C18 column (10 µm 250x50 ID mm) using a gradient of 0-25 % Acetonitrile in H2O/MeCN/NH3 95/5/0.2 buffer over 20 minutes with a flow of 100 mL/min. Cis-methyl 2-(3,4-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.361 g, 66 %) was isolated as a white solid. ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.84 – 2.14 (m, 4H), 2.52 – 2.62 (m, 1H), 2.71 – 2.80 (m, 1H), 2.95 – 3.05 (m, 1H), 3.09 – 3.20 (m, 1H), 3.64 (s, 3H), 3.95 – 4.06 (m, 1H), 4.20 – 4.30 (m, 1H), 5.74 (s, 1H), 6.77 – 6.83 (m, 1H), 6.90 – 6.98 (m, 1H), 6.98 – 7.09 (m, 1H). MS m/z 353 $(M+H)^+$

Step 3: (2R,4S)-Methyl 2-(3,4-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate and (2S,4R)-methyl 2-(3,4-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate

Cis-methyl 2-(3,4-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.36 g, 3.87 mmol) was subjected to chiral preparative HPLC (Column: Chiralpak AD (250x20), 5 µm particle size, mobile phase: Heptane/EtOH/FA 90/10/0.2, flow rate 18 mL/min) to yield (2R,4S)-methyl 2-(3,4-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (550 mg (40 %), Chiral purity 98.2 %ee, Optical rotation $[\alpha]_D^{20} = +15.0$ (acetonitrile, c=1) and (2S,4R)-methyl 2-(3,4-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (596 mg, 44 %), Chiral purity 99.4 %ee, Optical rotation $[\alpha]_D^{20} = -13.2$ (acetonitrile, c=1)

Step 4: 5-((2R,4S)-2-(3,4-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-Methyl 2-(3,4-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (550 mg, 1.56 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 15 mL, 85.65 mmol) and the mixture stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx I, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4S)-2-(3,4-difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one (183 mg, 40 %). ^{1}H NMR (600 MHz, cd_3od) δ 1.41 (q, 1H), 1.67 (dq, 1H), 1.99 – 2.08 (m, 2H), 2.77 – 2.95 (m, 4H), 3.17 – 3.24 (m, 1H), 3.26 – 3.34 (m, 1H), 5.49 (s, 1H), 7.00 – 7.05 (m, 1H), 7.14 – 7.22 (m, 2H). HRMS Calculated for $[C_{15}H_{16}F_2N_2O_2+H]^+$: 295.1258. Found: 295.1253

Example 121

5-((2S,4R)-2-(3,4-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

(2S,4R)-Methyl 2-(3,4-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (596 mg, 1.69 mmol) (from example 120, step 3) was dissolved in hydrogen bromide (33 % in acetic acid, 15 mL, 85.65 mmol) and the mixture stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative

HPLC (Instrument: FractionLynx I, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2S,4R)-2-(3,4-difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one (136 mg, 27%). ^{1}H NMR (600 MHz, cd_3od) δ 1.42 (q, 1H), 1.68 (dq, 1H), 2.04 (t, 2H), 2.78 – 2.95 (m, 4H), 3.19 – 3.25 (m, 1H), 3.29 – 3.35 (m, 1H), 5.49 (s, 1H), 7.00 – 7.05 (m, 1H), 7.14 – 7.22 (m, 2H). HRMS Calculated for $[C_{15}H_{16}F_2N_2O_2+H]^+$: 295.1258. Found: 295.1264

Example 122

5-((2S,4S)-2-(3,4-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(3,4-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Trans-methyl 2-(3,4-difluorobenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (0.278 g, 0.73 mmol) (from example 120, step 1) was dissolved in MeOH (3 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (0.029 g, 0.73 mmol) dissolved in water (0.300 mL) was added during 10 min and the yellow solution continued to stir at -40°C for 20 min. Hydroxylamine (50 % by weight in water, 0.044 mL, 0.73 mmol) was added during 8 min. The resulting solution was stirred at -40°C for 3 h 15 min. The mixture was then rapidly poured into a prewarmed (80°C) solution of 6 M hydrogen chloride (4 mL, 24.00 mmol) and the mixture continued to stir at 80°C for 20 min. The solvent was evaporated and DCM/water added. The phases were separated and the organic phase passed through a phase separator and evaporated to yield a yellow semi-solid. The compound was purified by preparative HPLC on a XBridge C18 column (10 µm 250x50 ID mm) using a gradient of 0-25 % Acetonitrile in H2O/MeCN/NH3 95/5/0.2 buffer over 20 minutes with a flow of 100 mL/min. Trans-methyl 2-(3,4-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (83 mg, 34 %) was isolated. ^{1}H NMR (400 MHz, $cdcl_3$) δ 1.47 – 2.14 (m, 4H), 2.71 – 3.14 (m, 4H), 3.43-3.75 (m, 3H), 4.01 – 4.78 (m, 2H), 5.65 (s, 1H), 6.78-7.14 (m, 3H). MS m/z 353 $(M+H)^+$

Step 2: (2S,4S)-Methyl 2-(3,4-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate and (2R,4R)-methyl 2-(3,4-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Trans-methyl 2-(3,4-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-

carboxylate (83 mg, 0.24 mmol) was subjected to chiral preparative HPLC (Column: ReproSil (250x20), 8 µm particle size, mobile phase: Heptane/(MTBE/MeOH 95/5) 70/30, flow rate 18 mL/min) to yield (2S,4S)-methyl 2-(3,4-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (45 mg, 54 %), Chiral purity 99.6 %ee and (2R,4R)-methyl 2-(3,4-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (32 mg, 38%), Chiral purity 99.9 %ee.

Step 3: 5-((2S,4S)-2-(3,4-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

(2S,4S)-Methyl 2-(3,4-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (45 mg, 0.13 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 1 mL, 5.71 mmol) and the mixture stirred at room temperature. After 17 h more hydrogen bromide (33 % in acetic acid, 0.5 mL, 2.85 mmol) was added and the reaction continued at room temperature for a total of 24 h. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx III, Mobilphase: gradient 5-95% MeCN in 0.2% NH3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2S,4S)-2-(3,4-difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one (8.5 mg, 22%). ^{1}H NMR (600 MHz, cd_3od) δ 1.71 – 1.79 (m, 1H), 1.96 – 2.04 (m, 1H), 2.04 – 2.12 (m, 2H), 2.79 – 2.92 (m, 2H), 2.95 – 3.03 (m, 1H), 3.14 – 3.36 (m, 3H), 5.51 (s, 1H), 7.00 – 7.04 (m, 1H), 7.13 – 7.24 (m, 2H). HRMS Calculated for $[C_{15}H_{16}F_2N_2O_2+H]^+$: 295.1258. Found: 295.1276

Example 123

5-((2R,4R)-2-(3,4-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4R)-Methyl 2-(3,4-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (32.5 mg, 0.09 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 0.8 mL, 4.57 mmol) and the mixture stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx III, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4R)-2-(3,4-difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one (10.4 mg, 38%). ^{1}H NMR (600 MHz, cd_3od) δ 1.71 – 1.78 (m, 1H), 1.96 – 2.04 (m, 1H), 2.05 – 2.12 (m, 2H), 2.80 – 2.92 (m, 2H), 2.96 – 3.03 (m, 1H), 3.15 – 3.25 (m, 2H), 3.26 –

3.35 (m, 1H), 5.50 (s, 1H), 6.99 – 7.05 (m, 1H), 7.13 – 7.23 (m, 2H). HRMS Calculated for $[C_{15}H_{16}F_2N_2O_2+H]^+$: 295.1258. Found: 295.1267

Example 124

5-((2R,4S)-2-(2,5-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(2,5-difluorobenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate and cis-methyl 2-(2,5-difluorobenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate

To a mixture of 2-(2,5-difluorobenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (7.4 g, 23.62 mmol) (reference compound 54) in anhydrous methyl-THF (150 mL) was added di(1H-imidazol-1-yl)methanone (5.74 g, 35.43 mmol) at room temperature under nitrogen. The suspension was stirred at room temperature for 4 h (flask 1). To a mixture of potassium 3-ethoxy-3-oxopropanoate (7.24 g, 42.52 mmol) in anhydrous methyl-THF (150 mL) was added magnesium chloride (4.05 g, 42.52 mmol) at room temperature under nitrogen. The mixture was heated at 50°C for 4 h, and then allowed to cool to room temperature (flask 2). The suspension in flask 1 was added to the suspension in flask 2. The reaction mixture was stirred at room temperature for 48 h. The mixture was acidified to pH 1 with 4 M HCl and then water and MTBE was added. The organic phase was separated, washed with water, satd $NaHCO_3$, dried and evaporated. The diastereomers were separated by flash chromatography on silica gel using iso-hexane/EtOAc (100:15 and 100:50) as eluent. Trans-methyl 2-(2,5-difluorobenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (1.6 g, 18 %) and cis-methyl 2-(2,5-difluorobenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (6.2 g, 69 %) were isolated as oils. Cis-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.20 – 1.32 (m, 3H), 1.64 – 2.00 (m, 4H), 2.67 – 3.15 (m, 4H), 3.48 (s, 2H), 3.58 (s, 3H), 3.87 – 3.99 (m, 1H), 4.07 – 4.32 (m, 3H), 6.82 – 7.01 (m, 3H). Trans-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.22 – 1.32 (m, 3H), 1.45 – 2.01 (m, 4H), 2.52 – 3.12 (m, 4H), 3.41 – 3.74 (m, 5H), 4.04 – 4.34 (m, 3H), 4.48 – 4.74 (m, 1H), 6.82 – 7.06 (m, 3H). MS m/z 384 $(M+H)^+$

Step 2: Cis-methyl 2-(2,5-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 2-(2,5-difluorobenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (2.241 g, 5.85 mmol) was dissolved in MeOH (20 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (0.234 g, 5.85 mmol) dissolved in water (2.000 mL) was added during 10 min and the colourless solution continued to stir at -40°C for 20 min. Hydroxylamine (50 % by weight in water, 0.358 mL, 5.85 mmol) was added during 8 min. The resulting solution was stirred at -40°C for 3 h. The mixture was then transferred into a prewarmed (80°C) solution of 6 M hydrogen chloride (30 mL, 180.00 mmol) and the mixture continued to stir at 80°C for 20 min. The solvent was evaporated and DCM/water added. The phases were separated and the organic phase passed through a phase separator and evaporated to yield a yellow semi-solid. The compound was purified by preparative HPLC in 3 injections on a XBridge C18 column (10 µm 250x50 ID mm) using a gradient of 0-20 % Acetonitrile in H2O/MeCN/NH3 95/5/0.2 buffer over 20 minutes with a flow of 100 mL/min. Cis-methyl 2-(2,5-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.259 g, 61 %) was isolated as a white solid. ^{1}H NMR (400 MHz, cd_3od) δ 1.88 – 2.13 (m, 4H), 2.63 – 2.83 (m, 2H), 2.99 – 3.10 (m, 1H), 3.23 – 3.34 (m, 1H), 3.45 (s, 3H), 3.88 – 4.00 (m, 1H), 4.35 – 4.46 (m, 1H), 5.85 (d, 1H), 6.88 – 7.06 (m, 3H). MS m/z 353 $(M+H)^+$

Step 3: (2R,4S)-Methyl 2-(2,5-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate and (2S,4R)-methyl 2-(2,5-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate

Cis-methyl 2-(2,5-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.259 g, 3.58 mmol) was subjected to chiral preparative HPLC (Column: Chiralpak AD (250x20), 5 µm particle size, mobile phase: Heptane/EtOH/FA 90/10/0.2, flow rate 18 mL/min) to yield (2R,4S)-methyl 2-(2,5-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (505 mg, 40 %), Chiral purity 98.8 %ee, Optical rotation $[\alpha]_D^{20} = -5.7$ (acetonitrile, c=1) and (2S,4R)-methyl 2-(2,5-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (499 mg, 39.6 %), Chiral purity 98.8 %ee, Optical rotation $[\alpha]_D^{20} + 3.5$ (acetonitrile, c=1).

Step 4: 5-((2R,4S)-2-(2,5-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-methyl 2-(2,5-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (505 mg, 1.43 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 10 mL, 57.10 mmol) and the mixture stirred at room temperature for 22 h. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx III, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4S)-2-(2,5-difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one 299 mg (71%). ^{1}H NMR (600 MHz, cd_3od) δ 1.49 (q, 1H), 1.71 (dq, 1H), 1.99 – 2.08 (m, 2H), 2.82 – 3.00 (m, 4H), 3.24 – 3.31 (m, 1H), 3.31 – 3.37 (m, 1H), 5.50 (s, 1H), 6.99 – 7.13 (m, 3H). HRMS Calculated for $[C_{15}H_{16}F_2N_2O_2+H]^+$: 295.1258. Found: 295.1244

Example 125

5-((2S,4R)-2-(2,5-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

(2S,4R)-Methyl 2-(2,5-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (499 mg, 1.42 mmol) (from example 124, step 3) was dissolved in hydrogen bromide (33 % in acetic acid, 10 mL, 57.10 mmol) and the mixture stirred at room temperature for 22 h. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx III, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2S,4R)-2-(2,5-difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one (292 mg, 70 %). ^{1}H NMR (600 MHz, cd_3od) δ 1.49 (q, 1H), 1.71 (dq, 1H), 2.00 – 2.08 (m, 2H), 2.83 – 2.91 (m, 2H), 2.93 – 3.00 (m, 2H), 3.25 – 3.31 (m, 1H), 3.33 – 3.37 (m, 1H), 5.50 (s, 1H), 6.99 – 7.12 (m, 3H). HRMS Calculated for $[C_{15}H_{16}F_2N_2O_2+H]^+$: 295.1258. Found: 295.1254

Example 126

5-(Trans-2-(2,5-difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(2,5-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Trans-methyl 2-(2,5-difluorobenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (0.611 g, 1.59 mmol) (from example 124, step 1) was dissolved in MeOH (5 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (0.064 g, 1.59 mmol) dissolved in water (0.500

mL) was added during 10 min and the colourless solution continued to stir at -40°C for 20 min. Hydroxylamine (50 % by weight in water, 0.098 mL, 1.59 mmol) was added during 8 min. The resulting solution was stirred at -40°C for 3 h. The mixture was then transferred into a prewarmed (80°C) solution of 6 M hydrogen chloride (8 mL, 48.00 mmol) and the mixture continued to stir at 80°C for 20 min. The solvent was evaporated and DCM/water added. The phases were separated and the organic phase passed through a phase separator and evaporated to yield crude trans-methyl 2-(2,5-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.552 g, 98%) as a yellow semi-solid. MS m/z 353 $(M+H)^+$

Step 2: 5-(Trans-2-(2,5-difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

Trans-methyl 2-(2,5-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (148 mg, 0.42 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 3 mL, 17.13 mmol) and the solution stirred at room temperature overnight. The solvent was evaporated and the residue was purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-(trans-2-(2,5-difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one (54.7 mg, 44 %). ^{1}H NMR (400 MHz, cd_3od) δ 1.90 – 2.00 (m, 1H), 2.10 – 2.25 (m, 3H), 3.05 (d, 2H), 3.09 – 3.19 (m, 1H), 3.34 – 3.45 (m, 2H), 3.51 – 3.61 (m, 1H), 5.81 (d, 1H), 7.02 – 7.21 (m, 3H). HRMS Calculated for $[C_{15}H_{16}F_2N_2O_2+H]^+$: 295.1258. Found: 295.1278

Example 127

5-((2R,4S)-2-(2,6-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(2,6-difluorobenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate and cis-methyl 2-(2,6-difluorobenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate

2-(2,6-Difluorobenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (4.72 g, 15.07 mmol) (reference compound 55) was dissolved in methyl THF (108 mL) and di(1H-imidazol-1-yl)methanone (3.66 g, 22.60 mmol) was added. The suspension was stirred at room temperature for 3 h 45 min under nitrogen (flask 1). In a separate flask was to a suspension of potassium 3-ethoxy-3-oxopropanoate (4.62 g, 27.12 mmol) in methyl THF (108 mL) magnesium chloride (2.58 g, 27.12 mmol) added. The suspension was stirred with a large

stirring bar for 3.5 h at 50°C under nitrogen (flask 2). The suspension in flask 1 was added to the suspension in flask 2 and the reaction mixture was then stirred at room temperature overnight. The reaction mixture was acidified to pH 1 with 2 M HCl. MTBE and water were added and the phases were separated. The organic phase was washed with water, satd $NaHCO_3$ and water before it was dried and concentrated. The residue was purified in 2 runs by automated flash chromatography on a Biotage® KP-SIL 340g column. A gradient from 15 % to 50 % of EtOAc in heptane over 8 CV (3 CV initial waste + 5 CV collected) was used as mobile phase. Trans-methyl 2-(2,6-difluorobenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (0.405 g, 7 %) and cis-methyl 2-(2,6-difluorobenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (2.404 g, 41 %) were isolated. Cis-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.20 – 1.33 (m, 3H), 1.68 – 2.05 (m, 4H), 2.65 – 2.89 (m, 2H), 2.93 – 3.16 (m, 2H), 3.49 (s, 5H), 3.96 (dd, 1H), 4.14 – 4.22 (m, 2H), 4.27 – 4.40 (m, 1H), 6.77 – 6.89 (m, 2H), 7.09 – 7.20 (m, 1H). MS m/z 384 $(M+H)^+$. Trans-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.22 – 1.34 (m, 3H), 1.41 – 2.01 (m, 4H), 2.75 – 3.20 (m, 4H), 3.37 – 3.70 (m, 5H), 4.02 – 4.32 (m, 3H), 4.55 – 4.85 (m, 1H), 6.81 – 6.92 (m, 2H), 7.11 – 7.23 (m, 1H). MS m/z 384 $(M+H)^+$

Step 2: Cis-methyl 2-(2,6-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 2-(2,6-difluorobenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (2.404 g, 6.27 mmol) was dissolved in MeOH (21 mL) and cooled to -40°C under nitrogen atmosphere. Sodium hydroxide (0.251 g, 6.27 mmol) dissolved in water (2.100 mL) was added over 8 min. After 20 min with stirring, hydroxylamine (50 % by weight in water, 0.384 mL, 6.27 mmol) was added over 6 minutes and the solution was stirred for 3.5 hours at -40°C. The reaction mixture was then rapidly poured into a prewarmed (80°C) solution of 6 M hydrogen chloride (32.3 mL, 193.76 mmol) and the mixture continued to stir at 80°C for 25 min. The solvent was evaporated and the crude mixture was redissolved in DCM/water. The organic phase was dried and concentrated. The compound was purified by preparative HPLC on a XBridge C18 column (10 µm 250x50 ID mm) using a gradient of 0-20% Acetonitrile in H2O/MeCN/NH3 95/5/0.2 buffer over 20 minutes with a flow of 100 mL/min. Cis-methyl 2-(2,6-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.232 g, 55.8 %) was isolated as a white solid. ^{1}H NMR (400 MHz, cd$_3$od) δ 1.94 – 2.04 (m, 2H), 2.08 – 2.16 (m, 2H), 2.63 – 2.73 (m, 1H), 2.81 – 2.91 (m, 1H), 2.98 – 3.09 (m, 1H), 3.24 – 3.37 (m,

4H), 3.88 – 3.99 (m, 1H), 4.41 – 4.54 (m, 1H), 5.81 (s, 1H), 6.82 – 6.92 (m, 2H), 7.16 – 7.26 (m, 1H). MS m/z 353 $(M+H)^+$

Step 3: (2R,4S)-Methyl 2-(2,6-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate and (2S,4R)-methyl 2-(2,6-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate

Cis-methyl 2-(2,6-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.232 g, 3.5 mmol) was subjected to chiral preparative HPLC (Column: Chiralpak AD (250x20), 5 µm particle size, mobile phase: Heptane/EtOH/FA 90/10/0.2, flow rate 18 mL/min) to yield (2R,4S)-methyl 2-(2,6-difluorobenzyl)-4-(3-oxo-2,3-dihydro-isoxazol-5-yl)piperidine-1-carboxylate (370 mg, 30 %), Chiral purity 99.2 %ee, Optical rotation $[\alpha]_D^{20} = -24.4$ (acetonitrile, c=1) and (2S,4R)-methyl 2-(2,6-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate yield (344 mg, 28 %), Chiral purity 97.6 %ee. Optical rotation $[\alpha]_D^{20} = +22.9$ (acetonitrile, c=1)

Step 4: 5-((2R,4S)-2-(2,6-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-methyl 2-(2,6-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (370 mg, 1.05 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 8 mL, 45.68 mmol) and the mixture stirred at room temperature for 24 h. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx III, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4S)-2-(2,6-difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one (254 mg, 82 %). ^{1}H NMR (600 MHz, cd_3od) δ 1.47 (q, 1H), 1.67 (qd, 1H), 2.02 (dd, 2H), 2.78 – 3.02 (m, 4H), 3.16 – 3.24 (m, 1H), 3.27 – 3.33 (m, 1H), 5.49 (s, 1H), 6.98 (t, 2H), 7.27 – 7.37 (m, 1H). HRMS Calculated for $[C_{15}H_{16}F_2N_2O_2+H]^+$: 295.1258. Found: 295.1248

Example 128

5-((2S,4R)-2-(2,6-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

(2S,4R)-Methyl 2-(2,6-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (344 mg, 0.98 mmol) (from example 127, step 3) was dissolved in hydrogen

bromide (33 % in acetic acid, 8 mL, 45.68 mmol) and the mixture stirred at room temperature for 24 h. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx III, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2S,4R)-2-(2,6-difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one (222 mg, 77 %). ^{1}H NMR (600 MHz, cd_3od) δ 1.47 (q, 1H), 1.68 (dq, 1H), 1.96 – 2.07 (m, 2H), 2.79 – 3.02 (m, 4H), 3.18 – 3.25 (m, 1H), 3.27 – 3.34 (m, 1H), 5.49 (s, 1H), 6.95 – 7.01 (m, 2H), 7.28 – 7.36 (m, 1H). HRMS Calculated for $[C_{15}H_{16}F_2N_2O_2+H]^+$: 295.1258. Found: 295.1240

Example 129

5-(Trans-2-(2,6-difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(2,6-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Trans-methyl 2-(2,6-difluorobenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (0.399 g, 1.04 mmol) (from example 127, step 1) was dissolved in MeOH (3.5 mL) and cooled to -40°C under nitrogen atmosphere. Sodium hydroxide (0.306 mL, 1.04 mmol) was added over 5 min. After 45 min with stirring, hydroxylamine (50 % by weight in water, 0.064 mL, 1.04 mmol) was added over one minute and the solution was stirred for 3.5 hours at -40°C. The reaction mixture was then rapidly poured into a prewarmed (80°C) solution of 6 M hydrogen chloride (5.36 mL, 32.16 mmol) and the mixture continued to stir at 80°C for 20 min. The solvent was evaporated and the crude mixture redissolved in DCM and washed with water. The organic phase was dried and concentrated to give crude trans-methyl 2-(2,6-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.331 g, 90 %). MS m/z 353 $(M+H)^+$

Step 2: 5-(Trans-2-(2,6-difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

Trans-methyl 2-(2,6-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.329 g, 0.93 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 7.5 mL, 42.82 mmol) and the mixture was stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm

OBD 19*150 mm) to yield 5-(trans-2-(2,6-difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one (4.6 mg, 1.7 %). HRMS Calculated for $[C_{15}H_{16}F_2N_2O_2+H]^+$: 295.1258. Found: 295.1257

Example 130

5-((2R,4S)-2-(3,5-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(3,5-difluorobenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate and cis-methyl 2-(3,5-difluorobenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate

2-(3,5-Difluorobenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (6.87 g, 21.93 mmol) (reference compound 56) was dissolved in methyl THF (150 mL) and di(1H-imidazol-1-yl)methanone (5.33 g, 32.89 mmol) was added. The suspension was stirred at room temperature for 3 hours under nitrogen (flask 1). In a separate flask was to potassium 3-ethoxy-3-oxopropanoate (6.72 g, 39.47 mmol) in methyl THF (150 mL) magnesium chloride (3.76 g, 39.47 mmol) added. The suspension was stirred with a large stirring bar for 3 h at 50°C (flask 2). The suspension in flask 1 was added to the suspension in flask 2 and the reaction mixture was then stirred at room temperature for 3 days. The reaction mixture was acidified to pH 1 with 2 M HCl. MTBE and water were added and the phases were separated. The organic phase was washed with water, satd NaHCO3 and water before it was dried and concentrated. 60 % of the residue was purified in 2 runs by automated flash chromatography on a Biotage® KP-SIL 340g column. A gradient from 20 % to 60 % of EtOAc in heptane over 8 CV (3 CV initial waste + 5 CV collected) was used as mobile phase. Trans-methyl 2-(3,5-difluorobenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (0.92 g, 20 %) and cis-methyl 2-(3,5-difluorobenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (2.66 g, 57 %). Cis-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.19 – 1.33 (m, 3H), 1.62 – 2.00 (m, 4H), 2.65 – 2.78 (m, 2H), 2.86 – 3.14 (m, 2H), 3.47 (s, 2H), 3.66 (s, 3H), 3.86 – 3.98 (m, 1H), 4.13 – 4.24 (m, 3H), 6.60 – 6.77 (m, 3H). MS m/z 384 $(M+H)^+$ .Trans-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.21 – 1.34 (m, 3H), 1.43 – 2.02 (m, 4H), 2.68 – 3.06 (m, 4H), 3.46 (s, 2H), 3.51 – 3.75 (m, 3H), 4.03 – 4.34 (m, 3H), 4.45 – 4.73 (m, 1H), 6.61 – 6.83 (m, 3H). MS m/z 384 $(M+H)^+$

Step 2: Cis-methyl 2-(3,5-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 2-(3,5-difluorobenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (2.662 g, 6.94 mmol) was dissolved in MeOH (24 mL) and cooled to -40°C under nitrogen atmosphere. Sodium hydroxide (0.278 g, 6.94 mmol) dissolved in water (2.400 mL) was added over 13 min. After 20 min with stirring, hydroxylamine (50 % by weight in water, 0.425 mL, 6.94 mmol) was added over 9 minutes and the solution was stirred for 3.5 hours at -40°C. The reaction mixture was then rapidly poured into a prewarmed (80°C) solution of 6 M hydrogen chloride (35.8 mL, 214.55 mmol) and the mixtured continued to stir at 80°C for 25 min. The solvent was evaporated and the crude mixture was redissolved in DCM/water. The organic phase was dried and concentrated. The compound was purified by preparative HPLC in 2 injections on a XBridge C18 column (10 µm 250x50 ID mm) using a gradient of 0-25% Acetonitrile in H2O/MeCN/NH3 95/5/0.2 buffer over 20 minutes with a flow of 100 mL/min. Cis-methyl 2-(3,5-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.604 g, 65.6 %) was isolated as a white solid. ^{1}H NMR (400 MHz, cd_3od) δ 1.91 – 2.07 (m, 4H), 2.62 – 2.80 (m, 2H), 2.97 – 3.04 (m, 1H), 3.23 – 3.34 (m, 1H), 3.54 (s, 3H), 3.89 – 3.99 (m, 1H), 4.26 – 4.36 (m, 1H), 5.73 (s, 1H), 6.69 – 6.79 (m, 3H). MS m/z 353 $(M+H)^+$

Step 3: (2R,4S)-Methyl 2-(3,5-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate and (2S,4R)-methyl 2-(3,5-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate

Cis-methyl 2-(3,5-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.604 g, 4.56 mmol) was subjected to chiral preparative HPLC (Column: Chiralpak AD (250x20), 5 µm particle size, mobile phase: Heptane/EtOH 90/10, flow rate 18 mL/min) to yield (2R,4S)-methyl 2-(3,5-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (645 mg, 40 %), Chiral purity 99.2 %ee, Optical rotation $[\alpha]_D^{20} = +13.1$ (MeOH, c=1) and (2S,4R)-methyl 2-(3,5-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (789 mg, 49%), Chiral purity 99.6 %ee, Optical rotation $[\alpha]_D^{20} = -10.1$ (MeOH, c=1)

Step 4: 5-((2R,4S)-2-(3,5-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-Methyl 2-(3,5-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.645 g, 1.83 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 14.43 mL, 82.38 mmol) and the mixture was stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx III, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4S)-2-(3,5-difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one (153 mg, 28%). ^{1}H NMR (600 MHz, dmso) δ 1.01 – 1.11 (m, 1H), 1.26 – 1.38 (m, 1H), 1.68 – 1.78 (m, 2H), 2.41 – 2.77 (m, 5H), 2.91 – 2.99 (m, 1H), 5.67 (s, 1H), 6.92 (d, 2H), 6.99 (s, 1H). HRMS Calculated for $[C_{15}H_{16}F_2N_2O_2+H]^+$: 295.1258. Found: 295.1249

Example 131

5-((2S,4R)-2-(3,5-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

(2S,4R)-Methyl 2-(3,5-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.789 g, 2.24 mmol) (from example 130, step 3) was dissolved in hydrogen bromide (33 % in acetic acid, 17.65 mL, 100.77 mmol) and the mixture was stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx III, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2S,4R)-2-(3,5-difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one (123 mg, 19%). ^{1}H NMR (600 MHz, dmso) δ 1.07 (q, 1H), 1.33 (dq, 1H), 1.71 – 1.78 (m, 2H), 2.49 – 2.56 (m, 1H), 2.57 – 2.71 (m, 3H), 2.72 – 2.78 (m, 1H), 2.94 – 2.99 (m, 1H), 5.67 (s, 1H), 6.89 – 6.94 (m, 2H), 7.00 (tt, 1H). HRMS Calculated for $[C_{15}H_{16}F_2N_2O_2+H]^+$: 295.1258. Found: 295.1248

Example 132

5-((2S,4S)-2-(3,5-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(3,5-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Trans-methyl 2-(3,5-difluorobenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (0.927 g, 2.42 mmol) (from example 130, step 1) was dissolved in MeOH (8 mL) and cooled to -40°C under nitrogen atmosphere. Sodium hydroxide (0.097 g, 2.42 mmol) dissolved in water (0.800 mL) was added over 7 min. After 20 min with stirring, hydroxylamine (50 % by weight in water, 0.148 mL, 2.42 mmol) was added over 4.5 minutes and the solution was stirred for 3.5 hours at -40°C. The reaction mixture was then rapidly poured into a prewarmed (80°C) solution of 6 M hydrogen chloride (12.45 mL, 74.71 mmol) and the mixture continued to stir at 80°C for 20 min. The solvent was evaporated and the crude mixture redissolved in DCM and washed with water. The organic phase was dried and concentrated. The compound was purified by preparative HPLC on a XBridge C18 column (10 µm 250x50 ID mm) using a gradient of 0-25% Acetonitrile in H2O/MeCN/NH3 95/5/0.2 buffer over 20 minutes with a flow of 100 mL/min. Trans-methyl 2-(3,5-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.648 g, 76 %) was isolated as a white solid. ^{1}H NMR (400 MHz, cd_3od) δ 1.45 – 2.12 (m, 4H), 2.80 – 3.35 (m, 4H), 3.35 – 3.70 (m, 3H), 4.12 (s, br., 1H), 4.62 (s, br., 1H), 5.71 (s, 1H), 6.77 (t, 1H), 6.87 (s, br., 2H). MS m/z 353 $(M+H)^+$

Step 2: (2S,4S)-Methyl 2-(3,5-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate and (2R,4R)-methyl 2-(3,5-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Trans-methyl 2-(3,5-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.648 g, 1.84 mmol) was subjected to chiral preparative HPLC (Column: Chiralpak AD (250x20), 5 µm particle size, mobile phase: Heptane/EtOH 70/30, flow rate 18 mL/min) to yield (2S,4S)-methyl 2-(3,5-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate 249 mg (38%), Chiral purity 99.9 %ee, Optical rotation $[\alpha]_D^{20} = +27.1$ (acetonitrile, c=1) and (2R,4R)-methyl 2-(3,5-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (244 mg, 37%), Chiral purity 99.9 %ee, Optical rotation $[\alpha]_D^{20} = -26.4$ (acetonitrile, c=1)

Step 3: 5-((2S,4S)-2-(3,5-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

(2S,4S)-Methyl 2-(3,5-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.249 g, 0.71 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 5.57 mL, 31.80 mmol) and the mixture was stirred at room temperature overnight. The solvent

was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2S,4S)-2-(3,5-difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one (34 mg, 16 %). ^{1}H NMR (400 MHz, cd_3od) δ 1.70 – 2.16 (m, 4H), 2.84 – 3.43 (m, 6H), 5.57 (s, 1H), 6.81 – 7.02 (m, 3H). HRMS Calculated for $[C_{15}H_{16}F_2N_2O_2+H]^+$: 295.1258. Found: 295.1254

Example 133

5-((2R,4R)-2-(3,5-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4R)-Methyl 2-(3,5-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.244 g, 0.69 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 5.46 mL, 31.16 mmol) and the mixture was stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4R)-2-(3,5-difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one (51 mg, 25 %). ^{1}H NMR (600 MHz, dmso) δ 1.44 – 1.51 (m, 1H), 1.65 – 1.80 (m, 3H), 2.52 – 2.60 (m, 1H), 2.65 – 2.70 (m, 2H), 2.76 – 2.83 (m, 1H), 2.86 – 2.94 (m, 1H), 3.09 – 3.14 (m, 1H), 5.74 (s, 1H), 6.90 – 6.95 (m, 2H), 7.00 (tt, 1H). HRMS Calculated for $[C_{15}H_{16}F_2N_2O_2+H]^+$: 295.1258. Found: 295.1276

Example 134

5-((2R,4S)-2-(2,4-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(2,4-difluorobenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate and cis-methyl 2-(2,4-difluorobenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate

Magnesium chloride (4.55 g, 47.75 mmol) and potassium 3-ethoxy-3-oxopropanoate (8 g, 47.00 mmol) were dissolved in methyl THF (100 mL) under nitrogen and the resulting suspension was stirred at 50°C with an oversized stirring bar for 6 h 30 min, then cooled to room temperature (flask 1). To a suspension of 2-(2,4-difluorobenzyl)-1-

(methoxycarbonyl)piperidine-4-carboxylic acid (7.48 g, 23.88 mmol) (reference compound 57) in methyl THF (100 mL) was added di(1H-imidazol-1-yl)methanone (5.81 g, 35.81 mmol) under nitrogen. The resulting mixture was stirred at room temperature for 1 h 20min (flask 2). The contents of flask 2 is transferred into flask 1 by transfer needle. Wash with methyl THF (30 mL). The resulting suspension was stirred at room temperature for 16 h. 3.8 M HCl was added (ca. 200 mL) and the resulting biphasic mixture stirred vigorously for 30 min. Water and MTBE were added and the phases separated. The organic phase was washed with water, satd $NaHCO_3$ and water, then dried over $MgSO_4$ and evaporated. The residue was purified via Biotage (Biotage® KP-SIL 340g column, 1 CV 20% EtOAc in heptanes, then 20% => 60% over 7 CV). Trans-methyl 2-(2,4-difluorobenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (1.18 g, 13 %) and cis-methyl 2-(2,4-difluorobenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (4.17 g, 45 %) were isolated as yellow oils. Cis-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.20 – 1.32 (m, 3H), 1.59 – 1.99 (m, 4H), 2.66 – 3.12 (m, 4H), 3.48 (s, 2H), 3.55 (s, 3H), 3.89 – 3.98 (m, 1H), 4.07 – 4.29 (m, 3H), 6.71 – 6.83 (m, 2H), 7.05 – 7.17 (m, 1H). MS m/z 384 $(M+H)^+$. Trans-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.19 – 1.35 (m, 3H), 1.42 – 2.02 (m, 4H), 2.65 – 3.11 (m, 4H), 3.38 – 3.75 (m, 5H), 4.02 – 4.34 (m, 3H), 4.45 – 4.70 (m, 1H), 6.73 – 6.89 (m, 2H), 7.03 – 7.34 (m, 1H). MS m/z 384 $(M+H)^+$

Step 2: <u>Cis-methyl 2-(2,4-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate</u>

Cis-methyl 2-(2,4-difluorobenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (2.46 g, 6.42 mmol) was dissolved in MeOH (20 mL) and cooled to -40°C. Sodium hydroxide (0.257 g, 6.42 mmol) dissolved in water (2 mL) was added over 5 min and the resulting solution was stirred at -40°C for 20 min. Then hydroxylamine (50 % by weight in water, 0.4 mL, 6.53 mmol) was added over 1 min and stirring continued at -40°C for 1 h 15 min. The reaction mixture was then transferred into a prewarmed (80°C) solution of 6 M hydrogen chloride (30 mL, 180.00 mmol) and the mixture was continued to be stirred at 80°C for 35 min. Then cooled to room temperature. Methanol was evaporated, then water was added. Extracted three times with DCM. Combined organic layers dried over $MgSO_4$ and evaporated. The residue was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x50 ID mm) using a gradient of 15-60% Acetonitrile in H2O/MeCN/Acetic Acid 95/5/0.2 buffer over 30 minutes with a flow of 100 mL/min. Cis-methyl 2-(2,4-difluorobenzyl)-4-(3-oxo-2,3-

dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.62 g, 72 %) was isolated as a colorless foam. ^{1}H NMR (400 MHz, cd_3od) δ 1.90 – 2.10 (m, 4H), 2.65 – 2.80 (m, 2H), 3.04 (p, 1H), 3.19 – 3.34 (m, 1H), 3.44 (s, 3H), 3.94 (ddd, 1H), 4.32 – 4.44 (m, 1H), 5.85 (s, 1H), 6.78 – 6.90 (m, 2H), 7.09 – 7.20 (m, 1H). MS m/z 353 $(M+H)^+$

Step 3: (2R,4S)-Methyl 2-(2,4-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate and (2S,4R)-methyl 2-(2,4-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate

Cis-methyl 2-(2,4-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.62 g, 4.6 mmol) was subjected to chiral preparative HPLC (Column: Chiralpak AD (250x20), 5 µm particle size, mobile phase: Heptane/EtOH/FA 90/10/0.2, flow rate 18 mL/min) to yield (2R,4S)-methyl 2-(2,4-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (799 mg, 49 %), Chiral purity 99.9 %ee, Optical rotation $[\alpha]_D^{20} = -4.0$ (acetonitrile, c=1) and (2S,4R)-methyl 2-(2,4-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (734 mg, 45 %), Chiral purity 99.5 %ee, Optical rotation $[\alpha]_D^{20} = +4.5$ (acetonitrile, c=1).

Step 4: 5-((2R,4S)-2-(2,4-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-Methyl 2-(2,4-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (399 mg, 1.13 mmol) was dissolved in hydrogen bromide (33 % in acetic acid (8.2 mL, 46.87 mmol) and stirred at room temperature for 16 h. The solvent was removed in vacuo and the residue purified by preparative HPLC (Instrument: FractionLynx III, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4S)-2-(2,4-difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one (146 mg, 44 %). ^{1}H NMR (400 MHz, cd_3od) δ 1.43 (q, 1H), 1.67 (dq, 1H), 1.99 – 2.12 (m, 2H), 2.79 – 2.97 (m, 4H), 3.14 – 3.24 (m, 1H), 3.27 – 3.35 (m, 1H), 5.52 (s, 1H), 6.91 – 7.02 (m, 2H), 7.27 – 7.36 (m, 1H). HRMS Calculated for $[C_{15}H_{16}F_2N_2O_2+H]^+$: 295.1258. Found: 295.1252

Example 135

5-((2S,4R)-2-(2,4-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

(2S,4R)-Methyl 2-(2,4-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate 367 mg, 1.04 mmol) (from example 134, step 3) was dissolved in hydrogen bromide (33 % in acetic acid, 8.2 mL, 46.87 mmol) and stirred at room temperature for 16 h. The solvent was removed in vacuo and the residue purified by preparative HPLC (Instrument: FractionLynx III, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2S,4R)-2-(2,4-difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one (144 mg, 47 %). ^{1}H NMR (400 MHz, cd_3od) δ 1.43 (q, 1H), 1.67 (dq, 1H), 2.01 – 2.11 (m, 2H), 2.79 – 2.96 (m, 4H), 3.14 – 3.23 (m, 1H), 3.27 – 3.35 (m, 1H), 5.52 (s, 1H), 6.92 – 7.01 (m, 2H), 7.28 – 7.35 (m, 1H). HRMS Calculated for $[C_{15}H_{16}F_2N_2O_2+H]^+$: 295.1258. Found: 295.1259

Example 136

Step 1: Trans-methyl 2-(2,4-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Trans-methyl 2-(2,4-difluorobenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (1.18 g, 3.08 mmol) (from example 134, step 1) was dissolved in MeOH (15 mL) and cooled to -40°C. Sodium hydroxide (0.123 g, 3.08 mmol) dissolved in water (1.7 mL) was added over 1 min and the resulting solution was stirred at -40°C for 20 min. Then hydroxylamine (50 % by weight in water, 0.2 mL, 3.26 mmol) was added over 1 min and stirring continued at -40°C for 2 h. The reaction mixture was then transferred into a prewarmed (80°C) solution of 6 M hydrogen chloride (30 mL, 180.00 mmol) and the mixture was continued to be stirred at 80°C for 1 h. Then cooled to room temperature. Methanol was evaporated, then water was added. Extracted three times with DCM. Combined organic layers dried over $MgSO_4$ and evaporated. Crude trans-methyl 2-(2,4-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.1 g, 101 %) was isolated as a pale orange foam. ^{1}H NMR (500 MHz, $cdcl_3$) δ 1.43 – 2.15 (m, 4H), 2.66 – 3.23 (m, 4H), 3.39 – 3.79 (m, 3H), 4.04 – 4.41 (m, 1H), 4.45 – 4.78 (m, 1H), 5.67 (s, 1H), 6.73 – 6.90 (m, 2H), 7.03 – 7.37 (m, 1H). MS m/z 353 $(M+H)^+$

Step 2: 5-(Trans-2-(2,4-difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

Trans-methyl 2-(2,4-difluorobenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.25 g, 0.71 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 6.21 mL, 35.48 mmol) and stirred at room temperature for 16 h. The solvents were evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-(trans-2-(2,4-difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one (94.6 mg, 45%). ^{1}H NMR (600 MHz, dmso) δ 1.43 – 1.51 (m, 1H), 1.63 – 1.78 (m, 3H), 2.52 – 2.60 (m, 1H), 2.65 (d, 2H), 2.76 – 2.87 (m, 2H), 3.08 – 3.13 (m, 1H), 5.67 (s, 1H), 6.98 (td, 1H), 7.12 (td, 1H), 7.27 – 7.34 (m, 1H). HRMS Calculated for $[C_{15}H_{16}F_2N_2O_2+H]^+$: 295.1258. Found: 295.1265

Example 137

5-((2R,4S)-2-(3-Fluoro-5-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3-fluoro-5-(trifluoromethyl)benzyl)-piperidine-1-carboxylate and cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3-fluoro-5-(trifluoromethyl)benzyl)piperidine-1-carboxylate

Magnesium chloride (2.3 g, 24.16 mmol) and potassium 3-ethoxy-3-oxopropanoate (4 g, 23.50 mmol) were suspended in methyl THF (70 mL) under nitrogen and the resulting suspension was stirred at 50°C with an oversized stirring bar for 18 h, then cooled to room temperature (flask 1). To a suspension of 2-(3-fluoro-5-(trifluoromethyl)benzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (4.58 g, 12.61 mmol) (reference compound 58) in methyl THF (70.0 mL) was added di(1H-imidazol-1-yl)methanone (3.36 g, 20.72 mmol) under nitrogen. The resulting mixture was stirred at room temperature for 2 h (flask 2). The contents of flask 2 is transferred into flask 1 by transfer needle. Wash with methyl THF (30 mL). Resulting suspension stirred at room temperature for 72 h. 3.8 M HCl was added (ca. 200 mL) and the resulting biphasic mixture stirred vigorously for 30 min. MTBE was added and the phases separated. The organic phase was washed with water, satd $NaHCO_3$ and water, then dried over $MgSO_4$ and evaporated. The residue was purified via Biotage (Biotage® KP-SIL 340g column, 1 CV 20% EtOAc in heptanes, then 20% => 60% over 7 CV). Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3-fluoro-5-(trifluoromethyl)benzyl)-piperidine-1-carboxylate (758 mg, 14 %) and cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3-fluoro-5-

(trifluoromethyl)benzyl)piperidine-1-carboxylate (2.52 g, 46 %) were isolated. Cis-isomer: ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.20 – 1.28 (m, 3H), 1.64 – 1.95 (m, 4H), 2.68 – 2.81 (m, 2H), 2.95 (dd, 1H), 3.02 (ddd, 1H), 3.45 (s, 2H), 3.59 (s, 3H), 3.84 – 3.96 (m, 1H), 4.06 – 4.23 (m, 3H), 7.04 – 7.11 (m, 1H), 7.15 (d, 1H), 7.19 – 7.24 (m, 1H). MS m/z 434 $(M+H)^+$. Trans-isomer: ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.20 – 1.29 (m, 3H), 1.43 – 1.99 (m, 4H), 2.75 – 2.89 (m, 1H), 2.89 – 3.04 (m, 3H), 3.36 – 3.72 (m, 5H), 4.03 – 4.33 (m, 3H), 4.49 – 4.72 (m, 1H), 6.98 – 7.20 (m, 2H), 7.20 – 7.28 (m, 1H).

Step 2: Cis-methyl 2-(3-fluoro-5-(trifluoromethyl)benzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3-fluoro-5-(trifluoromethyl)benzyl)piperidine-1-carboxylate (2.52 g, 5.81 mmol) was dissolved in MeOH (20 mL) and cooled to -40°C. Sodium hydroxide (.246 g, 6.15 mmol) dissolved in water (2.2 mL) was added over 1 min and the resulting solution was stirred at -40°C for 20 min. Then hydroxylamine (50 % by weight in water, 0.38 mL, 6.20 mmol) was added over 1 min and stirring continued at -40°C for 2 h 20 min. The reaction mixture was then transferred into a prewarmed (80°C) solution of 6 M hydrogen chloride (40 mL, 240.00 mmol) and the mixture was continued to be stirred at 80°C for 1h. Then cooled to room temperature. Methanol was evaporated, then water was added. Extracted three times with DCM. Combined organic layers dried over $MgSO_4$ and evaporated. The compound was purified by preparative HPLC in 3 injections on a XBridge C18 column (10 µm 250x50 ID mm) using a gradient of 0-35 % Acetonitrile in H2O/MeCN/NH3 95/5/0.2 buffer over 25 minutes with a flow of 100 mL/min. Cis-methyl 2-(3-fluoro-5-(trifluoromethyl)benzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.52 g, 65 %) was isolated as a colorless foam. ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.87 – 2.10 (m, 4H), 2.61 – 2.67 (m, 1H), 2.80 – 2.87 (m, 1H), 2.97 – 3.04 (m, 1H), 3.13 – 3.21 (m, 1H), 3.60 (s, 3H), 3.96 – 4.04 (m, 1H), 4.26 – 4.32 (m, 1H), 5.74 (s, 1H), 7.00 (d, 1H), 7.11 – 7.16 (m, 2H). MS m/z 403 $(M+H)^+$

Step 3: (2R,4S)-Methyl 2-(3-fluoro-5-(trifluoromethyl)benzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate and (2S,4R)-methyl 2-(3-fluoro-5-(trifluoromethyl)benzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-Methyl 2-(3-fluoro-5-(trifluoromethyl)benzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate (1.47 g, 3.66 mmol) was subjected to chiral preparative HPLC

(Column: Chiralcel OJ (250x20), 5 μm particle size, mobile phase: Heptane/EtOH 90/10, flow rate 18 mL/min) to yield (2R,4S)-methyl 2-(3-fluoro-5-(trifluoromethyl)benzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (703 mg, 47.8 %), Chiral purity 99.3 %ee, Optical rotation $[\alpha]_D^{20} = +5.5$ (acetonitrile, c=1) and (2S,4R)-methyl 2-(3-fluoro-5-(trifluoromethyl)benzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (675 mg, 45.9 %), Chiral purity 99.7 %ee, Optical rotation $[\alpha]_D^{20} = -5.1$ (acetonitrile, c=1)

Step 4: 5-((2R,4S)-2-(3-Fluoro-5-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-Methyl 2-(3-fluoro-5-(trifluoromethyl)benzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.703 g, 1.75 mmol) was dissolved in hydrogen bromide (33 % in AcOH, 5 mL, 71.37 mmol) and stirred at room temperature overnight. The solvents were evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN, pH 10, Column: Xbridge Prep C18 5μm OBD 19*150 mm) to yield 5-((2R,4S)-2-(3-fluoro-5-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one (375 mg, 62 %). ^{1}H NMR (600 MHz, dmso) δ 1.08 (q, 1H), 1.31 (dq, 1H), 1.71 – 1.80 (m, 2H), 2.48 – 2.54 (m, 1H), 2.63 – 2.80 (m, 4H), 2.92 – 2.99 (m, 1H), 5.65 (s, 1H), 7.37 – 7.46 (m, 3H). HRMS Calculated for $[C_{16}H_{16}F_4N_2O_2+H]^+$: 345.1226. Found: 345.1228

Example 138

5-((2S,4R)-2-(3-Fluoro-5-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one

(2S,4R)-Methyl 2-(3-fluoro-5-(trifluoromethyl)benzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.675 g, 1.68 mmol) (from example 137, step 3) was dissolved in hydrogen bromide (33 % in AcOH, 5 mL, 71.37 mmol) and stirred at room temperature overnight. The solvents were evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN, pH 10, Column: Xbridge Prep C18 5μm OBD 19*150 mm) to yield 5-((2S,4R)-2-(3-fluoro-5-(trifluoromethyl)benzyl)-piperidin-4-yl)isoxazol-3(2H)-one (443 mg, 77 %). ^{1}H NMR (600 MHz, dmso) δ 1.08 (q, 1H), 1.31 (qd, 1H), 1.75 (t, 2H), 2.48 – 2.54 (m, 1H), 2.64 – 2.79 (m, 4H), 2.96 (d, 1H), 5.65 (s, 1H), 7.38 – 7.46 (m, 3H). HRMS Calculated for $[C_{16}H_{16}F_4N_2O_2+H]^+$: 345.1226. Found: 345.1212.

Example 139

5-(Trans-2-(3-fluoro-5-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(3-fluoro-5-(trifluoromethyl)benzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3-fluoro-5-(trifluoromethyl)benzyl)piperidine-1-carboxylate (0.75 g, 1.73 mmol) (from example 137, step 1) was dissolved in MeOH (15 mL) and cooled to -40°C. Sodium hydroxide (0.073 g, 1.82 mmol) dissolved in water (1 mL) was added over 1 min and the resulting solution was stirred at -40°C for 20 min. Then hydroxylamine (50 % by weight in water, 0.115 mL, 1.88 mmol) was added over 1 min and stirring continued at -40°C for 2 h 20 min. The reaction mixture was then transferred into a prewarmed (80°C) solution of 6 M hydrogen chloride (30 mL, 180.00 mmol) and the mixture was continued to be stirred at 80°C for 1h. Then cooled to room temperature. Methanol was evaporated, then water was added. Extracted three times with DCM. Combined organic layers dried over $MgSO_4$ and evaporated. Trans-methyl 2-(3-fluoro-5-(trifluoromethyl)benzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (658 mg, 95 %) was isolated as an off-white solid. MS m/z 403 $(M+H)^+$

Step 2: 5-(Trans-2-(3-fluoro-5-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one

Trans-methyl 2-(3-fluoro-5-(trifluoromethyl)benzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.255 g, 0.63 mmol) was dissolved in hydrogen bromide (33% in acetic acid, 5 mL, 71.37 mmol) and stirred at room temperature for 1 week. The solvents were evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx III, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column:Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-(trans-2-(3-fluoro-5-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one (172 mg, 79 %). ^1H NMR (600 MHz, dmso) δ 1.43 – 1.51 (m, 1H), 1.62 – 1.80 (m, 3H), 2.51 – 2.58 (m, 1H), 2.71 – 2.82 (m, 3H), 2.86 – 2.94 (m, 1H), 3.07 – 3.14 (m, 1H), 5.72 (s, 1H), 7.37 – 7.46 (m, 3H). HRMS Calculated for $[C_{16}H_{16}F_4N_2O_2+H]^+$: 345.1226. Found: 345.1241

Example 140

5-((2R,4S)-2-(3-Fluoro-4-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3-fluoro-4-(trifluoromethyl)benzyl)-piperidine-1-carboxylate and cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3-fluoro-4-(trifluoromethyl)benzyl)piperidine-1-carboxylate

Magnesium chloride (3.25 g, 34.13 mmol) and potassium 3-ethoxy-3-oxopropanoate (5.82 g, 34.19 mmol) were suspended under a nitrogen atmosphere in methyl THF (100 mL) and stirred with an oversized stirring bar at 50°C for18 h, then cooled to room temperature (flask 1). To a suspension of 2-(3-fluoro-4-(trifluoromethyl)benzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (6.56 g, 18.06 mmol) (reference compound 59) in methyl THF (100 mL) was added di(1H-imidazol-1-yl)methanone (4.77 g, 29.42 mmol) under nitrogen. The resulting mixture was stirred at room temperature for 2 h (flask 2). The contents of flask 2 is transferred into flask 1 by transfer needle. Wash with methyl THF (30 mL). Resulting suspension stirred at room temperature for 18 h. 3.8 M HCl was added (ca. 200 mL) and the resulting biphasic mixture stirred vigorously for 30 min. MTBE was added and the phases separated. The organic phase was washed with water, satd $NaHCO_3$ and water, then dried over $MgSO_4$ and evaporated. The residue was purified via Biotage (Biotage® KP-SIL 340g column, 1 CV 20% EtOAc in heptanes, then 20% => 60% over 7 CV). Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3-fluoro-4-(trifluoromethyl)benzyl)piperidine-1-carboxylate (0.794 g, 10 %) and cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3-fluoro-4-(trifluoromethyl)-benzyl)piperidine-1-carboxylate (3.57 g, 45 %) were isolated as pale yellow oils. Cis-isomer: MS m/z 434 $(M+H)^+$. Trans-isomer: MS m/z 434 $(M+H)^+$

Step 2: Cis-methyl 2-(3-fluoro-4-(trifluoromethyl)benzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3-fluoro-4-(trifluoromethyl)benzyl)piperidine-1-carboxylate (2.033 g, 4.69 mmol) was dissolved in MeOH (20 mL) and cooled to -40°C. Sodium hydroxide (0.188 g, 4.69 mmol) dissolved in water (2.4 mL) was added over 1 min and the resulting solution was stirred at -40°C for 20 min. Then hydroxylamine (50 % by weight in water, 0.3 mL, 4.90 mmol) was added over 1 min and stirring continued at -40°C for 2 h 20 min. The reaction mixture was then transferred into a prewarmed (80°C) solution of 6 M hydrogen chloride (40 mL, 240.00 mmol) and the mixture was continued to be stirred at 80°C for 1 h. Then cooled to room temperature. Methanol was evaporated, then water was

added. Extracted three times with DCM. Combined organic layers dried over $MgSO_4$ and evaporated. Product was pale yellow oil. The compound was purified by preparative HPLC in 3 injections on a XBridge C18 column (10 µm 250x50 ID mm) using a gradient of 0-35 % Acetonitrile in H2O/MeCN/NH3 95/5/0.2 buffer over 25 minutes with a flow of 100 mL/min. Cis-methyl 2-(3-fluoro-4-(trifluoromethyl)benzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate (1.32 g, 70%) was isolated as a colorless foam. ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.84 – 1.99 (m, 3H), 1.99 – 2.10 (m, 1H), 2.62 (dd, 1H), 2.82 (dd, 1H), 2.92 – 3.06 (m, 1H), 3.10 – 3.19 (m, 1H), 3.59 (s, 3H), 3.93 – 4.03 (m, 1H), 4.19 – 4.34 (m, 1H), 5.73 (s, 1H), 6.91 – 6.99 (m, 2H), 7.46 (t, 1H). MS m/z 403 $(M+H)^+$

Step 3: (2R,4S)-Methyl 2-(3-fluoro-4-(trifluoromethyl)benzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate and (2S,4R)-methyl 2-(3-fluoro-4-(trifluoromethyl)benzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 2-(3-fluoro-4-(trifluoromethyl)benzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate (1.32 g, 3.28 mmol) was subjected to chiral preparative HPLC (Column: Chiralpak AD (250x20), 5 µm particle size, mobile phase: Heptane/EtOH 85/15, flow rate 18 mL/min) to yield (2R,4S)-methyl 2-(3-fluoro-4-(trifluoromethyl)benzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (594 mg, 46 %), Chiral purity 99.5 %ee, Optical rotation $[\alpha]_D^{20} = +9.1$ (acetonitrile, c=1) and (2S,4R)-methyl 2-(3-fluoro-4-(trifluoromethyl)benzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (589 mg, 45 %), Chiral purity 99.2 %ee, Optical rotation $[\alpha]_D^{20} = -8.8$ (acetonitrile, c=1)

Step 4: 5-((2R,4S)-2-(3-Fluoro-4-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-Methyl 2-(3-fluoro-4-(trifluoromethyl)benzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (594 mg, 1.48 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 10 mL, 57.10 mmol) and the mixture stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx III, Mobilphase: gradient 5-95% MeCN in 0.2% NH3, pH10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4S)-2-(3-fluoro-4-(trifluoromethyl)benzyl)-piperidin-4-yl)isoxazol-3(2H)-one (338 mg, 66 %).^{1}H NMR (600 MHz, dmso) δ 1.08 (q, 1H), 1.32 (qd, 1H), 1.71 – 1.79 (m, 2H), 2.45 – 2.72 (m, 4H), 2.72 – 2.80 (m, 1H), 2.96 (d, 1H),

5.68 (s, 1H), 7.23 (d, 1H), 7.35 (d, 1H), 7.65 (t, 1H). HRMS Calculated for $[C_{16}H_{16}F_4N_2O_2+H]^+$: 345.1226. Found: 345.1232

Example 141

5-((2S,4R)-2-(3-Fluoro-4-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one

(2S,4R)-Methyl 2-(3-fluoro-4-(trifluoromethyl)benzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (589 mg, 1.46 mmol) (from example 140, step 3) was dissolved in hydrogen bromide (33 % in acetic acid, 10 mL, 57.10 mmol) and the mixture stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx III, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2S,4R)-2-(3-fluoro-4-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one (329 mg, 65 %). ^{1}H NMR (600 MHz, cd_3od) δ 1.66 (q, 1H), 1.81 (dq, 1H), 2.17 – 2.25 (m, 2H), 3.00 – 3.15 (m, 4H), 3.47 – 3.52 (m, 1H), 3.56 – 3.62 (m, 1H), 5.76 (s, 1H), 7.28 (dd, 2H), 7.67 (t, 1H). HRMS Calculated for $[C_{16}H_{16}F_4N_2O_2+H]^+$: 345.1226. Found: 345.1225

Example 142

5-(Trans-2-(3-fluoro-4-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(3-fluoro-4-(trifluoromethyl)benzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3-fluoro-4-(trifluoromethyl)benzyl)piperidine-1-carboxylate (0.781 g, 1.80 mmol) (from example 140, step 1) was dissolved in MeOH (15 mL) and cooled to -40°C. Sodium hydroxide (0.072 g, 1.80 mmol) dissolved in water (1 mL) was added over 1 min and the resulting solution was stirred at -40°C for 20 min. Then hydroxylamine (50 % by weight in water, 0.12 mL, 1.96 mmol) was added over 1 min and stirring continued at -40°C for 2 h 15 min. The reaction mixture was then transferred into a prewarmed (80°C) solution of 6 M hydrogen chloride (30 mL, 180.00 mmol) and the mixture was continued to be stirred at 80°C for 1h. Then cooled to room temperature. Methanol was evaporated, then water was added. Extracted three times with DCM. Combined organic layers

dried over $MgSO_4$ and evaporated. Crude trans-methyl 2-(3-fluoro-4-(trifluoromethyl)-benzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (678 mg, 94 %) was isolated as an off-white foam. MS m/z 403 $(M+H)^+$

Step 2: 5-(Trans-2-(3-fluoro-4-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one

Trans-methyl 2-(3-fluoro-4-(trifluoromethyl)benzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate (0.224 g, 0.56 mmol) was dissolved in hydrogen bromide (33% in acetic acid, 5 mL, 71.37 mmol) and stirred at room temperature for 1 week. The solvents were evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx III, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column:Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-(trans-2-(3-fluoro-4-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one (160 mg, 83%). ^1H NMR (600 MHz, dmso) δ 1.48 (ddd, 1H), 1.63 – 1.81 (m, 3H), 2.51 – 2.59 (m, 1H), 2.70 – 2.82 (m, 3H), 2.88 – 2.95 (m, 1H), 3.07 – 3.14 (m, 1H), 5.72 (s, 1H), 7.21 (d, 1H), 7.33 (d, 1H), 7.63 (t, 1H). HRMS Calculated for $[C_{16}H_{16}F_4N_2O_2+H]^+$: 345.1226. Found: 345.1241

Example 143

5-((2R,4S)-2-(3,4,5-Trifluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3,4,5-trifluorobenzyl)piperidine-1-carboxylate and cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3,4,5-trifluorobenzyl)piperidine-1-carboxylate

1-(Methoxycarbonyl)-2-(3,4,5-trifluorobenzyl)piperidine-4-carboxylic acid (3.42 g, 10.32 mmol) (reference compound 60) was dissolved in methyl THF (60 mL) and di(1H-imidazol-1-yl)methanone (2.51 g, 15.49 mmol) added. The suspension was stirred at room temperature under nitrogen for 6 h (flask 1). In a separate flask potassium 3-ethoxy-3-oxopropanoate (3.16 g, 18.58 mmol) was suspended in methyl THF (60.0 mL) and magnesium chloride (1.769 g, 18.58 mmol) added. The suspension was stirred under nitrogen for 6 h (flask 2). The white suspension in flask 2 was then added to the brown suspension in flask 1. The resulting suspension was stirred at room temperature for 18 h. The mixture was acidified to pH 1 with 3 M HCl. MTBE (250 mL) and water (250 mL) were added, shaken and the phases separated. The organic phase was washed with water (250 mL), satd NaHCO3 (250 mL) and brine (250

mL), dried with Na_2SO_4, filtered and evaporated in vacuo. The residue was purified by automated flash chromatography on a Biotage® KP-SIL 100g column. A gradient 20 % EtOAc in heptane over 2 CV followed by 20 % to 60 % of EtOAc in heptane over 8 CV was used as mobile phase. Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3,4,5-trifluorobenzyl)-piperidine-1-carboxylate (0.309 g, 7.46 %) and cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3,4,5-trifluorobenzyl)piperidine-1-carboxylate (1.967 g, 47.5 %) were isolated. Cis-isomer: ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.19 – 1.30 (m, 3H), 1.62 – 1.96 (m, 4H), 2.61 – 2.68 (m, 1H), 2.68 – 2.76 (m, 1H), 2.80 – 2.87 (m, 1H), 2.96 – 3.04 (m, 1H), 3.46 (s, 2H), 3.65 (s, 3H), 3.83 – 3.94 (m, 1H), 4.09 – 4.20 (m, 3H), 6.76 – 6.84 (m, 2H). MS m/z 402 $(M+H)^+$. Trans-isomer: MS m/z 402 $(M+H)^+$

Step 2: Cis-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3,4,5-trifluorobenzyl)piperidine-1-carboxylate

Cis-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3,4,5-trifluorobenzyl)piperidine-1-carboxylate (1.967 g, 4.90 mmol) was dissolved in MeOH (20 mL) and cooled to - 40°C under nitrogen. Sodium hydroxide (1.290 mL, 4.90 mmol) in water (2.000 mL) was added and the mixture stirred at - 40°C for 20 min. Hydroxylamine (50 % by weight in water, 0.300 mL, 4.90 mmol) was added and stirring continued at - 40°C for 3.5 h. The reaction mixture was then transferred to a preheated 80°C solution of 6 M hydrogen chloride (25.3 mL, 151.92 mmol) and heating was continued for 20 min. The solvent was then evaporated. DCM (150 mL) and water (150 mL) were added, shaken and the phases separated. The organic phase was dried with a phase separator and evaporated in vacuo. The compound was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x50 ID mm) using a gradient of 10-55% Acetonitrile in H2O/MeCN/AcOH 95/5/0.2 buffer over 30 minutes with a flow of 100 mL/min. Cis-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3,4,5-trifluorobenzyl)piperidine-1-carboxylate (1.354 g, 74.6 %) was isolated as a white solid. ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.84 – 2.10 (m, 4H), 2.48 – 2.54 (m, 1H), 2.69 – 2.76 (m, 1H), 2.96 – 3.03 (m, 1H), 3.10 – 3.18 (m, 1H), 3.64 (s, 3H), 3.94 – 4.01 (m, 1H), 4.18 – 4.25 (m, 1H), 5.73 (s, 1H), 6.69 – 6.75 (m, 2H). MS m/z 369 $(M-H)^-$

Step 3: (2R,4S)-Methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3,4,5-trifluorobenzyl)-piperidine-1-carboxylate and (2S,4R)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3,4,5-trifluorobenzyl)piperidine-1-carboxylate

Cis-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3,4,5-trifluorobenzyl)piperidine-1-carboxylate (1.354 g, 3.68 mmol) was subjected to chiral preparative HPLC (Column: Chiralpak AD (250x20 mm), 5 µm particle size, mobile phase: Heptane/EtOH/FA 80/20/0.1, flow rate 18 mL/min) to yield (2R,4S)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3,4,5-trifluorobenzyl)piperidine-1-carboxylate (584 mg, 43 %), Chiral purity 99.3 %ee, Optical rotation $[\alpha]_D^{20} = +13.0$ (acetonitrile, c=1.0) and (2S,4R)-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3,4,5-trifluorobenzyl)piperidine-1-carboxylate (598 mg, 44 %), Chiral purity 99.2 %ee, Optical rotation $[\alpha]_D^{20} = -12.5$ (acetonitrile, c=1.0)

Step 4: 5-((2R,4S)-2-(3,4,5-Trifluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-Methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3,4,5-trifluorobenzyl)piperidine-1-carboxylate (584 mg, 1.58 mmol) was dissolved in hydrogen bromide (33 % in AcOH, 7 mL, 302.80 mmol) and stirred at room temperature for 20 h. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4S)-2-(3,4,5-trifluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one (325 mg, 66 %). ^{1}H NMR (600 MHz, dmso) δ 1.05 (q, 1H), 1.31 (dq, 1H), 1.71 – 1.78 (m, 2H), 2.34 – 3.78 (m, 6H), 5.68 (s, 1H), 7.12 – 7.20 (m, 2H). HRMS Calculated for $[C_{15}H_{15}F_3N_2O_2+H]^+$: 313.1164. Found: 313.1172

Example 144

5-((2S,4R)-2-(3,4,5-Trifluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

(2S,4R)-Methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3,4,5-trifluorobenzyl)piperidine-1-carboxylate (598 mg, 1,61 mmol) (from example 143, step 3) was dissolved in hydrogen bromide (33 % in AcOH, 7 mL, 99,92 mmol) and stirred at room temperature for 20 h. The solvent was evaporated in vacuo and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2S,4R)-2-(3,4,5-trifluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one (357 mg, 70.8 %). ^{1}H NMR (600 MHz, dmso) δ 1.05 (q, 1H), 1.32 (dq,

1H), 1.70 – 1.78 (m, 2H), 2.33 – 3.58 (m, 6H), 5.68 (s, 1H), 7.12 – 7.19 (m, 2H). HRMS Calculated for $[C_{15}H_{15}F_3N_2O_2+H]^+$: 313.1164. Found: 313.1158

Example 145

5-(Trans-2-(3,4,5-trifluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3,4,5-trifluorobenzyl)piperidine-1-carboxylate

Trans-methyl 4-(3-ethoxy-3-oxopropanoyl)-2-(3,4,5-trifluorobenzyl)piperidine-1-carboxylate (309 mg, 0.77 mmol) (from example 143, step 1) was dissolved in MeOH (5 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (0.203 mL, 0.77 mmol) in water (0.500 mL) was added and the mixture was stirred at -40°C for 20 min. Hydroxylamine (50 % in water, 0.047 mL, 0.77 mmol) was added and stirring contiuned at -40°C for 3 h. The reaction mixture was then transferred to a preheated 80°C solution of 6 M hydrogen chloride (3.98 mL, 23.87 mmol) and heating was continued for 20 min. The solvent was then evaporated. DCM (50 mL) and water (50 mL) were added, shaken and the phases separated. The organic phase was dried with a phase separator and evaporated in vacuo. The compound was purified by preparative HPLC on a Kromasil C8 column (10 µm 250x20 ID mm) using a gradient of 10-55 % Acetonitrile in H2O/MeCN/AcOH 95/5/0.2 buffer, over 30 minutes with a flow of 19 mL/min. Trans-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3,4,5-trifluorobenzyl)-piperidine-1-carboxylate (111 mg, 38.9 %) was isolated. MS m/z 371 $(M+H)^+$

Step 2: 5-(Trans-2-(3,4,5-trifluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one

Trans-methyl 4-(3-oxo-2,3-dihydroisoxazol-5-yl)-2-(3,4,5-trifluorobenzyl)piperidine-1-carboxylate (111 mg, 0.3 mmol) was stirred in hydrogen bromide (33 % in AcOH, 2 mL, 86.51 mmol) for 18 h. The reaction mixture was evaporated in vacuo and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-(trans-2-(3,4,5-trifluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one (20.17 mg, 21.5 %). ^{1}H NMR (600 MHz, dmso) δ 1.43 – 1.49 (m, 1H), 1.65 – 1.79 (m, 3H), 2.33 – 3.75 (m, 6H), 5.75 (s, 1H), 7.12 – 7.19 (m, 2H). HRMS Calculated for $[C_{15}H_{15}F_3N_2O_2+H]^+$: 313.1164. Found: 313.1147

Example 146

5-((2R,4S)-2-(3,5-Di-tert-butylbenzyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(3,5-di-tert-butylbenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate and cis-methyl 2-(3,5-di-tert-butylbenzyl)-4-(3-ethoxy-3-oxopropanoyl)-piperidine-1-carboxylate

2-(3,5-Di-tert-butylbenzyl)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (3.723 g, 9.56 mmol) (reference compound 61) was dissolved in methyl THF (70 mL) and di(1H-imidazol-1-yl)methanone (2.325 g, 14.34 mmol) added. The suspension was stirred at room temperature under nitrogen overnight (flask 1). In a separate flask potassium 3-ethoxy-3-oxopropanoate (2.93 g, 17.20 mmol) was suspended in methyl THF (70.0 mL) and magnesium chloride (1.638 g, 17.20 mmol) added. The suspension was stirred at 50°C under nitrogen overnight using an oversized stirring bar (flask 2). The yellow suspension in flask 1 was now added to the white suspension in flask 2. The resulting white suspension was stirred under nitrogen at room temperature for 2 days. The mixture was acidified to pH 1 with 3.8 M HCl and MTBE and water added. The phases were separated and the organic phase washed with water, satd $NaHCO_3$ and water. Evaporated the solvents to yield a yellow oil. The diastereomers were separated in 2 runs on Biotage (0 % => 40 % EtOAc in heptane, 8 CV; Biotage® KP-SIL 340g column). Trans-methyl 2-(3,5-di-tert-butylbenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (0.734 g, 17 %) and cis-methyl 2-(3,5-di-tert-butylbenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (2.027 g, 46 %) were isolated as colorless oils. Cis-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.19 – 1.35 (m, 21H), 1.63 – 1.99 (m, 4H), 2.62 – 3.05 (m, 4H), 3.46 (s, 2H), 3.57 – 3.64 (m, 3H), 3.88 – 3.97 (m, 1H), 4.07 – 4.26 (m, 3H), 6.97 – 7.01 (m, 2H), 7.24 – 7.28 (m, 1H). MS m/z 460 $(M+H)^+$. Trans-isomer: ^{1}H NMR (400 MHz, cdcl$_3$) δ 1.11 – 1.39 (m, 21H), 1.40 – 2.02 (m, 4H), 2.52 – 3.14 (m, 4H), 3.33 – 3.55 (m, 3H), 3.64 (s, br., 2H), 3.98 – 4.35 (m, 3H), 4.37-4.80 (m, 1H), 6.91 – 7.12 (m, 2H), 7.24 – 7.30 (m, 1H). MS m/z 460 $(M+H)^+$

Step 2: Cis-methyl 2-(3,5-di-tert-butylbenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 2-(3,5-di-tert-butylbenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (2.03 g, 4.42 mmol) was dissolved in MeOH (16 mL) and cooled to -40°C under nitrogen.

Sodium hydroxide (0.177 g, 4.42 mmol) dissolved in water (1.600 mL) was added during 10 min and the colourless solution continued to stir at -40°C for 20 min. Hydroxylamine (50 % by weight in water, 0.271 mL, 4.42 mmol) was added during 8 min. The resulting solution was stirred at -40°C for 3.5 h. The mixture was then transferred into a prewarmed (80°C) solution of 6 M hydrogen chloride (20 mL, 120.00 mmol) and the mixture continued to stir at 80°C for 20 min. DCM and water were added. The phases were separated and the organic phase passed through a phase separator and evaporated to yield a yellow semi-solid. The compound was purified by preparative HPLC in 3 injections on a XBridge C18 column (10 µm 250x50 ID mm) using a gradient of 10-50 % Acetonitrile in H2O/MeCN/NH3 95/5/0.2 buffer over 20 minutes with a flow of 100 mL/min. Cis-methyl 2-(3,5-di-tert-butylbenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.358 g, 72 %) was isolated as a white solid. ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.22 – 1.33 (m, 18H), 1.80 – 2.10 (m, 4H), 2.59 – 2.67 (m, 1H), 2.71 – 2.78 (m, 1H), 2.92 – 2.98 (m, 1H), 3.07 – 3.15 (m, 1H), 3.55 (s, 3H), 3.97 (dd, 1H), 4.18 – 4.27 (m, 1H), 5.68 (s, 1H), 6.92 (d, 2H), 7.22 (s, 1H). MS m/z 429 $(M+H)^+$

Step 3: <u>(2R,4S)-Methyl 2-(3,5-di-tert-butylbenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)-piperidine-1-carboxylate and (2S,4R)-methyl 2-(3,5-di-tert-butylbenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate</u>

Cis-methyl 2-(3,5-di-tert-butylbenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.358 g, 3.16 mmol) was subjected to chiral preparative HPLC (Column: Chiralcel OJ (250x20), 5 µm particle size, mobile phase: Heptane/EtOH/FA 90/10/0.1, flow rate 18 mL/min) to yield (2R,4S)-methyl 2-(3,5-di-tert-butylbenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (550 mg, 40 %), Chiral purity 99.6 %ee, Optical rotation $[\alpha]_D^{20} = +14.7$ (acetonitrile, c=1) and (2S,4R)-methyl 2-(3,5-di-tert-butylbenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (619 mg, 45 %), Chiral purity 99.7 %ee, Optical rotation $[\alpha]_D^{20} = -11.2$ (acetonitrile, c=1)

Step 4: <u>5-((2R,4S)-2-(3,5-Di-tert-butylbenzyl)piperidin-4-yl)isoxazol-3(2H)-one</u>

(2R,4S)-Methyl 2-(3,5-di-tert-butylbenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (550 mg, 1.28 mmol) was dissolved in hydrogen bromide (33 % in acetic acid (10 mL, 57.10 mmol) and the mixture stirred at room temperature overnight. The solvent was

evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx III, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4S)-2-(3,5-di-tert-butylbenzyl)piperidin-4-yl)isoxazol-3(2H)-one (315 mg, 66%). ^{1}H NMR (600 MHz, cd_3od) δ 1.30 (s, 18H), 1.58 – 1.67 (m, 1H), 1.80 (dq, 1H), 2.17 – 2.27 (m, 2H), 2.85 – 3.14 (m, 4H), 3.41 – 3.51 (m, 2H), 5.73 (s, 1H), 7.07 – 7.13 (m, 2H), 7.36 – 7.40 (m, 1H). HRMS Calculated for $[C_{23}H_{34}N_2O_2+H]^+$: 371.2698. Found: 371.2714

Example 147

5-((2S,4R)-2-(3,5-Di-tert-butylbenzyl)piperidin-4-yl)isoxazol-3(2H)-one

(2S,4R)-Methyl 2-(3,5-di-tert-butylbenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (619 mg, 1.44 mmol) (from example 146, step 3) was dissolved in hydrogen bromide (33 % in acetic acid, 10 mL, 57.10 mmol) and the mixture stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx III, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2S,4R)-2-(3,5-di-tert-butylbenzyl)piperidin-4-yl)isoxazol-3(2H)-one (330 mg, 61 %). ^{1}H NMR (600 MHz, cd_3od) δ 1.30 (s, 18H), 1.63 (q, 1H), 1.80 (dq, 1H), 2.19 – 2.27 (m, 2H), 2.86 – 3.18 (m, 4H), 3.43 – 3.56 (m, 2H), 5.73 (s, 1H), 7.10 (d, 2H), 7.37 – 7.40 (m, 1H). HRMS Calculated for $[C_{23}H_{34}N_2O_2+H]^+$: 371.2698. Found: 371.2693

Example 148

5-(Trans-2-(3,5-di-tert-butylbenzyl)piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-(3,5-di-tert-butylbenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Trans-methyl 2-(3,5-di-tert-butylbenzyl)-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (0.734 g, 1.60 mmol) was dissolved in MeOH (5 mL) and cooled to -40°C under nitrogen. Sodium hydroxide (0.064 g, 1.60 mmol) dissolved in water (0.500 mL) was added during 10 min and the colourless solution continued to stir at -40°C for 20 min.

Hydroxylamine (50 % by weight in water, 0.098 mL, 1.60 mmol) was added during 8 min. The resulting solution was stirred at -40°C for 4 h. The mixture was then transferred into a prewarmed (80°C) solution of 6 M hydrogen chloride (8 mL, 48.00 mmol) and the mixture continued to stir at 80°C for 20 min. DCM and water were added. The phases were separated and the organic phase passed through a phase separator and evaporated to yield crude trans-methyl 2-(3,5-di-tert-butylbenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.723 g, 106 %) as a yellow semi-solid. MS m/z 429 $(M+H)^+$

Step 2: 5-(Trans-2-(3,5-di-tert-butylbenzyl)piperidin-4-yl)isoxazol-3(2H)-one

Trans-Methyl 2-(3,5-di-tert-butylbenzyl)-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (155 mg, 0.36 mmol) was dissolved in hydrogen bromide (33 % in acetic acid, 3 mL, 17.13 mmol) and the mixture stirred at room temperature overnight. The solvent was evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx III, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-(trans-2-(3,5-di-tert-butylbenzyl)piperidin-4-yl)isoxazol-3(2H)-one (69 mg, 51 %). ^{1}H NMR (600 MHz, DMSO) δ 1.26 (s, 18H), 1.45 – 1.53 (m, 1H), 1.69 – 1.87 (m, 3H), 2.58 – 2.72 (m, 3H), 2.83 – 2.93 (m, 2H), 3.09 – 3.16 (m, 1H), 5.64 (s, 1H), 6.99 (d, 2H), 7.18 – 7.23 (m, 1H). HRMS Calculated for $[C_{23}H_{34}N_2O_2+H]^+$: 371.2698. Found: 371.2688

Example 149

5-((2R,4S)-2-Benzyl-2,3,4,5,6-d_5-piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-benzyl-2,3,4,5,6-d_5-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate and cis-methyl 2-benzyl-2,3,4,5,6-d_5-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate

Magnesium chloride (3.13 g, 32.90 mmol) and potassium 3-ethoxy-3-oxopropanoate (5.60 g, 32.90 mmol) suspended in THF (100 mL) were stirred with an oversized stirring bar at 50°C under nitrogen for 18h, then cooled to room temperature (flask 1). To a suspension of 2-benzyl-2,3,4,5,6-d_5-1-(methoxycarbonyl)piperidine-4-carboxylic acid (5.16 g, 18.28 mmol) (reference compound 62) in methyl THF (100 mL) was added di(1H-imidazol-1-yl)methanone (4.77 g, 29.42 mmol) under nitrogen. The resulting mixture was stirred at room temperature

for 19 h (flask 2). The contents of flask 2 is transferred into flask 1 by transfer needle. Wash with THF (35 mL). Resulting suspension stirred at room temperature for 24 h. 3.8 M HCl was added (ca. 200 mL) and the resulting biphasic mixture stirred vigorously for 30 min. MTBE was added and the phases separated. The aqueous phase extraced once more with MTBE. The combined organic layers dried over $MgSO_4$ and evaporated. The residue was purified via Biotage (Biotage® KP-SIL 340g column, 1 CV 20% EtOAc in heptanes, then 20% => 60% over 7 CV). Trans-methyl 2-benzyl-2,3,4,5,6-d_5-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (1.15 g, 18 %) and cis-methyl 2-benzyl-2,3,4,5,6-d_5-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (2.27 g, 35 %) were isolated as pale yellow oils. Cis-isomer: ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.19 – 1.28 (m, 3H), 1.60 – 1.92 (m, 4H), 2.63 – 2.77 (m, 2H), 2.85 – 3.04 (m, 2H), 3.42 (s, 2H), 3.61 (s, 3H), 3.85 – 3.94 (m, 1H), 4.05 – 4.22 (m, 3H). MS m/z 353 $(M+H)^+$. Trans-isomer: ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.19 – 1.31 (m, 3H), 1.39 – 1.66 (m, 2H), 1.67 – 1.98 (m, 2H), 2.71 – 3.07 (m, 4H), 3.33 – 3.73 (m, 5H), 3.99 – 4.33 (m, 3H), 4.57 (d, br., 1H). MS m/z 353 $(M+H)^+$

Step 2: Cis-methyl 2-benzyl-2,3,4,5,6-d_5-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 2-benzyl-2,3,4,5,6-d_5-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (2.27 g, 6.44 mmol) was dissolved in MeOH (20 mL) and cooled to -40°C. Sodium hydroxide (0.258 g, 6.44 mmol) dissolved in water (2 mL) was added over 2 min and the resulting solution was stirred at -40°C for 25 min. Then hydroxylamine (50 % by weight in water, 0.41 mL, 6.69 mmol) was added over 1 min and stirring continued at -50 to -40°C for 1 h 40 min. The reaction mixture was then transferred into a prewarmed (80°C) solution of 6 M hydrogen chloride (30 mL, 180.00 mmol) and the mixture was continued to be stirred at 80°C for 30 min. Then cooled to room temperature. Methanol was evaporated, then water was added. Extracted three times with DCM. Combined organic layers dried over $MgSO_4$ and evaporated. The compound was purified in 3 injections by preparative HPLC on a XBridge C18 column (10 µm 250x50 ID mm) using a gradient of 0-25% Acetonitrile in H2O/MeCN/NH3 95/5/0.2 buffer over 23 minutes with a flow of 100 mL/min. Cis-methyl 2-benzyl-2,3,4,5,6-d_5-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.458 g, 70 %) was isolated as a colorless solid. ^{1}H NMR (600 MHz, cdcl$_3$) δ 1.79 – 1.97 (m, 3H), 1.99 – 2.12 (m, 1H), 2.62 (dd, 1H), 2.81 (dd, 1H), 2.89 – 2.99 (m, 1H), 3.07 – 3.17 (m, 1H), 3.59 (s, 3H), 3.98 (dd, 1H), 4.20 – 4.30 (m, 1H), 5.69 (s, 1H). MS m/z 322 $(M+H)^+$

Step 3: (2R,4S)-Methyl 2-benzyl-2,3,4,5,6-d_5-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate and (2S,4R)-methyl 2-benzyl-2,3,4,5,6-d_5-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Cis-methyl 2-benzyl-2,3,4,5,6-d_5-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.25 g, 3.89 mmol) was subjected to chiral preparative HPLC (Column: Chiralcel OD (250x20), 5 µm particle size, mobile phase: Heptane/EtOH/FA 90/10/0.1, flow rate 18 mL/min) to yield (2R,4S)-methyl 2-benzyl-2,3,4,5,6-d_5-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (502 mg, 40 %), Chiral purity 98.9 %ee, Optical rotation $[\alpha]_D^{20} = +23.7$ (acetonitrile, c=1) and (2S,4R)-methyl 2-benzyl-2,3,4,5,6-d_5-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (512 mg, 41 %), Chiral purity 99.1 %ee, Optical rotation $[\alpha]_D^{20} = -22.2$ (acetonitrile, c=1).

Step 4: 5-((2R,4S)-2-Benzyl-2,3,4,5,6-d_5-piperidin-4-yl)isoxazol-3(2H)-one

(2R,4S)-Methyl 2-benzyl-2,3,4,5,6-d_5-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.502 g, 1.56 mmol) was dissolved in hydrogen bromide (33 % in AcOH, 10 mL, 142.75 mmol) and stirred at room temperature for 20h, then solvents evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2R,4S)-2-benzyl-2,3,4,5,6-d_5-piperidin-4-yl)isoxazol-3(2H)-one. HRMS Calculated for $[C_{15}H_{13}D_5N_2O_2+H]^+$: 264.1760. Found: 264.1751

Example 150

5-((2S,4R)-2-Benzyl-2,3,4,5,6-d_5-piperidin-4-yl)isoxazol-3(2H)-one

(2S,4R)-Methyl 2-benzyl-2,3,4,5,6-d_5-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.512 g, 1.59 mmol) (from example 149, step 3) was dissolved in hydrogen bromide (33% in acetic acid, 10 mL, 142.75 mmol) and stirred at room temperature for 20 h, then solvents evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-((2S,4R)-2-benzyl-2,3,4,5,6-d_5-piperidin-4-

yl)isoxazol-3(2H)-one. HRMS Calculated for $[C_{15}H_{13}D_5N_2O_2+H]^+$: 264.1760. Found: 264.1749

Example 151

5-(Trans-2-benzyl-2,3,4,5,6-d_5-piperidin-4-yl)isoxazol-3(2H)-one

Step 1: Trans-methyl 2-benzyl-2,3,4,5,6-d_5-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate

Trans-methyl 2-benzyl-2,3,4,5,6-d_5-4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (1.15 g, 3.26 mmol) (from example 149, step 1) was dissolved in MeOH (20 mL) and cooled to -40C. Sodium hydroxide (0.131 g, 3.26 mmol) dissolved in water (2 mL) was added over 1 min and the resulting solution was stirred at -40°C for 20 min. Hydroxylamine (50 % by weight in water, 0.208 mL, 3.39 mmol) was added over 1 min and stirring continued at -50 to -40°C for 1h. The reaction mixture was then transferred into a prewarmed (80°C) solution of 6 M hydrogen chloride (30 mL, 180.00 mmol) and the mixture was continued to be stirred at 80°C for 40 min. Then cooled to room temperature. Methanol was evaporated, then water was added. Extracted three times with DCM. Combined organic layers dried over $MgSO_4$ and evaporated to yield crude cis-methyl 2-benzyl-2,3,4,5,6-d_5-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (1.06 g, 101 %) as an orange foam. MS m/z 322 $(M+H)^+$

Step 2: 5-(Trans-2-benzyl-2,3,4,5,6-d_5-piperidin-4-yl)isoxazol-3(2H)-one

Cis-methyl 2-benzyl-2,3,4,5,6-d_5-4-(3-oxo-2,3-dihydroisoxazol-5-yl)piperidine-1-carboxylate (0.204 g, 0.63 mmol) was dissolved in hydrogen bromide (33% in acetic acid, 6 mL, 34.26 mmol) and stirred at room temperature for 20 h, then solvents evaporated and the residue purified by preparative HPLC (Instrument: FractionLynx II, Mobilphase: gradient 5-95% MeCN in 0.2% NH_3, pH 10, Column: Xbridge Prep C18 5µm OBD 19*150 mm) to yield 5-(trans-2-benzyl-2,3,4,5,6-d_5-piperidin-4-yl)isoxazol-3(2H)-one (29 mg, 23 %). HRMS Calculated for $[C_{15}H_{13}D_5N_2O_2+H]^+$: 264.1760. Found: 264.1747

General procedures for the preparation of crystalline forms of the examples

Method A – neutral form

The substance is slurried in water at room temperature over a prolonged period, then collected by filtration.

Method B – neutral form

The substance is slurried in a mixture of methanol and dichloromethane. The solvents are allowed to evaporate slowly.

Method C – HCl salt

The substance is dissolved in 1 M HCl at room temperature. The formed HCl salt is collected by filtration.

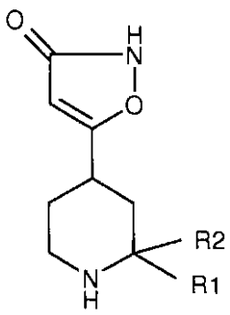
Method D – HCl salt

The substance is dissolved in 1.25 M HCl in methanol. The solvent is allowed to evaporate slowly.

Crystal forms of examples 14 and 104 were prepared according to method A. Crystal forms of examples 55, 65, 115 and 143 were prepared according to method B. Crystal forms of HCl salts of examples 14 and 104 were prepared according to method C. Crystal forms of HCl salts of examples 10, 18, 55, 65 and 143 were prepared according to method D.

Claims

1. A compound of formula I:



I

or a pharmaceutically suitable salt thereof, wherein,

R1 and R2 independently are hydrogen, deuterium, aryl, hetero aryl, C1-C8 alkyl, optionally being substituted with one or more substituents independently being R3,

R3 is an aryl, hetero aryl, fluorine(s), a C1-C6 alkyl containing one or more fluorine, a C1-C6 alkyl containing one or more deuterium, a C1-C6 alkyl containing hydroxy, the aryl and heteroaryl optionally being substituted with one or more halogen, a fluorinated alkoxy, a fluorinated alkyl, a sulfonyl, one or more deuterium, a C1-6 alkyl, a C1-6 alkoxy, a nitrile,

or R3 is a C1-6 alkyl optionally substituted with one or more of the following groups: COOR4, OCOR4, CONR5R6, NR5COR6, OR4;

wherein, R4 is a C1-10 alkyl optionally substituted with one or more fluorine, deuterium, alkoxy, arylcarboxylate, alkyl carboxylate ;

R5 and R6 are independently selected from hydrogen, alkyl or they may together form a 4-8 membered carbon ring;

or R1 and R2 form a 3-10 membered carbon ring optionally comprising O or N and optionally substituted with a C1-10 alkyl or aryl, hetero aryl optionally substituted with R3.

2. A compound according to claim 1,or a pharmaceutically suitable salt thereof, wherein,

R1 and R2 independently are hydrogen, deuterium, hetero aryl, C1-C8 alkyl, optionally being substituted with one or more substituents independently being R3,

R3 is an aryl, hetero aryl, fluorine(s), a C1-C6 alkyl containing one or more fluorine, a C1-C6 alkyl containing one or more deuterium, a C1-C6 alkyl containing hydroxy, the aryl and heteroaryl optionally being substituted with one or more halogen, a fluorinated alkoxy, a fluorinated alkyl, a sulfonyl, one or more deuterium, a C1-6 alkyl, a C1-6 alkoxy, a nitrile,

or R3 is a C1-6 alkyl optionally substituted with one or more of the following groups: COOR4, OCOR4, CONR5R6, NR5COR6, OR4;

wherein, R4 is a C1-10 alkyl optionally substituted with one or more fluorine, deuterium, alkoxy, arylcarboxylate, alkyl carboxylate ;

R5 and R6 are independently selected from hydrogen, alkyl or they may together form a 4-8 membered carbon ring;

or R1 and R2 form a 3-10 membered carbon ring optionally comprising O or N and optionally substituted with a C1-10 alkyl or aryl, hetero aryl optionally substituted with R3.

3. A compound according to claim 1 selected from one or more of the following compounds:
5-((2S,4S)-2-Benzylpiperidin-4-yl)isoxazol-3(2H)-one;
5-((2R,4R)-2-Benzylpiperidin-4-yl)isoxazol-3(2H)-one;
5-((2R,4S)-2-Benzylpiperidin-4-yl)isoxazol-3(2H)-one;
5-((2S,4R)-2-Benzylpiperidin-4-yl)isoxazol-3(2H)-one;
5-((2R,4S)-2-Isobutylpiperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-Isobutylpiperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4S)-2-Isobutylpiperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-Phenethylpiperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-Phenethylpiperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4S)-2-Phenethylpiperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4S)-2-(4-tert-Butylbenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(4-tert-Butylbenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4S)-2-Neopentylpiperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-Neopentylpiperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-Methylpiperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-Methylpiperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4S)-2-Methylpiperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4S)-2-(2-Methyl-2-phenylpropyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(2-Methyl-2-phenylpropyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(Cyclohexylmethyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4R)-2-(Cyclohexylmethyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4S)-2-(Cyclohexylmethyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(3,4-Difluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(3,4-difluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(4-Fluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(4-fluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(4-Chlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(4-Chlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(4-chlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(3-(Trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(3-(Trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(3-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(4-(Trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(4-(Trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(3-tert-Butylphenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(4-tert-butylphenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(4-(Methylsulfonyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((Trans-2-(4-(methylsulfonyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(6-(Trifluoromethyl)pyridin-3-yl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(6-(trifluoromethyl)pyridin-3-yl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(5-tert-Butylthiophen-2-yl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(5-tert-Butylthiophen-2-yl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(2,4-Difluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(4-Chloro-2-fluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(4-chloro-2-fluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(2-Chloro-4-fluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(2-chloro-4-fluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(4-Chloro-3-fluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(4-chloro-3-fluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(2,4-Dichlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(2,4-Dichlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4S)-2-(2,4-Dichlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4R)-2-(2,4-Dichlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(3,5-Dichlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(3,5-Dichlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(3,5-dichlorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(2-Fluoro-4-(trifluoromethoxy)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(2-fluoro-4-(trifluoromethoxy)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(3,4,5-Trifluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(3,4,5-Trifluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(3,4,5-trifluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(2,4,5-Trifluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4S)-2-(2,4,5-Trifluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(4-Chloro-3,5-difluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(4-chloro-3,5-difluorophenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(3-Methyl-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(3-Methyl-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(3-methyl-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(3,5-Difluoro-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(3,5-difluoro-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(2-Methyl-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(2-Fluoro-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(2-fluoro-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(3-fluoro-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(3-Fluoro-4-(trifluoromethyl)phenyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-phenylpiperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4S)-2-phenylpiperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-Cyclohexylpiperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4S)-2-Cyclohexylpiperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(2-Methyl-2H-tetrazol-5-yl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(2-methyl-2H-tetrazol-5-yl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(1-Methyl-1H-tetrazol-5-yl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(Cyclohexyloxymethyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(Cyclohexyloxymethyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(cyclohexyloxymethyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(Difluoromethyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(difluoromethyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4S)-2-((4,4-Difluorocyclohexyl)methyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4R)-2-((4,4-Difluorocyclohexyl)methyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-((4,4-difluorocyclohexyl)methyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4S)-2-(4-Fluorophenethyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4R)-2-(4-Fluorophenethyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(4-fluorophenethyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4S)-2-(3,3-Dimethylbutyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(3,3-Dimethylbutyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(4-Fluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4S)-2-(4-Fluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(3-Fluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4S)-2-(3-Fluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(2-Fluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4S)-2-(2-Fluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4R)-2-(2-Fluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(4-(Trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4S)-2-(4-(Trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4R)-2-(4-(Trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(3-(Trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(3-(Trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(3-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(2-(Trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(2-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(2-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(4-(Trifluoromethoxy)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(4-Chlorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(4-chlorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(4-(Methylsulfonyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(4-(Methylsulfonyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(4-(methylsulfonyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(3,4-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(3,4-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4S)-2-(3,4-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4R)-2-(3,4-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(2,5-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(2,5-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(2,5-difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(2,6-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(2,6-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(2,6-difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(3,5-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(3,5-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4S)-2-(3,5-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4R)-2-(3,5-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(2,4-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(2,4-Difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(2,4-difluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(3-Fluoro-5-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(3-Fluoro-5-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(3-fluoro-5-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(3-Fluoro-4-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(3-Fluoro-4-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(3-fluoro-4-(trifluoromethyl)benzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(3,4,5-Trifluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(3,4,5-Trifluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(3,4,5-trifluorobenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-(3,5-Di-tert-butylbenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-(3,5-Di-tert-butylbenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-(3,5-di-tert-butylbenzyl)piperidin-4-yl)isoxazol-3(2H)-one;

5-((2R,4S)-2-Benzyl-2,3,4,5,6-d_5-piperidin-4-yl)isoxazol-3(2H)-one;

5-((2S,4R)-2-Benzyl-2,3,4,5,6-d_5-piperidin-4-yl)isoxazol-3(2H)-one;

5-(Trans-2-benzyl-2,3,4,5,6-d_5-piperidin-4-yl)isoxazol-3(2H)-one.

4. A pharmaceutical composition comprising at least one compound according any of to claims 1-3 and a pharmaceutically acceptable carrier or diluent.

5. A method for treatment or prophylaxis of a disease or condition in which modulation of fibrinolysisis is beneficial comprising administering to a warm-blooded animal in need of such treatment a therapeutically effective amount of at least one compound in accordance with any of claims 1-3.

6. The method according to claim 5, wherein said disease or condition is selected from inherited bleeding disorders, stroke, menorrhagia and liver diseases.

7. The use of a compound according to any of claims 1-3 for the treatment or prophylaxis of a disease or condition in which modulation of fibrinolysis is beneficial.

8. The use according to claim 7, wherein said disease or condition is selected from inherited bleeding disorders, stroke, menorrhagia and liver diseases.

9. The use of a compound according to any of claims 1-3 in the manufacture of a medicament for the treatment or prophylaxis of a disease or condition in which modulation of fibrinolysis is beneficial.

10. The use according to claim 9, wherein said disease is selected from inherited bleeding disorders, stroke, menorrhagia and liver diseases.

Figure 1: XRPD pattern for example 55

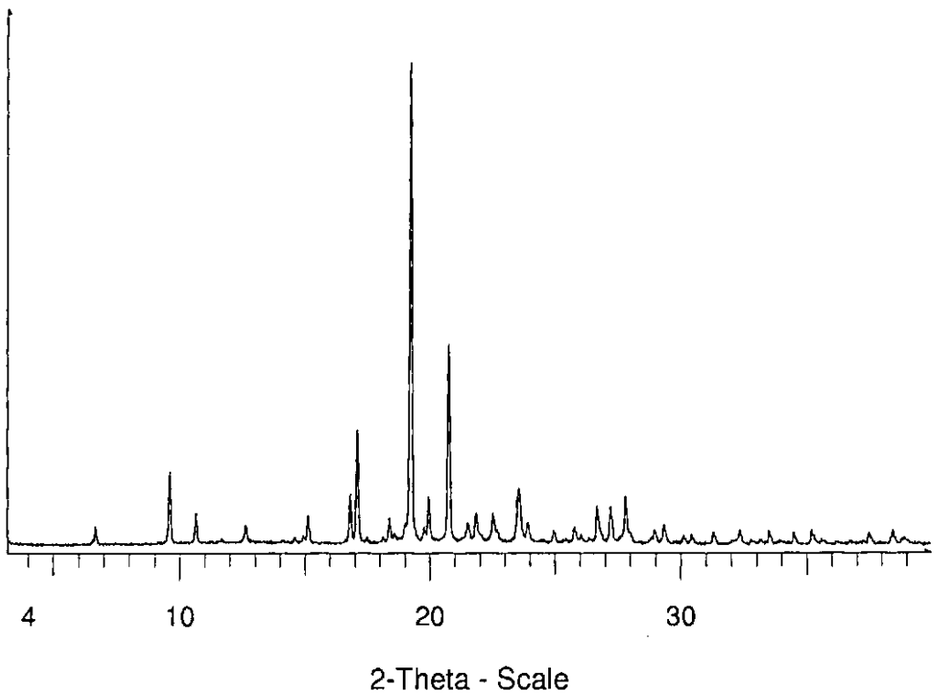


Figure 2: XRPD pattern for example 55 HCl salt

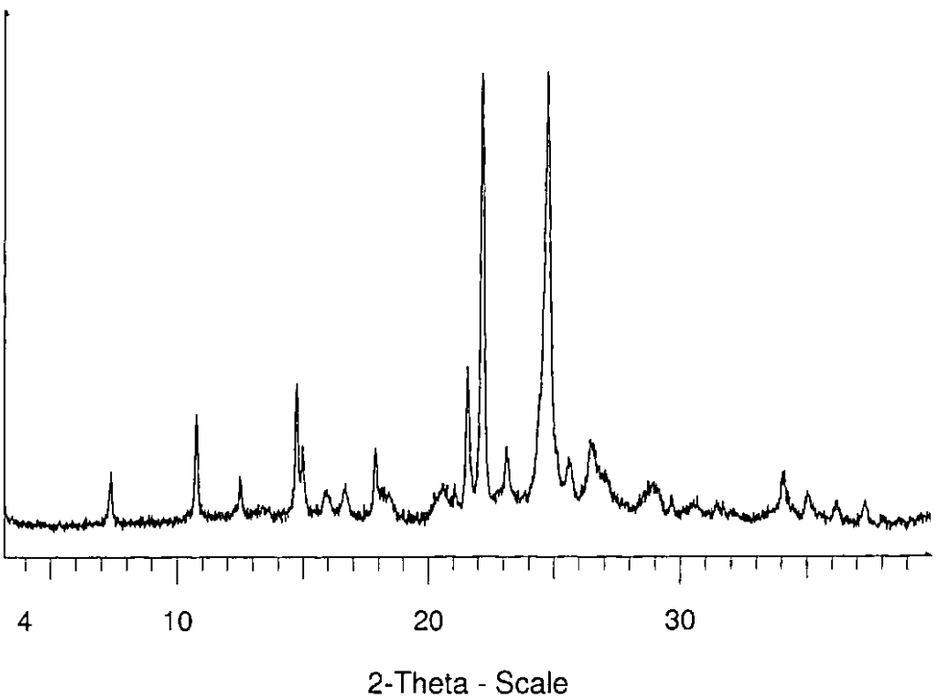


Figure 3: XRPD pattern for example 143

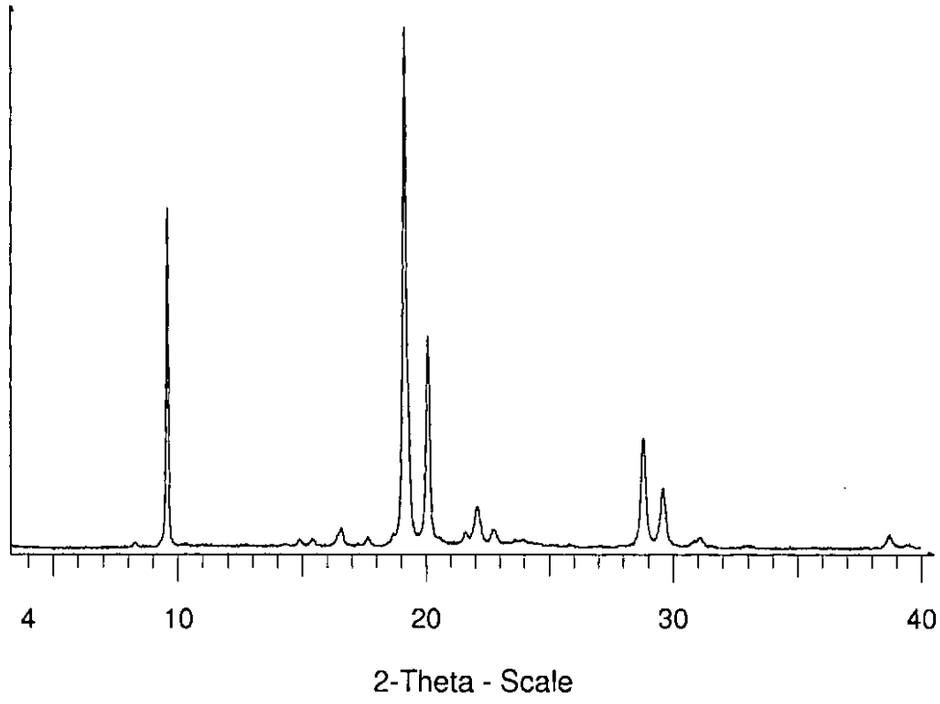


Figure 4: XRPD pattern for example 143 HCl salt

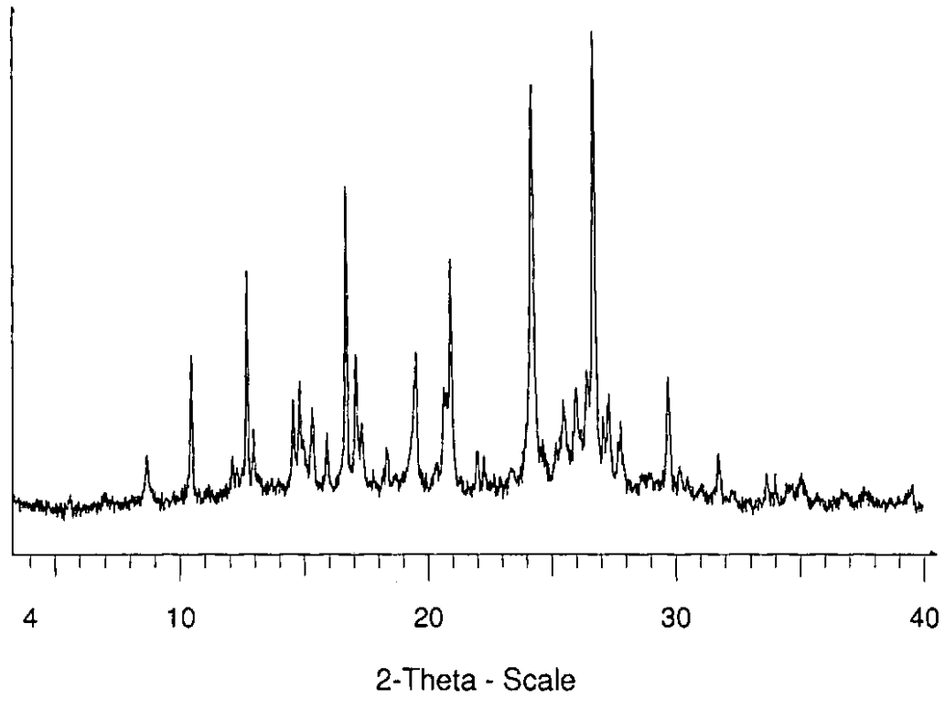


Figure 5: XRPD pattern for example 104

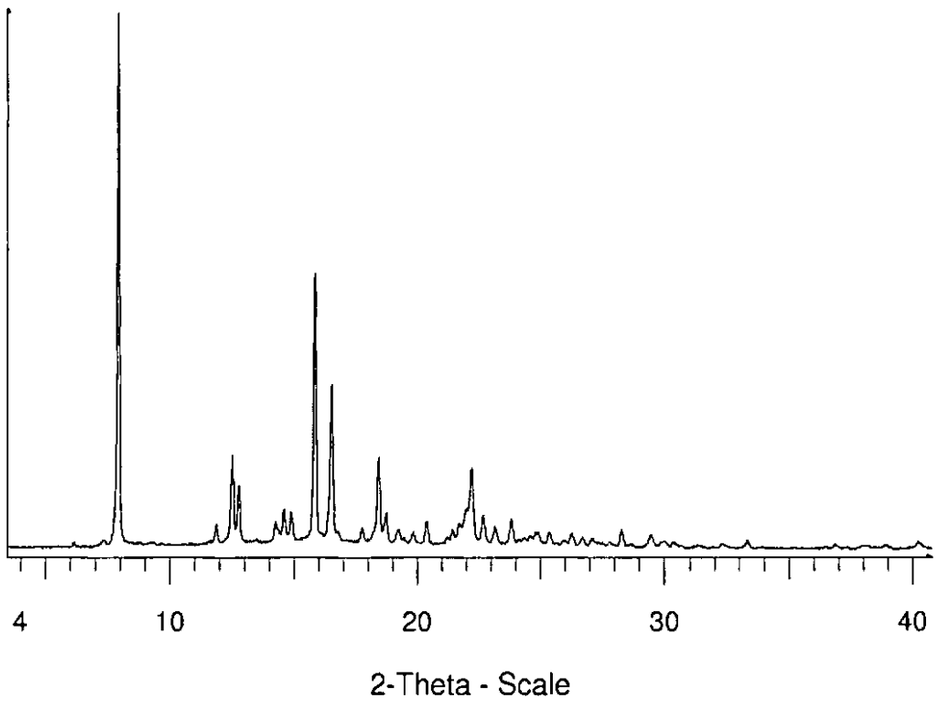


Figure 6: XRPD pattern for example 104 HCl salt

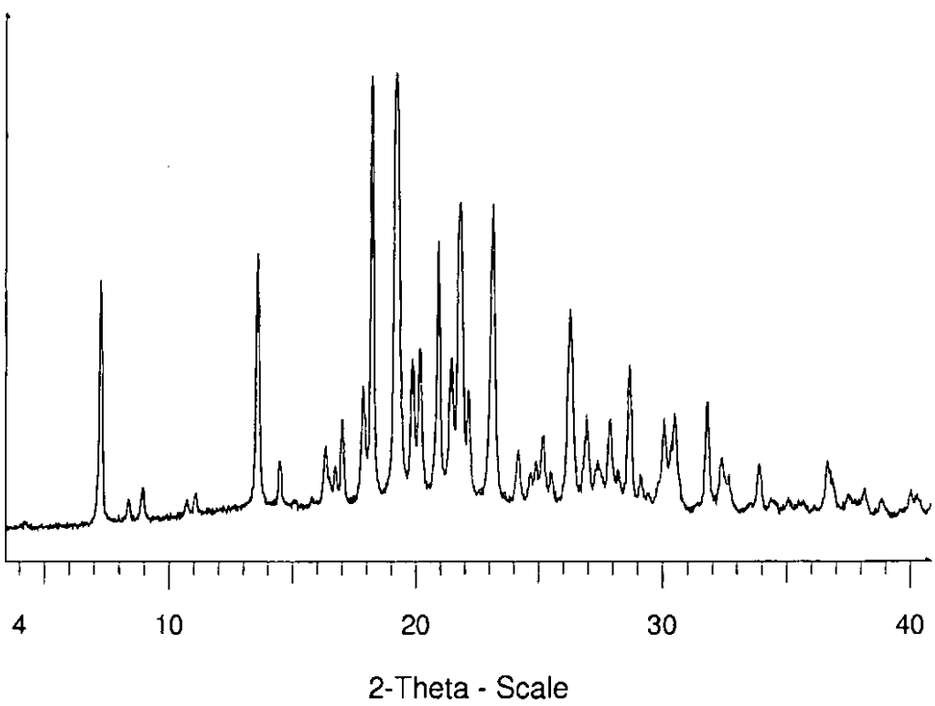


Figure 7: XRPD pattern for example 65

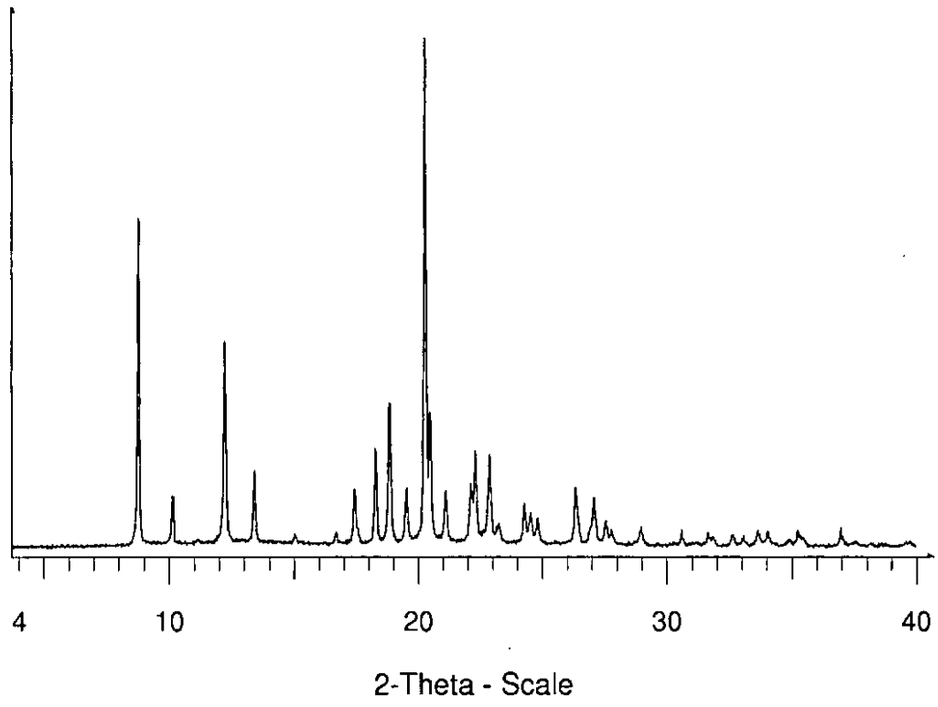


Figure 8: XRPD pattern for example 65 HCl salt

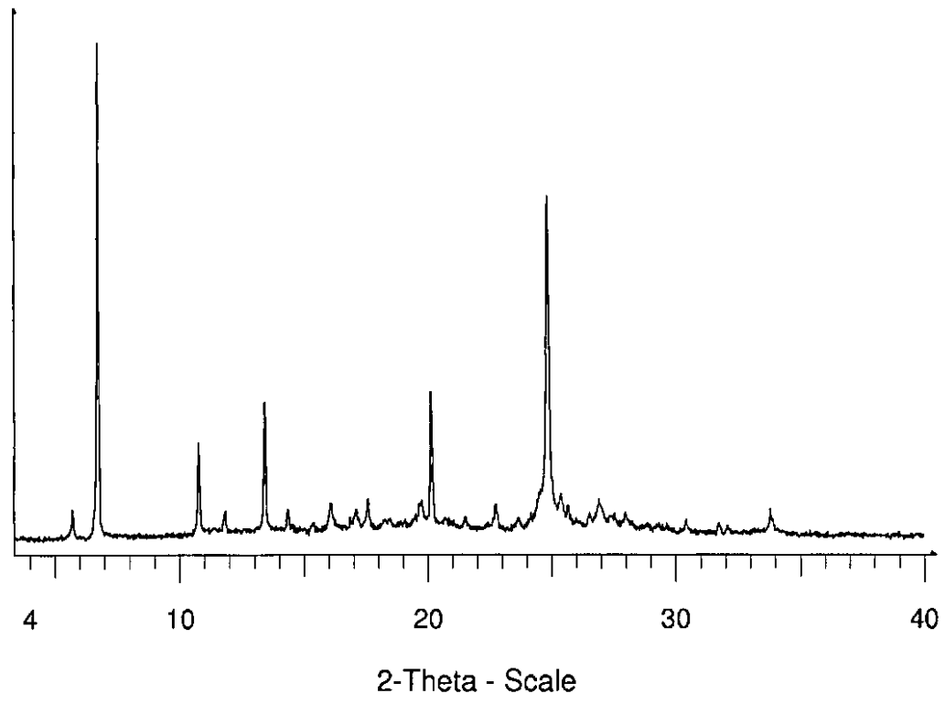


Figure 9: XRPD pattern for example 14

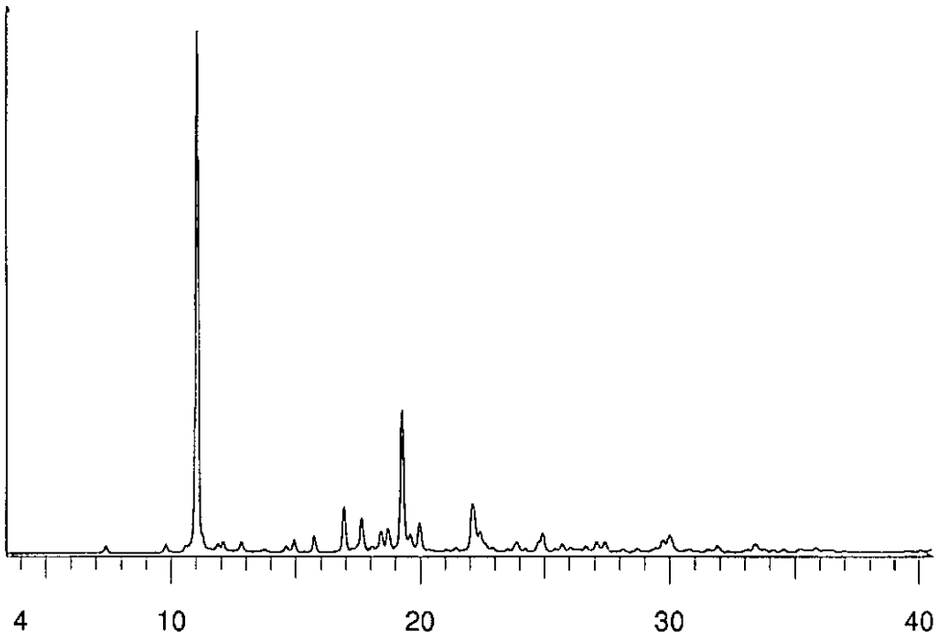


Figure 10: XRPD pattern for example 14 HCl salt

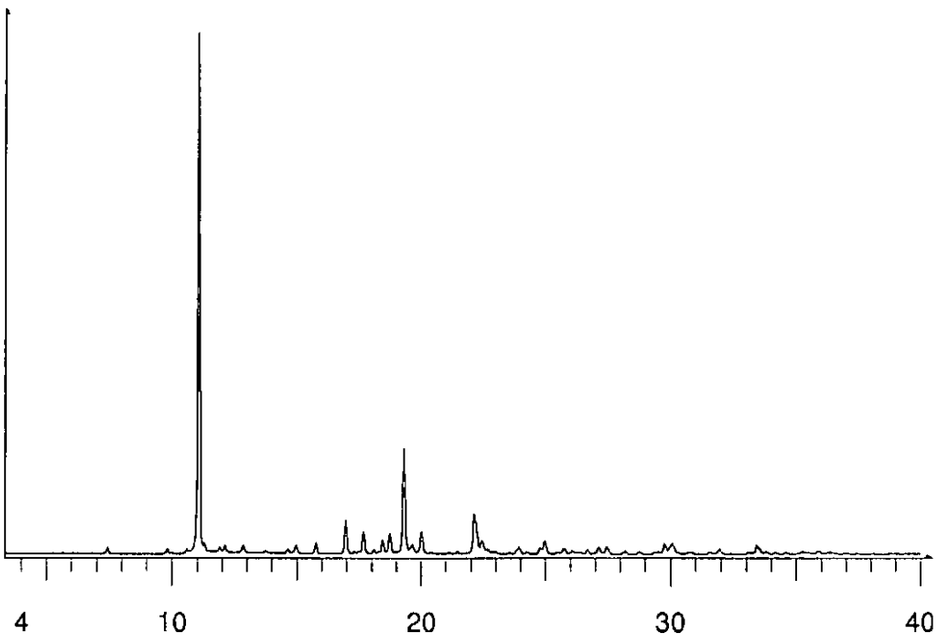


Figure 11: XRPD pattern for example 18 HCl salt

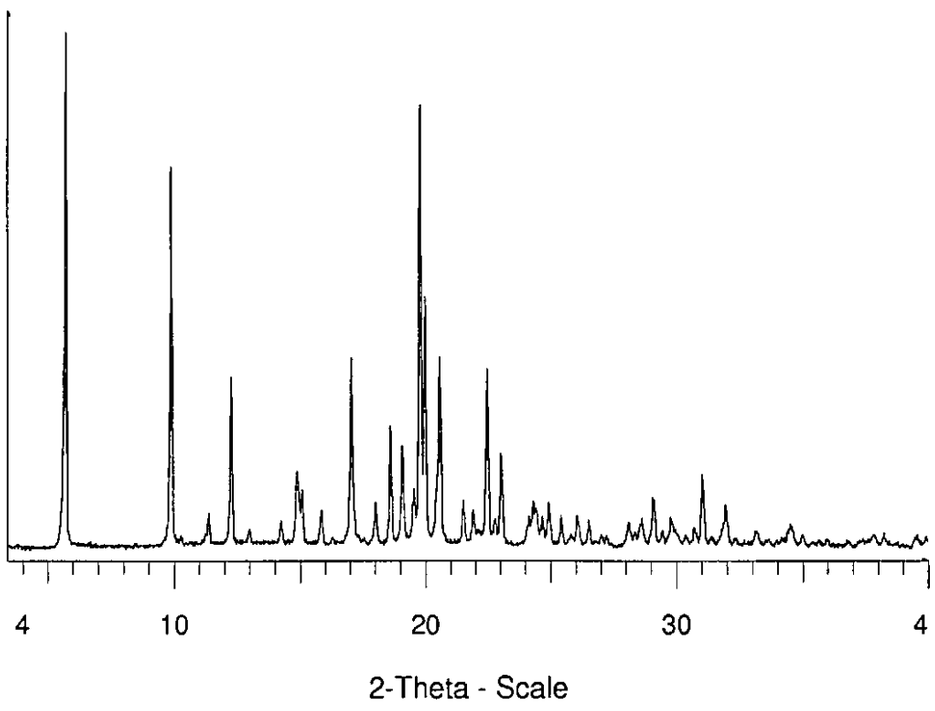


Figure 12: XRPD pattern for example 115

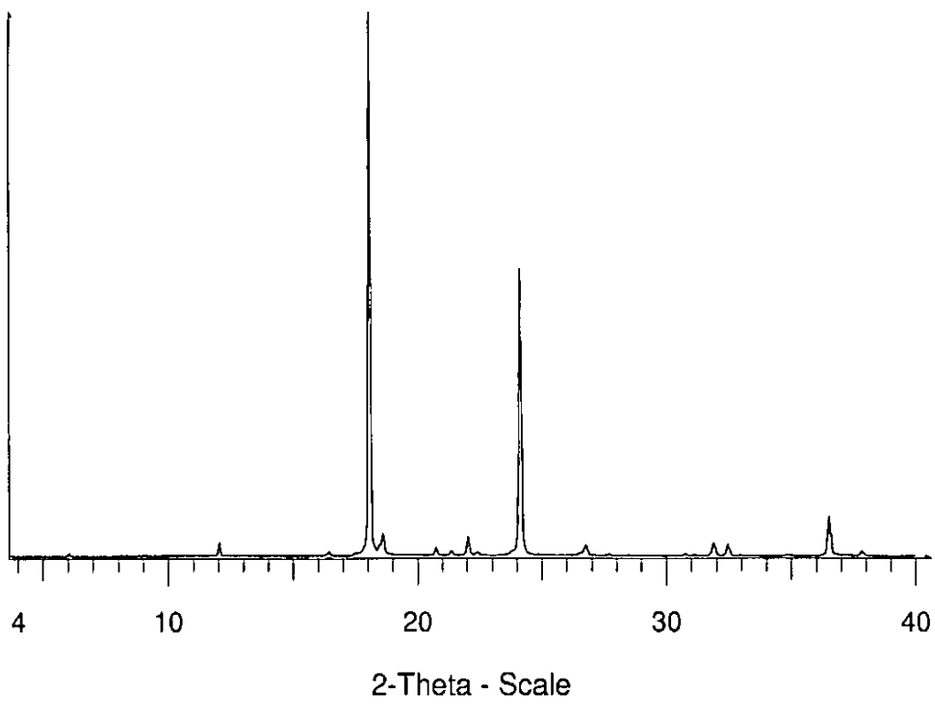
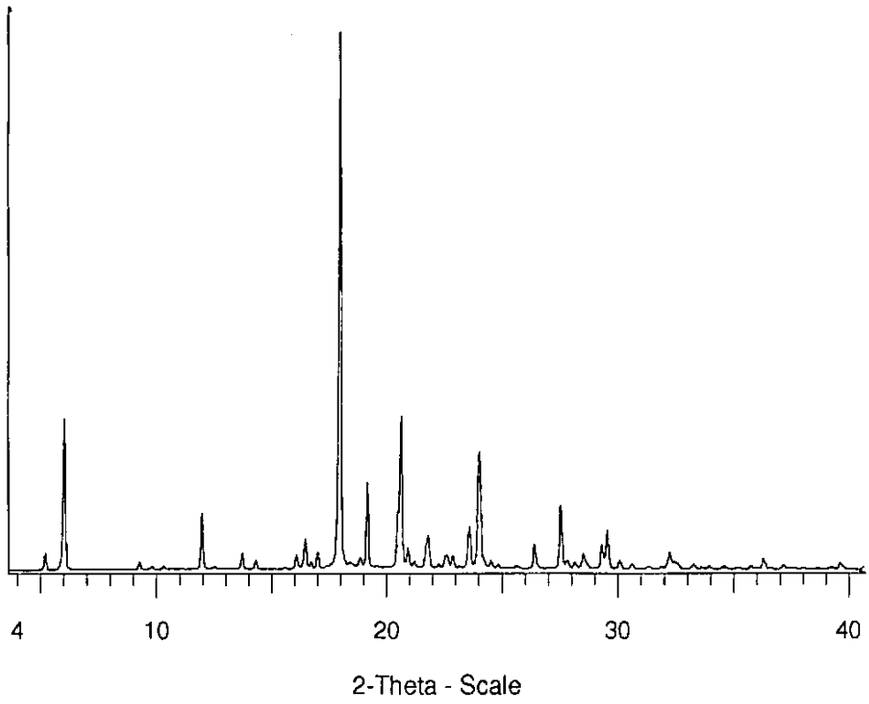


Figure 13: XRPD pattern for example 10 HCl salt



INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2010/050375

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet

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)

IPC:A61K, A61P, C07D

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

SE, DK, FI, NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, PAJ, WPI data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 20080081803 A1 (MERCK AND CO), 3 April 2008 (2008-04-03); page 50, paragraph [0602] - page 50, paragraph [0602]; Intermediate 44	1-2
A	WO 9514683 A1 (THE DU PONT MERCK PHARMACEUTICAL COMPANY), 1 June 1995 (1995-06-01); claims 1-10	1-10
X	3(2H)-Isoxazolone, 5-(4-piperidinyl)-, bromide (1:1), Retrieved from: STN International File Registry; CHEMCATS, RN 884230-75-5	1-2

☐ 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 application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
05-07-2010	06-07-2010

Name and mailing address of the ISA/SE	Authorized officer
Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. + 46 8 666 02 86	Carolina Gomez Lagerlöf Telephone No. + 46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2010/050375

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.: 5-6
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 5-6 relate to a method for treatment of the human or animal body by surgery or by therapy, as well as diagnostic methods, see PCT rule 39.1(iv). Nevertheless, a search has been made for these claims. The search has been directed to the technical content of the claims.

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:

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 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.:

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.

Continuation of: second sheet

International Patent Classification (IPC)

C07D 413/04 (2006.01)
A61K 31/4523 (2006.01)
A61P 7/04 (2006.01)

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Use the application number as username. The password is **YZUZRBXLRO**.

Paper copies can be ordered at a cost of 50 SEK per copy from PRV InterPat (telephone number 08-782 28 85).

Cited literature, if any, will be enclosed in paper form.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/SE2010/050375

US	20080081803	A1	03/04/2008	US	7598243	B2	06/10/2009
WO	9514683	A1	01/06/1995	AT	198748	T	15/02/2001
				AU	1098095	A	13/06/1995
				AU	695853	B2	27/08/1998
				BR	9408137	A	12/08/1997
				CA	2174838	A1	01/06/1995
				CZ	9601419	A3	13/11/1996
				DE	69426604	D1	22/02/2001
				DK	730590	T3	19/03/2001
				EP	0730590	B1	17/01/2001
				ES	2154326	T3	01/04/2001
				FI	962184	A	23/05/1996
				GR	3035610	T3	29/06/2001
				HR	940952	A2	30/04/1997
				HU	74690	A2	28/01/1997
				IL	111721	A	01/06/2000
				JP	9505590	T	03/06/1997
				NO	309768	B1	26/03/2001
				NO	962096	A	23/05/1996
				NZ	276633	A	27/04/1998
				PL	314591	A1	16/09/1996
				PL	182303	B1	31/12/2001
				RU	2149871	C1	27/05/2000
				SK	66696	A3	06/11/1996
				TW	483895	B	21/04/2002
				US	5849736	A	15/12/1998

Análogos de isoxazol-3(2*H*)-ona como agentes terapéuticos

Campo de la invención

La presente invención se refiere a compuestos de fórmula I, a una composición farmacéutica que los comprende y a su uso en el tratamiento de enfermedades o afecciones relacionadas con la fibrinólisis, por ejemplo, trastornos hemorrágicos hereditarios, accidente cerebrovascular, menorragia y enfermedades hepáticas, y en el tratamiento del angioedema hereditario.

Antecedentes

La hemorragia es un problema clínico común en traumatismos, cirugía, trastornos hemorrágicos, accidente cerebrovascular, menorragia y enfermedades hepáticas. El tratamiento de la hemorragia incluye agentes en la hemostasia primaria y secundaria, así como también la inhibición de la fibrinólisis.

El sistema fibrinolítico comprende un zimógeno inactivo, el plasminógeno (PLG), que puede activarse para obtener la enzima activa plasmina (PLN). La PLN degrada la fibrina insoluble en fragmentos de fibrina solubles. El resultado de esta actividad es la disolución del coágulo de fibrina. La activación del plasminógeno a plasmina se produce en la superficie del coágulo después de unirse a la fibrina. Los mediadores de la activación son el activador de plasminógeno tipo uroquinasa (u-PA) o el activador tisular de plasminógeno (t-PA).

La activación del proceso fibrinolítico puede utilizarse para tratar afecciones trombóticas. Por el contrario, la inhibición de la fibrinólisis se puede utilizar, y de hecho se utiliza, para el tratamiento de afecciones hemorrágicas. Existen diversos objetivos posibles para la inhibición de la fibrinólisis. Algunos ejemplos son la activación del inhibidor del activador del plasminógeno 1 (PAI-1), la inhibición de la actividad de u-PA y/o t-PA, la inhibición de la actividad de PLN y la activación de la antiplasmina. La inhibición

específica de los sitios proteolíticos en tPA, uPA y PLN es difícil. Sin embargo, se ha demostrado que el control de la hemorragia a través de la inhibición de la unión entre la plasmina (o plasminógeno) y la fibrina mediante análogos de lisina representa un mecanismo de acción seguro y eficaz en humanos.

La inhibición de la fibrinólisis a través de un mimético de lisina es un concepto validado para reducir la pérdida de sangre sin aumentar el riesgo de complicaciones trombóticas, por ejemplo, después de una cirugía, en la menorragia, en la hemofilia y en la enfermedad de von Willebrand.

Los posibles usos de los compuestos son el bloqueo de la proteólisis inducida por plasmina como un patomecanismo universal de propagación del cáncer y enfermedades cardiovasculares, inflamatorias y muchas otras.

Los antifibrinolíticos también han sido utilizados con éxito para tratar el angioedema hereditario. En esta enfermedad, la piel o mucosa alrededor de la boca, garganta y lengua se inflama rápidamente. La inflamación puede ocurrir en otros lugares, como las extremidades o los genitales. Por razones que no son bien conocidas, los antifibrinolíticos se pueden utilizar como un tratamiento profiláctico o intensivo para el angioedema hereditario.

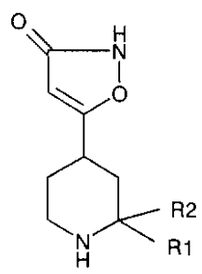
El ácido tranexámico, el compuesto que se encuentra actualmente en el mercado para tratar la menorragia, requiere dosis múltiples y muy elevadas, y tiene efectos secundarios gastrointestinales. Su uso se ha descrito en "Tranexamic acid. A review of its use in surgery and other indications"; Dunn, C.J.; Goa K.L.; Drugs 1999, junio 57(6): 1005-1032.

Objetivo de la invención

Un objetivo de la invención es proporcionar un compuesto farmacéutico para prevenir o tratar la hemorragia excesiva, presentando el tratamiento o la terapia preventiva una o más mejoras, tales como una eficacia, selectividad, permeabilidad y duración mejoradas, menos efectos secundarios y una biodisponibilidad mejorada.

Descripción de la invención:

La presente invención proporciona un compuesto de fórmula I:



I

o una sal farmacéuticamente aceptable de este, donde

R1 y R2 son independientemente hidrógeno, deuterio, arilo, heteroarilo, alquilo C1-C8, y están opcionalmente sustituidos con uno o más sustituyentes que son independientemente R3,

R3 es un arilo, heteroarilo, uno o más átomos de flúor, un alquilo C1-C6 que contiene uno o más átomos de flúor, un alquilo C1-C6 que contiene uno o más átomos de deuterio, un alquilo C1-C6 que contiene hidroxi, estando el arilo y el heteroarilo opcionalmente sustituidos con uno o más halógenos, un alcoxi fluorado, un alquilo fluorado, un sulfonilo, uno o más átomos de deuterio, un alquilo C1-C6, un alcoxi C1-C6, un nitrilo,

o R3 es un alquilo C1-C6 opcionalmente sustituido con uno o más de los siguientes grupos: COOR4, OCOR4, CONR5R6, NR5COR6, OR4;

donde R4 es un alquilo C1-C10 opcionalmente sustituido con uno o más átomos de flúor, deuterio, alcoxi, carboxilato de arilo, carboxilato de alquilo;

R5 y R6 se seleccionan independientemente entre hidrógeno, alquilo o pueden formar conjuntamente un anillo de carbono de 4-8 miembros;

o R1 y R2 forman un anillo de carbono de 3-10 miembros que comprende opcionalmente O o N y está opcionalmente sustituido

con un alquilo o arilo C1-C10, heteroarilo opcionalmente sustituido con R3.

De acuerdo con una realización de la invención, R1 y R2 pueden ser independientemente hidrógeno, deuterio, heteroarilo, alquilo C1-C8, y pueden estar opcionalmente sustituidos con uno o más sustituyentes que son independientemente R3,

R3 es un arilo, heteroarilo, uno o más átomos de flúor, un alquilo C1-C6 que contiene uno o más átomos de flúor, un alquilo C1-C6 que contiene uno o más átomos de deuterio, un alquilo C1-C6 que contiene hidroxi, estando el arilo y el heteroarilo opcionalmente sustituidos con uno o más halógenos, un alcoxi fluorado, un alquilo fluorado, un sulfonilo, uno o más átomos de deuterio, un alquilo C1-C6, un alcoxi C1-C6, un nitrilo,

o R3 es un alquilo C1-C6 opcionalmente sustituido con uno o más de los siguientes grupos: COOR4, OCOR4, CONR5R6, NR5COR6, OR4;

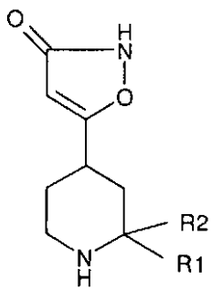
donde R4 es un alquilo C1-C10 opcionalmente sustituido con uno o más átomos de flúor, deuterio, alcoxi, carboxilato de arilo, carboxilato de alquilo;

R5 y R6 se seleccionan independientemente entre hidrógeno, alquilo o pueden formar conjuntamente un anillo de carbono de 4-8 miembros;

o R1 y R2 forman un anillo de carbono de 3-10 miembros que comprende opcionalmente O o N y está opcionalmente sustituido con un alquilo o arilo C1-C10, heteroarilo opcionalmente sustituido con R3.

