SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-043260- -00000-0000
Fecha: 2011-04-07 17:02:53 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 414

PCT BT

Industria y Comercio
SUPERINTENDENCIA

11-43260

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIRECCIÓN DE NUEVAS CREACIONES

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: COMPUESTOS HETEROAROMATICOS FUSIONADOS Y ESPIROCÍCLICOS PARA EL TRATAMIENTO DE INFECCIONES BACTERIANAS

SOLICITANTE: ASTRAZENECA AB

DIRECCIÓN: S-SE-151 85 Södertälje, Suecia

APODERADO: CARLOS R. OLARTE

BOGOTÁ 07 de Abril de 2011

P2011/000061

14-05-2011
No

OLARTEMOURE

OLARTE MOURE & ASOCIA

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-043260- -00000-0000
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PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2011/000061**

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:** Diagonal 34 No. 5-28 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/GB2009/051363 Fecha Octubre 13, 2009

Publicación Internacional No. WO 2010/043893 Fecha Abril 22, 2010

(6) **Título (54)** **COMPUESTOS HETEROAROMATICOS FUSIONADOS Y ESPIROCÍCLICOS PARA EL TRATAMIENTO DE INFECCIONES BACTERIANAS**

Clasificación Internacional (51) C07D 471/22, C07D 498/22, C07D 513/22, A61P 31/04, A61K 31/535

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

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Octubre 14, 2008	61/105.189

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

(10) **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. Declaraciòn bajo la Regla 4.17 (ii) del PCT.G
- [ ] Declaraciones.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

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

LISTA DE INVENTORES

PCT/GB2009/051363

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Nacionalidad: Canadiense

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 Minjusticia

Apostilla adjunta:

APOSTILLE
(Convention du La Haye du 5 octobre 1961)

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

Certificación:

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

Fecha: 13 de Noviembre de 2007.

Traductor: Jorge Enrique Sierra Reyes.

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

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

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

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

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

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. **Country :** **Sweden**

   This public document

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

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

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

   Notary Public in Stockholm

Certified

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

7. **by** Björn Sandin

   Notary Public

8. **No** 4071

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

NOTARIUS PUBLICUS I STOCKHOLM
BJÖRN SANDIN

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. Rodrígue
Lina Mosquer
Catalina Barbastefan

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

Power of Attorney

The undersigned,

domiciled in

AstraZeneca AB

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,

domiciliado en

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

Signature/Firma: Anders Burén
Authorized Signatory

Date/Fecha: 24 OCTOBER 2007

City,Country/Ciudad,País: SÖDERTÄLJE

NOTARIUS PUBLICUS i STOCKHOLM
ANNE-MARIE BONDE

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
Authorized Signatory

OLARTE RAISBECK
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 (llegible)

Certificado de Existencia

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

AstraZeneca AB

Registro No. 556011-7482

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

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

(Firmado) Anna-Karin Östin.

Hay un sello de Bolagsverket

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

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

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 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:**

NOTARIUS PUBLICUS I STOCKHOLM

BJÖRN SANDIN

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

11426

The Ministry for Foreign Affairs in Stockholm hereby certifies that

Mr. Anna-Karin Bäck

Swedish Companies Registration Office, Sundsvall

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

Fee Stockholm this 14th day of August 07

Kr 60/- PAID

Agneta Lodelius

MINISTRY FOR FOREIGN AFFAIRS

EMBASSY OF SUDAN STOCKHOLM

SIGNATURE OF Agneta Lodelius

AND STAMP OF : SE MFA

SIGNATURE : Mohamed Hussein

DATE : 20-08-07

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 April 2010 (22.04.2010)

PCT

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WO 2010/043893 A1

(51) International Patent Classification:
C07D 471/22 (2006.01) *A61P 31/04* (2006.01)
C07D 498/22 (2006.01) *A61K 31/535* (2006.01)
C07D 513/22 (2006.01)

(21) International Application Number:
PCT/GB2009/051363

(22) International Filing Date:
13 October 2009 (13.10.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/105,189 14 October 2008 (14.10.2008) US

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

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

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BARVIAN, Kevin** [US/US]; AstraZeneca R&D Boston, 35 Gatehouse Drive, Waltham, Massachusetts 02451 (US). **BASARAB, Gregory, Steven** [US/US]; AstraZeneca R&D Boston, 35 Gatehouse Drive, Waltham, MA 02451 (US). **GOWRAVARAM, Madhusudhan, Reddy** [US/US]; AstraZeneca R&D Boston, 35 Gatehouse Drive, Waltham, Massachusetts 02451 (US). **HAUCK, Sheila, Irene** [US/US]; AstraZeneca R&D Boston, 35 Gatehouse Drive, Waltham, Massachusetts 02451 (US). **ZHOU, Fei** [CA/US]; AstraZeneca R&D Boston, 35 Gatehouse Drive, Waltham, Massachusetts 02451 (US).

(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, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

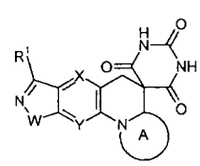
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, 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).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) Title: FUSED, SPIROCYCLIC HETEROAROMATIC COMPOUNDS FOR THE TREATMENT OF BACTERIAL INFECTIONS



(I)

(57) Abstract: The present invention relates to compounds of Formula (I); to pharmaceutically acceptable salts thereof, to methods of using them to treat bacterial infections, and to methods for their preparation.

WO 2010/043893 A1

FUSED, SPIROCYCLIC HETEROAROMATIC COMPOUNDS FOR THE TREATMENT OF BACTERIAL INFECTIONS

Field of the Invention

The present invention relates to novel substituted heterocycles, their pharmaceutical compositions and methods of use. In addition, the present invention relates to therapeutic methods for the treatment of bacterial infections.

Background of the Invention

The international microbiological and infectious disease community continues to express serious concern that the continuing evolution of antibacterial resistance could result in bacterial strains against which currently available antibacterial agents will be ineffective. The outcome of such an occurrence could have considerable morbidity and mortality. In general, bacterial pathogens may be classified as either Gram-positive or Gram-negative pathogens. Antibiotic compounds with effective activity against both Gram-positive and Gram-negative pathogens are generally regarded as having a broad spectrum of activity.

Gram-positive pathogens are of particular concern because of the development of resistant strains that are both difficult to treat and difficult to eradicate from the hospital environment once established. Examples of such strains are methicillin resistant *Staphylococcus aureus* (MRSA), methicillin resistant coagulase-negative *staphylococci* (MRCNS), penicillin resistant *Streptococcus pneumoniae* and multiple resistant *Enterococcus faecium*. Resistance is increasing at a steady rate rendering many agents less effective in the treatment of Gram-positive pathogens. In addition, there is increasing resistance to agents such as β-lactams, quinolones and macrolides used for the treatment of upper respiratory tract infections caused by Gram-negative strains including *H. influenzae* and *M. catarrhalis*. In addition, nosocomial Gram-negative pathogens, such as *Pseudomonas aeruginosa*, are difficult to treat due to resistance development. Consequently, in order to overcome the threat of widespread multi-drug resistant organisms, there is an on-going need to develop new antibacterials.

Deoxyribonucleic acid (DNA) gyrase is a member of the type II family of topoisomerases that control the topological state of DNA in cells (Champoux, J. J.; 2001. Ann. Rev. Biochem. 70: 369-413). Type II topoisomerases use the free energy from adenosine triphosphate (ATP)

hydrolysis to alter the topology of DNA by introducing transient double-stranded breaks in the DNA, catalyzing strand passage through the break and resealing the DNA. DNA gyrase is an essential and conserved enzyme in bacteria and is unique among topoisomerases in its ability to introduce negative supercoils into DNA. The enzyme consists of two subunits, encoded by *gyrA* and *gyrB*, forming an A_2B_2 tetrameric complex. The A subunit of gyrase (GyrA) is involved in DNA breakage and resealing and contains a conserved tyrosine residue that forms the transient covalent link to DNA during strand passage. The B subunit (GyrB) catalyzes the hydrolysis of ATP and interacts with the A subunit to translate the free energy from hydrolysis to the conformational change in the enzyme that enables strand-passage and DNA resealing.

Another conserved and essential type II topoisomerase in bacteria, called topoisomerase IV, is primarily responsible for separating the linked closed circular bacterial chromosomes produced in replication. This enzyme is closely related to DNA gyrase and has a similar tetrameric structure formed from subunits homologous to Gyr A and to Gyr B. The overall sequence identity between gyrase and topoisomerase IV in different bacterial species is high. Therefore, compounds that target bacterial type II topoisomerases have the potential to inhibit two targets in cells, DNA gyrase and topoisomerase IV; as is the case for existing quinolone antibacterials (Maxwell, A. 1997, Trends Microbiol. 5: 102-109).

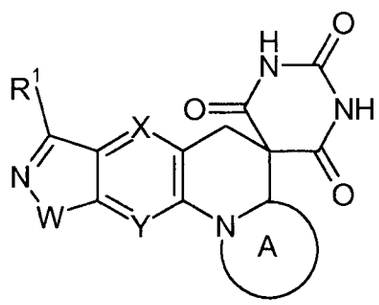
Antibacterials targeting DNA gyrase are well established in the art, including examples such as the quinolones and the coumarins. The quinolones (*e.g.* ciprofloxacin) are broad-spectrum antibacterials that inhibit the DNA breakage and reunion activity of the enzyme and trap the GyrA subunit covalently complexed with DNA (Drlica, K., and X. Zhao, 1997, Microbiol. Molec. Biol. Rev. 61: 377-392). Members of this class of antibacterials also inhibit topoisomerase IV and as a result, the primary target of these compounds varies among species. Although the quinolones are successful antibacterials, resistance generated primarily by mutations in the target (DNA gyrase and topoisomerase IV) is becoming an increasing problem in several organisms, including *S. aureus* and *Streptococcus pneumoniae* (Hooper, D. C., 2002, The Lancet Infectious Diseases 2: 530-538). In addition, quinolones, as a chemical class, suffer from toxic side effects, including arthropathy that prevents their use in children (Lipsky, B. A. and Baker, C. A., 1999, Clin. Infect. Dis. 28: 352-364). Furthermore, the potential for

cardiotoxicity, as predicted by prolongation of the QT_c interval, has been cited as a toxicity concern for quinolones.

There are several known natural product inhibitors of DNA gyrase that compete with ATP for binding the GyrB subunit (Maxwell, A. and Lawson, D.M. 2003, Curr. Topics in Med. Chem. 3: 283-303). The coumarins are natural products isolated from *Streptomyces spp.*, examples of which are novobiocin, chlorobiocin and coumermycin A1. Although these compounds are potent inhibitors of DNA gyrase, their therapeutic utility is limited due to toxicity in eukaryotes and poor penetration in Gram-negative bacteria (Maxwell, A. 1997, Trends Microbiol. 5: 102-109). Another natural product class of compounds that targets the GyrB subunit is the cyclothialidines, which are isolated from *Streptomyces filipensis* (Watanabe, J. et al 1994, J. *Antibiot.* 47: 32-36). Despite potent activity against DNA gyrase, cyclothialidine is a poor antibacterial agent showing activity only against some eubacterial species (Nakada, N, 1993, *Antimicrob. Agents Chemother.* 37: 2656-2661).

Summary of the Invention

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



Formula (I)

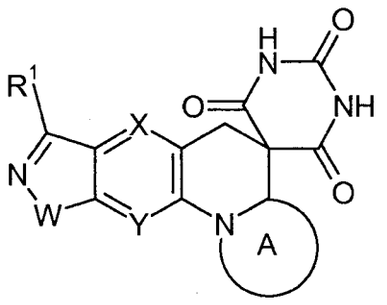
and to pharmaceutically acceptable salts thereof.

Typical compounds of Formula (I) are believed to inhibit bacterial DNA gyrase and are therefore of interest for their antibacterial effects. The inventive compounds are believed to be active against a variety of bacterial organisms, including both Gram positive and Gram negative aerobic

and anaerobic bacteria.

Detailed Description of the Invention

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



Formula (I)

and to pharmaceutically acceptable salts thereof, wherein:

Ring A is fused 5- to 7-membered non-aromatic heterocyclic ring, wherein said fused 5- to 7-membered non-aromatic heterocyclic ring is optionally substituted on carbon with one or more R^4, and wherein any -NH- moiety of said 5- to 7-membered heterocyclic ring is optionally substituted with R^{4*};

W is selected from -O-, -NH-, -S-, and $-S(O)_2-$;

X is selected from N and C-R^2;

Y is selected from N and C-R^3;

R^1 is selected from H, halo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, heterocyclyl, $-OR^{1a}$, $-SR^{1a}$, $-N(R^{1a})_2$, $-N(R^{1a})C(O)R^{1b}$, $-N(R^{1a})N(R^{1a})_2$, $-NO_2$, $-N(R^{1a})OR^{1a}$, $-ON(R^{1a})_2$, -C(O)H, $-C(O)R^{1b}$, $-C(O)_2R^{1a}$, $-C(O)N(R^{1a})_2$, $-C(O)N(R^{1a})(OR^{1a})$, $-OC(O)N(R^{1a})_2$, $-N(R^{1a})C(O)_2R^{1a}$, $-N(R^{1a})C(O)N(R^{1a})_2$, $-OC(O)R^{1b}$, $-S(O)R^{1b}$, $-S(O)_2R^{1b}$, $-S(O)_2N(R^{1a})_2$, $-N(R^{1a})S(O)_2R^{1b}$, $-C(R^{1a})=N(R^{1a})$, and $-C(R^{1a})=N(OR^{1a})$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, and heterocyclyl are optionally substituted on carbon with one or more R^{10}, and wherein any -NH- moiety of said heterocyclyl is optionally substituted with R^{10*};

R^{1a} in each occurrence is independently selected from H, C_{1-6}alkyl, carbocyclyl, and heterocyclyl, wherein said C_{1-6}alkyl, carbocyclyl, and heterocyclyl in each occurrence are optionally and independently substituted on carbon with one or more R^{10}, and wherein any -NH-

moiety of said heterocyclyl is optionally substituted with R^{10*};

R^{1b} in each occurrence is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, and heterocyclyl, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, and heterocyclyl in each occurrence are optionally and independently substituted on carbon with one or more R^{10}, and wherein any -NH- moiety of said heterocyclyl is optionally substituted with R^{10*};

R^2 is selected from H, halo, and -CN;

R^3 is selected from H, halo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $-OR^{3a}$, $-SR^{3a}$, and $-N(R^{3a})_2$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, and C_{2-6}alkynyl are optionally substituted on carbon with one or more R^{30};

R^{3a} in each occurrence is independently selected from H and C_{1-6}alkyl, wherein said C_{1-6}alkyl in each occurrence is optionally and independently substituted on carbon with one or more R^{30};

R^4 in each occurrence is independently selected from halo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, heterocyclyl, $-OR^{4a}$, $-SR^{4a}$, $-N(R^{4a})_2$, $-N(R^{4a})C(O)R^{4b}$, $-N(R^{4a})N(R^{4a})_2$, $-NO_2$, $-N(R^{4a})-OR^{4a}$, $-O-N(R^{4a})_2$, -C(O)H, $-C(O)R^{4b}$, $-C(O)_2R^{4a}$, $-C(O)N(R^{4a})_2$, $-C(O)N(R^{4a})(OR^{4a})$ $-OC(O)N(R^{4a})_2$, $-N(R^{4a})C(O)_2R^{4a}$, $-N(R^{4a})C(O)N(R^{4a})_2$, $-OC(O)R^{4b}$, $-S(O)R^{4b}$, $-S(O)_2R^{4b}$, $-S(O)_2N(R^{4a})_2$, $-N(R^{4a})S(O)_2R^{4b}$, $-C(R^{4a})=N(R^{4a})$, and $-C(R^{4a})=N(OR^{4a})$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, and heterocyclyl are optionally substituted on carbon with one or more R^{40}, and wherein any -NH- moiety of said heterocyclyl is optionally substituted with R^{40*};

R^{4*} in each occurrence is independently selected from C_{1-6}alkyl, carbocyclyl, heterocyclyl, -C(O)H, $-C(O)R^{4b}$, $-C(O)_2R^{4a}$, $-C(O)N(R^{4a})_2$, $-S(O)R^{4b}$, $-S(O)_2R^{4b}$, $-S(O)_2N(R^{4a})_2$, $-C(R^{4a})=N(R^{4a})$, and $-C(R^{4a})=N(OR^{4a})$, wherein said C_{1-6}alkyl, carbocyclyl, and heterocyclyl in each occurrence are optionally and independently substituted on carbon with one or more R^{40}, and wherein any -NH- moiety of said heterocyclyl is optionally substituted with R^{40*};

R^{4a} in each occurrence is independently selected from H, C_{1-6}alkyl, carbocyclyl, and heterocyclyl, wherein said C_{1-6}alkyl, carbocyclyl, and heterocyclyl in each occurrence are optionally and independently substituted on carbon with one or more R^{40}, and wherein any -NH- moiety of said heterocyclyl is optionally substituted with R^{40*};

R^{4b} in each occurrence is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, and heterocyclyl, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, and

heterocyclyl in each occurrence are optionally and independently substituted on carbon with one or more R^{40}, and wherein any -NH- moiety of said heterocyclyl is optionally substituted with R^{40*};

R^{10} in each occurrence is independently selected from halo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, heterocyclyl, $-OR^{10a}$, $-SR^{10a}$, $-N(R^{10a})_2$, $-N(R^{10a})C(O)R^{10b}$, $-N(R^{10a})N(R^{10a})_2$, $-NO_2$, $-N(R^{10a})-OR^{10a}$, $-O-N(R^{10a})_2$, -C(O)H, $-C(O)R^{10b}$, $-C(O)_2R^{10a}$, $-C(O)N(R^{10a})_2$, $-C(O)N(R^{10a})(OR^{10a})$, $-OC(O)N(R^{10a})_2$, $-N(R^{10a})C(O)_2R^{10a}$, $-N(R^{10a})C(O)N(R^{10a})_2$, $-OC(O)R^{10b}$, $-S(O)R^{10b}$, $-S(O)_2R^{10b}$, $-S(O)_2N(R^{10a})_2$, $-N(R^{10a})S(O)_2R^{10b}$, $-C(R^{10a})=N(R^{10a})$, and $-C(R^{10a})=N(OR^{10a})$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, and heterocyclyl in each occurrence are optionally and independently substituted on carbon with one or more R^a, and wherein any -NH- moiety of said heterocyclyl is optionally substituted with R^{a*};

R^{10*} in each occurrence is independently selected from C_{1-6}alkyl, carbocyclyl, heterocyclyl, -C(O)H, $-C(O)R^{10b}$, $-C(O)_2R^{10a}$, $-C(O)N(R^{10a})_2$, $-S(O)R^{10b}$, $-S(O)_2R^{10b}$, $-S(O)_2N(R^{10a})_2$, $-C(R^{10a})=N(R^{10a})$, and $-C(R^{10a})=N(OR^{10a})$, wherein said C_{1-6}alkyl, carbocyclyl, and heterocyclyl in each occurrence are optionally and independently substituted on carbon with one or more R^a, and wherein any -NH- moiety of said heterocyclyl is optionally substituted with R^{a*};

R^{10a} in each occurrence is independently selected from H, C_{1-6}alkyl, carbocyclyl, and heterocyclyl, wherein said C_{1-6}alkyl, carbocyclyl, and heterocyclyl in each occurrence are optionally and independently substituted on carbon with one or more R^a, and wherein any -NH- moiety of said heterocyclyl is optionally substituted with R^{a*};

R^{10b} in each occurrence is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, and heterocyclyl, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, and heterocyclyl in each occurrence are optionally and independently substituted on carbon with one or more R^a, and wherein any -NH- moiety of said heterocyclyl is optionally substituted with R^{a*};

R^{30} in each occurrence is independently selected from halo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $-OR^{30a}$, $-SR^{30a}$, and $-N(R^{30a})_2$;

R^{30a} in each occurrence is independently selected from H and C_{1-6}alkyl;

R^{40} in each occurrence is independently selected from halo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, heterocyclyl, $-OR^{40a}$, $-SR^{40a}$, $-N(R^{40a})_2$, $-N(R^{40a})C(O)R^{40b}$, $-N(R^{40a})N(R^{40a})_2$, $-NO_2$, $-N(R^{40a})-OR^{40a}$, $-O-N(R^{40a})_2$, -C(O)H, $-C(O)R^{40b}$, $-C(O)_2R^{40a}$, $-C(O)N(R^{40a})_2$, $-C(O)N(R^{40a})(OR^{40a})$, $-OC(O)N(R^{40a})_2$, $-N(R^{40a})C(O)_2R^{40a}$, $-N(R^{40a})C(O)N(R^{40a})_2$,

$-OC(O)R^{40b}$, $-S(O)R^{40b}$, $-S(O)_2R^{40b}$, $-S(O)_2N(R^{40a})_2$, $-N(R^{40a})S(O)_2R^{40b}$, $-C(R^{40a})=N(R^{40a})$, and $-C(R^{40a})=N(OR^{40a})$;

$\mathbf{R^{40*}}$ in each occurrence is independently selected from C_{1-6}alkyl, carbocyclyl, heterocyclyl, $-C(O)H$, $-C(O)R^{40b}$, $-C(O)_2R^{40a}$, $-C(O)N(R^{40a})_2$, $-S(O)R^{40b}$, $-S(O)_2R^{40b}$, $-S(O)_2N(R^{40a})_2$, $-C(R^{40a})=N(R^{40a})$, and $-C(R^{40a})=N(OR^{40a})$;

$\mathbf{R^{40a}}$ in each occurrence is independently selected from H, C_{1-6}alkyl, carbocyclyl, and heterocyclyl;

$\mathbf{R^{40b}}$ in each occurrence is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, and heterocyclyl;

$\mathbf{R^{a}}$ in each occurrence is independently selected from halo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, heterocyclyl, $-OR^m$, $-SR^m$, $-N(R^m)_2$, $-N(R^m)C(O)R^n$, $-N(R^m)N(R^m)_2$, $-NO_2$, $-N(R^m)-OR^m$, $-O-N(R^m)_2$, $-C(O)H$, $-C(O)R^n$, $-C(O)_2R^m$, $-C(O)N(R^m)_2$, $-C(O)N(R^m)(OR^m)$, $-OC(O)N(R^m)_2$, $-N(R^m)C(O)_2R^m$, $-N(R^m)C(O)N(R^m)_2$, $-OC(O)R^n$, $-S(O)R^n$, $-S(O)_2R^n$, $-S(O)_2N(R^m)_2$, $-N(R^m)S(O)_2R^n$, $-C(R^m)=N(R^m)$, and $-C(R^m)=N(OR^m)$;

$\mathbf{R^{a*}}$ in each occurrence is independently selected from C_{1-6}alkyl, carbocyclyl, heterocyclyl, $-C(O)H$, $-C(O)R^n$, $-C(O)_2R^m$, $-C(O)N(R^m)_2$, $-S(O)R^n$, $-S(O)_2R^n$, $-S(O)_2N(R^m)_2$, $-C(R^m)=N(R^m)$, and $-C(R^m)=N(OR^m)$;

$\mathbf{R^{m}}$ in each occurrence is independently selected from H, C_{1-6}alkyl, carbocyclyl, and heterocyclyl; and

$\mathbf{R^{n}}$ in each occurrence is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, and heterocyclyl.

Alkyl - As used herein the term "alkyl" refers to both straight and branched chain saturated hydrocarbon radicals having the specified number of carbon atoms. References to individual alkyl groups such as "propyl" are specific for the straight chain version only and references to individual branched chain alkyl groups such as 'isopropyl' are specific for the branched chain version only. In one aspect, "alkyl" is methyl.

Alkylene - As used herein the term "alkylene" refers to both straight and branched chain saturated hydrocarbon diradicals having the specified number of carbon atoms. For example, "C_{1-6}alkylene" includes groups such as C_{1-3}alkylene, methylene, ethylene, propylene,

isopropylene, butylene, pentylene, and hexylene.

Alkenyl – As used herein, the term "alkenyl" refers to both straight and branched chain hydrocarbon radicals having the specified number of carbon atoms and containing at least one carbon-carbon double bond. For example, "C_{2-6}alkenyl" includes groups such as C_{2-5}alkenyl, C_{2-4}alkenyl, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl, 2-heptenyl, and 2-methyl-1-heptenyl.

Alkenylene – As used herein, the term "alkenylene" refers to both straight and branched chain hydrocarbon radicals having the specified number of carbon atoms and containing at least one carbon-carbon double bond. In one aspect, "alkenylene" may be ethene-1,2-diyl.

Alkynyl – As used herein, the term "alkynyl" refers to both straight and branched chain hydrocarbon radicals having the specified number of carbon atoms and containing at least one carbon-carbon triple bond. For example, "C_{2-8}alkynyl" includes groups such as C_{2-6}alkynyl, C_{2-4}alkynyl, ethynyl, 2-propynyl, 2-methyl-2-propynyl, 3-butynyl, 4-pentynyl, 5-hexynyl, 2-heptynyl, and 4-methyl-5-heptynyl.

Alkynylene – As used herein, the term "alkynylene" refers to both straight and branched chain hydrocarbon radicals having the specified number of carbon atoms and containing at least one carbon-carbon triple bond. In one aspect, "alkynylene" may be ethyne-1,2-diyl.

Halo – As used herein, the term "halo" is intended to include fluoro, chloro, bromo and iodo. In one aspect, the "halo" may refer fluoro, chloro, and bromo. In another aspect, "halo" may refer to fluoro and chloro. In still another aspect, "halo" may refer to fluoro. In yet another aspect, "halo" may refer to chloro.

Carbocyclyl – As used herein, the term "carbocyclyl" refers to a saturated, partially saturated, or unsaturated, mono or bicyclic carbon ring that contains 3-12 atoms, wherein one or more -CH_2- groups may optionally be replaced by a corresponding number of -C(O)- groups. In one aspect, the term "carbocyclyl" may refer to a monocyclic ring containing 5 or 6 atoms or a bicyclic ring

containing 9 or 10 atoms. Illustrative examples of "carbocyclyl" include adamantyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, 1-oxocyclopentyl, phenyl, naphthyl, tetralinyl, indanyl or 1-oxoindanyl. In one aspect, "carbocyclyl" may be phenyl. In another aspect, "carbocyclyl" may be selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, and cyclohexyl. In still another aspect, carbocyclyl may be phenyl.

3- to 6-Membered Carbocyclyl - In one aspect, "carbocyclyl" may be "3- to 6-membered carbocyclyl." The term "3- to 6-membered carbocyclyl" refers to a saturated or partially saturated monocyclic carbon ring containing 3 to 6 ring atoms, of which one or more $-CH_2-$ groups may be optionally replaced with a corresponding number of -C(O)- groups. Illustrative examples of "3- to 6-membered carbocyclyl" include cyclopropyl, cyclobutyl, cyclopentyl, oxocyclopentyl, cyclopentenyl, cyclohexyl, and phenyl. In another aspect, "3- to 6-membered carbocyclyl" may be cyclopropyl and phenyl. In still another aspect, "3- to 6-membered carbocyclyl" may be phenyl.

3- to 5-Membered Carbocyclyl - In one aspect, "carbocyclyl" and "3- to 6-membered carbocyclyl" may be "3- to 5-membered carbocyclyl." The term "3- to 5-membered carbocyclyl" refers to a saturated or partially saturated monocyclic carbon ring containing 3 to 5 ring atoms, of which one or more $-CH_2-$ groups may be optionally replaced with a corresponding number of -C(O)- groups. Illustrative examples of "3- to 5-membered carbocyclyl" include cyclopropyl, cyclobutyl, cyclopentyl, and cyclopentenyl. In one aspect, "3- to 5-membered carbocyclyl" may be cyclopropyl.

Heterocyclyl – As used herein, the term "heterocyclyl" refers to a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 4 to 12 atoms of which at least one atom is selected from nitrogen, sulfur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein one or more $-CH_2-$ groups can optionally be replaced with a corresponding number of -C(O)- groups. Ring sulfur atoms may be optionally oxidized to form S-oxides. Ring nitrogen atoms may be optionally oxidized to form N-oxides. Illustrative examples of the term "heterocyclyl" include benzimidazolyl, 1,3-benzodioxolyl, benzofuranyl, 1-benzothiophenyl, 1,3-benzothiazolyl, 1,3-benzoxazolyl, dioxidotetrahydrothiophenyl, 3,5-dioxopiperidinyl,

imidazolyl, indolyl, isoquinolone, isothiazolyl, isoxazolyl, morpholinyl, 1,2,4-oxadiazolyl, oxoimidazolidinyl, 2-oxopyrrolidinyl, 2-oxotetrahydrofuranyl, 2-oxo-1,3-thiazolidinyl, piperazinyl, piperidylpiperidinyl, pyranyl, pyrazolyl, pyridinyl, pyrrolyl, pyrrolidinyl, pyrrolinyl, pyrimidyl, pyrazinyl, pyrazolyl, pyridazinyl, 4-pyridone, quinolyl, tetrazolyl, tetrahydrofuranyl, tetrahydropyranyl, thiazolyl, 1,3,4-thiadiazolyl, thiazolidinyl, thienyl, thiomorpholino, 4*H*-1,2,4-triazolyl, pyridine-*N*-oxide and quinoline-*N*-oxide. In one aspect of the invention the term "heterocyclyl" may refer to a saturated, partially saturated, or unsaturated, monocyclic ring containing 5 or 6 atoms of which at least one atom is chosen from nitrogen, sulfur or oxygen, and may, unless otherwise specified, be carbon or nitrogen linked, and a ring nitrogen atom may be optionally oxidized to form an N-oxide.

4- to 6- Membered Heterocyclyl - In one aspect, "heterocycl" may be "4- to 6-membered heterocyclyl." The term "4- to 6-membered heterocyclyl" refers to a saturated, partially saturated, or unsaturated, monocyclic ring containing 4 to 6 ring atoms, of which at least one ring atom is selected from nitrogen, sulfur, and oxygen, and of which a $-CH_2-$ group may be optionally replaced by a -C(O)- group. Unless otherwise specified, "4- to 6-membered heterocyclyl" groups may be carbon or nitrogen linked. Ring nitrogen atoms may be optionally oxidized to form an N-oxide. Ring sulfur atoms may be optionally oxidized to form S-oxides. Illustrative examples of "4- to 6-membered heterocyclyl" include, but are not limited to, azetidin-1-yl, dioxidotetrahydrothiophenyl, 2,4-dioxoimidazolidinyl, 3,5-dioxopiperidinyl, furanyl, imidazolyl, isothiazolyl, isoxazolyl, morpholinyl, oxazolyl, oxetanyl, oxoimidazolidinyl, 3-oxo-1-piperazinyl, 2-oxopyrrolidinyl, 2-oxotetrahydrofuranyl, oxo-1,3-thiazolidinyl, piperazinyl, piperidyl, 2*H*-pyranyl, pyrazolyl, pyridinyl, pyrrolyl, pyrrolidinyl, pyrimidinyl, pyrazinyl, pyrazolyl, pyridazinyl, 4-pyridonyl, tetrahydrofuranyl, tetrahydropyranyl, thiazolyl, 1,3,4-thiadiazolyl, thiazolidinyl, thiomorpholinyl, thiophenyl, 4*H*-1,2,4-triazolyl, and pyridine-*N*-oxidyl.

5- or 6-Membered Heterocyclyl - In one aspect, "heterocyclyl" and "4- to 6-membered heterocyclyl" may be "5- or 6-membered heterocyclyl," which refers to a saturated, partially saturated, or unsaturated, monocyclic ring containing 5 or 6 ring atoms, of which at least one ring atom is selected from nitrogen, sulfur, and oxygen, and of which one or more $-CH_2-$ groups may

be optionally replaced with a corresponding number of -C(O)- groups. Unless otherwise specified, "5- or 6-membered heterocyclyl" groups may be carbon or nitrogen linked. Ring nitrogen atoms may be optionally oxidized to form an N-oxide. Ring sulfur atoms may be optionally oxidized to form S-oxides. Illustrative examples of "5- or 6-membered heterocyclyl" include dioxidotetrahydrothiophenyl, 2,4-dioxoimidazolidinyl, 3,5-dioxopiperidinyl, furanyl, imidazolyl, isothiazolyl, isoxazolyl, morpholinyl, oxazolyl, oxoimidazolidinyl, 2-oxopyrrolidinyl, 2-oxotetrahydrofuranyl, oxo-1,3-thiazolidinyl, piperazinyl, piperidinyl, 2*H*-pyranyl, pyrazolyl, pyridinyl, pyrrolyl, pyrrolidinyl, pyrrolidinyl, pyrimidinyl, pyrazinyl, pyrazolyl, pyridazinyl, 4-pyridonyl, tetrazolyl, tetrahydrofuranyl, tetrahydropyranyl, thiazolyl, 1,3,4-thiadiazolyl, 1,34-thiazolidinyl, thiomorpholinyl, thiophenyl, 4*H*-1,2,4-triazolyl, and pyridine-*N*-oxidyl.

6-Membered Heterocyclyl – In one aspect, "heterocyclyl," "4- to 6-membered heterocyclyl," and "5- or 6-membered heterocyclyl" may be "6-membered heterocyclyl," which refers to a saturated, partially saturated, or unsaturated, monocyclic ring containing 6 ring atoms, of which at least one ring atom is selected from nitrogen, sulfur, and oxygen, and of which one or more $-CH_2-$ groups may be optionally replaced with a corresponding number of -C(O)- groups. Unless otherwise specified, "6-membered heterocyclyl" groups may be carbon or nitrogen linked. Ring nitrogen atoms may be optionally oxidized to form an N-oxide. Ring sulfur atoms may be optionally oxidized to form S-oxides. Illustrative examples of "6-membered heterocyclyl" include 3,5-dioxopiperidinyl, morpholinyl, 3-oxo-1-piperazinyl, piperazinyl, piperidinyl, 2*H*-pyranyl, pyrazinyl, pyridazinyl, pyridinyl, and pyrimidinyl.

5 or 6-Membered Non-Aromatic Heterocyclyl – In one aspect, "heterocyclyl" and "5- or 6-membered heterocyclyl" may be "5 or 6-membered non-aromatic heterocyclyl." The term "5- or 6-membered non-aromatic heterocyclyl" is intended to refer to a saturated or partially saturated, monocyclic, non-aromatic heterocyclyl ring containing 5 or 6 ring atoms, of which at least one ring atom is selected from nitrogen, sulfur, and oxygen, and which may, unless otherwise specified, be carbon or nitrogen linked, and of which one or more $-CH_2-$ group can optionally be replaced with a corresponding number of -C(O)- groups. Ring sulfur atoms may be optionally oxidized to form S-oxides. Ring nitrogen atoms may be optionally oxidized to form N-oxides. Illustrative examples of "5 or 6-membered non-aromatic heterocyclyl" include

dioxidotetrahydrothiophenyl, 2,4-dioxoimidazolidinyl, 3,5-dioxopiperidinyl, morpholinyl, oxoimidazolidinyl, 2-oxopyrrolidinyl, 2-oxotetrahydrofuranyl, oxo-1,3-thiazolidinyl, piperazinyl, piperidinyl, 2*H*-pyranyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydropyranyl, thiomorpholinyl, and thiazolidinyl.

5- or 6-Membered Heteroaryl – In one aspect, "heterocyclyl" and "5- or 6-membered heterocyclyl" may be "5- or 6-membered heteroaryl." The term "5- or 6-membered heteroaryl" is intended to refer to a monocyclic, aromatic heterocyclyl ring containing 5 or 6 ring atoms, of which at least one ring atom is selected from nitrogen, sulfur, and oxygen. Unless otherwise specified, "5- or 6-membered heteroaryl" groups may be carbon or nitrogen linked. Ring nitrogen atoms may be optionally oxidized to form an N-oxide. Ring sulfur atoms may be optionally oxidized to form S-oxides. Illustrative examples of "5- or 6-membered heteroaryl" include furanyl, imidazolyl, isothiazolyl, isoxazole, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyridinyl, pyrrolyl, tetrazolyl, 1,3,4-thiadiazolyl, thiazolyl, thiophenyl, 4*H*-1,2,4-triazolyl.

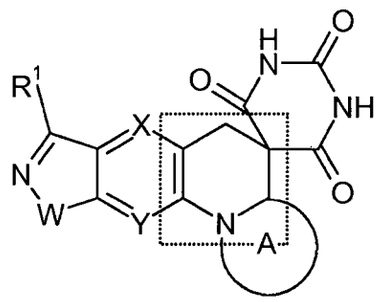
6-Membered Heteroaryl – In one aspect, "heterocyclyl," 5- or 6-membered heterocyclyl," "6-membered heterocyclyl," and "5- or 6-membered heteroaryl" may be "6-membered heteroaryl." The term "6-membered heteroaryl" is intended to refer to a monocyclic, aromatic heterocyclyl ring containing 6 ring atoms. Ring nitrogen atoms may be optionally oxidized to form an N-oxide. Illustrative examples of "6-membered heteroaryl" include pyrazinyl, pyridazinyl, pyrimidinyl, and pyridinyl.

Fused 5- to 7-Membered Heterocycle – For the purposes of Ring A, the term "fused 5- to 7-membered heterocycle" is intended to refer to a non-aromatic monocyclic ring containing 5 or 7 ring atoms, which shares two atoms, a carbon and nitrogen, with the piperidine ring of Formula (I) to which it is fused, forming a bicyclic ring system. The "fused 5- to 7-membered heterocycle" may contain, in addition to the bridgehead nitrogen shown in Formula (I), one or more ring heteroatom moieties selected from -O-, -NH-, and -S-. Ring sulfur atoms may be optionally oxidized to form S-oxides, ring nitrogen atoms may be optionally oxidized to form N-oxides, and one or more $-CH_2-$ groups can optionally be replaced by a corresponding number of

-C(O)- or -C=N(OR^{4a})- groups. Illustrative examples of the term "fused 5- to 7-membered heterocycle" include fused azepane, fused 3,5-dioxopiperidine, fused morpholine, fused oxopiperidine, fused 2-oxopyrrolidine, fused oxo-1,3-thiazolidine, fused piperazine, fused piperidine, fused pyrrolidine, fused thiazolidine, and fused thiomorpholine. In one aspect, "fused 5- to 7-membered heterocycle" is fused morpholine.

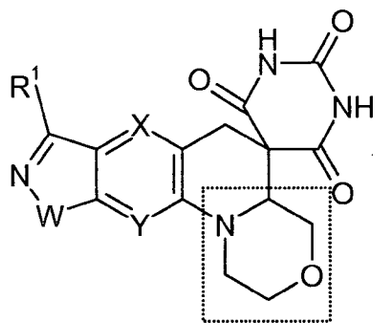
Fused 6- Membered Heterocycle – In one aspect "fused 5 to 7-membered heterocycle" may be "fused 6-membered heterocycle." The term "fused 6-membered heterocycle" is intended to refer to a non-aromatic monocyclic ring containing 6 ring atoms, which shares two atoms, a carbon and nitrogen, with the piperidine ring to which it is fused, forming a bicyclic ring system. The "fused 6-membered heterocycle" may contain, in addition to the bridgehead nitrogen shown in Formula (I), one or more ring heteroatom moieties selected from -O-, -NH-, and -S-. Ring sulfur atoms may be optionally oxidized to form S-oxides, ring nitrogen atoms may be optionally oxidized to form N-oxides, and one or more -CH_2- groups can optionally be replaced by a corresponding number of -C(O)- or -C=N(OR^{4a})- groups. Illustrative examples of the term "fused 6-membered heterocycle" include, fused 3,5-dioxopiperidine, fused morpholine, fused oxopiperidine, fused piperazine, fused piperidine, and fused thiomorpholine. In one aspect, "fused 6-membered heterocycle" is fused morpholine.

To resolve any potential ambiguity in the discussion of "fused 5- to 7-membered heterocycle" and "fused 6-membered heterocycle" above the term "piperidine ring" is intended to denote the nitrogen-containing, six-membered ring enclosed by the dotted lines in the following structure:



To resolve any potential ambiguity in the discussion of "fused 5- to 7-membered heterocycle" and "fused 6-membered heterocycle" above, the term "fused morpholine" is intended to denote the 6-membered oxygen- and nitrogen-containing ring enclosed by the dotted lines in the

following structure:



The morpholine ring may be optionally substituted as indicated hereinabove and hereinbelow.

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

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

Pharmaceutically Acceptable - As used herein, the phrase "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

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

Leaving Group – As used herein, the phrase "leaving group" is intended to refer to groups readily displaceable by a nucleophile such as an amine nucleophile, and alcohol nucleophile, or a thiol nucleophile. Examples of suitable leaving groups include halo, such as fluoro, chloro, bromo, and sulfonyloxy group, such as methanesulfonyloxy and toluene-4-sulfonyloxy.

Protecting Group – As used herein, the term "protecting group" is intended to refer to those groups used to prevent selected reactive groups (such as carboxy, amino, hydroxy, and mercapto groups) from undergoing undesired reactions.

Illustrative examples of suitable protecting groups for a hydroxy group include acyl groups; alkanoyl groups such as acetyl; aroyl groups, such as benzoyl; silyl groups, such as trimethylsilyl; and arylmethyl groups, such as benzyl. The deprotection conditions for the above hydroxy protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively a silyl group such as trimethylsilyl may be removed, for example, by fluoride or by aqueous acid; or an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation in the presence of a catalyst such as palladium-on-carbon.

Illustrative examples of suitable protecting groups for an amino group include acyl groups; alkanoyl groups such as acetyl; alkoxycarbonyl groups, such as methoxycarbonyl, ethoxycarbonyl, and *t*-butoxycarbonyl; arylmethoxycarbonyl groups, such as benzyloxycarbonyl;

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

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

Compounds of Formula (I) may form stable pharmaceutically acceptable acid or base salts, and in such cases administration of a compound as a salt may be appropriate. Examples of acid addition salts include acetate, adipate, ascorbate, benzoate, benzenesulfonate, bicarbonate, bisulfate, butyrate, camphorate, camphorsulfonate, choline, citrate, cyclohexyl sulfamate, diethylenediamine, ethanesulfonate, fumarate, glutamate, glycolate, hemisulfate, 2-hydroxyethyl-sulfonate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, hydroxymaleate, lactate, malate, maleate, methanesulfonate, meglumine, 2-naphthalenesulfonate, nitrate, oxalate, pamoate, persulfate, phenylacetate, phosphate, diphosphate, picrate, pivalate, propionate, quinate, salicylate, stearate, succinate, sulfamate, sulfanilate, sulfate, tartrate, tosylate (p-toluenesulfonate), trifluoroacetate, and undecanoate. Examples of base salts include ammonium salts; alkali metal salts such as sodium, lithium and potassium salts; alkaline earth metal salts such as aluminum, calcium and magnesium salts; salts with organic bases such as

dicyclohexylamine salts and N-methyl-D-glucamine; and salts with amino acids such as arginine, lysine, ornithine, and so forth. Also, basic nitrogen-containing groups may be quaternized with such agents as: lower alkyl halides, such as methyl, ethyl, propyl, and butyl halides; dialkyl sulfates such as dimethyl, diethyl, dibutyl; diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl halides; arylalkyl halides such as benzyl bromide and others. Non-toxic physiologically-acceptable salts are preferred, although other salts may be useful, such as in isolating or purifying the product.

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

Some compounds of Formula (I) may have chiral centres and/or geometric isomeric centres (E- and Z- isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomers and geometric isomers. The invention further relates to any and all tautomeric forms of the compounds of Formula (I).

It is also to be understood that certain compounds of Formula (I) can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms.

Additional embodiments of the invention are as follows. These additional embodiments relate to compounds of Formula (I) and pharmaceutically acceptable salts thereof. Such specific substituents may be used, where appropriate, with any of the definitions, claims or embodiments defined hereinbefore or hereinafter. All the embodiments disclosed hereinabove and hereinbelow are illustrative, and are not to be read as limiting the scope of the invention as defined by the claims.

Ring A

In one aspect, **Ring A** is fused 6-membered heterocycle, wherein said fused 6-membered

heterocycle is optionally substituted on carbon with one or more R^4; and
$\mathbf{R^4}$ is $C_{1\text{-}6}$alkyl.

In another aspect, **Ring A** is fused morpholine, wherein said fused morpholine is optionally substituted with one or more $\mathbf{R^4}$; and
$\mathbf{R^4}$ is $C_{1\text{-}6}$alkyl.

In still another aspect, **Ring A** is fused morpholine, wherein said fused morpholine is optionally substituted with one or more $\mathbf{R^4}$; and
$\mathbf{R^4}$ is methyl.

In yet another aspect, **Ring A**, together with the piperidine ring to which it is fused, forms octahydropyrido[2,1-*c*][1,4]oxazine, wherein said octahydropyrido[2,1-*c*][1,4]oxazine is optionally substituted with one or more R^4; and
$\mathbf{R^4}$ is methyl.

In a further aspect, **Ring A**, together with the piperidine ring to which it is fused, forms 1,3-dimethyloctahydropyrido[2,1-*c*][1,4]oxazine.

In still a further aspect, **Ring A**, together with the piperidine ring to which it is fused, forms (1*R*,3*S*)-1,3-dimethyloctahydropyrido[2,1-*c*][1,4]oxazine.

W

In one aspect, **W** is -O-.

X

In one aspect, **X** is C-H.

Y

In one aspect, **Y** is C-R^3; and
$\mathbf{R^3}$ is halo.

In another aspect, **Y** is C-R^3; and

$\mathbf{R^3}$ is selected from fluoro and chloro.

In still another aspect, **Y** is C-R^3; and

$\mathbf{R^3}$ is fluoro.

$\mathbf{R^1}$

In one aspect, $\mathbf{R^1}$ is selected from C_{1-6}alkyl, 3- to 5-membered carbocyclyl, 5- or 6-membered heterocyclyl, $-OR^{1a}$, $-SR^{1a}$, $-N(R^{1a})_2$, $-N(R^{1a})C(O)R^{1b}$, $-C(O)N(R^{1a})_2$, $-C(O)R^{1b}$, $-C(O)_2R^{1a}$, $-C(O)N(R^{1a})_2$, $-C(O)N(R^{1a})(OR^{1a})$, and $-S(O)_2R^{1b}$, wherein said C_{1-6}alkyl, 3 to 5-membered carbocyclyl, and 5- or 6-membered heterocyclyl are optionally substituted on carbon with one or more R^{10}, and wherein any -NH- moiety of said 5- or 6-membered heterocyclyl is optionally substituted with R^{10*};

$\mathbf{R^{1a}}$ in each occurrence is independently selected from H, C_{1-6}alkyl, 3- to 5-membered carbocyclyl, and 5- or 6-membered heterocyclyl, wherein said C_{1-6}alkyl, 3- to 5-membered carbocyclyl, and 5- or 6-membered heterocyclyl in each occurrence are optionally and independently substituted with one or more R^{10}, wherein any -NH- moiety of said 5- or 6-membered heterocyclyl is optionally substituted with R^{10*};

$\mathbf{R^{1b}}$ in each occurrence is independently selected from C_{1-6}alkyl and 4- to 6-membered heterocyclyl, wherein said C_{1-6}alkyl and 4- to 6-membered heterocyclyl are optionally and independently substituted on carbon with one or more R^{10}, and wherein any -NH- moiety of said 4- to 6-membered heterocyclyl is optionally substituted with R^{10*};

$\mathbf{R^{10}}$ in each occurrence is independently selected from halo, -CN, C_{1-6}alkyl, 3- to 6-membered carbocyclyl, 5- or 6-membered heterocyclyl, $-OR^{10a}$, $-SR^{10a}$, $-N(R^{10a})_2$, $-N(R^{10a})C(O)R^{10b}$, $-C(O)_2R^{10a}$, $-C(O)N(R^{10a})_2$, wherein said C_{1-6}alkyl, 3- to 6-membered carbocyclyl, and 5- or 6-membered heterocyclyl in each occurrence are optionally substituted with one or more R^a, and wherein any -NH- moiety of said 5- or 6-membered heterocyclyl is optionally substituted with R^{a*};

$\mathbf{R^{10*}}$ in each occurrence is independently selected from C_{1-6}alkyl and $-C(O)R^{10b}$;

$\mathbf{R^{10a}}$ in each occurrence is independently selected from H and C_{1-6}alkyl, wherein said C_{1-6}alkyl in

each occurrence is optionally and independently substituted with one or more R^a;

$\mathbf{R^{10b}}$ is C_{1-6}alkyl;

$\mathbf{R^a}$ in each occurrence is independently selected from halo, -CN, and $-OR^m$;

$\mathbf{R^{a*}}$ is C_{1-6}alkyl; and

$\mathbf{R^m}$ in each occurrence is independently selected from H and C_{1-6}alkyl.

In another aspect, $\mathbf{R^1}$ is selected from C_{1-6}alkyl, 3- to 5-membered carbocyclyl, 5- or 6-membered heterocyclyl, and $-C(O)N(R^{1a})_2$, wherein said C_{1-6}alkyl, 3 to 5-membered carbocycyl, and 5- or 6-membered heterocyclyl are optionally substituted on carbon with one or more R^{10}, and wherein any -NH- moiety of said 5- or 6-membered heterocyclyl is optionally substituted with R^{10*};

$\mathbf{R^{1a}}$ in each occurrence is independently selected from H and C_{1-6}alkyl, wherein said C_{1-6}alkyl in each occurrence is optionally and independently substituted with one or more R^{10};

$\mathbf{R^{10}}$ in each occurrence is independently selected from halo, -CN, C_{1-6}alkyl, 5- or 6-membered heterocyclyl, $-OR^{10a}$, $-SR^{10a}$, $-N(R^{10a})_2$, $-N(R^{10a})C(O)R^{10b}$, $-C(O)_2R^{10a}$, $-C(O)N(R^{10a})_2$; wherein said C_{1-6}alkyl in each occurrence is optionally and independently subsituted with one or more R^a;

$\mathbf{R^{10*}}$ in each occurrence is independently selected from C_{1-6}alkyl and $-C(O)R^{10b}$;

$\mathbf{R^{10a}}$ in each occurrence is independently selected from H and C_{1-6}alkyl, wherein said C_{1-6}alkyl in each occurrence is optionally and independently substituted with one or more R^a;

$\mathbf{R^{10b}}$ is C_{1-6}alkyl;

$\mathbf{R^a}$ in each occurrence is independently selected from $-OR^m$ and halo; and

$\mathbf{R^m}$ in each occurrence is independently selected from H and C_{1-6}alkyl.

In still another aspect, $\mathbf{R^1}$ is selected from C_{1-6}alkyl, 5- or 6-membered heterocyclyl, and $-C(O)N(R^{1a})_2$, wherein said C_{1-6}alkyl and 5- or 6-membered heterocyclyl are optionally substituted with one or more R^{10}, and wherein any -NH- moiety of said 5- or 6-membered heterocyclyl is optionally substituted with R^{10*};

$\mathbf{R^{1a}}$ in each occurrence is independently selected from H and C_{1-6}alkyl, wherein said C_{1-6}alkyl in each occurrence is optionally and independently substituted with one or more R^{10};

$\mathbf{R^{10}}$ in each occurrence is independently selected from halo, -CN, $-SR^{10a}$, and $-N(R^{10a})_2$;

$\mathbf{R^{10*}}$ is C_{1-6}alkyl; and

$\mathbf{R^{10a}}$ in each occurrence is independently selected from H and C_{1-6}alkyl.