La palabra alquilo incluye alquilos lineales, alquilos ramificados y alquilos formados por un anillo de 3-8 miembros. La palabra heteroarilo es una variante de un sistema de anillo de cinco o seis miembros con uno o más heteroátomos, es decir, que no sean C, seleccionados entre N, O o S.

De acuerdo con otro aspecto de la invención, se proporciona un compuesto de fórmula Ia:



Ia

o una sal farmacéuticamente aceptable de este, donde

R1 y R2 son independientemente hidrógeno, alquilo C1-C8, y están opcionalmente sustituidos con R3,

R3 es un arilo, estando el arilo opcionalmente sustituido con uno o más átomos de flúor, u OR4,

R4 es un alquilo C1-C6.

De acuerdo con otro aspecto de la invención, se proporciona un compuesto seleccionado entre uno o más de los siguientes compuestos:

5-((2*S*,4*S*)-2-Bencilpiperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*R*)-2-Bencilpiperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-Bencilpiperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-Bencilpiperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-Isobutilpiperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-Isobutilpiperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*S*)-2-Isobutilpiperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-Fenetilpiperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-Fenetilpiperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*S*)-2-Fenetilpiperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*S*)-2-(4-*tert*-Butilbencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(4-*tert*-Butilbencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*S*)-2-Neopentilpiperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-Neopentilpiperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-Metilpiperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-Metilpiperidin-4-il)isoxazol-3(2*H*)-ona;
5-((2*S*,4*S*)-2-Metilpiperidin-4-il)isoxazol-3(2*H*)-ona;
5-((2*S*,4*S*)-2-(2-Metil-2-fenilpropil)piperidin-4-il)isoxazol-3(2*H*)-ona;
5-((2*R*,4*S*)-2-(2-Metil-2-fenilpropil)piperidin-4-il)isoxazol-3(2*H*)-ona;
5-((2*R*,4*S*)-2-(Ciclohexilmetil)piperidin-4-il)isoxazol-3(2*H*)-ona;
5-((2*R*,4*R*)-2-(Ciclohexilmetil)piperidin-4-il)isoxazol-3(2*H*)-ona;
5-((2*S*,4*S*)-2-(Ciclohexilmetil)piperidin-4-il)isoxazol-3(2*H*)-ona;
5-((2*R*,4*S*)-2-(3,4-Difluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;
5-(*Trans*-2-(3,4-difluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;
5-((2*R*,4*S*)-2-(4-Fluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;
5-(*Trans*-2-(4-fluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;
5-((2*R*,4*S*)-2-(4-Clorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;
5-((2*S*,4*R*)-2-(4-Clorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;
5-(*Trans*-2-(4-clorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;
5-((2*R*,4*S*)-2-(3-(Trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;
5-((2*S*,4*R*)-2-(3-(Trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;
5-(*Trans*-2-(3-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;
5-((2*R*,4*S*)-2-(4-(Trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(4-(Trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(3-*tert*-Butilfenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(4-*tert*-butilfenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(4-(Metilsulfonil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((*Trans*-2-(4-(metilsulfonil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(6-(Trifluorometil)piridin-3-il)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(6-(trifluorometil)piridin-3-il)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(5-*tert*-Butiltiofen-2-il)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(5-*tert*-Butiltiofen-2-il)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(2,4-Difluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(4-Cloro-2-fluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(4-cloro-2-fluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(2-Cloro-4-fluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(2-cloro-4-fluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(4-Cloro-3-fluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(4-cloro-3-fluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(2,4-Diclorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(2,4-Diclorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*S*)-2-(2,4-Diclorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*R*)-2-(2,4-Diclorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(3,5-Diclorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(3,5-Diclorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(3,5-diclorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(2-Fluoro-4-(trifluorometoxi)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(2-fluoro-4-(trifluorometoxi)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(3,4,5-Trifluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(3,4,5-Trifluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(3,4,5-trifluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(2,4,5-Trifluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*S*)-2-(2,4,5-Trifluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(4-Cloro-3,5-difluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(4-cloro-3,5-difluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(3-Metil-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(3-Metil-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(3-metil-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(3,5-Difluoro-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(3,5-difluoro-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(2-Metil-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(2-Fluoro-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(2-fluoro-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(3-Fluoro-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(3-Fluoro-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-Fenilpiperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*S*)-2-Fenilpiperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-Ciclohexilpiperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*S*)-2-Ciclohexilpiperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(2-Metil-2*H*-tetrazol-5-il)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(2-metil-2*H*-tetrazol-5-il)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(1-Metil-1*H*-tetrazol-5-il)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(Ciclohexiloximetil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(Ciclohexiloximetil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(ciclohexiloximetil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(Difluorometil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(difluorometil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*S*)-2-((4,4-Difluorociclohexil)metil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*R*)-2-((4,4-Difluorociclohexil)metil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-((4,4-difluorociclohexil)metil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*S*)-2-(4-Fluorofenetil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*R*)-2-(4-Fluorofenetil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(4-fluorofenetil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*S*)-2-(3,3-Dimetilbutil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(3,3-Dimetilbutil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(4-Fluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*S*)-2-(4-Fluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(3-Fluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*S*)-2-(3-Fluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(2-Fluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*S*)-2-(2-Fluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*R*)-2-(2-Fluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(4-(Trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*S*)-2-(4-(Trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*R*)-2-(4-(Trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(3-(Trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(3-(Trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(3-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(2-(Trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(2-(Trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(2-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(4-(Trifluorometoxi)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(4-(trifluorometoxi)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(4-Clorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(4-clorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(4-(Metilsulfonil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(4-(Metilsulfonil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(4-(metilsulfonil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(3,4-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(3,4-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*S*)-2-(3,4-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*R*)-2-(3,4-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(2,5-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(2,5-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(2,5-difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(2,6-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(2,6-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(2,6-difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(3,5-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(3,5-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*S*)-2-(3,5-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*R*)-2-(3,5-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(2,4-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(2,4-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(2,4-difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(3-Fluoro-5-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(3-Fluoro-5-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(3-fluoro-5-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(3-Fluoro-4-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(3-Fluoro-4-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(3-fluoro-4-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(3,4,5-Trifluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(3,4,5-Trifluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(3,4,5-trifluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(3,5-Di-*tert*-butilbencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(3,5-Di-*tert*-butilbencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(3,5-di-*tert*-butilbencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-Bencil-2,3,4,5,6-d_5-piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-Bencil-2,3,4,5,6-d_5-piperidin-4-il)isoxazol-3(2*H*)-ona;

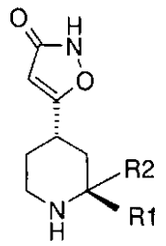
5-(*Trans*-2-bencil-2,3,4,5,6-d_5-piperidin-4-il)isoxazol-3(2*H*)-ona.

Los compuestos de fórmula I pueden presentarse en formas estereoisoméricas y/o tautoméricas. Se debe entender que todos los enantiómeros, diastereoisómeros, racematos, tautómeros y sus mezclas están incluidos dentro del alcance de la invención.

Los diferentes isómeros pueden tener diferente actividad biológica. Puede ocurrir que diferentes compuestos de fórmula general I muestren la actividad biológica más elevada con una

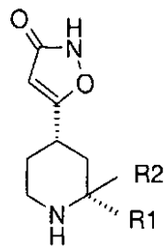
configuración diferente. Por ejemplo, puede suceder que la configuración (2*R*,4*S*) presente la actividad biológica más elevada para un compuesto, pero que para otro compuesto, la configuración (2*S*,4*S*) presente la actividad más elevada.

De acuerdo con un aspecto de la invención, se proporciona un compuesto de fórmula II con la siguiente configuración:



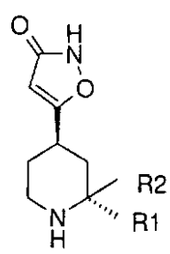
II

De acuerdo con un aspecto de la invención, se proporciona un compuesto de fórmula III con la siguiente configuración:



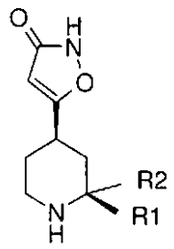
III

De acuerdo con un aspecto de la invención, se proporciona un compuesto de fórmula IV con la siguiente configuración:



IV

De acuerdo con un aspecto de la invención, se proporciona un compuesto de fórmula V con la siguiente configuración:



V

De acuerdo con otro aspecto de la invención, se proporciona una composición farmacéutica que comprende al menos un compuesto y un portador o diluyente farmacéuticamente aceptable.

De acuerdo con otro aspecto de la invención, se proporciona un método para el tratamiento o la profilaxis de una enfermedad o afección, tal como hemorragia intensa, trastornos hemorrágicos hereditarios o adquiridos, accidente cerebrovascular, menorragia y enfermedades hepáticas, en la cual la modulación de la fibrinólisis es beneficiosa, y para el tratamiento del angioedema hereditario, que comprende la administración de una cantidad terapéuticamente eficaz de al menos un compuesto de fórmula I a un animal de sangre caliente que necesite dicho tratamiento. Otras áreas de utilización del compuesto de acuerdo con la fórmula I son la curación de heridas, la reducción de pérdida de sangre en relación con una cirugía, incluida la cirugía dental, y el tratamiento de pacientes que están siendo tratados con anticoagulantes, por ejemplo, en la preparación para una cirugía. El compuesto también se puede utilizar para reducir la transfusión sanguínea necesaria en diferentes situaciones. El compuesto se puede utilizar adicionalmente en el tratamiento profiláctico de la

enfermedad de von Willebrand, la hemofilia o en el caso de pacientes anticoagulados.

De acuerdo con otro aspecto de la invención, se proporciona un método donde dicha enfermedad o afección se selecciona entre trastornos hemorrágicos hereditarios, accidente cerebrovascular, menorragia y enfermedades hepáticas.

De acuerdo con otro aspecto de la invención, se proporciona el tratamiento o la profilaxis de una enfermedad o afección en la cual la modulación de la fibrinólisis es beneficiosa.

De acuerdo con otro aspecto de la invención, se proporciona donde dicha enfermedad o afección se selecciona entre trastornos hemorrágicos hereditarios, accidente cerebrovascular, menorragia y enfermedades hepáticas.

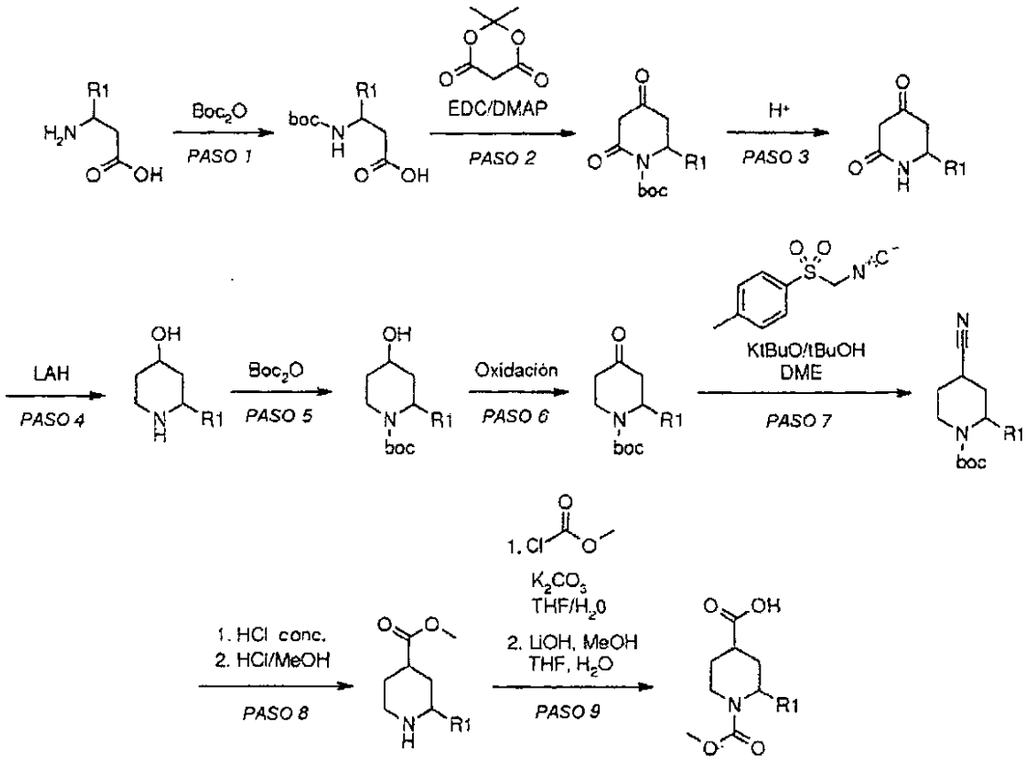
De acuerdo con otro aspecto de la invención, se proporciona el uso de un compuesto de acuerdo con la invención en la producción de un medicamento para el tratamiento o la profilaxis de una enfermedad o afección en la cual la modulación de la fibrinólisis es beneficiosa.

De acuerdo con otro aspecto de la invención, se proporciona el tratamiento o la profilaxis donde dicha enfermedad se selecciona entre trastornos hemorrágicos hereditarios, accidente cerebrovascular, menorragia y enfermedades hepáticas.

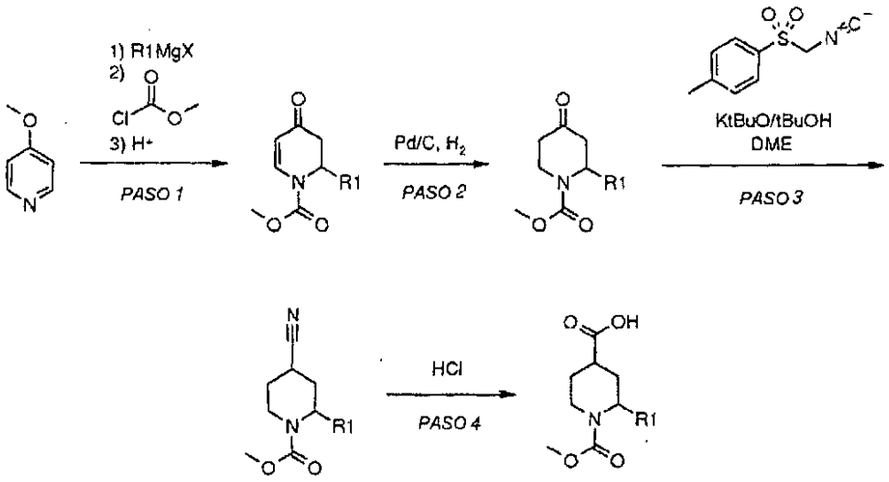
Los compuestos de fórmula I-V se pueden preparar mediante la siguiente ruta:

Esquema A. Preparación de los intermedios

MÉTODO A

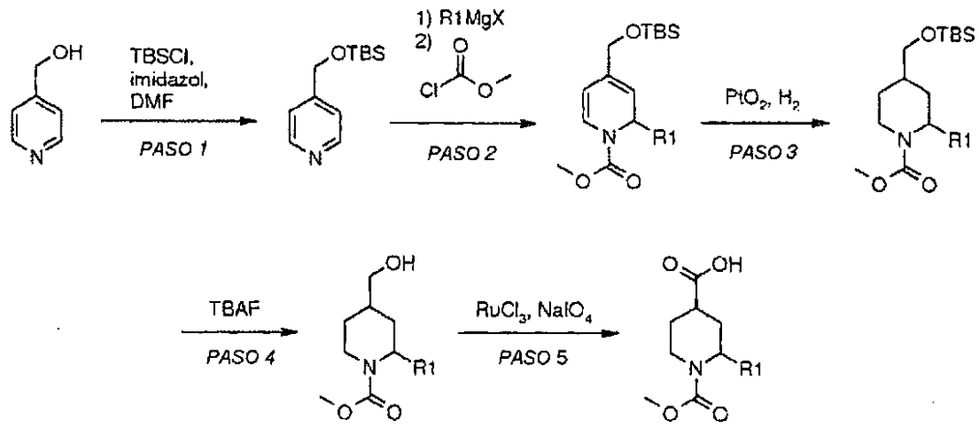


MÉTODO B

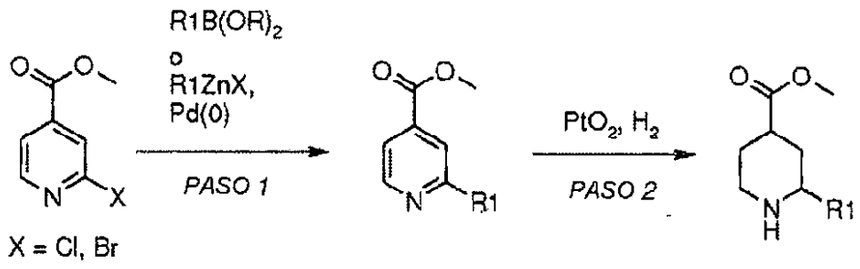


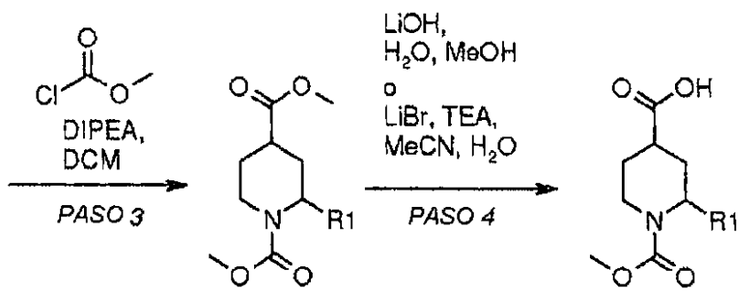
5

MÉTODO C

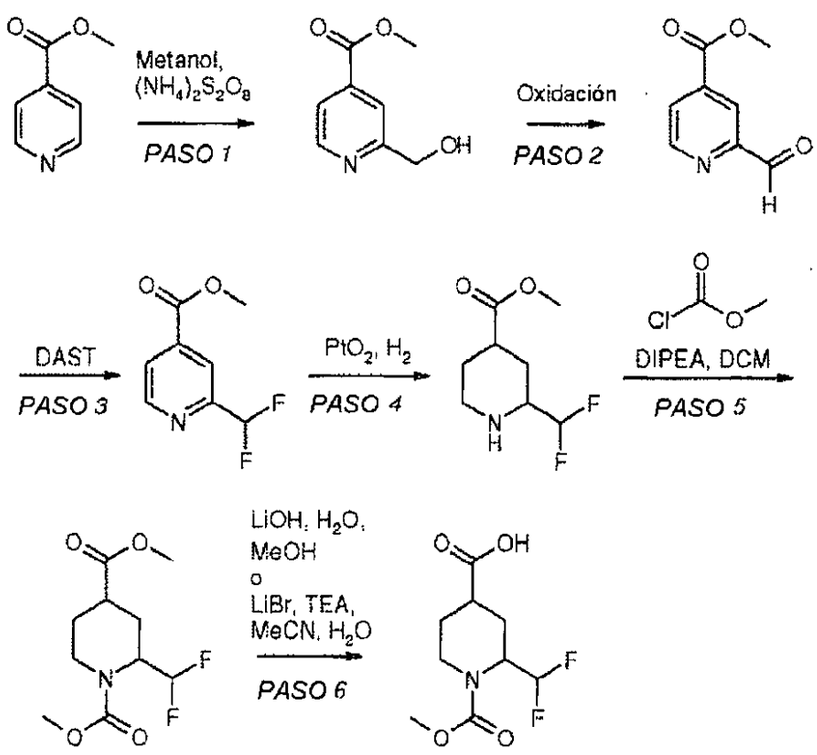


MÉTODO D

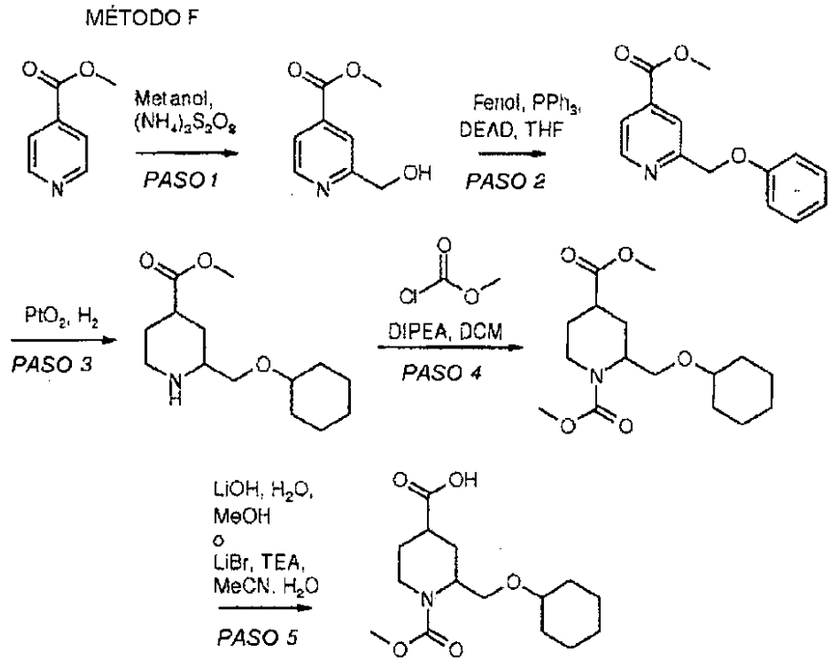




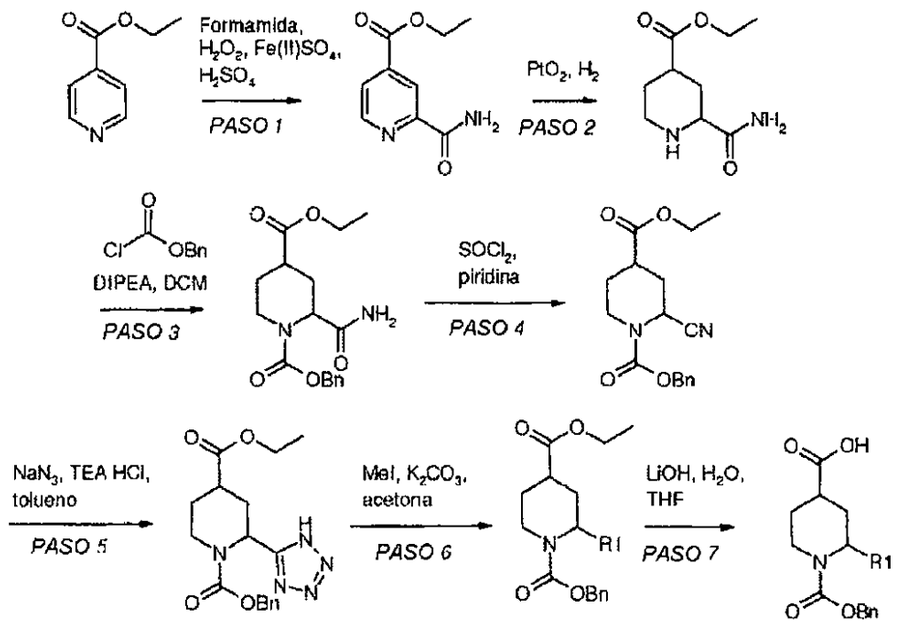
MÉTODO E



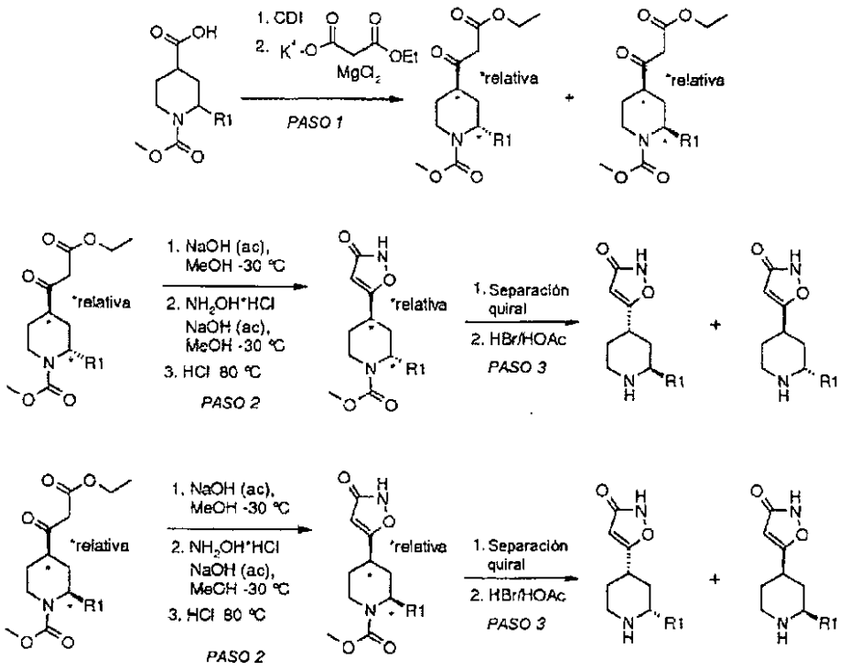
MÉTODO F



MÉTODO G


Formamida, H_2O_2, $Fe(II)SO_4$, H_2SO_4
PASO 1
PtO_2, H_2
PASO 2
Cl OBn
DIPEA, DCM
PASO 3
$SOCl_2$, piridina
PASO 4
NaN_3, TEA HCl, tolueno
PASO 5
MeI, K_2CO_3, acetona
PASO 6
LiOH, H_2O, THF
PASO 7
R1 = 1-metil-1H-tetrazol-5-ilo
y
2-metil-2H-tetrazol-5-ilo

Esquema B. Formación de 5-isoxazol-3-onas



NOTA: Las asignaciones estereoquímicas marcadas con asteriscos se deberán interpretar como definitivas para las configuraciones relativas de los átomos de carbono marcados, pero no como sus configuraciones absolutas, a menos que se indique expresamente de otro modo.

Será evidente para un experto en la materia que los procesos descritos anteriormente no son el único modo de producir los compuestos de acuerdo con la invención, sino que un experto en la materia podría cambiar el orden de las secuencias, las condiciones de reacción y otros parámetros adecuadamente. Algunos ejemplos de parámetros que se pueden modificar son el uso de diferentes disolventes, ácidos y bases, y diferentes temperaturas, entre otros parámetros, para proteger un grupo amina, hidroxilo u otros posibles grupos reactivos. Los grupos protectores adecuados y las condiciones de los procesos para introducir y eliminar dichos grupos son, en general, bien conocidos en la materia. Remítase, por ejemplo, a "Protective groups on Organic Synthesis", 3.ª edición (1999) de Greene y Wuts.

La resolución de los enantiómeros se puede llevar a cabo en cualquier etapa mediante el uso, por ejemplo, de separación en columna, mediante recristalización utilizando un ácido o una base quiral. La resolución también se puede llevar a cabo mediante una reacción enzimáticamente selectiva. Como alternativa, los enantiómeros se pueden sintetizar estereoespecíficamente.

Para los usos, métodos, medicamentos y composiciones mencionados en la presente, la cantidad utilizada del compuesto de fórmula I-V, o de sus sales o mezclas farmacéuticamente aceptables, y la dosis administrada pueden variar dependiendo del compuesto de fórmula I-V, o de sus sales o mezclas farmacéuticamente aceptables, utilizadas; y/o la vía de administración y/o tratamiento deseados. Sin embargo, en general, se obtienen resultados satisfactorios cuando se administra una dosis diaria de un compuesto de acuerdo con la fórmula I-V, o de sus sales o mezclas farmacéuticamente aceptables, de aproximadamente 0.1 mg a aproximadamente 400 mg/kg de peso corporal del animal. Dichas dosis se pueden administrar en dosis divididas de 1 a 4 veces al día o en una forma de liberación sostenida. Para el ser humano, la dosis total diaria puede variar, por ejemplo, de entre aproximadamente 5 mg y aproximadamente 7000 mg, y más particularmente de entre aproximadamente 10 mg y aproximadamente 1500 mg. Las formas farmacéuticas unitarias adecuadas para la administración oral generalmente comprenden, por ejemplo, de entre aproximadamente 2 mg y aproximadamente 1400 mg de al menos un compuesto de acuerdo con la fórmula I-V, o de sus sales o mezclas farmacéuticamente aceptables, en combinación con al menos un portador, lubricante y/o diluyente farmacéutico sólido y/o líquido.

El nivel de dosis y la frecuencia de dosis específicos para cualquier sujeto en particular, sin embargo, puede variar y generalmente depende de diversos factores, incluidos, sin carácter limitante, por ejemplo, la biodisponibilidad del o de los compuestos específicos de fórmula I-V, o de sus sales o

mezclas farmacéuticamente aceptables, en la forma administrada; la estabilidad metabólica y la duración de la acción del o los compuestos específicos de fórmula I-V, o de sus sales o mezclas farmacéuticamente aceptables; la especie, edad, peso corporal, estado de salud general, sexo y dieta del sujeto; la vía y el momento de la administración; la tasa de excreción; la combinación de fármacos; y la gravedad de la afección en particular.

El o los compuestos de acuerdo con la fórmula I-V, o sus sales o mezclas farmacéuticamente aceptables, se pueden administrar utilizando cualquier medio adecuado para la afección que se ha de tratar y la cantidad de compuesto de fórmula I-V, o de sus sales o mezclas farmacéuticamente aceptables, que ha de ser administrada.

El o los compuestos de acuerdo con la fórmula I-V, o sus sales o mezclas farmacéuticamente aceptables, se pueden administrar en forma de una composición farmacéutica convencional mediante cualquier vía, incluidas, sin carácter limitante, por ejemplo, la vía oral, intramuscular, subcutánea, tópica, intranasal, epidural, intraperitoneal, intratorácica, intravenosa, intratecal, intracerebroventricular, a través de un dispositivo intrauterino y mediante inyección en las articulaciones, mediante aplicación de un dispositivo tal como un parche o un tapón para el tratamiento tópico, tal como la hemorragia nasal.

En una realización, la vía de administración es oral, intravenosa, a través de un dispositivo intrauterino o intramuscular.

Un compuesto de fórmula I-V, o sus sales o mezclas farmacéuticamente aceptables, se pueden utilizar por sí solos o en forma de preparados medicinales apropiados para la administración enteral o parenteral.

Las composiciones farmacéuticas sólidas aceptables incluyen, sin carácter limitante, por ejemplo, polvos, comprimidos, gránulos dispersables, cápsulas, sellos y supositorios.

En una composición farmacéutica sólida, los portadores farmacéuticamente aceptables incluyen, pero no se limitan a, por ejemplo, al menos un sólido, al menos un líquido y mezclas de estos. El portador sólido también puede ser un diluyente, un saborizante, un solubilizante, un lubricante, un agente de suspensión, un aglutinante, un material encapsulante y/o un agente disgregante de comprimidos. Los portadores adecuados incluyen, sin carácter limitante, por ejemplo, carbonato de magnesio, estearato de magnesio, talco, lactosa, azúcar, pectina, dextrina, almidón, tragacanto, metilcelulosa, carboximetilcelulosa de sodio, cera con un punto de fusión bajo, manteca de cacao y mezclas de estos.

Se puede preparar un polvo, por ejemplo, mezclando un sólido finamente dividido con al menos un compuesto de fórmula I-V finamente dividido, o sus sales o mezclas farmacéuticamente aceptables.

Se puede preparar un comprimido, por ejemplo, mezclando al menos un compuesto de acuerdo con la fórmula I-V, o sus sales o mezclas farmacéuticamente aceptables, en proporciones adecuadas con un portador farmacéuticamente aceptable que tenga las propiedades aglutinantes necesarias y compactándolos para obtener la forma y el tamaño deseados.

Se puede preparar un supositorio, por ejemplo, mezclando al menos un compuesto de fórmula I-V, o sus sales o mezclas farmacéuticamente aceptables, con al menos un excipiente no irritante adecuado que sea líquido a temperatura rectal pero sólido a temperaturas inferiores a la temperatura rectal, donde primero se funde el excipiente no irritante y el compuesto de fórmula I se dispersa en él. La mezcla homogénea fundida se vierte posteriormente en moldes de tamaño conveniente, y se deja enfriar y solidificar. Los ejemplos de excipientes no irritantes incluyen, sin carácter limitante, por ejemplo, manteca de cacao, gelatina glicerinada, aceites vegetales hidrogenados, mezclas de polietilenglicoles de diferentes pesos moleculares y ésteres de ácidos grasos de polietilenglicol.

Las composiciones farmacéuticas líquidas aceptables incluyen, sin carácter limitante, por ejemplo, soluciones, suspensiones y emulsiones.

Los ejemplos de composiciones farmacéuticas líquidas adecuadas para la administración parenteral incluyen, sin carácter limitante, por ejemplo, soluciones estériles acuosas o propilenglicólicas acuosas de al menos un compuesto de acuerdo con la fórmula I-V, o de sus sales o mezclas farmacéuticamente aceptables; y soluciones polietilenglicólicas acuosas de al menos un compuesto de acuerdo con la fórmula I-V, o de sus sales o mezclas farmacéuticamente aceptables.

Las soluciones acuosas para administración oral se pueden preparar disolviendo al menos un compuesto de acuerdo con la fórmula I-V, o sus sales o mezlas farmacéuticamente aceptables, en agua y añadiendo colorantes, agentes saborizantes, estabilizadores y/o agentes espesantes adecuados según se desee.

Las suspensiones acuosas para administración oral se pueden preparar dispersando al menos un compuesto de fórmula I-V finamente dividido, o sus sales o mezclas farmacéuticamente aceptables, en agua junto con un material viscoso tal como, por ejemplo, una goma sintética natural, resina, metilcelulosa y carboximetilcelulosa de sodio.

En una realización, la composición farmacéutica contiene de aproximadamente un 0.05% a aproximadamente un 99% p (por ciento en peso) de al menos un compuesto de acuerdo con la fórmula I-V, o de sus sales o mezclas farmacéuticamente aceptables. Todos los porcentajes en peso están basados en la composición total.

En otra realización, la composición farmacéutica contiene de aproximadamente un 0.10% a aproximadamente un 50% p (por ciento en peso) de al menos un compuesto de acuerdo con la fórmula I-V, o de sus sales o mezclas farmacéuticamente aceptables. Todos los porcentajes en peso están basados en la composición total.

También se proporciona en la presente un proceso para preparar una composición farmacéutica, que comprende mezclar o combinar los ingredientes y dar forma de comprimidos o supositorios a los ingredientes mezclados; encapsular los ingredientes en cápsulas; o disolver los ingredientes para formar soluciones inyectables.

Se puede utilizar un compuesto de acuerdo con la presente invención combinado con otros agentes para tratar las afecciones descritas anteriormente. Algunos ejemplos de estos son los agentes antiinflamatorios no esteroideos, tales como los inhibidores de AINES y los tratamientos hormonales, tales como progesterona y/o estrógeno, agentes antiplaquetarios o anticoagulantes para evitar efectos secundarios, factores de coagulación tales como el factor VII y el factor VIII, el factor de von Willebrand.

Método de ensayo

El método de ensayo utilizado para la evaluación de la actividad biológica de los compuestos de acuerdo con la invención fue el ensayo de solución amortiguadora de lisis de coágulo.

Las mediciones de la inhibición de plasminógeno se llevaron a cabo en una mezcla de reacción de 200 µL que contenía 15 mM de HEPES, pH 7.4, 100 mM de NaCl, 0.008% de Tween-80, 13 µg/mL de Glu-plasminógeno humano (Chromogenix, Italia), 1.7 mg/mL de fibrinógeno humano (Aniara, EE. UU.), 0.02 nM de activador tisular de plasminógeno de cadena simple humano (Biopool, Suecia), 1% de DMSO y 0.05 NIH U/mL de trombina humana (Sigma, EE. UU.).

Las sustancias evaluadas se añadieron a la mezcla de reacción en un 10% de DMSO. La reacción se inició con la adición de trombina.

La formación y degradación de la fibrina se siguieron en un espectrofotómetro a 405 nm durante 15 h a 37 °C.

Actividad biológica

Se evaluó de acuerdo con el ensayo de solución amortiguadora de lisis de coágulo descrito anteriormente.

El Ejemplo 1 presentó un valor de CI_{50} de 2.85 µM. El Ejemplo 2 presentó un valor de CI_{50} de 169 µM. El Ejemplo 3 presentó un valor de CI_{50} de 1.16 µM. El Ejemplo 4 presentó un valor de CI_{50} de 150 µM. El Ejemplo 5 presentó un valor de CI_{50} de 2.86 µM. El Ejemplo 6 presentó un valor de CI_{50} de 47.5 µM. El Ejemplo 7 presentó un valor de CI_{50} de 2.62 µM. El Ejemplo 8 presentó un valor de CI_{50} de 2.36 µM. El Ejemplo 9 presentó un valor de CI_{50} de 16.5 µM. El Ejemplo 10 presentó un valor de CI_{50} de 1.46 µM. El Ejemplo 11 presentó un valor de CI_{50} de 4.3 µM. El Ejemplo 12 presentó un valor de CI_{50} de 2.25 µM. El Ejemplo 13 presentó un valor de CI_{50} de 1.28 µM. El Ejemplo 14 presentó un valor de CI_{50} de 1.15 µM. El Ejemplo 15 presentó un valor de CI_{50} de 5.2 µM. El Ejemplo 16 presentó un valor de CI_{50} de 56.2 µM. El Ejemplo 17 presentó un valor de CI_{50} de 4.65 µM. El Ejemplo 18 presentó un valor de CI_{50} de 1.6 µM. El Ejemplo 19 presentó un valor de CI_{50} de 1.6 µM. El Ejemplo 20 presentó un valor de CI_{50} de 5.1 µM. El Ejemplo 21 presentó un valor de CI_{50} de 107 µM. El Ejemplo 22 presentó un valor de CI_{50} de 1.2 µM. El Ejemplo 23 presentó un valor de CI_{50} de 1 µM. El Ejemplo 24 presentó un valor de CI_{50} de 42.8 µM. El Ejemplo 25 presentó un valor de CI_{50} de 2.5 µM. El Ejemplo 26 presentó un valor de CI_{50} de 73.8 µM. El Ejemplo 27 presentó un valor de CI_{50} de 1.5 µM. El Ejemplo 28 presentó un valor de CI_{50} de 283 µM. El Ejemplo 29 presentó un valor de CI_{50} de 24 µM. El Ejemplo 30 presentó un valor de CI_{50} de 0.7 µM. El Ejemplo 31 presentó un valor de CI_{50} de 33.1 µM. El Ejemplo 32 presentó un valor de CI_{50} de 23.6 µM. El Ejemplo 33 presentó un valor de CI_{50} de 1.43 µM. El Ejemplo 34 presentó un valor de CI_{50} de 150 µM. El Ejemplo 35 presentó un valor de CI_{50} de 14.4 µM. El Ejemplo 36 presentó un valor de CI_{50} de 1.9 µM. El Ejemplo 37 presentó un valor de CI_{50} de 228 µM. El Ejemplo 38 presentó un valor de CI_{50} de 1.5 µM. El Ejemplo 39 presentó un valor de CI_{50} de 97.3 µM. El Ejemplo 40 presentó un valor de CI_{50} de 1.5 µM. El Ejemplo 41 presentó un valor de CI_{50} de 40.9 µM. El Ejemplo 42 presentó un valor de CI_{50} de 34.9 µM. El Ejemplo 43 presentó un valor de CI_{50} de 77.5 µM. El Ejemplo 44 presentó un valor de CI_{50} de 2.3

μM. El Ejemplo 45 presentó un valor de CI_{50} de 2.35 μM. El Ejemplo 46 presentó un valor de CI_{50} de 90.7 μM. El Ejemplo 47 presentó un valor de CI_{50} de 1.4 μM. El Ejemplo 48 presentó un valor de CI_{50} de 44.3 μM. El Ejemplo 49 presentó un valor de CI_{50} de 2 μM. El Ejemplo 50 presentó un valor de CI_{50} de 5.3 μM. El Ejemplo 51 presentó un valor de CI_{50} de 0.9 μM. El Ejemplo 52 presentó un valor de CI_{50} de 1940 μM. El Ejemplo 53 presentó un valor de CI_{50} de 72.9 μM. El Ejemplo 54 presentó un valor de CI_{50} de 372 μM. El Ejemplo 55 presentó un valor de CI_{50} de 0.6 μM. El Ejemplo 56 presentó un valor de CI_{50} de 43.8 μM. El Ejemplo 57 presentó un valor de CI_{50} de 40 μM. El Ejemplo 58 presentó un valor de CI_{50} de 2.1 μM. El Ejemplo 59 presentó un valor de CI_{50} de 70.7 μM. El Ejemplo 60 presentó un valor de CI_{50} de 1.9 μM. El Ejemplo 61 presentó un valor de CI_{50} de 858 μM. El Ejemplo 62 presentó un valor de CI_{50} de 7.1 μM. El Ejemplo 63 presentó un valor de CI_{50} de 3.22 μM. El Ejemplo 64 presentó un valor de CI_{50} de 31.4 μM. El Ejemplo 65 presentó un valor de CI_{50} de 2.2 μM. El Ejemplo 66 presentó un valor de CI_{50} de 7.5 μM. El Ejemplo 67 presentó un valor de CI_{50} de 1.3 μM. El Ejemplo 68 presentó un valor de CI_{50} de 81.1 μM. El Ejemplo 69 presentó un valor de CI_{50} de 92.5 μM. El Ejemplo 70 presentó un valor de CI_{50} de 2.5 μM. El Ejemplo 71 presentó un valor de CI_{50} de 11.6 μM. El Ejemplo 72 presentó un valor de CI_{50} de 0.6 μM. El Ejemplo 73 presentó un valor de CI_{50} de 1.54 μM. El Ejemplo 74 presentó un valor de CI_{50} de 52.2 μM. El Ejemplo 75 presentó un valor de CI_{50} de 3.1 μM. El Ejemplo 76 presentó un valor de CI_{50} de 190 μM. El Ejemplo 77 presentó un valor de CI_{50} de 8 μM. El Ejemplo 78 presentó un valor de CI_{50} de 64.2 μM. El Ejemplo 79 presentó un valor de CI_{50} de 3.3 μM. El Ejemplo 80 presentó un valor de CI_{50} de 44 μM. El Ejemplo 81 presentó un valor de CI_{50} de 1.6 μM. El Ejemplo 82 presentó un valor de CI_{50} de 20.3 μM. El Ejemplo 83 presentó un valor de CI_{50} de 42 μM. El Ejemplo 84 presentó un valor de CI_{50} de 1.7 μM. El Ejemplo 85 presentó un valor de CI_{50} de 173 μM. El Ejemplo 86 presentó un valor de CI_{50} de 15.6 μM. El Ejemplo 87 presentó un valor de CI_{50} de 10.7 μM. El Ejemplo 88 presentó un valor de CI_{50} de 31.2

μM. El Ejemplo 89 presentó un valor de CI_{50} de 1.5 μM. El Ejemplo 90 presentó un valor de CI_{50} de 102 μM. El Ejemplo 91 presentó un valor de CI_{50} de 5.9 μM. El Ejemplo 92 presentó un valor de CI_{50} de 1.1 μM. El Ejemplo 93 presentó un valor de CI_{50} de 69.8 μM. El Ejemplo 94 presentó un valor de CI_{50} de 4.6 μM. El Ejemplo 95 presentó un valor de CI_{50} de 1.04 μM. El Ejemplo 96 presentó un valor de CI_{50} de 7.3 μM. El Ejemplo 97 presentó un valor de CI_{50} de 0.7 μM. El Ejemplo 98 presentó un valor de CI_{50} de 2.51 μM. El Ejemplo 99 presentó un valor de CI_{50} de 0.81 μM. El Ejemplo 100 presentó un valor de CI_{50} de 1.93 μM. El Ejemplo 101 presentó un valor de CI_{50} de 4.7 μM. El Ejemplo 102 presentó un valor de CI_{50} de 2.18 μM. El Ejemplo 103 presentó un valor de CI_{50} de 94 μM. El Ejemplo 104 presentó un valor de CI_{50} de 1.5 μM. El Ejemplo 105 presentó un valor de CI_{50} de 7.2 μM. El Ejemplo 106 presentó un valor de CI_{50} de 88.8 μM. El Ejemplo 107 presentó un valor de CI_{50} de 1.7 μM. El Ejemplo 108 presentó un valor de CI_{50} de 70.5 μM. El Ejemplo 109 presentó un valor de CI_{50} de 5 μM. El Ejemplo 110 presentó un valor de CI_{50} de 1.2 μM. El Ejemplo 111 presentó un valor de CI_{50} de 31.3 μM. El Ejemplo 112 presentó un valor de CI_{50} de 5.5 μM. El Ejemplo 113 presentó un valor de CI_{50} de 1.1 μM. El Ejemplo 114 presentó un valor de CI_{50} de 6.5 μM. El Ejemplo 115 presentó un valor de CI_{50} de 0.8 μM. El Ejemplo 116 presentó un valor de CI_{50} de 5.6 μM. El Ejemplo 117 presentó un valor de CI_{50} de 0.8 μM. El Ejemplo 118 presentó un valor de CI_{50} de 225 μM. El Ejemplo 119 presentó un valor de CI_{50} de 10.7 μM. El Ejemplo 120 presentó un valor de CI_{50} de 0.89 μM. El Ejemplo 121 presentó un valor de CI_{50} de 120 μM. El Ejemplo 122 presentó un valor de CI_{50} de 4.4 μM. El Ejemplo 123 presentó un valor de CI_{50} de 147 μM. El Ejemplo 124 presentó un valor de CI_{50} de 1.2 μM. El Ejemplo 125 presentó un valor de CI_{50} de 92.9 μM. El Ejemplo 126 presentó un valor de CI_{50} de 3.6 μM. El Ejemplo 127 presentó un valor de CI_{50} de 1.4 μM. El Ejemplo 128 presentó un valor de CI_{50} de 31.4 μM. El Ejemplo 129 presentó un valor de CI_{50} de 10.2 μM. El Ejemplo 130 presentó un valor de CI_{50} de 1.1 μM. El Ejemplo 131 presentó un valor de CI_{50} de 128 μM. El

Ejemplo 132 presentó un valor de CI_{50} de 2.2 µM. El Ejemplo 133 presentó un valor de CI_{50} de 120 µM. El Ejemplo 134 presentó un valor de CI_{50} de 0.85 µM. El Ejemplo 135 presentó un valor de CI_{50} de 69.1 µM. El Ejemplo 136 presentó un valor de CI_{50} de 4.94 µM. El Ejemplo 137 presentó un valor de CI_{50} de 1 µM. El Ejemplo 138 presentó un valor de CI_{50} de 123 µM. El Ejemplo 139 presentó un valor de CI_{50} de 2.9 µM. El Ejemplo 140 presentó un valor de CI_{50} de 0.6 µM. El Ejemplo 141 presentó un valor de CI_{50} de 69.5 µM. El Ejemplo 142 presentó un valor de CI_{50} de 1.8 µM. El Ejemplo 143 presentó un valor de CI_{50} de 0.9 µM. El Ejemplo 144 presentó un valor de CI_{50} de 88.2 µM. El Ejemplo 145 presentó un valor de CI_{50} de 4.3 µM. El Ejemplo 146 presentó un valor de CI_{50} de 6.6 µM. El Ejemplo 147 presentó un valor de CI_{50} de 44.6 µM. El Ejemplo 148 presentó un valor de CI_{50} de 2.7 µM. El Ejemplo 149 presentó un valor de CI_{50} de 0.9 µM. El Ejemplo 150 presentó un valor de CI_{50} de 87 µM. El Ejemplo 151 presentó un valor de CI_{50} de 7.7 µM.

Difracción de rayos X en polvo

El patrón de difracción de rayos X en polvo (que se denomina en la presente DRXP o DRX) se determinó colocando una muestra sobre un portador con ruido de fondo cero de silicio monocristalino y extendiendo la muestra para formar una capa fina. La muestra se centrifugó (para mejorar la estadística del recuento) y se irradió con rayos X generados por un tubo de cobre que funcionaba a 30 kV y 50 mA, utilizando un difractómetro theta-2 theta D8 Advance de Bruker con un detector VÅNTEC-1. Se utilizaron rendijas de divergencia variables automáticas.

Los análisis de difracción de rayos X se llevaron a cabo de acuerdo con los métodos estándar, que se pueden encontrar, por ejemplo, en *Molecular Crystals and Molecules*, Academic Press, Nueva York (1973), de Kitaigorodsky, A.I.; *Chemical Crystallography*, Clarendon Press, Londres (1948), de Bunn, C.W.; o *X-ray Diffraction Procedures*, John Wiley & Sons, Nueva York (1974), de Klug, H.P. y Alexander, L.E. Los datos de difracción de rayos X en polvo no se corrigieron mediante el

uso de una referencia interna. Las mediciones se llevaron a cabo con rendijas variables.

Se sobreentenderá que los valores 2-theta del patrón de difracción de rayos X en polvo pueden variar ligeramente de un aparato a otro y también dependiendo de las variaciones en la preparación de la muestra y de la variación de lote a lote, y por lo tanto los valores indicados no se deben interpretar como absolutos. También se sobreentenderá que las intensidades relativas de los picos pueden variar dependiendo de los efectos de la orientación, de manera que las intensidades mostradas en las curvas de DRX incluidas en la presente son ilustrativas y no se deben utilizar en comparaciones absolutas.

Los compuestos pueden cristalizar como un solvato (incluidos los hidratos y los solvatos mixtos) o como una forma no solvatada. Las moléculas de disolvente pueden estar unidas más o menos fuertemente en la estructura. Pueden aparecer transformaciones entre formas no solvatadas y solvatos o entre solvatos estequiométricos y no estequiométricos. Las transformaciones pueden ser tanto reversibles como irreversibles. La humedad relativa o la presencia de otros disolventes es un factor que puede afectar al patrón de difracción de rayos X en polvo en mayor o menor medida, dependiendo de la cantidad de disolvente presente en la estructura.

En las Figuras 1-13 se muestran los patrones de difracción de rayos X en polvo de una muestra típica de los ejemplos 10, 14, 18, 55, 65, 104, 115 y 143.

Ejemplos

Lista de abreviaturas utilizadas en los ejemplos:

AcOH - ÁCIDO ACÉTICO
VC - VOLUMEN DE LA COLUMNA
DME - 1,2-DIMETOXIETANO
DEE - ÉTER DIETÍLICO
DMF - *N*,*N*-DIMETILFORMAMIDA
DIPEA - *N*,*N*-DIISOPROPILETILAMINA
DCM - DICLOROMETANO
dppf - 1,1'-BIS(DIFENILFOSFINO)FERROCENO
DMAP - 4-DIMETILAMINOPIRIDINA
EDC - 1-ETIL-3-(3-DIMETILAMINOPROPIL)CARBODIIMIDA
EtOH - ETANOL
AF - ÁCIDO FÓRMICO
h - HORA(S)
min - MINUTO(S)
MTBE - Éter *tert*-butil metílico
IPA - ALCOHOL ISOPROPÍLICO
LAH - HIDRURO DE ALUMINIO Y LITIO
TEA - TRIETILAMINA
THF - TETRAHIDROFURANO
TBDMSCl - *TERT*-BUTILDIMETILCLOROSILANO
TBAF - FLUORURO DE TETRABUTILAMONIO
MeOH - METANOL
EtOAc - ACETATO DE ETILO
Ph - FENILO
sat. - SATURADO

Preparación de los compuestos de referencia

Compuesto de referencia 1

Ácido 2-bencil-1-(metoxicarbonil)piperidin-4-carboxílico

Paso 1: 2-Bencil-4-cianopiperidin-1-carboxilato de *tert*-butilo:

A una solución del éster *tert*-butílico del ácido 2-bencil-4-oxo-piperidin-1-carboxílico (15 g, 51.8 mmol) (de SYNTECH) en DME (250 mL) en una atmósfera de nitrógeno, se añadieron simultáneamente isocianuro de toluen-4-sulfonilmetilo (15.2 g, 77.7 mmol, en 250 mL de DME) y *tert*-butóxido de potasio (156 mL, 1 M en *tert*-butanol) durante 1 h, de manera que la temperatura se mantuviera por debajo de -10 °C. La solución se agitó a -10 °C durante 2 h y a continuación se dejó que alcanzara la temperatura ambiente durante 16 h. Se añadió H_2O (400 mL) a la mezcla de reacción, la solución se agitó durante 20 min y a continuación se extrajo con DEE (x3) y EtOAc (x3). Las fases orgánicas combinadas se secaron con Na_2SO_4 y se evaporaron. El residuo se purificó mediante cromatografía en columna utilizando EtOAc/heptano (gradiente de 10-60% de EtOAc) para obtener 2-bencil-4-cianopiperidin-1-carboxilato de *tert*-butilo (11.85 g, 76%). ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.38 - 1.46 (m, 9H), 1.63 - 2.14 (m, 4H), 2.62 - 3.33 (m, 4H), 4.17 (m, 1H), 4.48 (m, 1H), 7.11 - 7.41 (m, 5H); MS m/z 301 $(M+H)^+$.

Paso 2: 2-Bencilpiperidin-4-carboxilato de metilo:

Se añadió HCl conc. (43 mL) a 2-bencil-4-cianopiperidin-1-carboxilato de *tert*-butilo (11.85 g, 39.5 mmol). Después de agitar durante 20 min, la solución se transfirió a viales de reacción para microondas y se calentó hasta 140 °C durante 30 min en un reactor de microondas de nodo único. Se evaporaron los disolventes. El residuo se disolvió en HCl (1.25 M en MeOH, 50 mL) y la suspensión se calentó a reflujo durante 1 h. La eliminación de los disolventes proporcionó un aceite, que se disolvió en $NaHCO_3$ sat. (aprox. 80 mL) y posteriormente se neutralizó con $NaHCO_3$ sólido. La fase acuosa se extrajo con DCM (x3), el cual se secó utilizando un separador de fases y se evaporó para proporcionar 2-bencilpiperidin-4-carboxilato de metilo (7.36 g, 80%) como un aceite. ^{1}H RMN (600 MHz, $CDCl_3$) δ

1.18 - 2.40 (m, 5H), 2.47 - 3.15 (m, 5H), 3.66 - 2.69 (2 s, integral total, 3H), 7.15 - 7.35 (m, 5H); MS m/z 234 $(M+H)^+$.

Paso 3: Ácido 2-bencil-1-(metoxicarbonil)piperidin-4-carboxílico

A una solución de 2-bencilpiperidin-4-carboxilato de metilo (7.36 g, 31.55 mmol) y DIPEA (11.02 mL, 63.09 mmol) en DCM (200 mL), se añadió cloroformiato de metilo (3.18 mL, 41.01 mmol) en 100 mL de DCM durante 1 h. La mezcla de reacción se agitó durante 40 min, a continuación se lavó con $NaHCO_3$ saturado, se secó utilizando un separador de fases y se evaporó. El residuo se disolvió en THF (80 mL) y a continuación se añadieron LiOH (1.0 g, 42.0 mmol), MeOH (60 mL) y agua (60 mL). La mezcla de reacción se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 72 h. Después de evaporar los disolventes, el residuo se disolvió en agua. El pH se ajustó hasta alcanzar un valor < 2 mediante adición de HCl (10%). A continuación, la fase acuosa se extrajo con DCM (x5). Las fases orgánicas combinadas se secaron utilizando un separador de fases y se evaporaron para obtener el ácido 2-bencil-1-(metoxicarbonil)piperidin-4-carboxílico como un aceite. MS m/z 276 $(M-H)^-$.

Compuesto de referencia 2

Ácido 2-isobutil-1-(metoxicarbonil)piperidin-4-carboxílico

Paso 1: Ácido 3-(*tert*-butoxicarbonilamino)-5-metilhexanoico

A una solución de DL-β-homoleucina (45 g, 0.31 mol) en NaOH 1 N (1 L) a 0 °C, se añadió gota a gota una solución de $(Boc)_2O$ (87.8 g, 0.403 mol) en 1,4-dioxano (500 mL). La mezcla de reacción se agitó a temperatura ambiente durante toda la noche, se enfrió hasta 0 °C y se neutralizó con HCl 1 N (aprox. 1000 mL). El sólido se filtró y se secó al vacío para proporcionar el ácido 3-(*tert*-butoxicarbonilamino)-5-metilhexanoico (48.0 g, 63%) como un sólido.

Paso 2: 2-Isobutil-4,6-dioxopiperidin-1-carboxilato de *tert*-butilo

A una solución agitada de ácido 3-(*tert*-butoxicarbonilamino)-5-metilhexanoico (44.0 g, 0.179 mol) en DCM (800 mL) a 0 °C, se añadieron clorhidrato de EDC (51.56 g, 0.269 mol), DMAP (32.8 g, 0.269 mol) y ácido de Meldrum (25.8 g, 0.179 mol). La mezcla de reacción se agitó a temperatura ambiente durante 3 h, se lavó con $KHSO_4$ 1 N (500 mL), se secó con Na_2SO_4 y se concentró. El residuo se disolvió en acetato de etilo anhidro (1.5 L) y se calentó a reflujo durante toda la noche. La mezcla de reacción se lavó con $KHSO_4$ 1 N (500 mL), salmuera (500 mL), se secó con Na_2SO_4 y se concentró. El residuo se purificó mediante cromatografía en columna utilizando éter de petróleo y EtOAc (65:35) como eluyente para proporcionar el ácido 3-(*tert*-butoxicarbonilamino)-5-metilhexanoico como un sólido (35 g, 72%).

Paso 3: 6-Isobutilpiperidin-2,4-diona

Se añadió HCl (3 M en 1,4-dioxano, 100 mL) a una solución de 2-isobutil-4,6-dioxopiperidin-1-carboxilato de *tert*-butilo (30 g, 0.114 mol) en 1,4 dioxano anhidro (300 mL) y se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se concentró y se purificó mediante cristalización utilizando éter dietílico para proporcionar 6-isobutilpiperidin-2,4-diona (14 g, 74%) como un sólido blanco.

Paso 4: 2-Isobutilpiperidin-4-ol

Se añadió gota a gota una solución de 6-isobutilpiperidin-2,4-diona (14.0 g, 0.083 mol) en THF (100 mL) en una atmósfera de N_2 a una suspensión enfriada con hielo y agitada de LAH (16.1 g, 0.414 mol) en THF (100 mL). La mezcla de reacción se calentó hasta temperatura ambiente y se agitó en una atmósfera de N_2 durante 48 h. La mezcla de reacción se enfrió hasta 0 °C y se detuvo con agua (16.1 mL), NaOH 1 N (16.1 mL) y agua (16.1 mL). La mezcla de reacción se filtró y el sólido se lavó con THF caliente (100 mL). El filtrado se concentró para proporcionar 2-isobutilpiperidin-4-ol como un sólido (9 g, crudo).

Paso 5: 4-Hidroxi-2-isobutilpiperidin-1-carboxilato de *tert*-butilo

Se añadió una solución 50:50 de THF y $NaHCO_3$ sat. (100 mL) a 2-isobutilpiperidin-4-ol (9.0 g, 0.057 mol) y la mezcla se enfrió hasta 0 °C. Se añadió gota a gota una solución de $(Boc)_2O$ (13.7 g, 0.063 mol) en THF (50 mL). La solución resultante se agitó a temperatura ambiente durante toda la noche. La mezcla de reacción se concentró y se extrajo con EtOAc (100 mL). La fase orgánica se lavó con agua (100 mL), salmuera (100 mL), se secó con Na_2SO_4 y se concentró. El producto concentrado se purificó mediante cromatografía en columna utilizando un 20% de EtOAc en éter de petróleo para proporcionar una mezcla de dos compuestos. La mezcla se purificó adicionalmente mediante HPLC preparativa para proporcionar 4-hidroxi-2-isobutilpiperidin-1-carboxilato de *tert*-butilo como un líquido de color amarillo claro (4.5 g, 39.5%).

Paso 6: Éster *tert*-butílico del ácido 2-isobutil-4-oxopiperidin-1-carboxílico

A una solución agitada de 4-hidroxi-2-isobutilpiperidin-1-carboxilato de *tert*-butilo (4.6 g, 0.018 mol) en DCM (50 mL) a 0 °C, se añadió en porciones 1,1,1-triacetoxi-1,1-dihidro-1,2-benciodoxol-3(1*H*)-ona (9.1 g, 0.02146 mol) y la solución resultante se calentó hasta temperatura ambiente y se agitó en una atmósfera de N_2 durante toda la noche. La mezcla de reacción se detuvo con una solución de $NaHCO_3$ sat. (50 mL) y se filtró a través de un lecho de Celite®. El filtrado se extrajo varias veces con DCM (50 mL), las fases orgánicas combinadas se lavaron con agua (50 mL), salmuera (50 mL), se secaron con Na_2SO_4 y se concentraron. El producto concentrado se purificó mediante cromatografía en columna utilizando un 10% de EtOAc en éter de petróleo para proporcionar el producto con una pureza determinada mediante HPLC del 90%. El producto impuro se purificó adicionalmente mediante HPLC preparativa para proporcionar el éster *tert*-butílico del ácido 2-isobutil-4-oxopiperidin-1-carboxílico como un líquido (2.1 g, 46%).

Paso 7: 4-Ciano-2-isobutilpiperidin-1-carboxilato de *tert*-butilo

El compuesto se preparó como se ha descrito en el Paso 1 del Compuesto de referencia 1, a partir del éster *tert*-butílico del ácido 2-isobutil-4-oxopiperidin-1-carboxílico (4.55 g, 17.8 mmol), isocianuro de toluen-4-sulfonilmetilo (5.2 g, 26.7 mmol) y *tert*-butóxido de potasio (53.4 mL, 1 M en *tert*-butanol), para proporcionar 4-ciano-2-isobutilpiperidin-1-carboxilato de *tert*-butilo crudo. MS m/z 267 $(M+H)^+$.

Paso 8: Éster metílico del ácido 2-isobutilpiperidin-4-carboxílico

El compuesto se preparó como se ha descrito en el Paso 2 del Compuesto de referencia 1, a partir de 4-ciano-2-isobutilpiperidin-1-carboxilato de *tert*-butilo crudo (6.43 g, aprox. 24.2 mmol), para proporcioanr el éster metílico del ácido 2-isobutilpiperidin-4-carboxílico crudo. MS m/z 200 $(M+H)^+$.

Paso 9: Ácido 2-isobutil-1-(metoxicarbonil)piperidin-4-carboxílico

El compuesto se preparó como se ha descrito en el Paso 3 del Compuesto de referencia 1, a partir del éster metílico del ácido 2-isobutilpiperidin-4-carboxílico crudo (2.6 g, 13.0 mmol), DIPEA (4.55 mL, 26.1 mmol), cloroformiato de metilo (1.31 mL, 17.0 mmol) y posteriormente LiOH (1.3 equivalentes), para proporcionar el ácido 2-isobutil-1-(metoxicarbonil)piperidin-4-carboxílico crudo. MS m/z 242 $(M-H)^-$.

Compuesto de referencia 3

Ácido 1-(metoxicarbonil)-2-fenetilpiperidin-4-carboxílico

Paso 1: 4-Oxo-2-fenetil-3,4-dihidropiridin-1(2*H*)-carboxilato de metilo

Se disolvió 4-metoxipiridina (9.30 mL, 91.64 mmol) en THF (150 mL) en una atmósfera de nitrógeno y se enfrió hasta -15 °C. Se añadió gota a gota cloruro de fenetilmagnesio (93 mL, 93.47 mmol, 1 M en THF) y se formó una suspensión. Después de agitar a -20 °C durante 30 minutos, se añadió cloroformiato de metilo (9.23 mL, 119.13 mmol) durante 1 minuto. Se continuó agitando a -10 °C durante 1 h y a continuación se añadió HCl

(10%). La mezcla se agitó durante 20 minutos y a continuación se concentró. La fase acuosa se extrajo con éter (x2) y la fase orgánica se secó ($MgSO_4$) y se evaporó para proporcionar 4-oxo-2-fenetil-3,4-dihidropiridin-1(2*H*)-carboxilato de metilo (21.7 g, 82%) como un aceite. ^1H RMN (600 MHz, $CDCl_3$) δ 1.98 (m, 2H), 2.54 (m, 2H), 2.69 (m, 1H), 2.81 (m, 1H), 3.83 (s, 3H), 4.62 (m, 1H), 5.33 (m, 1H), 7.12 - 7.38 (m, 5H), 7.72 (m, 1H); MS m/z 260 $(M+H)^+$.

Paso 2: 4-Oxo-2-fenetilpiperidin-1-carboxilato de metilo:

Se hidrogenó 4-oxo-2-fenetil-3,4-dihidropiridin-1(2*H*)-carboxilato de metilo (21.7 g, aprox. 75 mmol) con Pd/C (5%) en EtOAc a 5 bar durante 20 h. La mezcla se filtró a través de un lecho de sílice y a continuación se evaporó para obtener el producto como un aceite (19.8 g). ^1H RMN (600 MHz, $CDCl_3$) δ 1.69 (m, 1H), 1.80 (m, 1H), 2.26 (m, 2H), 2.41 (m, 1H), 2.47 - 2.70 (m, 3H), 3.16 (m, 1H), 3.69 (m, 3H), 4.15-4.48 (m a, 2H), 7.14-7.30 (m, 5H). MS 262 m/z $(M+H)^+$.

Paso 3: 4-Ciano-2-fenetilpiperidin-1-carboxilato de metilo:

A una solución de 4-oxo-2-fenetilpiperidin-1-carboxilato de metilo (19.8 g, 75.7 mmol) en DME (250 mL) en una atmósfera de nitrógeno, se añadieron simultáneamente isocianuro de toluen-4-sulfonilmetilo (16.6 g, 85.0 mmol, en 250 mL de DME) y *tert*-butóxido de potasio (197 mL, 1 M en *tert*-butanol) durante 1 h, de manera que la temperatura se mantuviera por debajo de -10 °C. A continuación, la mezcla se agitó a -10 °C durante 2 h y se dejó que alcanzara la temperatura ambiente durante 16 h. Se añadió H_2O (400 mL) a la mezcla de reacción naranja, se agitó durante 20 min y a continuación se extrajo con éter (x3) y EtOAc (x3). Las fases orgánicas se combinaron, se secaron con Na_2SO_4 y se evaporaron para proporcionar 24.8 g de residuo. La cromatografía flash utilizando EtOAc/heptano (gradiente de 30-80% de EtOAc) proporcionó el producto (13.2 g, 64%) como una mezcla de diastereómeros (isómero *cis* mayoritario). MS m/z 273 $(M+H)^+$. Isómero *trans*: ^1H RMN (600 MHz, $CDCl_3$) δ 1.71 (m, 2H),

1.84 - 2.09 (m, 4H), 2.47 - 2.68 (m, 2H), 2.71 - 2.92 (m, 2H), 3.70 (s, 3H), 4.12 (m a, 1H), 4.45 (m a, 1H), 7.01 - 7.40 (m, 5H). Isómero *cis*: ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.76 (m, 1H), 1.88 (m, 1H), 1.92 - 2.07 (m, 2H), 2.07 - 2.15 (m, 1H), 2.24 - 2.38 (m, 1H), 2.55 - 2.72 (m, 2H), 2.96 (m, 1H), 3.16 - 3.29 (m, 1H), 3.69 (s, 3H), 4.10 (m, 1H), 4.35 (m, 1H), 7.15 - 7.35 (m, 5H).

Paso 4: Ácido 1-(metoxicarbonil)-2-fenetilpiperidin-4-carboxílico

Se añadió HCl 6 M a 4-ciano-2-fenetilpiperidin-1-carboxilato de metilo (13.2 g, 48.5 mmol) en un vial de reacción para microondas. La mezcla se calentó hasta 100 °C durante 30 min en un reactor de microondas de nodo único. La fase acuosa se extrajo con EtOAc y la fase orgánica resultante se lavó una vez con HCl al 10%, se secó con $MgSO_4$ y se evaporó para proporcionar 3.47 g de producto crudo. MS m/z 290 $(M-H)^-$.

Compuesto de referencia 4

Ácido 2-(4-*tert*-butilbencil)-1-(metoxicarbonil)piperidin-4-carboxílico

Paso 1: 4-((*tert*-Butildimetilsililoxi)metil)piridina

Se añadió TBDMSCl (42.6 g, 0.29 mol) a una solución de piridin-4-ilmetanol (25.7 g, 0.24 mol) e imidazol (19.8 g, 0.29 mol) en DMF anhidro (300 mL) y DCM anhidro (33 mL) en una atmósfera de nitrógeno. La solución se agitó durante 18 h y durante este periodo de tiempo se formó un precipitado. La mezcla de reacción se concentró mediante la eliminación de los componentes volátiles (aproximadamente 100 mL) y a continuación se añadió agua (500 mL). La mezcla resultante se extrajo con heptano:EtOAc 1:1 (200 mL x3). Las fases orgánicas combinadas se lavaron con salmuera (x2), se secaron ($MgSO_4$), se filtraron y se evaporaron para obtener 4-((*tert*-butildimetilsililoxi)metil)piridina (51.70 g, 98%) como un aceite. ^{1}H RMN (600 MHz, $CDCl_3$) δ -0.01 (s, 6H), 0.82 (s, 9H), 4.63 (s, 2H), 7.14 (m, 2H), 8.43 (m, 2H).

Paso 2: 2-(4-*tert*-Butilbencil)-4-((*tert*-butildimetilsililoxi)metil)piridin-1(2*H*)-carboxilato de metilo

A una suspensión de 4-(*tert*-butildimetilsililoxi)metil)piridina (5.33 g, 23.86 mmol) en THF (50 mL) enfriada hasta -30 °C, se añadió bromuro de (4-*tert*-butilbencil)magnesio (105 mL, 26.25 mmol, 0.25 M en THF) durante 10 minutos. Se añadió gota a gota cloroformiato de metilo (2.443 mL, 31.02 mmol) durante 10 minutos. Se permitió que la mezcla de reacción alcanzara 0 °C durante 2 h. Se evaporaron los disolventes orgánicos, la mezcla de reacción se diluyó con acetato de etilo y a continuación se lavó con HCl 1 N y salmuera. La fase orgánica se secó con $MgSO_4$ y se evaporó para proporcionar 9 g de un residuo crudo, que se purificó en 2 porciones iguales mediante cromatografía en columna automatizada (Biotage, 340 g de KP-SIL), eluyente: gradiente 0-50% de heptano/EtOAc, para proporcionar el producto (6.5 g, 64%) como un aceite claro. ^{1}H RMN (400 MHz, $CDCl_3$) (complejo) δ -0.07 - 0.21 (m, 6H), 0.9 - 1.30 (m, 18H), 2.0 - 7.4 (m, 15H). MS m/z 431 $(M+H)^+$.

Paso 3: 2-(4-*tert*-Butilbencil)-4-((*tert*-butildimetilsililoxi)metil)piperidin-1-carboxilato de metilo

Se añadió óxido de platino (IV) (0.07 g, 0.31 mmol) a una solución de 2-(4-*tert*-butilbencil)-4-((*tert*-butildimetilsililoxi)metil)piridin-1(2*H*)-carboxilato de metilo (6.5 g, 15.13 mmol) en acetato de etilo (50 mL). La suspensión se hidrogenó en una atmósfera de H_2 de 6 bar durante 20 h. La mezcla se filtró a través de Celite y los disolventes se evaporaron para obtener el producto (6.27 g, 96%) como un aceite. ^{1}H RMN (400 MHz, $CDCl_3$) δ -0.07 - 0.18 (m, 6H), 0.77 - 1.01 (m, 9H), 1.28 - 1.37 (m, 9H), 1.36 - 1.87 (m, 4H), 2.58 - 2.74 (m, 1H), 2.88 - 3.06 (m, 2H), 3.40 - 3.55 (m, 3H), 3.60 - 3.72 (m, 3H), 3.78 - 4.10 (m, 2H), 7.14 - 7.32 (m, 4H). MS m/z 434 $(M+H)^+$.

Paso 4: 2-(4-*tert*-Butilbencil)-4-(hidroximetil)piperidin-1-carboxilato de metilo:

A una suspensión de 2-(4-*tert*-butilbencil)-4-((*tert*-butildimetilsililoxi)metil)piperidin-1-carboxilato de metilo (6.27 g, 14.46 mmol) en tetrahidrofurano (15 mL), se añadió fluoruro de tetrabutilamonio (18.79 mL, 18.79 mmol, 1 M en THF) y la mezcla de reacción se agitó a temperatura ambiente durante 90 minutos. Los disolventes se evaporaron, el residuo se disolvió en acetato de etilo y se lavó con $NaHCO_3$ sat. (x1) y a continuación con salmuera (x2). La fase orgánica se secó con $MgSO_4$ y se evaporó. El residuo se purificó mediante cromatografía en columna automatizada (Biotage, (340 g de KP-SIL), eluyente: EtOAc/heptano, gradiente de 20-90% de EtOAc) para proporcionar el producto (3.21 g, 70%) como un aceite. ^1H RMN (400 MHz, $CDCl_3$) δ 1.30 (s, 9H), 1.42 - 1.50 (m, 2H), 1.65 - 1.91 (m, 2H), 2.68 (m, 1H), 2.89 - 3.07 (m, 2H), 3.39 - 3.62 (m, 3H), 3.67 (m, 3H), 3.87 (m, 1H), 4.07 (m, 1H), 7.11 (m, 2H), 7.30 (m, 2H). MS m/z 320 $(M+H)^+$.

Paso 5: Ácido 2-(4-*tert*-butilbencil)-1-(metoxicarbonil)piperidin-4-carboxílico

A una solución de 2-(4-*tert*-butilbencil)-4-(hidroximetil)piperidin-1-carboxilato de metilo (2.9 g, 9.08 mmol) en tetracloruro de carbono (18 mL), se añadieron peryodato de sodio (5.83 g, 27.24 mmol) y agua (27 mL). Se añadió acetonitrilo (18 mL) a esta mezcla y a continuación cloruro de rutenio (III) (0.041 g, 0.20 mmol). La mezcla bifásica resultante se agitó enérgicamente a temperatura ambiente durante 2 h. La mezcla de reacción se diluyó con agua y DCM y la fase acuosa se extrajo con DCM (x3). Las fases orgánicas combinadas se secaron con $MgSO_4$ y se evaporaron para obtener el producto como un aceite (3.0 g, 98%). MS m/z 332 $(M-H)^-$.

Compuesto de referencia 5

Ácido 1-(metoxicarbonil)-2-neopentilpiperidin-4-carboxílico

Paso 1: 4-((*tert*-Butildimetilsililoxi)metil)-2-neopentilpiridin-1(2*H*)carboxilato de metilo

El compuesto se preparó como se ha descrito en el Paso 2 del Compuesto de referencia 4, partiendo de 4-(*tert*-butildimetilsililoxi)metil)piridina, preparada como se ha descrito en el Paso 1 del Compuesto de referencia 4, cloruro de neopentilmagnesio (40.5 mL, 40.5 mmol, 1 M en THF) y cloroformiato de metilo (3.77 mL, 47.9 mmol). El residuo se purificó mediante cromatografía flash en columna automatizada en una columna Biotage® con 340 g de KP-SIL. Se utilizó un gradiente de 15:1 a 10:1 de heptano:EtOAc como fase móvil para obtener el compuesto del título (9.3 g, 71%): ^{1}H RMN (400 MHz, $CDCl_3$) δ -0.00 (s, 3H), 0.09 (s, 3H), 0.87 (s, 18H), 1.09 - 1.81 (m, 2H), 1.94 - 2.44 (m, 1H), 3.70 (s, 3H), 4.22 - 4.90 (m, 2H), 5.12 - 5.61 (m, 1H), 5.69 - 5.97 (m, 1H), 6.25 - 6.79 (m, 1H). MS m/z 354 $(M+H)^+$.

Paso 2: 4-((*tert*-Butildimetilsililoxi)metil)-2-neopentilpiperidin-1-carboxilato de metilo

El compuesto se preparó como se ha descrito en el Paso 3 del Compuesto de referencia 4, partiendo de 4-((*tert*-butildimetilsililoxi)metil)-2-neopentilpiridin-1(2*H*)-carboxilato de metilo, para proporcionar el compuesto del título. MS m/z 358 $(M+H)^+$.

Paso 3: 4-(Hidroximetil)-2-neopentilpiperidin-1-carboxilato de metilo

El compuesto se preparó como se ha descrito en el Paso 4 del Compuesto de referencia 4, partiendo de 4-((*tert*-butildimetilsililoxi)metil)-2-neopentilpiperidin-1-carboxilato de metilo y TBAF (34.2 mL, 34.2 mmol, 1 M en THF). El residuo se purificó mediante cromatografía flash en columna automatizada en una columna Biotage® con 340 g de KP-SIL. Se utilizó un gradiente de 30% a 100% de EtOAc en heptano como eluyente, para proporcionar el compuesto del título.

Paso 5: Ácido 1-(metoxicarbonil)-2-neopentilpiperidin-4-carboxílico

El compuesto se preparó como se ha descrito en el Paso 5 del Compuesto de referencia 4, partiendo de 4-(hidroximetil)-2-neopentilpiperidin-1-carboxilato de metilo, peryodato de sodio

(15.0 g, 70.3 mmol) y cloruro de rutenio (III) (0.11 g, 0.52 mmol), para proporcionar el compuesto del título. MS m/z 256 $(M-H)^-$.

Compuesto de referencia 6

Ácido 1-(metoxicarbonil)-2-metilpiperidin-4-carboxílico

Paso 1: 4-((*tert*-Butildimetilsililoxi)metil)-2-metilpiridin-1(2*H*)-carboxilato de metilo

El compuesto se preparó como se ha descrito en el Paso 2 del Compuesto de referencia 4, partiendo de 4-(*tert*-butildimetilsililoxi)metil)piridina, preparada como se ha descrito en el Paso 1 del Compuesto de referencia 4, cloruro de metilmagnesio (3 M en THF) (13.1 mL, 39.4 mmol, 1 M en THF) y cloroformiato de metilo (3.61 mL, 46.7 mmol). El residuo se purificó mediante cromatografía en columna (Biotage, heptano:EtOAc, utilizando un gradiente de 0-15% de EtOAc; columna snap 360), para proporcionar el compuesto del título como un aceite ligeramente amarillo (2.48 g, 23%): ^{1}H RMN (400 MHz, $CDCl_3$) δ -0.03 (d, 6H), 0.66 - 1.04 (m, 12H), 1.84 (m, 1H), 2.20 - 2.70 (m, 1H), 3.62 (s, 3H), 4.31 (m, 1H), 5.63 (m, 1H), 5.83 (m, 1H), 6.50 (m, 1H). MS m/z 298 $(M+H)^+$.

Paso 2: 4-((*tert*-Butildimetilsililoxi)metil)-2-metilpiperidin-1-carboxilato de metilo

El compuesto se preparó como se ha descrito en el Paso 3 del Compuesto de referencia 4, partiendo de 4-((*tert*-butildimetilsililoxi)metil)-2-metilpiridin-1(2*H*)-carboxilato de metilo, para proporcionar el compuesto del título. MS m/z 302 $(M+H)^+$.

Paso 3: 4-(Hidroximetil)-2-metilpiperidin-1-carboxilato de metilo

El compuesto se preparó como se ha descrito en el Paso 4 del Compuesto de referencia 4, partiendo de 4-((*tert*-butildimetilsililoxi)metil)-2-metilpiperidin-1-carboxilato de metilo y TBAF (10.65 mL, 10.65 mmol, 1 M en THF). El residuo se purificó mediante cromatografía en columna (Biotage, gradiente de 40%-90% de EtOAc en heptano, columna snap 340), para proporcionar el compuesto del título. ^{1}H RMN (400 MHz, $CDCl_3$) δ

0.95 - 1.42 (m, 3H), 1.68 - 1.95 (m, 3H), 3.08 (m, 1H), 3.39 - 3.53 (m, 2H), 3.61 (m, 1H), 3.68 (s, 3H), 3.71 - 3.87 (m, 1H), 3.87 - 4.08 (m, 1H), 4.30 - 4.62 (m, 1H).

Paso 5: Ácido 1-(metoxicarbonil)-2-metilpiperidin-4-carboxílico

El compuesto se preparó como se ha descrito en el Paso 5 del Compuesto de referencia 4, partiendo de 4-(hidroximetil)-2-metilpiperidin-1-carboxilato de metilo, peryodato de sodio (3.53 g, 16.5 mmol) y cloruro de rutenio (III) (0.025 g, 0.12 mmol), para proporcionar el compuesto del título. MS m/z 200 $(M-H)^-$.

Compuesto de referencia 7

Ácido 1-(metoxicarbonil)-2-(2-metil-2-fenilpropil)piperidin-4-carboxílico

Paso 1: 4-((*tert*-Butildimetilsililoxi)metil)-2-(2-metil-2-fenilpropil)piridin-1(2*H*)-carboxilato de metilo

El compuesto se preparó como se ha descrito en el Paso 2 del Compuesto de referencia 4, partiendo de 4-(*tert*-butildimetilsililoxi)metil)piridina, preparada como se ha descrito en el Paso 1 del Compuesto de referencia 4, cloruro de (2-metil-2-fenilpropil)magnesio (0.5 M en THF, 93 mL, 46.6 mmol) y cloroformiato de metilo (3.61 mL, 46.7 mmol), para obtener el producto (17.5 g). MS m/z 416 $(M+H)^+$.

Paso 2: 4-((*tert*-Butildimetilsililoxi)metil)-2-(2-metil-2-fenilpropil)piperidin-1-carboxilato de metilo

El compuesto se preparó como se ha descrito en el Paso 3 del Compuesto de referencia 4, partiendo de 4-((*tert*-butildimetilsililoxi)metil)-2-(2-metil-2-fenilpropil)piridin-1(2*H*)-carboxilato de metilo crudo (17.5 g), para proporcionar el compuesto del título (16.5 g). MS m/z 420 $(M+H)^+$.

Paso 3: 4-(Hidroximetil)-2-(2-metil-2-fenilpropil)piperidin-1-carboxilato de metilo

El compuesto se preparó como se ha descrito en el Paso 4 del Compuesto de referencia 4, partiendo de 4-((*tert*-butildimetilsililoxi)metil)-2-(2-metil-2-fenilpropil)piperidin-1-carboxilato de metilo crudo (16.5 g) y TBAF (46.5 mL, 46.6

mmol, 1 M en THF). El residuo se purificó mediante cromatografía en columna (Biotage, gradiente de 40-65% de EtOAc en heptano, columna snap 340, 2 purificaciones), para proporcionar el compuesto del título. MS m/z 306 $(M+H)^+$.

Paso 4: Ácido 1-(metoxicarbonil)-2-(2-metil-2-fenilpropil)piperidin-4-carboxílico

El compuesto se preparó como se ha descrito en el Paso 5 del Compuesto de referencia 4, partiendo de 4-(hidroximetil)-2-(2-metil-2-fenilpropil)piperidin-1-carboxilato de metilo (8.0 g, 26.2 mmol), peryodato de sodio (16.8 g, 78.6 mmol) y cloruro de rutenio (III) (0.12 g, 0.58 mmol), para proporcionar el compuesto del título (7.24 g, 87%). MS m/z 318 $(M-H)^-$.

Compuesto de referencia 8

Ácido 2-(ciclohexilmetil)-1-(metoxicarbonil)piperidin-4-carboxílico

Paso 1: 2-Bencilisonicotinato de metilo

Se disolvieron 2-cloroisonicotinato de metilo (4.29 g, 25 mmol) y $Pd(PPh_3)_4$ (1.156 g, 1.00 mmol) en THF (60 mL) para proporcionar una solución amarilla. A continuación, se añadió bromuro de bencilzinc (II) (0.5 M en THF) (75 mL, 37.50 mmol). La mezcla marrón resultante se calentó hasta 60 °C en un baño de aceite durante 18 h. La mezcla de reacción se detuvo añadiendo metanol, a continuación se diluyó con acetato de etilo y se lavó con NH_4Cl sat. y agua. Las fases orgánicas combinadas se secaron con $MgSO_4$ y se evaporaron. El residuo se purificó a través de 160 g de sílice en una columna Thompsson de Biotage, utilizando un eluyente isocrático de heptanos/acetato de etilo de 9:1 en 1 VC y a continuación un gradiente lineal de 9:1-75:25 en 6 VC. Las fracciones que contenían el producto se evaporaron para obtener 2-bencilisonicotinato de metilo como un líquido naranja. ^1H RMN (400 MHz, $CDCl_3$) δ 3.91 (s, 3H), 4.22 (s, 2H), 7.19 - 7.34 (m, 5H), 7.66 (dd, 1H), 7.69 (d, 1H), 8.70 (d, 1H).

Paso 2: 2-(Ciclohexilmetil)piperidin-4-carboxilato de metilo

Se añadieron 2-bencilisonicotinato de metilo (1.29 g, 5.67 mmol) y PtO_2 (0.13 g, 0.57 mmol) a ácido acético (50 mL). La mezcla de reacción se hidrogenó en un hidrogenador Büchi a 8 bar y temperatura ambiente durante 3 días. Se añadió metanol (100 mL) y se filtró el catalizador. Se evaporó el disolvente. El producto crudo se repartió entre Na_2CO_3 (ac.) y acetato de etilo. La fase orgánica se aisló, se secó con Na_2SO_4, se filtró a través de Celite® y se evaporó el disolvente. ^1H RMN (600 MHz, $CDCl_3$) δ 0.78 - 0.91 (m, 2H), 1.04 - 1.27 (m, 5H), 1.27 - 1.38 (m, 1H), 1.48 (ddd, 2H), 1.63 (dd, 5H), 1.80 - 1.93 (m, 2H), 2.36 (tt, 1H), 2.51 - 2.57 (m, 1H), 2.61 (td, 1H), 3.11 (ddd, 1H), 3.64 (s, 3H).

Paso 3: 2-(Ciclohexilmetil)piperidin-1,4-dicarboxilato de dimetilo

Se añadieron 2-(ciclohexilmetil)piperidin-4-carboxilato de metilo (1.79 g, 7.48 mmol), cloroformiato de metilo (1.06 g, 11.2 mmol) y DIPEA (1.93 g, 15.0 mmol) a diclorometano (60 mL) a temperatura ambiente y se agitó durante 2 h. La mezcla de reacción se diluyó con éter dietílico y se lavó con agua. La fase orgánica se secó con $MgSO_4$, se filtró a través de Celite® y se evaporó el disolvente. Producto crudo: 2.2 g. ^1H RMN (400 MHz, $CDCl_3$) δ 0.71 - 0.97 (m, 2H), 1.02 - 1.28 (m, 5H), 1.38 (dt, 1H), 1.69 (ddd, 6H), 1.98 (ddd, 3H), 2.52 - 2.61 (m, 1H), 3.01 - 3.16 (m, 1H), 3.67 (s, 3H), 3.69 (s, 3H), 3.81 - 3.94 (m, 1H), 4.13 - 4.31 (m, 1H).

Paso 4: Ácido 2-(ciclohexilmetil)-1-(metoxicarbonil)piperidin-4-carboxílico

Se disolvió 2-(ciclohexilmetil)piperidin-1,4-dicarboxilato de dimetilo (2.20 g, 7.40 mmol) en THF (25 mL) y agua (25 mL). Se añadió LiOH (0.266 g, 11.1 mmol) y la mezcla resultante se agitó a temperatura ambiente durante toda la noche y se calentó a reflujo durante 30 min. La mezcla de reacción se repartió entre $KHSO_4$ 1 M y éter dietílico. La fase orgánica se secó (Na_2SO_4), se filtró a través de Celite® y se evaporó el disolvente. El producto crudo se volvió a disolver en THF (25 mL) y agua (25 mL). Se añadió LiOH (0.23 g) al matraz de

reacción. La mezcla de reacción se agitó durante toda la noche. La reacción se trató como se ha descrito anteriormente, para obtener el producto. ^{1}H RMN (600 MHz, $CDCl_3$) δ 0.85 (ddd, 2H), 1.19 (dddd, 5H), 1.38 - 1.48 (m, 1H), 1.61 (d, 4H), 1.72 (tt, 2H), 1.97 (cd, 3H), 2.56 - 2.65 (m, 1H), 3.02 - 3.14 (m, 1H), 3.67 (d, 3H), 3.88 (d, 1H), 4.22 (s, 1H).

Compuesto de referencia 9

Ácido 2-(3,4-difluorofenil)-1-(metoxicarbonil)piperidin-4-carboxílico

Paso 1: 2-(3,4-Difluorofenil)isonicotinato de metilo

Una mezcla de 2-cloroisonicotinato de metilo (5 g, 29.14 mmol), ácido 3,4-difluorofenilborónico (5.06 g, 32.05 mmol), carbonato de potasio (2.416 g, 17.48 mmol) y $PdCl_2$(dppf) (1.066 g, 1.46 mmol) se agitó en metanol (30 mL) y se calentó en un reactor de microondas de nodo único a 100 °C durante 30 min. El disolvente se evaporó al vacío. Se añadieron DCM (400 mL) y $NaHCO_3$ (ac.) al 8% (400 mL), se agitó y se separaron las fases. La fase acuosa se extrajo con DCM (400 mL). Las fases orgánicas combinadas se secaron con un separador de fases y se evaporaron al vacío. El residuo se purificó mediante cromatografía flash automatizada en tres columnas Biotage® con 100 g de KP-SIL. Se utilizó como fase móvil un gradiente de 5 % de EtOAc en heptano en 2 VC y a continuación de 5 % a 20 % de EtOAc en heptano en 9 VC. Se aisló 2-(3,4-difluorofenil)isonicotinato de metilo (5.82 g, 80%) como un sólido blanco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 4.00 (s, 3H), 7.23 - 7.33 (m, 1H), 7.76 - 7.84 (m, 2H), 7.90 - 8.00 (m, 1H), 8.21 - 8.27 (m, 1H), 8.82 (dd, 1H).

Paso 2: Clorhidrato de 2-(3,4-difluorofenil)piperidin-4-carboxilato de metilo

Se disolvió 2-(3,4-difluorofenil)isonicotinato de metilo (5.821 g, 23.36 mmol) en cloruro de hidrógeno (1.25 M en MeOH) (37.4 mL, 46.72 mmol) y se agitó a temperatura ambiente durante 30 min. El disolvente se evaporó al vacío. La sal de HCl remanente se volvió a disolver en MeOH (20 mL), se añadió óxido de platino (IV) (0.159 g, 0.70 mmol) y la mezcla de reacción se hidrogenó en un hidrogenador Büchi a 5 bar y temperatura

ambiente durante 6 h. El catalizador se filtró, se lavó con MeOH y el filtrado se evaporó al vacío para proporcionar el clorhidrato de 2-(3,4-difluorofenil)piperidin-4-carboxilato de metilo (6.10 g, 90%) como un sólido de color claro. MS m/z 256 $(M+H)^+$.

Paso 3: 2-(3,4-Difluorofenil)piperidin-1,4-dicarboxilato de dimetilo

Se disolvieron el clorhidrato de 2-(3,4-difluorofenil)piperidin-4-carboxilato de metilo (6.1 g, 20.91 mmol) y DIPEA (9.13 mL, 52.28 mmol) en DCM (30 mL). Se añadió cloroformiato de metilo (1.944 mL, 25.09 mmol) y la reacción se agitó a temperatura ambiente durante 1.5 h. Se añadió DCM (170 mL). La fase orgánica se lavó con HCl 0.1 M (2 x 200 mL) y $NaHCO_3$ sat. (200 mL), se secó con un separador de fases y se evaporó al vacío, para proporcionar 2-(3,4-difluorofenil)piperidin-1,4-dicarboxilato de dimetilo (6.58 g, 100%) como un aceite de color oscuro. MS m/z 314 $(M+H)^+$.

Paso 4: Ácido 2-(3,4-difluorofenil)-1-(metoxicarbonil)piperidin-4-carboxílico

Se disolvió 2-(3,4-difluorofenil)piperidin-1,4-dicarboxilato de dimetilo (6.578 g, 21.00 mmol) en THF (40 mL) y agua (0.800 mL). Se añadieron bromuro de litio (14.59 g, 167.97 mmol) y TEA (11.71 mL, 83.98 mmol) y la reacción se agitó a 80 °C durante 3 h. La mezcla de reacción se enfrió hasta temperatura ambiente y se evaporó parte del disolvente al vacío. Se añadieron EtOAc (150 mL) y agua (150 mL), se agitó y se separaron las fases. La fase orgánica se extrajo con agua (150 mL). Las fases acuosas combinadas se acidificaron con HCl 3 M hasta un pH de 1 y se extrajeron con EtOAc (2x300 mL). Las fases orgánicas combinadas se secaron con Na_2SO_4, se filtraron y se evaporaron al vacío para proporcionar el ácido 2-(3,4-difluorofenil)-1-(metoxicarbonil)piperidin-4-carboxílico (5.66 g, 90%) como un aceite de color marrón claro. MS m/z 298 $(M+H)^+$.

Compuesto de referencia 10

Ácido 2-(4-fluorofenil)-1-(metoxicarbonil)piperidin-4-

carboxílico

Paso 1: Clorhidrato de 2-(4-fluorofenil)isonicotinato de metilo

Se mezclaron 2-cloroisonicotinato de metilo (4.5 g, 26.23 mmol), ácido 4-fluorofenilborónico (4.51 g, 32.26 mmol), carbonato de potasio (2.247 g, 16.26 mmol) y $PdCl_2$(dppf) (0.380 g, 0.52 mmol) en metanol (30 mL) en dos viales para microondas de 20 mL. Los viales se taparon y se calentaron a 100 °C durante 10 min en un reactor de microondas de nodo único. Se eliminaron los sólidos mediante filtración y se evaporó el filtrado para proporcionar una suspensión de color rojo oscuro. Se añadió HCl (1.25 M en metanol, 100 mL) al residuo. La mezcla se agitó a 45 °C durante 4 h y a continuación se concentró. Se añadió $NaHCO_3$ sat. (100 mL), mientras se enfriaba con un baño de hielo, y se extrajo con DCM (3 x 100 mL). Las fases orgánicas combinadas se lavaron con salmuera, se hicieron pasar a través de un separador de fases y se evaporaron, para proporcionar un sólido marrón. El crudo se disolvió en MTBE (180 mL) y se filtraron parte de los sólidos. Se enfrió con hielo-agua, se añadió gota a gota cloruro de hidrógeno (4 M en dioxano, 10 mL, 40 mmol) mientras se agitaba y se formó una suspensión. La suspensión se agitó a 0 °C durante 10 min. El sólido se aisló mediante filtración y se lavó con MTBE para proporcionar el clorhidrato de 2-(4-fluorofenil)isonicotinato de metilo (6.4 g, 91%) como un sólido beis. ^{1}H RMN (400 MHz, CD3OD) δ 4.07 (s, 3H), 7.37 - 7.51 (m, 2H), 8.02 - 8.13 (m, 2H), 8.37 (dd, 1H), 8.71 (d, 1H), 8.97 (dd, 1H). MS m/z 232 $(M+H)^+$.

Paso 2: 2-(4-Fluorofenil)piperidin-4-carboxilato de metilo

Se disolvió el clorhidrato de 2-(4-fluorofenil)isonicotinato de metilo (6.4 g, 23.91 mmol) en metanol (100 mL) y se añadió óxido de platino (IV) (0.271 g, 1.20 mmol). La mezcla resultante se hidrogenó en un hidrogenador Büchi a temperatura ambiente y 5 bar durante 21 h. El catalizador se filtró, se lavó con MeOH y se evaporó el filtrado. Se añadieron DCM y $NaHCO_3$ sat. y se separaron las

fases. La fase orgánica se lavó con salmuera, se hizo pasar a través de un separador de fases y se evaporó, para proporcionar un aceite marrón. El residuo se purificó mediante cromatografía flash automatizada en una columna Biotage® con 100 g de KP-SIL. Se utilizó como fase móvil un gradiente de 0% a 5% de MeOH en DCM (que contenía un 1% de Et_3N) en 10 VC y a continuación se eluyó isocráticamente con un 5% de MeOH en DCM (que contenía un 1% de Et_3N). Se aisló 2-(4-fluorofenil)piperidin-4-carboxilato de metilo (4.2 g, 74%). MS m/z 238 $(M+H)^+$.

Paso 3: 2-(4-Fluorofenil)piperidin-1,4-dicarboxilato de dimetilo

Se disolvió 2-(4-fluorofenil)piperidin-4-carboxilato de metilo (7.4 g, 31.19 mmol) en DCM (100 mL) y se añadió DIPEA (6.52 mL, 37.43 mmol) y a continuación cloroformiato de metilo (2.95 mL, 37.43 mmol) a 0 °C. La solución se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se lavó con HCl 0.1 M y $NaHCO_3$ sat. La fase orgánica se hizo pasar a través de un separador de fases y se evaporó, para proporcionar 2-(4-fluorofenil)piperidin-1,4-dicarboxilato de dimetilo (8.07 g, 97%) como un aceite marrón. MS m/z 296 $(M+H)^+$.

Paso 4: Ácido 2-(4-fluorofenil)-1-(metoxicarbonil)piperidin-4-carboxílico

Se disolvió 2-(4-fluorofenil)piperidin-1,4-dicarboxilato de dimetilo (8.97 g, 30.38 mmol) en acetonitrilo (60 mL) y agua (1.200 mL), a continuación se añadió bromuro de litio (21.10 g, 243.00 mmol). Se añadió trietilamina (16.84 mL, 121.50 mmol) y la suspensión marrón resultante se calentó a reflujo durante 1 h. Se añadieron agua (120 mL) y MTBE (120 mL). La fase orgánica se extrajo con agua (2 x 25 mL). La fase acuosa recogida se acidificó hasta un pH de 1 con HCl 6 M y se extrajo con MTBE (2 x 150 mL). Las fases orgánicas combinadas se lavaron con agua (25 mL), se secaron con Na_2SO_4 anhidro y se evaporaron. Se aisló el ácido 2-(4-fluorofenil)-1-(metoxicarbonil)piperidin-4-carboxílico (8.4 g, 98%) como un aceite marrón.

Compuesto de referencia 11

Ácido 2-(4-clorofenil)-1-(metoxicarbonil)piperidin-4-

carboxílico

Paso 1: Clorhidrato de 2-(4-clorofenil)isonicotinato de metilo

Se mezclaron 2-bromoisonicotinato de metilo (3.39 g, 15.69 mmol), ácido 4-clorofenilborónico (3.68 g, 23.54 mmol), carbonato de potasio (3.25 g, 23.54 mmol) y $PdCl_2$(dppf) (0.341 g, 0.47 mmol) en metanol (30 mL) en dos viales diferentes para microondas de 20 mL. Los viales se taparon y se calentaron a 100 °C durante 10 min en un reactor de microondas de nodo único. Se añadieron agua y DCM, y se separaron las fases. La fase acuosa (pH de 9) se extrajo con DCM y las fases orgánicas combinadas se lavaron con salmuera, se pasaron a través de un separador de fases y se evaporaron, para proporcionar un sólido naranja. El sólido se disolvió en MTBE y a continuación se añadió HCl (4 M en dioxano), para proporcionar el clorhidrato de 2-(4-clorofenil)isonicotinato de metilo crudo (4.3 g). MS m/z 248 $(M+H)^+$.

Paso 2: 2-(4-Clorofenil)piperidin-4-carboxilato de metilo

Se disolvió el clorhidrato de 2-(4-clorofenil)isonicotinato de metilo (4.46 g, 15.69 mmol) en MeOH (40 mL) y se añadió óxido de platino (IV) (0.356 g, 1.57 mmol). La mezcla resultante se hidrogenó en un hidrogenador Büchi a temperatura ambiente y 5 bar durante 1 h. El catalizador se filtró, se lavó con MeOH y se evaporó el eluato, para obtener un sólido marrón. El sólido se disolvió en DCM y se lavó con K_2CO_3 1 M y salmuera. La fase orgánica se secó a través de un separador de fases y se evaporó. El residuo se disolvió en DCM y se introdujo en columnas de intercambio catiónico SCX-2 (4 columnas de 10 g). Cada columna se lavó con DCM, MeOH y a continuación se eluyó con NH_3/MeOH (1 VC de cada uno). La fase de NH_3/MeOH se evaporó, para proporcionar 2-(4-clorofenil)piperidin-4-carboxilato de metilo (3.13 g, 79%). MS m/z 254 $(M+H)^+$.

Paso 3: 2-(4-Clorofenil)piperidin-1,4-dicarboxilato de dimetilo

Se disolvió 2-(4-clorofenil)piperidin-4-carboxilato de

metilo (3.13 g, 12.34 mmol) en DCM (50 mL) y a continuación se añadió DIPEA (5.39 mL, 30.84 mmol). Se añadió cloroformiato de metilo (1.360 mL, 17.27 mmol) gota a gota a la disolución. La mezcla se agitó a temperatura ambiente durante 3 h. La mezcla se lavó con HCl 0.1 M (2*100 mL) y $NaHCO_3$ sat. (100 mL), a continuación se secó a través de un separador de fases y se evaporó, para proporcionar 2-(4-clorofenil)piperidin-1,4-dicarboxilato de dimetilo (3.97 g, cuant.) como un aceite naranja. MS m/z 312 $(M+H)^+$.

Paso 4: Ácido 2-(4-clorofenil)-1-(metoxicarbonil)piperidin-4-carboxílico

Se disolvió 2-(4-clorofenil)piperidin-1,4-dicarboxilato de dimetilo (3.97 g, 12.73 mmol) en acetonitrilo (55 mL) y agua (1.1 mL), a continuación se añadió bromuro de litio (8.85 g, 101.87 mmol). Se añadió Et_3N (7.10 mL, 50.94 mmol) y la suspensión amarilla resultante se calentó a reflujo durante 2 h. Se añadieron agua (100 mL) y MTBE (150 mL). Las fases se separaron y la fase orgánica se extrajo con agua (2 x). Las fases acuosas recogidas se acidificaron hasta un pH de 1 con HCl 3.8 M y se extrajeron con MTBE (2 x). Las fases orgánicas combinadas se secaron con Na_2SO_4, se filtraron y se evaporaron, para proporcionar el ácido 2-(4-clorofenil)-1-(metoxicarbonil)piperidin-4-carboxílico (3.49 g, 92%) como un semisólido amarillo. MS m/z 298 $(M+H)^+$.

Compuesto de referencia 12

Ácido 1-(metoxicarbonil)-2-(3-(trifluorometil)fenil)piperidin-4-carboxílico

Paso 1: 2-(3-(Trifluorometil)fenil)isonicotinato de metilo

Se mezclaron 2-bromoisonicotinato de metilo (2.71 g, 12.57 mmol), ácido 3-(trifluorometil)fenilborónico (3.58 g, 18.85 mmol), carbonato de potasio (2.61 g, 18.85 mmol) y $PdCl_2$(dppf) (0.162 g, 0.25 mmol) en metanol (30 mL) en dos viales para microondas de 20 mL. Los viales se taparon y se calentaron a 100 °C durante 10 min en un reactor de microondas de nodo único. Se añadieron DCM y agua, y se separaron las fases. La fase acuosa (pH de 9) se extrajo con DCM y las fases orgánicas

combinadas se lavaron con salmuera, se pasaron a través de un separador de fases y se evaporaron, para proporcionar un sólido marrón. El residuo se disolvió en DCM y se introdujo en una columna de intercambio catiónico SCX-2. La columna se lavó con DCM, MeOH y a continuación se eluyó con NH_3/MeOH (1 VC de cada uno). La fase de NH_3/MeOH se evaporó, para proporcionar 2-(3-(trifluorometil)fenil)isonicotinato de metilo (2.6 g, 73%). MS m/z 282 $(M+H)^+$.

Paso 2: 2-(3-(Trifluorometil)fenil)piperidin-4-carboxilato de metilo

Se disolvió 2-(3-(trifluorometil)fenil)isonicotinato de metilo (2.6 g, 9.25 mmol) en ácido acético (40 mL) y se añadió óxido de platino (IV) (0.210 g, 0.92 mmol). La mezcla resultante se hidrogenó en un hidrogenador Büchi a temperatura ambiente y 5 bar durante 3 h. El catalizador se filtró, se lavó con MeOH y se evaporó el eluato. Se añadieron DCM y K_2CO_3 1 M, y se separaron las fases. La fase orgánica se lavó con salmuera, se hizo pasar a través de un separador de fases y se evaporó, para proporcionar 2-(3-(trifluorometil)fenil)piperidin-4-carboxilato de metilo (1.4 g, 52%) como un aceite marronoso. MS m/z 288 $(M+H)^+$.

Paso 3: 2-(3-(Trifluorometil)fenil)piperidin-1,4-dicarboxilato de dimetilo

Se disolvió 2-(3-(trifluorometil)fenil)piperidin-4-carboxilato de metilo (1.4 g, 4.87 mmol) en DCM (50 mL) y a continuación se añadió DIPEA (2.128 mL, 12.18 mmol). Se añadió cloroformiato de metilo (0.537 mL, 6.82 mmol) gota a gota a la disolución. La mezcla de reacción se agitó a temperatura ambiente durante 4 h, se lavó con HCl 0.1 M (100 mL) y $NaHCO_3$ sat. (100 mL), se secó a través de un separador de fases y se evaporó, para proporcionar 2-(3-(trifluorometil)fenil)piperidin-1,4-dicarboxilato de dimetilo (1.7 g, cuant.) como un aceite naranja. MS m/z 346 $(M+H)^+$.

Paso 4: Ácido 1-(metoxicarbonil)-2-(3-(trifluorometil)fenil)piperidin-4-carboxílico

Se disolvió 2-(3-(trifluorometil)fenil)piperidin-1,4-dicarboxilato de dimetilo (1.7 g, 4.92 mmol) en acetonitrilo (22 mL) y agua (0.440 mL), a continuación se añadió bromuro de litio (3.42 g, 39.38 mmol). Se añadió Et_3N (2.74 mL, 19.69 mmol) y la suspensión amarilla resultante se calentó a reflujo durante 2 h. Se añadieron agua (50 mL) y MTBE (150 mL). Las fases se separaron y la fase orgánica se extrajo con agua (2 veces). Las fases acuosas recogidas se acidificaron hasta un pH de 1 con HCl 3.8 M y se extrajeron con MTBE (2 veces). Las fases orgánicas combinadas se secaron con Na_2SO_4, se filtraron y se evaporaron, para proporcionar el ácido 1-(metoxicarbonil)-2-(3-(trifluorometil)fenil)piperidin-4-carboxílico (1.48 g, 91%) como un semisólido amarillento. MS m/z 332 $(M+H)^+$.

Compuesto de referencia 13

Ácido 1-(metoxicarbonil)-2-(4-(trifluorometil)fenil)piperidin-4-carboxílico

Paso 1: 2-(4-(Trifluorometil)fenil)isonicotinato de metilo

Se mezclaron 2-cloroisonicotinato de metilo (5 g, 29.14 mmol), ácido 4-(trifluorometil)fenilborónico (8.30 g, 43.71 mmol), carbonato de potasio (6.04 g, 43.71 mmol) y $PdCl_2$(dppf) (0.633 g, 0.87 mmol) en metanol (30 mL) en dos viales para microondas de 20 mL. Se añadieron dos gotas de agua a uno de los viales y los viales se taparon y se calentaron a 100 °C durante 10 min en un reactor de microondas de nodo único. Se eliminaron los sólidos mediante filtración y se evaporó el filtrado para proporcionar una suspensión de color rojo oscuro. Se añadieron DCM y agua, y se separaron las fases. La fase acuosa (pH de 9) se extrajo con DCM y las fases orgánicas combinadas se lavaron con salmuera, se pasaron a través de un separador de fases y se evaporaron, para proporcionar un sólido marrón. El crudo se disolvió en MTBE (180 mL) y los residuos sólidos se separaron por filtración. Se añadió gota a gota cloruro de hidrógeno (4 M en dioxano, 7.29 mL, 29.14 mmol) mientras se agitaba y se formó una suspensión. La suspensión se agitó a temperatura ambiente durante 2.5 h. El sólido se aisló mediante filtración y se lavó con MTBE. Se añadieron MTBE y

$NaHCO_3$ sat. al sólido, la fase orgánica se secó (Na_2SO_4), se filtró y se evaporó, para proporcionar 2-(4-(trifluorometil)fenil)isonicotinato de metilo (5.75 g, 70%) como un sólido beis. ^1H RMN (400 MHz, $CDCl_3$) δ 4.00 (s, 3H), 7.75 (d, 2H), 7.84 (dd, 1H), 8.18 (d, 2H), 8.33 (s, 1H), 8.87 (dd, 1H). MS m/z 282 $(M+H)^+$.

Paso 2: 2-(4-(Trifluorometil)fenil)piperidin-4-carboxilato de metilo

Se disolvió 2-(4-(trifluorometil)fenil)isonicotinato de metilo (4.985 g, 17.73 mmol) en ácido acético (45 mL) y se añadió óxido de platino (IV) (0.232 g, 1.02 mmol). La mezcla resultante se hidrogenó en un hidrogenador Büchi a temperatura ambiente y 5 bar durante 5 h. Se añadió más óxido de platino (IV) (0.116 g, 0.51 mmol) y se continuó la hidrogenación a 5 bar durante 1 h. El catalizador se filtró, se lavó con MeOH y se evaporó el eluato. Se añadieron DCM y K_2CO_3 al 10%, y se separaron las fases. La fase orgánica se lavó con salmuera, se hizo pasar a través de un separador de fases y se evaporó, para proporcionar 2-(4-(trifluorometil)fenil)piperidin-4-carboxilato de metilo (5.04 g, 99%) como un aceite marrón. MS m/z 288 $(M+H)^+$.

Paso 3: 2-(4-(Trifluorometil)fenil)piperidin-1,4-dicarboxilato de dimetilo

Se disolvió 2-(4-(trifluorometil)fenil)piperidin-4-carboxilato de metilo (4.973 g, 17.31 mmol) en DCM (100 mL), a continuación se añadió DIPEA (3.62 mL, 20.77 mmol) y después cloroformiato de metilo (1.636 mL, 20.77 mmol). La solución se agitó a temperatura ambiente durante 1 h 45 min. La mezcla de reacción se lavó con HCl 0.1 M y $NaHCO_3$ sat. La fase orgánica se hizo pasar a través de un separador de fases y se evaporó, para proporcionar 2-(4-(trifluorometil)fenil)piperidin-1,4-dicarboxilato de dimetilo crudo (6.05 g, 101%) como un aceite marrón. MS m/z 346 $(M+H)^+$.

Paso 4: Ácido 1-(metoxicarbonil)-2-(4-(trifluorometil)fenil)piperidin-4-carboxílico

Se disolvió 2-(4-(trifluorometil)fenil)piperidin-1,4-

dicarboxilato de dimetilo (5.996 g, 17.36 mmol) en acetonitrilo (60 mL) y agua (1.200 mL), a continuación se añadió bromuro de litio (12.06 g, 138.91 mmol). Se añadió trietilamina (9.63 mL, 69.46 mmol) y la suspensión marrón resultante se calentó a reflujo durante 1 h. Se añadieron agua y MTBE. La fase orgánica se extrajo con agua (x2). Las fases acuosas combinadas se acidificaron hasta un pH de 1 con HCl ac. 3.8 M y a continuación se extrajeron con MTBE (x2). Las fases orgánicas combinadas se lavaron con agua y se evaporaron. Las trazas de agua se eliminaron formando un azeótropo con MeCN. Se aisló el ácido 1-(metoxicarbonil)-2-(4-(trifluorometil)fenil)piperidin-4-carboxílico (5.71 g, 99%) como un aceite marrón. MS m/z 332 $(M+H)^+$.

Compuesto de referencia 14

Ácido 2-(3-*tert*-butilfenil)-1-(metoxicarbonil)piperidin-4-carboxílico

Paso 1: 2-(3-*tert*-Butilfenil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano

Se disolvió 1-bromo-3-*tert*-butilbenceno (4.48 g, 21 mmol) en DMSO (150 mL) y se añadieron 4,4,4',4',5,5,5',5'-octametil-2,2'-bi(1,3,2-dioxaborolano) (5.87 g, 23.10 mmol), acetato de potasio (6.18 g, 63.00 mmol) y $Pd(PPh_3)_4$ (1.213 g, 1.05 mmol). La suspensión marrón resultante se calentó hasta 80 °C en una atmósfera de nitrógeno. Después de 9 h, se añadieron agua y éter dietílico, y se separaron las fases. Se evaporó la fase orgánica y se eliminó el agua formando un azeótropo con MeCN. El residuo se purificó dos veces en una columna Biotage (0 => 20% de EtOAc en heptano, 5 VC; columna Biotage® con 340 g de KP-SIL) para proporcionar un aceite amarillo. Se volvió a purificar en una columna Biotage (0 => 20 % de EtOAc en heptano, 8 VC; columna Biotage® con 340 g de KP-SIL). Se aisló 2-(3-*tert*-butilfenil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano (3.39 g, 62%) como un aceite amarillo. ^1H RMN (600 MHz, $CDCl_3$) δ 1.32 (s, 9H), 1.33 (s, 12H), 7.29 (t, 1H), 7.47 - 7.50 (m, 1H), 7.61 (d, 1H), 7.81 (s, 1H).

Paso 2: Clorhidrato de 2-(3-*tert*-butilfenil)isonicotinato

de metilo

Se mezclaron 2-cloroisonicotinato de metilo (1.7 g, 9.91 mmol), 2-(3-*tert*-butilfenil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano (3.393 g, 13.04 mmol), carbonato de potasio (2.054 g, 14.86 mmol) y $PdCl_2$(dppf) (0.215 g, 0.30 mmol) en metanol (14 mL) en un vial para microondas de 20 mL. El vial se tapó y se calentó hasta 100 °C durante 10 min en un reactor de microondas de nodo único. La mezcla de reacción se suspendió en metanol, se eliminó el sólido mediante filtración y se evaporó el filtrado, para proporcionar una suspensión de color rojo oscuro. Se añadieron DCM y agua, y se separaron las fases. La fase acuosa (pH de 9) se extrajo con DCM y las fases orgánicas combinadas se lavaron con salmuera, se pasaron a través de un separador de fases y se evaporaron, para proporcionar un sólido marrón. El sólido se disolvió en MTBE (100 mL) y los residuos sólidos se eliminaron por filtración. Se añadió gota a gota cloruro de hidrógeno (4 M en dioxano, 3.50 mL, 13.99 mmol) mientras se agitaba y se formó una suspensión. La suspensión se agitó a temperatura ambiente durante 3 días. El sólido se aisló mediante filtración y se lavó con MTBE, para proporcionar el clorhidrato de 2-(3-*tert*-butilfenil)isonicotinato de metilo (2.14 g, 70%) como un sólido marronoso. ^{1}H RMN (600 MHz, CD_3OD) δ 1.41 (s, 9H), 4.07 (s, 3H), 7.62 (t, 1H), 7.77 - 7.80 (m, 2H), 8.00 - 8.02 (m, 1H), 8.37 - 8.40 (m, 1H), 8.69 - 8.71 (m, 1H), 8.94 - 8.97 (m, 1H).

Paso 3: 2-(3-*tert*-Butilfenil)piperidin-4-carboxilato de metilo

Se disolvió el clorhidrato de 2-(3-*tert*-butilfenil)isonicotinato de metilo (3 g, 9.81 mmol) en metanol (100 mL) y se añadió óxido de platino (IV) (0.111 g, 0.49 mmol). La mezcla resultante se hidrogenó en un hidrogenador Büchi a temperatura ambiente y 5 bar durante 13 h. Se añadió óxido de platino (IV) (40 mg) a la mezcla y se hidrogenó la mezcla en un hidrogenador Büchi a temperatura ambiente y 5 bar durante 1 h. El catalizador se filtró, se lavó con MeOH y se evaporó el eluato. Se añadieron DCM y $NaHCO_3$ sat. y se

separaron las fases. Se lavó con salmuera, se hizo pasar a través de un separador de fases y se evaporó, para proporcionar 2-(3-*tert*-butilfenil)piperidin-4-carboxilato de metilo (2.56 g, 95%) como un aceite marrón.

Paso 4: 2-(3-*tert*-Butilfenil)piperidin-1,4-dicarboxilato de dimetilo

Se disolvió 2-(3-*tert*-butilfenil)piperidin-4-carboxilato de metilo (2.56 g, 9.30 mmol) en DCM (100 mL) y se añadió DIPEA (2.429 mL, 13.94 mmol) y a continuación cloroformiato de metilo (0.9 mL, 11.43 mmol) a 0 °C. La solución se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se lavó con HCl ac. 1 M (pH de 4) y a continuación con salmuera y $NaHCO_3$ sat. La fase orgánica se hizo pasar a través de un separador de fases y se evaporó, para proporcionar 2-(3-*tert*-butilfenil)piperidin-1,4-dicarboxilato de dimetilo (3.17 g, cuant.) como un aceite marrón.

Paso 5: Ácido 2-(3-*tert*-butilfenil)-1-(metoxicarbonil)piperidin-4-carboxílico

Se disolvió 2-(3-*tert*-butilfenil)piperidin-1,4-dicarboxilato de dimetilo (3.17 g, 9.51 mmol) en acetonitrilo (60 mL) y agua (1.200 mL), a continuación se añadió bromuro de litio (6.61 g, 76.06 mmol) en una porción. Se añadió trietilamina (5.27 mL, 38.03 mmol) y la suspensión marrón resultante se calentó a reflujo durante 1.5 h. Se añadieron agua (120 mL) y MTBE (120 mL). La fase orgánica se extrajo con agua (2 x 25 mL). La fase acuosa recogida se acidificó hasta un pH de 1 con HCl 0.5 M (30 mL) y se extrajo con MTBE (2 x 150 mL). Las fases orgánicas combinadas se lavaron con agua (25 mL), se secaron con Na_2SO_4 y se evaporaron. Se aisló el ácido 2-(3-*tert*-butilfenil)-1-(metoxicarbonil)piperidin-4-carboxílico (2.73 g, 90%) como una espuma.

Compuesto de referencia 15

Ácido 2-(4-*tert*-butilfenil)-1-(metoxicarbonil)piperidin-4-carboxílico

Paso 1: Clorhidrato de 2-(4-*tert*-butilfenil)isonicotinato de metilo

Se mezclaron 2-cloroisonicotinato de metilo (7 g, 40.80 mmol), ácido 4-*tert*-butilfenilborónico (10 g, 56.17 mmol), carbonato de potasio (3.5 g, 25.32 mmol) y $PdCl_2$(dppf) (0.9 g, 1.24 mmol) en metanol (30 mL) en dos porciones iguales en viales para microondas de 20 mL. Los viales se taparon y se calentaron a 100 °C durante 10 min en un reactor de microondas de nodo único. Se eliminaron los sólidos mediante filtración y se evaporó el filtrado para proporcionar una suspensión de color rojo oscuro. Se añadieron DCM y salmuera, y se separaron las fases. La fase acuosa (pH de 9) se extrajo con DCM y las fases orgánicas combinadas se secaron con $MgSO_4$ y se evaporaron. El crudo se disolvió en MTBE (180 mL) y los residuos sólidos se eliminaron por filtración. Se añadió gota a gota cloruro de hidrógeno (4 M en dioxano, 10.20 mL, 40.80 mmol) mientras se agitaba y se formó una suspensión. La suspensión se agitó a temperatura ambiente durante 1 h. El sólido se aisló mediante filtración y se lavó con MTBE. Se aisló el clorhidrato de 2-(4-*tert*-butilfenil)isonicotinato de metilo (9.6 g, 77%) como un sólido de color marrón oscuro. ^{1}H RMN (400 MHz, DMSO) δ 1.30 (s, 9H), 3.92 (s, 3H), 7.53 (d, 2H), 7.80 (dd, 1H), 8.04 (d, 2H), 8.29 (s, 1H), 8.85 (d, 1H), 9.86 (a, 1H). MS m/z 270 $(M+H)^+$.

Paso 2: Clorhidrato de 2-(4-*tert*-butilfenil)piperidin-4-carboxilato de metilo

A una solución del clorhidrato de 2-(4-*tert*-butilfenil)isonicotinato de metilo (9.6 g, 31.39 mmol) en MeOH (100 mL), se añadió óxido de platino (IV) (0.713 g, 3.14 mmol). La mezcla resultante se hidrogenó en un hidrogenador Büchi a 5 bar. Después de 8 h, la mezcla de reacción se filtró a través de un cartucho de filtración de tierras de diatomeas, el residuo se lavó con metanol y se evaporó el filtrado. Se aisló el clorhidrato de 2-(4-*tert*-butilfenil)piperidin-4-carboxilato de metilo (9.66 g, 99%) como un sólido marrón. ^{1}H RMN (400 MHz, DMSO) δ 1.26 (s, 9H), 1.88 - 2.15 (m, 4H), 2.82 - 2.92 (m, 1H), 3.03 - 3.16 (m, 1H), 3.27 - 3.38 (m, 1H), 3.61 (s, 3H), 4.22 - 4.29 (m, 1H), 7.42 - 7.53 (m, 4H), 9.43 (a, 2H). MS m/z 276

$(M+H)^+$.

Paso 3: 2-(4-*tert*-Butilfenil)piperidin-1,4-dicarboxilato de dimetilo

A una suspensión del clorhidrato de 2-(4-*tert*-butilfenil)piperidin-4-carboxilato de metilo (9.66 g, 30.98 mmol) en diclorometano (100 mL), se añadió DIPEA (12 mL, 68.89 mmol). La mezcla de reacción se enfrió en un baño de hielo y se añadió gota a gota cloroformiato de metilo (2.8 mL, 35.56 mmol) durante 5 min. La mezcla de reacción se agitó durante 18 h a temperatura ambiente y se lavó con HCl 3.8 N. La fase acuosa se extrajo con DCM. Las fases orgánicas combinadas se secaron con $MgSO_4$ y se evaporaron. Se aisló 2-(4-*tert*-butilfenil)piperidin-1,4-dicarboxilato de dimetilo (10.6 g, cuant.) como un aceite de color marrón oscuro. MS m/z 334 $(M+H)^+$.

Paso 4: Ácido 2-(4-*tert*-butilfenil)-1-(metoxicarbonil)piperidin-4-carboxílico

A una solución de 2-(4-*tert*-butilfenil)piperidin-1,4-dicarboxilato de dimetilo (10.937 g, 32.80 mmol) en MeCN (100 mL), se añadieron bromuro de litio (6.58 mL, 262.42 mmol), trietilamina (18.19 mL, 131.21 mmol) y agua (2 mL). La mezcla resultante se calentó a reflujo durante 3 h y a continuación se enfrió a temperatura ambiente. Se evaporaron los disolventes y el residuo se disolvió en agua. La fase acuosa se lavó con MTBE y a continuación se acidificó añadiendo HCl 3.8 N. La fase acuosa se extrajo tres veces con DCM. Las fases orgánicas combinadas se secaron con $MgSO_4$ y se evaporaron. Se aisló el ácido 2-(4-*tert*-butilfenil)-1-(metoxicarbonil)piperidin-4-carboxílico (9.5 g, 91%) como una espuma de color marrón claro. MS m/z 320 $(M+H)^+$.

Compuesto de referencia 16

Ácido 1-(metoxicarbonil)-2-(4-(metilsulfonil)fenil)piperidin-4-carboxílico

Paso 1: 2-(4-(Metilsulfonil)fenil)isonicotinato de metilo

Se disolvieron 2-cloroisonicotinato de metilo (5 g, 29.14 mmol), ácido 4-(metilsulfonil)fenilborónico (7.58 g, 37.88 mmol), carbonato de potasio (2.416 g, 17.48 mmol) y $PdCl_2$(dppf)

(0.633 g, 0.87 mmol) en metanol (30 mL) y se repartieron en dos viales para microondas. Cada vial se calentó hasta 100 °C en un reactor de microondas de nodo único durante 35 min. Se añadieron DCM (250 mL) y agua (250 mL), se agitó y se separaron las fases. La fase acuosa se extrajo con DCM (250 mL). Las fases orgánicas combinadas se lavaron con salmuera (500 mL), se secaron con un separador de fases y se evaporaron al vacío. El residuo se purificó mediante cromatografía flash automatizada en dos columnas Biotage® con 340 g de KP-SIL. Se utilizó como fase móvil un gradiente de 20 - 70% de EtOAc en heptano en 10 VC y a continuación 70% de EtOAc en heptano en 5 VC. El producto se recogió utilizando una longitud de onda de 253 nm. Las fracciones de producto se recogieron y se evaporaron al vacío, para proporcionar 2-(4-(metilsulfonil)fenil)isonicotinato de metilo (5.66 g, 66.7%) como un sólido blanco. ^{1}H RMN (600 MHz, $CDCl_3$) δ 3.09 (s, 3H), 3.98 (s, 3H), 7.85 (dd, 1H), 8.05 (d, 2H), 8.25 (d, 2H), 8.34 (s, 1H), 8.86 (t, 1H).

Paso 2: Clorhidrato de 2-(4-(Metilsulfonil)fenil)piperidin-4-carboxilato de metilo

Se suspendió 2-(4-(metilsulfonil)fenil)isonicotinato de metilo (5.663 g, 19.44 mmol) en MeOH (20 mL) y se añadió cloruro de hidrógeno (1.25 M en MeOH, 40 mL, 50.00 mmol). La mezcla se agitó a temperatura ambiente durante 20 min y a continuación se evaporó al vacío. La sal de HCl se suspendió en MeOH (100 mL) y se añadió óxido de platino (IV) (0.221 g, 0.97 mmol). La mezcla se hidrogenó en un hidrogenador Büchi a temperatura ambiente y 5 bar durante 2 h. El catalizador se filtró y se lavó con MeOH. El filtrado se evaporó al vacío, para proporcionar el clorhidrato de 2-(4-(metilsulfonil)fenil)piperidin-4-carboxilato de metilo (5.84 g, 90%) como un sólido blanco. MS m/z 298 $(M+H)^+$.

Paso 3: 2-(4-(Metilsulfonil)fenil)piperidin-1,4-dicarboxilato de dimetilo

Se disolvieron el clorhidrato de 2-(4-(metilsulfonil)fenil)piperidin-4-carboxilato de metilo (5.2 g,

15.58 mmol) y DIPEA (6.78 mL, 38.94 mmol) en DCM (40 mL) y se añadió cloroformiato de metilo (1.472 mL, 18.69 mmol). La reacción se agitó a temperatura ambiente durante 50 min. Se añadió DCM (160 mL). La fase orgánica se lavó con HCl 0.1 M (2 x 200 mL) y $NaHCO_3$ sat. (200 mL), se secó con un separador de fases y se evaporó al vacío, para proporcionar 2-(4-metilsulfonil)fenil)piperidin-1,4-dicarboxilato de dimetilo crudo (5.95 g, 108%). MS m/z 356 $(M+H)^+$.

Paso 4: Ácido 1-(metoxicarbonil)-2-(4-(metilsulfonil)fenil)piperidin-4-carboxílico

Se disolvió 2-(4-(metilsulfonil)fenil)piperidin-1,4-dicarboxilato de dimetilo (5.952 g, 16.75 mmol) en acetonitrilo (50 mL) y agua (1.000 mL), a continuación se añadió bromuro de litio (11.64 g, 133.98 mmol). Se añadió trietilamina (9.29 mL, 66.99 mmol) y la mezcla de reacción se calentó a reflujo durante 1.5 h. Se añadieron MTBE (150 mL) y agua (150 mL), se agitó y se separaron las fases. La fase orgánica se extrajo con agua (2x200 mL). Las fases acuosas combinadas se acidificaron hasta un pH de 1 con HCl 3 M y se extrajeron con MTBE (2x500 mL). Las fases orgánicas combinadas se secaron con Na_2SO_4, se filtraron y se evaporaron al vacío para proporcionar el ácido 1-(metoxicarbonil)-2-(4-metilsulfonil)fenil)piperidin-4-carboxílico (4.76 g, 83%). MS m/z 342 $(M+H)^+$.

Compuesto de referencia 17

Ácido 1-(metoxicarbonil)-2-(6-(trifluorometil)piridin-3-il)piperidin-4-carboxílico

Paso 1: Clorhidrato de 6'-(trifluorometil)-2,3'-bipiridin-4-carboxilato de metilo

Se mezclaron 2-cloroisonicotinato de metilo (3 g, 17.48 mmol), ácido 6-(trifluorometil)piridin-3-ilborónico (5.01 g, 26.23 mmol), carbonato de potasio (1.450 g, 10.49 mmol) y $PdCl_2$(dppf) (0.380 g, 0.52 mmol) en metanol (30 mL) en dos viales diferentes para microondas de 20 mL. Los viales se taparon y se calentaron a 100 °C durante 10 min en un reactor de microondas de nodo único. Se añadieron agua y DCM, y se separaron las fases. La fase acuosa (pH de 9) se extrajo con

DCM y las fases orgánicas combinadas se lavaron con salmuera, se pasaron a través de un separador de fases y se evaporaron, para proporcionar un sólido naranja. El sólido se diluyó con MTBE y a continuación se añadió HCl (4 M en dioxano) para obtener una suspensión. El sólido se aisló mediante filtración para proporcionar el clorhidrato de 6'-(trifluorometil)-2,3'-bipiridin-4-carboxilato de metilo (3.2 g, 57%). MS m/z 283 $(M+H)^+$.

Paso 2: Clorhidrato de 2-(6-(trifluorometil)piridin-3-il)piperidin-4-carboxilato de metilo

Se disolvió el clorhidrato de 6'-(trifluorometil)-2,3'-bipiridin-4-carboxilato de metilo (2.5 g, 7.86 mmol) en MeOH (20 mL) y se añadió óxido de platino (IV) (0.036 g, 0.16 mmol). La mezcla resultante se hidrogenó en un hidrogenador Büchi a temperatura ambiente y 5 bar durante 1 h. Se añadió catalizador adicional y se continuó la hidrogenación durante 1 h. El catalizador se filtró, se lavó con MeOH y se evaporó el eluato, para proporcionar el clorhidrato de 2-(6-(trifluorometil)piridin-3-il)piperidin-4-carboxilato de metilo (2.2 g, 86%) como un sólido marrón. MS m/z 289 $(M+H)^+$.

Paso 3: 2-(6-(Trifluorometil)piridin-3-il)piperidin-1,4-dicarboxilato de dimetilo

Se disolvió el clorhidrato de 2-(6-(trifluorometil)piridin-3-il)piperidin-4-carboxilato de metilo (3 g, 9.24 mmol) en DCM (50 mL) y DIPEA (4.03 mL, 23.10 mmol). Se añadió cloroformiato de metilo (1.019 mL, 12.93 mmol) gota a gota a la disolución. La mezcla se agitó a temperatura ambiente durante 10 minutos. La mezcla se lavó con HCl 0.1 M (2x100 mL) y $NaHCO_3$ sat. (100 mL), a continuación se secó a través de un separador de fases y se evaporó, para proporcionar 2-(6-(trifluorometil)piridin-3-il)piperidin-1,4-dicarboxilato de dimetilo crudo (3 g, 94%) como un aceite de color marrón oscuro. MS m/z 347 $(M+H)^+$.

Paso 4: Ácido 1-(metoxicarbonil)-2-(6-(trifluorometil)piridin-3-il)piperidin-4-carboxílico

Se disolvió 2-(6-(trifluorometil)piridin-3-il)piperidin-1,4-dicarboxilato de dimetilo crudo (2.9 g, 8.38 mmol) en acetonitrilo (35 mL) y agua (0.700 mL), a continuación se añadió bromuro de litio (2.91 g, 33.50 mmol). Se añadió Et_3N (2.334 mL, 16.75 mmol) y la suspensión amarilla resultante se calentó a reflujo durante 1 h. Se añadieron agua (100 mL) y MTBE (150 mL). Las fases se separaron y la fase orgánica se extrajo con agua (2 veces). Las fases acuosas recogidas se acidificaron hasta un pH de 1 con HCl 3.8 M y se extrajeron con MTBE (2 veces). Las fases orgánicas combinadas se secaron con Na_2SO_4, se filtraron y se evaporaron, para proporcionar el ácido 1-(metoxicarbonil)-2-(6-(trifluorometil)piridin-3-il)piperidin-4-carboxílico crudo (2.5 g, 90%) como un sólido amarillento. MS m/z 333 $(M+H)^+$.

Compuesto de referencia 18

Ácido 2-(5-*tert*-butiltiofen-2-il)-1-(metoxicarbonil)piperidin-4-carboxílico

Paso 1: 2-(5-*tert*-Butiltiofen-2-il)isonicotinato de metilo

Se agitaron 2-cloroisonicotinato de metilo (175 mg, 1.02 mmol), 2-(5-*tert*-butiltiofen-2-il)-4,4,5,5-tetrametil-1,3,2-dioxaborolano (300 mg, 1.13 mmol), K_2CO_3 (85 mg, 0.61 mmol) y $PdCl_2$(dppf) (37.3 mg, 0.05 mmol) en metanol (2 mL) y se calentaron en un reactor de microondas de nodo único hasta 100 °C durante 30 min. Se añadieron DCM (50 mL) y agua (50 mL), se agitó y se separaron las fases. La fase acuosa se extrajo con DCM (50 mL). Las fases orgánicas combinadas se secaron con un separador de fases y se evaporaron al vacío. El residuo se purificó mediante cromatografía flash automatizada en una columna Biotage® con 50 g de KP-SIL. Se utilizó como fase móvil un gradiente de 5% de EtOAc en heptano en 2 VC y a continuación de 5% a 20% de EtOAc en heptano en 9 VC. El producto se recogió utilizando una longitud de onda de 295 nm. Las fracciones de producto se recogieron y se evaporaron al vacío, para proporcionar 2-(5-*tert*-butiltiofen-2-il)isonicotinato de metilo (213 mg, 76%). ^1H RMN (600 MHz, $CDCl_3$) δ 1.41 (s, 9H), 3.96 (s, 3H), 6.85 (d, 1H), 7.50 (s, 1H), 7.61 (d, 1H), 8.13 (s, 1H),

8.64 (d, 1H). MS m/z 276 $(M+H)^+$.

Paso 2: Clorhidrato de 2-(5-*tert*-butiltiofen-2-il)piperidin-4-carboxilato de metilo

Se disolvió 2-(5-*tert*-butiltiofen-2-il)isonicotinato de metilo (2.02 g, 7.34 mmol) en cloruro de hidrógeno (1.25 M en MeOH, 11.74 mL, 14.67 mmol) y se agitó a temperatura ambiente durante 30 min. El disolvente se evaporó al vacío. El residuo se disolvió en MeOH (20 mL), se añadió óxido de platino (IV) (0.050 g, 0.22 mmol) y la mezcla de reacción se hidrogenó en un hidrogenador Büchi a 5 bar y temperatura ambiente durante 3 h. Se añadió óxido de platino (IV) adicional (0.050 g, 0.22 mmol) y se continuó la hidrogenación durante 3 h. La mezcla de reacción se filtró a través de celite, se lavó con MeOH y se evaporó el filtrado al vacío. El residuo se volvió a disolver en MeOH (15 mL) y se añadió óxido de platino (IV) (0.167 g, 0.73 mmol). La hidrogenación se continuó durante 3 h. Se añadió óxido de platino (IV) adicional (0.167 g, 0.73 mmol) y se continuó la hidrogenación durante 2 h. La mezcla de reacción se filtró a través de celite, se lavó con MeOH y se evaporó el filtrado al vacío, para proporcionar el clorhidrato de 2-(5-*tert*-butiltiofen-2-il)piperidin-4-carboxilato de metilo (2.360 g, 101%) como un aceite negro. MS m/z 282 $(M+H)^+$.

Paso 3: 2-(5-*tert*-Butiltiofen-2-il)piperidin-1,4-dicarboxilato de dimetilo

Se disolvieron el clorhidrato de 2-(5-*tert*-butiltiofen-2-il)piperidin-4-carboxilato de metilo (2.36 g, 7.42 mmol) y DIPEA (3.24 mL, 18.56 mmol) en DCM (30 mL). Se añadió cloroformiato de metilo (0.690 mL, 8.91 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 1 h. Se añadió DCM (170 mL). La fase orgánica se lavó con HCl 0.1 M (2 x 200 mL) y $NaHCO_3$ sat. (200 mL), se secó con un separador de fases y se evaporó al vacío, para proporcionar 2-(5-*tert*-butiltiofen-2-il)piperidin-1,4-dicarboxilato de dimetilo (2.490 g, 99%) como un aceite oscuro. MS m/z 340 $(M+H)^+$.

Paso 4: Ácido 2-(5-*tert*-butiltiofen-2-il)-1-(metoxicarbonil)piperidin-4-carboxílico

Se disolvió 2-(5-*tert*-butiltiofen-2-il)piperidin-1,4-dicarboxilato de dimetilo (2.49 g, 7.34 mmol) en acetonitrilo (20 mL). Se añadieron agua (0.400 mL) y bromuro de litio (5.10 g, 58.68 mmol). Después de 5 min, se añadió TEA (4.09 mL, 29.34 mmol) y la reacción se calentó a reflujo durante 1 h. Se añadieron MTBE (150 mL) y agua (150 mL), se agitó y se separaron las fases. La fase orgánica se extrajo con agua (150 mL). Las fases acuosas combinadas se acidificaron con HCl 3 M hasta un pH de 1 y se extrajeron con MTBE (2 x 300 mL). Las fases orgánicas combinadas se secaron con Na_2SO_4, se filtraron y se evaporaron al vacío para proporcionar el ácido 2-(5-*tert*-butiltiofen-2-il)-1-(metoxicarbonil)piperidin-4-carboxílico (1.125 g, 47.1%) como una espuma blanca. MS m/z 326 $(M+H)^+$.

Compuesto de referencia 19

Ácido 2-(2,4-difluorofenil)-1-(metoxicarbonil)piperidin-4-carboxílico

Paso 1: Clorhidrato de 2-(2,4-difluorofenil)isonicotinato de metilo

Se mezclaron 2-cloroisonicotinato de metilo (3 g, 17.48 mmol), ácido 2,4-difluorofenilborónico (4.14 g, 26.23 mmol), carbonato de potasio (1.812 g, 13.11 mmol) y $PdCl_2$(dppf) (0.380 g, 0.52 mmol) en metanol (30 mL) en dos viales diferentes para microondas de 20 mL. Los viales se taparon y se calentaron a 100 °C durante 10 min en un reactor de microondas de nodo único. Se añadieron agua y DCM, y se separaron las fases. La fase acuosa (pH de 9) se extrajo con DCM y las fases orgánicas combinadas se lavaron con salmuera, se pasaron a través de un separador de fases y se evaporaron, para proporcionar un sólido marrón. El sólido se disolvió en MTBE y se agitó durante 15 minutos, a continuación se filtró. La fase de MTBE naranja se trató con cloruro de hidrógeno (4 M en dioxano, 4.37 mL, 17.48 mmol) y se agitó durante 1 h a temperatura ambiente. El sólido formado se aisló mediante filtración. Se aisló el clorhidrato de 2-(2,4-difluorofenil)isonicotinato de metilo (4.0 g, 80%) como un sólido anaranjado. MS m/z 250 $(M+H)^+$.

Paso 2: Clorhidrato de 2-(2,4-difluorofenil)piperidin-4-

carboxilato de metilo

Se disolvió el clorhidrato de 2-(2,4-difluorofenil)isonicotinato de metilo (3.93 g, 13.76 mmol) en MeOH (40 mL) y se añadió óxido de platino (IV) (0.312 g, 1.38 mmol). La mezcla resultante se hidrogenó en un hidrogenador Büchi a temperatura ambiente y 5 bar durante 2 h. El catalizador se filtró, se lavó con MeOH y se evaporó el eluato, para obtener el clorhidrato de 2-(2,4-difluorofenil)piperidin-4-carboxilato de metilo (2.34 g, 58%) como un sólido amarillento. MS m/z 256 $(M+H)^+$.

Paso 3: 2-(2,4-Difluorofenil)piperidin-1,4-dicarboxilato de dimetilo

Se disolvió el clorhidrato de 2-(2,4-difluorofenil)piperidin-4-carboxilato de metilo (2.34 g, 8.02 mmol) en DCM (50 mL) y a continuación se añadió DIPEA (3.50 mL, 20.05 mmol). Se añadió cloroformiato de metilo (0.884 mL, 11.23 mmol) gota a gota a la disolución. La mezcla se agitó a temperatura ambiente durante 4 h, se lavó con HCl 0.1 M (100 mL) y $NaHCO_3$ sat. (100 mL), a continuación se secó a través de un separador de fases y se evaporó, para proporcionar 2-(2,4-difluorofenil)piperidin-1,4-dicarboxilato de dimetilo (2.38 g, 95%) como un aceite naranja.

Paso 4: Ácido 2-(2,4-difluorofenil)-1-(metoxicarbonil)piperidin-4-carboxílico

Se disolvió 2-(2,4-difluorofenil)piperidin-1,4-dicarboxilato de dimetilo (2.38 g, 7.60 mmol) en acetonitrilo (35 mL) y agua (0.700 mL), a continuación se añadió bromuro de litio (5.28 g, 60.77 mmol). Se añadió Et_3N (4.24 mL, 30.39 mmol) y la suspensión amarilla resultante se calentó a reflujo durante 2 h. Se añadieron agua (50 mL) y MTBE (150 mL). Las fases se separaron y la fase orgánica se extrajo con agua (2 veces). Las fases acuosas recogidas se acidificaron hasta un pH de 1 con HCl 3.8 M y se extrajeron con MTBE (2 veces). Las fases orgánicas combinadas se secaron con Na_2SO_4, se filtraron y se evaporaron, para proporcionar el ácido 2-(2,4-difluorofenil)-1-(metoxicarbonil)piperidin-4-carboxílico (2.27

g, cuant.) como un semisólido amarillento. MS m/z 300 $(M+H)^+$.

Compuesto de referencia 20

Ácido 2-(4-cloro-2-fluorofenil)-1-(metoxicarbonil)piperidin-4-carboxílico

Paso 1: Clorhidrato de 2-(4-cloro-2-fluorofenil)isonicotinato de metilo

Se mezclaron 2-cloroisonicotinato de metilo (4 g, 23.31 mmol), ácido 4-cloro-2-fluorofenilborónico (6.10 g, 34.97 mmol), carbonato de potasio (2.416 g, 17.48 mmol) y $PdCl_2$(dppf) (0.506 g, 0.70 mmol) en metanol (30 mL) en dos viales diferentes para microondas de 20 mL. Los viales se taparon y se calentaron a 100 °C durante 10 min en un reactor de microondas de nodo único. Se añadieron agua y DCM, y se separaron las fases. La fase acuosa (pH de 9) se extrajo con DCM y las fases orgánicas combinadas se lavaron con salmuera, se pasaron a través de un separador de fases y se evaporaron, para proporcionar un sólido de color naranja oscuro. El sólido se disolvió en MTBE y se agitó durante 15 minutos, a continuación se filtró. La fase de MTBE naranja se trató con cloruro de hidrógeno (4 M en dioxano, 5.83 mL, 23.31 mmol) y se agitó durante 1 h a temperatura ambiente. El precipitado se aisló mediante filtración, para proporcionar el clorhidrato de 2-(4-cloro-2-fluorofenil)isonicotinato de metilo (7.22 g, cuant.) como un sólido anaranjado. MS m/z 266 $(M+H)^+$.

Paso 2: 2-(4-Cloro-2-fluorofenil)piperidin-4-carboxilato de metilo

Se disolvió el clorhidrato de 2-(4-cloro-2-fluorofenil)isonicotinato de metilo (7.26 g, 24.03 mmol) en MeOH (100 mL) y se añadió óxido de platino (IV) (0.546 g, 2.40 mmol). La mezcla resultante se hidrogenó en un hidrogenador Büchi a temperatura ambiente y 5 bar durante 1 h. El catalizador se filtró, se lavó con MeOH y se evaporó el eluato, para proporcionar el clorhidrato de 2-(4-cloro-2-fluorofenil)piperidin-4-carboxilato de metilo (7.45 g, cuant.) como un sólido marrón. MS m/z 272 $(M+H)^+$.

Paso 3: 2-(4-Cloro-2-fluorofenil)piperidin-1,4-

dicarboxilato de dimetilo

Se disolvió 2-(4-cloro-2-fluorofenil)piperidin-4-carboxilato de metilo (7.45 g, 27.42 mmol) en DCM (120 mL) y a continuación se añadió DIPEA (11.97 mL, 68.55 mmol). Se añadió cloroformiato de metilo (3.02 mL, 38.39 mmol) gota a gota a la disolución. La mezcla se agitó a temperatura ambiente durante 3 h. La mezcla se lavó con HCl 0.1 M (2x100 mL) y $NaHCO_3$ sat. (100 mL), a continuación se secó a través de un separador de fases y se evaporó, para proporcionar 2-(4-cloro-2-fluorofenil)piperidin-1,4-dicarboxilato de dimetilo (7.77 g, 86%) como un aceite naranja. MS m/z 330 $(M+H)^+$.

Paso 4: Ácido 2-(4-cloro-2-fluorofenil)-1-(metoxicarbonil)piperidin-4-carboxílico

Se disolvió 2-(4-cloro-2-fluorofenil)piperidin-1,4-dicarboxilato de dimetilo (7.77 g, 23.56 mmol) en acetonitrilo (100 mL) y agua (2.000 mL), a continuación se añadió bromuro de litio (16.37 g, 188.51 mmol). Se añadió Et_3N (13.14 mL, 94.25 mmol) y la suspensión amarilla resultante se calentó a reflujo durante 2 h. Se añadieron agua (200 mL) y MTBE (300 mL). Las fases se separaron y la fase orgánica se extrajo con agua (2 veces). Las fases acuosas recogidas se acidificaron hasta un pH de 1 con HCl 3.8 M y se extrajeron con MTBE (2 veces). Las fases orgánicas combinadas se secaron con $MgSO_4$, se filtraron y se evaporaron para proporcionar el ácido 2-(4-cloro-2-fluorofenil)-1-(metoxicarbonil)piperidin-4-carboxílico (7.28 g, 98%) como un semisólido amarillo. MS m/z 316 $(M+H)^+$.

Compuesto de referencia 21

Ácido 2-(2-cloro-4-fluorofenil)-1-(metoxicarbonil)piperidin-4-carboxílico

Paso 1: Clorhidrato de 2-(2-cloro-4-fluorofenil)isonicotinato de metilo

Se mezclaron 2-cloroisonicotinato de metilo (3.5 g, 20.40 mmol), ácido 2-cloro-4-fluorofenilborónico (3.91 g, 22.44 mmol), carbonato de potasio (2.114 g, 15.30 mmol) y $PdCl_2(dppf)$ (0.443 g, 0.61 mmol) en metanol (30 mL) en dos viales diferentes para microondas de 20 mL. Los viales se taparon y se

calentaron a 100 °C durante 10 min en un reactor de microondas de nodo único. Se añadieron agua y DCM, y se separaron las fases. La fase acuosa (pH de 9) se extrajo con DCM y las fases orgánicas combinadas se lavaron con salmuera, se pasaron a través de un separador de fases y se evaporaron, para proporcionar un sólido de color marrón oscuro. El sólido se disolvió en MTBE y se agitó durante 15 minutos, a continuación se filtró. La fase de MTBE se trató con cloruro de hidrógeno (4 M en dioxano, 5.10 mL, 20.40 mmol) y se agitó durante 1 h a temperatura ambiente. El precipitado se aisló mediante filtración. Se obtuvo 2-(2-cloro-4-fluorofenil)isonicotinato de metilo (2.350 g, 38.1%) como un sólido de color amarillo claro. ^{1}H RMN (400 MHz, $CDCl_3$) δ 4.13 (s, 3H), 7.24 - 7.33 (m, 1H), 7.36 (d, 1H), 7.82 - 8.03 (m, 1H), 8.34 (s a, 1H), 8.56 (s a, 1H), 9.08 (s a, 1H). MS m/z 266 $(M+H)^+$.

Paso 2: Clorhidrato de 2-(2-cloro-4-fluorofenil)piperidin-4-carboxilato de metilo

Se disolvió el clorhidrato de 2-(2-cloro-4-fluorofenil)isonicotinato de metilo (2.35 g, 7.78 mmol) en metanol (50 mL) y se añadió óxido de platino (IV) (0.177 g, 0.78 mmol). La mezcla de reacción se hidrogenó en un hidrogenador Büchi a temperatura ambiente y 5 bar durante 9 h. El catalizador se eliminó por filtración y se evaporó el disolvente. El residuo se disolvió en metanol (50.0 mL) y se añadió óxido de platino (IV) (144 mg, 0.63 mmol). Se continuó la hidrogenación a temperatura ambiente y 5 bar durante 4 h. El catalizador se eliminó por filtración y se evaporó el disolvente. Se obtuvo el clorhidrato de 2-(2-cloro-4-fluorofenil)piperidin-4-carboxilato de metilo crudo (2.4 g, 100%) como un sólido amarillo. MS m/z 272 $(M+H)^+$.

Paso 3: 2-(2-Cloro-4-fluorofenil)piperidin-1,4-dicarboxilato de dimetilo

Se disolvió el clorhidrato de 2-(2-cloro-4-fluorofenil)piperidin-4-carboxilato de metilo (2.4 g, 7.79 mmol) en diclorometano (50 mL) para obtener una solución incolora. Se añadieron DIPEA (3.39 mL, 19.47 mmol) y

cloroformiato de metilo (0.736 mL, 9.35 mmol) y la mezcla se agitó a temperatura ambiente durante 14 h. Se añadió HCl 0.1 M y la fase acuosa se extrajo con DCM. Las fases orgánicas combinadas se filtraron a través de un separador de fases y se evaporaron. Se obtuvo 2-(2-cloro-4-fluorofenil)piperidin-1,4-dicarboxilato crudo (2.5 g, 97%) como un aceite amarillo. MS m/z 330 $(M+H)^+$.

Paso 4: Ácido 2-(2-cloro-4-fluorofenil)-1-(metoxicarbonil)piperidin-4-carboxílico

Se disolvió 2-(2-cloro-4-fluorofenil)piperidin-1,4-dicarboxilato de dimetilo (2.5 g, 7.58 mmol) en acetonitrilo (50 mL) y agua (1 mL), a continuación se añadió bromuro de litio (5.27 g, 60.65 mmol). Se añadió trietilamina (4.20 mL, 30.33 mmol) y la suspensión resultante se calentó a reflujo durante 7 h. Se añadieron MTBE (170 mL) y agua (90 mL), se separaron las fases y se extrajo la fase orgánica con agua. Las fases acuosas combinadas se acidificaron con HCl 3.8 M y se extrajeron con EtOAc. Las fases orgánicas combinadas se secaron con Na_2SO_4 y se evaporaron. Se aisló el ácido 2-(2-cloro-4-fluorofenil)-1-(metoxicarbonil)piperidin-4-carboxílico (2.130 g, 89%) como un sólido marrón. MS m/z 316 $(M+H)^+$.

Compuesto de referencia 22

Ácido 2-(4-cloro-3-fluorofenil)-1-(metoxicarbonil)piperidin-4-carboxílico

Paso 1: 2-(4-Cloro-3-fluorofenil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano

Se suspendieron 4-bromo-1-cloro-2-fluorobenceno (4 g, 19.10 mmol), 4,4,4',4',5,5,5',5'-octametil-2,2'-bi(1,3,2-dioxaborolano) (5.63 g, 22.15 mmol), $PdCl_2$(dppf) (0.691 g, 0.95 mmol) y acetato de potasio (3.75 g, 38.20 mmol) en DMSO (40 mL) y se calentaron hasta 80 °C durante 4 h. Se dejó que la mezcla de reacción se enfriara hasta temperatura ambiente. Se diluyó con EtOAc (400 mL) y se filtró a través de celite. La fase orgánica se lavó con agua (3x500 mL) y salmuera (500 mL), se secó con un separador de fases y se evaporó al vacío. El residuo se purificó mediante cromatografía flash automatizada

en 2 columnas Biotage® con 100 g de KP-SIL. Se utilizó como fase móvil un gradiente de 0% a 30% de EtOAc en heptano en 15 VC. El producto se recogió utilizando una longitud de onda de 258 nm. Se aisló 2-(4-cloro-3-fluorofenil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano (2.100 g, 42.9%) como un aceite incoloro. ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.32 (s, 12H), 7.37 (t, 1H), 7.48 (d, 1H), 7.52 (d, 1H).

Paso 2: 2-(4-Cloro-3-fluorofenil)isonicotinato de metilo

Se combinaron 2-cloroisonicotinato de metilo (1.2 g, 6.99 mmol), carbonato de potasio (0.580 g, 4.20 mmol) y $PdCl_2$(dppf) (0.122 g, 0.17 mmol) en un vial para microondas. Se añadió 2-(4-cloro-3-fluorofenil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano (2.1 g, 8.19 mmol) disuelto en MeOH (15 mL). La mezcla de reacción se calentó en un reactor de microondas de nodo único a 100 °C durante 15 min. Se añadieron DCM (125 mL) y agua (125 mL), se agitó y se separaron las fases. La fase acuosa se extrajo con DCM (125 mL). Las fases orgánicas combinadas se lavaron con salmuera (250 mL), se secaron con un separador de fases y se evaporaron al vacío. El residuo se purificó mediante cromatografía flash automatizada en una columna Biotage® con 100 g de KP-SIL. Se utilizó como fase móvil un gradiente de 10% de EtOAc en heptano en 3 VC y a continuación de 10% a 50% de EtOAc en heptano en 12 VC. El producto se recogió utilizando una longitud de onda de 253 nm. Se aisló 2-(4-cloro-3-fluorofenil)isonicotinato de metilo (1.473 g, 79%) como un sólido blanco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 4.00 (s, 3H), 7.48 - 7.54 (m, 1H), 7.76 - 7.83 (m, 2H), 7.88 - 7.94 (m, 1H), 8.24 - 8.27 (m, 1H), 8.83 (dd, 1H).

Paso 3: Clorhidrato de 2-(4-cloro-3-fluorofenil)piperidin-4-carboxilato de metilo

Se suspendió 2-(4-cloro-3-fluorofenil)isonicotinato de metilo (1.473 g, 5.54 mmol) en MeOH (30 mL) y se añadió cloruro de hidrógeno (1.25 M en MeOH, 9.86 mL, 11.09 mmol) gota a gota mientras se agitaba. Después de 15 min, se evaporó el disolvente, se volvió a disolver la sal de HCl en MeOH (10 mL) y se añadió óxido de platino (IV) (0.063 g, 0.28 mmol). La

mezcla resultante se hidrogenó en un hidrogenador Büchi a temperatura ambiente y 5 bar durante 1.5 h. Se añadió óxido de platino (IV) (0.038 g, 0.17 mmol) y se continuó la hidrogenación durante 1 h. El catalizador se filtró y se lavó con MeOH. El disolvente se evaporó al vacío, para proporcionar el clorhidrato de 2-(4-cloro-3-fluorofenil)piperidin-4-carboxilato de metilo (1.639 g, 96%) como un sólido blanco. MS m/z 272 $(M+H)^+$.

Paso 4: 2-(4-Cloro-3-fluorofenil)piperidin-1,4-dicarboxilato de dimetilo

Se disolvieron el clorhidrato de 2-(4-cloro-3-fluorofenil)piperidin-4-carboxilato de metilo (1.639 g, 5.32 mmol) y DIPEA (2.316 mL, 13.30 mmol) en DCM (10 mL). Se añadió gota a gota cloroformiato de metilo (0.503 mL, 6.38 mmol) y la reacción se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se diluyó con DCM (100 mL), se lavó con HCl 0.1 M (2 x 75 mL), y $NaHCO_3$ sat. (100 mL), se hizo pasar a través de un separador de fases y se evaporó al vacío, para proporcionar 2-(4-cloro-3-fluorofenil)piperidin-1,4-dicarboxilato de dimetilo (1.625 g, 93%) como un aceite incoloro. MS m/z 330 $(M+H)^+$.

Paso 5: Ácido 2-(4-cloro-3-fluorofenil)-1-(metoxicarbonil)piperidin-4-carboxílico

Se disolvió 2-(4-cloro-3-fluorofenil)piperidin-1,4-dicarboxilato de dimetilo (1.625 g, 4.93 mmol) en acetonitrilo (20 mL) y agua (0.400 mL), se añadió bromuro de litio (3.42 g, 39.42 mmol). A continuación, se añadió trietilamina (2.73 mL, 19.71 mmol) y la reacción se calentó a reflujo durante 1.5 h. Se añadieron agua (200 mL) y MTBE (150 mL), se agitó y se separaron las fases. La fase orgánica se extrajo con agua (2x200 mL). Las fases acuosas combinadas se acidificaron con HCl 3 M hasta un pH de 1 y a continuación se extrajeron con MTBE (2x500 mL). Las fases orgánicas combinadas se secaron con Na_2SO_4, se filtraron y se evaporaron al vacío para proporcionar el ácido 2-(4-cloro-3-fluorofenil)-1-(metoxicarbonil)piperidin-4-carboxílico (1.430 g, 92%). MS m/z 314 $(M-H)^-$.

Compuesto de referencia 23

Ácido 2-(2,4-diclorofenil)-1-(metoxicarbonil)piperidin-4-carboxílico

Paso 1: 2-(2,4-Diclorofenil)isonicotinato de metilo

Se repartieron carbonato de potasio (1.812 g, 13.11 mmol), 2-cloroisonicotinato de metilo (3 g, 17.48 mmol), ácido 2,4-diclorofenilborónico (5.00 g, 26.23 mmol), $PdCl_2$(dppf) (0.380 g, 0.52 mmol) y MeOH (30.6 mL) en dos viales para microondas de 20 mL y se calentaron hasta 100 °C durante 35 min en un reactor de microondas de nodo único. La mezcla de reacción se diluyó con agua y DCM, se extrajo con DCM y se evaporó. Se purificó mediante cromatografía flash automatizada utilizando 5% de EtOAc en heptano -> 30% de EtOAc en 15 VC a 280 nm. Se aisló 2-(2,4-diclorofenil)isonicotinato de metilo (2.3 g, 47%) como un sólido blanco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 3.98 (s, 3H), 7.37 (dd, 1H), 7.53 (d, 1H), 7.57 (d, 1H), 7.86 (dd, 1H), 8.20 (s, 1H), 8.87 (d, 1H). MS m/z 282 $(M+H)^+$.

Paso 2: Clorhidrato de 2-(2,4-diclorofenil)piperidin-4-carboxilato de metilo

Se disolvió el clorhidrato de 2-(2,4-diclorofenil)isonicotinato de metilo (2.60 g, 8.15 mmol) en MeOH (50 mL), se añadió óxido de platino (IV) (0.019 g, 0.08 mmol) y se hidrogenó en un hidrogenador Büchi a 5 bar durante 90 min. La mezcla de reacción se filtró y se evaporó, para obtener el clorhidrato de 2-(2,4-diclorofenil)piperidin-4-carboxilato de metilo crudo (2.8 g) como un sólido blanco. MS m/z 288 $(M+H)^+$.

Paso 3: 2-(2,4-Diclorofenil)piperidin-1,4-dicarboxilato de dimetilo

Se diluyó el clorhidrato de 2-(2,4-diclorofenil)piperidin-4-carboxilato de metilo (2.8 g, 8.63 mmol) con DCM (24.18 mL). Se añadieron DIPEA (3.76 mL, 21.56 mmol) y cloroformiato de metilo (0.815 mL, 10.35 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 30 min, a continuación se lavó con 3 x HCl 0.1 M y salmuera. Se filtró a través de un separador de fases. Se evaporó para proporcionar 2-(2,4-

diclorofenil)piperidin-1,4-dicarboxilato de dimetilo (2.78 g, 93%) como un aceite. MS m/z 346 $(M+H)^+$.

Paso 4: Ácido 2-(2,4-diclorofenil)-1-(metoxicarbonil)piperidin-4-carboxílico

Se disolvió 2-(2,4-diclorofenil)piperidin-1,4-dicarboxilato de dimetilo (2.78 g, 8.03 mmol) en acetonitrilo (27.1 mL) y agua (0.542 mL). Se añadieron bromuro de litio (5.58 g, 64.24 mmol) y trietilamina (4.48 mL, 32.12 mmol) y la mezcla resultante se calentó a reflujo durante 4 h, se diluyó con agua y MTBE y la fase orgánica se extrajo con agua. Las fases acuosas combinadas se acidificaron con HCl 3 M, se extrajeron con MTBE, se secaron con $MgSO_4$, se filtraron y se evaporaron, para obtener el ácido 2-(2,4-diclorofenil)-1-(metoxicarbonil)piperidin-4-carboxílico (2.440 g, 91 %) como una espuma. MS m/z 332 $(M+H)^+$.

Compuesto de referencia 24

Ácido 2-(3,5-diclorofenil)-1-(metoxicarbonil)piperidin-4-carboxílico

Paso 1: 2-(3,5-Diclorofenil)isonicotinato de metilo

Se repartieron carbonato de potasio (2.416 g, 17.48 mmol), 2-cloroisonicotinato de metilo (5 g, 29.14 mmol), 2-(3,5-diclorofenil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano (10.34 g, 37.88 mmol), $PdCl_2$(dppf) (0.633 g, 0.87 mmol) y MeOH (45.7 mL) en tres viales para microondas de 20 mL, y se calentaron hasta 100 °C en un reactor de microondas de nodo único durante 20 min. La mezcla de reacción se diluyó con agua y DCM, la fase acuosa se extrajo con DCM y las fases orgánicas combinadas se evaporaron. Se purificó mediante cromatografía flash automatizada utilizando 5% de EtOAc en heptano -> 30% de EtOAc en 15 VC a 280 nm. Se aisló 2-(3,5-diclorofenil)isonicotinato de metilo (6.1 g, 74%) como un polvo blanco. ^1H RMN (400 MHz, $CDCl_3$) δ 4.01 (s, 3H), 7.44 (t, 1H), 7.84 (dd, 1H), 7.96 (d, 2H), 8.23 - 8.28 (m, 1H), 8.85 (dd, 1H).

Paso 2: Clorhidrato de 2-(3,5-diclorofenil)piperidin-4-carboxilato de metilo

Se disolvió el clorhidrato de 2-(3,5-

diclorofenil)isonicotinato de metilo (6.88 g, 21.6 mmol) en MeOH (50 mL), se añadió óxido de platino (IV) (0.049 g, 0.22 mmol) y se hidrogenó en un hidrogenador Büchi a 5 bar durante 4 h. La mezcla de reacción se filtró, se lavó con MeOH hasta que se disolvió todo el producto y se evaporó. Se aisló el clorhidrato de 2-(3,5-diclorofenil)piperidin-4-carboxilato de metilo (4.8 g, 69%) como un sólido amarillento. MS m/z 288 $(M+H)^+$.

Paso 3: 2-(3,5-Diclorofenil)piperidin-1,4-dicarboxilato de dimetilo

Se disolvió el clorhidrato de 2-(3,5-diclorofenil)piperidin-4-carboxilato de metilo (4.8 g, 14.79 mmol) en DCM (41.5 mL) y DIPEA (6.46 mL, 36.97 mmol). Se añadió cloroformiato de metilo (1.374 mL, 17.74 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 1 h, a continuación se diluyó con DCM y se lavó con HCl 0.3 M y salmuera. La fase orgánica se filtró a través de un separador de fases y se evaporó, para obtener 2-(3,5-diclorofenil)piperidin-1,4-dicarboxilato de dimetilo (5.3 g) como un aceite. MS m/z 346 $(M+H)^+$.

Paso 4: Ácido 2-(3,5-diclorofenil)-1-(metoxicarbonil)piperidin-4-carboxílico

Se disolvió 2-(3,5-diclorofenil)piperidin-1,4-dicarboxilato de dimetilo (5.3 g, 15.31 mmol) en acetonitrilo (51.7 mL). Se añadieron agua (1.033 mL), bromuro de litio (10.64 g, 122.47 mmol) y trietilamina (8.53 mL, 61.24 mmol) y la mezcla resultante se calentó a reflujo durante 2.5 h. Se diluyó con agua y MTBE. La fase acuosa se extrajo con agua. Las fases acuosas combinadas se acidificaron con HCl 3 M, se extrajeron con MTBE, se secaron con $MgSO_4$, se filtraron y se evaporaron, para obtener el ácido 2-(3,5-diclorofenil)-1-(metoxicarbonil)piperidin-4-carboxílico (4.60 g, 90%) como una espuma verdosa. MS m/z 330 $(M-H)^-$.

Compuesto de referencia 25

Ácido 2-(2-fluoro-4-(trifluorometoxi)fenil)-1-(metoxicarbonil)piperidin-4-carboxílico

Paso 1: 2-(2-Fluoro-4-(trifluorometoxi)fenil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano

Se disolvió 1-bromo-2-fluoro-4-(trifluorometoxi)benceno (7.41 g, 28.61 mmol) en DMSO (50 mL). Se añadieron 4,4,4',4',5,5,5',5'-octametil-2,2'-bi(1,3,2-dioxaborolano) (8.43 g, 33.19 mmol), $PdCl_2$(dppf) (1.035 g, 1.43 mmol) y acetato de potasio (5.62 g, 57.22 mmol) y la mezcla se calentó en un baño de aceite a 80 °C durante 15 h. La mezcla de reacción se diluyó con acetato de etilo y se lavó con agua. La fase orgánica se secó con Na_2SO_4 y se evaporó. El residuo se purificó mediante cromatografía flash automatizada en una columna Biotage® con 340 g de KP-SIL. Se utilizó como fase móvil un gradiente de 0% a 25% de EtOAc en heptano en 10 VC. Se obtuvo 2-(2-fluoro-4-(trifluorometoxi)fenil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano (5.38 g, 61.4%) como un sólido incoloro.

Paso 2: 2-(2-Fluoro-4-(trifluorometoxi)fenil)isonicotinato de metilo

Se mezclaron 2-cloroisonicotinato de metilo (3 g, 17.48 mmol), 2-(2-fluoro-4-(trifluorometoxi)fenil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano (5.37 g, 17.55 mmol), carbonato de potasio (1.812 g, 13.11 mmol) y $PdCl_2$(dppf) (0.380 g, 0.52 mmol) en metanol (30 mL) en dos viales diferentes para microondas de 20 mL. Los viales se taparon y se calentaron a 100 °C durante 10 min en un reactor de microondas de nodo único. Se añadieron agua y DCM, y se separaron las fases. La fase acuosa se extrajo con DCM y las fases orgánicas combinadas se filtraron a través de un separador de fases y se evaporaron, para proporcionar un sólido de color marrón oscuro. El residuo se purificó mediante cromatografía flash automatizada en una columna Biotage® con 340 g de KP-SIL. Se utilizó como fase móvil un gradiente de 8:1 a 3:1 de EtOAc en heptano en 10 VC. Se obtuvo 2-(2-fluoro-4-(trifluorometoxi)fenil)isonicotinato de metilo (4.48 g, 81%) como un sólido incoloro. ^{1}H RMN (600 MHz, $CDCl_3$) δ 3.96 (s, 3H), 7.07 (d, 1H), 7.14 (d, 1H), 7.79 - 7.84 (m, 1H), 8.03 - 8.09 (m, 1H), 8.31 (s, 1H), 8.82 - 8.88 (m,

1H). MS m/z 316 $(M+H)^+$.

Paso 3: Clorhidrato de 2-(2-fluoro-4-(trifluorometoxi)fenil)piperidin-4-carboxilato de metilo

Se disolvió 2-(2-fluoro-4-(trifluorometoxi)fenil)isonicotinato de metilo (4.47 g, 14.18 mmol) en metanol y se añadió cloruro de hidrógeno (1.25 M en metanol, 17.02 mL, 21.27 mmol). Se evaporó el disolvente y se volvió a disolver el residuo en metanol (50 mL). Se añadió óxido de platino (IV) (0.322 g, 1.42 mmol) y la mezcla se hidrogenó a temperatura ambiente y 5 bar durante 5 h. El catalizador se filtró y se evaporó el disolvente. Se obtuvo el clorhidrato de 2-(2-fluoro-4-(trifluorometoxi)fenil)piperidin-4-carboxilato de metilo crudo (4.97 g, 98%) como un sólido incoloro. MS m/z 322 $(M+H)^+$.

Paso 4: 2-(2-fluoro-4-(trifluorometoxi)fenil)piperidin-1,4-dicarboxilato de dimetilo

Se disolvió el clorhidrato de 2-(2-fluoro-4-(trifluorometoxi)fenil)piperidin-4-carboxilato de metilo (4.97 g, 13.89 mmol) en diclorometano (50 mL) y DIPEA (6.05 mL, 34.73 mmol). Se añadió cloroformiato de metilo (1.313 mL, 16.67 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 4 h. Se añadió HCl 0.1 M y la fase acuosa se extrajo con DCM. Las fases orgánicas combinadas se filtraron a través de un separador de fases y se evaporaron. Se obtuvo 2-(2-fluoro-4-(trifluorometoxi)fenil)piperidin-1,4-dicarboxilato de dimetilo crudo (5.39 g, 102%) como un aceite amarillo. MS m/z 380 $(M+H)^+$.

Paso 5: Ácido 2-(2-fluoro-4-(trifluorometoxi)fenil)-1-(metoxicarbonil)piperidin-4-carboxílico

Se disolvió 2-(2-fluoro-4-(trifluorometoxi)fenil)piperidin-1,4-dicarboxilato de dimetilo (5.35 g, 14.10 mmol) en acetonitrilo (100 mL) y agua (2.000 mL), a continuación se añadió bromuro de litio (9.80 g, 112.84 mmol). Se añadió trietilamina (7.82 mL, 56.42 mmol) y la suspensión resultante se calentó a reflujo durante 7 h. Se añadieron MTBE (350 mL) y agua (180 mL), se separaron las fases

y se extrajo la fase orgánica con agua. Las fases acuosas combinadas se acidificaron con HCl 3.8 M y se extrajeron con EtOAc. Las fases orgánicas combinadas se secaron con Na_2SO_4 y se evaporaron. Se obtuvo el ácido 2-(2-fluoro-4-(trifluorometoxi)fenil)-1-(metoxicarbonil)piperidin-4-carboxílico (5.09 g, 99%) como un sólido incoloro. MS m/z 364 $(M-H)^-$.

Compuesto de referencia 26

Ácido 1-(metoxicarbonil)-2-(3,4,5-trifluorofenil)piperidin-4-carboxílico

Paso 1: 2-(3,4,5-Trifluorofenil)isonicotinato de metilo

Se mezclaron 2-bromoisonicotinato de metilo (4 g, 18.52 mmol), ácido 3,4,5-trifluorofenilborónico (4.89 g, 27.77 mmol), carbonato de potasio (3.84 g, 27.77 mmol) y $PdCl_2$(dppf) (0.402 g, 0.56 mmol) en metanol (30 mL) en dos viales diferentes para microondas de 20 mL. Los viales se taparon y se calentaron a 100 °C durante 10 min en un reactor de microondas de nodo único. Se añadieron agua y DCM, y se separaron las fases. La fase acuosa (pH de 9) se extrajo con DCM y las fases orgánicas combinadas se lavaron con salmuera, se pasaron a través de un separador de fases y se evaporaron, para proporcionar un sólido marrón. El residuo se disolvió en DCM y se purificó mediante cromatografía de intercambio catiónico SCX-2. Se aisló 2-(3,4,5-trifluorofenil)isonicotinato de metilo (2.62 g, 52%) como un sólido amarillento. MS m/z 268 $(M+H)^+$.

Paso 2: Clorhidrato de 2-(3,4,5-trifluorofenil)piperidin-4-carboxilato de metilo

Se disolvió 2-(3,4,5-trifluorofenil)isonicotinato de metilo (2.62 g) en MTBE y a continuación se añadió HCl (4 M en dioxano, 15 mL). Se evaporaron los disolventes para obtener el clorhidrato de 2-(3,4,5-trifluorofenil)isonicotinato de metilo (2.94 g, 9.68 mmol), que se disolvió en MeOH (40 mL) y se añadió óxido de platino (IV) (0.220 g, 0.97 mmol). La mezcla resultante se hidrogenó en un hidrogenador Büchi a temperatura ambiente y 5 bar durante 1 h. El catalizador se filtró, se lavó con MeOH y se evaporó el eluato, para proporcionar el

clorhidrato de 2-(3,4,5-trifluorofenil)piperidin-4-carboxilato de metilo (2.75 g, 92%) como un sólido marrón. MS m/z 274 $(M+H)^+$.

Paso 3: 2-(3,4,5-Trifluorofenil)piperidin-1,4-dicarboxilato de dimetilo

Se disolvió el clorhidrato de 2-(3,4,5-trifluorofenil)piperidin-4-carboxilato de metilo (2.75 g, 8.88 mmol) en DCM (50 mL) y a continuación se añadió DIPEA (3.88 mL, 22.20 mmol). Se añadió cloroformiato de metilo (0.979 mL, 12.43 mmol) gota a gota a la disolución. La mezcla se agitó a temperatura ambiente durante 4 h. La mezcla se lavó con HCl (0.1 M, 100 mL) y $NaHCO_3$ sat. (100 mL), a continuación se secó a través de un separador de fases y se evaporó, para proporcionar 2-(3,4,5-trifluorofenil)piperidin-1,4-dicarboxilato de dimetilo (2.77 g, 94%) como un aceite naranja.

Paso 4: Ácido 1-(metoxicarbonil)-2-(3,4,5-trifluorofenil)piperidin-4-carboxílico

Se disolvió 2-(3,4,5-trifluorofenil)piperidin-1,4-dicarboxilato de dimetilo (2.77 g, 8.36 mmol) en acetonitrilo (35 mL) y agua (0.700 mL), a continuación se añadió bromuro de litio (5.81 g, 66.89 mmol). Se añadió Et_3N (4.66 mL, 33.45 mmol) y la suspensión amarilla resultante se calentó a reflujo durante 2 h. Se añadieron agua (50 mL) y MTBE (150 mL). Las fases se separaron y la fase orgánica se extrajo con agua (2 veces). Las fases acuosas recogidas se acidificaron hasta un pH de 1 con HCl 3.8 M y con MTBE (2 veces). Las fases orgánicas combinadas se secaron con Na_2SO_4, se filtraron y se evaporaron, para proporcionar el ácido 1-(metoxicarbonil)-2-(3,4,5-trifluorofenil)piperidin-4-carboxílico (2.23 g, 84%) como un semisólido amarillento. MS m/z 316 $(M-H)^-$.

Compuesto de referencia 27

Ácido 1-(metoxicarbonil)-2-(2,4,5-trifluorofenil)piperidin-4-carboxílico

Paso 1: 2-(2,4,5-Trifluorofenil)isonicotinato de metilo

Se mezclaron 2-cloroisonicotinato de metilo (3.25 g, 18.94 mmol), ácido 2,4,5-trifluorofenilborónico (5.00 g, 28.41 mmol),

carbonato de potasio (3.93 g, 28.41 mmol) y $PdCl_2$(dppf) (0.411 g, 0.57 mmol) en metanol (20 mL) en dos viales para microondas de 20 mL. Los viales se taparon y se calentaron a 100 °C durante 10 min en un reactor de microondas de nodo único. La mezcla de reacción se suspendió en metanol, se filtró y se evaporó el filtrado, para proporcionar una suspensión de color rojo oscuro. Se añadieron DCM y agua, y se separaron las fases. La fase acuosa (pH de 9) se extrajo con DCM y las fases orgánicas combinadas se lavaron con salmuera, se pasaron a través de un separador de fases y se evaporaron, para proporcionar un sólido marrón. El sólido marrón crudo se disolvió en MTBE (120 mL) y los residuos sólidos se separaron por filtración. Se añadió gota a gota cloruro de hidrógeno (4 M en dioxano, 4.74 mL, 18.94 mmol) y se formó una suspensión. La suspensión se agitó a temperatura ambiente durante 45 min. El sólido se aisló mediante filtración y se lavó con MTBE. Se añadieron MTBE y $NaHCO_3$ sat. La fase orgánica se secó con Na_2SO_4, se filtró y se evaporó, para proporcionar 2-(2,4,5-trifluorofenil)isonicotinato de metilo (1.676 g, 33%) como un sólido beis. El filtrado de MTBE se lavó con $NaHCO_3$ sat., se secó con Na_2SO_4, se filtró y se evaporó para proporcionar un sólido marrón. El residuo se purificó en una columna Biotage (0 => 20 % de EtOAc en heptano, 6 VC; columna Biotage® con 100 g de KP-SIL) para proporcionar 2-(2,4,5-trifluorofenil)isonicotinato de metilo (0.86 g, 17%) como un sólido blanco. ^{1}H RMN (600 MHz, $CDCl_3$) δ 3.97 (s, 3H), 7.00 - 7.07 (m, 1H), 7.81 (dd, 1H), 7.90 - 7.97 (m, 1H), 8.32 - 8.33 (m, 1H), 8.83 (dd, 1H). MS m/z 268 $(M+H)^+$.

Paso 2: 2-(2,4,5-Trifluorofenil)piperidin-4-carboxilato de metilo

Se disolvió 2-(2,4,5-trifluorofenil)isonicotinato de metilo (2.509 g, 9.39 mmol) en ácido acético (25 mL) y se añadió óxido de platino (IV) (0.107 g, 0.47 mmol). La mezcla resultante se hidrogenó en un hidrogenador Büchi a temperatura ambiente y 5 bar durante 6 h. El catalizador se filtró, se lavó con MeOH y se evaporó el eluato. Se añadieron DCM y K_2CO_3 al

10%, y se separaron las fases. La fase orgánica se lavó con salmuera, se hizo pasar a través de un separador de fases y se evaporó, para proporcionar 2-(2,4,5-trifluorofenil)piperidin-4-carboxilato de metilo (2.434 g, 95%) como un aceite marrón. MS m/z 274 $(M+H)^+$.

Paso 3: 2-(2,4,5-Trifluorofenil)piperidin-1,4-dicarboxilato de dimetilo

Se disolvió 2-(2,4,5-(trifluorofenil)piperidin-4-carboxilato de metilo (2.232 g, 8.17 mmol) en DCM (50 mL) y DIPEA (1.707 mL, 9.80 mmol), a continuación se añadió cloroformiato de metilo (0.965 mL, 12.25 mmol). La solución se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se lavó con HCl 0.1 M y $NaHCO_3$ sat., se hizo pasar a través de un separador de fases y se evaporó, para proporcionar 2-(2,4,5-trifluorofenil)piperidin-1,4-dicarboxilato de dimetilo crudo (2.971 g, cuant.) como un aceite marrón. MS m/z 332 $(M+H)^+$.

Paso 4: Ácido 1-(metoxicarbonil)-2-(2,4,5-trifluorofenil)piperidin-4-carboxílico

Se disolvió 2-(2,4,5-trifluorofenil)piperidin-1,4-dicarboxilato de dimetilo (2.971 g, 8.97 mmol) en acetonitrilo (30 mL) y agua (0.600 mL), a continuación se añadió bromuro de litio (6.23 g, 71.74 mmol). Se añadió trietilamina (4.97 mL, 35.87 mmol) y la suspensión marrón resultante se calentó a reflujo. Se añadió agua y MTBE. La fase orgánica se extrajo con agua (x2). Las fases acuosas recogidas se acidificaron hasta un pH de 1 con HCl 3.8 M y a continuación se extrajeron con MTBE (x2). Las fases orgánicas combinadas se lavaron con agua y se evaporaron. Las trazas de agua se eliminaron formando un azeótropo con MeCN. Se aisló el ácido 1-(metoxicarbonil)-2-(2,4,5-(trifluorofenil)piperidin-4-carboxílico (2.388 g, 84%) como un aceite amarillo. MS m/z 318 $(M+H)^+$.

Compuesto de referencia 28

Ácido 2-(4-cloro-3,5-difluorofenil)-1-(metoxicarbonil)piperidin-4-carboxílico

Paso 1: 2-(4-Cloro-3,5-difluorofenil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano

A 5-bromo-2-cloro-1,3-difluorobenceno (4.8 g, 21.11 mmol) disuelto en DMSO (40 mL), se añadieron 4,4,4',4',5,5,5',5'-octametil-2,2'-bi(1,3,2-dioxaborolano) (6.22 g, 24.48 mmol), $PdCl_2$(dppf) (0.764 g, 1.06 mmol) y acetato de potasio (4.14 g, 42.21 mmol). La mezcla de reacción se calentó en un baño de aceite a 80 °C durante 10 h, a continuación se diluyó con acetato de etilo y se lavó con agua. La fase orgánica se secó con Na_2SO_4 y se evaporó. El residuo se purificó mediante cromatografía flash automatizada en una columna Biotage® con 340 g de KP-SIL. Se utilizó como fase móvil un gradiente de 0% a 30% de EtOAc en heptano en 10 VC. Se aisló 2-(4-cloro-3,5-difluorofenil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano (4.01 g, 69%).

Paso 2: Clorhidrato de 2-(4-cloro-3,5-difluorofenil)isonicotinato de metilo

Se repartieron 2-cloroisonicotinato de metilo (3.01 g, 17.53 mmol), $PdCl_2$(dppf) (0.317 g, 0.44 mmol) y carbonato de potasio (1.322 mL, 21.91 mmol) en partes iguales en 3 viales para microondas. Se disolvió 2-(4-cloro-3,5-difluorofenil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano (4.01 g, 14.61 mmol) en metanol (45 mL) para obtener una solución incolora. La solución se dividió en 3 porciones iguales y se añadió a los viales. Los viales se taparon y se calentaron en un reactor de microondas de nodo único a 100 °C durante 10 min cada uno. Se combinó el contenido de los viales y se evaporó el disolvente. El residuo se disolvió en DCM y se lavó con agua. La fase orgánica se filtró a través de un separador de fases y se evaporó. El residuo se disolvió en MTBE y los residuos sólidos se eliminaron por filtración. Se añadió cloruro de hidrógeno (4 M en dioxano, 3.65 mL, 14.61 mmol) y se aisló el precipitado, para proporcionar el clorhidrato de 2-(4-cloro-3,5-difluorofenil)isonicotinato de metilo (1.72 g, 42%) como un sólido. ^{1}H RMN (400 MHz, $CDCl_3$) δ 4.06 (s, 3H), 7.86 (d, 2H), 8.09 (d, 1H), 8.39 (s, 1H), 8.96 (d, 1H). MS m/z 284 $(M+H)^+$.

Paso 3: 2-(4-Cloro-3,5-difluorofenil)piperidin-4-carboxilato de metilo

Se disolvió el clorhidrato de 2-(4-cloro-3,5-difluorofenil)isonicotinato de metilo (1.94 g, 6.06 mmol) en metanol. Se añadió óxido de platino (IV) (0.138 g, 0.61 mmol) y la mezcla se hidrogenó a temperatura ambiente y 5 bar en un hidrogenador Büchi durante 7 h. El catalizador se eliminó por filtración y se evaporó el disolvente. Se obtuvo el clorhidrato de 2-(4-cloro-3,5-difluorofenil)piperidin-4-carboxilato de metilo (1.820 g, 92%) como un aceite incoloro. MS m/z 290 $(M+H)^+$.

Paso 4: 2-(4-Cloro-3,5-difluorofenil)piperidin-1,4-dicarboxilato de dimetilo

Se disolvió el clorhidrato de 2-(4-cloro-3,5-difluorofenil)piperidin-4-carboxilato de metilo (1.82 g, 5.58 mmol) en diclorometano (50 mL). Se añadieron DIPEA (2.430 mL, 13.95 mmol) y cloroformiato de metilo (0.527 mL, 6.70 mmol) y la mezcla se agitó a temperatura ambiente durante 3 h. Se añadió HCl 0.1 M y la fase acuosa se extrajo con DCM. Las fases orgánicas combinadas se filtraron a través de un separador de fases y se evaporaron, para proporcionar 2-(4-cloro-3,5-difluorofenil)piperidin-1,4-dicarboxilato de dimetilo (1.83 g, 94%). MS m/z 348 $(M+H)^+$.

Paso 5: Ácido 2-(4-cloro-3,5-difluorofenil)-1-(metoxicarbonil)piperidin-4-carboxílico

Se disolvió 2-(4-cloro-3,5-difluorofenil)piperidin-1,4-dicarboxilato de dimetilo (1.83 g, 5.26 mmol) en acetonitrilo (30 mL) y agua (0.600 mL), a continuación se añadió bromuro de litio (3.66 g, 42.10 mmol). Se añadió trietilamina (2.92 mL, 21.05 mmol) y la suspensión resultante se calentó a reflujo durante 4 h. Se añadieron MTBE (100 mL) y agua (50 mL), se separaron las fases y se extrajo la fase orgánica con agua. Las fases acuosas combinadas se acidificaron hasta un pH de 1 con HCl 3.8 M y se extrajeron con MTBE. Las fases orgánicas combinadas se secaron con Na_2SO_4 y se evaporaron, para proporcionar el ácido 2-(4-cloro-3,5-difluorofenil)-1-(metoxicarbonil)piperidin-4-carboxílico (1.600 g, 91%) como un sólido de color amarillo claro. MS m/z 332 $(M-H)^-$.

Compuesto de referencia 29

Ácido 1-(metoxicarbonil)-2-(3-metil-4-(trifluorometil)fenil)piperidin-4-carboxílico

Paso 1: 4,4,5,5-Tetrametil-2-(3-metil-4-(trifluorometil)fenil)-1,3,2-dioxaborolano

Se combinaron 4-bromo-2-metil-1-(trifluorometil)benceno (3.3 g, 13.8 mmol), 4,4,4',4',5,5,5',5'-octametil-2,2'-bi(1,3,2-dioxaborolano) (4.07 g, 16.01 mmol), acetato de potasio (2.71 g, 27.61 mmol) y $PdCl_2$(dppf) (0.5 g, 0.69 mmol) en DMF (60 mL) y se repartieron en tres viales para microondas. Las mezclas de reacción se calentaron en un reactor de microondas de nodo único hasta 100 °C durante 10 min. Las mezclas de reacción se diluyeron con acetato de etilo y se filtraron a través de celite. El filtrado se lavó con agua (3 x) y salmuera. La fase orgánica se aisló, se secó con Na_2SO_4, se filtró a través de celite y se evaporó el disolvente. Se realizó una cromatografía en columna automatizada utilizando un aparato Biotage. Se realizó la elución utilizando un gradiente de heptano - acetato de etilo, empezando con un 0% de acetato de etilo y aumentando el porcentaje hasta un 30%. Se aisló 4,4,5,5-tetrametil-2-(3-metil-4-(trifluorometil)fenil)-1,3,2-dioxaborolano (1.66 g, 42%). ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.33 (s, 12H), 2.47 (s, 3H), 7.57 (d, 1H), 7.66 - 7.70 (m, 2H).

Paso 2: 2-(3-Metil-4-(trifluorometil)fenil)isonicotinato de metilo

Se mezclaron 2-cloroisonicotinato de metilo (0.996 g, 5.80 mmol), carbonato de potasio (1.042 g, 7.54 mmol), 4,4,5,5-tetrametil-2-(3-metil-4-(trifluorometil)fenil)-1,3,2-dioxaborolano (1.66 g, 5.80 mmol) y $PdCl_2$(dppf) (0.105 g, 0.15 mmol) en metanol (20 mL) en dos viales para microondas. Los viales se taparon y se calentaron a 100 °C durante 10 min en un reactor de microondas de nodo único. La solución se dividió entre agua y acetato de etilo. La fase orgánica se aisló, se secó con Na_2SO_4, se filtró a través de celite y se evaporó el disolvente. Se realizó una cromatografía en columna automatizada utilizando un equipo Biotage. Se realizó la

elución utilizando un gradiente de heptano - acetato de etilo, de 0% a 50%. Se aisló 2-(3-metil-4-(trifluorometil)fenil)isonicotinato de metilo (1.22 g, 71%). ^{1}H RMN (600 MHz, $CDCl_3$) δ 2.57 (s, 3H), 3.99 (s, 3H), 7.70 (d, 1H), 7.81 (dd, 1H), 7.91 (d, 1H), 7.98 (s, 1H), 8.29 (s, 1H), 8.84 (d, 1H).

Paso 3: 2-(3-metil-4-(trifluorometil)fenil)piperidin-4-carboxilato de metilo

Se disolvió 2-(3-metil-4-(trifluorometil)fenil)isonicotinato de metilo (2.32 g, 7.86 mmol) en ácido acético (150 mL) y se añadió óxido de platino (IV) (36 mg, 0.16 mmol). Se hidrogenó en un hidrogenador Büchi a temperatura ambiente y 6 bar durante 2 h. El catalizador se filtró. Se añadió más óxido de platino (IV) y se continuó la hidrogenación hasta que se consumió el material de partida. Se filtró el catalizador y se evaporó el disolvente, para proporcionar 2-(3-metil-4-(trifluorometil)fenil)piperidin-4-carboxilato de metilo crudo (2.60 g, 110%).

Paso 4: 2-(3-Metil-4-(trifluorometil)fenil)piperidin-1,4-dicarboxilato de dimetilo

Se disolvió 2-(4-(trifluorometil)bencil)piperidin-4-carboxilato de metilo (2.9 g, 9.62 mmol) en DIPEA (1.866 g, 14.44 mmol) y diclorometano (50 mL). Se añadió gota a gota cloroformiato de metilo (1.091 g, 11.55 mmol) y la mezcla resultante se agitó a temperatura ambiente durante toda la noche. Se añadieron $KHSO_4$ 1 M y éter dietílico y se separaron las fases. La fase orgánica se lavó con Na_2CO_3, se secó con $MgSO_4$, se filtró a través de celite y se evaporó, para proporcionar 2-(3-metil-4-(trifluorometil)fenil)piperidin-1,4-dicarboxilato de dimetilo (3.09 g, 89%).

Paso 5: Ácido 1-(metoxicarbonil)-2-(3-metil-4-(trifluorometil)fenil)piperidin-4-carboxílico

Se disolvió 2-(3-metil-4-(trifluorometil)fenil)piperidin-1,4-dicarboxilato de dimetilo (3.09 g, 8.60 mmol) en acetonitrilo (30 mL) y agua (0.6 mL), se añadió bromuro de litio (5.97 g, 68.79 mmol). Se añadió trietilamina (3.48 g,

34.40 mmol) y la suspensión resultante se calentó a reflujo durante 1 h. Se añadieron agua (60 mL) y MTBE. La fase orgánica se extrajo con agua (x 2). Se añadió MTBE a la fase acuosa recogida, la solución se acidificó hasta un pH de 1 con HCl y a continuación se extrajo con MTBE (x 2). La fase orgánica se secó con Na_2SO_4, se filtró a través de celite y se evaporó el disolvente, para proporcionar el ácido 1-(metoxicarbonil)-2-(3-metil-4-(trifluorometil)fenil)piperidin-4-carboxílico (2.65 g, 7.67 mmol).

Compuesto de referencia 30

Ácido 2-(3,5-difluoro-4-(trifluorometil)fenil)-1-(metoxicarbonil)piperidin-4-carboxílico

Paso 1: 2-(3,5-Difluoro-4-(trifluorometil)fenil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano

Se suspendieron 5-bromo-1,3-difluoro-2-(trifluorometil)benceno (4.7 g, 18.01 mmol), $PdCl_2$(dppf) (0.652 g, 0.90 mmol) y acetato de potasio (3.53 g, 36.02 mmol) en MeOH (20 mL), se repartieron en dos viales para microondas y se calentaron a 120 °C en un reactor de microondas de nodo único durante 20 min. La mezcla de reacción se diluyó con EtOAc (400 mL), se lavó con agua (400 mL) y salmuera (400 mL), se secó con Na_2SO_4, se filtró y se evaporó al vacío. El residuo se purificó mediante cromatografía flash automatizada en 2 columnas Biotage® con 100 g de KP-SIL. Se utilizó como fase móvil un gradiente de 0% a 30% de EtOAc en heptano en 12 VC. El producto se recogió utilizando una longitud de onda de 265 nm. Se aisló 2-(3,5-difluoro-4-(trifluorometil)fenil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano (3.30 g, 59.5%) como un sólido blanco. ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.32 (s, 12H), 7.37 (d, 2H).

Paso 2: 2-(3,5-(Difluoro-4-trifluorometil)fenil)isonicotinato de metilo

Se añadieron 2-cloroisonicotinato de metilo (1.838 g, 10.71 mmol), carbonato de potasio (0.888 g, 6.43 mmol) y $PdCl_2$(dppf) (0.233 g, 0.32 mmol) a un vial para microondas. Se añadió 2-(3,5-difluoro-4-(trifluorometil)fenil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano (3.3 g, 10.71 mmol) disuelto en

MeOH (15 mL) y la reacción se calentó en un reactor de microondas de nodo único a 100 °C durante un total de 40 min. Se añadieron DCM (100 mL) y agua (100 mL), se agitó y se separaron las fases. La fase acuosa se extrajo con DCM (100 mL). Las fases orgánicas combinadas se lavaron con salmuera (200 mL), se secaron con un separador de fases y se evaporaron al vacío. El residuo se purificó mediante cromatografía flash automatizada en una columna Biotage® con 100 g de KP-SIL. Se utilizó como fase móvil un gradiente de 5 % de EtOAc en heptano en 3 VC y a continuación de 5 % a 30 % de EtOAc en heptano en 9 VC. El producto se recogió utilizando una longitud de onda de 250 nm. Se aisló 2-(3,5-difluoro-4-(trifluorometil)fenil)isonicotinato de metilo (1.810 g, 53%) como un sólido blanco. ^{1}H RMN (600 MHz, $CDCl_3$) δ 3.99 (s, 3H), 7.74 (d, 2H), 7.86 - 7.89 (m, 1H), 8.27 (s, 1H), 8.86 (d, 1H).

Paso 3: Clorhidrato de 2-(3,5-difluoro-4-(trifluorometil)fenil)piperidin-4-carboxilato de metilo

Se disolvió 2-(3,5-difluoro-4-(trifluorometil)fenil)isonicotinato de metilo (3.147 g, 9.92 mmol) en MeOH (20 mL) y se añadió cloruro de hidrógeno (1.25 M en MeOH, 23.81 mL, 29.76 mmol). La reacción se agitó a temperatura ambiente durante 2 h y se evaporó. Se añadieron metanol (20 mL) y óxido de platino (IV) (0.113 g, 0.50 mmol) y la solución se hidrogenó en un hidrogenador Büchi a temperatura ambiente y 5 bar durante 4.5 h. Se añadió óxido de platino (IV) (0.113 g, 0.50 mmol) y se continuó la hidrogenación durante 4 h. El catalizador se filtró y se lavó con MeOH. El filtrado se evaporó al vacío, para proporcionar el clorhidrato de 2-(3,5-difluoro-4-(trifluorometil)fenil)piperidin-4-carboxilato de metilo (3.12 g, 87%) como un sólido blanco. MS m/z 324 $(M+H)^+$.

Paso 4: 2-(3,5-difluoro-4-(trifluorometil)fenil)piperidin-1,4-dicarboxilato de dimetilo

Se disolvieron el clorhidrato de 2-(3,5-difluoro-4-(trifluorometil)fenil)piperidin-4-carboxilato de metilo (3.118 g, 8.67 mmol) y DIPEA (3.02 mL, 17.34 mmol) en DCM (30 mL). Se añadió cloroformiato de metilo (1.024 mL, 13.00 mmol) y la

reacción se agitó a temperatura ambiente durante 1.5 h. Se añadió cloroformiato de metilo adicional (0.341 mL, 4.33 mmol) y se continuó agitando durante 0.5 h. Se añadió DCM (170 mL). La fase orgánica se lavó con HCl 0.1 M (2x200 mL) y $NaHCO_3$ sat. (200 mL), se secó con un separador de fases y se evaporó al vacío, para proporcionar 2-(3,5-difluoro-4-(trifluorometil)fenil)piperidin-1,4-dicarboxilato de dimetilo (2.85 g, 86%) como un aceite incoloro. MS m/z 382 $(M+H)^+$.

Paso 5: Ácido 2-(3,5-difluoro-4-(trifluorometil)fenil)-1-(metoxicarbonil)piperidin-4-carboxílico

Se disolvió 2-(3,5-difluoro-4-(trifluorometil)fenil)piperidin-1,4-dicarboxilato de dimetilo (2.851 g, 7.48 mmol) en acetonitrilo (25 mL) y agua (2.5 mL), a continuación se añadió bromuro de litio (5.19 g, 59.82 mmol) y después trietilamina (4.15 mL, 29.91 mmol). La mezcla de reacción se calentó a reflujo durante 1 h. Se añadieron MTBE (150 mL) y agua (150 mL), se agitó y se separaron las fases. La fase orgánica se extrajo con agua (2x150 mL). Las fases acuosas combinadas se acidificaron con HCl 3 M hasta un pH de 1 y se extrajeron con MTBE (2x450 mL). Las fases orgánicas combinadas se secaron con Na_2SO_4, se filtraron y se evaporaron al vacío, para proporcionar el ácido 2-(3,5-difluoro-4-(trifluorometil)fenil)-1-(metoxicarbonil)piperidin-4-carboxílico (2.363 g, 86%). MS m/z 368 $(M+H)^+$.

Compuesto de referencia 31

Ácido 1-(metoxicarbonil)-2-(2-metil-4-(trifluorometil)fenil)piperidin-4-carboxílico

Paso 1: Clorhidrato de 2-(2-metil-4-(trifluorometil)fenil)isonicotinato de metilo

Se repartieron carbonato de potasio (2.66 g, 19.23 mmol), 2-cloroisonicotinato de metilo (5.5 g, 32.05 mmol), ácido 2-metil-4-(trifluorometil)fenilborónico (8.50 g, 41.67 mmol), $PdCl_2$(dppf) (0.696 g, 0.96 mmol) y MeOH (50.3 mL) en tres viales para microondas y se calentaron en un reactor de microondas de nodo único a 100 °C durante 20 min. Se diluyeron con DCM, se filtraron y se evaporaron. Se purificaron mediante

cromatografía flash utilizando 5% de EtOAc en heptano -> 20% de EtOAc en 10 VC a 280 nm. El residuo se disolvió en éter, se añadió cloruro de hidrógeno (4 M en dioxano, 8.01 mL, 32.05 mmol) y se evaporaron los disolventes, para proporcionar el clorhidrato de 2-(2-metil-4-(trifluorometil)fenil)isonicotinato de metilo (9.15 g, 86%) como un sólido blanco. ^{1}H RMN (400 MHz, CD_3OD) δ 2.41 (s, 3H), 4.03 (s, 3H), 7.63 - 7.76 (m, 3H), 8.27 (dd, 1H), 8.33 (dd, 1H), 8.99 (dd, 1H). MS m/z 296 $(M+H)^+$.

Paso 2: Clorhidrato de 2-(2-metil-4-(trifluorometil)fenil)piperidin-4-carboxilato de metilo

Se disolvió el clorhidrato de 2-(2-metil-4-(trifluorometil)fenil)isonicotinato de metilo (9 g, 27.13 mmol) en MeOH (50 mL), se añadió óxido de platino (IV) (0.185 g, 0.81 mmol) y la mezcla resultante se hidrogenó en un hidrogenador Büchi a 5 bar durante 5 h. El catalizador se filtró y se evaporó el filtrado, para obtener el clorhidrato de 2-(2-metil-4-(trifluorometil)fenil)piperidin-4-carboxilato de metilo (8 g, 87%) como un sólido amarillento. MS m/z 302 $(M+H)^+$.

Paso 3: 2-(2-Metil-4-(trifluorometil)fenil)piperidin-1,4-dicarboxilato de dimetilo

Se disolvieron el clorhidrato de 2-(2-metil-4-(trifluorometil)fenil)piperidin-4-carboxilato de metilo (8.2 g, 24.28 mmol) y DIPEA (10.60 mL, 60.69 mmol) en diclorometano (100 mL). Se añadió cloroformiato de metilo (2.257 mL, 29.13 mmol) y la reacción se agitó a temperatura ambiente durante 1 h. Se añadió DCM (100 mL). La fase orgánica se lavó dos veces con HCl 1 M y agua, se secó con Na_2SO_4 y se evaporó, para proporcionar 2-(2-metil-4-(trifluorometil)fenil)piperidin-1,4-dicarboxilato de dimetilo (8.9 g, cuant.). MS m/z 360 $(M+H)^+$.

Paso 4: Ácido 1-(metoxicarbonil)-2-(2-metil-4-(trifluorometil)fenil)piperidin-4-carboxílico

Se disolvió 2-(2-metil-4-(trifluorometil)fenil)piperidin-1,4-dicarboxilato de dimetilo (8.9 g, 24.77 mmol) en acetonitrilo (80 mL). Se añadieron agua (1.6 mL), bromuro de litio (17.21 g, 198.14 mmol) y trietilamina (13.73 mL, 99.07 mmol). La mezcla se calentó a reflujo durante 2.5 h. Después de

enfriarla, se diluyó con agua, se extrajo con EtOAc dos veces y las fases orgánicas combinadas se lavaron con agua. Las fases acuosas combinadas se acidificaron con HCl 2 M y se extrajeron tres veces con EtOAc. Las fases orgánicas combinadas se secaron con Na_2SO_4, se filtraron y se evaporaron, para obtener el ácido 1-(metoxicarbonil)-2-(2-metil-4-(trifluorometil)fenil)piperidin-4-carboxílico (7.79 g, 91%). MS m/z 344 $(M-H)^-$.

Compuesto de referencia 32

Ácido 2-(2-fluoro-4-(trifluorometil)fenil)-1-(metoxicarbonil)piperidin-4-carboxílico

Paso 1: Clorhidrato de 2-(2-fluoro-4-(trifluorometil)fenil)isonicotinato de metilo

Se mezclaron 2-cloroisonicotinato de metilo (2.8 g, 16.32 mmol), ácido 2-fluoro-4-(trifluorometil)fenilborónico (5.09 g, 24.48 mmol), carbonato de potasio (1.692 g, 12.24 mmol) y $PdCl_2$(dppf) (0.354 g, 0.49 mmol) en metanol (30 mL) en dos viales diferentes para microondas de 20 mL. Los viales se taparon y se calentaron a 100 °C durante 10 min en un reactor de microondas de nodo único. Se añadieron agua y DCM, y se separaron las fases. La fase acuosa (pH de 9) se extrajo con DCM y las fases orgánicas combinadas se lavaron con salmuera, se pasaron a través de un separador de fases y se evaporaron, para proporcionar un sólido de color naranja oscuro. El sólido se disolvió en MTBE y se agitó durante 15 minutos, a continuación se filtró. La fase de MTBE naranja se trató con cloruro de hidrógeno (4 M en dioxano, 4.08 mL, 16.32 mmol) y se agitó durante 1 h a temperatura ambiente. El precipitado se aisló mediante filtración. Se aisló el clorhidrato de 2-(2-fluoro-4-(trifluorometil)fenil)isonicotinato de metilo (5.4 g, 99%) como un sólido anaranjado. MS m/z 300 $(M+H)^+$.

Paso 2: Clorhidrato de 2-(2-fluoro-4-(trifluorometil)fenil)piperidin-4-carboxilato de metilo

Se disolvió el clorhidrato de 2-(2-fluoro-4-(trifluorometil)fenil)isonicotinato de metilo (5.4 g, 16.09 mmol) en MeOH (40 mL) y se añadió óxido de platino (IV) (0.365

g, 1.61 mmol). La mezcla resultante se hidrogenó en un hidrogenador Büchi a temperatura ambiente y 5 bar durante 2 h. El catalizador se filtró, se lavó con MeOH y se evaporó el eluato, para proporcionar el clorhidrato de 2-(2-fluoro-4-(trifluorometil)fenil)piperidin-4-carboxilato de metilo (5.1 g, 93%) como un sólido marronoso. MS m/z 306 $(M+H)^+$.

Paso 3: 2-(2-Fluoro-4-(trifluorometil)fenil)piperidin-1,4-dicarboxilato de dimetilo

Se disolvió 2-(2-fluoro-4-(trifluorometil)fenil)piperidin-4-carboxilato de metilo (5.50 g, 16.09 mmol) en DCM (100 mL) y a continuación se añadió DIPEA (7.03 mL, 40.23 mmol). Se añadió cloroformiato de metilo (1.774 mL, 22.53 mmol) gota a gota a la disolución. La mezcla se agitó a temperatura ambiente durante 4 h. La mezcla se lavó con HCl 0.1 M (100 mL) y $NaHCO_3$ sat. (100 mL), a continuación se secó a través de un separador de fases y se evaporó, para proporcionar 2-(2-fluoro-4-(trifluorometil)fenil)piperidin-1,4-dicarboxilato de dimetilo (5.33 g, 91%) como un aceite marrón.

Paso 4: Ácido 2-(2-fluoro-4-(trifluorometil)fenil)-1-(metoxicarbonil)piperidin-4-carboxílico

Se disolvió 2-(2-fluoro-4-(trifluorometil)fenil)piperidin-1,4-dicarboxilato de dimetilo (5.33 g, 14.67 mmol) en acetonitrilo (35 mL) y agua (0.700 mL), a continuación se añadió bromuro de litio (10.19 g, 117.37 mmol). Se añadió Et_3N (8.18 mL, 58.68 mmol) y la suspensión amarilla resultante se calentó a reflujo durante 1 h. Se añadieron agua (50 mL) y MTBE (150 mL). Las fases se separaron y la fase orgánica se extrajo con agua (2 veces). Las fases acuosas recogidas se acidificaron hasta un pH de 1 con HCl 3.8 M y se extrajeron con MTBE (2 veces). Las fases orgánicas combinadas se secaron con Na_2SO_4, se filtraron y se evaporaron, para proporcionar el ácido 2-(2-fluoro-4-(trifluorometil)fenil)-1-(metoxicarbonil)piperidin-4-carboxílico (4.82 g, 94%) como un sólido amarillento. MS m/z 348 $(M-H)^-$.

Compuesto de referencia 33

Ácido 2-(3-fluoro-4-(trifluorometil)fenil)-1-

(metoxicarbonil)piperidin-4-carboxílico

Paso 1: 2-(3-Fluoro-4-(trifluorometil)fenil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano

Se disolvió 4-bromo-2-fluoro-1-(trifluorometil)benceno (5.08 g, 20.91 mmol) en DMSO (40 mL), a continuación se añadieron 4,4,4',4',5,5,5',5'-octametil-2,2'-bi(1,3,2-dioxaborolano) (6.16 g, 24.25 mmol), $PdCl_2$(dppf) (0.756 g, 1.05 mmol) y acetato de potasio (4.10 g, 41.81 mmol) y la mezcla se calentó en un baño de aceite a 80 °C durante 10 h. La mezcla de reacción se diluyó con acetato de etilo y se lavó con agua. La fase orgánica se secó con Na_2SO_4 y se evaporó. El residuo se purificó mediante cromatografía flash automatizada en una columna Biotage® con 340 g de KP-SIL. Se utilizó como fase móvil un gradiente de 0% a 20 % de EtOAc en heptano en 10 VC. Se aisló 2-(3-fluoro-4-(trifluorometil)fenil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano (3.72 g, 61%).

Paso 2: 2-(3-(Fluoro-4-trifluorometil)fenil)isonicotinato de metilo

Se repartieron 2-cloroisonicotinato de metilo (2.86 g, 16.67 mmol), $PdCl_2$(dppf) (0.278 g, 0.38 mmol) y carbonato de potasio (1.161 mL, 19.24 mmol) en partes iguales en 3 viales para microondas. Se repartió 2-(3-fluoro-4-(trifluorometil)fenil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano (3.72 g, 12.82 mmol) disuelto en metanol (45 mL) en 3 porciones iguales y se añadió a los viales. Los viales se taparon y se calentaron en un reactor de microondas de nodo único a 100 °C durante 10 min cada uno. Se combinó el contenido de los viales y se evaporó el disolvente. El residuo se disolvió en DCM y se lavó con agua. La fase orgánica se filtró a través de un separador de fases y se evaporó. El residuo se purificó mediante cromatografía flash automatizada en una columna Biotage® con 340 g de KP-SIL. Se utilizó como fase móvil heptano:EtOAc 7:1 en 10 VC. Se aisló 2-(3-fluoro-4-(trifluorometil)fenil)isonicotinato de metilo crudo (2.92 g, 76%). MS m/z 300 $(M+H)^+$.

Paso 3: 2-(3-fluoro-4-(trifluorometil)fenil)piperidin-4-

carboxilato de metilo

Se disolvió 2-(3-fluoro-4-(trifluorometil)fenil)isonicotinato de metilo (2.9 g, 9.69 mmol) en metanol y se añadió cloruro de hidrógeno (1.25 M en metanol, 11.63 mL, 14.54 mmol). Se evaporó el disolvente y se volvió a disolver el residuo en metanol (50 mL), se añadió óxido de platino (IV) (0.220 g, 0.97 mmol) y la mezcla de reacción se hidrogenó a 5 bar y temperatura ambiente en un hidrogenador Büchi durante 2 h. El catalizador se eliminó mediante filtración y se evaporó el disolvente, para proporcionar el clorhidrato de 2-(3-fluoro-4-(trifluorometil)fenil)piperidin-4-carboxilato de metilo (3.12 g, 94%). MS m/z 306 $(M+H)^+$.

Paso 4: 2-(3-Fluoro-4-(trifluorometil)fenil)piperidin-1,4-dicarboxilato de dimetilo

Se disolvió el clorhidrato de 2-(3-fluoro-4-(trifluorometil)fenil)piperidin-4-carboxilato (3.12 g, 10.22 mmol) en diclorometano (50 mL), a continuación se añadieron DIPEA (4.45 mL, 25.55 mmol) y cloroformiato de metilo (0.966 mL, 12.26 mmol) y la mezcla se agitó a temperatura ambiente durante 3 h. Se añadió HCl 0.1 M y la fase acuosa se extrajo con DCM. Las fases orgánicas combinadas se filtraron a través de un separador de fases y se evaporaron, para proporcionar 2-(3-fluoro-4-(trifluorometil)fenil)piperidin-1,4-dicarboxilato de dimetilo (3.2 g, 86%). MS m/z 364 $(M+H)^+$.

Paso 5: Ácido 2-(3-fluoro-4-(trifluorometil)fenil)-1-(metoxicarbonil)piperidin-4-carboxílico

Se disolvió 2-(3-fluoro-4-(trifluorometil)fenil)piperidin-1,4-dicarboxilato de dimetilo (3.2 g, 8.81 mmol) en acetonitrilo (40 mL) y agua (0.800 mL), a continuación se añadió bromuro de litio (6.12 g, 70.46 mmol). Se añadió trietilamina (4.88 mL, 35.23 mmol) y la solución resultante se calentó a reflujo durante 5 h. Se añadieron MTBE (110 mL) y agua (60 mL), se separaron las fases y se extrajo la fase orgánica con agua. Las fases acuosas combinadas se acidificaron hasta un pH de 1 con HCl 3.8 M y se extrajeron con MTBE. Las

fases orgánicas combinadas se secaron con Na_2SO_4 y se evaporaron, para proporcionar el ácido 2-(3-fluoro-4-(trifluorometil)fenil)-1-(metoxicarbonil)piperidin-4-carboxílico (3.07 g, cuant.). MS m/z 348 $(M-H)^-$.

Compuesto de referencia 34

Ácido 1-(metoxicarbonil)-2-fenilpiperidin-4-carboxílico

Paso 1: 2-Fenilisonicotinato de metilo

Se mezclaron 2-cloroisonicotinato de metilo (2.5 g, 14.57 mmol), ácido fenilborónico (2.66 g, 21.86 mmol), carbonato de potasio (3.02 g, 21.86 mmol) y $PdCl_2$(dppf) (0.316 g, 0.44 mmol) en metanol (15 mL) en un vial para microondas de 20 mL. Se añadieron dos gotas de agua y el vial se tapó y se calentó a 100 °C durante 10 min en un reactor de microondas de nodo único. Se eliminaron los sólidos mediante filtración y se evaporó parte del filtrado para proporcionar una suspensión de color rojo oscuro. Se añadieron DCM y agua, y se separaron las fases. La fase acuosa (pH de 9) se extrajo con DCM y las fases orgánicas combinadas se lavaron con salmuera, se pasaron a través de un separador de fases y se evaporaron, para proporcionar un aceite de color rojo oscuro. El compuesto se purificó a través de una columna Biotage, SNAP con 340 g de KP-SIL, utilizando un eluyente isocrático de heptano/acetato de etilo 9:1 en 2 VC y a continuación un gradiente lineal de heptano/acetato de etilo de 9:1 a 6:4 en 5 VC, para proporcionar 2-fenilisonicotinato de metilo (1.83 g, 58%) como un aceite incoloro. ^1H RMN (400 MHz, $CDCl_3$) δ 3.98 (s, 3H), 7.39 - 7.54 (m, 3H), 7.76 (dd, 1H), 8.01 - 8.09 (m, 2H), 8.29 (s, 1H), 8.82 (d, 1H). MS m/z 214 $(M+H)^+$.

Paso 2: 2-Fenilpiperidin-4-carboxilato de metilo

Se disolvió 2-fenilisonicotinato de metilo (1.83 g, 8.58 mmol) en ácido acético (20 mL) y se añadió óxido de platino (IV) (0.097 g, 0.43 mmol). La mezcla resultante se hidrogenó en un hidrogenador Büchi a temperatura ambiente y 5 bar durante 2.5 h. El catalizador se filtró, se lavó con MeOH y se evaporó el eluato. Se añadieron DCM y K_2CO_3 al 10%, y se separaron las fases. La fase acuosa se extrajo con DCM y las fases orgánicas

combinadas se lavaron con salmuera, se pasaron a través de un separador de fases y se evaporaron, para proporcionar 2-fenilpiperidin-4-carboxilato de metilo (2.131 g) como un aceite amarillo. MS m/z 220 $(M+H)^+$.

Paso 3: 2-Fenilpiperidin-1,4-dicarboxilato de dimetilo

Se disolvió 2-fenilpiperidin-4-carboxilato de metilo (4.33 g, 19.75 mmol) en DCM (150 mL) y DIPEA (3.78 mL, 21.72 mmol), a continuación se añadió cloroformiato de metilo (1.710 mL, 21.72 mmol). La solución se agitó a temperatura ambiente durante 1 h 45 min. Se añadieron DIPEA (1.720 mL, 9.87 mmol) y cloroformiato de metilo (0.777 mL, 9.87 mmol) adicionales y se procedió con la reacción durante 30 min más. La mezcla de reacción se lavó con HCl 0.1 M y $NaHCO_3$ sat. La fase orgánica se hizo pasar a través de un separador de fases y se evaporó, para proporcionar 2-fenilpiperidin-1,4-dicarboxilato de dimetilo (5.88 g, cuant.) como un aceite amarillo. MS m/z 278 $(M+H)^+$.

Paso 4: Ácido 1-(metoxicarbonil)-2-fenilpiperidin-4-carboxílico

Se disolvió 2-fenilpiperidin-1,4-dicarboxilato de dimetilo (5.88 g, 21.20 mmol) en acetonitrilo (60 mL) y agua (1.2 mL), a continuación se añadió bromuro de litio (4.25 mL, 169.63 mmol). Se añadió trietilamina (11.76 mL, 84.81 mmol) y la suspensión amarilla resultante se calentó a reflujo durante 1 h. Se añadieron agua (60 mL) y MTBE. La fase orgánica se extrajo con agua (x2). Se añadió MTBE a la fase acuosa recogida, la solución se acidificó hasta un pH de 1 con HCl ac. 3.8 M y a continuación se extrajo con MTBE (x2). Las fases orgánicas combinadas se lavaron con agua y se evaporaron. Las trazas de agua se eliminaron formando un azeótropo con MeCN. Se aisló el ácido 1-(metoxicarbonil)-2-fenilpiperidin-4-carboxílico (5.25 g, 94%) como un semisólido amarillento. MS m/z 264 $(M+H)^+$.

Compuesto de referencia 35

Ácido 2-ciclohexil-1-(metoxicarbonil)piperidin-4-carboxílico

Paso 1: Clorhidrato de 2-ciclohexilpiperidin-4-carboxilato

de metilo

Se disolvió 2-fenilisonicotinato de metilo (3.182 g, 14.92 mmol) (procedente del Paso 1 del Compuesto de referencia 34) en MeOH (30 mL) y se añadió cloruro de hidrógeno (1.25 M en MeOH, 14.33 mL, 17.91 mmol). Se evaporaron los disolventes para proporcionar un sólido amarillento. El residuo se disolvió en MeOH (60 mL) y se añadió óxido de platino (IV) (0.102 g, 0.45 mmol). A continuación, la mezcla resultante se hidrogenó en un hidrogenador Büchi a 8 bar durante 5 h. Se añadió más óxido de platino (IV) (121 mg) y se continuó la hidrogenación durante toda la noche a 8 bar (15 h). Se añadió óxido de platino (IV) (120 mg) y se continuó la hidrogenación a 60 °C durante 5 horas. Se añadió óxido de platino (IV) (120 mg) y se continuó la hidrogenación a 60 °C durante toda la noche (15 h). La mezcla de reacción se filtró a través de un cartucho de filtración con tierras de diatomeas y se lavó con metanol. Se evaporaron los disolventes y el residuo se secó al vacío para obtener un sólido blanco. Se volvió a disolver el residuo en MeOH (60 mL). Se añadió óxido de platino (IV) (340 mg) y se continuó la hidrogenación a 8 bar y 60 °C durante toda la noche (22 h). La mezcla de reacción se filtró a través de un cartucho de filtración con tierras de diatomeas y se lavó con metanol. Se evaporaron los disolventes y el residuo se secó al vacío para obtener el clorhidrato de 2-ciclohexilpiperidin-4-carboxilato de metilo (3.50 g, 89%) como un sólido blanco. MS m/z 226 $(M+H)^+$.

Paso 2: 2-Ciclohexilpiperidin-1,4-dicarboxilato de dimetilo

Se añadió cloroformiato de metilo (1.344 mL, 17.36 mmol) en DCM (50 mL) a una solución del clorhidrato de 2-ciclohexilpiperidin-4-carboxilato de metilo (3.50 g, 13.35 mmol) y DIPEA (1.88 mL, 10.76 mmol) en DCM (100 mL). La solución de reacción se agitó durante 3 h. Se añadieron 1.88 mL de DIPEA y 1.345 mL de cloroformiato de metilo y se procedió con la reacción durante toda la noche (16 h). La fase orgánica se lavó con $NaHCO_3$ sat. Se separaron las fases y se secó la

fase orgánica utilizando un separador de fases, para obtener 2-ciclohexilpiperidin-1,4-dicarboxilato de dimetilo crudo (4.90 g). MS m/z 284 $(M+H)^+$.

Paso 3: Ácido 2-ciclohexil-1-(metoxicarbonil)piperidin-4-carboxílico

Se disolvió 2-ciclohexilpiperidin-1,4-dicarboxilato de dimetilo (4.90 g, crudo) en acetonitrilo (30 mL) y agua (0.600 mL). Se añadieron bromuro de litio (9.28 g, 106.80 mmol) y trietilamina (7.40 mL, 53.40 mmol) y la mezcla se calentó a reflujo durante 2 h. Se añadieron agua (60 mL) y MTBE. La fase orgánica se extrajo con agua (x2). Se añadió MTBE a las fases acuosas recogidas, la solución se acidificó hasta un pH de 1 con HCl 2 M y a continuación se extrajo con MTBE (x2). Las fases orgánicas combinadas se secaron con Na_2SO_4 y se evaporaron, para obtener el ácido 2-ciclohexil-1-(metoxicarbonil)piperidin-4-carboxílico (3.28 g, 91% (en dos pasos)) como un semisólido amarillento. MS m/z 270 $(M+H)^+$.

Compuesto de referencia 36

Ácido 1-(benciloxicarbonil)-2-(2-metil-2*H*-tetrazol-5-il)piperidin-4-carboxílico

Paso 1: 2-Carbamoilisoniotinato de etilo

A una solución de isonicotinato de etilo (10 g, 66.15 mmol) y ácido sulfúrico concentrado (3.53 mL, 66.15 mmol) en formamida (80 mL, 2012.41 mmol), se añadieron de manera separada y simultánea peróxido de hidrógeno al 30% (2.399 mL, 99.23 mmol) y sulfato de hierro (II) heptahidratado en polvo (27.6 g, 99.23 mmol) durante 15 min, con una agitación eficaz y con refrigeración utilizando un baño de hielo. Tras completar la adición, se retiró el baño de hielo y se continuó agitando durante 2 h. Se añadió 2-hidroxipropan-1,2,3-tricarboxilato de sodio (132 mL, 132.31 mmol) (citrato de trisodio) y se ajustó el pH de la mezcla a un pH de 8 mediante la adición de $NaHCO_3$ sat. La mezcla resultante se extrajo con DCM tres veces y los extractos orgánicos combinados se lavaron con agua fría, se secaron con Na_2SO_4 y se evaporaron. El residuo sólido contenía una porción minoritaria del producto. El producto crudo se

sometió al mismo tratamiento anterior dos veces más, antes de conseguir obtener la mayor parte del producto deseado en el producto crudo, el cual se recristalizó en EtOH. Rendimiento: 4.3 g. Las aguas madres se purificaron en una columna Biotage utilizando heptano/EtOAc de 80/20 - 10/90 y se obtuvieron 0.8 g más de producto. Se aisló 2-carbamoilisonicotinato de etilo (5.1 g, 40%). ^{1}H RMN (400 MHz, DMSO) δ 1.34 (t, 3H), 4.37 (c, 2H), 7.79 (s, 1H), 8.00 (d, 1H), 8.22 (s, 1H), 8.40 (s, 1H), 8.83 (d, 1H). MS m/z 195 $(M+H)^+$.

Paso 2: Clorhidrato de 2-carbamoilpiperidin-4-carboxilato de etilo

Se suspendió 2-carbamoilisonicotinato de etilo (4.24 g, 21.83 mmol) en MeOH (50 mL) y se añadieron HCl en MeOH (17.47 mL, 21.83 mmol) y óxido de platino (IV) (0.248 g, 1.09 mmol). La mezcla se hidrogenó a 5 bar en un aparato de hidrogenación Büchi. Después de 3 h, todavía había material de partida sin reaccionar. Se añadió óxido de platino (IV) (0.14 g, 0.62 mmol) y se procedió con la reacción durante 2 h, a continuación se añadió óxido de platino (IV) (0.387 g, 1.70 mmol) y se agitó la reacción durante toda la noche. La mezcla de reacción se filtró y se evaporó para obtener el clorhidrato de 2-carbamoilpiperidin-4-carboxilato de etilo (3.93 g, 90%). ^{1}H RMN (400 MHz, DMSO) δ 1.16 (t, 3H), 1.31 - 1.63 (m, 2H), 1.86 (d, 1H), 2.26 (d, 1H), 2.54 - 2.66 (m, 1H), 2.74 - 2.88 (m, 1H), 3.10 - 3.19 (m, 1H), 3.47 - 3.56 (m, 1H), 4.06 (c, 2H), 7.38 (s, 1H), 7.71 (s, 1H). MS m/z 201 $(M+H)^+$.

Paso 3: 2-Carbamoilpiperidin-1,4-dicarboxilato de 1-bencilo y 4-etilo

Se suspendió el clorhidrato de 2-carbamoilpiperidin-4-carboxilato de etilo (2 g, 7.86 mmol) en diclorometano (25 mL) y se añadió DIPEA (3.43 mL, 19.65 mmol) y a continuación cloroformiato de bencilo (1.161 mL, 8.25 mmol) gota a gota. La reacción se agitó durante 1 h, a continuación se lavó con 25 mL de HCl 2 M y agua, se secó con Na_2SO_4 y se evaporó. El producto crudo se purificó en una columna Biotage de 100 g con heptano/EtOAc en 4 VC y a continuación con 100% de EtOAc en 10

VC. Se aisló 2-carbamoilpiperidin-1,4-dicarboxilato de 1-bencilo y 4-etilo (1.99 g, 76%). ^{1}H RMN (400 MHz, DMSO) δ 1.16 (t, 3H), 1.57 - 1.69 (m, 1H), 1.81 - 1.92 (m, 1H), 1.95 - 2.07 (m, 1H), 2.21 - 2.32 (m, 1H), 2.58 - 2.67 (m, 1H), 3.29 - 3.45 (m, 1H), 3.69 - 3.77 (m, 1H), 3.92 - 4.06 (m, 2H), 4.34 (t, 1H), 4.99 - 5.08 (m, 2H), 6.95 (s, 1H), 7.25 - 7.38 (m, 6H). MS m/z 335 $(M+H)^+$.

Paso 4: 2-Cianopiperidin-1,4-dicarboxilato de 1-bencilo y 4-etilo

Se disolvió 2-carbamoilpiperidin-1,4-dicarboxilato de 1-bencilo y 4-etilo (2.4 g, 7.18 mmol) en piridina (50 mL, 618.21 mmol). La mezcla se enfrió en un baño de hielo, se añadió gota a gota $SOCl_2$ (3.14 mL, 43.07 mmol) y se dejó durante toda la noche a temperatura ambiente. La mezcla de reacción se evaporó y se repartió entre HCl diluido y DCM. La fase acuosa se extrajo con DCM y las fases orgánicas combinadas se lavaron con agua, se secaron con Na_2SO_4 y se evaporaron. Se aisló 2-cianopiperidin-1,4-dicarboxilato de 1-bencilo y 4-etilo (2.25 g, 99%). ^{1}H RMN (400 MHz, DMSO) δ 1.21 (t, 3H), 1.54 - 1.66 (m, 1H), 1.98 - 2.12 (m, 2H), 2.29 - 2.37 (m, 1H), 2.83 - 2.91 (m, 1H), 3.04 - 3.16 (m, 1H), 3.83 - 3.91 (m, 1H), 4.02 - 4.18 (m, 2H), 5.13 (s, 2H), 5.25 - 5.31 (m, 1H), 7.28 - 7.40 (m, 5H).

Paso 5: 2-(1*H*-Tetrazol-5-il)piperidin-1,4-dicarboxilato de 1-bencilo y 4-etilo

Se disolvió 2-cianopiperidin-1,4-dicarboxilato de 1-bencilo y 4-etilo (2.5 g, 7.90 mmol) en tolueno (50 mL) y se añadieron azida de sodio (0.822 g, 12.64 mmol) y clorhidrato de trietilamina (1.740 g, 12.64 mmol) y la mezcla se calentó a 95 °C durante toda la noche. Se dejó enfriar la mezcla de reacción hasta temperatura ambiente y se lavó con HCl 2 M. La fase acuosa se extrajo con EtOAc y las fases orgánicas combinadas se secaron con Na_2SO_4 y se evaporaron, para proporcionar 2-(1*H*-tetrazol-5-il)piperidin-1,4-dicarboxilato de 1-bencilo y 4-etilo (2.8 g, 99%). MS m/z 360 $(M+H)^+$.

Paso 6: 2-(2-Metil-2*H*-tetrazol-5-il)piperidin-1,4-dicarboxilato de 1-bencilo y 4-etilo y 2-(1-metil-1*H*-tetrazol-5-il)piperidin-1,4-dicarboxilato de 1-bencilo y 4-etilo

Se disolvió 2-(1*H*-tetrazol-5-il)piperidin-1,4-dicarboxilato de 1-bencilo y 4-etilo (3.45 g, 9.60 mmol) en acetona (20 mL) y se añadieron yodometano (2.99 mL, 48.00 mmol) y K_2CO_3 (3.98 g, 28.80 mmol). La mezcla se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se repartió entre agua y EtOAc. La fase acuosa se extrajo 2 veces con EtOAc y las fases orgánicas combinadas se lavaron con agua y se evaporaron. El producto crudo se purificó en una columna Biotage de 100 g con heptano/EtOAc de 88/12 - 0/100 en 12 volúmenes de columna (VC). Se aislaron 2-(2-metil-2*H*-tetrazol-5-il)piperidin-1,4-dicarboxilato de 1-bencilo y 4-etilo (1.84 g, 51%) y 2-(1-metil-1*H*-tetrazol-5-il)piperidin-1,4-dicarboxilato de 1-bencilo y 4-etilo (1.14 g, 32%). Isómero 2-metilo: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.15 (t, 3H), 1.75 - 1.87 (m, 1H), 2.02 - 2.11 (m, 1H), 2.27 - 2.37 (m, 1H), 2.66 - 2.78 (m, 2H), 3.55 - 3.65 (m, 1H), 3.75 - 3.86 (m, 1H), 3.90 - 3.99 (m, 1H), 4.01 - 4.09 (m, 1H), 4.25 (s, 3H), 5.13 (c, 2H), 5.55 - 5.62 (m, 1H), 7.25 - 7.38 (m, 5H). MS m/z 374 $(M+H)^+$. Isómero 3-metilo: MS m/z 374 $(M+H)^+$.

Paso 7: Ácido 1-(benciloxicarbonil)-2-(2-metil-2*H*-tetrazol-5-il)piperidin-4-carboxílico

Se disolvió 2-(2-metil-2*H*-tetrazol-5-il)piperidin-1,4-dicarboxilato de 1-bencilo y 4-etilo (0.92 g, 2.36 mmol) en THF (10 mL) y agua (10 mL) y se añadió LiOH (0.239 g, 9.98 mmol). La mezcla se agitó a temperatura ambiente durante 1 h 10 min, a continuación se diluyó con agua y se acidificó con HCl 2 M. La fase acuosa se extrajo 3 veces con EtOAc, las fases orgánicas combinadas se secaron con Na_2SO_4 y se evaporaron, para proporcionar el ácido 1-(benciloxicarbonil)-2-(2-metil-2*H*-tetrazol-5-il)piperidin-4-carboxílico (828 mg, cuant.). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.80 - 1.91 (m, 1H), 2.01 - 2.11 (m, 1H), 2.34 (dt, 1H), 2.63 - 2.79 (m, 2H), 3.55 - 3.65 (m, 1H), 4.01 - 4.09 (m, 1H), 4.24 (s, 3H), 5.13 (d, 2H), 5.60 (dd, 1H), 7.27 -

7.39 (m, 5H). MS m/z 346 $(M+H)^+$.

Compuesto de referencia 37

Ácido 1-(benciloxicarbonil)-2-(1-metil-1*H*-tetrazol-5-il)piperidin-4-carboxílico

Se disolvió 2-(1-metil-1*H*-tetrazol-5-il)piperidin-1,4-dicarboxilato de 1-bencilo y 4-etilo (1.14 g, 2.93 mmol) (procedente del Paso 6 del Compuesto de referencia 36) en THF (10 mL) y agua (10 mL) y se añadió LiOH (0.280 g, 11.69 mmol). La mezcla se agitó a temperatura ambiente durante 30 min, a continuación se diluyó con agua y se acidificó con HCl 2 M. La fase acuosa se extrajo 3 veces con EtOAc, las fases orgánicas combinadas se secaron con Na_2SO_4 y se evaporaron, para proporcionar el ácido 1-(benciloxicarbonil)-2-(1-metil-1*H*-tetrazol-5-il)piperidin-4-carboxílico (990 mg, 98%). ^1H RMN (400 MHz, $CDCl_3$) δ 1.89 - 2.01 (m, 1H), 2.15 - 2.24 (m, 1H), 2.27 - 2.36 (m, 1H), 2.50 - 2.61 (m, 1H), 2.78 (q, 1H), 3.68 - 3.80 (m, 1H), 3.91 - 4.09 (m, 4H), 5.08 (c, 2H), 5.44 (t, 1H), 7.23 - 7.39 (m, 5H). MS m/z 346 $(M+H)^+$.

Compuesto de referencia 38

Ácido 2-(ciclohexiloximetil)-1-(metoxicarbonil)piperidin-4-carboxílico

Paso 1: 2-(hidroximetil)isonicotinato de metilo

La reacción se llevó a cabo en 2 matraces de fondo redondo diferentes de 1000 mL. A una solución de isonicotinato de metilo (70 g, 510.44 mmol) y ácido sulfúrico (2.340 mL, 43.90 mmol) en MeOH (700 mL) a reflujo, se añadió una solución de peroxidisulfato de amonio (210 g, 918.80 mmol) en agua (350 mL) durante 20 min. La reacción se calentó a reflujo durante 20 min y a continuación se dejo enfriar hasta temperatura ambiente. El sólido se filtró y lavó con MeOH. Se eliminó el MeOH del filtrado a presión reducida y a continuación se neutralizó añadiendo por pasos cuidadosamente Na_2CO_3 sólido, a la vez que se enfriaba con hielo. La solución acuosa se extrajo con acetato de etilo y las fases orgánicas combinadas se secaron con Na_2SO_4 y se evaporaron. El residuo de color marrón oscuro se trató con ciclohexano (3 x 300 mL) y la fase de ciclohexano

se decantó. El residuo de color marrón oscuro remanente se purificó mediante cromatografía flash automatizada en 2 columnas Biotage® con 340 g de KP-SIL. Se utilizó como fase móvil un gradiente de 25 % a 100 % de EtOAc en heptano en 10 VC. Se aisló 2-(hidroximetil)isonicotinato de metilo (27.5 g, 32%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 3.90 (s, 3H), 4.78 (s, 2H), 7.57 - 7.90 (m, 2H), 8.64 (s, 1H). MS m/z 168 $(M+H)^+$.

Paso 2: 2-(Fenoximetil)isonicotinato de metilo

Se disolvió 2-(hidroximetil)isonicotinato de metilo (2.232 g, 13.35 mmol) en THF (15 mL) y se añadieron fenol (1.426 mL, 16.02 mmol) y trifenilfosfina (3.71 mL, 16.02 mmol). La mezcla se enfrió hasta 0 °C. Se añadió gota a gota (*E*)-diazen-1,2-dicarboxilato de diisopropilo (3.24 g, 16.02 mmol), se retiró el baño de hielo y la reacción se agitó a temperatura ambiente durante 2 h. Se evaporó el disolvente y el residuo se purificó mediante cromatografía flash automatizada en una columna Biotage® con 340 g de KP-SIL. Se utilizó como fase móvil EtOAc en heptano 4:1 en 10 VC. Se aisló 2-(fenoximetil)isonicotinato de metilo (2.65 g, 82%).^{1}H RMN (400 MHz, $CDCl_3$) δ 3.96 (s, 3H), 5.26 (s, 2H), 6.95 - 7.04 (m, 3H), 7.27 - 7.34 (m, 2H), 7.76 - 7.80 (m, 1H), 8.10 (s, 1H), 8.75 (d, 1H). MS m/z 244 $(M+H)^+$.

Paso 3: 2-(Ciclohexiloximetil)piperidin-4-carboxilato de metilo

Se disolvió 2-(fenoximetil)isonicotinato de metilo (2.6 g, 10.69 mmol) en ácido acético (50 mL), a continuación se añadió óxido de platino (IV) (0.243 g, 1.07 mmol) y la mezcla se hidrogenó en un hidrogenador Büchi a 5 bar y temperatura ambiente durante 6 h. El catalizador se eliminó mediante filtración y se evaporó el disolvente. El residuo se disolvió en DCM y la fase orgánica se lavó con $NaHCO_3$ sat. La fase acuosa se extrajo con DCM, las fases orgánicas combinadas se filtraron a través de un separador de fases y se evaporaron. Se aisló 2-(ciclohexiloximetil)piperidin-4-carboxilato de metilo (2 g, 73%).

Paso 4: 2-(Ciclohexiloximetil)piperidin-1,4-dicarboxilato de dimetilo

Se disolvió 2-(ciclohexiloximetil)piperidin-4-carboxilato de metilo (2.13 g, 8.34 mmol) en diclorometano (50 mL). Se añadieron DIPEA (2.034 mL, 11.68 mmol) y cloroformiato de metilo (0.788 mL, 10.01 mmol) y la mezcla se agitó a temperatura ambiente durante 3 h. Se añadió NH_4Cl 0.1 M y la fase acuosa se extrajo con DCM. Las fases orgánicas combinadas se filtraron a través de un separador de fases y se evaporaron. Se aisló 2-(ciclohexiloximetil)piperidin-1,4-dicarboxilato de dimetilo (2.54 g, 97%). MS m/z 314 $(M+H)^+$.

Paso 5: Ácido 2-(ciclohexiloximetil)-1-(metoxicarbonil)piperidin-4-carboxílico

Se disolvió 2-(ciclohexiloximetil)piperidin-1,4-dicarboxilato de dimetilo (2.54 g, 8.1 mmol) en acetonitrilo (35 mL) y agua (0.7 mL), a continuación se añadió bromuro de litio (5.63 g, 64.80 mmol). Se añadió trietilamina (4.49 mL, 32.40 mmol) y la suspensión resultante se calentó a reflujo durante 4 h. Se añadieron MTBE (100 mL) y agua (50 mL), se separaron las fases y se extrajo la fase orgánica con agua. Las fases acuosas combinadas se acidificaron hasta un pH de 1 con HCl 3.8 M y se extrajeron con MTBE. Las fases orgánicas combinadas se secaron con Na_2SO_4 y se evaporaron. Se aisló el ácido 2-(ciclohexiloximetil)-1-(metoxicarbonil)piperidin-4-carboxílico (2.43 g, cuant.). MS m/z 300 $(M+H)^+$.

Compuesto de referencia 39

Ácido 2-(difluorometil)-1-(metoxicarbonil)piperidin-4-carboxílico

Paso 1: 2-Formilisonicotinato de metilo

Se disolvió 2-(hidroximetil)isonicotinato de metilo (8.36 g, 50 mmol) (procedente del Paso 1 del Compuesto de referencia 38) en diclorometano (150 mL). Se añadió peryodinano de Dess-Martin (25 g, 58.94 mmol) y la mezcla se agitó a temperatura ambiente durante 2 h 30 min. Se disolvió tiosulfato de sodio (59.3 g, 375.00 mmol) en $NaHCO_3$ sat. y se añadió a la mezcla de reacción. La suspensión se agitó enérgicamente a temperatura ambiente durante 15 min, se añadió DCM y se separaron las fases. La fase acuosa se extrajo con DCM dos veces y las fases

orgánicas combinadas se secaron con $MgSO_4$ y se evaporaron. El residuo se purificó mediante cromatografía flash automatizada en una columna Biotage® con 340 g de KP-SIL. Se utilizó como fase móvil un gradiente de heptanos:EtOAc de 80:20 a 65:35 en 5 VC. Se aisló 2-formilisonicotinato de metilo (7 g, 85%) como un sólido blanquecino. ^1H RMN (400 MHz, $CDCl_3$) δ 4.00 (s, 3H), 8.09 (dd, 1H), 8.49 (s, 1H), 8.95 (d, 1H), 10.15 (s, 1H). MS m/z 165 $(M+H)^+$.

Paso 2: 2-(Difluorometil)isonicotinato de metilo

Se disolvió 2-formilisonicotinato de metilo (2.51 g, 15.20 mmol) en diclorometano (50 mL) y se enfrió hasta 0 °C. Se añadió gota a gota trifluoruro de dietilaminoazufre (DAST) (2.61 mL, 19.76 mmol). Se retiró el baño de refrigeración y la mezcla se agitó a temperatura ambiente durante 2 h. Se añadió $NaHCO_3$ sat. a 0 °C y se separaron las fases. La fase acuosa se extrajo con DCM. Las fases orgánicas combinadas se filtraron a través de un separador de fases y se evaporaron. El residuo se purificó mediante cromatografía flash automatizada en una columna Biotage® con 50 g de KP-SIL. Se utilizó como fase móvil EtOAc en heptano 5:1 en 10 VC. Se aisló 2-(difluorometil)isonicotinato de metilo (2.4 g, 84%). ^1H RMN (400 MHz, $CDCl_3$) δ 4.00 (s, 3H), 6.70 (t, 1H), 7.97 (d, 1H), 8.19 (s, 1H), 8.82 (d, 1H).

Paso 3: 2-(Difluorometil)piperidin-4-carboxilato de metilo

Se disolvió 2-(difluorometil)isonicotinato de metilo (2.4 g, 12.82 mmol) en ácido acético (40 mL). Se añadió óxido de platino (IV) (0.291 g, 1.28 mmol) y la mezcla se hidrogenó a temperatura ambiente y 5 bar durante 7 h en un aparato de hidrogenación Büchi. El catalizador se eliminó por filtración, se añadió óxido de platino (IV) nuevo (210 mg, 0.92 mmol) y se continuó la hidrogenación a temperatura ambiente y 5 bar durante 6 h. El catalizador se eliminó por filtración y se evaporó el disolvente. El residuo se disolvió en DCM y la fase orgánica se lavó con $NaHCO_3$ sat. La fase acuosa se extrajo con DCM, las fases orgánicas combinadas se filtraron a través de un separador de fases y se evaporaron. Se aisló 2-

(difluorometil)piperidin-4-carboxilato de metilo (1.85 g, 75%). MS m/z 194 $(M+H)^+$.

Paso 4: 2-(Difluorometil)piperidin-1,4-dicarboxilato de dimetilo

Se disolvió 2-(difluorometil)piperidin-4-carboxilato de metilo (1.85 g, 9.58 mmol) en diclorometano (50 mL), se añadieron DIPEA (2.335 mL, 13.41 mmol) y cloroformiato de metilo (0.905 mL, 11.49 mmol) y la mezcla se agitó a temperatura ambiente durante 3 h. Se añadió NH_4Cl 0.1 M y la fase acuosa se extrajo con DCM. Las fases orgánicas combinadas se filtraron a través de un separador de fases y se evaporaron. Se aisló 2-(difluorometil)piperidin-1,4-dicarboxilato de dimetilo crudo (2.35 g, 98%).

Paso 5: Ácido 2-(difluorometil)-1-(metoxicarbonil)piperidin-4-carboxílico

Se disolvió 2-(difluorometil)piperidin-1,4-dicarboxilato de dimetilo (2.35 g, 9.35 mmol) en THF (35 mL) y se añadió hidróxido de litio 1 M (12.16 mL, 12.16 mmol) en agua. La mezcla se agitó a temperatura ambiente durante 3 h, a continuación se añadieron HCl 1 M y DCM, y se separaron las fases. La fase acuosa se extrajo con DCM, las fases orgánicas combinadas se secaron mediante la filtración a través de un separador de fases y se evaporaron. Se aisló el ácido 2-(difluorometil)-1-(metoxicarbonil)piperidin-4-carboxílico (2.2 g, 99%). MS m/z 275 $(M-H)^-$.

Compuesto de referencia 40

Ácido 2-((4,4-difluorociclohexil)metil)-1-(metoxicarbonil)piperidin-4-carboxílico

Paso 1: (4,4-Difluorociclohexil)metanol

Se disolvió 4,4-difluorociclohexanocarboxilato de etilo (10 g, 52.03 mmol) en THF (100 mL) y se enfrió hasta 1 °C en una atmósfera de nitrógeno. Se añadió LAH (57.2 mL, 57.23 mmol) gota a gota a la solución a una velocidad tal que la temperatura se mantuviera por debajo de 10 °C. Se dejó que la mezcla resultante alcanzara 20 °C y se agitó a esta temperatura durante aproximadamente 1 h. A continuación, la mezcla de

reacción se enfrió hasta 10 °C, se detuvo cuidadosamente con la adición lenta y secuencial de 2.2 mL de agua, 2.2 mL de NaOH acuoso al 15% p/v y 6.6 mL de agua y se agitó durante 30 min a 20 °C. Los sólidos se eliminaron por filtración y se lavaron con THF. La solución de reacción se secó con $MgSO_4$ y se evaporó al vacío para obtener (4,4-difluorociclohexil)metanol crudo (7.22 g, 92%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.21 - 1.38 (m, 2H), 1.44 (s, 1H), 1.51 - 1.90 (m, 5H), 2.04 - 2.18 (m, 2H), 3.52 (d, 2H).

Paso 2: 4-(Bromometil)-1,1-difluorociclohexano

Se disolvieron (4,4-difluorociclohexil)metanol (7.22 g, 48.08 mmol) y trifenilfosfina (25.2 g, 96.16 mmol) en DCM (75 mL) y se enfriaron hasta 0 °C en una atmósfera de nitrógeno. Se disolvió tetrabromuro de carbono (31.9 g, 96.16 mmol) en DCM (75 mL) y se añadió a la mezcla de reacción. La mezcla se agitó a temperatura ambiente durante toda la noche. Se evaporó el disolvente. Se añadió pentano (250 mL) al residuo orgánico, lo que provocó la precipitación del óxido de trifenilfosfina. Se filtraron los sólidos blanquecinos. El filtrado se evaporó y se purificó en una columna flash de sílice ISOLUTE (50 g). Se utilizó como eluyente pentano y a continuación EtOAc:pentano (1% de EtOAc). Se aisló 4-(bromometil)-1,1-difluorociclohexano (5.48 g, 54%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.32 - 1.46 (m, 2H), 1.64 - 1.84 (m, 3H), 1.90 - 1.99 (m, 2H), 2.05 - 2.18 (m, 2H), 3.31 (d, 2H).

Paso 3: Bromuro de ((4,4-difluorociclohexil)metil)zinc (II)

Se añadió zinc en polvo (1.43 g, 21.87 mmol) a un matraz anhidro y se calentó a 70 °C al vacío durante 30 min. Se añadió DMA (29 mL) anhidra y yodo (0.092 g, 0.37 mmol) y la mezcla se calentó a 70 °C hasta que desapareció el color marrón rojizo (aprox. 5 minutos). Se añadió 4-(bromometil)-1,1-difluorociclohexano (3.1 g, 14.55 mmol) y se continuó calentando durante aproximadamente 42 h. La solución resultante se utilizó en la siguiente transformación.

Paso 4: 2-((4,4-Difluorociclohexil)metil)isonicotinato de

metilo

Se añadió tetrahidrofurano (10 mL) a 2-cloroisonicotinato de metilo (1.664 g, 9.7 mmol) y bis(tri-*tert*-butilfosfina)paladio (0) (198 mg, 0.38 mmol) en una atmósfera de nitrógeno. A la solución resultante, se le añadió bromuro de ((4,4-difluorociclohexil)metil)zinc (II) (14.55 mmol, 0.5 M en 29 mL de DMA) recién preparado y la mezcla marrón resultante se calentó hasta 60 °C durante 4 h. La mezcla de reacción se diluyó con acetato de etilo y se lavó con $NaHCO_3$ sat. (2 veces), NH_4Cl sat. y salmuera. La fase orgánica se secó con $MgSO_4$, se filtró y se evaporó. El residuo se disolvió en DCM y se introdujo en una columna de intercambio catiónico SCX-2. La columna se lavó con DCM, MeOH y a continuación se eluyó con NH_3/MeOH. La fase de NH_3/MeOH se evaporó, para obtener 2-((4,4-difluorociclohexil)metil)isonicotinato de metilo (2 g, 67%) como un aceite amarillo. ^1H RMN (400 MHz, $CDCl_3$) δ 1.30 - 1.46 (m, 2H), 1.58 - 1.79 (m, 4H), 1.87 - 2.14 (m, 3H), 2.82 (d, 2H), 3.96 (s, 3H), 7.65 - 7.73 (m, 2H), 8.70 (d, 1H). MS m/z 270 $(M+H)^+$.

Paso 5: Clorhidrato de 2-((4,4-difluorociclohexil)metil)piperidin-4-carboxilato de metilo

Se trató 2-((4,4-difluorociclohexil)metil)isonicotinato de metilo (5 g, 18.6 mmol) con HCl (4 M en dioxano) y se evaporó, para obtener el clorhidrato de 2-((4,4-difluorociclohexil)metil)isonicotinato de metilo (5.6 g, 18.32 mmol), el cual se disolvió en MeOH (100 mL) y a continuación se añadió óxido de platino (IV) (0.416 g, 1.83 mmol). La mezcla se hidrogenó en un hidrogenador Büchi a 5 bar durante toda la noche. El catalizador se filtró y los disolventes se evaporaron, para proporcionar el clorhidrato de 2-((4,4-difluorociclohexil)metil)piperidin-4-carboxilato de metilo (5.1 g, 89%). MS m/z 276 $(M+H)^+$.

Paso 6: 2-((4,4-Difluorociclohexil)metil)piperidin-1,4-dicarboxilato de dimetilo

Se disolvió el clorhidrato de 2-((4,4-difluorociclohexil)metil)piperidin-4-carboxilato de metilo (5.1

g, 16.36 mmol) en DCM (150 mL) y a continuación se añadió DIPEA (7.14 mL, 40.89 mmol). Se añadió cloroformiato de metilo (1.803 mL, 22.90 mmol) gota a gota a la disolución. La mezcla se agitó a temperatura ambiente durante 2 h. La mezcla se lavó con HCl 0.1 M (100 mL) y $NaHCO_3$ sat. (100 mL), a continuación se secó a través de un separador de fases y se evaporó, para proporcionar 2-((4,4-difluorociclohexil)metil)piperidin-1,4-dicarboxilato de dimetilo crudo (5.7 g, 105%).

Paso 7: Ácido 2-((4,4-difluorociclohexil)metil)-1-(metoxicarbonil)piperidin-4-carboxílico

Se disolvió 2-((4,4-difluorociclohexil)metil)piperidin-1,4-dicarboxilato de dimetilo (5.7 g, 17.10 mmol) en acetonitrilo (75 mL) y agua (1.5 mL), a continuación se añadió bromuro de litio (11.88 g, 136.78 mmol). Se añadió Et_3N (9.53 mL, 68.39 mmol) a la disolución. La suspensión amarilla resultante se calentó a reflujo durante 2 h. Se añadieron agua (100 mL) y MTBE (300 mL). Las fases se separaron y la fase orgánica se extrajo con agua (2 veces). Las fases acuosas recogidas se acidificaron hasta un pH de 1 con HCl 3.8 M y se extrajeron con MTBE (2 veces). Las fases orgánicas combinadas se secaron con Na_2SO_4, se filtraron y se evaporaron, para proporcionar el ácido 2-((4,4-difluorociclohexil)metil)-1-(metoxicarbonil)piperidin-4-carboxílico (4.82 g, 88%) como un sólido blanco.

Compuesto de referencia 41

Ácido 2-(4-fluorofenetil)-1-(metoxicarbonil)piperidin-4-carboxílico

Paso 1: (*E*)-2-(4-fluoroestiril)isonicotinato de metilo

Se repartieron 2-cloroisonicotinato de metilo (5.5 g, 32.05 mmol), ácido (*E*)-4-fluoroestirilborónico (7.98 g, 48.08 mmol), fosfato de potasio (3.93 mL, 48.08 mmol) y $PdCl_2$(dppf) (0.464 g, 0.64 mmol) en 5 porciones iguales y cada porción se colocó en un recipiente de reacción para microondas. Los recipientes se sometieron al vacío y se volvieron a rellenar con nitrógeno. Se añadió metanol (15 mL) a cada recipiente, los recipientes se sellaron y se calentaron en un reactor de

microondas de nodo único a 100 °C durante 10 min cada uno. Se recuperó el contenido de los recipientes y se añadieron agua y DCM, se separaron las fases y la fase acuosa se extrajo con DCM. Las fases orgánicas combinadas se filtraron a través de un separador de fases y se evaporaron. El residuo se purificó mediante cromatografía flash automatizada en una columna Biotage® con 340 g de KP-SIL. Se utilizó como fase móvil un gradiente de 6:1 a 4:1 de EtOAc en heptano en 15 VC. Se aisló (*E*)-2-(4-fluoroestiril)isonicotinato de metilo (3.88 g, 47%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 3.98 (s, 3H), 7.04 - 7.18 (m, 3H), 7.52 - 7.62 (m, 2H), 7.63 - 7.71 (m, 2H), 7.93 (s, 1H), 8.74 (d, 1H). MS m/z 258 $(M+H)^+$.

Paso 2: 2-(4-Fluorofenetil)isonicotinato de metilo

Se disolvió (*E*)-2-(4-fluoroestiril)isonicotinato de metilo (3.6 g, 13.99 mmol) en metanol (200 mL). Se añadió paladio sobre carbón (0.149 g, 1.40 mmol) y la mezcla se hidrogenó a presión atmosférica y temperatura ambiente durante 18 h. El catalizador se filtró y se evaporó el filtrado. Se aisló 2-(4-fluorofenetil)isonicotinato de metilo (3.63 g, 99%). MS m/z 260 $(M+H)^+$.

Paso 3: 2-(4-Fluorofenetil)piperidin-4-carboxilato de metilo

Se disolvió 2-(4-fluorofenetil)isonicotinato de metilo (3.8 g, 14.66 mmol) en ácido acético (150 mL) y se añadió óxido de platino (IV) (0.25 g, 1.10 mmol). La mezcla se hidrogenó en un aparato de hidrogenación Büchi a temperatura ambiente y 5 bar durante 5 h. El catalizador se eliminó por filtración y se evaporó el disolvente. El residuo se disolvió en DCM y se lavó con $NaHCO_3$ sat. La fase orgánica se filtró a través de un separador de fases y se evaporó. Se aisló 2-(4-fluorofenetil)piperidin-4-carboxilato de metilo (3.89 g, cuant.). MS m/z 266 $(M+H)^+$.

Paso 4: 2-(4-Fluorofenetil)piperidin-1,4-dicarboxilato de dimetilo

Se disolvió 2-(4-fluorofenetil)piperidin-4-carboxilato de metilo (3.89 g, 14.65 mmol) en diclorometano (150 mL). Se

añadió DIPEA (3.06 mL, 17.58 mmol) y a continuación cloroformiato de metilo (1.615 mL, 20.51 mmol). La mezcla se agitó a temperatura ambiente durante 2 h. Se añadieron HCl 0.1 M y DCM. Las fases se separaron y la fase acuosa se extrajo con DCM. Las fases orgánicas combinadas se lavaron con $NaHCO_3$ sat., se filtraron a través de un separador de fases y se evaporaron. Se aisló 2-(4-fluorofenetil)piperidin-1,4-dicarboxilato de dimetilo (3.19 g, 67%). MS m/z 324 $(M+H)^+$.

Paso 5: Ácido 2-(4-fluorofenetil)-1-(metoxicarbonil)piperidin-4-carboxílico

Se disolvió 2-(4-fluorofenetil)piperidin-1,4-dicarboxilato de dimetilo (3.18 g, 9.83 mmol) en acetonitrilo (35 mL) y agua (0.7 mL), a continuación se añadió bromuro de litio (6.83 g, 78.67 mmol). Se añadió trietilamina (5.45 mL, 39.34 mmol) y la suspensión resultante se calentó a reflujo durante 5 h. Se añadieron MTBE y agua, se separaron las fases y se extrajo la fase orgánica con agua. Las fases acuosas combinadas se acidificaron hasta un pH de 1 con HCl 3.8 M y se extrajeron con MTBE. Las fases orgánicas combinadas se lavaron con agua, se secaron con Na_2SO_4 y se evaporaron. Se aisló el ácido 2-(4-fluorofenetil)-1-(metoxicarbonil)piperidin-4-carboxílico crudo (4.37 g). MS m/z 310 $(M+H)^+$.

Compuesto de referencia 42

Ácido 2-(3,3-dimetilbutil)-1-(metoxicarbonil)piperidin-4-carboxílico

Paso 1: 4-((*tert*-Butildimetilsililoxi)metil)-2-(3,3-dimetilbutil)piridin-1(2*H*)-carboxilato de metilo

Se disolvió 4-((*tert*-butildimetilsililoxi)metil)piridina (5.58 g, 25 mmol) (procedente del Paso 1 del Compuesto de referencia 4) en THF anhidro (50 mL) en una atmósfera de nitrógeno y la mezcla se enfrió hasta -15 °C. Se añadió cloruro de (3,3-dimetilbutil)magnesio (0.5 M en THF) (50 mL, 25 mmol) gota a gota durante 20 min para proporcionar una solución amarilla, que se agitó a -15 °C durante 30 min. A continuación, se añadió cloroformiato de metilo (2.5 mL, 32 mmol) durante 1 min. Se procedió con la reacción a -15 °C durante 30 min y a

continuación la mezcla se enfrió hasta -60 °C. La reacción tardó 2 h en alcanzar la temperatura ambiente. Se añadió agua (20 mL) y el disolvente se evaporó. La fase acuosa se extrajo con DCM (x2) y las fases orgánicas combinadas se hicieron pasar a través de un separador de fases. El disolvente se evaporó para obtener un aceite amarillo. El residuo se purificó en una columna Biotage (0 => 10 % de EtOAc en heptano) para proporcionar 4-((*tert*-butildimetilsililoxi)metil)-2-(3,3-dimetilbutil)piridin-1(2*H*)-carboxilato de metilo (3.67 g, 44%) como un aceite incoloro. MS m/z 368 $(M+H)^+$.

Paso 2: 4-((*tert*-Butildimetilsililoxi)metil)-2-(3,3-dimetilbutil)piperidin-1-carboxilato de metilo

Se añadió óxido de platino (IV) (224 mg, 1 mmol) a una solución de 4-((*tert*-butildimetilsililoxi)metil)-2-(3,3-dimetilbutil)piridin-1(2*H*)-carboxilato de metilo (3.63 g, 9.87 mmol) en acetato de etilo (60 mL). Se hidrogenó a 6 bar en un hidrogenador Büchi durante 3.5 h. El catalizador se filtró y se evaporó el filtrado, para proporcionar 4-((*tert*-butildimetilsililoxi)metil)-2-(3,3-dimetilbutil)piperidin-1-carboxilato de metilo (3.62 g, 99%) como un aceite incoloro. MS m/z 372 $(M+H)^+$.

Paso 3: 2-(3,3-Dimetilbutil)-4-(hidroximetil)piperidin-1-carboxilato de metilo

Se disolvió 4-((*tert*-butildimetilsililoxi)metil)-2-(3,3-dimetilbutil)piperidin-1-carboxilato de metilo (3.606 g, 9.7 mmol) en THF (50 mL) y se añadió TBAF (1M en THF) (13 mL, 13 mmol). Se agitó a temperatura ambiente durante 3.5 h. Se evaporó el disolvente. Se volvió a disolver en DCM y se lavó con $NaHCO_3$ sat. La fase orgánica se hizo pasar a través de un separador de fases y se evaporó, para proporcionar un aceite. El residuo se purificó en una columna Biotage (eluyente: 30-70% de EtOAc en heptano) para proporcionar 2-(3,3-dimetilbutil)-4-(hidroximetil)piperidin-1-carboxilato de metilo (2.45 g, 98%) como un aceite incoloro. MS m/z 258 $(M+H)^+$.

Paso 4: Ácido 2-(3,3-dimetilbutil)-1-(metoxicarbonil)piperidin-4-carboxílico

Se disolvió 2-(3,3-dimetilbutil)-4-(hidroximetil)piperidin-1-carboxilato de metilo (2.44 g, 9.49 mmol) en CCl_4 (20 mL) y acetonitrilo (20 mL). Se añadió peryodato de sodio (6.09 g, 28.5 mmol) y a continuación agua (30 mL) y cloruro de rutenio (III) (43 mg, 0.21 mmol). La suspensión resultante se agitó a temperatura ambiente durante 3 h 50 min. La mezcla de reacción se diluyó con DCM (100 mL) y agua (100 mL). La fase acuosa se extrajo con DCM (x3) y las fases orgánicas combinadas se hicieron pasar a través de un separador de fases y se evaporaron, para proporcionar el ácido 2-(3,3-dimetilbutil)-1-(metoxicarbonil)piperidin-4-carboxílico crudo (2.42 g, 94%) como un sólido negro. MS m/z 272 $(M+H)^+$.

Compuesto de referencia 43

Ácido 2-(4-fluorobencil)-1-(metoxicarbonil)piperidin-4-carboxílico

Paso 1: 2-(4-Fluorobencil)isonicotinato de metilo

En una atmósfera de nitrógeno, se disolvieron 2-cloroisonicotinato de metilo (5.6 g, 32.64 mmol) y $Pd(PPh_3)_4$(0.754 g, 0.65 mmol) en THF (100 mL) y se añadió cloruro de (4-fluorobencil)zinc (II) (0.5 M en THF) (100 mL, 50.00 mmol). La solución marrón se agitó a 60 °C durante 19 h. La reacción se detuvo añadiendo metanol (50.0 mL). La solución se diluyó con EtOAc y se lavó con NH_4Cl (ac.) y agua. La fase orgánica se evaporó, se disolvió en DCM, se lavó con NH_4Cl (ac.) y a continuación se secó pasándola a través de un separador de fases. El disolvente se evaporó para proporcionar un aceite marrón. El compuesto se purificó dos veces en una columna Biotage, SNAP con 340 g de KP-SIL, utilizando un eluyente isocrático de heptano/acetato de etilo 8:2 en 2 VC y a continuación un gradiente lineal de heptano/acetato de etilo de 8:2 a 5:5 en 5 VC, para proporcionar 7.08 g de 2-(4-fluorobencil)isonicotinato de metilo (88%) como un aceite amarillo. ^1H RMN (400 MHz, $CDCl_3$) δ 3.92 (s, 3H), 4.18 (s, 2H), 6.94 - 7.02 (m, 2H), 7.19 - 7.27 (m, 2H), 7.65 - 7.69 (m, 2H), 8.68 - 8.71 (m, 1H). MS m/z 246 $(M+H)^+$.

Paso 2: 2-(4-Fluorobencil)piperidin-4-carboxilato de

metilo

Se disolvió 2-(4-fluorobencil)isonicotinato de metilo (5.06 g, 20.63 mmol) en ácido acético (50 mL) y se añadió óxido de platino (IV) (0.234 g, 1.03 mmol). La mezcla resultante se hidrogenó en un hidrogenador Büchi durante toda la noche a temperatura ambiente y 5 bar. El catalizador se filtró, se lavó con MeOH y se evaporó el eluato. Se añadieron DCM y K_2CO_3 al 10%, y se separaron las fases. La fase acuosa se extrajo con DCM y las fases orgánicas combinadas se lavaron con salmuera, se pasaron a través de un separador de fases y se evaporaron, para proporcionar 2-(4-fluorobencil)piperidin-4-carboxilato de metilo (3.816 g, 73.6%) como un aceite amarillo. MS m/z 252 $(M+H)^+$.

Paso 3: 2-(4-Fluorobencil)piperidin-1,4-dicarboxilato de dimetilo

Se disolvió 2-(4-fluorobencil)piperidin-4-carboxilato de metilo (4.981 g, 19.82 mmol) en DCM (150 mL) y DIPEA (4.14 mL, 23.79 mmol), a continuación se añadió cloroformiato de metilo (1.873 mL, 23.79 mmol). La solución se agitó a temperatura ambiente durante 50 min. Se añadió más cloroformiato de metilo (unas gotas) y se procedió con la reacción a temperatura ambiente durante 1 h. La mezcla de reacción se lavó con HCl 0.1 M $NaHCO_3$ sat. La fase orgánica se hizo pasar a través de un separador de fases y se evaporó, para proporcionar 2-(4-fluorobencil)piperidin-1,4-dicarboxilato de dimetilo (5.82 g, 95%) como un aceite amarillo. MS m/z 310 $(M+H)^+$.

Paso 4: Ácido 2-(4-fluorobencil)-1-(metoxicarbonil)piperidin-4-carboxílico

Se disolvió 2-(4-fluorobencil)piperidin-1,4-dicarboxilato de dimetilo (5.797 g, 18.74 mmol) en acetonitrilo (60 mL) y agua (1.2 mL), a continuación se añadió bromuro de litio (13.02 g, 149.92 mmol). Se añadió trietilamina (10.39 mL, 74.96 mmol) y la suspensión amarilla resultante se calentó a reflujo durante 1.5 h. Se añadieron agua (60 mL) y MTBE (120 mL). La fase orgánica se extrajo con agua (x2). Las fases acuosas recogidas se acidificaron hasta un pH de 1 con HCl 3.8 M y a

continuación se extrajeron con MTBE (x2). Las fases orgánicas combinadas se lavaron con agua y se evaporaron. Las trazas de agua se eliminaron formando un azeótropo con MeCN. Se aisló el ácido 2-(4-fluorobencil)-1-(metoxicarbonil)piperidin-4-carboxílico (4.43 g, 80%) como un sólido beis. MS m/z 296 $(M+H)^+$.

Compuesto de referencia 44

Ácido 2-(3-fluorobencil)-1-(metoxicarbonil)piperidin-4-carboxílico

Paso 1: 2-(3-Fluorobencil)isonicotinato de metilo

En una atmósfera de nitrógeno, se disolvieron 2-cloroisonicotinato de metilo (5.6 g, 32.64 mmol) y $Pd(PPh_3)_4$(0.754 g, 0.65 mmol) en THF (100 mL) y se añadió cloruro de (3-fluorobencil)zinc (II) (0.5 M en THF) (100 mL, 50.00 mmol). La solución marrón se agitó a 60 °C durante 4 h. La reacción se detuvo añadiendo metanol (50 mL), se diluyó con EtOAc y se lavó con NH_4Cl. La fase orgánica se secó con Na_2SO_4, se filtró y se evaporó para obtener un aceite amarillo. El compuesto se purificó dos veces en una columna Biotage, SNAP con 340 g de KP-SIL, utilizando un eluyente isocrático de heptano/acetato de etilo 8:2 en 2 VC y a continuación un gradiente lineal de heptano/acetato de etilo de 8:2 a 5:5 en 5 VC, para proporcionar 2-(3-fluorobencil)isonicotinato de metilo (6.766 g, 85%) como un aceite amarillo. ^1H RMN (400 MHz, $CDCl_3$) δ 3.93 (s, 3H), 4.21 (s, 2H), 6.88 - 7.00 (m, 2H), 7.02 - 7.07 (m, 1H), 7.22 - 7.30 (m, 1H), 7.66 - 7.73 (m, 2H), 8.68 - 8.73 (m, 1H). MS m/z 246 $(M+H)^+$.

Paso 2: 2-(3-Fluorobencil)piperidin-4-carboxilato de metilo

Se disolvió 2-(3-fluorobencil)isonicotinato de metilo (6.766 g, 27.59 mmol) en ácido acético (70 mL) y se añadió óxido de platino (IV) (0.313 g, 1.38 mmol). La mezcla resultante se hidrogenó en un hidrogenador Büchi a temperatura ambiente y 5 bar durante 4.5 h. Se añadió más óxido de platino (IV) (0.313 g, 1.38 mmol) y se continuó la hidrogenación a 5 bar durante 2 h 40 min. El catalizador se filtró, se lavó con

MeOH y se evaporó el eluato. Se añadieron DCM y K_2CO_3 al 10%, y se separaron las fases. La fase acuosa se extrajo con DCM y las fases orgánicas combinadas se lavaron con salmuera, se pasaron a través de un separador de fases y se evaporaron, para proporcionar 2-(3-fluorobencil)piperidin-4-carboxilato de metilo crudo (7.6 g, 110%) como un aceite marrón. MS m/z 252 $(M+H)^+$.

Paso 3: 2-(3-Fluorobencil)piperidin-1,4-dicarboxilato de dimetilo

Se disolvió 2-(3-fluorobencil)piperidin-4-carboxilato de metilo (7.6 g, 30.24 mmol) en DCM (200 mL) y DIPEA (6.32 mL, 36.29 mmol), a continuación se añadió cloroformiato de metilo (3.3 mL, 41.91 mmol). La solución se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se lavó con HCl 0.1 M y $NaHCO_3$ sat. La fase orgánica se hizo pasar a través de un separador de fases y se evaporó, para proporcionar 2-(3-fluorobencil)piperidin-1,4-dicarboxilato de dimetilo (9.30 g, 99%) como un aceite marrón. MS m/z 310 $(M+H)^+$.

Paso 4: Ácido 2-(3-fluorobencil)-1-(metoxicarbonil)piperidin-4-carboxílico

Se disolvió 2-(3-fluorobencil)piperidin-1,4-dicarboxilato de dimetilo (9.153 g, 29.59 mmol) en acetonitrilo (100 mL) y agua (2 mL), a continuación se añadió bromuro de litio (20.56 g, 236.72 mmol). Se añadió trietilamina (16.41 mL, 118.36 mmol) y la suspensión marrón resultante se calentó a reflujo durante 2 h. Se añadieron agua (100 mL) y MTBE (300 mL). La fase orgánica se extrajo con agua (x2). Las fases acuosas recogidas se acidificaron hasta un pH de 1 con HCl 3.8 M y a continuación se extrajeron con MTBE (x2). Las fases orgánicas combinadas se lavaron con agua, se secaron con Na_2SO_4, se filtraron a través de un filtro con Celite y se evaporaron. Se aisló el ácido 2-(3-fluorobencil)-1-(metoxicarbonil)piperidin-4-carboxílico (7.07 g, 81%) como un sólido amarillo. MS m/z 296 $(M+H)^+$.