In one aspect, **R^1** is selected from 3- to 5-membered carbocyclyl and 5- or 6-membered heterocyclyl, wherein said 3 to 5-membered carbocycyl and 5- or 6-membered heterocyclyl are optionally substituted on carbon with one or more R^{10}, and wherein any -NH- moiety of said 5- or 6-membered heterocyclyl is optionally substituted with R^{10*};

R^{10} in each occurrence is independently selected from halo, -CN, C_{1-6}alkyl, 5- or 6-membered heterocyclyl, $-OR^{10a}$, $-SR^{10a}$, $-N(R^{10a})_2$, $-N(R^{10a})C(O)R^{10b}$, $-C(O)_2R^{10a}$, $-C(O)N(R^{10a})_2$; wherein said C_{1-6}alkyl is optionally subsituted with one or more R^a;

R^{10*} in each occurrence is independently selected from C_{1-6}alkyl and $-C(O)R^{10b}$;

R^{10a} in each occurrence is independently selected from H and C_{1-6}alkyl, wherein said C_{1-6}alkyl in each occurrence is optionally and independently substituted with one or more R^a;

R^{10b} is C_{1-6}alkyl;

R^a in each occurrence is independently selected from $-OR^m$ and halo; and

R^m in each occurrence is independently selected from H and C_{1-6}alkyl.

In yet another aspect, **R^1** is selected from 5- or 6-membered heterocyclyl, wherein said 5- or 6-membered heterocyclyl is optionally substituted on carbon with one or more R^{10}, and wherein any -NH- moiety of said 5- or 6-membered heterocyclyl is optionally substituted with R^{10*};

R^{10} in each occurrence is independently selected from halo, -CN, C_{1-6}alkyl, 5- or 6-membered heterocyclyl, $-OR^{10a}$, $-SR^{10a}$, $-N(R^{10a})_2$, $-N(R^{10a})C(O)R^{10b}$, $-C(O)_2R^{10a}$, $-C(O)N(R^{10a})_2$; wherein said C_{1-6}alkyl is optionally subsituted with one or more R^a;

R^{10*} in each occurrence is independently selected from C_{1-6}alkyl and $-C(O)R^{10b}$;

R^{10a} in each occurrence is independently selected from H and C_{1-6}alkyl, wherein said C_{1-6}alkyl in each occurrence is optionally and independently substituted with one or more R^a;

R^{10b} is C_{1-6}alkyl;

R^a in each occurrence is independently selected from $-OR^m$ and halo; and

R^m in each occurrence is independently selected from H and C_{1-6}alkyl.

In a further aspect, **R^1** is selected from $-C(O)R^{1b}$, $-C(O)_2R^{1a}$, $-C(O)N(R^{1a})_2$, and $-C(O)N(R^{1a})(OR^{1a})$;

R^{1a} in each occurrence is independently selected from H, C_{1-6}alkyl, 3- to 5-membered

carbocyclyl, and 5- or 6-membered heterocyclyl, wherein said C_{1-6}alkyl is optionally substituted with one or more R^{10}, and wherein any -NH- moiety of said 5- or 6-membered heterocyclyl is optionally substituted with R^{10*};

$\mathbf{R^{1b}}$ in each occurrence is independently selected from C_{1-6}alkyl and 4- to 6-membered heterocyclyl, wherein said 4- to 6-membered heterocyclyl is optionally substituted on carbon with one or more R^{10}, and wherein any -NH- moiety of said 4- to 6-membered heterocyclyl is optionally substituted with R^{10*};

$\mathbf{R^{10}}$ in each occurrence is independently selected from halo, -CN, 3- to 6-membered carbocyclyl, 5- or 6-membered heterocyclyl, $-OR^{10a}$, and $-N(R^{10a})C(O)R^{10b}$, wherein said 3- to 6-membered carbocyclyl is optionally substituted on carbon with one or more R^a, and wherein any -NH- moiety of said 5- or 6-membered heterocyclyl is optionally substituted with R^{a*};

$\mathbf{R^{10*}}$ is C_{1-6}alkyl;

$\mathbf{R^{10a}}$ is C_{1-6}alkyl;

$\mathbf{R^{10b}}$ is C_{1-6}alkyl;

$\mathbf{R^a}$ is -CN; and

$\mathbf{R^{a*}}$ is C_{1-6}alkyl.

In still a further aspect, $\mathbf{R^1}$ is selected from $-C(O)N(R^{1a})_2$;

$\mathbf{R^{1a}}$ in each occurrence is independently selected from H, C_{1-6}alkyl, and 3 to 5-membered carbocyclyl, wherein said C_{1-6}alkyl is optionally substituted with one or more R^{10};

$\mathbf{R^{10}}$ in each occurrence is independently selected from halo, 3- to 6-membered carbocyclyl, 5- or 6-membered heterocyclyl, and $-OR^{10a}$, wherein said 3- to 6-membered carbocyclyl is optionally substituted on carbon with one or more R^a, and wherein any -NH- moiety of said 5- or 6-membered heterocyclyl is optionally substituted with R^{a*};

$\mathbf{R^{10a}}$ is C_{1-6}alkyl;

$\mathbf{R^a}$ is -CN; and

$\mathbf{R^{a*}}$ is C_{1-6}alkyl.

In yet a further aspect, $\mathbf{R^1}$ is selected from $-C(O)N(R^{1a})_2$;

$\mathbf{R^{1a}}$ in each occurrence is independently selected from H and C_{1-6}alkyl.

In one aspect, $\mathbf{R^1}$ is selected from C_{1-6}alkyl, 3- to 6-membered carbocyclyl, 5- or 6-membered heterocyclyl, $-NH_2$, and $-N(H)C(O)R^{1b}$; and
$\mathbf{R^{1b}}$ is C_{1-6}alkyl.

In another aspect, $\mathbf{R^1}$ is selected from C_{1-6}alkyl and $-C(O)N(R^{1a})_2$;
$\mathbf{R^{1a}}$ in each occurrence is independently selected from H and C_{1-6}alkyl, wherein said C_{1-6}alkyl in each occurrence is optionally substituted with one or more R^{10}; and
$\mathbf{R^{10}}$ is halo.

In still another aspect, $\mathbf{R^1}$ is selected from C_{1-6}alkyl, 3- to 6-membered carbocyclyl, 6-membered heterocyclyl, $-NH_2$, and $-N(H)C(O)R^{1b}$; and
$\mathbf{R^{1b}}$ is C_{1-6}alkyl.

In a further aspect, $\mathbf{R^1}$ is C_{1-6}alkyl, wherein said C_{1-6}alkyl is optionally substituted with one or more R^{10}; and
$\mathbf{R^{10}}$ in each occurrence is independently selected from halo and $-OR^{10a}$;
$\mathbf{R^{10a}}$ in each occurrence is independently selected from H and C_{1-6}alkyl.

In yet a further aspect, $\mathbf{R^1}$ is C_{1-6}alkyl, wherein said C_{1-6}alkyl is optionally substituted with one or more halo.

In still a further aspect, $\mathbf{R^1}$ is selected from aminocarbonyl, 2-aminopyrimidin-4-yl, 2-cyanopyrimidin-4-yl, 3,3-difluoroazetidin-1-yl, [(2,2-difluoroethyl)amino]carbonyl, difluoromethyl, (isopropylamino)carbonyl, methyl, (methylamino)carbonyl, 2-(methylsulfanyl)pyrimidin-4-yl, 1-methyl-1*H*-1,2,4-triazol-5-yl, pyrazin-2-yl, pyridazin-3-yl, pyrimidin-4-yl, pyrimdin-2-yl, 1,3-thiazol-2-yl, 1*H*-1,2,4-triazol-1-yl, 2*H*-1,2,3-triazol-2-yl, and trifluoromethyl.

In one aspect, $\mathbf{R^1}$ is selected from methyl, phenyl, cyclopropyl, pyridinyl, $-NH_2$, and $-N(H)C(O)R^{1b}$; and
$\mathbf{R^{1b}}$ is methyl.

In another aspect, $\mathbf{R^1}$ is selected from methyl, phenyl, cyclopropyl, pyridin-2-yl, $-NH_2$, and $-N(H)C(O)R^{1b}$; and

$\mathbf{R^{1b}}$ is methyl.

In still another aspect, $\mathbf{R^1}$ is selected from methyl, (methylamino)carbonyl, and [(2,2-difluoroethyl)amino]carbonyl.

Ring A, W, X, Y, and $\mathbf{R^1}$

In one aspect, **Ring A** is fused 6-membered heterocycle, wherein said fused 6-membered heterocycle is optionally substituted on carbon with one or more R^4;

W is -O-;

X is C-H

Y is $C\text{-}R^3$;

$\mathbf{R^1}$ is selected from $C_{1\text{-}6}$alkyl, 3- to 6-membered carbocyclyl, 5- or 6-membered heterocyclyl, $-NH_2$, and $-N(H)C(O)R^{1b}$;

$\mathbf{R^{1b}}$ is $C_{1\text{-}6}$alkyl;

$\mathbf{R^3}$ is halo; and

$\mathbf{R^4}$ is $C_{1\text{-}6}$alkyl.

In another aspect, **Ring A** is fused morpholine, wherein said fused morpholine is optionally substituted with one or more $\mathbf{R^4}$;

W is -O-;

X is C-H

Y is $C\text{-}R^3$;

$\mathbf{R^1}$ is selected from $C_{1\text{-}6}$alkyl, 3- to 6-membered carbocyclyl, 6-membered heterocyclyl, $-NH_2$, and $-N(H)C(O)R^{1b}$;

$\mathbf{R^{1b}}$ is $C_{1\text{-}6}$alkyl;

$\mathbf{R^3}$ is halo; and

$\mathbf{R^4}$ is $C_{1\text{-}6}$alkyl.

In still another aspect, **Ring A**, together with the piperidine ring to which it is fused, forms 1,3-dimethyloctahydropyrido[2,1-*c*][1,4]oxazine;

W is -O-;

X is C-H;

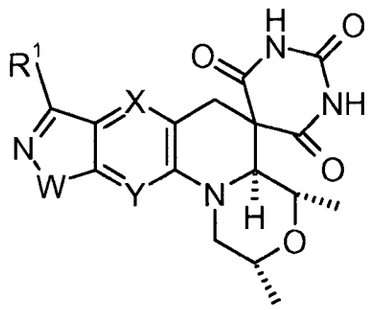
Y is C-R^3;

$\mathbf{R^1}$ is selected from methyl, phenyl, cyclopropyl, pyridin-2-yl, $-NH_2$, and $-N(H)C(O)R^{1b}$;

$\mathbf{R^{1b}}$ is methyl; and

$\mathbf{R^3}$ is fluoro.

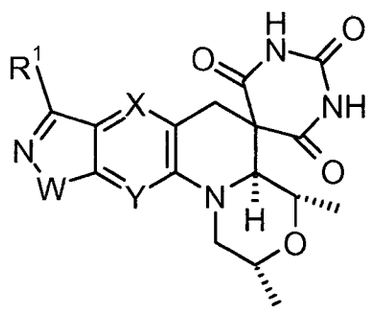
In yet another aspect, the compound of Formula (I) is a compound of Formula (Ia):



Formula (Ia)

or a pharmaceutically acceptable salt thereof, wherein **W**, **X**, **Y**, and $\mathbf{R^1}$ are as described hereinabove.

In yet another aspect, the compound of Formula (I) is a compound of Formula (Ia):



Formula (Ia)

or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R^1}$ is as described hereinabove, and wherein:

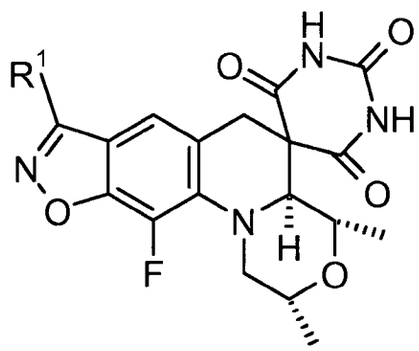
W is -O-;

X is C-H;

Y is C-R^3; and

$\mathbf{R^3}$ is halo.

In a further aspect, the compound of Formula (I) is a compound of Formula (Ib):



Formula (Ib)

or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R^1}$ is as described hereinabove.

In still a further aspect, present invention provides a compound of Formula (I) selected from the Examples, free bases thereof, and pharmaceutically acceptable salts thereof.

In yet a further aspect, the present invention provides a compound selected from:
(2*R*,4*S*,4a*S*)-8-Amino-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
(2*R*,4*S*,4a*S*)-11-Fluoro-2,4,8-trimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
(2*R*,4*S*,4a*S*)-11-Fluoro-2,4-dimethyl-8-phenyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
(2*R*,4*S*,4a*S*)-8-Cyclopropyl-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-11-Fluoro-2,4-dimethyl-8-pyridin-2-yl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

N-[(2*R*,4*S*,4a*S*)-11-Fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidin]-8-yl]acetamide;

(2*R*,4*S*,4a*S*)-11-chloro-2,4,8-trimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-8-(4-acetylpiperazin-1-yl)-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-8-(benzylamino)-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-8-[(1,3-thiazol-2-ylmethyl)amino]-1,2,4,4a-tetrahydro-2'H,6*H*-spiro[1,4-oxazino[4,3-a][1,2]oxazolo[4,5-g]quinoline-5,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione;

(2*R*,4*S*,4a*S*)-11-fluoro-8-[(1*H*-imidazol-4-ylmethyl)amino]-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-8-{[(1-methyl-1*H*-pyrazol-4-yl)methyl]amino}-1,2,4,4a-tetrahydro-2'H,6*H*-spiro[1,4-oxazino[4,3-a][1,2]oxazolo[4,5-g]quinoline-5,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-8-{[(5-methyl-1,2-oxazol-3-yl)methyl]amino}-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-8-[(pyridin-2-ylmethyl)amino]-1,2,4,4a-tetrahydro-2'H,6*H*-spiro[1,4-oxazino[4,3-a][1,2]oxazolo[4,5-g]quinoline-5,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione;

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-8-[(pyridin-3-ylmethyl)amino]-1,2,4,4a-tetrahydro-2'H,6*H*-spiro[1,4-oxazino[4,3-a][1,2]oxazolo[4,5-g]quinoline-5,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-8-[(pyridin-4-ylmethyl)amino]-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-8-[(cyclopropylmethyl)amino]-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-8-[(cyclohexylmethyl)amino]-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-

spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-8-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

tert-butyl 4-[(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidin]-8-yl]piperazine-1-carboxylate;

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-8-(piperazin-1-yl)-1,2,4,4a-tetrahydro-2'H,6*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-8-(morpholin-4-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-8-(diethylamino)-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-8-(dimethylamino)-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-8-(pyrrolidin-1-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-8-(azepan-1-yl)-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-8-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

N-{1-[(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-1*H*-pyrazol-3-yl}acetamide;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-8-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-8-[3-(difluoromethyl)-5-methyl-1*H*-pyrazol-1-yl]-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-8-(propylamino)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-8-[benzyl(methyl)amino]-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

3-amino-1-[(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-1*H*-pyrazole-4-carbonitrile;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-8-[4-(pyrimidin-4-yl)-1*H*-pyrazol-1-yl]-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-8-[4-(pyrazin-2-yl)-1*H*-pyrazol-1-yl]-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-11-fluoro-8-(4-iodo-1*H*-pyrazol-1-yl)-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

ethyl 1-[(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-1*H*-pyrazole-4-carboxylate;

(2*R*,4*S*,4a*S*)-11-chloro-2,4-dimethyl-8-(pyridin-2-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-11-chloro-8-cyclopropyl-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-11-chloro-2,4-dimethyl-8-(6-methylpyridin-3-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-11-chloro-2,4-dimethyl-8-(1,3-thiazol-5-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-11-chloro-2,4-dimethyl-8-(pyrimidin-2-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-11-chloro-2,4-dimethyl-8-(pyrimidin-4-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-11-chloro-2,4-dimethyl-8-(pyrimidin-5-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-

oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
(2*R*,4*S*,4a*S*)-11-chloro-2,4-dimethyl-8-(pyridazin-4-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
(2*R*,4*S*,4a*S*)-11-chloro-2,4-dimethyl-8-(pyridin-4-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
(2*R*,4*S*,4a*S*)-11-chloro-2,4-dimethyl-8-(pyridin-3-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione
(2*R*,4*S*,4a*S*)-11-chloro-2,4-dimethyl-8-(1,3-thiazol-2-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
(2*R*,4*S*,4a*S*)-11-chloro-8-(methoxymethyl)-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-8-[methyl(propyl)amino]-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)trione;
(2*R*,4*S*,4a*S*)-11-fluoro-8-methoxy-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
(2*R*,4S,4a*S*)-8-(benzyloxy)-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'H,6*H*-spiro[1,4-oxazino[4,3-a][1,2]oxazolo[4,5-g]quinoline-5,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione;
(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-8-(1*H*-1,2,4-triazol-1-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-8-(3-methyl-1*H*-1,2,4-triazol-1-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
1-[(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-1*H*-1,2,4-triazole-3-carbonitrile;
(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-8-(2*H*-1,2,3-triazol-2-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-8-(1*H*-1,2,3-triazol-1-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
(2*R*,4*S*,4a*S*)-11-fluoro-8-(1*H*-imidazol-1-yl)-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-8-[4-(trifluoromethyl)-1*H*-imidazol-1-yl]-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-8-(4-methyl-1*H*-pyrazol-1-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-8-(4-chloro-1*H*-pyrazol-1-yl)-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-8-(methylsulfanyl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-8-(3,5-dimethyl-1*H*-pyrazol-1-yl)-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-8-(1*H*-pyrazol-4-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-8-(2-methyl-1,3-oxazol-4-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-8-(5-methyl-1,2-oxazol-3-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-8-(3,5-dimethyl-1,2-oxazol-4-yl)-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*R*)-11-fluoro-2,4-dimethyl-8-(1-methyl-1*H*-imidazol-2-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-8-(1-methyl-1*H*-imidazol-4-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-8-(1-methyl-1*H*-imidazol-5-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-8-(4-methyl-1,3-thiazol-5-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-8-(4-methyl-1,2,3-thiadiazol-5-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-

trione;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-8-(pyridazin-3-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-8-(pyrimidin-4-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4,8-trimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]thiazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-8-(pyridin-2-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]thiazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4,8-trimethyl-1,2,3,4,4a,6-hexahydro-1'*H*-spiro[isoxazolo[4,5-g]pyrido[1,2-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*R*,4*S*,4a*S*)-8-(3-chloropyrazin-2-yl)-11-fluoro-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*R*,4*S*,4a*S*)-8-(6-chloropyrazin-2-yl)-11-fluoro-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-8-(5-(methylthio)pyrazin-2-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*R*,4*S*,4a*S*)-8-((1*H*-1,2,4-triazol-1-yl)methyl)-11-fluoro-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-8-(pyridin-4-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*R*,4S,4a*S*)-11-fluoro-8-(5-hydroxy-1,3,4-oxadiazol-2-yl)-2,4-dimethyl-1,2,4,4a-tetrahydro-2'H,6*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-8-[4-(morpholin-4-ylcarbonyl)-1,3-thiazol-2-yl]-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-8-[4-(morpholin-4-ylcarbonyl)-1,3-thiazol-5-yl]-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

2-[(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-

spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-*N*,*N*-dimethyl-1,3-thiazole-4-carboxamide;

2-[(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-*N*,*N*-dimethyl-1,3-thiazole-5-carboxamide;

5-[(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-1,3-thiazole-4-carbonitrile;

(2*R*,4*S*,4a*S*)-11-chloro-2,4-dimethyl-8-(1-methyl-1*H*-imidazol-2-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-2,4,11-trimethyl-8-(1,3-thiazol-2-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(6-methylpyridin-3-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-8-(trifluoromethyl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*R*,4S,4a*S*)-8-(difluoromethyl)-11-fluoro-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*R*,4S,4a*S*)-*N*-(2,2-difluoroethyl)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;

(2*R*,4S,4a*S*)-8-(3,3-difluoroazetidine-1-carbonyl)-11-fluoro-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-8-(thiazol-2-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*R*,4S,4a*S*)-11-fluoro-8-(furan-2-yl)-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-8-(thiazol-5-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*R*,4S,4a*S*)-11-fluoro-8-(2-fluorophenyl)-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-8-(tetrahydro-2*H*-pyran-4-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*R*,4*S*,4a*S*)-2,4,11-trimethyl-8-(pyrazin-2-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

tert-butyl (2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidin]-8-yl carbonate;

(2*R*,4*S*,4a*S*)-8-acetyl-9,10-difluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4S,4a*S*)-2-ethyl-11-fluoro-4,8-dimethyl-1,2,4,4a-tetrahydro-2'H,6*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione;

(2*R*,4*R*,4a*S*)-11-fluoro-4-(methoxymethyl)-2,8-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*S*,4a*S*)-11-fluoro-2-(methoxymethyl)-4,8-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4S,4a*S*)-11-chloro-2,4-dimethyl-8-(pyridyin-2-yl)-2,4,4*a*,6-tetrahydro-1*H* ,1'*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*) – trione;

(2*R*,4S,4a*S*)-11-chloro-2,4-dimethyl-8-(pyridyin-4-yl)-2,4,4*a*,6-tetrahydro-1*H*, 1'*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)-trione;

(2*R*,4S,4a*S*)-11-chloro-2,4-dimethyl-8-(pyridyin-3-yl)-2,4,4*a*,6-tetrahydro-1*H*, 1'*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)-trione;

(2*R*,4S,4a*S*)-11-chloro-2,4-dimethyl-8-(pyrazin-2-yl)-2,4,4*a*,6-tetrahydro-1*H*, 1'*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)-trione;

(2*R*,4S,4a*S*)-11-chloro-2,4-dimethyl-8-(thiazol-2-yl)-2,4,4*a*,6-tetrahydro-1*H*, 1'*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)-trione;

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-8-(1-methyl-1*H*-imidazol-2-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*R*,4S,4a*S*)-11-Chloro-2,4-dimethyl-8-(4-methylthiazol-2-yl)-2,4,4*a*,6-tetrahydro-1*H*, 1'*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)-trione;

(2*R*,4S,4a*S*)-11-Chloro-2,4-dimethyl-8-(1-methyl –1*H*-imidazol-2-yl)-2,4,4*a*,6-tetrahydro-1*H*, 1'*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)-

trione;

(2*R*,4S,4a*S*)-11-chloro-2,4-dimethyl-8-(thiazol-5-yl)-2,4,4*a*,6-tetrahydro-1*H*, 1'*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)-trione;

(2*R*,4S,4a*S*)-11-chloro-2,4-dimethyl-8-(2,4-dichlorothiazol-5-yl)-2,4,4*a*,6-tetrahydro-1*H*, 1'*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)-trione;

(2*R*,4S,4a*S*)-11-Chloro-2,4-dimethyl-8-(2-methylthiazol-5-yl)-2,4,4*a*,6-tetrahydro-1*H*, 1'*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)-trione;

(2*R*,4S,4a*S*)-11-chloro-2,4-dimethyl-8-(1-methyl-1*H*-1,2,4-triazol-5-yl)-2,4,4*a*,6-tetrahydro-1*H*, 1'*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)-trione;

(2*R*,4S,4a*S*)-11-chloro-2,4-dimethyl-8-(2-bromothiazol-5-yl)-2,4,4*a*,6-tetrahydro-1*H*, 1'*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)-trione;

(2*R*,4S,4a*S*)-11-chloro-2,4-dimethyl-8-(pyrazin-2-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

4-((2*R*,4S,4a*S*)-11-chloro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4*a*,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-8-yl)-2-fluorobenzonitrile;

(2*R*,4S,4a*S*)-11-Chloro-2,4-dimethyl-8-(5-methylthiazol-2-yl)-2,4,4*a*,6-tetrahydro-1*H*, 1'*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)-trione;

5-((2*R*,4S,4a*S*)-11-chloro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naphthyridine-5,5'-pyrimidine]-8-yl)picolinamide;

(2*R*,4S,4a*S*)-11-Chloro-2,4,8-trimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*R*,4S,4a*S*)-11-Chloro-*N*,2,4-trimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naphthyridine-5,5'-pyrimidine]-8-carboxamide;

(2*R*,4S,4a*S*)-11-chloro-*N*-ethyl-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naphthyridine-5,5'-pyrimidine]-8-carboxamide;

(2*R*,4S,4a*S*)-Chloro-*N*-isopropyl-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naphthyridine-5,5'-pyrimidine]-8-carboxamide;

(2*R*,4S,4a*S*)-*N*-*tert*-butyl-11-chloro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-

1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naphthyridine-5,5'-pyrimidine]-8-carboxamide;

(2*R*,4S,4a*S*)-11-Chloro-2,4-dimethyl-*N*-neopentyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naphthyridine-5,5'-pyrimidine]-8-carboxamide;

(2*R*,4S,4a*S*)-11-Chloro-8-(3,3-difluoroazetidine-1-carbonyl)-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*R*,4S,4a*S*)-*N*-benzyl-11-chloro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naphthyridine-5,5'-pyrimidine]-8-carboxamide;

(2*R*,4S,4a*S*)-11-chloro-*N*-(4-cyanobenzyl)-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naphthyridine-5,5'-pyrimidine]-8-carboxamide;

(2*R*,4S,4a*S*)-11-chloro-*N*-(3-cyanobenzyl)-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naphthyridine-5,5'-pyrimidine]-8-carboxamide;

(2*R*,4S,4a*S*)-ethyl 11-fluoro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxylate;

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-8-(morpholine-4-carbonyl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*R*,4S,4a*S*)-11-fluoro-*N*,*N*,2,4-tetramethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;

(2*R*,4S,4a*S*)-11-fluoro-*N*-methoxy-*N*,2,4-trimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;

(2*R*,4S,4a*S*)-*N*-ethyl-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;

(2*R*,4S,4a*S*)-*N*-ethyl-11-fluoro-*N*,2,4-trimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;

(2*R*,4S,4a*S*)-11-fluoro-*N*,2,4-trimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-8-(4-methyl-3-oxopiperazine-1-carbonyl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-^{1}*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;

(2*R*,4S,4a*S*)-11-fluoro-2,4-diethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;

(2*R*,4S,4a*S*)-11-fluoro-*N*-(2-methoxyethyl)-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;

(2*R*,4S,4a*S*)-*N*-*tert*-butyl-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;

(2*R*,4S,4a*S*)-8-[(1,1-dioxidothiomorpholin-4-yl)carbonyl]-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione;

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-*N*-(tetrahydro-2*H*-pyran-4-yl)-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;

(2*R*,4S,4a*S*)-11-fluoro-*N*-isopropyl-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-8-(pyrimidin-2-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2S,4S,4a*S*)-11-fluoro-4,8-dimethyl-2-(trifluoromethyl)-1,2,4,4a-tetrahydro-2'H,6*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione;

(2*R*,4S,4a*S*)-*N*-cyclopropyl-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;

(2*R*,4S,4a*S*)-11-fluoro-8-(4-methoxypiperidine-1-carbonyl)-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*R*,4S,4a*S*)-*N*-(cyclopropylmethyl)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-8-(1,2-oxazinan-2-ylcarbonyl)-1,2,4,4a-tetrahydro-2'H,6*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione;

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-*N*-(thiophen-2-ylmethyl)-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-*N*-(pyridin-4-ylmethyl)-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;

(2*R*,4S,4a*S*)-*N*-(cyclohexylmethyl)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;

(2*R*,4S,4a*S*)-8-(4,4-difluoropiperidine-1-carbonyl)-11-fluoro-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*R*,4S,4a*S*)-8-(3,3-difluoropyrrolidine-1-carbonyl)-11-fluoro-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-*N*-(1-methylazetidin-3-yl)-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;

N-(1-((2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-ylcarbonyl)azetidin-3-yl)acetamide;

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-*N*-((1-methyl-1*H*-pyrazol-3-yl)methyl)-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-*N*-((1-methyl-1*H*-pyrazol-5-yl)methyl)-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;

(2*R*,4S,4a*S*)-*N*-(1,3-dimethoxy-2-(methoxymethyl)propan-2-yl)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;

1-((2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-

spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-ylcarbonyl)azetidine-3-carbonitrile;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-8-(pyrazin-2-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-8-(5-morpholinopyrazin-2-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*R*,4S,4a*S*)-11-fluoro-8-(6-methoxypyrazin-2-yl)-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-8-(2-(methylthio)pyrimidin-4-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-8-(2-(methylsulfonyl)pyrimidin-4-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*R*,4S,4a*S*)-11-fluoro-8-(2-(2-methoxyethylamino)pyrimidin-4-yl)-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*R*,4S,4a*S*)-11-fluoro-8-(2-(2-hydroxyethylamino)pyrimidin-4-yl)-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*R*,4S,4a*S*)-11-fluoro-8-(2-methoxypyrimidin-4-yl)-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

4-((2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-yl)pyrimidine-2-carbonitrile;

(2*R*,4S,4a*S*)-8-(2-aminopyrimidin-4-yl)-11-fluoro-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*R*,4*S*,4a*S*)-11-fluoro-8-(2-hydroxypyrimidin-4-yl)-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4S,4a*S*)-11-Fluoro-2,4-dimethyl-8-(2-morpholinopyrimidin-4-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*R*,4S,4a*S*)-8-(6-(Dimethylamino)pyrazin-2-yl)-11-fluoro-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*R*,4S,4a*S*)-11-Fluoro-2,4-dimethyl-8-(1-methyl-1*H*-1,2,4-triazol-5-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*R*,4*S*,4a*S*)-11-Fluoro-2,4-dimethyl-8-(piperazin-1-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4S,4a*S*)-8-Chloro-11-fluoro-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*R*,4*S*,4a*S*)-11-Fluoro-2,4-dimethyl-8-(methylsulfinyl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-11-Fluoro-2,4-dimethyl-8-(methylsulfonyl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*R*,4*S*,4a*S*)-11-Fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-8-carbonitrile;

ethyl 2-[(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-1,3-thiazole-4-carboxylate;

(2*R*,4S,4a*S*)-11-fluoro-8-(hydroxymethyl)-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

1-[(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-1*H*-pyrazole-4-carboxylic acid;

1-[(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-*N*,*N*-dimethyl-1*H*-pyrazole-4-carboxamide;

1-[(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-*N*-methyl-1*H*-pyrazole-4-carboxamide;

1-[(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-1*H*-pyrazole-4-carboxamide;

(2*R*,4*S*,4a*S*)-11-fluoro-8-[4-(hydroxymethyl)-1*H*-pyrazol-1-yl]-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-

trione,
or a pharmaceutically acceptable salt thereof.

In yet a further aspect, the present invention provides a compound selected from:
(2*S*,4*R*,4a*R*)-8-Amino-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
(2*S*,4*R*,4a*R*)-11-Fluoro-2,4,8-trimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
(2*S*,4*R*,4a*R*)-11-Fluoro-2,4-dimethyl-8-phenyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
(2*S*,4*R*,4a*R*)-8-Cyclopropyl-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
(2*S*,4*R*,4a*R*)-11-Fluoro-2,4-dimethyl-8-pyridin-2-yl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
(2*S*,4*R*,4a*R*)-11-Fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidin]-8-yl]acetamide;
(2*S*,4*R*,4a*R*)-11-chloro-2,4,8-trimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
(2*S*,4*R*,4a*R*)-8-(4-acetylpiperazin-1-yl)-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
(2*S*,4*R*,4a*R*)-8-(benzylamino)-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-[(1,3-thiazol-2-ylmethyl)amino]-1,2,4,4a-tetrahydro-2'H,6*H*-spiro[1,4-oxazino[4,3-a][1,2]oxazolo[4,5-g]quinoline-5,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione;
(2*S*,4*R*,4a*R*)-11-fluoro-8-[(1*H*-imidazol-4-ylmethyl)amino]-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-{[(1-methyl-1*H*-pyrazol-4-yl)methyl]amino}-1,2,4,4a-tetrahydro-2'H,6*H*-spiro[1,4-oxazino[4,3-a][1,2]oxazolo[4,5-g]quinoline-5,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-{[(5-methyl-1,2-oxazol-3-yl)methyl]amino}-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-[(pyridin-2-ylmethyl)amino]-1,2,4,4a-tetrahydro-2'H,6*H*-spiro[1,4-oxazino[4,3-a][1,2]oxazolo[4,5-g]quinoline-5,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-[(pyridin-3-ylmethyl)amino]-1,2,4,4a-tetrahydro-2'H,6*H*-spiro[1,4-oxazino[4,3-a][1,2]oxazolo[4,5-g]quinoline-5,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-[(pyridin-4-ylmethyl)amino]-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-8-[(cyclopropylmethyl)amino]-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-8-[(cyclohexylmethyl)amino]-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

tert-butyl 4-[(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidin]-8-yl]piperazine-1-carboxylate;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-(piperazin-1-yl)-1,2,4,4a-tetrahydro-2'H,6*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-(morpholin-4-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-8-(diethylamino)-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-8-(dimethylamino)-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-(pyrrolidin-1-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-8-(azepan-1-yl)-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

N-{1-[(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-1*H*-pyrazol-3-yl}acetamide;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-8-[3-(difluoromethyl)-5-methyl-1*H*-pyrazol-1-yl]-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-(propylamino)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-8-[benzyl(methyl)amino]-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

3-amino-1-[(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-1*H*-pyrazole-4-carbonitrile;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-[4-(pyrimidin-4-yl)-1*H*-pyrazol-1-yl]-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-[4-(pyrazin-2-yl)-1*H*-pyrazol-1-yl]-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-8-(4-iodo-1*H*-pyrazol-1-yl)-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

ethyl 1-[(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-1*H*-pyrazole-4-carboxylate;

(2*S*,4*R*,4a*R*)-11-chloro-2,4-dimethyl-8-(pyridin-2-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-

oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
(2*S*,4*R*,4a*R*)-11-chloro-8-cyclopropyl-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
(2*S*,4*R*,4a*R*)-11-chloro-2,4-dimethyl-8-(6-methylpyridin-3-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
(2*S*,4*R*,4a*R*)-11-chloro-2,4-dimethyl-8-(1,3-thiazol-5-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
(2*S*,4*R*,4a*R*)-11-chloro-2,4-dimethyl-8-(pyrimidin-2-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
(2*S*,4*R*,4a*R*)-11-chloro-2,4-dimethyl-8-(pyrimidin-4-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
(2*S*,4*R*,4a*R*)-11-chloro-2,4-dimethyl-8-(pyrimidin-5-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
(2*S*,4*R*,4a*R*)-11-chloro-2,4-dimethyl-8-(pyridazin-4-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
(2*S*,4*R*,4a*R*)-11-chloro-2,4-dimethyl-8-(pyridin-4-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
(2*S*,4*R*,4a*R*)-11-chloro-2,4-dimethyl-8-(pyridin-3-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
(2*S*,4*R*,4a*R*)-11-chloro-2,4-dimethyl-8-(1,3-thiazol-2-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
(2*S*,4*R*,4a*R*)-11-chloro-8-(methoxymethyl)-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-[methyl(propyl)amino]-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)trione;
(2*S*,4*R*,4a*R*)-11-fluoro-8-methoxy-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
(2*S*,4*R*,4a*R*)l-8-(benzyloxy)-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'H,6*H*-spiro[1,4-oxazino[4,3-a][1,2]oxazolo[4,5-g]quinoline-5,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-(1*H*-1,2,4-triazol-1-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-(3-methyl-1*H*-1,2,4-triazol-1-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-1*H*-1,2,4-triazole-3-carbonitrile;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-(2*H*-1,2,3-triazol-2-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-(1*H*-1,2,3-triazol-1-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-8-(1*H*-imidazol-1-yl)-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-[4-(trifluoromethyl)-1*H*-imidazol-1-yl]-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-(4-methyl-1*H*-pyrazol-1-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-8-(4-chloro-1*H*-pyrazol-1-yl)-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-(methylsulfanyl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-8-(3,5-dimethyl-1*H*-pyrazol-1-yl)-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-(1*H*-pyrazol-4-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-(2-methyl-1,3-oxazol-4-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-(5-methyl-1,2-oxazol-3-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-8-(3,5-dimethyl-1,2-oxazol-4-yl)-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-

2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-(1-methyl-1*H*-imidazol-2-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-(1-methyl-1*H*-imidazol-4-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-(1-methyl-1*H*-imidazol-5-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-(4-methyl-1,3-thiazol-5-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-(4-methyl-1,2,3-thiadiazol-5-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-(pyridazin-3-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-(pyrimidin-4-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4,8-trimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]thiazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-(pyridin-2-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]thiazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4,8-trimethyl-1,2,3,4,4a,6-hexahydro-1'*H*-spiro[isoxazolo[4,5-g]pyrido[1,2-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*S*,4*R*,4a*R*)-8-(3-chloropyrazin-2-yl)-11-fluoro-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*S*,4*R*,4a*R*)-8-(6-chloropyrazin-2-yl)-11-fluoro-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-(5-(methylthio)pyrazin-2-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*S*,4*R*,4a*R*)-8-((1*H*-1,2,4-triazol-1-yl)methyl)-11-fluoro-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-(pyridin-4-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione

(2*S*,4*R*,4a*R*)-11-fluoro-8-(5-hydroxy-1,3,4-oxadiazol-2-yl)-2,4-dimethyl-1,2,4,4a-tetrahydro-2'H,6*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-[4-(morpholin-4-ylcarbonyl)-1,3-thiazol-2-yl]-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-[4-(morpholin-4-ylcarbonyl)-1,3-thiazol-5-yl]-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-*N*,*N*-dimethyl-1,3-thiazole-4-carboxamide;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-*N*,*N*-dimethyl-1,3-thiazole-5-carboxamide;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-1,3-thiazole-4-carbonitrile;

(2*S*,4*R*,4a*R*)-11-chloro-2,4-dimethyl-8-(1-methyl-1*H*-imidazol-2-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-2,4,11-trimethyl-8-(1,3-thiazol-2-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-(6-methylpyridin-3-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(trifluoromethyl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*S*,4*R*,4a*R*)-8-(difluoromethyl)-11-fluoro-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*S*,4*R*,4a*R*)-*N*-(2,2-difluoroethyl)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-

carboxamide;
(2*S*,4*R*,4a*R*)-8-(3,3-difluoroazetidine-1-carbonyl)-11-fluoro-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;
(2*S*,4*R*,4a*R*)-11-fluoro-8-(furan-2-yl)-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-(thiazol-5-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;
(2*S*,4*R*,4a*R*)-11-fluoro-8-(2-fluorophenyl)-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-(tetrahydro-2*H*-pyran-4-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;
(2*S*,4*R*,4a*R*)-2,4,11-trimethyl-8-(pyrazin-2-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
tert-butyl (2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidin]-8-yl carbonate;
(2*S*,4*R*,4a*R*)-8-acetyl-9,10-difluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
(2*S*,4*R*,4a*R*)-2-ethyl-11-fluoro-4,8-dimethyl-1,2,4,4a-tetrahydro-2'H,6*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione;
(2*S*,4*S*,4a*R*)-11-fluoro-4-(methoxymethyl)-2,8-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
(2*R*,4*R*,4a*R*)-11-fluoro-2-(methoxymethyl)-4,8-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
(2*S*,4*R*,4a*R*)-11-chloro-2,4-dimethyl-8-(pyridyin-2-yl)-2,4,4*a*,6-tetrahydro-1*H* ,1'*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*) – trione;
(2*S*,4*R*,4a*R*)-11-chloro-2,4-dimethyl-8-(pyridyin-4-yl)-2,4,4*a*,6-tetrahydro-1*H*, 1'*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)-trione;
(2*S*,4*R*,4a*R*)-11-chloro-2,4-dimethyl-8-(pyridyin-3-yl)-2,4,4*a*,6-tetrahydro-1*H*, 1'*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)-trione;
(2*S*,4*R*,4a*R*)-11-chloro-2,4-dimethyl-8-(pyrazin-2-yl)-2,4,4*a*,6-tetrahydro-1*H*, 1'*H*-

spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)-trione;
(2*S*,4*R*,4a*R*)-11-chloro-2,4-dimethyl-8-(thiazol-2-yl)-2,4,4*a*,6-tetrahydro-1*H*, 1'*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)-trione;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-(1-methyl-1*H*-imidazol-2-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;
(2*S*,4*R*,4a*R*)-11-Chloro-2,4-dimethyl-8-(4-methylthiazol-2-yl)-2,4,4*a*,6-tetrahydro-1*H*, 1'*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)-trione;
(2*S*,4*R*,4a*R*)-11-Chloro-2,4-dimethyl-8-(1-methyl –1*H*-imidazol-2-yl)-2,4,4*a*,6-tetrahydro-1*H*, 1'*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)-trione;
(2*S*,4*R*,4a*R*)-11-chloro-2,4-dimethyl-8-(thiazol-5-yl)-2,4,4*a*,6-tetrahydro-1*H*, 1'*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)-trione;
(2*S*,4*R*,4a*R*)-11-chloro-2,4-dimethyl-8-(2,4-dichlorothiazol-5-yl)-2,4,4*a*,6-tetrahydro-1*H*, 1'*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)-trione;
(2*S*,4*R*,4a*R*)-11-Chloro-2,4-dimethyl-8-(2-methylthiazol-5-yl)-2,4,4*a*,6-tetrahydro-1*H*, 1'*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)-trione;
(2*S*,4*R*,4a*R*)-11-chloro-2,4-dimethyl-8-(1-methyl-1*H*-1,2,4-triazol-5-yl)-2,4,4*a*,6-tetrahydro-1*H*, 1'*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)-trione;
(2*S*,4*R*,4a*R*)-11-chloro-2,4-dimethyl-8-(2-bromothiazol-5-yl)-2,4,4*a*,6-tetrahydro-1*H*, 1'*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)-trione;
(2*S*,4*R*,4a*R*)-11-chloro-2,4-dimethyl-8-(pyrazin-2-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;
4-((2*S*,4*R*,4a*R*)-11-chloro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4*a*,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-8-yl)-2-fluorobenzonitrile;
(2*S*,4*R*,4a*R*)-11-Chloro-2,4-dimethyl-8-(5-methylthiazol-2-yl)-2,4,4*a*,6-tetrahydro-1*H*, 1'*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)-trione;
5-((2*S*,4*R*,4a*R*)-11-chloro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naphthyridine-5,5'-pyrimidine]-8-yl)picolinamide;
(2*S*,4*R*,4a*R*)-11-Chloro-2,4,8-trimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-

g][1,4]oxazino[4,3-a][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'H)-trione;
(2*S*,4*R*,4a*R*)-11-Chloro-*N*,2,4-trimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naphthyridine-5,5'-pyrimidine]-8-carboxamide;
(2*S*,4*R*,4a*R*)-11-chloro-*N*-ethyl-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naphthyridine-5,5'-pyrimidine]-8-carboxamide;
(2*S*,4*R*,4a*R*)-Chloro-*N*-isopropyl-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naphthyridine-5,5'-pyrimidine]-8-carboxamide;
(2*S*,4*R*,4a*R*)-*N*-*tert*-butyl-11-chloro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naphthyridine-5,5'-pyrimidine]-8-carboxamide;
(2*S*,4*R*,4a*R*)-11-Chloro-2,4-dimethyl-*N*-neopentyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naphthyridine-5,5'-pyrimidine]-8-carboxamide;
(2*S*,4*R*,4a*R*)-11-Chloro-8-(3,3-difluoroazetidine-1-carbonyl)-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'H)-trione;
(2*S*,4*R*,4a*R*)-*N*-benzyl-11-chloro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naphthyridine-5,5'-pyrimidine]-8-carboxamide;
(2*S*,4*R*,4a*R*)-11-chloro-*N*-(4-cyanobenzyl)-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naphthyridine-5,5'-pyrimidine]-8-carboxamide;
(2*S*,4*R*,4a*R*)-11-chloro-*N*-(3-cyanobenzyl)-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naphthyridine-5,5'-pyrimidine]-8-carboxamide;
(2*S*,4*R*,4a*R*)-ethyl 11-fluoro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxylate;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-(morpholine-4-carbonyl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;
(2*S*,4*R*,4a*R*)-11-fluoro-*N*,*N*,2,4-tetramethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-

spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;
(2*S*,4*R*,4a*R*)-11-fluoro-*N*-methoxy-*N*,2,4-trimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;
(2*S*,4*R*,4a*R*)-*N*-ethyl-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;
(2*S*,4*R*,4a*R*)-*N*-ethyl-11-fluoro-*N*,2,4-trimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;
(2*S*,4*R*,4a*R*)-11-fluoro-*N*,2,4-trimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-(4-methyl-3-oxopiperazine-1-carbonyl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-^{1}*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;
(2*S*,4*R*,4a*R*)-11-fluoro-*N*-(2-methoxyethyl)-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;
(2*S*,4*R*,4a*R*)-*N*-*tert*-butyl-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;
(2*S*,4*R*,4a*R*)-8-[(1,1-dioxidothiomorpholin-4-yl)carbonyl]-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-*N*-(tetrahydro-2*H*-pyran-4-yl)-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;
(2*S*,4*R*,4a*R*)-11-fluoro-*N*-isopropyl-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-(pyrimidin-2-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;
(2*S*,4*R*,4a*R*)-11-fluoro-4,8-dimethyl-2-(trifluoromethyl)-1,2,4,4a-tetrahydro-2'H,6*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione;

(2*S*,4*R*,4a*R*)-*N*-cyclopropyl-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;

(2*S*,4*R*,4a*R*)-11-fluoro-8-(4-methoxypiperidine-1-carbonyl)-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*S*,4*R*,4a*R*)-*N*-(cyclopropylmethyl)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-(1,2-oxazinan-2-ylcarbonyl)-1,2,4,4a-tetrahydro-2'H,6*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-*N*-(thiophen-2-ylmethyl)-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-*N*-(pyridin-4-ylmethyl)-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;

(2*S*,4*R*,4a*R*)-*N*-(cyclohexylmethyl)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;

(2*S*,4*R*,4a*R*)-8-(4,4-difluoropiperidine-1-carbonyl)-11-fluoro-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*S*,4*R*,4a*R*)-8-(3,3-difluoropyrrolidine-1-carbonyl)-11-fluoro-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-*N*-(1-methylazetidin-3-yl)-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;

N-(1-((2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-ylcarbonyl)azetidin-3-yl)acetamide;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-*N*-((1-methyl-1*H*-pyrazol-3-yl)methyl)-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-*N*-((1-methyl-1*H*-pyrazol-5-yl)methyl)-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;

(2*S*,4*R*,4a*R*)-*N*-(1,3-dimethoxy-2-(methoxymethyl)propan-2-yl)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-ylcarbonyl)azetidine-3-carbonitrile;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-(pyrazin-2-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-8-(6-(Dimethylamino)pyrazin-2-yl)-11-fluoro-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*S*,4*R*,4a*R*)-11-Fluoro-2,4-dimethyl-8-(piperazin-1-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-11-Fluoro-2,4-dimethyl-8-(methylsulfinyl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione;

(2*S*,4*R*,4a*R*)-11-Fluoro-2,4-dimethyl-8-(methylsulfonyl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

(2*S*,4*R*,4a*R*)-11-Fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-8-carbonitrile;

ethyl 2-[(2*S*,4*R*,4a*R*)11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-1,3-thiazole-4-carboxylate;

(2*S*,4*R*,4a*R*)-11-fluoro-8-(hydroxymethyl)-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-1*H*-pyrazole-4-carboxylic acid;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-*N*,*N*-dimethyl-1*H*-pyrazole-4-carboxamide;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-*N*-methyl-1*H*-pyrazole-4-carboxamide;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-1*H*-pyrazole-4-carboxamide;

(2*S*,4*R*,4a*R*)-11-fluoro-8-[4-(hydroxymethyl)-1*H*-pyrazol-1-yl]-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione,

or a pharmaceutically acceptable salt thereof.

Biological Activity

Typical compounds of Formula (I) are believed to inhibit bacterial DNA gyrase and are therefore of interest for their antibacterial effects. The inventive compounds are believed to be active against a variety of bacterial organisms, including both Gram positive and Gram negative aerobic and anaerobic bacteria.

These properties may be assessed using, for example, the assay shown below.

DNA Gyrase Supercoiling Activity Fluorescence Polarisation Assay

In a black, 384-well polystyrene assay plate, 30 microliters/well of 5 nM *Escherichia coli* DNA gyrase A/B tetramer and 130 micrograms/ml of topologically relaxed plasmid containing the triplex-forming sequence TTCTTCTTCTTCTTCTTCTTCTTC in an assay buffer consisting of 35 mM Tris-HCl (pH 7.5), 24 mM KCl, 4 mM $MgCl_2$, 2 mM dithiothreitol, 1.8 mM spermidine, 5% (v/v) glycerol, 200 nM bovine serum albumin, 0.8% dimethylsulfoxide, and 0.3 mM ATP may be incubated at ambient temperature for (typically 30 minutes) in the absence or presence of 5 -10 different concentrations of test compound. The supercoiling reactions may be quenched by the addition of 10 microliters/well of 40 nM oligodeoxynucleotide probe in 3X triplex-forming buffer consisting of 150 mM NaCl, and 150 mM sodium acetate at pH 3.5. The oligodeoxynucleotide probe may be 5'-BODIPY-FL-labeled TTCTTCTTC. After 60 minutes, the fluorescence anisotropy of the BODIPY-FL may be measured in a Tecan Ultra plate reader, using 485 nm excitation and 535 nm emission filters equipped with polarizers. The IC_{50} may be

determined by nonlinear regression using two control reactions. The first contains no test compound but 0.8% DMSO (100% activity) while the second control reaction contains 5μM Ciprofloxacin and 0.8% DMSO (0% activity).

When tested in an in-vitro assay based on the DNA gyrase supercoiling activity fluorescence polarisation assay described above, the *E. coli* DNA gyrase supercoiling IC_{50} assay inhibitory activity of the following Examples was measured at the indicated IC_{50}. A hyphen indicates that an IC_{50} measurement is not provided for that particular compound, and is not meant to imply that the particular compound does not possess IC_{50} activity.

Example	**IC_{50} (μM)**
1	0.5
2	0.4
2(a)	83
2(b)	0.3
3	0.4
4	0.3
5	0.2
6	0.8
7	0.4
8	8.3
9	1.7
10	1.9
11	0.8
12	1.2
13	1.7
14	2.0
15	1.0
16	2.4

17	1.4
18	2.9
19	2.9
20	20
21	2.4
22	2.6
23	4.3
24	0.3
25	1.5
26	3.7
27	7.1
28	3.1
29	-
30	5.4
31	2.2
32	0.6
33	1.0
34	16.3
35	30
36	2.1
37	8.5
38	0.8
39	0.6
40	1.6
41	0.8
42	1.2
43	0.5
44	1.0

45	1.6
46	1.0
47	0.3
48	1.0
49	1.7
50	0.5
51	1.0
52	2.4
53	2.8
53(a)	0.2
53(b)	20
54	2.0
55	2.6
56	0.7
57	1.5
58	0.5
59	6.6
60	1.2
61	9.3
62	0.9
63	2.7
64	0.8
65	1.1
66	0.4
67	3.2
68	0.7
69	17
70	0.5

71	0.9
72	0.9
73	0.5
74	-
74(a)	27
74(b)	0.3
75	0.2
76	-
77	0.3
78	0.8
79	0.8
80	1.7
81	3.0
82	0.2
83	-
84	-
85	17
86	5.0
87	6.7
88	1.2
89	1.3
90	-
91	1.9
92	1.4
92(a)	65
92(b)	0.6
93	0.7
93(a)	56

93(b)	0.4
94	1.6
94(a)	51
94(b)	0.8
95	0.3
95(a)	1.0
95(b)	-
96	0.7
97	0.7
98	0.4
99	0.4
100	4.1
101	1.4
102	2.7
103 + 104	0.2
105	0.7
106	1.1
107	1.4
108	0.8
109	0.5
110	3.0
111	0.7
111(a)	83
111(b)	1.1
112	-
113	2.5
114	5.2
115	1.1

116	2.0
117	2.0
118	-
119	3.1
120	0.2
121	0.6
122	0.5
123	5.8
124	1.8
125	0.7
126	0.5
127	19
128	19
129	31
130	30
131	4.4
132	7.7
133	13
134	1.0
135	3.3
136	2.8
137	2.3
138	1.7
139	7.6
140	1.1
140(a)	0.9
141	4.9
142	0.3

142(a)	1.7
143	1.0
144	2.9
145	5.2
146	4.9
147	3.9
147(a)	0.9
147(b)	-
148	0.9
148(a)	83
148(b)	0.4
149	4.4
150	1.3
151	5.5
152	2.1
153	3.7
154	1.5
155	1.2
156	1.5
157	6.4
158	1.4
159	1.4
160	1.0
161	1.3
162	2.1
163	17
164	1.2
165	0.4

165(a)	7.8
165(b)	0.2
166(a)	83
166(b)	6.9
167	1.1
168	0.6
169	-
170	0.7
171	0.3
172	0.9
173	0.1
174	0.5
175	0.9
176	3.2
177	5.0
178	1.3
179	2.0
180	0.2
181	3.3
182	2.4
183	12
184	-
185	1.4
186	7.6
187	3.3
188	2.7
189	2.2
190	2.1

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In one aspect there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use as a medicament.