Compuesto de referencia 45

Ácido 2-(2-fluorobencil)-1-(metoxicarbonil)piperidin-4-carboxílico

Paso 1: 2-(2-Fluorobencil)isonicotinato de metilo

En una atmósfera de nitrógeno, se disolvieron 2-cloroisonicotinato de metilo (5.2 g, 30.31 mmol) y $Pd(PPh_3)_4$ (0.700 g, 0.61 mmol) en THF (100 mL), se añadió cloruro de (2-fluorobencil)zinc (II) (0.5 M en THF) (90 mL, 45.00 mmol) y la solución marrón se agitó a 60 °C durante 18 h. La reacción se detuvo añadiendo metanol (50.0 mL). La solución se diluyó con EtOAc, se lavó con NH_4Cl (ac.) se secó con Na_2SO_4 y a continuación se evaporó. El compuesto se purificó dos veces en una columna Biotage, SNAP con 340 g de KP-SIL, utilizando un eluyente isocrático de heptano/acetato de etilo 8:2 en 2 VC y a continuación un gradiente lineal de heptano/acetato de etilo de 8:2 a 5:5 en 5 VC, para obtener 2-(2-fluorobencil)isonicotinato de metilo (5.42 g, 73%) como un aceite amarillo. ^1H RMN (400 MHz, $CDCl_3$) 3.92 (s, 3H), 4.25 (s, 2H), 7.00 - 7.13 (m, 2H), 7.18 - 7.30 (m, 2H), 7.64 - 7.74 (m, 2H), 8.69 (d, 1H). MS m/z 246 $(M+H)^+$.

Paso 2: 2-(2-Fluorobencil)piperidin-4-carboxilato de metilo

Se disolvió 2-(2-fluorobencil)isonicotinato de metilo (5.42 g, 22.08 mmol) en ácido acético (50 mL) y se añadió óxido de platino (IV) (0.251 g, 1.10 mmol). La mezcla resultante se hidrogenó en un hidrogenador Büchi durante 4 h a temperatura ambiente y 5 bar. El catalizador se filtró, se lavó con MeOH y se evaporó el eluato. Se añadieron DCM y K_2CO_3 al 10%, y se separaron las fases. La fase acuosa se extrajo con DCM y las fases orgánicas combinadas se lavaron con agua, se pasaron a través de un separador de fases y se evaporaron, para proporcionar 2-(2-fluorobencil)piperidin-4-carboxilato de metilo (4.49 g, 81%) MS m/z 252 $(M+H)^+$.

Paso 3: 2-(2-Fluorobencil)piperidin-1,4-dicarboxilato de dimetilo

A una solución de 2-(2-fluorobencil)piperidin-4-carboxilato de metilo (4.49 g, 17.85 mmol) y DIPEA (9.35 mL, 53.55 mmol) en DCM (100 mL), se añadió cloroformiato de metilo (1.798 mL, 23.21 mmol) en DCM (50 mL). La mezcla de reacción se

agitó durante 1.5 h. La fase orgánica se lavó con $NaHCO_3$ sat. Se separaron las fases y se secó la fase orgánica utilizando un separador de fases, para proporcionar 2-(2-fluorobencil)piperidin-1,4-dicarboxilato de dimetilo crudo (6.16 g, 112%). MS m/z 310 $(M+H)^+$.

Paso 4: Ácido 2-(2-fluorobencil)-1-(metoxicarbonil)piperidin-4-carboxílico

Se disolvió 2-(2-fluorobencil)piperidin-1,4-dicarboxilato de dimetilo (6.16 g, crudo) en acetonitrilo (45 mL) y agua (0.9 mL). Se añadieron bromuro de litio (13.84 g, 159.39 mmol) y trietilamina (11.05 mL, 79.69 mmol) y la mezcla se calentó a reflujo durante toda la noche. Se añadieron agua (90 mL) y MTBE. La fase orgánica se extrajo con agua (x2). Se añadió MTBE a la fase acuosa recogida, la solución se acidificó hasta un pH de 1 con HCl 2 M y a continuación se extrajo con MTBE (x2). Las fases orgánicas combinadas se secaron con Na_2SO_4 y se evaporaron, para obtener el ácido 2-(2-fluorobencil)-1-(metoxicarbonil)piperidin-4-carboxílico (4.48 g, 76%) como un semisólido amarillento. MS m/z 296 $(M+H)^+$.

Compuesto de referencia 46

Ácido *cis*-1-(metoxicarbonil)-2-(4-(trifluorometil)bencil)piperidin-4-carboxílico

Paso 1: 2-(4-(Trifluorometil)bencil)isonicotinato de metilo

Se disolvieron 2-cloroisonicotinato de metilo (18 g, 104.91 mmol) y $Pd(PPh_3)_4$ (2.43 g, 2.10 mmol) en THF (300 mL). Se añadió cloruro de (4-trifluorometil)bencil)zinc (II) (0.5 M en THF) (273 mL, 137 mmol) a la solución amarilla y el matraz se calentó hasta 60 °C durante toda la noche. La mezcla de reacción se detuvo añadiendo metanol. La solución se diluyó con acetato de etilo y se lavó con NH_4Cl (ac.) y agua. La fase orgánica se secó con Na_2SO_4, se filtró a través de celite y se evaporó el disolvente. El crudo se cromatografió utilizando un equipo Biotage. Eluyente: acetato de etilo-heptano, empezando desde 0-100 y aplicando un gradiente lineal hasta 100-0. Se aisló 2-(4-(trifluorometil)bencil)isonicotinato de metilo (11.5

g, 37.1%). ^{1}H RMN (600 MHz, $CDCl_3$) δ 3.91 (s, 3H), 4.25 (s, 2H), 7.36 (d, 2H), 7.54 (d, 2H), 7.66 - 7.70 (m, 2H), 8.68 (d, 1H).

Paso 2: 2-(4-(Trifluorometil)bencil)piperidin-4-carboxilato de metilo

Se disolvió 2-(4-(trifluorometil)bencil)isonicotinato de metilo (11.5 g, 38.95 mmol) en ácido acético (200 mL) y metanol (100 mL). Se añadió óxido de platino (IV) (0.177 g, 0.78 mmol) y la mezcla se hidrogenó en un hidrogenador Büchi a temperatura ambiente y 7 bar durante 6 h. El catalizador se filtró. Se añadió óxido de platino (IV) nuevo (0.18 g, 0.78 mmol) y se continuó la hidrogenación a 9 bar durante 7 h. El catalizador se filtró, se evaporó el disolvente y el residuo se repartió entre acetato de etilo y Na_2CO_3 (ac.). La fase orgánica se secó con $MgSO_4$, se filtró a través de celite y se evaporó el disolvente. Se aisló 2-(4-(trifluorometil)bencil)piperidin-4-carboxilato de metilo (9.5 g, 81%).

Paso 3: 2-(4-(Trifluorometil)bencil)piperidin-1,4-dicarboxilato de dimetilo

Se disolvió 2-(4-(trifluorometil)bencil)piperidin-4-carboxilato de metilo (9.5 g, 31.53 mmol) en DIPEA (8.24 mL, 47.29 mmol) y diclorometano (150 mL). Se añadió cloroformiato de metilo (3.58 g, 37.50 mmol) gota a gota y la mezcla de reacción se agitó a temperatura ambiente durante 1 h, se diluyó con éter y se lavó con HCl 1 M. La fase orgánica se lavó con Na_2CO_3 (ac.), se secó con $MgSO_4$, se filtró a través de celite y se evaporó el disolvente, para proporcionar 2-(4-(trifluorometil)bencil)piperidin-1,4-dicarboxilato de dimetilo (10.9 g, 96%).

Paso 4: Ácido 1-(metoxicarbonil)-2-(4-(trifluorometil)bencil)piperidin-4-carboxílico

Se disolvió 2-(4-(trifluorometil)bencil)piperidin-1,4-dicarboxilato de dimetilo (10.9 g, 30.33 mmol) en acetonitrilo (80 mL) y agua (1.6 mL), a continuación se añadieron bromuro de litio (21.07 g, 242.67 mmol) y trietilamina (16.82 mL, 121.33 mmol) y la suspensión amarilla resultante se calentó a reflujo.

Se añadieron agua (60 mL) y MTBE. La fase orgánica se extrajo con agua (x2). Se añadió MTBE a la fase acuosa recogida, la solución se acidificó hasta un pH de 1 con HCl y a continuación se extrajo con MTBE (x2). La fase orgánica se secó con Na_2SO_4, se filtró a través de celite y se evaporó el disolvente, para proporcionar el ácido 1-(metoxicarbonil)-2-(4-(trifluorometil)bencil)piperidin-4-carboxílico (9.14 g, 87%).

Paso 5: Ácido *cis*-1-(metoxicarbonil)-2-(4-(trifluorometil)bencil)piperidin-4-carboxílico

Se suspendió el ácido 1-(metoxicarbonil)-2-(4-(trifluorometil)bencil)piperidin-4-carboxílico (14.65 g, 42.43 mmol) en MTBE (150 mL) y se calentó a reflujo durante 1 min, a continuación se agitó a temperatura ambiente durante 3 días. Se aisló el sólido y se secó al vacío. Se aisló el ácido *cis*-1-(metoxicarbonil)-2-(4-(trifluorometil)bencil)piperidin-4-carboxílico (9.3 g, 63.5%). ^{1}H RMN (600 MHz, CD_3OD) δ 1.68 - 1.77 (m, 1H), 1.90 - 1.97 (m, 1H), 1.99 - 2.10 (m, 2H), 2.58 - 2.64 (m, 1H), 2.83 - 2.89 (m, 1H), 2.93 - 3.00 (m, 1H), 3.16 - 3.31 (m, 1H), 3.43 (s, 3H), 3.86 - 3.92 (m, 1H), 4.31 - 4.36 (m, 1H), 7.36 (d, 2H), 7.53 (d, 2H).

Compuesto de referencia 47

Ácido 1-(metoxicarbonil)-2-(4-(trifluorometil)bencil)piperidin-4-carboxílico

Paso 1: 4-Ciano-2-(4-(trifluorometil)bencil)piperidin-1-carboxilato de metilo

A una solución de 4-oxo-2-(4-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (8.75 g, 27.75 mmol) (Syngene) en DME (100 mL) en una atmósfera de nitrógeno, se añadieron simultáneamente 1-(isocianometilsulfonil)-4-metilbenceno (8.13 g, 41.63 mmol) en 100 mL de DME y *tert*-butóxido de potasio (83 mL, 83.26 mmol) (1 M) durante 30 min a una temperatura de -20 a -10 °C. La solución se agitó a -20 °C durante 2 h y a continuación se dejó calentar hasta temperatura ambiente durante toda la noche. Se añadió agua (200 mL) a la mezcla de reacción naranja, la solución se agitó durante 20 min y a continuación se extrajo

con éter dietílico (3x) y EtOAc (3x). Las fases orgánicas combinadas se lavaron una vez con salmuera, a continuación se secaron con Na_2SO_4 y se evaporaron, para proporcionar un aceite marrón. El aceite se purificó mediante cromatografía flash en gel de sílice utilizando como eluyente un gradiente de 20-60% de EtOAc en heptano. Se aisló 4-ciano-2-(4-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (7.96 g, 87.9%) como un aceite amarillo.

Paso 2: Ácido 1-(metoxicarbonil)-2-(4-(trifluorometil)bencil)piperidin-4-carboxílico

Se calentaron 4-ciano-2-(4-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (2.1 g, 6.44 mmol), peróxido de hidrógeno (5 mL, 206.78 mmol) e hidróxido de potasio (3.61 g, 54.36 mmol) en agua (50 mL) hasta 80 °C durante toda la noche. Se añadieron HCl 1 M y EtOAc a la mezcla de reacción. La fase orgánica se aisló, se secó con Na_2SO_4, se filtró a través de Celite y se evaporó el disolvente, para proporcionar el ácido 1-(metoxicarbonil)-2-(4-(trifluorometil)bencil)piperidin-4-carboxílico (1.67 g, 75%).

Compuesto de referencia 48

Ácido 1-(metoxicarbonil)-2-(3-(trifluorometil)bencil)piperidin-4-carboxílico

Paso 1: 2-(3-(Trifluorometil)bencil)isonicotinato de metilo

Se disolvieron 2-cloroisonicotinato de metilo (8.1 g, 47.21 mmol) y $Pd(PPh_3)_4$ (1.091 g, 0.94 mmol) en THF (150 mL) en una atmósfera de nitrógeno. Se añadió cloruro de (3-trifluorometil)bencil)zinc (II) (0.5 M en THF) (142 mL, 71 mmol) a la solución naranja y el matraz se calentó hasta 60 °C durante toda la noche. La mezcla de reacción se detuvo añadiendo metanol (50 mL) y la mayor parte del disolvente se eliminó mediante evaporación. El residuo se diluyó con acetato de etilo y se lavó con NH_4Cl (ac.) y agua. La fase orgánica se secó con Na_2SO_4, se filtró a través de celite y se evaporó el disolvente. El crudo se cromatografió utilizando un equipo Biotage. Eluyente: acetato de etilo-heptano, empezando desde

20-80 y aplicando un gradiente lineal hasta 40-60. Se aisló 2-(3-(trifluorometil)bencil)isonicotinato de metilo (12.83 g, 92%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 3.93 (s, 3H), 4.27 (s, 2H), 7.37 - 7.56 (m, 4H), 7.66 - 7.75 (m, 2H), 8.67 - 8.76 (m, 1H).

Paso 2: 2-(3-(Trifluorometil)bencil)piperidin-4-carboxilato de metilo

Se añadieron 2-(3-(trifluorometil)bencil)isonicotinato de metilo (12.83 g, 43.45 mmol) y óxido de platino (IV) (0.197 g, 0.87 mmol) a ácido acético (150 mL). La mezcla de reacción se hidrogenó en un hidrogenador Büchi durante 6 h a temperatura ambiente y 5 bar. El catalizador se filtró y se añadió óxido de platino (IV) nuevo (0.26 g). Se continuó la hidrogenación durante toda la noche a 6 bar. Se filtró el catalizador y se evaporó el disolvente. El residuo se disolvió en acetato de etilo y se lavó con Na_2CO_3 (ac.). La fase orgánica se aisló, se secó con $MgSO_4$, se filtró a través de celite y se evaporó el disolvente. Se aisló 2-(3-(trifluorometil)bencil)piperidin-4-carboxilato de metilo crudo (14. 4 g, 110%).

Paso 3: 2-(3-(Trifluorometil)bencil)piperidin-1,4-dicarboxilato de dimetilo

Se disolvió 2-(3-(trifluorometil)bencil)piperidin-4-carboxilato de metilo (6.0 g, 19.91 mmol) en DIPEA (6.94 mL, 39.83 mmol) y diclorometano (150 mL). Se añadió cloroformiato de metilo (2.258 g, 23.90 mmol) gota a gota. Se añadió éter y la mezcla de reacción se lavó con HCl 1 M y Na_2CO_3 (ac.). La fase orgánica se secó con $MgSO_4$, se filtró a través de celite y se evaporó el disolvente, para proporcionar 2-(3-(trifluorometil)bencil)piperidin-1,4-dicarboxilato de dimetilo (6.1 g, 85%).

Paso 4: Ácido 1-(metoxicarbonil)-2-(3-(trifluorometil)bencil)piperidin-4-carboxílico

Se disolvieron 2-(3-(trifluorometil)bencil)piperidin-1,4-dicarboxilato de dimetilo (6.1 g, 16.98 mmol) y LiBr (11.79 g, 135.8 mmol) en acetonitrilo (60 mL) y agua (1.2 mL). Se añadió trietilamina (9.41 mL, 67.90 mmol) y la suspensión resultante se calentó a reflujo durante 1 h, a continuación se enfrió

hasta temperatura ambiente y se agitó durante toda la noche. Se disolvió entre acetato de etilo y HCl 3 M. La fase acuosa se extrajo una vez con acetato de etilo. Las fases orgánicas combinadas se secaron con Na_2SO_4, se filtraron a través de celite y se evaporó el disolvente, para proporcionar el ácido 1-(metoxicarbonil)-2-(3-(trifluorometil)bencil)piperidin-4-carboxílico (5.8 g, 99%).

Compuesto de referencia 49

Ácido 1-(metoxicarbonil)-2-(2-(trifluorometil)bencil)piperidin-4-carboxílico

Paso 1: Bromuro de (2-(trifluorometil)bencil)zinc (II)

En un matraz anhidro, se suspendió zinc en polvo (2.489 g, 38.07 mmol) en tetrahidrofurano anhidro (50 mL) en una atmósfera de nitrógeno. La suspensión resultante se calentó hasta 60 °C, a continuación se añadió 1,2-dibromoetano (0.126 mL, 1.46 mmol) y se agitó a esta temperatura durante 15 min. Se enfrió hasta temperatura ambiente, a continuación se añadió clorotrimetilsilano (0.149 mL, 1.17 mmol) y se agitó durante 20 min. Se añadió 1-(bromometil)-2-(trifluorometil)benceno (4.46 mL, 29.28 mmol) en THF (2 mL) gota a gota y se continuó agitando a temperatura ambiente durante 4 h. Se dejó de agitar para permitir que el precipitado se asentara. El líquido sobrenadante se utilizó en la siguiente transformación.

Paso 2: 2-(2-(Trifluorometil)bencil)isonicotinato de metilo

Se añadió bromuro de (2-(trifluorometil)bencil)zinc(II) (8.91 g, 29.28 mmol) recién preparado en tetrahidrofurano (50 mL) a una solución de 2-cloroisonicotinato de metilo (3.35 g, 19.52 mmol) y bis(tri-*tert*-butilfosfina)Pd (0) (0.399 g, 0.78 mmol) en tetrahidrofurano (50 mL) en un matraz anhidro con atmósfera de nitrógeno. La mezcla roja resultante se calentó hasta 60 °C durante toda la noche (16 h). Después de enfriar hasta temperatura ambiente, la reacción se detuvo añadiendo NH_4Cl ac. al 10% y se diluyó con acetato de etilo. Después de separar las fases, la fase orgánica se lavó con salmuera, se secó con $MgSO_4$ y se evaporó. El residuo se disolvió en 100 mL

de MTBE. Se filtraron los residuos insolubles y se evaporó el filtrado. La purificación en una columna Biotage, SNAP con 340 g de KP-SIL, utilizando un eluyente isocrático de heptano/acetato de etilo 8:2 en 1 VC y a continuación un gradiente lineal de heptano/acetato de etilo de 8:2 a 5:5 en 6 VC proporcionó 2-(2-(trifluorometil)bencil)isonicotinato de metilo (4.61 g, 80%) como un aceite amarillo. ^{1}H RMN (400 MHz, $CDCl_3$) δ 3.91 (s, 3H), 4.43 (s, 2H), 7.28 - 7.40 (m, 2H), 7.47 (t, 1H), 7.54 - 7.65 (m, 1H), 7.65 - 7.72 (m, 2H), 8.71 (d, 1H). MS m/z 296 $(M+H)^+$.

Paso 3: 2-(2-(Trifluorometil)bencil)piperidin-4-carboxilato de metilo

Se disolvió 2-(2-(trifluorometil)bencil)isonicotinato de metilo (4.613 g, 15.62 mmol) en ácido acético (40 mL) y se añadió óxido de platino (IV) (0.26 g, 1.14 mmol). La mezcla resultante se hidrogenó en un hidrogenador Büchi durante 3 h a temperatura ambiente y 5 bar. Se añadió más óxido de platino (IV) (160 mg) y se continuó la hidrogenación a temperatura ambiente y 5 bar durante 2 h. El catalizador se filtró, se lavó con MeOH y se evaporó el eluato. Se añadieron DCM y K_2CO_3 al 10%, y se separaron las fases. La fase acuosa se extrajo con DCM y las fases orgánicas combinadas se lavaron con agua, se pasaron a través de un separador de fases y se evaporaron, para proporcionar 2-(2-(trifluorometil)bencil)piperidin-4-carboxilato de metilo (4.20 g, 89%) como un aceite amarillo. MS m/z 302 $(M+H)^+$.

Paso 4: 2-(2-(Trifluorometil)bencil)piperidin-1,4-dicarboxilato de dimetilo

Se añadió cloroformiato de metilo (1.399 mL, 18.07 mmol) en DCM (40 mL) a una solución de 2-(2-(trifluorometil)bencil)piperidin-4-carboxilato de metilo (4.19 g, 13.9 mmol) y DIPEA (7.28 mL, 41.69 mmol) en DCM (60 mL). La mezcla de reacción se agitó durante 1.5 h a temperatura ambiente y a continuación se lavó con $NaHCO_3$ sat. Se separaron las fases y se secó la fase orgánica utilizando un separador de fases, para obtener 2-(2-(trifluorometil)bencil)piperidin-1,4-

dicarboxilato de dimetilo crudo (5.42 g, 109%). MS m/z 360 $(M+H)^+$.

Paso 5: Ácido 1-(metoxicarbonil)-2-(2-(trifluorometil)bencil)piperidin-4-carboxílico

Se disolvió 2-(2-(trifluorometil)bencil)piperidin-1,4-dicarboxilato de dimetilo crudo (5.42 g, 15.15 mmol) en acetonitrilo (40 mL) y agua (0.800 mL). Se añadieron bromuro de litio (9.66 g, 111.20 mmol) y trietilamina (7.71 mL, 55.60 mmol) y la mezcla se calentó a reflujo durante 1 h 45 min. Se añadieron agua (90 mL) y MTBE. La fase orgánica se extrajo con agua. Se añadió MTBE a la fase acuosa recogida, la solución se acidificó hasta un pH de 1 con HCl 2 M y a continuación se extrajo con MTBE (x2). Las fases orgánicas combinadas se secaron con Na_2SO_4 y se evaporaron, para obtener el ácido 1-(metoxicarbonil)-2-(2-(trifluorometil)bencil)piperidin-4-carboxílico (4.72 g, 98%) como un semisólido amarillento. MS m/z 346 $(M+H)^+$.

Compuesto de referencia 50

Ácido 1-(metoxicarbonil)-2-(4-(trifluorometoxi)bencil)piperidin-4-carboxílico

Paso 1: Bromuro de (4-(trifluorometoxi)bencil)zinc (II)

En un matraz anhidro, se suspendió zinc en polvo (0.769 g, 11.76 mmol) en tetrahidrofurano anhidro (20 mL) en una atmósfera de nitrógeno. La suspensión resultante se calentó hasta 60 °C, a continuación se añadió 1,2-dibromoetano (0.042 mL, 0.49 mmol) y se agitó a esta temperatura durante 15 min. Se enfrió hasta temperatura ambiente, a continuación se añadió clorotrimetilsilano (0.050 mL, 0.39 mmol) y se agitó a temperatura ambiente durante 1 h. A continuación, se añadió 1-(bromometil)-4-(trifluorometoxi)benceno (2.5 g, 9.80 mmol) en tetrahidrofurano (5 mL) durante 2 min y después se continuó agitando a temperatura ambiente durante 22 h. Se dejó de agitar para permitir que los sólidos se asentaran. El líquido sobrenadante se utilizó en la siguiente transformación.

Paso 2: 2-(4-(Trifluorometoxi)bencil)isonicotinato de metilo

A una solución de 2-cloroisonicotinato de metilo (4.80 g, 28 mmol) y $Pd(PPh_3)_4$ (0.647 g, 0.56 mmol) en tetrahidrofurano (50 mL) en un matraz anhidro con atmósfera de nitrógeno, se añadió una solución recién preparada de bromuro de (4-(trifluorometoxi)bencil)zinc (II) (12.56 g, 39.20 mmol) en tetrahidrofurano (90 mL). La mezcla de color amarillo intenso resultante se calentó hasta 60 °C durante 2 h 30 min y a continuación se enfrió hasta temperatura ambiente. La reacción se detuvo añadiendo $NaHCO_4$ acuoso al 10%. Se diluyó con acetato de etilo. Después de separar las fases, la fase orgánica se lavó con salmuera, se secó con $MgSO_4$ y se evaporó. El residuo se suspendió en 50 mL de MTBE y se sonicó, a continuación se filtraron los residuos insolubles amarillos y se lavaron con MTBE. Se incrementó el volumen del filtrado hasta aproximadamente 150 mL, a continuación se añadieron 5 mL de MeOH y después cloruro de hidrógeno (4 M en dioxano) (7.00 mL, 28.00 mmol). Se formó un precipitado incoloro, que se volvió a disolver a continuación. Se evaporaron los disolventes. El residuo se disolvió en aproximadamente 15 mL de DCM y a continuación se añadieron MTBE y heptanos. Se formó un aceite, el cual se lavó y, después de unos minutos, se empezó a formar un sólido. Se sonicó y a continuación se agitó a temperatura ambiente durante 20 min. Se separó el sólido formado, se lavó con MTBE y se secó. Se disolvió el sólido en DCM y se lavó con K_2CO_3 al 10%. Después de separar las fases, la fase acuosa se extrajo con DCM. Las fases orgánicas combinadas se secaron con $MgSO_4$ y se evaporaron. Se aisló 2-(4-(trifluorometoxi)bencil)isonicotinato de metilo (8.04 g, 92%) como un aceite de color amarillo claro. ^1H RMN (400 MHz, $CDCl_3$) δ 3.93 (s, 3H), 4.22 (s, 2H), 7.11 - 7.17 (m, 2H), 7.24 - 7.31 (m, 2H), 7.67 - 7.72 (m, 2H), 8.68 - 8.72 (m, 1H). MS m/z 312 $(M+H)^+$.

Paso 3: 2-(4-(Trifluorometoxi)bencil)piperidin-4-carboxilato de metilo

A una solución de 2-(4-(trifluorometoxi)bencil)isonicotinato de metilo (8.04 g, 25.83

mmol) en ácido acético (40 mL), se añadió óxido de platino (IV) (0.343 g, 1.51 mmol) y la mezcla resultante se hidrogenó a 5 bar en un hidrogenador Büchi durante 5 h. La mezcla de reacción se filtró a través de un cartucho de filtración con tierras de diatomeas y el catalizador se lavó con metanol. Se evaporaron los disolventes, se disolvió el residuo en DCM y se lavó con Na_2CO_3 al 10%. Después de separar las fases, la fase acuosa se extrajo con DCM. Las fases orgánicas combinadas se secaron con $MgSO_4$ y se evaporaron. Se aisló 2-(4-(trifluorometoxi)bencil)piperidin-4-carboxilato de metilo (8.19 g, 100%) como un aceite de color marrón oscuro. MS m/z 318 $(M+H)^+$.

Paso 4: 2-(4-(Trifluorometoxi)bencil)piperidin-1,4-dicarboxilato de dimetilo

A una solución de 2-(4-(trifluorometoxi)bencil)piperidin-4-carboxilato de metilo (8.19 g, 25.81 mmol) en DCM (100 mL), se añadió DIPEA (5.40 mL, 30.97 mmol) y después cloroformiato de metilo (2.236 mL, 28.39 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 30 min. Se evaporaron los disolventes y el residuo se repartió entre acetato de etilo y HCl 3.8 M. Después de separar las fases, la fase acuosa se extrajo con acetato de etilo. Las fases orgánicas combinadas se secaron con $MgSO_4$ y se evaporaron para obtener un aceite amarillo. Se aisló 2-(4-(trifluorometoxi)bencil)piperidin-1,4-dicarboxilato de dimetilo (9.72 g, 100%). MS m/z 376 $(M+H)^+$.

Paso 5: Ácido 1-(metoxicarbonil)-2-(4-(trifluorometoxi)bencil)piperidin-4-carboxílico

A una solución de 2-(4-(trifluorometoxi)bencil)piperidin-1,4-dicarboxilato de dimetilo (9.72 g, 25.90 mmol) en MeCN (80 mL) y agua (1.6 mL), se añadieron bromuro de litio (18.2 g, 209.57 mmol) y trietilamina (15 mL, 108.21 mmol). La mezcla resultante se calentó a reflujo durante 3 h y a continuación se enfrió a temperatura ambiente. Se añadieron agua y MTBE. La fase orgánica se extrajo con agua dos veces. Se ajustó el pH de las fases acuosas recogidas hasta un pH de 1 con HCl 3.8 M y se extrajeron con DCM (3 x). La mezcla se filtró a través de un

cartucho de filtración con tierras de diatomeas. Las fases orgánicas combinadas se secaron con $MgSO_4$ y se evaporaron. Se aisló el ácido 1-(metoxicarbonil)-2-(4-(trifluorometoxi)bencil)piperidin-4-carboxílico (8.75 g, 94%) como un sólido de color amarillo claro. MS m/z 360 $(M-H)^-$.

Compuesto de referencia 51

Ácido 2-(4-clorobencil)-1-(metoxicarbonil)piperidin-4-carboxílico

Paso 1: 2-(4-Clorobencil)-4-cianopiperidin-1-carboxilato de *tert*-butilo

A una solución de 2-(4-clorobencil)-4-oxopiperidin-1-carboxilato de *tert*-butilo (8.737 g, 26.98 mmol) en DME (200 mL) en una atmósfera de nitrógeno, se añadieron simultáneamente 1-(isocianometilsulfonil)-4-metilbenceno (7.90 g, 40.47 mmol) en 200 mL DME y *tert*-butóxido de potasio (81 mL, 80.94 mmol) durante 1 hora, de manera que la temperatura nunca estuviera por encima de 0 °C. La solución se agitó a -20 °C durante 2 h y a continuación se dejó calentar hasta temperatura ambiente durante toda la noche. Se añadió agua (200 mL) a la mezcla de reacción naranja, la solución se agitó durante 20 min y a continuación se extrajo con éter dietílico (3x) y EtOAc (3x). Las fases orgánicas se combinaron, se secaron con Na_2SO_4 y se evaporaron, para obtener un residuo marrón. Se purificó adicionalmente en una columna Biotage (columna con 340 g, 3 purificaciones, heptano/EtOAc, gradiente de 20-60% de EtOAc) para obtener 2-(4-clorobencil)-4-cianopiperidin-1-carboxilato de *tert*-butilo (5.54 g, 61%). ^1H RMN (400 MHz, $CDCl_3$) δ, 1.21 - 1.50 (m, 9H), 1.58 - 2.14 (m, 4H), 2.55 - 3.27 (m, 4H), 4.06 - 4.25 (m, 1H), 4.34-4.60 (m, 1H), 7.02 - 7.34 (m, 4H). MS m/z 235, 237 $(M-C5H8O2+H)^+$.

Paso 2: Clorhidrato del ácido 2-(4-clorobencil)piperidin-4-carboxílico

Se añadió HCl conc. (20 mL, 651.11 mmol) a 2-(4-clorobencil)-4-cianopiperidin-1-carboxilato de *tert*-butilo (5.54 g, 16.55 mmol) y la mezcla se agitó durante 20 minutos. La mezcla se transfirió a un vial para microondas de 20 mL. El

vial se tapó y se calentó hasta 140 °C durante 30 min en un reactor de microondas de nodo único. La concentración de la solución de reacción proporcionó el clorhidrato del ácido 2-(4-clorobencil)piperidin-4-carboxílico crudo (5.34 g, 111%). MS m/z 254, 256 $(M+H)^+$.

Paso 3: 2-(4-Clorobencil)piperidin-4-carboxilato de metilo

Se añadió HCl (1.25 M en MeOH, 60 mL) al clorhidrato del ácido 2-(4-clorobencil)piperidin-4-carboxílico crudo (5.34 g, 20.9 mmol). La suspensión resultante se calentó a reflujo durante 2 h y a continuación se concentró para obtener un sólido amarillento. El residuo se disolvió en $NaHCO_3$ sat. (100 mL). La fase acuosa se extrajo con DCM (x3), las fases orgánicas combinadas se secaron con un separador de fases y se evaporaron, para proporcionar 2-(4-clorobencil)piperidin-4-carboxilato de metilo (3.85 g, 87%) como un aceite marrón. MS m/z 268, 270 $(M+H)^+$.

Paso 4: 2-(4-Clorobencil)piperidin-1,4-dicarboxilato de dimetilo

A una solución de 2-(4-clorobencil)piperidin-4-carboxilato de metilo (3.72 g, 13.2 mmol) y DIPEA (4.85 mL, 27.78 mmol) en DCM (100 mL), se añadió cloroformiato de metilo (1.431 mL, 18.48 mmol) en DCM (50 mL) durante 30 minutos. La mezcla de reacción se agitó durante toda la noche (16 h). La fase orgánica se lavó con $NaHCO_3$ sat., se secó utilizando un separador de fases y se evaporó, para proporcionar 2-(4-clorobencil)piperidin-1,4-dicarboxilato de dimetilo (4.74 g, 110%) como un aceite amarillo. MS m/z 326, 328 $(M+H)^+$.

Paso 5: Ácido 2-(4-clorobencil)-1-(metoxicarbonil)piperidin-4-carboxílico

Se disolvió 2-(4-clorobencil)piperidin-1,4-dicarboxilato de dimetilo (4.74 g, 14.55 mmol) en tetrahidrofurano (15 mL) y a continuación se añadieron LiOH (0.430 g, 17.97 mmol), MeOH (10 mL) y agua (10 mL). La mezcla de reacción se agitó a temperatura ambiente durante toda la noche. Se evaporaron los disolventes y el residuo se disolvió en agua. El pH se ajustó hasta alcanzar un valor < 2 añadiendo HCl 2 M. El producto

resultó ser muy poco soluble y los intentos de extraer la fase acuosa con DCM y acetato de etilo fracasaron. En su lugar, la mezcla se concentró y a continuación se filtró, se lavó con agua y se secó, para obtener un material sólido amarillo. La fase acuosa contenía parte del producto, se extrajo con DCM (x3) y se secó con un separador de fases para obtener aproximadamente 500 mg. Se aisló el ácido 2-(4-clorobencil)-1-(metoxicarbonil)piperidin-4-carboxílico crudo (4.27 g, cuant.). MS m/z 312, 314 $(M+H)^+$.

Compuesto de referencia 52

Ácido 1-(metoxicarbonil)-2-(4-(metilsulfonil)bencil)piperidin-4-carboxílico

Paso 1: Bromuro de (4-(metilsulfonil)bencil)zinc (II)

Se suspendió zinc en polvo (2.81 g, 42.97 mmol) en THF (50 mL) en una atmósfera de nitrógeno y se calentó hasta 60 °C. Se añadió 1,2-dibromoetano (0.336 g, 1.79 mmol) y se agitó durante 15 min a 60 °C. Se enfrió hasta temperatura ambiente, se añadió TMSCl (0.156 g, 1.43 mmol) y se agitó durante 15 min a temperatura ambiente. Se añadió 1-(bromometil)-4-(metilsulfonil)benceno (8.92 g, 35.81 mmol) disuelto en THF (50 mL) durante 15 min y la mezcla resultante se agitó a temperatura ambiente durante toda la noche. Se dejó de agitar y se utilizó el líquido sobrenadante en la siguiente reacción.

Paso 2: 2-(4-(Metilsulfonil)bencil)isonicotinato de metilo

Se disolvieron 2-cloroisonicotinato de metilo (5.12 g, 29.84 mmol) y $Pd(PPh_3)_4$ (1.379 g, 1.19 mmol) en THF (50 mL) en una atmósfera de nitrógeno. Se añadió bromuro de 4-(metilsulfonil)bencil)zinc (II) (11.26 g, 35.81 mmol) recién preparado en THF (100 mL) y la mezcla de reacción se calentó hasta 60 °C durante 3 h. Se añadió agua (20 mL). Se diluyó con $NaHCO_3$ (ac.) y se extrajo con éter dietílico. La fase orgánica se lavó con NaCl (ac.), se secó con Na_2SO_4, se filtró y se evaporó. Se purificó utilizando un equipo Biotage. Se utilizó como eluyente acetato de etilo y hexano. Gradiente: de 0% a 100% de acetato de etilo. Se aisló 2-(4-(metilsulfonil)bencil)isonicotinato de metilo (8.0 g, 88%). ^1H

RMN (600 MHz, $CDCl_3$) δ 3.00 (s, 3H), 3.92 (s, 3H), 4.28 (s, 2H), 7.45 (d, 2H), 7.68 - 7.72 (m, 2H), 7.85 (d, 2H), 8.69 (d, 1H). MS m/z 306 $(M+H)^+$.

Paso 3: 2-(4-(Metilsulfonil)bencil)piperidin-4-carboxilato de metilo

Se disolvió 2-(4-(metilsulfonil)bencil)isonicotinato de metilo (8.0 g, 26.2 mmol) en ácido acético (250 mL). Se añadió carbón activo y se agitó durante 30 min. Se filtró el carbón activo. Se añadió PtO_2 (0.119 g, 0.52 mmol) a la solución y la mezcla de reacción se hidrogenó en un hidrogenador Büchi durante toda la noche a temperatura ambiente y 9 bar. Se filtró el catalizador. Se evaporó el disolvente. El crudo se repartió entre Na_2CO_3 (ac.) y acetato de etilo. La fase orgánica se secó con Na_2SO_4, se filtró a través de celite y se evaporó, para proporcionar 2-(4-(metilsulfonil)bencil)piperidin-4-carboxilato de metilo (5.38 g, 65.9%).

Paso 4: 2-(4-(Metilsulfonil)bencil)piperidin-1,4-dicarboxilato de dimetilo

Se disolvió 2-(4-(metilsulfonil)bencil)piperidin-4-carboxilato de metilo (5.88 g, 18.88 mmol) en DIPEA (4.93 mL, 28.32 mmol) y diclorometano (150 mL). Se añadió gota a gota cloroformiato de metilo (2.141 g, 22.66 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante toda la noche. Se evaporó el disolvente y el residuo se repartió entre $KHSO_4$ 1 M y éter dietílico. La fase orgánica se secó con Na_2SO_4, se filtró a través de celite y se evaporó, para proporcionar 2-(4-(metilsulfonil)bencil)piperidin-1,4-dicarboxilato de dimetilo (5.5 g, 79%).

Paso 5: Ácido 1-(metoxicarbonil)-2-(4-(metilsulfonil)bencil)piperidin-4-carboxílico

Se disolvió 2-(4-(metilsulfonil)bencil)piperidin-1,4-dicarboxilato de dimetilo (5.5 g, 14.89 mmol) en acetonitrilo (50 mL) y agua (1 mL), a continuación se añadieron bromuro de litio (10.34 g, 119.10 mmol) y trietilamina (8.25 mL, 59.55 mmol) y la suspensión resultante se calentó a reflujo durante 2 h. Se añadieron agua y MTBE. La fase orgánica se extrajo con

agua (x2). Se añadió acetato de etilo a la fase acuosa recogida, la solución se acidificó hasta un pH de 1 con HCl y a continuación se extrajo con acetato de etilo dos veces. La fase orgánica se secó (Na_2SO_4), se filtró a través de celite y se evaporó, para proporcionar el ácido 1-(metoxicarbonil)-2-(4-(metilsulfonil)bencil)piperidin-4-carboxílico (4.2 g, 79%). MS m/z 354 $(M-H)^-$.

Compuesto de referencia 53

Ácido 2-(3,4-difluorobencil)-1-(metoxicarbonil)piperidin-4-carboxílico

Paso 1: 2-(3,4-Difluorobencil)isonicotinato de metilo

Se disolvieron 2-cloroisonicotinato de metilo (5.6 g, 32.64 mmol) y $Pd(PPh_3)_4$ (0.754 g, 0.65 mmol) en THF (100 mL) en una atmósfera de nitrógeno. Se añadió bromuro de (3,4-difluorobencil)zinc (II) (0.5 M en THF) (100 mL, 50.00 mmol) y la solución marrón se agitó a 60 °C durante toda la noche. La reacción se detuvo añadiendo metanol (50 mL). La solución se diluyó con EtOAc y se lavó con NH_4Cl (ac.). La fase orgánica se secó con $MgSO_4$, se filtró y se evaporó para proporcionar un aceite amarillo. El compuesto se purificó en una columna Biotage, SNAP con 340 g de KP-SIL, utilizando un eluyente isocrático de heptano/acetato de etilo 8:2 en 2 VC y a continuación un gradiente lineal de heptano/acetato de etilo de 8:2 a 5:5 en 6 VC, para proporcionar 2-(3,4-difluorobencil)isonicotinato de metilo (7.7 g, 90%) como un aceite amarillo. ^1H RMN (400 MHz, $CDCl_3$) δ 3.93 (s, 3H), 4.16 (s, 2H), 6.94 - 7.01 (m, 1H), 7.02 - 7.12 (m, 2H), 7.66 - 7.71 (m, 2H), 8.70 (dd, 1H). MS m/z 264 $(M+H)^+$.

Paso 2: 2-(3,4-Difluorobencil)piperidin-4-carboxilato de metilo

Se disolvió 2-(3,4-difluorobencil)isonicotinato de metilo (7.7 g, 29.25 mmol) en ácido acético (75 mL) y se añadió óxido de platino (IV) (0.332 g, 1.46 mmol). La mezcla resultante se hidrogenó en un hidrogenador Büchi a temperatura ambiente y 5 bar durante 4 h 45 min. Se añadió más óxido de platino (IV) (0.166 g, 0.73 mmol) y se continuó la hidrogenación a 5 bar

durante 2 h. Se añadió más óxido de platino (IV) (0.166 g, 0.73 mmol) y se continuó la hidrogenación a 5 bar durante 1 h 20 min. El catalizador se filtró, se lavó con MeOH y se evaporó el eluato. Se añadieron DCM y K_2CO_3 al 10%, y se separaron las fases. La fase orgánica se lavó con salmuera, se hizo pasar a través de un separador de fases y se evaporó, para proporcionar 2-(3,4-difluorobencil)piperidin-4-carboxilato de metilo crudo (8.133 g, 103%) como un aceite marrón. MS m/z 270 $(M+H)^+$.

Paso 3: 2-(3,4-Difluorobencil)piperidin-1,4-dicarboxilato de dimetilo

Se disolvió 2-(3,4-difluorobencil)piperidin-4-carboxilato de metilo (8.115 g, 30.14 mmol) en DCM (200 mL) y DIPEA (6.30 mL, 36.16 mmol), a continuación se añadió cloroformiato de metilo (3.3 mL, 41.91 mmol). La solución se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se lavó con HCl 0.1 M y $NaHCO_3$ sat. La fase orgánica se hizo pasar a través de un separador de fases y se evaporó. El residuo se volvió a disolver en éter/pentano, 80/20, la solución se lavó con HCl 1 M 5 veces, a continuación con $NaHCO_3$ sat. y salmuera, se secó con $MgSO_4$, se filtró y se evaporó, para proporcionar 2-(3,4-difluorobencil)piperidin-1,4-dicarboxilato de dimetilo (7.05 g, 71%). MS m/z 328 $(M+H)^+$.

Paso 4: Ácido 2-(3,4-difluorobencil)-1-(metoxicarbonil)piperidin-4-carboxílico

Se disolvió 2-(3,4-difluorobencil)piperidin-1,4-dicarboxilato de dimetilo (7.010 g, 21.42 mmol) en acetonitrilo (75 mL) y agua (1.5 mL). Se añadieron bromuro de litio (14.88 g, 171.33 mmol) y trietilamina (11.87 mL, 85.66 mmol) y la suspensión amarilla resultante se calentó a reflujo durante 3 h. Se añadieron agua (100 mL) y MTBE (300 mL). La fase orgánica se extrajo con agua (x2). Las fases acuosas recogidas se acidificaron hasta un pH de 1 con HCl 3.8 M y a continuación se extrajeron con MTBE (x2). Las fases orgánicas combinadas se lavaron con agua, se secaron con Na_2SO_4, se filtraron y se evaporaron, para proporcionar el ácido 2-(3,4-difluorobencil)-1-(metoxicarbonil)piperidin-4-carboxílico (6.62 g, 99%) como un

sólido amarillo. MS m/z 314 $(M+H)^+$.

Compuesto de referencia 54

Ácido 2-(2,5-difluorobencil)-1-(metoxicarbonil)piperidin-4-carboxílico

Paso 1: 2-(2,5-Difluorobencil)isonicotinato de metilo

A una solución de 2-cloroisonicotinato de metilo (5.6 g, 32.64 mmol) y $Pd(PPh_3)_4$ (0.754 g, 0.65 mmol) en THF anhidro (100 mL), se añadió bromuro de (2,5-difluorobencil)zinc (II) (0.5 M en THF) (100 mL, 50.00 mmol) gota a gota en una atmósfera de nitrógeno. La mezcla de reacción se calentó a 60 °C durante 15 h. La mezcla de reacción se detuvo añadiendo metanol (50 mL) y a continuación se filtró. Se evaporó el disolvente a presión reducida. El residuo se disolvió en acetato de etilo y se lavó con una solución sat. de NH_4Cl y salmuera, a continuación se secó. Se evaporó el disolvente a presión reducida. El residuo se suspendió en etanol, se filtró y se lavó el sólido con etanol. El filtrado se concentró. El residuo se disolvió en MTBE (150 mL), a continuación se añadieron HCl (4 M en dioxano, 8.15 mL) y MeOH (7.5 mL). La suspensión resultante se agitó durante 20 min, se separó el sólido, se lavó con MTBE (x2) y se secó al aire. El sólido se disolvió en DCM (200 mL) y se lavó con $NaHCO_3$ sat. La fase orgánica se secó con un separador de fases y se evaporó, para proporcionar 2-(2,5-difluorobencil)isonicotinato de metilo (6.8 g, 79%). MS m/z 264 $(M+H)^+$.

Paso 2: 2-(2,5-Difluorobencil)piperidin-4-carboxilato de metilo

Se hidrogenó una mezcla de 2-(2,5-difluorobencil)isonicotinato de metilo (6.8 g, 25.83 mmol) y óxido de platino (IV) (0.293 g, 1.29 mmol) en ácido acético (68 mL) en un hidrogenador Büchi a temperatura ambiente y 5 bar durante 5 h. Se añadió más PtO_2 (190 mg) y se continuó la hidrogenación a temperatura ambiente y 5 bar durante 80 min adicionales. La mezcla de reacción se filtró a través de Celite y el catalizador se lavó con metanol. El filtrado se concentró, el residuo se disolvió en DCM, se lavó con $NaHCO_3$ sat. y la

fase orgánica se secó utilizando un separador de fases. Se evaporó el disolvente a presión reducida. El residuo se disolvió en isohexano/éter y se filtró. Se evaporaron los disolventes al vacío para proporcionar 2-(2,5-difluorobencil)piperidin-4-carboxilato de metilo (6.65 g, 96%). MS m/z 270 $(M+H)^+$.

Paso 3: 2-(2,5-Difluorobencil)piperidin-1,4-dicarboxilato de dimetilo

A una solución de 2-(2,5-(difluorobencil)piperidin-4-carboxilato de metilo (6.65 g, 24.69 mmol) en DCM (100 mL) y DIPEA (5.16 mL, 29.63 mmol), se añadió cloroformiato de metilo (2.53 mL, 32.10 mmol) gota a gota a temperatura ambiente en una atmósfera de nitrógeno. La mezcla de reacción se agitó a temperatura ambiente durante 1 h. La reacción se detuvo con HCl 0.15 M (250 mL). La fase orgánica se separó, se lavó con $NaHCO_3$ sat., se secó utilizando un separador de fases y se evaporó, para proporcionar 2-(2,5-difluorobencil)piperidin-1,4-dicarboxilato de dimetilo (8.1 g, 100%). MS m/z 328 $(M+H)^+$.

Paso 4: Ácido 2-(2,5-difluorobencil)-1-(metoxicarbonil)piperidin-4-carboxílico

A una solución de 2-(2,5-(difluorobencil)piperidin-1,4-dicarboxilato de dimetilo (8.08 g, 24.69 mmol) en acetonitrilo (85 mL) y agua (1.7 mL), se añadieron bromuro de litio (4.95 mL, 197.48 mmol) y trietilamina (13.69 mL, 98.74 mmol). La mezcla de reacción se calentó a reflujo durante 2.5 h y a continuación se dejó enfriar hasta temperatura ambiente. Se añadieron agua (150 mL) y MTBE (300 mL). Se separó la fase acuosa y la fase orgánica se extrajo dos veces con agua. Las fases acuosas se combinaron y se añadió HCl 4.0 M hasta obtener un pH de 1. La fase acuosa se extrajo con MTBE (300 mL x 2). Las fases orgánicas se combinaron, se lavaron con salmuera, se secaron con Na_2SO_4 y se evaporaron a presión reducida, para obtener el ácido 2-(2,5-difluorobencil)-1-(metoxicarbonil)piperidin-4-carboxílico (7.4 g, 96%). MS m/z 314 $(M+H)^+$.

Compuesto de referencia 55

Ácido 2-(2,6-difluorobencil)-1-(metoxicarbonil)piperidin-4-carboxílico

Paso 1: 2-(2,6-Difluorobencil)isonicotinato de metilo

En una atmósfera de nitrógeno, se disolvieron 2-cloroisonicotinato de metilo (5.600 g, 32.64 mmol) y $Pd(PPh_3)_4$ (0.754 g, 0.65 mmol) en THF (100 mL), se añadió bromuro de (2,6-difluorobencil)zinc (II) (0.5 M en THF) (100 mL, 50.00 mmol) y la solución resultante se agitó a 60 °C durante 4 h, antes de enfriarla hasta temperatura ambiente y detener la reacción con metanol (50.0 mL). La mezcla se diluyó con EtOAc y se lavó con NH_4Cl sat. La fase orgánica se secó con $MgSO_4$, se filtró y se evaporó. El producto crudo se disolvió en MTBE (200 mL), se filtraron los sólidos y se añadió HCl (4 M en dioxano, 8.16 mL, 32.64 mmol) gota a gota. La mezcla se agitó durante 10 minutos, antes de filtrar el precipitado, lavarlo con MTBE y disolverlo en MTBE / $NaHCO_3$ sat. La fase orgánica se secó con $MgSO_4$, se filtró y se evaporó para obtener 2-(2,6-difluorobencil)isonicotinato de metilo (5.03 g, 58.6%) como un sólido blanco. ^1H RMN (400 MHz, $CDCl_3$) δ 3.92 (s, 3H), 4.29 (s, 2H), 6.87 - 6.97 (m, 2H), 7.18 - 7.29 (m, 1H), 7.61 - 7.73 (m, 2H), 8.63 - 8.70 (m, 1H). MS m/z 264 $(M+H)^+$.

Paso 2: 2-(2,6-Difluorobencil)piperidin-4-carboxilato de metilo

Se disolvió 2-(2,6-difluorobencil)isonicotinato de metilo (5.031 g, 19.11 mmol) en ácido acético (49 mL) y se añadió óxido de platino (IV) (0.217 g, 0.96 mmol). La mezcla se hidrogenó en un hidrogenador Büchi a temperatura ambiente y 5 bar durante 5 h. Se añadió más óxido de platino (IV) (0.108 g, 0.48 mmol) y se continuó la hidrogenación durante 1 h. Se añadió óxido de platino (IV) adicional (0.108 g, 0.48 mmol) y la mezcla se volvió a hidrogenar durante 1.5 h. Se añadió más óxido de platino (IV) (0.108 g, 0.48 mmol). Después de un total de 8.5 h, la mezcla de reacción se filtró a través de celite y el catalizador se lavó con MeOH. El eluato se concentró y se añadieron DCM y K_2CO_3 1 M. Se separaron las fases y la fase orgánica se lavó con salmuera, antes de secarla y concentrarla,

para proporcionar 2-(2,6-difluorobencil)piperidin-4-carboxilato de metilo (5.01 g, 97%). MS m/z 270 $(M+H)^+$.

Paso 3: 2-(2,6-Difluorobencil)piperidin-1,4-dicarboxilato de dimetilo

Se disolvió 2-(2,6-difluorobencil)piperidin-4-carboxilato de metilo (5.008 g, 18.60 mmol) en DCM (121 mL), se añadió DIPEA (3.89 mL, 22.32 mmol) y a continuación cloroformiato de metilo (2.050 mL, 26.04 mmol). Después de 3.5 h a temperatura ambiente, la solución se lavó con HCl 0.1 M y $NaHCO_3$ sat. La fase orgánica se secó y se concentró, para proporcionar 2-(2,6-difluorobencil)piperidin-1,4-dicarboxilato de dimetilo (5.98 g, 98%). MS m/z 328 $(M+H)^+$.

Paso 4: Ácido 2-(2,6-difluorobencil)-1-(metoxicarbonil)piperidin-4-carboxílico

Se disolvió 2-(2,6-difluorobencil)piperidin-1,4-dicarboxilato de dimetilo (5.98 g, 18.27 mmol) en acetonitrilo (50 mL) y agua (1 mL), a continuación se añadieron bromuro de litio (12.69 g, 146.16 mmol) y trietilamina (10.13 mL, 73.08 mmol). La suspensión se calentó a reflujo durante 3.5 h, a continuación se añadieron agua (60 mL) y MTBE (180 mL). La fase orgánica se extrajo con agua (x2). Las fases acuosas combinadas se acidificaron hasta un pH de 1 con HCl 3.8 M y se extrajeron con MTBE (x2). Las fases orgánicas combinadas se lavaron con agua, se secaron con $MgSO_4$, se filtraron a través de celite y se concentraron, para obtener el ácido 2-(2,6-difluorobencil)-1-(metoxicarbonil)piperidin-4-carboxílico (4.72 g, 82%) como un sólido de color amarillo claro. MS m/z 314 $(M+H)^+$.

Compuesto de referencia 56

Ácido 2-(3,5-difluorobencil)-1-(metoxicarbonil)piperidin-4-carboxílico

Paso 1: 2-(3,5-Difluorobencil)isonicotinato de metilo

En una atmósfera de nitrógeno, se disolvieron 2-cloroisonicotinato de metilo (5.600 g, 32.64 mmol) y $Pd(PPh_3)_4$ (0.754 g, 0.65 mmol) en THF (100 mL), a continuación se añadió cloruro de (3,5-difluorobencil)zinc (II) (0.5 M en THF, 100 mL, 50.00 mmol) y la solución resultante se agitó a 60 °C durante 3

h, antes de enfriarla hasta temperatura ambiente y detener la reacción con metanol (50.0 mL). La mezcla se diluyó con EtOAc y se lavó con NH_4Cl sat. La fase orgánica se secó y se concentró. El residuo se purificó mediante cromatografía flash automatizada en una columna Biotage® con 340 g de KP-SIL, utilizando como fase móvil un eluyente isocrático de heptano/EtOAc 8:2 en 2 VC y a continuación un gradiente de 20% a 50% de EtOAc en heptano en 6 VC. Se aisló 2-(3,5-difluorobencil)isonicotinato de metilo (7.42 g, 86%) como un aceite. ^1H RMN (400 MHz, $CDCl_3$) δ 3.94 (s, 3H), 4.18 (s, 2H), 6.66 (tt, 1H), 6.74 - 6.82 (m, 2H), 7.67 - 7.75 (m, 2H), 8.67 - 8.75 (m, 1H). MS m/z 264 $(M+H)^+$.

Paso 2: 2-(3,5-Difluorobencil)piperidin-4-carboxilato de metilo

Se disolvió 2-(3,5-difluorobencil)isonicotinato de metilo (7.417 g, 28.18 mmol) en ácido acético (72 mL) y se añadió óxido de platino (IV) (0.320 g, 1.41 mmol). La mezcla se hidrogenó en un hidrogenador Büchi a temperatura ambiente y 5 bar durante 5 h. La mezcla de reacción se filtró a través de celite y el catalizador se lavó con MeOH. El eluato se concentró y se añadieron DCM y K_2CO_3 1 M. Se separaron las fases y la fase orgánica se lavó con salmuera, antes de secarla y concentrarla, para proporcionar 2-(3,5-difluorobencil)piperidin-4-carboxilato de metilo (7.08 g, 93%). MS m/z 270 $(M+H)^+$.

Paso 3: 2-(3,5-Difluorobencil)piperidin-1,4-dicarboxilato de dimetilo

Se disolvió 2-(3,5-difluorobencil)piperidin-4-carboxilato de metilo (7.082 g, 26.30 mmol) en DCM (170 mL) y DIPEA (5.50 mL, 31.56 mmol), a continuación se añadió cloroformiato de metilo (2.88 mL, 36.58 mmol). La mezcla se agitó a temperatura ambiente durante 3 h y a continuación se añadió cloroformiato de metilo adicional (0.7 mL, 8.89 mmol). La solución se agitó durante 30 min y a continuación se lavó con HCl 0.1 M y $NaHCO_3$ sat. La fase orgánica se secó y se concentró, para obtener 2-

(3,5-difluorobencil)piperidin-1,4-dicarboxilato de dimetilo (8.55 g, 99%). MS m/z 328 $(M+H)^+$.

Paso 4: Ácido 2-(3,5-difluorobencil)-1-(metoxicarbonil)piperidin-4-carboxílico

Se disolvió 2-(3,5-difluorobencil)piperidin-1,4-dicarboxilato de dimetilo (8.459 g, 25.84 mmol) en acetonitrilo (85 mL) y agua (1.7 mL). Se añadieron bromuro de litio (17.95 g, 206.74 mmol) y trietilamina (14.33 mL, 103.37 mmol). La suspensión se calentó a reflujo durante 1.5 h, antes de añadir agua (100 mL) y MTBE (300 mL). La fase orgánica se extrajo con agua (x2). Las fases acuosas combinadas se acidificaron hasta un pH de 1 con HCl 3.8 M y se extrajeron con MTBE (x2). Las fases orgánicas combinadas se lavaron con agua, se secaron con $MgSO_4$, se filtraron a través de celite y se concentraron. El producto crudo se volvió a disolver en MTBE y se lavó con HCl 0.1 M (x2) y agua. La fase orgánica se secó con $MgSO_4$ y se concentró, para obtener el ácido 2-(3,5-difluorobencil)-1-(metoxicarbonil)piperidin-4-carboxílico (6.88 g, 85%). MS m/z 314 $(M+H)^+$.

Compuesto de referencia 57

Ácido 2-(2,4-difluorobencil)-1-(metoxicarbonil)piperidin-4-carboxílico

Paso 1: 2-(2,4-Difluorobencil)isonicotinato de metilo

En una atmósfera de nitrógeno, se disolvieron 2-cloroisonicotinato de metilo (5.2 g, 30.31 mmol) y $Pd(PPh_3)_4$ (0.700 g, 0.61 mmol) en THF (100 mL), se añadió cloruro de (2,4-difluorobencil)zinc (II) (0.5 M en THF, 90 mL, 45.00 mmol) y la solución marrón se agitó a 60 °C durante toda la noche (18 h). La reacción se detuvo añadiendo metanol (50.0 mL). La solución se diluyó con EtOAc, se lavó con NH_4Cl (ac.) y salmuera y se secó con Na_2SO_4 para obtener un aceite rojo. El crudo se volvió a disolver en MTBE (200 mL) y se filtraron los sólidos. Se añadió gota a gota cloruro de hidrógeno (4 M en dioxano, 7.58 mL, 30.31 mmol) mientras se agitaba y se formó una suspensión. La suspensión se agitó a temperatura ambiente durante 15 min. El sólido se aisló mediante filtración y se

lavó con MTBE. El sólido se disolvió en MTBE / $NaHCO_3$ sat. Se separaron las fases, la fase orgánica se secó con Na_2SO_4, se filtró y se evaporó, para proporcionar 2-(2,4-difluorobencil)isonicotinato de metilo (7.011 g, 88%) como un aceite rojo. ^1H RMN (400 MHz, $CDCl_3$) δ 3.93 (s, 3H), 4.20 (s, 2H), 6.77 - 6.88 (m, 2H), 7.18 - 7.25 (m, 1H), 7.62 - 7.73 (m, 2H), 8.69 (dd, 1H). MS m/z 264 $(M+H)^+$.

Paso 2: 2-(2,4-Difluorobencil)piperidin-4-carboxilato de metilo

Se disolvió 2-(2,4-difluorobencil)isonicotinato de metilo (7.011 g, 26.63 mmol) en ácido acético (50 mL) y se añadió óxido de platino (IV) (0.302 g, 1.33 mmol). La mezcla resultante se hidrogenó en un hidrogenador Büchi durante 4.5 h a temperatura ambiente y 5 bar. Se añadió óxido de platino (IV) (174 mg) y se continuó la hidrogenación a temperatura ambiente y 5 bar durante 2 h. Se añadió óxido de platino (IV) adicional (185 mg) y se continuó la hidrogenación a temperatura ambiente y 5 bar durante 2 h. El catalizador se filtró, se lavó con MeOH y se evaporó el eluato. Se añadieron DCM y K_2CO_3 al 10%, y se separaron las fases. La fase acuosa se extrajo con DCM y las fases orgánicas combinadas se lavaron con agua, se pasaron a través de un separador de fases y se evaporaron, para proporcionar 2-(2,4-(difluorobencil)piperidin-4-carboxilato de metilo (7.103 g, 99%) como un aceite amarillo. MS m/z 270 $(M+H)^+$.

Paso 3: 2-(2,4-Difluorobencil)piperidin-1,4-dicarboxilato de dimetilo

A una solución de 2-(2,4-(difluorobencil)piperidin-4-carboxilato de metilo (7.1 g, 26.37 mmol) en DCM (100 mL), se añadió DIPEA (6.5 mL, 37.32 mmol) y después cloroformiato de metilo (2.3 mL, 29.21 mmol) gota a gota. Después de completar la adición, la mezcla de reacción se agitó a temperatura ambiente durante 4 h y a continuación se añadió HCl 2 M. La fase orgánica se diluyó con MTBE, la mezcla bifásica se filtró para eliminar los residuos insolubles y, después de separar las fases, la fase orgánica se lavó con salmuera y con $NaHCO_3$ sat.,

se secó con $MgSO_4$ y se evaporó, para obtener 2-(2,4-difluorobencil)piperidin-1,4-dicarboxilato de dimetilo (8.51 g, 99%) como un aceite oscuro. MS m/z 328 $(M+H)^+$.

Paso 4: Ácido 2-(2,4-difluorobencil)-1-(metoxicarbonil)piperidin-4-carboxílico

A una suspensión de bromuro de litio (18.06 g, 207.99 mmol) en acetonitrilo (80 mL) y agua (1.6 mL), se añadió trietilamina (14.42 mL, 104.00 mmol) y a continuación 2-(2,4-difluorobencil)piperidin-1,4-dicarboxilato de dimetilo (8.51 g, 26.00 mmol) en acetonitrilo (40 mL). La mezcla resultante se calentó a reflujo durante 2 h 30 min, a continuación se enfrió hasta temperatura ambiente y se añadieron agua y MTBE. La fase orgánica se extrajo con agua dos veces. Se ajustó el pH de las fases acuosas recogidas hasta un pH de 1 con HCl 3.8 M y a continuación se extrajeron con DCM (3x). Las fases orgánicas combinadas se secaron con $MgSO_4$ y se evaporaron, para proporcionar el ácido 2-(2,4-difluorobencil)-1-(metoxicarbonil)piperidin-4-carboxílico (7.48 g, 92%) como un sólido naranja. MS m/z 314 $(M+H)^+$.

Compuesto de referencia 58

Ácido 2-(3-fluoro-5-(trifluorometil)bencil)-1-(metoxicarbonil)piperidin-4-carboxílico

Paso 1: Bromuro de (3-fluoro-5-(trifluorometil)bencil)zinc (II)

En un matraz anhidro, se suspendió zinc en polvo (1.526 g, 23.34 mmol) en THF anhidro (12.5 mL) en una atmósfera de nitrógeno. La suspensión resultante se calentó hasta 60 °C, a continuación se añadió 1,2-dibromoetano (0.084 mL, 0.97 mmol) y se agitó a esta temperatura durante 15 min. Se enfrió hasta temperatura ambiente, a continuación se añadió clorotrimetilsilano (0.099 mL, 0.78 mmol) y se agitó a temperatura ambiente durante 20 min. A continuación, se añadió 1-(bromometil)-3-fluoro-5-(trifluorometoxi)benceno (5 g, 19.45 mmol) disuelto en THF anhidro (12.5 mL) durante 7 min y se continuó agitando a temperatura ambiente durante 1 h, a continuación se dejó de agitar para permitir que los sólidos se

asentaran. El líquido sobrenadante se utilizó en la siguiente transformación.

Paso 2: 2-(3-Fluoro-5-(trifluorometil)bencil)isonicotinato de metilo

Se disolvieron 2-cloroisonicotinato de metilo (3.0 g, 17.48 mmol) y $Pd(PPh_3)_4$ (0.606 g, 0.52 mmol) en THF (50 mL) en una atmósfera de nitrógeno. Se añadió bromuro de (3-fluoro-5-(trifluorometil)bencil)zinc (II) (5.41 g, 19.45 mmol) recién preparado en THF (25 mL) a la solución amarilla y el matraz se calentó hasta 60 °C durante toda la noche. La mezcla de reacción se detuvo añadiendo metanol. La solución se diluyó con acetato de etilo y se lavó con NH_4Cl y agua. La fase orgánica se secó con Na_2SO_4, se filtró a través de celite y se evaporó el disolvente. El residuo se cromatografió utilizando un equipo Biotage. Eluyente: acetato de etilo-heptano, empezando desde 20-80 y aplicando un gradiente lineal hasta 60-40. Se aisló 2-(3-fluoro-5-(trifluorometil)bencil)isonicotinato de metilo (4.1 g, 75%). ^1H RMN (400 MHz, $CDCl_3$) δ 3.94 (s, 3H), 4.25 (s, 2H), 7.13 - 7.22 (m, 2H), 7.33 (s, 1H), 7.69 - 7.75 (m, 2H), 8.70 - 8.74 (m, 1 H). MS m/z 314 $(M+H)^+$.

Paso 3: 2-(3-Fluoro-5-(trifluorometil)bencil)piperidin-4-carboxilato de metilo

A una solución de 2-(3-fluoro-5-(trifluorometoxi)bencil)isonicotinato de metilo (4.5 g, 14.37 mmol) en ácido acético (50 mL), se añadió óxido de platino (IV) (0.36 g, 1.59 mmol) y la mezcla resultante se hidrogenó a 5 bar en un hidrogenador Büchi durante 3 h 45 min. La mezcla de reacción se filtró a través de un cartucho de filtración con tierras de diatomeas y el catalizador se lavó con metanol. Se evaporaron los disolventes, se volvió a disolver el residuo en DCM y se lavó con Na_2CO_3 al 10%. Después de separar las fases, la fase acuosa se extrajo con DCM. Las fases orgánicas combinadas se secaron con $MgSO_4$ y se evaporaron. Se aisló 2-(3-fluoro-5-(trifluorometil)bencil)piperidin-4-carboxilato de metilo (4.11 g, 90%) como un aceite de color amarillo claro, que solidificó parcialmente en reposo. MS m/z 320 $(M+H)^+$.

Paso 4: 2-(3-Fluoro-5-(trifluorometil)bencil)piperidin-1,4-dicarboxilato de dimetilo

A una solución de 2-(3-fluoro-5-(trifluorometil)bencil)piperidin-4-carboxilato de metilo (4.10 g, 12.84 mmol) en DCM (50 mL) enfriada en un baño de hielo, se añadió DIPEA (3.5 mL, 20.09 mmol) y después cloroformiato de metilo (1.112 mL, 14.12 mmol). Después de completar la adición, la mezcla de reacción se agitó a temperatura ambiente durante 2 h. Se evaporaron los disolventes y el residuo se repartió entre acetato de etilo y HCl 3.8 M. Después de separar las fases, se lavó la fase orgánica con salmuera, se secó con $MgSO_4$ y se evaporó, para proporcionar 2-(3-fluoro-5-(trifluorometil)bencil)piperidin-1,4-dicarboxilato de dimetilo crudo (4.94 g, 102%) como un aceite de color amarillo claro. MS m/z 378 $(M+H)^+$.

Paso 5: Ácido 2-(3-fluoro-5-(trifluorometil)bencil)-1-(metoxicarbonil)piperidin-4-carboxílico

A una solución de 2-(3-fluoro-5-(trifluorometil)bencil)piperidin-1,4-dicarboxilato de dimetilo (4.94 g, 13.09 mmol) en acetonitrilo (60 mL) y agua (1.2 mL), se añadieron bromuro de litio (9.10 g, 104.74 mmol) y trietilamina (7.26 mL, 52.37 mmol). La mezcla resultante se calentó a reflujo durante 2 h y a continuación se enfrió hasta temperatura ambiente. Se añadió agua y se eliminó el acetonitrilo mediante evaporación. La fase acuosa se diluyó adicionalmente con agua y a continuación se lavó con MTBE. La fase orgánica se extrajo con agua. Las fases acuosas combinadas se acidificaron con HCl 3.8 M y se formó un precipitado incoloro. La fase acuosa se extrajo con DCM tres veces. Las fases orgánicas combinadas se secaron con $MgSO_4$ y se evaporaron. Se aisló el ácido 2-(3-fluoro-5-(trifluorometil)bencil)-1-(metoxicarbonil)piperidin-4-carboxílico (4.58 g, 96%) como un aceite viscoso de color amarillo claro. MS m/z 364 $(M+H)^+$.

Compuesto de referencia 59

Ácido 2-(3-fluoro-4-(trifluorometil)bencil)-1-

(metoxicarbonil)piperidin-4-carboxílico

Paso 1: Bromuro de (3-fluoro-4-(trifluorometil)bencil)zinc (II)

En un matraz anhidro, se suspendió zinc en polvo (3.05 g, 46.69 mmol) en tetrahidrofurano anhidro (25 mL) en una atmósfera de nitrógeno. La suspensión resultante se calentó hasta 60 °C, a continuación se añadió 1,2-dibromoetano (0.168 mL, 1.95 mmol) y se agitó a esta temperatura durante 15 min. Se enfrió hasta temperatura ambiente, a continuación se añadió clorotrimetilsilano (0.2 mL, 1.58 mmol) y se agitó a temperatura ambiente durante 1 h 15 min. A continuación, se añadió 4-(bromometil)-2-fluoro-1-(trifluorometil)benceno (10 g, 38.91 mmol) en tetrahidrofurano (5 mL) en 6 porciones iguales cada 10 minutos con un baño de hielo. Después de completar la adición, se retiró el baño de hielo y la mezcla de reacción se agitó a temperatura ambiente durante 18 h. A continuación, se dejó de agitar para que los sólidos se asentaran. El líquido sobrenadante se utilizó en la siguiente transformación.

Paso 2: 2-(3-Fluoro-4-(trifluorometil)bencil)isonicotinato de metilo

A una solución de 2-cloroisonicotinato de metilo (5.15 g, 30 mmol) y $Pd(PPh_3)_4$ (0.693 g, 0.60 mmol) en tetrahidrofurano (40 mL) en un matraz anhidro con atmósfera de nitrógeno, se añadió bromuro de (3-fluoro-4-(trifluorometil)bencil)zinc (II) recién preparado (12.55 g, 38.91 mmol) en tetrahidrofurano (50 mL). La mezcla de color amarillo intenso resultante se calentó hasta 60 °C durante 2 h 20 min y a continuación se enfrió hasta temperatura ambiente. La reacción se detuvo añadiendo NH_4Cl al 10%. Se diluyó con acetato de etilo. Después de separar las fases, la fase orgánica se lavó con salmuera, se secó con $MgSO_4$ y se evaporó. El residuo se suspendió en 150 mL de MTBE y se sonicó, a continuación se filtraron los residuos insolubles amarillos y se lavaron con MTBE. Se incrementó el volumen del filtrado hasta aproximadamente 200 mL y a continuación se añadió cloruro de hidrógeno (7.50 mL, 30.00 mmol) (4M en dioxano) gota a gota. Se formó un precipitado incoloro. La

suspensión resultante se agitó durante aproximadamente 1 h y a continuación se sonicó durante 2 min. Se separó el sólido formado, se lavó con MTBE y se secó. Se disolvió el sólido en DCM y se lavó con K_2CO_3 al 10%. Después de separar las fases, la fase acuosa se extrajo con DCM. Las fases orgánicas combinadas se secaron con $MgSO_4$ y se evaporaron. Se aisló 2-(3-fluoro-4-(trifluorometil)bencil)isonicotinato de metilo (8.26 g, 88%) como un aceite de color naranja claro. ^{1}H RMN (400 MHz, $CDCl_3$) δ 3.94 (s, 3H), 4.24 (s, 2H), 7.06 - 7.18 (m, 2H), 7.52 (t, 1H), 7.69 - 7.75 (m, 2H), 8.68 - 8.75 (m, 1H). MS m/z 314 $(M+H)^+$.

Paso 3: 2-(3-Fluoro-4-(trifluorometil)bencil)piperidin-4-carboxilato de metilo

A una solución de 2-(3-fluoro-4-(trifluorometil)bencil)isonicotinato de metilo (8.26 g, 26.37 mmol) en ácido acético (50 mL), se añadió óxido de platino (IV) (0.44 g, 1.94 mmol) y la mezcla resultante se hidrogenó a 5 bar en un hidrogenador Büchi durante 8 h. La mezcla de reacción se filtró a través de un cartucho de filtración con tierras de diatomeas y el catalizador se lavó con metanol. Se evaporaron los disolventes, el residuo se disolvió en DCM y se lavó con Na_2CO_3 al 10%. Después de separar las fases, la fase acuosa se extrajo con DCM. Las capas orgánicas combinadas se secaron con $MgSO_4$ y se evaporaron. Se aisló 2-(3-fluoro-4-(trifluorometil)bencil)piperidin-4-carboxilato de metilo (8.4 g, 100%) como un aceite de color amarillo claro, que solidificó parcialmente en reposo. MS m/z 320 $(M+H)^+$.

Paso 4: 2-(3-Fluoro-4-(trifluorometil)bencil)piperidin-1,4-dicarboxilato de dimetilo

A una solución de 2-(3-fluoro-4-(trifluorometil)bencil)piperidin-4-carboxilato de metilo (5.96 g, 18.67 mmol) en DCM (100 mL) enfriada en un baño de hielo, se añadió DIPEA (4 mL, 22.96 mmol) y después cloroformiato de metilo (1.617 mL, 20.53 mmol). Después de completar la adición, la mezcla de reacción se agitó a temperatura ambiente durante 2 h. Se evaporaron los disolventes y el residuo se repartió entre

acetato de etilo y HCl 3.8 M. Después de separar las fases, la fase orgánica se lavó con salmuera, a continuación se secó con $MgSO_4$ y se evaporó. Se aisló 2-(3-fluoro-4-(trifluorometil)bencil)piperidin-1,4-dicarboxilato de dimetilo (7.17 g, 102%) como un aceite de color amarillo claro.

Paso 5: Ácido 2-(3-fluoro-4-(trifluorometil)bencil)-1-(metoxicarbonil)piperidin-4-carboxílico

A una solución de 2-(3-fluoro-4-(trifluorometil)bencil)piperidin-1,4-dicarboxilato de dimetilo (7.17 g, 19.00 mmol) en acetonitrilo (60 mL) y agua (1.2 mL), se añadieron bromuro de litio (13.20 g, 152.02 mmol) y trietilamina (10.54 mL, 76.01 mmol). La mezcla resultante se calentó a reflujo durante 2 h y a continuación se enfrió hasta temperatura ambiente. Se añadió agua y se eliminó el acetonitrilo mediante evaporación. La fase acuosa se diluyó adicionalmente con agua y a continuación se lavó con MTBE. La fase orgánica se extrajo con agua. Las fases acuosas combinadas se acidificaron con HCl 3.8 M y se formó un precipitado incoloro. Los sólidos se extrajeron 6 veces con DCM. La fase acuosa se volvió a extraer dos veces con DCM. Las fases orgánicas combinadas se secaron con $MgSO_4$ y se evaporaron. Se obtuvo el ácido 2-(3-fluoro-4-(trifluorometil)bencil)-1-(metoxicarbonil)piperidin-4-carboxílico (6.56 g, 95%) como un sólido blanquecino. MS m/z 364 $(M+H)^+$.

Compuesto de referencia 60

Ácido 1-(metoxicarbonil)-2-(3,4,5-trifluorobencil)piperidin-4-carboxílico

Paso 1: Bromuro de (3,4,5-trifluorobencil)zinc (II)

Se añadieron zinc en polvo (2.62 g, 40.00 mmol) y cloruro de litio (1.696 g, 40.00 mmol) a un matraz anhidro y se calentaron hasta 150 °C al vacío durante 30 min. Se dejó que el matraz alcanzara la temperatura ambiente. Se añadieron THF (20 mL) y 1,2-dibromoetano (0.115 mL, 1.33 mmol). La mezcla se calentó hasta que se observó ebullición y a continuación se dejó que el matraz alcanzara la temperatura ambiente. Se añadió clorotrimetilsilano (0.034 mL, 0.27 mmol) y se volvió a

calentar la mezcla hasta observar ebullición. Se enfrió el matraz con un baño de hielo y se añadió gota a gota 5-(bromometil)-1,2,3-trifluorobenceno (6 g, 26.67 mmol) disuelto en THF (5 mL). Se retiró el baño de hielo y se agitó la reacción a temperatura ambiente durante 20 h. Se dejó que los sólidos se asentaran y se utilizó el líquido sobrenadante en la siguiente transformación.

Paso 2: Clorhidrato de 2-(3,4,5-trifluorobencil)isonicotinato de metilo

Se disolvió 2-cloroisonicotinato de metilo (3.5 g, 20.40 mmol) en THF (30 mL) en una atmósfera de nitrógeno. Se añadió bis(tri-*tert*-butilfosfina)Pd (0) (0.208 g, 0.41 mmol). A continuación, se añadió bromuro de (3,4,5-trifluorobencil)zinc (II) recién preparado (1.06 M en THF) (25.1 mL, 26.65 mmol) y la mezcla de reacción se agitó a 60 °C durante 3 h. Se añadió agua (15 mL) y se evaporó el THF. La mezcla de reacción se diluyó con $NaHCO_3$ sat. y se extrajo con EtOAc (3x). Las fases orgánicas combinadas se lavaron con $NaHCO_3$ sat., agua, NH_4Cl y salmuera, se secaron con Na_2SO_4, se filtraron y se evaporaron al vacío para proporcionar un aceite rojo (5 g). Se añadió MTBE (70 mL), se filtraron los residuos insolubles y se lavaron con MTBE (10 mL). Se añadió cloruro de hidrógeno (4 M en dioxano, 5.10 mL, 20.40 mmol) gota a gota al filtrado y se formó un precipitado naranja. La mezcla se enfrió con un baño de hielo. El precipitado se filtró, se lavó con MTBE frío y se secó al vacío, para proporcionar el clorhidrato de 2-(3,4,5-trifluorobencil)isonicotinato de metilo (4.00 g, 61.7%) como un sólido naranja. ^1H RMN (600 MHz, CD_3OD) δ 4.02 (s, 3H), 4.45 (s, 2H), 7.13 - 7.22 (m, 2H), 8.24 - 8.32 (m, 2H), 8.87 - 8.93 (m, 1H). MS m/z 282 $(M+H)^+$.

Paso 3: Clorhidrato de 2-(3,4,5-trifluorobencil)piperidin-4-carboxilato de metilo

Se disolvió el clorhidrato de 2-(3,4,5-trifluorobencil)isonicotinato de metilo (4 g, 12.59 mmol) en MeOH (45 mL) y se añadió óxido de platino (IV) (0.143 g, 0.63 mmol). La mezcla resultante se hidrogenó en un hidrogenador

Büchi a temperatura ambiente y 5 bar durante 3 h. Se añadió óxido de platino (IV) adicional (0.029 g, 0.13 mmol) y se continuó la hidrogenación durante 20 min. El catalizador se filtró y se lavó con MeOH. El filtrado se evaporó al vacío, para proporcionar el clorhidrato de 2-(3,4,5-trifluorobencil)piperidin-4-carboxilato de metilo (3.96 g, 97%) como un sólido marrón. MS m/z 288 $(M+H)^+$.

Paso 4: 2-(3,4,5-Trifluorobencil)piperidin-1,4-dicarboxilato de dimetilo

Se disolvieron el clorhidrato de 2-(3,4,5-trifluorobencil)piperidin-4-carboxilato de metilo (3.957 g, 12.22 mmol) y DIPEA (4.68 mL, 26.89 mmol) en DCM (20 mL) y se añadió cloroformiato de metilo (1.059 mL, 13.45 mmol). La reacción se agitó a temperatura ambiente durante 18 h, se diluyó con DCM (200 mL), se lavó con HCl 0.1 M (2x200 mL) y $NaHCO_3$ sat. (200 mL), se secó a través de un separador de fases y se evaporó al vacío, para proporcionar 2-(3,4,5-(trifluorobencil)piperidin-1,4-dicarboxilato de dimetilo (4.01 g, 95%) como un aceite marrón. MS m/z 346 $(M+H)^+$.

Paso 5: Ácido 1-(metoxicarbonil)-2-(3,4,5-trifluorobencil)piperidin-4-carboxílico

Se disolvió 2-(3,4,5-trifluorobencil)piperidin-1,4-dicarboxilato de dimetilo (4.01 g, 11.61 mmol) en acetonitrilo (40 mL) y agua (0.8 mL). Se añadió bromuro de litio (2.329 mL, 92.90 mmol) y a continuación trietilamina (6.44 mL, 46.45 mmol). La reacción se calentó a reflujo durante 2 h. La reacción se enfrió hasta temperatura ambiente. Se añadieron agua (200 mL) y MTBE (150 mL), se agitó y se separaron las fases. La fase orgánica se extrajo con agua (2x150 mL). Las fases acuosas combinadas se acidificaron con HCl 3 M hasta un pH de 1 y a continuación se extrajeron con MTBE (2x400 mL). Las fases orgánicas combinadas se secaron con Na_2SO_4, se filtraron y se evaporaron al vacío, para proporcionar el ácido 1-(metoxicarbonil)-2-(3,4,5-trifluorobencil)piperidin-4-carboxílico (3.42 g, 89%) como una espuma de color marrón claro. MS m/z 330 $(M-H)^-$.

Compuesto de referencia 61

Ácido 2-(3,5-di-*tert*-butilbencil)-1-(metoxicarbonil)piperidin-4-carboxílico

Paso 1: Bromuro de (3,5-di-*tert*-butilbencil)zinc (II)

En un matraz anhidro, se suspendió zinc en polvo (2.493 g, 38.13 mmol) en tetrahidrofurano anhidro (23 mL) en una atmósfera de nitrógeno. La suspensión resultante se calentó hasta 60 °C, a continuación se añadió 1,2-dibromoetano (0.137 mL, 1.59 mmol) y se agitó a esta temperatura durante 15 min. Se enfrió hasta temperatura ambiente, a continuación se añadió clorotrimetilsilano (0.161 mL, 1.27 mmol) y se agitó a temperatura ambiente durante 45 min. A continuación, se añadió 1-(bromometil)-3,5-di-*tert*-butilbenceno) (9 g, 31.77 mmol) disuelto en tetrahidrofurano anhidro (23.00 mL) durante 10 min. Se continuó agitando a temperatura ambiente durante 16 h, a continuación se dejó de agitar para permitir que los sólidos se asentaran. El líquido sobrenadante se utilizó en la siguiente transformación.

Paso 2: 2-(3,5-di-*tert*-Butilbencil)isonicotinato de metilo

A una solución de 2-cloroisonicotinato de metilo (4 g, 23.31 mmol) y $Pd(PPh_3)_4$ (0.539 g, 0.47 mmol) en tetrahidrofurano (120 mL) en un matraz anhidro con atmósfera de nitrógeno, se añadió una solución recién preparada de bromuro de (3,5-di-*tert*-butilbencil)zinc (II) recién preparado (11.08 g, 31.78 mmol) en tetrahidrofurano (46 mL). La solución de color amarillo intenso resultante se calentó hasta 60 °C durante 35 min, a continuación se agitó a temperatura ambiente durante 1 h. La reacción se detuvo añadiendo metanol (50 mL). La solución se diluyó con EtOAc y se lavó con NH_4Cl. La fase orgánica se secó con $MgSO_4$, se filtró y se evaporó para proporcionar un aceite marrón. El crudo se volvió a disolver en MTBE (180 mL) y se filtraron los sólidos. Se añadió gota a gota cloruro de hidrógeno (4 M en dioxano, 6.42 mL, 25.66 mmol) mientras se agitaba y se formó una suspensión. La suspensión se agitó a temperatura ambiente durante 10 min. El sólido se aisló mediante filtración y se lavó con MTBE. Se volvió a disolver en

MTBE / $NaHCO_3$ sat. Se separaron las fases, la fase orgánica se secó con Na_2SO_4, se filtró y se evaporó, para proporcionar 2-(3,5-di-*tert*-butilbencil)isonicotinato de metilo (7.132 g, 90%) como un aceite marrón. ^1H RMN (600 MHz, $CDCl_3$) δ 1.28 (s, 18H), 3.89 (s, 3H), 4.19 (s, 2H), 7.11 (d, 2H), 7.27 (t, 1H), 7.64 (dd, 1H), 7.71 (s, 1H), 8.68 (d, 1H). MS m/z 340 $(M+H)^+$.

Paso 3: 2-(3,5-di-*tert*-Butilbencil)piperidin-4-carboxilato de metilo

Se disolvió 2-(3,5-di-*tert*-butilbencil)isonicotinato de metilo (3.538 g, 10.42 mmol) en ácido acético (30 mL) y se añadió óxido de platino (IV) (0.118 g, 0.52 mmol). La mezcla resultante se hidrogenó en un hidrogenador Büchi a temperatura ambiente y 5 bar durante 5 h 45 min. El catalizador se filtró, se lavó con MeOH y se evaporó el eluato. Se añadieron DCM y K_2CO_3 al 10%, y se separaron las fases. La fase orgánica se lavó con salmuera, se hizo pasar a través de un separador de fases y se evaporó, para proporcionar 2-(3,5-di-*tert*-butilbencil)piperidin-4-carboxilato de metilo (3.80 g, 106%) como un aceite beis. MS m/z 346 $(M+H)^+$.

Paso 4: 2-(3,5-di-*tert*-Butilbencil)piperidin-1,4-dicarboxilato de dimetilo

Se disolvió 2-(3,5-di-*tert*-butilbencil)piperidin-4-carboxilato de metilo (3.691 g, 10.68 mmol) en DCM (80 mL), se añadió DIPEA (2.233 mL, 12.82 mmol) y después cloroformiato de metilo (1.262 mL, 16.02 mmol). La solución se agitó a temperatura ambiente durante 1.5 h. La mezcla de reacción se lavó con HCl 0.1 M y $NaHCO_3$ sat. La fase orgánica se hizo pasar a través de un separador de fases y se evaporó, para proporcionar 2-(3,5-di-*tert*-butilbencil)piperidin-1,4-dicarboxilato de dimetilo (3.91 g, 91%) como un aceite amarillo. MS m/z 404 $(M+H)^+$.

Paso 5: Ácido 2-(3,5-di-*tert*-butilbencil)-1-(metoxicarbonil)piperidin-4-carboxílico

Se disolvió 2-(3,5-di-*tert*-butilbencil)piperidin-1,4-dicarboxilato de dimetilo (3.886 g, 9.63 mmol) en acetonitrilo (40 mL) y agua (0.8 mL), a continuación se añadieron bromuro de

litio (6.69 g, 77.04 mmol) y trietilamina (5.34 mL, 38.52 mmol) y la suspensión amarilla resultante se calentó a reflujo. Después de 5 h, se añadieron agua (100 mL) y MTBE (250 mL). La fase orgánica se extrajo con agua (x2). Las fases acuosas recogidas se acidificaron hasta un pH de 1 con HCl 3.8 M y a continuación se extrajeron con MTBE (x3). Las fases orgánicas combinadas se lavaron con agua, se secaron con Na_2SO_4, se filtraron y se evaporaron, para proporcionar el ácido 2-(3,5-di-*tert*-butilbencil)-1-(metoxicarbonil)piperidin-4-carboxílico (3.723 g, 99%) como una goma amarilla. MS m/z 390 $(M+H)^+$.

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Ácido 2-bencil-2,3,4,5,6-d_5-1-(metoxicarbonil)piperidin-4-carboxílico

Paso 1: Bromuro de bencil-2,3,4,5,6-d_5 zinc (II)

En un matraz anhidro, se suspendió zinc en polvo (2.4 g, 36.70 mmol) en tetrahidrofurano anhidro (40 mL) en una atmósfera de nitrógeno. La suspensión resultante se calentó hasta 60 °C, a continuación se añadió 1,2-dibromoetano (0.125 mL, 1.45 mmol) y se agitó a esta temperatura durante 20 min. Se enfrió hasta temperatura ambiente, a continuación se añadió clorotrimetilsilano (0.15 mL, 1.18 mmol) y se agitó a temperatura ambiente durante 30 min. A continuación, se añadió bromuro de bencilo-2,3,4,5,6-d_5 (5 g, 28.40 mmol) (99.2% deuterado) en porciones durante 30 min y a continuación se continuó agitando a temperatura ambiente durante 18 h. Se dejó de agitar para permitir que el precipitado se asentara. El líquido sobrenadante se utilizó en la siguiente transformación.

Paso 2: 2-Bencil-2,3,4,5,6-d_5 isonicotinato de metilo

A una solución de 2-cloroisonicotinato de metilo (3.95 g, 23 mmol) y $Pd(PPh_3)_4$ (0.532 g, 0.46 mmol) en tetrahidrofurano (40 mL) en un matraz anhidro con atmósfera de nitrógeno, se añadió bromuro de bencil-2,3,4,5,6-d_5 zinc (II) recién preparado (6.86 g, 28.4 mmol) en tetrahidrofurano (50 mL). La mezcla de color amarillo intenso resultante se calentó hasta 60 °C durante 2 h. Después de enfriarla a temperatura ambiente, la reacción se detuvo añadiendo NH_4Cl al 10%. Se diluyó con

acetato de etilo. Después de separar las fases, la fase orgánica se lavó con salmuera, se secó con $MgSO_4$ y se evaporó. El residuo se suspendió en MTBE (50 mL) y se sonicó, se filtraron los residuos insolubles amarillos y se lavaron con MTBE. Se incrementó el volumen del filtrado hasta aproximadamente 150 mL, a continuación se añadieron 5 mL de MeOH y después cloruro de hidrógeno (5.75 mL, 23.00 mmol) (4 M en dioxano). Se formó un precipitado incoloro. La mezcla se agitó durante 10 min, se sonicó durante 5 min, a continuación los sólidos se separaron y se lavaron con MTBE. El sólido se transfirió a un embudo de separación con MeOH y se diluyó con MTBE. A continuación, se añadió Na_2CO_3 al 10% y se agitó enérgicamente. Después de separar las fases, la fase orgánica se lavó con salmuera, se secó con $MgSO_4$ y se evaporó. Se aisló 2-bencil-2,3,4,5,6-d_5 isonicotinato de metilo (4.78 g, 89%) como un aceite de color amarillo claro. ^1H RMN (400 MHz, $CDCl_3$) δ 3.92 (s, 3H), 4.23 (s, 2H), 7.65 - 7.71 (m, 2H), 8.66 - 8.74 (m, 1H). MS m/z 233 $(M+H)^+$.

Paso 3: 2-Bencil-2,3,4,5,6-d_5 piperidin-4-carboxilato de metilo

Se disolvió 2-bencil-2,3,4,5,6-d_5 isonicotinato de metilo (4.69 g, 20.19 mmol) en ácido acético (3 mL) y se añadió óxido de platino (IV) (0.364 g, 1.60 mmol). La mezcla resultante se hidrogenó en un hidrogenador Büchi a 4 bar durante 4 h. La mezcla de reacción se filtró a través de un cartucho de filtración con tierras de diatomeas, se lavó con metanol y se evaporaron los disolventes. El residuo se disolvió en MTBE y se lavó con $NaHCO_3$ sat. Antes de separar las fases, se ajustó el pH de la fase acuosa hasta un pH de 9 añadiendo K_2CO_3 al 10%. La fase orgánica se secó con $MgSO_4$ y se evaporó, para proporcionar 2-bencil-2,3,4,5,6-d_5 piperidin-4-carboxilato de metilo (4.6 g, 96%) como un aceite amarillo. MS m/z 239 $(M+H)^+$.

Paso 4: 2-Bencil-2,3,4,5,6-d_5 piperidin-1,4-dicarboxilato de dimetilo

A una solución de 2-bencil-2,3,4,5,6-d_5 piperidin-4-carboxilato de metilo (4.6 g, 19.30 mmol) y DIPEA (5 mL, 28.71

mmol) en DCM (75 mL), se añadió cloroformiato de metilo (1.8 mL, 22.86 mmol) gota a gota. Se continuó agitando a temperatura ambiente durante 45 min y a continuación se evaporaron los disolventes. El residuo se repartió entre MTBE y HCl 1 N. La fase orgánica se lavó con salmuera y $NaHCO_3$ sat., a continuación se secó con $MgSO_4$ y se evaporó, para proporcionar 2-bencil-2,3,4,5,6-d_5 piperidin-1,4-dicarboxilato de dimetilo (5.55 g, 97%) como un aceite de color amarillo claro. MS m/z 297 $(M+H)^+$.

Paso 5: Ácido 2-bencil-2,3,4,5,6-d_5-1-(metoxicarbonil)piperidin-4-carboxílico

Se disolvió 2-bencil-2,3,4,5,6,-d_5 piperidin-1,4-dicarboxilato de dimetilo (5.55 g, 18.73 mmol) en acetonitrilo (60 mL) y agua (1,2 mL), a continuación se añadieron bromuro de litio (13.01 g, 149.81 mmol) y trietilamina (10.38 mL, 74.91 mmol). La suspensión amarilla resultante se calentó a reflujo. Después de 2 h 10 min, la mezcla de reacción se enfrió hasta temperatura ambiente, a continuación se añadieron agua y MTBE. La fase orgánica se extrajo con agua dos veces. Se ajustó el pH de las fases acuosas recogidas hasta un pH de 1 con HCl 3.8 M y a continuación se extrajeron con DCM (3x). Las fases orgánicas combinadas se secaron con $MgSO_4$ y se evaporaron, para proporcionar el ácido 2-bencil-2,3,4,5,6-d_5-1-(metoxicarbonil)piperidin-4-carboxílico (5.16 g, 98%) como un sólido blanquecino. MS m/z 283 $(M+H)^+$.

Preparación de los Ejemplos de Compuestos. Formación de 5-isoxazol-3-onas

Ejemplo 1

5-((2*S*,4*S*)-2-Bencilpiperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-bencil-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo y *cis*-2-bencil-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo

Se agitó una suspensión de cloruro de magnesio (3.11 g, 32.66 mmol) y malonato de etilo y potasio (8.34 g, 48.99 mmol) en THF anhidro (70 mL) en una atmósfera de nitrógeno a 50 °C durante 4 h (matraz 1). En otro matraz, se añadió carbonildiimidazol (6.35 g, 39.19 mmol) en porciones a una suspensión del ácido 2-bencil-1-(metoxicarbonil)piperidin-4-carboxílico (9.057 g, 32.66 mmol) (compuesto de referencia 1) en THF anhidro (70 mL) a 5 °C en una atmósfera de nitrógeno. La mezcla de reacción se agitó durante 1 h a 5 °C (matraz 2). A continuación, el contenido del matraz 2 se añadió gota a gota al matraz 1 y la mezcla resultante se agitó durante 24 h. La mezcla de reacción se concentró y el residuo se repartió entre EtOAc y H_2O. La fase acuosa se extrajo una vez con EtOAc, las fases orgánicas combinadas se lavaron con H_2O y Na_2CO_3 sat., a continuación se secaron con Na_2SO_4 y se evaporaron para obtener 11.02 g de aceite. La purificación utilizando cromatografía en columna automatizada (Biotage) (2 purificaciones - columna de 340 g, gradiente de 10-60% de EtOAc/heptano) proporcionó *trans*-2-bencil-4-(3-etoxi-3-oxopropanoil)piperidina-1-carboxilato de metilo (6.35 g): ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.27 (m, 3H), 1.41 - 1.66 (m, 3H), 1.70 - 2.11 (m, 2H), 2.53 - 3.10 (m, 4H), 3.55 (d, 4H), 4.19 (dd, 3H), 4.42 - 4.99 (m, 1H), 7.08 - 7.37 (m, 5H); MS m/z 348 $(M+H)^+$ y *cis*-2-bencil-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (2.15 g): ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.25 (m, 3H), 1.61 - 1.96 (m, 4H), 2.64 - 2.79 (m, 2H), 2.80 - 3.10 (m, 2H), 3.44 (s, 2H), 3.63 (s, 3H),

3.84 - 4.00 (m, 1H), 4.03 - 4.25 (m, 3H), 7.15 - 7.42 (m, 5H); MS m/z 348 $(M+H)^+$.

Paso 2: *Trans*-2-bencil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se añadió una solución de *trans*-2-bencil-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (6.35 g, 18.3 mmol) en MeOH (2 mL) a una solución de NaOH (0.77 g, 19.4 mmol) en MeOH/H_2O (15 mL/0.9 mL) a -30 °C. Después de 10 minutos, se añadió una solución de clorhidrato de hidroxilamina (2.54 g, 36.6 mmol) y NaOH (1.46 g, 36.6 mmol) en MeOH (18 mL) y H_2O (18 mL). Se continuó agitando a -30 °C durante 30 minutos. A continuación, la mezcla de reacción se vertió sobre HCl concentrado (20 mL) que estaba a 80 °C. La solución se agitó durante 30 minutos. El disolvente orgánico se evaporó y la fase acuosa se extrajo con DEE (x3). La fase orgánica se secó con Na_2SO_4 y se evaporó para proporcionar un sólido, 3.68 g, que se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x20 DI en mm), utilizando un gradiente de 20-70% de acetonitrilo en un tampón 95/5/0.2 de H_2O/MeCN/AF, durante 18 minutos con un flujo de 19 mL/minuto. Se aisló *trans*-2-bencil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (2.54 g, 54.6%) como un sólido. ^1H RMN (600 MHz, $CDCl_3$) δ 1.50 - 2.21 (m, 4H), 2.91 (m, 2H), 3.10 (m, 2H), 3.58 (d, 3H), 4.04 - 4.41 (m, 1H), 4.43 - 4.82 (m, 1H), 5.55 - 5.84 (m, 1H), 7.15 - 7.30 (m, 5H); MS m/z 317 $(M+H)^+$.

Paso 3: (2*S*,4*S*)-2-Bencil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se llevó a cabo una separación quiral del *trans*-2-bencil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo racémico (2.54 g, 8.04 mmol), utilizando Chiralcel IA y fase móvil 80/20/0.4/0.1 de heptano/EtOH/AF, para obtener (2*S*,4*S*)-2-bencil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.99 g).

Paso 4: 5-((2*S*,4*S*)-2-Bencilpiperidin-4-il)isoxazol-3(2*H*)-ona

Se añadió HBr (33% en HOAc, 20 mL) a (2*S*,4*S*)-2-bencil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.99 g) y la solución se agitó durante 8 h. Los componentes volátiles se concentraron y el residuo se purificó mediante HPLC preparativa en una columna XBridge C18 (10 µm 250x50 DI en mm), utilizando un gradiente de 0-40 % de acetonitrilo en un tampón 95/5/0.2 de H_2O/MeCN/NH_3 durante 15 minutos con un flujo de 100 mL/minuto. Se aisló el compuesto del título (0.62 g, 30%). ^{1}H RMN (600 MHz, DMSO) δ 1.47 (m, 1H), 1.67 - 1.83 (m, 3H), 2.51 - 2.67 (m, 3H), 2.74 - 2.89 (m, 2H), 3.04 - 3.15 (m, 1H), 5.67 (s, 1H), 7.21 (m, 5H); $[\alpha]^{20}_D$ +47.0 (MeOH/H_2O 1:1, c = 1); HRMS calculado para $[C_{15}H_{19}N_2O_2]$+: 259.1447; Experimental: 259.1449.

Ejemplo 2

5-((2*R*,4*R*)-2-Bencilpiperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: (2*R*,4*R*)-2-Bencil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo El compuesto del título se obtuvo en la preparación del Paso 3 del Ejemplo 1 (0.93 g).

Paso 2: 5-((2*R*,4*R*)-2-Bencilpiperidin-4-il)isoxazol-3(2*H*)-ona

Siguiendo el mismo procedimiento que se ha descrito en el Paso 4 del Ejemplo 1 y utilizando ((2*R*,4*R*)-2-bencil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidina-1-carboxilato de metilo, se obtuvo el compuesto del título (0.55 g, 27%). $[\alpha]^{20}_D$ -43.0 (MeOH/H_2O 1:1, c = 1); HRMS calculado para $[C_{15}H_{19}N_2O_2]$+: 259.1447; experimental: 259,1449.

Ejemplo 3

5-((2*R*,4*S*)-2-Bencilpiperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Cis*-2-bencil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se añadió una solución de *cis*-2-bencil-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (2.15 g, 6.18 mmol) (procedente del Paso 1 del Ejemplo 1) en MeOH (0.75 mL) a una solución de NaOH (0.26 g, 6.55 mmol) en MeOH/H_2O (5 mL/0.3 mL) a -30 °C. Después de 10 minutos, se añadió una solución de

clorhidrato de hidroxilamina (0.86 g, 12.4 mmol) y NaOH (0.49 g, 12.4 mmol) en MeOH (6.1 mL) y H_2O (6.1 mL). Se continuó agitando a -30 °C durante 30 minutos. A continuación, la mezcla de reacción se vertió sobre HCl concentrado (7 mL) que estaba a 80°C. La solución se agitó durante 30 minutos. El disolvente orgánico se evaporó y la fase acuosa se extrajo con éter (x3). Las fases orgánicas combinadas se secaron con Na_2SO_4 y se evaporaron para proporcionar un sólido, 2.2 g. El compuesto se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x20 DI en mm), utilizando un gradiente de 20-70% de acetonitrilo en un tampón 95/5/0.2 de H_2O/MeCN/AF, durante 18 minutos con un flujo de 19 mL/minuto. Se aisló el compuesto del título (1.1 g, 57%). ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.76 - 2.15 (m, 4H), 2.63 (m, 1H), 2.82 (m, 1H), 2.87 - 3.03 (m, 1H), 3.03 - 3.22 (m, 1H), 3.61 (s, 3H), 3.99 (m, 1H), 4.19 - 4.33 (m, 1H), 5.71 (s, 1H), 7.01 - 7.37 (m, 5H). MS m/z 317 $(M+H)^+$.

Paso 2: (2*R*,4*S*)-2-Bencil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se llevó a cabo una separación quiral del *cis*-2-bencil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo racémico (1.1 g), utilizando Chiralcel OD y una fase móvil 90/10/0.1 de heptano/EtOH/AF a 40 °C, para obtener (2*R*,4*S*)-2-bencil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.47 g).

Paso 3: 5-((2*R*,4*S*)-2-Bencilpiperidin-4-il)isoxazol-3(2*H*)-ona

Se añadió HBr (33% en HOAc, 10 mL) a (2*R*,4*S*)-2-bencil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.47 g) y la solución se agitó durante 16 h. Los componentes volátiles se concentraron y el residuo se purificó mediante HPLC preparativa en una columna XBridge C18 (10 µm 250x50 DI en mm), utilizando un gradiente de 0-40% de acetonitrilo en un tampón 95/5/0.2 de H_2O/MeCN/NH_3 durante 15 minutos con un flujo de 100 mL/minuto. Se aisló el compuesto del título (0.26 g, 29%): ^{1}H RMN (600 MHz, DMSO) δ 1.07 (m,

1H), 1.26 - 1.45 (m, 1H), 1.75 (m, 2H), 2.53 (m, 2H), 2.58 - 2.67 (m, 2H), 2.69 (m, 1H), 2.97 (m, 1H), 5.66 (s, 1H), 7.08 - 7.34 (m, 5H); $[\alpha]^{20}_{D}$ +67.8 (MeOH/H_2O 1:1, c = 1); HRMS calculado para $[C_{15}H_{19}N_2O_2]$+: 259.1447; experimental: 259.1442.

Ejemplo 4

5-((2*S*,4*R*)-2-Bencilpiperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: (2*S*,4*R*)-2-Bencil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El compuesto del título se obtuvo en el Paso 2 del Ejemplo 3 (0.47 g).

Paso 2: 5-((2*S*,4*R*)-2-Bencilpiperidin-4-il)isoxazol-3(2*H*)-ona

Siguiendo el mismo procedimiento que se ha descrito en el Paso 3 del Ejemplo 3 y utilizando (2*S*,4*R*)-2-bencil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo, se obtuvo el compuesto del título (0.23 g, 26%); HRMS calculado para $[C_{15}H_{19}N_2O_2]$+: 259.1447; experimental: 259.1433.

Ejemplo 5

5-((2*R*,4*S*)-2-Isobutilpiperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-isobutil-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo y *cis*-2-isobutil-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo

Los compuestos se prepararon como se ha descrito en el Paso 1 del Ejemplo 1, partiendo del ácido 2-isobutil-1-(metoxicarbonil)piperidin-4-carboxílico crudo (2.28 g, 9.4 mmol) (Compuesto de referencia 2), cloruro de magnesio (0.95 g, 9.95 mmol), malonato de etilo y potasio (2.5 g, 14.9 mmol) y carbonildiimidazol (1.98 g, 12.2 mmol), para obtener *trans*-2-isobutil-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (1.60 g, 54%). Isómero *trans*: ^{1}H RMN (500 MHz, $CDCl_3$) δ 0.91 (m, 6H), 1.29 (t, 3H), 1.42 - 1.98 (m, 6H), 2.48 - 2.84 (m, 3H), 3.48 (s, 2H), 3.70 (s, 3H), 3.98 - 4.28 (m, 3H), 4.30 - 4.60 (m, 1H); MS m/z 314 $(M+H)^+$ y *cis*-2-isobutil-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (0.59 g, 20%).

Isómero *cis*: ^{1}H RMN (500 MHz, $CDCl_3$) δ 0.80 (d, 3H), 0.83 (d, 3H), 1.09 (m, 1H), 1.20 (t, 3H), 1.31 - 1.54 (m, 2H), 1.60 (m, 1H), 1.69 - 1.86 (m, 2H), 1.98 (m, 1H), 2.56 - 2.68 (m, 1H), 2.91 - 3.04 (m, 1H), 3.44 (s, 2H), 3.60 (s, 3H), 3.78 (m, 1H), 4.00 - 4.17 (m, 3H); MS m/z 314 $(M+H)^+$.

Paso 2: *Trans*-2-isobutil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El compuesto se preparó como se ha descrito en el Paso 2 del Ejemplo 1, partiendo de *trans*-2-isobutil-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (1.60 g, 5.0 mmol), para obtener el producto (1.02 g, 71%): ^{1}H RMN (500 MHz, $CDCl_3$) δ 0.95 (m, 6H), 1.32 (m, 1H), 1.54 (s, 2H), 1.71 (m, 2H), 1.84 - 2.05 (m, 2H), 3.04 (m, 2H), 3.72 (s, 3H), 4.23 (s, 1H), 4.44 (s, 1H), 5.65 (s, 1H); MS m/z 283 $(M+H)^+$.

Paso 3: *Trans*-5-(2-isobutilpiperidin-4-il)isoxazol-3(2H)-ona

Se agitó *trans*-2-isobutil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo racémico (0.39 g, 1.3 mmol) en HBr (33% en HOAc) durante 16 h. Los componentes volátiles se concentraron y el residuo se purificó mediante HPLC preparativa en una columna XBridge C18 (10 µm 250x50 DI en mm), utilizando un gradiente de 0-25% de acetonitrilo en un tampón 95/5/0.2 de H_2O/MeCN/NH_3 durante 10 minutos con un flujo de 100 mL/minuto. Se aisló el compuesto del título (0.26 g). ^{1}H RMN (600 MHz, D_2O) δ 0.76 (d, 3H), 0.79 (d, 3H), 1.14 (m, 1H), 1.33 - 1.41 (m, 1H), 1.45 (m, 1H), 1.59 (m, 1H), 1.76 (m, 1H), 1.98 (m, 1H), 2.06 (m, 1H), 2.21 (m, 1H), 3.04 (m, 2H), 3.14 - 3.31 (m, 4H), 5.67 (s, 1H).

Paso 4: 5-((2*R*,4*S*)-2-Isobutilpiperidin-4-il)isoxazol-3(2*H*)-ona

Se llevó a cabo una separación quiral de la mezcla racémica de *trans*-5-(2-isobutilpiperidin-4-il)isoxazol-3(2*H*)-ona, utilizando Chiralcel CI y una fase móvil 60/40/0.4/0.2 de heptano/EtOH/AF/TEA, para obtener el compuesto del título (117

mg, 40%). $[\alpha]^{20}_D$ +21.1(H_2O, c = 1); HRMS calculado para $[C_{12}H_{21}N_2O_2]$+: 225.1603; experimental: 225.1599.

Ejemplo 6

5-((2*S*,4*R*)-2-Isobutilpiperidin-4-il)isoxazol-3(2*H*)-ona

El compuesto del título se obtuvo a partir del Paso 4 del Ejemplo 5 (113 mg, 39%). HRMS calculado para $[C_{12}H_{21}N_2O_2]$+: 225.1603; experimental: 225.1596.

Ejemplo 7

5-((2*S*,4*S*)-2-Isobutilpiperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Cis*-2-isobutil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El compuesto se preparó como se ha descrito en el Paso 2 del Ejemplo 5, partiendo de *cis*-2-isobutil-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo, obtenido en el Paso 1 del Ejemplo 5 (0.59 g, 1.9 mmol), para obtener el compuesto del título (0.29 g, 51%). ^{1}H RMN (600 MHz, $CDCl_3$) δ 0.85 (2 d, 6H), 1.15 (m, 1H), 1.29 - 1.40 (m, 1H), 1.50 (m, 1H), 1.82 - 1.93 (m, 2H), 2.04 (m, 2H), 2.91 - 3.05 (m, 1H), 3.06 - 3.20 (m, 1H), 3.69 (s, 3H), 3.93 (m, 1H), 4.17 (m, 1H), 5.70 (s, 1H). MS m/z 283 $(M+H)^+$.

Paso 2: *Cis*-5-(2-isobutilpiperidin-4-il)isoxazol-3(2*H*)-ona

Se agitó *cis*-2-isobutil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo racémico (0.29 g, 1.03 mmol) en HBr (12 mL, 33% en HOAc) durante 24 h. Los componentes volátiles se concentraron y el residuo se purificó mediante HPLC preparativa en una columna XBridge C18 (10 µm 250x50 DI en mm), utilizando un gradiente de 0-25% de acetonitrilo en un tampón 95/5/0.2 de H_2O/MeCN/NH_3 durante 10 minutos con un flujo de 100 mL/min. Se aisló el compuesto del título (160 mg). ^{1}H RMN (600 MHz, D_2O) δ 0.79 (2 d, 6H), 1.34 - 1.51 (m, 3H), 1.54 - 1.72 (m, 2H), 2.13 (m, 1H), 2.25 (m, 1H), 2.99 (m, 2H), 3.21 (m, 1H), 3.38 (m, 1H), 5.61 (s, 1H).

Paso 3: 5-((2*S*,4*S*)-2-Isobutilpiperidin-4-il)isoxazol-3(2*H*)-ona

Se llevó a cabo una separación quiral de la mezcla racémica de *cis*-5-(2-isobutilpiperidin-4-il)isoxazol-3(2*H*)-ona, utilizando Chiralpak IC y una fase móvil 60/40/0.4/0.2 de heptano/EtOH/AF/TEA, para obtener el compuesto del título (85 mg, 37%). $[\alpha]^{20}_{D}$ +19.5 (H_2O, c = 1); HRMS calculado para $[C_{12}H_{21}N_2O_2]+$: 225.1603; experimental: 225.1593.

Ejemplo 8

5-((2*R*,4*S*)-2-Fenetilpiperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-4-(3-etoxi-3-oxopropanoil)-2-fenetilpiperidin-1-carboxilato de metilo y *cis*-4-(3-etoxi-3-oxopropanoil)-2-fenetilpiperidin-1-carboxilato de metilo

Los compuestos se prepararon como se ha descrito en el Paso 1 del Ejemplo 1, partiendo del ácido 1-(metoxicarbonil)-2-fenetilpiperidin-4-carboxílico crudo (5.7 g, 19.6 mmol) (Compuesto de referencia 3), cloruro de magnesio (1.86 g, 19.6 mmol), malonato de etilo y potasio (4.99 g, 29.3 mmol) y carbonildiimidazol (3.81 g, 23.5 mmol), para obtener *trans*-4-(3-etoxi-3-oxopropanoil)-2-fenetilpiperidin-1-carboxilato de metilo (2.56 g, 36%) y *cis*-4-(3-etoxi-3-oxopropanoil)-2-fenetilpiperidin-1-carboxilato de metilo (0.29 g, 4%). Isómero *trans*: ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.28 (m, 3H), 1.49 (m, 1H), 1.60 - 1.93 (m, 4H), 2.01 (m, 1H), 2.57 (m, 2H), 2.84 (m, 2H), 3.42 (m, 2H), 3.69 (s, 3H), 4.00 - 4.63 (m, 4H), 7.08 - 7.41 (m, 5H). MS m/z 362 $(M+H)^+$. Isómero *cis*: ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.25 (t, 3H), 1.63 - 1.82 (m, 3H), 1.91 (m, 3H), 2.00 - 2.12 (m, 1H), 2.53 - 2.66 (m, 2H), 2.71 (m, 1H), 3.09 (m, 1H), 3.49 (s, 2H), 3.69 (s, 3H), 3.89 (m, 1H), 4.08 (m, 1H), 4.17 (q, 2H), 7.15 - 7.31 (m, 5H). MS m/z 362 $(M+H)^+$.

Paso 2: *Trans*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-fenetilpiperidin-1-carboxilato de metilo

Los compuestos se prepararon como se ha descrito en el Paso 2 del Ejemplo 1, partiendo de *trans*-4-(3-etoxi-3-oxopropanoil)-2-fenetilpiperidin-1-carboxilato de metilo (2.53 g, 7.0 mmol), para obtener el compuesto del título (1.35 g, 58%). ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.55 (m, 1H), 1.79 (m, 2H), 2.03

(m, 3H), 2.58 (m, 2H), 3.01 (m, 2H), 3.70 (s, 3H), 4.01 - 4.60 (m 2H), 5.62 (s, 1H), 7.05 - 7.40 (m, 5H). MS m/z 331 $(M+H)^+$.

Paso 3: (2*R*,4*S*)-4-(3-Oxo-2,3-dihidroisoxazol-5-il)-2-fenetilpiperidin-1-carboxilato de metilo

Como se describe en el Paso 3 del Ejemplo 1, se llevó a cabo una separación quiral del *trans*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-fenetilpiperidin-1-carboxilato de metilo racémico (1.35 g, 4.09 mmol), utilizando Chiralpak AD y una fase móvil 80/20 de heptano/EtOH/TEA a 30 °C, para obtener (2*R*,4*S*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-fenetilpiperidin-1-carboxilato de metilo (0.53 g, 1.6 mmol).

Paso 4: 5-((2*R*,4*S*)-2-Fenetilpiperidin-4-il)isoxazol-3(2*H*)-ona

Partiendo de (2*R*,4*S*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-fenetilpiperidin-1-carboxilato de metilo (0.53 g) y siguiendo el procedimiento del Paso 4 del Ejemplo 1, se obtuvo el compuesto del título (0.30 g, 28%). ^{1}H RMN (600 MHz, DMSO) δ 1.47 (m, 1H), 1.55 (m, 1H), 1.62 (m, 1H), 1.70 (m, 2H), 1.86 (m, 1H), 2.58 (m, 4H), 2.76 (m, 1H), 3.06 (m, 1H), 5.70 (s, 1H), 7.15 - 7.32 (m, 5H). $[\alpha]^{20}_D$ +24.6 (MeOH/H_2O 1:1, c = 1); HRMS calculado para $[C_{16}H_{21}N_2O_2]$+: 273.1603; experimental: 273.1598.

Ejemplo 9

5-((2*S*,4*R*)-2-Fenetilpiperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: (2*S*,4*R*)-4-(3-Oxo-2,3-dihidroisoxazol-5-il)-2-fenetilpiperidin-1-carboxilato de metilo

El compuesto del título se obtuvo a partir de la preparación en el Paso 3 del Ejemplo 8 (0.62 g, 1.87 mmol).

Paso 2: 5-((2*S*,4*R*)-2-Fenetilpiperidin-4-il)isoxazol-3(2*H*)-ona

Siguiendo el mismo procedimiento que se ha descrito en el Paso 4 del Ejemplo 8 y partiendo de (2*S*,4*R*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-fenetilpiperidin-1-carboxilato de metilo, se obtuvo el compuesto del título (0.62 g, 24%): $[\alpha]^{20}_D$

-23.0 (MeOH/H_2O 1:1, c = 1); HRMS calculado para $[C_{16}H_{21}N_2O_2]+$: 273.1603; experimental: 273.1592.

Ejemplo 10

5-((2*S*,4*S*)-2-Fenetilpiperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Cis*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-fenetilpiperidin-1-carboxilato de metilo

El compuesto se preparó como se ha descrito en el Paso 2 del Ejemplo 1, partiendo de *cis*-4-(3-etoxi-3-oxopropanoil)-2-fenetilpiperidin-1-carboxilato de metilo, procedente del Paso 1 del Ejemplo 8 (0.29 g, 0.82 mmol), para obtener el compuesto del título (0.07 g, 26%). ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.65 (m, 1H), 1.79 - 2.14 (m, 5H), 2.60 (m, 2H), 3.00 (m, 1H), 3.20 (m, 1H), 3.70 (s, 3H), 3.92 (m, 1H), 4.10 (m, 1H), 5.71 (s, 1H), 7.10 - 7.29 (m, 5H); MS m/z 331 $(M+H)^+$.

Paso 2: (2*S*,4*S*)-4-(3-Oxo-2,3-dihidroisoxazol-5-il)-2-fenetilpiperidin-1-carboxilato de metilo

Siguiendo el procedimiento descrito en el Paso 3 del Ejemplo 1, se llevó a cabo una separación quiral del *cis*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-fenetilpiperidin-1-carboxilato de metilo racémico (0.07 g, 0.22 mmol), utilizando Chiralcel CI y una fase móvil 80/20 de heptano/IPA a 40 °C, para obtener (2*S*,4*S*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-fenetilpiperidin-1-carboxilato de metilo (0.032 g, 0.1 mmol) y (2*R*,4*R*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-fenetilpiperidin-1-carboxilato de metilo (0.03 g, 0.09 mmol).

Paso 3: 5-((2*S*,4*S*)-2-Fenetilpiperidin-4-il)isoxazol-3(2*H*)-ona

Partiendo de (2*S*,4*S*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-fenetilpiperidin-1-carboxilato de metilo (0.032 g) y siguiendo el procedimiento descrito en el Paso 4 del Ejemplo 1, se pudo obtener el compuesto del título (12.6 mg, 21%): ^{1}H RMN (400 MHz, DMSO) δ 1.15 (m, 1H), 1.38 (m, 1H), 1.60 (m, 2H), 1.79 (m, 1H), 1.95 (m, 1H), 2.45 - 2.75 (m, 5H), 3.05 (m, 1H), 5.77 (s, 1H), 7.15 - 7.30 (m, 5H). $[\alpha]^{20}_D$ +54.1 (MeOH/H_2O 1:1, c = 1);

HRMS calculado para $[C_{16}H_{21}N_2O_2]+$: 273.1603; experimental: 273.1601.

Ejemplo 11

5-((2*S*,4*S*)-2-(4-*tert*-Butilbencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(4-*tert*-butilbencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo y *cis*-2-(4-*tert*-butilbencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo

Los compuestos se prepararon como se ha descrito en el Paso 1 del Ejemplo 1, partiendo del ácido 2-(4-*tert*-butilbencil)-1-(metoxicarbonil)piperidin-4-carboxílico crudo (3.07 g, 9.2 mmol) (Compuesto de referencia 4), cloruro de magnesio (0.88 g, 9.2 mmol) y malonato de etilo y potasio (2.35 g, 13.8 mmol) y a continuación carbonildiimidazol (1.98 g, 12.2 mmol), para obtener *trans*-2-(4-*tert*-butilbencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (0.55 g, 15%) y *cis*-2-(4-*tert*-butilbencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (1.65 g, 44%). Isómero *trans*: ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.08 - 1.32 (m, 12H), 1.32 -1.78 (m, 4H), 2.53 - 3.06 (m, 4H), 3.30 - 3.62 (m, 5H), 3.93 - 4.61 (m, 4H), 7.03 - 7.36 (m, 4H); MS m/z 404 $(M+H)^+$. Isómero *cis*: ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.21 - 1.35 (m, 12H), 1.59 - 1.79 (m, 1H), 1.79 - 1.99 (m, 3H), 2.69 (m, 2H), 2.84 - 2.94 (m, 1H), 2.94 - 3.07 (m, 1H), 3.45 (s, 2H), 3.61 (m, 3H), 3.92 (m, 1H), 4.08 - 4.22 (m, 3H), 7.09 (m, 2H), 7.25 - 7.32 (m, 2H); MS m/z 404 $(M+H)^+$.

Paso 2: *Trans*-2-(4-*tert*-butilbencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El compuesto se preparó como se ha descrito en el Paso 2 del Ejemplo 1, partiendo de *trans*-2-(4-*tert*-butilbencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (0.54 g, 1.34 mmol), para obtener *trans*-2-(4-*tert*-butilbencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.24 g, 48%); ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.29 (s, 9H), 1.41 -

1.60 (m, 2H), 1.89 - 2.09 (m, 2H), 2.87 (m, 2H), 3.03 - 3.20 (m, 2H), 3.42 - 3.73 (m, 3H), 4.06 - 4.32 (m, 1H), 4.45 - 4.77 (m, 1H), 5.63 (s, 1H), 7.02 - 7.17 (m, 2H), 7.31 (m, 2H); MS m/z 373 $(M+H)^+$.

Paso 3: (2*S*,4*S*)-2-(4-*tert*-Butilbencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Siguiendo el procedimiento descrito en el Paso 3 del Ejemplo 1, se llevó a cabo una separación quiral del *trans*-2-(4-*tert*-butilbencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo racémico (0.24 g, 0.64 mmol), utilizando Chiralcel AD y una fase móvil 80/20/0.1 de heptano/EtOH/AF, para obtener (2*S*,4*S*)-2-(4-*tert*-butilbencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.106 g, 0.28 mmol).

Paso 4: 5-((2*S*,4*S*)-2-(4-*tert*-Butilbencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Partiendo de (2*S*,4*S*)-2-(4-*tert*-butilbencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.106 g, 0.28 mmol) y siguiendo el procedimiento descrito en el Paso 4 del Ejemplo 1, se obtuvo el compuesto del título (50.3 mg, 25%): ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.29 (s, 9H), 1.43 - 1.74 (m, 1H), 1.81 - 2.07 (m, 3H), 2.60 (m, 3H), 2.82 (m, 2H), 3.11 (m, 1H), 5.71 (s, 1H), 7.08 (d, 2H), 7.27 (d, 2H); $[\alpha]^{20}_D$ +56.7 (MeOH/H_2O 1:1, c = 1); HRMS calculado para $[C_{19}H_{27}N_2O_2]$+: 315.2072; experimental: 315.2069.

Ejemplo 12

5-((2*R*,4*S*)-2-(4-*tert*-Butilbencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Cis*-2-(4-*tert*-butilbencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Los compuestos se prepararon como se ha descrito en el Paso 2 del Ejemplo 1, partiendo de *cis*-2-(4-*tert*-butilbencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (1.64 g, 4.06 mmol), para obtener *cis*-2-(4-*tert*-butilbencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-piperidin-1-carboxilato de

metilo (0.69 g, 47%). ^{1}H RMN (500 MHz, $CDCl_3$) δ 1.31 (s, 9H), 1.84 - 1.93 (m, 2H), 1.96 (m, 1H), 2.10 (m, 1H), 2.62 (m, 1H), 2.82 (m, 2H), 2.97 (m, 1H), 3.08 - 3.24 (m, 1H), 3.62 (s, 3H), 4.02 (m, 1H), 4.18 - 4.34 (m, 1H), 5.73 (s, 1H), 7.06 (m, 2H), 7.23 - 7.38 (m, 2H). MS m/z 373 $(M+H)^+$.

Paso 2: (2*R*,4*S*)-2-(4-*tert*-Butilbencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Siguiendo el procedimiento descrito en el Paso 3 del Ejemplo 1, se llevó a cabo una separación quiral del *cis*-2-(4-*tert*-butilbencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo racémico (0.69 g, 1.85 mmol), utilizando Chiralcel AD y una fase móvil 80/20/0.1 de heptano/EtOH/AF, para obtener (2*R*,4*S*)-2-(4-*tert*-butilbencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.32 g, 0.86 mmol).

Paso 3: 5-((2*R*,4*S*)-2-(4-*tert*-Butilbencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Utilizando (2*R*,4*S*)-2-(4-*tert*-butilbencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.32 g, 0.86 mmol) y siguiendo el procedimiento descrito en el Paso 4 del Ejemplo 1, se pudo obtener el compuesto del título (0.125 g, 22%). ^{1}H RMN (600 MHz, DMSO) δ 1.05 (m, 1H), 1.23 (m, 9H), 1.34 (m, 1H), 1.74 (m, 2H), 2.50 - 2.80 (m, 5H), 2.96 (m, 1H), 5.63 (s, 1H), 7.08 (m, 2H), 7.27 (m, 2H). $[\alpha]^{20}_D$ -7.5 ($CHCl_3$ c = 0.2). HRMS calculado para $[C_{19}H_{27}N_2O_2]$+: 315.2072; experimental: 315.2058.

Ejemplo 13

5-((2*S*,4*S*)-2-Neopentilpiperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-4-(3-etoxi-3-oxopropanoil)-2-neopentilpiperidin-1-carboxilato de metilo

El compuesto se preparó como se ha descrito en el Paso 1 del Ejemplo 1, partiendo del ácido 1-(metoxicarbonil)-2-neopentilpiperidin-4-carboxílico crudo (4.95 g, 19.2 mmol) (Compuesto de referencia 5), cloruro de magnesio (2.381 g, 25.01 mmol), malonato de etilo y potasio (5.57 g, 32.70 mmol) y

carbonildiimidazol (3.74 g, 23.08 mmol), para obtener *cis*-4-(3-etoxi-3-oxopropanoil)-2-neopentilpiperidin-1-carboxilato de metilo (2.40 g, 38%) y *trans*-4-(3-etoxi-3-oxopropanoil)-2-neopentilpiperidin-1-carboxilato de metilo (1.2 g, 19%). Isómero *cis*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 0.93 (m, 9H), 1.18 (m, 1H), 1.28 (t, 3H), 1.52 - 1.65 (m, 1H), 1.65 - 1.83 (m, 2H), 1.89 (m, 1H), 2.12 (m, 1H), 2.69 (m, 1H), 3.11 (m, 1H), 3.52 (s, 2H), 3.69 (s, 3H), 3.87 (m, 1H), 4.15 - 4.24 (m, 2H), 4.27 (m, 1H); MS m/z 328 $(M+H)^+$.

Paso 2: *Trans*-2-neopentil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Los compuestos se prepararon como se ha descrito en el Paso 2 del Ejemplo 1, partiendo de *trans*-4-(3-etoxi-3-oxopropanoil)-2-neopentilpiperidin-1-carboxilato de metilo (4.49 g, 13.7 mmol), para obtener *trans*-2-neopentil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.26 g, 31%). ^{1}H RMN (600 MHz, $CDCl_3$) δ 0.94 (s, 9H), 1.34 (m, 1H), 1.40 - 1.62 (m, 1H), 1.71 (m, 2H), 1.83 (m, 1H), 1.97 (m, 1H), 3.05 (m, 2H), 3.70 (s, 3H), 4.01 - 4.31 (m, 1H), 4.44 - 4.74 (m, 1H), 5.62 (s, 1H). MS m/z 297 $(M+H)^+$.

Paso 3: (2*S*,4*S*)-2-Neopentil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Siguiendo el procedimiento descrito en el Paso 3 del Ejemplo 1, se llevó a cabo una separación quiral del *trans*-2-neopentil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo racémico (1.26 g, 4.26 mmol), utilizando Chiralcel OD y una fase móvil 80/20/0.1 de heptano/IPA/AF, para obtener (2*S*,4*S*)-2-neopentil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.64 g, 2.16 mmol).

Paso 4: (2*S*,4*S*)-5-(2-Neopentilpiperidin-4-il)isoxazol-3(2*H*)-ona

Partiendo de (2*S*,4*S*)-2-neopentil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.64 g, 2.16 mmol) y siguiendo el procedimiento descrito en el Paso 4 del Ejemplo 1, se obtuvo el compuesto del título (0.44 g, 85%):

^{1}H RMN (600 MHz, DMSO) δ 0.86 (s, 9H), 1.17 (dd, 1H), 1.27 (dd, 1H), 1.45 (m, 1H), 1.68 (m, 2H), 1.81 (m, 1H), 2.59 (m, 1H), 2.67 (m, 1H), 2.73 (m, 1H), 3.04 (m, 2H), 5.71 (s, 1H); $[\alpha]^{20}_D$ +18.4 (MeOH/H_2O 1:1, c = 1); HRMS calculado para $[C_{13}H_{23}N_2O_2]$+: 239.1759; experimental: 239.1742.

Ejemplo 14

5-((2*R*,4*S*)-2-Neopentilpiperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Cis*-2-neopentil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El compuesto se preparó como se ha descrito en el Paso 2 del Ejemplo 1, partiendo de *cis*-4-(3-etoxi-3-oxopropanoil)-2-neopentilpiperidin-1-carboxilato de metilo (2.68 g, 8.19 mmol), para obtener *cis*-2-neopentil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.60 g, 66%): ^{1}H RMN (400 MHz, $CDCl_3$) δ 0.89 (s, 9H), 1.18 (dd, 1H), 1.45 (dd, 1H), 1.80 - 1.92 (m, 2H), 1.97 - 2.17 (m, 2H), 2.94 - 3.02 (m, 1H), 3.11 - 3.23 (m, 1H), 3.71 (s, 3H), 3.88 - 3.99 (m, 1H), 4.22 - 4.32 (m, 1H), 5.72 (s, 1H); m/z (MH^+) 297.

Paso 2: (2*R*,4*S*)-2-Neopentil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Siguiendo el procedimiento descrito en el Paso 3 del Ejemplo 1, se llevó a cabo una separación quiral del *cis*-2-neopentil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo racémico (1.60 g, 5.4 mmol), utilizando Chiralcel IC y una fase móvil 60/40/0.1 de heptano/IPA/AF, para obtener (2*R*,4*S*)-2-neopentil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.8 g, 2.7 mmol).

Paso 3: 5-((2*R*,4*S*)-2-Neopentilpiperidin-4-il)isoxazol-3(2*H*)-ona

Partiendo de (2*R*,4*S*)-2-neopentil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.8 g, 2.7 mmol) y siguiendo el procedimiento descrito en el Paso 4 del Ejemplo 1, se obtuvo el compuesto del título (0.44 g, 69%): ^{1}H RMN (600 MHz, DMSO-d6) δ 0.89 (s, 9H), 1.18 (m, 2H), 1.50 (m, 2H), 1.82-1.90 (m, 2H), 2.70-2.85 (m, 3H), 3.08 (m, 1H),

5.71 (s, 1H). $[\alpha]^{20}_D$ +43.8 (MeOH/H_2O 1:1, c = 1); HRMS calculado para $[C_{13}H_{23}N_2O_2]$+: 239.1759; experimental: 239.1753.

Ejemplo 15

5-((2*R*,4*S*)-2-Metilpiperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-4-(3-etoxi-3-oxopropanoil)-2-metilpiperidin-1-carboxilato de metilo y *cis*-4-(3-etoxi-3-oxopropanoil)-2-metilpiperidin-1-carboxilato de metilo

Los compuestos se prepararon como se ha descrito en el Paso 1 del Ejemplo 1, partiendo del ácido 1-(metoxicarbonil)-2-metilpiperidin-4-carboxílico crudo (0.90 g, 4.47 mmol) (Compuesto de referencia 6), cloruro de magnesio (0.42 g, 4.47 mmol) y malonato de etilo y potasio (1.14 g, 6.71 mmol) y a continuación carbonildiimidazol (0.87 g, 5.47 mmol), para obtener *trans*-4-(3-etoxi-3-oxopropanoil)-2-metilpiperidin-1-carboxilato de metilo (0.31 g, 26%) y *cis*-4-(3-etoxi-3-oxopropanoil)-2-metilpiperidin-1-carboxilato de metilo (0.50 g, 41%). Isómero *trans*: ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.18 (dd, 3H), 1.23 - 1.31 (m, 3H), 1.47 (m, 1H), 1.65 - 1.78 (m, 2H), 1.85 (m, 1H), 2.82 (m, 1H), 2.91 (m, 1H), 3.48 (s, 2H), 3.68 (s, 3H), 3.99 - 4.14 (m, 1H), 4.15 - 4.23 (m, 2H), 4.57 (m, 1H). Isómero *cis*: ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.13 (d, 3H), 1.22 - 1.32 (m, 3H), 1.63 - 1.73 (m, 1H), 1.78 - 1.94 (m, 2H), 1.95 - 2.07 (m, 1H), 2.67 - 2.76 (m, 1H), 3.04 - 3.16 (m, 1H), 3.50 (s, 2H), 3.68 (s, 3H), 3.79 - 3.91 (m, 1H), 4.12 (m, 1H), 4.15 (m, 2H).

Paso 2: *Trans*-2-metil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El compuesto se preparó como se ha descrito en el Paso 2 del Ejemplo 1, partiendo de *trans*-4-(3-etoxi-3-oxopropanoil)-2-metilpiperidin-1-carboxilato de metilo (0.31 g, 1.15 mmol), para obtener *trans*-2-metil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.149 g, 54%); ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.21 (m, 3H), 1.49 - 1.59 (m, 1H), 1.76 (m, 1H), 1.86 (m, 1H), 1.99 (m, 1H), 3.02 (m, 2H), 3.69 (m, 3H), 4.13 (m, 1H), 4.59 (m, 1H), 5.64 (s, 1H). MS m/z 241 $(M+H)^+$.

Paso 3: (2*R*,4*S*)-2-Metil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Siguiendo el procedimiento descrito en el Paso 3 del Ejemplo 1, se llevó a cabo una separación quiral del *trans*-2-metil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo racémico (0.149 g, 0.62 mmol), utilizando Chiralcel OJ y una fase móvil 80/20 de heptano/EtOH a 22 °C, para obtener (2*R*,4*S*)-2-metil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.051 g, 0.21 mmol).

Paso 4: 5-((2*R*,4*S*)-2-Metilpiperidin-4-il)isoxazol-3(2*H*)-ona

Partiendo de (2*R*,4*S*)-2-metil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.051 g, 0.21 mmol) y siguiendo el procedimiento descrito en el Paso 4 del Ejemplo 1, se obtuvo el compuesto del título (32 mg, 84 %): ^{1}H RMN (600 MHz, CD3OD) δ 1.31 (d, 3H), 1.79 - 1.89 (m, 1H), 2.02 - 2.25 (m, 3H), 3.04 - 3.13 (m, 1H), 3.26 (d, 2H), 3.38 (m, 1H), 5.66 (s, 1H); $[\delta]^{20}_D$ +8.4 (MeOH/H_2O 1:1, c = 1).

Ejemplo 16

5-((2*S*,4*R*)-2-Metilpiperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: (2*S*,4*R*)-2-metil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se obtuvo el compuesto del título a partir del Paso 3 del Ejemplo 15 (62 mg, 0.26 mmol).

Paso 2: 5-((2*S*,4*R*)-2-Metilpiperidin-4-il)isoxazol-3(2*H*)-ona

Utilizando el mismo procedimiento descrito en el Paso 4 del Ejemplo 1 y partiendo de (2*S*,4*R*)-2-metil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (62 mg, 0.26 mmol), se obtuvo el compuesto del título (30 mg 64%).

Ejemplo 17

5-((2*S*,4*S*)-2-Metilpiperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Cis*-2-metil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El compuesto se preparó como se ha descrito en el Paso 2 del Ejemplo 1, partiendo de *cis*-4-(3-etoxi-3-oxopropanoil)-2-metilpiperidin-1-carboxilato de metilo (0.49 g, 1.83 mmol), para obtener *cis*-2-metil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.23 g, 52%); ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.08 (d, 3H), 1.86 (m, 2H), 2.05 (m, 2H), 2.96 - 3.02 (m, 1H), 3.12 - 3.30 (m, 1H), 3.69 (s, 3H), 3.83 - 3.99 (m, 1H), 4.19 (m, 1H), 5.70 (s, 1H); MS m/z 241 $(M+H)^+$.

Paso 2: (2*S*,4*S*)-2-Metil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Siguiendo el procedimiento descrito en el Paso 3 del Ejemplo 1, se llevó a cabo una separación quiral del *cis*-2-metil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo racémico (0.23 g, 0.96 mmol), utilizando Chiralcel IC y una fase móvil 70/30 de heptano/IPA, para obtener (2*S*,4*S*)-2-metil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.101 g, 0.42 mmol).

Paso 3: 5-((2*S*,4*S*)-2-Metilpiperidin-4-il)isoxazol-3(2*H*)-ona

Partiendo de (2*S*,4*S*)-2-metil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.101 g, 0.42 mmol) y siguiendo el procedimiento descrito en el Paso 4 del Ejemplo 1, se obtuvo el compuesto del título (0.046 g, 60%) ^{1}H RMN (600 MHz, CD3OD) δ 1.32 - 1.44 (d, 3H), 1.65 (m, 1H), 1.84 (m, 1H), 2.24 (m, 2H), 3.08 - 3.23 (m, 2H), 3.34 - 3.52 (m, 2H), 5.82 (s, 1H); $[\alpha]^{20}_D$ +0 (MeOH/H_2O 1:1, c = 1).

Ejemplo 18

5-((2*S*,4*S*)-2-(2-Metil-2-fenilpropil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-4-(3-etoxi-3-oxopropanoil)-2-(2-metil-2-fenilpropil)piperidin-1-carboxilato de metilo y *cis*-4-(3-etoxi-3-oxopropanoil)-2-(2-metil-2-fenilpropil)piperidin-1-carboxilato de metilo

Los compuestos se prepararon como se ha descrito en el Paso 1 del Ejemplo 1, partiendo del ácido 1-(metoxicarbonil)-2-

(2-metil-2-fenilpropil)piperidin-4-carboxílico crudo (7.24 g, 22.7 mmol) (Compuesto de referencia 7), cloruro de magnesio (2.16 g, 22.7 mmol) y malonato de etilo y potasio (5.79 g, 34 mmol) y a continuación carbonildiimidazol (4.41 g, 27.2 mmol), para obtener *trans*-4-(3-etoxi-3-oxopropanoil)-2-(2-metil-2-fenilpropil)piperidin-1-carboxilato de metilo (1.59 g, 18%) y *cis*-4-(3-etoxi-3-oxopropanoil)-2-(2-metil-2-fenilpropil)piperidin-1-carboxilato de metilo (2.38 g, 27%). Isómero *trans*: ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.20 - 1.50 (m, 10H), 1.59 - 1.84 (m, 2H), 1.90 (m, 2H), 2.50 - 2.89 (m, 2H), 3.16 (m, 2H), 3.58 (m, 4H), 4.17 (m, 4H), 7.06 - 7.51 (m, 5H). Isómero *cis*: ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.20 - 1.41 (m, 10H), 1.57 - 1.74 (m, 3H), 1.79 (d, 1H), 2.03 (m, 1H), 2.53 (m, 1H), 2.83 - 3.02 (m, 1H), 3.40 (m, 2H), 3.48 - 3.68 (m, 4H), 4.03 (m, 1H), 4.12 - 4.22 (m, 2H), 7.18 - 7.44 (m, 5H).

Paso 2: *Trans*-2-(2-metil-2-fenilpropil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El compuesto se preparó como se ha descrito en el Paso 2 del Ejemplo 1, partiendo de *trans*-4-(3-etoxi-3-oxopropanoil)-2-(2-metil-2-fenilpropil)piperidin-1-carboxilato de metilo (1.58 g, 4.06 mmol), para obtener *trans*-2-(2-metil-2-fenilpropil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.82 g, 56%); ^{1}H RMN (600 MHz, CDCl3) δ 1.29 - 1.65 (m, 6H), 1.67 - 1.98 (m, 4H), 2.10 (m, 2H), 2.88 (m, 2H), 3.57 (s, 3H), 3.70 - 4.18 (m, 1H), 4.18 - 4.67 (m, 1H), 5.45 (s, 1H), 7.17-7.31 (m, 5H); MS m/z 359 $(M+H)^+$.

Paso 3: (2*S*,4*S*)-2-(2-Metil-2-fenilpropil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se llevó a cabo una separación quiral del *trans*-2-(2-metil-2-fenilpropil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo racémico (0.82 g, 2.28 mmol), utilizando Chiralcel IC y una fase móvil 80/20 de heptano/IPA a 40 °C, para obtener (2*S*,4*S*)-2-(2-metil-2-fenilpropil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.361 g, 1.01 mmol).

Paso 4: 5-((2*S*,4*S*)-2-(2-Metil-2-fenilpropil)piperidin-4-il)isoxazol-3(2*H*)-ona

Partiendo de (2*S*,4*S*)-2-(2-metil-2-fenilpropil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.361 g, 1.01 mmol) y siguiendo el procedimiento descrito en el Paso 4 del Ejemplo 1, se obtuvo el compuesto del título (0.21 g, 69%) ^{1}H RMN (600 MHz, DMSO) δ 1.24 (m, 7H), 1.45 (m, 1H), 1.59 (m, 2H), 1.69 (m, 2H), 2.42 (m, 1H), 2.59 (m, 2H), 2.87 (m, 1H), 5.36 (s, 1H), 7.12 (m, 1H), 7.21 - 7.36 (m, 4H); $[\alpha]^{20}_D$ +66.7 (MeOH/H_2O 1:1, c = 1); HRMS calculada para $[C_{18}H_{25}N_2O_2]$+: 301.1916; experimental: 301.1888.

Ejemplo 19

5-((2*R*,4*S*)-2-(2-Metil-2-fenilpropil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Cis*-2-(2-metil-2-fenilpropil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El compuesto se preparó como se ha descrito en el Paso 2 del Ejemplo 1, partiendo de *cis*-4-(3-etoxi-3-oxopropanoil)-2-(2-metil-2-fenilpropil)piperidin-1-carboxilato de metilo (2.38 g, 6.11 mmol), para obtener *cis*-2-(2-metil-2-fenilpropil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.93 g, 42%); ^{1}H RMN (500 MHz, $CDCl_3$) δ 1.31 (s, 3H), 1.37 (s, 3H), 1.53 - 1.67 (m, 2H), 1.77 (m, 2H), 1.90 - 2.01 (m, 2H), 2.80 - 2.91 (m, 1H), 2.95 - 3.06 (m, 1H), 3.60 (s, 3H), 3.69 (m, 1H), 4.01 - 4.15 (m, 1H), 5.63 (s, 1H), 7.17 (m, 1H), 7.30 (m, 4H); MS m/z 359 $(M+H)^+$.

Paso 2: (2*R*,4*S*)-2-(2-Metil-2-fenilpropil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se llevó a cabo una separación quiral del *cis*-2-(2-metil-2-fenilpropil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo racémico (0.93 g, 2.59 mmol), utilizando Chiralcel IC y una fase móvil 80/20 de heptano/IPA a una temperatura de 40 °C, para obtener (2*R*,4*S*)-2-(2-metil-2-fenilpropil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.432 g, 1.21 mmol).

Paso 3: 5-((2*R*,4*S*)-2-(2-Metil-2-fenilpropil)piperidin-4-il)isoxazol-3(2*H*)-ona

Partiendo de (2*R*,4*S*)-2-(2-metil-2-fenilpropil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.432 g, 1.21 mmol) y siguiendo el procedimiento descrito en el Paso 4 del Ejemplo 1, se obtuvo el compuesto del título (0.16 g, 43%); ^{1}H RMN (600 MHz, DMSO) δ 1.08 (m, 1H), 1.28 (s, 3H), 1.34 (m, 4H), 1.46 (m, 1H), 1.76 - 1.83 (m, 1H), 1.83 - 1.97 (m, 2H), 2.73 (m, 1H), 2.86 (m, 1H), 2.97 (m, 1H), 3.17 (m, 1H), 5.46 (s, 1H), 7.16 (m, 1H), 7.28 (m, 2H), 7.35 (m, 2H); $[\alpha]^{20}_D$ +57.9 (MeOH/H_2O 1:1, c = 1); HRMS calculado para $[C_{18}H_{25}N_2O_2]$+: 301.1916; experimental: 301.1892.

Ejemplo 20

5-((2*R*,4*S*)-2-(Ciclohexilmetil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: 2-(Ciclohexilmetil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo

Se añadieron malonato de etilo y potasio (1.75 g, 10.3 mmol) y $MgCl_2$ (0.665 g, 6.88 mmol) a THF anhidro (50 mL). El matraz de reacción se agitó enérgicamente durante 4 h a 50 °C (matraz 1). Se añadieron el ácido 2-(ciclohexilmetil)-1-(metoxicarbonil)piperidin-4-carboxílico (1.95 g, 6.88 mmol) (compuesto de referencia 8) y carbonildiimidazol (1.34 g, 8.26 mmol) a THF anhidro (50 mL) a 5 °C (matraz 2). El contenido del matraz 2 se añadió al matraz 1 a temperatura ambiente. La mezcla de reacción se evaporó para eliminar la mayor parte del THF. El crudo se repartió entre agua y éter dietílico. La fase orgánica se aisló, se secó con $MgSO_4$, se filtró a través de Celite® y se evaporó el disolvente. El residuo se purificó mediante cromatografía en columna automatizada utilizando un equipo Biotage. La elución en gradiente utilizando acetato de etilo-heptano se inició en 15-85 y finalizó en 40-60, para obtener *trans*-2-(ciclohexilmetil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (0.38 g, 16%) y *cis*-2-(ciclohexilmetil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-

carboxilato de metilo (1.28 g, 53%). Isómero *trans*: ^{1}H RMN (600 MHz, $CDCl_3$) δ 0.88 (d, 2H), 0.99 - 1.32 (m, 8H), 1.38 - 1.56 (m, 2H), 1.68 (dd, 8H), 2.80 (t, 2H), 3.45 (s, 2H), 3.66 (s, 3H), 3.93 - 4.21 (m, 3H), 4.47 (d, 1H). Isómero *cis*: ^{1}H RMN (600 MHz, $CDCl_3$) δ 0.72 - 0.95 (m, 2H), 1.04 - 1.31 (m, 8H), 1.38 - 1.49 (m, 1H), 1.53 - 1.69 (m, 6H), 1.70 - 1.92 (m, 3H), 2.02 (dt, 1H), 2.61 - 2.71 (m, 1H), 2.95 - 3.07 (m, 1H), 3.48 (s, 2H), 3.66 (s, 3H), 3.85 (dd, 1H), 4.09 - 4.21 (m, 3H).

Paso 2: (2*R*,4*S*)-2-(Ciclohexilmetil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Una solución de 2-(ciclohexilmetil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (1.5 g, 4.2 mmol) en MeOH (4 mL), se añadió a una solución de NaOH (221 mg, 5.5 mmol) en MeOH/H_2O (4 mL/ 0.25 mL) a -30 °C. Después de 10 minutos, se añadió hidroxilamina-HCl (0.59 g, 8.5 mmol) y NaOH (0.339 g, 8.5 mmol) en MeOH (5 mL) y H_2O (5 mL). Se continuó agitando a -30 °C durante 30 minutos. La solución de la reacción se vertió sobre HCl 6 M (6 mL) a 80 °C y se calentó durante 30 minutos. La mezcla de reacción se repartió entre agua y acetato de etilo. La fase orgánica se aisló, se secó con Na_2SO_4, se filtró a través de Celite® y se evaporó el disolvente. Crudo: 1.7 g. La purificación utilizando cromatografía de fase inversa proporcionó 0.3 g, con un rendimiento del 22%. La separación quiral, utilizando Chiralcel OJ y una fase móvil 80/20 de heptano/etanol a 40 °C, proporcionó (2*R*,4*S*)-2-(ciclohexilmetil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.11 g). ^{1}H RMN (600 MHz, $CDCl_3$) δ 0.91 (d, 2H), 1.06 - 1.39 (m, 5H), 1.68 (dt, 7H), 1.85 (s, 2H), 1.94 (s, 1H), 2.99 (t, 2H), 3.68 (s, 3H), 4.11 (d, 1H), 4.50 (d, 1H), 5.60 (s, 1H). $[\alpha]^{20}_D$ +3.2 (MeCN, c = 1).

Paso 3: 5-((2*R*,4*S*)-2-(Ciclohexilmetil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se añadió HBr (33% en ácido acético) (7 mL) a un matraz de reacción que contenía (2*R*,4*S*)-2-(ciclohexilmetil)-4-(3-oxo-2,3-

dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.11 g, 0.34 mmol). La reacción se agitó enérgicamente durante toda la noche. Se evaporó el disolvente. La purificación utilizando HPLC preparativa (pH = 11, columna pequeña, muestra disuelta en metanol/agua (50/50), gradiente de 0-40, 20 minutos) proporcionó el compuesto del título (62 mg, rendimiento del 69%). ^{1}H RMN (600 MHz, CD_3OD) δ 0.94 (s, 2H), 1.18 (s, 1H), 1.27 (s, 2H), 1.35 - 1.55 (m, 3H), 1.57 - 1.80 (m, 6H), 2.01 (s, 1H), 2.13 (s, 1H), 2.24 (s, 1H), 3.09 (s, 1H), 3.22 (s, 3H), 5.53 (s, 1H).

Ejemplo 21

5-((2*R*,4*R*)-2-(Ciclohexilmetil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: (2*R*,4*R*)-2-(Ciclohexilmetil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo y (2*S*,4*S*)-2-(ciclohexilmetil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se añadió gota a gota una solución de *cis*-2-(ciclohexilmetil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo, procedente de un preparado del Paso 1 del Ejemplo 20 (1.28 g, 3.62 mmol) en MeOH (3 mL), a una solución de NaOH (0.159 g) en MeOH/H_2O (3 mL/0.2 mL) a -30 °C. Después de agitar durante 10 minutos, se añadió una solución de clorhidrato de hidroxilamina (0.50 g, 7.24 mmol) y NaOH (0.29 g, 7.24 mmol) en metanol/agua (5 mL/5 mL) a -30 °C. Se continuó agitando durante 30 minutos a -30 °C. La solución se añadió gota a gota a HCl (6M) a 80 °C. Se agitó durante 30 minutos a 80 °C. La mezcla de reacción se repartió entre agua y acetato de etilo. La fase orgánica se aisló, se secó con Na_2SO_4, se filtró a través de Celite® y se evaporó el disolvente. La cromatografía de fase inversa acídica, utilizando un gradiente de 35% a 75% de acetonitrilo, proporcionó *cis*-2-(ciclohexilmetil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.62 g, 53.1%). La separación quiral utilizando Chiralpac IC y una fase móvil 80/20 de heptano/alcohol isopropílico a una temperatura de 40 °C proporcionó (2*R*,4*R*)-2-(ciclohexilmetil)-4-(3-oxo-2,3-

dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.28 g) con un 98.5% de ee y (2*S*,4*S*)-2-(ciclohexilmetil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.27 g) con un 98.5% de ee. ^{1}H RMN (600 MHz, $CDCl_3$, *RR*) δ 0.67 - 0.88 (m, 2H), 0.98 - 1.20 (m, 5H), 1.28 (dd, 1H), 1.56 (dd, 5H), 1.75 - 1.86 (m, 2H), 1.92 - 2.06 (m, 2H), 2.87 - 2.99 (m, 1H), 3.02 - 3.15 (m, 1H), 3.65 (s, 3H), 3.88 (dd, 1H), 4.15 (q, 1H), 5.65 (d, 1H). $[\alpha]^{20}_D$ -30.7 (MeCN, c = 1); ^{1}H RMN (600 MHz, $CDCl_3$, *SS*) δ 0.70 - 0.87 (m, 2H), 0.97 - 1.20 (m, 5H), 1.28 (dd, 1H), 1.51 - 1.65 (m, 5H), 1.77 - 1.85 (m, 2H), 1.96 - 2.05 (m, 2H), 2.87 - 2.96 (m, 1H), 3.03 - 3.14 (m, 1H), 3.65 (s, 3H), 3.88 (dd, 1H), 4.15 (q, 1H), 5.65 (d, 1H) $[\alpha]^{20}_D$ +29.9 (MeCN, c = 1).

Paso 2: 5-((2*R*,4*R*)-2-(Ciclohexilmetil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se añadió HBr (33% en ácido acético) (5 mL) a (2*R*,4*R*)-2-(ciclohexilmetil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.28 g, 0.87 mmol). La reacción se agitó enérgicamente durante toda la noche. Se evaporó el disolvente. La purificación se llevó a cabo utilizando LC prep. (pH = 11, columna pequeña, sin inyección de tipo sándwich, muestra disuelta en metanol/agua (50/50), gradiente de 15-55, 20 minutos). Se obtuvo el compuesto del título (57 mg, 25%). ^{1}H RMN (400 MHz, CD_3OD) δ 0.78 - 0.95 (m, 2H), 1.17 (dd, 3H), 1.28 - 1.48 (m, 4H), 1.63 (dd, 6H), 2.04 (d, 1H), 2.12 (d, 1H), 2.85 (t, 1H), 2.96 (dd, 1H), 3.13 (s, 1H), 3.31 (d, 1H), 5.40 (s, 1H).

Ejemplo 22

5-((2*S*,4*S*)-2-(Ciclohexilmetil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se añadió HBr (33% en ácido acético) (5 ml) a (2*S*,4*S*)-2-(ciclohexilmetil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo, procedente de un preparado del Paso 1 del Ejemplo 21 (0.27 g, 0.85 mmol). La reacción se agitó enérgicamente durante toda la noche. Se evaporó el disolvente.

La purificación utilizando HPLC preparativa (pH = 11, columna pequeña, muestra disuelta en acetonitrilo/agua (40/60), gradiente de 15-55, 20 minutos) proporcionó el compuesto del título (75 mg, 33%). ^{1}H RMN (600 MHz, CD_3OD) δ 0.80 - 0.95 (m, 2H), 1.03 - 1.27 (m, 3H), 1.29 - 1.47 (m, 4H), 1.53 - 1.72 (m, 6H), 2.05 (d, 1H), 2.13 (d, 1H), 2.82 - 2.90 (m, 1H), 2.97 (td, 1H), 3.13 (s, 1H), 3.31 (d, 1H), 5.40 (s, 1H).

Ejemplo 23

5-((2*R*,4*S*)-2-(3,4-Difluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(3,4-difluorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo y *cis*-2-(3,4-difluorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo

Se disolvió el ácido 2-(3,4-difluorofenil)-1-(metoxicarbonil)piperidin-4-carboxílico (5.655 g, 18.90 mmol) (compuesto de referencia 9) en THF (60 mL) y se añadió di(1*H*-imidazol-1-il)metanona (4.60 g, 28.34 mmol). La suspensión se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 5 h (matraz 1). En otro matraz, se suspendieron la sal potásica del ácido 3-etoxi-3-oxopropanoico (6.47 g, 37.79 mmol) y cloruro de magnesio (3.60 g, 37.79 mmol) en THF (60 mL) y se agitó con un imán grande a 50 °C en una atmósfera de nitrógeno durante 5 h. A continuación, la suspensión blanca del matraz 2 se añadió al matraz 1. La suspensión blanca densa se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se acidificó añadiendo HCl 3 M hasta pH 1. El disolvente se evaporó al vacío. Se añadieron EtOAc (250 mL) y agua, se agitó y se separaron las fases. La fase orgánica se lavó con agua (200 mL), $NaHCO_3$ sat. (200 mL) y salmuera (200 mL), se secó con un separador de fases y se evaporó al vacío. El residuo se purificó mediante cromatografía flash automatizada en una columna Biotage® con 100 g de KP-SIL. Se utilizó como fase móvil un gradiente de 10 % de EtOAc en heptano en 2 VC y a continuación de 10 % a 40 % de EtOAc en heptano en 9 VC. Se obtuvieron el *cis*-2-(3,4-difluorofenil)-4-(3-etoxi-3-

oxopropanoil)piperidin-1-carboxilato de metilo (5.23 g, 74,9%) y el *trans*-2-(3,4-difluorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (0.502 g, 7.19%). Isómero *cis*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.23 - 1.30 (m, 3H), 1.74 - 2.18 (m, 3H), 2.22 - 2.30 (m, 1H), 2.82 - 2.91 (m, 1H), 3.24 - 3.37 (m, 1H), 3.44 (d, 2H), 3.65 (s, 3H), 4.05 - 4.22 (m, 1H), 4.18 (q, 2H), 4.85 - 4.98 (m, 1H), 6.90 - 6.97 (m, 1H), 6.98 - 7.05 (m, 1H), 7.05 - 7.14 (m, 1H). MS m/z 370 $(M+H)^+$. Isómero *trans*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.23 - 1.32 (m, 3H), 1.51 - 2.02 (m, 3H), 2.42 - 2.53 (m, 1H), 2.59 - 2.71 (m, 1H), 2.77 - 2.88 (m, 1H), 3.47 (d, 2H), 3.76 (s, 3H), 4.19 (c, 2H), 4.14 - 4.33 (m, 1H), 5.47 - 5.66 (m, 1H), 6.90 - 6.97 (m, 1H), 6.99 - 7.07 (m, 1H), 7.11 - 7.20 (m, 1H). MS m/z 370 $(M+H)^+$.

Paso 2: *Cis*-2-(3,4-difluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *cis*-2-(3,4-difluorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (5.23 g, 14.16 mmol) en MeOH (50 mL) y se enfrió hasta -40 °C. Se añadió hidróxido sódico (3.73 mL, 14.16 mmol) disuelto en agua (5.00 mL) y la reacción se agitó a -40 °C durante 40 min. Se añadió hidroxilamina (0.868 mL, 14.16 mmol) y se continuó agitando durante 3.5 h a -40 °C. Posteriormente, la mezcla de reacción se añadió a una solución calentada previamente a 80 °C de ácido clorhídrico 6 M (73.2 mL, 438.95 mmol) y se agitó durante 20 min. El disolvente se concentró al vacío. Se añadieron DCM (200 mL) y agua (150 mL), se agitó y se separaron las fases. La fase acuosa se extrajo con DCM (150 mL). Las fases orgánicas combinadas se secaron con un separador de fases y se evaporaron al vacío. El compuesto se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x50 DI en mm) utilizando un gradiente de 20-60% de acetonitrilo en un tampón 95/5/0.2 de H_2O/MeCN/AcOH en 25 minutos con un flujo de 100 mL/min. Se aisló *cis*-2-(3,4-difluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (3.41 g, 71.2%) como un sólido blanco. ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.81 - 1.88 (m, 1H),

2.08 - 2.18 (m, 1H), 2.19 - 2.28 (m, 1H), 2.30 - 2.38 (m, 1H), 3.02 - 3.11 (m, 1H), 3.32 - 3.40 (m, 1H), 3.67 (s, 3H), 4.09 - 4.18 (m, 1H), 5.02 - 5.08 (m, 1H), 5.56 (s, 1H), 6.86 - 6.92 (m, 1H), 6.95 - 7.01 (m, 1H), 7.03 - 7.10 (m, 1H). MS m/z 339 $(M+H)^+$.

Paso 3: (2*R*,4*S*)-2-(3,4-Difluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El *cis*-2-(3,4-difluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (3.41 g, 10 mmol) se sometió a HPLC preparativa quiral (columna: Lux Cell2 (250x30), tamaño de partícula: 5 µm, fase móvil: 15% de MeOH en CO_2 (175 bar), velocidad de flujo: 130 mL/min, temperatura: 40 °C) para proporcionar (2*R*,4*S*)-2-(3,4-difluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.70 g, 50%), pureza quiral: 99.0 % de ee, rotación óptica $[\alpha]_D^{20} = +49.9$ (acetonitrilo, c=1). ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.81 - 1.87 (m, 1H), 2.09 - 2.17 (m, 1H), 2.20 - 2.28 (m, 1H), 2.31 - 2.37 (m, 1H), 3.02 - 3.09 (m, 1H), 3.32 - 3.41 (m, 1H), 3.67 (s, 3H), 4.10 - 4.16 (m, 1H), 5.03 - 5.08 (m, 1H), 5.56 (s, 1H), 6.87 - 6.92 (m, 1H), 6.95 - 7.01 (m, 1H), 7.03 - 7.09 (m, 1H).

Paso 4: 5-((2*R*,4*S*)-2-(3,4-Difluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-2-(3,4-difluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.7 g, 5.03 mmol) en ácido bromhídrico (al 33% en AcOH, 25 mL, 151.92 mmol) y se agitó a temperatura ambiente durante 20 h. El disolvente se evaporó al vacío. El compuesto se purificó mediante HPLC preparativa en una columna XBridge C18 (10 µm 250x50 DI en mm) utilizando un gradiente de 5-30% de acetonitrilo en un tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 25 minutos con un flujo de 100 mL/min. El compuesto se volvió a purificar mediante HPLC preparativa en una columna XBridge C18 (10 µm 250x50 DI en mm) utilizando un gradiente de 0-30% de acetonitrilo en un tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 25 minutos con un flujo de 100 mL/min. Se aisló 5-((2*R*,4*S*)-2-(3,4-

difluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona (0.923 g, 65.5%) como un sólido blanco. ^{1}H RMN (600 MHz, CD_3OD) δ 1.66 - 1.76 (m, 2H), 2.09 (d, 1H), 2.19 (d, 1H), 2.96 - 3.07 (m, 2H), 3.28 - 3.35 (señales omitidas), 3.90 - 3.95 (m, 1H), 5.65 (s, 1H), 7.20 - 7.29 (m, 2H), 7.34 - 7.39 (m, 1H). HRMS calculado para $[C_{14}H_{14}F_2N_2O_2+H]^+$: 281.1101; experimental: 281.1106.

Ejemplo 24

5-(*Trans*-2-(3,4-difluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(3,4-difluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *trans*-2-(3,4-difluorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (502 mg, 1.36 mmol) (procedente del Paso 1 del Ejemplo 23) en MeOH (5 mL) y se enfrió hasta -40 °C. Se añadió hidróxido sódico (0.358 mL, 1.36 mmol) disuelto en agua (0.500 mL) y la reacción se agitó a -40 °C durante 20 min. Se añadió hidroxilamina (0.083 mL, 1.36 mmol) y se continuó agitando durante 3.5 h a - 40 °C. Posteriormente, la mezcla de reacción se añadió a una solución calentada previamente a 80 °C de ácido clorhídrico (7.02 mL, 42.13 mmol) y se agitó durante 20 min. El disolvente se evaporó al vacío. Se añadieron DCM (50 mL) y agua (50 mL), se agitó y se separaron las fases. La fase acuosa se extrajo con DCM (50 mL). Las fases orgánicas combinadas se secaron con un separador de fases y se evaporaron al vacío. El compuesto se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x50 DI en mm) utilizando un gradiente de 20-60% de acetonitrilo en un tampón 95/5/0.2 de H_2O/MeCN/AcOH en 25 minutos con un flujo de 100 mL/min. Se aisló *trans*-2-(3,4-difluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (242 mg, 52.6%) como un sólido blanco. ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.60 - 1.72 (m, 1H), 1.94 (d, 1H), 1.98 - 2.07 (m, 1H), 2.60 (d, 1H), 2.78 - 2.94 (m, 2H), 3.77 (s, 3H), 4.25 (s, 1H), 5.51 - 5.71 (m, 2H), 6.94 - 6.99 (m, 1H), 7.02 - 7.09 (m, 1H), 7.17 (dd, 1H). MS m/z 337 $(M-H)^-$.

Paso 2: 5-(*Trans*-2-(3,4-difluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió *trans*-2-(3,4-difluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (242 mg, 0.72 mmol) en ácido bromhídrico (al 33% en AcOH, 4 mL, 24.31 mmol) y se agitó a temperatura ambiente durante 20 h. El disolvente se evaporó al vacío. El residuo se purificó mediante HPLC preparativa (instrumento: Agilent, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5µm OBD 19*150 mm) para proporcionar 5-(*trans*-2-(3,4-difluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona (137 mg, 68%). ^{1}H RMN (600 MHz, DMSO) δ 1.74 - 1.81 (m, 2H), 1.84 - 1.89 (m, 1H), 1.98 - 2.03 (m, 1H), 2.65 - 2.71 (m, 1H), 2.81 (dt, 1H), 3.09 - 3.13 (m, 1H), 3.70 (dd, 1H), 5.96 (s, 1H), 7.18 - 7.22 (m, 1H), 7.30 - 7.36 (m, 1H), 7.39 - 7.44 (m, 1H). HRMS calculado para $[C_{14}H_{14}F_2N_2O_2+H]^+$: 281.1101; experimental: 281.1114.

Ejemplo 25

5-((2*R*,4*S*)-2-(4-Fluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-4-(3-etoxi-3-oxopropanoil)-2-(4-fluorofenil)piperidin-1-carboxilato de metilo y *cis*-4-(3-etoxi-3-oxopropanoil)-2-(4-fluorofenil)piperidin-1-carboxilato de metilo

Se disolvió el ácido 2-(4-difluorofenil)-1-(metoxicarbonil)piperidin-4-carboxílico (8.4 g, 29.86 mmol) (compuesto de referencia 10) en metil-THF (120 mL) y se añadió di(1*H*-imidazol-1-il)metanona (7.26 g, 44.80 mmol). La suspensión se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 2 h (matraz 1). En otro matraz, se suspendió 3-etoxi-3-oxopropanoato de potasio (9.15 g, 53.75 mmol) en metil-THF (120 mL) y se añadió cloruro de magnesio (5.12 g, 53.75 mmol). La suspensión se agitó a 50 °C en atmósfera de nitrógeno durante 3 h utilizando un imán muy grande (matraz 2). A continuación, la suspensión beis del matraz 1 se añadió a la suspensión blanca del matraz 2. La suspensión beis resultante

se agitó en una atmósfera de nitrógeno a temperatura ambiente durante 23 h. La mezcla se acidificó hasta pH 1 con HCl 3 M (50 mL) y se añadieron MTBE (200 mL) y agua (70 mL). Se separaron las fases y la fase orgánica se extrajo con agua (30 mL), $NaHCO_3$ sat. (30 mL) y agua (30 mL), se secó con Na_2SO_4 y se evaporó. Los diastereoisómeros se separaron en una columna Biotage (20 % => 55 % de EtOAc en heptano, 8 CV; columna Biotage® con 340 g de KP-SIL) para proporcionar *trans*-4-(3-etoxi-3-oxopropanoil)-2-(4-fluorofenil)piperidin-1-carboxilato de metilo (1.26 g, 12%) y *cis*-4-(3-etoxi-3-oxopropanoil)-2-(4-fluorofenil)piperidin-1-carboxilato de metilo (6.58 g, 62%) como aceites incoloros. Isómero *cis*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.27 (t, 3H), 1.83 - 2.14 (m, 3H), 2.27 (ddd, 1H), 2.80 - 2.93 (m, 1H), 3.26 - 3.50 (m, 3H), 3.64 (s, 3H), 4.10 - 4.22 (m, 3H), 4.93 - 5.01 (m, 1H), 6.95 - 7.05 (m, 2H), 7.14 - 7.22 (m, 2H). MS m/z 352 $(M+H)^+$. Isómero *trans*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.18 - 1.33 (m, 3H), 1.50 - 1.89 (m, 2H), 1.90 - 2.02 (m, 1H), 2.47 - 2.59 (m, 1H), 2.59 - 2.72 (m, 1H), 2.79 - 2.91 (m, 1H), 3.47 (s, 2H), 3.76 (s, 3H), 4.08 - 4.30 (m, 3H), 5.50 - 5.69 (s a, 1H), 6.98 - 7.10 (m, 2H), 7.10 - 7.23 (m, 2H). MS m/z 350 $(M-H)^-$.

Paso 2: <u>*Cis*-2-(4-fluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo</u>

Se disolvió *cis*-4-(3-etoxi-3-oxopropanoil)-2-(4-fluorofenil)piperidin-1-carboxilato de metilo (6.58 g, 18.7 mmol) en MeOH (50 mL) y se enfrió hasta -40 °C en una atmósfera de nitrógeno. Se añadió hidróxido sódico (0.749 g, 18.73 mmol) disuelto en agua (5.00 mL) durante 10 min y se continuó agitando la solución incolora a -40 °C durante 20 min. Se añadió hidroxilamina (al 50 % en peso en agua, 1.148 mL, 18.73 mmol) durante 8 min. La solución resultante se agitó a -40 °C durante 3 h 20 min. La mezcla se transfirió a una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (94 mL, 561.80 mmol) y se continuó agitando la mezcla a 80 °C durante 20 min. El disolvente se evaporó y se añadieron DCM/agua. Las fases se separaron y la fase orgánica se hizo pasar a través de

un separador de fases y se evaporó para proporcionar 5.8 g de un sólido amarillo. Se purificaron 2.9 g de este sólido mediante HPLC preparativa en 3 inyecciones en una columna XBridge C18 (10 µm 250x50 DI en mm) utilizando un gradiente de 30-75% de acetonitrilo en un tampón 95/5/0.2 de H_2O/MeCN/HOAc en 15 minutos con un flujo de 100 mL/min. Se aisló *cis*-2-(4-fluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.7 g, 28%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.79 - 1.90 (m, 1H), 2.08 - 2.40 (m, 3H), 3.01 - 3.12 (m, 1H), 3.32 - 3.44 (m, 1H), 3.67 (s, 3H), 4.15 (ddd, 1H), 5.05 - 5.14 (m, 1H), 5.54 (s, 1H), 6.92 - 7.02 (m, 2H), 7.10 - 7.18 (m, 2H). MS m/z 321 $(M+H)^+$.

Paso 3: (2*R*,4*S*)-2-(4-Fluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El *cis*-2-(4-fluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.7 g, 5,3 mmol) se sometió a HPLC preparativa quiral (columna: Chiralcel OJ (250x20), tamaño de partícula: 20 µm, fase móvil: EtOH, velocidad de flujo: 118 mL/min) para proporcionar (2*R*,4*S*)-2-(4-fluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (860 mg, 50%), pureza quiral: 99.9% de ee, rotación óptica $[\alpha]_D^{20} = +57.0$ (acetonitrilo, c=1).

Paso 4: 5-((2*R*,4*S*)-2-(4-Fluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-2-(4-fluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.86 g, 2.68 mmol) en bromuro de hidrógeno (al 33% en ácido acético, 15.52 mL, 88.60 mmol) y la solución se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (instrumento: Agilent, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: XBridge Prep C18 5 µm OBD 19*150 mm) y en una columna XBridge C18 (10 µm 250x19 DI en mm), utilizando un gradiente de 0 - 30% de acetonitrilo en un tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 20 minutos con un flujo de 19 mL/min. Se aisló

5-((2*R*,4*S*)-2-(4-fluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona (167 mg, 23%). ^{1}H RMN (400 MHz, DMSO) δ 1.27 - 1.53 (m, 2H), 1.81 - 1.98 (m, 2H), 2.67 - 2.77 (m, 1H), 2.78 - 2.91 (m, 1H), 3.10 (d, 1H), 3.63 (d, 1H), 5.67 - 5.77 (m, 1H), 7.04 -7.16 (m, 2H), 7.34 - 7.45 (m, 2H). HRMS calculado para $[C_{14}H_{15}FN_2O_2+H]^+$: 263.1196. Experimental: 263.1201.

Ejemplo 26

5-(*Trans*-2-(4-fluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(4-fluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *trans*-4-(3-etoxi-3-oxopropanoil)-2-(4-fluorofenil)piperidin-1-carboxilato de metilo (1.26 g, 3.59 mmol) (procedente del Paso 1 del Ejemplo 25) en MeOH (50 mL) y se enfrió hasta -40 °C en una atmósfera de nitrógeno. Se añadió hidróxido sódico (0.143 g, 3.59 mmol) disuelto en agua (5.00 mL) durante 5 min y se continuó agitando la solución incolora a -40 °C durante 20 min. Se añadió hidroxilamina (al 50 % en peso en agua, 0.220 mL, 3.59 mmol) durante 8 min. La solución resultante se agitó a -40 °C durante 3 h 20 min. La mezcla se transfirió a una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (17.93 mL, 107.58 mmol) y se continuó agitando la mezcla a 80 °C durante 20 min. El disolvente se evaporó y se añadieron DCM/agua. Las fases se separaron y la fase orgánica se hizo pasar a través de un separador de fases y se evaporó para proporcionar *trans*-2-(4-fluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.1 g, 95%) como un sólido marrón, 1.1 g. MS m/z 321 $(M+H)^+$.

Paso 2: 5-(*Trans*-2-(4-fluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió *trans*-2-(4-fluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.3 g, 0.94 mmol) en bromuro de hidrógeno (al 33% en ácido acético, 6 mL, 34.26 mmol) y la solución se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (instrumento: Agilent, fase

móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm). Se aisló 5-(*trans*-2-(4-fluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona (54 mg, 22%). ^{1}H RMN (400 MHz, DMSO) δ 1.75 - 2.10 (m, 4H), 2.67 - 2.77 (m, 1H), 2.80 - 2.89 (m, 1H), 3.11 - 3.18 (m, 1H), 3.70 (d, 1H), 5.94 (s, 1H), 7.07 - 7.15 (m, 2H), 7.36 - 7.43 (m, 2H). HRMS calculado para $[C_{14}H_{15}FN_2O_2+H]^+$: 263.1196. Experimental: 263.1201.

Ejemplo 27

5-((2*R*,4*S*)-2-(4-Clorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(4-clorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo y *cis*-2-(4-clorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo

Se disolvió el ácido 2-(4-clorofenil)-1-(metoxicarbonil)piperidin-4-carboxílico (3.49 g, 11.72 mmol) (compuesto de referencia 11) en metil-THF (120 mL) y a continuación se añadió di(1*H*-imidazol-1-il)metanona (2.85 g, 17.58 mmol). La mezcla se agitó a temperatura ambiente en atmósfera de nitrógeno durante 3 h (matraz 1). En otro matraz, se suspendió 3-etoxi-3-oxopropanoato de potasio (3.59 g, 21.10 mmol) en metil-THF (120 mL) y a continuación se añadió cloruro de magnesio (2.009 g, 21.10 mmol). La suspensión se agitó a 50 °C en una atmósfera de nitrógeno durante 3 h utilizando un imán grande (matraz 2). El contenido del matraz 1 se transfirió al matraz 2. La suspensión blanca resultante se agitó a temperatura ambiente en una atmósfera de nitrógeno durante toda la noche. La mezcla se acidificó hasta pH 1 con HCl 3.8 M y a continuación se añadieron MTBE (50 mL) y agua (50 mL). Las fases se separaron, y la fase orgánica se lavó con agua, $NaHCO_3$ sat. y salmuera. La fase orgánica se secó con Na_2SO_4, se filtró y se evaporó para obtener un aceite amarillento. El residuo se purificó mediante cromatografía en columna automatizada en una columna Biotage (340 g) con un gradiente de 20-60% de EtOAc en *n*-heptano (8 VC), para proporcionar *trans*-2-(4-clorofenil)-4-

(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (205 mg, 5%) y *cis*-2-(4-clorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (2.27 g, 53%). Isómero *cis*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.21 - 1.32 (m, 3H), 1.82 - 2.15 (m, 3H), 2.22 - 2.31 (m, 1H), 2.81 - 2.92 (m, 1H), 3.26 - 3.49 (m, 3H), 3.63 (s, 3H), 4.06 - 4.22 (m, 3H), 4.91 - 4.99 (m, 1H), 7.11 - 7.18 (m, 2H), 7.24 - 7.31 (m, 2H). MS m/z 366 $(M-H)^-$. Isómero *trans*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.16 - 1.33 (m, 3H), 1.47 - 2.02 (m, 3H), 2.43 - 2.70 (m, 2H), 2.75 - 2.91 (m, 1H), 3.42 - 3.48 (m, 2H), 3.74 (s, 3H), 4.00 - 4.39 (m, 3H), 5.45 - 5.71 (s a, 1H), 7.14 (d, 2H), 7.29 - 7.35 (m, 2H). MS m/z 368 $(M+H)^+$.

Paso 2: <u>*Cis*-2-(4-clorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo</u>

Se disolvió *cis*-2-(4-clorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (2.11 g, 5.74 mmol) en MeOH (24 mL) y se enfrió hasta -40 °C en una atmósfera de nitrógeno. Se añadió hidróxido sódico (1.687 mL, 5.74 mmol) durante 10 min y la solución amarilla se continuó agitando a -40 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.352 mL, 5.74 mmol) durante 8 min. La solución resultante se agitó a -40 °C durante 3 h. A continuación, la mezcla se vertió rápidamente sobre una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (29.5 mL, 177.26 mmol) y la mezcla se continuó agitando a 80 °C durante 20 min. El disolvente se evaporó y se añadieron DCM/agua. Las fases se separaron y la fase orgánica se hizo pasar a través de un separador de fases y se evaporó para proporcionar un sólido blanco. El compuesto se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x50 DI en mm) utilizando un gradiente de 10-60% de acetonitrilo en un tampón 95/5/0.2 de H_2O/MeCN/AcOH en 30 minutos con un flujo de 100 mL/min. Se aisló *cis*-2-(4-clorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (923 mg, 47%). MS m/z 337 $(M+H)^+$.

Paso 3: <u>(2*R*,4*S*)-2-(4-Clorofenil)-4-(3-oxo-2,3-</u>

dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo y (2*S*,4*R*)-2-(4-clorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El *cis*-2-(4-clorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (923 mg, 2.75 mmol) se sometió a HPLC preparativa quiral (columna: ReproSil (250x50), tamaño de partícula de 8 µm, fase móvil: EtOH, velocidad de flujo: 100 mL/min) para proporcionar (2*R*,4*S*)-2-(4-clorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (447 mg, 48%), pureza quiral: 99.9% de ee, rotación óptica $[\alpha]_D^{20} = +67.7$ (acetonitrilo, c=1), ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.79 - 1.89 (m, 1H), 2.07 - 2.40 (m, 3H), 3.01 - 3.11 (m, 1H), 3.33 - 3.43 (m, 1H), 3.66 (s, 3H), 4.10 - 4.19 (m, 1H), 5.07 (dd, 1H), 5.55 (s, 1H), 7.08 - 7.14 (m, 2H), 7.23 - 7.28 (m, 2H) y (2*S*,4*R*)-2-(4-clorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-piperidin-1-carboxilato de metilo (458 mg, 49%), pureza quiral: 99.6% de ee, rotación óptica $[\alpha]_D^{20} = -67.6$ (acetonitrilo, c=1), ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.79 - 1.88 (m, 1H), 2.07 - 2.38 (m, 3H), 3.02 - 3.10 (m, 1H), 3.33 - 3.43 (m, 1H), 3.66 (s, 3H), 4.11 - 4.18 (m, 1H), 5.04 - 5.09 (m, 1H), 5.54 (s, 1H), 7.09 - 7.13 (m, 2H), 7.23 - 7.28 (m, 2H).

Paso 4: 5-((2*R*,4*S*)-2-(4-Clorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-2-(4-clorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.447 g, 1.33 mmol) en ácido bromhídrico (al 33% en ácido acético, 10.46 mL, 59.73 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*S*)-2-(4-clorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona (233 mg, 63%). ^{1}H RMN (600 MHz, DMSO) δ 1.32 (c, 1H), 1.44 (dc, 1H), 1.82 - 1.88 (m, 1H), 1.90 - 1.97 (m, 1H), 2.71 (dt, 1H), 2.80 - 2.88 (m, 1H), 3.06 - 3.12 (m,

1H), 3.63 (dd, 1H), 5.70 (s, 1H), 7.31 - 7.35 (m, 2H), 7.35 - 7.40 (m, 2H). HRMS calculado para $[C_{14}H_{15}ClN_2O_2+H]^+$: 279.0900. Experimental: 279.0905.

Ejemplo 28

5-((2*S*,4*R*)-2-(4-Clorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*S*,4*R*)-2-(4-clorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.458 g, 1.36 mmol) (procedente del Paso 3 del Ejemplo 27) en ácido bromhídrico (al 33% en ácido acético, 10.72 mL, 61.20 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*S*,4*R*)-2-(4-clorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona (198 mg, 52%). ^{1}H RMN (600 MHz, DMSO) δ 1.32 (c, 1H), 1.44 (dc, 1H), 1.83 - 1.88 (m, 1H), 1.91 - 1.96 (m, 1H), 2.71 (dt, 1H), 2.84 (tt, 1H), 3.07 - 3.11 (m, 1H), 3.63 (dd, 1H), 5.70 (s, 1H), 7.31 - 7.40 (m, 4H). HRMS calculado para $[C_{14}H_{15}N_2O_2+H]^+$: 279.0900. Experimental: 279.0887.

Ejemplo 29

5-(*Trans*-2-(4-clorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(4-clorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *trans*-2-(4-clorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (184 mg, 0.50 mmol) (procedente del Paso 1 del Ejemplo 27) en MeOH (2 mL) y se enfrió hasta -40 °C en una atmósfera de nitrógeno. Se añadió hidróxido sódico (0.147 mL, 0.50 mmol) durante 10 min y la solución amarilla se continuó agitando a -40 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.031 mL, 0.50 mmol) durante 8 min. La solución resultante se agitó a -40 °C durante 3 h. A continuación, la mezcla se vertió rápidamente sobre una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (2.58 mL, 15.46 mmol) y la mezcla se continuó

agitando a 80 °C durante 20 min. El disolvente se evaporó y se añadieron DCM/agua. Las fases se separaron y la fase orgánica se hizo pasar a través de un separador de fases y se evaporó para proporcionar *trans*-2-(4-clorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (155 mg, 92%) como un aceite amarillento. MS m/z 337 $(M+H)^+$.

Paso 2: 5-(*Trans*-2-(4-clorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió *trans*-2-(4-clorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (155 mg, 0.46 mmol) en ácido bromhídrico (al 33% en ácido acético, 3.63 mL, 20.71 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-(*trans*-2-(4-clorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona (23.5 mg, 18%). ^{1}H RMN (600 MHz, DMSO) δ 1.74 - 1.83 (m, 2H), 1.84 - 1.91 (m, 1H), 1.96 - 2.03 (m, 1H), 2.70 (dt, 1H), 2.79 - 2.86 (m, 1H), 3.09 - 3.15 (m, 1H), 3.69 (dd, 1H), 5.89 - 5.98 (m, 1H), 7.32 - 7.36 (m, 2H), 7.36 - 7.41 (m, 2H). HRMS calculado para $[C_{14}H_{15}ClN_2O_2+H]^+$: 279.0900. Experimental: 279.0889.

Ejemplo 30

5-((2*R*,4*S*)-2-(3-(Trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-4-(3-etoxi-3-oxopropanoil)-2-(3-(trifluorometil)fenil)piperidin-1-carboxilato de metilo y *cis*-4-(3-etoxi-3-oxopropanoil)-2-(3-(trifluorometil)fenil)piperidin-1-carboxilato de metilo

Se disolvió el ácido 1-(metoxicarbonil)-2-(3-(trifluorometil)fenil)piperidin-4-carboxílico (1.479 g, 4.46 mmol) (compuesto de referencia 12) en metil-THF (50 mL) y a continuación se añadió di(1*H*-imidazol-1-il)metanona (1.086 g, 6.70 mmol). La mezcla se agitó a temperatura ambiente en atmósfera de nitrógeno durante 3 h (matraz 1). En otro matraz,

se suspendió 3-etoxi-3-oxopropanoato de potasio (1.368 g, 8.04 mmol) en metil-THF (50.0 mL) y a continuación se añadió cloruro de magnesio (0.765 g, 8.04 mmol). La suspensión se agitó a 50 °C en una atmósfera de nitrógeno durante 3 h utilizando un imán grande (matraz 2). El contenido del matraz 1 se transfirió al matraz 2. La suspensión blanca resultante se agitó a temperatura ambiente en una atmósfera de nitrógeno durante toda la noche. La mezcla se acidificó hasta pH 1 con HCl 3.8 M y a continuación se añadieron MTBE (50 mL) y agua (50 mL). Las fases se separaron, y la fase orgánica se lavó con agua, $NaHCO_3$ sat. y salmuera. La capa orgánica se secó con Na_2SO_4, se filtró y se evaporó para obtener un aceite amarillento. El residuo se purificó mediante cromatografía en columna automatizada en una columna Biotage (340 g) con un gradiente de 20-55% de EtOAc en *n*-heptano (8 VC), para proporcionar *trans*-4-(3-etoxi-3-oxopropanoil)-2-(3-(trifluorometil)fenil)-piperidin-1-carboxilato de metilo (157 mg, 9%) y *cis*-4-(3-etoxi-3-oxopropanoil)-2-(3-(trifluorometil)fenil)piperidin-1-carboxilato de metilo (679 mg, 38%). Isómero *cis*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.19 - 1.27 (m, 3H), 1.75 - 2.20 (m, 3H), 2.23 - 2.32 (m, 1H), 2.82 - 2.94 (m, 1H), 3.26 - 3.48 (m, 3H), 3.61 (s, 3H), 4.05 - 4.21 (m, 3H), 4.91 - 5.04 (m, 1H), 7.35 - 7.50 (m, 4H). MS m/z 402 $(M+H)^+$. Isómero *trans*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.16 - 1.32 (m, 3H), 1.46 - 2.09 (m, 4H), 2.48 - 2.90 (m, 2H), 3.40 - 3.50 (m, 2H), 3.75 (s, 3H), 4.02 - 4.42 (m, 3H), 5.65 (s a, 1H), 7.36 - 7.56 (m, 4H). MS m/z 402 $(M+H)^+$.

Paso 2: *Cis*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3-(trifluorometil)fenil)piperidin-1-carboxilato de metilo

Se disolvió *cis*-4-(3-etoxi-3-oxopropanoil)-2-(3-(trifluorometil)fenil)piperidin-1-carboxilato de metilo (679 mg, 1.69 mmol) en MeOH (8 mL) y se enfrió hasta -40 °C en una atmósfera de nitrógeno. Se añadió hidróxido sódico (0.498 mL, 1.69 mmol) disuelto en agua (0.800 mL) durante 10 min y la solución amarilla se continuó agitando a -40 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.104 mL, 1.69 mmol) durante 8 min. La solución resultante se agitó a -40 °C

durante 3 h. A continuación, la mezcla se vertió rápidamente sobre una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (8.71 mL, 52.27 mmol) y la mezcla se continuó agitando a 80 °C durante 20 min. El disolvente se evaporó y se añadieron DCM/agua. Las fases se separaron y la fase orgánica se hizo pasar a través de un separador de fases y se evaporó para proporcionar un sólido blanco. El compuesto se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x50 DI en mm) utilizando un gradiente de 10-60% de acetonitrilo en un tampón 95/5/0.2 de H_2O/MeCN/AcOH en 30 minutos con un flujo de 100 mL/min. Se aisló *cis*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3-(trifluorometil)fenil)piperidin-1-carboxilato de metilo (311 mg, 50%). MS m/z 371 $(M+H)^+$.

Paso 3: (2*R*,4*S*)-4-(3-Oxo-2,3-dihidroisoxazol-5-il)-2-(3-(trifluorometil)fenil)piperidin-1-carboxilato de metilo y (2*S*,4*R*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3-(trifluorometil)fenil)piperidin-1-carboxilato de metilo

El *cis*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3-(trifluorometil)fenil)piperidin-1-carboxilato de metilo (311 mg, 0.84 mmol) se sometió a HPLC preparativa quiral (columna: Chiralpak IC (250x20), tamaño de partícula: 5 µm, fase móvil: 40/60 de heptano/IPA, velocidad de flujo: 12 mL/min) para proporcionar (2*R*,4*S*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3-(trifluorometil)fenil)piperidin-1-carboxilato de metilo (155 mg, 50%), pureza quiral: 99.9% de ee, rotación óptica $[\alpha]_D^{20} = +54.4$ (acetonitrilo, c=1), ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.78 - 1.90 (m, 1H), 2.08 - 2.42 (m, 3H), 3.01 - 3.13 (m, 1H), 3.34 - 3.48 (m, 1H), 3.65 (s, 3H), 4.09 - 4.22 (m, 1H), 5.08 - 5.19 (m, 1H), 5.53 (s, 1H), 7.31 - 7.50 (m, 4H) y (2*S*,4*R*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3-(trifluorometil)fenil)piperidin-1-carboxilato de metilo (152 mg, 49%), pureza quiral: 99.9% de ee, rotación óptica $[\alpha]_D^{20} = -55.7$ (acetonitrilo, c=1), ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.80 - 1.90 (m, 1H), 2.11 - 2.32 (m, 2H), 2.33 - 2.42 (m, 1H), 3.02 - 3.12 (m, 1H), 3.36 - 3.47 (m, 1H), 3.66 (s, 3H), 4.12 - 4.21 (m, 1H), 5.11 - 5.17 (m, 1H), 5.53 (s,

1H), 7.33 - 7.48 (m, 4H).

Paso 4: 5-((2*R*,4*S*)-2-(3-(Trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3-(trifluorometil)fenil)piperidin-1-carboxilato de metilo (0.155 g, 0.42 mmol) en ácido bromhídrico (al 33% en ácido acético, 3.30 mL, 18.83 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*S*)-2-(3-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona (43 mg, 33%). ^{1}H RMN (600 MHz, DMSO) δ 1.35 (c, 1H), 1.47 (dc, 1H), 1.87 (d, 1H), 2.00 (d, 1H), 2.69 - 2.77 (m, 1H), 2.83 - 2.91 (m, 1H), 3.08 - 3.14 (m, 1H), 3.75 (d, 1H), 5.74 (s, 1H), 7.50 - 7.55 (m, 1H), 7.55 - 7.59 (m, 1H), 7.64 - 7.68 (m, 1H), 7.71 (s, 1H). HRMS calculado para $[C_{15}H_{15}F_3N_2O_2+H]^+$: 313.1164. Experimental: 313.1144.

Ejemplo 31

5-((2*S*,4*R*)-2-(3-(Trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*S*,4*R*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3-(trifluorometil)fenil)piperidin-1-carboxilato de metilo (0.152 g, 0.42 mmol) (procedente del Paso 3 del Ejemplo 30) en ácido bromhídrico (al 33% en ácido acético, 3.30 mL, 18.83 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*S*,4*R*)-2-(3-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona (28 mg, 22%). ^{1}H RMN (600 MHz, DMSO) δ 1.35 (c, 1H), 1.47 (cd, 1H), 1.87 (d, 1H), 2.00 (d, 1H), 2.73 (dt, 1H), 2.84 - 2.91 (m, 1H), 3.09 - 3.14 (m, 1H), 3.75 (d, 1H), 5.74 (s, 1H), 7.50 - 7.54 (m, 1H), 7.55 - 7.58 (m, 1H), 7.66 (d, 1H),

7.71 (s, 1H). HRMS calculado para $[C_{15}H_{15}F_3N_2O_2+H]^+$: 313.1164. Experimental: 313.1158.

Ejemplo 32

5-(*Trans*-2-(3-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3-(trifluorometil)fenil)piperidin-1-carboxilato de metilo

Se disolvió *trans*-4-(3-etoxi-3-oxopropanoil)-2-(3-(trifluorometil)fenil)piperidin-1-carboxilato de metilo (157 mg, 0.39 mmol) (procedente del Paso 1 del Ejemplo 30) en MeOH (2 mL) y se enfrió hasta -40 °C en una atmósfera de nitrógeno. Se añadió hidróxido sódico (0.115 mL, 0.39 mmol) disuleto en agua (0.200 mL) durante 10 min y la solución amarilla se continuó agitando a -40 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.024 mL, 0.39 mmol) durante 8 min. La solución resultante se agitó a -40 °C durante 3 h 15 min. A continuación, la mezcla se vertió rápidamente sobre una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (2.014 mL, 12.09 mmol) y la mezcla se continuó agitando a 80 °C durante 20 min. El disolvente se evaporó y se añadieron DCM/agua. Las fases se separaron y la fase orgánica se hizo pasar a través de un separador de fases y se evaporó para proporcionar *trans*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3-(trifluorometil)fenil))piperidin-1-carboxilato de metilo crudo (128 mg, 88%) como un sólido blanco. MS m/z 371 $(M+H)^+$.

Paso 2: 5-(*Trans*-2-(3-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió *trans*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3-(trifluorometil)fenil)piperidin-1-carboxilato de metilo (0.128 g, 0.35 mmol) en ácido bromhídrico (al 33% en ácido acético, 2.72 mL, 15.55 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-(*trans*-2-(3-

(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona (31 mg, 28%). ^{1}H RMN (600 MHz, DMSO) δ 1.77 - 1.86 (m, 2H), 1.86 - 1.93 (m, 1H), 2.01 - 2.08 (m, 1H), 2.71 (dt, 1H), 2.81 - 2.87 (m, 1H), 3.11 - 3.16 (m, 1H), 3.76 - 3.83 (m, 1H), 5.99 (s, 1H), 7.50 - 7.55 (m, 1H), 7.55 - 7.59 (m, 1H), 7.64 - 7.68 (m, 1H), 7.72 (s, 1H). HRMS calculado para $[C_{15}H_{15}F_3N_2O_2+H]^+$: 313.1164. Experimental: 313.1153.

Ejemplo 33

5-((2*R*,4*S*)-2-(4-(Trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-4-(3-etoxi-3-oxopropanoil)-2-(4-(trifluorometil)fenil)piperidin-1-carboxilato de metilo y *cis*-4-(3-etoxi-3-oxopropanoil)-2-(4-(trifluorometil)fenil)piperidin-1-carboxilato de metilo

Se disolvió el ácido 1-(metoxicarbonil)-2-(4-(trifluorometil)fenil)piperidin-4-carboxílico (5.629 g, 16.99 mmol) (compuesto de referencia 13) en metil-THF (120 mL) y se añadió di(1*H*-imidazol-1-il)metanona (4.13 g, 25.49 mmol). La suspensión se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 3 h 45 min (matraz 1). En otro matraz, se suspendió 3-etoxi-3-oxopropanoato de potasio (5.21 g, 30.58 mmol) en metil-THF (120 mL) y se añadió cloruro de magnesio (2.91 g, 30.58 mmol). La suspensión se agitó a 50 °C en atmósfera de nitrógeno durante 3.5 h utilizando un imán muy grande (matraz 2). A continuación, la suspensión beis del matraz 1 se añadió a la suspensión blanca del matraz 2. La suspensión beis resultante se agitó en una atmósfera de nitrógeno a temperatura ambiente durante 23 h. La mezcla se acidificó hasta pH 1 con HCl 3.8 M y se añadieron MTBE y agua. Las fases se separaron y la fase orgánica se extrajo con agua, $NaHCO_3$ sat. y agua. La fase orgánica se evaporó y las trazas de agua se eliminaron formando un azeótropo con MeCN, para obtener un aceite marrón. Los diastereoisómeros se separaron mediante 2 purificaciones en una columna Biotage (20% => 55% de EtOAc en heptano, 8 VC; columna Biotage® con 340 g de KP-SIL). Se aislaron *trans*-4-(3-etoxi-3-oxopropanoil)-2-(4-

(trifluorometil)fenil)piperidin-1-carboxilato de metilo (0.474 g, 7%) y *cis*-4-(3-etoxi-3-oxopropanoil)-2-(4-(trifluorometil)fenil)piperidin-1-carboxilato de metilo (3.532 g, 52%) como aceites incoloros. Isómero *cis*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.26 (t, 3H), 1.72 - 2.22 (m, 3H), 2.29 (ddd, 1H), 2.83 - 2.96 (m, 1H), 3.29 - 3.49 (m, 3H), 3.64 (s, 3H), 4.07 - 4.23 (m, 3H), 4.92 - 5.06 (m, 1H), 7.32 (d, 2H), 7.58 (d, 2H). MS m/z 402 $(M+H)^+$. Isómero *trans*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.13 - 1.26 (m, 3H), 1.43 - 1.60 (m, 1H), 1.64 - 1.85 (m, 1H), 1.95 (dt, 1H), 2.44 - 2.61 (m, 2H), 2.73 - 2.85 (m, 1H), 3.39 (s, 2H), 3.70 (s, 3H), 3.99 - 4.36 (m, 3H), 5.59 (s a, 1H), 7.28 (d, 2H), 7.56 (d, 2H). MS m/z 402 $(M+H)^+$.

Paso 2: <u>*Cis*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(4-(trifluorometil)fenil)piperidin-1-carboxilato de metilo</u>

Se disolvió *cis*-4-(3-etoxi-3-oxopropanoil)-2-(4-(trifluorometil)fenil)piperidin-1-carboxilato de metilo (2.307 g, 5.75 mmol) en MeOH (20 mL) y se enfrió hasta -40 °C en una atmósfera de nitrógeno. Se añadió hidróxido sódico (0.230 g, 5.75 mmol) disuelto en agua (2 mL) durante 10 min y se continuó agitando la solución incolora a -40 °C durante 20 min. Se añadió hidroxilamina (al 50 % en peso en agua, 0.352 mL, 5.75 mmol) durante 8 min. La solución resultante se agitó a -40 °C durante 3 h 20 min. A continuación, la mezcla se transfirió a una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (30 mL, 180.00 mmol) y se continuó agitando la mezcla a 80 °C durante 20 min. El disolvente se evaporó y se añadieron DCM/agua. Las fases se separaron, y la fase orgánica se hizo pasar a través de un separador de fases y se evaporó para proporcionar un sólido amarillo. El compuesto se purificó mediante HPLC preparativa en 3 inyecciones en una columna XBridge C18 (10 µm 250x50 DI en mm) utilizando un gradiente de 0-25% de acetonitrilo en un tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 20 minutos con un flujo de 100 mL/min. Se aisló *cis*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(4-(trifluorometil)fenil)piperidin-1-carboxilato de metilo (1.682 g, 79%) como un sólido blanco. ^{1}H RMN (400 MHz, CD_3OD) δ 1.83 - 1.94 (m, 1H), 2.16 - 2.29 (m,

2H), 2.34 - 2.43 (m, 1H), 3.06 - 3.18 (m, 1H), 3.51 (ddd, 1H), 3.64 (s, 3H), 4.12 (ddd, 1H), 5.10 - 5.22 (m, 1H), 5.57 (s, 1H), 7.40 (d, 2H), 7.58 (d, 2H). MS m/z 371 $(M+H)^+$.

Paso 3: (2*R*,4*S*)-4-(3-Oxo-2,3-dihidroisoxazol-5-il)-2-(4-(trifluorometil)fenil)piperidin-1-carboxilato de metilo y (2*R*,4*S*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(4-(trifluorometil)fenil)piperidin-1-carboxilato de metilo

El *cis*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(4-(trifluorometil)fenil)piperidin-1-carboxilato de metilo (1.682 g, 4.54 mmol) se sometió a HPLC preparativa quiral (columna: Chiralpak IA (250x30), tamaño de partícula: 5 µm, fase móvil: 15% de MeOH en CO_2 (175 bar), velocidad de flujo: 130 mL/min, temperatura: 40 °C) para proporcionar (2*R*,4*S*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(4-(trifluorometil)fenil)piperidin-1-carboxilato de metilo (580 mg, 34%), pureza quiral: 99.9% de ee, rotación óptica $[\alpha]_D^{20} = +53.3$ (acetonitrilo, c=1) y (2*S*,4*R*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(4-(trifluorometil)fenil)piperidin-1-carboxilato de metilo (591 mg, 35%), pureza quiral: 98.8% de ee, rotación óptica $[\alpha]_D^{20} = -74.2$ (acetonitrilo, c=1).

Paso 4: 5-((2*R*,4*S*)-2-(4-(Trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(4-(trifluorometil)fenil)piperidin-1-carboxilato de metilo (580 mg, 1.57 mmol) en ácido bromhídrico (al 33% en ácido acético, 12 mL, 68.52 mmol) y la mezcla se agitó a temperatura ambiente durante 17 h. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*S*)-2-(4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona (341 mg, 70%). ^{1}H RMN (600 MHz, CD_3OD) δ 1.68 - 1.79 (m, 2H), 2.10 (d, 1H), 2.21 (d, 1H), 2.98 - 3.10 (m, 2H), 3.35 (d, 1H), 3.99 - 4.07 (m, 1H), 5.64 (s, 1H), 7.60 (d, 2H), 7.66 (d, 2H). HRMS calculado para $[C_{15}H_{15}F_3N_2O_2+H]^+$: 313.1164.

Experimental: 313.1150.

Ejemplo 34

5-((2*S*,4*R*)-2-(4-(Trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*S*,4*R*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(4-(trifluorometil)fenil)piperidin-1-carboxilato de metilo (591 mg, 1.60 mmol) (procedente del Paso 3 del Ejemplo 33) en ácido bromhídrico (al 33% en ácido acético, 12 mL, 68.52 mmol) y la mezcla se agitó a temperatura ambiente. Después de 24 h, se añadió más ácido bromhídrico (al 33% en ácido acético, 5 mL, 28.55 mmol) y se procedió con la reacción a temperatura ambiente durante un total de 1.5 días. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (instrumento: FractionLynx III, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*S*,4*R*)-2-(4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona (337 mg, 67%). ^{1}H RMN (600 MHz, CD_3OD) δ 1.69 - 1.78 (m, 2H), 2.09 (d, 1H), 2.21 (d, 1H), 2.99 - 3.09 (m, 2H), 3.32 - 3.38 (m, 1H), 4.01 - 4.04 (m, 1H), 5.63 (s, 1H), 7.59 (d, 2H), 7.66 (d, 2H). HRMS calculado para $[C_{15}H_{15}F_3N_2O_2+H]^+$: 313.1164. Experimental: 313.1156.

Ejemplo 35

5-(*Trans*-2-(4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(4-(trifluorometil)fenil)piperidin-1-carboxilato de metilo

Se disolvió *trans*-4-(3-etoxi-3-oxopropanoil)-2-(4-(trifluorometil)fenil)piperidin-1-carboxilato de metilo (0.467 g, 1.16 mmol) (procedente del Paso 1 del Ejemplo 33) en MeOH (4 mL) y se enfrió hasta -40 °C en una atmósfera de nitrógeno. Se añadió hidróxido sódico (0.047 g, 1.16 mmol) disuelto en agua (0.4 mL) durante 10 min y se continuó agitando la solución incolora a -40 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.071 mL, 1.16 mmol) durante 8 min. La solución resultante se agitó a -40 °C durante 3.5 h. A

continuación, la mezcla se transfirió a una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (6 mL, 36.00 mmol) y se continuó agitando la mezcla a 80 °C durante 20 min. El disolvente se evaporó y se añadieron DCM/agua. Las fases se separaron y la fase orgánica se hizo pasar a través de un separador de fases y se evaporó para proporcionar *trans*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(4-(trifluorometil)fenil)piperidin-1-carboxilato de metilo crudo (0.432 g, cuant.) como un aceite amarillo. MS m/z 371 $(M+H)^+$.

Paso 2: 5-(*Trans*-2-(4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió *trans*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(4-(trifluorometil)fenil)piperidin-1-carboxilato de metilo (148 mg, 0.40 mmol) en ácido bromhídrico (al 33% en ácido acético, 3 mL, 17.13 mmol) y la solución se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-(*trans*-2-(4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona (50 mg, 40%). ^{1}H RMN (600 MHz, DMSO) δ 1.75 - 1.83 (m, 2H), 1.84 - 1.92 (m, 1H), 2.00 - 2.06 (m, 1H), 2.70 (dt, 1H), 2.79 - 2.86 (m, 1H), 3.09 - 3.15 (m, 1H), 3.77 (d, 1H), 5.95 (s, 1H), 7.59 (d, 2H), 7.64 (d, 2H). HRMS calculado para $[C_{15}H_{15}F_3N_2O_2+H]^+$: 313.1164. Experimental: 313.1166.

Ejemplo 36

5-((2*R*,4*S*)-2-(3-*tert*-Butilfenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: 2-(3-*tert*-Butilfenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo

Se disolvió el ácido 2-(3-*tert*-butilfenil)-1-(metoxicarbonil)piperidin-4-carboxílico (2.73 g, 8.55 mmol) (compuesto de referencia 14) en metil-THF (40 mL) y se añadió di(1*H*-imidazol-1-il)metanona (2.079 g, 12.82 mmol). La suspensión se agitó a temperatura ambiente en atmósfera de

nitrógeno durante 2 h (matraz 1). En otro matraz, se suspendió 3-etoxi-3-oxopropanoato de potasio (2.62 g, 15.39 mmol) en metil-THF (60 mL) y se añadió cloruro de magnesio (1.465 g, 15.39 mmol). La suspensión se agitó a 50 °C en atmósfera de nitrógeno durante 3 h utilizando un imán muy grande (matraz 2). A continuación, la suspensión beis del matraz 1 se añadió a la suspensión blanca del matraz 2. La suspensión beis resultante se agitó en atmósfera de nitrógeno a temperatura ambiente durante 23 h. La mezcla se acidificó hasta pH 1 con HCl 0.5 M (100 mL) y se añadió MTBE (200 mL). Las fases se separaron y la fase orgánica se extrajo con agua (30 mL), $NaHCO_3$ sat. (30 mL) y agua (30 mL), se secó con Na_2SO_4 anhidro y se evaporó para proporcionar 2-(3-*tert*-butilfenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo crudo (3.14 g, 95%) como un aceite marrón.

Paso 2: *Cis*-2-(3-*tert*-butilfenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió 2-(3-*tert*-butilfenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (3.14 g, 8.06 mmol) en MeOH (50 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (0.322 g, 8.06 mmol) disuelto en agua (5.00 mL) durante 5 min y se continuó agitando la mezcla incolora a -40 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.494 mL, 8.06 mmol) durante 8 min. La solución resultante se agitó a -55 °C durante 6 h 30 min. A continuación, la mezcla se transfirió a una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (60 mL, 360.00 mmol) y se continuó agitando la mezcla a 80 °C durante 20 min. El disolvente se evaporó y se añadieron DCM/agua. Las fases se separaron, y la fase orgánica se hizo pasar a través de un separador de fases y se evaporó para proporcionar un aceite marrón. El crudo se purificó mediante HPLC preparativa en 3 inyecciones en una columna XBridge C18 (10 µm 250x50 DI en mm) utilizando un gradiente de 40-85% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/HOAc en 25 minutos con un flujo de 100 mL/min. Se aisló *cis*-2-(3-*tert*-butilfenil)-

4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (690 mg, 24%). ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.29 (s, 9H), 1.81 - 1.88 (m, 1H), 2.14 - 2.21 (m, 1H), 2.22 - 2.31 (m, 1H), 2.35 - 2.42 (m, 1H), 3.03 - 3.10 (m, 1H), 3.37 - 3.44 (m, 1H), 3.66 (s, 3H), 4.16 - 4.22 (m, 1H), 5.12 - 5.16 (m, 1H), 5.48 (s, 1H), 6.97 - 7.01 (m, 1H), 7.17 (s, 1H), 7.21 - 7.25 (m, 2H). MS m/z 359 $(M+H)^+$.

Paso 3: (2*R*,4*S*)-2-(3-*tert*-Butilfenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El *cis*-2-(3-*tert*-butilfenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (690 mg, 1.93 mmol) se sometió a HPLC preparativa quiral (columna: ReproSil (250x50), tamaño de partícula de 8 µm, fase móvil: 40/60 de heptano/EtOH, velocidad de flujo: 118 mL/min) para proporcionar (2*R*,4*S*)-2-(3-*tert*-butilfenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (340 mg, 49%), pureza quiral: 99.9% de e.e., rotación óptica $[\alpha]_D^{20} = +55.8$ (acetonitrilo, c=1).

Paso 4: 5-((2*R*,4*S*)-2-(3-*tert*-Butilfenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-2-(3-*tert*-butilfenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.340 g, 0.95 mmol) en ácido bromhídrico (al 33% en ácido acético, 5.49 mL, 31.35 mmol) y la solución se agitó a temperatura ambiente durante la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*S*)-2-(3-*tert*-butilfenil)piperidin-4-il)isoxazol-3(2*H*)-ona (107 mg, 37%). ^{1}H RMN (400 MHz, DMSO) δ 1.26 (s, 9H), 1.32 - 1.43 (m, 1H), 1.43 - 1.54 (m, 1H), 1.81 - 1.90 (m, 1H), 1.90 - 1.99 (m, 1H), 2.68 - 2.78 (m, 1H), 2.80 - 2.91 (m, 1H), 3.08 - 3.16 (m, 1H), 3.59 - 3.66 (m, 1H), 5.72 (s, 1H), 7.13 - 7.29 (m, 3H), 7.37 (s, 1H). HRMS calculado para $[C_{18}H_{24}N_2O_2+H]+$: 301.1916. Experimental: 301.1909.

Ejemplo 37

5-(*Trans*-2-(4-*tert*-butilfenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(4-*tert*-butilfenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo

Se suspendieron cloruro de magnesio (5.38 g, 56.51 mmol) y 3-etoxi-3-oxopropanoato de potasio (9.62 g, 56.51 mmol) en metil-THF (100 mL) y se calentó hasta 50 °C en atmósfera de nitrógeno durante 18 h utilizando un imán muy grande; posteriormente se enfrió hasta temperatura ambiente (matraz 1). En otro matraz, se añadió di(1*H*-imidazol-1-il)metanona (7.23 g, 44.62 mmol) a una suspensión del ácido 2-(4-*tert*-butilfenil)-1-(metoxicarbonil)piperidin-4-carboxílico (9.5 g, 29.74 mmol) (compuesto de referencia 15) en metil-THF (100 mL) en atmósfera de nitrógeno. La mezcla resultante se agitó a temperatura ambiente durante 4 h (matraz 2). Posteriormente, el contenido del matraz 2 se transfirió al matraz 1 con una aguja de transferencia. Se lavó con metil-THF (30 mL). La suspensión resultante se agitó a temperatura ambiente durante 18 h. Se añadió HCl 3.8 M (ca. 150 mL) y la mezcla bifásica resultante se agitó vigorosamente durante 2 h. Las fases se separaron. La fase orgánica se lavó con agua, $NaHCO_3$ sat. y salmuera, a continuación se secó con $MgSO_4$, y se evaporó. El residuo se purificó en una columna Biotage en dos porciones iguales (columna Biotage® con 340 g de KP-SIL, 1 VC de 20% de EtOAc en heptanos, seguido de 20% => 60% en 7 VC). Se aisló *trans*-2-(4-*tert*-butilfenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (1.09 g, 9.4%) como un aceite de color amarillo claro. ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.22 - 1.31 (m, 3H), 1.31 (s, 9H), 1.50 - 1.99 (m, 4H), 2.50 - 2.96 (m, 2H), 3.47 (s, 2H), 3.74 (s, 3H), 4.08 - 4.23 (m, 3H), 5.46 - 5.71 (m, 1H), 7.09 - 7.16 (m, 2H), 7.34 - 7.40 (m, 2H).

Paso 2: *Trans*-2-(4-*tert*-butilfenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *trans*-2-(4-*tert*-butilfenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (1.09 g, 2.80 mmol) en MeOH (10 mL) y se enfrió hasta -40 °C. Se añadió

hidróxido sódico (0.112 g, 2.80 mmol) disuelto en agua (1.2 mL) en 1 min y la solución resultante se agitó a -40 °C durante 20 min. A continuación, se añadió hidroxilamina (al 50% en agua, 0.178 mL, 2.91 mmol) en 1 min y se continuó agitando a -40 °C durante 3 h. La mezcla de reacción se transfirió posteriormente a una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (30 mL, 180.00 mmol) y se continuó agitando la mezcla a 80 °C durante 1h. A continuación se enfrió hasta temperatura ambiente. Se evaporó el metanol y después se añadió agua. Se extrajo tres veces con DCM. Las capas orgánicas combinadas se secaron con $MgSO_4$ y se evaporaron. Se aisló *trans*-2-(4-*tert*-butilfenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo crudo (910 mg, 90%) como una espuma blanquecina. ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.32 (s, 9H), 1.46 - 2.23 (m, 3H), 2.46 - 3.05 (m, 3H), 3.74 (s, 3H), 3.98 - 4.43 (m, 1H), 5.48 - 5.72 (m, 2H), 7.10 - 7.22 (m, 2H), 7.35 - 7.45 (m, 2H). MS m/z 359 $(M+H)^+$.

Paso 3: 5-(*Trans*-2-(4-*tert*-butilfenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió *trans*-2-(4-*tert*-butilfenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.26 g, 0.73 mmol) en ácido bromhídrico (al 33% en ácido acético, 5 mL, 71.37 mmol) y se agitó a temperatura ambiente durante 18 h. Los disolventes se evaporaron y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-(*trans*-2-(4-*tert*-butilfenil)piperidin-4-il)isoxazol-3(2*H*)-ona (182 mg, 84%). ^{1}H RMN (600 MHz, DMSO) δ 1.23 (s, 9H), 1.76 - 1.85 (m, 2H), 1.86 - 1.93 (m, 1H), 1.96 - 2.03 (m, 1H), 2.71 (td, 1H), 2.81 - 2.88 (m, 1H), 3.10 - 3.15 (m, 1H), 3.65 (dd, 1H), 5.90 (s, 1H), 7.24 - 7.33 (m, 4H). HRMS calculado para $[C_{18}H_{24}N_2O_2+H]^+$: 301.1916. Experimental: 301.1919.

Ejemplo 38

5-((2*R*,4*S*)-2-(4-(Metilsulfonil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-4-(3-etoxi-3-oxopropanoil)-2-(4-(metilsulfonil)fenil)piperidin-1-carboxilato de metilo y *cis*-4-(3-etoxi-3-oxopropanoil)-2-(4-(metilsulfonil)fenil)piperidin-1-carboxilato de metilo

Se disolvió el ácido 1-(metoxicarbonil)-2-(4-(metilsulfonil)fenil)piperidin-4-carboxílico (4.756 g, 13.93 mmol) en metil-THF (70 mL) y se añadió di(1*H*-imidazol-1-il)metanona (3.39 g, 20.90 mmol). Se formó un precipitado blanco espeso. Se añadió metil-THF (70.0 mL) y la suspensión se agitó en atmósfera de nitrógeno a temperatura ambiente durante 6 h (matraz 1). En otro matraz, se suspendió 3-etoxi-3-oxopropanoato de potasio (4.74 g, 27.86 mmol) en metil-THF (70.0 mL) y se añadió cloruro de magnesio (2.65 g, 27.86 mmol). Se calentó a 50 °C en atmósfera de nitrógeno durante 6 h (matraz 2). A continuación, la suspensión blanca del matraz 2 se añadió a la suspensión blanca densa del matraz 1. La suspensión se agitó a temperatura ambiente durante 16 h. La temperatura se incrementó hasta 50 °C durante 6 h. Se añadieron más 3-etoxi-3-oxopropanoato de potasio (4.74 g, 27.86 mmol) y cloruro de magnesio (2.65 g, 27.86 mmol) en MeTHF (15 mL) junto con dioxano (60 mL). La reacción se agitó a 50 °C durante 18 h. La mezcla de reacción se acidificó hasta pH 1 con HCl 3 M. La fase orgánica se lavó con agua (2x400 mL), $NaHCO_3$ sat. (400 mL) y salmuera (400 mL), se secó con Na_2SO_4, se filtró y se evaporó al vacío. El residuo se purificó mediante cromatografía flash automatizada en una columna Biotage® con 100g de KP-SIL. Se utilizó como fase móvil un gradiente de 50% de EtOAc en heptano en 2 VC seguido de 50% a 80% de EtOAc en heptano en 10 VC. Se aislaron *cis*-4-(3-etoxi-3-oxopropanoil)-2-(4-(metilsulfonil)fenil)piperidin-1-carboxilato de metilo (2.70 g, 47.1%) y *trans*-4-(3-etoxi-3-oxopropanoil)-2-(4-(metilsulfonil)fenil)piperidin-1-carboxilato de metilo (0.505 g, 8.81%). Isómero *cis*: RMN: ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.25 (t, 3H), 1.80 - 1.95 (m, 2H), 2.04 - 2.16 (m, 1H), 2.23 - 2.32 (m, 1H), 2.84 - 2.95 (m, 1H), 3.02 (s, 3H), 3.29 - 3.38 (m, 1H), 3.38 - 3.48 (m, 2H), 3.63 (s, 3H), 4.10 - 4.21 (m, 3H), 4.95 -

5.04 (m, 1H), 7.40 (d, 2H), 7.88 (d, 2H). MS m/z 410 $(M-H)^-$. Isómero *trans*: ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.23 (t, 3H), 1.12 - 2.26 (m, 3H), 2.51 - 2.62 (m, 2H), 2.83 (td, 1H), 3.04 (s, 3H), 3.40 - 3.48 (s, 2H), 3.75 (s, 3H), 4.07 - 4.38 (m, 1H), 4.15 (c, 2H), 5.49 - 5.77 (m, 1H), 7.41 (d, 2H), 7.93 (d, 2H). MS m/z 412 $(M+H)^+$.

Paso 2: *Cis*-2-(4-(metilsulfonil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se suspendió *cis*-4-(3-etoxi-3-oxopropanoil)-2-(4-(metilsulfonil)fenil)piperidin-1-carboxilato de metilo (2.6 g, 6.32 mmol) en MeOH (100 mL). Se añadió DCM (40 mL) y la reacción se enfrió hasta -40 °C. Se añadió hidróxido sódico 3.8 M (1.663 mL, 6.32 mmol) en agua (10.00 mL) y la reacción se agitó a -40 °C durante 20 min. Se añadió hidroxilamina (al 50% en agua, 0.387 mL, 6.32 mmol) y la reacción se agitó a -40 °C durante 3 h. A continuación, la mezcla de reacción se añadió a una solución calentada previamente a 80 °C de ácido clorhídrico 6 M (63.2 mL, 379.13 mmol) y la reacción se agitó durante 30 min. El disolvente se evaporó al vacío. Se añadieron DCM (250 mL) y agua (250 mL), se agitó y se separaron las fases. La fase orgánica se secó con un separador de fases y se evaporó al vacío. El compuesto se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x50 DI en mm) utilizando un gradiente de 15-45% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/AcOH en 30 minutos con un flujo de 100 mL/min. Se aisló *cis*-2-(4-(metilsulfonil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.200 g, 49.9%) como un sólido blanco. ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.85 - 1.91 (m, 1H), 2.18 - 2.29 (m, 2H), 2.35 - 2.41 (m, 1H), 2.98 (s, 3H), 3.00 - 3.13 (m, 1H), 3.38 - 3.44 (m, 1H), 3.67 (s, 3H), 4.13 - 4.19 (m, 1H), 5.20 (t, 1H), 5.47 (s, 1H), 7.34 (d, 2H), 7.83 (d, 2H). MS m/z 381 $(M+H)^+$.

Paso 3: (2*R*,4*S*)-2-(4-(Metilsulfonil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El *cis*-2-(4-(metilsulfonil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.200

g, 3.16 mmol) se sometió a HPLC preparativa quiral (columna: ReproSil (250x50), tamaño de partícula de 8 µm, fase móvil: EtOH, velocidad de flujo: 120 mL/min) para proporcionar (2*R*,4*S*)-2-(4-(metilsulfonil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (536 mg, 45%), pureza quiral: 99.9% de ee, rotación óptica $[\alpha]_D^{20} = +59.5$ (acetonitrilo, c=1), ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.78 - 1.85 (m, 1H), 2.12 - 2.23 (m, 2H), 2.29 - 2.37 (m, 1H), 2.93 (s, 3H), 3.02 - 3.08 (m, 1H), 3.33 - 3.41 (m, 1H), 3.61 (s, 3H), 4.07 - 4.13 (m, 1H), 5.14 (t, 1H), 5.44 (s, 1H), 7.31 (d, 2H), 7.77 (d, 2H).

Paso 4: 5-((2*R*,4*S*)-2-(4-(Metilsulfonil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-2-(4-(metilsulfonil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (536 mg, 1.41 mmol) en ácido bromhídrico (al 33% en AcOH, 5 mL, 71.37 mmol) y se agitó a temperatura ambiente durante 20 h. La mezcla de reacción se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx III, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*S*)-2-(4-(metilsulfonil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona (309 mg, 68%), ^{1}H RMN (600 MHz, DMSO) δ 1.39 (c, 1H), 1.49 (dc, 1H), 1.87 - 1.93 (m, 1H), 2.01 (d, 1H), 2.76 (t, 1H), 2.87 - 2.94 (m, 1H), 3.11 - 3.19 (m, 1H), 3.17 (s, 3H), 3.80 (d, 1H), 5.74 (s, 1H), 7.64 (d, 2H), 7.85 (d, 2H). HRMS calculado para $[C_{15}H_{18}N_2O_4S+H]+$: 323.1065. Experimental: 323.1042.

Ejemplo 39

5-((*Trans*-2-(4-(metilsulfonil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(4-(metilsulfonil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se suspendió *trans*-4-(3-etoxi-3-oxopropanoil)-2-(4-(metilsulfonil)fenil)piperidin-1-carboxilato de metilo (505 mg,

1.23 mmol) (del paso 1 del ejemplo 38) en MeOH (5 mL) y se enfrió hasta -40 °C. Se añadió hidróxido sódico 3.8 M (0.323 mL, 1.23 mmol) en agua. 20 min después, se añadió hidroxilamina (al 50% en agua, 0.075 mL, 1.23 mmol) y se continuó agitando a -40 °C durante 3 h. A continuación, la mezcla de reacción se añadió a una solución calentada previamente a 80 °C de ácido clorhídrico 6 M (6.14 mL, 36.82 mmol) y se agitó durante 20 min. El disolvente se evaporó al vacío. Se añadieron DCM (50 mL) y agua (50 mL), se agitó y se separaron las fases. La fase orgánica se secó con un separador de fases y se evaporó al vacío. El residuo se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x20 DI en mm) utilizando un gradiente de 15-40% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/AcOH en 25 minutos con un flujo de 19 mL/min. Se aisló *trans*-2-(4-(metilsulfonil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (301 mg, 64.5%). ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.61 - 1.73 (m, 1H), 1.91 - 1.99 (m, 1H), 2.05 - 2.14 (m, 1H), 2.66 - 2.82 (m, 2H), 2.91 (t, 1H), 3.05 (s, 3H), 3.77 (s, 3H), 4.12 - 4.46 (m, 1H), 5.60 - 5.80 (m, 2H), 7.44 (d, 2H), 7.95 (d, 2H). MS m/z 381 $(M+H)^+$.

Paso 2: 5-((*Trans*-2-(4-(metilsulfonil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió *trans*-2-(4-(metilsulfonil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (301 mg, 0.79 mmol) en ácido bromhídrico (al 33% en ácido acético, 2 mL, 28.55 mmol) y se agitó a temperatura ambiente durante 20 h. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-(*trans*-2-(4-(metilsulfonil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona (119 mg, 47%), HRMS calculado para $[C_{15}H_{18}N_2O_4S+H]+$: 323.1065. Experimental: 323.1054.

Ejemplo 40

5-((2*R*,4*S*)-2-(6-(Trifluorometil)piridin-3-il)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-4-(3-etoxi-3-oxopropanoil)-2-(6-(trifluorometil)piridin-3-il)piperidin-1-carboxilato de metilo y *cis*-4-(3-etoxi-3-oxopropanoil)-2-(6-(trifluorometil)piridin-3-il)piperidin-1-carboxilato de metilo

Se disolvió el ácido 1-(metoxicarbonil)-2-(6-(trifluorometil)piridin-3-il)piperidin-4-carboxílico (2.5 g, 3.76 mmol) (compuesto de referencia 17) en metil-THF (80 mL) y a continuación se añadió di(1*H*-imidazol-1-il)metanona (1.098 g, 6.77 mmol). La mezcla se agitó a temperatura ambiente en atmósfera de nitrógeno durante 3 h (matraz 1). En otro matraz, se suspendió 3-etoxi-3-oxopropanoato de potasio (1.153 g, 6.77 mmol) en metil-THF (80 mL) y a continuación se añadió cloruro de magnesio (0.645 g, 6.77 mmol). La suspensión se agitó a 50 °C en atmósfera de nitrógeno durante 3 h utilizando un imán grande (matraz 2). 3 h después, el contenido del matraz 1 se transfirió al matraz 2. La suspensión blanca resultante se agitó a temperatura ambiente en atmósfera de nitrógeno durante toda la noche. La mezcla se acidificó hasta pH 1 con HCl 3.8 M y a continuación se añadieron MTBE (50 mL) y agua (50 mL). Las fases se separaron, y la capa orgánica se lavó con agua, $NaHCO_3$ sat. y salmuera. La capa orgánica se secó con Na_2SO_4, se filtró y se evaporó para obtener un aceite amarillento. El producto se purificó en una columna Biotage (340 g) con 1 VC con 20% de EtOAc en *n*-heptano seguido de un gradiente de 20-60% (8 VC). Se aislaron *trans*-4-(3-etoxi-3-oxopropanoil)-2-(6-(trifluorometil)piridin-3-il)piperidin-1-carboxilato de metilo (70 mg, 5%) y *cis*-4-(3-etoxi-3-oxopropanoil)-2-(6-(trifluorometil)piridin-3-il)piperidin-1-carboxilato de metilo (1.085 g, 72%). Isómero *cis*: MS m/z 403 $(M+H)^+$. Isómero *trans*: ^1H RMN (400 MHz, $CDCl_3$) δ 1.18 - 1.31 (m, 3H), 1.53 - 1.72 (m, 1H), 1.82 - 1.93 (m, 1H), 2.00 - 2.13 (m, 1H), 2.49 - 2.69 (m, 2H), 2.82 (dt, 1H), 3.46 (d, 2H), 3.76 (s, 3H), 4.10 - 4.40 (m, 3H), 5.72 (s a, 1H), 7.64 - 7.77 (m, 2H), 8.63 (s, 1H). MS m/z 403 $(M+H)^+$.

Paso 2: *Cis*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(6-(trifluorometil)piridin-3-il)piperidin-1-carboxilato de metilo

Se disolvió *cis*-4-(3-etoxi-3-oxopropanoil)-2-(6-(trifluorometil)piridin-3-il)piperidin-1-carboxilato de metilo (1.085 g, 2.70 mmol) en MeOH (12 mL) y se enfrió hasta -45 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (0.793 mL, 2.70 mmol) durante 10 min y la solución amarilla se continuó agitando a -45 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.165 mL, 2.70 mmol) durante 8 min. La solución resultante se agitó a -45 °C durante 3 h. A continuación, la mezcla se vertió rápidamente sobre una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (13.89 mL, 83.32 mmol) y la mezcla se continuó agitando a 80 °C durante 20 min. El disolvente se evaporó y se añadieron DCM/agua. Las fases se separaron, y la fase orgánica se hizo pasar a través de un separador de fases y se evaporó para proporcionar un sólido blanco. El compuesto se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x50 DI en mm) utilizando un gradiente de 10-60% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/AcOH en 30 minutos con un flujo de 100 mL/min. Se aisló *cis*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(6-(trifluorometil)piridin-3-il)piperidin-1-carboxilato de metilo (160 mg, 16%). MS m/z 372 $(M+H)^+$.

Paso 3: <u>(2*R*,4*S*)-4-(3-Oxo-2,3-dihidroisoxazol-5-il)-2-(6-(trifluorometil)piridin-3-il)piperidin-1-carboxilato de metilo</u>

El *cis*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(6-(trifluorometil)piridin-3-il)piperidin-1-carboxilato de metilo (160 mg, 0.43 mmol) se sometió a HPLC preparativa quiral (columna: CelluCoat (250x50 mm), tamaño de partícula: 10 µm, fase móvil: 50/50 de heptano/EtOH, velocidad de flujo: 120 mL/min) para proporcionar (2*R*,4*S*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(6-(trifluorometil)piridin-3-il)piperidin-1-carboxilato de metilo (74.5 mg, 47%), pureza quiral: 99.9% de ee, rotación óptica $[\alpha]_D^{20} = +32.0$ (acetonitrilo, c=0.1).

Paso 4: <u>5-((2*R*,4*S*)-2-(6-(Trifluorometil)piridin-3-il)piperidin-4-il)isoxazol-3(2*H*)-ona</u>

Se disolvió (2*R*,4*S*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(6-(trifluorometil)piridin-3-il)piperidin-1-carboxilato de metilo (74.5 mg, 0.20 mmol) en ácido bromhídrico (al 33% en ácido acético, 1.58 mL, 9.03 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*S*)-2-(6-(trifluorometil)piridin-3-il)piperidin-4-il)isoxazol-3(2*H*)-ona (43 mg, 68%), ^{1}H RMN (600 MHz, DMSO) δ 1.36 - 1.53 (m, 2H), 1.89 (d, 1H), 2.04 (d, 1H), 2.70 - 2.78 (m, 1H), 2.90 (tt, 1H), 3.09 - 3.16 (m, 1H), 3.83 (d, 1H), 5.75 (s, 1H), 7.84 (d, 1H), 8.04 (dd, 1H), 8.75 (d, 1H). HRMS calculado para $[C_{14}H_{14}F_3N_3O_2+H]^+$: 314.1116. Experimental: 314.1134

Ejemplo 41

5-(*Trans*-2-(6-(trifluorometil)piridin-3-il)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(6-(trifluorometil)piridin-3-il)piperidin-1-carboxilato de metilo

Se disolvió *trans*-4-(3-etoxi-3-oxopropanoil)-2-(6-(trifluorometil)piridin-3-il)piperidin-1-carboxilato de metilo (70 mg, 0.17 mmol) (del paso 1 del ejemplo 40) en MeOH (1 mL) y se enfrió hasta -45 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (0.051 mL, 0.17 mmol) durante 10 min y la solución amarilla se continuó agitando a -45 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 10.66 µL, 0.17 mmol) durante 8 min. La solución resultante se agitó a -45 °C durante 3 h. A continuación, la mezcla se vertió rápidamente sobre una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (0.896 mL, 5.38 mmol) y la mezcla se continuó agitando a 80 °C durante 20 min. El disolvente se evaporó y se añadieron DCM/agua. Las fases se separaron, y la fase orgánica se hizo pasar a través de un separador de fases y se evaporó para proporcionar *trans*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(6-(trifluorometil)piridin-3-il)piperidin-1-carboxilato de

metilo (60 mg, cuant.) como un aceite amarillento. MS m/z 372 $(M+H)^+$.

Paso 2: 5-(*Trans*-2-(6-(trifluorometil)piridin-3-il)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió *trans*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(6-(trifluorometil)piridin-3-il)piperidin-1-carboxilato de metilo (60 mg, 0.16 mmol) en ácido bromhídrico (al 33% en ácido acético, 1.27 mL, 7.27 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-(*trans*-2-(6-(trifluorometil)piridin-3-il)piperidin-4-il)isoxazol-3(2*H*)-ona (11.4 mg, 23%), ^{1}H RMN (400 MHz, DMSO) δ 1.77 - 1.99 (m, 3H), 2.06 - 2.16 (m, 1H), 2.69 - 2.80 (m, 1H), 2.83 - 2.94 (m, 1H), 3.07 - 3.59 (m, 1H), 3.94 (d, 1H), 6.03 (s, 1H), 7.86 (d, 1H), 8.08 (d, 1H), 8.78 (s, 1H). HRMS calculado para $[C_{14}H_{14}F_3N_3O_2+H]^+$: 314.1116. Experimental: 314.1122

Ejemplo 42

5-((2*R*,4*S*)-2-(5-*tert*-Butiltiofen-2-il)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Cis*-2-(5-*tert*-butiltiofen-2-il)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo

Se disolvió el ácido 2-(5-*tert*-butiltiofen-2-il)-1-(metoxicarbonil)piperidin-4-carboxílico (1.125 g, 3.46 mmol) (compuesto de referencia 18) en THF (30 mL) y se añadió di(1*H*-imidazol-1-il)metanona (0.911 g, 5.62 mmol). La suspensión se agitó a temperatura ambiente en atmósfera de nitrógeno durante 6 h (matraz 1). En otro matraz, se suspendieron la sal potásica del ácido 3-etoxi-3-oxopropanoico (1.509 g, 8.82 mmol) y cloruro de magnesio (0.84 g, 8.82 mmol) en THF (30 mL) y se agitó a 50 °C en atmósfera de nitrógeno durante 20 h utilizando un imán muy grande (matraz 2). A continuación, la suspensión blanca del matraz 2 se añadió al matraz 1. La suspensión blanca densa se agitó a temperatura ambiente durante 18 h. La mezcla

de reacción se acidificó añadiendo HCl 3 M hasta pH 1. El disolvente se evaporó al vacío. Se añadieron MTBE (250 mL) y agua, se agitó y se separaron las fases. La fase orgánica se lavó con agua (200 mL), $NaHCO_3$ sat. (200 mL) y salmuera (200 mL), se secó con un separador de fases y se evaporó al vacío. El residuo se purificó mediante cromatografía flash automatizada en una columna Biotage® con 100 g de KP-SIL. Se utilizó como fase móvil un gradiente de 10% de EtOAc en heptano en 2 VC seguido de 10% a 40% de EtOAc en heptano en 9 VC. Se aisló *cis*-2-(5-*tert*-butiltiofen-2-il)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (0.963 g, 70.4%). Isómero *cis*: MS m/z 396 $(M+H)^+$.

Paso 2: *Cis*-2-(5-*tert*-butiltiofen-2-il)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *cis*-2-(5-*tert*-butiltiofen-2-il)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (963 mg, 2.43 mmol) en metanol (15 mL) y se enfrió hasta -40 °C. Se añadió NaOH (0.641 mL, 2.43 mmol) disuelto en agua (1 mL) y se agitó durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.149 mL, 2.43 mmol) y la reacción se agitó a -40 °C durante 3 h. Posteriormente, la mezcla de reacción se añadió a una solución calentada previamente a 80 °C de HCl 6 M (12.58 mL, 75.48 mmol) y se agitó durante 20 min. El disolvente se evaporó al vacío. Se añadieron DCM (150 mL) y agua (150 mL), se agitó y se separaron las fases. La fase acuosa se extrajo con DCM (150 mL). Las fases orgánicas combinadas se secaron con un separador de fases y se evaporaron al vacío. El compuesto se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x50 DI en mm) utilizando un gradiente de 35-75% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/AcOH en 25 minutos con un flujo de 100 mL/min. Se aisló *cis*-2-(5-*tert*-butiltiofen-2-il)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (436 mg, 49.1%) como un sólido blanco. MS m/z 363 $(M-H)^-$.

Paso 3: (2*R*,4*S*)-2-(5-*tert*-Butiltiofen-2-il)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo y

(2*S*,4*R*)-2-(5-*tert*-butiltiofen-2-il)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El *cis*-2-(5-*tert*-butiltiofen-2-il)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (436 mg, 1.2 mmol) se sometió a HPLC preparativa quiral (columna: CelluCoat (250x20 mm), tamaño de partícula: 5 µm, fase móvil: 80/20 de heptano/EtOH, velocidad de flujo: 18 mL/min) para proporcionar (2*R*,4*S*)-2-(5-*tert*-butiltiofen-2-il)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (212 mg, 49%), pureza quiral: 98.7% de ee, rotación óptica $[\alpha]_D^{20} = +3.0$ (acetonitrilo, c=1.0), ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.34 (s, 9H), 1.55 - 1.68 (m, 1H), 1.90 - 2.04 (m, 2H), 2.49 (d, 1H), 3.12 (s a, 2H), 3.76 (s, 3H), 4.19 (d a, 1H), 5.60 - 5.87 (m, 2H), 6.59 - 6.69 (m, 2H) y (2*S*,4*R*)-2-(5-*tert*-butiltiofen-2-il)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (210 mg, 48%), pureza quiral: 99.3% de ee, rotación óptica $[\alpha]_D^{20} = -1.1$ (acetonitrilo, c=1.0), ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.33 (s, 9H), 1.54 - 1.66 (m, 1H), 1.88 - 2.03 (m, 2H), 2.48 (d, 1H), 3.11 (s a, 2H), 3.74 (s, 3H), 4.17 (d a, 1H), 5.58 - 5.85 (m, 2H), 6.58 - 6.67 (m, 2H).

Paso 4: 5-((2*R*,4*S*)-2-(5-*tert*-Butiltiofen-2-il)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-2-(5-*tert*-butiltiofen-2-il)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (50 mg, 0.14 mmol) en ácido bromhídrico (al 33% en ácido acético, 1 mL, 6.08 mmol) y se agitó a temperatura ambiente durante 24 h. El disolvente se evaporó al vacío y el residuo se purificó mediante HPLC preparativa en una columna XBridge C18 (10 µm 250x19 DI en mm) utilizando un gradiente de 10-50% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 25 minutos con un flujo de 19 mL/min. Se aisló 5-((2*R*,4*S*)-2-(5-*tert*-butiltiofen-2-il)piperidin-4-il)isoxazol-3(2*H*)-ona (4.00 mg, 9.52%) como un sólido blanco. ^{1}H RMN (400 MHz, CD_3OD) δ 1.36 (s, 9H), 1.99 - 2.17 (m, 2H), 2.20 - 2.31 (m, 1H), 2.36 - 2.44 (m, 1H), 3.05 - 3.21 (m, 2H), 3.28 - 3.37 (m, 1H), 4.37 (dd,

1H), 5.70 (d, 1H), 6.77 (d, 1H), 6.93 (d, 1H). HRMS calculado para $[C_{16}H_{22}N_2O_2S+H]^+$: 307.1480. Experimental: 307.1502.

Ejemplo 43

5-((2*S*,4*R*)-2-(5-*tert*-Butiltiofen-2-il)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*S*,4*R*)-2-(5-*tert*-butiltiofen-2-il)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (50 mg, 0.14 mmol) (del paso 3 del ejemplo 42) en ácido bromhídrico (al 33% en AcOH, 1 mL, 6.08 mmol) y se agitó a temperatura ambiente durante 20 h. El disolvente se evaporó al vacío. El compuesto se purificó mediante HPLC preparativa en una columna XBridge C18 (10 µm 250x19 DI en mm) utilizando un gradiente de 10-50% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 25 minutos con un flujo de 19 mL/min. Se aisló 5-((2*S*,4*R*)-2-(5-*tert*-butiltiofen-2-il)piperidin-4-il)isoxazol-3(2*H*)-ona (7.00 mg, 16.65%) como un sólido blanco. ^{1}H RMN (600 MHz, CD_3OD) δ 1.36 (s, 9H), 2.03 - 2.12 (m, 1H), 2.12 - 2.19 (m, 1H), 2.26 - 2.33 (m, 1H), 2.40 - 2.46 (m, 1H), 3.09 - 3.17 (m, 1H), 3.18 - 3.24 (m, 1H), 3.34 - 3.40 (m, 1H), 4.38 - 4.44 (m, 1H), 5.75 (s, 1H), 6.78 (d, 1H), 6.96 (d, 1H).

Ejemplo 44

5-((2*R*,4*S*)-2-(2,4-Difluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Cis*-2-(2,4-difluorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo

Se disolvió el ácido 2-(2,4-difluorofenil)-1-(metoxicarbonil)piperidin-4-carboxílico (2.20 g, 7.35 mmol) (compuesto de referencia 19) en metil-THF (70 mL) y a continuación se añadió di(1*H*-imidazol-1-il)metanona (2.146 g, 13.23 mmol). La mezcla se agitó a temperatura ambiente en atmósfera de nitrógeno durante 5 h (matraz 1). En otro matraz, se suspendió 3-etoxi-3-oxopropanoato de potasio (2.252 g, 13.23 mmol) en metil-THF (70.0 mL) y a continuación se añadió cloruro de magnesio (1.260 g, 13.23 mmol). La suspensión se agitó a 50 °C en atmósfera de nitrógeno durante 5 h utilizando un imán grande (matraz 2). 3 h después, el contenido del matraz 1 se

transfirió al matraz 2. La suspensión blanca resultante se agitó a temperatura ambiente en atmósfera de nitrógeno durante toda la noche. La mezcla se acidificó hasta pH 1 con HCl 3.8 M y a continuación se añadieron MTBE (50 mL) y agua (50 mL). Las fases se separaron, y la capa orgánica se lavó con agua, $NaHCO_3$ sat. y salmuera. La capa orgánica se secó con Na_2SO_4, se filtró y se evaporó para obtener un aceite amarillento. El producto se purificó en una columna Biotage (340 g) con 1 VC de EtOAc en heptano (20%) seguido de un gradiente de 20-60% de EtOAc en *n*-heptano (8 VC). La columna se acondicionó con 20% de EtOAc en *n*-heptano (1 VC). Se aisló *cis*-2-(2,4-difluorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (870 mg, 32%). MS m/z 370 $(M+H)^+$.

Paso 2: *Cis*-2-(2,4-difluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *cis*-2-(2,4-difluorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (870 mg, 2.36 mmol) en MeOH (9 mL) y se enfrió hasta -45 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (0.693 mL, 2.36 mmol) durante 10 min y la solución amarilla se continuó agitando a -45 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.144 mL, 2.36 mmol) durante 8 min. La solución resultante se agitó a -45 °C durante 3 h. A continuación, la mezcla se vertió rápidamente sobre una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (12.13 mL, 72.78 mmol) y la mezcla se continuó agitando a 80 °C durante 20 min. El disolvente se evaporó y se añadieron DCM/agua. Las fases se separaron, y la fase orgánica se hizo pasar a través de un separador de fases y se evaporó para proporcionar un sólido blanco. El compuesto se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x50 DI en mm) utilizando un gradiente de 10-60% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/AcOH en 30 minutos con un flujo de 100 mL/min. Se aisló *cis*-2-(2,4-difluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (397 mg, 49%). MS m/z 339 $(M+H)^+$.

Paso 3: (2*R*,4*S*)-2-(2,4-Difluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El *cis*-2-(2,4-difluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (397 mg, 1.17 mmol) se sometió a HPLC preparativa quiral (columna: CelluCoat (250x50 mm), tamaño de partícula: 10 µm, fase móvil: 60/40 de heptano/EtOH, velocidad de flujo: 120 mL/min) para proporcionar (2*R*,4*S*)-2-(2,4-difluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (187 mg, 47%), pureza quiral: 99.1% de ee, rotación óptica $[\alpha]_D^{20} = +65.0$ (acetonitrilo, c=0.5), ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.82 - 1.92 (m, 1H), 2.02 - 2.14 (m, 1H), 2.23 - 2.40 (m, 2H), 3.01 - 3.13 (m, 1H), 3.44 - 3.55 (m, 1H), 3.63 (s, 3H), 4.11 - 4.21 (m, 1H), 5.16 (dd, 1H), 5.61 (s, 1H), 6.74 - 6.83 (m, 2H), 7.06 - 7.15 (m, 1H).

Paso 4: 5-((2*R*,4*S*)-2-(2,4-Difluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-2-(2,4-difluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (187 mg, 0.55 mmol) en ácido bromhídrico (al 33% en ácido acético, 4.36 mL, 24.87 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*S*)-2-(2,4-difluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona (93 mg, 60%). ^{1}H RMN (600 MHz, DMSO) δ 1.36 (c, 1H), 1.46 (dc, 1H), 1.83 - 1.89 (m, 1H), 1.90 - 1.95 (m, 1H), 2.72 (dt, 1H), 2.89 (tt, 1H), 3.06 - 3.12 (m, 1H), 3.89 (dd, 1H), 5.73 (s, 1H), 7.03 (dt, 1H), 7.11 - 7.17 (m, 1H), 7.52 - 7.59 (m, 1H). HRMS calculado para $[C_{14}H_{14}F_2N_2O_2+H]^+$: 281.1101. Experimental: 281.1106.

Ejemplo 45

5-((2*R*,4*S*)-2-(4-Cloro-2-fluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(4-cloro-2-fluorofenil)-4-(3-etoxi-3-

oxopropanoil)piperidin-1-carboxilato de metilo y *cis*-2-(4-cloro-2-fluorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo

Se disolvió el ácido 2-(4-cloro-2-fluorofenil)-1-(metoxicarbonil)piperidin-4-carboxílico (6.49 g, 20.56 mmol) (compuesto de referencia 20) en metil-THF (250 mL) y a continuación se añadió di(1*H*-imidazol-1-il)metanona (5.00 g, 30.83 mmol). La mezcla se agitó a temperatura ambiente en atmósfera de nitrógeno durante 3 h (matraz 1). En otro matraz, se suspendió 3-etoxi-3-oxopropanoato de potasio (6.30 g, 37.00 mmol) en metil-THF (250 mL) y a continuación se añadió cloruro de magnesio (3.52 g, 37.00 mmol). La suspensión se agitó a 50 °C en atmósfera de nitrógeno durante 3 h utilizando un imán grande (matraz 2). 3 h después, el contenido del matraz 1 se transfirió al matraz 2. La suspensión blanca resultante se agitó a temperatura ambiente en atmósfera de nitrógeno durante toda la noche. La mezcla se acidificó hasta pH 1 con HCl 3.8 M y a continuación se añadieron MTBE (50 mL) y agua (50 mL). Las fases se separaron, y la capa orgánica se lavó con agua, $NaHCO_3$ sat. y salmuera. La capa orgánica se secó con Na_2SO_4, se filtró y se evaporó para obtener un aceite amarillento. El producto se purificó en una columna Biotage (340 g) con 1 VC con 20% de EtOAc en heptano seguido de un gradiente de 20-60% de EtOAc en *n*-heptano (8 VC). La columna se acondicionó con 20% de EtOAc en *n*-heptano (1 VC). Se aislaron *trans*-2-(4-cloro-2-fluorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (0.5 g, 6%) y *cis*-2-(4-cloro-2-fluorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (2.31 g, 29%). Isómero *cis*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.27 (t, 3H), 1.79 - 1.99 (m, 2H), 2.03 - 2.21 (m, 1H), 2.23 - 2.32 (m, 1H), 2.84 - 2.95 (m, 1H), 3.33 - 3.51 (m, 3H), 3.62 (s, 3H), 4.12 - 4.23 (m, 3H), 4.98 - 5.21 (m, 1H), 6.98 - 7.24 (m, 3H). MS m/z 386 $(M+H)^+$. Isómero *trans*:^{1}H RMN (400 MHz, $CDCl_3$) δ 1.22 (t, 3H), 1.57 - 1.69 (m, 1H), 1.86 - 2.01 (m, 2H), 2.36 - 2.62 (m, 2H), 3.07 - 3.18 (m, 1H), 3.44 (s, 2H), 3.70 (s, 3H), 4.10 - 4.21 (m, 2H), 4.32 (a, 1H), 5.67 (a, 1H), 7.02 - 7.14 (m, 3H). MS

m/z 386 $(M+H)^+$.

Paso 2: *Cis*-2-(4-cloro-2-fluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *cis*-2-(4-cloro-2-fluorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (2.31 g, 5.99 mmol) en MeOH (24 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (1.761 mL, 5.99 mmol) durante 10 min y la solución amarilla se continuó agitando a -40 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.367 mL, 5.99 mmol) durante 8 min. La solución resultante se agitó a -40 °C durante 3 h. A continuación, la mezcla se vertió rápidamente sobre una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (30.8 mL, 185.01 mmol) y la mezcla se continuó agitando a 80 °C durante 20 min. El disolvente se evaporó y se añadieron DCM/agua. Las fases se separaron, y la fase orgánica se hizo pasar a través de un separador de fases y se evaporó para proporcionar un sólido amarillento. El compuesto se purificó mediante HPLC preparativa en una columna XBridge C18 (10 µm 250x50 DI en mm) utilizando un gradiente de 10-55% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 30 minutos con un flujo de 100 mL/min. Posteriormente, se aisló *cis*-2-(4-cloro-2-fluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1 g, 47%). MS m/z 355 $(M+H)^+$.

Paso 3: (2*R*,4*S*)-2-(4-Cloro-2-fluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El *cis*-2-(4-cloro-2-fluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1 g, 2.82 mmol) se sometió a HPLC preparativa quiral (columna: CelluCoat (250x50), tamaño de partícula: 10 µm, fase móvil: 50/50 de heptano/IPA, velocidad de flujo: 120 mL/min) para proporcionar (2*R*,4*S*)-2-(4-cloro-2-fluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (504 mg, 50%), pureza quiral: 99.7% de ee, rotación óptica $[\alpha]_D^{20} = +65.5$ (acetonitrilo, c=1).

Paso 4: 5-((2*R*,4*S*)-2-(4-Cloro-2-fluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-2-(4-cloro-2-fluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.504 g, 1.42 mmol) en ácido bromhídrico (al 33% en ácido acético, 11.20 mL, 63.93 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*S*)-2-(4-cloro-2-fluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona (313 mg, 74%). ^{1}H RMN (600 MHz, DMSO) δ 1.35 (c, 1H), 1.46 (dc, 1H), 1.86 (d, 1H), 1.94 (d, 1H), 2.73 (dt, 1H), 2.90 (tt, 1H), 3.10 (td, 1H), 3.91 (d, 1H), 5.73 (s, 1H), 7.25 (dd, 1H), 7.34 (dd, 1H), 7.55 (t, 1H). HRMS calculado para $[C_{14}H_{14}ClFN_2O_2+H]+$: 297.0806. Experimental: 297.0786.

Ejemplo 46

5-(*Trans*-2-(4-cloro-2-fluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(4-cloro-2-fluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *trans*-2-(4-cloro-2-fluorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (500 mg, 1.30 mmol) (del paso 1 del ejemplo 45) en MeOH (6 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (0.381 mL, 1.30 mmol) durante 10 min y la solución amarilla se continuó agitando a -40 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.079 mL, 1.30 mmol) durante 8 min. La solución resultante se agitó a -40 °C durante 3 h. A continuación, la mezcla se vertió rápidamente sobre una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (6.67 mL, 40.05 mmol) y la mezcla se continuó agitando a 80 °C durante 20 min. El disolvente se evaporó y se añadieron DCM/agua. Las fases se separaron y la fase orgánica se hizo pasar a través de un separador de fases y se evaporó

para proporcionar *trans*-2-(4-cloro-2-fluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo crudo (0.45 g, 98%) como una película seca amarillenta. MS m/z 355 $(M+H)^+$.

Paso 2: 5-(*Trans*-2-(4-cloro-2-fluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*S*,4*S*)-2-(4-cloro-2-fluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.45 g, 1.27 mmol) en ácido bromhídrico (al 33% en ácido acético, 10.00 mL, 57.08 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-(*trans*-2-(4-cloro-2-fluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona (82 mg, 22%). ^{1}H RMN (400 MHz, DMSO) δ 1.66 - 1.77 (m, 1H), 1.77 - 1.90 (m, 1H), 1.92 - 2.00 (m, 1H), 2.02 - 2.10 (m, 1H), 2.63 - 2.79 (m, 1H), 2.88 - 2.97 (m, 1H), 3.03 - 3.86 (señales omitidas), 3.95 (d, 1H), 5.88 (s, 1H), 7.27 (dd, 1H), 7.35 (dd, 1H), 7.56 (t, 1H). HRMS calculado para $[C_{14}H_{14}ClFN_2O_2+H]+$: 297.0806. Experimental: 297.0806.

Ejemplo 47

5-((2*R*,4*S*)-2-(2-Cloro-4-fluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: 2-(2-Cloro-4-fluorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo

Se disolvió el ácido 2-(2-cloro-2-fluorofenil)-1-(metoxicarbonil)piperidin-4-carboxílico (2.13 g, 6.75 mmol) (compuesto de referencia 21) en metil-THF (50 mL) en atmósfera de nitrógeno y se añadió di(1*H*-imidazol-1-il)metanona (1.641 g, 10.12 mmol). La suspensión se agitó a temperatura ambiente durante 3 h (matraz 1). En otro matraz, se suspendió 3-etoxi-3-oxopropanoato de potasio (2.067 g, 12.14 mmol) en metil-THF (25 mL) y se añadió cloruro de magnesio (1.156 g, 12.14 mmol). La suspensión se agitó a 50 °C en atmósfera de nitrógeno durante

15 h utilizando un imán muy grande. El contenido del matraz 1 se añadió al matraz 2 y la suspensión blanca resultante se agitó a temperatura ambiente durante 20 h. En otro matraz, se suspendió 3-etoxi-3-oxopropanoato de potasio (1.033 g, 6.07 mmol) en metil-THF (25 mL) y se añadió cloruro de magnesio (0.578 g, 6.07 mmol). La suspensión se agitó a 50 °C durante 15 h y después se añadió a la mezcla de reacción. La mezcla se agitó a temperatura ambiente durante 15 h. Se añadieron HCl 0.1 M y DCM, y las dos fases se separaron. La fase acuosa se extrajo con DCM, las fases orgánicas combinadas se filtraron a través de un separador de fases y se evaporaron. El residuo se purificó en una columna Biotage (gradiente 2:1->1:1 de heptano:EtOAc, columna Biotage® con 340 g de KP-SIL, 10 VC). Se aisló 2-(2-cloro-4-fluorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (1.655 g, 63.6%) como un aceite incoloro. MS m/z 386 $(M+H)^+$.

Paso 2: 2-(2-Cloro-4-fluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió 2-(2-cloro-4-fluorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (1.655 g, 4.29 mmol) en MeOH (22 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (0.180 g, 4.50 mmol) disuelto en agua (2.200 mL) y la mezcla se agitó a -40 °C durante 15 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.276 mL, 4.50 mmol). La solución resultante se agitó a -40 °C durante 1 h. Posteriormente, la mezcla se transfirió con una pipeta a una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (22.16 mL, 132.98 mmol) y la mezcla se agitó a 80 °C durante 15 min. Se añadieron agua y DCM y se separaron las fases. La fase acuosa se extrajo con DCM, las fases orgánicas combinadas se filtraron a través de un separador de fases y se evaporaron. El compuesto se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x50 DI en mm) utilizando un gradiente de 15-55% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/AF en 25 minutos con un flujo de 100 mL/min (3 purificaciones). Se proporcionó

2-(2-cloro-4-fluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.995 g, 65.4%) como un sólido blanco. MS m/z 355 $(M+H)^+$.

Paso 3: (2*R*,4*S*)-2-(2-Cloro-4-fluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo y *trans*-2-(2-cloro-4-fluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El 2-(2-cloro-4-fluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.995 g, 2.81 mmol) se sometió a cromatografía quiral: Separación 1: HPLC preparativa quiral (columna: Chiralpak IA (250x50 mm), tamaño de partícula: 20 µm, fase móvil: 70/30 de heptano/EtOH, velocidad de flujo: 120 mL/min). Separación 2: HPLC preparativa quiral (columna: CelluCoat (250x50 mm), tamaño de partícula: 10 µm, fase móvil: 90/10 de heptano/EtOH, velocidad de flujo: 120 mL/min). Se aisló (2*R*,4*S*)-2-(2-cloro-4-fluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (382 mg, 38%), pureza quiral: 98.9% de ee, rotación óptica $[\alpha]_D^{20} = +71.2$ (acetonitrilo, c=0.5). Se aisló *trans*-2-(2-cloro-4-fluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (130 mg, 13%).

Paso 4: 5-((2*R*,4*S*)-2-(2-Cloro-4-fluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-2-(2-cloro-4-fluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (382 mg, 1.08 mmol) en ácido bromhídrico (al 33% en ácido acético, 8.5 mL, 48.46 mmol) y se agitó a temperatura ambiente durante 16 h. El disolvente se eliminó al vacío y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*S*)-2-(2-cloro-4-fluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona (304 mg, 95%). ^{1}H RMN (600 MHz, DMSO) δ 1.24 (c, 1H), 1.47 (dc, 1H), 1.85 - 1.91 (m, 1H), 1.97 - 2.02 (m, 1H), 2.75 (dt, 1H), 2.87 (tt, 1H), 3.09 - 3.14 (m, 1H),

3.97 (d, 1H); 5.73 (d, 1H), 7.19 (dt, 1H), 7.37 (dd, 1H), 7.66 (dd, 1H). HRMS calculado para $[C_{14}H_{14}ClFN_2O_2+H]^+$: 297.0806. Experimental: 297.0834.

Ejemplo 48

5-(*Trans*-2-(2-cloro-4-fluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió *trans*-2-(2-cloro-4-fluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (130 mg, 0.37 mmol) (del paso 3 del ejemplo 47) en ácido bromhídrico (al 33% en ácido acético, 2.9 mL, 16.49 mmol) y se agitó a temperatura ambiente durante 16 h. El disolvente se eliminó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-(*trans*-2-(2-cloro-4-fluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona (94 mg, 86%). ^{1}H RMN (600 MHz, DMSO) δ 1.50 - 1.60 (m, 1H), 1.79 - 1.88 (m, 1H), 1.95 - 2.01 (m, 1H), 2.06 - 2.12 (m, 1H), 2.70 (t, 1H), 2.88 - 2.96 (m, 1H), 3.20 - 3.24 (m, 1H), 4.01 (d, 1H), 5.95 (d, 1H), 7.21 (dt, 1H), 7.37 (dd, 1H), 7.68 (dd, 1H). HRMS calculado para $[C_{14}H_{14}ClFN_2O_2+H]^+$: 297.0806. Experimental: 297.0823.

Ejemplo 49

5-((2*R*,4*S*)-2-(4-Cloro-3-fluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(4-cloro-3-fluorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo y *cis*-2-(4-cloro-3-fluorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo

Se disolvió el ácido 2-(4-cloro-3-fluorofenil)-1-(metoxicarbonil)piperidin-4-carboxílico (1.430 g, 4.53 mmol) (compuesto de referencia 22) en metil-THF (20 mL) y se añadió di(1*H*-imidazol-1-il)metanona (1.102 g, 6.79 mmol). La reacción se agitó a temperatura ambiente durante 6 h (matraz 1). En otro matraz, se suspendió 3-etoxi-3-oxopropanoato de potasio (1.388 g, 8.15 mmol) en metil-THF (20.00 mL) y se añadió cloruro de magnesio (0.776 g, 8.15 mmol). La suspensión se agitó a 50 °C

durante 6 h (matraz 2). La suspensión blanca del matraz 2 se añadió al matraz 1. Se formó una suspensión blanca. La suspensión se agitó a temperatura ambiente durante 18 h. La suspensión se acidificó hasta pH 1 con HCl 3 M. Se añadieron MTBE (100 mL) y agua (150 mL), se agitó y se separaron las fases. La fase orgánica se lavó con agua (150 mL), $NaHCO_3$ sat. (150 mL) y salmuera (150 mL), se secó con Na_2SO_4, se filtró y se evaporó al vacío. El residuo se purificó mediante cromatografía flash automatizada en una columna Biotage® con 100 g de KP-SIL. Se utilizó como fase móvil un gradiente de 20% de EtOAc en heptano en 2 VC seguido de 20%-60% de EtOAc en heptano en 10 VC. Se aislaron *cis*-2-(4-cloro-3-fluorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (1.153 g, 66.0%) y *trans*-2-(4-cloro-3-fluorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (0.107 g, 6.12%) como aceites incoloros. Isómero *cis*: ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.19 - 1.30 (m, 3H), 1.73 - 1.97 (m, 2H), 2.00 - 2.16 (m, 1H), 2.20 - 2.27 (m, 1H), 2.81 - 2.89 (m, 1H), 3.24 - 3.48 (m, 3H), 3.60 - 3.65 (m, 3H), 4.04 - 4.20 (m, 3H), 4.84 - 4.98 (m, 1H), 6.86 - 7.01 (m, 2H), 7.28 - 7.34 (m, 1H). MS m/z 386 $(M+H)^+$. Isómero *trans*: ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.19 - 1.29 (m, 3H), 1.38 - 2.98 (m, 6H), 3.39 - 3.49 (m, 2H), 3.63 - 3.82 (m, 3H), 4.00 - 4.37 (m, 3H), 5.56 (s a, 1H), 6.86 - 7.02 (m, 2H), 7.33 - 7.39 (m, 1H). MS m/z 386 $(M+H)^+$.

Paso 2: <u>*Cis*-2-(4-cloro-3-fluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo</u>

Se disolvió *cis*-2-(4-cloro-3-fluorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (1.731 g, 4.49 mmol) en MeOH (20 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (1.181 mL, 4.49 mmol) disuelto en agua (2 mL) y la reacción se agitó a -40 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.247 mL, 4.49 mmol) gota a gota y se continuó agitando durante 3 h. La mezcla se transfirió posteriormente a una solución calentada previamente a 80 °C de ácido clorhídrico 6 M (23.18 mL, 139.09 mmol) y se continuó agitando a 80 °C durante 20 min. El

disolvente se evaporó y se añadieron DCM (200 mL) y agua (200 mL). Las fases se agitaron, se separaron, y la fase orgánica se secó con un separador de fases y se evaporó al vacío. El compuesto se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x50 DI en mm) utilizando un gradiente de 10-60% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/AcOH en 30 minutos con un flujo de 100 mL/min. Se aisló *cis*-2-(4-cloro-3-fluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.921 g, 57.9%) como un sólido blanco. ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.79 - 1.87 (m, 1H), 2.06 - 2.15 (m, 1H), 2.19 - 2.28 (m, 1H), 2.30 - 2.37 (m, 1H), 3.00 - 3.09 (m, 1H), 3.31 - 3.40 (m, 1H), 3.66 (s, 3H), 4.07 - 4.16 (m, 1H), 5.00 - 5.07 (m, 1H), 5.56 (s, 1H), 6.87 - 6.91 (m, 1H), 6.95 (dd, 1H), 7.29 (t, 1H). MS m/z 355 $(M+H)^+$.

Paso 3: (2*R*,4*S*)-2-(4-Cloro-3-fluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El *cis*-2-(4-cloro-3-fluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.921 g, 2.6 mmol) se sometió a HPLC preparativa quiral (columna: CelluCoat (250x50 mm), tamaño de partícula: 10 µm, fase móvil: 1/1 de heptano/EtOH, velocidad de flujo: 120 mL/min) para proporcionar (2*R*,4*S*)-2-(4-cloro-3-fluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (446 mg, 48%), pureza quiral: 99.9% de ee, rotación óptica $[\alpha]_D^{20} = +61.8$ (acetonitrilo, c=0.5).

Paso 4: 5-((2*R*,4*S*)-2-(4-Cloro-3-fluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-2-(4-cloro-3-fluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (446 mg, 1.26 mmol) en ácido bromhídrico (al 33% en AcOH, 6.8 mL, 38.97 mmol) y se agitó a temperatura ambiente durante 20 h. El disolvente se evaporó posteriormente y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar

5-((2*R*,4*S*)-2-(4-cloro-3-fluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona (266 mg, 71%). ^{1}H RMN (600 MHz, DMSO) δ 1.31 (c, 1H), 1.44 (dc, 1H), 1.82 - 1.89 (m, 1H), 1.94 - 2.00 (m, 1H), 2.70 (dt, 1H), 2.84 (tt, 1H), 3.06 - 3.12 (m, 1H), 3.66 (dd, 1H), 5.72 (s, 1H), 7.23 (dd, 1H), 7.38 (dd, 1H), 7.49 (t, 1H). HRMS calculado para $[C_{14}H_{14}ClFN_2O_2+H]^+$: 297.0806. Experimental: 297.0795.

Ejemplo 50

5-(*Trans*-2-(4-cloro-3-fluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(4-cloro-3-fluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *trans*-2-(4-cloro-3-fluorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (171 mg, 0.44 mmol) (del paso 1 del ejemplo 49) en MeOH (2 mL) y se enfrió hasta -40 °C. Se añadió hidróxido sódico (0.117 mL, 0.44 mmol) disuelto en agua (0.200 mL) gota a gota y la solución se agitó duarante 20 min. Posteriormente, se añadió hidroxilamina (al 50% en peso en agua, 0.024 mL, 0.44 mmol) y se continuó agitando durante 3.5 h. A continuación, la mezcla se transfirió a una solución calentada previamente a 80 °C de ácido clorhídrico 6 M (2.290 mL, 13.74 mmol) y se continuó agitando a 80 °C durante 20 min. El disolvente se evaporó al vacío y se añadieron DCM (50 mL) y agua (50 mL). Las fases se agitaron, se separaron, y la fase orgánica se secó con un separador de fases y se evaporó al vacío. El compuesto se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x20 DI en mm) utilizando un gradiente de 10-60% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/AcOH en 30 minutos con un flujo de 19 mL/min. Se aisló (2*S*,4*S*)-2-(4-cloro-3-fluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (49.0 mg, 31.2%) como un sólido blanco. ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.58 - 1.70 (m, 1H), 1.85 - 2.06 (m, 2H), 2.60 (d, 1H), 2.73 - 2.96 (m, 2H), 3.73 (s, 3H), 4.04 - 4.44 (m, 1H), 5.42 - 5.78 (m, 2H), 6.92 - 7.05 (m, 2H), 7.38 (t, 1H). MS m/z 355 $(M+H)^+$.

Paso 2: 5-(*Trans*-2-(4-cloro-3-fluorofenil)piperidin-4-

il)isoxazol-3(2*H*)-ona

Se disolvió *trans*-2-(4-cloro-3-fluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (49 mg, 0.14 mmol) en ácido bromhídrico (al 33% en AcOH, 2 mL, 11.42 mmol) y se agitó a temperatura ambiente durante 5 h. La reacción se calentó hasta 50 °C durante 3 h. La mezcla de reacción se evaporó al vacío y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-(*trans*-2-(4-cloro-3-fluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona (23 mg, 56%). ^{1}H RMN (600 MHz, DMSO) δ 1.72 - 1.81 (m, 2H), 1.82 - 1.89 (m, 1H), 1.97 - 2.04 (m, 1H), 2.64 - 2.71 (m, 1H), 2.77 - 2.83 (m, 1H), 3.06 - 3.12 (m, 1H), 3.72 (dd, 1H), 5.96 (s, 1H), 7.23 (dd, 1H), 7.40 (dd, 1H), 7.49 (t, 1H). HRMS calculado para $[C_{14}H_{14}ClFN_2O_2+H]^+$: 297.0806. Experimental: 297.0807.

Ejemplo 51

5-((2*R*,4*S*)-2-(2,4-Diclorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: 2-(2,4-Diclorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo

Se disolvió el ácido 2-(2,4-diclorofenil)-1-(metoxicarbonil)piperidin-4-carboxílico (2.44 g, 7.35 mmol) (compuesto de referencia 23) en metil-THF (36.7 mL) y se añadió di(1*H*-imidazol-1-il)metanona (1.787 g, 11.02 mmol). La suspensión se agitó a temperatura ambiente en atmósfera de nitrógeno durante 6 h (matraz 1). En otro matraz, se suspendió 3-etoxi-3-oxopropanoato de potasio (2.250 g, 13.22 mmol) en metil-THF (36.7 mL) y se añadió cloruro de magnesio (1.259 g, 13.22 mmol). La suspensión se agitó en atmósfera de nitrógeno durante 6 h (matraz 2). A continuación, la suspensión blanca del matraz 2 se añadió a la suspensión marrón del matraz 1. La suspensión resultante se agitó a temperatura ambiente durante 40 h. La mezcla se acidificó hasta pH 1 con HCl 3 M. Se añadieron agua y metil-THF, y se separaron las fases. La capa

orgánica se lavó con agua, $NaHCO_3$ sat. y salmuera, se secó con $MgSO_4$, se filtró y se evaporó. Se purificó mediante cromatografía flash utilizando 20% de EtOAc en heptano -> 50% de EtOAc en 10 VC, 3 VC con el 50%. Se purificó de nuevo mediante cromatografía flash utilizando 20% de EtOAc en EtOAc -> 30% de EtOAc en 12 VC. Se aisló 2-(2,4-diclorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (1.55 g, 52%).

Paso 2: 2-(2,4-Diclorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió 2-(2,4-diclorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (1.55 g, 3.85 mmol) en MeOH (15.79 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (1.014 mL, 3.85 mmol) en agua (1.579 mL) y la mezcla se agitó a -40 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.236 mL, 3.85 mmol) y se continuó agitando a -40 °C durante 3.5 h. La mezcla de reacción se transfirió posteriormente a una solución calentada previamente a 80 °C de ácido clorhídrico 6 M (19.91 mL, 119.45 mmol) y se continuó calentando durante 20 min. A continuación se evaporó el disolvente. Se añadieron DCM y agua, se agitó y se separaron las fases. La fase orgánica se secó con un separador de fases y se evaporó al vacío. El compuesto se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x50 DI en mm) utilizando un gradiente de 25-65% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/AcOH en 30 minutos con un flujo de 100 mL/min. Se aisló 2-(2,4-diclorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.870 g, 60.8%) como un sólido blanco. MS m/z 371 $(M+H)^+$.