In one aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Acinetobacter baumanii*. In another aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Aeromis hydrophila*. In still another aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Bacillus anthracis*. In yet another aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Bacteroides fragilis*. In a further aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Bordatella pertussis*. In still a further aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Burkholderia cepacia*. In yet a further aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Chlamyida pneumoniae*. In one aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Citrobacter freundii*. In another aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Clostridium difficile*. In still another aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Enterobacter cloacae*. In yet another aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Enterococcus faecalis*. In a further aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Enterococcus faecium*. In still a further aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Enterobacter aerogenes*. In yet a further aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Escherichia coli*. In one aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Fusobacterium necrophorum*. In another aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Haemophilus influenzae*. In still another aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Haemophilus parainfluenzae*. In yet another aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Haemophilus somnus*. In a further aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Klebsiella oxytoca*. In still a further aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection

caused by *Klebsiella pneumoniae*. In yet a further aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Legionella pneumophila*. In one aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Listeria monocytogenes*. In another aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Moraxella catarrhalis*. In still another aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Morganella morganii*. In yet another aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Mycoplasma pneumoniae*. In a further aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Neisseria gonorrhoeae*. In still a further aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Neisseria meningitidis*. In yet a further aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Pasteurella multocida*. In one aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Proteus mirabilis*. In another aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Proteus vulgaris*. In still another aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Pseudomonas aeruginosa*. In yet another aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Salmonella typhi*. In a further aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Salmonella typhimurium*. In still a further aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Serratia marcesens*. In yet a further aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Shigella flexneria*. In one aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Shigella dysenteriae*. In another aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Staphylococcus aureus*. In still another aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Staphylococcus epidermidis*. In yet another aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Staphylococcus haemolyticus*. In a further aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Staphylococcus intermedius*. In still a further aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Staphylococcus saprophyticus*. In yet a further aspect, the terms "infection" and

"bacterial infection" may refer to a bacterial infection caused by *Stenotrophomonas maltophila*. In one aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Streptococcus agalactiae*. In another aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Streptococcus mutans*. In a still another aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Streptococcus pneumoniae*. In yet another aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Streptococcus pyrogenes*.

In one aspect, the terms "infection and "bacterial infection" may refer to a bacterial infection caused by a bacteria of the genus *Aeromonas*. In another aspect, the terms "infection and "bacterial infection" may refer to a bacterial infection caused by a bacteria of the genus *Acinetobacter*. In still another aspect, the terms "infection and "bacterial infection" may refer to a bacterial infection caused by a bacteria of the genus *Bacillus*. In yet another aspect, the terms "infection and "bacterial infection" may refer to a bacterial infection caused by a bacteria of the genus *Bacteroides*. In a further aspect, the terms "infection and "bacterial infection" may refer to a bacterial infection caused by a bacteria of the genus *Bordetella*. In still a further aspect, the terms "infection and "bacterial infection" may refer to a bacterial infection caused by a bacteria of the genus *Burkholderia*. In yet a further aspect, the terms "infection and "bacterial infection" may refer to a bacterial infection caused by a bacteria of the genus *Chlamydophila*. In one aspect, the terms "infection and "bacterial infection" may refer to a bacterial infection caused by a bacteria of the genus *Citrobacter*. In another aspect, the terms "infection and "bacterial infection" may refer to a bacterial infection caused by a bacteria of the genus *Clostridium*. In still another aspect, the terms "infection and "bacterial infection" may refer to a bacterial infection caused by a bacteria of the genus *Enterobacter*. In yet another aspect, the terms "infection and "bacterial infection" may refer to a bacterial infection caused by a bacteria of the genus *Enterococcus*. In a further aspect, the terms "infection and "bacterial infection" may refer to a bacterial infection caused by a bacteria of the genus *Escherichia*. In still a further aspect, the terms "infection and "bacterial infection" may refer to a bacterial infection caused by a bacteria of the genus *Flavobacterium*. In yet a further aspect, the terms "infection and "bacterial infection" may refer to a bacterial infection caused by a bacteria of the genus *Fusobacterium*. In one aspect, the terms "infection and "bacterial infection" may refer to a bacterial infection caused

by a bacteria of the genus *Haemophilus*. In one aspect, the terms "infection and "bacterial infection" may refer to a bacterial infection caused by a bacteria of the genus *Klebsiella*. In another aspect, the terms "infection and "bacterial infection" may refer to a bacterial infection caused by a bacteria of the genus *Legionella*. In still another aspect, the terms "infection and "bacterial infection" may refer to a bacterial infection caused by a bacteria of the genus *Listeria*. In yet another aspect, the terms "infection and "bacterial infection" may refer to a bacterial infection caused by a bacteria of the genus *Morganella*. In a further aspect, the terms "infection and "bacterial infection" may refer to a bacterial infection caused by a bacteria of the genus *Moraxella*. In still a further aspect, the terms "infection and "bacterial infection" may refer to a bacterial infection caused by a bacteria of the genus *Mycoplasma*. In yet a further aspect, the terms "infection and "bacterial infection" may refer to a bacterial infection caused by a bacteria of the genus *Neisseria*. In one aspect, the terms "infection and "bacterial infection" may refer to a bacterial infection caused by a bacteria of the genus *Pasteurella*. In another aspect, the terms "infection and "bacterial infection" may refer to a bacterial infection caused by a bacteria of the genus *Peptococci*. In still another aspect, the terms "infection and "bacterial infection" may refer to a bacterial infection caused by a bacteria of the genus *Peptostreptococci*. In yet another aspect, the terms "infection and "bacterial infection" may refer to a bacterial infection caused by a bacteria of the genus *Prevotella*. In a further aspect, the terms "infection and "bacterial infection" may refer to a bacterial infection caused by a bacteria of the genus *Proteus*. In still a further aspect, the terms "infection and "bacterial infection" may refer to a bacterial infection caused by a bacteria of the genus *Pseudomonas*. In still another aspect, the terms "infection and "bacterial infection" may refer to a bacterial infection caused by a bacteria of the genus *Salmonella*. In yet a further aspect, the terms "infection and "bacterial infection" may refer to a bacterial infection caused by a bacteria of the genus *Serratia*. In one aspect, the terms "infection and "bacterial infection" may refer to a bacterial infection caused by a bacteria of the genus *Shigella*. In yet another aspect, the terms "infection and "bacterial infection" may refer to a bacterial infection caused by a bacteria of the genus *Staphylococcus*. In another aspect, the terms "infection and "bacterial infection" may refer to a bacterial infection caused by a bacteria of the genus *Stenotrophomonas*. In still another aspect, the terms "infection and "bacterial infection" may refer to a bacterial infection caused by a bacteria of the genus *Streptococcus*.

In one aspect, the terms "infection" and "bacterial infection" may refer to a gynecological infection. In another aspect the terms "infection" and "bacterial infection" may refer to a respiratory tract infection (RTI). In still another, the terms "infection" and "bacterial infection" may refer to a sexually transmitted disease. In yet another aspect, the terms "infection" and "bacterial infection" may refer to a urinary tract infection. In a further aspect, the terms "infection" and "bacterial infection" may refer to acute exacerbation of chronic bronchitis (ACEB). In yet a further aspect, the terms "infection" and "bacterial infection" may refer to acute otitis media. In one aspect, the terms "infection" and "bacterial infection" may refer to acute sinusitis. In another aspect, the terms "infection" and "bacterial infection" may refer to an infection caused by drug resistant bacteria. In still another aspect, the terms "infection" and "bacterial infection" may refer to catheter-related sepsis. In yet another aspect, the terms "infection" and "bacterial infection" may refer to chancroid. In a further aspect, the terms "infection" and "bacterial infection" may refer to chlamydia. In still a further aspect, the terms "infection" and "bacterial infection" may refer to community-acquired pneumonia (CAP). In yet a further aspect, the terms "infection" and "bacterial infection" may refer to complicated skin and skin structure infection. In one aspect, the terms "infection" and "bacterial infection" may refer to uncomplicated skin and skin structure infection. In another aspect, the terms "infection" and "bacterial infection" may refer to endocarditis. In still another aspect, the terms "infection" and "bacterial infection" may refer to febrile neutropenia. In yet another aspect, the terms "infection" and "bacterial infection" may refer to gonococcal cervicitis. In a further aspect, the terms "infection" and "bacterial infection" may refer to gonococcal urethritis. In still a further aspect, the terms "infection" and "bacterial infection" may refer to hospital-acquired pneumonia (HAP). In yet another aspect, the terms "infection" and "bacterial infection" may refer to osteomyelitis. In a further aspect, the terms "infection" and "bacterial infection" may refer to sepsis. In still a further aspect, the terms "infection" and "bacterial infection" may refer to syphilis.

In one aspect, there is provided the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the production of a bacterial DNA gyrase inhibitory effect, in a warm-blooded animal such as man.

In another aspect, there is provided the use a compound of Formula (I), or a pharmaceutically

acceptable salt thereof, in the manufacture of a medicament for the treatment of a bacterial infection in a warm-blooded animal such as man.

In still another aspect, there is provided the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of urinary tract infections, pneumonia, prostatitis, skin and soft tissue infections, and intra-abdominal infections, in a warm-blooded animal such as man.

In yet another aspect, there is provided a method for producing a bacterial DNA gyrase inhibitory effect in a warm-blooded animal such as man, said method comprising administering to said animal an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In a further aspect, there is provided a method for treating a bacterial infection in a warm-blooded animal such as man, said method comprising administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

In still a further aspect, there is provided a method for treating urinary tract infections, pneumonia, prostatitis, skin and soft tissue infections, and intra-abdominal infections, in a warm-blooded animal such as man, said method comprising administering to said animal an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In yet a further aspect, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in producing a bacterial DNA gyrase inhibitory effect in a warm-blooded animal such as man.

In one aspect, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in treating a bacterial infection in a warm-blooded animal, such as man.

In another aspect, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in treating urinary tract infections, pneumonia, prostatitis, skin and soft tissue

infections, and intra-abdominal infections, in a warm-blooded animal such as man.

In still another aspect, there is provided a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, diluent, or excipient.

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

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

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

Compositions for oral use may be in the form of hard gelatin capsules in which the active

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

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

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

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

suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavoring and coloring agents, may also be present.

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

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

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

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

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

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 4 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

In addition to the compounds of the present invention, the pharmaceutical composition of this invention may also contain or be co-administered (simultaneously, sequentially or separately) with one or more known drugs selected from other clinically useful classes of antibacterial agents (for example, macrolides, quinolones, ß-lactams or aminoglycosides) and/or other anti-infective agents (for example, an antifungal triazole or amphotericin). These may include carbapenems, for example meropenem or imipenem, to broaden the therapeutic effectiveness. Compounds of this invention may also contain or be co-administered with bactericidal/permeability-increasing protein (BPI) products or efflux pump inhibitors to improve activity against gram negative bacteria and bacteria resistant to antimicrobial agents.

As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular disease state will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. Preferably a daily dose in the range of 1-50 mg/kg is employed. Accordingly, the optimum dosage may be determined by the practitioner who is treating any particular patient.

In addition to its use in therapeutic medicine, the compound of Formulas (I) and its pharmaceutically acceptable salts are also useful as pharmacological tools in the development and standardization of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of DNA gyrase in laboratory animals such as cats, dogs, rabbits, monkeys, rats and

mice, as part of the search for new therapeutic agents.

If not commercially available, the necessary starting materials for the procedures such as those described herein may be made by procedures which are selected from standard organic chemical techniques, techniques which are analogous to the synthesis of known, structurally similar compounds, or techniques which are analogous to the described procedure or the procedures described in the Examples.

It is noted that many of the starting materials for synthetic methods as described herein are commercially available and/or widely reported in the scientific literature, or could be made from commercially available compounds using adaptations of processes reported in the scientific literature. The reader is further referred to *Advanced Organic Chemistry*, 5th Edition, by Jerry March and Michael Smith, published by John Wiley & Sons **2001**, for general guidance on reaction conditions and reagents.

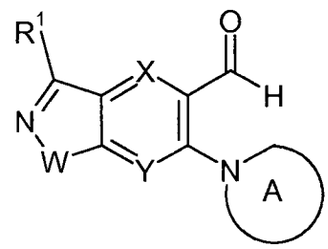
Compounds of Formula (I) may be prepared in a variety of ways. The processes shown below illustrates a method for synthesizing compounds of Formula (I) (wherein **Ring A**, **W**, **X**, **Y**, and $\mathbf{R^1}$, unless otherwise defined, are as defined hereinabove). The reactions are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being effected. Also, in the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reactions proposed. Such restrictions to the substituents, which are compatible with the reaction conditions, will be readily apparent to one skilled in the art and alternate methods must then be used. The Schemes and Processes are not intended to present an exhaustive list of methods for preparing the compounds of Formula (I); rather, additional techniques of which the skilled chemist is aware may be also be used for the compounds' synthesis. The claims are not intended to be limited to the structures shown in the Schemes and Processes.

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

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

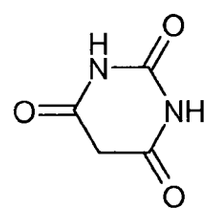
In one aspect, compounds of Formula (I), or pharmaceutically acceptable salts thereof, may be prepared by:

Process A - reacting a compound of Formula (A1):



Formula (A1)

with barbituric acid:



,

and thereafter if necessary:

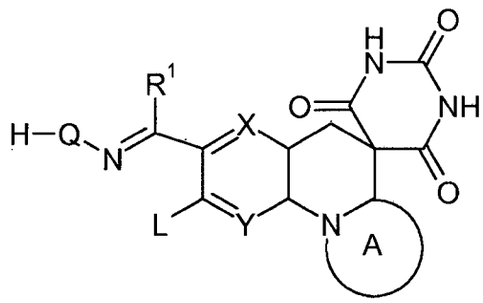
i) converting a compound of Formula (I) into another compound of Formula (I);

ii) removing any protecting groups; and/or

iii) forming a pharmaceutically acceptable salt.

In another aspect, compounds of Formula (Ib), which are compounds of Formula (I) in which **W** is -O- or -NH-, or pharmaceutically acceptable salts thereof, may be prepared by:

Process B – reacting a compound of Formula (A3):



Formula (A3)

with a suitable ring-forming agent,

and thereafter if necessary:

i) converting a compound of Formula (I) into another compound of Formula (I);

ii) removing any protecting groups; and/or

iii) forming a pharmaceutically acceptable salt,

wherein

L is a leaving group, as discussed hereinabove; and

Q is selected from -O- and -NH-.

Process A

The reaction of **Process A** may be carried out in one or two separate reaction steps by reaction of a compound of Formula (A1) with a compound of Formula (A2) under standard Knoevenagel reaction conditions to form an intermediate olefin. Solvents suitable for such a reaction include alcohols such as methanol, isopropanol, and butanol, hydrocarbon solvents such as toluene and benzene and ethereal solvents such as dioxane and dimethoxyethane. Typical temperatures can range from about 60°C to about 120°C. The Knoevenagel reaction may be catalyzed by a base such as triethylamine or pyrrolidine or an organic salt such as piperidinium acetate. Oftentimes

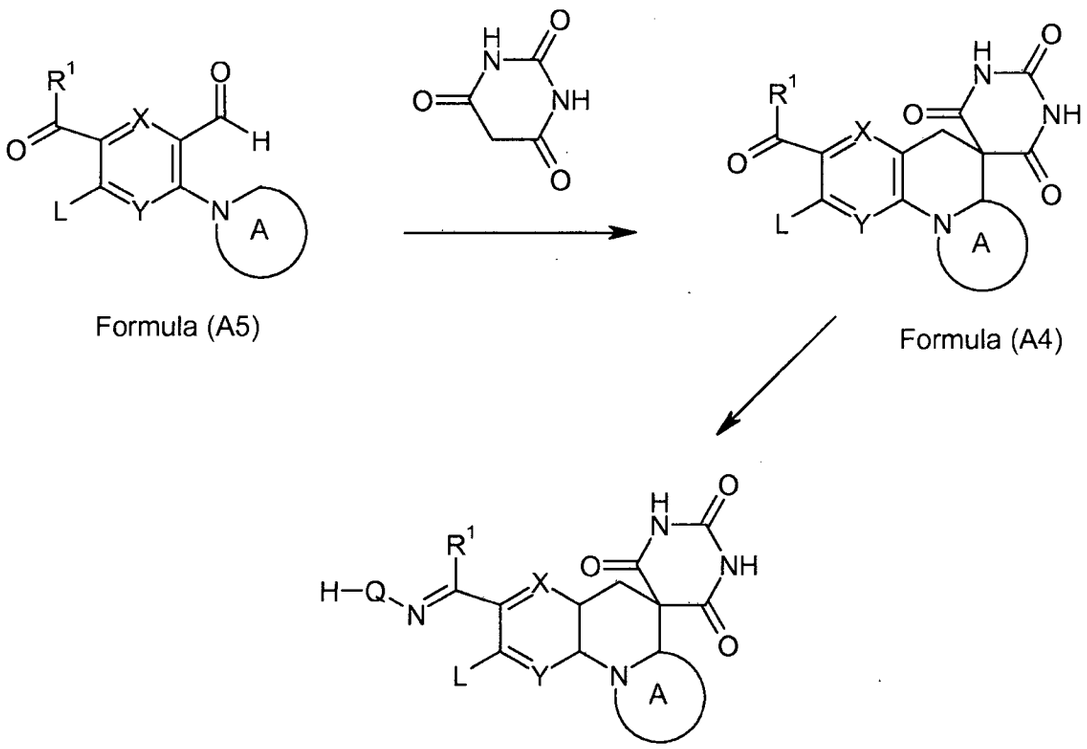
under the reaction conditions, the intermediate olefin (Knoevenagel adduct) rearranges to a compound of Formula (A1), the rearrangement being due to what is sometimes referred to as the "tertiary amine effect." If the rearrangement does not occur, the temperature of the reaction may be increased and/or solvents can be exchanged to more polar solvents such as dimethylformamide and dimethylsulfoxide. Increased reaction temperature may then range from about 70°C to about 180° C.

Process B

The reaction shown for Process B can be run in protic solvents such as MeOH, EtOH or IPA or ethereal solvents such as THF and dioxane or aprotic solvents such as DMF or acetonitrile depending on the nature of the base. Reaction temperatures can vary from room temperature to 130 °C. Illustrtative examples of the "ring-forming agent" include carbonate bases such as $CsCO_3$ and Na_2CO_3, alkoxides such as NaOMe and NaOEt, amines such as triethylamine and DBU and hydride bases such as NaH.

Scheme 1 depicts a procedure by which compounds of Formula (A3) may be prepared.

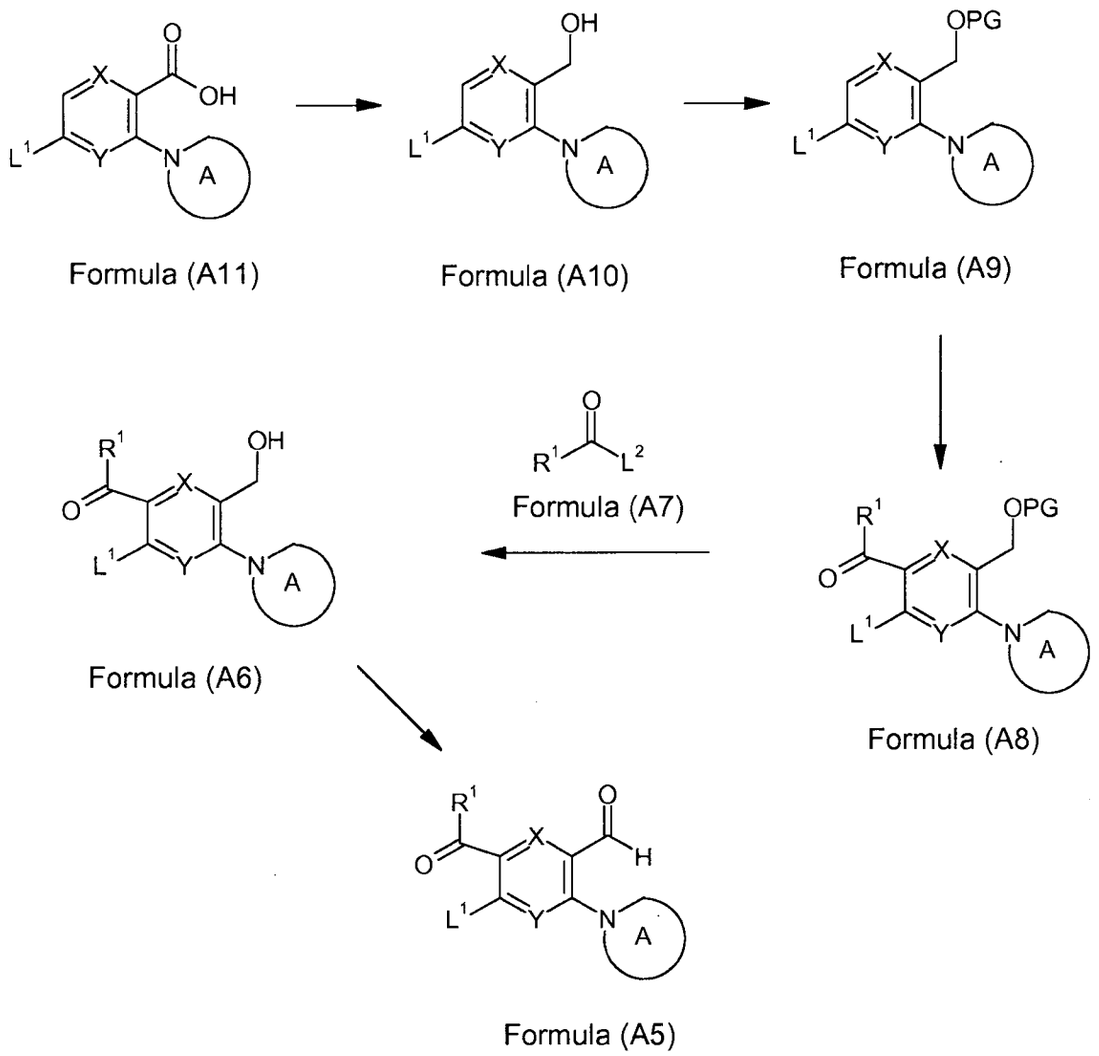
Scheme 1



Compounds of Formula (A5) may be reacted with barbituric acid under the conditions described for the reaction of **Process A**, providing a compound of Formula (A4). The compound of Formula (A3) may be obtained by reaction of the compound of Formula (A4) with hydroxylamine hydrochloride or hydrazine optionally in the presence of a catalyst or reagent such as sodium acetate, sodium bicarbonate, or pyridine at temperatures ranging from room temperature to 130 °C in suitable solvents including protic solvents such as methanol or ethanol, polar solvents such as DMF or DMSO, ethereal solvents such as THF or dioxane and aromatic solvents such as toluene or pyridine. Oftentimes under the reaction conditions, the intermediate compounds A3 cyclize to compounds of Formula A (W is O or NH).

Scheme 2 depicts a process by which compounds of Formula (A5) are prepared. Leaving group $\mathbf{L^1}$ typically include halogens such as fluorine, chlorine or bromine or sulfonic esters such as trifluomethanesulfonyloxy.

Scheme 2



Compounds of Formula (A5) may be prepared from compounds of Formula (A11) using the synthesis showed in Scheme 2. Reduction of the acid group of the compound of Formula (A11) to an alcohol may be accomplished using typical reducing agents such as borane, sodium borohydride and iodine, and ethyl chloroformate and lithium borohydride under standard reducing conditions, providing the compound of Formula (A10). Protection of the compound of Formula (A10) under typical conditions with standard alcohol protecting groups, including silyl protecting groups such as TBMS, provides the compound of Formula (A9). The R^1-(CO)- moiety may be added by reaction of the compound of Formula (A9) with a compound of Formula (A7) under basic conditions, providing the compound of Formula (A6). Typical leaving groups

(designated by L^2) suitable for such a reaction include amines such as dimethylamine and (N-methoxy)-methylamine, alcohols such as methanol or ethanol or halides such as chloride or bromide. Bases suitable for such a reaction include alkyllithiums such *s*-butyllithium and *n*-butyllithium and amines such a lithium diisopropylamine, lithium hexamethyldisilazine and lithium tetramethylpiperidine. Oxidation of the alcohol of the compound of Formula (A6) using an oxidizing agent such as MnO_2, pyrdinium chlorochromate, the Dess-Martin periodinane and DMF/oxalyl chloride.DMSO provides the compound of Formula (A5).

In any of the above-mentioned pharmaceutical compositions, processes, methods, uses, medicaments, and manufacturing features of the instant invention, any of the alternate embodiments of the compounds of the invention described herein also apply.

Examples

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

(i) temperatures are given in degrees Celsius (°C); operations are carried out at room temperature or ambient temperature, that is, in a range of 18-25 °C;

(ii) organic solutions were dried over anhydrous magnesium sulfate; evaporation of organic solvent was carried out using a rotary evaporator under reduced pressure (4.5 – 30 mmHg) with a bath temperature of up to 60 °C;

(iii) chromatography means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates;

(iv) in general, the course of reactions was followed by TLC or liquid chromatography/mass spectroscopy (LC/MS) and reaction times are given for illustration only;

(v) final products have satisfactory proton nuclear magnetic resonance (NMR) spectra and/or mass spectra data;

(vi) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vii) when given, NMR data is in the form of delta values for major diagnostic protons,

given in part per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz in DMSO-d_6 unless otherwise stated;

(viii) chemical symbols have their usual meanings;

(ix) solvent ratio was given in volume : volume (v/v) terms;

(x) an ISCO Combiflash refers to flash chromatography on silica gel using Isco Combiflash® separation system: RediSep normal phase flash column, flow rate, 30-40 ml/min;

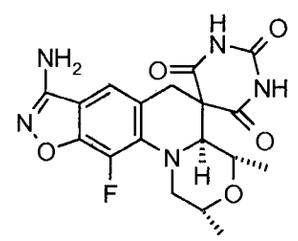
(xi) the following abbreviations may have been used:

BINAP	2,2'-bis(diphenylphosphino)-1,1'-binapthyl
Boc_2O	*tert*-butyloxycarbonyl anhydride
DAST	Diethylaminosulfur trifluoride
DCM	dichloromethane
DIPEA	*N, N*-diisopropylethylamine
DMAc	*N,N*-dimethylacetamide
DMF	*N,N*-dimethylformamide
dppf	1,1'-bis(diphenylphosphino)ferrocene
DMAP	4-dimethylaminopyridine
DMSO	dimethylsulfoxide
ee	enantiomeric excess
EtOAc	ethyl acetate
Et_2O	diethyl ether
GC	gas chromatography
HATU	O-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HPLC	high-performance liquid chromatography
hr	hours
LDA	Lithium diisopropylamide
mins	minutes
NMO	4-methylmorpholine-N-oxide
NMP	*N*-methylpyrrolidone
o/n	overnight

$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)
*i*PrOH	*i*-propanol
rac.	rracemic
SEM	1-((2-(trimethylsilyl)ethoxy)methyl
TBME	*tert*-butylmethyl ether
TEA	triethylamine
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TMS	trimethyl silyl
Tosyl, Ts	para-toluenesulfonyl
TPAP	tetrapropylammonium perruthenate
Xantphos	9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene

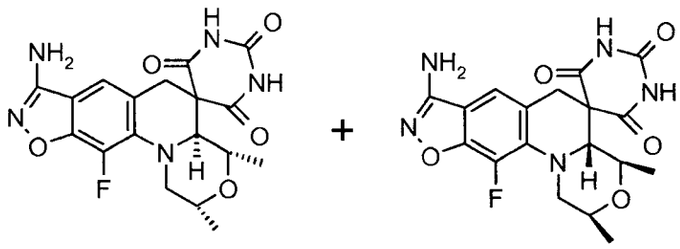
In those instances in which a compound name includes "rel," as in, for example, "(2*R*,4*S*,4a*S*)-rel-8-amino-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione," it is to be understood that such a designation implies that the indicated compound is in the form of a racemic mixture. In the indicated example, the name indicates that the compound is in the form of a racemic mixture of two enantiomers: the (2*R*,4*S*,4a*S*) enantiomer and the (2*S*,4*R*,4a*R*) enantiomer.

Additionally, the structural depiction of a (2*R*, 4*S*, 4a*S*) enantiomer preceded by a "(±)" sign indicates that the compound is present in the form a racemic mixture containing the (2*R*,4*S*,4a*S*) enantiomer and the (2*S*,4*R*,4a*R*) enantiomer of the compound. For example, the structure shown for **Example 1**:

(±) 

indicates that the title compound is present as a racemic mixture of the following two

enantiomers:



The examples are illustrative and are not to be read as limiting the scope of the invention as defined by the claims.

Intermediate 1

2-((2*R*,6*S*)-2,6-dimethyl-morpholin-4-yl)-3,4-difluoro-benzoic acid

To a stirred solution of 2,3,4-trifluorobenzoic acid (25.0 g, 142 mmol) in THF (250 mL), was added lithium bis(trimethylsilyl)amide (1M in THF, 156 mL, 156 mmol) at -78° C under nitrogen atmosphere and the solution stirred for 45 min. To this was added a premixed solution of cis-2,6-dimethylmorpholine (17.4 mL, 142 mmol) and lithium bis(trimethylsilyl)amide (1M in THF, 156 mL, 156 mmol) (which was stirred for 45 minutes at -78 °C, before the addition was made) and stirring continued for 1 h at -78 °C. It was brought to room temperature and stirring continued for additional 12 hours. Solvents were evaporated and the residue dissolved in ethyl acetate, which was washed with 1N HCl, water and brine. The organic layer was dried and concentrated to give the title compound as semi-solid. Yield: 27.5 g, (72 %).

MS (ES) $M+H^+$: 271.2 for $C_{13}H_{15}F_2NO_3$

^1H NMR (400 MHz – $CDCl_3$) δ: 1.2 (s, 6H), 2.9 (d, 2H), 3.1 (d, 2H), 3.9 (m, 2H), 7.2 (s, 1H), 7.3 (t, 1H), 8.1 (m, 1H).

Intermediate 2

[2-((2*R*,6*S*)-2,6-dimethyl-morpholin-4-yl)-3,4-difluoro-phenyl]-methanol

To a stirred and ice-bath cooled solution of 2-((2*R*,6*S*)-2,6-dimethyl-morpholin-4-yl)-3,4-difluoro-benzoic acid (**Intermediate 1,** 27.0 g, 99.6 mmol) in THF (250 mL) was added sodium borohydride (12.56 g, 358.6 mmol) in small portions, followed by iodine (32.5 g, 139.4 mmol) in THF (250 mL). The addition was carried out such that the temperature maintained below 10

°C. The mixture brought to room temperature and refluxed for 12 hours. It was cooled and then quenched with methanol (250 mL). Solvents were evaporated and the residue treated with 2M NaOH (500 mL) for 2 hours. The aqueous layer extracted with ethyl acetate (3x 150 mL), and the combined organic phases were washed with water and brine before being dried (Na_2SO_4) and concentrated to give the title compound as a gummy solid. MS (ES) MH^+: 257.2 for $C_{13}H_{17}F_2NO_2$

^1H NMR (400 MHz, $CDCl_3$) δ: 1.24 (s, 6H), 3.0 (d, 3H), 3.1 (d, 2H), 3.9 (m, 2H), 4.78 (s, 2H), 6.9 (d, 1H), 7.0 (t, 1H).

Intermediate 3

(2*R*,6*S*)-4-[6-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-2,3-difluorophenyl]-2,6-dimethylmorpholine

To an ice cooled and stirred solution of [2-((2*R*,6*S*)-2,6-dimethyl-morpholin-4-yl)-3,4-difluoro-phenyl]-methanol (**Intermediate 2,** 27.0 g, 105 mmol) in CH_2Cl_2 was added imidazole (8.5 g, 126 mmol) followed by *t*-butyl chlorodiphenylsilane (30 mL, 115 mmol) over a period of 15 min. The mixture was brought to room temperature and stirred for 12 h during which tlc showed the disappearance of starting material. The reaction mixture diluted with CH_2Cl_2 and washed successively with 1 N HCl (1x 250mL), water and brine. The organic layer dried (Na_2SO_4), filtered and concentrated. The residue was purified over a silica gel flash column using a gradient of ethyl acetate in pet. ether to give the title compound as a white solid. Yield: 45 g (94 %).

MS (ES) MH^+: 495.6 for $C_{29}H_{35}F_2NO_2Si$

^1H NMR (400 MHz, $CDCl_3$) δ: 1.1 (s, 15 H), 2.6 (d, 2 H), 2.8 (m, 2H), 3.5 (t, 2H), 4.7 (s, 2H), 7.0 (q, 1H); 7.3 (t, 1H), 7.4 (m, 10H).

Intermediate 4

5-(*tert*-butyl-diphenyl-silanyloxymethyl)-4-((2*R*,6*S*)-2,6-dimethyl-morpholin-4-yl)-2,3-difluoro-benzaldehyde

To a stirred solution of (2*R*,6*S*)-4-[6-({[*tert*-Butyl(diphenyl)silyl]oxy}methyl)-2,3-difluorophenyl]-2,6-dimethylmorpholine (**Intermediate 3,** 15.0 g, 30.0 mmol) in THF (150 mL)

was added *sec*-butyllithium (1.4 M in cyclohexane, 66.4 mL, 93 mmol) at -78 °C under a nitrogen atmosphere. After stirring for 1 h at this temperature, DMF (3.4 mL, 45 mmol) was added dropwise such that the temperature was maintained below -60 °C. After stirring for ½ h, reaction mixture treated with saturated aqueous NH_4Cl solution and the aqueous layer extracted with EtOAc (2 X 100 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated. The residue was purified over a silica gel flash column using a gradient of ethyl acetate in pet. ether to give the title compound as a yellow solid.

MS (ES) MH^+: 523.6 for $C_{30}H_{35}F_2NO_3Si$

^1H NMR (400 MHz – $CDCl_3$) δ: 1.1 (s, 15H), 2.8 (m, 4H), 3.4 (m, 2H), 4.6 (s, 2H), 7.3 (t, 4H), 7.4 (t, 2H), 7.6 (d, 4H), 7.8 (s, 1H), 10.2 (s, 1H).

Intermediate 5

1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}-*N*-hydroxymethanimine

To an ice-bath cooled and stirred solution of 5-(*tert*-Butyl-diphenyl-silanyloxymethyl)-4-((2*R*,6*S*)-2,6-dimethyl-morpholin-4-yl)-2,3-difluoro-benzaldehyde (**Intermediate 4,** 9.1 g, 17 mmol) in THF was added DIPEA (4.5 mL, 26 mmol) followed by hydroxylamine hydrochloride (1.3 g, 19 mmol) over a period of 15 min. The mixture was brought to room temperature and stirred for 12 hours. The reaction mixture was diluted with CH_2Cl_2 and washed successively with 1 N HCl (1x 250mL), water and brine. The organic layer dried (Na_2SO_4), filtered and concentrated. The residue was purified over a silica gel flash column using a gradient of ethyl acetate in pet. ether to give the title compound as white solid. Yield: 8.9 g, (86 %).

MS (ES) MH^+: 539.6 for $C_{30}H_{36}F_2N_2O_3Si$.

Intermediate 6

5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorobenzonitrile

A mixture of (*E*)-1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}-*N*-hydroxymethanimine (**Intermediate 5**, 8.0 g, 14.8 mmol) and acetic anhydride (10 mL) was stirred at 130 ° C for 12 hours. the reaction mixture cooled to room temperature and concentrated, and the residue was purified over a silica

gel flash column using a gradient of ethyl acetate in pet. ether to give the title compound as yellow solid. Yield: 6.5 g, (85 %).

MS (ES) MH^+: 521.2 for $C_{30}H_{34}F_2N_2O_2Si$

^1H NMR (300 MHz,$CDCl_3$) δ: 1.1 (s, 6H), 1.3 (s, 9H), 2.8(d, 2H), 2.9 (m, 2H), 3.5 (d, 2H), 4.7 (s, 2H), 7.3 (s, 1H), 7.4 (s, 1H), 7.6 (d, 1H).

Intermediate 7

{3-amino-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-1,2-benzisoxazol-5-yl}methanol

To an ice-bath cooled and stirred solution of 5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorobenzonitrile (**Intermediate 6,** 500 mg, 0.96 mmol) in DMF was added *t*-BuOK (161 mg, 1.4 mmol) followed by acetohydroxamic acid (108 mg, 1.4 mmol). The mixture was brought to room temperature and stirred for 12 hours. The reaction mixture was diluted with EtOAc and washed successively with 1 N HCl (1x 250mL), water and brine. The organic layer was dried (Na_2SO_4), filtered and concentrated. The residue was purified over silica gel flash column using a gradient of ethyl acetate in pet. ether to give the title compound as a white solid. Yield: 200 mg, (70 %).

MS (ES) MH^+: 296.6 for $C_{14}H_{18}FN_3O_3$

^1H NMR (400 MHz,$CDCl_3$) δ: 1.1 (s, 6H), 2.8 (d, 2H), 2.9 (m, 2H), 3.6 (t, 2H), 4.7 (s, 2H), 5.3 (t, 1H), 6.5(s, 2H), 7.8 (d, 1H).

Intermediate 8

3-amino-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-1,2-benzisoxazole-5-carbaldehyde

To an ice-cooled solution of {3-amino-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-1,2-benzisoxazol-5-yl}methanol (**Intermediate 7**, 200 mg, 0.67 mmol) in CH_2Cl_2/CH_3CN mixture (4 mL, 1:1 v/v) was added NMO (119 mg, 1.0 mmol) followed TPAP (23 mg, 0.06 mmol) and mixture stirred for 2 h at room temperature. The reaction mixture filtered thorough a silica gel bed and washed with EtOAc. The organic phase concentrated under reduced pressure to give the title compound as a yellow solid. Yield: 100 mg, (50 %).

MS (ES) MH^+: 294.6 for $C_{14}H_{16}FN_3O_3$.

Intermediate 9

1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}ethanone

To a stirred solution of (2*R*,6*S*)-4-[6-({[*tert*-Butyl(diphenyl)silyl]oxy}methyl)-2,3-difluorophenyl]-2,6-dimethylmorpholine (**Intermediate 3,** 15.0 g, 30.0 mmol) in THF (150 mL) was added *sec*-butyllithium (1.4 M in cyclohexane, 66.4 mL, 93 mmol) at -78 °C under a nitrogen atmosphere. After stirring for 1 h, *N*-methoxy-*N*-methyl-acetamide (3.4 mL, 45 mmol) was added and, after stirring for ½ h at -78 °C, the solution was allowed reach room temperature with stirring continuing for 12 hours. The reaction mixture treated with saturated aqueous NH_4Cl solution and the aqueous layer extracted by EtOAc (2 X 100 mL). The organic phases were combined, dried (Na_2SO_4) and concentrated. The residue was purified over a silica gel flash column using a gradient of ethyl acetate in pet. ether to give the title compound as yellow solid.

Yield: 13.2 g (82%)

MS (ES) MH^+: 538.6 for $C_{31}H_{37}F_2NO_3Si$

^1H NMR (400 MHz, $CDCl_3$) δ: 1.1 (s, 15H), 2.8 (m, 4H), 3.4 (m, 2H), 4.6 (s, 2H), 7.3 (t, 4H), 7.4 (t, 2H), 7.6 (d, 4H), 7.8 (s, 1H), 10.2 (s, 1H).

Intermediate 10

1-[4-((2*R*,6*S*)-2,6-dimethyl-morpholin-4-yl)-2,3-difluoro-5-hydroxymethyl-phenyl]-ethanone

A mixture of 1-[5-(*tert*-butyl-diphenyl-silanyloxymethyl)-4-((2*R*,6*S*)-2,6-dimethyl-morpholin-4-yl)-2,3-difluoro-phenyl]-ethanone (**Intermediate 9,** 7.2 g, 28 mmol) and 4N HCl in dry dioxane (75 mL) was stirred at room temperature for 12 hours. The reaction mixture was treated with cold water (20 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic phases combined were dried (Na_2SO_4) and concentrated. The residue was purified over a silica gel flash column using a gradient of ethyl acetate in pet. ether to give the title compound as yellow solid.

Yield: 3.4 g (42%).

MS (ES) MH^+: 300 for $C_{15}H_{19}F_2NO_3$

^1H NMR (400 MHz, $CDCl_3$) δ: 1.1 (s, 15H), 2.5 (d, 2H), 2.7 (t, 2H), 2.8 (s, 2H), 4.7 (s, 2H), 5.2 (t, 1H), 7.3 (t, 1H), 7.4 (s, 10H).

Intermediate 11

5-acetyl-2-((2*R*,6*S*)-2,6-dimethyl-morpholin-4-yl)-3,4-difluoro-benzaldehyde

To an ice-cooled solution of 1-[4-((2*R*,6*S*)-2,6-dimethyl-morpholin-4-yl)-2,3-difluoro-5-hydroxymethyl-phenyl]-ethanone (**Intermediate 10,** 3.2 g, 9.72 mmol) in CH_2Cl_2/CH_3CN mixture (20 mL, 1:1 v/v) was added NMO (2.2 g, 19.44 mmol) followed by TPAP (340 mg, 0.97 mmol) and mixture stirred for 2 hours at room temperature. The reaction mixture filtered thorough silica gel bed and washed with EtOAc. The organic phase concentrated under reduced pressure to give the title compound as a yellow crystalline solid. Yield: 3.0 g (94%).

MS(ES) MH^+: 298.2 for $C_{15}H_{17}F_2NO_3$

^1H NMR (400 MHz, $CDCl_3$): δ 1.2 (d, 6H); 2.1 (s, 3H), 3.0 (d, 2H), 3.1 (t, 2H), 3.8 (s, 2H), 5.1 (s, 2H), 7.6 (t 1H), 10.2 (s, 1H).

Intermediate 12

(2*R*,4*S*,4a*S*)-rel-8-acetyl-9,10-difluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

To a solution of 5-acetyl-2-((2*R*,6*S*)-2,6-dimethyl-morpholin-4-yl)-3,4-difluoro-benzaldehyde (**Intermediate 11,** 3.0 g, 9.17 mmol) in IPA was added barbituric acid (1.4 g, 11.00 mmol), and the mixture was heated at 85 °C for 12 hours. Solvents were evaporated and the residue was purified over neutral alumina using a gradient of methanol in CH_2Cl_2 to give the title compound as a racemic mixture in the form of an off-white solid. Yield: 3.0 g (75%).

MS (ES) MH^+: 408.2 for $C_{19}H_{19}F_2N_3O_5$

^1H NMR (400 MHz – DMSO-d_6) δ: 0.8 (d, 3H), 1.1 (d, 3H), 2.1 (s, 3H), 2.8 (d, 1H), 3.0 (t, 1H), 3.5 (d, 1H), 3.6 (m, 1H), 3.7 (d, 1H), 3.9 (d, 1H), 4.1 (d, 1H), 7.2 (d, 1H), 11.5 (s, 1H), 11.8 (s,1H).

Intermediates 13 to **15** were prepared from the indicated starting materials using a method similar to the one described for the syntheses of **Intermediate 12**. Each was obtained as a racemic mixture.

Intermediate 13

(2*R*,4*S*,4a*S*)-rel-9,10-difluoro-2,4-dimethyl-8-(phenylcarbonyl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

Starting material: 2-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3,4-difluoro-5-(phenylcarbonyl)benzaldehyde (**Intermediate 26**).

MS(ES)MH^+: 470.2 for $C_{24}H_{21}F_2N_3O_5$

^1H NMR (400 MHz, DMSO-d_6) δ: 0.8 (d, 3H), 1.1 (d, 3H), 2.9 (d, 1H), 3.1 (t, 1H), 3.6 (m, 2H), 3.8 (m, 1H), 3.9 (d, 1H), 4.1 (d, 1H), 7.1 (d, 1H), 7.5 (m, 2H), 7.6 (m, 3H), 11.5 (s, 1H), 11.8 (s,1H):

Intermediate 14

(2*R*,4*S*,4a*S*)-rel-9,10-difluoro-2,4-dimethyl-8-(pyridin-2-ylcarbonyl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

Starting material: 2-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3,4-difluoro-5-(pyridin-2-ylcarbonyl)benzaldehyde (**Intermediate 27**).

MS (ES) MH^+: 471.2 for $C_{23}H_{20}F_2N_4O_5$

Intermediate 15

(2*R*,4*S*,4a*S*)-rel-8-(cyclopropylcarbonyl)-9,10-difluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

Starting material: 5-(Cyclopropylcarbonyl)-2-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3,4-difluorobenzaldehyde (**Intermediate 28**).

MS (ES) MH^+: 434.1 for $C2_1H_{21}F_2N_3O_5$

Intermediate 16

(2*R*,4*S*,4a*S*)-rel-9,10-difluoro-8-[(1*E*)-*N*-hydroxyethanimidoyl]-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

To a solution of (2*R*,4*S*,4a*S*)-rel-8-acetyl-9,10-difluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione (**Intermediate 12,** 250 mg, 0.63 mmol) in MeOH, was added hydroxylamine hydrochloride (88 mg, 1.3 mmol) and the mixture heated to 85 °C for 12 hours. After cooling to room temperature, solvent was removed, and the residue was purified via normal phase HPLC (95:5: Hexane:IPA) to give the title compound as a racemic mixture in the form of a pale yellow solid. Yield: 50 mg (20%).

MS (ES) MH^+: 423.2 for $C_{19}H_{20}F_2N4O_5$

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 2.0 (d, 3H), 2.8 (d, 1H), 3.0 (t, 1H), 3.3 (d, 1H), 3.6 (d, 1H), 3.7 (t, 1H), 3.8 (t, 1H), 4.0 (d, 1H), 4.1 (d, 2H), 6.8 (d, 1H), 11.1 (s,1H), 11.4 (s, 1H), 11.8 (s, 1H).

Intermediate 17

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(phenyl)methanol

To a stirred solution of (2*R*,6*S*)-4-[6-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-2,3-difluorophenyl]-2,6-dimethylmorpholine (**Intermediate 3,** 1 g, 2.0 mmol) in anhydrous THF (10 mL), *s*-butyllithium (4.5 ml, 1.4M in cyclohexane, 6.3 mmol) was added and stirred for 2h at -78 °C. Benzaldehyde (685 mg, 0.0064 mmol) in THF (5 mL) was added dropwise and the solution was stirred for additional 1h. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was washed with brine and dried (Na_2SO_4), and solvent was removed. The residue was purified over a silica gel chromatography column using ethyl acetate-pet. ether gradient, providing the title compound.

Yield: 1.1 g, (92%)

MS (ES) MH^+: 602.2 for $C_{36}H_{41}F_2NO_3Si$

Intermediates 18 to **19** were prepared from the indicated starting materials using a method similar to the one described for the syntheses of **Intermediate 17**. Each was obtained as a racemic mixture.

Intermediate 18

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(pyridin-2-yl)methanol

Starting material: (2*R*,6*S*)-4-[6-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-2,3-difluorophenyl]-2,6-dimethylmorpholine (**Intermediate 3**) and pyridine-2-carboxaldehyde.

MS (ES) MH^+: 603.2 for $C_{35}H_{40}F_2N_2O_3Si$

Intermediate 19

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(cyclopropyl)methanol

Starting material: (2*R*,6*S*)-4-[6-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-2,3-difluorophenyl]-2,6-dimethylmorpholine (**Intermediate 3**) and cylopropyl carboxaldehyde.

MS (ES) MH^+: 566.2 for $C_{33}H_{41}F_2NO_3Si$

Intermediate 20

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(phenyl)methanone

NMO (428 mg, 0.0037 mmol) and TPAP (65 mg, 0.0002 mmol) were added to a stirred solution of {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(phenyl)methanol (**Intermediate 17,** 1.1 g, 0.002 mmol) in CH_2Cl_2:CH_3CN (1:1, 10 mL) 0 °C. The mixture was allowed to warm to room temperature with stirring for 12 hours. The solvents were removed, and the residue was purified over a silica gel chromatography column using an ethyl acetate-pet. ether gradient, providing the title compound. Yield: 1 g, (92 %)

MS (ES) MH^+: 600.2 for $C_{36}H_{39}F_2NO_3Si$

Intermediate 21

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(pyridin-2-yl)methanone

PCC (1.07 g, 0.005 mmol) was added to a solution of {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(pyridin-2-yl)methanol (**Intermediate 18**, 1.8 g, 0.002 mmol) in anhydrous DMC (15 mL) at 0 °C and the mixture was allowed to stir for 1h at room temperature. The reaction mixture was filtered and the solvents were removed under vacuum and the residue was purified over silica gel chromatography column using an ethyl acetate-pet. ether gradient, providing the title compound. Yield: 1.5 g (83 %).MS (ES) MH^+: 603.2 for $C_{35}H_{40}F_2N_2O_3Si$

Intermediate 22 was prepared from the indicated starting materials using a method similar to the one described for the syntheses of **Intermediate 21**:

Intermediate 22

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(cyclopropyl)methanone

Starting material: {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(cyclopropyl)methanol (**Intermediate 19**).

MS (ES) MH^+: 564.2 for $C_{33}H_{39}F_2NO_3Si$

Intermediate 23

{4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluoro-5-(hydroxymethyl)phenyl}(phenyl)methanone

tert-Butyl ammonium fluoride (435 mg, 0.002 mmol) was added in small portions to a stirred solution of {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(phenyl)methanone (**Intermediate 20,** 1 g, 0.002 mmol) in anhydrous THF (10 mL) at 0 °C and stirring was continued for 1h with warming to room temperature. The solvent was removed and the residue was purified over a silica gel chromatography column using ethyl acetate-pet. ether gradient, providing the title compound. Yield: 450 mg, (75%)

MS (ES) MH^+: 362.2 for $C_{20}H_{21}F_2NO_3$

Intermediates 24 and **25** were prepared from the indicated starting materials using a method similar to the one described for the syntheses of **Intermediate 23**:

Intermediate 24

{4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluoro-5-(hydroxymethyl)phenyl}(pyridin-2-yl)methanone

Starting material: {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(pyridin-2-yl)methanol (**Intermediate 18**).

MS (ES) MH^+: 363.2 for $C_{19}H_{20}F_2N_2O_3$

Intermediate 25

cyclopropyl{4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluoro-5-(hydroxymethyl)phenyl}methanone

Starting material: {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(cyclopropyl)methanone (**Intermediate 22**).