Paso 3: (2*R*,4*S*)-2-(2,4-Diclorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo, (2*S*,4*R*)-2-(2,4-diclorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo, (2*S*,4*S*)-2-(2,4-diclorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo y (2*R*,4*R*)-2-(2,4-diclorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El 2-(2,4-diclorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.870 g, 2.34 mmol) se sometió a HPLC preparativa quiral: Separación 1: Los enantiómeros se separaron utilizando HPLC preparativa quiral (columna: ReproSil (250x50 mm), tamaño de partícula: 8 µm, fase móvil: 60/40/0.1 de heptano/EtOH/AF, velocidad de flujo: 120 mL/min) para proporcionar una mezcla de un enantiómero *cis* y uno *trans*. Separación 2: Los enantiómeros se separaron utilizando HPLC preparativa quiral (columna: CelluCoat (250x20 mm), tamaño de partícula: 5 µm, fase móvil: 80/20/0.1 de heptano/IPA/AF, velocidad de flujo: 18 mL/min). Se aisló (2*R*,4*S*)-2-(2,4-diclorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (334 mg, 38%). Pureza quiral: 99.7% de de, rotación óptica $[\alpha]_D^{20} = +64.0$ (acetonitrilo, c=1.0), ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.79 - 1.92 (m, 2H), 2.25 - 2.48 (m, 2H), 3.02 - 3.13 (m, 1H), 3.53 - 3.64 (m, 4H), 4.12 - 4.21 (m, 1H), 5.16 (dd, 1H), 5.64 (s, 1H), 7.12 - 7.22 (m, 2H), 7.36 (d, 1H). Se aisló (2*S*,4*R*)-2-(2,4-diclorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (340 mg, 39%). Pureza quiral: 99.9% de de, rotación óptica $[\alpha]_D^{20} = -65.1$ (acetonitrilo, c=1.0), ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.79 - 1.92 (m, 2H), 2.26 - 2.38 (m, 1H), 2.39 - 2.48 (m, 1H), 3.03 - 3.13 (m, 1H), 3.53 - 3.64 (m, 4H), 4.12 - 4.22 (m, 1H), 5.16 (dd, 1H), 5.64 (s, 1H), 7.13 - 7.22 (m, 2H), 7.36 (d, 1H). Se aisló (2*S*,4*S*)-2-(2,4-diclorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (67 mg, 8%). Pureza quiral: 98.7% de de, rotación óptica $[\alpha]_D^{20} = +11.5$ (acetonitrilo, c=1.0), ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.72 (dc, 1H), 2.01 - 2.19 (m, 2H), 2.40 - 2.49 (m, 1H), 2.74 (tt, 1H), 3.43 (dt, 1H), 3.66 (s, 3H), 4.40 (d a, 1H), 5.61 - 5.71 (m, 2H), 7.14 - 7.24 (m, 2H), 7.40 (d, 1H). Se aisló (2*R*,4*R*)-2-(2,4-diclorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (75 mg, 9%). Pureza quiral: 98.5% de de, rotación óptica $[\alpha]_D^{20} = -10.9$ (acetonitrilo, c=1.0), ^{1}H RMN (400 MHz, $CDCl_3$)

δ 1.72 (dc, 1H), 2.01 - 2.19 (m, 2H), 2.40 - 2.49 (m, 1H), 2.74 (tt, 1H), 3.43 (dt, 1H), 3.68 (s, 3H), 4.40 (d a, 1H), 5.61 - 5.71 (m, 2H), 7.14 - 7.24 (m, 2H), 7.41 (d, 1H).

Paso 4: 5-((2*R*,4*S*)-2-(2,4-Diclorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se diluyó (2*R*,4*S*)-2-(2,4-diclorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (334 mg, 0.90 mmol) con ácido bromhídrico (al 33% en AcOH, 4.7 mL, 26.99 mmol) y se agitó a temperatura ambiente durante 24 h. Se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*S*)-2-(2,4-diclorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona (173 mg, 61%). ^{1}H RMN (600 MHz, DMSO) δ 1.22 (c, 1H), 1.47 (dc, 1H), 1.85 - 1.90 (m, 1H), 1.97 - 2.02 (m, 1H), 2.74 (dt, 1H), 2.87 (tt, 1H), 3.09 - 3.14 (m, 1H), 3.96 (dd, 1H), 5.73 (d, 1H), 7.40 (dd, 1H), 7.54 (d, 1H), 7.64 (d, 1H). HRMS calculado para $[C_{14}H_{14}Cl_2N_2O_2+H]^+$: 313.0511. Experimental: 313.0493.

Ejemplo 52

5-((2*S*,4*R*)-2-(2,4-Diclorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se diluyó (2*S*,4*R*)-2-(2,4-diclorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (340 mg, 0.92 mmol) (del paso 3 del ejemplo 51) con ácido bromhídrico (al 33% en AcOH, 4812 µL, 27.48 mmol) y se agitó a temperatura ambiente durante 24 h. Se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*S*,4*R*)-2-(2,4-diclorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona. ^{1}H RMN (600 MHz, DMSO) δ 1.22 (c, 1H), 1.47 (dc, 1H), 1.84 - 1.90 (m, 1H), 1.96 - 2.03 (m, 1H), 2.74 (dt, 1H), 2.87 (tt, 1H), 3.07 - 3.15 (m, 1H), 3.96 (dd, 1H), 5.73 (s, 1H), 7.40 (dd, 1H), 7.54 (d, 1H), 7.64 (d, 1H). HRMS calculado para $[C_{14}H_{14}Cl_2N_2O_2+H]^+$: 313.0511. Experimental: 313.0490.

Ejemplo 53

5-((2*S*,4*S*)-2-(2,4-Diclorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se diluyó (2*S*,4*S*)-2-(2,4-diclorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (67 mg, 0.18 mmol) (del paso 3 del ejemplo 51) con ácido bromhídrico (al 33% en AcOH, 948 µL, 5.41 mmol) y se agitó a temperatura ambiente durante 24 h. Se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*S*,4*S*)-2-(2,4-diclorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona (36 mg, 64%). ^{1}H RMN (600 MHz, DMSO) δ 1.46 - 1.54 (m, 1H), 1.77 - 1.85 (m, 1H), 1.93 - 1.99 (m, 1H), 2.05 - 2.11 (m, 1H), 2.67 (dt, 1H), 2.86 - 2.92 (m, 1H), 3.18 - 3.22 (m, 1H), 3.98 (dd, 1H), 5.93 (d, 1H), 7.40 (dd, 1H), 7.53 (d, 1H), 7.66 (d, 1H). HRMS calculado para $[C_{14}H_{14}Cl_2N_2O_2+H]^+$: 313.0511. Experimental: 313.0499.

Ejemplo 54

5-((2*R*,4*R*)-2-(2,4-Diclorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se diluyó (2*R*,4*R*)-2-(2,4-diclorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (75 mg, 0.20 mmol) (del paso 3 del ejemplo 51) con ácido bromhídrico (al 33% en AcOH, 1062 µL, 6.06 mmol) y se agitó a temperatura ambiente durante 24 h. Se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*R*)-2-(2,4-diclorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona (38 mg, 60%). ^{1}H RMN (600 MHz, DMSO) δ 1.47 - 1.54 (m, 1H), 1.78 - 1.85 (m, 1H), 1.93 - 1.99 (m, 1H), 2.05 - 2.11 (m, 1H), 2.67 (dt, 1H), 2.86 - 2.92 (m, 1H), 3.18 - 3.22 (m, 1H), 3.98 (dd, 1H), 5.93 (d, 1H), 7.41 (dd, 1H), 7.53 (d, 1H), 7.66 (d, 1H). HRMS calculado para $[C_{14}H_{14}Cl_2N_2O_2+H]^+$: 313.0511. Experimental: 313.0494.

Ejemplo 55

5-((2*R*,4*S*)-2-(3,5-Diclorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(3,5-diclorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo y *cis*-2-(3,5-diclorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo

Se disolvió el ácido 2-(3,5-diclorofenil)-1-(metoxicarbonil)piperidin-4-carboxílico (4.6 g, 13.85 mmol) (compuesto de referencia 24) en metil-THF (69.2 mL) y se añadió di(1*H*-imidazol-1-il)metanona (3.37 g, 20.77 mmol). La suspensión se agitó a temperatura ambiente durante toda la noche en atmósfera de nitrógeno (matraz 1). En otro matraz, se suspendió 3-etoxi-3-oxopropanoato de potasio (4.24 g, 24.93 mmol) en metil-THF (69.2 mL) y se añadió cloruro de magnesio (2.373 g, 24.93 mmol). La suspensión se agitó a 50 °C durante toda la noche en atmósfera de nitrógeno (matraz 2). A continuación, la suspensión blanca del matraz 2 se añadió a la suspensión marrón del matraz 1. La suspensión resultante se agitó a temperatura ambiente durante 40 h. La mezcla se acidificó hasta pH 1 con HCl 3 M. Se añadieron agua y metil-THF. Las fases se separaron, la capa orgánica se lavó con agua, $NaHCO_3$ sat. y salmuera, se secó con $MgSO_4$, se filtró y se evaporó. Se purificó mediante cromatografía flash utilizando 20% de EtOAc en heptano -> 50% de EtOAc en 10 VC, 3 VC con el 50%. Se aislaron *trans*-2-(3,5-diclorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (0.6 g, 11%) y *cis*-2-(3,5-diclorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (3.57 g, 64%). Isómero *cis*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.22 - 1.32 (m, 3H), 1.79 - 1.94 (m, 2H), 2.03 - 2.17 (m, 1H), 2.20 - 2.29 (m, 1H), 2.82 - 2.93 (m, 1H), 3.24 - 3.34 (m, 1H), 3.46 (d, 2H), 3.64 - 3.68 (m, 3H), 4.10 - 4.23 (m, 3H), 4.83 - 4.92 (m, 1H), 7.06 - 7.09 (m, 2H), 7.22 - 7.25 (m, 1H). MS m/z 402 $(M+H)^+$. Isómero *trans*: MS m/z 402 $(M+H)^+$.

Paso 2: *Cis*-2-(3,5-diclorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *cis*-2-(3,5-diclorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (3.57 g, 8.87 mmol) en MeOH (36.4 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (2.335 mL, 8.87 mmol) en agua (3.64 mL) y la mezcla se agitó a -40 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.544 mL, 8.87 mmol) y se continuó agitando a -40 °C durante 3.5 h. La mezcla de reacción se transfirió posteriormente a una solución calentada previamente a 80 °C de ácido clorhídrico 6 M (45.9 mL, 275.11 mmol) y se continuó agitando durante 20 min. A continuación se evaporó el disolvente. Se añadieron DCM y agua, se agitó y se separaron las fases. La fase orgánica se secó con un separador de fases y se evaporó al vacío. El compuesto se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x50 DI en mm) utilizando un gradiente de 25-65% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/AcOH en 30 minutos con un flujo de 100 mL/min. Se aisló *cis*-2-(3,5-diclorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (2.000 g, 60.7%) como un sólido blanco. ^{1}H RMN (400 MHz, CD_3OD) δ 1.82 - 1.93 (m, 1H), 2.13 - 2.27 (m, 2H), 2.30 - 2.39 (m, 1H), 3.06 - 3.16 (m, 1H), 3.42 - 3.53 (m, 1H), 3.66 (s, 3H), 4.04 - 4.12 (m, 1H), 5.06 (dd, 1H), 5.64 (d, 1H), 7.14 - 7.18 (m, 2H), 7.27 (t, 1H). MS m/z 371 $(M+H)^+$.

Paso 3: (2*R*,4*S*)-2-(3,5-Diclorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo y (2*S*,4*R*)-2-(3,5-diclorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El *cis*-2-(3,5-diclorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (2.000 g, 5.4 mmol) se sometió a HPLC preparativa quiral (columna: CelluCoat (250x50 mm), tamaño de partícula: 10 µm, fase móvil: 70/30 de heptano/EtOH, velocidad de flujo: 120 mL/min) para proporcionar (2*R*,4*S*)-2-(3,5-diclorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.05 g, 50%), pureza quiral: 99.6% de ee, rotación óptica $[\alpha]_D^{20} = +67.1$ (acetonitrilo,

c=1.0), y (2*S*,4*R*)-2-(3,5-diclorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.06 g, 50%), pureza quiral: 97.6% de ee, rotación óptica $[\alpha]_D^{20} = -58.4$ (acetonitrilo, c=1.0).

Paso 4: 5-((2*R*,4*S*)-2-(3,5-Diclorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-2-(3,5-diclorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1 g, 2.69 mmol) en ácido bromhídrico (al 33% en AcOH, 4.67 mL, 80.82 mmol). Se agitó durante toda la noche y se evaporó, y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*S*)-2-(3,5-diclorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona (607 mg, 72%). ^{1}H RMN (600 MHz, DMSO) δ 1.32 (c, 1H), 1.44 (dc, 1H), 1.84 - 1.89 (m, 1H), 1.97 - 2.03 (m, 1H), 2.70 (dt, 1H), 2.80 - 2.87 (m, 1H), 3.06 - 3.12 (m, 1H), 3.67 (dd, 1H), 5.75 (s, 1H), 7.42 (d, 2H), 7.44 (t, 1H). HRMS calculado para $[C_{14}H_{14}Cl_2N_2O_2+H]^+$: 313.0511. Experimental: 313.0513.

Ejemplo 56

5-((2*S*,4*R*)-2-(3,5-Diclorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*S*,4*R*)-2-(3,5-diclorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1 g, 2.69 mmol) (del paso 3 del ejemplo 55) en ácido bromhídrico (al 33% en AcOH, 4.67 mL, 80.82 mmol) y se agitó durante toda la noche. Se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*S*,4*R*)-2-(3,5-diclorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona (509 mg, 60%). ^{1}H RMN (600 MHz, DMSO) δ 1.32 (c, 1H), 1.44 (dc, 1H), 1.84 - 1.89 (m, 1H), 1.97 - 2.02 (m, 1H), 2.70 (dt, 1H), 2.84 (tt, 1H), 3.07 - 3.12 (m, 1H), 3.67 (dd, 1H), 5.75 (s,

1H), 7.42 (d, 2H), 7.44 (t, 1H). HRMS calculado para $[C_{14}H_{14}Cl_2N_2O_2+H]^+$: 313.0511. Experimental: 313.0516.

Ejemplo 57

5-(*Trans*-2-(3,5-diclorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(3,5-diclorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *trans*-2-(3,5-diclorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (0.6 g, 1.49 mmol) (del paso 1 del ejemplo 55) en MeOH (6.11 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (0.393 mL, 1.49 mmol) en agua (0.611 mL) y la mezcla se agitó a -40 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.091 mL, 1.49 mmol) y se continuó agitando a -40 °C durante 3.5 h. La mezcla de reacción se transfirió posteriormente a una solución calentada previamente a 80 °C de ácido clorhídrico 6 M (7.71 mL, 46.24 mmol) y se continuó calentando durante 20 min. A continuación se evaporó el disolvente. Se añadieron DCM y agua, se agitó y se separaron las fases. La fase orgánica se secó con un separador de fases y se evaporó para proporcionar *trans*-2-(3,5-diclorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo crudo (300 mg, 54%). MS m/z 371 $(M+H)^+$.

5-(*Trans*-2-(3,5-diclorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se diluyó *trans*-2-(3,5-diclorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (300 mg, 0.81 mmol) con ácido bromhídrico (al 33% en AcOH, 4.3 mL, 24.24 mmol) y se agitó a temperatura ambiente durante 48 h. Se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-(*trans*-2-(3,5-diclorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona (162 mg, 64%). ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.77 - 2.17 (m, 4H), 2.66 - 2.74 (m, 1H), 2.82 - 2.89 (m, 1H), 3.12 - 3.18 (m, 1H), 3.79 (d, 1H),

6.06 (s, 1H), 7.44 - 7.51 (m, 3H). HRMS calculado para $[C_{14}H_{14}Cl_2N_2O_2+H]^+$: 313.0511. Experimental: 313.0513.

Ejemplo 58

5-((2*R*,4*S*)-2-(2-Fluoro-4-trifluorometoxi)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-4-(3-etoxi-3-oxopropanoil)-2-(2-fluoro-4-(trifluorometoxi)fenil)piperidin-1-carboxilato de metilo y *cis*-4-(3-etoxi-3-oxopropanoil)-2-(2-fluoro-4-(trifluorometoxi)fenil)piperidin-1-carboxilato de metilo

Se disolvió el ácido 2-(2-fluoro-4-(trifluorometoxi)fenil)-1-(metoxicarbonil)piperidin-4-carboxílico (4.07 g, 11.14 mmol) (compuesto de referencia 25) en metil-THF (100 mL) en atmósfera de nitrógeno y se añadió di(1*H*-imidazol-1-il)metanona (2.71 g, 16.71 mmol). La suspensión se agitó a temperatura ambiente durante 5 h (matraz 1). En otro matraz, se suspendió 3-etoxi-3-oxopropanoato de potasio (3.41 g, 20.06 mmol) en metil-THF (50 mL) y se añadió cloruro de magnesio (1.910 g, 20.06 mmol). La suspensión se agitó a 50 °C en atmósfera de nitrógeno durante 15 h utilizando un imán muy grande (matraz 2). El contenido del matraz 1 se añadió al matraz 2 y la suspensión blanca resultante se agitó a temperatura ambiente durante 20 h. Se añadieron HCl 0.1 M y DCM, y se separaron las fases. La fase acuosa se extrajo con DCM, las fases orgánicas combinadas se filtraron a través de un separador de fases y se evaporaron. El residuo se purificó en una columna Biotage (gradiente 3:1->1:1 de heptano:EtOAc, columna Biotage® con 340 g de KP-SIL, 10 VC). Se aislaron *cis*-4-(3-etoxi-3-oxopropanoil)-2-(2-fluoro-4-(trifluorometoxi)fenil)piperidin-1-carboxilato de metilo (3.44 g, 70.9%) y *trans*-4-(3-etoxi-3-oxopropanoil)-2-(2-fluoro-4-(trifluorometoxi)fenil)piperidin-1-carboxilato de metilo (0.420 g, 8.66%) como aceites incoloros. Isómero *cis*: ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.23 - 1.28 (m, 3H), 1.77 - 1.96 (m, 2H), 2.03 - 2.14 (m, 1H), 2.24 - 2.31 (m, 1H), 2.84 - 2.93 (m, 1H), 3.32 - 3.48 (m, 3H), 3.57 - 3.65 (m, 3H), 4.08 - 4.20 (m, 3H), 5.03 - 5.12 (m, 1H), 6.89 - 6.98 (m, 2H), 7.13 - 7.21 (m, 1H). MS m/z 436

$(M+H)^+$. Isómero *trans*: ^1H RMN (600 MHz, $CDCl_3$) δ 1.16 - 1.28 (m, 3H), 1.62 (dc, 1H), 1.85 - 2.00 (m, 2H), 2.37 - 2.60 (m, 2H), 3.12 (dt, 1H), 3.43 (s, 2H), 3.68 (s a, 3H), 4.08 - 4.20 (m, 2H), 4.25 (s a, 1H), 5.68 (s a, 1H), 6.92 - 7.01 (m, 2H), 7.13 (t, 1H). MS m/z 436 $(M+H)^+$.

Paso 2: *Cis*-2-(2-fluoro-4-(trifluorometoxi)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *cis*-4-(3-etoxi-3-oxopropanoil)-2-(2-fluoro-4-(trifluorometoxi)fenil)piperidin-1-carboxilato de metilo (3.22 g, 7.40 mmol) en MeOH (30 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (0.311 g, 7.77 mmol) disuelto en agua (3.00 mL) y la mezcla se agitó a -40 °C durante 15 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.476 mL, 7.77 mmol). La solución resultante se agitó a -40 °C durante 1 h. Posteriormente, la mezcla se transfirió a una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (38.2 mL, 229.28 mmol) y la mezcla se agitó a 80 °C durante 15 min. Se añadieron agua y DCM y se separaron las fases. La fase acuosa se extrajo con DCM, las fases orgánicas combinadas se filtraron a través de un separador de fases y se evaporaron. El compuesto se purificó mediante HPLC preparativa (4 purificaciones) en una columna Kromasil C8 (10 µm 250x50 DI en mm) utilizando un gradiente de 25-65% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/AcOH en 25 minutos con un flujo de 100 mL/min. Se aisló *cis*-2-(2-fluoro-4-(trifluorometoxi)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.82 g, 61%). ^1H RMN (600 MHz, $CDCl_3$) δ 1.82 - 1.91 (m, 1H), 2.03 - 2.13 (m, 1H), 2.22 - 2.41 (m, 2H), 3.01 - 3.10 (m, 1H), 3.43 - 3.53 (m, 1H), 3.63 (s, 3H), 4.11 - 4.21 (m, 1H), 5.19 (dd, 1H), 5.59 (s, 1H), 6.89 - 6.95 (m, 2H), 7.14 (t, 1H). MS m/z 405 $(M+H)^+$.

Paso 3: *(2R,4S)*-2-(2-Fluoro-4-(trifluorometoxi)fenil)-4-(3-oxo-2,3-dihidro-isoxazol-5-il)piperidin-1-carboxilato de metilo

El *cis*-2-(2-fluoro-4-(trifluorometoxi)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.82 g,

4.5 mmol) se sometió a HPLC preparativa quiral (columna: CelluCoat (250x50 mm), tamaño de partícula: 10 µm, fase móvil: 1/1 de heptano/EtOH, velocidad de flujo: 120 mL/min) para proporcionar (2*R*,4*S*)-2-(2-fluoro-4-(trifluorometoxi)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (917 mg, 50%), pureza quiral: 99.9% de ee, rotación óptica $[\alpha]_D^{20} = +49.7$ (acetonitrilo, c=1.0).

Paso 4: 5-((2*R*,4*S*)-2-(2-Fluoro-4-(trifluorometoxi)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-2-(2-fluoro-4-(trifluorometoxi)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (458 mg, 1.13 mmol) en ácido bromhídrico (al 33% en ácido acético, 8.93 mL, 50.98 mmol) y se agitó a temperatura ambiente durante 16 h. El disolvente se eliminó al vacío y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*S*)-2-(2-fluoro-4-(trifluorometoxi)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona (246 mg, 63%). ^{1}H RMN (600 MHz, DMSO) δ 1.37 (c, 1H), 1.47 (dc, 1H), 1.84 - 1.90 (m, 1H), 1.93 - 1.99 (m, 1H), 2.74 (dt, 1H), 2.87 - 2.94 (m, 1H), 3.07 - 3.13 (m, 1H), 3.94 (dd, 1H), 5.74 (s, 1H), 7.18 - 7.22 (m, 1H), 7.28 - 7.33 (m, 1H), 7.66 (t, 1H); HRMS calculado para $[C_{15}H_{14}F_4N_2O_3+H]^+$: 347.1019. Experimental: 347.0995.

Ejemplo 59

5-(*Trans*-2-(2-fluoro-4-(trifluorometoxi)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(2-fluoro-4-(trifluorometoxi)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *trans*-4-(3-etoxi-3-oxopropanoil)-2-(2-fluoro-4-(trifluorometoxi)fenil)piperidin-1-carboxilato de metilo (420 mg, 0.96 mmol) (del paso 1 del ejemplo 58) en MeOH (4 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (40.5 mg, 1.01 mmol) disuelto en agua (0.400

mL) y la mezcla se agitó a -40 °C durante 15 min. Se añadió hidroxilamina (al 50% en peso en agua, 62 µL, 1.01 mmol). La solución resultante se agitó a -40 °C durante 1 h. Posteriormente, la mezcla se transfirió a una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (4.98 mL, 29.91 mmol) y la mezcla se agitó a 80 °C durante 15 min. Se añadieron agua y DCM, y se separaron las fases. La fase acuosa se extrajo con DCM, las fases orgánicas combinadas se filtraron a través de un separador de fases y se evaporaron. Se proporcionó *trans*-2-(2-fluoro-4-(trifluorometoxi)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo crudo (365 mg, 94%) como un aceite incoloro. MS m/z 405 $(M+H)^+$.

Paso 2: 5-(*Trans*-2-(2-fluoro-4-(trifluorometoxi)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió *trans*-2-(2-fluoro-4-(trifluorometoxi)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (365 mg, 0.90 mmol) en ácido bromhídrico (al 33% en ácido acético, 7.115 mL, 40.62 mmol) y se agitó a temperatura ambiente durante 16 h. El disolvente se eliminó al vacío y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-(*trans*-2-(2-fluoro-4-(trifluorometoxi)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona (185 mg, 59%). ^{1}H RMN (600 MHz, DMSO) δ 1.64 - 1.72 (m, 1H), 1.77 - 1.85 (m, 1H), 1.91 - 1.97 (m, 1H), 2.02 - 2.08 (m, 1H), 2.69 (dt, 1H), 2.86 - 2.92 (m, 1H), 3.17 - 3.22 (m, 1H), 3.95 (dd, 1H), 5.87 (d, 1H), 7.19 - 7.23 (m, 1H), 7.28 - 7.32 (m, 1H), 7.66 (t, 1H); HRMS calculado para $[C_{15}H_{14}F_4N_2O_3+H]^+$: 347.1019. Experimental: 347.1002.

Ejemplo 60

5-((2*R*,4*S*)-2-(3,4,5-Trifluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-4-(3-etoxi-3-oxopropanoil)-2-(3,4,5-trifluorofenil)piperidin-1-carboxilato de metilo y *cis*-4-(3-etoxi-3-oxopropanoil)-2-(3,4,5-trifluorofenil)piperidin-1-

carboxilato de metilo

Se disolvió el ácido 1-(metoxicarbonil)-2-(3,4,5-trifluorofenil)piperidin-4-carboxílico (1.94 g, 6.11 mmol) (compuesto de referencia 26) en metil-THF (70 mL) y a continuación se añadió di(1*H*-imidazol-1-il)metanona (1.487 g, 9.17 mmol). La mezcla se agitó a temperatura ambiente en atmósfera de nitrógeno durante 3 h (matraz 1). En otro matraz, se suspendió 3-etoxi-3-oxopropanoato de potasio (1.873 g, 11.01 mmol) en metil-THF (70.0 mL) y a continuación se añadió cloruro de magnesio (1.048 g, 11.01 mmol). La suspensión se agitó a 50 °C en atmósfera de nitrógeno durante 3 h utilizando un imán grande (matraz 2). Posteriormente, el contenido del matraz 1 se transfirió al matraz 2. La suspensión blanca resultante se agitó a temperatura ambiente en atmósfera de nitrógeno durante toda la noche. La mezcla se acidificó hasta pH 1 con HCl 3.8 M y a continuación se añadieron MTBE (50 mL) y agua (50 mL). Las fases se separaron y la capa orgánica se lavó con agua, $NaHCO_3$ sat. y salmuera. La capa orgánica se secó con Na_2SO_4, se filtró y se evaporó para obtener un aceite amarillento. El producto se purificó en una columna Biotage (340 g) con un gradiente de 20-60% de EtOAc en *n*-heptano (8 VC). La columna se acondicionó con 20% de EtOAc en *n*-heptano (1 VC). Se aislaron *trans*-4-(3-etoxi-3-oxopropanoil)-2-(3,4,5-trifluorofenil)piperidin-1-carboxilato de metilo (59 mg, 2.5%) y *cis*-4-(3-etoxi-3-oxopropanoil)-2-(3,4,5-trifluorofenil)piperidin-1-carboxilato de metilo (810 mg, 34%). Isómero *cis*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.07 - 1.18 (m, 3H), 1.60 - 2.43 (m, 4H), 2.71 - 2.83 (m, 1H), 3.12 - 3.27 (m, 1H), 3.36 (s, 2H), 3.52 (s, 3H), 3.91 - 4.09 (m, 3H), 4.72 - 4.83 (m, 1H), 6.71 - 6.81 (m, 2H). MS m/z 388 $(M+H)^+$. Isómero *trans*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.20 - 1.30 (m, 3H), 1.47 - 2.01 (m, 3H), 2.35 - 2.47 (m, 1H), 2.55 - 2.68 (m, 1H), 2.79 (dt, 1H), 3.42 - 3.49 (m, 2H), 3.75 (s, 3H), 4.09 - 4.37 (m, 3H), 5.52 (s a, 1H), 6.78 - 6.89 (m, 2H). MS m/z 388 $(M+H)^+$.

Paso 2: *Cis*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3,4,5-trifluorofenil)piperidin-1-carboxilato de metilo

Se disolvió *cis*-4-(3-etoxi-3-oxopropanoil)-2-(3,4,5-

trifluorofenil)piperidin-1-carboxilato de metilo (810 mg, 2.09 mmol) en MeOH (8 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (0.615 mL, 2.09 mmol) durante 10 min y la solución amarilla se continuó agitando a -40 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.128 mL, 2.09 mmol) durante 8 min. La solución resultante se agitó a -40 °C durante 3 h. A continuación, la mezcla se vertió rápidamente sobre una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (10.77 mL, 64.62 mmol) y la mezcla se continuó agitando a 80 °C durante 20 min. El disolvente se evaporó y se añadieron DCM/agua. Las fases se separaron y la fase orgánica se hizo pasar a través de un separador de fases y se evaporó para proporcionar un sólido blanco. El compuesto se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x50 DI en mm) utilizando un gradiente de 10-60% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/AcOH en 30 minutos con un flujo de 100 mL/min. Se aisló *cis*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3,4,5-trifluorofenil)piperidin-1-carboxilato de metilo (355 mg, 48%). MS m/z 357 $(M+H)^+$.

Paso 3: (2*R*,4*S*)-4-(3-Oxo-2,3-dihidroisoxazol-5-il)-2-(3,4,5-trifluorofenil)piperidin-1-carboxilato de metilo y (2*S*,4*R*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3,4,5-trifluorofenil)piperidin-1-carboxilato de metilo

El *cis*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3,4,5-trifluorofenil)piperidin-1-il)piperidin-1-carboxilato de metilo (355 mg, 1 mmol) se sometió a HPLC preparativa quiral (columna: CelluCoat (250x20), tamaño de partícula: 5 µm, fase móvil: 60/40 de heptano/EtOH, velocidad de flujo: 18 mL/min) para proporcionar (2*R*,4*S*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3,4,5-trifluorofenil)piperidin-1-carboxilato de metilo (164 mg, 46%), pureza quiral: 98.7% de ee, rotación óptica $[\alpha]_D^{20} = +60.6$ (acetonitrilo, c=0.5), ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.80 - 1.90 (m, 1H), 1.99 - 2.40 (m, 3H), 3.00 - 3.13 (m, 1H), 3.29 - 3.42 (m, 1H), 3.69 (s, 3H), 4.07 - 4.19 (m, 1H), 4.97 - 5.07 (m,

1H), 5.60 (s, 1H), 6.75 - 6.85 (m, 2H), y (2*S*,4*R*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3,4,5-trifluorofenil)piperidin-1-carboxilato de metilo (160 mg, 45%), pureza quiral: 99.9% de ee, rotación óptica $[\alpha]_D^{20} = -52.9$ (acetonitrilo, c=1), ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.81 - 1.90 (m, 1H), 2.05 - 2.15 (m, 1H), 2.19 - 2.38 (m, 2H), 3.02 - 3.11 (m, 1H), 3.30 - 3.40 (m, 1H), 3.69 (s, 3H), 4.09 - 4.18 (m, 1H), 4.99 - 5.05 (m, 1H), 5.60 (s, 1H), 6.76 - 6.84 (m, 2H).

Paso 4: 5-((2*R*,4*S*)-2-(3,4,5-Trifluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3,4,5-trifluorofenil)piperidin-1-carboxilato de metilo (164 mg, 0.46 mmol) en ácido bromhídrico (al 33% en ácido acético, 3.63 mL, 20.71 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*S*)-2-(3,4,5-trifluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona (93 mg, 67%). ^{1}H RMN (600 MHz, DMSO) δ 1.29 (c, 1H), 1.43 (dc, 1H), 1.82 - 1.89 (m, 1H), 1.96 - 2.02 (m, 1H), 2.70 (dt, 1H), 2.79 - 2.87 (m, 1H), 3.05 - 3.12 (m, 1H), 3.64 (dd, 1H), 5.72 (s, 1H), 7.26 - 7.34 (m, 2H). HRMS calculado para $[C_{14}H_{13}F_3N_2O_2+H]^+$: 299.1007. Experimental: 299.1002.

Ejemplo 61

5-((2*S*,4*R*)-2-(3,4,5-Trifluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*S*,4*R*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3,4,5-trifluorofenil)piperidin-1-carboxilato de metilo (160 mg, 0.45 mmol) (del paso 3 del ejemplo 60) en ácido bromhídrico (al 33% en ácido acético, 3.54 mL, 20.21 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil:

gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*S*,4*R*)-2-(3,4,5-trifluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona (85 mg, 63%), ^{1}H RMN (600 MHz, DMSO) δ 1.29 (c, 1H), 1.43 (cd, 1H), 1.83 - 1.88 (m, 1H), 1.97 - 2.02 (m, 1H), 2.70 (td, 1H), 2.80 - 2.87 (m, 1H), 3.06 - 3.12 (m, 1H), 3.64 (dd, 1H), 5.73 (s, 1H), 7.27 - 7.34 (m, 2H). HRMS calculado para $[C_{14}H_{13}F_3N_2O_2+H]^+$: 299.1007. Experimental: 299.1037.

Ejemplo 62

5-(*Trans*-2-(3,4,5-trifluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3,4,5-trifluorofenil)piperidin-1-carboxilato de metilo

Se disolvió *trans*-4-(3-etoxi-3-oxopropanoil)-2-(3,4,5-trifluorofenil)piperidin-1-carboxilato de metilo (59 mg, 0.15 mmol) (del paso 1 del ejemplo 60) en MeOH (1 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (0.045 mL, 0.15 mmol) durante 10 min y la solución amarilla se continuó agitando a -40 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 9.33 µL, 0.15 mmol) durante 8 min. La solución resultante se agitó a -40 °C durante 3 h 15 min. A continuación, la mezcla se vertió rápidamente sobre una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (0.784 mL, 4.71 mmol) y la mezcla se continuó agitando a 80 °C durante 20 min. El disolvente se evaporó y se añadieron DCM/agua. Las fases se separaron, la fase orgánica se hizo pasar a través de un separador de fases y se evaporó para proporcionar *trans*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3,4,5-trifluorofenil)piperidin-1-carboxilato de metilo crudo (53 mg, cuant.) como un aceite amarillento. MS m/z 357 $(M+H)^+$.

Paso 2: 5-(*Trans*-2-(3,4,5-trifluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió *trans*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3,4,5-trifluorofenil)piperidin-1-carboxilato de metilo (53.4 mg, 0.15 mmol) en ácido bromhídrico (al 33% en ácido acético,

1.18 mL, 6.75 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-(*trans*-2-(3,4,5-trifluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona (11 mg, 25%). ^{1}H RMN (600 MHz, DMSO) δ 1.72 - 1.88 (m, 3H), 1.97 - 2.04 (m, 1H), 2.61 - 2.69 (m, 1H), 2.76 - 2.83 (m, 1H), 3.06 - 3.11 (m, 1H), 3.69 - 3.75 (m, 1H), 5.98 (s, 1H), 7.28 - 7.36 (m, 2H). HRMS calculado para $[C_{14}H_{13}F_3N_2O_2+H]^+$: 299.1007. Experimental: 299.1031.

Ejemplo 63

5-((2*R*,4*S*)-2-(2,4,5-Trifluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Cis*-4-(3-etoxi-3-oxopropanoil)-2-(2,4,5-trifluorofenil)piperidin-1-carboxilato de metilo

Se disolvió el ácido 1-(metoxicarbonil)-2-(2,4,5-trifluorofenil)piperidin-4-carboxílico (2.388 g, 7.53 mmol) (compuesto de referencia 27) en metil-THF (50 mL) y se añadió di(1*H*-imidazol-1-il)metanona (1.831 g, 11.29 mmol). La suspensión se agitó a temperatura ambiente en atmósfera de nitrógeno durante 6 h (matraz 1). En otro matraz, se suspendió 3-etoxi-3-oxopropanoato de potasio (2.306 g, 13.55 mmol) en metil-THF (50.0 mL) y se añadió cloruro de magnesio (1.290 g, 13.55 mmol). La suspensión se agitó a 50 °C en atmósfera de nitrógeno durante 5.5 h utilizando un imán muy grande (matraz 2). A continuación, la suspensión del matraz 1 se añadió a la suspensión blanca del matraz 2. La suspensión beis resultante se agitó a temperatura ambiente en atmósfera de nitrógeno durante toda la noche. La mezcla se acidificó hasta pH 1 con HCl 3.8 M, y se añadieron MTBE y agua. Las fases se separaron y la fase orgánica se lavó con agua, $NaHCO_3$ sat. y agua, y se evaporó. Las trazas de agua se eliminaron mediante la formación de un azeótropo con MeCN para proporcionar un aceite amarillo. El residuo se purificó en una columna Biotage (20% => 50% de EtOAc en heptano, 8 VC; columna Biotage® con 340 g de KP-SIL).

Se aisló *cis*-4-(3-etoxi-3-oxopropanoil)-2-(2,4,5-trifluorofenil)piperidin-1-carboxilato de metilo (1.877 g, 64%) como un aceite incoloro. ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.19 - 1.29 (m, 3H), 1.49 - 2.19 (m, 3H), 2.22 - 2.29 (m, 1H), 2.82 - 2.91 (m, 1H), 3.34 (ddd, 1H), 3.39 - 3.48 (m, 2H), 3.62 (s, 3H), 4.05 - 4.20 (m, 3H), 5.00 - 5.06 (m, 1H), 6.85 - 7.00 (m, 2H). MS m/z 388 $(M+H)^+$.

Paso 2: *Cis*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(2,4,5-trifluorofenil)piperidin-1-carboxilato de metilo y *trans*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(2,4,5-trifluorofenil)piperidin-1-carboxilato de metilo

Se disolvió *cis*-4-(3-etoxi-3-oxopropanoil)-2-(2,4,5-trifluorofenil)piperidin-1-carboxilato de metilo (1.888 g, 4.87 mmol) en MeOH (18 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (0.195 g, 4.87 mmol) disuelto en agua (1.800 mL) durante 10 min y se continuó agitando la solución incolora a -40 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.299 mL, 4.87 mmol) durante 8 min. La solución resultante se agitó a -40 °C durante 3 h 20 min. A continuación, la mezcla se transfirió a una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (24 mL, 144.00 mmol) y se continuó agitando la mezcla a 80 °C durante 20 min. El disolvente se evaporó y se añadieron DCM/agua. Las fases se separaron, y la fase orgánica se hizo pasar a través de un separador de fases y se evaporó para proporcionar un aceite amarillo. El compuesto se purificó mediante HPLC preparativa en 3 inyecciones en una columna XBridge C18 (10 µm 250x50 DI en mm) utilizando un gradiente de 5-30% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 20 minutos con un flujo de 100 mL/min. Se obtuvo una mezcla de *cis*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(2,4,5-trifluorofenil)piperidin-1-carboxilato de metilo y *trans*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(2,4,5-trifluorofenil)piperidin-1-carboxilato de metilo (1.027 g, 59%) como un sólido blanco después de liofilizar. MS m/z 357 $(M+H)^+$.

Paso 3: (2*R*,4*S*)-4-(3-Oxo-2,3-dihidroisoxazol-5-il)-2-(2,4,5-trifluorofenil)piperidin-1-carboxilato de metilo y (2*S*,4*S*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(2,4,5-trifluorofenil)piperidin-1-carboxilato de metilo

La mezcla de *cis*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(2,4,5-trifluorofenil)piperidin-1-carboxilato de metilo y *trans*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(2,4,5-trifluorofenil)piperidin-1-carboxilato de metilo (1.027 g, 2.88 mmol) se sometió a HPLC preparativa quiral (columna: CelluCoat (250x20), tamaño de partícula: 5 µm, fase móvil: 80/20 de heptano/IPA, velocidad de flujo: 18 mL/min) para proporcionar (2*R*,4*S*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(2,4,5-trifluorofenil)piperidin-1-carboxilato de metilo (259 mg, 25%), pureza quiral: 99.9% de A, rotación óptica $[\alpha]_D^{20} = +50.3$ (acetonitrilo, c=1), y (2*S*,4*S*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(2,4,5-trifluorofenil)piperidin-1-carboxilato de metilo (203 mg, 20%), pureza quiral: 99.9% de A, rotación óptica $[\alpha]_D^{20} = +4.5$ (acetonitrilo, c=1).

Paso 4: 5-((2*R*,4*S*)-2-(2,4,5-Trifluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(2,4,5-trifluorofenil)piperidin-1-carboxilato de metilo (259 mg, 0.73 mmol) en ácido bromhídrico (al 33% en ácido acético, 4 mL, 22.84 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*S*)-2-(2,4,5-trifluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona (161 mg, 74%). ^{1}H RMN (600 MHz, DMSO) δ 1.36 (c, 1H), 1.45 (dc, 1H), 1.83 - 1.90 (m, 1H), 1.91 - 1.97 (m, 1H), 2.74 (dt, 1H), 2.90 (tt, 1H), 3.06 - 3.13 (m, 1H), 3.91 (d, 1H), 5.74 (d, 1H), 7.44 - 7.57 (m, 2H). HRMS calculado para $[C_{14}H_{13}F_3N_2O_2+H]^+$: 299.1007. Experimental: 299.1021.

Ejemplo 64

5-((2*S*,4*S*)-2-(2,4,5-Trifluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*S*,4*S*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(2,4,5-trifluorofenil)piperidin-1-carboxilato de metilo (203 mg, 0.57 mmol) (del paso 4 del ejemplo 63) en ácido bromhídrico (al 33% en ácido acético, 4 mL, 22.84 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*S*,4*S*)-2-(2,4,5-trifluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona (138 mg, 81%). ^{1}H RMN (600 MHz, DMSO) δ 1.62 - 1.70 (m, 1H), 1.80 (tt, 1H), 1.90 - 1.96 (m, 1H), 2.00 - 2.06 (m, 1H), 2.68 (dt, 1H), 2.85 - 2.91 (m, 1H), 3.20 (s a, 1H), 3.90 (d, 1H), 5.86 (d, 1H), 7.43 - 7.56 (m, 2H). HRMS calculado para $[C_{14}H_{13}F_3N_2O_2+H]^+$: 299.1007. Experimental: 299.1023.

Ejemplo 65

5-((2*R*,4*S*)-2-(4-Cloro-3,5-difluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(4-Cloro-3,5-difluorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo y *cis*-2-(4-cloro-3,5-difluorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo

Se disolvió el ácido 2-(4-cloro-3,5-difluorofenil)-1-(metoxicarbonil)piperidin-4-carboxílico (1.6 g, 4.79 mmol) (compuesto de referencia 28) en metil-THF (30 mL) en atmósfera de nitrógeno y se añadió di(1*H*-imidazol-1-il)metanona (1.166 g, 7.19 mmol). La suspensión se agitó a temperatura ambiente durante 3 h (matraz 1). En otro matraz, se suspendió 3-etoxi-3-oxopropanoato de potasio (1.469 g, 8.63 mmol) en metil-THF (15 mL) y se añadió cloruro de magnesio (0.822 g, 8.63 mmol). La suspensión se agitó a 50 °C en atmósfera de nitrógeno durante 7 h utilizando un imán muy grande (matraz 2). El contenido del matraz 1 se añadió al matraz 2 y la suspensión blanca resultante se agitó a temperatura ambiente durante 20 h. En

otro matraz, se suspendió 3-etoxi-3-oxopropanoato de potasio (0.734 g, 4.32 mmol) en metil-THF (15 mL) y se añadió cloruro de magnesio (0.411 g, 4.32 mmol). La suspensión se agitó a 50 °C durante 5 h y después se añadió a la mezcla de reacción. La mezcla se agitó a temperatura ambiente durante 15 h. Se añadieron HCl 0.1 M y DCM, y las fases se separaron. La fase acuosa se extrajo con DCM, las fases orgánicas combinadas se filtraron a través de un separador de fases y se evaporaron. El residuo se purificó mediante cromatografía en columna de sílice (2:1 de heptano:EtOAc, columna Biotage® con 340 g de KP-SIL, 10 VC). Se aislaron *cis*-2-(4-cloro-3,5-difluorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (1.448 g, 74.8%) y *trans*-2-(4-cloro-3,5-difluorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (0.178 g, 9.19%) como aceites incoloros. Isómero *cis*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.23 - 1.32 (m, 3H), 1.74 - 2.19 (m, 3H), 2.20 - 2.30 (m, 1H), 2.82 - 2.92 (m, 1H), 3.23 - 3.34 (m, 1H), 3.46 (s, 2H), 3.63 - 3.69 (m, 3H), 4.04 - 4.23 (m, 3H), 4.84 - 4.95 (m, 1H), 6.81 - 6.90 (m, 2H). MS m/z 404 $(M+H)^+$. Isómero *trans*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.20 - 1.33 (m, 3H), 1.48 - 1.92 (m, 2H), 1.92 - 2.04 (m, 1H), 2.36 - 2.51 (m, 1H), 2.54 - 2.70 (m, 1H), 2.82 (dt, 1H), 3.47 (d, 2H), 3.73 (s, 3H), 4.08 - 4.45 (m, 3H), 5.56 (s a, 1H), 6.86 (d, 2H). MS m/z 404 $(M+H)^+$.

Paso 2: <u>*Cis*-2-(4-cloro-3,5-difluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo</u>

Se disolvió *cis*-2-(4-cloro-3,5-difluorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (1.445 g, 3.58 mmol) en MeOH (14 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (0.150 g, 3.76 mmol) disuelto en agua (1.4 mL) y la mezcla se agitó a -40 °C durante 15 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.230 mL, 3.76 mmol). La solución resultante se agitó a -40 °C durante 1 h. Posteriormente, la mezcla se transfirió a una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (18.49 mL, 110.93 mmol) y la mezcla se agitó a 80 °C durante 20 min. Se añadieron agua y DCM, y se separaron las fases. La fase

acuosa se extrajo con DCM, las fases orgánicas combinadas se filtraron a través de un separador de fases y se evaporaron. El compuesto se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x50 DI en mm) utilizando un gradiente de 15-55% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/AF en 30 minutos con un flujo de 100 mL/min. Los compuestos se detectaron mediante UV a 220 nm. Se proporcionó *cis*-2-(4-cloro-3,5-difluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.831 g, 62.3%) como un sólido incoloro. ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.80 - 1.87 (m, 1H), 2.04 - 2.15 (m, 1H), 2.19 - 2.28 (m, 1H), 2.30 - 2.36 (m, 1H), 3.00 - 3.09 (m, 1H), 3.30 - 3.39 (m, 1H), 3.66 (s, 3H), 4.07 - 4.16 (m, 1H), 4.98 - 5.05 (m, 1H), 5.59 (s a, 1H), 6.80 (d, 2H). MS m/z 273 $(M+H)^+$.

Paso 3: (2*R*,4*S*)-2-(4-Cloro-3,5-difluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El *cis*-2-(4-cloro-3,5-difluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (830 mg, 2.23 mmol) se sometió a HPLC preparativa quiral (columna: CelluCoat (250x50 mm), tamaño de partícula: 10 µm, fase móvil: 50/50 de heptano/EtOH, velocidad de flujo: 120 mL/min) para proporcionar (2*R*,4*S*)-2-(4-cloro-3,5-difluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (390 mg, 47%), pureza quiral: 99.7% de ee, rotación óptica $[\alpha]_D^{20} = +55.9$ (acetonitrilo, c=1.0).

Paso 4: 5-((2*R*,4*S*)-2-(4-Cloro-3,5-difluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-2-(4-cloro-3,5-difluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.39 g, 1.05 mmol) en ácido bromhídrico (al 33% en ácido acético, 10 mL, 142.75 mmol) y se agitó a temperatura ambiente durante 18 h. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar

5-((2*R*,4*S*)-2-(4-cloro-3,5-difluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona (272 mg, 83%). ^{1}H RMN (600 MHz, DMSO) δ 1.29 (c, 1H), 1.43 (dc, 1H), 1.82 - 1.89 (m, 1H), 1.97 - 2.04 (m, 1H), 2.70 (dt, 1H), 2.84 (tt, 1H), 3.06 - 3.12 (m, 1H), 3.68 (dd, 1H), 5.73 (s, 1H), 7.31 (d, 2H). HRMS calculado para $[C_{14}H_{13}ClF_2N_2O_2+H]^+$: 315.0712. Experimental: 315.0707.

Ejemplo 66

5-(*Trans*-2-(4-cloro-3,5-difluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(4-cloro-3,5-difluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *trans*-2-(4-cloro-3,5-difluorofenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (178 mg, 0.44 mmol) (del paso 1 del ejemplo 65) en MeOH (2 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (18.51 mg, 0.46 mmol) disuelto en agua (0.200 mL) y la mezcla se agitó a -40 °C durante 15 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.028 mL, 0.46 mmol). La solución resultante se agitó a -40 °C durante 1 h. La mezcla se transfirió a una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (2.278 mL, 13.67 mmol) y la mezcla se agitó a 80 °C durante 20 min. Se añadieron agua y DCM, y se separaron las fases. La fase acuosa se extrajo con DCM, las fases orgánicas combinadas se filtraron a través de un separador de fases y se evaporaron. Se aisló *trans*-2-(4-cloro-3,5-difluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo crudo (158 mg, 96%) como un aceite amarillo claro. MS m/z 273 $(M+H)^+$.

Paso 2: 5-(*Trans*-2-(4-cloro-3,5-difluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió *trans*-2-(4-cloro-3,5-difluorofenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (157 mg, 0.42 mmol) en ácido bromhídrico (al 33% en ácido acético, 3.32 mL, 18.95 mmol) y se agitó a temperatura ambiente durante 16 h. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase

móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-(*trans*-2-(4-cloro-3,5-difluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona (26 mg, 19%). ^{1}H RMN (600 MHz, DMSO) δ 1.75 - 2.11 (m, 4H), 2.66 - 2.77 (m, 1H), 2.81 - 2.95 (m, 1H), 3.14 (s a, 1H), 3.86 (s a, 1H), 6.03 (s, 1H), 7.32 - 7.42 (m, 2H). HRMS calculado para $[C_{14}H_{13}ClF_2N_2O_2+H]^+$: 315.0712. Experimental: 315.0715.

Ejemplo 67

5-((2*R*,4*S*)-2-(3-Metil-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-4-(3-etoxi-3-oxopropanoil)-2-(3-metil-4-(trifluorometil)fenil)piperidin-1-carboxilato de metilo y *cis*-4-(3-etoxi-3-oxopropanoil)-2-(3-metil-4-(trifluorometil)fenil)piperidin-1-carboxilato de metilo

Se añadieron malonato de etilo y potasio (1.567 g, 9.21 mmol) y $MgCl_2$ (0.731 g, 7.67 mmol) a THF anhidro (50 mL). El matraz de reacción se agitó vigorosamente durante 4 h a 50 °C (matraz 1). Se añadieron el ácido 1-(metoxicarbonil)-2-(3-metil-4-(trifluorometil)fenil)piperidin-4-carboxílico (2.65 g, 7.67 mmol) (compuesto de referencia 29) y carbonildiimidazol (1.867 g, 11.51 mmol) a THF anhidro (50 mL) a temperatura ambiente (matraz 2). El contenido del matraz 2 se añadió al matraz 1 y la mezcla resultante se agitó a temperatura ambiente durante toda la noche. La mezcla de reacción se disolvió entre agua y éter dietílico. La fase orgánica se aisló, se secó con Na_2SO_4, se filtró a través de celite y el disolvente se evaporó. Para la cromatografía se utilizó el equipo Biotage. Se utilizó un gradiente de elución de acetato de etilo-heptano que partió de 0-100 y terminó en 100-0. Se aislaron *trans*-4-(3-etoxi-3-oxopropanoil)-2-(3-metil-4-(trifluorometil)fenil)piperidin-1-carboxilato de metilo (0.69 g, 22%) y *cis*-4-(3-etoxi-3-oxopropanoil)-2-(3-metil-4-(trifluorometil)fenil)piperidin-1-carboxilato de metilo (1.40 g, 44%). Isómero *cis*: ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.25 (t, 3H), 1.00 - 2.29 (m, 4H), 2.44 (s, 3H), 2.47 - 2.95 (m, 1H), 3.27 -

3.34 (m, 1H), 3.37 - 3.48 (m, 2H), 3.62 (s, 3H), 3.66 - 4.20 (m, 3H), 4.88 - 4.96 (m, 1H), 7.05 - 7.11 (m, 2H), 7.50 - 7.54 (m, 1H). Isómero *trans*: ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.22 (t, 3H), 1.47 - 2.03 (m, 4H), 2.47 (s, 3H), 2.49 - 2.89 (m, 2H), 3.40 - 3.47 (m, 2H), 3.74 (s, 3H), 4.15 (c, 2H), 4.11 - 4.36 (m, 1H), 5.37 - 5.75 (m, 1H), 7.06 - 7.13 (m, 2H), 7.57 (d, 1H).

Paso 2: Cis-2-(3-metil-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *cis*-4-(3-etoxi-3-oxopropanoil)-2-(3-metil-4-(trifluorometil)fenil)piperidin-1-carboxilato de metilo (1.4 g, 3.37 mmol) en MeOH (20 mL) y se enfrió hasta -40 °C. Se añadió NaOH (0.135 g, 3.37 mmol) disuelto en agua (2 mL) durante 10 min y se continuó agitando la solución incolora resultante a -40 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.223 g, 3.37 mmol) gota a gota. La solución resultante se agitó a -40 °C durante 30 min. Posteriormente, la mezcla se transfirió a una solución calentada previamente (80 °C) de HCl 6 M y la mezcla se continuó agitando a 80 °C durante 20 min. La mezcla se disolvió entre éter dietílico y agua. Las fases se separaron y la fase orgánica se secó con Na_2SO_4, se filtró a través de celite y se eliminó el disolvente. Se purificó mediante HPLC preparativa. Se utilizó un gradiente de elución de acetonitrilo-tampón ácido que partió de 40-60 y terminó en 55-45. Se aisló *cis*-2-(3-metil-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.37 g, 29%). ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.80 - 1.87 (m, 1H), 2.07 - 2.28 (m, 2H), 2.31 - 2.38 (m, 1H), 2.41 (s, 3H), 3.03 - 3.10 (m, 1H), 3.35 - 3.43 (m, 1H), 3.66 (s, 3H), 4.13 - 4.19 (m, 1H), 5.09 (t, 1H), 5.52 (s, 1H), 7.02 - 7.06 (m, 2H), 7.49 (d, 1H). MS m/z 385 $(M+H)^+$.

Paso 3: (2*R*,4*S*)-2-(3-Metil-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo y (2*S*,4*R*)-2-(3-metil-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El *cis*-2-(3-metil-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.37 g,

0.96 mmol) se sometió a HPLC preparativa quiral (columna: CelluCoat OJ (250x50), tamaño de partícula: 10 µm, fase móvil: 50/50 de heptano/EtOH, velocidad de flujo: 120 mL/min) para proporcionar (2*R*,4*S*)-2-(3-metil-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (177 mg, 48%), pureza quiral: 99.2% de ee, rotación óptica $[\alpha]_D^{20} = +57.1$ (acetonitrilo, c=1), ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.78 - 1.85 (m, 1H), 2.08 - 2.16 (m, 1H), 2.17 - 2.26 (m, 1H), 2.29 - 2.36 (m, 1H), 2.39 (s, 3H), 3.01 - 3.09 (m, 1H), 3.34 - 3.42 (m, 1H), 3.64 (s, 3H), 4.09 - 4.17 (m, 1H), 5.07 (t, 1H), 5.50 (s, 1H), 7.01 - 7.07 (m, 2H), 7.47 (d, 1H), 10.63 (a, 1H), y (2*S*,4*R*)-2-(3-metil-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (168 mg, 45%), pureza quiral: 99.9% de ee, rotación óptica $[\alpha]_D^{20} = -57.1$ (acetonitrilo, c=1), ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.79 - 1.86 (m, 1H), 2.10 - 2.18 (m, 1H), 2.19 - 2.27 (m, 1H), 2.31 - 2.37 (m, 1H), 2.41 (s, 3H), 3.02 - 3.09 (m, 1H), 3.35 - 3.42 (m, 1H), 3.65 (s, 3H), 4.11 - 4.18 (m, 1H), 5.08 (t, 1H), 5.51 (s, 1H), 7.02 - 7.07 (m, 2H), 7.48 (d, 1H).

Paso 4: <u>5-((2*R*,4*S*)-2-(3-Metil-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona</u>

Se disolvió (2*R*,4*S*)-2-(3-metil-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.177 g, 0.46 mmol) en HBr (al 33% en ácido acético, 5.6 g, 22.84 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*S*)-2-(3-metil-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona (0.082 g, 55%). ^{1}H RMN (600 MHz, DMSO) δ 1.31 - 1.39 (m, 1H), 1.41 - 1.50 (m, 1H), 1.84 - 1.90 (m, 1H), 1.95 - 2.00 (m, 1H), 2.40 (d, 3H), 2.57 - 2.59 (m, 1H), 2.83 - 2.90 (m, 1H), 3.08 - 3.13 (m, 1H), 3.68 (d, 1H), 5.72 (s, 1H), 7.35 (d, 1H), 7.43 (s,

1H), 7.57 (d, 1H). HRMS calculado para $[C_{16}H_{17}F_3N_2O_2+H]^+$: 327.1320. Experimental: 327.1311.

Ejemplo 68

5-((2*S*,4*R*)-2-(3-Metil-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*S*,4*R*)-2-(3-metil-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.168 g, 0.44 mmol) (del paso 3 del ejemplo 67) en HBr (al 33% en ácido acético, 5.6 g, 22.84 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*S*,4*R*)-2-(3-metil-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona (0.068 g, 48%). ^{1}H RMN (600 MHz, DMSO) δ 1.31 - 1.40 (m, 1H), 1.41 - 1.50 (m, 1H), 1.85 - 1.90 (m, 1H), 1.95 - 2.00 (m, 1H), 2.40 (s, 3H), 2.69 - 2.76 (m, 1H), 2.83 - 2.90 (m, 1H), 3.08 - 3.13 (m, 1H), 3.68 (d, 1H), 5.73 (s, 1H), 7.36 (d, 1H), 7.43 (s, 1H), 7.57 (d, 1H). HRMS calculado para $[C_{16}H_{17}F_3N_2O_2+H]^+$: 327.1320. Experimental: 327.1318.

Ejemplo 69

5-(*Trans*-2-(3-metil-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(3-metil-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *trans*-4-(3-etoxi-3-oxopropanoil)-2-(3-metil-4-(trifluorometil)fenil)piperidin-1-carboxilato de metilo (0.69 g, 1.66 mmol) (del paso 1 del ejemplo 67) en MeOH (8 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió NaOH (0.066 g, 1.66 mmol) disuelto en agua (0.7 mL) durante 10 min y la solución incolora resultante se continuó agitando a -40 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.110 g, 1.66 mmol) gota a gota. La solución resultante se agitó a -40 °C durante 30 min. Posteriormente, la mezcla se transfirió a una solución calentada previamente (80 °C) de HCl

6 M y la mezcla se continuó agitando a 80 °C durante 20 min. La mezcla se disolvió entre éter dietílico y agua. Las fases se separaron y la fase orgánica se secó con Na_2SO_4, se filtró a través de celite y se evaporó para proporcionar *trans*-2-(3-metil-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo crudo (0.54 g, 85%). ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.60 - 1.72 (m, 1H), 1.89 - 1.97 (m, 1H), 1.99 - 2.07 (m, 1H), 2.48 (s, 3H), 2.58 - 2.71 (m, 1H), 2.80 (s, 1H), 2.93 (t, 1H), 3.73 (s, 3H), 4.23 (s, 1H), 5.49 - 5.73 (m, 2H), 7.06 - 7.16 (m, 2H), 7.60 (d, 1H).

Paso 2: 5-(*Trans*-2-(3-metil-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió *trans*-2-(3-metil-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.139 g, 0.36 mmol) en HBr (al 33% en ácido acético, 5.60 g, 22.84 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-(*trans*-2-(3-metil-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona (0.075 g, 64%). ^{1}H RMN (600 MHz, DSMO) δ 1.76 - 1.85 (m, 2H), 1.85 - 1.93 (m, 1H), 1.99 - 2.07 (m, 1H), 2.40 (d, 2H), 2.67 - 2.75 (m, 1H), 2.80 - 2.89 (m, 1H), 3.10 - 3.17 (m, 1H), 3.68 - 3.78 (m, 1H), 5.96 (s, 1H), 7.36 (d, 1H), 7.43 (s, 1H), 7.57 (d, 1H). HRMS calculado para $[C_{16}H_{17}F_3N_2O_2+H]^+$: 327.1320. Experimental: 327.1298.

Ejemplo 70

5-((2*R*,4*S*)-2-(3,5-Difluoro-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(3,5-difluoro-4-(trifluorometil)fenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo y *cis*-2-(3,5-difluoro-4-(trifluorometil)fenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo

Se disolvió el ácido 2-(3,5-difluoro-4-

(trifluorometil)fenil)-1-(metoxicarbonil)piperidin-4-carboxílico (2.363 g, 6.43 mmol) (compuesto de referencia 30) en metil-THF (30 mL) y se añadió di(1*H*-imidazol-1-il)metanona (1.565 g, 9.65 mmol). La suspensión se agitó a temperatura ambiente en atmósfera de nitrógeno durante 20 h (matraz 1). En otro matraz, se suspendieron 3-etoxi-3-oxopropanoato de potasio (2.190 g, 12.87 mmol) y cloruro de magnesio (1.225 g, 12.87 mmol) en metil-THF (30.0 mL) y se agitó a 50 °C en atmósfera de nitrógeno utilizando un imán muy grande durante 20 h (matraz 2). A continuación, la suspensión blanca del matraz 2 se añadió al matraz 1. La suspensión blanca densa se agitó a temperatura ambiente durante 24 h. La mezcla de reacción se acidificó añadiendo HCl 3 M hasta pH 1. Se añadieron MTBE (250 mL) y agua, se agitó y se separaron las fases. La fase orgánica se lavó con agua (200 mL), $NaHCO_3$ sat. (200 mL) y salmuera (200 mL), se secó con un separador de fases y se evaporó al vacío. El residuo se purificó mediante cromatografía flash automatizada en una columna Biotage® con 100 g de KP-SIL. Se utilizó como fase móvil un gradiente de 40% de EtOAc en heptano en 2 VC y a continuación de 40% a 80% de EtOAc en heptano en 10 VC. Se aislaron *cis*-2-(3,5-difluoro-4-(trifluorometil)fenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (1.489 g, 52.9%) y *trans*-2-(3,5-difluoro-4-(trifluorometil)fenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (0.110 g, 3.91%). Isómero *cis*: ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.25 (t, 3H), 1.49 - 2.28 (m, 4H), 2.80 - 2.91 (m, 1H), 3.23 - 3.31 (m, 1H), 3.44 (s, 2H), 3.65 (s, 3H), 4.07 - 4.14 (m, 1H), 4.17 (c, 2H), 4.86 - 4.95 (m, 1H), 6.83 (d, 2H). Isómero *trans*: ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.24 (t, 3H), 1.54 - 1.60 (m, 1H), 1.73 - 1.89 (m, 1H), 1.96 - 2.03 (m, 1H), 2.38 - 2.47 (m, 1H), 2.53 - 2.62 (m, 1H), 2.76 - 2.84 (m, 1H), 3.40 - 3.49 (m, 2H), 3.75 (s, 3H), 4.17 (c, 2H), 4.15 - 4.42 (m, 1H), 5.40 - 5.71 (m, 1H), 6.87 (d, 2H).

Paso 2: <u>*Cis*-2-(3,5-difluoro-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo</u>

Se disolvió *cis*-2-(3,5-difluoro-4-(trifluorometil)fenil)-

4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (1.489 g, 3.40 mmol) en MeOH (15 mL) y se enfrió hasta -40 °C. Se añadió hidróxido sódico (0.896 mL, 3.40 mmol) disuelto en agua (1.500 mL) y la reacción se agitó a -40 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.209 mL, 3.40 mmol) y se continuó agitando durante 3.5 h a -40 °C. Posteriormente, la mezcla de reacción se añadió a una solución calentada previamente a 80 °C de ácido clorhídrico (17.59 mL, 105.54 mmol) y se agitó durante 20 min. El disolvente se evaporó al vacío. Se añadieron DCM (100 mL) y agua (100 mL), se agitó y se separaron las fases. La fase orgánica se secó con un separador de fases y se evaporó al vacío. El compuesto se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x50 DI en mm) utilizando un gradiente de 20-65% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/AcOH en 30 minutos con un flujo de 100 mL/min. Se aisló *cis*-2-(3,5-difluoro-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.594 g, 42.9%) como un sólido blanco. ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.82 - 1.89 (m, 1H), 2.08 - 2.16 (m, 1H), 2.19 - 2.27 (m, 1H), 2.32 - 2.38 (m, 1H), 3.04 - 3.11 (m, 1H), 3.34 - 3.41 (m, 1H), 3.68 (s, 3H), 4.09 - 4.15 (m, 1H), 5.04 - 5.08 (m, 1H), 5.57 (s, 1H), 6.80 (d, 2H).

Paso 3: (2*R*,4*S*)-2-(3,5-Difluoro-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidro-isoxazol-5-il)piperidin-1-carboxilato de metilo

El *cis*-2-(3,5-difluoro-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (465 mg, 1.14 mmol) se sometió a HPLC preparativa quiral (columna: CelluCoat (250x50), tamaño de partícula: 10 µm, fase móvil: 60/40 de heptano/EtOH, velocidad de flujo: 120 mL/min) para proporcionar (2*R*,4*S*)-2-(3,5-difluoro-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (226 mg, 48%), pureza quiral: 99.8% de ee, rotación óptica $[\alpha]_D^{20} = +48.2$ (acetonitrilo, c=1), ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.82 - 1.88 (m, 1H), 2.07 - 2.14 (m, 1H), 2.19 - 2.27 (m, 1H),

2.32 - 2.38 (m, 1H), 3.04 - 3.10 (m, 1H), 3.34 - 3.41 (m, 1H), 3.68 (s, 3H), 4.09 - 4.15 (m, 1H), 5.04 - 5.08 (m, 1H), 5.58 (s, 1H), 6.80 (d, 2H).

Paso 4: 5-((2*R*,4*S*)-2-(3,5-Difluoro-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-2-(3,5-difluoro-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (226 mg, 0.56 mmol) en ácido bromhídrico (al 33% en AcOH, 5 mL, 30.38 mmol) y se agitó a temperatura ambiente durante 20 h. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*S*)-2-(3,5-difluoro-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona (133 mg, 68%). ^{1}H RMN (600 MHz, DMSO) δ 1.30 (c, 1H), 1.43 (dc, 1H), 1.84 - 1.89 (m, 1H), 2.02 - 2.07 (m, 1H), 2.70 (dt, 1H), 2.86 (tt, 1H), 3.07 - 3.13 (m, 1H), 3.75 (dd, 1H), 5.73 (s, 1H), 7.37 (d, 2H). HRMS calculado para $[C_{15}H_{13}F_5N_2O_2+H]^+$: 349.0975. Experimental: 349.0972.

Ejemplo 71

5-(*Trans*-2-(3,5-difluoro-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(3,5-difluoro-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *trans*-2-(3,5-difluoro-4-(trifluorometil)fenil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (110 mg, 0.25 mmol) (del paso 1 del ejemplo 70) en MeOH (5 mL) y se enfrió hasta -40 °C. Se añadió hidróxido sódico (0.066 mL, 0.25 mmol) disuelto en agua (0.500 mL). 20 min después a -40 °C, se añadió hidroxilamina (al 50% en peso en agua, 7.71 µL, 0.25 mmol) y se continuó agitando durante 4 h. A continuación, la mezcla de reacción se añadió a una solución calentada previamente a 80 °C de ácido clorhídrico 6 M (1.299 mL, 7.80 mmol) y se agitó durante 1 h. El disolvente

se evaporó al vacío. Se añadieron DCM (50 mL) y agua (50 mL), se agitó y se separaron las fases. La fase orgánica se secó con un separador de fases y se evaporó al vacío. El compuesto se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x20 DI en mm) utilizando un gradiente de 20-65% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/AcOH en 30 minutos con un flujo de 19 mL/min. Se aisló *trans*-2-(3,5-difluoro-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (7.00 mg, 6.85%) como un sólido blanco. ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.61 - 1.73 (m, 1H), 1.90 - 2.01 (m, 1H), 2.06 (dt, 1H), 2.56 (d, 1H), 2.76 (t, 1H), 2.89 (t, 1H), 3.78 (s, 3H), 4.13 - 4.47 (m, 1H), 5.46 - 5.74 (m, 1H), 5.68 (s, 1H), 6.89 (d, 2H). MS m/z 407 $(M+H)^+$.

Paso 2: 5-(*Trans*-2-(3,5-difluoro-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió *trans*-2-(3,5-difluoro-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (26 mg, 0.06 mmol) en ácido bromhídrico (al 33% en AcOH, 2 mL, 0.06 mmol) y se agitó a temperatura ambiente durante 20 h. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-(*trans*-2-(3,5-difluoro-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona (7.00 mg, 31%). ^{1}H RMN (600 MHz, DMSO) δ 1.73 - 1.88 (m, 3H), 2.02 - 2.08 (m, 1H), 2.64 - 2.70 (m, 1H), 2.77 - 2.83 (m, 1H), 3.06 - 3.11 (m, 1H), 3.83 - 3.86 (m, 1H), 6.02 (s, 1H), 7.42 (d, 2H). HRMS calculado para $[C_{15}H_{13}F_5N_2O_2+H]^+$: 349.0975. Experimental: 349.0983.

Ejemplo 72

5-((2*R*,4*S*)-2-(2-Metil-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Cis*-4-(3-etoxi-3-oxopropanoil)-2-(2-metil-4-(trifluorometil)fenil)piperidin-1-carboxilato de metilo

Se disolvió el ácido 1-(metoxicarbonil)-2-(2-metil-4-(trifluorometil)fenil)piperidin-4-carboxílico (7.79 g, 22.56 mmol) (compuesto de referencia 31) en THF (60 mL) y a continuación se añadió di(1*H*-imidazol-1-il)metanona (5.49 g, 33.84 mmol). La reacción se agitó durante toda la noche a temperatura ambiente (matraz 1). En otro matraz, se suspendieron 3-etoxi-3-oxopropanoato de potasio (7.68 g, 45.12 mmol) y cloruro de magnesio anhidro (4.30 g, 45.12 mmol) en THF (60.0 mL) y se agitó a 50 °C en atmósfera de nitrógeno durante toda la noche, y posteriormente se dejó enfriar hasta temperatura ambiente (matraz 2). El contenido del matraz 1 se añadió al matraz 2 y se agitó en atmósfera de nitrógeno durante 48 h. La reacción se detuvo añadiendo HCl 2 M. La mezcla se extrajo tres veces con EtOAc, las fases orgánicas combinadas se evaporaron y se purificaron mediante cromatografía en columna de sílice (columna Biotage de 100 g con 88/12-33/67 de heptano/EtOAc en 9 volúmenes de columna) para proporcionar *cis*-4-(3-etoxi-3-oxopropanoil)-2-(2-metil-4-(trifluorometil)fenil)piperidin-1-carboxilato de metilo (6.28 g, 67%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.23 - 1.33 (m, 3H), 1.68 - 1.97 (m, 2H), 2.08 - 2.21 (m, 2H), 2.44 (s, 3H), 2.87 - 2.98 (m, 1H), 3.46 (s, 2H), 3.44 - 3.66 (m, 1H), 3.58 (s, 3H), 4.15 - 4.29 (m, 3H), 4.91 - 5.01 (m, 1H), 7.24 - 7.32 (m, 1H), 7.36 - 7.43 (m, 2H). MS m/z 416 $(M+H)^+$.

Paso 2: <u>*Cis*-2-(2-metil-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo</u>.

Se disolvió *cis*-4-(3-etoxi-3-oxopropanoil)-2-(2-metil-4-(trifluorometil)fenil)piperidin-1-carboxilato de metilo (6.28 g, 15.12 mmol) en MeOH (60 mL) y se enfrió hasta -40 °C. Se disolvió NaOH 3.8 M (3.98 mL, 15.12 mmol) en agua (6 mL) y se añadió a la mezcla, y la reacción se agitó a -40 °C durante 40 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.926 mL, 15.12 mmol) y se continuó agitando durante 3.5 h a -40 °C. Posteriormente, la mezcla de reacción se añadió a una solución caliente calentada previamente a 80 °C de HCl 6 M (76 mL, 453.53 mmol) y se agitó durante 20 min. La mezcla de reacción

se repartió entre agua y DCM. La fase acuosa se extrajo 2 veces con DCM y las fases orgánicas combinadas se secaron y se evaporaron. El compuesto se purificó dos veces mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x50 DI en mm) utilizando un gradiente de 35-75% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/AcOH en 30 minutos con un flujo de 100 mL/min. Se aisló *cis*-2-(2-metil-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (3.2 g, 55%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.81 - 1.93 (m, 2H), 2.21 - 2.42 (m, 2H), 2.44 (s, 3H), 3.03 - 3.13 (m, 1H), 3.59 (s, 3H), 3.63 - 3.75 (m, 1H), 4.12 - 4.20 (m, 1H), 5.02 (dd, 1H), 5.65 (s, 1H), 7.30 (d, 1H), 7.37 - 7.44 (m, 2H). MS m/z 383 $(M-H)^-$.

Paso 3: (2*R*,4*S*)-2-(2-Metil-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El *cis*-2-(2-metil-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (3.2 g, 8.33 mmol) se sometió a HPLC preparativa quiral (columna: CelluCoat (250x50), tamaño de partícula: 10 µm, fase móvil: 75/25 de heptano/EtOH, velocidad de flujo: 120 mL/min) para proporcionar (2*R*,4*S*)-2-(2-metil-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.45 g, 45%), pureza quiral: 99.3% de ee, rotación óptica $[\alpha]_D^{20} = +49.0$ (acetonitrilo, c=1), ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.79 - 1.95 (m, 2H), 2.20 - 2.40 (m, 2H), 2.44 (s, 3H), 3.02 - 3.15 (m, 1H), 3.59 (s, 3H), 3.63 - 3.76 (m, 1H), 4.11 - 4.22 (m, 1H), 5.02 (dd, 1H), 5.65 (s, 1H), 7.24 - 7.32 (m, 1H), 7.36 - 7.43 (m, 2H).

Paso 4: 5-((2*R*,4*S*)-2-(2-Metil-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-2-(2-metil-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.45 g, 3.77 mmol) en ácido bromhídrico (al 33% en AcOH, 19.82 mL, 113.18 mmol) y se agitó durante toda la noche. La mezcla se evaporó y purificó en una columna Kromasil C8 (10

µm 250x50 DI en mm) utilizando un gradiente de 15-55% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 20 minutos con un flujo de 100 mL/min. Se aisló 5-((2*R*,4*S*)-2-(2-metil-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona (810 mg, 65%) como un polvo blanco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.35 (c, 1H), 1.52 (dc, 1H), 1.88 - 2.01 (m, 2H), 2.42 (s, 3H), 2.75 - 2.85 (m, 1H), 2.89 - 3.00 (m, 1H), 3.12 - 3.18 (m, 1H), 3.93 (d, 1H), 5.76 (s, 1H), 7.49 - 7.54 (m, 2H), 7.73 (d, 1H). HRMS calculado para $[C_{16}H_{17}F_3N_2O_2+H]^+$: 327.1320. Experimental: 327.1312.

Ejemplo 73

5-((2*R*,4*S*)-2-(2-Fluoro-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-4-(3-etoxi-3-oxopropanoil)-2-(2-fluoro-4-(trifluorometil)fenil)piperidin-1-carboxilato de metilo y *cis*-4-(3-etoxi-3-oxopropanoil)-2-(2-fluoro-4-(trifluorometil)fenil)piperidin-1-carboxilato de metilo

Se disolvió el ácido 2-(2-fluoro-4-(trifluorometil)fenil)-1-(metoxicarbonil)piperidin-4-carboxílico (4.82 g, 13.80 mmol) en metil-THF (120 mL) y a continuación se añadió di(1*H*-imidazol-1-il)metanona (4.03 g, 24.84 mmol). La mezcla se agitó a temperatura ambiente en atmósfera de nitrógeno durante 5 h (matraz 1). En otro matraz, se suspendió 3-etoxi-3-oxopropanoato de potasio (4.23 g, 24.84 mmol) en metil-THF (120 mL) y a continuación se añadió cloruro de magnesio (2.365 g, 24.84 mmol). La suspensión se agitó a 50 °C en atmósfera de nitrógeno durante 5 h utilizando un imán grande (matraz 2). El contenido del matraz 1 se transfirió al matraz 2. La suspensión blanca resultante se agitó a temperatura ambiente en atmósfera de nitrógeno durante toda la noche. La mezcla se acidificó hasta pH 1 con HCl 3.8 M y a continuación se añadieron MTBE (50 mL) y agua (50 mL). Las fases se separaron y la capa orgánica se lavó con agua, $NaHCO_3$ sat. y salmuera. La capa orgánica se secó con Na_2SO_4, se filtró y se evaporó para obtener un aceite amarillento. El residuo se purificó mediante cromatografía en sílice (Biotage (340 g) con 1 VC de EtOAc en heptano (20%)

seguido de un gradiente de 20-60% de EtOAc en *n*-heptano (8 VC)). La columna se acondicionó con 20% de EtOAc en *n*-heptano (1 VC). Se aislaron *trans*-4-(3-etoxi-3-oxopropanoil)-2-(2-fluoro-4-(trifluorometil)fenil)piperidin-1-carboxilato de metilo (413 mg, 7%) y *cis*-4-(3-etoxi-3-oxopropanoil)-2-(2-fluoro-4-(trifluorometil)fenil)piperidin-1-carboxilato de metilo (2.83 g, 49%). Isómero *cis*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.22 - 1.32 (m, 3H), 1.81 - 1.96 (m, 2H), 2.06 - 2.18 (m, 1H), 2.27 - 2.36 (m, 1H), 2.87 - 2.97 (m, 1H), 3.34 - 3.51 (m, 3H), 3.58 - 3.66 (m, 3H), 4.14 - 4.23 (m, 3H), 5.15 (dd, 1H), 7.25 - 7.40 (m, 3H). MS m/z 420 $(M+H)^+$. Isómero *trans*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.18 - 1.31 (m, 3H), 1.58 - 1.72 (m, 1H), 1.87 - 2.06 (m, 2H), 2.40 - 2.60 (m, 2H), 3.17 (dt, 1H), 3.45 (s, 2H), 3.73 (s a, 3H), 4.08 - 4.23 (m, 2H), 4.34 (s a, 1H), 5.75 (s a, 1H), 7.22 - 7.43 (m, 3H). MS m/z 420 $(M+H)^+$.

Paso 2: *Cis*-2-(2-fluoro-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *cis*-4-(3-etoxi-3-oxopropanoil)-2-(2-fluoro-4-(trifluorometil)fenil)piperidin-1-carboxilato de metilo (3 g, 7.15 mmol) en MeOH (25 mL) y se enfrió hasta -45 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (2.104 mL, 7.15 mmol) durante 10 min y la solución amarilla se continuó agitando a -45 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.438 mL, 7.15 mmol) durante 8 min. La solución resultante se agitó a -45 °C durante 3 h. A continuación, la mezcla se vertió rápidamente sobre una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (36.8 mL, 221.05 mmol) y la mezcla se continuó agitando a 80 °C durante 20 min. El disolvente se evaporó y se añadieron DCM/agua. Las fases se separaron, y la fase orgánica se hizo pasar a través de un separador de fases y se evaporó para proporcionar un sólido amarillento. El compuesto se purificó mediante HPLC preparativa en una columna XBridge C18 (10 µm 250x50 DI en mm) utilizando un gradiente de 10-60% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 20 minutos con un flujo de 100 mL/min. Se aisló *cis*-2-(2-fluoro-4-

(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (2.12 g, 76%) como un aceite incoloro. MS m/z 389 $(M+H)^+$.

Paso 3: (2*R*,4*S*)-2-(2-Fluoro-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El *cis*-2-(2-fluoro-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (2.12 g, 5.46 mmol) se sometió a HPLC preparativa quiral (columna: CelluCoat (250x50 mm), tamaño de partícula: 10 µm, fase móvil: 50/50 de heptano/EtOH, velocidad de flujo: 120 mL/min)) para proporcionar (2*R*,4*S*)-2-(2-fluoro-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (958 mg, 45%), pureza quiral: 99.9% de ee, rotación óptica $[\alpha]_D^{20} = +48.0$ (acetonitrilo, c=1.0), ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.84 - 1.95 (m, 1H), 2.04 - 2.15 (m, 1H), 2.24 - 2.45 (m, 2H), 3.04 - 3.15 (m, 1H), 3.47 - 3.58 (m, 1H), 3.65 (s, 3H), 4.14 - 4.23 (m, 1H), 5.25 (dd, 1H), 5.61 (s, 1H), 7.23 - 7.37 (m, 3H).

Paso 4: 5-((2*R*,4*S*)-2-(2-Fluoro-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-2-(2-fluoro-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.96 g, 2.47 mmol) en ácido bromhídrico (al 33% en ácido acético, 19.48 mL, 111.25 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*S*)-2-(2-fluoro-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona (687 mg, 84%). ^{1}H RMN (600 MHz, DMSO) δ 1.36 (c, 1H), 1.48 (dc, 1H), 1.84 - 1.92 (m, 1H), 1.94 - 2.02 (m, 1H), 2.75 (dt, 1H), 2.92 (tt, 1H), 3.08 - 3.15 (m, 1H), 4.00 (d, 1H), 5.73 (s, 1H), 7.53 - 7.62 (m, 2H), 7.78 (t, 1H). HRMS calculado para $[C_{15}H_{14}F_4N_2O_2+H]^+$: 331.1070. Experimental: 331.1086.

Ejemplo 74

5-(*Trans*-2-(2-fluoro-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(2-fluoro-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *trans*-4-(3-etoxi-3-oxopropanoil)-2-(2-fluoro-4-(trifluorometil)fenil)piperidin-1-carboxilato de metilo (430 mg, 1.03 mmol) (del paso 1 del ejemplo 73) en MeOH (3 mL) y se enfrió hasta -45 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (0.302 mL, 1.03 mmol) durante 10 min y la solución amarilla se continuó agitando a -45 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.063 mL, 1.03 mmol) durante 8 min. La solución resultante se agitó a -45 °C durante 3 h. A continuación, la mezcla se vertió rápidamente sobre una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (5.28 mL, 31.68 mmol) y la mezcla se continuó agitando a 80 °C durante 20 min. El disolvente se evaporó y se añadieron DCM/agua. Las fases se separaron y la fase orgánica se hizo pasar a través de un separador de fases y se evaporó para proporcionar un aceite amarillento. Se aisló *trans*-2-(2-fluoro-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo crudo (398 mg, cuant.). MS m/z 387 $(M-H)^-$.

Paso 2: 5-(*Trans*-2-(2-fluoro-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió *trans*-2-(2-fluoro-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (400 mg, 1.03 mmol) en ácido bromhídrico (al 33% en ácido acético, 8.12 mL, 46.35 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-(*trans*-2-(2-fluoro-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona (146 mg, 43%). ^{1}H RMN (600 MHz, DMSO) δ 1.63 - 1.71 (m, 1H), 1.78 -

1.86 (m, 1H), 1.91 - 1.99 (m, 1H), 2.04 - 2.11 (m, 1H), 2.69 (dt, 1H), 2.87 - 2.93 (m, 1H), 3.19 - 3.23 (m, 1H), 4.00 (d, 1H), 5.88 (d, 1H), 7.53 - 7.61 (m, 2H), 7.77 (t, 1H). HRMS calculado para $[C_{15}H_{14}F_4N_2O_2+H]^+$: 331.1070. Experimental: 331.1074.

Ejemplo 75

5-((2*R*,4*S*)-2-(3-Fluoro-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: 4-(3-Etoxi-3-oxopropanoil)-2-(3-fluoro-4-(trifluorometil)fenil)piperidin-1-carboxilato de metilo

Se disolvió el ácido 2-(3-fluoro-4-(trifluorometil)fenil)-1-(metoxicarbonil)piperidin-4-carboxílico (3.07 g, 8.8 mmol) (compuesto de referencia 33) en metil-THF (60 mL) en atmósfera de nitrógeno y se añadió di(1*H*-imidazol-1-il)metanona (2.140 g, 13.20 mmol). La suspensión se agitó a temperatura ambiente durante 3 h (matraz 1). En otro matraz, se suspendió 3-etoxi-3-oxopropanoato de potasio (2.70 g, 15.84 mmol) en metil-THF (30 mL) y se añadió cloruro de magnesio (1.508 g, 15.84 mmol). La suspensión se agitó a 50 °C en atmósfera de nitrógeno durante 22 h utilizando un imán muy grande (matraz 2). El contenido del matraz 1 se transfirió al matraz 2 y la suspensión blanca resultante se agitó a temperatura ambiente durante 20 h. En otro matraz, se suspendió 3-etoxi-3-oxopropanoato de potasio (1.348 g, 7.92 mmol) en metil-THF (30 mL) y se añadió cloruro de magnesio (0.754 g, 7.92 mmol). La suspensión se agitó a 50 °C durante 5 h y después se añadió a la mezcla de reacción. La mezcla se agitó a temperatura ambiente durante 15 h. Se añadieron HCl 0.1 M y DCM, y las fases se separaron. La fase acuosa se extrajo con DCM, las fases orgánicas combinadas se filtraron a través de un separador de fases y se evaporaron. El residuo se purificó en una columna Biotage (gradiente 5:1 de heptano:EtOAc, columna Biotage® con 340 g de KP-SIL, 10 VC). Se aisló el producto 4-(3-etoxi-3-oxopropanoil)-2-(3-fluoro-4-(trifluorometil)fenil)piperidin-1-carboxilato de metilo (2.190 g, 59.3%) como un aceite incoloro. MS m/z 420 $(M+H)^+$.

Paso 2: 2-(3-Fluoro-4-(trifluorometil)fenil)-4-(3-oxo-2,3-

dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió 4-(3-etoxi-3-oxopropanoil)-2-(3-fluoro-4-(trifluorometil)fenil)piperidin-1-carboxilato de metilo (2.19 g, 5.22 mmol) en MeOH (20 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (0.219 g, 5.48 mmol) disuelto en agua (2.000 mL) y la mezcla se agitó a -40 °C durante 15 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.336 mL, 5.48 mmol). La solución resultante se agitó a -40 °C durante 1 h. Posteriormente, la mezcla se transfirió a una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (27.0 mL, 161.89 mmol) y la mezcla se agitó a 80 °C durante 20 min. Se añadieron agua y DCM y se separaron las fases. La fase acuosa se extrajo con DCM, las fases orgánicas combinadas se filtraron a través de un separador de fases y se evaporaron. El compuesto se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x50 DI en mm) utilizando un gradiente de 15-55% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/AF en 25 minutos con un flujo de 100 mL/min. Se proporcionó el 2-(3-fluoro-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.670 g, 33.0%) como un sólido incoloro. ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.82 - 1.93 (m, 1H), 2.12 - 2.44 (m, 3H), 3.04 - 3.16 (m, 1H), 3.35 - 3.46 (m, 1H), 3.69 (s, 3H), 4.11 - 4.21 (m, 1H), 5.09 - 5.18 (m, 1H), 5.56 (s, 1H), 6.97 - 7.09 (m, 2H), 7.52 (t, 1H). MS m/z 387 $(M-H)^-$.

Paso 3: (2*R*,4*S*)-2-(3-Fluoro-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo y (2*S*,4*R*)-2-(3-fluoro-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El 2-(3-fluoro-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (670 mg, 1.73 mmol) se sometió a HPLC preparativa quiral (columna: CelluCoat (250x50), tamaño de partícula: 10 µm, fase móvil: 50/50 de heptano/EtOH, velocidad de flujo: 120 mL/min) para proporcionar (2*R*,4*S*)-2-(3-fluoro-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

(319 mg, 47%), pureza quiral: 99.9% de ee, rotación óptica $[\alpha]_D^{20} = +53.4$ (acetonitrilo, c=0.5), y (2*S*,4*R*)-2-(3-fluoro-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (332 mg, 49%), pureza quiral: 99.3% de ee, rotación óptica $[\alpha]_D^{20} = -47.6$ (acetonitrilo, c=0.5).

Paso 4: 5-((2*R*,4*S*)-2-(3-Fluoro-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-2-(3-fluoro-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (319 mg, 0.82 mmol) en ácido bromhídrico (al 33% en ácido acético, 6.5 mL, 36.97 mmol) y se agitó a temperatura ambiente durante 16 h. El disolvente se eliminó al vacío y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*S*)-2-(3-fluoro-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona (150 mg, 55%). ^{1}H RMN (600 MHz, DMSO) δ 1.33 (c, 1H), 1.45 (dc, 1H), 1.84 - 1.90 (m, 1H), 1.99 - 2.05 (m, 1H), 2.72 (dt, 1H), 2.83 - 2.91 (m, 1H), 3.07 - 3.14 (m, 1H), 3.72 - 3.79 (m, 1H), 5.73 (s, 1H), 7.41 (d, 1H), 7.48 (d, 1H), 7.70 (t, 1H). HRMS calculado para $[C_{15}H_{14}F_4N_2O_2+H]^+$: 331.1070. Experimental: 331.1058.

Ejemplo 76

5-((2*S*,4*R*)-2-(3-Fluoro-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*S*,4*R*)-2-(3-fluoro-4-(trifluorometil)fenil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (332 mg, 0.85 mmol) en ácido bromhídrico (al 33% en ácido acético, 6.74 mL, 38.47 mmol) y se agitó a temperatura ambiente durante 16 h. El disolvente se eliminó al vacío y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm)

para proporcionar 5-((2*S*,4*R*)-2-(3-fluoro-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona (174 mg, 62%). ^{1}H RMN (600 MHz, DMSO) δ 1.32 (c, 1H), 1.45 (dc, 1H), 1.85 - 1.90 (m, 1H), 2.00 - 2.04 (m, 1H), 2.72 (dt, 1H), 2.87 (tt, 1H), 3.08 - 3.13 (m, 1H), 3.73 - 3.77 (m, 1H), 5.73 (s, 1H), 7.41 (d, 1H), 7.48 (d, 1H), 7.70 (t, 1H). HRMS calculado para $[C_{15}H_{14}F_4N_2O_2+H]^+$: 331.1070. Experimental: 331.1067.

Ejemplo 77

5-((2*R*,4*S*)-2-Fenilpiperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-4-(3-etoxi-3-oxopropanoil)-2-fenilpiperidin-1-carboxilato de metilo y *cis*-4-(3-etoxi-3-oxopropanoil)-2-fenilpiperidin-1-carboxilato de metilo.

Se disolvió el ácido 1-(metoxicarbonil)-2-fenilpiperidin-4-carboxílico (5.133 g, 19.50 mmol) (compuesto de referencia 34) en metil-THF (90 mL) y a continuación se añadió di(1*H*-imidazol-1-il)metanona (4.74 g, 29.24 mmol). La suspensión se agitó a temperatura ambiente durante toda la noche en atmósfera de nitrógeno (matraz 1). En otro matraz, se suspendió 3-etoxi-3-oxopropanoato de potasio (5.97 g, 35.09 mmol) en metil-THF (90 mL) y se añadió cloruro de magnesio (3.34 g, 35.09 mmol). La suspensión se agitó a temperatura ambiente durante toda la noche en atmósfera de nitrógeno (matraz 2). A continuación, la suspensión amarillenta del matraz 1 se añadió a la suspensión blanca del matraz 2. La suspensión blanca resultante se agitó en atmósfera de nitrógeno a temperatura ambiente durante 6 h 30 min. Mientras tanto, se suspendió 3-etoxi-3-oxopropanoato de potasio (5.97 g, 35.09 mmol) en metil-THF (90 mL) y se añadió cloruro de magnesio (3.34 g, 35.09 mmol). La suspensión se agitó a 50 °C en atmósfera de nitrógeno durante 2 h y después se añadió a la mezcla de reacción. La suspensión blanca resultante se agitó a temperatura ambiente en atmósfera de nitrógeno durante 3 días. La mezcla se acidificó hasta pH 1 con HCl 1 M y se añadió MTBE. Las fases se separaron y la fase orgánica se lavó con agua, $NaHCO_3$ sat. y agua. Los disolventes se evaporaron para proporcionar un aceite amarillo. Los

diastereoisómeros se separaron mediante cromatografía en columna sobre sílice (Biotage, gradiente 0% => 50% de EtOAc en heptano; columna Biotage® con 340 g de KP-SIL) para proporcionar *trans*-4-(3-etoxi-3-oxopropanoil)-2-fenilpiperidin-1-carboxilato de metilo (1.14 g, 19%) y *cis*-4-(3-etoxi-3-oxopropanoil)-2-fenilpiperidin-1-carboxilato de metilo (3.77 g, 62%). Isómero *cis*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.22 - 1.31 (m, 3H), 1.84 - 2.11 (m, 3H), 2.26 - 2.35 (m, 1H), 2.82 - 2.92 (m, 1H), 3.28 - 3.48 (m, 3H), 3.63 (s, 3H), 4.12 - 4.21 (m, 3H), 4.96 - 5.04 (m, 1H), 7.17 - 7.35 (m, 5H). MS m/z 334 $(M+H)^+$. Isómero *trans*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.13 - 1.25 (m, 3H), 1.44 - 1.95 (m, 3H), 2.45 - 2.66 (m, 2H), 2.78 - 2.88 (m, 1H), 3.39 (s, 2H), 3.68 (s, 3H), 3.98 - 4.34 (m, 3H), 5.55 (s a, 1H), 7.10 - 7.23 (m, 3H), 7.26 - 7.34 (m, 2H). MS m/z 334 $(M+H)^+$.

Paso 2: <u>*Cis*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-fenilpiperidin-1-carboxilato de metilo</u>

Se disolvió *cis*-4-(3-etoxi-3-oxopropanoil)-2-fenilpiperidin-1-carboxilato de metilo (1.913 g, 5.74 mmol) en MeOH (15 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (0.230 g, 5.74 mmol) disuelto en agua (1.500 mL) durante 5 min y se continuó agitando la solución incolora a -40 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.352 mL, 5.74 mmol) durante 8 min. La solución resultante se agitó a -40°C durante 2 h 15 min. A continuación, la mezcla se vertió rápidamente sobre una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (24 mL, 144.00 mmol) y se continuó agitando la mezcla a 80 °C durante 20 min. El disolvente se evaporó y se añadieron MTBE/agua. Las fases se separaron y la fase orgánica se evaporó para proporcionar un aceite amarillento. El compuesto se purificó mediante HPLC preparativa en 2 inyecciones en una columna XBridge C18 (10 µm 250x50 DI en mm) utilizando un gradiente de 0-30% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 20 minutos con un flujo de 100 mL/min. Se aisló *cis*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-

fenilpiperidin-1-carboxilato de metilo (1.344 g, 77%) como un sólido blanco. ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.77 - 1.85 (m, 1H), 2.10 - 2.18 (m, 1H), 2.19 - 2.28 (m, 1H), 2.32 - 2.39 (m, 1H), 3.01 - 3.08 (m, 1H), 3.37 (ddd, 1H), 3.64 (s, 3H), 4.15 (ddd, 1H), 5.08 - 5.13 (m, 1H), 5.48 (s, 1H), 7.13 - 7.20 (m, 3H), 7.27 (t, 2H). MS m/z 303 $(M+H)^+$.

Paso 3: (2*R*,4*S*)-4-(3-Oxo-2,3-dihidroisoxazol-5-il)-2-fenetilpiperidin-1-carboxilato de metilo

El *cis*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-fenilpiperidin-1-carboxilato de metilo racémico (1.34 g, 4.42 mmol) se sometió a HPLC preparativa quiral (columna: ReproSil (250x20), tamaño de partícula: 8 µm, fase móvil: EtOH, velocidad de flujo: 100 mL/min) para proporcionar (2*R*,4*S*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-fenilpiperidin-1-carboxilato de metilo (621 mg, 46%), pureza quiral: 99.9% de ee, rotación óptica $[\alpha]_D^{20} = +65.8$ (acetonitrilo, c=1).

Paso 4: 5-((2*R*,4*S*)-2-Fenilpiperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-fenilpiperidin-1-carboxilato de metilo (621 mg, 2.05 mmol) en ácido bromhídrico (al 33% en ácido acético, 7 mL, 99.92 mmol) y la mezcla se agitó a temperatura ambiente durante 24 h. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*S*)-2-fenilpiperidin-4-il)isoxazol-3(2*H*)-ona (306 mg, 61%) (la muestra aislada contenía DMSO). ^{1}H RMN (400 MHz, CD_3OD) δ 1.76 - 2.02 (m, 2H), 2.11 - 2.30 (m, 2H), 3.05 - 3.21 (m, 2H), 3.41 - 3.49 (m, 1H), 4.14 (dd, 1H), 5.56 (s, 1H), 7.27 - 7.48 (m, 5H). HRMS calculado para $[C_{14}H_{16}N_2O_2+H]^+$: 245.1290. Experimental: 245.1270.

Ejemplo 78

5-((2*S*,4*S*)-2-Fenilpiperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-

fenilpiperidin-1-carboxilato de metilo

Se disolvió *trans*-4-(3-etoxi-3-oxopropanoil)-2-fenilpiperidin-1-carboxilato de metilo (1.104 g, 3.31 mmol) (del paso 1 del ejemplo 77) en MeOH (10 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (0.132 g, 3.31 mmol) disuelto en agua (1.000 mL) durante 10 min y se continuó agitando la solución incolora a -40 °C durante 30 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.203 mL, 3.31 mmol) durante 6 min. La solución resultante se agitó a -40 °C durante 2 h 30 min. A continuación, la mezcla se vertió rápidamente sobre una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (14 mL, 84.00 mmol) y se continuó agitando la mezcla a 80 °C durante 20 min. El disolvente se evaporó y se añadieron MTBE/agua. Las fases se separaron y la fase orgánica se evaporó para proporcionar un aceite marrón. El residuo se purificó mediante HPLC preparativa en una columna XBridge C18 (10 µm 250x50 DI en mm) utilizando un gradiente de 0-30% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 20 minutos con un flujo de 100 mL/min. Se aisló *trans*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-fenilpiperidin-1-carboxilato de metilo (722 mg, 72%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.66 (dc, 1H), 1.86 - 2.09 (m, 2H), 2.72 (d, 1H), 2.79 - 3.03 (m, 2H), 3.78 (s, 3H), 4.26 (s a, 1H), 5.68 (s a, 2H), 7.20 - 7.32 (m, 3H), 7.34 - 7.43 (m, 2H). MS m/z 303 $(M+H)^+$.

Paso 2: (2*S*,4*S*)-4-(3-Oxo-2,3-dihidroisoxazol-5-il)-2-fenilpiperidin-1-carboxilato de metilo

El *trans*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-fenilpiperidin-1-carboxilato de metilo racémico (772 mg, 2.55 mmol) se sometió a HPLC preparativa quiral (columna: Chiralpak AD (250x20), tamaño de partícula: 5 µm, fase móvil: 75/25 de heptano/EtOH, velocidad de flujo: 15 mL/min) para proporcionar (2*S*,4*S*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-fenilpiperidin-1-carboxilato de metilo (249 mg, 32%), rotación óptica $[\alpha]_D^{20} = +23.0$ (acetonitrilo, c=1), pureza quiral: 99.7% de ee.

Paso 3: 5-((2*S*,4*S*)-2-Fenilpiperidin-4-il)isoxazol-3(2*H*)-

ona

Se disolvió (2*S*,4*S*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-fenilpiperidin-1-carboxilato de metilo (249 mg, 0.82 mmol) en ácido bromhídrico (al 33% en ácido acético, 3 mL, 42.82 mmol) y la mezcla se agitó a temperatura ambiente durante 16 h. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*S*,4*S*)-2-fenilpiperidin-4-il)isoxazol-3(2*H*)-ona (255 mg, 127%) (la muestra aislada contenía DMSO). ^{1}H RMN (400 MHz, $CDCl_3$) δ 2.10 - 2.43 (m, 4H), 3.21 (dt, 1H), 3.26 - 3.35 (m, 1H), 3.35 - 3.43 (m, 1H), 4.17 (dd, 1H), 5.73 (s, 1H), 7.34 - 7.48 (m, 5H). HRMS calculado para $[C_{14}H_{16}N_2O_2+H]^+$: 245.1290. Experimental: 245.1271.

Ejemplo 79

5-((2*R*,4*S*)-2-Ciclohexilpiperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-ciclohexil-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo y *cis*-2-ciclohexil-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo

Se agitó una suspensión de cloruro de magnesio (2.085 g, 21.89 mmol) y malonato de etilo y potasio (3.73 g, 21.89 mmol) en THF anhidro (80 mL) en atmósfera de nitrógeno a 50 °C durante 2.5 h (matraz 1). En otro matraz, se añadió di(1*H*-imidazol-1-il)metanona (2.96 g, 18.24 mmol) en porciones a una solución de ácido 2-ciclohexil-1-(metoxicarbonil)piperidin-4-carboxílico (3.28 g, 12.16 mmol) (compuesto de referencia 35) en THF anhidro (20 mL) a 0 °C y se creó una atmósfera de nitrógeno. Se retiró el baño de hielo y la solución se agitó a temperatura ambiente durante 2 h (matraz 2). Posteriormente, el contenido del matraz 1 se añadió al matraz 2 y la mezcla resultante se agitó durante toda la noche (20 h). La mezcla de reacción se concentró y el residuo se disolvió en EtOAc y H_2O. La fase acuosa se extrajo una vez con EtOAc y las fases orgánicas combinadas se lavaron con agua y Na_2CO_3 al 10%, y

posteriormente se secaron con Na_2SO_4. La fase orgánica se lavó con NaOH 0.1 M, se volvió a secar y se evaporó para proporcionar un aceite amarillo. El compuesto se purificó aún más con una columna Biotage, 2 purificaciones, SNAP con 340 g de KP-SIL, gradiente lineal de 9:1 a 1:1 de heptanos/acetato de etilo en 7 VC. Se aislaron *trans*-2-ciclohexil-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (349 mg, 6.9%) y *cis*-2-ciclohexil-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (2.501, 49%). Isómero *cis*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 0.90 - 1.29 (m, 5H), 1.26 (t, 3H), 1.37 - 2.05 (m, 10H), 2.57 - 2.70 (m, 1H), 2.85-3.02 (m, 1H), 3.48 (s, 2H), 3.67 (s, 3H), 3.71-3.84 (m, 1H), 3.86-3.99 (m, 1H), 4.18 (c, 2H). MS m/z 340 $(M+H)^+$. Isómero *trans*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 0.80 - 1.30 (m, 5H), 1.26 (t, 3H), 1.33 - 1.90 (m, 9H), 1.96-2.12 (m, 1H), 2.69 - 2.86 (m, 2H), 3.46 (s, 2H), 3.67 (s, 3H), 3.84-4.33 (m, 2H), 4.21 (c, 2H). MS m/z 340 $(M+H)^+$.

Paso 2: <u>*Cis*-2-ciclohexil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo</u>

Se disolvió *cis*-2-ciclohexil-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (1.644 g, 4.84 mmol) en MeOH (15 mL) y se enfrió hasta -40 °C. Se añadió hidróxido sódico (0.194 g, 4.84 mmol) disuelto en agua (1.500 mL) gota a gota y se continuó agitando la solución incolora a -40 °C durante 30 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.297 mL, 4.84 mmol) gota a gota. La solución resultante se agitó a -40 °C durante 3 h. Posteriormente, la mezcla se vertió rápidamente sobre una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (21 mL, 126.00 mmol) y la mezcla se continuó agitando a 80 °C durante 20 min. El disolvente se evaporó y se añadieron MTBE/agua. Las fases se separaron y la fase orgánica se secó con Na_2SO_4 y se evaporó para proporcionar una espuma amarillenta. El compuesto se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x50 DI en mm) utilizando dos inyecciones con un gradiente de 15-75% de acetonitrilo en tampón 95/5/0.2 de

H_2O/MeCN/AcOH en 30 minutos con un flujo de 100 mL/min. Se aisló *cis*-2-ciclohexil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (814 mg, 55%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 0.83-0.98 (m, 2H), 1.01-1.16 (m, 3H), 1.25-1.40 (m, 1H), 1.50 - 1.88 (m, 6H), 1.95 - 2.13 (m, 3H), 2.88-3.07 (m, 2H), 3.70 (s, 3H), 3.79 - 3.89 (m, 1H), 3.95-4.07 (m, 1H), 5.70 (s, 1H). MS m/z 309 $(M+H)^+$.

Paso 3: (2*R*,4*S*)-2-Ciclohexil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

1 *cis*-2-ciclohexil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (814 mg, 2.66 mmol) se sometió a HPLC preparativa quiral (columna: Chiralpak IC (250x20), tamaño de partícula: 5 µm, fase móvil: 60/40 de heptano/IPA, velocidad de flujo: 15 mL/min) para proporcionar (2*R*,4*S*)-2-ciclohexil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (427 mg, 50%), pureza quiral: 99.9% de ee, rotación óptica $[\alpha]_D^{20} = +38.5$ (acetonitrilo, c=1).

Paso 4: 5-((2*R*,4*S*)-2-Ciclohexilpiperidin-4-il)isoxazol-3(2*H*)-ona

Se agitó (2*R*,4*S*)-2-ciclohexil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.427 g, 1.38 mmol) en HBr (al 33% en AcOH) durante toda la noche (19 horas). Se evaporaron los disolventes y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx I, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*S*)-2-ciclohexilpiperidin-4-il)isoxazol-3(2*H*)-ona (228 mg, 66%). ^{1}H RMN (400 MHz, CD_3OD) δ 1.05-1.42 (m, 5H), 1.49-1.66 (m, 2H), 1.67 - 1.91 (m, 6H), 2.17-2.26 (m, 1H), 2.26-2.35 (m, 1H), 2.97 - 3.19 (m, 3H), 3.43-3.52 (m, 1H), 5.70 (s, 1H), 8.51 (s, 1H). HRMS calculado para $[C_{14}H_{22}N_2O_2+H]^+$: 251.1760. Experimental: 251.1750.

Ejemplo 80

5-((2*S*,4*S*)-2-Ciclohexilpiperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-ciclohexil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *trans*-2-ciclohexil-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (349 mg, 1.03 mmol) (del paso 1 del ejemplo 79) en MeOH (5 mL) y se enfrió hasta -40 °C. Se añadió hidróxido sódico (41.1 mg, 1.03 mmol) disuelto en agua (0.500 mL) gota a gota y se continuó agitando la solución incolora a -40 °C durante 30 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.063 mL, 1.03 mmol) gota a gota. La solución resultante se agitó a -40 °C durante 2 h 20 min. Posteriormente, la mezcla se vertió rápidamente sobre una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (5 mL, 30.00 mmol) y la mezcla se continuó agitando a 80 °C durante 20 min. El disolvente se evaporó y se añadieron MTBE/agua. Las fases se separaron y la fase orgánica se secó con Na_2SO_4 y se evaporó para proporcionar un aceite amarillo. El compuesto se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x50 DI en mm) utilizando un gradiente de 15-75% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/AcOH en 30 minutos con un flujo de 100 mL/min. Se aisló *trans*-2-ciclohexil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (170 mg, 53%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 0.82-1.08 (m, 2H), 1.08-1.32 (m, 3H), 1.45-1.83 (m, 8H), 1.89-2.02 (m, 1H), 2.12-2.23 (m, 1H), 2.79-3.04 (m, 2H), 3.70 (s, 3H), 3.87-4.83 (m, 2H), 5.64 (s, 1H). MS m/z 309 $(M+H)^+$.

Paso 2: (2*S*,4*S*)-2-Ciclohexil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El *trans*-2-ciclohexil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (212 mg, 0.69 mmol) se sometió a HPLC preparativa quiral (columna: Chiralcel OJ (250x20), tamaño de partícula: 5 µm, fase móvil: EtOH, velocidad de flujo: 12 mL/min) para proporcionar (2*S*,4*S*)-2-ciclohexil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (79 mg, 37%), pureza quiral: 99.3% de ee,

rotación óptica $[\alpha]_D^{20} = +5.1$ (acetonitrilo, c=1).

Paso 3: 5-((2*S*,4*S*)-2-Ciclohexilpiperidin-4-il)isoxazol-3(2*H*)-ona

Se agitó (2*S*,4*S*)-2-ciclohexil-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (79 mg, 0.26 mmol) en HBr (al 33% en AcOH) durante toda la noche. Los disolventes se evaporaron y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx I, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna:Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 22 mg de 5-((2*S*,4*S*)-2-ciclohexilpiperidin-4-il)isoxazol-3(2*H*)-ona (35%). ^{1}H RMN (400 MHz, CD_3OD) δ 1.00-1.39 (m, 5H), 1.51-1.64 (m, 1H), 1.64 - 1.93 (m, 6H), 1.96-2.11 (m, 1H), 2.15-2.25 (m, 1H), 2.26-2.35 (m, 1H), 2.92 - 3.02 (m, 1H), 3.03-3.16 (m, 1H), 3.22-3.33 (m, 2H), 5.57 (s, 1H). HRMS calculado para $[C_{14}H_{22}N_2O_2+H]+$: 251.1760. Experimental: 251.1754.

Ejemplo 81

5-((2*R*,4*S*)-2-(2-Metil-2*H*-tetrazol-5-il)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: 4-(3-Etoxi-3-oxopropanoil)-2-(2-metil-2H-tetrazol-5-il)piperidin-1-carboxilato de bencilo

Se disolvió el ácido 1-(benciloxicarbonil)-2-(2-metil-2*H*-tetrazol-5-il)piperidin-4-carboxílico (0.828 g, 2.40 mmol) (compuesto de referencia 36) en THF (7 mL) y a continuación se añadió di(1*H*-imidazol-1-il)metanona (0.583 g, 3.60 mmol). La reacción se agitó durante toda la noche a temperatura ambiente (matraz 1). En otro matraz, se suspendieron 3-etoxi-3-oxopropanoato de potasio (0.816 g, 4.80 mmol) y cloruro de magnesio anhidro (0.457 g, 4.80 mmol) en THF (7.00 mL) y se agitó a 50 °C en atmósfera de nitrógeno durante toda la noche, y posteriormente se dejó enfriar hasta temperatura ambiente (matraz 2). El contenido del matraz 1 se añadió al matraz 2 y se agitó en atmósfera de nitrógeno durante todo el fin de semana (72 h). La reacción se detuvo añadiendo HCl 2 M. La mezcla se extrajo tres veces con EtOAc, las fases orgánicas

combinadas se evaporaron y se purificaron en una columna Biotage de 50 g con 88/12-100/0 de heptano/EtOAc en 12 VC. Se aisló 4-(3-etoxi-3-oxopropanoil)-2-(2-metil-2*H*-tetrazol-5-il)piperidin-1-carboxilato de bencilo (499 mg, 59%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.22 - 1.31 (m, 3H), 1.72 - 1.83 (m, 1H), 2.00 - 2.08 (m, 1H), 2.41 (dt, 1H), 2.70 - 2.78 (m, 1H), 2.88 - 2.95 (m, 1H), 3.35 - 3.63 (m, 3H), 3.99 - 4.07 (m, 1H), 4.12 - 4.20 (m, 2H), 4.28 (s, 3H), 5.11 - 5.21 (m, 2H), 5.59 (t, 1H), 7.27 - 7.40 (m, 5H). MS m/z 416 $(M+H)^+$.

Paso 2: 2-(2-Metil-2*H*-tetrazol-5-il)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de bencilo

Se disolvió 4-(3-etoxi-3-oxopropanoil)-2-(2-metil-2*H*-tetrazol-5-il)piperidin-1-carboxilato de bencilo (0.499 g, 1.20 mmol) en MeOH (6 mL) y se enfrió hasta -40 °C. Se añadió NaOH 3.8 M (0.316 mL, 1.20 mmol) disuelto en agua (0.6 mL) y la reacción se agitó a -40 °C durante 40 min. Se añadió hidroxilamina (el 50% en peso en agua, 0.074 mL, 1.20 mmol) y se continuó agitando durante 3.5 h a -40 °C. Posteriormente, la mezcla de reacción se añadió a una solución calentada previamente a 80 °C de HCl 6 M (6.01 mL, 36.03 mmol) y se agitó durante 20 min. La mezcla de reacción se repartió entre agua y DCM. La fase acuosa se extrajo 2 veces con DCM y las fases orgánicas combinadas se secaron y se evaporaron. El compuesto se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x50 DI en mm) utilizando un gradiente de 15-55% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 20 minutos con un flujo de 100 mL/min. Se aisló 2-(2-metil-2*H*-tetrazol-5-il)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de bencilo (327 mg, 71%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.96 - 2.15 (m, 2H), 2.41 (dt, 1H), 2.64 - 2.74 (m, 1H), 3.12 - 3.19 (m, 1H), 3.61 - 3.72 (m, 1H), 4.07 - 4.20 (m, 4H), 5.13 (s, 2H), 5.43 (s, 1H), 5.58 - 5.64 (m, 1H), 7.25 - 7.41 (m, 5H). MS m/z 385 $(M+H)^+$.

Paso 3: (2*R*,4*S*)-2-(2-Metil-2*H*-tetrazol-5-il)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de bencilo y

trans-2-(2-metil-2*H*-tetrazol-5-il)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de bencilo

El 2-(2-metil-2*H*-tetrazol-5-il)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de bencilo (866 mg, 2.25 mmol) se sometió a HPLC preparativa quiral: Los isómeros *cis* se separaron de los isómeros *trans* utilizando HPLC preparativa (columna: Chiralcel OJ (250x20), tamaño de partícula: 5 µm, fase móvil: 65/45/0.1 de heptano/EtOH/DEA, velocidad de flujo: 18 mL/min). Los enantiómeros *cis* se separaron utilizando HPLC preparativa quiral (columna: Chiralpak AD (250x20), tamaño de partícula: 5 µm, fase móvil: 50/50/0.1 de heptano/IPA/DEA, velocidad de flujo: 15 mL/min) para proporcionar (2*R*,4*S*)-2-(2-metil-2*H*-tetrazol-5-il)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de bencilo (301 mg, 35%), pureza quiral: 99.1% de ee, rotación óptica $[\alpha]_D^{20} = +28.9$ (acetonitrilo, c=1), ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.96 - 2.13 (m, 2H), 2.39 (dt, 1H), 2.61 - 2.71 (m, 1H), 3.10 (q, 1H), 3.62 - 3.72 (m, 1H), 4.09 (dt, 1H), 4.18 (s, 3H), 5.12 (d, 2H), 5.33 (s, 1H), 5.56 (t, 1H), 7.21 - 7.36 (m, 5H), y se aislaron *trans*-2-(2-metil-2*H*-tetrazol-5-il)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de bencilo (99 mg, 11%).

Paso 4: 5-((2*R*,4*S*)-2-(2-Metil-2*H*-tetrazol-5-il)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-2-(2-metil-2*H*-tetrazol-5-il)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de bencilo (301 mg, 0.78 mmol) en ácido bromhídrico (al 33% en AcOH) (4.1 mL, 23.49 mmol) y se dejó reaccionar durante 1 h. La mezcla se evaporó y el residuo se repartió entre agua y EtOAc. La fase acuosa se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x50 DI en mm) utilizando un gradiente de 0-15% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 20 minutos con un flujo de 100 mL/min. Se aisló 5-((2*R*,4*S*)-2-(2-metil-2H-tetrazol-5-il)piperidin-4-il)isoxazol-3(2*H*)-ona (143 mg, 73%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.70 (cd, 1H), 1.85 (c,

1H), 2.04 - 2.12 (m, 1H), 2.43 - 2.50 (m, 1H), 2.91 - 3.02 (m, 2H), 3.33 - 3.41 (m, 1H), 4.18 (dd, 1H), 4.32 (s, 3H), 5.68 (s, 1H). HRMS calculado para $[C_{10}H_{14}N_6O_2+H]^+$: 251.1256. Experimental: 251.1233.

Ejemplo 82

5-(*Trans*-2-(2-metil-2*H*-tetrazol-5-il)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió *trans*-2-(2-metil-2*H*-tetrazol-5-il)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de bencilo (99 mg, 0.26 mmol) (del paso 3 del ejemplo 81) en ácido bromhídrico (al 33% en AcOH, 1.35 mL, 7.73 mmol) y se dejó reaccionar durante 1 h. La mezcla se evaporó y el residuo se repartió entre agua y EtOAc. La fase acuosa se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x50 DI en mm) utilizando un gradiente de 0-15% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 20 minutos con un flujo de 100 mL/min. 5-(*Trans*-2-(2-metil-2*H*-tetrazol-5-il)piperidin-4-il)isoxazol-3(2*H*)-ona (45 mg, 70%). ^{1}H RMN (400 MHz, CD_3OD) δ 1.83 - 2.05 (m, 2H), 2.21 - 2.31 (m, 1H), 2.36 - 2.44 (m, 1H), 2.93 - 3.06 (m, 2H), 3.17 - 3.25 (m, 1H), 4.37 (s, 3H), 4.49 (t, 1H), 5.77 (s, 1H). HRMS calculado para $[C_{10}H_{14}N_6O_2+H]^+$: 251.1256. Experimental: 251.1262.

Ejemplo 83

5-((2*R*,4*S*)-2-(1-Metil-1*H*-tetrazol-5-il)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Cis*-4-(3-etoxi-3-oxopropanoil)-2-(1-metil-1*H*-tetrazol-5-il)piperidin-1-carboxilato de bencilo

Se disolvió el ácido 1-(benciloxicarbonil)-2-(1-metil-1*H*-tetrazol-5-il)piperidin-4-carboxílico (0.495 g, 1.43 mmol) (compuesto de referencia 37) en THF (4 mL) y a continuación se añadió di(1*H*-imidazol-1-il)metanona (0.349 g, 2.15 mmol). La reacción se agitó durante toda la noche a temperatura ambiente (matraz 1). En otro matraz, se suspendieron 3-etoxi-3-oxopropanoato de potasio (0.488 g, 2.87 mmol) y cloruro de magnesio anhidro (0.273 g, 2.87 mmol) en THF (4.00 mL) y se agitó a 50 °C en atmósfera de nitrógeno durante toda la noche,

y posteriormente se dejó enfriar hasta temperatura ambiente (matraz 2). El contenido del matraz 1 se añadió al matraz 2 y se agitó en atmósfera de nitrógeno durante todo el fin de semana (72 h). La reacción se detuvo añadiendo HCl 2 M. La mezcla se extrajo tres veces con EtOAc, las fases orgánicas combinadas se evaporaron y se purificaron en una columna Biotage de 50 g con 88/12-100/0 de heptano/EtOAc en 12 VC. Se aisló *cis*-4-(3-etoxi-3-oxopropanoil)-2-(1-metil-1*H*-tetrazol-5-il)piperidin-1-carboxilato de bencilo (482 mg, 81%). ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.25 (t, 3H), 1.89 - 1.97 (m, 1H), 2.05 - 2.12 (m, 1H), 2.28 - 2.34 (m, 1H), 2.59 - 2.66 (m, 1H), 2.93 (q, 1H), 3.35 - 3.41 (m, 1H), 3.62 (dd, 2H), 3.85 - 3.98 (m, 4H), 4.16 (c, 2H), 5.09 (c, 2H), 5.36 - 5.42 (m, 1H), 7.21 - 7.37 (m, 5H). MS m/z 416 $(M+H)^+$.

Paso 2: 2-(1-Metil-1*H*-tetrazol-5-il)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de bencilo

Se disolvió 4-(3-etoxi-3-oxopropanoil)-2-(1-metil-1*H*-tetrazol-5-il)piperidin-1-carboxilato de bencilo (0.947 g, 2.28 mmol) en MeOH (10 mL) y se enfrió hasta -40 °C. Se añadió NaOH 3.8 M (0.600 mL, 2.28 mmol) disuelto en agua (1 mL) y la reacción se agitó a -40 °C durante 40 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.140 mL, 2.28 mmol) y se continuó agitando durante 3.5 h a -40 °C. Posteriormente, la mezcla de reacción se añadió a una solución caliente calentada previamente a 80 °C de HCl 6 M (11.40 mL, 68.38 mmol) y se agitó durante 20 min. La mezcla de reacción se repartió entre agua y DCM. La fase acuosa se extrajo 2 veces con DCM y las fases orgánicas combinadas se secaron y se evaporaron. El compuesto se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x50 DI en mm) utilizando un gradiente de 15-55% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 20 minutos con un flujo de 100 mL/min. Se aisló 2-(1-metil-1*H*-tetrazol-5-il)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de bencilo (488 mg, 56%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.86 - 1.99 (m, 1H), 2.18 - 2.30 (m, 1H), 2.33 - 2.54 (m, 2H), 3.01 - 3.12 (m, 1H), 3.78 - 4.09 (m, 5H), 5.05 (s, 2H), 5.20 -

5.30 (m, 1H), 5.67 (s, 1H), 7.20 - 7.27 (m, 2H), 7.27 - 7.39 (m, 3H). MS m/z 385 $(M+H)^+$.

Paso 3: (2*R*,4*S*)-2-(1-Metil-1*H*-tetrazol-5-il)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de bencilo

El 2-(1-metil-1*H*-tetrazol-5-il)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de bencilo (488 mg, 1.27 mmol) se sometió a HPLC preparativa quiral (Columna: Chiralpak AS (250x20), tamaño de partícula: 5 µm, fase móvil: 60/40/0.1 de heptano/EtOH/DEA, velocidad de flujo: 18 mL/min) para proporcionar (2*R*,4*S*)-2-(1-metil-1*H*-tetrazol-5-il)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de bencilo (231 mg, 47%), pureza quiral: 98% de ee, rotación óptica $[\alpha]_D^{20} = +14.5$ (acetonitrilo, c=1).

Paso 4: 5-((2*R*,4*S*)-2-(1-Metil-1*H*-tetrazol-5-il)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-2-(1-metil-1*H*-tetrazol-5-il)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de bencilo (0.231 g, 0.60 mmol) en ácido bromhídrico (al 33% en AcOH, 5.26 mL, 30.05 mmol) y se dejó reaccionar durante 1 h. La mezcla se evaporó y el residuo se repartió entre agua y EtOAc. La fase acuosa se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x50 DI en mm) utilizando un gradiente de 0-10% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 20 minutos con un flujo de 100 mL/min. Los compuestos se detectaron mediante UV a 220 nm. Se recogieron las fracciones que contenían el producto (que contenían DMSO) y se evaporó el acetonitrilo. La fase acuosa se liofilizó. La mayor parte del DMSO seguía estando presente, así que el residuo se disolvió en 2 mL de MeOH y se introdujo en una columna SCX-2 de 2 g y la columna se lavó con MeOH. La amina se liberó haciendo pasar 10 mL de trietilamina al 10% en MeOH a través de la columna. El disolvente se evaporó y el residuo se liofilizó en agua para proporcionar 5-((2*R*,4*S*)-2-(1-metil-1*H*-tetrazol-5-il)piperidin-4-il)isoxazol-3(2*H*)-ona (100 mg, 67%). ^{1}H RMN (400 MHz, DMSO) δ 1.47 (dc, 1H), 1.70 - 1.81 (m, 1H), 1.87 (d, 1H), 2.12 (d, 1H),

2.74 (dt, 1H), 2.92 - 3.02 (m, 1H), 3.04 - 3.13 (m, 1H), 4.09 (s, 3H), 4.18 (dd, 1H), 5.78 (s, 1H). HRMS calculado para [(2 x $C_{10}H_{14}N_6O_2$)+H]$^+$: 501.2435. Experimental: 501.2418.

Ejemplo 84

5-((2*R*,4*S*)-2-(Ciclohexiloximetil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(ciclohexiloximetil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo y *cis*-2-(ciclohexiloximetil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo

Se disolvió el ácido 2-(ciclohexiloximetil)-1-(metoxicarbonil)piperidin-4-carboxílico (2.425 g, 8.1 mmol) (compuesto de referencia 38) en metil-THF (60 mL) en atmósfera de nitrógeno y se añadió di(1*H*-imidazol-1-il)metanona (1.970 g, 12.15 mmol). La suspensión se agitó a temperatura ambiente durante 3 h (matraz 1). En otro matraz, se suspendió 3-etoxi-3-oxopropanoato de potasio (2.482 g, 14.58 mmol) en metil-THF (30 mL) y se añadió cloruro de magnesio (1.388 g, 14.58 mmol). La suspensión se agitó a 50 °C en atmósfera de nitrógeno durante 22 h utilizando un imán muy grande (matraz 2). El contenido del matraz 1 se añadió al matraz 2 y la suspensión blanca resultante se agitó a temperatura ambiente durante 20 h. En otro matraz, se suspendió 3-etoxi-3-oxopropanoato de potasio (1.241 g, 7.29 mmol) en metil-THF (30 mL) y se añadió cloruro de magnesio (0.694 g, 7.29 mmol). La suspensión se agitó a 50 °C durante 5 h y después se añadió a la mezcla de reacción. La mezcla se agitó a temperatura ambiente durante 15 h. Se añadieron HCl 0.1 M y DCM, y las fases se separaron. La fase acuosa se extrajo con DCM, las fases orgánicas combinadas se filtraron a través de un separador de fases y se evaporaron. El residuo se purificó en una columna Biotage (gradiente 5:1 de heptano:EtOAc, columna Biotage® con 340 g de KP-SIL, 10 VC). Se aislaron *trans*-2-(ciclohexiloximetil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (210 mg, 7%) y *cis*-2-(ciclohexiloximetil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (1.13 g, 38%). Isómero *cis*: ^{1}H RMN (400

MHz, $CDCl_3$) δ 1.14 - 2.14 (m, 17H), 2.70 - 2.79 (m, 1H), 3.11 - 3.30 (m, 2H), 3.34 - 3.62 (m, 4H), 3.69 (s, 3H), 3.82 - 3.91 (m, 1H), 4.07 - 4.24 (m, 3H). MS m/z 370 $(M+H)^+$. Isómero *trans*: ^1H RMN (400 MHz, $CDCl_3$) δ 1.16 - 2.19 (m, 17H), 2.80 - 3.10 (m, 2H), 3.16 - 3.32 (m, 1H), 3.44 - 3.64 (m, 4H), 3.66 - 3.74 (m, 3H), 3.97 - 4.27 (m, 3H), 4.33 - 4.57 (m, 1H). MS m/z 370 $(M+H)^+$.

Paso 2: *Cis*-2-(ciclohexiloximetil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *cis*-2-(ciclohexiloximetil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (1.13 g, 3.06 mmol) en MeOH (14 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (0.128 g, 3.21 mmol) disuelto en agua (1.400 mL) y la mezcla se agitó a -40 °C durante 15 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.197 mL, 3.21 mmol). La solución resultante se agitó a -40 °C durante 1 h. La mezcla se transfirió a una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (15.80 mL, 94.82 mmol) y la mezcla se agitó a 80 °C durante 20 min. Se añadieron agua y DCM, y se separaron las fases. La fase acuosa se extrajo con DCM, las fases orgánicas combinadas se filtraron a través de un separador de fases y se evaporaron. El compuesto se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x50 DI en mm) utilizando un gradiente de 15-55% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/AcOH en 25 minutos con un flujo de 100 mL/min. Se aisló *cis*-2-(ciclohexiloximetil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (423 mg, 41%). ^1H RMN (400 MHz, $CDCl_3$) δ 1.12 - 2.15 (m, 14H), 2.93 - 3.04 (m, 1H), 3.10 - 3.31 (m, 2H), 3.35 - 3.50 (m, 2H), 3.70 (s, 3H), 3.83 - 3.94 (m, 1H), 4.05 - 4.15 (m, 1H), 5.75 (s, 1H). MS m/z 339 $(M+H)^+$.

Paso 3: (2*R*,4*S*)-2-(Ciclohexiloximetil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo y (2*S*,4*R*)-2-(ciclohexiloximetil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El *cis*-2-(ciclohexiloximetil)-4-(3-oxo-2,3-

dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (423 mg, 1.25 mmol) se sometió a HPLC preparativa quiral (columna: Chiralpak IC (250x20), tamaño de partícula: 5 µm, fase móvil: 70/30 de heptano/EtOH, velocidad de flujo: 18 mL/min)) para proporcionar (2*R*,4*S*)-2-(ciclohexiloximetil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (190 mg, 45%), pureza quiral: 98.3% de ee, rotación óptica $[\alpha]_D^{20} = +55.9$ (acetonitrilo, c=1) y (2*S*,4*R*)-2-(ciclohexiloximetil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (194 mg, 46%), pureza quiral: 98.6% de ee, rotación óptica $[\alpha]_D^{20} = -55.4$ (acetonitrilo, c=1).

Paso 4: 5-((2*R*,4*S*)-2-(Ciclohexiloximetil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-2-(ciclohexiloximetil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (190 mg, 0.56 mmol) en ácido bromhídrico (al 33% en ácido acético, 4.43 mL, 25.27 mmol) y se agitó a temperatura ambiente durante 16 h. El disolvente se eliminó al vacío y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*S*)-2-(ciclohexiloximetil)piperidin-4-il)isoxazol-3(2*H*)-ona (5 mg, 3%). ^{1}H RMN (600 MHz, DMSO) δ 1.03 - 1.25 (m, 6H), 1.32 - 1.48 (m, 2H), 1.55 - 1.68 (m, 2H), 1.70 - 1.90 (m, 4H), 2.56 - 2.66 (m, 1H), 2.68 - 2.79 (m, 2H), 2.99 - 3.06 (m, 1H), 3.06 - 3.83 (m, 3H), 5.70 (s, 1H). HRMS calculado para $[C_{15}H_{24}N_2O_3+H]^+$: 281.1865. Experimental: 281.1860.

Ejemplo 85

5-((2*S*,4*R*)-2-(Ciclohexiloximetil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*S*,4*R*)-2-(ciclohexiloximetil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (194 mg, 0.57 mmol) (del paso 3 del ejemplo 84) en ácido bromhídrico (al 33% en ácido acético, 4.52 mL, 25.80 mmol) y se agitó a temperatura ambiente durante 16 h. El disolvente se eliminó al

vacío y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*S*,4*R*)-2-(ciclohexiloximetil)piperidin-4-il)isoxazol-3(2*H*)-ona (4.5 mg, 3%). ^{1}H RMN (600 MHz, DMSO) δ 1.04 - 1.24 (m, 6H), 1.33 - 1.46 (m, 2H), 1.57 - 1.66 (m, 2H), 1.73 - 1.88 (m, 4H), 2.56 - 2.67 (m, 1H), 2.68 - 2.80 (m, 2H), 2.99 - 3.06 (m, 1H), 3.07 - 3.84 (m, 3H), 5.70 (s, 1H). HRMS calculado para $[C_{15}H_{24}N_2O_3+H]^+$: 281.1865. Experimental: 281.1893.

Ejemplo 86

5-(*Trans*-2-(ciclohexiloximetil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(ciclohexiloximetil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *trans*-2-(ciclohexiloximetil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (210 mg, 0.57 mmol) (del paso 1 del ejemplo 84) en MeOH (3 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (23.87 mg, 0.60 mmol) disuelto en agua (0.300 mL) y la mezcla se agitó a -40 °C durante 15 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.037 mL, 0.60 mmol). La solución resultante se agitó a -40 °C durante 1 h. La mezcla se transfirió a una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (2.94 mL, 17.62 mmol) y la mezcla se agitó a 80 °C durante 20 min. Se añadieron agua y DCM y se separaron las fases. La fase acuosa se extrajo con DCM, las fases orgánicas combinadas se filtraron a través de un separador de fases y se evaporaron. El compuesto se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x50 DI en mm) utilizando un gradiente de 15-55% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/AcOH en 20 minutos con un flujo de 100 mL/min. Se aisló *trans*-2-(ciclohexiloximetil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (121 mg, 63%). MS m/z 339 $(M+H)^+$.

Paso 2: 5-(*Trans*-2-(ciclohexiloximetil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió *trans*-2-(ciclohexiloximetil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (121 mg, 0.36 mmol) en ácido bromhídrico (al 33% en ácido acético, 2.75 mL, 15.69 mmol) y se agitó a temperatura ambiente durante 16 h. El disolvente se evaporó al vacío y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-(*trans*-2-(ciclohexiloximetil)piperidin-4-il)isoxazol-3(2*H*)-ona (15 mg, 15%). ^{1}H RMN (600 MHz, DMSO) δ 1.09 - 1.25 (m, 5H), 1.38 - 1.53 (m, 2H), 1.55 - 1.65 (m, 2H), 1.65 - 1.83 (m, 5H), 2.55 - 2.63 (m, 1H), 2.69 - 2.80 (m, 2H), 3.02 - 3.88 (m, 4H), 5.76 (s, 1H). HRMS calculado para $[C_{15}H_{24}N_2O_3+H]^+$: 281.1865. Experimental: 281.1879.

Ejemplo 87

5-((2*R*,4*S*)-2-(Difluorometil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(difluorometil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo y *cis*-2-(difluorometil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo

Se disolvió el ácido 2-(difluorometil)-1-(metoxicarbonil)piperidin-4-carboxílico (2.2 g, 9.27 mmol) (compuesto de referencia 39) en metil-THF (60 mL) en atmósfera de nitrógeno y se añadió di(1*H*-imidazol-1-il)metanona (2.256 g, 13.91 mmol). La suspensión se agitó a temperatura ambiente durante 3 h (matraz 1). En otro matraz, se suspendió 3-etoxi-3-oxopropanoato de potasio (2.84 g, 16.69 mmol) en metil-THF (60 mL) y se añadió cloruro de magnesio (1.590 g, 16.69 mmol). La suspensión se agitó a 50 °C en atmósfera de nitrógeno durante 22 h utilizando un imán muy grande (matraz 2). El contenido del matraz 1 se añadió al matraz 2 y la suspensión blanca resultante se agitó a temperatura ambiente durante 20 h. En otro matraz, se suspendió 3-etoxi-3-oxopropanoato de potasio

(0.71 g, 4.17 mmol) en metil-THF (30 mL) en atmósfera de nitrógeno y se añadió cloruro de magnesio (0.41 g, 4.31 mmol). La suspensión se agitó vigorosamente a 50 °C durante 6 h. La suspensión se añadió a la mezcla de reacción y se continuó agitando a temperatura ambiente durante 17 h. Se añadieron NH_4Cl sat. y DCM, y las fases se separaron. La fase acuosa se extrajo con DCM, las fases orgánicas combinadas se filtraron a través de un separador de fases y se evaporaron. El residuo se purificó mediante cromatografía flash automatizada en una columna Biotage® con 340 g de KP-SIL. Se utilizó como fase móvil un gradiente de 5:1 a 1:1 de EtOAc en heptano en 15 VC. Se asilaron *trans*-2-(difluorometil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (203 mg, 7%) y *cis*-2-(difluorometil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (1.38 g, 48%). Isómero *cis*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.29 (t, 3H), 1.47 - 2.09 (m, 4H), 2.70 - 2.83 (m, 1H), 3.05 - 3.18 (m, 1H), 3.51 (d, 2H), 3.73 (s, 3H), 3.91 - 4.02 (m, 1H), 4.20 (c, 2H), 4.11 - 4.30 (m, 1H), 5.91 (dt, 1H). MS m/z 308 $(M+H)^+$. Isómero *trans*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.28 (t, 3H), 1.39 - 2.32 (m, 4H), 2.88 - 3.23 (m, 2H), 3.51 (s, 2H), 3.73 (s, 3H), 4.20 (c, 2H), 4.11 - 4.70 (m, 2H), 5.88 (t, 1H). MS m/z 308 $(M+H)^+$.