MS (ES) MH^+: 326.2 for $C_{17}H_{21}F_2NO_3$

Intermediate 26

2-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3,4-difluoro-5-(phenylcarbonyl)benzaldehyde

NMO (295 mg, 0.0025 mmol) and TPAP (44 mg, 0.0001 mmol) were added to a stirred solution of {4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluoro-5-(hydroxymethyl)phenyl}(phenyl)methanone (**Intermediate 23,** 450 mg, 0.001 mmol) in anhydrous CH_2Cl_2:CH_3CN (1:1, 10 mL) at 0°C, and the mixture was stirred for 12 hours with warming to room temperature. The solvents were removed and the residue was purified over a silica gel chromatography column using ethyl acetate-pet. ether gradient, providing the title compound. Yield: 340 mg, (76 %)

MS (ES) MH^+: 360.2 for $C_{20}H_{19}F_2NO_3$

Intermediate 27

2-[(2*R*,6*S*)-2,6-cimethylmorpholin-4-yl]-3,4-difluoro-5-(pyridin-2-ylcarbonyl)benzaldehyde

PCC (297 mg, 0.002 mmol) was added to a solution of {4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluoro-5-(hydroxymethyl)phenyl}(pyridin-2-yl)methanone (**Intermediate 24**, 500 mg, 0.001 mmol) in anhydrous CH_2Cl_2 (5 mL), at 0 °C and the mixture was stired with warming to room temperature for 1h. The reaction mixture was filtered, the solvents were removed, and the residue was purified over silica gel chromatography column using ethyl acetate-pet. ether gradient, providing the title compound. Yield: 350 mg, (70 %).

MS (ES) MH^+: 361.2 for $C_{19}H_{18}F_2N_2O_3$

Intermediate 28 was prepared from the indicated starting materials using a method similar to the one described for the syntheses of **Intermediate 27**:

Intermediate 28

5-(cyclopropylcarbonyl)-2-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3,4-difluorobenzaldehyde

Starting material: cyclopropyl{4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluoro-5-(hydroxymethyl)phenyl}methanone (**Intermediate 25**).

MS (ES) MH^+: 324.2 for $C_{17}H_{19}F_2NO_3$

Intermediate 29

(2*R*,4*S*,4a*S*)-rel-9,10-difluoro-8-[(*E*)-(hydroxyimino)(phenyl)methyl]-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

Hydroxylamine hydrochloride (77 mg, 0.001 mmol) was added to a solution of (2*R*,4*S*,4a*S*)-rel-9,10-difluoro-2,4-dimethyl-8-(phenylcarbonyl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione (**Intermediate 13,** 280 mg, 0.6 mmol) in methanol:pyridine (1:1, 3 mL) and the solution was heated to 90 °C for 12 hours. Solvents were removed and the residue was subjected to silica gel column chromatography using a gradient of ethyl acetate in pet. ether to give the title compound as a racemic mixture. Yield: 120 mg (42 %).

MS (ES) MH^+: 485.2 for $C_{24}H_{22}F_2N_4O_5$

^{1}H NMR (400 MHz – DMSO-d_6) δ: 0.8 (d, 3H), 1.2 (d, 3H), 2.8 (d, 1H), 3.0 (m, 1H), 3.4 (d, 1H), 3.6 (m, 1H), 3.7 (m, 1H), 3.8 (d, 1H), 4.0 (d, 1H), 6.6 (d, 1H), 7.4 (s, 5H), 11.5 (s, 2H).

Intermediates 30 and **31** were prepared from the indicated starting materials using a method similar to the one described for the syntheses of **Intermediate 29**. Each was obtained as a racemic mixture.

Intermediate 30

(2*R*,4*S*,4a*S*)-rel-9,10-difluoro-8-[(*Z*)-(hydroxyimino)(pyridin-2-yl)methyl]-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

Starting material: (2*R*,4*S*,4a*S*)-rel-9,10-Difluoro-2,4-dimethyl-8-(pyridin-2-ylcarbonyl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione (**Intermediate 14**).

MS (ES) MH^+: 486.3 for $C_{23}H_{21}F_2N_5O_5$

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.8 (d, 3H), 1.1 (d, 3H), 2.9 (d, 1H), 3.0 (m, 1H), 3.4 (d, 1H), 3.6 (m, 1H), 3.7 (m, 1H), 3.8 (d, 1H), 4.0 (d, 1H), 6.65 (d, 1H), 7.3 (m, 1H), 7.8 (m, 2H) , 8.4 (d, 1H), 11.5 (s, 1H), 11.8 (s, 1H), 11.8 (d, 1H).

Intermediate 31

(2*R*,4*S*,4a*S*)-rel-8-[(*E*)-cyclopropyl(hydroxyimino)methyl]-9,10-difluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

Starting material: (2*R*,4*S*,4a*S*)-rel-8-(Cyclopropylcarbonyl)-9,10-difluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione (**Intermediate 15**).

MS (ES) MH^+: 449.1 for $C_{21}H_{22}F_2N_4O_5$

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.3 (m, 1H), 0.8 (d, 2H), 0.85 (d, 3H), 1.1 (d, 3H), 2.3 (m, 1H), 2.9 (d, 1H), 3.0 (m, 1H), 3.3 (m, 1H), 3.6 (m, 1H), 3.7 (m, 1H), 3.8 (d, 1H), 4.0 (d, 1H), 6.55 (d, 1H), 11.1 (s, 3H).

Intermediate 32

1-(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoro-2-(propan-2-ylideneaminooxy)phenyl)ethanone

To a stirred solution of propan-2-one oxime (913 mg, 12.50 mmol) in THF (15 ml) was added KOtBu (935 mg, 8.33 mmol) at room temperature. After stirring for 45 minutes, 1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}ethanone (**Intermediate 9,** 2240 mg, 4.17 mmol) dissolved in10 ml of THF was added. After stirring for 3 hours reaction quenched with saturated aqueous ammonium chloride solution and extracted with EtOAc. The organic layer was dried (Na_2SO_4), filtered, and concentrated to give the crude title compound (2.5 g). LCMS and NMR indicates >90% purity. Used in the next step without any further purification.

MS (ES): 591 (M+H) for $C_{34}H_{43}FN_2O_4Si$

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.0-1.1 (s and d, 15H), 2.0 (s, 3H), 2.1 (s, 3H), 2.5-2.95 (m, 7H), 3.3-3.6 (m, 2H), 4.7 (s, 2H), 7.3-7.5 (m, 6H), 7.55 - 7.8 (m, 5H).

Intermediate 33

(6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-methylbenzo[d]isoxazol-5-yl)methanol

To a stirred solution of 1-(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoro-2-(propan-2-ylideneaminooxy)phenyl)ethanone (**Intermediate 32**, 77 mg, 0.13 mmol, crude reaction product from above reaction) dissolved in ethanol (5 ml) was treated with 5 ml of 5% aqueous HCl at 75° C for 2 hours. Reaction quenched with 10% aqueous sodium bicarbonate solution and extracted with EtOAc. The organic layer washed with water, dried, and concentrated. The residue purified over a silica gel flash coulmn (elution with 50-70% EtOAc in hexanes) to give the title compound (15 mg, 39 %).

MS (ES): 295 (M+H) for $C_{15}H_{19}FN_2O_3$

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.2 (d, 6H), 2.5 (s, 3H), 2.8-3.2 (m, 5H), 3.7- 3.95 (m, 2H), 4.8 (s, 2H), 7.3 (s, 1H).

Intermediate 34

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-methylbenzo[d]isoxazole-5-carbaldehyde

To a stirred solution of (6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-methylbenzo[d]isoxazol-5-yl)methanol (**Intermediate 33,** 0.65 g, 2.21 mmol) in CH_2Cl_2 (30 ml) was added MnO_2 (3.84 g, 44.17 mmol). After stirring for 3 days at room temperature MnO_2 was filtered and washed with CH_2Cl_2. The filtrate was concentrated and dried to give the title compound (0.547 g, 85 %).

MS (ES): 293 (M+H) for $C_{15}H_{17}FN_2O_3$

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1. 2 (d, 6H) 2.6 (s, 3H) 2.9 - 3.2 (m, 4H) 3.7-4.0 (m, 2H), 7.9 (s, 1H), 10.4 (s, 1H).

Intermediates 35 and 36 were prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 1**:

Intermediate 35

3-chloro-2-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-4-fluorobenzoic acid

Starting materials: 3-chloro-2,4-difluorobenzoic acid and cis-2,6-dimethylmorpholine.

MS (ES) MH^+: 288 for $C_{13}H_{15}ClFNO_3$

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.1 (d, 6H), 2.5 (d, 2H), 3.1(t, 2H), 3.4 (m, 2H), 6.9 (d, 1H), 7.0 (t, 1H), 13.2 (br, 1H).

Intermediate 36

2-((2*R*,6*R*)-2,6-dimethylmorpholino)-3,4-difluorobenzoic acid

Starting materials: 2,3,4-trifluorobenzoic acid and (2*R*,6*R*)-2,6-dimethylmorpholine (BASF).

MS (ES) MH^+: 272 for $C_{13}H_{15}F_2NO_3$

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.17 (d, 6H), 2.84 (dd, 2H), 3.20 (d, 2H), 3.86-4.19 (m, 2H), 7.14-7.40 (m, 1H), 7.44-7.61 (m, 1H), 14.14 (s, 1H).

Intermediates 37 and 38 were prepared from the indicated starting material, I_2 and $NaBH_4$ using a method similar to the one described for the synthesis of **Intermediate 2**:

Intermediate 37

{3-chloro-2-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-4-fluorophenyl}methanol

Starting material: 3-chloro-2-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-4-fluorobenzoic acid (**Intermediate 35**).

MS (ES) MH^+: 274 for $C_{13}H_{17}ClFNO_2$

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.1 (d, 6H), 2.5 (d, 2H), 3.1(t, 2H), 3.4 (m, 2H), 4.78 (s, 2H), 6.9 (d, 1H), 7.0 (t, 1H).

Intermediate 38

(2-((2*R*,6*R*)-2,6-dimethylmorpholino)-3,4-difluorophenyl)methanol

Starting material: 2-((2*R*,6*R*)-2,6-dimethylmorpholino)-3,4-difluorobenzoic acid (**Intermediate 36**).

MS (ES) MH^+: 258 for $C_{13}H_{17}F_2NO_2$

^{1}H NMR (300 MHz, $CDCl_3$) δ: ppm 1.32 (d, 6H), 2.73-3.41 (m, 4H), 4.00-4.29 (m, 2H), 4.60-4.89 (m, 2H), 6.78-7.19 (m, 2H).

Intermediate 39

1-(dimethoxymethyl)-2,3,4-trifluorobenzene

A solution of 2,3,4-trifluorobenzaldehyde (25 g, 156.16 mmol), 2,2-dimethoxypropane (58.1 ml, 468.48 mmol), and 4-methylbenzenesulfonic acid (0.269 g, 1.56 mmol) was stirred at room temperature overnight. The reaction mixture diluted with ether and washed successively with aq. sodium bicarbonate solution, water, and brine. The organic layer dried over sodium sulfate and concentrated. The residue wasdistilled under high vacuum to give the title compound (23.07 g, 71.7 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.36 (s, 6H), 5.54 (s, 1H), 6.8-7.1 (m, 1H), 7.1-7.4 (m, 1H).

Intermediate 40

3-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-fluoropicolinic acid

A solution of 3,5-difluoropicolinic acid (20.5 g, 128.86 mmol), cis-2,6-dimethylmorpholine (63.5 ml, 515.43 mmol) and DIEA (45.0 ml, 257.72 mmol) in THF (200 ml) was stirred at room temperature for 3 days. The mixture was diluted with EtOAc and extracted 3 times with aqueous Na_2CO_3. The aqueous layer was acidified with 1N HCl to bring pH to about 3 and was then saturated with NaCl before being extracted 10 times with EtOAc. The EtOAc layers were dried ($MgSO_4$) and solvent was removed to give 33.5 g of product as a solid.

MS (ES) $(M-H)^-$: 253 for $C_{12}H_{15}FN_2O_3$.

^{1}H NMR (DMSO-d^6): 1.1 (d, 6H), 2.5 (m, 2H), 3.2 (d, 2H), 3.7 (m 2H), 7.5 (d, 1H), 8.1 (s, 1H), 13.3 (s, broad, 1H).

Intermediate 41

(3-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-fluoropyridin-2-yl)methanol

Ethyl chloroformate (4.04 ml, 42.05 mmol) was added to a solution of 3-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-fluoropicolinic acid (**Intermediate 40,** 8.91 g, 35.04 mmol) and TEA (5.86 ml, 42.05 mmol) cooled in an ice water bath. After completion of the addtion, the reaction mixture was allowed to warm to room temperature with stirring for 1 hour. Lithium borohydride (1.985 g, 91.11 mmol) was added portionwise and the mixture was stirred for 1 hour. The mixture was quenched first with water and then with 1N HCl. It was then taken up in EtOAc and aqueous Na_2CO_3. The organic layer was separated and washed with brine. The combined aqueous layers were extracted with EtOAc 3 times, each extract being washed with brine. The combined EtOAc layers were dried ($MgSO_4$) and concentrated to give an oil that slowly

solidified. The residue was recrystallized from cyclohexane to give product as a white solid. The mother liquor was concentrated and the residue was chromatographed on silica gel (100% CH_2Cl_2 followed by gradient elution to 50% EtOAc in CH_2Cl_2) to give additional product as a white solid. Total yield of 5.6 g.

MS (ES) MH^+: 241 for $C_{12}H_{17}FN_2O_2$.

^1H NMR (DMSO-d^6): 1.1 (d, 6H), 2.4 (t, 2H), 3.1 (d, 2H), 3.7-3.8 (m, 2H), 4.5 (d, 2H), 5.1 (t, 1H), 7.4 (d, 1H), 8.2 (s, 1H).

Intermediates 42 to 44 were prepared from the indicated starting material and *t*-butyl chloro diphenylsilane using a method similar to the one described for the synthesis of **Intermediate 3**:

Intermediate 42

(2*R*,6*S*)-4-[6-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-2-chloro-3-fluorophenyl]-2,6-dimethylmorpholine

Starting material: {3-chloro-2-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-4-fluorophenyl}methanol (**Intermediate 37**).

MS (ES) MH^+: 496 for $C_{29}H_{35}F_2NO_2Si$

^1H NMR (400 MHz, $CDCl_3$) δ: 1.0 (s, 15H), 1.1(s, 9H), 2.5 (d, 2H), 3.1 (t, 2H), 3.4 (m, 2H); 4.7 (s, 2H), 7.0 (t, 1H), 7.3 (t, 1H), 7.4 (m, 10H).

Intermediate 43

(2*R*,6*R*)-4-(6-((*tert*-butyldiphenylsilyloxy)methyl)-2,3-difluorophenyl)-2,6-dimethylmorpholine

Starting material: (2-((2*R*,6*R*)-2,6-dimethylmorpholino)-3,4-difluorophenyl)methanol (**Intermediate 38**).

MS (ES) MH^+: 496 for $C_{29}H_{35}F_2NO_2Si$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.04 (d, 6H) 1.09 (s, 9H), 2.44-2.77 (m, 2H), 2.82-3.15 (m, 2H), 3.72-4.03 (m, 2H), 4.62-4.93 (m, 2H), 6.91-7.12 (m, 1H), 7.29-7.52 (m, 7H), 7.57-7.76 (m, 4H).

Intermediate 44

(2*R*,6*S*)-4-(2-((*tert*-Butyldiphenylsilyloxy)methyl)-5-fluoropyridin-3-yl)-2,6-dimethylmorpholine

Starting material: (3-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-fluoropyridin-2-yl)methanol

(**Intermediate 41**).

MS (ES) MH^+: 479 for $C_{28}H_{35}FNO_2Si$.

^1H NMR ($CDCl_3$): δ 1.0 (s, 9H), 1.15 (d, 6H, 2.4 (t, 2H), 3.0 (d, 2H), 3.6-3.7 (m, 2H), 4.8 (s, 2H), 7.0 (d, 1H), 7.4 (m, 6H), 7.7 (m, 4H), 8.2 (s, 1H).

Intermediate 45

(2*R*,6*S*)-4-(2-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-fluoropyridin-3-yl)-2,6-dimethylmorpholine

A solution of diisopropylamine (3.51 ml, 24.65 mmol) in THF (30 ml) was cooled in a dry ice-acetone bath. A solution of n-butyllithium (2.5 M in hexanes, 9.28 ml, 23.20 mmol) was added and the mixture was warmed to 0 °C and recooled in a dry ice-acetone bath. The solution was added to a second solution of (2*R*,6*S*)-4-(2-((*tert*-butyldiphenylsilyloxy)methyl)-5-fluoropyridin-3-yl)-2,6-dimethylmorpholine (**Intermediate 44**, 6.94 g, 14.50 mmol) in THF (30 ml) cooled in a dry ice-acetone bath. The mixture was stirred for 45 minutes before the solution was transfered via cannula to a solution of hexachloroethane (2.79 ml, 24.65 mmol) in 60 ml THF also cooled in a dry ice-acetone bath. The mixture was allowed to warm to room temperature before being diluted with EtOAc and washed with water and brine. The combined aqueous layers were extracted again with EtOAc, which was washed with brine. Drying ($MgSO_4$) of the combined EtOAc extracts and removal of solvent gave a gummy solid that was chromatographed on silica gel (50% hexanes in CH_2Cl_2 followed by gradient elution to 100% CH_2Cl_2) to afford product as an oil that slowly solidified (5.26 g yield). MS (ES) MH^+: 513 for $C_{28}H_{34}ClFN_2O_2Si$.

^1H NMR ($CDCl_3$): δ 1.0 (s, 9H), 1.15 (d, 6H, 2.4 (t, 2H), 3.0 (d, 2H), 3.6-3.7 (m, 2H), 4.8 (s, 2H), 7.0 (d, 1H), 7.4 (m, 6H), 7.7 (m, 4H), 8.2 (s, 1H).

Intermediate 46

2,4-difluoro-3-methylbenzoic acid

To a stirred solution of diisopropylamine (1.7 g, 16.4 mmol) in THF 2.6 M solution of n-BuLi (1.1 g, 16.4 mmol) was added at -30°C and the mixture was stirred for an hour at the same temperature. To this mixture a solution of 2,4-difluorobenzoic acid (1.0 g, 6.3 mmol) in THF was added slowly at -78°C, followed by methyl iodide (2.2 g, 15.7 mmol) and it was stirred for another 2 h at the same temperature and allowed to attain the room temperature. The reaction

mixture was treated with saturated aqueous NH_4Cl solution and the aqueous layer extracted with ethylacetate (3 x 25 mL). The organic phases were combined and dried over anhydrous sodium sulfate. After removal of solvent, the residue was purified over a silica gel flash column using a gradient of ethyl acetate in pet. ether to give product as a white solid. Yield: 0.77 g (70%)
MS (ES) MH^+: 172 for $C_8H_6F_2O_2$
^1H NMR (400 MHz, $CDCl_3$) δ: 2.2 (s, 3H), 7.0 (m, 1H), 7.9 (m, 1H).

Intermediate 47

methyl 3-chloro-2-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-4-fluorobenzoate

To a stirred solution of 3-chloro-2-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-4-fluorobenzoic acid (**Intermediate 35,** 10.0 g, 34.8 mmol) in methanol (50 mL) was added concentrated H_2SO_4 (1 mL) and the solution was refluxed for 12 hours. The reaction mixture was concentrated and diluted with EtOAc (100 mL). The organic layer washed with H_2O (2x 20 mL), dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatrography with ethyl acetate- pet. ether to give product as a solid. Yield: 9.0 g (86%)
MS (ES) MH^+: 303 for $C_{14}H_{17}ClFNO_3$.

Intermediate 48

tert-butyldiphenyl(2,3,4-trifluorobenzyloxy)silane

tert-Butylchlorodiphenylsilane (8.86 ml, 34 mmol) was added slowly via syringe to a solution of (2,3,4-trifluorophenyl)methanol (5.0 g, 31 mmol) and imidazole (2.53 g, 37.2 mmol) in CH_2Cl_2 (30 ml) cooled in an ice water bath. The mixture warmed to room temperature and stir overnight. Solvent was removed and the residue was partitioned between Et_2O and water. The Et_2O was separated and washed with brine, and the combined aqueous layers were twice more extracted with Et_2O, which was washed with brine. Drying ($MgSO_4$) and removal of solvent gave an oil that was chromatographed on silica gel (50% CH_2Cl_2 in hexanes followed by gradient elution to 100% CH_2Cl_2) to isolate an oil that slowly solidified to afford 11.9 g (96%) of a white solid.
^1H NMR: δ 7.7 (m, 4H), 7.4 (m, 6H), 7.3 (m, 1H), 7.0 (m, 1H), 4.8 (s, 1H), 1.1 (s, 9H).

Intermediate 49

N-methoxy-*N*,1-dimethyl-1*H*-1,2,4-triazole-5-carboxamide

A mixture of 1-methyl-1*H*-1,2,4-triazole (3.15 mL, 55.56 mmol) and methoxy(methyl)carbamic chloride (7.55 g, 61.11 mmol) in acetonitrile (60 mL) was cooled in an ice water bath before addition of TEA (8.52 mL, 61.11 mmol). The mixture was allowed to slowly warm to room temperature and was then stirred overnight. The material was diluted with ether and solids were filtered and rinsed well with ether. The filtrate was concentrated and the residue was taken up in ether. Insoluble solids were filtered off and rinsed well with additional ether. The filtrate was concentrated to give and oil that was chromatographed on silica gel (100% CH_2Cl_2 followed by gradient elution to 40% EtOAc in CH_2Cl_2) to afford product as an oil that slowly solidified. 6.13 g (65% yield).

MS ES^+ (MH): 171

^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 3.4 (br. s., 3H) 3.9 (s, 3H) 4.1 (br. s., 3H) 7.9 (s, 1H).

Intermediate 50

N-methoxy-*N*-methylpyrazine-2-carboxamide

To a 500 ml round bottom flask, pyrazine-2-carboxylic acid (58g, 467.37 mmol) was suspended in dry CH_2Cl_2 (250ml): oxalyl chloride (50.1 ml, 560.85 mmol) was added along with a few drops of DMF, and the mixture was stirred at room temperature for 12 hours. N, O-Dimethylhydroxylamine hydrochloride (54.7 g, 560.85 mmol) was added, and the resultant mixture was cooled down to 5°C. Triethylamine (195 ml, 1402.12 mmol) was added via a droping funnel, and the reaction mixture was stirred at room temperature for 30 minutes before being filtered. The filter cake was washed with EtOAc, and the combinded filtrate was washed with saturated sodium bicarbonate and brine, concentrated to an oil and dried under high vaccum to give the desired product (72g).

MS (ES) MH^+: 168 for $C_7H_9N_3O_2$

Intermediate 51

6-chloro-*N*-methoxy-*N*-methylpyrazine-2-carboxamide

To a 100 ml round bottom flask, 6-chloropyrazine-2-carboxylic acid (1g, 6.31 mmol) was suspended in dry CH_2Cl_2 (30ml). Oxalyl chloride (3.78 ml, 7.57 mmol) was added along with a few drop of DMF, the mixture was stirred at room temperature for 12 hrs, N, O-Dimethylhydroxylamine hydrochloride (0.800 g, 8.20 mmol) was added, the resulting mixture was cooled down to 5°C, TEA (2.64 ml, 18.92 mmol) was added via a droping funal, the reaction mixture was stirred at room temperature for 30 minutes, filtered and the filter cake was washed with EtOAc, the combinded filtrate was washed with saturated sodium bicarbonate and brine, concentrated to an oil, purified on silica gel with Hexanes/EtOAc solventsto give product (1.06g).
MS (ES) MH^+: 202 for $C_7H_8ClN_3O_2$

Intermediates 52 to 55 were prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 50**:

Intermediate 52

N-methoxy-*N*-methyl-5-morpholinopyrazine-2-carboxamide

Starting material: 5-morpholinopyrazine-2-carboxylic acid

MS (ES) MH^+: 253 for $C_{11}H_{16}N_4O_3$

Intermediate 53

3-chloro-*N*-methoxy-*N*-methylpyrazine-2-carboxamide

Starting material: 3-chloropyrazine-2-carboxylic acid

MS (ES) MH^+: 202 for $C_7H_8ClN_3O_2$

Intermediate 54

5-chloro-*N*-methoxy-*N*-methylpyrazine-2-carboxamide

Starting material: 5-chloropyrazine-2-carboxylic acid

Intermediate 55

N,6-Dimethoxy-*N*-methylpyrazine-2-carboxamide

Starting material: 6-methoxypyrazine-2-carboxylic acid

MS (ES) MH^+: 198 for $C_8H_{11}N_3O_3$

Intermediate 56

Ethyl 2-(methoxy(methyl)amino)-2-oxoacetate

To a solution of N,O-dimethylhydroxylamine hydrochloride (10 g, 102.52 mmol) and ethyl chlorooxoacetate (13.77 ml, 123.02 mmol) in dichloromethane (163 ml) at 0 °C was added triethylamine (28.6 ml, 205.04 mmol) drop wise. The reaction was stirred at room temperature for 1.5 hrs. The reaction was quenched with 20 ml of methanol, and then concentrated. The resulting solid was triturated with THF and filtered away. The filtrate was concentrated. The residue was vacuum distilled bulb to bulb. At approximately 85 °C impurities were collected and then discarded. The title compound was colleted at approximately 120 °C as a neat oil (11.6 g, 72.0 mmol, 70.2 %).

MS (ES) MH^+: 162 for $C_6H_{11}NO_4$

^1H NMR (300 MHz, DMSO-d_6) δ ppm 1.27 (t, 3H) 3.17 (s, 3H) 3.70 (s, 3H) 4.29 (q, 2H)

Intermediate 57

2,4-difluoro-5-[hydroxy(1,3-thiazol-2-yl)methyl]-3-methylbenzoic acid

A solution of 1.9 M n-BuLi (3.8 ml, 7.2 mmol) in hexanes was added at -30°C to a stirred solution of 2,2,6,6-tetramethylpiperidine (1.2 g, 9.0 mmol) in THF and the mixture was stirred for an hour at the same temperature. After cooling to -78°C, a solution of 2,4-difluoro-3-methylbenzoic acid (**Intermediate 46**, 0.5 g, 3.0 mmol) in THF was added slowly at and the mixture was stirred for another 2 h at the same temperature. To this mixture, a solution of thiazole-2-carboxaldehyde (0.8 g, 7.2 mmol) in THF was added dropwise over aperiod of 10 mins and the mixture was brought to the room temperature. The reaction mixture was quenched with 1.5N hydrochloric acid and the organic layer was separated, the aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organic layer was dried over sodium sulfate. Removal of solvent afforded the title compound as colorless product. Yield: 0.42 g (51%).

MS (ES) MH^+: 285 for $C_{12}H_9F_2NO_3S$

Intermediate 58 was prepared from the indicated starting materials using a method similar to the one described for the synthesis of 2,4-difluoro-5-[hydroxy(1,3-thiazol-2-yl)methyl]-3-methylbenzoic acid (**Intermediate 57**):

Intermediate 58

2,4-difluoro-3-methyl-5-(pyrazin-2-ylcarbonyl)benzoic acid

Starting materials: 2,4-difluoro-3-methylbenzoic acid (**Intermediate 46**) and *N*-methoxy-*N*-methylpyrazine-2-carboxamide.

MS (ES) MH^+: 278 for $C_{13}H_8F_2N_2O_3$

^1H NMR (400 MHz, $CDCl_3$) δ: 2.1 (s, 3H), 7.8 (t, 1H), 8.8 (s, 1H), 8.9 (t, 1H), 9.3 (d, 1H), 13.6 (s, 1H).

Intermediate 59

2,4-difluoro-3-methyl-5-(1,3-thiazol-2-ylcarbonyl)benzoic acid

A stirred mixture of 2,4-difluoro-5-[hydroxy(pyrazin-2-yl)methyl]-3-methylbenzoic acid (**Intermediate 57**, 0.43 g, 1.5 mmol) in 1,4-dioxane (10 mL), MnO_2 (0.65 g, 7.4 mmol) was was refluxed for 5 hours. The reaction mixture was cooled to room temperature and filtered through celite and the solvent was removed by vacuum to afford product. Yield: 0.4 g (95%).

MS (ES) MH^+: 283 for $C_{12}H_7F_2NO_3S$

Intermediate 60

2-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-4-fluoro-3-methyl-5-(1,3-thiazol-2-ylcarbonyl)benzoic acid

In a sealed tube, a mixture of 2,4-difluoro-3-methyl-5-(1,3-thiazol-2-ylcarbonyl)benzoic acid (**Intermediate 59**, 0.4 g, 1.4 mmol), cis-2,6-dimethylmorpholine (0.25 g, 2.1 mmol) and diisopropylethylamine (0.55 g, 4.2 mmol) in acetonitrile (1 mL) were heated at 90°C overnight. The solvents were removed under vacuum and the residue was taken up in ethyl acetate, which was washed with 1.5N hydrochloric acid and dried over sodium sulfate. Removal of ethyl acetate afforded crude product that was purified by silica gel column chromatography (eluent: 3% methanol in chloroform) to afford product. Yield: 0.31 g (58 %).

MS (ES) MH^+: 378.2 for $C_{18}H_{19}FN_2O_4S$

Intermediate 61 was prepared from the indicated starting materials using a method similar to the one described for the synthesis of 2-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-4-fluoro-3-methyl-5-(1,3-thiazol-2-ylcarbonyl)benzoic acid (**Intermediate 60**):

Intermediate 61

2-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-4-fluoro-3-methyl-5-(pyrazin-2-ylcarbonyl)benzoic acid

Starting material: 2,4-difluoro-3-methyl-5-(pyrazin-2-ylcarbonyl)benzoic acid **Intermediate 58**).

MS (ES) MH^+: 383 for $C_{19}H_{20}FN_3O_4$

^1H NMR (400 MHz, DMSO-d6) δ: 1.2 (d, 6H), 2.5 (s, 3H), 3.0 (d, 2H), 3.2 (t, 2H), 3.9 (m, 2H), 8.5 (d, 1H), 8.6 (t, 1H), 8.8 (d, 1H), 9.3 (s, 1H).

Intermediate 62

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}(pyridin-2-yl)methanol

To a stirred solution of (2*R*,6*S*)-4-[6-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-2-chloro-3-fluorophenyl]-2,6-dimethylmorpholine (**Intermediate 42,** 2.0 g, 3.9 mmol) in anhydrous THF (10 mL), *sec*-Butyl lithium (1.4 M in cyclohexane, 2.1 eq) was added and the solution was stirred for ½ h at -78 °C. Pyridine-2-carbaldehyde (0.74 mL, 7.8 mmol) in THF (5 mL) was added dropwise and the solution was stirred for additional 1h. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulphate. The solvent was removed under vacuum and the residue was purified over silica gel chromatography column using ethyl acetate-pet. ether gradient to obtain product. Yield: 900 mg, (37%)

MS (ES) MH^+: 619 for $C_{35}H_{40}ClFN_2O_3Si$;

Intermediates 63 to 70 were prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 62**:

Intermediate 63

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}(1,3-thiazol-5-yl)methanol

Starting materials: (2*R*,6*S*)-4-[6-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-2-chloro-3-fluorophenyl]-2,6-dimethylmorpholine (**Intermediate 42**), 1,3-thiazole-5-carbaldehyde and lithium 2,2,6,6-tetramethylpiperidide.

MS (ES) MH^+: 625 for $C_{33}H_{38}ClFN_2O_3Si$;

Intermediate 64

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}(pyridin-4-yl)methanol

Starting materials: (2*R*,6*S*)-4-[6-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-2-chloro-3-fluorophenyl]-2,6-dimethylmorpholine (**Intermediate 42**), 4-pyridine carboaldehyde and lithium 2,2,6,6-tetramethylpiperidide.

MS (ES) MH^+: 619 for $C_{35}H_{40}ClFN_2O_3Si$;

Intermediate 65

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}(pyridin-3-yl)methanol

Starting material: (2*R*,6*S*)-4-[6-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-2-chloro-3-fluorophenyl]-2,6-dimethylmorpholine (**Intermediate 42**), pyridine-3-carboaldehyde and LDA

MS (ES) MH^+: 619 for $C_{35}H_{40}ClFN_2O_3Si$;

Intermediate 66

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}(1,3-thiazol-2-yl)methanol

Starting material: (2*R*,6*S*)-4-[6-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-2-chloro-3-fluorophenyl]-2,6-dimethylmorpholine (**Intermediate 42**), 1,3-thiazole-2-carbaldehyde and lithium 2,2,6,6-tetramethylpiperidide.

MS (ES) MH^+: 626 for $C_{33}H_{38}ClFN_2O_3SSi$;

Intermediate 67

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}(1-methyl-1*H*-imidazol-2-yl)methanol

Starting material: (2*R*,6*S*)-4-[6-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-2-chloro-3-fluorophenyl]-2,6-dimethylmorpholine (**Intermediate 42**), 1-methyl-imidazole-2-carbaldehyde and *n*-BuLi

MS (ES) MH^+: 622 for $C_{34}H_{41}ClFN_3O_3Si$;

Intermediate 68

methyl 3-chloro-5-[cyclopropyl(hydroxy)methyl]-2-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-4-fluorobenzoate

Starting materials: methyl 3-chloro-2-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-4-fluorobenzoate (**Intermediate 47**), cyclopropyl carbaldehyde and LDA.

MS (ES) MH^+: 372 for $C_{18}H_{23}ClFNO_4$

Intermediate 69

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(1-methyl-1*H*-imidazol-5-yl)methanol

Starting materials: (2*R*,6*S*)-4-[6-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-2,3-difluorophenyl]-2,6-dimethylmorpholine (**Intermediate 3**), 1-methyl-imidazole-5-carbaldehyde (116 mg, 1.06 mmol) and *sec*-butyllithium.

MS (ES) MH^+: 605 for $C_{34}H_{41}F_2N_3O_3Si$;

Intermediate 70

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(4-methyl-1,3-thiazol-5-yl)methanol

Starting materials: (2*R*,6*S*)-4-[6-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-2,3-difluorophenyl]-2,6-dimethylmorpholine (**Intermediate 3**, 1.0 g, 2.02 mmol), 4-methyl-1,3-thiazole-5-carbaldehyde and *sec*-butyllithium

MS (ES) MH^+: 623 for $C_{34}H_{40}F_2N_2O_3SSi$

Intermediate 71

(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*R*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)(2-(methylthio)pyrimidin-4-yl)methanol

Starting materials: (2*R*,6*R*)-4-(6-((*tert*-butyldiphenylsilyloxy)methyl)-2,3-difluorophenyl)-2,6-dimethylmorpholine (**Intermediate 43,** 7.36 g, 14.84 mmol) in t-BuOMe (20 mL) was added s-BuLi (12.45 mL, 16.19 mmol) at -75 °C under nitrogen atmosphere. After stirring for 20 minutes at this temperature, it was then transfered via canula to a solution of 2-(methylthio)pyrimidine-4-carbaldehyde (2.08g, 13.49 mmol) in t-BuOMe (20 mL) (precooled down to -70°C), the mixture was then stirred for 0.5 hour at -70 °C, quenched with saturated aqueouse ammonium chloride solution and extracted with ethylacetate, dried and concentrated, purified by flash column chromatography on silica gel with Hex/EtOAc to give the desired product(3.024g).
MS (ES) MH^+: 650 for $C_{35}H_{41}F_2N_3O_3SSi$

Intermediate 72

(5-((*tert*-Butyldiphenylsilyloxy)methyl)-3-chloro-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2-fluorophenyl)(pyrazin-2-yl)methanone

A solution of butyllithium, 2.5M in hexanes (1.718 mL, 4.30 mmol) was added dropwise to a solution of 2,2,6,6-tetramethylpiperidine (0.802 mL, 4.73 mmol) in 15 ml THF at -78 °C. The flask was removed from the -78 °C bath, and stirred at ca 0 °C for 10 minutes, then recooled to -78 °C to give a pale yellow solution of LiTMP. A solution of (2*R*,6*S*)-4-[6-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-2-chloro-3-fluorophenyl]-2,6-dimethylmorpholine (**Intermediate 42**, 1.1 g, 2.15 mmol) 20 ml THF was cannulated into the LiTMP solution to give a yellow solution which was stirred at -78 for about 1 hour; then *N*-methoxy-*N*-methylpyrazine-2-carboxamide (1.077 g, 6.44 mmol) was added. The mixture was stirred at -78 °C. After 5 hours the reaction was worked up by adding saturated NH_4Cl to the -78 °C solution and extracting with EtOAc (3X). After drying over $MgSO_4$, concentration of the mixture gave material that was purified on SiO_2 using 0-10% acetone/hexanes to recover 891 mg (67%) of the title compound as a yellow oil.
MS (ES) MH^+: 618 for $C_{34}H_{37}ClFN_3O_3Si$

^{1}H NMR (CD_2Cl_2) δ: 1.0-1.1 (overlapping m, 15H), 2.5-2.7 (m, 2H), 3.0-3.2 (m, 2H), 3.3-3.4 (m, 2H), 4.8 (s, 2H), 7.3-7.5 (m, 6H), 7.6-7.7 (m, 4H), 7.9 (br s, 1H), 8.6 (m, 1H), 8.7 (d, 1H), 9.2 (br s, 1H).

Intermediate 73

(6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)(1-methyl-1*H*-imidazol-2-yl)methanol

Diisopropylamine (0.868 mL, 6.14 mmol) was added dropwise to a stirring solution of 2.5M butyllithium in hexanes (2.339 mL, 5.85 mmol) in THF (20 mL) at -78°C. The solution was warmed to 0°C for 10 minutes and then cooled again to -78°C. Cannulation of the LDA at -78°C into (2*R*,6*S*)-4-(2-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-fluoropyridin-3-yl)-2,6-dimethylmorpholine (**Intermediate 45,** 1.5 g, 2.92 mmol) in THF (10mL) at -78°C. Allowed dark solution to stir for 20 minutes then cannulated into a stirring solution of 1-methyl-1*H*-imidazole-2-carbaldehyde (0.644 g, 5.85 mmol) in THF (10mL) at -78°C. The solution was allowed to warm to –50 °C then quenched with saturated ammonium chloride solution. The mixture was extracted with ethyl acetate and washed resulting organics with brine. After drying the organics over sodium sulfate, filtering, and evacuating the filtrate under vacuum, a crude yellow oil was obtained. The crude oil was purified on silica using 40% ethyl acetate in n-hexane to give 1.2 g (66%) of the title compound as oil.

MS (ES) MH^+: 623 for $C_{33}H_{40}ClFN_4O_3Si$

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.0 (s, 9H), 1.1 (d, 6H), 2.8 (br.s., 2H), 3.1 (br.s., 2H), 3.6 (br.s., 2H), 3.7 (s, 3H), 5.0 (br.s., 2H), 6.0 (br.s., 1H), 6.8 (br.s., 1H), 6.9 (d, 1H) 7.3–7.4 (m, 6H), 7.6 – 7.7 (m, 4H), 9.1(s, 1H).

Intermediates 74 to 79 were prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 73**:

Intermediate 74

(6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)(thiazol-5-yl)methanol

Starting materials: (2*R*,6*S*)-4-(2-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-fluoropyridin-3-yl)-2,6-dimethylmorpholine (**Intermediate 45**) and thiazole-5-carbaldehyde.

MS (ES) MH^+: 626 for $C_{32}H_{37}ClFN_3O_3SiS$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.0 (s, 9H), 1.1–1.2 (m, 6H), 2.7 – 2.8 (m, 2H), 3.1 (br.s., 2H), 3.7 (br.s., 2H), 4.8 (br.s., 2H), 6.2 (s, 1H), 7.2 (br.s., 1H), 7.3–7.4 (m, 6H), 7.6–7.7 (m, 4H), 8.5 (s, 1H), 9.1(s, 1H).

Intermediate 75

(6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)(2-methylthiazol-5-yl)methanol

Starting materials: (2*R*,6*S*)-4-(2-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-fluoropyridin-3-yl)-2,6-dimethylmorpholine (**Intermediate 45**) and 2-methylthiazole-5-carbaldehyde.

MS (ES) MH^+: 640 for $C_{33}H_{39}ClFN_3O_3SiS$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.0 (s, 9H), 1.1–1.2 (m, 6H), 2.6 (s, 3H), 2.7–2.8 (m, 2H), 3.1 (br.s., 2H), 3.7 (br.s., 2H), 4.8 (br.s., 2H), 6.1 (s, 1H), 7.2 (br.s., 1H), 7.3–7.5 (m, 6H), 7.6–7.7 (m, 4H), 8.2 (s, 1H).

Intermediate 76

4-((6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)(hydroxy)methyl)-2-fluorobenzonitrile

Starting materials: (2*R*,6*S*)-4-(2-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-fluoropyridin-3-yl)-2,6-dimethylmorpholine (**Intermediate 45**) and 2-fluoro-4-formylbenzonitrile.

MS (ES) MH^+: 662 for $C_{36}H_{38}ClF_2N_3O_3Si$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.0 (s, 9H), 1.1–1.2 (m, 6H), 2.7 (br.s., 2H), 3.1 (br.s., 2H), 3.6 (br.s., 2H), 4.8 (br.s., 2H), 5.9 (s, 1H), 6.1 (s, 1H), 7.2–7.5 (m, 6H), 7.5 (dd, 1H), 7.6 (br.s., 2H), 7.6–7.7 (m, 4H).

Intermediate 77

(6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)(5-methylthiazol-2-yl)methanol

Starting materials: (2*R*,6*S*)-4-(2-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-fluoropyridin-3-yl)-2,6-dimethylmorpholine (**Intermediate 45**) and 5-methylthiazole-2-carbaldehyde.

MS (ES) MH^+: 640 for $C_{33}H_{39}ClFN_3O_3SiS$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.0 (s, 9H), 1.1–1.2 (m, 6H), 2.4 (d, 3H), 2.7 (br.s., 2H), 3.1 (br.s., 2H), 3.6 (br.s., 2H), 4.8 (br.s., 2H), 5.0 (s, 1H), 6.1 (s, 1H), 7.2 (s, 1H), 7.3–7.5 (m, 6H), 7.6–7.7 (m, 4H).

Intermediate 78

(2-bromothiazol-5-yl)(6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)methanol

Starting materials: 2*R*,6*S*)-4-(2-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-fluoropyridin-3-yl)-2,6-dimethylmorpholine (**Intermediate 45**) and 2-bromothiazole-5-carbaldehyde.

MS (ES) MH^+: 705 for $C_{32}H_{36}ClFBrN_3O_3SiS$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.0 (s, 9H), 1.1–1.2 (m, 6H), 2.7 (br.s., 2H), 3.1 (br.s., 2H), 3.7 (br.s., 2H), 4.8 (br.s., 2H), 6.1 (d, 1H,) 7.3–7.5 (m, 6H), 7.6–7.7 (m, 4H), 8.1(s, 1H), 9.9 (m, 1H).

Intermediate 79

(6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)(2,4-dichlorothiazol-5-yl)methanol

Starting materials: (2*R*,6*S*)-4-(2-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-fluoropyridin-3-yl)-2,6-dimethylmorpholine (**Intermediate 45**) and 2,4-dichlorothiazole-5-carbaldehyde.

MS (ES) MH^+: 694 for $C_{32}H_{35}Cl_3FN_3O_3SiS$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.0 (s, 9H), 1.1–1.2 (m, 6H), 2.8 (br.s., 2H), 3.1 (br.s., 2H), 3.7 (br.s., 2H), 4.8 (br.s., 2H), 6.2 (d, 1H), 7.3–7.5 (m, 6H), 7.6–7.7 (m, 4H).

Intermediate 80 and Intermediate 81

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}[4-(morpholin-4-ylcarbonyl)-1,3-thiazol-2-yl]methanol (**Intermediate 80**) and {5-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}[4-(morpholin-4-ylcarbonyl)-1,3-thiazol-5-yl]methanol (**Intermediate 81**).

Morpholin-4-yl(1,3-thiazol-4-yl)methanone (1.0 g, 5.05 mmol) in anhydrous THF (10 mL) was added to a stirred solution of LiTMP (3.2 eq, generated from n-butyllithium and 2,2,6,6-tetramethylpiperidine in 10 ml THF) at -78 °C, and the mixture was stirred for 2 hours at -78 °C. A solution of 5-(*tert*-butyl-diphenyl-silanyloxymethyl)-4-((2*R*,6*S*)-2,6-dimethyl-morpholin-4-yl)-2,3-difluoro-benzaldehyde (**Intermediate 4,** 2.6 g, 5.05 mmol) in THF (10 mL) was added dropwise and the mixture was stirred for an additional 1 hour at -78 °C. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer were washed with brine and dried over anhydrous sodium sulphate. The solvent was removed under vacuum and the residue was purified on a silica gel column using ethyl acetate-pet. ether gradient to give two products: **Intermediate 80** and **Intermediate 81**. Yield: 600 mg (17 %).

Intermediate 80 MS (ES) MH^+: 722 for $C_{38}H_{45}F_2N_3O_5SSi$.

Intermediate 81 MS (ES) MH^+: 722 for $C_{38}H_{45}F_2N_3O_5SSi$;

Intermediates 82 to 84 were prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 80 and Intermediate 81**:

Intermediate 82

2-[{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(hydroxy)methyl]-*N*,*N*-dimethyl-1,3-thiazole-4-carboxamide

Starting material: 5-(*tert*-Butyl-diphenyl-silanyloxymethyl)-4-((2*R*,6*S*)-2,6-dimethyl-morpholin-4-yl)-2,3-difluoro-benzaldehyde (**Intermediate 4**) and *N*,*N*-dimethyl-1,3-thiazole-4-carboxamide.

MS (ES) MH^+: 680 for $C_{36}H_{43}F_2N_3O_4SSi$

Intermediate 83

2-[{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(hydroxy)methyl]-*N*,*N*-dimethyl-1,3-thiazole-5-carboxamide

Starting material: 5-(*tert*-Butyl-diphenyl-silanyloxymethyl)-4-((2*R*,6*S*)-2,6-dimethyl-morpholin-4-yl)-2,3-difluoro-benzaldehyde (**Intermediate 4**) and *N*,*N*-dimethyl-1,3-thiazole-5-carboxamide

MS (ES) MH^+: 680 for $C_{36}H_{43}F_2N_3O_4SSi$

Intermediate 84

5-[{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(hydroxy)methyl]-1,3-thiazole-4-carbonitrile

Starting material: 5-(*tert*-Butyl-diphenyl-silanyloxymethyl)-4-((2*R*,6*S*)-2,6-dimethyl-morpholin-4-yl)-2,3-difluoro-benzaldehyde (**Intermediate 4**) and 4-cyano-1,3-thiazole.

MS (ES) MH^+: 634 for $C_{34}H_{37}F_2N_23O_3SSi$.

Intermediate 85

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}(pyridin-2-yl)methanone

To the solution of {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}(pyridin-2-yl)methanol (**Intermediate 62**, 100 mg, 0.165 mmol) in anhydrous DCM (5 mL) was added NMO (37 mg, 0.323 mmol) and TPAP (0.1 eq) at 0 °C and the mixture was allowed to stir for 1 hour at room temperature. The reaction mixture was filtered and the solvents were removed under vacuum and the residue was purified over silica gel chromatography column using ethyl acetate-pet. ether gradient to give product as a solid. Yield: 90 mg, (90 %).

MS (ES) MH^+: 617 for $C_{35}H_{38}ClFN_2O_3Si$

Intermediates 86 to 96 were prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 85**:

Intermediate 86

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}(1,3-thiazol-5-yl)methanone

Starting material: {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}(1,3-thiazol-5-yl)methanol (**Intermediate 63**).

MS (ES) MH^+: 623 for $C_{33}H_{36}ClFN_2O_3Si$

Intermediate 87

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}(pyridin-4-yl)methanone

Starting material: {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}(pyridin-4-yl)methanol (**Intermediate 64**).

MS (ES) MH^+: 617 for $C_{35}H_{38}ClFN_2O_3Si$

Intermediate 88

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}(pyridin-3-yl)methanone

Starting material: {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}(pyridin-3-yl)methanol (**Intermediate 65**).

MS (ES) MH^+: 617 for $C_{35}H_{38}ClFN_2O_3Si$

Intermediate 89

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}(1,3-thiazol-2-yl)methanone

Starting material: {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}(1,3-thiazol-2-yl)methanol (**Intermediate 66**).

MS (ES) MH^+: 623 for $C_{33}H_{36}ClFN_2O_3Si$

Intermediate 90

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}(1-methyl-1*H*-imidazol-2-yl)methanone

Starting material: {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}(1-methyl-1*H*-imidazol-2-yl)methanol (**Intermediate 67**)

MS (ES) MH^+: 620 for $C_{34}H_{39}ClFN_3O_3Si$

Intermediate 91

methyl 3-chloro-5-(cyclopropylcarbonyl)-2-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-4-fluorobenzoate

Starting material: methyl 3-chloro-5-[cyclopropyl(hydroxy)methyl]-2-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-4-fluorobenzoate (**Intermediate 68**).

MS (ES) MH^+: 370 for $C_{18}H_{21}ClFNO_4$

Intermediate 92

{2-[{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(hydroxy)methyl]-1,3-thiazol-4-yl}(morpholin-4-yl)methanone

Starting material: {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}[4-(morpholin-4-ylcarbonyl)-1,3-thiazol-2-yl]methanol (**Intermediate 80**)

MS (ES) MH^+: 720 for $C_{38}H_{43}F_2N_3O_5SSi$

Intermediate 93

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}{4-[hydroxy(morpholin-4-yl)methyl]-1,3-thiazol-5-yl}methanone

Starting material: {5-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}[4-(morpholin-4-ylcarbonyl)-1,3-thiazol-5-yl]methanol (**Intermediate 81**)

MS (ES) MH^+: 720 for $C_{38}H_{43}F_2N_3O_5SSi$

Intermediate 94

2-({5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}carbonyl)-*N*,*N*-dimethyl-1,3-thiazole-4-carboxamide

Starting material: 2-[{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(hydroxy)methyl]-*N*,*N*-dimethyl-1,3-thiazole-4-carboxamide (**Intermediate 82**)

MS (ES) MH^+: 678 for $C_{36}H_{41}F_2N_3O_4SSi$

Intermediate 95

2-({5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}carbonyl)-*N*,*N*-dimethyl-1,3-thiazole-5-carboxamide

Starting material: 2-[{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(hydroxy)methyl]-*N*,*N*-dimethyl-1,3-thiazole-5-carboxamide (**Intermediate 83**)

MS (ES) MH^+: 678 for $C_{36}H_{41}F_2N_3O_4SSi$

Intermediate 96

5-({5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}carbonyl)-1,3-thiazole-4-carbonitrile

Starting material: 5-[{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(hydroxy)methyl]-1,3-thiazole-4-carbonitrile (**Intermediate 84**).

MS (ES) MH^+: 632 for $C_{34}H_{35}F_2N_23O_3SSi$.

Intermediate 97

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(1-methyl-1*H*-imidazol-5-yl)methanone

To the solution of {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(1-methyl-1*H*-imidazol-5-yl)methanol (**Intermediate 69**, 50 mg, 0.08 mmol) in anhydrous DCM (5 mL), MnO_2 (143 mg, 1.65 mmol) was added at 0 °C and allowed to stir for 1 hour at room temperature. The reaction mixture was filtered and the solvents were removed under vacuum and the residue was purified over silica gel chromatography column using ethyl acetate-pet. ether gradient to give solid. Yield: 37 mg, (75 %).

MS (ES) MH^+: 604 for $C_{34}H_{39}F_2N_3O_3Si$.

Intermediate 98 was prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 97**:

Intermediate 98

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(4-methyl-1,3-thiazol-5-yl)methanone

Starting material: {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(4-methyl-1,3-thiazol-5-yl)methanol e (**Intermediate 70**)

MS (ES) MH^+: 621 for $C_{34}H_{38}F_2N_2O_3SSi$

Intermediate 99

(6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)(1-methyl-1*H*-imidazol-2-yl)methanone

To a stirring solution of (6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)(1-methyl-1*H*-imidazol-2-yl)methanol (1.2 g, 1.93 mmol, **Intermediate 73**) in dichloromethane (20 mL) was added Manganese(IV)oxide (0.670 g, 7.70 mmol). The mixture was allowed to stir overnight at room temperature. The reaction was filtered through Celite®, and the filtrate concentrated under vacuum to give clear oil. The oil was purified on short bed of silica using 20-30% ethyl acetate in n-hexane to give 1.0 g (84%) the title compound as oil.

MS (ES) MH^+: 621 for $C_{33}H_{38}ClFN_4O_3Si$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.1 (s, 9H), 1.2 (d, 6H), 2.9 (br.s, 2H), 3.2 (m, 2H), 3.8 (br.s., 2H), 4.2 (s, 2H), 4.9 (s, 2H), 7.3–7.4 (m, 4H), 7.4–7.5 (m, 5H), 7.8 (d, 4H).

Intermediates 100 to 106 were prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 99**:

Intermediate 100

(6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)(thiazol-5-yl)methanone

Starting material: (6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)(thiazol-5-yl)methanol (**Intermediate 74**).

MS (ES) MH^+: 624 for $C_{32}H_{35}ClFN_3O_3SiS$

^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.9-1.0 (s, 9H), 1.1 (d, 6H), 3.0–3.1 (m, 4H), 3.7 (br.s, 2H), 4.9 (s, 2H), 7.3–7.4 (m, 6H), 7.5 – 7.7 (m, 4H), 8.8–8.9 (m, 2H).

Intermediate 101

(6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)(2-methylthiazol-5-yl)methanone

Starting material: (6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)(2-methylthiazol-5-yl)methanol (**Intermediate 75**).

MS (ES) MH^+: 638 for $C_{33}H_{37}ClFN_3O_3SiS$

^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.9-1.0 (m, 9H), 1.1 (d, 6H), 2.7 (s, 3H), 3.0 (br.s, 2H), 3.0–3.1 (m, 2H), 3.7 (br.s, 2H), 4.9 (s, 2H), 7.3–7.4 (m, 6H), 7.5–7.7 (m, 4H), 8.6 (s, 1H).

Intermediate 102

4-(6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropicolinoyl)-2-fluorobenzonitrile

Starting material: 4-((6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)(hydroxy)methyl)-2-fluorobenzonitrile (**Intermediate 76**).

MS (ES) MH^+: 660 for $C_{36}H_{36}ClF_2N_3O_3Si$

^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.9–1.1 (m, 9H), 1.2 (d, 6H), 1.8 (td, 3H), 3.1 (d, 2H), 3.6–3.7 (m, 4H), 4.8 (s, 2H), 7.2–7.3 (m, 2H), 7.3–7.5 (m, 2H), 7.5–7.6 (m, 5H), 7.7 (d, 2H).

Intermediate 103

(6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)(5-methylthiazol-2-yl)methanone

Starting material: (6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)(5-methylthiazol-2-yl)methanol (**Intermediate 77**)

MS (ES) MH^+: 638 for $C_{33}H_{37}ClFN_3O_3SiS$

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.0 (s, 9H), 1.1–1.2 (m, 6H), 2.5 (s, 3H), 2.9–3.0 (m, 2H), 3.0–3.1 (m, 2H), 3.7 (d, 2H), 4.9 (s, 2H), 7.3–7.5 (m, 6H), 7.6–7.7 (m, 4H), 7.8 (d, 1H).

Intermediate 104

(2-bromothiazol-5-yl)(6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)methanone

Starting material: (2-bromothiazol-5-yl)(6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)methanol (**Intermediate 78).**

MS (ES) MH^+: 703 for $C_{32}H_{34}ClFBrN_3O_3SiS$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.0 (s, 9H), 1.1–1.2 (m, 6H), 2.9–3.0 (m, 2H), 3.0–3.1 (m, 2H), 3.7 (d, 2H), 4.9 (s, 2H), 7.3–7.5 (m, 6H), 7.6–7.7 (m, 4H), 8.4 (s, 1H).

Intermediate 105

(6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)(2,4-dichlorothiazol-5-yl)methanone

Starting material: (6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)(2,4-dichlorothiazol-5-yl)methanol (**Intermediate 79).**

MS (ES) MH^+: 692 for $C_{32}H_{33}Cl_3FN_3O_3SiS$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.0 (s, 9H), 1.1–1.2 (m, 6H), 2.8 (br.s., 2H), 3.1 (br.s., 2H), 3.7 (br.s., 2H), 4.8 (s, 2H), 7.3–7.5 (m, 6H), 7.6 – 7.7 (m, 4H).

Intermediate 106

(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*R*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)(2-(methylthio)pyrimidin-4-yl)methanone

Starting material: (5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*R*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)(2-(methylthio)pyrimidin-4-yl)methanol (**Intermediate 71**).

MS (ES) MH^+: 648 (M+H) for $C_{35}H_{39}F_2N_3O_3SSi$

Intermediate 107

methyl 5-acetyl-3-chloro-2-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-4-fluorobenzoate

To a stirred solution of LDA (3.1 eq) at -50°C in THF was added methyl 3-chloro-2-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-4-fluorobenzoate (**Intermediate 47,** 1.5 g, 4.96 mmol) in anhydrous THF (10 mL) dropwise and the solution was stirred for 1h at -50 °C. *N*-methoxy-*N*-

methylacetamide (1.66 g, 14.9 mmol) in THF (5 mL) was added dropwise and stirring was continued for additional 1h. The reaction mixture was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulphate. The solvent was removed under vacuum and the residue was purified over silica gel chromatography column using ethyl acetate-pet. ether gradient to obtain the title compound. Yield: 800 mg, (47%)

MS (ES) MH^+: 344 for $C_{16}H_{19}ClFNO_4$

Intermediates 108 to 113 were prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 107**:

Intermediate 108

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}(6-methylpyridin-3-yl)methanone

Starting materials: (2*R*,6*S*)-4-[6-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-2-chloro-3-fluorophenyl]-2,6-dimethylmorpholine (**Intermediate 42**) and *N*-methoxy-6,*N*-dimethyl-nicotinamide.

MS (ES) MH^+: 631 for $C_{36}H_{40}ClFN_2O_3Si$.

Intermediate 109

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}(pyrimidin-2-yl)methanone

Starting materials: (2*R*,6*S*)-4-[6-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-2-chloro-3-fluorophenyl]-2,6-dimethylmorpholine (**Intermediate 42**) and *N*-methoxy-*N*-methylpyrimidine-2-carboxamide.

MS (ES) MH^+: 618 for $C_{34}H_{37}ClFN_3O_3Si$.

Intermediate 110

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}(pyrimidin-4-yl)methanone

Starting materials: (2*R*,6*S*)-4-[6-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-2-chloro-3-fluorophenyl]-2,6-dimethylmorpholine (**Intermediate 42**) and *N*-methoxy-*N*-methylpyrimidine-4-carboxamide

MS (ES) MH^+: 618 for $C_{34}H_{37}ClFN_3O_3Si$.

Intermediate 111

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}(pyrimidin-5-yl)methanone

Starting material: (2*R*,6*S*)-4-[6-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-2-chloro-3-fluorophenyl]-2,6-dimethylmorpholine (**Intermediate 42**) and *N*-methoxy-*N*-methylpyrimidine-5-carboxamide.

MS (ES) MH^+: 618 for $C_{34}H_{37}ClFN_3O_3Si$.

Intermediate 112

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}(pyridazin-4-yl)methanone

Starting materials: (2*R*,6*S*)-4-[6-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-2-chloro-3-fluorophenyl]-2,6-dimethylmorpholine (**Intermediate 42**) and *N*-methoxy-*N*-methylpyridazine-4-carboxamide

MS (ES) MH^+: 618 for $C_{34}H_{37}ClFN_3O_3Si$

Intermediate 113

1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}-2-methoxyethanone

Starting material: (2*R*,6*S*)-4-[6-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-2-chloro-3-fluorophenyl]-2,6-dimethylmorpholine (**Intermediate 42**) and *N*,2-dimethoxy-*N*-methylacetamide.

MS (ES) MH^+: 583 for $C_{32}H_{39}ClFNO_4Si$.

Intermediate 114 and Intermediate 115

Ethyl 2-(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)-2-oxoacetate (**Intermediate 114**) and 2-(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)-*N*-methoxy-*N*-methyl-2-oxoacetamide (**Intermediate 115**)

(2*R*,6*S*)-4-(6-((*tert*-butyldiphenylsilyloxy)methyl)-2,3-difluorophenyl)-2,6-dimethylmorpholine (**Intermediate 3**, 0.5 g, 1.01 mmol) was dissolved in THF (10 ml) and cooled to -78°C. Sec-butyl lithium (1.552 ml, 2.02 mmol) was added drop wise over ~20 minutes and stirred at -78°C for 1 hr. A solution of ethyl 2-(methoxy(methyl)amino)-2-oxoacetate (**Intermediate 56**) (0.406 g, 2.52 mmol) in 10ml of THF was added drop wise over 15 minutes. The reaction was stirred at –78 °C for 30 minutes and then quenched cold with 3 ml sat NH_4Cl. The reaction was allowed to warm to room temperature, was diluted with water and extracted three times with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography using a gradient of hexanes to ethyl acetate to give the first eluting compound, **Intermediate 114** (2.38 g, 3.99 mmol, 39.6 %):

MS (ES) MH^+: 596 for $C_{33}H_{39}F_2NO_5Si$

^1H NMR (300 MHz, DMSO-d_6) δ ppm 1.0 (d, 6H), 1.04 (s, 9H), 1.3 (t, 3H), 2.6-2.75 (m, 2H), 2.9 (d, 2H), 3.3 (m, 2H), 4.4 (q, 2H), 4.7 (s, 2H), 7.4-7.6 (m, 10H) 7.85 (d, 1H).

and the second eluting compound, **Intermediate 115** (1.8 g, 2.95 mmol, 29.2 %):

(1.8 g, 2.95 mmol, 29.2 %):

MS (ES) MH^+: 611 for $C_{33}H_{40}F_2N_2O_5Si$

^1H NMR (300 MHz, DMSO-d_6) δ ppm 1.0 (d, 6H), 1.04 (s, 9H), 2.7 (t, 2H), 2.9 (d, 2H), 3.25 (s, 3H), 3.3 (m, 2H), 3.33 (s, 3H), 3.6 (s, 2H), 7.4-7.5 (m, 6H), 7.6 (d, 4H), 7.87 (d, 1H).

Intermediate 114 was also be prepared according to the following method:

Intermediate 114 (Alternate Synthesis)

Ethyl 2-(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)-2-oxoacetate

(2*R*,6*S*)-4-[6-({[*tert*-Butyl(diphenyl)silyl]oxy}methyl)-2,3-difluorophenyl]-2,6-dimethylmorpholine (**Intermediate 3**, 0.5 g, 1.01 mmol) was dissolved in 10 ml of THF and cooled to -78°C. Sec-butyl lithium (1.358 ml, 1.77 mmol) was added drop wise over 5 minutes. The reaction stirred at -78°C for 1.5 hours. The reaction mixture was cannulated into a -78°C cooled flask containing diethyl oxalate (1.370 ml, 10.09 mmol) in 10 ml of THF. The reaction was allowed to stir at -78°C for 30 minutes; quenched cold with 1 ml sat NH_4Cl and allowed to warm to room temp. The reaction was diluted with water and extracted twice with ethyl acetate. The organic layers were combined and washed twice with brine, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography using a gradient of hexanes to ethyl acetate to give the title compound (486mg, 81% yield) contaminated with diethyl oxalate. This material was taken to the next step without further purifcation.
MS (ES) MH^+: 596 for $C_{33}H_{39}F_2NO_5Si$

Intermediates 116 and 117 were prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 114** (Alternative Synthesis):

Intermediate 116

Ethyl 2-(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*R*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)-2-oxoacetate

Starting materials: (2*R*,6*R*)-4-(6-((*tert*-butyldiphenylsilyloxy)methyl)-2,3-difluorophenyl)-2,6-dimethylmorpholine (11.96 g, 24.13 mmol) (**Intermediate 43**) and diethyl oxalate.
MS (ES) MH^+: 596 for $C_{33}H_{39}F_2NO_5Si$

Intermediate 117

Ethyl 2-(5-(dimethoxymethyl)-2,3,4-trifluorophenyl)-2-oxoacetate

Startng materials: 1-(dimethoxymethyl)-2,3,4-trifluorobenzene (**Intermediate 39**) and diethyl oxalate.

^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.4-1.5 (m, 3H), 3.35-3.4 (m, 6H), 4.5 (q, 2H), 7.3 (s, 1H), 7.9-8.0 (m, 1H).

Intermediate 118

2-(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)-2-oxoacetic acid

Ethyl 2-(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)-2-oxoacetate (**Intermediate 114**, 0.785 g, 3.00 mmol) was dissolved in ethanol (60 ml) and stirred at room temperature with 1ml of 10% KOH. After 3 hours the reaction appears to have gone approximately 40-50% by LCMS. An additional 1ml of 10% KOH was added and the reaction was stirred at room temperature for 30 minutes. The reaction has 70-80% by LCMS. An additional 1ml of 10% KOH was added and the reaction was stirred at room temperature for 60 minutes. The reaction was made acidic with acetic acid, diluted with water and extracted three times with ethyl acetate. The organic layers were washed twice with brine, dried over $MgSO_4$ and concentrated. The resulting sticky oil was dissolved in ethyl acetate, washed with sat. $NaHCO_3$, dried over $MgSO_4$ and concentrated. The resulting oil was dried under vacuum for 2 hours to give the title compound as a yellow solid.

MS (ES) MH^+: 568 for $C_{31}H_{35}F_2NO_5Si$

^1H NMR (300 MHz, DMSO-d_6) δ ppm 0.96 (d, 6H), 1.02 (s, 9H), 2.6-2.7 (m, 2H), 2.7-2.8 (m, 2H), 3.2-3.3 (m, 2H), 4.7 (s, 2H), 7.4-7.5 (m, 6H), 7.6 (d, 4H), 7.87 (d, 1H).

Intermediate 119

1-(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)-2-morpholinoethane-1,2-dione

2-(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)-2-oxoacetic acid (**Intermediate 118,** 150 mg, 0.26 mmol), HATU (121 mg, 0.32 mmol), morpholine (0.025 ml, 0.29 mmol) and triethylamine (0.055 ml, 0.40 mmol) in DMF (5 ml) were stirred at room temperature for 1 hour. The reaction was diluted with water and extracted twice with ethyl acetate. The organic layers were washed three times with brine, dried over $MgSO_4$ and concentrated to give an oil. The oil was purified by silica gel column chromatography using a gradient of hexanes to ethyl acetate to give the title compound (130 mg, 0.204 mmol, 77 %)

MS (ES) MH^+: 637 for $C_{35}H_{42}F_2N_2O_5Si$

^{1}H NMR (300 MHz, CHLOROFORM-d) δ ppm 1.0-1.2 (m, 15H),, 2.7-2.9 (m, 4H), 3.5 (m, 4H), 3.7-3.9 (m, 6H), 4.7 (s, 2H), 7.4-7.5 (m, 6H), 7.7 (d, 4H), 7.95 (d, 1H).

Intermediate 120

2-(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)-*N*,*N*-dimethyl-2-oxoacetamide

2-(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)-2-oxoacetic acid (**Intermediate 118**, 250 mg, 0.44 mmol), HATU (335 mg, 0.88 mmol), triethylamine (0.184 ml, 1.32 mmol) and 2.0M dimethylamine (0.440 ml, 0.88 mmol) in THF were stirred in DMF (5 ml) in a closed vial for 16 hours. The reaction was diluted with water and extracted 3x with ethyl acetate. The organic layers were washed 3x with brine, dried over $MgSO_4$ and concentrated to give an oil. The oil was purified by silica gel column chromatography using a gradient of hexanes to ethyl acetate. Fractions were combined and concentrated to give the title compound (195 mg, 0.328 mmol, 74.5 %)

MS (ES) MH^+: 595 for $C_{33}H_{40}F_2N_2O_4Si$

^{1}H NMR (300 MHz, CHLOROFORM-d) δ ppm 1.0-1.1 (m, 15H), 2.7-2.9 (m, 4H), 3.0 (s, 3H), 3.1 (s, 3H), 3.45 (m, 2H), 4.65 (s, 2H), 7.3-7.5 (m, 6H), 7.7 (d, 4H), 7.9 (d, 1H).

Intermediate 121

Ethyl 2-(6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)-2-oxoacetate

A solution of n-butyllithium, 2.5M in hexanes (3.43 mL, 8.58 mmol) was added.dropwise to a solution of diisopropylamine (1.333 mL, 9.35 mmol) in 15 ml THF at -78 °C. The flask was removed from the -78 degree bath, and placed in an ice bath. Stirred at ca 0 °C for 10 minutes, then recooled to -78 °C to give a pale yellow solution of LDA. The LDA was added by cannulation (over less than 5 min) to a pre-cooled -78 °C solution of (2*R*,6*S*)-4-(2-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-fluoropyridin-3-yl)-2,6-dimethylmorpholine (**Intermediate 45**, 2 g, 3.90 mmol) in THF, 20 ml, to give a brown solution. The solution was stirred at -78 for about 1 hour, then cannulated over about 5 minutes to a -78 °C solution of diethyl oxalate (1.588 mL, 11.69 mmol) in 20 ml THF to give a yellow solution. The solution was stirred at -78 °C. After about 2.5h hours, the yellow solution was worked up by addition of

saturated NH4Cl to the -78 °C solution, and extracted with EtOAc (3X). The organic phase was dried over $MgSO_4$, and concentrated to a yellow oil. The crude was purified by chromatography on SiO_2 using 0-25% EtOAc/hexanes to give 2.3 g (96%) yellow solid, A portion was recrystallized from EtOAc/hexanes.

MS (ES) MH^+: 613 for $C_{32}H_{38}ClFN_2O_5Si$

^1H NMR (300 MHz, DMSO-d_6) δ: 0.9-1.1 (overlapping multiplet, 15H), 1.2 (t, 3H), 2.9-3.0 (m, 2H), 3.1-3.2 (m, 2H). 3.5-3.7 (m, 2H), 4.2 (q, 2H), 4.8 (s, 2H), 7.4-7.6 (m, 10H).

Intermediate 122

(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)(furan-2-yl)methanone

To a stirred solution of (2*R*,6*S*)-4-(6-((*tert*-butyldiphenylsilyloxy)methyl)-2,3-difluorophenyl)-2,6-dimethylmorpholine (**Intermediate 3,** 1 g, 2.02 mmol) in THF (8 mL) was added sBuLi (1.3 M in cyclohexane/hexanes, 3.1 ml, 4.03 mmol) at -70°C under nitrogen atmosphere. After stirring for 1 h at this temperature, *N*-methoxy-*N*-methylfuran-2-carboxamide (0.939 g, 6.05 mmol) was added in 3 ml of THF. After stirring for 1½ h at -70°C, the reaction quenched with sat. ammonium chloride solution and the aqueous layer extracted by ethyl acetate (2 X 100 mL). The organic phases were combined, dried (Na_2SO_4), and concentrated. The residue purified over a silica gel flash column using a gradient of ethyl acetate in hexanes to give the title compound (0.90 g, 76 %).

MS (ES) MH^+: 590 for $C_{34}H_{37}F_2NO_4Si$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.05 (s, 9H), 1.08 (d, 6H), 2.59-2.93 (m, 4H), 3.35-3.58 (m, 2H), 4.71 (s, 2H), 6.58 (dd,1H), 7.18 (d, 1H), 7.32-7.48 (m, 6H), 7.57-7.74 (m, 6H).

Intermediates 123 to 138 were prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 122**:

Intermediate 123

(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)(thiazol-5-yl)methanone

Starting materials: (2*R*,6*S*)-4-(6-((*tert*-butyldiphenylsilyloxy)methyl)-2,3-difluorophenyl)-2,6-dimethylmorpholine (**Intermediate 3**) and *N*-methoxy-*N*-methylthiazole-5-carboxamide.

MS (ES) MH^+: 607 for $C_{33}H_{36}F_2N_2O_3SSi$

^1H NMR (300 MHz, $CDCl_3$) δ: 0.99-1.14 (overlapping doublet and singlet, 15H), 2.67-2.94 (m, 4H), 3.38-3.57 (m, 2H), 4.70 (s, 2H), 7.28-7.51 (m, 6H), 7.54-7.74 (m, 5H), 8.26 (d, 1H), 9.08 (s, 1H).

Intermediate 124

(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)(6-methylpyridin-3-yl)methanone

Starting materials (2*R*,6*S*)-4-(6-((*tert*-butyldiphenylsilyloxy)methyl)-2,3-difluorophenyl)-2,6-dimethylmorpholine (**Intermediate 3** and *N*-methoxy-*N*,6-dimethylnicotinamide.

MS (ES) MH^+: 615 for $C_{36}H_{40}F_2N_2O_3Si$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.00-1.12 (overlapping doublet and singlet,15H), 2.67 (s, 3H), 2.69-2.93 (m, 4H), 3.32-3.61 (m, 2H), 4.70 (s, 2H), 7.25-7.71 (m, 12H), 8.02 (d, 1H), 8.88 (s, 1H).

Intermediate 125

(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)(2-fluorophenyl)methanone

Starting materials: (2*R*,6*S*)-4-(6-((*tert*-butyldiphenylsilyloxy)methyl)-2,3-difluorophenyl)-2,6-dimethylmorpholine (**Intermediate 3**) and 2-fluoro-*N*-methoxy-*N*-methylbenzamide.

MS (ES) MH^+: 618 for $C_{36}H_{38}F_3NO_3Si$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.01 (s, 9H), 1.07 (d, 6H), 2.59-2.93 (m, 4H), 3.30-3.59 (m, 2H), 4.67 (s, 2H), 6.99-7.81 (m, 15H).

Intermediate 126

(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)(tetrahydro-2*H*-pyran-4-yl)methanone

Starting materials: (2*R*,6*S*)-4-(6-((*tert*-butyldiphenylsilyloxy)methyl)-2,3-difluorophenyl)-2,6-dimethylmorpholine (**Intermediate 3**) and *N*-methoxy-*N*-methyltetrahydro-2*H*-pyran-4-carboxamide.

MS (ES) MH^+: 608 for $C_{35}H_{43}F_2NO_4Si$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.04-1.11 (overlaping singlet and doublet, 15H), 1.73-1.90 (m, 4H), 2.62-2.93 (m, 4H), 3.19-3.36 (m, 1H), 3.39-3.59 (m, 4H), 3.95-4.08 (m, 2H), 4.67 (s, 2H), 7.30-7.52 (m, 6H), 7.58-7.72 (m, 4H), 7.78 (d, 1H).

Intermediate 127

1-(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)-2-chloroethanone

Starting materials (2*R*,6*S*)-4-(6-((*tert*-butyldiphenylsilyloxy)methyl)-2,3-difluorophenyl)-2,6-dimethylmorpholine (**Intermediate 3**) and 2-chloro-*N*-methoxy-*N*-methylacetamide.

MS (ES) MH^+: 572 for $C_{31}H_{36}ClF_2NO_3Si$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.05-1.16 (overlapping doublet and singlet, 15H), 2.70-2.92 (m, 4H), 3.34-3.61 (m, 2H), 4.67 (s, 2H) 4.71 (d, 2H), 7.35-7.53 (m, 6H), 7.60-7.74 (m, 4H) 7.97 (dd, 1.98 Hz, 1H).

Intermediate 128

(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)(pyridin-4-yl)methanone

Starting materials: (2*R*,6*S*)-4-(6-((*tert*-butyldiphenylsilyloxy)methyl)-2,3-difluorophenyl)-2,6-dimethylmorpholine (**Intermediate 3**) and *N*-methoxy-*N*-methylisonicotinamide.

MS (ES) MH^+: 601 for $C_{35}H_{38}F_2N_2O_3Si$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.03 (s, 9H), 1.09 (d, 6H), 2.65-2.95 (m, 4H), 3.38-3.59 (m, 2H), 4.68 (s, 2H), 7.28-7.47 (m, 6H), 7.52-7.68 (m, 7H), 8.80 (d, 2H).

Intermediate 129

1-(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)-2,2-difluoroethanone

Starting materials: (2*R*,6*S*)-4-(6-((*tert*-butyldiphenylsilyloxy)methyl)-2,3-difluorophenyl)-2,6-dimethylmorpholine (**Intermediate 3**) and 2,2-difluoro-*N*-methoxy-*N*-methylacetamide.

MS (ES) MH^+: 574 for $C_{31}H_{35}F_4NO_3Si$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.05-1.10 (overlapping doublet and singlet, 15H), 2.71-2.92 (m, 4H), 3.37-3.55 (m, 2H), 4.63 (s, 2H), 6.12-6.57 (m, 1H), 7.31-7.49 (m, 6H), 7.58-7.70 (m, 4H), 7.93 (dd, 1.79 Hz, 1H).

Intermediate 130

1-(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)-2,2,2-trifluoroethanone

Starting materials (2*R*,6*S*)-4-(6-((*tert*-butyldiphenylsilyloxy)methyl)-2,3-difluorophenyl)-2,6-dimethylmorpholine (**Intermediate 3**) and 2,2,2-trifluoro-*N*-methoxy-*N*-methylacetamide. Compound exists in the hydrated form.

MS (ES) MH^+: 610 for $C_{31}H_{34}F_5NO_3Si.H_2O$

Intermediate 131

(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*R*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)(thiazol-2-yl)methanone

Starting materials (2*R*,6*R*)-4-(6-((*tert*-butyldiphenylsilyloxy)methyl)-2,3-difluorophenyl)-2,6-dimethylmorpholine (**Intermediate 43**) and *N*-methoxy-*N*-methylthiazole-2-carboxamide (MTBE was used as solvent instead of THF).

MS (ES) MH^+: 607 for $C_{33}H_{36}F_2N_2O_3SSi$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.05 (d, 6H) 1.07 (s, 9H), 2.58-2.80 (m, 2H), 2.91-3.21 (m, 2H), 3.78-3.96 (m, 2H), 4.64-4.94 (m, 2 H, 7.30-8.20 (m, 13H).

Intermediate 132

1-(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*R*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)-2,2-difluoroethanone

Starting materials (2*R*,6*R*)-4-(6-((*tert*-butyldiphenylsilyloxy)methyl)-2,3-difluorophenyl)-2,6-dimethylmorpholine (**Intermediate 43**) and 2,2-difluoro-*N*-methoxy-*N*-methylacetamide (MTBE was used as solvent instead of THF).

MS (ES) MH^+: 574 for $C_{31}H_{35}F_4NO_3Si$

^1H NMR (300 MHz, $CDCl_3$) δ: 0.99-1.17 (oerlapping doublet and singlet, 15H), 2.58-2.85 (m, 2H), 2.97-3.20 (m, 2H), 3.76-3.99 (m, 2H), 4.57-4.82 (m, 2H), 6.36 (t, 1H), 7.30-8.10 (m, 11H).

Intermediate 133

(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*R*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)(pyrazin-2-yl)methanone

Starting material: *N*-methoxy-*N*-methylpyrazine-2-carboxamide (**Intermediate 50**)

MS (ES) MH^+: 602 for $C_{34}H_{37}F_2N_3O_3Si$

Intermediate 134

(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*R*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)(5-morpholinopyrazin-2-yl)methanone

Starting material: *N*-methoxy-*N*-methyl-5-morpholinopyrazine-2-carboxamide (**Intermediate 52**)

MS (ES) MH^+: 740 for $C_{41}H_{50}FN_5O_5Si$

Intermediate 135

(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)(3-chloropyrazin-2-yl)methanone

Starting material: 3-chloro-*N*-methoxy-*N*-methylpyrazine-2-carboxamide (**Intermediate 53**)

MS (ES) MH^+: 637 for $C_{34}H_{36}ClF_2N_3O_3Si$

Intermediate 136

(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)(6-chloropyrazin-2-yl)methanone

Starting material: 6-chloro-*N*-methoxy-*N*-methylpyrazine-2-carboxamide (**Intermediate 51**)

MS (ES) MH^+: 637 for $C_{34}H_{36}ClF_2N_3O_3Si$

Intermediate 137

(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)(5-chloropyrazin-2-yl)methanone

Starting material:5-chloro-*N*-methoxy-*N*-methylpyrazine-2-carboxamide (**Intermediate 54).**

MS (ES) MH^+: 637 for $C_{34}H_{36}ClF_2N_3O_3Si$

Intermediate 138

(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*R*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)(6-methoxypyrazin-2-yl)methanone

Starting material: *N*,6-dimethoxy-*N*-methylpyrazine-2-carboxamide (**Intermediate 55**)

MS (ES) MH^+: 632 for $C_{35}H_{39}F_2N_3O_4Si$

Intermediate 139

1-(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone

Potassium carbonate (1208 mg, 8.74 mmol) was added to a mixture of 1-(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)-2-chloroethanone (**Intermediate 127**, 500 mg, 0.87 mmol) and 1*H*-1,2,4-triazole (66.4 mg, 0.96 mmol) dissolved in 15 ml of Acetonitrile. The mixture was stirred at room temperature for 3 hours. Potassium carbonate was filtered from the mixture, and the filtrate was diluted with water and extracted with ethyl acetate (2 X 100 mL). The organic phases were combined, dried (Na_2SO_4), and concentrated. The crude residue (482 mg, 91%) contained mainly desired title compound and was used in the next step without further purification.

MS (ES) MH^+: 605 for $C_{33}H_{38}F_2N_4O_3Si$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.02-1.12 (overlapping singlet and doublet, 15H), 2.67-2.91 (m, 4H), 3.35-3.54 (m, 2H), 4.63 (s, 2H), 5.56 (d, 2H), 7.29-8.32 (m, 13H).

Intermediate 140

(6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)(pyridin-2-yl)methanone

Diisopropylamine (0.925 mL, 6.55 mmol) was added dropwise to a stirring solution of 2.5M n-butyllithium in hexane (2.495 mL, 6.24 mmol) in THF (10 mL) at -78°C. Allowed solution to warm to 0°C for 10 minutes then cooled again to -78°C. Cannulated the prepared LDA at -78°C into (2*R*,6*S*)-4-(2-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-fluoropyridin-3-yl)-2,6-dimethylmorpholine (**Intermediate 45,** 1.6 g, 3.12 mmol) in THF (10mL) at -78°C . Allowed the dark solution to stir for 20 minutes and then cannulated into a stirring solution of *N*-methoxy-*N*-methylpicolinamide (1.05 g, 6.24 mmol) in THF (10mL) at -78°C. Allowed the solution to warm to –50 °C and then quenched with saturated ammonium chloride solution. Extracted mixture with ethyl acetate and washed resulting organics with brine. Dried organics over sodium sulfate, filtered, and evacuated filtrate under vacuum to give crude yellow oil. The crude oil was purified on silica using 10-30% acetone in n-hexane as eluant to give 1.3g (67%) of the title compound as oil.

MS (ES) MH^+: 618 for $C_{34}H_{37}ClFN_3O_3Si$

^1H NMR (300 MHz, $CDCl_3$) δ: 0.9 (s, 9H), 1.0 (d, 6H), 2.7–2.9 (m, 2H), 2.9–3.1 (m, 2H), 3.6 (br.s., 2H), 4.8 (s, 2H), 7.1–7.3 (m, 4H), 7.3-7.4 (m, 2H), 7.5-7.6 (m, 5H), 7.9–8.1 (m, 2H), 8.5–8.6 (m, 1H).

Intermediates 141 to 148 were prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 140**:

Intermediate 141

(6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)(pyridin-4-yl)methanone

Starting material: (2*R*, 6*S*)-4-(2-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-fluoropyridin-3-yl)-2,6-dimethylmorpholine (1.5 g, 2.92 mmol) (**Intermediate 45**) and *N*-methoxy-*N*-methylisonicotinamide.

MS (ES) MH^+: 621 for $C_{34}H_{37}ClFN_3O_3Si$

Intermediate 142

(6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)(pyridin-3-yl)methanone

Starting material: (2*R*, 6*S*)-4-(2-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-fluoropyridin-3-yl)-2,6-dimethylmorpholine (**Intermediate 45**) and *N*-methoxy-*N*-methylnicotinamide.
MS (ES) MH^+: 618 for $C_{34}H_{37}ClFN_3O_3Si$:
^1H NMR (300 MHz, $CDCl_3$) δ: 0.9-1.0 (m, 9H), 1.2 (dd, 6H), 3.0-3.1 (m, 4H), 3.7 (d, 2H), 4.8 (m, 2H), 7.2–7.3 (m, 4H), 7.4 (td, 3H), 7.6 (m, 3H), 7.7 (dd, 2H), 8.6–8.7 (m, 2H).

Intermediate 143

(6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)(pyrazin-2-yl)methanone

Starting material: (2-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-fluoropyridin-3-yl)-2,6-dimethylmorpholine (**Intermediate 45**) and *N*-methoxy-*N*-methylpyrazine-2-carboxamide.
MS (ES) MH^+: 619 for $C_{33}H_{36}ClFN_4O_3Si$
^1H NMR (300 MHz, $CDCl_3$) δ: 0.9-1.0 (m, 9H), 1.1–1.2 (m, 6H,) 2.9-3.1 (m, 2H), 3.2 (t, 2H), 3.7 (br.s., 2H), 4.8 (s, 2H), 7.2–7.3 (m, 4H), 7.3–7.4 (m, 2H), 7.6–7.7 (m, 4H), 8.2 (m, 1H), 8.8 (m, 1H), 9.1(d, 1H).

Intermediate 144

(6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)(thiazol-2-yl)methanone

Starting material: (2-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-fluoropyridin-3-yl)-2,6-dimethylmorpholine (**Intermediate 45**) and *N*-methoxy-*N*-methylthiazole-2-carboxamide.
MS (ES) MH^+: 624 for $C_{32}H_{35}ClFN_3O_3SiS$
^1H NMR (300 MHz, $CDCl_3$) δ: 1.0 (s, 9H), 1.1 (d, 6H), 3.0 (br.s, 2H), 3.1–3.2 (m, 2H), 3.7 (br.s., 2H), 4.9 (s, 2H), 7.2–7.5 (m, 6H), 7.5–7.6 (m, 4H), 8.1 (s, 1H).

Intermediate 145

(6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)(4-methylthiazol-2-yl)methanone

Starting material: (2-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-fluoropyridin-3-yl)-2,6-dimethylmorpholine (**Intermediate 45**) and *N*-methoxy-*N*,4-dimethylthiazole-2-carboxamide.
MS (ES) MH^+: 638 for $C_{33}H_{37}ClFN_3O_3SiS$

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.0 (s, 9H), 1.1 (d, 6H), 2.5 (s, 3H), 3.0 (br.s, 2H), 3.1– 3.2 (m, 2H), 3.7 (dd, 2H), 4.9 (s, 2H), 7.2–7.5 (m, 6H), 7.5–7.6 (m, 4H), 7.6 (s, 1H).

Intermediate 146

(6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)(1-methyl-1*H*-1,2,4-triazol-5-yl)methanone

Starting material: (2*R*,6*S*)-4-(2-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-fluoropyridin-3-yl)-2,6-dimethylmorpholine (**Intermediate 45**) and *N*-methoxy-*N*,1-dimethyl-1*H*-1,2,4-triazole-5-carboxamide (**Intermediate 49**).

MS (ES) MH^+: 622 for $C_{32}H_{37}ClFN_5O_3Si$

^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.9 -1.0 (m, 9H) 1.2 (d, 6H) 2.8–3.0 (m, 2H) 3.0 (d, 2H) 3.7 (d, 2H) 4.3 (s, 2H) 4.8 (s, 2H) 7.2–7.3 (m, 4H) 7.3–7.6 (m, 3H) 7.7 (d, 4H) 7.9 (s, 1H).

Intermediate 147

5-(6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropicolinoyl)picolinonitrile

Starting material: (2*R*,6*S*)-4-(2-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-fluoropyridin-3-yl)-2,6-dimethylmorpholine (**Intermediate 45**) and 6-cyano-*N*-methoxy-*N*-methylnicotinamide.

MS (ES) MH^+: 643 for $C_{35}H_{36}ClFN_4O_3Si$

^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.9–1.1 (m, 9H), 1.2 (d, 6H), 3.0–3.1 (m, 2H), 3.6–3.7 (m, 2H), 3.6–3.7 (m, 2H), 4.7–4.8 m, 2H), 7.2–7.3 (m, 4H), 7.5–7.6 (m, 5H), 7.6–7.7 (m, 2H), 8.3 (dd, 1H), 9.1 (d, 1H).

Intermediate 148

1-(6-((*tert*-Butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)ethanone

Starting materials: (2*R*,6*S*)-4-(2-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-fluoropyridin-3-yl)-2,6-dimethylmorpholine (**Intermediate 45**) and *N*-methoxy-*N*-methylacetamide.

MS (ES) MH^+: 555 for $C_{30}H_{36}ClFN_2O_3Si$

^{1}H NMR (300 MHz, CD_2Cl_2) δ: 1.05 (s, 9H), 1.1 (d, 6H), 2.6 (s, 3H), 3.0-3.2 (m, 4H), 3.7-3.8 (m, 2H), 4.9 (s, 2H), 7.4-7.5 (m 6H), 7.7-7.8 (m, 4H).

Intermediate 149

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(2-methyl-1,3-oxazol-4-yl)methanone

sec-Butyl lithium (1.4 M in cyclohexane, 3.2 eq) was added to a stirred solution of (2*R*,6*S*)-4-[6-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-2,3-difluorophenyl]-2,6-dimethylmorpholine (**Intermediate 3,** 1.0 g, 2.02 mmol) in anhydrous THF (10 mL) at -78 °C, and the mixture was stirred for 2h. *N*-methoxy-*N*,2-dimethyl-1,3-oxazole-4-carboxamide (1.0g, 6.46 mmol) in THF (5 mL) was added dropwise and stirring was continued for an additional 1h. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulphate. The solvent was removed under vacuum and the residue was purified by silica gel chromatography using ethy lacetate-pet. ether gradient to obtain product. Yield: 600 mg, (50%)

MS (ES) MH^+: 605 for $C_{34}H_{38}F_2N_2O_4Si$

^1H NMR (400 MHz, DMSO-d_6) δ: 1.0 (m, 15H), 2.5 (s, 3H), 2.7 (m, 2H), 2.8 (d, 2H), 4.8 (s, 2H), 7.4 (m, 6H), 7.6 (t, 4H), 7.7(d, 1H), 8.8(s, 1H).

Intermediates 150 to 156 were prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 149**:

Intermediate 150

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(5-methyl-1,2-oxazol-3-yl)methanone

Starting materials: (2*R*,6*S*)-4-[6-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-2,3-difluorophenyl]-2,6-dimethylmorpholine (**Intermediate 3**) and *N*-methoxy-*N*,5-dimethyl-1,2-oxazole-3-carboxamide

MS (ES) MH^+: 605 for $C_{34}H_{38}F_2N_2O_4Si$

Intermediate 151

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(3,5-dimethyl-1,2-oxazol-4-yl)methanone

Starting materials: (2*R*,6*S*)-4-[6-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-2,3-difluorophenyl]-2,6-dimethylmorpholine (**Intermediate 3**) and *N*-methoxy-*N*,3,5-trimethyl-1,2-oxazole-4-carboxamide

MS (ES) MH^+: 619.5 for $C_{35}H_{40}F_2N_2O_4Si$

Intermediate 152

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(1-methyl-1*H*-imidazol-2-yl)methanone

Starting materials: (2*R*,6*S*)-4-[6-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-2,3-difluorophenyl]-2,6-dimethylmorpholine (**Intermediate 3**) and *N*-methoxy-*N*,1-dimethyl-1*H*-imidazole-2-carboxamide

MS (ES) MH^+: 604 for $C_{34}H_{39}F_2N_3O_3Si$;

Intermediate 153

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(1-methyl-1*H*-imidazol-4-yl)methanone

Starting materials: (2*R*,6*S*)-4-[6-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-2,3-difluorophenyl]-2,6-dimethylmorpholine (**Intermediate 3**) and *N*-methoxy-*N*,1-dimethyl-1*H*-imidazole-4-carboxamide

MS (ES) MH^+: 604.2 for $C_{34}H_{39}F_2N_3O_3Si$;

Intermediate 154

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(4-methyl-1,2,3-thiadiazol-5-yl)methanone

Starting materials: (2*R*,6*S*)-4-[6-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-2,3-difluorophenyl]-2,6-dimethylmorpholine (**Intermediate 3**) and *N*-methoxy-*N*,4-dimethyl-1,2,3-thiadiazole-5-carboxamide

MS (ES) MH^+: 622 for $C_{33}H_{37}F_2N_3O_3SSi$

Intermediate 155

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl} (pyridazin-3-yl)methanone

Starting material: (2*R*,6*S*)-4-[6-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-2,3-difluorophenyl]-2,6-dimethylmorpholine (**Intermediate 3**) and *N*-methoxy-*N*-methylpyridazine-3-carboxamide

MS (ES) MH^+: 602 for $C_{34}H_{37}F_2N_3O_3Si$;

Intermediate 156

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(pyrimidin-4-yl)methanone

Starting material: (2*R*,6*S*)-4-[6-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-2,3-difluorophenyl]-2,6-dimethylmorpholine (**Intermediate 3**) and *N*-methoxy-*N*-methylpyrimidine-4-carboxamide

MS (ES) MH^+: 602 for $C_{34}H_{37}F_2N_3O_3Si$;

Intermediate 157

{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-methyl-1,2-benzothiazol-5-yl}methanol

A mixture of 1-[5-(*tert*-Butyldiphenylsilanyloxymethyl)-4-[(2*R*,6*S*)-2,6-dimethyl-morpholin-4-yl]-2,3-difluorophenyl]ethanone (**Intermediate 9**, 0.5 g, 0.92 mmol), sulfur powder (0.06 g, 1.8 mmol), potassium iodide (0.08 g, 0.4 mmol) and 25% aqueous ammonia solution (10 mL) in DMSO (10 mL) was heated in a sealed tube at 100°C for 4 hours. The reaction mixture was cooled and water was added. The mixture was extracted with ethyl acetate, which was dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (1:9 ethyl acetate:hexanes) to afford product as a yellow solid. Yield: 0.18 g (63%).

MS (ES) MH^+: 311 for $C_{15}H_{19}FN_2O_2S$

^1H NMR (400 MHz, Methanol-d_4): δ 1.2 (d, 6H), 2.5 (s, 3H), 3.0 (m, 4H), 3.8 (m, 2H), 4.8 (s, 2H), 8.0 (s, 1H).

Intermediate 158 was prepared from the indicated starting material using a method similar to the one described for the synthesis of **Intermediate 157**:

Intermediate 158

{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(pyridin-2-yl)-1,2-benzothiazol-5-yl}methanol

Starting material: {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(pyridin-2-yl)methanone (**Intermediate 21**)

MS (ES) MH^+: 374 for $C_{19}H_{20}FN_3O_2S$

^1H NMR (400 MHz, $CDCl_3$) δ: 1.25 (d, 6H), 2.7 (m, 2H), 3.0 (d, 2H), 3.1 (t, 2H), 3.8 (m, 2H), 4.9 (s, 2H), 7.5 (m, 1H), 7.9 (t, 1H), 8.3 (d, 1H), 8.8 (d, 1H), 8.9 (s, 1H).

Intermediate 159

1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}-2,2,2-trifluoro-*N*-hydroxyethanimine

Pyridine (2597 µl, 32.11 mmol) was added to a mixture of 1-(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)-2,2,2-trifluoroethanone (**Intermediate 130,** 1900 mg, 3.21 mmol) and hydroxylamine hydrochloride (223 mg, 3.21 mmol) in 50 ml of ethanol and the solution was heated at 80°C for 40 hours. The reaction mixture was concentrated, diluted with water, and extracted with ethyl acetate. The organic phases were combined, dried (Na_2SO_4), and concentrated to give the crude title compound (1.95 g, 98%), which was used in the next step without further purification.

MS (ES) MH^+: 607 for $C_{31}H_{35}F_5N_2O_3Si$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.03-1.15 (m, 15H), 2.56-2.91 (m, 4H), 3.33-3.59 (m, 2H), 4.58-4.80 (m, 2H), 7.27-7.51 (m, 7H), 7.57-7.74 (m, 4H).

Intermediates 160 to 164 were prepared from the indicated starting material using a method similar to the one described for the synthesis of **Intermediate 159**:

Intermediate 160

1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}-2,2-difluoro-*N*-hydroxyethanimine

Starting material: 1-(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)-2,2-difluoroethanone (**Intermediate 129**).

MS (ES) MH^+: 589 for $C_{31}H_{36}F_4N_2O_3Si$

Intermediate 161

1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}-*N*-hydroxy-1-pyridin-4-ylmethanimine

Starting material: (5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)(pyridin-4-yl)methanone (**Intermediate 128**).

MS (ES) MH^+: 616 for $C_{35}H_{39}F_2N_3O_3Si$

Intermediate 162

1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}-1-furan-2-yl-*N*-hydroxymethanimine

Starting material: (5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)(furan-2-yl)methanone (**Intermediate 122**).

MS (ES) MH^+: 605 for $C_{34}H_{38}F_2N_2O_4Si$

Intermediate 163

1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}-*N*-hydroxy-2-(1*H*-1,2,4-triazol-1-yl)ethanimine

Starting material: 1-(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone (**Intermediate 139**).

MS (ES) MH^+: 620 for $C_{33}H_{39}F_2N_5O_3Si$

Intermediate 164

1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*R*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}-2,2-difluoro-*N*-hydroxyethanimine

Starting material: 1-(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*R*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)-2,2-difluoroethanone (**Intermediate 132**).

MS (ES) MH^+: 589 for $C_{31}H_{36}F_4N_2O_3Si$

Intermediate 165

Ethyl 2-(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)-2-(hydroxyimino)acetate

Ethyl 2-(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)-2-oxoacetate (**Intermediate 114**, 2.808 g, 4.71 mmol) and hydroxylamine hydrochloride (0.360 g, 5.18 mmol) were dissolved in pyridine (40 ml) and stirred at 115 °C for 16 hours. The reaction was concentrated to remove excess pyridine. The residue was dissolved in ethyl acetate and washed with water and brine 3x. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography using a gradient of hexanes to ethyl acetate to give the title compound as a mixture of oxime isomers (1.924 g, 3.15 mmol, 66.8 %).

MS (ES) MH^+: 611 for $C_{33}H_{40}F_2N_2O_5Si$ (2 peaks by LCMS).

^1H NMR (300 MHz, DMSO-d_6) δ ppm 0.9-1.1 (m, 15H), 1.15-1.3 (m, 3H), 2.6-2.8 (m, 4H), 4.2-4.35 (m, 2H), 4.7-4.8 (m, 2H), 7.3-7.65 (m, 11H).

Intermediates 166 and 167 were prepared from the indicated starting material using a method similar to the one described for the synthesis of **Intermediate 165**:

Intermediate 166

Ethyl 2-(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*R*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)-2-(hydroxyimino)acetate

Starting material: ethyl 2-(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*R*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)-2-oxoacetate (**Intermediate 116**)

MS (ES) MH^+: 611 for $C_{33}H_{40}F_2N_2O_5Si$

Intermediate 167

Ethyl 2-(5-(dimethoxymethyl)-2,3,4-trifluorophenyl)-2-(hydroxyimino)acetate

Starting material: ethyl 2-(5-(dimethoxymethyl)-2,3,4-trifluorophenyl)-2-oxoacetate (**Intermediate 117**).

MS (ES) $M^+(-CH_3O)$: 290

Intermediate 168

2-(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)-2-(hydroxyimino)-1-morpholinoethanone

1-(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)-2-morpholinoethane-1,2-dione (**Intermediate 119**, 130 mg, 0.20 mmol) in pyridine was stirred at 115 °C for 16 hours. The reaction was allowed to cool to room temperature and then concentrated. The residue was dissolved in ethyl acetate, diluted with water and made acidic with 1N HCl. The mixture was extracted twice with ethyl acetate. The organic layers were washed twice with brine, dried over $MgSO_4$ and concentrated to give the title compound as an oil which was dried under vacuum. The residue was carried forward without further purification.

MS (ES) MH^+: 652 for $C_{35}H_{43}F_2N_3O_5Si$

Intermediates 169 and 170 were prepared from the indicated starting material using a method similar to the one described for the synthesis of **Intermediate 168**:

Intermediate 169

2-(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)-2-(hydroxyimino)-*N*,*N*-dimethylacetamide

Starting material: 2-(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)-*N*,*N*-dimethyl-2-oxoacetamide (**Intermediate 120**).

MS (ES) MH^+: 610 for $C_{33}H_{41}F_2N_3O_4Si$

Intermediate 170

2-(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)-2-(hydroxyimino)-*N*-methoxy-*N*-methylacetamide

Starting material: 2-(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)-*N*-methoxy-*N*-methyl-2-oxoacetamide (**Intermediate 115**).

MS (ES) MH^+: 626 for $C_{33}H_{41}F_2N_3O_5Si$

Intermediate 171

methyl 3-chloro-2-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-4-fluoro-5-[*N*-hydroxyethanimidoyl]benzoate

To a solution of methyl 5-acetyl-3-chloro-2-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-4-fluorobenzoate (**Intermediate 107,** 800 mg, 2.32 mmol) in methanol:Pyridine (1:1, 6 mL) was added hydroxylamine hydrochloride (223 mg, 3.48 mmol) and the mixture was stirred at room temperature for 12 hours. Solvents were removed under vacuum and the residue was subjected to silica gel column chromatography using a gradient of ethyl aacetate in pet. ether to give title compound. Yield: 700 mg (87%).

MS (ES) MH^+: MS (ES) MH^+: 359 for $C_{16}H_{20}ClFN_2O_4$

Intermediates 172 to 196 were prepared from the indicated starting material and hydroxylamine hydrochloride using a method similar to the one described for the synthesis of **Intermediate 171**:

Intermediate 172

1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}-*N*-hydroxy-1-(pyridin-2-yl)methanimine

Starting material: {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}(pyridin-2-yl)methanone (**Intermediate 85**).

MS (ES) MH^+: 632 for $C_{35}H_{39}ClFN_3O_3Si$

Intermediate 173

1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}-*N*-hydroxy-1-(6-methylpyridin-3-yl)methanimine

Starting material: {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}(6-methylpyridin-3-yl)methanone (**Intermediate 108**).

MS (ES) MH^+: 646 for $C_{36}H_{41}ClFN_3O_3Si$.

Intermediate 174

1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}-*N*-hydroxy-1-(1,3-thiazol-5-yl)methanimine

Starting material: {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}(1,3-thiazol-5-yl)methanone (**Intermediate 86**).
MS (ES) MH^+: 638 for $C_{33}H_{37}ClFN_3O_3SSi$

Intermediate 175

1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}-*N*-hydroxy-1-(pyridin-4-yl)methanimine
Starting material: {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}(pyridin-4-yl)methanone (**Intermediate 87**).
MS (ES) MH^+: 632 for $C_{35}H_{39}ClFN_3O_3Si$

Intermediate 176

1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}-*N*-hydroxy-1-(pyridin-3-yl)methanimine
Starting material: {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}(pyridin-3-yl)methanone (**Intermediate 88**).
MS (ES) MH^+: 632 for $C_{35}H_{39}ClFN_3O_3Si$

Intermediate 177

1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}-*N*-hydroxy-1-(1,3-thiazol-2-yl)methanimine
Starting material: {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}(1,3-thiazol-2-yl)methanone (**Intermediate 89**).
MS (ES) MH^+: 638 for $C_{33}H_{37}ClFN_3O_3SSi$

Intermediate 178

1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}-*N*-hydroxy-1-(1-methyl-1*H*-imidazol-2-yl)methanimine
Starting material: {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}(1-methyl-1*H*-imidazol-2-yl)methanone (**Intermediate 90**).