Paso 2: *Cis*-2-(difluorometil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *cis*-2-(difluorometil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (1.38 g, 4.49 mmol) en MeOH (20 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (0.180 g, 4.49 mmol) disuelto en agua (2.000 mL) y la mezcla se agitó a -40 °C durante 15 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.275 mL, 4.49 mmol). La solución resultante se agitó a -40 °C durante 1 h. Posteriormente, la mezcla se transfirió a una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (23.20 mL, 139.22 mmol) y la mezcla se agitó a 80 °C durante 20 min. Se añadieron agua y DCM, y se separaron las

fases. La fase acuosa se extrajo con DCM, las fases orgánicas combinadas se filtraron a través de un separador de fases y se evaporaron. El compuesto se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x50 DI en mm) utilizando un gradiente de 5-55% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/AcOH en 20 minutos con un flujo de 100 mL/min. Se aisló *cis*-2-(difluorometil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (650 mg, 52%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.77 - 1.88 (m, 1H), 2.03 - 2.24 (m, 3H), 2.93 - 3.03 (m, 1H), 3.22 - 3.33 (m, 1H), 3.75 (s, 3H), 3.92 - 4.02 (m, 1H), 4.21 - 4.34 (m, 1H), 5.73 (s, 1H), 5.92 (dt, 1H). MS m/z 275 $(M-H)^-$.

Paso 3: <u>(2*R*,4*S*)-2-(difluorometil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo</u>

El *cis*-2-(difluorometil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (650 mg, 2.35 mmol) se sometió a HPLC preparativa quiral (columna: Chiralpak AD (250x20), tamaño de partícula: 5 µm, fase móvil: 70/30 de heptano/EtOH, velocidad de flujo: 18 mL/min)) para proporcionar (2*R*,4*S*)-2-(difluorometil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (278 mg, 43%), pureza quiral: 99.5% de ee, rotación óptica $[\alpha]_D^{20} = +73.7$ (acetonitrilo, c=1), ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.75 - 1.86 (m, 1H), 2.01 - 2.21 (m, 3H), 2.91 - 3.01 (m, 1H), 3.20 - 3.30 (m, 1H), 3.72 (s, 3H), 3.89 - 4.01 (m, 1H), 4.18 - 4.33 (m, 1H), 5.72 (s, 1H), 5.88 (dt, 1H), 9.00 (a, 1H).

Paso 4: <u>5-((2*R*,4*S*)-2-(Difluorometil)piperidin-4-il)isoxazol-3(2*H*)-ona</u>

Se disolvió (2*R*,4*S*)- 2-(difluorometil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (278 mg, 1.01 mmol) en ácido bromhídrico (al 33% en ácido acético, 7.93 mL, 45.29 mmol) y se agitó a temperatura ambiente durante 16 h. El disolvente se eliminó al vacío y el compuesto se purificó mediante HPLC preparativa en una columna XBridge C18 (10 µm 250x19 DI en mm) utilizando un gradiente de 0-10% de

acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 20 minutos con un flujo de 19 mL/min. Se aisló 5-((2*R*,4*S*)-2-(difluorometil)piperidin-4-il)isoxazol-3(2*H*)-ona (224 mg). ^{1}H RMN (400 MHz, CD_3OD) δ 1.66 - 1.77 (m, 1H), 1.77 - 1.89 (m, 1H), 2.24 - 2.31 (m, 1H), 2.36 - 2.43 (m, 1H), 3.12 - 3.27 (m, 2H), 3.51 - 3.58 (m, 1H), 3.73 - 3.86 (m, 1H), 5.84 (s, 1H), 6.14 (dt, 1H). HRMS calculado para $[C_9H_{12}F_2N_2O_2+H]^+$: 219.0945. Experimental: 219.0950.

Ejemplo 88

5-(*Trans*-2-(difluorometil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(difluorometil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *trans*-2-(difluorometil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (203 mg, 0.66 mmol) (del paso 1 del ejemplo 87) en MeOH (3 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (26.4 mg, 0.66 mmol) disuelto en agua (0.300 mL) y la mezcla se agitó a -40 °C durante 15 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.040 mL, 0.66 mmol). La solución resultante se agitó a -40 °C durante 2 h. Posteriormente, la mezcla se transfirió a una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (3.41 mL, 20.48 mmol) y la mezcla se agitó a 80 °C durante 20 min. Se añadieron agua y DCM, y se separaron las fases. La fase acuosa se extrajo con DCM, las fases orgánicas combinadas se filtraron a través de un separador de fases y se evaporaron. El compuesto se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x20 DI en mm) utilizando un gradiente de 5-55% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/AcOH en 15 minutos con un flujo de 19 mL/min. Se aisló *trans*-2-(difluorometil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (122 mg, 67%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.35 - 1.65 (m, 1H), 1.68 - 1.82 (m, 1H), 1.87 - 2.12 (m, 1H), 2.30 - 2.45 (m, 1H), 2.70 - 3.22 (m, 2H), 3.74 (s, 3H), 4.10 - 4.74 (m, 2H), 5.69 (s, 1H), 5.75 - 6.09 (m, 1H). MS m/z 275 $(M-H)^-$.

Paso 2: 5-(*Trans*-2-(difluorometil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió *trans*-2-(difluorometil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (122 mg, 0.44 mmol) en ácido bromhídrico (al 33% en ácido acético, 8.21 mL, 46.87 mmol) y se agitó a temperatura ambiente durante 16 h. El disolvente se eliminó al vacío y el compuesto se purificó mediante HPLC preparativa en una columna XBridge C18 (10 µm 250x19 DI en mm) utilizando un gradiente de 0-10% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 20 minutos con un flujo de 19 mL/min. Se aisló 5-(*trans*-2-(difluorometil)piperidin-4-il)isoxazol-3(2*H*)-ona (86 mg, 89%). ^{1}H RMN (400 MHz, CD_3OD) δ 1.80 - 2.00 (m, 3H), 2.03 - 2.12 (m, 1H), 2.76 - 2.86 (m, 1H), 2.93 - 3.13 (m, 2H), 3.22 - 3.28 (m, 1H), 5.78 (s, 1H), 5.81 (dt, 1H). MS m/z 219 $(M+H)^+$.

Ejemplo 89

5-((2*S*,4*S*)-2-((4,4-Difluorociclohexil)metil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-((4,4-difluorociclohexil)metil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo y *cis*-2-((4,4-difluorociclohexil)metil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo

Se disolvió el ácido 2-((4,4-difluorociclohexil)metil)-1-(metoxicarbonil)piperidin-4-carboxílico (4.82 g, 15.09 mmol) (compuesto de referencia 40) en metil-THF (150 mL), a continuación se añadió di(1*H*-imidazol-1-il)metanona (3.67 g, 22.64 mmol). La mezcla se agitó a temperatura ambiente en atmósfera de nitrógeno durante 3 h (matraz 1). En otro matraz, se suspendió 3-etoxi-3-oxopropanoato de potasio (4.62 g, 27.17 mmol) en metil-THF (150 mL) y a continuación se añadió cloruro de magnesio (2.59 g, 27.17 mmol). La suspensión se agitó a 50 °C en atmósfera de nitrógeno durante 3 h utilizando un imán grande (matraz 2). El contenido del matraz 1 se transfirió al matraz 2. La suspensión amarilla resultante se agitó a temperatura ambiente en atmósfera de nitrógeno durante toda la

noche. La mezcla se acidificó hasta pH 1 con HCl 3.8 M y a continuación se añadieron MTBE (100 mL) y agua (100 mL). Las fases se separaron y la capa orgánica se lavó con agua, $NaHCO_3$ sat. y salmuera. La fase orgánica se secó con Na_2SO_4, se filtró y se evaporó para obtener un aceite incoloro. El residuo se purificó mediante cromatografía flash automatizada en una columna Biotage (340 g) con un gradiente de 20-50% (8 VC). La columna se acondicionó con 20% (1 VC). Se aislaron *trans*-2-((4,4-difluorociclohexil)metil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (300 mg, 5%) y *cis*-2-((4,4-difluorociclohexil)metil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (2.66 g, 45%). Isómero *cis*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.15 - 2.11 (m, 18H), 2.66 - 2.76 (m, 1H), 2.98 - 3.09 (m, 1H), 3.50 (s, 2H), 3.70 (s, 3H), 3.83 - 3.93 (m, 1H), 4.11 - 4.24 (m, 3H). MS m/z 390 $(M+H)^+$. Isómero *trans*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.15 - 2.13 (m, 18H), 2.77 - 2.94 (m, 2H), 3.49 (s, 2H), 3.70 (s, 3H), 3.97 - 4.33 (m, 3H), 4.34 - 4.65 (m, 1H).

Paso 2: *Cis*-2-((4,4-difluorociclohexil)metil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *cis*-2-((4,4-difluorociclohexil)metil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (2.66 g, 6.83 mmol) en MeOH (20 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (2.009 mL, 6.83 mmol) disuelto en agua (2.000 mL) durante 10 min y la solución amarilla se continuó agitando a -40 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.419 mL, 6.83 mmol) durante 8 min. La solución resultante se agitó a -40 °C durante 3 h. A continuación, la mezcla se vertió rápidamente sobre una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (30 mL, 180.00 mmol) y la mezcla se continuó agitando a 80 °C durante 20 min. El disolvente se evaporó y se añadieron DCM/agua. Las fases se separaron, y la fase orgánica se hizo pasar a través de un separador de fases y se evaporó para proporcionar un sólido blanco. El compuesto se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm

250x50 DI en mm) utilizando un gradiente de 5-55% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/AF en 30 minutos con un flujo de 100 mL/min. Se aisló *cis*-2-((4,4-difluorociclohexil)metil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.6 g, 65%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.10 - 2.12 (m, 15H), 2.96 - 3.05 (m, 1H), 3.08 - 3.19 (m, 1H), 3.71 (s, 3H), 3.87 - 4.00 (m, 1H), 4.14 - 4.24 (m, 1H), 5.72 (s, 1H). MS m/z 357 $(M-H)^-$.

Paso 3: (2*S*,4*S*)-2-((4,4-Difluorociclohexil)metil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo y (2*R*,4*R*)-2-((4,4-difluorociclohexil)metil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El *cis*-2-((4,4-difluorociclohexil)metil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.6 g, 4.46 mmol) se sometió a HPLC preparativa quiral (columna: CelluCoat (250x20), tamaño de partícula: 5 µm, fase móvil: 80/20 de heptano/IPA, velocidad de flujo: 18 mL/min) para proporcionar (2*S*,4*S*)-2-((4,4-difluorociclohexil)metil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (787 mg, 49%), pureza quiral: 99.8% de ee, rotación óptica $[\alpha]_D^{20} = +28.8$ (acetonitrilo, c=1), y (2*R*,4*R*)-2-((4,4-difluorociclohexil)metil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (752 mg, 47%), pureza quiral: 99.9% de ee, rotación óptica $[\alpha]_D^{20} = -30.2$ (acetonitrilo, c=1).

Paso 4: 5-((2*S*,4*S*)-2-((4,4-Difluorociclohexil)metil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*S*,4*S*)-2-((4,4-difluorociclohexil)metil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.787 g, 2.20 mmol) en ácido bromhídrico (al 33% en ácido acético, 17.31 mL, 98.82 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm

OBD 19*150 mm) para proporcionar 5-((2*S*,4*S*)-2-((4,4-difluorociclohexil)metil)piperidin-4-il)isoxazol-3(2*H*)-ona (424 mg, 64%). ^{1}H RMN (600 MHz, DMSO) δ 0.98 - 1.41 (m, 5H), 1.51 - 2.61 (m, 12H), 2.66 - 2.75 (m, 1H), 2.95 - 3.04 (m, 1H), 5.59 - 5.67 (m, 1H). HRMS calculado para $[C_{15}H_{22}F_2N_2O_2+H]^+$: 301.1728. Experimental: 301.1713.

Ejemplo 90

5-((2*R*,4*R*)-2-((4,4-Difluorociclohexil)metil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*R*)-2-((4,4-difluorociclohexil)metil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.752 g, 2.10 mmol) (del paso 3 del ejemplo 89) en ácido bromhídrico (al 33% en ácido acético, 16.54 mL, 94.42 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*R*)-2-((4,4-difluorociclohexil)metil)piperidin-4-il)isoxazol-3(2*H*)-ona (415 mg, 66%). HRMS calculado para $[C_{15}H_{22}F_2N_2O_2+H]^+$: 301.1728. Experimental: 301.1741.

Ejemplo 91

5-(*Trans*-2-((4,4-difluorociclohexil)metil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-((4,4-difluorociclohexil)metil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *trans*-2-((4,4-difluorociclohexil)metil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (300 mg, 0.77 mmol) (del paso 1 del ejemplo 89) en MeOH (3 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (0.227 mL, 0.77 mmol) disuelto en agua (0.300 mL) durante 10 min y la solución amarilla se continuó agitando a -40 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.047 mL, 0.77 mmol) durante 8 min. La solución resultante se agitó a -40 °C durante 3 h 15 min. A continuación, la mezcla se vertió rápidamente sobre una

solución calentada previamente (80 °C) de ácido clorhídrico 6 M (4 mL, 24.00 mmol) y la mezcla se continuó agitando a 80 °C durante 20 min. El disolvente se evaporó y se añadieron DCM/agua. Las fases se separaron, y la fase orgánica se hizo pasar a través de un separador de fases y se evaporó para proporcionar *trans*-2-((4,4-difluorociclohexil)metil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo crudo (267 mg, 97%) como un sólido amarillento. MS m/z 357 $(M-H)^-$.

Paso 2: 5-(*Trans*-2-((4,4-difluorociclohexil)metil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió *trans*-2-((4,4-difluorociclohexil)metil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.267 g, 0.75 mmol) en ácido bromhídrico (al 33% en ácido acético, 5.87 mL, 33.53 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-(*trans*-2-((4,4-difluorociclohexil)metil)piperidin-4-il)isoxazol-3(2*H*)-ona (63 mg, 28%). ^{1}H RMN (600 MHz, DMSO) δ 0.99 - 1.19 (m, 3H), 1.27 - 1.35 (m, 1H), 1.38 - 1.46 (m, 1H), 1.46 - 1.55 (m, 1H), 1.61 - 1.87 (m, 7H), 1.87 - 1.98 (m, 2H), 2.54 - 2.61 (m, 1H), 2.61 - 2.70 (m, 1H), 2.72 - 2.79 (m, 1H), 3.03 - 3.09 (m, 1H), 5.75 (s, 1H). HRMS calculado para $[C_{15}H_{22}F_2N_2O_2+H]^+$: 301.1728. Experimental: 301.1751.

Ejemplo 92

5-((2*S*,4*S*)-2-(4-Fluorofenetil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-4-(3-etoxi-3-oxopropanoil)-2-(4-fluorofenetil)piperidin-1-carboxilato de metilo y *cis*-4-(3-etoxi-3-oxopropanoil)-2-(4-fluorofenetil)piperidin-1-carboxilato de metilo

Se disolvió el ácido 2-(4-fluorofenetil)-1-(metoxicarbonil)piperidin-4-carboxílico (4.34 g, 14.03 mmol)

(compuesto de referencia 41) en metil-THF (100 mL) en atmósfera de nitrógeno y se añadió di(1*H*-imidazol-1-il)metanona (3.41 g, 21.05 mmol). La suspensión se agitó a temperatura ambiente durante 4 h (matraz 1). En otro matraz, se suspendió 3-etoxi-3-oxopropanoato de potasio (4.30 g, 25.25 mmol) en metil-THF (100 mL) y se añadió cloruro de magnesio (2.404 g, 25.25 mmol). La suspensión se agitó a 50 °C en atmósfera de nitrógeno durante 4 h utilizando un imán muy grande (matraz 2). El contenido del matraz 1 se añadió al matraz 2 y la mezcla (suspensión blanca) se agitó a temperatura ambiente durante 19 h. En otro matraz, se suspendió 3-etoxi-3-oxopropanoato de potasio (4.30 g, 25.25 mmol) en metil-THF (100 mL) y se añadió cloruro de magnesio (2.404 g, 25.25 mmol). La suspensión se agitó a 50 °C en atmósfera de nitrógeno durante 4 h utilizando un imán muy grande y después se añadió a la mezcla de reacción. La mezcla se agitó a temperatura ambiente durante otras 16 horas a temperatura ambiente. Se añadieron HCl 0.1 M y DCM, las fases se separaron y la fase acuosa se extrajo con DCM. Las fases orgánicas combinadas se lavaron con $NaHCO_3$ sat., se filtraron a través de un separador de fases y se evaporaron. El residuo se purificó mediante cromatografía flash automatizada en 2 columnas Biotage® con 340 g de KP-SIL, fase móvil: 2:1 de heptano:EtOAc en 4 VC seguido de un gradiente 2:1->1:1 de heptano:EtOAc en 6 VC. Se aislaron *trans*-4-(3-etoxi-3-oxopropanoil)-2-(4-fluorofenetil)piperidin-1-carboxilato de metilo (0.74 g, 14%) y *cis*-4-(3-etoxi-3-oxopropanoil)-2-(4-fluorofenetil)piperidin-1-carboxilato de metilo (3.17 g, 60%). Isómero *cis*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.24 (t, 3H), 1.50 - 2.11 (m, 6H), 2.48 - 2.65 (m, 2H), 2.67 - 7.77 (m, 1H), 3.03 - 3.14 (m, 1H), 3.50 (s, 2H), 3.69 (s, 3H), 3.84 - 3.93 (m, 1H), 4.07 (q, 1H), 4.12 - 4.22 (m, 2H), 6.95 (t, 2H), 7.08 - 7.16 (m, 2H). MS m/z 380 $(M+H)^+$. Isómero *trans*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.23 - 1.32 (m, 3H), 1.41 - 2.11 (m, 6H), 2.42 - 2.66 (m, 2H), 2.76 - 2.96 (m, 2H), 3.45 (s, 2H), 3.69 (s, 3H), 4.01 - 4.65 (m, 4H), 6.97 (t, 2H), 7.13 (s. a, 2H). MS m/z 380 $(M+H)^+$.

Paso 2: *Cis*-2-(4-fluorofenetil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *cis*-4-(3-etoxi-3-oxopropanoil)-2-(4-fluorofenetil)piperidin-1-carboxilato de metilo (3.15 g, 8.30 mmol) en MeOH (30 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (0.332 g, 8.30 mmol) disuelto en agua (3.00 mL) y la mezcla se agitó a -40 °C durante 15 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.509 mL, 8.30 mmol). La solución resultante se agitó a -40 °C durante 3 h. Posteriormente, la mezcla se transfirió a una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (42.9 mL, 257.36 mmol) y la mezcla se agitó a 80 °C durante 20 min. Se añadieron agua y DCM. Las fases se separaron y la fase orgánica se hizo pasar a través de un separador de fases y se evaporó. El compuesto (dividido en cuatro partes) se purificó mediante HPLC preparativa en una columna XBridge C18 (10 µm 250x50 DI en mm) utilizando un gradiente de 0-25% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 20 minutos con un flujo de 100 mL/min. Se aisló *cis*-2-(4-fluorofenetil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.9 g, 66%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.53 - 2.14 (m, 6H), 2.46 - 2.64 (m, 2H), 2.98 - 3.07 (m, 1H), 3.12 - 3.24 (m, 1H), 3.70 (s, 3H), 3.87 - 3.99 (m, 1H), 4.05 - 4.16 (m, 1H), 5.72 (s, 1H), 6.85 - 6.94 (m, 2H), 7.04 - 7.11 (m, 2H). MS m/z 349 $(M+H)^+$.

Paso 3: (2*S*,4*S*)-2-(4-Fluorofenetil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo y (2*R*,4*R*)-2-(4-fluorofenetil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El *cis*-2-(4-fluorofenetil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.4 g, 4 mmol) se sometió a HPLC preparativa quiral (columna: Chiralpak AD (250x20), tamaño de partícula: 5 µm, fase móvil: 80/20 de heptano/EtOH, velocidad de flujo: 18 mL/min) para proporcionar (2*S*,4*S*)-2-(4-fluorofenetil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (582 mg, 42%), pureza quiral: 99.9% de

ee, rotación óptica $[\alpha]_D^{20} = +51.6$ (acetonitrilo, c=1) y (2*R*,4*R*)-2-(4-fluorofenetil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (676 mg, 48%), pureza quiral: 99.4% de ee, rotación óptica $[\alpha]_D^{20} = -45.0$ (acetonitrilo, c=1).

Paso 4: 5-((2*S*,4*S*)-2-(4-Fluorofenetil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*S*,4*S*)-2-(4-fluorofenetil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (435 mg, 1.25 mmol) en ácido bromhídrico (al 33% en ácido acético, 9.84 mL, 56.19 mmol) para proporcionar una solución amarilla. La mezcla se agitó a temperatura ambiente durante 16 h, el disolvente se eliminó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*S*,4*S*)-2-(4-fluorofenetil)piperidin-4-il)isoxazol-3(2*H*)-ona (228 mg, 63%). ^{1}H RMN (400 MHz, CD_3OD) δ 1.48 (dd, 1H), 1.64 - 1.97 (m, 3H), 2.13 (d, 1H), 2.30 (d, 1H), 2.66 - 2.80 (m, 2H), 2.84 - 3.10 (m, 3H), 3.34 - 3.43 (m, 1H), 5.51 (s, 1H), 6.97 - 7.05 (m, 2H), 7.19 - 7.28 (m, 2H). HRMS calculado para $[C_{16}H_{19}FN_2O_2+H]^+$: 291.1509. Experimental: 291.1497.

Ejemplo 93

5-((2*R*,4*R*)-2-(4-Fluorofenetil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*R*)-2-(4-fluorofenetil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (507 mg, 1.46 mmol) (del paso 3 del ejemplo 92) en ácido bromhídrico (al 33% en ácido acético, 11.5 mL, 65.49 mmol) para proporcionar una solución amarilla. La mezcla se agitó a temperatura ambiente durante 16 h, el disolvente se eliminó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*R*)-2-(4-fluorofenetil)piperidin-4-il)isoxazol-3(2*H*)-ona (278 mg, 65%). ^{1}H RMN (400 MHz, CD_3OD) δ

1.48 (c, 1H), 1.70 (dc, 1H), 1.78 - 1.96 (m, 2H), 2.09 - 2.17 (m, 1H), 2.26 - 2.34 (m, 1H), 2.66 - 2.80 (m, 2H), 2.86 - 3.09 (m, 3H), 3.35 - 3.43 (m, 1H), 5.52 (s, 1H), 6.98 - 7.05 (m, 2H), 7.21 - 7.26 (m, 2H). HRMS calculado para $[C_{16}H_{19}FN_2O_2+H]^+$: 291.1509. Experimental: 291.1483.

Ejemplo 94

5-(*Trans*-2-(4-fluorofenetil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(4-fluorofenetil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *trans*-4-(3-etoxi-3-oxopropanoil)-2-(4-fluorofenetil)piperidin-1-carboxilato de metilo (730 mg, 1.92 mmol) (del paso 1 del ejemplo 92) en MeOH (7 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (77 mg, 1.92 mmol) disuelto en agua (0.700 mL) y la mezcla se agitó a -40 °C durante 15 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.118 mL, 1.92 mmol). La solución resultante se agitó a -40 °C durante 3 h. Posteriormente, la mezcla se transfirió a una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (9.94 mL, 59.64 mmol) y la mezcla se agitó a 80 °C durante 20 min. Se añadieron agua y DCM. Las fases se separaron, la fase acuosa se extrajo con DCM, y las capas orgánicas combinadas se hicieron pasar a través de un separador de fases y se evaporaron. El residuo se purificó mediante cromatografía flash automatizada en una columna Biotage® con 100 g de KP-SIL. Se utilizó como fase móvil DCM:MeOH:HCOOH=50:1:0.1 en 10 VC. Se aisló *trans*-2-(4-fluorofenetil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (550 mg, 82%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.01 - 2.13 (m, 6H), 2.48 - 2.70 (m, 2H), 2.88 - 3.08 (m, 2H), 3.70 (s, 3H), 3.98 - 4.69 (m, 2H), 5.64 (s, 1H), 6.91 - 7.02 (m, 2H), 7.06 - 7.21 (m, 2H). MS m/z 349 $(M+H)^+$.

Paso 2: 5-(*Trans*-2-(4-fluorofenetil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió *trans*-2-(4-fluorofenetil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (137 mg,

0.39 mmol) en ácido bromhídrico (al 33% en ácido acético, 3.1 mL, 17.70 mmol) para proporcionar una solución amarilla. La mezcla se agitó a temperatura ambiente durante 16 h, el disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-(*trans*-2-(4-fluorofenetil)piperidin-4-il)isoxazol-3(2*H*)-ona (80 mg, 70%). ^{1}H RMN (400 MHz, DMSO) δ 1.42 - 1.78 (m, 5H), 1.82 - 1.95 (m, 1H), 2.52 - 2.68 (m, 4H), 2.74 - 2.84 (m, 1H), 3.05 - 3.13 (m, 1H), 5.73 (s, 1H), 7.01 - 7.10 (m, 2H), 7.15 - 7.25 (m, 2H). HRMS calculado para $[C_{16}H_{19}FN_2O_2+H]^+$: 291.1509. Experimental: 291.1522.

Ejemplo 95

5-((2*S*,4*S*)-2-(3,3-Dimetilbutil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(3,3-dimetilbutil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo y *cis*-2-(3,3-dimetilbutil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo

Se agitó una suspensión de cloruro de magnesio (0.852 g, 8.94 mmol) y malonato de etilo y potasio (2.283 g, 13.42 mmol) en THF anhidro (40 mL) en atmósfera de nitrógeno a 50 °C durante 3.5 h (matraz 1). En otro matraz, se añadió carbonildiimidazol (1.740 g, 10.73 mmol) en porciones a una solución de ácido 2-(3,3-dimetilbutil)-1-(metoxicarbonil)piperidin-4-carboxílico (2.427 g, 8.94 mmol) (compuesto de referencia 42) en THF anhidro (40 mL) a 0 °C en atmósfera de nitrógeno. Esta solución se agitó durante 1.5 h (matraz 2). El contenido del matraz 1 se añadió en 10 min al matraz 2 y la mezcla resultante se agitó a temperatura ambiente durante 20 h. La mezcla de reacción se concentró y el residuo se disolvió en EtOAc y H_2O. La fase acuosa se extrajo una vez con EtOAc y las fases orgánicas combinadas se lavaron con H_2O y $NaHCO_3$ sat., y después se secaron con Na_2SO_4, se filtraron y se evaporaron para proporcionar un aceite negro. La separación en

una columna Biotage (columna de 340 g, gradiente de 20-30% de EtOAc en heptano, 7 VC) proporcionó *trans*-2-(3,3-dimetilbutil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (574 mg, 24%) y *cis*-2-(3,3-dimetilbutil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (1.74 g, 72%) como aceites amarillos. Isómero *cis*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 0.85 (s, 9H), 1.03 - 1.95 (m, 10H), 2.01 - 2.10 (m, 1H), 2.65 - 2.75 (m, 1H), 2.98 - 3.08 (m, 1H), 3.51 (s, 2H), 3.69 (s, 3H), 3.83 - 4.02 (m, 2H), 4.19 (c, 2H). MS m/z 342 $(M+H)^+$. Isómero *trans*: MS m/z 342 $(M+H)^+$.

Paso 2: *Cis*-2-(3,3-dimetilbutil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se añadió una solución de *cis*-2-(3,3-dimetilbutil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (1.78 g, 5.22 mmol) en MeOH (3.9 mL) a una solución de NaOH (288 mg, 7.2 mmol) en MeOH/H_2O (4.4 mL/0.3 mL) a -30 °C. Después de 10 min, se añadieron clorhidrato de hidroxilamina (726 mg, 10.45 mmol) y NaOH (418 mg, 10.45 mmol) en MeOH (5.2 mL) y H_2O (5.2 mL). Se continuó agitando a -30 °C durante 30 min. La solución de reacción se vertió sobre HCl 6 M (7.7 mL) a 80 °C y se calentó a 80 °C durante 1 h. Tras concentrar el disolvente orgánico, extraer con DCM (x2), secar con un separador de fases y evaporar, se obtuvo un aceite naranja. El compuesto se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x50 DI en mm) utilizando un gradiente de 30-60% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/AF en 30 minutos con un flujo de 100 mL/min. Se aisló *cis*-2-(3,3-dimetilbutil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (717 mg, 44%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 0.79 (s, 9H), 1.01 - 1.19 (m, 2H), 1.23 - 1.48 (m, 2H), 1.83 - 1.96 (m, 2H), 1.98 - 2.11 (m, 2H), 2.94 - 3.04 (m, 1H), 3.09 - 3.19 (m, 1H), 3.70 (s, 3H), 3.91 - 4.06 (m, 2H), 5.71 (d, 1H). MS m/z 311 $(M+H)^+$.

Paso 3: (2*S*,4*S*)-2-(3,3-dimetilbutil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El *cis*-2-(3,3-dimetilbutil)-4-(3-oxo-2,3-dihidroisoxazol-

5-il)piperidin-1-carboxilato de metilo (717 mg, 2.31 mmol) se sometió a HPLC preparativa quiral (columna: Chiralpak IC (250x20), tamaño de partícula: 5 µm, fase móvil: 80/20 de heptano/IPA, velocidad de flujo: 18 mL/min) para proporcionar (2*S*,4*S*)-2-(3,3-dimetilbutil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (341 mg, 48%), pureza quiral: 99.9% de ee, rotación óptica $[\alpha]_D^{20} = +36.5$ (acetonitrilo, c=1).

Paso 4: 5-((2*S*,4*S*)-2-(3,3-Dimetilbutil)piperidin-4-il)isoxazol-3(2*H*)-ona .

Se disolvió (2*S*,4*S*)-2-(3,3-dimetilbutil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (341 mg, 1.1 mmol) en ácido bromhídrico (al 33% en ácido acético, 20 mL) y la mezcla se agitó a temperatura ambiente durante 24 h. El disolvente se evaporó y el compuesto se purificó mediante HPLC preparativa en una columna XBridge C18 (10 µm 250x50 DI en mm) utilizando un gradiente de 5-30% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 15 minutos con un flujo de 100 mL/min. Se aisló 5-((2*S*,4*S*)-2-(3,3-dimetilbutil)piperidin-4-il)-isoxazol-3(2*H*)-ona (235 mg, 85%). ^{1}H RMN (600 MHz, CD_3OD) δ 0.90 (s, 9H), 1.22 - 1.34 (m, 2H), 1.43 - 1.78 (m, 4H), 2.10 (d, 1H), 2.22 (d, 1H), 2.85 - 2.94 (m, 1H), 2.98 - 3.07 (m, 2H), 3.40 (d, 1H), 5.46 (s, 1H). HRMS calculado para $[C_{14}H_{24}N_2O_2+H]^+$: 253.1916. Experimental: 253.1898.

Ejemplo 96

5-((2*R*,4*S*)-2-(3,3-Dimetilbutil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(3,3-dimetilbutil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se añadió una solución de *cis*-2-(3,3-dimetilbutil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (549 mg, 1.61 mmol) (del paso 1 del ejemplo 95) en MeOH (1.2 mL) a una solución de NaOH (70 mg, 1.75 mmol) en MeOH/H_2O (1.3 mL/0.08 mL) a -30 °C. Después de 10 min, se añadieron clorhidrato de hidroxilamina (223 mg, 3.22 mmol) y NaOH (129 mg, 3.22 mmol) en

MeOH (1.6 mL) y H_2O (1.6 mL). Se continuó agitando a -30 °C durante 30 min. La solución de reacción se vertió sobre HCl 6 M (2.4 mL) a 80 °C y se calentó a 80 °C durante 1 h. Tras concentrar el disolvente orgánico, extraer con DCM (x2), secar con un separador de fases y evaporar, se obtuvo un aceite naranja. El compuesto se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x50 DI en mm) utilizando un gradiente de 30-60% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/AF en 30 minutos con un flujo de 100 mL/min. Se aisló *trans*-2-(3,3-dimetilbutil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (194 mg, 39%) como un sólido blanco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 0.89 (s, 9H), 1.02 - 1.78 (m, 6H), 1.89 - 2.03 (m, 2H), 2.83 - 3.09 (m, 2H), 3.71 (s, 3H), 3.99 - 4.51 (m, 2H), 5.65 (s, 1H). MS m/z 311 $(M+H)^+$.

Paso 2: (2*R*,4*S*)-2-(3,3-dimetilbutil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El *trans*-2-(3,3-dimetilbutil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (194 mg, 0.63 mmol) se sometió a HPLC preparativa quiral (columna: Chiralpak IC (250x20), tamaño de partícula: 5 µm, fase móvil: 85/15 de heptano/IPA, velocidad de flujo: 18 mL/min) para proporcionar (2*R*,4*S*)-2-(3,3-dimetilbutil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (83 mg, 43%), pureza quiral: 99.3% de ee, rotación óptica $[\alpha]_D^{20} = -12.3$ (acetonitrilo, c=1).

Paso 3: 5-((2*R*,4*S*)-2-(3,3-Dimetilbutil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-2-(3,3-dimetilbutil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (62 mg, 0.2 mmol) en ácido bromhídrico (al 33% en ácido acético, 4 mL) y la mezcla se agitó a temperatura ambiente durante 18 h. El disolvente se evaporó y el compuesto se purificó mediante HPLC preparativa en una columna XBridge C18 (10 µm 250x19 DI en mm) utilizando un gradiente de 5-30% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 15 minutos con un flujo de 19

mL/min. Se aisló 5-((2*R*,4*S*)-2-(3,3-dimetilbutil)piperidin-4-il)isoxazol-3(2*H*)-ona (39.8 mg, 79%) como un sólido blanco. ^{1}H RMN (600 MHz, CD_3OD) δ 0.92 (s, 9H), 1.20 - 1.34 (m, 2H), 1.56 - 1.69 (m, 2H), 1.83 - 1.90 (m, 1H), 2.05 - 2.13 (m, 1H), 2.14 - 2.21 (m, 1H), 2.26 - 2.34 (m, 1H), 3.05 - 3.19 (m, 2H), 3.25 - 3.34 (m, 2H), 5.75 (s, 1H). HRMS calculado para $[C_{14}H_{24}N_2O_2+H]^+$: 253.1916. Experimental: 253.1925.

Ejemplo 97

5-((2*R*,4*S*)-2-(4-Fluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-4-(3-etoxi-3-oxopropanoil)-2-(4-fluorobencil)piperidin-1-carboxilato de metilo y *cis*-4-(3-etoxi-3-oxopropanoil)-2-(4-fluorobencil)piperidin-1-carboxilato de metilo

Se disolvió el ácido 2-(4-fluorobencil)-1-(metoxicarbonil)piperidin-4-carboxílico (4.428 g, 14.99 mmol) (compuesto de referencia 43) en metil-THF (100 mL) y se añadió di(1*H*-imidazol-1-il)metanona (3.65 g, 22.49 mmol). La suspensión se agitó a temperatura ambiente durante toda la noche en atmósfera de nitrógeno (matraz 1). En otro matraz, se suspendió 3-etoxi-3-oxopropanoato de potasio (4.59 g, 26.99 mmol) en metil-THF (100 mL) y se añadió cloruro de magnesio (2.57 g, 26.99 mmol). La suspensión se agitó a 50 °C en atmósfera de nitrógeno durante 3 h (matraz 2). A continuación, la suspensión amarillenta del matraz 1 se añadió a la suspensión blanca del matraz 2. La suspensión blanca resultante se agitó a temperatura ambiente en atmósfera de nitrógeno durante toda la noche. La mezcla se acidificó hasta pH 1 con HCl 3.8 M y se añadió MTBE. Las fases se separaron y la fase orgánica se extrajo con agua, $NaHCO_3$ sat. y agua. Los disolventes se evaporaron para proporcionar un aceite amarillo. Los diastereoisómeros se separaron en una columna Biotage (0% => 70% de EtOAc en heptano, 7 VC; columna Biotage® con 340 g de KP-SIL). Las fracciones mezcladas se purificaron de nuevo en una columna Biotage (30% => 65% de EtOAc en heptano, 10 VC; columna Biotage® con 50 g de KP-SIL). Se aislaron *trans*-4-(3-

etoxi-3-oxopropanoil)-2-(4-fluorobencil)piperidin-1-carboxilato de metilo (0.458 g, 10.36%) y *cis*-4-(3-etoxi-3-oxopropanoil)-2-(4-fluorobencil)piperidin-1-carboxilato de metilo (2.531 g, 57.3%). Isómero *cis*: ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.20 - 1.25 (m, 3H), 1.61 - 1.68 (m, 1H), 1.77 - 1.91 (m, 3H), 2.64 - 2.73 (m, 2H), 2.82 - 2.87 (m, 1H), 2.94 - 3.00 (m, 1H), 3.43 (s, 2H), 3.60 (s, 3H), 3.90 (dd, 1H), 4.11 - 4.17 (m, 3H), 6.91 - 6.96 (m, 2H), 7.08 - 7.13 (m, 2H). MS m/z 366 $(M+H)^+$. Isómero *trans*: ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.15 - 1.26 (m, 3H), 1.39 - 1.94 (m, 4H), 2.59 - 3.00 (m, 4H), 3.32 - 3.66 (m, 5H), 3.96 - 4.28 (m, 3H), 4.50 (d a, 1H), 6.88 - 6.95 (m, 2H), 6.99 - 7.18 (m, 2H). MS m/z 366 $(M+H)^+$.

Paso 2: <u>*Cis*-2-(4-fluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo</u>

Se disolvió *cis*-4-(3-etoxi-3-oxopropanoil)-2-(4-fluorobencil)piperidin-1-carboxilato de metilo (2.53 g, 6.92 mmol) en MeOH (20 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (0.277 g, 6.92 mmol) disuelto en agua (2.000 mL) durante 10 min y la solución incolora se continuó agitando a -40 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.424 mL, 6.92 mmol) durante 8 min. La solución resultante se agitó a -40 °C durante 2 h. A continuación, la mezcla se vertió rápidamente sobre una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (30 mL, 180.00 mmol) y la mezcla se continuó agitando a 80 °C durante 20 min. El disolvente se evaporó y se añadieron DCM/agua. Las fases se separaron, y la fase orgánica se hizo pasar a través de un separador de fases y se evaporó para proporcionar un sólido amarillo. El compuesto se purificó mediante HPLC preparativa en 3 inyecciones en una columna XBridge C18 (10 µm 250x50 DI en mm) utilizando un gradiente de 0-35% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 20 minutos con un flujo de 100 mL/min. Se aisló *cis*-2-(4-fluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.516 g, 65.5%) como un sólido blanco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.83 - 2.14 (m, 4H), 2.55 - 2.65 (m,

1H), 2.72 - 2.81 (m, 1H), 2.93 - 3.03 (m, 1H), 3.08 - 3.19 (m, 1H), 3.61 (s, 3H), 3.95 - 4.05 (m, 1H), 4.20 - 4.30 (m, 1H), 5.73 (s, 1H), 6.91 - 6.99 (m, 2H), 7.02 - 7.09 (m, 2H). MS m/z 335 $(M+H)^+$.

Paso 3: (2*R*,4*S*)-2-(4-fluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El *cis*-2-(4-fluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.516 g, 4.53 mmol) se sometió a HPLC preparativa quiral (columna: Chiralpak IC (250x20), tamaño de partícula: 5 µm, fase móvil: 50/50 de heptano/(95/5 de MTBE/MeOH) , velocidad de flujo: 18 mL/min) para proporcionar (2*R*,4*S*)-2-(4-fluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (647 mg, 43%), pureza quiral: 99.9% de ee, rotación óptica $[\alpha]_D^{20} = +17.8$ (acetonitrilo, c=1).

Paso 4: 5-((2*R*,4*S*)-2-(4-Fluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-2-(4-fluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (647 mg, 1.94 mmol) en ácido bromhídrico (al 33% en ácido acético, 15 mL, 85.65 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*S*)-2-(4-fluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona (360 mg, 67%). ^{1}H RMN (600 MHz, DMSO) δ 1.08 (c, 1H), 1.37 (dc, 1H), 1.73 - 1.81 (m, 2H), 2.44 - 2.73 (m, 5H), 2.96 - 3.03 (m, 1H), 5.70 (s, 1H), 7.07 - 7.14 (m, 2H), 7.21 - 7.27 (m, 2H). HRMS calculado para $[C_{15}H_{17}FN_2O_2+H]^+$: 277.1352. Experimental: 277.1333.

Ejemplo 98

5-((2*S*,4*S*)-2-(4-Fluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(4-fluorobencil)-4-(3-oxo-2,3-

dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *trans*-4-(3-etoxi-3-oxopropanoil)-2-(4-fluorobencil)piperidin-1-carboxilato de metilo (0.454 g, 1.24 mmol) (del paso 1 del ejemplo 97) en MeOH (5 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (0.050 g, 1.24 mmol) disuelto en agua (1 mL) durante 10 min y la solución incolora se continuó agitando a -40 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.076 mL, 1.24 mmol) durante 5 min. La solución resultante se agitó a -40 °C durante 2 h. A continuación, la mezcla se vertió rápidamente sobre una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (6 mL, 36.00 mmol) y la mezcla se continuó agitando a 80 °C durante 20 min. El disolvente se evaporó y se añadieron DCM/agua. Las fases se separaron y la fase orgánica se hizo pasar a través de un separador de fases y se evaporó para proporcionar un aceite amarillento. El compuesto se purificó mediante HPLC preparativa en una columna XBridge C18 (10 µm 250x50 DI en mm) utilizando un gradiente de 0-30% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 20 minutos con un flujo de 100 mL/min. Se aisló *trans*-2-(4-fluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.268 g, 64.5%) como un sólido blanco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.47 - 1.75 (m, 2H), 1.85 - 2.14 (m, 2H), 2.71 - 3.00 (m, 2H), 3.02 - 3.16 (m, 2H), 3.40 - 3.76 (m, 3H), 4.22 (d a, 1H), 4.59 (d a, 1H), 5.64 (s, 1H), 6.95 - 7.03 (m, 2H), 7.15 (s a, 2H). MS m/z 335 $(M+H)^+$.

Paso 2: (2*S*,4*S*)-2-(4-Fluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El *trans*-2-(4-fluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.268 g, 0.8 mmol) se sometió a HPLC preparativa quiral (columna: Chiralcel OJ (250x30), tamaño de partícula: 5 µm, fase móvil: 10% de EtOH en CO_2 (175 bar), velocidad de flujo: 150 mL/min) para proporcionar (2*S*,4*S*)-2-(4-fluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (81 mg,

30%), pureza quiral: 99.8% de ee, rotación óptica $[\alpha]_D^{20} = +29.3$ (acetonitrilo, c=1).

Paso 3: 5-((2*S*,4*S*)-2-(4-Fluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*S*,4*S*)-2-(4-fluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (81 mg, 0.24 mmol) en ácido bromhídrico (al 33% en ácido acético, 2 mL, 11.42 mmol) y la mezcla se agitó a temperatura ambiente durante 24 h; a continuación se añadió más ácido bromhídrico (al 33% en ácido acético, 0.5 mL) y se continuó agitando durante toda la noche. Posteriormente se añadió más ácido bromhídrico (al 33% en ácido acético, 1 mL) y se continuó agitando durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: Agilent, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*S*,4*S*)-2-(4-fluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona (46.9 g, 70%). ^{1}H RMN (400 MHz, CD_3OD) δ 1.73 - 1.83 (m, 1H), 1.98 - 2.17 (m, 3H), 2.81 - 3.10 (m, 3H), 3.20 - 3.28 (m, 2H), 3.32 - 3.41 (m, 1H), 5.48 (d, 1H), 7.01 - 7.09 (m, 2H), 7.20 - 7.27 (m, 2H). HRMS calculado para $[C_{15}H_{17}FN_2O_2+H]^+$: 277.1352. Experimental: 277.1346.

Ejemplo 99

5-((2*R*,4*S*)-2-(3-Fluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-4-(3-etoxi-3-oxopropanoil)-2-(3-fluorobencil)piperidin-1-carboxilato de metilo y *cis*-4-(3-etoxi-3-oxopropanoil)-2-(3-fluorobencil)piperidin-1-carboxilato de metilo

Se disolvió el ácido 2-(3-fluorobencil)-1-(metoxicarbonil)piperidin-4-carboxílico (7.112 g, 24.08 mmol) (compuesto de referencia 44) en metil-THF (150 mL) y se añadió di(1*H*-imidazol-1-il)metanona (5.86 g, 36.13 mmol). La suspensión se agitó a temperatura ambiente en atmósfera de nitrógeno durante 3.5 h (matraz 1). En otro matraz, se

suspendió 3-etoxi-3-oxopropanoato de potasio (7.38 g, 43.35 mmol) en metil-THF (150 mL) y se añadió cloruro de magnesio (4.13 g, 43.35 mmol). La suspensión se agitó a 50 °C en atmósfera de nitrógeno durante 3 h (matraz 2). A continuación, la suspensión naranja del matraz 1 se añadió a la suspensión blanca del matraz 2. La suspensión amarilla resultante se agitó a temperatura ambiente en atmósfera de nitrógeno durante 3 días. La mezcla se acidificó hasta pH 1 con HCl 3.8 M y se añadió MTBE. Las fases se separaron y la fase orgánica se extrajo con agua, $NaHCO_3$ sat. y agua. Los disolventes se evaporaron para proporcionar un aceite naranja. El 42% del aceite se purificó en una columna Biotage (20% => 50% de EtOAc en heptano en 6 VC + 50% en 4 VC; columna Biotage® con 340 g de KP-SIL) para proporcionar *trans*-4-(3-etoxi-3-oxopropanoil)-2-(3-fluorobencil)piperidin-1-carboxilato de metilo (664 mg, 18%) y cis-4-(3-etoxi-3-oxopropanoil)-2-(3-fluorobencil)piperidin-1-carboxilato de metilo (1.8 g, 49%). Isómero *cis*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.20 (t, 3H), 1.56 - 1.93 (m, 4H), 2.62 - 2.73 (m, 2H), 2.83 - 3.03 (m, 2H), 3.41 (s, 2H), 3.59 (s, 3H), 3.83 - 3.93 (m, 1H), 4.07 - 4.20 (m, 3H), 6.82 - 6.93 (m, 3H), 7.15 - 7.22 (m, 1H). MS m/z 366 $(M+H)^+$. Isómero *trans*: MS m/z 366 $(M+H)^+$.

Paso 2: <u>*Cis*-2-(3-fluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo</u>

Se disolvió *cis*-4-(3-etoxi-3-oxopropanoil)-2-(3-fluorobencil)piperidin-1-carboxilato de metilo (1.826 g, 5.00 mmol) en MeOH (20 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (0.200 g, 5.00 mmol) disuelto en agua (2.000 mL) durante 20 min y la solución amarilla se continuó agitando a -40 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.306 mL, 5.00 mmol) durante 8 min. La solución resultante se agitó a -40 °C durante 3.5 h. A continuación, la mezcla se vertió rápidamente sobre una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (25 mL, 150.00 mmol) y la mezcla se continuó agitando a 80 °C durante 20 min. El disolvente se evaporó y se

añadieron DCM/agua. Las fases se separaron, y la fase orgánica se hizo pasar a través de un separador de fases y se evaporó para proporcionar un semisólido marrón. El compuesto se purificó mediante HPLC preparativa en 2 inyecciones en una columna XBridge C18 (10 µm, 250x50 DI en mm) utilizando un gradiente de 0-25% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 20 minutos con un flujo de 100 mL/min. Se aisló *cis*-2-(3-fluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.141 g, 68%) como un sólido blanco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.83 - 2.15 (m, 4H), 2.58 - 2.67 (m, 1H), 2.77 - 2.86 (m, 1H), 2.93 - 3.03 (m, 1H), 3.10 - 3.21 (m, 1H), 3.63 (s, 3H), 3.96 - 4.05 (m, 1H), 4.22 - 4.32 (m, 1H), 5.73 (s, 1H), 6.81 - 6.95 (m, 3H), 7.18 - 7.27 (m, 1H). MS m/z 335 $(M+H)^+$.

Paso 3: (2*R*,4*S*)-2-(3-fluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El *cis*-2-(3-fluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.141 g, 3.42 mmol) se sometió a HPLC preparativa quiral (columna: Chiralpak IC (250x20), tamaño de partícula: 5 µm, fase móvil: 80/20 de heptano/THF, velocidad de flujo: 18 mL/min) para proporcionar (2*R*,4*S*)-2-(3-fluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (545 mg, 48%), pureza quiral: 99.7% de ee, rotación óptica $[\alpha]_D^{20} = +17.8$ (acetonitrilo, c=1).

Paso 4: 5-((2*R*,4*S*)-2-(3-Fluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-2-(3-fluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (545 mg, 1.63 mmol) en ácido bromhídrico (al 33% en ácido acético, 10 mL, 57.10 mmol) y la mezcla se agitó a temperatura ambiente durante 23 h. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx I, fase móvil: gradiente 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-

((2*R*,4*S*)-2-(3-fluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona (286 mg, 63.5%). ^{1}H RMN (400 MHz, DMSO) δ 1.09 (c, 1H), 1.36 (dc, 1H), 1.71 - 1.81 (m, 2H), 2.50 - 2.79 (m, 5H), 2.95 - 3.03 (m, 1H), 5.66 (s, 1H), 6.95 - 7.07 (m, 3H), 7.26 - 7.34 (m, 1H). HRMS calculado para $[C_{15}H_{17}FN_2O_2+H]^+$: 277.1352. Experimental: 277.1343.

Ejemplo 100

5-((2*S*,4*S*)-2-(3-Fluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(3-fluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *trans*-4-(3-etoxi-3-oxopropanoil)-2-(3-fluorobencil)piperidin-1-carboxilato de metilo (0.663 g, 1.81 mmol) (del paso 1 del ejemplo 99) en MeOH (8 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (0.073 g, 1.81 mmol) disuelto en agua (1 mL) durante 20 min y la solución amarilla se continuó agitando a -40 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.111 mL, 1.81 mmol) durante 5 min. La solución resultante se agitó a -40 °C durante 4 h. A continuación, la mezcla se vertió rápidamente sobre una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (9 mL, 54.00 mmol) y la mezcla se continuó agitando a 80 °C durante 20 min. El disolvente se evaporó y se añadieron DCM/agua. Las fases se separaron, y la fase orgánica se hizo pasar a través de un separador de fases y se evaporó para proporcionar un semisólido marrón. El compuesto se purificó mediante HPLC preparativa en una columna XBridge C18 (10 µm 250x50 DI en mm) utilizando un gradiente de 0-25% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 20 minutos con un flujo de 100 mL/min. Se aisló *trans*-2-(3-fluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (214 mg, 35%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.47 - 1.77 (m, 2H), 1.82 - 2.15 (m, 2H), 2.75 - 3.00 (m, 2H), 3.00 - 3.15 (m, 2H), 3.40 - 3.80 (m, 3H), 4.00 - 4.42 (m, 1H), 4.42 - 4.80 (m, 1H), 5.64 (s, 1H), 6.83 - 7.05 (m, 3H), 7.22 - 7.31 (m, 1H). MS m/z 335 $(M+H)^+$.

Paso 2: (2*S*,4*S*)-2-(3-Fluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El *trans*-2-(3-fluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (214 mg, 0.64 mmol) se sometió a HPLC preparativa quiral (columna: Chiralcel OJ (250x30), tamaño de partícula: 5 µm, fase móvil: 10% de EtOH en CO_2 (175 bar), velocidad de flujo: 150 mL/min) para proporcionar 77 mg de (2*S*,4*S*)-2-(3-fluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (38.5%), pureza quiral: 99.6% de ee, rotación óptica $[\alpha]_D^{20} = +64.9$ (acetonitrilo, c=1).

Paso 3: 5-((2*S*,4*S*)-2-(3-Fluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*S*,4*S*)-2-(3-fluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (77 mg, 0.23 mmol) en ácido bromhídrico (al 33% en ácido acético, 2 mL, 11.42 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: Agilent, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*S*,4*S*)-2-(3-fluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona (51.4 mg, 81%). ^{1}H RMN (400 MHz, CD_3OD) δ 1.74 - 1.84 (m, 1H), 1.98 - 2.16 (m, 3H), 2.84 - 3.10 (m, 3H), 3.19 - 3.29 (m, 2H), 3.35 - 3.44 (m, 1H), 5.50 (s, 1H), 6.96 - 7.07 (m, 3H), 7.29 - 7.37 (m, 1H). HRMS calculado para $[C_{15}H_{17}FN_2O_2+H]^+$: 277.1352. Experimental: 277.1357.

Ejemplo 101

5-((2*R*,4*S*)-2-(2-Fluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-4-(3-etoxi-3-oxopropanoil)-2-(2-fluorobencil)piperidin-1-carboxilato de metilo y *cis*-4-(3-etoxi-3-oxopropanoil)-2-(2-fluorobencil)piperidin-1-carboxilato de metilo

Se agitó una suspensión de cloruro de magnesio (2.60 g, 27.33 mmol) y malonato de etilo y potasio (4.65 g, 27.33 mmol) en THF anhidro (80 mL) en atmósfera de nitrógeno a 50 °C durante 2.5 h (matraz 1). En otro matraz, se añadió di(1*H*-imidazol-1-il)metanona (3.69 g, 22.77 mmol) en porciones a una solución de ácido 2-(2-fluorobencil)-1-(metoxicarbonil)piperidin-4-carboxílico (4.483 g, 15.18 mmol) (compuesto de referencia 45) en THF anhidro (20 mL) a 0 °C en atmósfera de nitrógeno. Se retiró el baño de hielo y la solución se agitó a temperatura ambiente durante 2 h (matraz 2). El contenido del matraz 1 se añadió lentamente al matraz 2 y la mezcla resultante se agitó durante 19 h en atmósfera de nitrógeno. La mezcla de reacción se concentró y el residuo se disolvió en EtOAc y H_2O. La fase acuosa se extrajo una vez con EtOAc y las fases orgánicas combinadas se lavaron con H_2O y Na_2CO_3 al 10%, y posteriormente se secaron con Na_2SO_4. El compuesto se purificó aún más con una columna Biotage, 2 purificaciones, SNAP con 340 g de KP-SIL, primero con 8:2 en 2 VC y después un gradiente lineal de 8:2 a 3:7 de heptanos/acetato de etilo en 7 VC. Se aislaron *trans*-4-(3-etoxi-3-oxopropanoil)-2-(2-fluorobencil)piperidin-1-carboxilato de metilo (1.145 g, 14%) y *cis*-4-(3-etoxi-3-oxopropanoil)-2-(2-fluorobencil)piperidin-1-carboxilato de metilo (3.19 g, 58%). Isómero *cis*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.20-1.30 (m, 3H), 1.63 - 1.99 (m, 4H), 2.63-2.76 (m, 1H), 2.77 - 3.13 (m, 3H), 3.46 (s, 2H), 3.53 (s, 3H), 3.85-3.99 (m, 1H), 4.17 (c, 2H), 4.22 - 4.32 (m, 1H), 6.93 - 7.08 (m, 2H), 7.09 - 7.22 (m, 2H). MS m/z 366 $(M+H)^+$. Isómero *trans*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.19 - 1.32 (m, 3H), 1.39-1.99 (m, 4H), 2.52 - 3.12 (m, 4H), 3.37 - 3.71 (m, 5H), 4.18 (c, 2H), 4.02 - 4.32 (m, 1H), 4.48-4.71 (m, 1H), 6.94 - 7.24 (m, 4H). MS m/z 366 $(M+H)^+$.

Paso 2: <u>*Cis*-2-(2-fluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo</u>

Se disolvió *cis*-4-(3-etoxi-3-oxopropanoil)-2-(2-fluorobencil)piperidin-1-carboxilato de metilo (1.95 g, 5.34

mmol) en MeOH (20 mL) y se enfrió hasta -40 °C. Se añadió hidróxido sódico (0.213 g, 5.34 mmol) disuelto en agua (2.000 mL) gota a gota y se continuó agitando la solución incolora a -40 °C durante 30 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.327 mL, 5.34 mmol) gota a gota. La solución resultante se agitó a -40 °C durante 3 h. Posteriormente, la mezcla se vertió rápidamente sobre una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (25 mL, 150.00 mmol) y la mezcla se continuó agitando a 80 °C durante 20 min. El disolvente se evaporó y se añadieron MTBE/agua. Las fases se separaron y la fase orgánica se secó con Na_2SO_4 y se evaporó para proporcionar una espuma amarillenta. El compuesto se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x50 DI en mm) utilizando dos inyecciones con un gradiente de 15-75% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/AcOH en 30 minutos con un flujo de 100 mL/min. Se aisló *cis*-2-(2-fluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.09 g, 61%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.80 - 2.17 (m, 4H), 2.72-2.87 (m, 2H), 2.91-3.02 (m, 1H), 3.12-3.24 (m, 1H), 3.52 (s, 3H), 3.95-4.05 (m, 1H), 4.29 - 4.40 (m, 1H), 5.72 (s, 1H), 6.94 - 7.12 (m, 3H), 7.12 - 7.20 (m, 1H). MS m/z 335 $(M+H)^+$.

Paso 3: (2*R*,4*S*)-2-(2-fluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El *cis*-2-(2-fluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.09 g, 3.26 mmol) se sometió a HPLC preparativa quiral (columna: Chiralpak AS (250x20), tamaño de partícula: 5 µm, fase móvil: 80/20 de heptano/EtOH, velocidad de flujo: 18 mL/min) para proporcionar (2*R*,4*S*)-2-(2-fluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (492 mg, 45%), pureza quiral: 98.2% de ee, rotación óptica $[\alpha]_D^{20} = -3$ (acetonitrilo, c=1).

Paso 4: 5-((2*R*,4*S*)-2-(2-Fluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se agitó (2*R*,4*S*)-2-(2-fluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (492 mg, 1.47 mmol) en ácido bromhídrico (al 33% en AcOH) durante toda la noche (19 h). Se evaporaron los disolventes y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx I, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*S*)-2-(2-fluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona (504 mg, 124%). La muestra contenía DMSO y ácido acético. ^{1}H RMN (400 MHz, CD_3OD) δ 1.50 - 1.65 (m, 1H), 1.69-1.84 (m, 1H), 2.08-2.22 (m, 2H), 2.89 - 3.18 (m, 4H), 3.38-3.51 (m, 2H), 5.66 (s, 1H), 7.11 - 7.23 (m, 2H), 7.28 - 7.41 (m, 2H). HRMS calculado para $[C_{15}H_{17}FN_2O_2+H]+$: 277.1352. Experimental: 277.1344.

Ejemplo 102

5-((2*S*,4*S*)-2-(2-Fluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(2-fluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *trans*-4-(3-etoxi-3-oxopropanoil)-2-(2-fluorobencil)piperidin-1-carboxilato de metilo (1.145 g, 3.13 mmol) (del paso 1 del ejemplo 101) en metanol (10 mL) y se enfrió hasta -40 °C. Se añadió hidróxido sódico (0.194 g, 4.84 mmol) disuelto en agua (1.000 mL) gota a gota y se continuó agitando a -40 °C durante 30 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.192 mL, 3.13 mmol) gota a gota. La solución resultante se agitó a -40 °C durante 2 h. Posteriormente, la mezcla se vertió rápidamente sobre una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (15 mL, 90.00 mmol) y la mezcla se continuó agitando a 80 °C durante 55 min. El disolvente se evaporó y se añadieron MTBE/agua. Las fases se separaron y la fase orgánica se secó con Na_2SO_4 y se evaporó para proporcionar una espuma amarilla. El compuesto se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x50 DI en mm) con un gradiente de 15-75% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/AcOH en

30 minutos con un flujo de 100 mL/min. Se aisló *trans*-2-(2-fluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (468 mg, 45%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.46-1.77 (m, 2H), 1.80-2.13 (m, 2H), 2.28-3.23 (m, 4H), 3.38-3.80 (m, 3H), 4.04 - 4.34 (m, 1H), 4.50 - 4.80 (m, 1H), 5.65 (s, 1H), 6.99-7.12 (m, 2H), 7.12-7.30 (m, 2H). MS m/z 335 $(M+H)^+$.

Paso 2: (2*S*,4*S*)-2-(2-Fluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo y (2*R*,4*R*)-2-(2-fluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El *trans*-2-(2-fluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (468 mg, 1.4 mmol) se sometió a HPLC preparativa quiral (columna: Chiralcel OJ (250x30), tamaño de partícula: 5 µm, fase móvil: 20% de EtOH en CO_2 (175 bar), velocidad de flujo: 130 mL/min, temperatura: 40 °C) para proporcionar (2*S*,4*S*)-2-(2-fluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (199 mg, 43%), pureza quiral: 98.5% de ee, rotación óptica $[\alpha]_D^{20} = +28.8$ (acetonitrilo, c=1) y (2*R*,4*R*)-2-(2-fluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (185 mg, 40%), pureza quiral: 99.7% de ee, rotación óptica $[\alpha]_D^{20} = -28.9$ (acetonitrilo, c=1).

Paso 3: 5-((2*S*,4*S*)-2-(2-Fluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se agitó (2S,4*S*)-2-(2-fluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (199 mg, 0.60 mmol) en ácido bromhídrico (al 33% en AcOH) durante toda la noche (17 h). Se evaporaron los disolventes y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx I, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*S*,4*S*)-2-(2-fluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona (115 mg, 70%). ^{1}H RMN (600 MHz, DMSO) δ 1.47-1.56 (m, 1H), 1.67-1.81 (m, 3H), 2.57-2.64 (m, 1H), 2.72

(d, 2H), 2.81-2.87 (m, 1H), 2.87 - 2.95 (m, 1H), 3.12-3.18 (m, 1H), 5.70 (s, 1H), 7.09 - 7.18 (m, 2H), 7.22-7.33 (m, 2H). HRMS calculado para $[C_{15}H_{17}FN_2O_2+H]+$: 277.1352. Experimental: 277.1352.

Ejemplo 103

5-((2*R*,4*R*)-2-(2-Fluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se agitó (2*R*,4*R*)-2-(2-fluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (185 mg, 0.55 mmol) (del paso 2 del ejemplo 102) en ácido bromhídrico (al 33% en AcOH) durante toda la noche (17 h). Se evaporaron los disolventes y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx I, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*R*)-2-(2-fluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona (75 mg, 49%). ^{1}H RMN (600 MHz, DMSO) δ 1.48 - 1.55 (m, 1H), 1.68 - 1.80 (m, 3H), 2.58 - 2.64 (m, 1H), 2.72 (d, 2H), 2.81 - 2.87 (m, 1H), 2.87 - 2.94 (m, 1H), 3.12 - 3.17 (m, 1H), 5.70 (s, 1H), 7.11 - 7.17 (m, 2H), 7.24 - 7.31 (m, 2H). HRMS calculado para $[C_{15}H_{17}FN_2O_2+H]+$: 277.1352. Experimental: 277.1357.

Ejemplo 104

5-((2*R*,4*S*)-2-(4-(Trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Cis*-4-(3-etoxi-3-oxopropanoil)-2-(4-(trifluorometil)bencil)piperidin-1-carboxilato de metilo

Se suspendieron cloruro de magnesio (7.39 g, 77.58 mmol) y 3-etoxi-3-oxopropanoato de potasio (13.20 g, 77.58 mmol) en metil-THF (100 mL) en atmósfera de nitrógeno y la suspensión resultante se calentó hasta 50 °C mientras se agitaba con un imán muy grande durante 4 h, posteriormente se enfrió hasta temperatura ambiente (matraz 1). En otro matraz, se añadió di(1*H*-imidazol-1-il)metanona (10 g, 61.67 mmol) al ácido *cis*-1-(metoxicarbonil)-2-(4-(trifluorometil)bencil)piperidin-4-carboxílico (14.1 g, 40.83 mmol) (compuesto de referencia 46) en metil-THF (100 mL) en atmósfera de nitrógeno. La mezcla

resultante se agitó a temperatura ambiente durante 4 h 30 min (matraz 2). Posteriormente, el contenido del matraz 2 se transfirió al matraz 1 con una aguja de transferencia y se lavó el matraz con metil-THF (40 mL). La suspensión resultante se agitó a temperatura ambiente durante 19 h 30 min. Se aplicaron ultrasonidos a 50 °C a más cloruro de magnesio (3.7 g, 38.86 mmol) y 3-etoxi-3-oxopropanoato de potasio (6.6 g, 38.78 mmol) en metil-THF (50 mL) durante 2 h 30 min y posteriormente se añadieron a la mezcla de reacción. Se agitó a temperatura ambiente durante 21 h. La mezcla de reacción se repartió entre HCl 2 M (ca. 150 mL) y MTBE. Se separaron las fases. La fase orgánica se lavó con salmuera y $NaHCO_3$ sat., a continuación se secó con $MgSO_4$ y se evaporó. Se aisló *cis*-4-(3-etoxi-3-oxopropanoil)-2-(4-(trifluorometil)bencil)piperidin-1-carboxilato de metilo crudo (14.9 g, 88%). ^1H RMN (400 MHz, $CDCl_3$) δ 1.21 - 1.30 (m, 3H), 1.63 - 2.04 (m, 4H), 2.67 - 2.86 (m, 2H), 2.93 - 3.09 (m, 2H), 3.46 (s, 2H), 3.60 (s, 3H), 3.85 - 3.98 (m, 1H), 4.11 - 4.26 (m, 3H), 7.30 (d, 2H), 7.53 (d, 2H). MS m/z 416 $(M+H)^+$.

Paso 2: <u>*Cis*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(4-(trifluorometil)bencil)piperidin-1-carboxilato de metilo</u>

Se disolvió *cis*-4-(3-etoxi-3-oxopropanoil)-2-(4-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (14.9 g, 35.87 mmol) en MeOH (120 mL) y se enfrió hasta -40 °C. Se añadió hidróxido sódico (1.495 g, 37.38 mmol) disuleto en agua (14.4 mL) en 2 min y la solución resultante se agitó a -40 °C durante 20 min. Posteriormente, se añadió hidroxilamina (al 50% en peso en agua, 2.2 mL, 35.90 mmol) en 1 min y se continuó agitando a una temperatura entre -40 °C y -45 °C durante 80 min. La mezcla de reacción se vertió posteriormente sobre una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (400 mL, 2400.00 mmol) y la mezcla se continuó agitando a 80 °C durante 1 h. A continuación se enfrió hasta temperatura ambiente. Se evaporó el metanol y después se añadió agua. Se extrajo tres veces con DCM. Las fases orgánicas combinadas se secaron con Na_2SO_4 y se evaporaron. Se aisló *cis*-4-(3-oxo-2,3-

dihidroisoxazol-5-yl)-2-(4-(trifluorometil)bencil)piperidin-1-carboxilato de metilo crudo (12.88 g, 94%). MS m/z 385 $(M+H)^+$.

Paso 3: (2*R*,4*S*)-4-(3-Oxo-2,3-dihidroisoxazol-5-il)-2-(4-(trifluorometil)bencil)piperidin-1-carboxilato de metilo

El *cis*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(4-(trifluorometil)bencil)piperidin-1-carboxilato de metilo crudo (12.88 g, 33.54 mmol) se purificó mediante HPLC preparativa (Columna: Kromasil-C18 (250x20), tamaño de partícula: 10 µm, fase móvil: 50/50/0.1 de MeCN/H_2O/FA, velocidad de flujo: 120 mL/min) para proporcionar *cis*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(4-(trifluorometil)bencil)piperidin-1-carboxilato de metilo puro (8.7 g) que se separó posteriormente utilizando HPLC preparativa quiral (Columna: Chiralpak AD (250x20), tamaño de partícula: 5 µm, fase móvil: 85/15 de heptano/EtOH/DEA, velocidad de flujo: 18 mL/min) para proporcionar (2*R*,4*S*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(4-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (3.90 g, 30%), pureza quiral: 98.5% de ee, rotación óptica $[\alpha]_D^{20} = +11.9$ (acetonitrilo, c=1). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.86 - 2.01 (m, 3H), 2.03 - 2.15 (m, 1H), 2.67 (dd, 1H), 2.85 (dd, 1H), 2.96 - 3.05 (m, 1H), 3.12 - 3.22 (m, 1H), 3.59 (s, 3H), 3.97 - 4.07 (m, 1H), 4.26 - 4.34 (m, 1H), 5.75 (s, 1H), 7.22 (d, 2H), 7.52 (d, 2H).

Paso 4: 5-((2*R*,4*S*)-2-(4-Trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(4-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (4.889 g, 12.72 mmol) en ácido bromhídrico (al 33% en AcOH, 30 mL, 428.24 mmol) y se agitó a temperatura ambiente durante 18 h. El compuesto se purificó mediante HPLC preparativa (2 inyecciones idénticas) en una columna XBridge C18 (10 µm 250x50 DI en mm) utilizando un gradiente de 05-40% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 20 minutos con un flujo de 100 mL/min. Las fracciones que contenían producto se liofilizaron y se trataron de nuevo con ácido

bromhídrico como se describe anteriormente. El compuesto se purificó mediante HPLC preparativa (3 inyecciones idénticas) en una columna XBridge C18 (10 µm 250x50 DI en mm) utilizando un gradiente de 05-40% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 20 minutos con un flujo de 100 mL/min. Se aisló 5-((2*R*,4*S*)-2-(4-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona (3.34 g, 80%) como un sólido incoloro. ^{1}H RMN (400 MHz, DMSO) δ 1.04 - 1.15 (m, 1H), 1.35 (cd, 1H), 1.72 - 1.80 (m, 2H), 2.49 - 2.58 (m, 1H), 2.61 - 2.81 (m, 4H), 2.94 - 3.02 (m, 1H), 5.66 (s, 1H), 7.42 (d, 2H), 7.62 (d, 2H). HRMS calculado para $[C_{16}H_{17}F_3N_2O_2+H]^+$: 327.1320. Experimental: 327.1305.

Ejemplo 105

5-((2*S*,4*S*)-2-(4-Trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-4-(3-etoxi-3-oxopropanoil)-2-(4-(trifluorometil)bencil)piperidin-1-carboxilato de metilo

Se añadieron malonato de etilo y potasio (1.065 g, 6.26 mmol) y $MgCl_2$ (0.496 g, 5.21 mmol) a THF anhidro (50 mL). La mezcla de reacción se agitó vigorosamente durante 4 h a 50 °C (matraz 1). Se añadieron el ácido 1-(metoxicarbonil)-2-(4-(trifluorometil)bencil)piperidin-4-carboxílico (1.8 g, 5.21 mmol) (compuesto de referencia 47) y carbonildiimidazol (1.268 g, 7.82 mmol) a THF anhidro (50 mL) a 5 °C (matraz 2). El contenido del matraz 2 se añadió al matraz 1 y la suspensión resultante se agitó a temperatura ambiente durante toda la noche. Se evaporó el THF y la mezcla de reacción se repartió entre agua y éter dietílico. La fase orgánica se aisló, se secó con Na_2SO_4, se filtró a través de celite y el disolvente se evaporó. Para la cromatografía se utilizó el equipo Biotage. Se utilizó un gradiente de elución de acetato de etilo-heptano que partió de 15-85 y terminó en 40-60. Se aisló *trans*-4-(3-etoxi-3-oxopropanoil)-2-(4-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (0.93 g, 42.9%). ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.20 - 1.29 (m, 3H), 1.46 - 1.99 (m, 4H), 2.74 - 3.04 (m, 4H), 3.34 - 3.70 (m, 5H), 4.01 - 4.32 (m, 3H), 4.60 (d, 1H),

7.22 - 7.38 (m, 2H), 7.51 - 7.56 (m, 2H). MS m/z 416 $(M+H)^+$.

Paso 2: *Trans*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(4-(trifluorometil)bencil)piperidin-1-carboxilato de metilo

Una solución de *trans*-4-(3-etoxi-3-oxopropanoil)-2-(4-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (0.4 g, 0.96 mmol) en metanol (3 mL) se añadió gota a gota a una solución de NaOH (0.042g, 1.06 mmol) en metanol/agua (3 mL/0.2 mL) a -30 °C. Después de agitar durante 10 min, se añadió una solución de clorhidrato de hidroxilamina (0.134 g, 1.93 mmol) y NaOH (0.077 g, 1.93 mmol) en metanol/agua (5 mL/5 mL) a -30 °C. Se continuó agitando durante 30 min a -30 °C. Se añadió HCl 6 M a 80 °C a la solución gota a gota. Se agitó 30 min a 80 °C. La mezcla de reacción se disolvió entre agua y acetato de etilo. La fase orgánica se aisló, se secó con Na_2SO_4, se filtró a través de celite y el disolvente se evaporó. Se purificó mediante cromatografía en fase inversa ácida con un gradiente de 35% a 75% de acetonitrilo. Se aisló *trans*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(4-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (205 mg, 55.4%). ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.63 (d, 2H), 1.98 (d, 2H), 2.81 - 3.14 (m, 4H), 3.55 (d, 3H), 4.21 (d, 1H), 4.63 (d, 1H), 5.63 (s, 1H), 7.22 - 7.37 (m, 2H), 7.54 (d, 2H). MS m/z 385 $(M+H)^+$.

Paso 3: (2*S*,4*S*)-4-(3-Oxo-2,3-dihidroisoxazol-5-il)-2-(4-(trifluorometil)bencil)piperidin-1-carboxilato de metilo y (2*R*,4*R*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(4-(trifluorometil)bencil)piperidin-1-carboxilato de metilo

El *trans*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(4-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (205 mg, 0.53 mmol) se sometió a HPLC preparativa quiral (columna: Chiralpak IC (250x20), tamaño de partícula: 5 µm, fase móvil: 90/10/0.1 de heptano/EtOH/AF, velocidad de flujo: 18 mL/min) para proporcionar (2*S*,4*S*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(4-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (77 mg, 38.5%), pureza quiral: 99.3% de ee, rotación óptica $[\alpha]_D^{20} = +34.6$ (acetonitrilo, c=1), y (2*R*,4*R*)-4-(3-oxo-2,3-

dihidroisoxazol-5-il)-2-(4-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (87 mg, 43.5%), pureza quiral: 99.9% de ee, rotación óptica $[\alpha]_D^{20} -30.2$ (acetonitrilo, c=1).

Paso 4: 5-((2*S*,4*S*)-2-(4-Trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se añadió ácido bromhídrico (al 33% en ácido acético, 5 mL) a un matraz de reacción que contenía (2*S*,4*S*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(4-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (77 mg, 0.20 mmol). La reacción se agitó vigorosamente durante toda la noche. Se evaporó el disolvente. La purificación utilizando PrepLC (pH=11, columna pequeña, muestra disuelta en MeOH, gradiente 5-45, 20 min) proporcionó 5-((2*S*,4*S*)-2-(4-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona (50 mg, 76%). ^{1}H RMN (600 MHz, CD_3OD) δ 1.73 - 1.79 (m, 1H), 1.98 - 2.12 (m, 3H), 2.93 (dd, 1H), 2.97 - 3.04 (m, 2H), 3.17 - 3.25 (m, 2H), 3.35 - 3.41 (m, 1H), 5.48 (s, 1H), 7.41 (d, 2H), 7.61 (d, 2H). HRMS calculado para $[C_{16}H_{17}F_3N_2O_2+H]^+$: 327.1320. Experimental: 327,1289.

Ejemplo 106

5-((2*R*,4*R*)-2-(4-Trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se añadió ácido bromhídrico (al 33% en ácido acético, 5 mL) a un matraz de reacción que contenía (2*R*,4*R*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(4-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (87 mg, 0.23 mmol). La reacción se agitó vigorosamente durante toda la noche. Se evaporó el disolvente. La purificación utilizando PrepLC (pH=11, columna pequeña, muestra disuelta en MeOH, gradiente 5-45, 20 min) proporcionó 5-((2*R*,4*R*)-2-(4-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona (48 mg, 65%). ^{1}H RMN (600 MHz, CD_3OD) δ 1.74 - 1.80 (m, 1H), 1.99 - 2.13 (m, 3H), 2.94 (dd, 1H), 2.98 - 3.05 (m, 2H), 3.19 - 3.26 (m, 2H), 3.36 - 3.42 (m, 1H), 5.50 (s, 1H), 7.42 (d, 2H), 7.62 (d, 2H). HRMS calculado para $[C_{16}H_{17}F_3N_2O_2+H]^+$: 327.1320. Experimental: 327,1289.

Ejemplo 107

5-((2*R*,4*S*)-2-(3-Trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-4-(3-etoxi-3-oxopropanoil)-2-(3-(trifluorometil)bencil)piperidin-1-carboxilato de metilo y *cis*-4-(3-etoxi-3-oxopropanoil)-2-(3-(trifluorometil)bencil)piperidin-1-carboxilato de metilo

Se añadieron malonato de etilo y potasio (3.42g, 20.16 mmol) y $MgCl_2$ (1.599 g, 16.80 mmol) a THF anhidro (50 mL). El matraz de reacción se agitó vigorosamente durante toda la noche a 50 °C (matraz 1). Se añadieron el ácido 1-(metoxicarbonil)-2-(3-(trifluorometil)bencil)piperidin-4-carboxílico (5.8 g, 16.80 mmol) (compuesto de referencia 48) y carbonildiimidazol (4.09 g, 25.19 mmol) a THF anhidro (50 mL) a 5 °C y se agitó durante toda la noche a temperatura ambiente (matraz 2). El contenido del matraz 2 se añadió al matraz 1 a temperatura ambiente y se agitó durante 3 días. La mezcla de reacción se disolvió entre agua y éter dietílico. La fase orgánica se evaporó para eliminar la mayor parte del THF. El crudo se disolvió de nuevo entre agua y éter dietílico. La fase orgánica se aisló, se secó con Na_2SO_4, se filtró a través de celite y el disolvente se evaporó. Para la cromatografía se utilizó el equipo Biotage. Se utilizó un gradiente de elución de acetato de etilo-heptano que partió de 0-100 y terminó en 100-0. Se aislaron *trans*-4-(3-etoxi-3-oxopropanoil)-2-(3-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (1.8 g, 26%) y *cis*-4-(3-etoxi-3-oxopropanoil)-2-(3-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (2.45 g, 35%). Isómero *cis*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.20 - 1.32 (m, 3H), 1.63 - 1.99 (m, 4H), 2.67 - 2.86 (m, 2H), 2.92 - 3.12 (m, 2H), 3.47 (s, 2H), 3.59 (s, 3H), 3.89 - 4.00 (m, 1H), 4.09 - 4.29 (m, 3H), 7.32 - 7.51 (m, 4H). MS m/z 416 $(M+H)^+$. Isómero *trans*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.19 - 1.35 (m, 3H), 1.42 - 2.08 (m, 4H), 2.51 - 3.09 (m, 4H), 3.35 - 3.78 (m, 5H), 4.04 - 4.38 (m, 3H), 4.47 - 4.79 (m, 1H), 7.23 - 7.56 (m, 4H). MS m/z 416 $(M+H)^+$.

Paso 2: *Cis*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3-(trifluorometil)bencil)piperidin-1-carboxilato de metilo

Se añadió una solución de *cis*-4-(3-etoxi-3-oxopropanoil)-2-(3-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (2.45 g, 5.90 mmol) en MeOH (7 mL) a una solución de NaOH (307 mg, 7.67 mmol) en MeOH/H_2O (8 mL/0.5 mL) a -30 °C. Después de 10 min, se añadieron clorhidrato de hidroxilamina (0.82 g, 11.80 mmol) y NaOH (472mg, 11.80 mmol) en MeOH (8 mL) y H_2O (8 mL). Se continuó agitando a -30 °C durante 30 min. La solución de reacción se vertió sobre HCl 6 M (60 mL) a 80 °C y se calentó durante 30 min. La mezcla de reacción se disolvió entre agua y acetato de etilo. La fase orgánica se aisló, se secó con Na_2SO_4, se filtró a través de celite y el disolvente se evaporó. Se purificó utilizando prepLC (pH=3, columna grande, 40-55% de MeCN en 20 min). Se aisló *cis*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (1.27 g, 56%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.86 - 2.15 (m, 4H), 2.68 (dd, 1H), 2.86 (dd, 1H), 2.96 - 3.06 (m, 1H), 3.12 - 3.25 (m, 1H), 3.58 (s, 3H), 3.95 - 4.08 (m, 1H), 4.25 - 4.37 (m, 1H), 5.75 (s, 1H), 7.23 - 7.32 (m, 1H), 7.35 - 7.41 (m, 2H), 7.43 - 4.49 (m, 1H). MS m/z 385 $(M+H)^+$.

Paso 3: <u>(2*R*,4*S*)-4-(3-Oxo-2,3-dihidroisoxazol-5-il)-2-(3-(trifluorometil)bencil)piperidin-1-carboxilato de metilo y (2*S*,4*R*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3-(trifluorometil)bencil)piperidin-1-carboxilato de metilo</u>

El *cis*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (1.27 g, 3.31 mmol) se sometió a HPLC preparativa quiral (columna: Chiralpak AD (250x20), tamaño de partícula: 5 µm, fase móvil: heptano/IPA/AF 90/10/0.1, velocidad de flujo: 18 mL/min) para proporcionar (2*R*,4*S*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (620 mg, 49%), pureza quiral: 99.7% de ee, rotación óptica $[\alpha]_D^{20} = +7.3$ (acetonitrilo, c=1), y (2*S*,4*R*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3-(trifluorometil)bencil)piperidin-1-carboxylato de metilo (640 mg, 50%), pureza quiral: 99.3% de ee, rotación óptica $[\alpha]_D^{20} = -6.3$ (acetonitrilo, c=1).

Paso 4: 5-((2*R*,4*S*)-2-(3-Trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (0.62 g, 1.61 mmol) en ácido bromhídrico (al 33% en ácido acético, 5 mL, 71.37 mmol) y se agitó a temperatura ambiente durante 41 h. La mezcla de reacción se evaporó y se comenzó de nuevo en las mismas condiciones. Después de 28 h, los disolventes se evaporaron y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx I, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*S*)-2-(3-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona (366 mg, 69%). ^{1}H RMN (600 MHz, DMSO) δ 1.07 - 1.17 (m, 1H), 1.32 - 1.41 (m, 1H), 1.73 - 1.81 (m, 2H), 2.48 - 2.58 (m, 1H), 2.63 - 2.79 (m, 4H), 2.96 - 3.02 (m, 1H), 5.67 (s, 1H), 7.50 - 7.60 (m, 4H). HRMS calculado para $[C_{16}H_{17}F_3N_2O_2+H]^+$: 327.1320. Experimental: 327.1328.

Ejemplo 108

5-((2*S*,4*R*)-2-(3-Trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*S*,4*R*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (0.64 g, 1.67 mmol) (del paso 3 del ejemplo 107) en ácido bromhídrico (al 33% en ácido acético, 5 mL, 71.37 mmol) y se agitó a temperatura ambiente durante 41 h. La mezcla de reacción se evaporó y se comenzó de nuevo en las mismas condiciones. Después de 28 h, los disolventes se evaporaron y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx I, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5µm OBD 19*150 mm) para proporcionar 5-((2*S*,4*R*)-2-(3-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona (368 mg, 68%). ^{1}H RMN (600 MHz, DMSO) δ 1.07 - 1.15 (m, 1H), 1.36 (dc, 1H), 1.74 - 1.80 (m, 2H), 2.54 - 2.58 (m, 1H), 2.64 - 2.79 (m, 4H), 2.96 - 3.01 (m, 1H), 5.66 (s, 1H), 7.50 - 7.59 (m,

4H). HRMS calculado para $[C_{16}H_{17}F_3N_2O_2+H]^+$: 327.1320. Experimental: 327.1333.

Ejemplo 109

5-(*Trans*-2-(3-trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3-(trifluorometil)bencil)piperidin-1-carboxilato de metilo

Se añadió una solución de *trans*-4-(3-etoxi-3-oxopropanoil)-2-(3-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (1.8 g, 4.33 mmol) (del paso 1 del ejemplo 107) en MeOH (7 mL) a una solución de NaOH (225 mg, 5.63 mmol) en $MeOH/H_2O$ (8 mL/0.5 mL) a -30 °C. Después de 10 min, se añadieron clorhidrato de hidroxilamina (0.602 g, 8.67 mmol) y NaOH (347mg, 8.67 mmol) en MeOH (7 mL) y H_2O (8 mL). Se continuó agitando a -30 °C durante 30 min. La solución de reacción se vertió sobre HCl 6 M (60 mL) a 80 °C y se calentó durante 30 min. La mezcla de reacción se disolvió entre agua y acetato de etilo. La fase orgánica se aisló, se secó con Na_2SO_4, se filtró a través de celite y el disolvente se evaporó. Se purificó utilizando prepLC (pH=3, columna grande, 25-55% de MeCN en 20 min). Se aisló *trans*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (1.06 g, 63.6%). ^1H RMN (400 MHz, $CDCl_3$) δ 1.49 - 2.17 (m, 4H), 2.80 - 3.22 (m, 4H), 3.34 - 3.76 (m, 3H), 4.07 - 4.40 (m, 1H), 4.52 - 4.84 (m, 1H), 5.65 (s, 1H), 7.28 - 7.54 (m, 4H). MS m/z 385 $(M+H)^+$.

Paso 2: 5-(*Trans*-2-(3-trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se añadió ácido bromhídrico (al 33% en ácido acético, 10 mL) a un matraz de reacción que contenía *trans*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (0.25 g, 0.65 mmol). La reacción se agitó vigorosamente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm)

para proporcionar 5-(*trans*-2-(3-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona (91 mg, 43%). ^{1}H RMN (600 MHz, CD_3OD) δ 1.94 - 2.05 (m, 1H), 2.11 - 2.30 (m, 3H), 3.09 - 3.26 (m, 3H), 3.37 - 3.47 (m, 2H), 3.58 - 3.66 (m, 1H), 5.83 (s, 1H), 7.53 - 7.67 (m, 4H). HRMS calculado para $[C_{16}H_{17}F_3N_2O_2+H]^+$: 327.1320. Experimental: 327.1322.

Ejemplo 110

5-((2*R*,4*S*)-2-(2-Trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-4-(3-etoxi-3-oxopropanoil)-2-(2-(trifluorometil)bencil)piperidin-1-carboxilato de metilo y *cis*-4-(3-etoxi-3-oxopropanoil)-2-(2-(trifluorometil)bencil)piperidin-1-carboxilato de metilo

Se disolvió el ácido 1-(metoxicarbonil)-2-(2-(trifluorometil)bencil)piperidin-4-carboxílico (4.718 g, 13.66 mmol) (compuesto de referencia 49) en metil-THF (100 mL) y se añadió di(1*H*-imidazol-1-il)metanona (3.32 g, 20.49 mmol). La suspensión se agitó a temperatura ambiente durante toda la noche en atmósfera de nitrógeno (matraz 1). En otro matraz, se suspendió 3-etoxi-3-oxopropanoato de potasio (4.19 g, 24.59 mmol) en metil-THF (100 mL) y se añadió cloruro de magnesio (2.342 g, 24.59 mmol). La suspensión se agitó a 50 °C en atmósfera de nitrógeno durante toda la noche utilizando un imán muy grande (matraz 2). A continuación, la suspensión amarilla del matraz 1 se añadió a la suspensión blanca del matraz 2. La suspensión blanca resultante se agitó a temperatura ambiente en atmósfera de nitrógeno durante 3 días. La mezcla se acidificó hasta pH 10 con HCl 3.8 M, y se añadieron MTBE (50 mL) y agua (50 mL). Las fases se separaron, y la fase orgánica se lavó con agua y $NaHCO_3$ sat. Los disolventes se evaporaron para proporcionar un aceite amarillo. Los diastereómeros se separaron en dos purificaciones en una columna Biotage (20% => 50% de EtOAc en heptano, 8 VC; columna Biotage® con 340 g de KP-SIL). Se aislaron *trans*-4-(3-etoxi-3-oxopropanoil)-2-(2-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (0.67 g, 12%) y *cis*-4-(3-etoxi-3-oxopropanoil)-2-(2-

(trifluorometil)bencil)piperidin-1-carboxilato de metilo (2.11 g, 37%) como aceites amarillos. Isómero *cis*: ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.22 (t, 3H), 1.65 - 1.99 (m, 4H), 2.65 - 2.73 (m, 1H), 2.85 - 2.91 (m, 1H), 2.95 - 3.02 (m, 1H), 3.15 (ddd, 1H), 3.35 (s, 3H), 3.46 (s, 2H), 4.01 (dd, 1H), 4.12 - 4.19 (m, 2H), 4.23 - 4.33 (m, 1H), 7.20 (d, 1H), 7.27 (t, 1H), 7.41 (t, 1H), 7.60 (d, 1H). MS m/z 416 $(M+H)^+$. Isómero *trans*: ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.13 - 1.27 (m, 3H), 1.41 - 1.97 (m, 5H), 2.79 - 3.67 (m, 8H), 4.01 - 4.33 (m, 3H), 4.64 (d a, 1H), 7.07 - 7.50 (m, 3H), 7.53 - 7.62 (m, 1H). MS m/z 416 $(M+H)^+$.

Paso 2: *Cis*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(2-(trifluorometil)bencil)piperidin-1-carboxilato de metilo

Se disolvió *cis*-4-(3-etoxi-3-oxopropanoil)-2-(2-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (2.062 g, 4.96 mmol) en MeOH (16 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (0.199 g, 4.96 mmol) disuelto en agua (1.600 mL) durante 10 min y se continuó agitando la solución incolora a -40 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.304 mL, 4.96 mmol) durante 8 min. La solución resultante se agitó a -40 °C durante 3.5 h. A continuación, la mezcla se transfirió a una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (25 mL, 150.00 mmol) y se continuó agitando la mezcla a 80 °C durante 20 min. Se añadieron DCM y agua. Las fases se separaron y la fase orgánica se hizo pasar a través de un separador de fases y se evaporó para proporcionar un semisólido amarillo. El compuesto se purificó mediante HPLC preparativa en 3 inyecciones en una columna XBridge C18 (10 µm 250x50 DI en mm) utilizando un gradiente de 5-30% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 20 minutos con un flujo de 100 mL/min. Se aisló *cis*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(2-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (1.30 g, 68%) como un sólido blanco. ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.79 - 1.95 (m, 2H), 1.95 - 2.14 (m, 2H), 2.79 - 2.98 (m, 3H), 3.17 - 3.27 (m, 1H), 3.34 (s, 3H), 4.04 (dd, 1H), 4.30 - 4.41 (m, 1H),

5.68 (s, 1H), 7.14 (d, 1H), 7.19 - 7.28 (m, 1H), 7.39 (t, 1H), 7.57 (d, 1H). MS m/z 385 $(M+H)^+$.

Paso 3: (2*R*,4*S*)-4-(3-Oxo-2,3-dihidroisoxazol-5-il)-2-(2-(trifluorometil)bencil)piperidin-1-carboxilato de metilo y (2*S*,4*R*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(2-(trifluorometil)bencil)piperidin-1-carboxilato de metilo

El *cis*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(2-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (1.30 g, 3.39 mmol) se sometió a HPLC preparativa quiral (columna: Chiralcel OJ (250x20), tamaño de partícula: 5 µm, fase móvil: 80/20/0.1 de heptano/EtOH/AF, velocidad de flujo: 18 mL/min) para proporcionar (2*R*,4*S*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(2-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (597 mg, 46%), pureza quiral: 99.6% de ee, rotación óptica $[\alpha]_D^{20} = -4.0$ (acetonitrilo, c=1), y (2*S*,4*R*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(2-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (624 mg, 48%), pureza quiral: 99.8% de ee, rotación óptica $[\alpha]_D^{20} = +6.1$ (acetonitrilo, c=1).

Paso 4: 5-((2*R*,4*S*)-2-(2-Trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(2-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (597 mg, 1.55 mmol) en ácido bromhídrico (al 33% en ácido acético, 10 mL, 57.10 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx III, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*S*)-2-(2-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona (358 mg, 71%). ^1H RMN (600 MHz, CD_3OD) δ 1.68 (c, 1H), 1.84 (cd, 1H), 2.11 (d, 1H), 2.22 (d, 1H), 3.02 - 3.20 (m, 3H), 3.21 - 3.32 (m, 1H), 3.51 (d, 1H), 3.57 - 3.67 (m, 1H), 5.74 (s, 1H), 7.44 - 7.56 (m, 2H), 7.64 (t, 1H), 7.74 (d, 1H). HRMS calculado para $[C_{16}H_{17}F_3N_2O_2+H]^+$: 327.1320. Experimental: 327.1328.

Ejemplo 111

5-((2*S*,4*R*)-2-(2-Trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*S*,4*R*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(2-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (624 mg, 1.62 mmol) en ácido bromhídrico (al 33% en ácido acético, 10 mL, 57.10 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx III, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*S*,4*R*)-2-(2-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona (359 mg, 68%). ^{1}H RMN (600 MHz, CD_3OD) δ 1.68 (c, 1H), 1.84 (dc, 1H), 2.11 (d, 1H), 2.22 (d, 1H), 3.04 - 3.19 (m, 3H), 3.23 - 3.30 (m, 4H), 3.49 - 3.54 (m, 1H), 3.59 - 3.66 (m, 1H), 5.74 (s, 1H), 7.48 (t, 1H), 7.52 (d, 1H), 7.64 (t, 1H), 7.74 (d, 1H). HRMS calculado para $[C_{16}H_{17}F_3N_2O_2+H]^+$: 327.1320. Experimental: 327.1321.

Ejemplo 112

5-(*Trans*-2-(2-trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(2-(trifluorometil)bencil)piperidin-1-carboxilato de metilo

Se disolvió *trans*-4-(3-etoxi-3-oxopropanoil)-2-(2-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (0.661 g, 1.59 mmol) en MeOH (5 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (0.064 g, 1.59 mmol) disuelto en agua (0.500 mL) durante 10 min y se continuó agitando la solución incolora a -40 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.098 mL, 1.59 mmol) durante 8 min. La solución resultante se agitó a -40 °C durante 3.5 h. A continuación, la mezcla se transfirió a una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (8 mL, 48.00 mmol) y se continuó agitando la mezcla a 80 °C durante 20 min. Se añadieron DCM y agua. Las fases se separaron

y la fase orgánica se hizo pasar a través de un separador de fases y se evaporó para proporcionar *trans*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(2-(trifluorometil)bencil)piperidin-1-carboxilato de metilo crudo (0.748 g, 122%) como un semisólido amarillo. MS m/z 385 $(M+H)^+$.

Paso 2: 5-(*Trans*-2-(2-trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió *trans*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(2-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (157 mg, 0.41 mmol) en ácido bromhídrico (al 33% en ácido acético, 3 mL, 17.13 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx III, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-(*trans*-2-(2-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona (53 mg, 40%). ^{1}H RMN (600 MHz, CD_3OD) δ 1.95 (ddd, 1H), 2.08 - 2.19 (m, 2H), 2.19 - 2.28 (m, 1H), 3.07 - 3.18 (m, 2H), 3.18 - 3.25 (m, 1H), 3.33 - 3.43 (m, 2H), 3.51 - 3.62 (m, 1H), 5.75 (d, 1H), 7.43 - 7.51 (m, 2H), 7.63 (t, 1H), 7.73 (d, 1H). HRMS calculado para $[C_{16}H_{17}F_3N_2O_2+H]^+$: 327.1320. Experimental: 327.1297.

Ejemplo 113

5-((2*R*,4*S*)-2-(4-Trifluorometoxi)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-4-(3-etoxi-3-oxopropanoil)-2-(4-(trifluorometoxi)bencil)piperidin-1-carboxilato de metilo y *cis*-4-(3-etoxi-3-oxopropanoil)-2-(4-(trifluorometoxi)bencil)piperidin-1-carboxilato de metilo

Se disolvió el ácido 1-(metoxicarbonil)-2-(4-(trifluorometoxi)bencil)piperidin-4-carboxílico (4.7 g, 13.01 mmol) (compuesto de referencia 50) en metil-THF (150 mL) y a continuación se añadió di(1*H*-imidazol-1-il)metanona (3.16 g, 19.51 mmol) en una porción. La mezcla se agitó a temperatura ambiente en atmósfera de nitrógeno durante 3 h (matraz 1). En otro matraz, se suspendió 3-etoxi-3-oxopropanoato de potasio

(3.99 g, 23.41 mmol) en metil-THF (150 mL) y a continuación se añadió cloruro de magnesio (2.229 g, 23.41 mmol). La suspensión se agitó a 50 °C en atmósfera de nitrógeno durante 3 h utilizando un imán grande (matraz 2). 3 h después, el contenido del matraz 1 se transfirió al matraz 2. La suspensión amarilla resultante se agitó a temperatura ambiente en atmósfera de nitrógeno durante toda la noche. La mezcla se acidificó hasta pH 1 con HCl 3.8 M y a continuación se añadieron MTBE (100 mL) y agua (100 mL). Las fases se separaron y la capa orgánica se lavó con agua, $NaHCO_3$ sat. y salmuera. La capa orgánica se secó con Na_2SO_4, se filtró y se evaporó para obtener un aceite amarillento. El producto se purificó en una columna Biotage (340 g) con un gradiente de 20-60% de EtOAc en *n*-heptano (8 VC). La columna se acondicionó con 20% de EtOAc en *n*-heptano (1 CV). Se aislaron *trans*-4-(3-etoxi-3-oxopropanoil)-2-(4-(trifluorometoxi)bencil)piperidin-1-carboxilato de metilo (679 mg, 12.1%) y *cis*-4-(3-etoxi-3-oxopropanoil)-2-(4-(trifluorometoxi)bencil)piperidin-1-carboxilato de metilo (2.457 g, 43.8%). Isómero *cis*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.19 - 1.32 (m, 3H), 1.64 - 1.98 (m, 4H), 2.67 - 2.78 (m, 2H), 2.86 - 3.11 (m, 2H), 3.47 (s, 2H), 3.59 (s, 3H), 3.87 - 3.98 (m, 1H), 4.07 - 4.23 (m, 3H), 7.09 - 7.16 (m, 2H), 7.16 - 7.23 (m, 2H). MS m/z 432 $(M+H)^+$. Isómero *trans*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.20 - 1.31 (m, 3H), 1.38 - 2.03 (m, 4H), 2.66 - 3.08 (m, 4H), 3.32 - 3.75 (m, 5H), 3.97 - 4.36 (m, 3H), 4.40 - 4.77 (m, 1H), 7.10 - 7.32 (m, 4H). MS m/z 432 $(M+H)^+$.

Paso 2: *Cis*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(4-(trifluorometoxi)bencil)piperidin-1-carboxilato de metilo

Se disolvió *cis*-4-(3-etoxi-3-oxopropanoil)-2-(4-(trifluorometoxi)bencil)piperidin-1-carboxilato de metilo (2.475 g, 5.74 mmol) en MeOH (20 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (1.687 mL, 5.74 mmol) disuelto en agua (2.000 mL) durante 10 min y la solución amarilla se continuó agitando a -40 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.352 mL, 5.74 mmol) durante 8 min. La solución resultante se agitó a -40 °C

durante 3 h. A continuación, la mezcla se vertió rápidamente sobre una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (29.5 mL, 177.28 mmol) y la mezcla se continuó agitando a 80 °C durante 20 min. El disolvente se evaporó y se añadieron DCM/agua. Las fases se separaron y la fase orgánica se hizo pasar a través de un separador de fases y se evaporó para proporcionar un sólido blanco. El compuesto se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x50 DI en mm) utilizando un gradiente de 10-60% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/AcOH en 30 minutos con un flujo de 100 mL/min. Se aisló *cis*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(4-(trifluorometoxi)bencil)piperidin-1-carboxilato de metilo (1.41 g, 61.4%). MS m/z 401 $(M+H)^+$.

Paso 3: (2*R*,4*S*)-4-(3-Oxo-2,3-dihidroisoxazol-5-il)-2-(4-(trifluorometoxi)bencil)piperidin-1-carboxilato de metilo

El *cis*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(4-(trifluorometoxi)bencil)piperidin-1-carboxilato de metilo (1.41 g, 3.53 mmol) se sometió a HPLC preparativa quiral (columna: Chiralpak AD (250x20), tamaño de partícula: 5 µm, fase móvil: 90/10 de heptano/EtOH, velocidad de flujo: 18 mL/min) para proporcionar (2*R*,4*S*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(4-(trifluorometoxi)bencil)piperidin-1-carboxilato de metilo (691 mg, 49%), pureza quiral: 99.0% de ee, rotación óptica $[\alpha]_D^{20} = +9.4$ (acetonitrilo, c=1), ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.84 - 2.14 (m, 4H), 2.56 - 2.66 (m, 1H), 2.72 - 2.82 (m, 1H), 2.94 - 3.04 (m, 1H), 3.09 - 3.21 (m, 1H), 3.57 (s, 3H), 3.96 - 4.06 (m, 1H), 4.21 - 4.32 (m, 1H), 5.74 (s, 1H), 7.06 - 7.15 (m, 4H).

Step 4: 5-((2*R*,4*S*)-2-(4-Trifluorometoxi)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(4-(trifluorometoxi)bencil)piperidin-1-carboxilato de metilo (0.690 g, 1.72 mmol) en ácido bromhídrico (al 33% en ácido acético, 13.58 mL, 77.56 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa

(Instrumento: FractionLynx III, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*S*)-2-(4-(trifluorometoxi)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona (55 mg, 9.4%). ^{1}H RMN (600 MHz, DMSO) δ 1.07 (c, 1H), 1.34 (dc, 1H), 1.69 - 1.78 (m, 2H), 2.45 - 2.74 (m, 5H), 2.93 - 2.99 (m, 1H), 5.64 (s, 1H), 7.20 - 7.25 (m, 2H), 7.26 - 7.32 (m, 2H). HRMS calculado para $[C_{16}H_{17}F_3N_2O_3+H]^+$: 343.1270. Experimental: 343.1241.

Ejemplo 114

5-(*Trans*-2-(4-trifluorometoxi)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(4-(trifluorometoxi)bencil)piperidin-1-carboxilato de metilo

Se disolvió *trans*-4-(3-etoxi-3-oxopropanoil)-2-(4-(trifluorometoxi)bencil)piperidin-1-carboxilato de metilo (679 mg, 1.57 mmol) (del paso 1 del ejemplo 113) en MeOH (10 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (0.463 mL, 1.57 mmol) disuelto en agua (1.000 mL) durante 10 min y la solución amarilla se continuó agitando a -40 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.096 mL, 1.57 mmol) durante 8 min. La solución resultante se agitó a -40 °C durante 3 h 15 min. A continuación, la mezcla se vertió rápidamente sobre una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (8.11 mL, 48.63 mmol) y la mezcla se continuó agitando a 80 °C durante 20 min. El disolvente se evaporó y se añadieron DCM/agua. Las fases se separaron y la fase orgánica se hizo pasar a través de un separador de fases y se evaporó para proporcionar un sólido blanco. Se aisló *trans*-4-(3-oxo-2,3-dihidroisoxazol-5-yl)-2-(4-(trifluorometoxi)bencil)piperidin-1-carboxilato de metilo crudo (603 mg, 96%). MS m/z 401 $(M+H)^+$.

Paso 2: 5-(*Trans*-2-(4-trifluorometoxi)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió *trans*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(4-(trifluorometoxi)bencil)piperidin-1-carboxilato de metilo

(0.603 g, 1.51 mmol) en ácido bromhídrico (al 33% en ácido acético, 11.87 mL, 67.78 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el compuesto se purificó mediante HPLC preparativa en una columna XBridge C18 (10 µm 250x50 DI en mm) utilizando un gradiente de 10-50% de acetonitrilo en tampón 95/5/0.2 de H_2O/AcN/NH_3 en 20 minutos con un flujo de 100 mL/min. Se aisló 5-(*trans*-2-(4-(trifluorometoxi)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona (200 mg, 38.8%) como un sólido blanco. ^{1}H RMN (400 MHz, DMSO) δ 1.47 - 1.60 (m, 1H), 1.68 - 1.87 (m, 3H), 2.43 - 4.01 (m, 6H), 5.73 (s, 1H), 7.20 - 7.40 (m, 4H). HRMS calculado para $[C_{16}H_{17}F_3N_2O_3+H]^+$: 343.1270. Experimental: 343.1260.

Ejemplo 115

5-((2*R*,4*S*)-2-(4-Clorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: 2-(4-Clorobencil)-4-((2,2-dimetil-4,6-dioxo-1,3-dioxan-5-ilideno)-(hidroxi)metil)piperidin-1-carboxilato de metilo

Se añadió diclorometano (200 mL) al ácido 2-(4-clorobencil)-1-(metoxicarbonil)piperidin-4-carboxílico (4.27 g, 13.7 mmol) (compuesto de referencia 51). La mezcla se enfrió con un baño de hielo. Se añadieron DMAP (2.008 g, 16.44 mmol), 2,2-dimetil-1,3-dioxan-4,6-diona (2.96 g, 20.54 mmol) y DIPEA (5.25 mL, 30.13 mmol) y posteriormente se añadió clorhidrato de *N*1-((etilimino)metileno)-*N*3,*N*3-dimetilpropan-1,3-diamina (5.25 g, 27.39 mmol). La mezcla se agitó a 0 °C durante 15 min, posteriormente la mezcla se calentó hasta temperatura ambiente y se agitó durante toda la noche. La fase orgáncia se lavó con HCl 1 M y una vez con agua. La capa orgánica se filtró a través de un separador de fases y se evaporó para proporcionar 2-(4-clorobencil)-4-((2,2-dimetil-4,6-dioxo-1,3-dioxan-5-ilideno)(hidroxi)metil)piperidin-1-carboxilato de metilo crudo (7.00 g, 117%). MS m/z 438, 440 $(M+H)^+$.

Paso 2: *Trans*-2-(4-clorobencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo y *cis*-2-(4-clorobencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato

de metilo

Se disolvió 2-(4-clorobencil)-4-((2,2-dimetil-4,6-dioxo-1,3-dioxan-5-ilideno)(hidroxi)metil)piperidin-1-carboxilato de metilo (7.00 g, 16 mmol) en EtOH (100 mL) para proporcinar una solución amarilla. La mezcla se calentó casi hasta refljo y se agitó durante 90 min. El disolvente se evaporó y el residuo se purificó en una columna Biotage (heptano:acetato de etilo, gradiente 20%->70% de acetato de etilo, 7 VC, columna de 340 g, dos purificaciones) para proporcionar *trans*-2-(4-clorobencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (780 mg, 13%) y *cis*-2-(4-clorobencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (1.45 g, 24%). Isómero *cis*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.14 - 1.31 (m, 3H), 1.56 - 1.95 (m, 4H), 2.59 - 3.08 (m, 4H), 3.43 (d, 2H), 3.59 (d, 3H), 3.80-3.95 (m, 1H), 4.00 - 4.22 (m, 3H), 7.05 - 7.11 (m, 2H), 7.18-7.24 (m, 2H). MS m/z 382, 384 $(M+H)^+$. Isómero *trans*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.26 (t, 3H), 1.39-1.99 (m, 4H), 2.46-3.06 (m, 4H), 3.35-3.72 (m, 5H), 3.95-4.32 (m, 3H), 4.40-4.72 (m, 1H), 6.99-7.37 (m, 4H). MS m/z 382, 384 $(M+H)^+$.

Paso 3: *Cis*-2-(4-clorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se añadió una solución de *cis*-2-(4-clorobencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (1.45 g, 3.80 mmol) en MeOH (10 mL) a una solución de hidróxido sódico (3.16 mL, 3.80 mmol) en MeOH/H_2O (2.981 mL/0.179 mL) a -30 °C. Después de 10 min, se añadió una solución de clorhidrato de hidroxilamina (0.528 g, 7.59 mmol) e hidróxido sódico (0.304 g, 7.59 mmol) en MeOH (10 mL) y H_2O (10 mL). Se continuó agitando a -30 °C durante 30 min. La solución de reacción se vertió sobre HCl 6 M (6.33 mL, 37.97 mmol) a 80 °C y se calentó a 80 °C durante 1 hora. Tras concentrar el disolvente orgánico, extraer con éter dietílico (x3), secar con Na_2SO_4 y evaporar, se obtuvo una espuma amarilla. Se purificó utilizando prepLC (2 inyecciones, pH=3, columna grande, 20-80% de MeCN en 30 min) para proporcionar *cis*-2-(4-clorobencil)-4-(3-oxo-2,3-

dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (557 mg, 41%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.83-2.00 (m, 3H), 2.02-2.12 (m, 1H), 2.59 (dd, 1H), 2.77 (dd, 1H), 2.97 - 3.02 (m, 1H), 3.08-3.20 (m, 1H), 3.62 (s, 3H), 4.00 (dd, 1H), 4.21 - 4.29 (m, 1H), 5.73 (s, 1H), 7.04 (d, 2H), 7.21 - 7.25 (m, 2H). MS m/z 351, 353 $(M+H)^+$.

Paso 4: (2*R*,4*S*)-2-(4-clorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El *cis*-2-(4-clorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (557 mg, 1.58 mmol) se sometió a HPLC preparativa quiral (columna: Chiralpak IC (250x20), tamaño de partícula: 5 µm, fase móvil: 50/50/0.1 de heptano/IPA/AF, velocidad de flujo: 15 mL/min) para proporcionar (2*R*,4*S*)-2-(4-clorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (253 mg, 45%), pureza quiral: 99.3% de ee, rotación óptica $[\alpha]_D^{20} = +16.2$ (acetonitrilo, c=1).

Paso 5: 5-((2*R*,4*S*)-2-(4-Clorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se agitó (2*R*,4*S*)-2-(4-clorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (253 mg, 0.72 mmol) en HBr (al 33% en AcOH) durante toda la noche (24 horas). Los disolventes se evaporaron y el residuo se purificó mediante HPLC preparativa en una columna XBridge C18 (10 µm 250x50 DI en mm) utilizando un gradiente de 5% a 45% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 20 minutos con un flujo de 100 mL/min. Se aisló 5-((2*R*,4*S*)-2-(4-clorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona (150 mg, 71%). ^{1}H RMN (400 MHz, CD_3OD) δ 1.37-1.50 (m, 1H), 1.61 - 1.77 (m, 1H), 2.01-2.13 (m, 2H), 2.78-2.98 (m, 4H), 3.18-3.28 (m, 1H), 3.28 - 3.36 (m, 1H), 5.51 (s, 1H), 7.24 (d, 2H), 7.34 (d, 2H). HRMS calculado para $[C_{15}H_{17}ClN_2O_2+H]^+$: 293.1057. Experimental: 293.1043.

Ejemplo 116

5-(*Trans*-2-(4-clorobencil)piperidin-4-il)isoxazol-3(2*H*)-

ona

Paso 1: *Trans*-2-(4-clorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se añadió una solución de 2-(4-clorobencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (780 mg, 2.04 mmol) (paso 2 del ejemplo 115) en MeOH (5 mL) a una solución de hidróxido sódico (1.705 mL, 2.05 mmol) en MeOH/H_2O (1.608 mL/0.097 mL) a -30 °C. Después de 10 min, se añadió una solución de clorhidrato de hidroxilamina (284 mg, 4.09 mmol) e hidróxido sódico (163 mg, 4.09 mmol) en MeOH (5 mL) y H_2O (5 mL). Se continuó agitando a -30 °C durante 30 min. La solución de reacción se vertió sobre HCl 6 M (3.40 mL, 20.43 mmol) a 80 °C y se calentó a 80 °C durante 30 min. Tras concentrar el disolvente orgánico, extraer con éter dietílico (x3), secar con Na_2SO_4 y evaporar, se obtuvo una espuma amarilla. Se purificó utilizando prepLC (pH=3, columna grande, 20-80% de MeCN en 30 min) para proporcionar *trans*-2-(4-clorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (272.5 mg, 38%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.44 - 2.18 (m, 4H), 2.70 - 3.01 (m, 2H), 3.02-3.14 (m, 2H), 3.42 - 3.76 (m, 3H), 4.04 - 4.37 (m, 1H), 4.39 - 4.79 (m, 1H), 5.64 (s, 1H), 7.05 - 7.31 (m, 4H). MS m/z 351, 353 $(M+H)^+$

Paso 2: 5-(*Trans*-2-(4-clorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se agitó 2-(4-clorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (347 mg, 0.99 mmol) en HBr (al 33% en AcOH) durante toda la noche (19 horas). Se evaporaron los disolventes y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-(*trans*-2-(4-clorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona (151 mg, 52%). ^{1}H RMN (400 MHz, TFA) δ 2.25-2.60 (m, 4H), 3.06-3.20 (m, 2H), 3.35 - 3.52 (m, 1H), 3.55-3.75 (s, 2H), 3.77 - 3.96 (m, 1H), 6.59 (s, 1H), 7.15-7.22 (m, 2H), 7.22-7.41 (m, 2H). HRMS calculado para $[C_{15}H_{17}ClN_2O_2+H]^+$: 293.1057. Experimental:

293.1031.

Ejemplo 117

5-((2*R*,4*S*)-2-(4-Metilsulfonil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: 4-(3-Etoxi-3-oxopropanoil)-2-(4-(metilsulfonil)bencil)piperidin-1-carboxilato de metilo

Se añadieron malonato de etilo y potasio (2.414 g, 14.18 mmol) y $MgCl_2$ (1.125 g, 11.82 mmol) a THF anhidro (75 mL). El matraz de reacción se agitó vigorosamente durante 4 h a 50 °C (matraz 1). Se añadieron el ácido 1-(metoxicarbonil)-2-(4-(metilsulfonil)bencil)piperidin-4-carboxílico (4.2 g, 11.82 mmol) (compuesto de referencia 51) y carbonildiimidazol (2.87 g, 17.73 mmol) a THF anhidro (75 mL) a temperatura ambiente (matraz 2). Se añadió más di(1*H*-imidazol-1-il)metanona (0.5 g) y después de 2 h, el contenido del matraz 2 se añadió al matraz 1 a temperatura ambiente y se agitó durante la noche. La mezcla de reacción se disolvió entre agua y éter dietílico. La fase orgánica se aisló, se secó con Na_2SO_4, se filtró a través de celite y el disolvente se evaporó. Para la cromatografía se utilizó el equipo Biotage. Se utilizó un gradiente de elución de acetato de etilo-heptano que partió de 10-90 y terminó en 100-0. Se aisló 4-(3-etoxi-3-oxopropanoil)-2-(4-(metilsulfonil)bencil)piperidin-1-carboxilato de metilo (3.99 g, 79%).

Paso 2: 2-(4-(Metilsulfonil)bencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió 4-(3-etoxi-3-oxopropanoil)-2-(4-(metilsulfonil)bencil)piperidin-1-carboxilato de metilo (3.99 g, 9.38 mmol) en MeOH (70 mL) y se enfrió hasta -30 °C. Se añadió NaOH (0.375 g, 9.38 mmol) disuelto en agua (7 mL) durante 10 min y se continuó agitando la solución incolora resultante a -30°C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.575 mL, 9.38 mmol) gota a gota. La solución resultante se agitó a -30 °C durante 30 min. Posteriormente, la mezcla se transfirió a una solución calentada previamente (80 °C) de HCl 6 M (30 mL, 180 mmol) y la

mezcla se continuó agitando a 80 °C durante 20 min. La mezcla se disolvió entre acetato de etilo y agua. La capa acuosa se extrajo tres veces más con acetato de etilo. Las capas orgánicas combinadas se secaron con Na_2SO_4, se filtraron a través de celite y el disolvente se evaporó. El residuo se purificó utilizando cromatografía en fase inversa, gradiente de tampón ácido y acetonitrilo, partiendo de 35% y terminando en 40%. Se aisló 2-(4-(metilsulfonil)bencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.05 g, 28.4%).

Paso 3: (2*R*,4*S*)-2-(4-(Metilsulfonil)bencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo, (2*S*,4*R*)-2-(4-(metilsulfonil)bencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo y *trans*-2-(4-(metilsulfonil)bencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El 2-(4-(metilsulfonil)bencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1 g, 2.54 mmol) se sometió a HPLC preparativa quiral en dos etapas (utilizando primero una columna: Chiralcel OJ (250x50), tamaño de partícula: 20 µm, fase móvil: 30/70/0.1 de heptano/IPA/AF, velocidad de flujo: 120 mL/min y utilizando posteriormente una columna: Chiralpak AD (250x50), tamaño de partícula: 20 µm, fase móvil: 40/60/0.1 de heptano/EtOH/AF, velocidad de flujo: 120 mL/min) para proporcionar (2*R*,4*S*)-2-(4-(metilsulfonil)bencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (231 mg, 23%), pureza quiral: 99.5% de ee, rotación óptica $[\alpha]_D^{20} = +10.1$ (acetonitrilo, c=1), ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.87 - 1.97 (m, 3H), 2.02 - 2.11 (m, 1H), 2.68 (dd, 1H), 2.88 (dd, 1H), 2.96 - 3.06 (m, 4H), 3.12 - 3.22 (m, 1H), 3.60 (s, 3H), 3.96 - 4.02 (m, 1H), 4.27 - 4.35 (m, 1H), 5.74 (s, 1H), 7.30 (d, 2H), 7.82 (d, 2H); (2*S*,4*R*)-2-(4-(metilsulfonil)bencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (225 mg, 22.5%), pureza quiral: 98.4% de ee, rotación óptica $[\alpha]_D^{20} = -11.4$

(acetonitrilo, c=1), ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.86 - 1.97 (m, 3H), 2.02 - 2.10 (m, 1H), 2.67 (dd, 1H), 2.87 (dd, 1H), 2.96 - 3.05 (m, 4H), 3.12 - 3.20 (m, 1H), 3.59 (s, 3H), 3.95 - 4.02 (m, 1H), 4.27 - 4.34 (m, 1H), 5.74 (s, 1H), 7.29 (d, 2H), 7.81 (d, 2H), y *trans*-2-(4-(metilsulfonil)bencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (185 mg, 18.5%).

Paso 4: 5-((2*R*,4*S*)-2-(4-Metilsulfonil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-2-(4-(metilsulfonil)bencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (231 mg, 0.59 mmol) en HBr (al 33% en ácido acético, 5 mL, 28.55 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*S*)-2-(4-(metilsulfonil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona (171 mg, 87%). ^{1}H RMN (600 MHz, DMSO) δ 1.06 - 1.15 (m, 1H), 1.30 - 1.39 (m, 1H), 1.76 (d, 2H), 2.43 -2.56 (señales omitidas), 2.62 - 2.81 (m, 4H), 2.95 - 3.00 (m, 1H), 3.16 (s, 3H), 5.68 (s, 1H), 7.46 (d, 2H), 7.80 (d, 2H). HRMS calculado para $[C_{16}H_{20}N_2O_4S+H]+$: 337.1222. Experimental: 337.1198.

Ejemplo 118

5-((2*S*,4*R*)-2-(4-Metilsulfonil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*S*,4*R*)-2-(4-(metilsulfonil)bencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (225 mg, 0.57mmol) en HBr (al 33% en ácido acético, 5 mL, 28.55 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*S*,4*R*)-2-(4-(metilsulfonil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona (91 mg, 47.4%).^{1}H RMN (600 MHz, DMSO) δ 1.05 - 1.14

(m, 1H), 1.30 - 1.38 (m, 1H), 1.72 - 1.79 (m, 2H), 2.39 - 2.56 (señales omitidas), 2.62 - 2.80 (m, 4H), 2.94 - 3.00 (m, 1H), 3.16 (s, 3H), 5.68 (s, 1H), 7.46 (d, 2H), 7.80 (d, 2H). HRMS calculado para $[C_{16}H_{20}N_2O_4S+H]+$: 337.1222. Experimental: 337.1198.

Ejemplo 119

5-(*Trans*-2-(4-metilsulfonil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió *trans*-2-(4-(metilsulfonil)bencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (185 mg, 0.47 mmol) en HBr (al 33% en ácido acético, 4 mL, 22.84 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-(*trans*-2-(4-(metilsulfonil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona (161 mg, 102%). ^{1}H RMN (600 MHz, DMSO) δ 1.65 - 1.97 (m, 4H), 2.34 - 2.63 (señales omitidas), 2.80 - 3.15 (m, 5H), 3.18 (s, 3H), 5.84 (s, 1H), 7.51 (d, 2H), 7.87 (d, 2H). HRMS calculado para $[C_{16}H_{20}N_2O_4S+H]+$: 337.1222. Experimental: 337.1236.

Ejemplo 120

5-((2*R*,4*S*)-2-(3,4-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(3,4-difluorobencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo y *cis*-2-(3,4-difluorobencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo

Se disolvió el ácido 2-(3,4-difluorobencil)-1-(metoxicarbonil)piperidin-4-carboxílico (6.62 g, 21.13 mmol) (compuesto de referencia 53) en metil-THF (150 mL) y se añadió di(1*H*-imidazol-1-il)metanona (5.14 g, 31.70 mmol). La suspensión se agitó a temperatura ambiente en atmósfera de nitrógeno durante 3.5 h (matraz 1). En otro matraz, se suspendió 3-etoxi-3-oxopropanoato de potasio (6.47 g, 38.03

mmol) en metil-THF (150 mL) y se añadió cloruro de magnesio (3.62 g, 38.03 mmol). La suspensión se agitó a 50 °C en atmósfera de nitrógeno durante 3 h utilizando un imán muy grande (matraz 2). A continuación, la suspensión amarilla del matraz 1 se añadió a la suspensión blanca del matraz 2. La suspensión amarilla resultante se agitó en atmósfera de nitrógeno a temperatura ambiente durante 4 h. La mezcla se acidificó hasta pH 1 con HCl 3.8 M, y se añadieron MTBE y agua. Las fases se separaron y la fase orgánica se extrajo con agua, $NaHCO_3$ sat. y agua. Los disolventes se evaporaron para proporcionar un aceite naranja. Los diastereómeros se separaron en dos purificaciones en una columna Biotage (20% => 50% de EtOAc en heptano, 8 VC; columna Biotage® con 340g de KP-SIL). Se aislaron *trans*-2-(3,4-difluorobencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (0.278 g, 3.4%) y *cis*-2-(3,4-difluorobencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (2.233 g, 27.6%) como aceites amarillos. Isómero *cis*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.21 - 1.29 (m, 3H), 1.61 - 1.98 (m, 4H), 2.63 - 2.78 (m, 2H), 2.82 - 3.11 (m, 2H), 3.47 (s, 2H), 3.64 (s, 3H), 3.86 - 3.97 (m, 1H), 4.12 - 4.23 (m, 3H), 6.85 - 6.92 (m, 1H), 6.95 - 7.13 (m, 2H). MS m/z 384 $(M+H)^+$. Isómero *trans*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.22 - 1.29 (m, 3H), 1.40 - 2.00 (m, 4H), 2.63 - 3.03 (m, 4H), 3.37 - 3.75 (m, 5H), 4.00 - 4.31 (m, 3H), 4.55 (d a, 1H), 6.77 - 7.12 (m, 3H). MS m/z 384 $(M+H)^+$.

Paso 2: <u>*Cis*-2-(3,4-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo</u>

Se disolvió *cis*-2-(3,4-difluorobencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (2.233 g, 5.82 mmol) en MeOH (20 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (0.233 g, 5.82 mmol) disuelto en agua (2.000 mL) durante 10 min y la solución amarilla se continuó agitando a -40 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.357 mL, 5.82 mmol) durante 8 min. La solución resultante se agitó a -40 °C durante 3 h. A continuación, la mezcla se vertió rápidamente

sobre una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (30 mL, 180.00 mmol) y la mezcla se continuó agitando a 80 °C durante 20 min. El disolvente se evaporó y se añadieron DCM/agua. Las fases se separaron y la fase orgánica se hizo pasar a través de un separador de fases y se evaporó para proporcionar un semisólido amarillo. El compuesto se purificó mediante HPLC preparativa en 3 inyecciones en una columna XBridge C18 (10 µm 250x50 DI en mm) utilizando un gradiente de 0-25% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 20 minutos con un flujo de 100 mL/min. Se aisló *cis*-2-(3,4-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.361 g, 66%) como un sólido blanco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.84 - 2.14 (m, 4H), 2.52 - 2.62 (m, 1H), 2.71 - 2.80 (m, 1H), 2.95 - 3.05 (m, 1H), 3.09 - 3.20 (m, 1H), 3.64 (s, 3H), 3.95 - 4.06 (m, 1H), 4.20 - 4.30 (m, 1H), 5.74 (s, 1H), 6.77 - 6.83 (m, 1H), 6.90 - 6.98 (m, 1H), 6.98 - 7.09 (m, 1H). MS m/z 353 $(M+H)^+$.

Paso 3: (2*R*,4*S*)-2-(3,4-Difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo y (2*S*,4*R*)-2-(3,4-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El *cis*-2-(3,4-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.36 g, 3.87 mmol) se sometió a HPLC preparativa quiral (columna: Chiralpak AD (250x20), tamaño de partícula: 5 µm, fase móvil: 90/10/0.2 de heptano/EtOH/AF, velocidad de flujo: 18 mL/min) para proporcionar (2*R*,4*S*)-2-(3,4-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (550 mg, 40%), pureza quiral: 98.2% de ee, rotación óptica $[\alpha]_D^{20} = +15.0$ (acetonitrilo, c=1) y (2*S*,4*R*)-2-(3,4-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (596 mg, 44%), pureza quiral: 99.4% de ee, rotación óptica $[\alpha]_D^{20} = -13.2$ (acetonitrilo, c=1).

Paso 4: 5-((2*R*,4*S*)-2-(3,4-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-2-(3,4-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (550 mg, 1.56 mmol) en ácido bromhídrico (al 33% en ácido acético, 15 mL, 85.65 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx I, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*S*)-2-(3,4-difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona (183 mg, 40%). ^{1}H RMN (600 MHz, CD_3OD) δ 1.41 (c, 1H), 1.67 (dc, 1H), 1.99 - 2.08 (m, 2H), 2.77 - 2.95 (m, 4H), 3.17 - 3.24 (m, 1H), 3.26 - 3.34 (m, 1H), 5.49 (s, 1H), 7.00 - 7.05 (m, 1H), 7.14 - 7.22 (m, 2H). HRMS calculado para $[C_{15}H_{16}F_2N_2O_2+H]^+$: 295.1258. Experimental: 295.1253.

Ejemplo 121

5-((2*S*,4*R*)-2-(3,4-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*S*,4*R*)-2-(3,4-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (596 mg, 1.69 mmol) (del paso 3 del ejemplo 120) en ácido bromhídrico (al 33% en ácido acético, 15 mL, 85.65 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx I, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*S*,4*R*)-2-(3,4-difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona (136 mg, 27%). ^{1}H RMN (600 MHz, CD_3OD) δ 1.42 (c, 1H), 1.68 (dc, 1H), 2.04 (t, 2H), 2.78 - 2.95 (m, 4H), 3.19 - 3.25 (m, 1H), 3.29 - 3.35 (m, 1H), 5.49 (s, 1H), 7.00 - 7.05 (m, 1H), 7.14 - 7.22 (m, 2H). HRMS calculado para $[C_{15}H_{16}F_2N_2O_2+H]^+$: 295.1258. Experimental: 295.1264.

Ejemplo 122

5-((2*S*,4*S*)-2-(3,4-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

Paso 1: *Trans*-2-(3,4-difluorobencil)-4-(3-oxo-2,3-

dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *trans*-2-(3,4-difluorobencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (0.278 g, 0.73 mmol) (del paso 1 del ejemplo 120) en MeOH (3 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (0.029 g, 0.73 mmol) disuelto en agua (0.300 mL) durante 10 min y se continuó agitando la solución amarilla a -40 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.044 mL, 0.73 mmol) durante 8 min. La solución resultante se agitó a -40 °C durante 3 h 15 min. A continuación, la mezcla se vertió rápidamente sobre una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (4 mL, 24.00 mmol) y se continuó agitando la mezcla a 80 °C durante 20 min. El disolvente se evaporó y se añadieron DCM/agua. Las fases se separaron y la fase orgánica se hizo pasar a través de un separador de fases y se evaporó para proporcionar un semisólido amarillo. El compuesto se purificó mediante HPLC preparativa en una columna XBridge C18 (10 µm 250x50 DI en mm) utilizando un gradiente de 0-25% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 20 minutos con un flujo de 100 mL/min. Se aisló *trans*-2-(3,4-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (83 mg, 34%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.47 - 2.14 (m, 4H), 2.71 - 3.14 (m, 4H), 3.43-3.75 (m, 3H), 4.01 - 4.78 (m, 2H), 5.65 (s, 1H), 6.78-7.14 (m, 3H). MS m/z 353 $(M+H)^+$.

Paso 2: (2*S*,4*S*)-2-(3,4-Difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo y (2*R*,4*R*)-2-(3,4-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El *trans*-2-(3,4-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (83 mg, 0.24 mmol) se sometió a HPLC preparativa quiral (columna: ReproSil (250x20), tamaño de partícula: 8 µm, fase móvil: 70/30 de heptano/(95/5 de MTBE/MeOH), velocidad de flujo: 18 mL/min) para proporcionar (2*S*,4*S*)-2-(3,4-difluorobencil)-4-(3-oxo-2,3-

dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (45 mg, 54%), pureza quiral: 99.6% de ee y (2*R*,4*R*)-2-(3,4-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (32 mg, 38%), pureza quiral: 99.9% de ee.

Paso 3: 5-((2*S*,4*S*)-2-(3,4-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*S*,4*S*)-2-(3,4-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (45 mg, 0.13 mmol) en ácido bromhídrico (al 33% en ácido acético, 1 mL, 5.71 mmol) y la mezcla se agitó a temperatura ambiente. Después de 17 h, se añadió más ácido bromhídrico (al 33% en ácido acético, 0.5 mL, 2.85 mmol) y la reacción continuó a temperatura ambiente durante un total de 24 h. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx III, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*S*,3,4*S*)-2-(3,4-difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona (8.5 mg, 22%). ^{1}H RMN (600 MHz, CD_3OD) δ 1.71 - 1.79 (m, 1H), 1.96 - 2.04 (m, 1H), 2.04 - 2.12 (m, 2H), 2.79 - 2.92 (m, 2H), 2.95 - 3.03 (m, 1H), 3.14 - 3.36 (m, 3H), 5.51 (s, 1H), 7.00 - 7.04 (m, 1H), 7.13 - 7.24 (m, 2H). HRMS calculado para $[C_{15}H_{16}F_2N_2O_2+H]^+$: 295.1258. Experimental: 295.1276.

Ejemplo 123

5-((2*R*,4*R*)-2-(3,4-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*R*)-2-(3,4-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (32.5 mg, 0.09 mmol) en ácido bromhídrico (al 33% en ácido acético, 0.8 mL, 4.57 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx III, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*R*)-2-(3,4-difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona (10.4 mg, 38%). ^{1}H RMN (600 MHz, CD_3OD) δ

1.71 - 1.78 (m, 1H), 1.96 - 2.04 (m, 1H), 2.05 - 2.12 (m, 2H), 2.80 - 2.92 (m, 2H), 2.96 - 3.03 (m, 1H), 3.15 - 3.25 (m, 2H), 3.26 - 3.35 (m, 1H), 5.50 (s, 1H), 6.99 - 7.05 (m, 1H), 7.13 - 7.23 (m, 2H). HRMS calculado para $[C_{15}H_{16}F_2N_2O_2+H]^+$: 295.1258. Experimental: 295.1267.

Ejemplo 124

5-((2*R*,4*S*)-2-(2,5-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(2,5-difluorobencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo y *cis*-2-(2,5-difluorobencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo

Se añadió di(1*H*-imidazol-1-il)metanona (5.74 g, 35.43 mmol) a una mezcla del ácido 2-(2,5-difluorobencil)-1-(metoxicarbonil)piperidin-4-carboxílico (7.4 g, 23.62 mmol) (compuesto de referencia 54) en metil-THF anhidro (150 mL) a temperatura ambiente en atmósfera de nitrógeno. La suspensión se agitó a temperatura ambiente durante 4 h (matraz 1). Se añadió cloruro de magnesio (4.05 g, 42.52 mmol) a una mezcla de 3-etoxi-3-oxopropanoato de potasio (7.24 g, 42.52 mmol) en metil-THF anhidro (150 mL) a temperatura ambiente en atmósfera de nitrógeno. La mezcla se calentó a 50 °C durante 4 h y después de dejó enfriar hasta temperatura ambiente (matraz 2). La suspensión del matraz 1 se añadió a la suspensión del matraz 2. La mezcla de reacción se agitó a temperatura ambiente durante 48 h. La mezcla se acidificó hasta pH 1 con HCl 4 M, y posteriormente se añadieron MTBE y agua. La fase orgánica se separó, se lavó con agua y $NaHCO_3$ sat., se secó y se evaporó. Los diastereómeros se separaron mediante cromatografía flash en gel de sílice utilizando isohexano/EtOAc (100:15 y 100:50) como eluyente. Se aislaron *trans*-2-(2,5-difluorobencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (1.6 g, 18%) y *cis*-2-(2,5-difluorobencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (6.2 g, 69%) como aceites. Isómero *cis*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.20 - 1.32 (m, 3H), 1.64 - 2.00 (m, 4H), 2.67 - 3.15 (m, 4H), 3.48 (s, 2H), 3.58 (s, 3H), 3.87 -

3.99 (m, 1H), 4.07 - 4.32 (m, 3H), 6.82 - 7.01 (m, 3H). Isómero *trans*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.22 - 1.32 (m, 3H), 1.45 - 2.01 (m, 4H), 2.52 - 3.12 (m, 4H), 3.41 - 3.74 (m, 5H), 4.04 - 4.34 (m, 3H), 4.48 - 4.74 (m, 1H), 6.82 - 7.06 (m, 3H). MS m/z 384 $(M+H)^+$.

Paso 2: *Cis*-2-(2,5-Difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *cis*-2-(2,5-difluorobencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (2.241 g, 5.85 mmol) en MeOH (20 mL) y se enfrió hasta -40°C en atmósfera de nitrógeno. Se añadió hidróxido sódico (0.234 g, 5.85 mmol) disuelto en agua (2.000 mL) durante 10 min y se continuó agitando la solución incolora a -40 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.358 mL, 5.85 mmol) durante 8 min. La solución resultante se agitó a -40 °C durante 3 h. A continuación, la mezcla se transfirió a una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (30 mL, 180.00 mmol) y se continuó agitando la mezcla a 80 °C durante 20 min. El disolvente se evaporó y se añadieron DCM/agua. Las fases se separaron y la fase orgánica se hizo pasar a través de un separador de fases y se evaporó para proporcionar un semisólido amarillo. El compuesto se purificó mediante HPLC preparativa en 3 inyecciones en una columna XBridge C18 (10 µm 250x50 DI en mm) utilizando un gradiente de 0-20% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 20 minutos con un flujo de 100 mL/min. Se aisló *cis*-2-(2,5-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.259 g, 61%) como un sólido blanco. ^{1}H RMN (400 MHz, CD_3OD) δ 1.88 - 2.13 (m, 4H), 2.63 - 2.83 (m, 2H), 2.99 - 3.10 (m, 1H), 3.23 - 3.34 (m, 1H), 3.45 (s, 3H), 3.88 - 4.00 (m, 1H), 4.35 - 4.46 (m, 1H), 5.85 (d, 1H), 6.88 - 7.06 (m, 3H). MS m/z 353 $(M+H)^+$.