MS (ES) MH^+: 635 for $C_{34}H_{40}ClFN_4O_3Si$

Intermediate 179

1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}-*N*-hydroxy-2-methoxyethanimine

Starting material: 1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}-2-methoxyethanone (**Intermediate 113**).

MS (ES) MH^+: 599 for $C_{32}H_{40}ClFN_2O_4Si$.

Intermediate 180

{2-[{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(hydroxyimino)methyl]-1,3-thiazol-4-yl}(morpholin-4-yl)methanone

Starting material: {2-[{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(hydroxy)methyl]-1,3-thiazol-4-yl}(morpholin-4-yl)methanone (**Intermediate 92**).

MS (ES) MH^+: MS (ES) MH^+: 620 for $C_{34}H_{39}F_2N_3O_4Si$;

Intermediate 181

{5-[{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(hydroxyimino)methyl]-1,3-thiazol-4-yl}(morpholin-4-yl)methanone

Starting material: {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}{4-[hydroxy(morpholin-4-yl)methyl]-1,3-thiazol-5-yl}methanone (**Intermediate 93**)

MS (ES) MH^+: 735.for $C_{38}H_{44}F_2N_4O_5SSi$

Intermediate 182

2-[{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(hydroxyimino)methyl]-*N*,*N*-dimethyl-1,3-thiazole-4-carboxamide

Starting material: 2-({5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}carbonyl)-*N*,*N*-dimethyl-1,3-thiazole-4-carboxamide (**Intermediate 94**).

MS (ES) MH^+: 693 for $C_{36}H_{42}F_2N_4O_4SSi$

Intermediate 183

2-[{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(hydroxyimino)methyl]-*N*,*N*-dimethyl-1,3-thiazole-5-carboxamide

Starting material: 2-({5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}carbonyl)-*N*,*N*-dimethyl-1,3-thiazole-5-carboxamide (**Intermediate 95**)

MS (ES) MH^+: 693 for $C_{36}H_{42}F_2N_4O_4SSi$

Intermediate 184

5-[{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(hydroxyimino)methyl]-1,3-thiazole-4-carbonitrile

Starting material: 5-({5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}carbonyl)-1,3-thiazole-4-carbonitrile (**Intermediate 96**)

MS (ES) MH^+: 647 for $C_{34}H_{36}F_2N_4O_3SSi$.

Intermediate 185

1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}-*N*-hydroxy-1-(2-methyl-1,3-oxazol-4-yl)methanimine

Starting material: {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(2-methyl-1,3-oxazol-4-yl)methanone (**Intermediate 149**).

MS (ES) MH^+: MS (ES) MH^+: 620 for $C_{34}H_{39}F_2N_3O_4Si$;

Intermediate 186

1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}-*N*-hydroxy-1-(5-methyl-1,2-oxazol-3-yl)methanimine

Starting material: {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(5-methyl-1,2-oxazol-3-yl)methanone

(Intermediate 150)

MS (ES) MH^+: 620 for $C_{34}H_{39}F_2N_3O_4Si$;

Intermediate 187

1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}-1-(3,5-dimethyl-1,2-oxazol-4-yl)-*N*-hydroxymethanimine

Starting material: {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(3,5-dimethyl-1,2-oxazol-4-yl)methanone

(Intermediate 151)

MS (ES) MH^+: 634 for $C_{35}H_{41}F_2N_3O_4Si$;

Intermediate 188

1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}-*N*-hydroxy-1-(1-methyl-1*H*-imidazol-2-yl)methanimine

Starting material: {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(1-methyl-1*H*-imidazol-2-yl)methanone

(Intermediate 152)

MS (ES) MH^+: 618 for $C_{34}H_{40}F_2N_4O_3Si$;

Intermediate 189

1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}-*N*-hydroxy-1-(1-methyl-1*H*-imidazol-4-yl)methanimine

Starting material: {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(1-methyl-1*H*-imidazol-4-yl)methanone

(Intermediate 153)

MS (ES) MH^+: 618 for $C_{34}H_{40}F_2N_4O_3Si$;

Intermediate 190

1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}-*N*-hydroxy-1-(1-methyl-1*H*-imidazol-5-yl)methanimine

Starting material: {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(1-methyl-1*H*-imidazol-5-yl)methanone (**Intermediate 97**)

MS (ES) MH^+: 618 for $C_{34}H_{40}F_2N_4O_3Si$;

Intermediate 191

1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}-*N*-hydroxy-1-(4-methyl-1,3-thiazol-5-yl)methanimine

Starting material: {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(4-methyl-1,3-thiazol-5-yl)methanone (**Intermediate 98**)

MS (ES) MH^+: 636 for $C_{34}H_{39}F_2N_3O_3SSi$

Intermediate 192

1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}-*N*-hydroxy-1-(4-methyl-1,2,3-thiadiazol-5-yl)methanimine

Starting material: {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(4-methyl-1,2,3-thiadiazol-5-yl)methanone (**Intermediate 154**)

MS (ES) MH^+: 637 for $C_{33}H_{38}F_2N_4O_3SSi$;

Intermediate 193

1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}-*N*-hydroxy-1-(pyridazin-3-yl)methanimine

Starting material: {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl} (pyridazin-3-yl)methanone (**Intermediate 155**)

MS (ES) MH^+: 617.2 for $C_{34}H_{38}F_2N_4O_3Si$;

Intermediate 194

1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}-*N*-hydroxy-1-(pyrimidin-4-yl)methanimine

Starting material: {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(pyrimidin-4-yl)methanone (**Intermediate 156**)

MS (ES) MH^+: 617 for $C_{34}H_{38}F_2N_4O_3Si$;

Intermediate 195

2-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-4-fluoro-5-[(hydroxyimino)(1,3-thiazol-2-yl)methyl]-3-methylbenzoic acid

Starting material: 2-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-4-fluoro-3-methyl-5-(1,3-thiazol-2-ylcarbonyl)benzoic acid (**Intermediate 60**).

MS (ES) MH^+: 393 for $C_{18}H_{20}FN_3O_4S$

Intermediate 196

2-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-4-fluoro-5-[(hydroxyimino)(pyrazin-2-yl)methyl]-3-methylbenzoic acid

Starting material: 2-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-4-fluoro-3-methyl-5-(pyrazin-2-ylcarbonyl)benzoic acid (**Intermediate 61**).

MS (ES) MH^+: 388 for $C_{19}H_{21}FN_4O_4$

Intermediate 197

ethyl 2-(6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)-2-(hydroxyimino)acetate

Ethyl 2-(6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)-2-oxoacetate (**Intermediate 121**, 13.4 g, 21.85 mmol) was slurried in isopropanol (150ml), and pyridine (124 ml, 1529.70 mmol) was added to give a yellow solution. Hydroxylamine hydrochloride (1.670 g, 24.04 mmol) was added, and the suspension was stirred at room temperature for approximately 16 hours. The resulting solution was concentrated to an oil. The residue was purified by chromatography on SiO_2 using 5-40 % EtOAc/hexane. A total of 11.93 g (87%) of the title product as a mixture of oxime isomers was obtained as a yellow oil.

MS (ES) MH^+: 628 for $C_{32}H_{39}CFN_3O_5Si$

Intermediate 198

{5-[(3-chloropyrazin-2-yl)(hydroxyimino)methyl]-2-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3,4-difluorophenyl}methanol

A mixture of (5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)(3-chloropyrazin-2-yl)methanone (**Intermediate 135,** ~150mg) and $NH_2OH.HCl$ in 10 ml of MeOH was stirred for 72 hours at room temperature,. The reaction mixture was diluted with EtOAc, washed with water and brine. After drying over anhydrous sodium sulfate, filtering and concentrating, the resultant residue was purified by silica gel column chromatography (Hexanes/EtOAc) to give product.(106mg).

MS (ES) MH^+: 413 for $C_{18}H_{19}ClF_2N_4O_3$

Intermediates 199 and 200 were prepared from the indicated starting material and hydroxylamine hydrochloride using a method similar to the one described for the synthesis of **Intermediate 198**:

Intermediate 199

1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}-1-(6-chloropyrazin-2-yl)-*N*-hydroxymethanimine

Starting material: (5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)(6-chloropyrazin-2-yl)methanone (**Intermediate 136**)

MS (ES) MH^+: 652 for $C_{34}H_{37}ClF_2N_4O_3Si$

Intermediate 200

1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}-1-(5-chloropyrazin-2-yl)-*N*-hydroxymethanimine

Starting material: (5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)(5-chloropyrazin-2-yl)methanone (**Intermediate 137**)

MS (ES) MH^+: 652 for $C_{34}H_{37}ClF_2N_4O_3Si$

Intermediate 201

(7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(pyridin-2-yl)isoxazolo[4,5-b]pyridin-5-yl)methanol

A solution of (6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)(pyridin-2-yl)methanone (**Intermediate 140**, 1.3 g, 2.10 mmol) and hydroxylamine hydrochloride (0.146 g, 2.10 mmol) in pyridine (10 mL) / methanol (20 mL) mixture was heated for 2 hours at 40 °C then cooled and concentrated under vacuum to give a crude yellow oil weighing 1.3g.

To the above oil was added DMF (30 mL) and cesium carbonate (0.801 g, 2.46 mmol). The slurry was heated at 40°C for 4 hours then cooled. The reaction mixture was quenched with water and extracted with ethyl acetate. The organics were washed with brine then dried organics over sodium sulfate, filtered, and filtrate evacuated under vacuum to give a crude yellow oil. The crude oil was purified on silica using 20-40% acetone in n-hexane to give 0.39g (51%) of the title compound as oil.

MS (ES) MH^+: 375 for $C_{18}H_{19}ClN_4O_3$

^1H NMR (300 MHz, DMSO-d_6) δ: 1.0–1.1 (m, 6H), 3.0 (d, 4H), 3.7–3.9 (m, 2H), 4.8 (td, 2H), 5.2 (br.s., 1H), 7.6 (td, 1H), 8.1 (td, 1H), 8.6 (d, 1H), 8.8 (dd, 1H).

Intermediates 202 and 203 were prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 201**:

Intermediate 202

(7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(pyridin-4-yl)isoxazolo[4,5-b]pyridin-5-yl)methanol

Starting material: (6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)(pyridin-4-yl)methanone (**Intermediate 141**).

MS (ES) MH^+: 375 for $C_{18}H_{19}ClN_4O_3$

^1H NMR (300 MHz, DMSO-d_6) δ: 1.0–1.1 (m, 6H), 3.0 (d, 4H), 3.7–3.8 (m, 2H), 4.8 (td, 2H), 5.3 (br.s., 1H), 8.4 (dd, 2H), 8.8 (dd, 2H).

Intermediate 203

(7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(pyridin-3-yl)isoxazolo[4,5-b]pyridin-5-yl)methanol

Starting material: (6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)(pyridin-3-yl)methanone (**Intermediate 142**).

MS (ES) MH^+: 375 for $C_{18}H_{19}ClN_4O_3$

^1H NMR (300 MHz, DMSO-d_6) δ: 1.0–1.1 (m, 6H), 3.0 (d, 4H), 3.7–3.9 (m, 2H), 4.8 (td, 2H), 5.2 (br.s., 1H), 7.9 (dd, 1H), 8.7-8.8 (m, 2H).

Intermediate 204

ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxylate

Sodium hydride (0.159 g, 3.97 mmol) was suspended in 20 ml of DMF and cooled in an ice bath. Ethyl 2-(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)-2-(hydroxyimino)acetate (**Intermediate 165**, 1.94 g, 3.18 mmol) was dissolved in 20ml of DMF and added to the reaction flask. The ice bath was removed and the reaction stirred at room temperature for 2 hours. The reaction was quenched with sat NH_4Cl (5 ml), diluted with water and extracted three times with ethyl acetate. The organic layers were combined, washed with water and brine 5x, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography using a gradient of hexanes to ethyl acetate to give the title compound (1.250 g, 66.6 %).

MS (ES) MH^+: 591 for $C_{33}H_{39}FN_2O_5Si$

^1H NMR (300 MHz, DMSO-d_6) δ ppm 1.0 (d, 6H), 1.1 (s, 9H), 1.4 (t, 3H), 2.6-2.8 (m, 4H), 4.5 (q, 2H), 4.9 (s, 2H), 7.4-7.5 (m, 6H), 7.6 (d, 4H), 8.1 (s, 1H).

Intermediates 205 and 206 were prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 204**:

Intermediate 205

5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-*N*-methoxy-*N*-methylbenzo[d]isoxazole-3-carboxamide

Starting material: 2-(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)-2-(hydroxyimino)-*N*-methoxy-*N*-methylacetamide (**Intermediate 170**).

MS (ES) MH^+: 606 for $C_{33}H_{40}FN_3O_5Si$

^1H NMR (300 MHz, CHLOROFORM-d) δ ppm 1.0-1.2 (m, 15H), 2.7 (d, 2H), 2.8-3.0 (m, 2H), 3.4-3.6 (m, 5H), 3.8 (s, 3H), 4.8 (s, 2H), 7.3-7.5 (m, 6H), 7.7 (d, 4H), 7.9 (br. s., 1H).

Intermediate 206

Ethyl 5-(dimethoxymethyl)-6,7-difluorobenzo[d]isoxazole-3-carboxylate

Starting material: ethyl 2-(5-(dimethoxymethyl)-2,3,4-trifluorophenyl)-2-(hydroxyimino)acetate (**Intermediate 167**).

MS (ES) $M^+(-CH_3O)$: 270

^1H NMR (300 MHz, CHLOROFORM-d) δ ppm 1.5 (t, 3H), 3.4 (s, 6H), 4.6 (q, 2H), 5.7 (s, 1H), 8.1 (d, 1H).

Intermediate 207

5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carbohydrazide

Ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxylate (**Intermediate 204**, 0.5 g, 0.85 mmol) in 4.5 ml ethanol was treated with anhydrous hydrazine (0.490 ml, 15.60 mmol) at room temperature for 2 hour. Reaction was diluted with dichloromethane and brine. Organic layer washed with water, dried over sodium sulfate, and concentrated. The residue purified on silica-gel column (elution 40% etoac in hexanes) to give 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carbohydrazide (0.354 g, 72.5 %).

MS (ES) MH^+:577 for $C_{31}H_{37}FN_4O_4Si$

Intermediate 208

5-(5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazol-3-yl)-1,3,4-oxadiazol-2(3H)-one

5-((*tert*-Butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carbohydrazide (**Intermediate 207**, 490 mg, 0.85 mmol) and di(1*H*-

imidazol-1-yl)methanone (207 mg, 1.27 mmol) were dissolved in 8ml of THF and was treated with DIEA (297 µl, 1.70 mmol) at room temperature for 16 hours. Reaction diluted with ethyl acetate and quenched with aq. Ammonium chloride solution. Organic layer was separated and washed with water, dried over sodium sulfate and concentrated to give 5-(5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazol-3-yl)-1,3,4-oxadiazol-2(3H)-one (495 mg, 97 %)

MS (ES) MH^+: 603 for $C_{32}H_{35}FN_4O_5Si$

^1H NMR (300 MHz, DMSO-d_6) δ: 1.1 (d, 6 H) 1.1 (s, 9 H) 2.5 - 3.0 (m, 4 H) 3.3 - 3.6 (m, 2 H) 4.8 (s, 2 H) 7.3 - 7.7 (m, 10 H) 8.1 (s, 1 H) 9.0 (s, 1 H)

Intermediate 209

5-(6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)benzo[d]isoxazol-3-yl)-1,3,4-oxadiazol-2(3H)-one

5-(5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazol-3-yl)-1,3,4-oxadiazol-2(3H)-one (**Intermediate 208,** 490 mg, 0.81 mmol) in 10 ml of THF was treated with TBAF (1M in THF;1626 µl, 1.63 mmol) at room temperature for 16 hours. Reaction quenched with aq ammonium chloride solution and Extracted with ethyl acetate. Crude product purified on column (50-80% etoac in hexanaes) to give 5-(6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)benzo[d]isoxazol-3-yl)-1,3,4-oxadiazol-2(3H)-one (235 mg, 79 %)

MS (ES) MH^+: 365 for $C_{16}H_{17}FN_4O_5$

^1H NMR (300 MHz, DMSO-d_6) δ: 1.1 (d, 6 H) 2.9 - 3.3 (m, 4 H) 3.7 - 3.9 (m, 2 H) 8.2 (s, 1 H) 10.3 (s, 1 H) 13.4 (s, 1 H)

Intermediate 210

ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxylate

Sodium hydride (0.723 g, 18.07 mmol) was suspended in 60 ml of DMF and cooled in an ice bath. Ethyl 2-(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*R*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)-2-(hydroxyimino)acetate (**Intermediate 166**, 8.827 g, 14.45 mmol) was dissolved in 30ml of DMF and added to the reaction flask. The ice bath was removed and the

reaction stirred at room temperature for 2 hours. LCMS analysis indicated that the reaction was incomplete, so an additional 100mg of NaH was added and the reaction stirred for 30 minutes. LCMS analysis indicated that the reaction was incomplete, so an additional 100mg of NaH was added and the reaction stirred for 30 minutes. The reaction was cooled in an ice bath and quenched drop wise with 5 ml of saturated NH_4Cl. The reaction was diluted with water and extracted three times with ethyl acetate. The organic layers were combined, washed 5x with brine, dried over $MgSO_4$ and concentrated to give an oil. The oil was purified by silica gel column chromatography using a gradient of hexanes to ethyl acetate. Fractions were combined and concentrated to give the title compound (5.156 g, 8.73 mmol, 60.4 %).

MS (ES) MH^+: 591 for $C_{33}H_{39}FN_2O_5Si$

^1H NMR (300 MHz, DMSO-d_6) δ ppm 0.94 (d, 6H) 1.10 (s, 9H) 1.38 (t, 3H) 2.59-2.73 (m, 2H) 2.91-3.10 (m, 2H) 3.77 (br. s., 2H) 4.49 (q, *J*=7.03 Hz, 2H) 4.84-5.03 (m, 2H) 7.36-7.54 (m, 6H) 7.63 (d, 4H) 8.14 (s, 1H)

Also isolated during the purification was ethyl (2Z)-(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*R*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)-2-(hydroxyimino)acetate as a single oxime isomer (1.22 g, 14%).

MS (ES) MH^+: 611 for $C_{33}H_{40}F_2N_2O_5Si$

Intermediate 211

Ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)isoxazolo[4,5-b]pyridine-3-carboxylate

Sodium hydride, 60% dispersion in mineral oil (0.063 g, 1.56 mmol) was added to a flask and DMF, 5 ml, was added to give a white slurry. The mixture was cooled in an ice bath. Ethyl 2-(6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)-2-(hydroxyimino)acetate (**Intermediate 197,** 0.786 g, 1.25 mmol) in 5ml DMF was added to the sodium hydride suspension. There was some gas evolution, and the mixture became an orange solution. The reaction was worked up after 1 hour. Then saturated NH4Cl solution was added; the mixture was extracted with EtOAc, and washed with water (3x). The combined organic phase was dried over $MgSO_4$ and concentrated. The residue was purified

by chromatography on SiO_2 using 0-40% EtOAc/hexanes to recover 544 mg (71%) of the title compound as a yellow foam.

MS (ES) MH^+: 608 for $C_{32}H_{38}ClN_3O_5Si$

^1H NMR (300 MHz, CD_2Cl_2) δ: 1.0-1.2 (overlapping multiplet, 15H), 1.5 (t, 3H), 2.8-2.9 (m, 2H), 3.1 (t, 2H), 3.7 (br s, 2H), 4. 6 (q, 2H), 5.0 (s, 2H), 7.3-7.8 (m, 10H).

Intermediate 212

5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-*N*-ethyl-7-fluorobenzo[d]isoxazole-3-carboxamide

Under a nitrogen atmosphere, trimethylaluminum (2M in toluene, 1206 µl, 2.41 mmol) was slowly added (gas evolution) to an ice cooled solution of ethylamine (2M in THF) (1206 µl, 2.41 mmol) in 7 ml of toluene. The reaction was allowed to warm to room temperature and stirred for 2 hours. Ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxylate, (**Intermediate 204**, 190 mg, 0.32 mmol) was added as a solution in toluene (3 ml). The reaction was stirred at 45 °C for 18 hours. The reaction was quenched drop wise (vigorous gas evolution) with 2 ml of 1N HCl. The crude reaction was filtered to remove solids, diluted with water and extracted twice with ethyl acetate. The organic layers were combined, washed twice with brine, dried over $MgSO_4$ and concentrated to give an oil. The oil was purified by silica gel column chromatorgraphy using a gradient of hexanes to ethyl acetate. Fractions were combined and concentrated to give the title compound. (170 mg, 0.288 mmol, 90 %).

MS (ES) MH^+: 590 for $C_{33}H_{40}FN_3O_4Si$

^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.0-1.2 (m, 15H), 1.3 (t, 3H), 2.7 (d, 2H), 2.88 (t, 2H), 3.45 (m, 2H), 3.5-3.7 (m, 2H), 4.8 (s, 2H), 6.9 (m, 1H), 7.35-7.5 (m, 6H), 7.0 (d, 4H), 8.3 (s, 1H).

Intermediates 213 to 240 were prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 212**:

Intermediate 213

5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-*N*-ethyl-7-fluoro-*N*-methylbenzo[d]isoxazole-3-carboxamide

Starting materials: Ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxylate (**Intermediate 204**) and *N*-methylethanamine hydrochloride

MS (ES) MH^+: 604 for $C_{34}H_{42}FN_3O_4Si$

^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.0-1.2 (m, 15H), 1.2-1.4 (m, 3H), 2.7 (d, 2H), 2.9 (t, 2H), 3.2 (d, 3H), 3.4-3.6 (m, 2H), 3.6-3.8 (m, 2H), 4.8 (s, 2H), 7.3-7.5 (m, 6H), 7.7 (d, 4H), 7.9 (br. s., 1H).

Intermediate 214

5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-*N*-methylbenzo[d]isoxazole-3-carboxamide

Starting materials: Ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxylate(**Intermediate 204**) and methylamine (2M in THF)

MS (ES) MH^+: 576 for $C_{32}H_{38}FN_3O_4Si$

^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.0-1.2 (m, 15H), 2.7 (d, 2H), 2.8-3.0 (m, 2H), 3.12 (d, 3H), 3.5 (m, 2H), 4.8 (s, 2H), 6.9-7.1 (m, 1H), 7.3-7.5 (m, 6H), 7.7 (d, 4H), 8.3 (s, 1H).

Intermediate 215

4-(5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carbonyl)-1-methylpiperazin-2-one

Starting materials: Ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxylate (**Intermediate 204**) and 1-methylpiperazin-2-one hydrochloride.

MS (ES) MH^+: 659 for $C_{36}H_{43}FN_4O_5Si$

Intermediate 216

(5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazol-3-yl)(3,3-difluoroazetidin-1-yl)methanone

Starting materials: ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxylate (**Intermediate 204**) and 3,3-difluoroazetidine hydrochloride.

MS (ES) MH^+: 638 for $C_{34}H_{38}F_3N_3O_4Si$

^1H NMR (300 MHz, CHLOROFORM-*d*) d ppm 1.0-1.2 (m, 15H), 2.67 (d, 2H), 2.8-3.0 (m, 2H), 3.4 (d, 2H), 4.6 (t, 2H), 5.0 (t, 2H), 7.3-7.5 (m, 6H), 7.7 (d, 4H), 8.2 (s, 1H).

Intermediate 217

5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxamide

Starting materials: Ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxylate (**Intermediate 204**) and ammonium chloride.

MS (ES) MH^+: 562 for $C_{31}H_{36}FN_3O_4Si$

Intermediate 218

5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-*N*-(2-methoxyethyl)benzo[d]isoxazole-3-carboxamide

Starting materials: Ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxylate (**Intermediate 204**) and 2-methoxyethanamine

MS (ES) MH^+: 620 for $C_{34}H_{42}FN_3O_5Si$

^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.0-1.2 (m, 15H), 2.7 (d, 2H), 2.8-2.95 (m, 2H), 3.4-3.5 (m, 5H), 3.6 (t, 2H), 3.7 (t, 2H), 4.8 (s, 2H), 7.35 – 7.5 (m, 6H), 7.7-7.8 (m, 4H), 8.26 (s, 1H).

Intermediate 219

N-tert-butyl-5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxamide

Starting materials: Ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxylate (**IIntermediate 204**) and 2-methylpropan-2-amine

MS (ES) MH^+: 618 for $C_{35}H_{44}FN_3O_4Si$

^1H NMR (300 MHz, CHLOROFORM-*d*) d ppm 1.0-1.2 (m, 15H), 1.55 (s, 9H), 2.7 (d, 2H), 2.8–3.0 (m, 2H), 3.4-3.55 (m, 2H), 4.8 (s, 2H), 6.75 (br. s., 1H), 7.3-7. (m, 6H), 7.7 (d, 4H), 8.2 (s, 1H).

Intermediate 220

5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-[(1,1-dioxidothiomorpholin-4-yl)carbonyl]-7-fluoro-1,2-benzisoxazole

Starting materials: Ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxylate (**Intermediate 204**) and thiomorpholine 1,1-dioxide

MS (ES) MH^+: 680 for $C_{35}H_{42}FN_3O_6SSi$

Intermediate 221

5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-*N*-(tetrahydro-2*H*-pyran-4-yl)benzo[d]isoxazole-3-carboxamide

Starting materials: Ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxylate (**Intermediate 204**) and tetrahydro-2*H*-pyran-4-amine

MS (ES) MH^+: 646 for $C_{36}H_{44}FN_3O_5Si$

^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.0-1.2 (m, 1H), 1.6-1.8 (m, 2H), 2.0-2.1 (m, 2H), 2.7 (d, 2H), 2.8–3.0 (m, 2H), 3.4-3.5 (m, 2H), 3.6 (t, 2H), 4.1 (d, 2H), 4.2-4.4 (m, 1H), 4.8 (s, 2H), 6.85 (d, 1H), 7.3-7.5 (m, 6H), 7.7 (d, 4H), 8.3 (s, 1H).

Intermediate 222

5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-*N*-isopropylbenzo[d]isoxazole-3-carboxamide

Starting materials:Ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxylate (**Intermediate 204**) and propan-2-amine

MS (ES) MH^+: 604.2 for $C_{34}H_{42}FN_3O_4Si$

^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.0-1.2 (m, 15H), 1.35 (d, 6H), 2.7 (d, 2H), 2.8-3.0 (m, 2H), 3.45 (m, 2H), 4.3-4.5 (m, 1H), 4.8 (s, 2H), 6.8 (d, 1H), 7.3-7.5 (m, 6H), 7.7 (d, 4H), 8.3 (s, 1H).

Intermediate 223

5-((*tert*-butyldiphenylsilyloxy)methyl)-*N*-cyclopropyl-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxamide

Starting materials: Ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxylate (**Intermediate 204**) and cyclopropanamine

MS (ES) MH^+: 602 for $C_{34}H_{40}FN_3O_4Si$

^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.7-0.8 (m, 2H), 0.9–1.0 (m, 2H), 1.1 (d, 6H), 1.1 (s, 9H), 2.7 (d, 2H), 2.8-2.95 (m, 2H), 2.95-3.1 (m, 1H), 3.4-3.55 (m, 2H), 4.8 (s, 2H), 7.0 (br. s., 1H), 7.3-7.5 (m, 6H), 7.7 (d, 4H), 8.3 (s, 1H).

Intermediate 224

(5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazol-3-yl)(4-methoxypiperidin-1-yl)methanone

Starting materials: Ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxylate (**Intermediate 204**) and 4-methoxypiperidine

MS (ES) MH^+: 660for $C_{37}H_{46}FN_3O_5Si$

^{1}H NMR (300 MHz, CHLOROFORM-*d*) d ppm 1.02-1.17 (m, 15H) 1.64-2.05 (m, 4H) 2.69 (d, *J*=11.30 Hz, 2H) 2.81-3.00 (m, 2H) 3.41 (s, 3H) 3.43-3.66 (m, 4H) 3.72-3.86 (m, 1H) 3.86-4.08 (m, 2H) 4.82 (s, 2H) 7.33-7.52 (m, 6H) 7.69 (d, *J*=6.78 Hz, 4H) 7.83 (s, 1H)

Intermediate 225

5-((*tert*-butyldiphenylsilyloxy)methyl)-*N*-(cyclopropylmethyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxamide

Starting materials: Ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxylate (**Intermediate 204**) and cyclopropylmethanamine

MS (ES) MH^+: 616 for $C_{35}H_{42}FN_3O_4Si$

Intermediate 226

5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(1,2-oxazinan-2-ylcarbonyl)-1,2-benzisoxazole

Starting materials: Ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxylate (**Intermediate 204**) and [1,2]oxazinane

MS (ES) MH^+: 632 for $C_{35}H_{42}FN_3O_5Si$

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.06-1.19 (m, 15H) 1.92 (br. s., 4H) 2.69 (d, *J*=10.55 Hz, 2H) 2.90 (t, *J*=9.42 Hz, 2H) 3.41-3.56 (m, 2H) 4.06 (br. s., 4H) 4.83 (s, 2H) 7.34-7.51 (m, 6H) 7.69 (d, *J*=6.78 Hz, 4H) 7.84 (br. s., 1H)

Intermediate 227

5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-*N*-(thiophen-2-ylmethyl)benzo[d]isoxazole-3-carboxamide

Starting materials: Ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxylate (**Intermediate 204**) and thiophen-2-ylmethanamine

MS (ES) MH^+: 658 for $C_{36}H_{40}FN_3O_4SSi$

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.11 (d, *J*=6.03 Hz, 6H) 1.16 (s, 9H) 2.71 (d, *J*=10.55 Hz, 2H) 2.83-3.00 (m, 2H) 3.39-3.56 (m, 2H) 4.85 (s, 2H) 4.92 (d, *J*=5.27 Hz, 2H) 6.98-7.06 (m, 1H) 7.08-7.16 (m, 1H) 7.25-7.36 (m, 2H) 7.36-7.52 (m, 6H) 7.73 (d, *J*=6.03 Hz, 4H) 8.29 (s, 1H)

Intermediate 228

(3,3-difluoroazetidin-1-yl)(5-(dimethoxymethyl)-6,7-difluorobenzo[d]isoxazol-3-yl)methanone

Starting materials: ethyl 5-(dimethoxymethyl)-6,7-difluorobenzo[d]isoxazole-3-carboxylate (**Intermediate 206**) and 3,3-difluoroazetidine hydrochloride.

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 3.4 (s, 6H) 4.6 (t, 2H) 5.0 (t, 2H) 5.7 (s, 1H) 8.2 (d, 1H).

Intermediate 229

5-(dimethoxymethyl)-6,7-difluoro-*N*-isopropylbenzo[d]isoxazole-3-carboxamide

Starting materials: ethyl 5-(dimethoxymethyl)-6,7-difluorobenzo[d]isoxazole-3-carboxylate (**Intermediate 206**) and isopropyl amine.

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.2 (d, 6H), 3.3 (s, 6H), 4.2 (dq, 1H), 5.7 (s, 1H), 8.0 (d, 1H), 9.1 (d, 1H)

Intermediate 230

5-((*tert*-Butyldiphenylsilyloxy)methyl)-7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-*N*-methylisoxazolo[4,5-b]pyridine-3-carboxamide

Starting materials: ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)isoxazolo[4,5-b]pyridine-3-carboxylate (**Intermediate 211**) and methylamine, 2M in THF.

MS (ES) MH^+: 593 for $C_{31}H_{37}ClN_4O_4Si$

^{1}H NMR (300 MHz, CD_2Cl_2) δ: 1.0-1.2 (overlapping multiplet, 15H), 2.7-2. 9 (m, 2H), 3.0 (d, 3H), 3.1-3.2 (m, 2H), 3.6-3.7 (m, 2H), 5.0 (s, 2H). 7.3-7.5 (m, 6H), 7.6-7.7 (m, 4H), 8.3 (br s, 1H).

Intermediate 231

5-((*tert*-Butyldiphenylsilyloxy)methyl)-7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-*N*-ethylisoxazolo[4,5-b]pyridine-3-carboxamide

Starting material: ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)isoxazolo[4,5-b]pyridine-3-carboxylate (**Intermediate 211**) and ethylamine.

MS (ES) MH^+: 607 for $C_{32}H_{39}ClN_4O_4Si$

^1H NMR (300 MHz, CD_2Cl_2) δ: 1.0-1.1 (overlapping multiplet, 15H), 1.2 (t, 3H), 2.7-2.9 (m, 2H), 3.1-3.2 (m, 2H), 3.4-3.5 (m, 2H), 3.6-3.7 (m, 2H), 5.0 (s, 2H), 7.3-7.5 (m, 6H), 7.6-7.7 (m, 4H), 8.4 (br s, 1H).

Intermediate 232

5-((*tert*-butyldiphenylsilyloxy)methyl)-7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-*N*-isopropylisoxazolo[4,5-b]pyridine-3-carboxamide

Starting material: ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)isoxazolo[4,5-b]pyridine-3-carboxylate (**Intermediate 211**) and isopropylamine.

MS (ES) MH^+: 621 for $C_{33}H_{41}ClN_4O_4Si$

^1H NMR (300 MHz, CD_2Cl_2) δ: 1.0-1.1 (overlapping multiplet, 15H), 1.2 (d, 6H), 2.7-2.8 (m, 2H), 3.1-3.2 (m, 2H), 3.5-3.7 (m, 2H), 4.3 (m, 1H), 5.0 (s, 2H), 7.3-7.5 (m, 6H), 7.6-7.7 (m, 4H), 8.15 (br s, 1H).

Intermediate 233

N-*tert*-Butyl-5-((*tert*-butyldiphenylsilyloxy)methyl)-7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)isoxazolo[4,5-b]pyridine-3-carboxamide

Starting material: ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)isoxazolo[4,5-b]pyridine-3-carboxylate (**Intermediate 211**) and *t*-butylamine.

MS (ES) MH^+: 635 for $C_{34}H_{43}ClN_4O_4Si$

^1H NMR (300 MHz, CD_2Cl_2) δ: 1.0 (s, 9H), 1.1 (d, 6H),1.4 (s, 9H), 2.7-2.8 (m, 2H), 3.1-3.2 (m, 2H), 3.5-3.7 (m, 2H), 5.0 (s, 2H), 7.3-7.5 (m, 6H), 7.6-7.9 (m, 4H), 8.1 (br s, 1H).

Intermediate 234

5-((*tert*-Butyldiphenylsilyloxy)methyl)-7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-*N*-neopentylisoxazolo[4,5-b]pyridine-3-carboxamide

Starting material: ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)isoxazolo[4,5-b]pyridine-3-carboxylate (**Intermediate 211**) and 2,2-dimethylpropan-1-amine.

MS (ES) MH^+: 649 for $C_{35}H_{45}ClN_4O_4Si$

Intermediate 235

(5-((*tert*-Butyldiphenylsilyloxy)methyl)-7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)isoxazolo[4,5-b]pyridin-3-yl)(3,3-difluoroazetidin-1-yl)methanone

Starting material: ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)isoxazolo[4,5-b]pyridine-3-carboxylate (**Intermediate 211**) and 3,3-difluoroazetidine-HCl.

MS (ES) MH^+: 655 for $C_{33}H_{37}ClF_2N_4O_4Si$,

^1H NMR (300 MHz, CD_2Cl_2) δ: 1.0 (s, 9H), 1.1 (d, 6H), 2.8-2.9 (m, 2H), 3.2 (t, 2H), 3.6-3.7 (m, 2H), 4.6 (t, 2H), 4.8 (t, 2H), 5.0 (s, 2H), 7.3-7.5 (m, 6H), 7.7-7.8 (m, 4H).

Intermediate 236

N-Benzyl-5-((*tert*-butyldiphenylsilyloxy)methyl)-7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)isoxazolo[4,5-b]pyridine-3-carboxamide

Starting material: ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)isoxazolo[4,5-b]pyridine-3-carboxylate (**Intermediate 211**) and benzylamine.

MS (ES) MH^+: 669 for $C_{37}H_{41}ClN_4O_4Si$

^1H NMR (300 MHz, CD_2Cl_2) δ: 1.0 (s, 9H), 1.1 (d, 6H), 2.7-2.8 (m, 2H), 3.1-3.2 (m, 2H), 3.5-3.7 (m, 2H), 4.6 (d, 2H), 5.0 (s, 2H), 7.2-7.5 (m, 11H), 7.6-7. 7 (m, 4H), 8.7 (br s, 1H).

Intermediate 237

5-((*tert*-Butyldiphenylsilyloxy)methyl)-7-chloro-*N*-(4-cyanobenzyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)isoxazolo[4,5-b]pyridine-3-carboxamide

Starting material: ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)isoxazolo[4,5-b]pyridine-3-carboxylate (**Intermediate 211**) and 4-(aminomethyl)benzonitrile.

MS (ES) MH^+: 694 for $C_{38}H_{40}ClN_5O_4Si$

^1H NMR (300 MHz, CD_2Cl_2) δ: 1.0 (s, 9H), 1.1 (d ,6H), 2.7-2.8 (m, 2H), 3.1-3.2 (m, 2H), 3.5-3.7 (m, 2H), 4.7 (d, 2H), 5.0 (br s, 2H), 7.2-7.4 (m, 8H), 7.5-7.6 (m, 6H), 8. 9 (br s).

Intermediate 238

5-((*tert*-Butyldiphenylsilyloxy)methyl)-7-chloro-*N*-(3-cyanobenzyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)isoxazolo[4,5-b]pyridine-3-carboxamide

Starting materials: ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)isoxazolo[4,5-b]pyridine-3-carboxylate (**Intermediate 211**) and 3-(aminomethyl)benzonitrile-HCl.

MS (ES) MH^+: 694 for $C_{38}H_{40}ClN_5O_4Si$

^1H NMR (300 MHz, CD_2Cl_2) δ: 1.0 (s, 9H), 1.1 (d , 6H), 2.7-2.8 (m, 2H), 3.1-3.2 (m, 2H), 3.5-3.7 (m, 2H), 4.6 (d, 2H), 5.0 (br s, 2H), 7.2-7.7 (m, 14H), 8.9 (br s).

Intermediate 239

N-(2,2-difluoroethyl)-5-(dimethoxymethyl)-6,7-difluorobenzo[d]isoxazole-3-carboxamide

Starting Material: ethyl 5-(dimethoxymethyl)-6,7-difluorobenzo[d]isoxazole-3-carboxylate (**Intermediate 206**)

MS (ES) $M^+(-CH_3O)$: 305

^1H NMR (300 MHz, DMSO-d_6) δ ppm 3.3 (s, 6 H), 3.6 - 3.9 (m, 2 H), 5.7 (s, 1 H), 6.0 - 6.5 (m, 1 H), 8.0 (d, 1 H), 9.6 (t, 1 H)

Intermediate 240

5-(dimethoxymethyl)-6,7-difluoro-*N*-methylbenzo[d]isoxazole-3-carboxamide

Starting Material: ethyl 5-(dimethoxymethyl)-6,7-difluorobenzo[d]isoxazole-3-carboxylate (**Intermediate 206**)

MS (ES) $M^+(-CH_3O)$: 255

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.9 (d, 3 H) 3.3 (s, 6 H) 5.7 (s, 1 H) 8.0 (d, 1 H) 9.1 (d, 1 H)

Intermediate 241

3-(3,3-difluoroazetidine-1-carbonyl)-6,7-difluorobenzo[d]isoxazole-5-carbaldehyde

(3,3-Difluoroazetidin-1-yl)(5-(dimethoxymethyl)-6,7-difluorobenzo[d]isoxazol-3-yl)methanone (**Intermediate 228,** 3.336 g, 9.58 mmol) was dissolved in a 4:1 THF:water mixture (62.5 ml) and heated at 75°C with tosic acid monohydrate (0.911 g, 4.79 mmol) for three hours. The reaction was allowed to cool to room temperature, diluted with ethyl acetate, washed 3x with saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography using a gradient of hexanes to ethyl acetate. Fractions were combined and concentrated to give the title compound (2.66 g, 8.83 mmol).

MS (ES) MH^+ 303 for $C_{12}H_6F_4N_2O_3$

^{1}H NMR (300 MHz, CHLOROFORM-d) δ ppm 4.64 (t, 2H) 5.0 (t, 2H) 8.61 (d, 1H) 10.36 (s, 1H)

Intermediates 242 to 244 were prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 241**:

Intermediate 242

6,7-difluoro-5-formyl-*N*-isopropylbenzo[d]isoxazole-3-carboxamide

Starting material: 5-(dimethoxymethyl)-6,7-difluoro-*N*-isopropylbenzo[d]isoxazole-3-carboxamide (**Intermediate 229**).

MS (ES) MH^+ 269 for $C_{12}H_{10}F_2N_2O_3$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.23 (d, 6H) 4.09-4.28 (m, 1H) 8.41 (d, 1H) 9.16 (d, 1H) 10.23 (s, 1H).

Intermediate 243

N-(2,2-difluoroethyl)-6,7-difluoro-5-formylbenzo[d]isoxazole-3-carboxamide

Starting Material: *N*-(2,2-difluoroethyl)-5-(dimethoxymethyl)-6,7-difluorobenzo[d]isoxazole-3-carboxamide (**Intermediate 239**).

MS (ES) MH^-: 289 for $C_{11}H_6F_4N_2O_3$

^1H NMR (300 MHz, DMSO-d_6) δ ppm 3.7 - 3.9 (m, 2 H), 5.9 - 6.5 (m, 1 H), 8.4 (d, 1 H), 9.6 - 9.7 (m, 1 H), 10.2 (s, 1 H)

Intermediate 244

6,7-difluoro-5-formyl-*N*-methylbenzo[d]isoxazole-3-carboxamide

Starting Material: 5-(dimethoxymethyl)-6,7-difluoro-*N*-methylbenzo[d]isoxazole-3-carboxamide (**Intermediate 240**)

MS (ES) MH^+: 241 for $C_{10}H_6F_2N_2O_3$

^1H NMR (300 MHz, DMSO-d_6) δ ppm 2.9 (d, 3 H), 8.4 (d, 1 H), 9.2 (d, 1 H), 10.2 (s, 1 H)

Intermediate 245

3-(3,3-difluoroazetidine-1-carbonyl)-6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-5-carbaldehyde

Diisopropylethylamine (1.432 ml, 8.20 mmol) and (2*R*,6*R*)-2,6-dimethylmorpholine (1.027 ml, 8.20 mmol) were added to a solution of 3-(3,3-difluoroazetidine-1-carbonyl)-6,7-difluorobenzo[d]isoxazole-5-carbaldehyde (**Intermediate 241,** 1.906 g, 6.31 mmol) in acetonitrile (50 ml). The reaction was stirred at reflux for 20 hours. The reaction was cooled to room temp, diluted with water and brine and extracted twice with ethyl acetate. The organic layers were combined, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography using a gradient of DCM to ethyl acetate. Fractions were combined and concentrated to give the title compound.

MS (ES) MH^+ 398.1 for $C_{18}H_{18}F_3N_3O_4$

^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.35 (d, 6H) 3.07 (dd, 5.65 Hz, 2H) 3.45 (d, 2H) 4.26 (m, 2H) 4.62 (t, 2H) 4.99 (t, 2H) 8.50 (s, 1H) 10.44 (s, 1H).

Intermediates 246 and 247 were prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 245**:

Intermediate 246

6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-5-formyl-*N*-isopropylbenzo[d]isoxazole-3-carboxamide

The title compound was prepared from 6,7-difluoro-5-formyl-*N*-isopropylbenzo[d]isoxazole-3-carboxamide (**Intermediate 242**) and (2*R*,6*R*)-2,6-dimethylmorpholine.

MS (ES) MH^+ 364 for $C_{18}H_{22}FN_3O_4$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.14-1.29 (m, 12H) 3.02 (dd, *J*=10.93, 2H) 3.40 (d, 2H) 4.05-4.26 (m, 3H) 8.22 (s, 1H) 9.05 (d, 1H) 10.35 (s, 1H).

Intermediate 247

6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-5-formyl-*N*-methylbenzo[d]isoxazole-3-carboxamide

Starting Material: 6,7-difluoro-5-formyl-*N*-methylbenzo[d]isoxazole-3-carboxamide (**Intermediate 244**).

MS (ES) MH^+: 336 for $C_{16}H_{18}FN_3O_4$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.2 (d, 6 H), 2.9 (d, 3 H), 2.9 - 3.1 (m, 2 H), 3.4 (d, 2 H), 4.1 - 4.2 (m, 2 H), 8.2 (s, 1 H), 9.1 (d, 1 H), 10.4 (s, 1 H).

Intermediate 247 was also be prepared according to the following procedure:

Intermediate 247 (Alternate synthesis)

6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-5-formyl-*N*-methylbenzo[d]isoxazole-3-carboxamide

Starting material: 6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)-*N*-methylbenzo[d]isoxazole-3-carboxamide (**Intermediate 280**)

MS (ES) MH^+: 336 for $C_{16}H_{18}FN_3O_4$

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.35 (d, *J*=6.78 Hz, 6H) 2.99-3.16 (m, 5H) 3.45 (d, *J*=12.06 Hz, 2H) 4.20-4.35 (m, 2H) 6.83 -6.96 (m, 1H) 8.54 (s, 1H) 10.44 (s, 1H).

Intermediate 248

N-(2,2-difluoroethyl)-6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-5-formylbenzo[d]isoxazole-3-carboxamide

N-(2,2-Difluoroethyl)-6,7-difluoro-5-formylbenzo[d]isoxazole-3-carboxamide (**Intermediate 243**, 2.86 g, 9.86 mmol) was dissolved in butyronitrile (50 mL) and water (2.5 mL). Potassium carbonate (1.362 g, 9.86 mmol) and (2*R*,6*R*)-2,6-dimethylmorpholine (1.481 mL, 11.83 mmol) were added and the reaction was stirred at 90°C for 4 hours. The crude reaction mixture was diluted with water, brine and ethyl acetate. The mixture was washed 2x with brine. The aqueous layer was back-extracted with ethyl acetate. The organic layers combined, dried over $MgSO_4$ and concentrated. The residue was dissolved in DCM and purified by silica gel column chromatography using a gradient of DCM to ethyl acetate. Fractions were combined and concentrated to give the title compound.

MS (ES) MH^+: 286 for $C_{17}H_{18}F_3N_3O_4$

^1H NMR (300 MHz, DMSO-d_6) δ ppm 1.2 (d, 6 H), 3.0 (m, 2 H), 3.4 (d, 2 H), 3.8 (m, 2 H), 4.1 - 4.2 (m, 2 H), 6.0 - 6.4 (m, 1 H), 8.2 (s, 1 H), 9.5 (t, *J*=5.7 Hz, 1 H), 10.3 (s, 1 H).

Intermediate 249

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)-*N*-(pyridin-4-ylmethyl)benzo[d]isoxazole-3-carboxamide

Trimethylaluminum (2M in Toluene, 2116 µl, 4.23 mmol) was slowly added (gas evolution) to a solution of pyridin-4-ylmethanamine (458 mg, 4.23 mmol) in toluene (10ml) at room temperature and under a nitrogen atmosphere. The reaction was stirred for 2 hours at room temperature. Ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxylate (**Intermediate 204,** 500 mg, 0.85 mmol) was added as a solution in 5 ml of toluene. The reaction was stirred at 45 °C for three days. The reaction was cooled to room temperature and then quenched drop wise with 3 ml of 1N HCl (vigorous gas evolution). The crude reaction was poured into a Biotage Isolute® HM-N tube (10ml capacity) packed with a small amount of glass wool to prevent clogging. A Biotage sodium sulfate column (2.5g) was attached to the bottom of the Isolute® tube. The reaction mixture was allowed to gravity elute through the tube and washed through with 2-3 column volumes of ethyl acetate. The eluent was concentrated. The residue was dissolved in THF (10 ml) and stirred at room

temperature with acetic acid (0.097 ml, 1.70 mmol) and TBAF (1N in THF, 0.935 ml, 0.94 mmol) for 16 hours. The reactions were diluted with 1 ml of water and shaken vigorously. The sample was added to a Varian Chem Elute® CE 1003 tube with a Biotage sodium sulfate column (2.5g) on the bottom of it. The sample was gravity eluted with 2-3 column volumes of ethyl acetate and concentrated. The residue purified by silica gel column chromatography. Fractions were combined and concentrated to give the title compound (241 mg, 0.552 mmol, 65%).
MS (ES) MH^+: 415 for $C_{21}H_{23}FN_4O_4$
^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.26 (d, *J*=6.03 Hz, 6H) 2.91-3.17 (m, 4H) 3.72-3.95 (m, 2H) 4.70-4.91 (m, 4H) 7.46 (d, *J*=5.27 Hz, 2H) 7.51 (br. s., 1H) 7.97 (s, 1H) 8.55-8.77 (m, 2H)

Intermediates 250 to 261 were prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 249**:

Intermediate 250

N-(cyclohexylmethyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)benzo[d]isoxazole-3-carboxamide

Starting materials: ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxylate (**Intermediate 204**) and cyclohexylmethanamine

MS (ES) MH^+: 420.3 for $C_{22}H_{30}FN_3O_4$

Intermediate 251

(4,4-difluoropiperidin-1-yl)(6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)benzo[d]isoxazol-3-yl)methanone

Starting materials: ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxylate (**Intermediate 204**) and 4,4-difluoropiperidine

MS (ES) MH^+: 428 for $C_{20}H_{24}F_3N_3O_4$

Intermediate 252

(3,3-difluoropyrrolidin-1-yl)(6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)benzo[d]isoxazol-3-yl)methanone

Starting material: 3,3-difluoropyrrolidine

MS (ES) MH^+: 414 for $C_{19}H_{22}F_3N_3O_4$

Intermediate 253

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)-*N*-(1-methylazetidin-3-yl)benzo[d]isoxazole-3-carboxamide

Starting materials: ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxylate (**Intermediate 204**) and 1-methylazetidin-3-amine

MS (ES) MH^+: 393 for $C_{19}H_{25}FN_4O_4$

Intermediate 254

N-(1-(6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)benzo[d]isoxazole-3-carbonyl)azetidin-3-yl)acetamide

Starting materials: ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxylate (**Intermediate 204**) and *N*-(azetidin-3-yl)acetamide

MS (ES) MH^+: 421 for $C_{20}H_{25}FN_4O_5$

Intermediate 255

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)-*N*-((1-methyl-1*H*-pyrazol-3-yl)methyl)benzo[d]isoxazole-3-carboxamide

Starting materials: ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxylate (**Intermediate 204**) and (1-methyl-1*H*-pyrazol-3-yl)methanamine

MS (ES) MH^+: 318 for $C_{20}H_{24}FN_5O_4$

Intermediate 256

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)-*N*-((1-methyl-1*H*-pyrazol-5-yl)methyl)benzo[d]isoxazole-3-carboxamide

Starting materials: ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxylate (**Intermediate 204**) and (1-methyl-1*H*-pyrazol-5-yl)methanamine

MS (ES) MH^+: 418. for $C_{20}H_{24}FN_5O_4$

Intermediate 257

N-(1,3-dimethoxy-2-(methoxymethyl)propan-2-yl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)benzo[d]isoxazole-3-carboxamide

Starting materials: ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxylate (**Intermediate 204**) and 1,3-dimethoxy-2-(methoxymethyl)propan-2-amine

MS (ES) MH^+: 470 for $C_{22}H_{32}FN_3O_7$

Intermediate 258

N-(2,2-difluoroethyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)benzo[d]isoxazole-3-carboxamide

Starting materials: ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxylate (**Intermediate 204**) and 2,2-difluoroethanamine

MS (ES) MH^+: 388 for $C_{17}H_{20}F_3N_3O_4$

Intermediate 259

1-(6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)benzo[d]isoxazole-3-carbonyl)azetidine-3-carbonitrile

Starting materials: ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxylate (**Intermediate 204**) and azetidine-3-carbonitrile

MS (ES) MH^+: 389 for $C_{19}H_{21}FN_4O_4$

Intermediate 260

5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-*N*-methylbenzo[d]isoxazole-3-carboxamide

Starting materials: ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxylate (**Intermediate 210**, 5.16 g, 8.73 mmol) and methylamine (2M in THF).

MS (ES) MH^+: 576 for $C_{32}H_{38}FN_3O_4Si$

^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.06 (d, 6H) 1.17 (s, 9H) 2.64-2.80 (m, 2H) 3.04-3.15 (m, 5H) 3.82-3.96 (m, 2H) 4.80-4.98 (m, 2H) 6.93 (br. s., 1H) 7.33-7.50 (m, 6H) 7.66-7.76 (m, 4H) 8.35 (s, 1H)

Intermediate 261

5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxamide

Starting materials: ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxylate (**Intermediate 210**) and ammonia (0.5 M in dioxane).

MS (ES) MH^+: 362.2 for $C_{31}H_{36}FN_3O_4Si$

Intermediate 262

ethyl 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)benzo [d]isoxazole-3-carboxylate

Ethyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxylate (**Intermediate 204**, 693 mg, 1.17 mmol) was dissolved in THF (3 ml) along with acetic acid (0.134 ml, 2.35 mmol). TBAF (1N in THF, 1.290 ml, 1.29 mmol) was added and the reaction was stirred at room temperature for 30 minutes. The reaction was diluted with water and extracted 2x with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography to give the title compound.

MS (ES) MH^+: 353 for $C_{17}H_{21}FN_2O_5$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.1 (d, 6H) 1.4 (t, 3H) 2.8 (t, 2H) 3.0 (d, 2H) 3.6-3.8 (m, 2H) 4.5 (q, 2H) 4.7 (d, 2H) 5.45 (t, 1H) 7.95 (s, 1H)

Intermediates 263 to 281 were prepared from the indicated starting materials using a method similar to the one described for the syntheses of **Intermediate 262**:

Intermediate 263

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)-*N*-methoxy-*N*-methylbenzo[d]isoxazole-3-carboxamide

Starting material: 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-*N*-methoxy-*N*-methylbenzo[d]isoxazole-3-carboxamide (**Intermediate 205**)

MS (ES) MH^+: 368 for $C_{17}H_{22}FN_3O_5$

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.26 (d, *J*=6.78 Hz, 6H) 2.93-3.04 (m, 2H) 3.04-3.16 (m, 2H) 3.49 (br. s., 3H) 3.87 (br. s., 5H) 4.83 (s, 2H) 7.70 (br. s., 1H)

Intermediate 264

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-*N*-ethyl-7-fluoro-5-(hydroxymethyl)benzo [d]isoxazole-3-carboxamide

Starting material: 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-*N*-ethyl-7-fluorobenzo[d]isoxazole-3-carboxamide (**Intermediate 212**).

MS (ES) MH^+: 352 for $C_{17}H_{22}FN_3O_4$

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.15-1.37 (m, 9H) 2.91-3.17 (m, 4H) 3.48-3.65 (m, 2H) 3.75-3.94 (m, 2H) 4.82 (s, 2H) 6.92 (br. s., 1H) 7.95 (s, 1H)

Intermediate 265

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-*N*-ethyl-7-fluoro-5-(hydroxymethyl)-*N*-methylbenzo[d]isoxazole-3-carboxamide

Starting material: 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-*N*-ethyl-7-fluoro-*N*-methylbenzo[d]isoxazole-3-carboxamide (**Intermediate 213**).

MS (ES) MH^+: 366 for $C_{18}H_{24}FN_3O_4$

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.24 (d, *J*=6.40 Hz, 6H) 1.26-1.34 (m, 3H) 2.89-3.01 (m, 2H) 3.01-3.14 (m, 2H) 3.15-3.34 (m, 3H) 3.68 (q, *J*=7.16 Hz, 2H) 3.76-3.91 (m, 2H) 4.79 (s, 2H) 7.68 (d, *J*=7.16 Hz, 1H)

Intermediate 266

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)-*N*-methylbenzo[d]isoxazole-3-carboxamide

Starting material: 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-*N*-methylbenzo[d]isoxazole-3-carboxamide (**Intermediate 214**)

MS (ES) MH^+: 338 for $C_{16}H_{20}FN_3O_4$

^{1}H NMR (300 MHz, CHLOROFORM-d) δ ppm 1.23 (d, J=6.78 Hz, 6H) 2.93-3.13 (m, 7H) 3.76-3.93 (m, 2H) 4.81 (s, 2H) 6.99 (br. s., 1H) 7.94 (s, 1H)

Intermediate 267

4-(6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)benzo[d]isoxazole-3-carbonyl)-1-methylpiperazin-2-one

Starting material: 4-(5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carbonyl)-1-methylpiperazin-2-one (**Intermediate 215**)

MS (ES) MH^+: 421 for $C_{20}H_{25}FN_4O_5$

Intermediate 268

(3,3-difluoroazetidin-1-yl)(6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)benzo[d]isoxazol-3-yl)methanone

Starting material: (5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazol-3-yl)(3,3-difluoroazetidin-1-yl)methanone (**Intermediate 216**).

MS (ES) MH^+: 400 for $C_{18}H_{20}F_3N_3O_4$

^{1}H NMR (300 MHz, CHLOROFORM-d) δ ppm 1.17 (d, J=6.03 Hz, 6H) 2.81-3.09 (m, 4H) 3.76 (br. s., 2H) 4.52 (t, J=12.06 Hz, 2H) 4.74 (s, 2

H) 4.90 (t, J=11.68 Hz, 2H) 7.85 (s, 1H)

Intermediate 269

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)benzo[d]isoxazole-3-carboxamide

Starting material: 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxamide (**Intermediate 217**)

MS (ES) MH^+: 324 for $C_{15}H_{18}FN_3O_4$

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.25 (d, *J*=6.03 Hz, 6H) 2.93-3.19 (m, 4H) 3.78-3.94 (m, 2H) 4.84 (s, 2H) 5.72 (br. s., 1H) 6.83 (br. s., 1H) 7.96 (s, 1H)

Intermediate 270

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)-*N*-(2-methoxyethyl)benzo[d]isoxazole-3-carboxamide

Starting material: 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-*N*-(2-methoxyethyl)benzo[d]isoxazole-3-carboxamide (**Intermediate 218**)

MS (ES) MH^+: 382 for $C_{18}H_{24}FN_3O_5$

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.23 (d, *J*=6.03 Hz, 6H) 2.89-3.15 (m, 4H) 3.41 (s, 3H) 3.60 (t, *J*=4.90 Hz, 2H) 3.70 (q, *J*=5.27 Hz, 2H) 3.83 (m , 2H) 4.81 (s, 2H) 7.93 (s, 1H)

Intermediate 271

N-tert-butyl-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)benzo[d]isoxazole-3-carboxamide

Starting material: *N-tert*-butyl-5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxamide (**Intermediate 219**)

MS (ES) MH^+: 380 for $C_{19}H_{26}FN_3O_4$

^{1}H NMR (300 MHz, CHLOROFORM-*d*) d ppm 1.23 (d, *J*=6.03 Hz, 6H) 1.51 (s, 9H) 2.90-3.15 (m, 4H) 3.83 (br. s., 2H) 4.80 (s, 2H) 6.78 (br. s., 1H) 7.95 (s, 1H)

Intermediate 272

{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-[(1,1-dioxidothiomorpholin-4-yl)carbonyl]-7-fluoro-1,2-benzisoxazol-5-yl}methanol

Starting material: 5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-[(1,1-dioxidothiomorpholin-4-yl)carbonyl]-7-fluoro-1,2-benzisoxazole (**Intermediate 220**)

MS (ES) MH^+: 442.0 for $C_{19}H_{24}FN_3O_6S$

^1H NMR (300 MHz, CHLOROFORM-d) δ ppm 1.26 (d, J=6.03 Hz, 6H) 2.91-3.03 (m, 2H) 3.03-3.16 (m, 2H) 3.19-3.33 (m, 4H) 3.79-3.91 (m, 2H) 4.32-4.42 (m, 2H) 4.42-4.52 (m, 2H) 4.84 (s, 4H) 7.74 (s, 1H)

Intermediate 273

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)-*N*-(tetrahydro-2*H*-pyran-4-yl)benzo[d]isoxazole-3-carboxamide

Starting material: 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-*N*-(tetrahydro-2*H*-pyran-4-yl)benzo[d]isoxazole-3-carboxamide (**Intermediate 221**)

MS (ES) MH^+: 408 for $C_{20}H_{26}FN_3O_5$

^1H NMR (300 MHz, CHLOROFORM-d) δ ppm 1.26 (d, J=6.78 Hz, 6H) 1.57-1.77 (m, J=11.77, 11.77, 11.49, 4.14 Hz, 2H) 2.05 (d, J=10.55 Hz, 2H) 2.98-3.18 (m, 4H) 3.57 (t, J=11.68 Hz, 2H) 3.90 (br. s., 2H) 4.05 (d, J=10.55 Hz, 2H) 4.19-4.34 (m, 1H) 4.87 (s, 2H) 6.84 (d, J=7.54 Hz, 1H) 7.96 (s, 1H)

Intermediate 274

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)-*N*-isopropylbenzo[d]isoxazole-3-carboxamide

Starting material: 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-*N*-isopropylbenzo[d]isoxazole-3-carboxamide (**Intermediate 222**)

MS (ES) MH^+: 366 for $C_{18}H_{24}FN_3O_4$

^1H NMR (300 MHz, CHLOROFORM-d) δ ppm 1.26 (d, J=6.78 Hz, 6H) 1.29-1.38 (m, 6H) 2.93-3.17 (m, 4H) 3.86 (m 2H) 4.26-4.41 (m, 1H) 4.84 (s, 2H) 6.76 (d, J=6.78 Hz, 1H) 7.97 (s, 1H)

Intermediate 275

N-cyclopropyl-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)benzo[d]isoxazole-3-carboxamide

.Starting material: 5-((*tert*-butyldiphenylsilyloxy)methyl)-*N*-cyclopropyl-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxamide (**Intermediate 223**)

MS (ES) MH^+: 364 for $C_{18}H_{22}FN_3O_4$

^1H NMR (300 MHz, CHLOROFORM-d) δ ppm 0.64-0.79 (m, 2H) 0.85-1.02 (m, 2H) 1.25 (d, J=6.78 Hz, 6H) 2.88-3.18 (m, 5H) 3.85 (m, 2H) 4.84 (s, 2H) 7.02 (br. s., 1H) 7.97 (s, 1H)

Intermediate 276

(6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)benzo[d]isoxazol-3-yl)(4-methoxypiperidin-1-yl)methanone

Starting material: (5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazol-3-yl)(4-methoxypiperidin-1-yl)methanone (**Intermediate 224**)

MS (ES) MH^+: 422 for $C_{21}H_{28}FN_3O_5$

^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.23 (d, *J*=6.03 Hz, 6H) 1.62-2.04 (m, 4H) 2.84-2.97 (m, 2H) 3.04 (t, *J*=9.80 Hz, 2H) 3.49-3.88 (m, 6H) 3.88-4.06 (m, 2H) 4.75 (d, *J*=6.03 Hz, 2H) 7.62 (s, 1H)

Intermediate 277

N-(cyclopropylmethyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)benzo[d]isoxazole-3-carboxamide

Starting material: 5-((*tert*-butyldiphenylsilyloxy)methyl)-*N*-(cyclopropylmethyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxamide (**Intermediate 225**)

MS (ES) MH^+: 378 for $C_{19}H_{24}FN_3O_4$

^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.25 (d, *J*=5.27 Hz, 2H) 0.45-0.60 (m, 2H) 0.94-1.09 (m, 1H) 1.17 (d, *J*=6.03 Hz, 6H) 2.84-2.96 (m, 2H) 2.96-3.10 (m, 2H) 3.20-3.39 (m, 2H) 3.65-3.88 (m, 2H) 4.75 (s, 2H) 6.95 (br. s., 1H) 7.88 (s, 1H)

Intermediate 278

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(1,2-oxazinan-2-ylcarbonyl)-1,2-benzisoxazol-5-yl}methanol

Starting material: 5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(1,2-oxazinan-2-ylcarbonyl)-1,2-benzisoxazole

(**Intermediate 226**)

MS (ES) MH^+: 394 for $C_{19}H_{24}FN_3O_5$

^1H NMR (300 MHz, CHLOROFORM-*d*) δppm 1.25 (d, *J*=6.03 Hz, 6H) 1.92 (br. s., 4H) 2.83-3.18 (m, 4H) 3.83 (br. s., 2H) 3.96-4.38 (m, 4H) 4.80 (s, 2H) 7.61 (br. s., 1H)

Intermediate 279

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)-*N*-(thiophen-2-ylmethyl)benzo[d]isoxazole-3-carboxamide

Starting materials: 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-*N*-(thiophen-2-ylmethyl)benzo[d]isoxazole-3-carboxamide (**Intermediate 227**)

MS (ES) MH^+: 420 for $C_{20}H_{22}FN_3O_4S$

Intermediate 280

6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)-*N*-methylbenzo[d]isoxazole-3-carboxamide

Starting material: 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-*N*-methylbenzo[d]isoxazole-3-carboxamide (**Intermediate 260**)

MS (ES) MH^+: 338 for $C_{16}H_{20}FN_3O_4$

^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.29-1.48 (m, 6H) 2.90-3.03 (m, 2H) 3.09 (d, *J*=5.27 Hz, 3H) 3.31 (br. s., 2H) 4.18 (m, 2H) 4.78-4.94 (m, 2H) 6.92 (br. s., 1H) 8.01 (s, 1H)

Intermediate 281

6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)benzo[d]isoxazole-3-carboxamide

Starting material: 5-((*tert*-butyldiphenylsilyloxy)methyl)-6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-3-carboxamide (**Intermediate 261**)

MS (ES) MH^+: 324 for $C_{15}H_{18}FN_3O_4$

^1H NMR (300 MHz, DMSO-d_6) δ ppm 1.23 (d, J=6.03 Hz, 6H) 2.82 (m, 2H) 3.19 (d, J=11.30 Hz, 2H) 3.95-4.13 (m, 2H) 4.64-4.80 (m, 2H) 5.43 (t, J=5.27 Hz, 1H) 7.97 (s, 1H) 8.10 (s, 1H) 8.45 (s, 1H)

Intermediate 282

(3-(6-chloropyrazin-2-yl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazol-5-yl)methanol

5-((*tert*-Butyldiphenylsilyloxy)methyl)-3-(6-chloropyrazin-2-yl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole (**Intermediate 329**, 320mg, 0.51 mmol) was dissolved in ethanol (10 ml) and was treated with 15 ml of 10% aq HCl, the mixture was heated at 70 °C for 1 hour. The reaction was cooled and diluted with EtOAc before being quenched with aqueous sodium bicarbonate solution. The mixture was extracted with EtOAc, which was washed with brine, dried ($MgSO_4$) and concentrated.

MS (ES) MH^+: 393 for $C_{18}H_{18}ClFN_4O_3$

Intermediate 283

(6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(5-(methylthio)pyrazin-2-yl)benzo[d]isoxazol-5-yl)methanol

1-{5-({[*tert*-Butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}-1-(5-chloropyrazin-2-yl)-*N*-hydroxymethanimine (**Intermediate 200,** 400mg, 0.61 mmol)in DMF (5 mL) was treated with sodium thiomethoxide (45.3 mg, 0.61 mmol) at room temperature, the mixture was stirred at room temperature for 10min. K_2CO_3 (5eq) was added and the mixture was heated to 100°C for 1hour. The reaction mixture was diluted with ethylacetate(20ml). Organic layer washed with water and brine, then dried over sodium sulfate, filtered, and the filtrate was concentrated, purified by silica gel column chromatography (Hexanses/EtOAc, gradiant) to give the desired product (97 mg, 39.0 %).

MS (ES) MH^+: 405 for $C_{19}H_{21}FN_4O_3S$

Intermediate 284 was prepared from the indicated starting materials using a method similar to the one described for the syntheses of **Intermediate 283**:

Intermediate 284

(6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-3-(2-(methylthio)pyrimidin-4-yl)benzo[d]isoxazol-5-yl)methanol

Starting material: (5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*R*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)(2-(methylthio)pyrimidin-4-yl)methanone

(**Intermediate 106**)

MS (ES) MH^+: 405 (M+H) for $C_{19}H_{21}FN_4O_3S$

Intermediate 285

(6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)benzo[d]isoxazol-3-yl)(morpholino)methanone

2-(5-((*tert*-Butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)-2-(hydroxyimino)-1-morpholinoethanone, (**Intermediate 168,** 133 mg, 0.20 mmol) was dissolved in DMF and stirred at 60 °C with cesium carbonate (332 mg, 1.02 mmol) for 6 hours. The reaction stirred at room temperature over 2 days. The reaction was diluted with water and extracted three times with ethyl acetate. The organic layers were combined and washed 5x with brine, dried over $MgSO_4$ and concentrated to give an oil. The oil was purified by silica gel column chromatography using a gradient of hexanes to ethyl acetate to give the title compound (34 mg, 0.086 mmol).

MS (ES) MH^+: 394 for $C_{19}H_{24}FN_3O_5$

^1H NMR (300 MHz, CHLOROFORM-d) δ ppm 1.25 (d, 6H), 2.9-3.0 (m, 2H), 3.0-3.2 (m, 2H), 3.7-3.9 (m, 8H), 3.9-4.0 (m, 2H), 4.8 (s, 2H), 7.7 (s, 1H).

Intermediates 286 to 301 were prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 285**:

Intermediate 286

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)-*N*,*N*-dimethylbenzo[d]isoxazole-3-carboxamide

2-(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)-2-(hydroxyimino)-*N*,*N*-dimethylacetamide (**Intermediate 169**).

MS (ES) MH^+: 352 for $C_{17}H_{22}FN_3O_4$

^{1}H NMR (300 MHz, CHLOROFORM-d) δ ppm 1.25 (d, 6H), 3.0-3.05 (m, 2H), 3.1 (m, 2H), 3.2 (s, 3H), 3.35 (s, 3H), 3.9 (m, 2H), 4.8 (s, 2H), 7.7 (s, 1H)

Intermediate 287

(6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(pyridin-4-yl)benzo[d]isoxazol-5-yl)methanol

Starting material: 1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}-*N*-hydroxy-1-pyridin-4-ylmethanimine (**Intermediate 161**).

MS (ES) MH^+: 358 for $C_{19}H_{20}FN_3O_3$

^{1}H NMR (300 MHz, $CDCl_3$) δ: ppm 1.23 (d, 6H), 2.87-3.17 (m, 4H), 3.37 (s, 1H), 3.71-3.92 (m, 2H), 4.85 (s, 2H), 7.64 (s, 1H), 7.86 (d, 2H), 8.84 (d, 2H).

Intermediate 288

(3-((1*H*-1,2,4-triazol-1-yl)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazol-5-yl)methanol

Starting material: 1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}-*N*-hydroxy-2-(1*H*-1,2,4-triazol-1-yl)ethanimine (**Intermediate 163**).

MS (ES) MH^+: 362 for $C_{17}H_{20}FN_5O_3$

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.21 (d, 6H), 2.76-3.13 (m, 5H), 3.60-3.93 (m, 2H), 4.75 (s, 2H) 5.72 (s, 2H), 7.36 (s, 1H), 7.99 (s, 1H), 8.23 (s, 1H).

Intermediate 289

(6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(furan-2-yl)benzo[d]isoxazol-5-yl)methanol

Starting material: 1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}-1-furan-2-yl-*N*-hydroxymethanimine (**Intermediate 162**).

MS (ES) MH^+: 347 for $C_{18}H_{19}FN_2O_4$

^{1}H NMR (300 MHz, $CDCl_3$) δ:1.23 (d, 6H), 2.89-3.17 (m, 4H), 3.72-3.92 (m, 2H), 4.84 (s, 2H) 6.63 (d, 1H), 7.19 (d, 1H), 7.70 (s, 1H), 7.78 (s, 1H).

Intermediate 290

(6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(trifluoromethyl)benzo[d]isoxazol-5-yl)methanol

Starting material: 1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}-2,2,2-trifluoro-*N*-hydroxyethanimine (**Intermediate 159**).

MS (ES) MH^+: 349 for $C_{15}H_{16}F_4N_2O_3$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.22 (d, 6H), 1.97 (broad peak, 1H), 2.85-3.15 (m, 4H), 3.66-3.93 (m, 2H), 4.82 (s, 2H) 7.55 (s, 1H).

Intermediate 291

(3-(difluoromethyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazol-5-yl)methanol

Starting material: 1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}-2,2-difluoro-*N*-hydroxyethanimine (**Intermediate 160**).

MS (ES) MH^+: 331 for $C_{15}H_{17}F_3N_2O_3$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.23 (d, 6H), 2.88-3.16 (m, 4H), 3.72-3.95 (m, 2H), 4.83 (s, 2H), 7.00 (t, 1H), 7.61 (s, 1H).

Intermediate 292

(3-(difluoromethyl)-6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazol-5-yl)methanol

Starting materials 1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*R*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}-2,2-difluoro-*N*-hydroxyethanimine (**Intermediate 164**).

MS (ES) MH^+: 331 for $C_{15}H_{17}F_3N_2O_3$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.34 (d, 6H) 2.79-3.41 (m, 4H) 4.02-4.28 (m, 2H) 4.68-5.07 (m, 2H) 7.00 (t, 1H) 7.66 (s, 1H).

Intermediate 293

7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-(hydroxymethyl)-*N*-methylisoxazolo[4,5-b]pyridine-3-carboxamide

Starting material: 5-((*tert*-butyldiphenylsilyloxy)methyl)-7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-*N*-methylisoxazolo[4,5-b]pyridine-3-carboxamide (**Intermediate 230**).

MS (ES) MH^+: 355 for $C_{15}H_{19}ClN_4O_4$

^1H NMR (300 MHz, DMSO-d_6) δ: 1.1 (d, 6H), 2.9 (d, 3H), 2.9-3.1 (m, 4H), 3.7-3.9 (m, 2H), 4.8 (d, 2H), 5.4 (br t, 1H). 8.9 (m, 1H).

Intermediate 294

7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-*N*-ethyl-5-(hydroxymethyl)isoxazolo[4,5-b]pyridine-3-carboxamide

Starting material: 5-((*tert*-butyldiphenylsilyloxy)methyl)-7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-*N*-ethylisoxazolo[4,5-b]pyridine-3-carboxamide (**Intermediate 231**).

MS (ES) MH^+: 369 for $C_{16}H_{21}ClN_4O_4$

^1H NMR (300 MHz, DMSO-d_6) δ: 1.1 (d, 6H), 1.2 (t, 3H), 2.9-3.1 (m, 4H), 3.3-3.5 (m, 2H), 3.7-3.9 (m, 2H), 4.8 (d, 2H), 5.3 (br t, 1H). 9.0 (m, 1H).

Intermediate 295

7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-(hydroxymethyl)-*N*-isopropylisoxazolo[4,5-b]pyridine-3-carboxamide

Starting material: 5-((*tert*-butyldiphenylsilyloxy)methyl)-7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-*N*-isopropylisoxazolo[4,5-b]pyridine-3-carboxamide (**Intermediate 232**).

MS (ES) MH^+: 383 for $C_{17}H_{23}ClN_4O_4$

^1H NMR (300 MHz CD_2Cl_2) δ: 1.2 (d, 6H), 1.3 (d, 6H), 2.8-2. 9 (m, 2H), 3.1-3.3 (m, 2H), 3.5 (br s, 1H), 3.8-3.9 (m, 2H), 4.3 (m, 1H), 4.9 (br s, 2H). 7.5 (br s, 1H).

Intermediate 296

N-tert-butyl-7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-(hydroxymethyl)isoxazolo[4,5-b]pyridine-3-carboxamide

Starting material: *N*-*tert*-butyl-5-((*tert*-butyldiphenylsilyloxy)methyl)-7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)isoxazolo[4,5-b]pyridine-3-carboxamide (**Intermediate 233**).

MS (ES) MH^+: 397 for $C_{18}H_{25}ClN_4O_4$

^1H NMR (300 MHz, CD_2Cl_2) δ: 1.2 (d, 6H), 1.5 (s, 9H), 2.7-2.9 (m, 2H), 3.2-3.3 (m, 2H), 3.4 (m, 1H), 3.7-3.9 (m, 2H), 4.9 (d, 2H), 7.6 (br s, 1H).

Intermediate 297

7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-(hydroxymethyl)-*N*-neopentylisoxazolo[4,5-b]pyridine-3-carboxamide

Starting material: 5-((*tert*-butyldiphenylsilyloxy)methyl)-7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-*N*-neopentylisoxazolo[4,5-b]pyridine-3-carboxamide (**Intermediate 234**).

MS (ES) MH^+: 411 for $C_{19}H_{27}ClN_4O_4$

^1H NMR (300 MHz, CD_2Cl_2) δ: 1.0 (s, 9H), 1.2 (d, 6H), 2.8-2.9 (m, 2H), 3.2-3.3 (m, 2H), 3.3-3.4 (overlapping m, 3H), 3.8-3.9 (m, 2H), 4.9 (d, 2H), 7.9 (br s 1H).

Intermediate 298

(7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-(hydroxymethyl)isoxazolo[4,5-b]pyridin-3-yl)(3,3-difluoroazetidin-1-yl)methanone

Starting material: (5-((*tert*-butyldiphenylsilyloxy)methyl)-7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)isoxazolo[4,5-b]pyridin-3-yl)(3,3-difluoroazetidin-1-yl)methanone (**Intermediate 235**).

MS (ES) MH^+: 417 for $C_{17}H_{19}ClF_2N_4O_4$

^1H NMR (300 MHz, CD_2Cl_2) δ: 1.2 (d, 6H), 2.8-2.9 (m, 2H), 3.1-3.3 (m, 2H), 3.8-3.9 (m, 2H), 3.9 (brs, 1H), 4.6 (t, 2H), 4.8-4.9 (m, 4H).

Intermediate 299

N-benzyl-7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-(hydroxymethyl)isoxazolo[4,5-b]pyridine-3-carboxamide

Starting material: *N*-benzyl-5-((*tert*-butyldiphenylsilyloxy)methyl)-7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)isoxazolo[4,5-b]pyridine-3-carboxamide (**Intermediate 236**).

MS (ES) MH^+: 431 for $C_{21}H_{23}ClN_4O_4$

^{1}H NMR (300 MHz, CD_2Cl_2) δ: 1.2 (d, 6H), 2.8-2.9 (m, 2H), 3.2-3. 3 (m, 2H), 3.8-3.9 (m, 2H), 4.7 (d, 2H), 4. 9 (s, 2H), 7.3-7.4 (m, 5H), 8.0 (br s, 1H).

Intermediate 300

7-chloro-*N*-(4-cyanobenzyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-(hydroxymethyl)isoxazolo[4,5-b]pyridine-3-carboxamide

Starting material: 5-((*tert*-butyldiphenylsilyloxy)methyl)-7-chloro-*N*-(4-cyanobenzyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)isoxazolo[4,5-b]pyridine-3-carboxamide (**Intermediate 237**).

MS (ES) MH^+: 456 for $C_{22}H_{22}ClN_5O_4$

^{1}H NMR (300 MHz, CD_2Cl_2) δ: 1.2 (d, 6H), 2. 8-2.9 (m, 2H), 3.1-3. 3 (m, 2H), 3.4 (m, 1H). 3.8-3.9 (m, 2H), 4.8, (d, 2H), 4.9 (d, 2H), 7.5 (d, 2H), 7.7 (d, 2H), 8.1 (br s, 1H).

Intermediate 301

7-chloro-*N*-(3-cyanobenzyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-(hydroxymethyl)isoxazolo[4,5-b]pyridine-3-carboxamide

Starting material: 5-((*tert*-butyldiphenylsilyloxy)methyl)-7-chloro-*N*-(3-cyanobenzyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)isoxazolo[4,5-b]pyridine-3-carboxamide (**Intermediate 238**).

MS (ES) MH^+: 456 for $C_{22}H_{22}ClN_5O_4$

^{1}H NMR (300 MHz, CD_2Cl_2) δ: 1.2 (d, 6H), 2.8-2.9 (m, 2H), 3.1-3. 3 (m, 2H), 3.4 (m, 1H). 3.7-3. 9 (m, 2H), 4.8, (d, 2H), 4.9 (m, 2H), 7.5 (t, 1H), 7.6-7.7 (m, 3H), 8.2 (m, 1H).

Intermediate 302

7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-methyl-1,2-benzoxazole-5-carboxylic acid

To a solution of methyl 3-chloro-2-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-4-fluoro-5-[*N*-hydroxyethanimidoyl]benzoate (**Intermediate 171**, 700 mg, 1.94 mmol) in DMF (4 mL) was added Cs_2CO_3 (1.9 g, 5.84 mmol) and the mixture was heated to 130 °C for 14 hours. The reaction mixture was cooled to room temperature and filtered through a celite bed. The solvent was removed under vacuum and the residue was purified by silica gel chromatography column using ethyl acetate-pet. ether gradient to obtain product. Yield: 250 mg, (41 %).

MS (ES) MH^+: 335 for $C_{15}H_{17}ClN_2O_4$

Intermediates 303 to 325 were prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 302**:

Intermediate 303

{7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(pyridin-2-yl)-1,2-benzoxazol-5-yl}methanol

Starting material: 1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}-*N*-hydroxy-1-(pyridin-2-yl)methanimine (**Intermediate 172**).

MS (ES) MH^+: 374 for $C_{19}H_{20}ClN_3O_3$

Intermediate 304

{7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(6-methylpyridin-3-yl)-1,2-benzoxazol-5-yl}methanol

Starting material: 1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}-*N*-hydroxy-1-(6-methylpyridin-3-yl)methanimine (**Intermediate 173**).

MS (ES) MH^+: 388.4 for $C_{20}H_{22}ClN_3O_3$.

Intermediate 305

{7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(1,3-thiazol-5-yl)-7,7a-dihydro-1,2-benzoxazol-5-yl}methanol

Starting material: 1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}-*N*-hydroxy-1-(1,3-thiazol-5-yl)methanimine (**Intermediate 174**)

MS (ES) MH^+: 382.2 for $C_{17}H_{20}ClN_3O_3S$

Intermediate 306

{7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(pyridin-4-yl)-1,2-benzoxazol-5-yl}methanol

Starting material: 1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}-*N*-hydroxy-1-(pyridin-4-yl)methanimine (**Intermediate 175**).

MS (ES) MH^+: 374 for $C_{19}H_{20}ClN_3O_3$

Intermediate 307

{7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(pyridin-3-yl)-1,2-benzoxazol-5-yl}methanol

Starting material: 1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}-*N*-hydroxy-1-(pyridin-3-yl)methanimine (**Intermediate 176**).

MS (ES) MH^+: 374 for $C_{19}H_{20}ClN_3O_3$

Intermediate 308

{7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(1,3-thiazol-2-yl)-1,2-benzoxazol-5-yl}methanol

Starting material: 1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}-*N*-hydroxy-1-(1,3-thiazol-2-yl)methanimine (**Intermediate 177**).

MS (ES) MH^+: 380 for $C_{17}H_{18}ClN_3O_3S$

Intermediate 309

{7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(1-methyl-1*H*-imidazol-2-yl)-1,2-benzoxazol-5-yl}methanol

Starting material: 1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}-*N*-hydroxy-1-(1-methyl-1*H*-imidazol-2-yl)methanimine (**Intermediate 178**).

MS (ES) MH^+: 377 for $C_{18}H_{21}ClN_4O_3$

Intermediate 310

{7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(methoxymethyl)-1,2-benzoxazol-5-yl}methanol

Starting material: (1*E*)-1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}-*N*-hydroxy-2-methoxyethanimine (**Intermediate 179**).

MS (ES) MH^+: 341 for $C_{16}H_{21}ClN_2O_4$

Intermediate 311

{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(2-methyl-1,3-oxazol-4-yl)-1,2-benzoxazol-5-yl}methanol

Starting material: 1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}-*N*-hydroxy-1-(2-methyl-1,3-oxazol-4-yl)methanimine (**Intermediate 185**)

MS (ES) MH^+: 362 for $C_{18}H_{20}FN_2O_4$

Intermediate 312

{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(5-methyl-1,2-oxazol-3-yl)-1,2-benzoxazol-5-yl}methanol

Starting material: 1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}-*N*-hydroxy-1-(5-methyl-1,2-oxazol-3-yl)methanimine (**Intermediate 186**)

MS (ES) MH^+: 362 for $C_{18}H_{20}FN_3O_4$;

Intermediate 313

{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(3,5-dimethyl-1,2-oxazol-4-yl)-7-fluoro-1,2-benzoxazol-5-yl}methanol

Starting material: 1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}-1-(3,5-dimethyl-1,2-oxazol-4-yl)-*N*-hydroxymethanimine (**Intermediate 187**)

MS (ES) MH^+: 376 for $C_{19}H_{22}FN_3O_4$;

Intermediate 314

{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(1-methyl-1*H*-imidazol-2-yl)-1,2-benzoxazol-5-yl}methanol

Starting material: 1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}-*N*-hydroxy-1-(1-methyl-1*H*-imidazol-2-yl)methanimine (**Intermediate 188**)

MS (ES) MH^+: 361 for $C_{18}H_{21}FN_4O_3$

Intermediate 315

{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(1-methyl-1*H*-imidazol-4-yl)-1,2-benzoxazol-5-yl}methanol

Starting material: 1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}-*N*-hydroxy-1-(1-methyl-1*H*-imidazol-4-yl)methanimine (**Intermediate 189**)

MS (ES) MH^+: 361.2 for $C_{18}H_{21}FN_4O_3$;

Intermediate 316

{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(1-methyl-1*H*-imidazol-5-yl)-1,2-benzoxazol-5-yl}methanol

Starting material: 1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}-*N*-hydroxy-1-(1-methyl-1*H*-imidazol-5-yl)methanimine (**Intermediate 190**)

MS (ES) MH^+: 361 for $C_{18}H_{21}FN_4O_3$;

Intermedate 317

{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(4-methyl-1,3-thiazol-5-yl)-1,2-benzoxazol-5-yl}methanol

Starting material: 1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}-*N*-hydroxy-1-(4-methyl-1,3-thiazol-5-yl)methanimine (**Intermediate 191**)

MS (ES) MH^+: 378 for $C_{18}H_{20}FN_3O_3S$

Intermediate 318

{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(4-methyl-1,2,3-thiadiazol-5-yl)-1,2-benzoxazol-5-yl}methanol

Starting material: 1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}-*N*-hydroxy-1-(4-methyl-1,2,3-thiadiazol-5-yl)methanimine (**Intermediate 192**)

MS (ES) MH^+: 379 for $C_{17}H_{19}FN_4O_3S$;

Intermediate 319

{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(pyridazin-3-yl)-1,2-benzoxazol-5-yl}methanol

Starting material: 1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}-*N*-hydroxy-1-(pyridazin-3-yl)methanimine (**Intermediate 193**)

MS (ES) MH^+: 359 for $C_{18}H_{19}FN_4O_3$;

Intermediate 320

{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(pyrimidin-4-yl)-1,2-benzoxazol-5-yl}methanol

Starting material: 1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}-*N*-hydroxy-1-(pyrimidin-4-yl)methanimine (**Intermediate 194**)

MS (ES) MH^+: 359 for $C_{18}H_{19}FN_4O_3$

Intermediate 321

(2-{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-5-(hydroxymethyl)-1,2-benzoxazol-3-yl}-1,3-thiazol-4-yl)(morpholin-4-yl)methanone

Starting material: {2-[{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(hydroxyimino)methyl]-1,3-thiazol-4-yl}(morpholin-4-yl)methanone (**Intermediate 180**).

MS (ES) MH^+: 477 for $C_{22}H_{25}FN_4O_4S$.

Intermediate 322

(5-{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-5-(hydroxymethyl)-1,2-benzoxazol-3-yl}-1,3-thiazol-4-yl)(morpholin-4-yl)methanone

Starting material: {5-[{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(hydroxyimino)methyl]-1,3-thiazol-4-yl}(morpholin-4-yl)methanone (**Intermediate 181**)

MS (ES) MH^+: 477 for $C_{22}H_{25}FN_4O_4S$.

Intermediate 323

2-{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-5-(hydroxymethyl)-1,2-benzoxazol-3-yl}-*N*,*N*-dimethyl-1,3-thiazole-4-carboxamide

Starting material: 2-[{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(hydroxyimino)methyl]-*N*,*N*-dimethyl-1,3-thiazole-4-carboxamide (**Intermediate 182**)

MS (ES) MH^+: 435.2 for $C_{20}H_{23}FN_4O_4S$

Intermediate 324

2-{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-5-(hydroxymethyl)-1,2-benzoxazol-3-yl}-*N*,*N*-dimethyl-1,3-thiazole-5-carboxamide

Starting material: 2-[{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(hydroxyimino)methyl]-*N*,*N*-dimethyl-1,3-thiazole-5-carboxamide (**Intermediate 183**)

MS (ES) MH^+: 435 for $C_{20}H_{23}FN_4O_4S$

Intermediate 325

5-{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-5-(hydroxymethyl)-1,2-benzoxazol-3-yl}-1,3-thiazole-4-carbonitrile

Starting material: 5-[{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(hydroxyimino)methyl]-1,3-thiazole-4-carbonitrile (**Intermediate 184**)

MS (ES) MH^+: 388 for $C_{18}H_{17}FN_4O_3S$.

Intermediate 326

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-methyl-3-(1,3-thiazol-2-yl)-1,2-benzoxazole-5-carboxylic acid

A solution of methyl 2-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-4-fluoro-5-[(hydroxyimino)(1,3-thiazol-2-yl)methyl]-3-methylbenzoic acid (**Intermediate 195**, 0.31 g, 0.8 mmol), K_2CO_3 (0.4 g, 2.3 mmol) and potassium iodide (0.03 g, 0.2 mmol) in DMF (10 mL) was heated at 130 °C for 12 hours. Solvents were removed under vacuum and the residue was treated with 1.5N hydrochloric acid and extracted with ethyl acetate, which was dried over sodium sulfate. Removal of solvent by vacuum afforded product. Yield: 0.18 g (62%).

MS (ES) MH^+: 373 for $C_{18}H_{19}N_3O_4S$

Intermediate 327 was prepared from the indicated starting material using a method similar to the one described for the synthesis of **Intermediate 326**:

Intermediate 327

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-methyl-3-(pyrazin-2-yl)-1,2-benzoxazole-5-carboxylic acid

Starting material: 2-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-4-fluoro-5-[(hydroxyimino) (pyrazin-2-yl)methyl]-3-methylbenzoic acid (**Intermediate 196**).

MS (ES) MH^+: 368 for $C_{19}H_{20}N_4O_4$

Intermediate 328

(3-(3-chloropyrazin-2-yl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazol-5-yl)methanol

{5-[(3-chloropyrazin-2-yl)(hydroxyimino)methyl]-2-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3,4-difluorophenyl}methanol (**Intermediate 198,** 106mg, 0.26 mmol) in MeCN (4 mL) was treated with K_2CO_3 (53.2 mg, 0.39 mmol) at 120 °C for 1hr. The mixture was diluted with EtOAc and

washed with water and brine. The EtOAc solution was dried over anhydrous sodium sulfate, filtered and concentrated to afford 90mg of product..
MS (ES) MH^+: 393 for $C_{18}H_{18}ClFN_4O_3$

Intermediate 329 was prepared from the indicated starting material using a method similar to the one described for the synthesis of **Intermediate 328**:

Intermediate 329
5-((*tert*-butyldiphenylsilyloxy)methyl)-3-(6-chloropyrazin-2-yl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole
Starting material: 1-{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}-1-(6-chloropyrazin-2-yl)-*N*-hydroxymethanimine (**Intermediate 199**)
MS (ES) MH^+: 632 for $C_{34}H_{36}ClFN_4O_3Si$

Intermediate 330
6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-methyl-3-(1,3-thiazol-2-yl)-1,2-benzoxazole-5-carbaldehyde
Oxalyl chloride (0.31 g, 2.4 mmol) was added to a stirred solution of 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-methyl-3-(1,3-thiazol-2-yl)-1,2-benzoxazole-5-carboxylic acid (**Intermediate 326**, 0.18 g, 0.4 mmol) and two drops DMF in dichloromethane (5 mL) at 0°C and the mixture was stirred at room temperature for 2 hours. Solvent was removed under reduced pressure and the residue was dissolved in THF (10 mL) and the solution was cooled to -78°C and 1M solution of lithium tri(*t*-butoxy)aluminium hydride (0.28 g, 1.1 mmol) was added slowly and it was stirred for 30 mins at the same temperature. The reaction was quenched with 1.5N hydrochloric acid and extracted with ethyl acetate, the combined organic layers were dried over sodium sulfate and the solvent was removed. The brown viscous oil thus obtained was purified by silica gel column chromatography (20% ethyl acetate in hexane) affording the product as yellow solid. Yield: 0.06 g (35%).
MS (ES) MH^+: 357 for $C_{18}H_{19}N_3O_3S$

Intermediate 331 was prepared from the indicated starting material using a method similar to the one described for the synthesis of **Intermediate 330**:

Intermediate 331

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-methyl-3-(pyrazin-2-yl)-1,2-benzoxazole-5-carbaldehyde

Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-methyl-3-(pyrazin-2-yl)-1,2-benzoxazole-5-carboxylic acid (**Intermediate 327**).

MS (ES) MH^+: 352 for $C_{19}H_{20}N_4O_3$

^1H NMR (400 MHz, $CDCl_3$) δ: 1.2 (d, 6H), 2.7 (s, 3H), 3.0 (d, 2H), 3.2 (t, 2H), 3.9 (m, 2H), 8.7 (s, 1H), 8.8 (s, 2H), 9.4 (s, 1H), 10.5 (s, 1H).

Intermediate 332

1-(5-((*tert*-butyldiphenylsilyloxy)methyl)-2,3,4-trifluorophenyl)ethanone

A solution of *s*-butyllithium (1.4 M in cyclohexane) (6.42 ml, 8.99 mmol) was added slowly to a solution of *tert*-butyldiphenyl(2,3,4-trifluorobenzyloxy)silane (**Intermediate 48,** 3 g, 7.49 mmol) in THF (30 ml) cooled in a dry ice-acetone bath to maintain a temperature below -60 °C. After stirring in the dry-ice acetone bath for 20 minutes, *N*-methoxy-*N*-methylacetamide (1.035 ml, 9.74 mmol) was added dropwise maintaining a tempterature below -60 °C. The mixture was stirred cold for 40 minutes before being quenched with NH_4Cl (aqueous) and warmed to room temperature. The solution was partitioned between EtOAc and water. The EtOAc was separated and washed with brine. The combined aqueous layers were extracted with EtOAc, which was washed with rine. The combined EtOAc was dried ($MgSO_4$) and concentrated to give an oil that was chromatographed on silica gel (10% CH_2Cl_2 in hexanes followed by gradient elution to 70% CH_2Cl_2 in hexanes) to give 2 materials, the first eluting component (0.76 g) being consistant with starting material and the second eluting component (2.05 g) being consistant with product.

^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.1 (s, 9H), 2.6 (d, 3H), 4.8 (s, 2H), 7.3-7.5 (m, 6H) 7.6-7.7 (m, 4H), 7.8-7.95 (m, 1H).

Intermediate 333 was prepared from the indicated starting material and *tert*-butyldiphenyl(2,3,4-trifluorobenzyloxy)silane (**Intermediate 48**) using a method similar to the one described for the synthesis of **Intermediate 332**:

Intermediate 333

(5-((*tert*-butyldiphenylsilyloxy)methyl)-2,3,4-trifluorophenyl)(1-methyl-1*H*-1,2,4-triazol-5-yl)methanone

Starting material: *N*-methoxy-*N*,1-dimethyl-1*H*-1,2,4-triazole-5-carboxamide (**Intermediate 49**)

MS ES^+ MH^+ 510 for $C_{27}H_{26}F_3N_3O_2Si$

^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.1 (s, 9H), 4.3 (s, 3H), 4.8 (s, 2H), 7.3-7.5 (m, 5H), 7.6-7.7 (m, 4H), 7.95 (s, 1H), 8.0 (m, 1H).

Intermediate 334

(6,7-difluoro-3-methyl-1,2-benzisoxazol-5-yl)methanol

To a stirred solution of propan-2-one oxime (1.73 g, 23.7 mmol) in THF (25 ml) was added potassium *t*-butoxide (1M solution in THF, 23.8 mL) at 0°C under nitrogen atmosphere and the mixture was stirred with warming to room temperature for 1 hour. The mixture was cooled to –78 °C and a solution of 1-(5-((*tert*-butyldiphenylsilyloxy)methyl)-2,3,4-trifluorophenyl)ethanone (**Intermediate 332**, 3.0 g, 6.8 mmol) in THF (15 mL) was added to the mixture and stirred for 20 minutes at -78 °C then at -20°C for 2 hours. The reeaction was quenched with a saturated aqueous NH_4Cl solution and extracted with EtOAc. The organic layer was dried (Na_2SO_4), filtered, and concentrated to give material that was used for the next step without any further purification. A stirred solution of the material dissolved in ethanol (130 ml) was treated with 5 ml of 5% aqueous HCl at 45 °C for 8 hours. The reaction quenched with 10% aqueous sodium bicarbonate solution and extracted with EtOAc. The organic layer washed with water, dried, and concentrated. The residue was purified over a silica gel flash coulmn (elution with 15-20% EtOAc in hexanes) to give title compound as yellow solid. Yield: 600 mg, (46%).

MS (ES) MH^+: 200 for $C_9H_7F_2NO_2$

^1H NMR (400 MHz, DMSO-d_6) δ: 2.6(s, 3H), 4.6 (d, 2H), 5.55 (s, 1H), 7.7 (d, 1H).

Intermediate 335 was prepared from the indicated starting material and propan-2-one oxime using a method similar to the one described for the synthesis of **Intermediate 334**:

Intermediate 335

(6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-3-(5-morpholinopyrazin-2-yl)benzo[d]isoxazol-5-yl)methanol

Starting material: (5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*R*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)(5-morpholinopyrazin-2-yl)methanone (**Intermediate 134**)

MS (ES) MH^+: 444 (M+H) for $C_{22}H_{26}FN_5O_4$

Intermediate 336

1-(6-((*tert*-Butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(propan-2-ylideneaminooxy)pyridin-2-yl)ethanone

Propan-2-one oxime (104 mg, 1.43 mmol) was dissolved in 2 ml THF, and potassium *tert*-butoxide, 1M in THF (1.427 mL, 1.43 mmol), was added to give a white mixture which was stirred at room temperature for 45 min. The mixture was cooled in an ice bath, and a solution of 1-(6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)ethanone (**Intermediate 148**, 660 mg, 1.19 mmol) in 3 ml THF was added to give a yellow solution. Stirred at 0 °C. After about.30 minutes, saturated NH_4Cl was added to quench the reaction, which was followed by extraction with EtOAc. The phases were separated, and the combined organic phase dried over $MgSO_4$ before concentrating to a pale yellow oil, 635 mg (88%).

MS (ES) MH^+: 608 for $C_{33}H_{42}ClN_3O_4Si$

Intermediates 337 to 344 were prepared from the indicated starting material and propan-2-one oxime using a method similar to the one described for the synthesis of **Intermediate 336**:

Intermediate 337

(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoro-2-(propan-2-ylideneaminooxy)phenyl)(thiazol-5-yl)methanone

Starting materials (5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)(thiazol-5-yl)methanone (**Intermediate 123**).

MS (ES) MH^+: 660 for $C_{36}H_{42}FN_3O_4SSi$

^1H NMR (300 MHz, $CDCl_3$) δ: 0.84-1.10 (overlapping doublet and singlet, 15H), 1.58-1.92 (6H), 2.43-2.97 (m, 4H), 3.24-3.60 (m, 2H) 4.68 (s, 2H), 7.23-7.45 (m,7H), 7.47-7.71 (m, 4H), 8.11 (s, 1H) 8.93 (s, 1H).

Intermediate 338

(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoro-2-(propan-2-ylideneaminooxy)phenyl)(6-methylpyridin-3-yl)methanone

Starting material: (5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)(6-methylpyridin-3-yl)methanone (**Intermediate 124**).

MS (ES) MH^+: 660 for $C_{39}H_{46}FN_3O_4Si$

^1H NM*R* (300 MHz, $CDCl_3$) δ: 1.01-1.11 (overlapping doublet and singlet, 15H), 1.62 (3H), 1.68(3H), 2.64 (s, 3H), 2.66-2.90 (m, 4H), 3.39-3.55 (m, 2H), 4.74 (s, 2H), 7.22 (d, 1H), 7.31-7.46 (m, 7H), 7.59-7.68 (m, 4H), 7.96 (d, 1H), 8.86 (s, 1H).

Intermediate 339

(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoro-2-(propan-2-ylideneaminooxy)phenyl)(2-fluorophenyl)methanone

Starting materials (5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)(2-fluorophenyl)methanone (**Intermediate 125**).

MS (ES) MH^+: 671 for $C_{39}H_{44}F_2N_2O_4Si$

^1H NM*R* (300 MHz, $CDCl_3$) δ: 1.03 (s, 9H), 1.07 (d, 6H), 1.53 (s, 3H), 1.73 (s, 3H), 2.55-2.91 (m, 4H), 3.30-3.64 (m, 2H), 4.73 (s, 2H), 6.94-7.74 (m, 15H).

Intermediate 340

(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoro-2-(propan-2-ylideneaminooxy)phenyl)(tetrahydro-2*H*-pyran-4-yl)methanone

Starting materials (5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)(tetrahydro-2*H*-pyran-4-yl)methanone (**Intermediate 126**).

MS (ES) MH^+: 661 for $C_{38}H_{49}FN_2O_5Si$

Intermediate 341

(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*R*)-2,6-dimethylmorpholino)-3-fluoro-2-(propan-2-ylideneaminooxy)phenyl)(thiazol-2-yl)methanone

Starting materials (5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*R*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)(thiazol-2-yl)methanone (**Intermediate 131**).

MS (ES) MH^+: $C_{36}H_{42}FN_3O_4SSi$

Intermediate 342

(5-((*tert*-Butyldiphenylsilyloxy)methyl)-3-chloro-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2-(propan-2-ylideneaminooxy)phenyl)(pyrazin-2-yl)methanone

Starting material: (5-((*tert*-butyldiphenylsilyloxy)methyl)-3-chloro-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2-fluorophenyl)(pyrazin-2-yl)methanone (**Intermediate 72**, 847 mg, 1.37 mmol).