Paso 3: (2*R*,4*S*)-2-(2,5-Difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo y (2*S*,4*R*)-2-(2,5-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El *cis*-2-(2,5-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.259 g, 3.58 mmol) se sometió a HPLC preparativa quiral (columna: Chiralpak AD (250x20), tamaño de partícula: 5 µm, fase móvil: 90/10/0.2 de heptano/EtOH/AF, velocidad de flujo: 18 mL/min) para proporcionar (2*R*,4*S*)-2-(2,5-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (505 mg, 40%), pureza quiral: 98.8% de ee, rotación óptica $[\alpha]_D^{20} = -5.7$ (acetonitrilo, c=1) y (2*S*,4*R*)-2-(2,5-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (499 mg, 39.6%), pureza quiral: 98.8% de ee, rotación óptica $[\alpha]_D^{20} +3.5$ (acetonitrilo, c=1).

Paso 4: 5-((2*R*,4*S*)-2-(2,5-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-2-(4-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (505 mg, 1.43 mmol) en ácido bromhídrico (al 33% en ácido acético, 10 mL, 57.10 mmol) y la mezcla se agitó a temperatura ambiente durante 22 h. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx III, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 299 mg de 5-((2*R*,4*S*)-2-(2,5-difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona (71%). ^{1}H RMN (600 MHz, CD_3OD) δ 1.49 (c, 1H), 1.71 (dc, 1H), 1.99 - 2.08 (m, 2H), 2.82 - 3.00 (m, 4H), 3.24 - 3.31 (m, 1H), 3.31 - 3.37 (m, 1H), 5.50 (s, 1H), 6.99 - 7.13 (m, 3H). HRMS calculado para $[C_{15}H_{16}F_2N_2O_2+H]^+$: 295.1258. Experimental: 295.1244.

Ejemplo 125

5-((2*S*,4*R*)-2-(2,5-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*S*,4*R*)-2-(2,5-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (499 mg, 1.42 mmol) (del paso 3 del ejemplo 124) en ácido bromhídrico (al 33% en ácido acético, 10 mL, 57.10 mmol) y la mezcla se

agitó a temperatura ambiente durante 22 h. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx III, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*S*,4*R*)-2-(2,5-difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona (292 mg, 70%). ^{1}H RMN (600 MHz, CD_3OD) δ 1.49 (c, 1H), 1.71 (dc, 1H), 2.00 - 2.08 (m, 2H), 2.83 - 2.91 (m, 2H), 2.93 - 3.00 (m, 2H), 3.25 - 3.31 (m, 1H), 3.33 - 3.37 (m, 1H), 5.50 (s, 1H), 6.99 - 7.12 (m, 3H). HRMS calculado para $[C_{15}H_{16}F_2N_2O_2+H]^+$: 295.1258. Experimental: 295.1254.

Ejemplo 126

5-(*Trans*-2-(2,5-difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(2,5-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *trans*-2-(2,5-difluorobencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (0.611 g, 1.59 mmol) (del paso 1 del ejemplo 124) en MeOH (5 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (0.064 g, 1.59 mmol) disuelto en agua (0.500 mL) durante 10 min y se continuó agitando la solución incolora a -40 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.098 mL, 1.59 mmol) durante 8 min. La solución resultante se agitó a -40 °C durante 3 h. A continuación, la mezcla se transfirió a una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (8 mL, 48.00 mmol) y se continuó agitando la mezcla a 80 °C durante 20 min. El disolvente se evaporó y se añadieron DCM/agua. Las fases se separaron y la fase orgánica se hizo pasar a través de un separador de fases y se evaporó para proporcionar *trans*-2-(2,5-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo crudo (0.552 g, 98%) como un semisólido amarillo. MS m/z 353 $(M+H)^+$.

Paso 2: 5-(*Trans*-2-(2,5-difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió *trans*-2-(2,5-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (148 mg, 0.42 mmol) en ácido bromhídrico (al 33% en ácido acético, 3 mL, 17.13 mmol) y la solución se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-(*trans*-2-(2,5-difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona (54.7 mg, 44%). ^{1}H RMN (400 MHz, CD_3OD) δ 1.90 - 2.00 (m, 1H), 2.10 - 2.25 (m, 3H), 3.05 (d, 2H), 3.09 - 3.19 (m, 1H), 3.34 - 3.45 (m, 2H), 3.51 - 3.61 (m, 1H), 5.81 (d, 1H), 7.02 - 7.21 (m, 3H). HRMS calculado para $[C_{15}H_{16}F_2N_2O_2+H]^+$: 295.1258. Experimental: 295.1278.

Ejemplo 127

5-((2*R*,4*S*)-2-(2,6-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(2,6-difluorobencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo y *cis*-2-(2,6-difluorobencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo

Se disolvió el ácido 2-(2,6-difluorobencil)-1-(metoxicarbonil)piperidin-4-carboxílico (4.72 g, 15.07 mmol) (compuesto de referencia 55) en metil-THF (108 mL) y se añadió di(1*H*-imidazol-1-il)metanona (3.66 g, 22.60 mmol). La suspensión se agitó a temperatura ambiente durante 3 h 45 min en atmósfera de nitrógeno (matraz 1). En otro matraz, se añadió cloruro de magnesio (2.58 g, 27.12 mmol) a una suspensión de 3-etoxi-3-oxopropanoato de potasio (4.62 g, 27.12 mmol) en metil-THF (108 mL). La suspensión se agitó con un imán grande durante 3.5 h a 50 °C en atmósfera de nitrógeno (matraz 2). La suspensión del matraz 1 se añadió a la suspensión del matraz 2 y a continuación la mezcla de reacción se agitó a temperatura ambiente durante toda la noche. La mezcla de reacción se acidificó hasta pH 1 con HCl 2 M. Se añadieron agua y MTBE, y se separaron las fases. La fase orgánica se lavó con agua,

$NaHCO_3$ sat. y agua, antes de secarla y concentrarla. El residuo se purificó dos veces mediante cromatografía flash automatizada en una columna Biotage® con 340g de KP-SIL. Se utilizó como fase móvil un gradiente de 15% a 50% de EtOAc en heptano en 8 VC (3 VC de desecho inicial + 5 VC recogidos). Se aislaron el *trans*-2-(2,6-difluorobencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (0.405 g, 7%) y *cis*-2-(2,6-difluorobencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (2.404 g, 41%). Isómero *cis*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.20 - 1.33 (m, 3H), 1.68 - 2.05 (m, 4H), 2.65 - 2.89 (m, 2H), 2.93 - 3.16 (m, 2H), 3.49 (s, 5H), 3.96 (dd, 1H), 4.14 - 4.22 (m, 2H), 4.27 - 4.40 (m, 1H), 6.77 - 6.89 (m, 2H), 7.09 - 7.20 (m, 1H). MS m/z 384 $(M+H)^+$. Isómero *trans*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.22 - 1.34 (m, 3H), 1.41 - 2.01 (m, 4H), 2.75 - 3.20 (m, 4H), 3.37 - 3.70 (m, 5H), 4.02 - 4.32 (m, 3H), 4.55 - 4.85 (m, 1H), 6.81 - 6.92 (m, 2H), 7.11 - 7.23 (m, 1H). MS m/z 384 $(M+H)^+$.

Paso 2: *Cis*-2-(2,6-Difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *cis*-2-(2,6-difluorobencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (2.404 g, 6.27 mmol) en MeOH (21 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (0.251 g, 6.27 mmol) disuelto en agua (2.100 mL) en 8 min. Después de agitar durante 20 min, se añadió hidroxilamina (al 50% en peso en agua, 0.384 mL, 6.27 mmol) en 6 minutos y la solución se agitó durante 3.5 horas a -40 °C. Posteriormente, la mezcla de reacción se vertió rápidamente en una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (32.3 mL, 193.76 mmol) y se continuó agitando la mezcla a 80 °C durante 25 min. El disolvente se evaporó y la mezcla cruda se redisolvió en DCM/agua. La fase orgánica se secó y se concentró. El compuesto se purificó mediante HPLC preparativa en una columna XBridge C18 (10 µm 250x50 DI en mm) utilizando un gradiente de 0-20% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 20 minutos con un flujo de 100 mL/min. Se aisló *cis*-2-(2,6-

difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.232 g, 55.8%) como un sólido blanco. ^{1}H RMN (400 MHz, CD_3OD) δ 1.94 - 2.04 (m, 2H), 2.08 - 2.16 (m, 2H), 2.63 - 2.73 (m, 1H), 2.81 - 2.91 (m, 1H), 2.98 - 3.09 (m, 1H), 3.24 - 3.37 (m, 4H), 3.88 - 3.99 (m, 1H), 4.41 - 4.54 (m, 1H), 5.81 (s, 1H), 6.82 - 6.92 (m, 2H), 7.16 - 7.26 (m, 1H). MS m/z 353 $(M+H)^+$.

Paso 3: (2*R*,4*S*)-2-(2,6-Difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo y (2*S*,4*R*)-2-(2,6-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El *cis*-2-(2,6-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.232 g, 3.5 mmol) se sometió a HPLC preparativa quiral (columna: Chiralpak AD (250x20), tamaño de partícula: 5 µm, fase móvil: 90/10/0.2 de heptano/EtOH/AF, velocidad de flujo: 18 mL/min) para proporcionar (2*R*,4*S*)-2-(2,6-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (370 mg, 30%), pureza quiral: 99.2% de ee, rotación óptica $[\alpha]_D^{20} = -24.4$ (acetonitrilo, c=1) y (2*S*,4*R*)-2-(2,6-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (344 mg, 28%), pureza quiral: 97.6% de ee. rotación óptica $[\alpha]_D^{20} = +22.9$ (acetonitrilo, c=1).

Paso 4: 5-((2*R*,4*S*)-2-(2,6-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,2,4*S*)-2-(2,6-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (370 mg, 1.05 mmol) en ácido bromhídrico (al 33% en ácido acético, 8 mL, 45.68 mmol) y la mezcla se agitó a temperatura ambiente durante 24 h. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx III, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*S*)-2-(2,6-difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona (254 mg, 82%). ^{1}H RMN (600 MHz, CD_3OD) δ 1.47 (c, 1H), 1.67

(cd, 1H), 2.02 (dd, 2H), 2.78 - 3.02 (m, 4H), 3.16 - 3.24 (m, 1H), 3.27 - 3.33 (m, 1H), 5.49 (s, 1H), 6.98 (t, 2H), 7.27 - 7.37 (m, 1H). HRMS calculado para $[C_{15}H_{16}F_2N_2O_2+H]^+$: 295.1258. Experimental: 295.1248.

Ejemplo 128

5-((2*S*,4*R*)-2-(2,6-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*S*,4*R*)-2-(2,6-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (344 mg, 0.98 mmol) (del paso 3 del ejemplo 127) en ácido bromhídrico (al 33% en ácido acético, 8 mL, 45.68 mmol) y la mezcla se agitó a temperatura ambiente durante 24 h. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx III, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*S*,4*R*)-2-(2,6-difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona (222 mg, 77%). ^{1}H RMN (600 MHz, CD_3OD) δ 1.47 (c, 1H), 1.68 (dc, 1H), 1.96 - 2.07 (m, 2H), 2.79 - 3.02 (m, 4H), 3.18 - 3.25 (m, 1H), 3.27 - 3.34 (m, 1H), 5.49 (s, 1H), 6.95 - 7.01 (m, 2H), 7.28 - 7.36 (m, 1H). HRMS calculado para $[C_{15}H_{16}F_2N_2O_2+H]^+$: 295.1258. Experimental: 295.1240.

Ejemplo 129

5-(*Trans*-2-(2,6-difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(2,6-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *trans*-2-(2,6-difluorobencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (0.399 g, 1.04 mmol) (del paso 1 del ejemplo 127) en MeOH (3.5 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (0.306 mL, 1.04 mmol) en 5 min. Después de agitar durante 45 min, se añadió hidroxilamina (al 50% en peso en agua, 0.064 mL, 1.04 mmol) en 1 minuto y la solución se agitó durante 3.5 horas a -40 °C. Posteriormente, la mezcla de reacción se vertió rápidamente en una solución calentada

previamente (80 °C) de ácido clorhídrico 6 M (5.36 mL, 32.16 mmol) y se continuó agitando la mezcla a 80 °C durante 20 min. El disolvente se evaporó y la mezcla cruda se redisolvió en DCM y se lavó con agua. La fase orgánica se secó y se concentró para obtener *trans*-2-(2,6-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo crudo (0.331 g, 90%). MS m/z 353 $(M+H)^+$.

Paso 2: 5-(*Trans*-2-(2,6-difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió *trans*-2-(2,6-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.329 g, 0.93 mmol) en ácido bromhídrico (al 33% en ácido acético, 7.5 mL, 42.82 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-(*trans*-2-(2,6-difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona (4.6 mg, 1.7%). HRMS calculado para $[C_{15}H_{16}F_2N_2O_2+H]^+$: 295.1258. Experimental: 295.1257.

Ejemplo 130

5-((2*R*,4*S*)-2-(3,5-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(3,5-difluorobencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo y *cis*-2-(3,5-difluorobencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo

Se disolvió el ácido 2-(3,5-difluorobencil)-1-(metoxicarbonil)piperidin-4-carboxílico (6.87 g, 21.93 mmol) (compuesto de referencia 56) en metil-THF (150 mL) y se añadió di(1*H*-imidazol-1-il)metanona (5.33 g, 32.89 mmol). La suspensión se agitó a temperatura ambiente durante 3 horas en atmósfera de nitrógeno (matraz 1). En otro matraz, se añadió cloruro de magnesio (3.76 g, 39.47 mmol) a 3-etoxi-3-oxopropanoato de potasio (6.72 g, 39.47 mmol) en metil-THF (150 mL). La suspensión se agitó con un imán grande durante 3 h a 50

°C (matraz 2). La suspensión del matraz 1 se añadió a la suspensión del matraz 2 y a continuación la mezcla de reacción se agitó a temperatura ambiente durante 3 días. La mezcla de reacción se acidificó hasta pH 1 con HCl 2 M. Se añadieron agua y MTBE, y se separaron las fases. La fase orgánica se lavó con agua, $NaHCO_3$ sat. y agua, antes de secarla y concentrarla. 60% del residuo se purificó dos veces mediante cromatografía flash automatizada en una columna Biotage® con 340g de KP-SIL. Se utilizó como fase móvil un gradiente de 20% a 60% de EtOAc en heptano en 8 VC (3 VC de desecho inicial + 5 VC recogidos). Se aislaron el *trans*-2-(3,5-difluorobencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (0.92 g, 20%) y *cis*-2-(3,5-difluorobencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (2.66 g, 57%). Isómero *cis*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.19 - 1.33 (m, 3H), 1.62 - 2.00 (m, 4H), 2.65 - 2.78 (m, 2H), 2.86 - 3.14 (m, 2H), 3.47 (s, 2H), 3.66 (s, 3H), 3.86 - 3.98 (m, 1H), 4.13 - 4.24 (m, 3H), 6.60 - 6.77 (m, 3H). MS m/z 384 $(M+H)^+$. Isómero *trans*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.21 - 1.34 (m, 3H), 1.43 - 2.02 (m, 4H), 2.68 - 3.06 (m, 4H), 3.46 (s, 2H), 3.51 - 3.75 (m, 3H), 4.03 - 4.34 (m, 3H), 4.45 - 4.73 (m, 1H), 6.61 - 6.83 (m, 3H). MS m/z 384 $(M+H)^+$.

Paso 2: *Cis*-2-(3,5-Difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *cis*-2-(3,5-difluorobencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (2.662 g, 6.94 mmol) en MeOH (24 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (0.278 g, 6.94 mmol) disuelto en agua (2.400 mL) en 13 min. Después de agitar durante 20 min, se añadió hidroxilamina (al 50% en peso en agua, 0.425 mL, 6.94 mmol) en 9 minutos y la solución se agitó durante 3.5 horas a -40 °C. Posteriormente, la mezcla de reacción se vertió rápidamente en una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (35.8 mL, 214.55 mmol) y se continuó agitando la mezcla a 80 °C durante 25 min. El disolvente se evaporó y la mezcla cruda se redisolvió en DCM/agua. La fase orgánica se secó y se concentró. El compuesto

se purificó mediante HPLC preparativa en 2 inyecciones en una columna XBridge C18 (10 µm 250x50 DI en mm) utilizando un gradiente de 0-25% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 20 minutos con un flujo de 100 mL/min. Se aisló *cis*-2-(3,5-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.604 g, 65.6%) como un sólido blanco. ^{1}H RMN (400 MHz, CD_3OD) δ 1.91 - 2.07 (m, 4H), 2.62 - 2.80 (m, 2H), 2.97 - 3.04 (m, 1H), 3.23 - 3.34 (m, 1H), 3.54 (s, 3H), 3.89 - 3.99 (m, 1H), 4.26 - 4.36 (m, 1H), 5.73 (s, 1H), 6.69 - 6.79 (m, 3H). MS m/z 353 $(M+H)^+$.

Paso 3: (2*R*,4*S*)-2-(3,5-Difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo y (2*S*,4*R*)-2-(3,5-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El *cis*-2-(3,5-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.604 g, 4.56 mmol) se sometió a HPLC preparativa quiral (columna: Chiralpak AD (250x20), tamaño de partícula: 5 µm, fase móvil: 90/10 de heptano/EtOH, velocidad de flujo: 18 mL/min) para proporcionar (2*R*,4*S*)-2-(3,5-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (645 mg, 40%), pureza quiral: 99.2% de ee, rotación óptica $[\alpha]_D^{20} = +13.1$ (MeOH, c=1) y (2*S*,4*R*)-2-(3,5-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (789 mg, 49%), pureza quiral: 99.6% de ee, rotación óptica $[\alpha]_D^{20} = -10.1$ (MeOH, c=1).

Paso 4: 5-((2*R*,4*S*)-2-(3,5-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-2-(3,5-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.645 g, 1.83 mmol) en ácido bromhídrico (al 33% en ácido acético, 14.43 mL, 82.38 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx III, fase móvil: gradiente de 5-95% de MeCN en NH_3

al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*S*)-2-(3,5-difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona (153 mg, 28%). ^{1}H RMN (600 MHz, DMSO) δ 1.01 - 1.11 (m, 1H), 1.26 - 1.38 (m, 1H), 1.68 - 1.78 (m, 2H), 2.41 - 2.77 (m, 5H), 2.91 - 2.99 (m, 1H), 5.67 (s, 1H), 6.92 (d, 2H), 6.99 (s, 1H). HRMS calculado para $[C_{15}H_{16}F_2N_2O_2+H]^+$: 295.1258. Experimental: 295.1249.

Ejemplo 131

5-((2*S*,4*R*)-2-(3,5-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*S*,4*R*)-2-(3,5-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.789 g, 2.24 mmol) (del paso 3 del ejemplo 130) en ácido bromhídrico (al 33% en ácido acético, 17.65 mL, 100.77 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx III, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*S*,4*R*)-2-(3,5-difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona (123 mg, 19%). ^{1}H RMN (600 MHz, DMSO) δ 1.07 (c, 1H), 1.33 (dc, 1H), 1.71 - 1.78 (m, 2H), 2.49 - 2.56 (m, 1H), 2.57 - 2.71 (m, 3H), 2.72 - 2.78 (m, 1H), 2.94 - 2.99 (m, 1H), 5.67 (s, 1H), 6.89 - 6.94 (m, 2H), 7.00 (tt, 1H). HRMS calculado para $[C_{15}H_{16}F_2N_2O_2+H]^+$: 295.1258. Experimental: 295.1248.

Ejemplo 132

5-((2*S*,4*S*)-2-(3,5-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(3,5-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *trans*-2-(3',5-difluorobencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (0.927 g, 2.42 mmol) (del paso 1 del ejemplo 130) en MeOH (8 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (0.097 g, 2.42 mmol) disuelto en agua (0.800 mL) en 7 min. Después de agitar durante 20 min, se añadió hidroxilamina

(al 50% en peso en agua, 0.148 mL, 2.42 mmol) en 4.5 minutos y la solución se agitó durante 3.5 horas a -40 °C. Posteriormente, la mezcla de reacción se vertió rápidamente en una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (12.45 mL, 74.71 mmol) y se continuó agitando la mezcla a 80 °C durante 20 min. El disolvente se evaporó, y la mezcla cruda se redisolvió en DCM y se lavó con agua. La fase orgánica se secó y se concentró. El compuesto se purificó mediante HPLC preparativa en una columna XBridge C18 (10 µm 250x50 DI en mm) utilizando un gradiente de 0-25% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 20 minutos con un flujo de 100 mL/min. Se aisló *trans*-2-(3,5-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.648 g, 76%) como un sólido blanco. ^{1}H RMN (400 MHz, CD_3OD) δ 1.45 - 2.12 (m, 4H), 2.80 - 3.35 (m, 4H), 3.35 - 3.70 (m, 3H), 4.12 (s a, 1H), 4.62 (s a, 1H), 5.71 (s, 1H), 6.77 (t, 1H), 6.87 (s a, 2H). MS m/z 353 $(M+H)^+$.

Paso 2: (2*S*,4*R*)-2-(3,5-Difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo y (2*R*,4*R*)-2-(3,5-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El *trans*-2-(3,5-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.648 g, 1.84 mmol) se sometió a HPLC preparativa quiral (columna: Chiralpak AD (250x20), tamaño de partícula: 5 µm, fase móvil: 70/30 de heptano/EtOH, velocidad de flujo: 18 mL/min) para proporcionar (2*S*,4*S*)-2-(3,5-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (249 mg, 38%), pureza quiral: 99.9% de ee, rotación óptica $[\alpha]_D^{20} = +27.1$ (acetonitrilo, c=1) y (2*R*,4*R*)-2-(3,5-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (244 mg, 37%), pureza quiral: 99.9% de ee, rotación óptica $[\alpha]_D^{20} = -26.4$ (acetonitrilo, c=1).

Paso 3: 5-((2*S*,4*S*)-2-(3,5-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*S*,4*S*)-2-(3,5-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.249 g, 0.71 mmol) en ácido bromhídrico (al 33% en ácido acético, 5.57 mL, 31.80 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*S*,4*S*)-2-(3,5-difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona (34 mg, 16%). ^{1}H RMN (400 MHz, CD_3OD) δ 1.70 - 2.16 (m, 4H), 2.84 - 3.43 (m, 6H), 5.57 (s, 1H), 6.81 - 7.02 (m, 3H). HRMS calculado para $[C_{15}H_{16}F_2N_2O_2+H]^+$: 295.1258. Experimental: 295.1254.

Ejemplo 133

5-((2*R*,4*R*)-2-(3,5-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*R*)-2-(3,5-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.244 g, 0.69 mmol) en ácido bromhídrico (al 33% en ácido acético, 5.46 mL, 31.16 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*R*)-2-(3,5-difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona (51 mg, 25%). ^{1}H RMN (600 MHz, DMSO) δ 1.44 - 1.51 (m, 1H), 1.65 - 1.80 (m, 3H), 2.52 - 2.60 (m, 1H), 2.65 - 2.70 (m, 2H), 2.76 - 2.83 (m, 1H), 2.86 - 2.94 (m, 1H), 3.09 - 3.14 (m, 1H), 5.74 (s, 1H), 6.90 - 6.95 (m, 2H), 7.00 (tt, 1H). HRMS calculado para $[C_{15}H_{16}F_2N_2O_2+H]^+$: 295.1258. Experimental: 295.1276.

Ejemplo 134

5-((2*R*,4*S*)-2-(2,4-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(2,4-difluorobencil)-4-(3-etoxi-3-

oxopropanoil)piperidin-1-carboxilato de metilo y *cis*-2-(2,4-difluorobencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo

Se disolvieron cloruro de magnesio (4.55 g, 47.75 mmol) y 3-etoxi-3-oxopropanoato de potasio (8 g, 47.00 mmol) en metil-THF (100 mL) en atmósfera de nitrógeno y la suspensión resultante se agitó a 50 °C mientras se agitaba con un imán muy grande durante 6 h 30 min, posteriormente se enfrió hasta temperatura ambiente (matraz 1). Se añadió di(1*H*-imidazol-1-il)metanona (5.81 g, 35.81 mmol) a una suspensión del ácido 2-(2,4-difluorobencil)-1-(metoxicarbonil)piperidin-4-carboxílico (7.48 g, 23.88 mmol) (compuesto de referencia 57) en metil-THF (100 mL) en atmósfera de nitrógeno. La mezcla resultante se agitó a temperatura ambiente durante 1 h 20 min (matraz 2). El contenido del matraz 2 se transfirió al matraz 1 con una aguja de transferencia. Se lavó con metil-THF (30 mL). La suspensión resultante se agitó a temperatura ambiente durante 16 h. Se añadió HCl 3.8 M (ca. 200 mL) y la mezcla bifásica resultante se agitó vigorosamente durante 30 min. Se añadieron agua y MTBE y las fases se separaron. La fase orgánica se lavó con agua y $NaHCO_3$ sat. y agua, a continuación se secó con $MgSO_4$ y se evaporó. El residuo se purificó en una columna Biotage (columna Biotage® con 340 g de KP-SIL, 1 VC de 20% de EtOAc en heptanos, seguido de 20% => 60% en 7 VC). Se aislaron *trans*-2-(2,4-difluorobencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (1.18 g, 13%) y *cis*-2-(2,4-difluorobencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (4.17 g, 45%) como aceites amarillos. Isómero *cis*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.20 - 1.32 (m, 3H), 1.59 - 1.99 (m, 4H), 2.66 - 3.12 (m, 4H), 3.48 (s, 2H), 3.55 (s, 3H), 3.89 - 3.98 (m, 1H), 4.07 - 4.29 (m, 3H), 6.71 - 6.83 (m, 2H), 7.05 - 7.17 (m, 1H). MS m/z 384 $(M+H)^+$. Isómero *trans*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.19 - 1.35 (m, 3H), 1.42 - 2.02 (m, 4H), 2.65 - 3.11 (m, 4H), 3.38 - 3.75 (m, 5H), 4.02 - 4.34 (m, 3H), 4.45 - 4.70 (m, 1H), 6.73 - 6.89 (m, 2H), 7.03 - 7.34 (m, 1H). MS m/z 384 $(M+H)^+$.

Paso 2: *Cis*-2-(2,4-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *cis*-2-(2,4-difluorobencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (2.46 g, 6.42 mmol) en MeOH (20 mL) y se enfrió hasta -40 °C. Se añadió hidróxido sódico (0.257 g, 6.42 mmol) disuleto en agua (2 mL) en 5 min y la solución resultante se agitó a -40 °C durante 20 min. Posteriormente, se añadió hidroxilamina (al 50% en peso en agua, 0.4 mL, 6.53 mmol) en 1 min y se continuó agitando a -40 °C durante 1 h 15 min. La mezcla de reacción se transfirió posteriormente sobre una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (30 mL, 180.00 mmol) y la mezcla se continuó agitando a 80 °C durante 35 min. A continuación, se enfrió hasta temperatura ambiente. Se evaporó el metanol y después se añadió agua. Se extrajo tres veces con DCM. Las capas orgánicas combinadas se secaron con $MgSO_4$ y se evaporaron. El residuo se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x50 DI en mm) utilizando un gradiente de 15-60% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/ácido acético en 30 minutos con un flujo de 100 mL/min. Se aisló *cis*-2-(2,4-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.62 g, 72%) como una espuma incolora. ^{1}H RMN (400 MHz, CD_3OD) δ 1.90 - 2.10 (m, 4H), 2.65 - 2.80 (m, 2H), 3.04 (q, 1H), 3.19 - 3.34 (m, 1H), 3.44 (s, 3H), 3.94 (ddd, 1H), 4.32 - 4.44 (m, 1H), 5.85 (s, 1H), 6.78 - 6.90 (m, 2H), 7.09 - 7.20 (m, 1H). MS m/z 353 $(M+H)^+$.

Paso 3: (2*R*,4*S*)-2-(2,4-Difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo y (2*S*,4*R*)-2-(2,4-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El *cis*-2-(2,4-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.62 g, 4.6 mmol) se sometió a HPLC preparativa quiral (columna: Chiralpak AD (250x20), tamaño de partícula: 5 µm, fase móvil:

90/10/0.2 de heptano/EtOH/AF, velocidad de flujo: 18 mL/min) para proporcionar (2*R*,4*S*)-2-(2,4-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (799 mg, 49%), pureza quiral: 99.9% de ee, rotación óptica $[\alpha]_D^{20} = -4.0$ (acetonitrilo, c=1) y (2*S*,4*R*)-2-(2,4-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (734 mg, 45%), pureza quiral: 99.5% de ee, rotación óptica $[\alpha]_D^{20} = +4.5$ (acetonitrilo, c=1).

Paso 4: 5-((2*R*,4*S*)-2-(2,4-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-(2,4-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (399 mg, 1.13 mmol) en ácido bromhídrico (al 33% en ácido acético, 8.2 mL, 46.87 mmol) y se agitó a temperatura ambiente durante 16 h. El disolvente se evaporó al vacío y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx III, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*S*)-2-(2,4-difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona (146 mg, 44%). ^{1}H RMN (400 MHz, CD_3OD) δ 1.43 (c, 1H), 1.67 (dc, 1H), 1.99 - 2.12 (m, 2H), 2.79 - 2.97 (m, 4H), 3.14 - 3.24 (m, 1H), 3.27 - 3.35 (m, 1H), 5.52 (s, 1H), 6.91 - 7.02 (m, 2H), 7.27 - 7.36 (m, 1H). HRMS calculado para $[C_{15}H_{16}F_2N_2O_2+H]^+$: 295.1258. Experimental: 295.1252.

Ejemplo 135

5-((2*S*,4*R*)-2-(2,4-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*S*,4*R*)-2-(2,4-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (367 mg, 1.04 mmol) (del paso 3 del ejemplo 134) en ácido bromhídrico (al 33% en ácido acético, 8.2 mL, 46.87 mmol) y se agitó a temperatura ambiente durante 16 h. El disolvente se evaporó al vacío y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx III, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm

OBD 19*150 mm) para proporcionar 5-((2*S*,4*R*)-2-(2,4-difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona (144 mg, 47%). ^{1}H RMN (400 MHz, CD_3OD) δ 1.43 (c, 1H), 1.67 (dc, 1H), 2.01 - 2.11 (m, 2H), 2.79 - 2.96 (m, 4H), 3.14 - 3.23 (m, 1H), 3.27 - 3.35 (m, 1H), 5.52 (s, 1H), 6.92 - 7.01 (m, 2H), 7.28 - 7.35 (m, 1H). HRMS calculado para $[C_{15}H_{16}F_2N_2O_2+H]^+$: 295.1258. Experimental: 295.1259.

Ejemplo 136

Paso 1: *Trans*-2-(2,4-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *trans*-2-(2,4-difluorobencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (1.18 g, 3.08 mmol) (del paso 1 del ejemplo 134) en MeOH (15 mL) y se enfrió hasta -40 °C. Se añadió hidróxido sódico (0.123 g, 3.08 mmol) disuleto en agua (1.7 mL) en 1 min y la solución resultante se agitó a -40 °C durante 20 min. Posteriormente, se añadió hidroxilamina (al 50% en peso en agua, 0.2 mL, 3.26 mmol) en 1 min y se continuó agitando a -40 °C durante 2 h. La mezcla de reacción se transfirió posteriormente sobre una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (30 mL, 180.00 mmol) y la mezcla se continuó agitando a 80 °C durante 1 h. A continuación, se enfrió hasta temperatura ambiente. Se evaporó el metanol y después se añadió agua. Se extrajo tres veces con DCM. Las capas orgánicas combinadas se secaron con $MgSO_4$ y se evaporaron. Se aisló *trans*-2-(2,4-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo crudo (1.1 g, 101%) como una espuma de color naranja pálido. ^{1}H RMN (500 MHz, $CDCl_3$) δ 1.43 - 2.15 (m, 4H), 2.66 - 3.23 (m, 4H), 3.39 - 3.79 (m, 3H), 4.04 - 4.41 (m, 1H), 4.45 - 4.78 (m, 1H), 5.67 (s, 1H), 6.73 - 6.90 (m, 2H), 7.03 - 7.37 (m, 1H). MS m/z 353 $(M+H)^+$.

Paso 2: 5-(*Trans*-2-(2,4-difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió *trans*-2-(2,4-difluorobencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.25 g, 0.71 mmol) en ácido bromhídrico (al 33% en ácido acético, 6.21

mL, 35.48 mmol) y se agitó a temperatura ambiente durante 16 h. Los disolventes se evaporaron y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-(*trans*-2-(2,4-difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona (94.6 mg, 45%). ^{1}H RMN (600 MHz, DMSO) δ 1.43 - 1.51 (m, 1H), 1.63 - 1.78 (m, 3H), 2.52 - 2.60 (m, 1H), 2.65 (d, 2H), 2.76 - 2.87 (m, 2H), 3.08 - 3.13 (m, 1H), 5.67 (s, 1H), 6.98 (td, 1H), 7.12 (td, 1H), 7.27 - 7.34 (m, 1H). HRMS calculado para $[C_{15}H_{16}F_2N_2O_2+H]^+$: 295.1258. Experimental: 295.1265.

Ejemplo 137

5-((2*R*,4*S*)-2-(3-Fluoro-5-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-4-(3-etoxi-3-oxopropanoil)-2-(3-fluoro-5-(trifluorometil)bencil)piperidin-1-carboxilato de metilo y *cis*-4-(3-etoxi-3-oxopropanoil)-2-(3-fluoro-5-(trifluorometil)bencil)piperidin-1-carboxilato de metilo

Se suspendieron cloruro de magnesio (2.3 g, 24.16 mmol) y 3-etoxi-3-oxopropanoato de potasio (4 g, 23.50 mmol) en metil-THF (70 mL) en atmósfera de nitrógeno y la suspensión resultante se agitó a 50 °C mientras se agitaba con un imán muy grande durante 18 h, posteriormente se enfrió hasta temperatura ambiente (matraz 1). Se añadió di(1*H*-imidazol-1-il)metanona (3.36 g, 20.72 mmol) a una suspensión del ácido 2-(3-fluoro-5-(trifluorometil)bencil)-1-(metoxicarbonil)piperidin-4-carboxílico (4.58 g, 12.61 mmol) (compuesto de referencia 58) en metil-THF (70.0 mL) en atmósfera de nitrógeno. La mezcla resultante se agitó a temperatura ambiente durante 2 h (matraz 2). El contenido del matraz 2 se transfirió al matraz 1 con una aguja de transferencia. Se lavó con metil-THF (30 mL). La suspensión resultante se agitó a temperatura ambiente durante 72 h. Se añadió HCl 3.8 M (ca. 200 mL) y la mezcla bifásica resultante se agitó vigorosamente durante 30 min. Se añadió MTBE y las fases se separaron. La fase orgánica se lavó con agua y $NaHCO_3$ sat. y agua, a continuación se secó con $MgSO_4$ y

se evaporó. El residuo se purificó en una columna Biotage (columna Biotage® con 340 g de KP-SIL, 1 VC de 20% de EtOAc en heptanos, seguido de 20% => 60% en 7 VC). Se aislaron *trans*-4-(3-etoxi-3-oxopropanoil)-2-(3-fluoro-5-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (758 mg, 14%) y *cis*-4-(3-etoxi-3-oxopropanoil)-2-(3-fluoro-5-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (2.52 g, 46%). Isómero *cis*: ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.20 - 1.28 (m, 3H), 1.64 - 1.95 (m, 4H), 2.68 - 2.81 (m, 2H), 2.95 (dd, 1H), 3.02 (ddd, 1H), 3.45 (s, 2H), 3.59 (s, 3H), 3.84 - 3.96 (m, 1H), 4.06 - 4.23 (m, 3H), 7.04 - 7.11 (m, 1H), 7.15 (d, 1H), 7.19 - 7.24 (m, 1H). MS m/z 434 $(M+H)^+$. Isómero *trans*: ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.20 - 1.29 (m, 3H), 1.43 - 1.99 (m, 4H), 2.75 - 2.89 (m, 1H), 2.89 - 3.04 (m, 3H), 3.36 - 3.72 (m, 5H), 4.03 - 4.33 (m, 3H), 4.49 - 4.72 (m, 1H), 6.98 - 7.20 (m, 2H), 7.20 - 7.28 (m, 1H).

Paso 2: *Cis*-2-(3-fluoro-5-(trifluorometil)bencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *cis*-4-(3-etoxi-3-oxopropanoil)-2-(3-fluoro-5--(trifluorometil)bencil)piperidin-1-carboxilato de metilo (2.52 g, 5.81 mmol) en MeOH (20 mL) y se enfrió hasta -40 °C. Se añadió hidróxido sódico (246 g, 6.15 mmol) disuleto en agua (2.2 mL) en 1 min y la solución resultante se agitó a -40 °C durante 20 min. Posteriormente, se añadió hidroxilamina (al 50% en peso en agua, 0.38 mL, 6.20 mmol) en 1 min y se continuó agitando a -40 °C durante 2 h 20 min. La mezcla de reacción se vertió posteriormente sobre una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (40 mL, 240.00 mmol) y la mezcla se continuó agitando a 80 °C durante 1 h. A continuación se enfrió hasta temperatura ambiente. Se evaporó el metanol y después se añadió agua. Se extrajo tres veces con DCM. Las capas orgánicas combinadas se secaron con $MgSO_4$ y se evaporaron. El compuesto se purificó mediante HPLC preparativa en 3 inyecciones en una columna XBridge C18 (10 µm 250x50 DI en mm) utilizando un gradiente de 0-35% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 25 minutos con un flujo de 100

mL/min. Se aisló *cis*-2-(3-fluoro-5-(trifluorometil)bencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.52 g, 65%) como una espuma incolora. ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.87 - 2.10 (m, 4H), 2.61 - 2.67 (m, 1H), 2.80 - 2.87 (m, 1H), 2.97 - 3.04 (m, 1H), 3.13 - 3.21 (m, 1H), 3.60 (s, 3H), 3.96 - 4.04 (m, 1H), 4.26 - 4.32 (m, 1H), 5.74 (s, 1H), 7.00 (d, 1H), 7.11 - 7.16 (m, 2H). MS m/z 403 $(M+H)^+$.

Paso 3: (2*R*,4*S*)-2-(3-Fluoro-5-(trifluorometil)bencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo y (2*S*,4*R*)-2-(3-fluoro-5-(trifluorometil)bencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El *cis*-2-(3-fluoro-5-(trifluorometil)bencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.47 g, 3.66 mmol) se sometió a HPLC preparativa quiral (columna: Chiralcel OJ (250x20), tamaño de partícula: 5 µm, fase móvil: Heptano/EtOH 90/10, velocidad de flujo: 18 mL/min) para proporcionar (2R,4S)-2-(3-fluoro-5-(trifluorometil)bencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (703 mg, 47.8%), pureza quiral: 99.3% de ee, rotación óptica $[\alpha]_D^{20} = +5.5$ (acetonitrilo, c=1) y (2*S*,4*R*)-2-(3-fluoro-5-(trifluorometil)bencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (675 mg, 45.9%), pureza quiral: 99.7% de ee, rotación óptica $[\alpha]_D^{20} = -5.1$ (acetonitrilo, c=1).

Paso 4: 5-((2*R*,4*S*)-2-(3-Fluoro-5-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-2-(3-fluoro-5-(trifluorometil)bencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.703 g, 1.75 mmol) en ácido bromhídrico (al 33% en AcOH, 5 mL, 71.37 mmol) y se agitó a temperatura ambiente durante toda la noche. Los disolventes se evaporaron y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente 5-95% de MeCN, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*S*)-2-(3-fluoro-5-(trifluorometil)bencil)piperidin-4-

il)isoxazol-3(2*H*)-ona (375 mg, 62%). ^{1}H RMN (600 MHz, DMSO) δ 1.08 (c, 1H), 1.31 (dc, 1H), 1.71 - 1.80 (m, 2H), 2.48 - 2.54 (m, 1H), 2.63 - 2.80 (m, 4H), 2.92 - 2.99 (m, 1H), 5.65 (s, 1H), 7.37 - 7.46 (m, 3H). HRMS calculado para $[C_{16}H_{16}F_4N_2O_2+H]^+$: 345.1226. Experimental: 345.1228.

Ejemplo 138

5-((2*S*,4*R*)-2-(3-Fluoro-5-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*S*,4*R*)-2-(3-fluoro-5-(trifluorometil)bencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.675 g, 1.68 mmol) (del paso 3 del ejemplo 137) en ácido bromhídrico (al 33% en AcOH, 5 mL, 71.37 mmol) y se agitó a temperatura ambiente durante toda la noche. Los disolventes se evaporaron y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente 5-95% de MeCN, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*S*,4*R*)-2-(3-fluoro-5-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona (443 mg, 77%). ^{1}H RMN (600 MHz, DMSO) δ 1.08 (c, 1H), 1.31 (cd, 1H), 1.75 (t, 2H), 2.48 - 2.54 (m, 1H), 2.64 - 2.79 (m, 4H), 2.96 (d, 1H), 5.65 (s, 1H), 7.38 - 7.46 (m, 3H). HRMS calculado para $[C_{16}H_{16}F_4N_2O_2+H]^+$: 345.1226. Experimental: 345.1212.

Ejemplo 139

5-(*Trans*-2-(3-fluoro-5-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(3-fluoro-5-(trifluorometil)bencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *trans*-4-(3-etoxi-3-oxopropanoil)-2-(3-fluoro-5--(trifluorometil)bencil)piperidin-1-carboxilato de metilo (0.75 g, 1.73 mmol) (del paso 1 del ejemplo 137) en MeOH (15 mL) y se enfrió hasta -40 °C. Se añadió hidróxido sódico (0.073 g, 1.82 mmol) disuleto en agua (1 mL) en 1 min y la solución resultante se agitó a -40 °C durante 20 min. Posteriormente, se añadió hidroxilamina (al 50% en peso en agua, 0.115 mL, 1.88 mmol) en 1 min y se continuó agitando a -40 °C durante 2 h 20 min. La mezcla de reacción se vertió posteriormente sobre una

solución calentada previamente (80 °C) de ácido clorhídrico 6 M (30 mL, 180.00 mmol) y la mezcla se continuó agitando a 80 °C durante 1 h. A continuación se enfrió hasta temperatura ambiente. Se evaporó el metanol y después se añadió agua. Se extrajo tres veces con DCM. Las capas orgánicas combinadas se secaron con $MgSO_4$ y se evaporaron. Se aisló *trans*-2-(3-fluoro-5-(trifluorometil)bencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (658 mg, 95%) como un sólido blanquecino. MS m/z 403 $(M+H)^+$.

Paso 2: 5-(*Trans*-2-(3-fluoro-5-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió *trans*-2-(3-fluoro-5-(trifluorometil)bencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.255 g, 0.63 mmol) en ácido bromhídrico (al 33% en ácido acético, 5 mL, 71.37 mmol) y se agitó a temperatura ambiente durante una semana. Los disolventes se evaporaron y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx III, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-(*trans*-2-(3-fluoro-5-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona (172 mg, 79%). ^1H RMN (600 MHz, DMSO) δ 1.43 - 1.51 (m, 1H), 1.62 - 1.80 (m, 3H), 2.51 - 2.58 (m, 1H), 2.71 - 2.82 (m, 3H), 2.86 - 2.94 (m, 1H), 3.07 - 3.14 (m, 1H), 5.72 (s, 1H), 7.37 - 7.46 (m, 3H). HRMS calculado para $[C_{16}H_{16}F_4N_2O_2+H]^+$: 345.1226. Experimental: 345.1241.

Ejemplo 140

5-((2*R*,4*S*)-2-(3-Fluoro-4-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-4-(3-etoxi-3-oxopropanoil)-2-(3-fluoro-4-(trifluorometil)bencil)piperidin-1-carboxilato de metilo y *cis*-4-(3-etoxi-3-oxopropanoil)-2-(3-fluoro-4-(trifluorometil)bencil)piperidin-1-carboxilato de metilo

Se suspendieron cloruro de magnesio (3.25 g, 34.13 mmol) y 3-etoxi-3-oxopropanoato de potasio (5.82 g, 34.19 mmol) en atmósfera de nitrógeno en metil-THF (100 mL) y se agitó con un

imán muy grande a 50 °C durante 18 h, posteriormente se enfrió hasta temperatura ambiente (matraz 1). Se añadió di(1*H*-imidazol-1-il)metanona (4.77 g, 29.42 mmol) a una suspensión del ácido 2-(3-fluoro-4-(trifluorometil)bencil)-1-(metoxicarbonil)piperidin-4-carboxílico (6.56 g, 18.06 mmol) (compuesto de referencia 59) en metil-THF (100 mL) en atmósfera de nitrógeno. La mezcla resultante se agitó a temperatura ambiente durante 2 h (matraz 2). El contenido del matraz 2 se transfirió al matraz 1 con una aguja de transferencia. Se lavó con metil-THF (30 mL). La suspensión resultante se agitó a temperatura ambiente durante 18 h. Se añadió HCl 3.8 M (ca. 200 mL) y la mezcla bifásica resultante se agitó vigorosamente durante 30 min. Se añadió MTBE y las fases se separaron. La fase orgánica se lavó con agua, $NaHCO_3$ sat. y agua, a continuación se secó con $MgSO_4$ y se evaporó. El residuo se purificó en una columna Biotage (columna Biotage® con 340 g de KP-SIL, 1 VC de 20% de EtOAc en heptanos, seguido de 20% => 60% en 7 VC). Se aislaron *trans*-4-(3-etoxi-3-oxopropanoil)-2-(3-fluoro-4-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (0.794 g, 10%) y *cis*-4-(3-etoxi-3-oxopropanoil)-2-(3-fluoro-4-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (3.57 g, 45%) como aceites de color amarillo pálido. Isómero *cis*: MS m/z 434 $(M+H)^+$. Isómero *trans*: MS m/z 434 $(M+H)^+$.

Paso 2: <u>*Cis*-2-(3-fluoro-4-(trifluorometil)bencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo</u>

Se disolvió *cis*-4-(3-etoxi-3-oxopropanoil)-2-(3-fluoro-4-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (2.033 g, 4.69 mmol) en MeOH (20 mL) y se enfrió hasta -40 °C. Se añadió hidróxido sódico (0.188 g, 4.69 mmol) disuleto en agua (2.4 mL) en 1 min y la solución resultante se agitó a -40 °C durante 20 min. Posteriormente, se añadió hidroxilamina (al 50% en peso en agua, 0.3 mL, 4.90 mmol) en 1 min y se continuó agitando a -40 °C durante 2 h 20 min. La mezcla de reacción se transfirió posteriormente sobre una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (40 mL, 240.00

mmol) y la mezcla se continuó agitando a 80 °C durante 1 h. A continuación, se enfrió hasta temperatura ambiente. Se evaporó el metanol y después se añadió agua. Se extrajo tres veces con DCM. Las capas orgánicas combinadas se secaron con $MgSO_4$ y se evaporaron. El producto fue un aceite de color amarillo pálido. El compuesto se purificó mediante HPLC preparativa en 3 inyecciones en una columna XBridge C18 (10 µm 250x50 DI en mm) utilizando un gradiente de 0-35% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 25 minutos con un flujo de 100 mL/min. Se aisló *cis*-2-(3-fluoro-4-(trifluorometil)bencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.32 g, 70%) como una espuma incolora. ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.84 - 1.99 (m, 3H), 1.99 - 2.10 (m, 1H), 2.62 (dd, 1H), 2.82 (dd, 1H), 2.92 - 3.06 (m, 1H), 3.10 - 3.19 (m, 1H), 3.59 (s, 3H), 3.93 - 4.03 (m, 1H), 4.19 - 4.34 (m, 1H), 5.73 (s, 1H), 6.91 - 6.99 (m, 2H), 7.46 (t, 1H). MS m/z 403 $(M+H)^+$.

Paso 3: (2*R*,4*S*)-2-(3-Fluoro-4-(trifluorometil)bencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo y (2*S*,4*R*)-2-(3-fluoro-4-(trifluorometil)bencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El *cis*-2-(3-fluoro-4-(trifluorometil)bencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.32 g, 3.28 mmol) se sometió a HPLC preparativa quiral (columna: Chiralpak AD (250x20), tamaño de partícula: 5 µm, fase móvil: Heptano/EtOH 85/15, velocidad de flujo: 18 mL/min) para proporcionar (2*R*,4*S*)-2-(3-fluoro-4-(trifluorometil)bencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (594 mg, 46%), pureza quiral: 99.5% de ee, rotación óptica $[\alpha]_D^{20} = +9.1$ (acetonitrilo, c=1) y (2*S*,4*R*)-2-(3-fluoro-4-(trifluorometil)bencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (589 mg, 45%), pureza quiral: 99.2% de ee, rotación óptica $[\alpha]_D^{20} = -8.8$ (acetonitrilo, c=1).

Paso 4: 5-((2*R*,4*S*)-2-(3-Fluoro-4-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-2-(3-fluoro-4-(trifluorometil)bencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (594 mg, 1.48 mmol) en ácido bromhídrico (al 33% en ácido acético, 10 mL, 57.10 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx III, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*S*)-2-(3-fluoro-4-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona (338 mg, 66%). ^{1}H RMN (600 MHz, DMSO) δ 1.08 (c, 1H), 1.32 (cd, 1H), 1.71 - 1.79 (m, 2H), 2.45 - 2.72 (m, 4H), 2.72 - 2.80 (m, 1H), 2.96 (d, 1H), 5.68 (s, 1H), 7.23 (d, 1H), 7.35 (d, 1H), 7.65 (t, 1H). HRMS calculado para $[C_{16}H_{16}F_4N_2O_2+H]^+$: 345.1226. Experimental: 345.1232.

Ejemplo 141

5-((2*S*,4*R*)-2-(3-Fluoro-4-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*S*,4*R*)-2-(3-fluoro-4-(trifluorometil)bencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (589 mg, 1.46 mmol) (del paso 3 del ejemplo 140) en ácido bromhídrico (al 33% en ácido acético, 10 mL, 57.10 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx III, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*S*,4*R*)-2-(3-fluoro-4-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona (329 mg, 65%). ^{1}H RMN (600 MHz, CD_3OD) δ 1.66 (c, 1H), 1.81 (dc, 1H), 2.17 - 2.25 (m, 2H), 3.00 - 3.15 (m, 4H), 3.47 - 3.52 (m, 1H), 3.56 - 3.62 (m, 1H), 5.76 (s, 1H), 7.28 (dd, 2H), 7.67 (t, 1H). HRMS calculado para $[C_{16}H_{16}F_4N_2O_2+H]^+$: 345.1226. Experimental: 345.1225.

Ejemplo 142

5-(*Trans*-2-(3-fluoro-4-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(3-fluoro-4-(trifluorometil)bencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *trans*-4-(3-etoxi-3-oxopropanoil)-2-(3-fluoro-4-(trifluorometil)bencil)piperidin-1-carboxilato de metilo (0.781 g, 1.80 mmol) (del paso 1 del ejemplo 140) en MeOH (15 mL) y se enfrió hasta -40 °C. Se añadió hidróxido sódico (0.072 g, 1.80 mmol) disuleto en agua (1 mL) en 1 min y la solución resultante se agitó a -40 °C durante 20 min. Posteriormente, se añadió hidroxilamina (al 50% en peso en agua, 0.12 mL, 1.96 mmol) en 1 min y se continuó agitando a -40 °C durante 2 h 15 min. La mezcla de reacción se vertió posteriormente sobre una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (30 mL, 180.00 mmol) y la mezcla se continuó agitando a 80 °C durante 1 h. A continuación se enfrió hasta temperatura ambiente. Se evaporó el metanol y después se añadió agua. Se extrajo tres veces con DCM. Las capas orgánicas combinadas se secaron con $MgSO_4$ y se evaporaron. Se aisló *trans*-2-(3-fluoro-4-(trifluorometil)bencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo crudo (678 mg, 94%) como una espuma blanquecina. MS m/z 403 $(M+H)^+$.

Paso 2: 5-(*Trans*-2-(3-fluoro-4-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió *trans*-2-(3-fluoro-4-(trifluorometil)bencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.224 g, 0.56 mmol) en ácido bromhídrico (al 33% en ácido acético, 5 mL, 71.37 mmol) y se agitó a temperatura ambiente durante una semana. Los disolventes se evaporaron y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx III, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-(*trans*-2-(3-fluoro-4-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona (160 mg, 83%). ^1H RMN (600 MHz, DMSO) δ 1.48 (ddd, 1H), 1.63 - 1.81 (m, 3H), 2.51 - 2.59 (m, 1H), 2.70 - 2.82 (m, 3H), 2.88 - 2.95 (m, 1H), 3.07 - 3.14 (m, 1H), 5.72 (s, 1H), 7.21 (d, 1H), 7.33

(d, 1H), 7.63 (t, 1H). HRMS calculado para $[C_{16}H_{16}F_4N_2O_2+H]^+$: 345.1226. Experimental: 345.1241.

Ejemplo 143

5-((2*R*,4*S*)-2-(3,4,5-Trifluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-4-(3-etoxy-3-oxopropanoil)-2-(3,4,5-trifluorobencil)piperidin-1-carboxilato de metilo y *cis*-4-(3-etoxi-3-oxopropanoil)-2-(3,4,5-trifluorobencil)piperidin-1-carboxilato de metilo

Se disolvió el ácido 1-(metoxicarbonil)-2-(3,4,5-trifluorobencil)piperidin-4-carboxílico (3.42 g, 10.32 mmol) (compuesto de referencia 60) en metil-THF (60 mL) y se añadió di(1*H*-imidazol-1-il)metanona (2.51 g, 15.49 mmol). La suspensión se agitó a temperatura ambiente en atmósfera de nitrógeno durante 6 h (matraz 1). En otro matraz, se suspendió 3-etoxi-3-oxopropanoato de potasio (3.16 g, 18.58 mmol) en metil-THF (60.0 mL) y se añadió cloruro de magnesio (1.769 g, 18.58 mmol). La suspensión se agitó en atmósfera de nitrógeno durante 6 h (matraz 2). A continuación, la suspensión blanca del matraz 2 se añadió a la suspensión marrón del matraz 1. La suspensión resultante se agitó a temperatura ambiente durante 18 h. La mezcla se acidificó hasta pH 1 con HCl 3 M. Se añadieron MTBE (250 mL) y agua (250 mL), se agitó y se separaron las fases. La fase orgánica se lavó con agua (250 mL), $NaHCO_3$ sat. (250 mL) y salmuera (250 mL), se secó con Na_2SO_4, se filtró y se evaporó al vacío. El residuo se purificó mediante cromatografía flash automatizada en una columna Biotage® con 100 g de KP-SIL. Se utilizó como fase móvil un gradiente de 20% de EtOAc en heptano en 2 VC y a continuación de 20% a 60% de EtOAc en heptano en 8 VC. Se aislaron *trans*-4-(3-etoxi-3-oxopropanoil)-2-(3,4,5-(trifluorobencil)piperidin-1-carboxilato de metilo (0.309 g, 7.46%) y *cis*-4-(3-etoxi-3-oxopropanoil)-2-(3,4,5-(trifluorobencil)piperidin-1-carboxilato de metilo (1.967 g, 47.5%). Isómero *cis*: ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.19 - 1.30 (m, 3H), 1.62 - 1.96 (m, 4H), 2.61 - 2.68 (m, 1H), 2.68 - 2.76 (m, 1H), 2.80 - 2.87 (m, 1H), 2.96 - 3.04

(m, 1H), 3.46 (s, 2H), 3.65 (s, 3H), 3.83 - 3.94 (m, 1H), 4.09 - 4.20 (m, 3H), 6.76 - 6.84 (m, 2H). MS m/z 402 $(M+H)^+$. Isómero *trans*: MS m/z 402 $(M+H)^+$.

Paso 2: *Cis*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3,4,5-(trifluorobencil)piperidin-1-carboxilato de metilo

Se disolvió *cis*-4-(3-etoxi-3-oxopropanoil)-2-(3,4,5-(trifluorobencil)piperidin-1-carboxilato de metilo (1.967 g, 4.90 mmol) en MeOH (20 mL) y se enfrió hasta 40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (1.290 mL, 4.90 mmol) en agua (2.000 mL) y la mezcla se agitó a -40 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.300 mL, 4.90 mmol) y se continuó agitando a -40 °C durante 3.5 h. La mezcla de reacción se transfirió posteriormente a una solución calentada previamente a 80 °C de ácido clorhídrico 6 M (25.3 mL, 151.92 mmol) y se continuó calentando durante 20 min. A continuación se evaporó el disolvente. Se añadieron DCM (150 mL) y agua (150 mL), se agitó y se separaron las fases. La fase orgánica se secó con un separador de fases y se evaporó al vacío. El compuesto se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x50 DI en mm) utilizando un gradiente de 10-55% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/AcOH en 30 minutos con un flujo de 100 mL/min. Se aisló *cis*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3,4,5-(trifluorobencil)piperidin-1-carboxilato de metilo (1.354 g, 74.6%) como un sólido blanco. ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.84 - 2.10 (m, 4H), 2.48 - 2.54 (m, 1H), 2.69 - 2.76 (m, 1H), 2.96 - 3.03 (m, 1H), 3.10 - 3.18 (m, 1H), 3.64 (s, 3H), 3.94 - 4.01 (m, 1H), 4.18 - 4.25 (m, 1H), 5.73 (s, 1H), 6.69 - 6.75 (m, 2H). MS m/z 369 $(M-H)^-$.

Paso 3: (2*R*,4*S*)-4-(3-Oxo-2,3-dihidroisoxazol-5-il)-2-(3,4,5-trifluorobencil)piperidin-1-carboxilato de metilo y (2*S*,4*R*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3,4,5-trifluorobencil)piperidin-1-carboxilato de metilo

El *cis*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3,4,5-(trifluorobencil)piperidin-1-carboxilato de metilo (1.354 g, 3.68 mmol) se sometió a HPLC preparativa quiral (columna:

Chiralpak AD (250x20 mm), tamaño de partícula: 5 µm, fase móvil: 80/20/0.1 de heptano/EtOH/AF, velocidad de flujo: 18 mL/min) para proporcionar (2*R*,4*S*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3,4,5-trifluorobencil)piperidin-1-carboxilato de metilo (584 mg, 43%), pureza quiral: 99.3% de ee, rotación óptica $[\alpha]_D^{20} = +13.0$ (acetonitrilo, c=1.0), y (2*S*,4*R*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3,4,5-trifluorobencil)piperidin-1-carboxilato de metilo (598 mg, 44%), pureza quiral: 99.2% de ee, rotación óptica $[\alpha]_D^{20} = -12.5$ (acetonitrilo, c=1.0).

Paso 4: 5-((2*R*,4*S*)-2-(3,4,5-Trifluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3,4,5-trifluorobencil)piperidin-1-carboxilato de metilo (584 mg, 1.58 mmol) en ácido bromhídrico (al 33% en AcOH, 7 mL, 302.80 mmol) y se agitó a temperatura ambiente durante 20 h. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*S*)-2-(3,4,5-trifluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona (325 mg, 66%). ^{1}H RMN (600 MHz, DMSO) δ 1.05 (c, 1H), 1.31 (dc, 1H), 1.71 - 1.78 (m, 2H), 2.34 - 3.78 (m, 6H), 5.68 (s, 1H), 7.12 - 7.20 (m, 2H). HRMS calculado para $[C_{15}H_{15}F_3N_2O_2+H]^+$: 313.1164. Experimental: 313.1172.

Ejemplo 144

5-((2*S*,4*R*)-2-(3,4,5-Trifluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*S*,4*R*)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3,4,5-trifluorobencil)piperidin-1-carboxilato de metilo (598 mg, 1.61 mmol) (del paso 3 del ejemplo 143) en ácido bromhídrico (al 33% en AcOH, 7 mL, 99.92 mmol) y se agitó a temperatura ambiente durante 20 h. El disolvente se evaporó al vacío y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm

OBD 19*150 mm) para proporcionar 5-((2*S*,4*R*)-2-(3,4,5-trifluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona (357 mg, 70.8%). ^{1}H RMN (600 MHz, DMSO) δ 1.05 (c, 1H), 1.32 (dc, 1H), 1.70 - 1.78 (m, 2H), 2.33 - 3.58 (m, 6H), 5.68 (s, 1H), 7.12 - 7.19 (m, 2H). HRMS calculado para $[C_{15}H_{15}F_3N_2O_2+H]^+$: 313.1164. Experimental: 313.1158.

Ejemplo 145

5-(*Trans*-2-(3,4,5-trifluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3,4,5-(trifluorobencil)piperidin-1-carboxilato de metilo

Se disolvió *trans*-4-(3-etoxi-3-oxopropanoil)-2-(3,4,5-trifluorobencil)piperidin-1-carboxilato de metilo (309 mg, 0.77 mmol) (del paso 1 del ejemplo 143) en MeOH (5 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (0.203 mL, 0.77 mmol) en agua (0.500 mL) y la mezcla se agitó a -40 °C durante 20 min. Se añadió hidroxilamina (al 50% en agua, 0.047 mL, 0.77 mmol) y se continuó agitando a -40 °C durante 3 h. La mezcla de reacción se transfirió posteriormente a una solución calentada previamente a 80 °C de ácido clorhídrico 6 M (3.98 mL, 23.87 mmol) y se continuó calentando durante 20 min. A continuación se evaporó el disolvente. Se añadieron DCM (50 mL) y agua (50 mL), se agitó y se separaron las fases. La fase orgánica se secó con un separador de fases y se evaporó al vacío. El compuesto se purificó mediante HPLC preparativa en una columna Kromasil C8 (10 µm 250x20 DI en mm) utilizando un gradiente de 10-55% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/AcOH en 30 minutos con un flujo de 19 mL/min. Se aisló el *trans*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3,4,5-(trifluorobencil)piperidin-1-carboxilato de metilo (111 mg, 38.9%). MS m/z 371 $(M+H)^+$.

Paso 2: 5-(*Trans*-2-(3,4,5-trifluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se agitó *trans*-4-(3-oxo-2,3-dihidroisoxazol-5-il)-2-(3,4,5-trifluorobencil)piperidin-1-carboxilato de metilo (111 mg, 0.3 mmol) en ácido bromhídrico (al 33% en AcOH, 2 mL, 86.51

mmol) durante 18 h. La mezcla de reacción se evaporó al vacío y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-(*trans*-2-(3,4,5-trifluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona (20.17 mg, 21.5%). ^{1}H RMN (600 MHz, DMSO) δ 1.43 - 1.49 (m, 1H), 1.65 - 1.79 (m, 3H), 2.33 - 3.75 (m, 6H), 5.75 (s, 1H), 7.12 - 7.19 (m, 2H). HRMS calculado para $[C_{15}H_{15}F_3N_2O_2+H]^+$: 313.1164. Experimental: 313.1147.

Ejemplo 146

5-((2*R*,4*S*)-2-(3,5-Di-*tert*-butilbencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(3,5-di-*tert*-butilbencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo y *cis*-2-(3,5-di-*tert*-butilbencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo

Se disolvió el ácido 2-(3,5-di-*tert*-butilbencil)-1-(metoxicarbonil)piperidin-4-carboxílico (3.723 g, 9.56 mmol) (compuesto de referencia 61) en metil-THF (70 mL) y se añadió di(1*H*-imidazol-1-il)metanona (2.325 g, 14.34 mmol). La suspensión se agitó a temperatura ambiente durante toda la noche en atmósfera de nitrógeno (matraz 1). En otro matraz, se suspendió 3-etoxi-3-oxopropanoato de potasio (2.93 g, 17.20 mmol) en metil-THF (70.0 mL) y se añadió cloruro de magnesio (1.638 g, 17.20 mmol). La suspensión se agitó a 50 °C en atmósfera de nitrógeno durante toda la noche utilizando un imán muy grande (matraz 2). A continuación, la suspensión amarilla del matraz 1 se añadió a la suspensión blanca del matraz 2. La suspensión blanca resultante se agitó a temperatura ambiente en atmósfera de nitrógeno durante 2 días. La mezcla se acidificó hasta pH 1 con HCl 3.8 M, y se añadieron MTBE y agua. Las fases se separaron y la fase orgánica se lavó con agua, $NaHCO_3$ sat. y agua. Los disolventes se evaporaron para proporcionar un aceite amarillo. Los diastereómeros se separaron en dos purificaciones en una columna Biotage (0% => 40% de EtOAc en heptano, 8 VC; columna Biotage® con 340g de KP-SIL). Se aislaron *trans*-2-(3,5-

di-*tert*-butilbencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (0.734 g, 17%) y *cis*-2-(3,5-di-*tert*-butilbencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (2.027 g, 46%) como aceites incoloros. Isómero *cis*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.19 - 1.35 (m, 21H), 1.63 - 1.99 (m, 4H), 2.62 - 3.05 (m, 4H), 3.46 (s, 2H), 3.57 - 3.64 (m, 3H), 3.88 - 3.97 (m, 1H), 4.07 - 4.26 (m, 3H), 6.97 - 7.01 (m, 2H), 7.24 - 7.28 (m, 1H). MS m/z 460 $(M+H)^+$. Isómero *trans*: ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.11 - 1.39 (m, 21H), 1.40 - 2.02 (m, 4H), 2.52 - 3.14 (m, 4H), 3.33 - 3.55 (m, 3H), 3.64 (s a, 2H), 3.98 - 4.35 (m, 3H), 4.37-4.80 (m, 1H), 6.91 - 7.12 (m, 2H), 7.24 - 7.30 (m, 1H). MS m/z 460 $(M+H)^+$.

Paso 2: <u>*Cis*-2-(3,5-di-*tert*-butilbencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo</u>

Se disolvió *cis*-2-(3,5-di-*tert*-butilbencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (2.03 g, 4.42 mmol) en MeOH (16 mL) y se enfrió hasta -40°C en atmósfera de nitrógeno. Se añadió hidróxido sódico (0.177 g, 4.42 mmol) disuelto en agua (1.600 mL) durante 10 min y se continuó agitando la solución incolora a -40 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.271 mL, 4.42 mmol) durante 8 min. La solución resultante se agitó a -40°C durante 3.5 h. A continuación, la mezcla se transfirió a una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (20 mL, 120.00 mmol) y se continuó agitando la mezcla a 80 °C durante 20 min. Se añadieron DCM y agua. Las fases se separaron y la fase orgánica se hizo pasar a través de un separador de fases y se evaporó para proporcionar un semisólido amarillo. El compuesto se purificó mediante HPLC preparativa en 3 inyecciones en una columna XBridge C18 (10 µm 250x50 DI en mm) utilizando un gradiente de 10-50% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 20 minutos con un flujo de 100 mL/min. Se aisló *cis*-2-(3,5-di-*tert*-butilbencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.358 g, 72%) como un sólido blanco. ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.22 - 1.33 (m, 18H), 1.80 - 2.10 (m, 4H), 2.59 - 2.67 (m, 1H), 2.71 -

2.78 (m, 1H), 2.92 - 2.98 (m, 1H), 3.07 - 3.15 (m, 1H), 3.55 (s, 3H), 3.97 (dd, 1H), 4.18 - 4.27 (m, 1H), 5.68 (s, 1H), 6.92 (d, 2H), 7.22 (s, 1H). MS m/z 429 $(M+H)^+$.

Paso 3: (2*R*,4*S*)-2-(3,5-Di-*tert*-butilbencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)-piperidin-1-carboxilato de metilo y (2*S*,4*R*)-2-(3,5-di-*tert*-butilbencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El *cis*-2-(3,5-di-*tert*-butilbencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.358 g, 3.16 mmol) se sometió a HPLC preparativa quiral (columna: Chiralcel OJ (250x20), tamaño de partícula: 5 µm, fase móvil: Heptano/EtOH/AF 90/10/0.1, velocidad de flujo: 18 mL/min) para proporcionar (2R,4S)-2-(3,5-di-tert-butilbencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (550 mg, 40%), pureza quiral: 99.6% de ee, rotación óptica $[\alpha]_D^{20} = +14.7$ (acetonitrilo, c=1) y (2*S*,4*R*)-2-(3,5-di-*tert*-butilbencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (619 mg, 45%), pureza óptica: 99.7% de ee, rotación óptica $[\alpha]_D^{20} = -11.2$ (acetonitrilo, c=1).

Paso 4: 5-((2*R*,4*S*)-2-(3,5-Di-*tert*-butilbencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-2-(3,5-di-*tert*-butilbencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (550 mg, 1.28 mmol) en ácido bromhídrico (al 33% en ácido acético, 10 mL, 57.10 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx III, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*S*)-2-(3,5-di-*tert*-butilbencil)piperidin-4-il)isoxazol-3(2*H*)-ona (315 mg, 66%). ^{1}H RMN (600 MHz, CD_3OD) δ 1.30 (s, 18H), 1.58 - 1.67 (m, 1H), 1.80 (dc, 1H), 2.17 - 2.27 (m, 2H), 2.85 - 3.14 (m, 4H), 3.41 - 3.51 (m, 2H), 5.73 (s, 1H), 7.07 - 7.13 (m, 2H), 7.36 - 7.40 (m, 1H). HRMS calculado para $[C_{23}H_{34}N_2O_2+H]^+$: 371.2698. Experimental: 371.2714.

Ejemplo 147

5-((2*S*,4*R*)-2-(3,5-Di-*tert*-butilbencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*S*,4*R*)-2-(3,5-di-*tert*-butilbencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (619 mg, 1.44 mmol) (del paso 3 del ejemplo 146) en ácido bromhídrico (al 33% en ácido acético, 10 mL, 57.10 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx III, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*S*,4*R*)-2-(3,5-di-*tert*-butilbencil)piperidin-4-il)isoxazol-3(2*H*)-ona (330 mg, 61%). ^{1}H RMN (600 MHz, CD_3OD) δ 1.30 (s, 18H), 1.63 (c, 1H), 1.80 (dc, 1H), 2.19 - 2.27 (m, 2H), 2.86 - 3.18 (m, 4H), 3.43 - 3.56 (m, 2H), 5.73 (s, 1H), 7.10 (d, 2H), 7.37 - 7.40 (m, 1H). HRMS calculado para $[C_{23}H_{34}N_2O_2+H]^+$: 371.2698. Experimental: 371.2693.

Ejemplo 148

5-(*Trans*-2-(3,5-di-*tert*-butilbencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-(3,5-di-*tert*-butilbencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *trans*-2-(3,5-di-*tert*-butilbencil)-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (0.734 g, 1.60 mmol) en MeOH (5 mL) y se enfrió hasta -40 °C en atmósfera de nitrógeno. Se añadió hidróxido sódico (0.064 g, 1.60 mmol) disuelto en agua (0.500 mL) durante 10 min y se continuó agitando la solución incolora a -40 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.098 mL, 1.60 mmol) durante 8 min. La solución resultante se agitó a -40°C durante 4 h. A continuación, la mezcla se transfirió a una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (8 mL, 48.00 mmol) y se continuó agitando la mezcla a 80 °C durante 20 min. Se añadieron DCM y agua. Las fases se separaron y la fase orgánica se hizo pasar a través de un separador de

fases y se evaporó para proporcionar *trans*-2-(3,5-di-*tert*-butilbencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo crudo (0.723 g, 106%) como un semisólido amarillo. MS m/z 429 $(M+H)^+$.

Paso 2: 5-(*Trans*-2-(3,5-di-*tert*-butilbencil)piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió *trans*-2-(3,5-di-*tert*-butilbencil)-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (155 mg, 0.36 mmol) en ácido bromhídrico (al 33% en ácido acético, 3 mL, 17.13 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. El disolvente se evaporó y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx III, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-(*trans*-2-(3,5-di-*tert*-butilbencil)piperidin-4-il)isoxazol-3(2*H*)-ona (69 mg, 51%). ^{1}H RMN (600 MHz, DMSO) δ 1.26 (s, 18H), 1.45 - 1.53 (m, 1H), 1.69 - 1.87 (m, 3H), 2.58 - 2.72 (m, 3H), 2.83 - 2.93 (m, 2H), 3.09 - 3.16 (m, 1H), 5.64 (s, 1H), 6.99 (d, 2H), 7.18 - 7.23 (m, 1H). HRMS calculado para $[C_{23}H_{34}N_2O_2+H]^+$: 371.2698. Experimental: 371.2688.

Ejemplo 149

5-((2*R*,4*S*)-2-Bencil-2,3,4,5,6-d_5-piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-bencil-2,3,4,5,6-d_5-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo y *cis*-2-bencil-2,3,4,5,6-d_5-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo

Se agitaron cloruro de magnesio (3.13 g, 32.90 mmol) y 3-etoxi-3-oxopropanoato de potasio (5.60 g, 32.90 mmol) suspendidos en THF (100 mL) en atmósfera de nitrógeno con un imán muy grande a 50 °C durante 18 h, posteriormente se enfrió hasta temperatura ambiente (matraz 1). Se añadió di(1*H*-imidazol-1-il)metanona (4.77 g, 29.42 mmol) a una suspensión del ácido 2-bencil-2,3,4,5,6-d_5-1-(metoxicarbonil)piperidin-4-carboxílico (5.16 g, 18.28 mmol) (compuesto de referencia 62) en metil-THF (100 mL) en atmósfera de nitrógeno. La mezcla

resultante se agitó a temperatura ambiente durante 19 h (matraz 2). El contenido del matraz 2 se transfirió al matraz 1 con una aguja de transferencia. Se lavó con THF (35 mL). La suspensión resultante se agitó a temperatura ambiente durante 24 h. Se añadió HCl 3.8 M (ca. 200 mL) y la mezcla bifásica resultante se agitó vigorosamente durante 30 min. Se añadió MTBE y las fases se separaron. La fase acuosa se extrajo una vez más con MTBE. Las fases orgánicas combinadas se secaron con $MgSO_4$ y se evaporaron. El residuo se purificó en una columna Biotage (columna Biotage® con 340 g de KP-SIL, 1 VC de 20% de EtOAc en heptanos, seguido de 20% => 60% en 7 VC). Se aislaron *trans*-2-bencil-2,3,4,5,6-d_5-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (1.15 g, 18%) y *cis*-2-bencil-2,3,4,5,6-d_5-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (2.27 g, 35%) como aceites de color amarillo pálido. Isómero *cis*: ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.19 - 1.28 (m, 3H), 1.60 - 1.92 (m, 4H), 2.63 - 2.77 (m, 2H), 2.85 - 3.04 (m, 2H), 3.42 (s, 2H), 3.61 (s, 3H), 3.85 - 3.94 (m, 1H), 4.05 - 4.22 (m, 3H). MS m/z 353 $(M+H)^+$. Isómero *trans*: ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.19 - 1.31 (m, 3H), 1.39 - 1.66 (m, 2H), 1.67 - 1.98 (m, 2H), 2.71 - 3.07 (m, 4H), 3.33 - 3.73 (m, 5H), 3.99 - 4.33 (m, 3H), 4.57 (d a, 1H). MS m/z 353 $(M+H)^+$.

Paso 2: <u>*Cis*-2-bencil-2,3,4,5,6-d_5-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo</u>

Se disolvió *cis*-2-bencil-2,3,4,5,6-d_5-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (2.27 g, 6.44 mmol) en MeOH (20 mL) y se enfrió hasta -40 °C. Se añadió hidróxido sódico (0.258 g, 6.44 mmol) disuleto en agua (2 mL) en 2 min y la solución resultante se agitó a -40 °C durante 25 min. Posteriormente, se añadió hidroxilamina (al 50% en peso en agua, 0.41 mL, 6.69 mmol) en 1 min y se continuó agitando a una temperatura de -50 °C a -40 °C durante 1 h 40 min. La mezcla de reacción se transfirió posteriormente a una solución calentada previamente (80 °C) de ácido clorhídrico 6 M (30 mL, 180.00 mmol) y la mezcla se continuó agitando a 80 °C durante 30 min. A continuación, se enfrió hasta temperatura ambiente. Se

evaporó el metanol y después se añadió agua. Se extrajo tres veces con DCM. Las capas orgánicas combinadas se secaron con $MgSO_4$ y se evaporaron. El compuesto se purificó en 3 inyecciones mediante HPLC preparativa en una columna XBridge C18 (10 µm 250x50 DI en mm) utilizando un gradiente de 0-25% de acetonitrilo en tampón 95/5/0.2 de H_2O/MeCN/NH_3 en 23 minutos con un flujo de 100 mL/min. Se aisló *cis*-2-bencil-2,3,4,5,6-d_5-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.458 g, 70%) como un sólido incoloro. ^{1}H RMN (600 MHz, $CDCl_3$) δ 1.79 - 1.97 (m, 3H), 1.99 - 2.12 (m, 1H), 2.62 (dd, 1H), 2.81 (dd, 1H), 2.89 - 2.99 (m, 1H), 3.07 - 3.17 (m, 1H), 3.59 (s, 3H), 3.98 (dd, 1H), 4.20 - 4.30 (m, 1H), 5.69 (s, 1H). MS m/z 322 $(M+H)^+$.

Paso 3: (2*R*,4*S*)-2-Bencil-2,3,4,5,6-d_5-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo y (2*S*,4*R*)-2-bencil-2,3,4,5,6-d_5-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

El *cis*-2-bencil-2,3,4,5,6-d_5-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (1.25 g, 3.89 mmol) se sometió a HPLC preparativa quiral (columna: Chiralcel OD (250x20), tamaño de partícula: 5 µm, fase móvil: 90/10/0.1 de heptano/EtOH/AF, velocidad de flujo: 18 mL/min) para proporcionar (2*R*,4*S*)-2-bencil-2,3,4,5,6-d_5-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (502 mg, 40%), pureza quiral: 98.9% de ee, rotación óptica $[\alpha]_D^{20} = +23.7$ (acetonitrilo, c=1) y (2*S*,4*R*)-2-bencil-2,3,4,5,6-d_5-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (512 mg, 41%), pureza quiral: 99.1% de ee, rotación óptica $[\alpha]_D^{20} = -22.2$ (acetonitrilo, c=1).

Paso 4: 5-((2*R*,4*S*)-2-Bencil-2,3,4,5,6-d_5-piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*R*,4*S*)-2-bencil-2,3,4,5,6-d_5-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.502 g, 1.56 mmol) en ácido bromhídrico (al 33% en AcOH, 10 mL, 142.75 mmol) y se agitó a temperatura ambiente durante 20 h,

posteriormente los disolventes se evaporaron y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*R*,4*S*)-2-bencil-2,3,4,5,6-d_5-piperidin-4-il)isoxazol-3(2*H*)-ona. HRMS calculado para $[C_{15}H_{13}D_5N_2O_2+H]^+$: 264.1760. Experimental: 264.1751.

Ejemplo 150

5-((2*S*,4*R*)-2-Bencil-2,3,4,5,6-d_5-piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió (2*S*,4*R*)-2-bencil-2,3,4,5,6-d_5-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.512 g, 1.59 mmol) (del paso 3 del ejemplo 149) en ácido bromhídrico (al 33% en ácido acético, 10 mL, 142.75 mmol) y se agitó a temperatura ambiente durante 20 h, posteriormente los disolventes se evaporaron y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-((2*S*,4*R*)-2-bencil-2,3,4,5,6-d_5-piperidin-4-il)isoxazol-3(2*H*)-ona. HRMS calculado para $[C_{15}H_{13}D_5N_2O_2+H]^+$: 264.1760. Experimental: 264.1749.

Ejemplo 151

5-(*Trans*-2-bencil-2,3,4,5,6-d_5-piperidin-4-il)isoxazol-3(2*H*)-ona

Paso 1: *Trans*-2-bencil-2,3,4,5,6-d_5-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo

Se disolvió *trans*-2-bencil-2,3,4,5,6-d_5-4-(3-etoxi-3-oxopropanoil)piperidin-1-carboxilato de metilo (1.15 g, 3.26 mmol) (del paso1 del ejemplo 149) en MeOH (20 mL) y se enfrió hasta -40 °C. Se añadió hidróxido sódico (0.131 g, 3.26 mmol) disuelto en agua (2 mL) en 1 min y la solución resultante se agitó a -40 °C durante 20 min. Se añadió hidroxilamina (al 50% en peso en agua, 0.208 mL, 3.39 mmol) en 1 min y se continuó agitando a una temperatura de -50 °C a -40 °C durante 1 h. La mezcla de reacción se transfirió posteriormente a una solución

calentada previamente (80 °C) de ácido clorhídrico 6 M (30 mL, 180.00 mmol) y se continuó agitando la mezcla a 80 °C durante 40 min. Posteriormente, se enfrió hasta temperatura ambiente. Se evaporó el metanol y después se añadió agua. Se extrajo tres veces con DCM. Las capas orgánicas combinadas se secaron con $MgSO_4$ y se evaporaron para proporcionar *cis*-2-bencil-2,3,4,5,6-d_5-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo curdo (1.06 g, 101%) como una espuma naranja. MS m/z 322 $(M+H)^+$.

Paso 2: 5-(*Trans*-2-bencil-2,3,4,5,6-d_5-piperidin-4-il)isoxazol-3(2*H*)-ona

Se disolvió *cis*-2-bencil-2,3,4,5,6-d_5-4-(3-oxo-2,3-dihidroisoxazol-5-il)piperidin-1-carboxilato de metilo (0.204 g, 0.63 mmol) en ácido bromhídrico (al 33% en ácido acético, 6 mL, 34.26 mmol) y se agitó a temperatura ambiente durante 20 h, posteriormente los disolventes se evaporaron y el residuo se purificó mediante HPLC preparativa (Instrumento: FractionLynx II, fase móvil: gradiente de 5-95% de MeCN en NH_3 al 0.2%, pH 10, columna: Xbridge Prep C18 5 µm OBD 19*150 mm) para proporcionar 5-(*trans*-2-bencil-2,3,4,5,6-d_5-piperidin-4-il)isoxazol-3(2*H*)-ona (29 mg, 23%). HRMS calculado para $[C_{15}H_{13}D_5N_2O_2+H]^+$: 264.1760. Experimental: 264.1747.

Procedimientos generales para preparar las formas critalinas de los ejemplos

Método A - forma neutra

La sustacia se suspende en agua a temperatura ambiente durante un periodo prolongado, posteriormente se separa por filtración.

Método B - forma neutra

La sustancia se suspende en una mezcla de metanol y diclorometano. Los disolventes se dejan evaporar lentamente.

Método C - sal de HCl

La sustancia se disuelve en HCl 1 M a temperatura ambiente. La sal de HCl formada se separa por filtración.

Método D - sal de HCl

La sustancia se disuelve en HCl 1.25 M en metanol. El disolvente se deja evaporar lentamente.

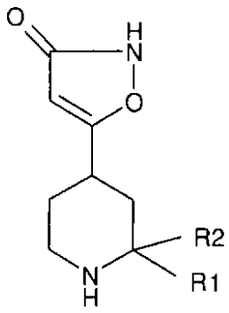
Las formas cristalinas de los ejemplos 14 y 104 se prepararon de acuerdo con el método A. Las formas cristalinas de los ejemplos 55, 65, 115 y 143 se prepararon de acuerdo con el método B. Las formas cristalinas de las sales de HCl de los ejemplos 14 y 104 se prepararon de acuerdo con el método C. Las formas cristalinas de las sales de HCl de los ejemplos 10, 18, 55, 65 y 143 se prepararon de acuerdo con el método D.

Se hace constar que, con relación a esta fecha, el mejor método conocido por la solicitante para llevar a la práctica la citada invención, es el que resulta claro de la presente descripción de la invención.

Reivindicaciones

Habiéndose descrito la invención como antecede, se reclama como propiedad lo contenido en las siguientes reivindicaciones:

1. Un compuesto de fórmula I:



I

o una sal farmacéuticamente aceptable de este, donde

R1 y R2 son independientemente hidrógeno, deuterio, arilo, heteroarilo, alquilo C1-C8, y están opcionalmente sustituidos con uno o más sustituyentes que son independientemente R3,

R3 es un arilo, heteroarilo, uno o más átomos de flúor, un alquilo C1-C6 que contiene uno o más átomos de flúor, un alquilo C1-C6 que contiene uno o más átomos de deuterio, un alquilo C1-C6 que contiene hidroxi, estando el arilo y el heteroarilo opcionalmente sustituidos con uno o más halógenos, un alcoxi fluorado, un alquilo fluorado, un sulfonilo, uno o más átomos de deuterio, un alquilo C1-C6, un alcoxi C1-C6, un nitrilo,

o R3 es un alquilo C1-C6 opcionalmente sustituido con uno o más de los siguientes grupos: COOR4, OCOR4, CONR5R6, NR5COR6, OR4;

donde R4 es un alquilo C1-C10 opcionalmente sustituido con uno o más átomos de flúor, deuterio, alcoxi, carboxilato de arilo, carboxilato de alquilo;

R5 y R6 se seleccionan independientemente entre hidrógeno, alquilo o pueden formar conjuntamente un anillo de carbono de 4-8 miembros;

o R1 y R2 forman un anillo de carbono de 3-10 miembros que comprende opcionalmente O o N y está opcionalmente sustituido

con un alquilo o arilo C1-C10, heteroarilo opcionalmente sustituido con R3.

2. Un compuesto de acuerdo con la reivindicación 1, o una sal farmacéuticamente aceptable de este, donde

R1 y R2 son independientemente hidrógeno, deuterio, heteroarilo, alquilo C1-C8, y están opcionalmente sustituidos con uno o más sustituyentes que son independientemente R3,

R3 es un arilo, heteroarilo, uno o más átomos de flúor, un alquilo C1-C6 que contiene uno o más átomos de flúor, un alquilo C1-C6 que contiene uno o más átomos de deuterio, un alquilo C1-C6 que contiene hidroxi, estando el arilo y el heteroarilo opcionalmente sustituidos con uno o más halógenos, un alcoxi fluorado, un alquilo fluorado, un sulfonilo, uno o más átomos de deuterio, un alquilo C1-C6, un alcoxi C1-C6, un nitrilo,

o R3 es un alquilo C1-C6 opcionalmente sustituido con uno o más de los siguientes grupos: COOR4, OCOR4, CONR5R6, NR5COR6, OR4;

donde R4 es un alquilo C1-C10 opcionalmente sustituido con uno o más átomos de flúor, deuterio, alcoxi, carboxilato de arilo, carboxilato de alquilo;

R5 y R6 se seleccionan independientemente entre hidrógeno, alquilo o pueden formar conjuntamente un anillo de carbono de 4-8 miembros;

o R1 y R2 forman un anillo de carbono de 3-10 miembros que comprende opcionalmente O o N y está opcionalmente sustituido con un alquilo o arilo C1-C10, heteroarilo opcionalmente sustituido con R3.

3. Un compuesto de acuerdo con la reivindicación 1 que se selecciona de uno o más de los siguientes compuestos:

5-((2*S*,4*S*)-2-Bencilpiperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*R*)-2-Bencilpiperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-Bencilpiperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-Bencilpiperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-Isobutilpiperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-Isobutilpiperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*S*)-2-Isobutilpiperidin-4-il)isoxazol-3(2*H*)-ona;
5-((2*R*,4*S*)-2-Fenetilpiperidin-4-il)isoxazol-3(2*H*)-ona;
5-((2*S*,4*R*)-2-Fenetilpiperidin-4-il)isoxazol-3(2*H*)-ona;
5-((2*S*,4*S*)-2-Fenetilpiperidin-4-il)isoxazol-3(2*H*)-ona;
5-((2*S*,4*S*)-2-(4-*tert*-Butilbencil)piperidin-4-il)isoxazol-3(2*H*)-ona;
5-((2*R*,4*S*)-2-(4-*tert*-Butilbencil)piperidin-4-il)isoxazol-3(2*H*)-ona;
5-((2*S*,4*S*)-2-Neopentilpiperidin-4-il)isoxazol-3(2*H*)-ona;
5-((2*R*,4*S*)-2-Neopentilpiperidin-4-il)isoxazol-3(2*H*)-ona;
5-((2*R*,4*S*)-2-Metilpiperidin-4-il)isoxazol-3(2*H*)-ona;
5-((2*S*,4*R*)-2-Metilpiperidin-4-il)isoxazol-3(2*H*)-ona;
5-((2*S*,4*S*)-2-Metilpiperidin-4-il)isoxazol-3(2*H*)-ona;
5-((2*S*,4*S*)-2-(2-Metil-2-fenilpropil)piperidin-4-il)isoxazol-3(2*H*)-ona;
5-((2*R*,4*S*)-2-(2-Metil-2-fenilpropil)piperidin-4-il)isoxazol-3(2*H*)-ona;
5-((2*R*,4*S*)-2-(Ciclohexilmetil)piperidin-4-il)isoxazol-3(2*H*)-ona;
5-((2*R*,4*R*)-2-(Ciclohexilmetil)piperidin-4-il)isoxazol-3(2*H*)-ona;
5-((2*S*,4*S*)-2-(Ciclohexilmetil)piperidin-4-il)isoxazol-3(2*H*)-ona;
5-((2*R*,4*S*)-2-(3,4-Difluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;
5-(*Trans*-2-(3,4-difluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;
5-((2*R*,4*S*)-2-(4-Fluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;
5-(*Trans*-2-(4-fluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;
5-((2*R*,4*S*)-2-(4-Clorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;
5-((2*S*,4*R*)-2-(4-Clorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(4-clorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(3-(Trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(3-(Trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(3-trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(4-(Trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(4-(Trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(3-*tert*-Butilfenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(4-*tert*-butilfenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(4-Metilsulfonil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((*Trans*-2-(4-(metilsulfonil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(6-(Trifluorometil)piridin-3-il)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(6-(trifluorometil)piridin-3-il)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(5-*tert*-Butiltiofen-2-il)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(5-*tert*-Butiltiofen-2-il)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(2,4-Difluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(4-Cloro-2-fluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(4-cloro-2-fluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(2-Cloro-4-fluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(2-cloro-2-fluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(4-Cloro-3-fluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(4-cloro-3-fluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(2,4-Diclorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(2,4-Diclorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*S*)-2-(2,4-Diclorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*R*)-2-(2,4-Diclorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(3,5-Diclorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(3,5-Diclorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(3,5-diclorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(2-Fluoro-4-(trifluorometoxi)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(2-fluoro-4-(trifluorometoxi)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(3,4,5-Trifluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(3,4,5-Trifluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(3,4,5-trifluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(2,4,5-Trifluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*S*)-2-(2,4,5-Trifluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(4-Cloro-3,5-difluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(4-cloro-3,5-difluorofenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(3-Metil-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(3-Metil-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(3-metil-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(3,5-Difluoro-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(3,5-difluoro-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(2-Metil-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(2-Fluoro-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(2-fluoro-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(3-Fluoro-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(3-Fluoro-4-(trifluorometil)fenil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-Fenilpiperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*S*)-2-Fenilpiperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-Ciclohexilpiperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*S*)-2-Ciclohexilpiperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(2-Metil-2*H*-tetrazol-5-il)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(2-metil-2*H*-tetrazol-5-il)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(1-Metil-1*H*-tetrazol-5-il)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(Ciclohexiloximetil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(Ciclohexiloximetil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(ciclohexiloximetil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(Difluorometil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(difluorometil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*S*)-2-((4,4-Difluorociclohexil)metil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*R*)-2-((4,4-Difluorociclohexil)metil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-((4,4-difluorociclohexil)metil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*S*)-2-(4-Fluorofenetil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*R*)-2-(4-Fluorofenetil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(4-fluorofenetil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*S*)-2-(3,3-Dimetilbutil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(3,3-Dimetilbutil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(4-Fluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*S*)-2-(4-Fluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(3-Fluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*S*)-2-(3-Fluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(2-Fluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*S*)-2-(2-Fluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*R*)-2-(2-Fluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(4-(Trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*S*)-2-(4-(Trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*R*)-2-(4-(Trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(3-(Trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(3-(Trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(3-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(2-(Trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(2-(Trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(2-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(4-(Trifluorometoxi)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(4-(trifluorometoxi)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(4-Clorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(4-clorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(4-(Metilsulfonil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(4-(Metilsulfonil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(4-(metilsulfonil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(3,4-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(3,4-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*S*)-2-(3,4-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*R*)-2-(3,4-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(2,5-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(2,5-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(2,5-difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(2,6-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(2,6-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(2,6-difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(3,5-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(3,5-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*S*)-2-(3,5-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*R*)-2-(3,5-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(2,4-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(2,4-Difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(2,4-difluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(3-Fluoro-5-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(3-Fluoro-5-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(3-fluoro-5-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(3-Fluoro-4-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(3-Fluoro-4-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(3-fluoro-4-(trifluorometil)bencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(3,4,5-Trifluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(3,4,5-Trifluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(3,4,5-trifluorobencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-(3,5-Di-*tert*-butilbencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-(3,5-Di-*tert*-butilbencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-(3,5-di-*tert*-butilbencil)piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*R*,4*S*)-2-Bencil-2,3,4,5,6-d_5-piperidin-4-il)isoxazol-3(2*H*)-ona;

5-((2*S*,4*R*)-2-Bencil-2,3,4,5,6-d_5-piperidin-4-il)isoxazol-3(2*H*)-ona;

5-(*Trans*-2-bencil-2,3,4,5,6-d_5-piperidin-4-il)isoxazol-3(2*H*)-ona.

4. Una composición farmacéutica que comprende al menos un compuesto de acuerdo con cualquiera de las reivindicaciones 1-3 y un portador o diluyente farmacéuticamente aceptable.

5. Un método para el tratamiento o la profilaxis de una enfermedad o afección en la que es beneficioso modular la fibrinólisis, que comprende administrar a un animal de sangre caliente que necesite dicho tratamiento una cantidad terapéuticamente eficaz de al menos un compuesto de acuerdo con cualquiera de las reivindicaciones 1-3.

6. El método de acuerdo con la reivindicación 5, donde dicha enfermedad o afección se selecciona entre trastornos hemorrágicos hereditarios, accidente cerebrovascular, menorragia y enfermedades hepáticas.

7. El uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1-3 para el tratamiento o la profilaxis de una enfermedad o afección en la que es beneficioso modular la fibrinólisis.

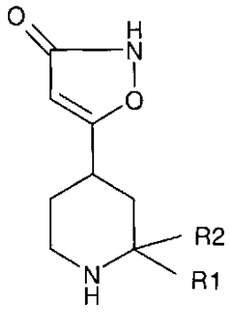
8. El uso de acuerdo con la reivindicación 7, donde dicha enfermedad o afección se selecciona entre trastornos hemorrágicos hereditarios, accidente cerebrovascular, menorragia y enfermedades hepáticas.

9. El uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1-3 en la fabricación de un medicamento para el tratamiento o la profilaxis de una enfermedad o afección en la que es beneficioso modular la fibrinólisis.

10. El uso de acuerdo con la reivindicación 9, donde dicha enfermedad se selecciona entre trastornos hemorrágicos hereditarios, accidente cerebrovascular, menorragia y enfermedades hepáticas.

Resumen

Un compuesto de Fórmula I



I

o una sal farmacéuticamente aceptable de este, donde

R1 y R2 son independientemente hidrógeno, deuterio, arilo, heteroarilo, alquilo C1-C8, y están opcionalmente sustituidos con uno o más sustituyentes que son independientemente R3,

R3 es un arilo, heteroarilo, uno o más átomos de flúor, un alquilo C1-C6 que contiene uno o más átomos de flúor, un alquilo C1-C6 que contiene uno o más átomos de deuterio, un alquilo C1-C6 que contiene hidroxi, estando el arilo y el heteroarilo opcionalmente sustituidos con uno o más halógenos, un alcoxi fluorado, un alquilo fluorado, un sulfonilo, uno o más átomos de deuterio, un alquilo C1-C6, un alcoxi C1-C6, un nitrilo,

o R3 es un alquilo C1-C6 opcionalmente sustituido con uno o más de los siguientes grupos: COOR4, OCOR4, CONR5R6, NR5COR6, OR4;

donde R4 es un alquilo C1-C10 opcionalmente sustituido con uno o más átomos de flúor, deuterio, alcoxi, carboxilato de arilo, carboxilato de alquilo;

R5 y R6 se seleccionan independientemente entre hidrógeno, alquilo o pueden formar conjuntamente un anillo de carbono de 4-8 miembros;

o R1 y R2 forman un anillo de carbono de 3-10 miembros que comprende opcionalmente O o N y está opcionalmente sustituido con un alquilo o arilo C1-C10, heteroarilo opcionalmente sustituido con R3.

Figura 1: Patrón de DRXP para el ejemplo 55

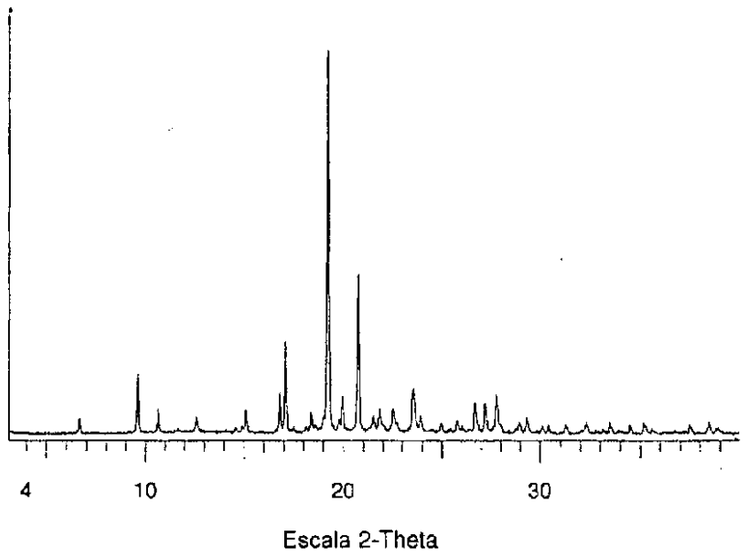


Figura 2: Patrón de DRXP para la sal de HCl del ejemplo 55

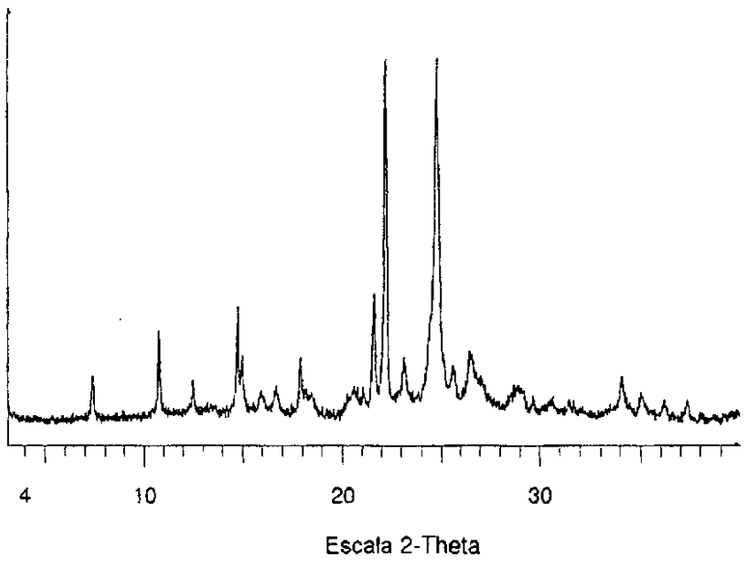


Figura 3: Patrón de DRXP para el ejemplo 143

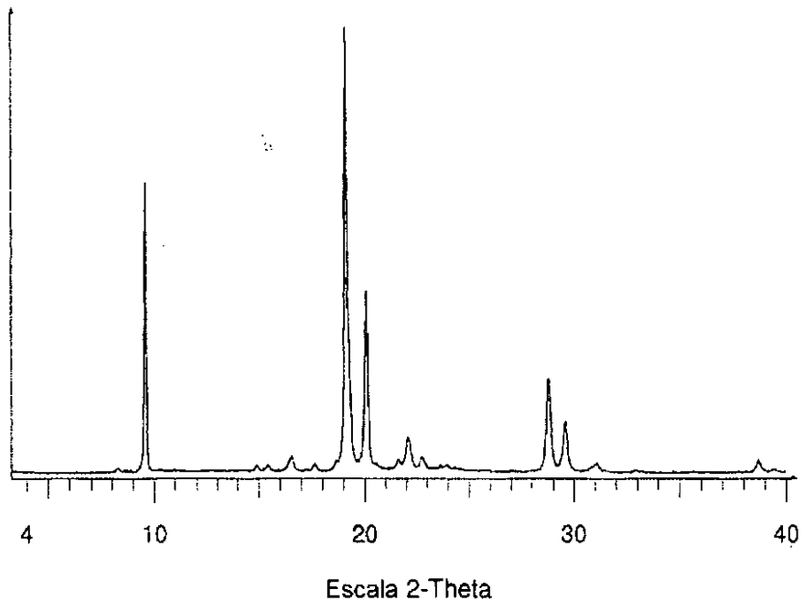


Figura 4: Patrón de DRXP para la sal de HCl del ejemplo 143

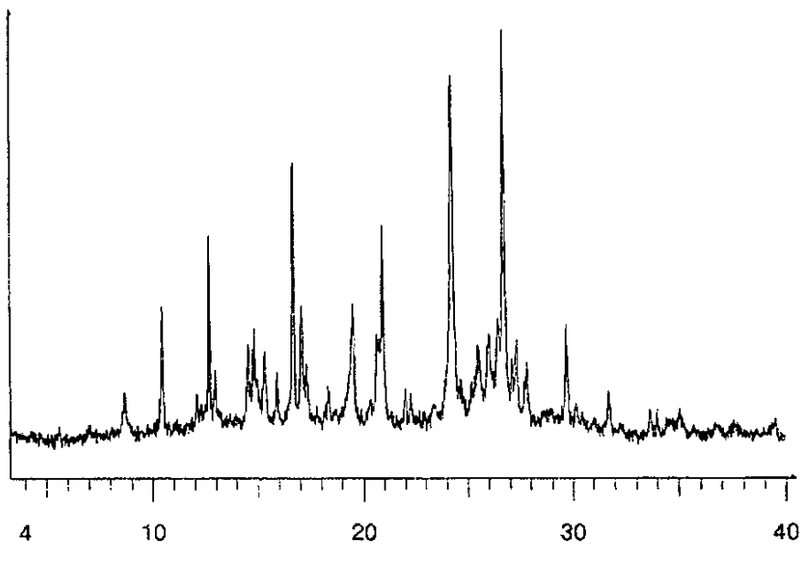


Figura 5: Patrón de DRXP para el ejemplo 104

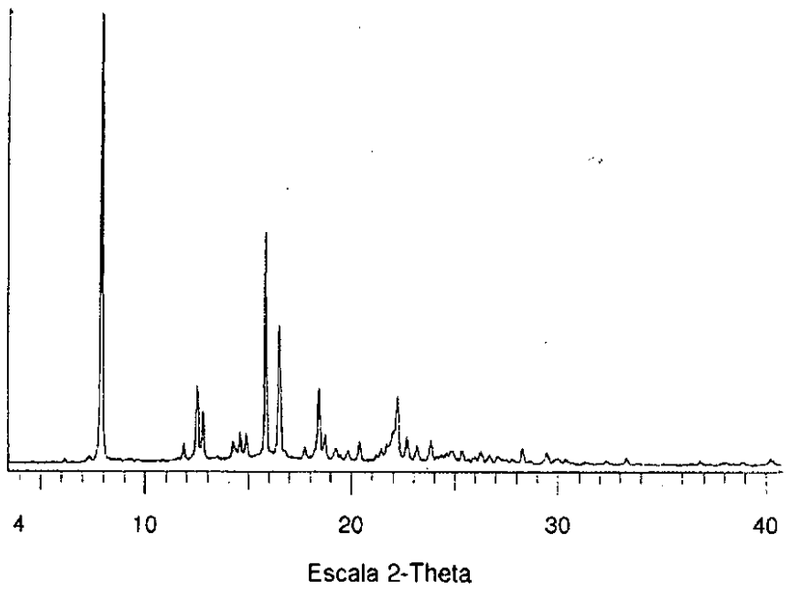


Figura 6: Patrón de DRXP para la sal de HCl del ejemplo 104

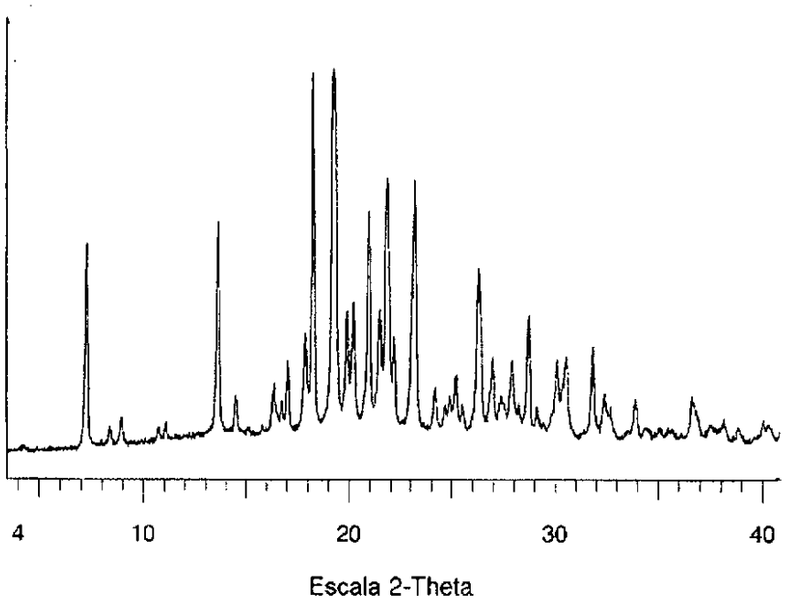


Figura 7: Patrón de DRXP para el ejemplo 65

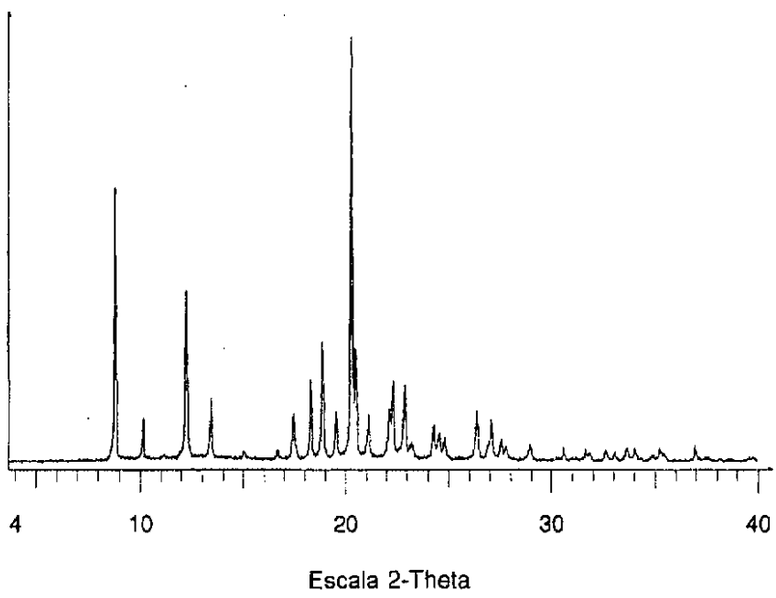


Figura 8: Patrón de DRXP para la sal de HCl del ejemplo 65

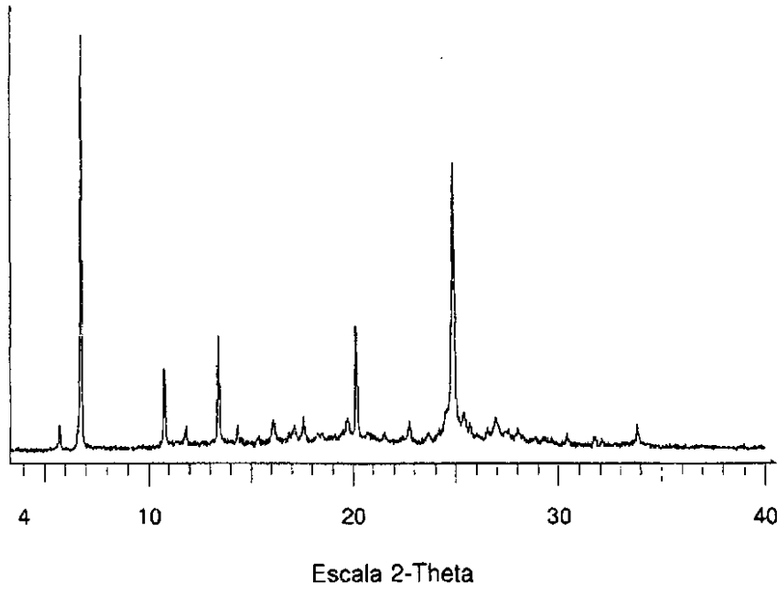


Figura 9: Patrón de DRXP para el ejemplo 14

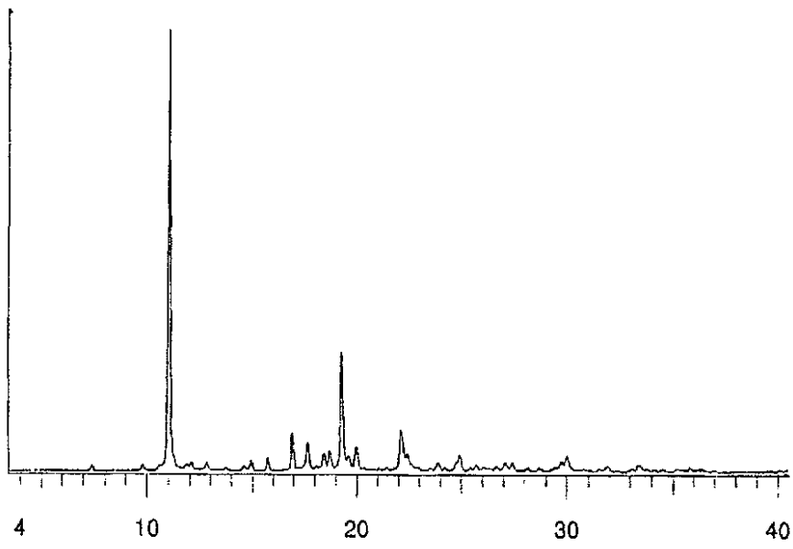


Figura 10: Patrón de DRXP para la sal de HCl del ejemplo 14

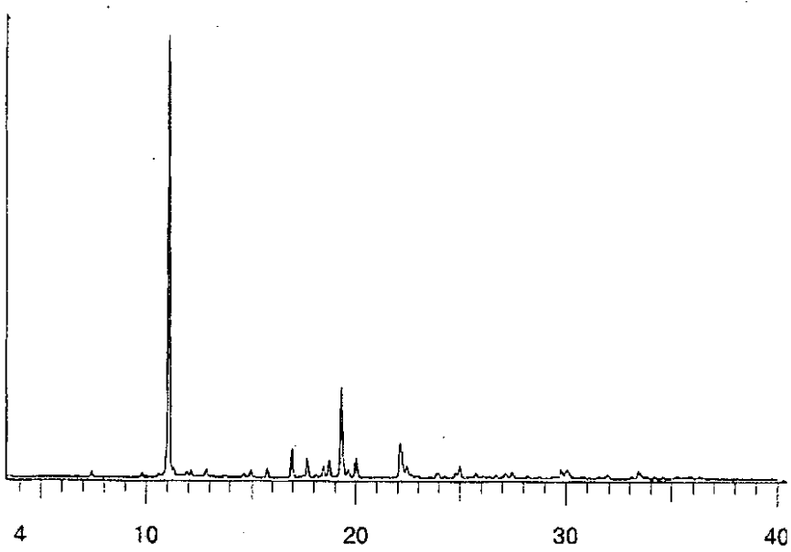


Figura 11: Patrón de DRXP para la sal de HCl del ejemplo 18

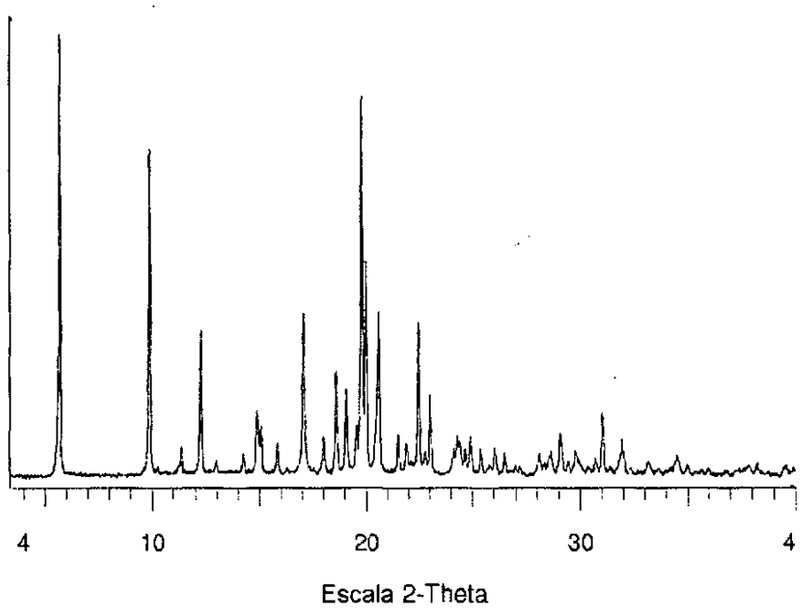


Figura 12: Patrón de DRXP para el ejemplo 115

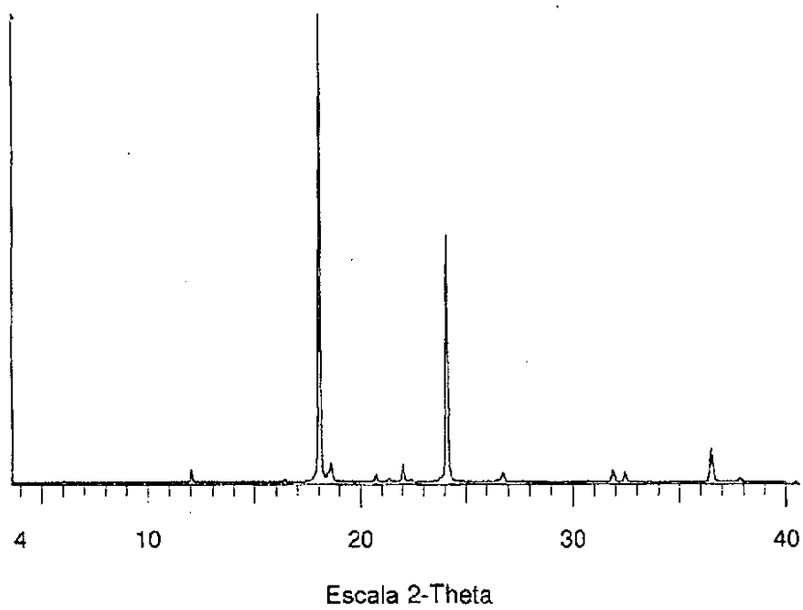
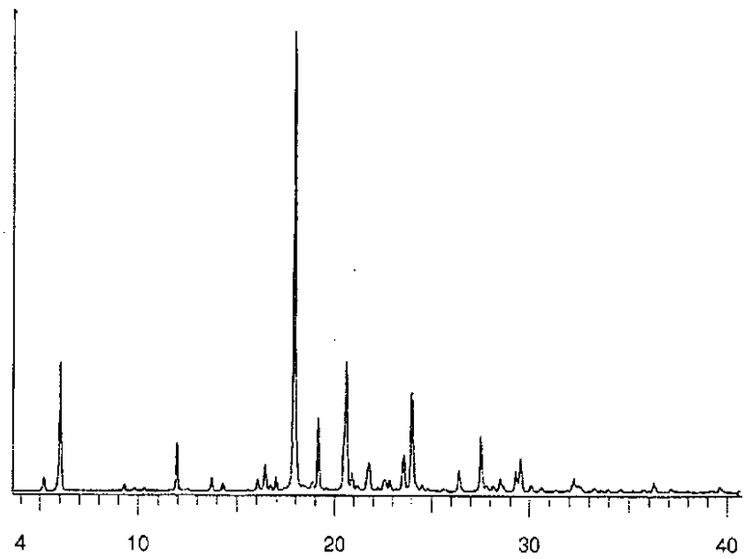


Figura 13: Patrón de DRXP para la sal de HCl del ejemplo 10



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(12) SOLICITUD INTERNACIONAL PUBLICADA EN VIRTUD DEL TRATADO DE COOPERACION EN MATERIA DE PATENTES (PCT)

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Oficina Internacional

(43) Fecha de publicación internacional
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PCT

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(71) Solicitante *(para todos los Estados designados salvo US)*: **ASTRAZENECA AB** [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventores; e

(75) Inventores/solicitantes *(sólo para US)*: **BOSTRÖM, Jonas** [SE/SE]; AstraZeneca R&D Mölndal, S-431 83 Mölndal (SE). **CHENG, Leifeng** [GB/SE]; AstraZeneca R&D Mölndal, S-431 83 Mölndal (SE). **FEX, Tomas** [SE/SE]; AstraZeneca R&D Mölndal, S-431 83 Mölndal (SE). **KARLE, Michael** [DE/SE]; AstraZeneca R&D Mölndal, S-431 83 Mölndal (SE). **PETTERSEN, Daniel** [SE/SE]; AstraZeneca R&D Mölndal, S-431 83 Mölndal (SE). **SCHELL, Peter** [DE/SE]; AstraZeneca R&D Mölndal, S-431 83 Mölndal (SE).

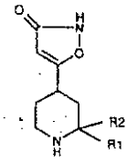
(74) Mandatario: **ASTRAZENECA INTELLECTUAL PROPERTY**; AstraZeneca AB, S-151 85 Södertälje (SE).

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

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

Publicada:
- *con informe de búsqueda internacional (Art. 21(3))*

(54) **Title**: METHOD AND APPARATUS FOR PRODUCING HEAT ENERGY AND CARBON DIOXIDE
(54) **Título**: MÉTODO Y APARATO PARA PRODUCIR ENERGÍA TÉRMICA Y DIÓXIDO DE CARBONO


(I)

(57) **Abstract** : Formula I or a pharmaceutically suitable salt thereof, wherein, R1 and R2 independently are hydrogen, deuterium, aryl, hetero aryl, C1-C8 alkyl, optionally being substituted with one or more substituents independently being R3, R3 is an aryl, hetero aryl, fluorine(s), a C1-C6 alkyl containing one or more fluorine, a C1-C6 alkyl containing one or more deuterium, a C1-C6 alkyl containing hydroxy, the aryl and heteroaryl optionally being substituted with one or more halogen, a fluorinated alkoxy, a fluorinated alkyl, a sulfonyl, one or more deuterium, a C1-6 alkyl, a C1-6 alkoxy, a nitrile, or R3 is a C1-6 alkyl optionally substituted with one or more of the following groups: COOR4, OCOR4, CONR5R6, NR5COR6, OR4; wherein, R4 is a C1-10 alkyl optionally substituted with one or more fluorine, deuterium, alkoxy, arylcarboxylate, alkyl carboxylate; R5 and R6 are independently selected from hydrogen, alkyl or they may together form a 4-8 membered carbon ring; or R1 and R2 form a 3-10 membered carbon ring optionally comprising O or N and optionally substituted with a C1-10 alkyl or aryl, hetero aryl optionally substituted with R3.

(57) **Resumen**: Un compuesto de fórmula I o una sal farmacéuticamente aceptable de este, donde R1 y R2 son independientemente hidrógeno, deuterio, arilo, heteroarilo, alquilo C1-C8, y están opcionalmente sustituidos con uno o más sustituyentes que son independientemente R3, R3 es un arilo, heteroarilo, uno o más átomos de flúor, un alquilo C1-C6 que contiene uno o más átomos de flúor, un alquilo C1-C6 que contiene uno o más átomos de deuterio, un alquilo C1-C6 que contiene hidroxi, estando el arilo y el heteroarilo opcionalmente sustituidos con uno o más halógenos, un alcoxi fluorado, un alquilo fluorado, un sulfonilo, uno o más átomos de deuterio, un alquilo C1-C6, un alcoxi C1-C6, un nitrilo, o R3 es un alquilo C1-C6 opcionalmente sustituido con uno o más de los siguientes grupos: COOR4, OCOR4, CONR5R6, NR5COR6, OR4; donde R4 es un alquilo C1-C10 opcionalmente sustituido con uno o más átomos de flúor, deuterio, alcoxi, carboxilato de arilo, carboxilato de alquilo; R5 y R6 se seleccionan independientemente entre hidrógeno, alquilo o pueden formar conjuntamente un anillo de carbono de 4-8 miembros; o R1 y R2 forman un anillo de carbono de 3-10 miembros que comprende opcionalmente O o N y está opcionalmente sustituido con un alquilo o arilo C1-C10, heteroarilo opcionalmente sustituido con R3.

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INFORME DE BÚSQUEDA INTERNACIONAL

Solicitud internacional Nº
PCT/SE2010/050375

A. CLASIFICACIÓN DEL OBJETO DE LA SOLICITUD

CIP: ver hoja extra

De acuerdo con la Clasificación Internacional de Patentes (CIP) o según la clasificación nacional y la CIP

B. SECTORES COMPRENDIDOS POR LA BÚSQUEDA

Documentación mínima consultada (sistema de clasificación, seguido de los símbolos de clasificación)

CIP:A61K, A61P, C07D

Otra documentación consultada, además de la documentación mínima, en la medida en que tales documentos formen parte de los sectores comprendidos por la búsqueda

SE, DK, FI, NO clases como arriba

Bases de datos electrónicas consultadas durante la búsqueda internacional (nombre de la base de datos y, si es posible, términos de búsqueda utilizados)

EPO-Internal, PAJ, WPI data, CHEM ABS Data

C. DOCUMENTOS CONSIDERADOS RELEVANTES

Categoría*	Documentos citados, con indicación, si procede, de las partes relevantes	Relevante para las reivindicaciones Nº
X	US 20080081803 A1 (MERCK AND CO), 3 de abril de 2008 (2008-04-03); página 50, párrafo [0602] - página 50, párrafo [0602]; intermedio 44 --	1-2
A	WO 9514683 A1 (THE DU PONT MERCK PHARMACEUTICAL COMPANY), 1 de junio de 1995 (1995-06-01); reivindicaciones 1-10 --	1-10
X	3(2H)-Isoxazolone, 5-(4-piperidinyl)-, bromide (1:1), Extraído de: STN International File Registry; CHEMCATS, RN 884230-75-5 -- -------	1-2

☐ En la continuación del recuadro C se relacionan otros documentos.

☒ Los documentos de familias de patentes se indican en el anexo.

* Categorías especiales de documentos citados:

"A" documento que define el estado general de la técnica no considerado como particularmente relevante

"E" documento anterior aunque publicado en la fecha de presentación internacional o en fecha posterior

"L" documento que puede plantear dudas sobre una reivindicación de prioridad o que se cita para determinar la fecha de publicación de otra cita o por una razón especial (como la indicada)

"O" documento que se refiere a una divulgación oral, a una utilización, a una exposición o a cualquier otro medio

"P" documento publicado antes de la fecha de presentación internacional pero con posterioridad a la fecha de prioridad reivindicada

"T" documento ulterior publicado con posterioridad a la fecha de presentación internacional o de prioridad, que no pertenece al estado de la técnica pertinente pero que se cita por permitir la comprensión del principio o teoría que constituye la base de la invención

"X" documento particularmente relevante; la invención reivindicada no puede considerarse nueva o que implique una actividad inventiva por referencia al documento aisladamente considerado

"Y" documento particularmente relevante; la invención reivindicada no puede considerarse que implique una actividad inventiva cuando el documento se asocia a otro u otros documentos de la misma naturaleza, resultando dicha combinación evidente para un experto en la materia

"&" documento que forma parte de la misma familia de patentes

Fecha en que se ha concluido la búsqueda internacional	Fecha de expedición del Informe de Búsqueda Internacional
05-07-2010	06-07-2010

Nombre y dirección postal de la Administración encargada de la Búsqueda Internacional	Funcionario autorizado
Patent- och registreringsverket Box 5055 S-102 42 ESTOCOLMO No. de Fax. + 46 8 666 02 86	Carolina Gomez Lagerlöf No. de Teléfono + 46 8 782 25 00

INFORME DE BÚSQUEDA INTERNACIONAL

Solicitud Internacional N°
PCT/SE2010/050375

Recuadro II **Observaciones cuando se estime que algunas reivindicaciones no pueden ser objeto de búsqueda (continuación del punto 2 de la primera hoja)**

Este informe de búsqueda internacional no se ha realizado en relación a ciertas reivindicaciones por los siguientes motivos:

1. ☒ Las reivindicaciones n°s: 5-6
se refieren a un objeto con respecto al cual esta Administración no está obligada a proceder a la búsqueda, a saber:

Las reivindicaciones 5-6 se relacionan con un método de tratamiento del cuerpo humano o animal mediante cirugía o terapia, así como con métodos de diagnósticos, veáse PCT Regla 39.1(iv). Sin embargo, una búsqueda ha sido realizada para estas reivindicaciones. La búsqueda se ha basado en el contenido técnico de las reivindicaciones.

2. ☐ Las reivindicaciones n°s:
se refieren a elementos de la solicitud nacional que no cumplen con los requisitos establecidos, de tal modo que no pueda efectuarse una búsqueda provechosa, concretamente:

3. ☐ Las reivindicaciones n°s:
son reivindicaciones dependientes y no están redactadas de conformidad con los párrafos segundo y tercero de la Regla 6.4(a)..

Recuadro III **Observaciones cuando falta unidad de invención (continuación del punto 3 de la primera hoja)**

La Administración encargada de la búsqueda internacional ha detectado varias invenciones en la presente solicitud nacional, a saber:

1. ☐ Dado que todas las tasas adicionales requeridas han sido satisfechas por el solicitante dentro del plazo, el presente informe de búsqueda de tipo internacional comprende todas las reivindicaciones que pueden ser objeto de búsqueda.

2. ☐ Dado que todas las reivindicaciones que pueden ser objeto de búsqueda podrían serlo sin realizar un esfuerzo que justifique tasas adicionales, esta Administración no requirió el pago de tasas adicionales.

3. ☐ Dada que tan sólo una parte de las tasas adicionales requeridas ha sido satisfecha dentro del plazo por el solicitante, el presente informe de búsqueda de tipo internacional comprende solamente aquellas reivindicaciones respecto de las cuales han sido satisfechas las tasas, concretamente las reivindicaciones n°s:

4. ☐ Ninguna de las tasas adicionales requeridas ha sido satisfecha por el solicitante dentro del plazo, en consecuencia, el presente informe de búsqueda de tipo internacional se limita a la invención mencionada en primer término en las reivindicaciones, cubierta por las reivindicaciones n°s:

Indicación en cuanto a la protesta

☐ Se acompañó a las tasas adicionales la protesta del solicitante y, en su caso, el pago de una tasa de protesta.

☐ Se acompañó a las tasas adicionales la protesta del solicitante, pero la tasa de protesta aplicable no se pagó en el plazo estabecido para ello.

☐ El pago de las tasas adicionales no ha sido acompañado de ninguna protesta.

INFORME DE BÚSQUEDA INTERNACIONAL

Solicitud internacional N°
PCT/SE2010/050375

Continuación de: la segunda hoja
Clasificación internacional de patentes (CIP)

C07D 413/04 (2006.01)
A61K 31/4523 (2006.01)
A61P 7/04 (2006.01)

Descargue los documentos de su patente en www.prv.se
Los documentos de patente citados se pueden descargar en www.prvf.se mediante los vínculos siguientes:

- En English/Searches and advisory services/Cited documents (servicio en inglés) o
- e-tjänster/anförda document (servicio en sueco).

Use el número de solicitud como número de usuario.
La contraseña es **YZUZRBXLRO**.

Las copias en papel se pueden ordenar a un costo de 50 SEK por copia a PVR InterPat (número de teléfono 08-782 28 85).

La bibliografía citada, si la hay, se adjuntará impresa.

INFORME DE BÚSQUEDA INTERNACIONAL
Información sobre miembros de la familia de patentes

Solicitud internacional Nº
PCT/SE2010/050375

US	20080081803	A1	03/04/2008	US	7598243	B2	06/10/2009
WO	9514683	A1	01/06/1995	AT	198748	T	15/02/2001
				AU	1098095	A	13/06/1995
				AU	695853	B2	27/08/1998
				BR	9408137	A	12/08/1997
				CA	2174838	A1	01/06/1995
				CZ	9601419	A3	13/11/1996
				DE	69426604	D1	22/02/2001
				DK	730590	T3	19/03/2001
				EP	0730590	B1	17/01/2001
				ES	2154326	T3	01/04/2001
				FI	962184	A	23/05/1996
				GR	3035610	T3	29/06/2001
				HR	940952	A2	30/04/1997
				HU	74690	A2	28/01/1997
				IL	111721	A	01/06/2000
				JP	9505590	T	03/06/1997
				NO	309768	B1	26/03/2001
				NO	962096	A	23/05/1996
				NZ	276633	A	27/04/1998
				PL	314591	A1	16/09/1996
				PL	182303	B1	31/12/2001
				RU	2149871	C1	27/05/2000
				SK	66696	A3	06/11/1996
				TW	483895	B	21/04/2002
				US	5849736	A	15/12/1998

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PATENT COOPERATION TREATY PCT/SE2010/050375

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

ASTRAZENECA INTELLECTUAL PROPERTY
AstraZeneca AB
S-151 85 Södertälje
SUÈDE

Date of mailing *(day/month/year)*
19 September 2011 (19.09.2011)

Applicant's or agent's file reference
103552-1P WO

IMPORTANT NOTIFICATION

International application No.
PCT/SE2010/050375

International filing date *(day/month/year)*
06 April 2010 (06.04.2010)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address	State of Nationality	State of Residence
CHENG, Leifeng AstraZeneca R&D Mölndal S-431 83 Mölndal Sweden	GB	SE
	Telephone No.	
	Facsimile No.	
	E-mail address	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☒ the nationality ☐ the residence

Name and Address	State of Nationality	State of Residence
CHENG, Leifeng AstraZeneca R&D China Building 7 No. 898 Halei Road Zhangjiang Hi-Tech Park Shanghai 201203 China	SE	CN
	Telephone No.	
	Facsimile No.	
	E-mail address ☐ Notifications by e-mail authorized	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☐ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Tholle Peter
Facsimile No. +41 22 338 70 80	e-mail pt03.pct@wipo.int Telephone No. +41 22 338 74 03

Form PCT/IB/306 (January 2009) I/T6GQFHCJ0

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 103552-1P WO	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/SE2010/050375	International filing date *(day/month/year)* 06-04-2010	(Earliest) Priority Date *(day/month/year)* 07-04-2009
Applicant ASTRAZENECA AB et al		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☐ 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:

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, 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/SE2010/050375

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.: 5-6
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 5-6 relate to a method for treatment of the human or animal body by surgery or by therapy, as well as diagnostic methods, see PCT rule 39.1(iv). Nevertheless, a search has been made for these claims. The search has been directed to the technical content of the claims.

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:

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 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.:

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/SE2010/050375

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet

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)

IPC:A61K, A61P, C07D

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

SE, DK, FI, NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, PAJ, WPI data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 20080081803 A1 (MERCK AND CO), 3 April 2008 (2008-04-03); page 50, paragraph [0602] - page 50, paragraph [0602]; Intermediate 44	1-2
A	WO 9514683 A1 (THE DU PONT MERCK PHARMACEUTICAL COMPANY), 1 June 1995 (1995-06-01); claims 1-10	1-10
X	3(2H)-Isoxazolone, 5-(4-piperidinyl)-, bromide (1:1), Retrieved from: STN International File Registry; CHEMCATS, RN 884230-75-5	1-2

☐ 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 application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
05-07-2010	06-07-2010

Name and mailing address of the ISA/SE	Authorized officer
Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. + 46 8 666 02 86	Carolina Gomez Lagerlöf Telephone No. + 46 8 782 25 00

International application No.
PCT/SE2010/050375

Continuation of: second sheet

International Patent Classification (IPC)

C07D 413/04 (2006.01)
A61K 31/4523 (2006.01)
A61P 7/04 (2006.01)

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The cited patent documents can be downloaded:

- From "Cited documents" found under our online services at www.prv.se (English version)
- From "Anförda dokument" found under "e-tjänster" at www.prv.se (Swedish version)

Use the application number as username. The password is **YZUZRBXLRO**.

Paper copies can be ordered at a cost of 50 SEK per copy from PRV InterPat (telephone number 08-782 28 85).

Cited literature, if any, will be enclosed in paper form.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/SE2010/050375

US	20080081803	A1	03/04/2008	US	7598243	B2	06/10/2009
WO	9514683	A1	01/06/1995	AT	198748	T	15/02/2001
				AU	1098095	A	13/06/1995
				AU	695853	B2	27/08/1998
				BR	9408137	A	12/08/1997
				CA	2174838	A1	01/06/1995
				CZ	9601419	A3	13/11/1996
				DE	69426604	D1	22/02/2001
				DK	730590	T3	19/03/2001
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				ES	2154326	T3	01/04/2001
				FI	962184	A	23/05/1996
				GR	3035610	T3	29/06/2001
				HR	940952	A2	30/04/1997
				HU	74690	A2	28/01/1997
				IL	111721	A	01/06/2000
				JP	9505590	T	03/06/1997
				NO	309768	B1	26/03/2001
				NO	962096	A	23/05/1996
				NZ	276633	A	27/04/1998
				PL	314591	A1	16/09/1996
				PL	182303	B1	31/12/2001
				RU	2149871	C1	27/05/2000
				SK	66696	A3	06/11/1996
				TW	483895	B	21/04/2002
				US	5849736	A	15/12/1998

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-132448- -00000-0000

Fecha: 2011-10-06 17:03:39 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 394

PATENTE DE INVENCIÓN ☐ MODE

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

Completa ☐ Incompleta ☐

PATENTE DE INVENCIÓN PCT ☒ MODELO DE UTILIDAD PCT ☐ Art.33 Decisión 486/00, Circular Única

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

Completa ☒ Incompleta ☐

DISEÑO INDUSTRIAL ☐ (Art. 119 Decisión 486/00)

- ☐ Indicación que se solicita Diseño industrial
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

ESQUEMA DE TRAZADO ☐ (Art. 92 Decisión 486/00)

- ☐ Indicación que se solicita un esquema de trazado
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica de un esquema de trazado
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