MS (ES) MH^+: 671 for $C_{37}H_{43}ClN_4O_4Si$

Intermediate 343

(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*R*)-2,6-dimethylmorpholino)-3-fluoro-2-(propan-2-ylideneaminooxy)phenyl)(pyrazin-2-yl)methanone

Starting material: (5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*R*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)(pyrazin-2-yl)methanone (**Intermediate 133**)

MS (ES) MH^+: 655 for $C_{37}H_{43}FN_4O_4Si$

Intermediate 344

(5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*R*)-2,6-dimethylmorpholino)-3-fluoro-2-(propan-2-ylideneaminooxy)phenyl)(6-methoxypyrazin-2-yl)methanone

Starting material: (5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*R*)-2,6-dimethylmorpholino)-2,3-difluorophenyl)(6-methoxypyrazin-2-yl)methanone (**Intermediate 138**)

MS (ES) MH^+: 685 for $C_{38}H_{45}FN_4O_5Si$

Intermediates 345 to 351 were prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 33**:

Intermediate 345

(6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(thiazol-5-yl)benzo[d]isoxazol-5-yl)methanol

Starting material: (5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoro-2-(propan-2-ylideneaminooxy)phenyl)(thiazol-5-yl)methanone (**Intermediate 337**).

MS (ES) MH^+: 364 for $C_{17}H_{18}FN_3O_3S$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.23 (d, 6H), 2.85-3.20 (m, 4H), 3.70-3.94 (m, 2H), 4.80 (s, 2H), 7.66 (s, 1H, 8.57 (s, 1H), 9.00 (s, 1H).

Intermediate 346

(6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(6-methylpyridin-3-yl)benzo[d]isoxazol-5-yl)methanol

Starting material: (5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoro-2-(propan-2-ylideneaminooxy)phenyl)(6-methylpyridin-3-yl)methanone (**Intermediate 338**).

MS (ES) MH^+: 372 for $C_{20}H_{22}FN_3O_3$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.22 (s, 3H), 1.24 (s, 3H), 2.68 (s, 3H), 2.82-3.22 (m, 4H), 3.29-3.55 (broad peak, 1H), 3.67-4.00 (m, 2H), 4.82 (s, 2H), 7.37 (d, 1H), 7.60 (s, 1H), 8.15 (d, 1H), 9.06 (s, 1H).

Intermediate 347

(6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(2-fluorophenyl)benzo[d]isoxazol-5-yl)methanol

Starting material: (5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoro-2-(propan-2-ylideneaminooxy)phenyl)(2-fluorophenyl)methanone (**Intermediate 339**).

MS (ES) MH^+: 375 for $C_{20}H_{20}F_2N_2O_3$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.23 (d, 6H), 2.90-3.18 (m, 4H), 3.69-3.94 (m, 2H), 4.81 (s, 2H), 7.25-7.88 (m, 5H).

Intermediate 348

(6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(tetrahydro-2*H*-pyran-4-yl)benzo[d]isoxazol-5-yl)methanol

Starting material: (5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoro-2-(propan-2-ylideneaminooxy)phenyl)(tetrahydro-2*H*-pyran-4-yl)methanone (**Intermediate 340**).

MS (ES) MH^+: 365 for $C_{19}H_{25}FN_2O_4$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.22 (d, 6H), 1.87-2.24 (m, 4H), 2.84-2.99 (m, 2H), 3.07 (t, 2H), 3.24-3.39 (m, 1H), 3.59 (t, 2H), 3.71-3.94 (m, 2H), 4.00-4.21 (m, 2H), 4.80 (s, 2H), 7.40 (s, 1H).

Intermediate 349

(6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-3-(thiazol-2-yl)benzo[d]isoxazol-5-yl)methanol

Starting material: (5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*R*)-2,6-dimethylmorpholino)-3-fluoro-2-(propan-2-ylideneaminooxy)phenyl)(thiazol-2-yl)methanone (**Intermediate 341**).

MS (ES) MH^+: 364 for $C_{17}H_{18}FN_3O_3S$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.35 (d, 6H), 2.90-3.08 (m, 2H), 3.20-3.47 (m, 2H), 4.04-4.29 (m, 2H), 4.76-4.99 (m, 2H), 7.57 (d, 1H), 8.09 (d, 1H), 8.18 (s, 1H).

Intermediate 350

(6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-3-(pyrazin-2-yl)benzo[d]isoxazol-5-yl)methanol

Starting material: (5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*R*)-2,6-dimethylmorpholino)-3-fluoro-2-(propan-2-ylideneaminooxy)phenyl)(pyrazin-2-yl)methanone (**Intermediate 343**).

MS (ES) MH^+: 359 for $C_{18}H_{19}FN_4O_3$

Intermediate 351

(6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-3-(6-methoxypyrazin-2-yl)benzo[d]isoxazol-5-yl)methanol

Starting material: (5-((*tert*-butyldiphenylsilyloxy)methyl)-4-((2*R*,6*R*)-2,6-dimethylmorpholino)-3-fluoro-2-(propan-2-ylideneaminooxy)phenyl)(6-methoxypyrazin-2-yl)methanone (**Intermediate 344**)

MS (ES) MH^+: 389 for $C_{19}H_{21}FN_4O_4$

Intermediate 352

(7-Chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-methylisoxazolo[4,5-b]pyridin-5-yl)methanol

1-(6-((*tert*-Butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(propan-2-ylideneaminooxy)pyridin-2-yl)ethanone (**Intermediate 336**, 821 mg, 1.35 mmol) was dissolved in 13ml of EtOH. Aqueous 1M HCl, (4.33 ml, 4.33 mmol) was added to give an immediate precipitate, which dissolved to give a hazy yellow solution. The mixture was heated at 75 °C. After 1 hour, 15 minutes, the reaction was cooled and diluted with with EtOAc. Added saturated $NaHCO_3$ to quench was followed by extraction 2X with EtOAc. The combined organic phase was dried over $MgSO_4$ and concentrated. The crude was purified on SiO2 using 15-40% EtOAc/hexanes. Recovered 389 mg (88%) of the title compound as white solid.

MS (ES) MH^+: 312 for $C_{14}H_{18}ClN_3O_3$

^1H NMR (300 MHz, CD_2Cl_2) δ: 1.2 (d, 6H), 2.6 (s, 3H), 2.7-2.8 (m, 2H), 3.2-3.3 (m, 2H), 3.7-3.9 (m, 2H), 4.0 (br s, 1H), 4.9 (d, 2H).

Intermediate 353 was prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 352**:

Intermediate 353

(7-Chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(pyrazin-2-yl)benzo[d]isoxazol-5-yl)methanol

Starting material: (5-((*tert*-Butyldiphenylsilyloxy)methyl)-3-chloro-4-((2*R*,6*S*)-2,6-dimethylmorpholino)-2-(propan-2-ylideneaminooxy)phenyl)(pyrazin-2-yl)methanone (**Intermediate 342**).

MS (ES) MH^+: 375 for $C_{18}H_{19}ClN_4O_3$

^1H NMR (DMSO-d_6) δ: 1.1 (d, 6H), 2.8-3.0 (m, 2H), 3.1-3.2 (m, 2H), 3.7-3.8 (m, 2H), 4.7-4.8 (m, 2H), 5.4 (m, 1H), 8.4 (br s, 1H), 8.9 (d, 1H), 9.0 (m, 1H), 9.4 (m, 1H).

Intermediate 354

7-chloro-3-cyclopropyl-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-1,2-benzoxazole-5-carboxylic acid

To a stirred solution of propan-2-one oxime (80 mg, 1.10 mmol) in THF (10 ml) was added potassium *t*-butoxide (1M solution in THF, 2.0 ml, 2.0 mmol) at -20 °C. After stirring for 45 minutes a solution of methyl 3-chloro-5-(cyclopropylcarbonyl)-2-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-4-fluorobenzoate (**Intermediate 91**) (370 mg, 1.0 mmol) in THF (5 mL) was added, and the mixture was stirred for 20 minutes at -20°C before warming to room temperature for 1 hour. The reaction was quenched with saturated aqueous ammonium chloride solution and extracted with EtOAc. The organic layer was dried (Na_2SO_4), filtered, and concentrated to give the crude material, which was used for the next step without any further purification. A stirred solution of crude material (500 mg) from above reaction dissolved in ethanol (20 ml) was treated with 5 ml of 5% aqueous HCl at 50 °C for 12 hours. The reaction quenched with 10% aqueous sodium bicarbonate solution and extracted with EtOAc. The organic layer washed with water, dried, and concentrated. The residue purified over a silica gel flash coulmn (elution with 50-70% EtOAc in hexanes) to give product. Yield: 100 mg (28 %).
MS (ESP): 295.4 for $C_{15}H_{19}FN_2O_3$

Intermediates 355 to 371 were prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 354**:

Intermediate 355

{7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(pyrimidin-2-yl)-1,2-benzoxazol-5-yl}methanol

Starting material: {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}(pyrimidin-2-yl)methanone (**Intermediate 109**)
MS (ES) MH^+: 375.2 for $C_{18}H_{19}ClN_4O_3$.

Intermediate 356

{7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(pyrimidin-4-yl)-1,2-benzoxazol-5-yl}methanol

Starting material: {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}(pyrimidin-4-yl)methanone (**Intermediate 110**)
MS (ES) MH^+: 375.2 for $C_{18}H_{19}ClN_4O_3$.

Intermediate 357

{7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(pyrimidin-5-yl)-1,2-benzoxazol-5-yl}methanol

Starting material: {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}(pyrimidin-5-yl)methanone (**Intermediate 111**).

MS (ES) MH^+: 375.2 for $C_{18}H_{19}ClN_4O_3$

Intermediate 358

{7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(pyridazin-4-yl)-1,2-benzoxazol-5-yl}methanol

Starting material: {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-3-chloro-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-fluorophenyl}(pyridazin-4-yl)methanone (**Intermediate 112**).

MS (ES) MH^+: 375.2 for $C_{18}H_{19}ClN_4O_3$

Intermediate 359

(6,7-difluoro-3-(1-methyl-1*H*-1,2,4-triazol-5-yl)benzo[d]isoxazol-5-yl)methanol

Starting material: (5-((*tert*-butyldiphenylsilyloxy)methyl)-2,3,4-trifluorophenyl)(1-methyl-1*H*-1,2,4-triazol-5-yl)methanone (**Intermediate 333**).

MS (ES) MH^+: 267 for $C_{11}H_8F_2N_4O_2$

^1H NMR (300 MHz, DMSO-d_6) δ ppm 4.3 (s, 3H), 4.7 (d, 2H), 5.7 (t, 1H), 8.3 (d, 1H), 8.4 (s, 1H).

Intermediate 360

(7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(pyrazin-2-yl)isoxazolo[4,5-b]pyridin-5-yl)methanol

Starting material: (6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)(pyrazin-2-yl)methanone (1.1 g, 1.78 mmol) (**Intermediate 143**).

MS (ES) MH^+: 376 for $C_{17}H_{18}ClN_5O_3$

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.0–1.1 (m, 6H), 3.0 (d, 4H), 3.7–3.9 (m, 2H), 4.8 (td, 2H), 5.2 (br.s., 1H), 8.7-8.8 (m, 2H), 9.5 (d, 1H).

Intermediate 361

(7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(thiazol-2-yl)isoxazolo[4,5-b]pyridin-5-yl)methanol

Starting material: (6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)(thiazol-2-yl)methanone (**Intermediate 144**).

MS (ES) MH^+: 381 for $C_{16}H_{17}ClN_4O_3S$

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.1–1.2 (m, 6H), 2.8 (br.s., 4H), 3.3 (br.s., 2H), 3.8 (br.s., 2H), 4.9 (s, 1H), 7.7 (d, 1H), 8.2 (d, 1H).

Intermediate 362

(7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(4-methylthiazol-2-yl)isoxazolo[4,5-b]pyridin-5-yl)methanol

Starting material: (6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)(4-methylthiazol-2-yl)methanone (**Intermediate 145**).

MS (ES) MH^+: 395 for $C_{17}H_{19}ClN_4O_3S$

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.1–1.2 (m, 6H), 2.7 (br.s., 4H), 2.8 (s, 3H), 3.3 (br.s., 2H), 3.8 (br.s., 2H), 4.9 (s, 1H), 7.5 (s, 1H).

Intermediate 363

(7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(1-methyl-1*H*-imidazol-2-yl)isoxazolo[4,5-b]pyridin-5-yl)methanol

Starting material: (6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)(1-methyl-1*H*-imidazol-2-yl)methanone (**Intermediate 99**).

MS (ES) MH^+: 378 for $C_{17}H_{20}ClN_5O_3$

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.1–1.2 (m, 6H), 2.8 (br.s., 4H), 3.2 (br.s., 2H), 3.8 (br.s., 2H), 4.0 (s, 3H), 4.9 (br.s., 1H), 7.1 (s, 1H), 7.3 (br.s., 1H).

Intermediate 364

(7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(thiazol-5-yl)isoxazolo[4,5-b]pyridin-5-yl)methanol

Starting material: (6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)(thiazol-5-yl)methanone (**Intermediate 100**).

MS (ES) MH^+: 381 for $C_{16}H_{17}ClN_4O_3S$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.1–1.2 (m, 6H), 2.8 (br.s., 2H), 3.3 (br.s., 2H), 3.8 (br.s., 2H), 4.9 (s, 2H), 9.0 (2s, 2H).

Intermediate 365

(7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(2-methylthiazol-5-yl)isoxazolo[4,5-b]pyridin-5-yl)methanol

Starting material: (6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)(2-methylthiazol-5-yl)methanone (**Intermediate 101**).

MS (ES) MH^+: 395 for $C_{16}H_{17}ClN_4O_3S$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.1–1.2 (m, 6H) 2.7–2.9 (m, 5H), 3.3 (br.s., 2H), 3.8 (br.s., 2H), 4.9 (s, 2H), 8.7 (s, 1H).

Intermediate 366

(7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(1-methyl-1*H*-1,2,4-triazol-5-yl)isoxazolo[4,5-b]pyridin-5-yl)methanol

Starting material: (6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)(1-methyl-1*H*-1,2,4-triazol-5-yl)methanone (**Intermediate 146**).

MS (ES) MH^+: 379 for $C_{16}H_{19}ClN_6O_3$

Intermediate 367

4-(7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-(hydroxymethyl)isoxazolo[4,5-b]pyridin-3-yl)-2-fluorobenzonitrile

Starting material: 4-(6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropicolinoyl)-2-fluorobenzonitrile (**Intermediate 102**).

MS (ES) MH^+: 417 for $C_{20}H_{18}ClN_4O_3$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.1–1.3 (m, 6H), 2.8 (br.s., 2H), 3.3 (br.s., 2H), 3.8 (br.s., 2H), 4.9 (s, 2H), 7.8 (dd, 1H), 8.2 – 8.4 (m, 2H).

Intermediate 368

(7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(5-methylthiazol-2-yl)isoxazolo[4,5-b]pyridin-5-yl)methanol

Starting material: (6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)(5-methylthiazol-2-yl)methanone (**Intermediate 103**).

MS (ES) MH^+: 395 for $C_{17}H_{19}ClN_4O_3S$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.1–1.2 (m, 6H), 2.5–2.7 (m, 3H), 2.8 (br.s., 2H), 3.3 (br.s., 2H), 3.8 (br.s., 2H), 4.9 (s, 2H), 7.8 (d, 1H).

Intermediate 369

5-(7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-(hydroxymethyl)isoxazolo[4,5-b]pyridin-3-yl)picolinonitrile

Starting material: 5-(6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropicolinoyl)picolinonitrile (**Intermediate 147**).

MS (ES) MH^+: 400 for $C_{19}H_{18}ClN_5O_3$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.1–1.2 (m, 6H), 2.8 (br.s., 2H), 3.3 (br.s., 2H), 3.8 (br.s., 2H), 4.9 (s, 2H), 8.8 (dd, 1H), 9.7 (d, 1H).

Intermediate 370

(3-(2-bromothiazol-5-yl)-7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)isoxazolo[4,5-b]pyridin-5-yl)methanol

Starting material: (2-bromothiazol-5-yl)(6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)methanone (**Intermediate 104**).

MS (ES) MH^+: 460 for $C_{16}H_{16}ClBrN_4O_3S$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.1–1.2 (m, 6H), 2.7–2.9 (m, 2H), 3.3 (br.s., 2H), 3.8 (br.s., 2H), 4.9 (s, 2H), 8.6 (s, 1H).

Intermediate 371

(7-chloro-3-(2,4-dichlorothiazol-5-yl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)isoxazolo[4,5-b]pyridin-5-yl)methanol

Starting material: (6-((*tert*-butyldiphenylsilyloxy)methyl)-4-chloro-5-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-fluoropyridin-2-yl)(2,4-dichlorothiazol-5-yl)methanone (**Intermediate 105**).

MS (ES) MH^+: 449 for $C_{16}H_{15}Cl_3N_4O_3S$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.1–1.2 (m, 6H), 2.7 – 2.9 (m, 2H), 3.3 (br.s., 2H), 3.8 (br.s., 2H), 4.9 (s, 2H).

Intermediate 372

{7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-methyl-1,2-benzoxazol-5-yl}methanol

To a stirred solution of $NaBH_4$ (78 mg, 2.43 mmol) in diglyme (1 mL) was added BF3 (1.6 mL, 2.59 mmol), and the thus generated diborane gas was purged into solution of 7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-methyl-1,2-benzoxazole-5-carboxylic acid (**Intermediate 302,** 250 mg, 0.8 mmol) in THF (1 mL). The mixture was stirred at room temperature for 30 minutes before being quenched with methanol (1 mL) and concentrated. The residue was purified by column chromatography to give product as solid. Yield: 130 mg (52%).

MS (ES) MH^+: 311 for $C_{15}H_{19}ClN_2O_3$.

Intermediate 373 was prepared from the indicated starting material using a method similar to the one described for the synthesis of **Intermediate 372**:

Intermediate 373

{7-chloro-3-cyclopropyl-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-1,2-benzoxazol-5-yl}methanol

Starting material: 7-chloro-3-cyclopropyl-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-1,2-benzoxazole-5-carboxylic acid (**Intermediate 354**).

MS (ES) MH^+: 337 for $C_{17}H_{21}ClN_2O_3$

Intermediate 374

6,7-difluoro-3-methylbenzo[d]isoxazole-5-carbaldehyde

To an ice-cooled solution of (6,7-difluoro-3-methyl-1,2-benzisoxazol-5-yl)methanol (**Intermediate 334,** 200 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) was added NMO (235 mg, 2.0 mmol) followed TPAP (35 mg, 0.1 mmol) and mixture stirred for 2 hours at room temperature. The reaction mixture filtered thorough silica gel bed and washed with EtOAc. The organic phase was concentrated under reduced pressure to give product as a yellow solid. Yield: 150 mg (76 %).

MS (ES) MH^+: 198 for $C_9H_5F_2NO_2$

^1H NMR (400 MHz, DMSO-d_6) δ: 2.5 (s, 3H), 8.3 (dd, 1H), 10.2 (s, 1H).

Intermediate 374 (Alternate method)

6,7-difluoro-3-methylbenzo[d]isoxazole-5-carbaldehyde

A mixture of (6,7-difluoro-3-methyl-1,2-benzisoxazol-5-yl)methanol (**Intermediate 334**, 0.7 g, 3.51 mmol) and manganese dioxide (6.11 g, 70.30 mmol) in CH_2Cl_2 (70 ml) was stirred at room temperature for 3 days. TLC shows conversion to a higher Rf spot with starting material. Addtional MnO_2 (5 g) was added and the mixture was heated to reflux for 24 hours. The mixture was filtered through celite and rinsed well with CH_2Cl_2. Solvent was removed from the filtrate to give 640 mg of product as a tan solid.

MS (ES) MH^+: 198 for $C_9H_5F_2NO_2$

^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 2.6 (s, 3H), 8.0 (d, 1H), 10.4 (s, 1H).

Intermediate 375

7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-methyl-1,2-benzoxazole-5-carbaldehyde

To the solution of {7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-methyl-1,2-benzoxazol-5-yl}methanol (**Intermediate 372**, 130 mg, 4.4 mmol) in anhydrous DCM (5 mL), was added NMO (103 mg, 8.8 mmol) and TPAP (31 mg, 0.88 mmol) at 0 °C and allowed to stir for 1h at room temperature. The reaction mixture was filtered and the solvents were removed under vacuum and the residue was purified over silica gel chromatography column using ethylacetate-pet. ether gradient to give solid. Yield: 35mg, (27 %).

MS (ES) MH^+: 309 for $C_{15}H_{17}ClN_2O_3$

Intermediates 376 to 393 were prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 375**:

Intermediate 376

7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(pyridin-2-yl)-1,2-benzoxazole-5-carbaldehyde

Starting material: {7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(pyridin-2-yl)-1,2-benzoxazol-5-yl}methanol (**Intermediate 303**)

MS (ES) MH^+: 372 for $C_{19}H_{18}ClN_3O_3$.

Intermediate 377

7-chloro-3-cyclopropyl-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-1,2-benzoxazole-5-carbaldehyde

Starting material: {7-chloro-3-cyclopropyl-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-1,2-benzoxazol-5-yl}methanol (**Intermediate 373**)

MS (ES) MH^+: 335 for $C_{17}H_{19}ClN_2O_3$.

Intermediate 378

7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(6-methylpyridin-3-yl)-1,2-benzoxazole-5-carbaldehyde

Starting material: {7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(6-methylpyridin-3-yl)-1,2-benzoxazol-5-yl}methanol (**Intermediate 304**)

MS (ES) MH^+: 386.4 for $C_{20}H_{20}ClN_3O_3$.

Intermediate 379

7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(1,3-thiazol-5-yl)-7,7a-dihydro-1,2-benzoxazole-5-carbaldehyde

Starting material: {7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(1,3-thiazol-5-yl)-7,7a-dihydro-1,2-benzoxazol-5-yl}methanol (**Intermediate 305**).

MS (ES) MH^+: 380 for $C_{17}H_{19}ClN_3O_3S$;

Intermediate 380

7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(pyrimidin-2-yl)-1,2-benzoxazole-5-carbaldehyde

Starting material: {7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(pyrimidin-2-yl)-1,2-benzoxazol-5-yl}methanol (**Intermediate 355**).

MS (ES) MH^+: 373 for $C_{18}H_{17}ClN_4O_3$

Intermediate 381

7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(pyrimidin-4-yl)-1,2-benzoxazole-5-carbaldehyde

Starting material: {7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(pyrimidin-4-yl)-1,2-benzoxazol-5-yl}methanol (**Intermediate 356**).

MS (ES) MH^+: 375.2 for $C_{18}H_{19}ClN_4O_3$.

Intermediate 382

7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(pyrimidin-5-yl)-1,2-benzoxazole-5-carbaldehyde

Starting material: {7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(pyrimidin-5-yl)-1,2-benzoxazol-5-yl}methanol (**Intermediate 357**).

MS (ES) MH^+: 373 for $C_{18}H_{17}ClN_4O_3$

Intermediate 383

7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(pyridazin-4-yl)-1,2-benzoxazole-5-carbaldehyde

Starting material: {7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(pyridazin-4-yl)-1,2-benzoxazol-5-yl}methanol (**Intermediate 358**).

MS (ES) MH^+: 373.2 for $C_{18}H_{17}ClN_4O_3$

Intermediate 384

7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(pyridin-4-yl)-1,2-benzoxazole-5-carbaldehyde

Starting material: {7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(pyridin-4-yl)-1,2-benzoxazol-5-yl}methanol (**Intermediate 306**)
MS (ES) MH^+: 372 for $C_{19}H_{18}ClN_3O_3$

Intermediate 385

7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(pyridin-3-yl)-1,2-benzoxazole-5-carbaldehyde

Starting material: {7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(pyridin-3-yl)-1,2-benzoxazol-5-yl}methanol (**Intermediate 307**).
MS (ES) MH^+: 372 for $C_{19}H_{18}ClN_3O_3$;

Intermediate 386

7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(1,3-thiazol-2-yl)-1,2-benzoxazole-5-carbaldehyde

Starting material: {7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(1,3-thiazol-2-yl)-1,2-benzoxazol-5-yl}methanol (**Intermediate 308**).
MS (ES) MH^+: 380 for $C_{17}H_{18}ClN_3O_3S$;

Intermediate 387

7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(1-methyl-1*H*-imidazol-2-yl)-1,2-benzoxazole-5-carbaldehyde

Starting material: {7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(1-methyl-1*H*-imidazol-2-yl)-1,2-benzoxazol-5-yl}methanol (**Intermediate 309**).
MS (ES) MH^+: 375.4 for $C_{18}H_{19}ClN_4O$;

Intermediate 388

7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(methoxymethyl)-1,2-benzoxazole-5-carbaldehyde

Starting material: {7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(methoxymethyl)-1,2-benzoxazol-5-yl}methanol (**Intermediate 310**)
MS (ES) MH^+: 339 for $C_{16}H_{19}ClN_2O_4$.

Intermediate 389

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[4-(morpholin-4-ylcarbonyl)-1,3-thiazol-2-yl]-1,2-benzoxazole-5-carbaldehyde

Starting material: (2-{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-5-(hydroxymethyl)-1,2-benzoxazol-3-yl}-1,3-thiazol-4-yl)(morpholin-4-yl)methanone (**Intermediate 321**).

MS (ES) MH^+: 475 for $C_{22}H_{23}FN_4O_4S$.

Intermediate 390

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[4-(morpholin-4-ylcarbonyl)-1,3-thiazol-5-yl]-1,2-benzoxazole-5-carbaldehyde

Starting material: (5-{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-5-(hydroxymethyl)-1,2-benzoxazol-3-yl}-1,3-thiazol-4-yl)(morpholin-4-yl)methanone (**Intermediate 322**)

MS (ES) MH^+: 475 for $C_{22}H_{23}FN_4O_4S$

Intermediate 391

2-{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-5-formyl-1,2-benzoxazol-3-yl}-*N*,*N*-dimethyl-1,3-thiazole-4-carboxamide

Starting material: 2-{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-5-(hydroxymethyl)-1,2-benzoxazol-3-yl}-*N*,*N*-dimethyl-1,3-thiazole-4-carboxamide (**Intermediate 323**)

MS (ES) MH^+: 433 for $C_{20}H_{21}FN_4O_4S$

Intermediate 392

2-{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-5-formyl-1,2-benzoxazol-3-yl}-*N*,*N*-dimethyl-1,3-thiazole-5-carboxamide

Starting material: 2-{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-5-(hydroxymethyl)-1,2-benzoxazol-3-yl}-*N*,*N*-dimethyl-1,3-thiazole-5-carboxamide (**Intermediate 324**)

MS (ES) MH^+: 433.2 for $C_{20}H_{21}FN_4O_4S$

Intermediate 393

5-{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-5-formyl-1,2-benzoxazol-3-yl}-1,3-thiazole-4-carbonitrile

Starting material: 5-{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-5-(hydroxymethyl)-1,2-benzoxazol-3-yl}-1,3-thiazole-4-carbonitrile (**Intermediate 325**)

MS (ES) MH^+: 386.4 for $C_{18}H_{15}FN_4O_3S$.

Intermediate 394

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(2-methyl-1,3-oxazol-4-yl)-1,2-benzoxazole-5-carbaldehyde

MnO_2 (227 mg, 2.8 mmol) was added at 0 °C to a solution of {6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(2-methyl-1,3-oxazol-4-yl)-1,2-benzoxazol-5-yl}methanol **Intermediate 311**, 50 mg, 0.13 mmol) in anhydrous DCM (5 mL), and the mixture was allowed to stir for 1h at room temperature. The reaction mixture was filtered and the solvents were removed under vacuum and the residue was purified by silica gel chromatography using ethyl acetate-pet. ether gradient to give product as a solid. Yield: 37 mg, (75 %).

MS (ES) MH^+: 360 for $C_{18}H_{18}FN_3O_4$

Intermediates 395 to 403 were prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 394**:

Intermediate 395

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(5-methyl-1,2-oxazol-3-yl)-1,2-benzoxazole-5-carbaldehyde

Starting material: {6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(5-methyl-1,2-oxazol-3-yl)-1,2-benzoxazol-5-yl}methanol (**Intermediate 312**)

MS (ES) MH^+: 360 for $C_{18}H_{18}FN_3O_4$

Intermediate 396

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(3,5-dimethyl-1,2-oxazol-4-yl)-7-fluoro-1,2-benzoxazole-5-carbaldehyde

Starting material: {6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(3,5-dimethyl-1,2-oxazol-4-yl)-7-fluoro-1,2-benzoxazol-5-yl}methanol (**Intermediate 313**)

MS (ES) MH^+: 374 for $C_{19}H_{20}FN_3O_4$

Intermediate 397

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(1-methyl-1*H*-imidazol-2-yl)-1,2-benzoxazole-5-carbaldehyde

Starting material: {6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(1-methyl-1*H*-imidazol-2-yl)-1,2-benzoxazol-5-yl}methanol (**Intermediate 314**)

MS (ES) MH^+: 359 for $C_{18}H_{19}FN_4O_3$;

Intermediate 398

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(1-methyl-1*H*-imidazol-4-yl)-1,2-benzoxazole-5-carbaldehyde

Starting material: {6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(1-methyl-1*H*-imidazol-4-yl)-1,2-benzoxazol-5-yl}methanol (**Intermediate 315**)

MS (ES) MH^+: 359 for $C_{18}H_{19}FN_4O_3$;

Intermediate 399

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(1-methyl-1*H*-imidazol-5-yl)-1,2-benzoxazole-5-carbaldehyde

Starting material: {6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(1-methyl-1*H*-imidazol-5-yl)-1,2-benzoxazol-5-yl}methanol (**Intermediate 316**)

MS (ES) MH^+: 359 for $C_{18}H_{19}FN_4O_3$;

Intermediate 400

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(4-methyl-1,3-thiazol-5-yl)-1,2-benzoxazole-5-carbaldehyde

Starting material: {6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(4-methyl-1,3-thiazol-5-yl)-1,2-benzoxazol-5-yl}methanol (**Intermedate 317**)

MS (ES) MH^+: 377 for $C_{18}H_{20}FN_3O_3S$;

Intermediate 401

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(4-methyl-1,2,3-thiadiazol-5-yl)-1,2-benzoxazole-5-carbaldehyde

Starting material: {6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(4-methyl-1,2,3-thiadiazol-5-yl)-1,2-benzoxazol-5-yl}methanol (**Intermediate 318**)

MS (ES) MH^+: 377.2 for $C_{17}H_{17}FN_4O_3S$

Intermediate 402

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(pyridazin-3-yl)-1,2-benzoxazole-5-carbaldehyde

Starting material: {6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(pyridazin-3-yl)-1,2-benzoxazol-5-yl}methanol (**Intermediate 319**)

MS (ES) MH^+: 357 for $C_{18}H_{17}FN_4O_3$

Intermediate 403

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(pyrimidin-4-yl)-1,2-benzoxazole-5-carbaldehyde

Starting material: {6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(pyrimidin-4-yl)-1,2-benzoxazol-5-yl}methanol (**Intermediate 320**)

MS (ES) MH^+: 357 for $C_{18}H_{17}FN_4O_3$

Intermediates 404 and 405 were prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 374** (Alternate Method):

Intermediate 404

6,7-difluoro-3-(1-methyl-1*H*-1,2,4-triazol-5-yl)benzo[d]isoxazole-5-carbaldehyde

Starting material: (6,7-difluoro-3-(1-methyl-1*H*-1,2,4-triazol-5-yl)benzo[d]isoxazol-5-yl)methanol (**Intermediate 359**).

MS (ES) MH^+: 266 for $C_{11}H_6F_2N_2O_4$

^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 4.4 (s, 3H), 8.1 (s, 1H), 8.8 (d, 1H), 10.4 (s, 1).

Intermediate 405

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)benzo[d]isoxazole-5-carbaldehyde

Starting material: 5-(6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)benzo[d]isoxazol-3-yl)-1,3,4-oxadiazol-2(3H)-one (**Intermediate 209**)

MS (ES) MH^+: 363 for $C_{16}H_{15}FN_4O_5$

Intermediate 406

7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(pyridin-2-yl)isoxazolo[4,5-b]pyridine-5-carbaldehyde

To a stirring solution of (7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(pyridin-2-yl)isoxazolo[4,5-b]pyridin-5-yl)methanol (**Intermediate 201**, 0.39 g, 1.04 mmol) in dichloromethane (20 mL) was added Manganese dioxode (0.543 g, 6.24 mmol). The mixture was allowed to stir 2 days at room temperature. The reaction was filtered over Celite®, and the filtrate concentrated under vacuum to give clear oil. The oil was purified on short bed of silica using 20-30% acetone in n-hexane to give 0.16 g (42%) of the title compound as a yellow solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.1 (m, 6H), 3.0–3.1 (m, 2H), 3.1–3.2 (m, 2H), 3.9 (td, 2H), 7.5 (dd, 1H), 7.9 (t, 1H), 8.6 (d, 1H), 8.9 (d, 1H), 10.2 (s, 1H).

Intermediates 407 to 438 were prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 406**:

Intermediate 407

7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(pyridin-4-yl)isoxazolo[4,5-b]pyridine-5-carbaldehyde

Starting material: (7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(pyridin-4-yl)isoxazolo[4,5-b]pyridin-5-yl)methanol (**Intermediate 202**).

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.1 (m, 6H), 3.0–3.1 (m, 2H), 3.1–3.2 (m, 2H), 3.9 (td, 2H), 8.3–8.4 (m, 2H), 8.8 (dd, 2H), 10.2 (s, 1H).

Intermediate 408

7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(pyridin-3-yl)isoxazolo[4,5-b]pyridine-5-carbaldehyde

Starting material: (7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(pyridin-3-yl)isoxazolo[4,5-b]pyridin-5-yl)methanol (**Intermediate 203**).

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.1 (m, 6H), 3.0–3.1 (m, 2H), 3.1–3.2 (m, 2H), 3.9 (td, 2H), 7.5 (dd, 1H), 8.7–8.8 (m, 2H), 9.7 (d, 1H), 10.2 (s, 1H)

Intermediate 409

7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(pyrazin-2-yl)isoxazolo[4,5-b]pyridine-5-carbaldehyde

Starting material: (7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(pyrazin-2-yl)isoxazolo[4,5-b]pyridin-5-yl)methanol (**Intermediate 360**).

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.1 (m, 6H), 3.0–3.1 (m, 2H), 3.1–3.2 (m, 2H), 3.9 (td, 2H), 8.7–8.9 (m, 2H), 9.8 (d, 1H), 10.2 (s, 1H).

Intermediate 410

7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(thiazol-2-yl)isoxazolo[4,5-b]pyridine-5-carbaldehyde

Starting material: (7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(thiazol-2-yl)isoxazolo[4,5-b]pyridin-5-yl)methanol (**Intermediate 361**).

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.1 (m, 6H), 2.9–3.0 (m, 2H), 3.1–3.2 (m, 2H), 3.9 (td, 2H), 7.7 (d, 1H), 8.2 (d, 1H), 10.2 (s, 1H).

Intermediate 411

7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(4-methylthiazol-2-yl)isoxazolo[4,5-b]pyridine-5-carbaldehyde

Starting material: (7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(4-methylthiazol-2-yl)isoxazolo[4,5-b]pyridin-5-yl)methanol (**Intermediate 362.**

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.1 (m, 6H), 2.5 (s, 3H), 2.8–3.0 (m, 2H), 3.1 – 3.2 (m, 2H), 3.8 (d, 2H), 7.8 (s, 1H), 10.2 (s, 1H).

Intermediate 412

7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(1-methyl-1*H*-imidazol-2-yl)isoxazolo[4,5-b]pyridine-5-carbaldehyde

Starting material: (7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(1-methyl-1*H*-imidazol-2-yl)isoxazolo[4,5-b]pyridin-5-yl)methanol (**Intermediate 363**).

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.1 (m, 6H), 2.9–3.0 (m, 2H), 3.1–3.2 (m, 2H), 3.9 (m, 2H), 4.1 (s, 3H), 7.1 (s, 1H), 7.4 (1H), 10.2 (s, 1H).

Intermediate 413

7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(thiazol-5-yl)isoxazolo[4,5-b]pyridine-5-carbaldehyde

Starting material: (7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(thiazol-5-yl)isoxazolo[4,5-b]pyridin-5-yl)methanol (**Intermediate 364**).

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.0 (m, 6H), 3.0–3.1 (m, 2H), 3.2 (m, 2H), 3.9–4.0 (m, 2H), 9.1 (s, 1H), 9.3 (s, 1H), 10.2 (s, 1H).

Intermediate 414

7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(2-methylthiazol-5-yl)isoxazolo[4,5-b]pyridine-5-carbaldehyde

Starting material: (7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(2-methylthiazol-5-yl)isoxazolo[4,5-b]pyridin-5-yl)methanol (**Intermediate 365**).

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.0 (m, 6H), 2.8 (s, 3H), 3.0–3.1 (m, 2H), 3.2 (m, 2H), 3.9–4.0 (m, 2H), 8.9 (s, 1H), 10.2 (s, 1H).

Intermediate 415

7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(1-methyl-1*H*-1,2,4-triazol-5-yl)isoxazolo[4,5-b]pyridine-5-carbaldehyde

Starting material: (7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(1-methyl-1*H*-1,2,4-triazol-5-yl)isoxazolo[4,5-b]pyridin-5-yl)methanol (**Intermediate 366**).

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.2 (m, 6H), 2.8–2.9 (m, 2H), 3.0–3.1 (m, 2H), 3.9 (td, 2H),

4.3 (s, 3H), 8.2 (s, 1H), 10.2 (s, 1H).

Intermediate 416

4-(7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-formylisoxazolo[4,5-b]pyridin-3-yl)-2-fluorobenzonitrile

Starting material: 4-(7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-(hydroxymethyl)isoxazolo[4,5-b]pyridin-3-yl)-2-fluorobenzonitrile (**Intermediate 367**).

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.1 – 1.3 (m, 6H), 2.9–3.1 (m, 2H), 3.1–3.2 (m, 2H), 3.9 (td, 2H), 7.8 (dd, 1H), 8.4–8.5 (m, 2H), 10.2 (s, 1H).

Intermediate 417

5-(7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-formylisoxazolo[4,5-b]pyridin-3-yl)picolinonitrile

Starting material: 5-(7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-(hydroxymethyl)isoxazolo[4,5-b]pyridin-3-yl)picolinonitrile (**Intermediate 369**).

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.2 (d, 6H), 3.1–3.2 (m, 4H), 3.9–4.1 (m, 2H), 7.9 (dd, 1H), 8.3–8.5 (m, 1H), 8.9–9.0 (m, 1H), 10.2 (s, 1H).

Intermediate 418

7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(5-methylthiazol-2-yl)isoxazolo[4,5-b]pyridine-5-carbaldehyde

Starting material: (7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(5-methylthiazol-2-yl)isoxazolo[4,5-b]pyridin-5-yl)methanol (0.49 g, 1.24 mmol, **Intermediate 368**)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.2 (d, 6H), 2.6 (s, 3H), 3.0–3.1 (m, 2H), 3.1–3.2 (m, 2H), 3.8–4.0 (m, 2H), 7.8 (d, 1H), 10.2 (s, 1H).

Intermediate 419

7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(2-bromothiazol-5-yl)isoxazolo[4,5-b]pyridine-5-carbaldehyde

Starting material: (3-(2-bromothiazol-5-yl)-7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)isoxazolo[4,5-b]pyridin-5-yl)methanol (**Intermediate 370**).

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.0 (m, 6H), 3.0–3.1 (m, 2H), 3.2 (m, 2H), 3.9–4.0 (m, 2H), 8.9 (s, 1H), 10.2 (s, 1H).

Intermediate 420

7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(2,4-dichlorothiazol-5-yl)isoxazolo[4,5-b]pyridine-5-carbaldehyde

Starting material: (7-chloro-3-(2,4-dichlorothiazol-5-yl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)isoxazolo[4,5-b]pyridin-5-yl)methanol (**Intermediate 371**).

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.0 (m, 6H), 3.0–3.1 (m, 2H), 3.2 (m, 2H), 3.9–4.0 (m, 2H), 10.2 (s, 1H).

Intermediate 421

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(6-methylpyridin-3-yl)benzo[d]isoxazole-5-carbaldehyde

Starting material: (6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(6-methylpyridin-3-yl)benzo[d]isoxazol-5-yl)methanol (**Intermediate 346**).

MS (ES) MH^+: 370 for $C_{20}H_{20}FN_3O_3$

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.23 (d, 6H), 2.70 (s, 3H), 2.98-3.28 (m, 4H), 3.74-4.00 (m, 2H), 7.40 (d, 1H), 8.03-8.33 (m, 2H), 9.09 (d, 1H), 10.38 (s, 1H).

Intermediate 422

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(thiazol-5-yl)benzo[d]isoxazole-5-carbaldehyde

Starting material: (6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(thiazol-5-yl)benzo[d]isoxazol-5-yl)methanol (**Intermediate 345**).

MS (ES) MH^+: 362 for $C_{17}H_{16}FN_3O_3S$

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.23 (d, 6H), 2.44-3.23 (m, 4H), 3.75-4.03 (m, 2H), 8.21 (s, 1H), 8.62 (s, 1H), 9.04 (s, 1H), 10.38 (s, 1H).

Intermediate 423

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(2-fluorophenyl)benzo[d]isoxazole-5-carbaldehyde

Starting material: (6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(2-fluorophenyl)benzo[d]isoxazol-5-yl)methanol (**Intermediate 347**).

MS (ES) MH^+: 373 for $C_{17}H_{16}FN_3O_3S$

^1H NMR (400 MHz, $CDCl_3$) δ: 1.23 (d, 6H), 2.94-3.30 (m, 4H), 3.79-3.97 (m, 2H), 7.27-7.86 (m, 4H), 8.09 (d, 1H), 10.37 (s, 1H).

Intermediate 424

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(tetrahydro-2*H*-pyran-4-yl)benzo[d]isoxazole-5-carbaldehyde

Starting material: (6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(tetrahydro-2*H*-pyran-4-yl)benzo[d]isoxazol-5-yl)methanol (**Intermediate 348**).

MS (ES) MH^+: 363 for $C_{19}H_{23}FN_2O_4$

^1H NMR (400 MHz, $CDCl_3$) δ: 1.22 (d, 6H), 1.91-2.19 (m, 4H), 2.98-3.21 (m, 4H), 3.25-3.41 (m, 1H), 3.53-3.67 (m, 2H), 3.75-3.97 (m, 2H), 4.06-4.16 (m, 2H), 8.00 (s, 1H), 10.37 (s, 1H).

Intermediate 425

3-((1*H*-1,2,4-triazol-1-yl)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-5-carbaldehyde

Starting material: (3-((1*H*-1,2,4-triazol-1-yl)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazol-5-yl)methanol (**Intermediate 288**).

MS (ES) MH^+: 360 for $C_{17}H_{18}FN_5O_3$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.08 (d, 6H), 2.81-3.24 (m, 4H), 3.67-3.94 (m, 2H), 6.00 (s, 2H), 7.93 (s, 1 H, 8.04 (s, 1H), 8.83 (s, 1H), 10.22 (s, 1H).

Intermediate 426

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(pyridin-4-yl)benzo[d]isoxazole-5-carbaldehyde

Starting material: (6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(pyridin-4-yl)benzo[d]isoxazol-5-yl)methanol (**Intermediate 287**).

MS (ES) MH^+: 356 for $C_{19}H_{18}FN_3O_3$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.24 (d, 6H), 3.03-3.27 (m, 4H), 3.77-4.01 (m, 2H), 7.87 (d, 2H), 8.20 (s, 1H), 8.86 (d, 2H), 10.38 (s, 1H).

Intermediate 427

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(furan-2-yl)benzo[d]isoxazole-5-carbaldehyde

Starting material: (6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(furan-2-yl)benzo[d]isoxazol-5-yl)methanol (**Intermediate 289**).

MS (ES) MH^+: 345 for $C_{18}H_{17}FN_2O_4$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.23 (d, 6H), 2.99-3.26 (m, 4H), 3.77-3.98 (m, 2H), 6.65 (dd, 1H), 7.24 (s, 1H), 7.73 (d, 1H), 8.38 (d, 1H), 10.39 (s, 1H).

Intermediate 428

3-(difluoromethyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-5-carbaldehyde

Starting material: (3-(difluoromethyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazol-5-yl)methanol (**Intermediate 291**).

MS (ES) MH^+: 329 for $C_{15}H_{15}F_3N_2O_3$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.22 (d, 6H), 3.04-3.23 (m, 4H), 3.80-3.99 (m, 2H), 7.00 (t, 1H), 8.15 (s, 1H), 10.34 (s, 1H).

Intermediate 429

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(trifluoromethyl)benzo[d]isoxazole-5-carbaldehyde

Starting material: (6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(trifluoromethyl)benzo[d]isoxazol-5-yl)methanol (**Intermediate 290**).

MS (ES) MH^+: 347 for $C_{15}H_{14}F_4N_2O_3$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.23 (d, 6H), 2.96-3.29 (m, 4H), 3.74-4.03 (m, 2H), 8.06 (s, 1H), 10.32 (s, 1H).

Intermediate 430

6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-3-(thiazol-2-yl)benzo[d]isoxazole-5-carbaldehyde

Starting material: (6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-3-(thiazol-2-yl)benzo[d]isoxazol-5-yl)methanol (**Intermediate 349**).

MS (ES) MH^+: 362 for $C_{17}H_{16}FN_3O_3S$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.33 (d, 6H), 2.89-3.22 (m, 2H), 3.31-3.52 (m, , 2H), 4.07-4.36 (m, 2H), 7.59 (d, 1H), 8.12 (d, 1H), 8.55-8.72 (s, 1H), 10.48 (s, 1H).

Intermediate 431

3-(difluoromethyl)-6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-5-carbaldehyde

Starting material: (3-(difluoromethyl)-6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazol-5-yl)methanol (**Intermediate 292**).

MS (ES) MH^+: 329 for $C_{15}H_{15}F_3N_2O_3$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.32 (d, 6H), 2.93-3.52 (m, 4H), 4.07-4.36 (m, 2H), 7.01 (t, 1H), 8.16 (s, 1H), 10.44 (s, 1H).

Intermediate 432

3-(3-chloropyrazin-2-yl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-5-carbaldehyde

Starting material: (3-(3-chloropyrazin-2-yl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazol-5-yl)methanol (**Intermediate 328**).

MS (ES) MH^+: 391 for $C_{18}H_{16}ClFN_4O_3$

Intermediate 433

6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-3-(5-morpholinopyrazin-2-yl)benzo[d]isoxazole-5-carbaldehyde

Starting material: (6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-3-(5-morpholinopyrazin-2-yl)benzo[d]isoxazol-5-yl)methanol (**Intermediate 335**).

MS (ES) MH^+: 442 (M+H) for $C_{22}H_{24}FN_5O_4$

Intermediate 434

3-(6-chloropyrazin-2-yl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-5-carbaldehyde

Starting material: (3-(6-chloropyrazin-2-yl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazol-5-yl)methanol (**Intermediate 282**)

MS (ES) MH^+: 391 for $C_{18}H_{16}ClFN_4O_3$

Intermediate 435

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(5-(methylthio)pyrazin-2-yl)benzo[d]isoxazole-5-carbaldehyde

Starting material: (6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(5-(methylthio)pyrazin-2-yl)benzo[d]isoxazol-5-yl)methanol (**Intermediate 283**)

MS (ES) MH^+: 403 for $C_{19}H_{19}FN_4O_3S$

Intermediate 436

6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-3-(6-methoxypyrazin-2-yl)benzo[d]isoxazole-5-carbaldehyde

Starting material: (6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-3-(6-methoxypyrazin-2-yl)benzo[d]isoxazol-5-yl)methanol (**Intermediate 351**)

MS (ES) MH^+: 387 for $C_{19}H_{19}FN_4O_4$

Intermediate 437

6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-3-(2-(methylthio)pyrimidin-4-yl)benzo[d]isoxazole-5-carbaldehyde

Starting material: (6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-3-(2-(methylthio)pyrimidin-4-yl)benzo[d]isoxazol-5-yl)methanol (**Intermediate 284**)

MS (ES) MH^+: 403 (M+H) for $C_{19}H_{19}FN_4O_3S$

Intermediate 438

6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-3-(pyrazin-2-yl)benzo[d]isoxazole-5-carbaldehyde

Starting material: (6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-3-(pyrazin-2-yl)benzo[d]isoxazol-5-yl)methanol (**Intermediate 350**).

MS (ES) MH^+: 357 for $C_{18}H_{17}FN_4O_3$

Intermediate 439

ethyl 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formylbenzo[d]isoxazole-3-carboxylate

Ethyl 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)benzo[d]isoxazole-3-carboxylate (**Intermediate 262**, 430 mg, 1.22 mmol) was dissolved in dichloromethane (100 ml). Manganese dioxide (2122 mg, 24.41 mmol) was added and the reaction was stirred vigorously overnight. The reaction was incomplete so an additional 2g of MnO_2 was added and the reaction was stirred for 4 hours. The reaction was still incomplete so an additional 2g of MnO2 was added and the reaction was stirred overnight. The reaction was filtered through celite and washed through with DCM and ethyl acetate. The filtrate was concentrated to give the title compound (350 mg, 0.999 mmol, 82 %)

MS (ES) MH^+: 351 for $C_{17}H_{19}FN_2O_5$

^{1}H NMR (300 MHz, CHLOROFORM-d) δ ppm 1.3 (d, 6H), 1.5 (t, 3H), 3.0-3.3 (m, 4H), 3.9 (br. s., 2H), 4.6 (q, 2H), 8.4 (s, 1H), 10.4 (s, 1H).

Intermediates 440 to 470were prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 439**:

Intermediate 440

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(morpholine-4-carbonyl)benzo[d]isoxazole-5-carbaldehyde

Starting material: (6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)benzo[d]isoxazol-3-yl)(morpholino)methanone (**Intermediate 285**).

MS (ES) MH^+: 392 for $C_{19}H_{22}FN_3O_5$

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.2 (d, 6H), 3.0-3.2 (m, 4H), 3.6-3.7 (m, 2H), 3.7-3.9 (m, 8H), 8.2 (s, 1H), 10.25 (s, 1H).

Intermediate 441

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formyl-*N*-methoxy-*N*-methylbenzo[d]isoxazole-3-carboxamide

Starting material: 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)-*N*-methoxy-*N*-methylbenzo[d]isoxazole-3-carboxamide (**Intermediate 263**)

MS (ES) MH^+: 366 for $C_{17}H_{20}FN_3O_5$

Intermediate 442

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-*N*-ethyl-7-fluoro-5-formylbenzo[d]isoxazole-3-carboxamide

Starting material: 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-*N*-ethyl-7-fluoro-5-(hydroxymethyl)benzo[d]isoxazole-3-carboxamide (**Intermediate 264**)

MS (ES) MH^+: 350 for $C_{17}H_{20}FN_3O_4$

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.23 (d, *J*=6.03 Hz, 6H) 1.31 (t, *J*=7.16 Hz, 3H) 3.02-3.22 (m, 4H) 3.48-3.65 (m, 2H) 3.82 -3.98 (m, 2H) 6.81-6.96 (br. s., 1H) 8.51 (s, 1H) 10.33 (s, 1H)

Intermediate 443

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-*N*-ethyl-7-fluoro-5-formyl-*N*-methylbenzo[d]isoxazole-3-carboxamide

Starting material: 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-*N*-ethyl-7-fluoro-5-(hydroxymethyl)-*N*-methylbenzo[d]isoxazole-3-carboxamide (**Intermediate 265**)

MS (ES) MH^+: 364 for $C_{18}H_{22}FN_3O_4$

Intermediate 444

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formyl-*N*-methylbenzo[d]isoxazole-3-carboxamide

Starting material: 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)-*N*-methylbenzo[d]isoxazole-3-carboxamide (**Intermediate 266**)

MS (ES) MH^+: 336 for $C_{16}H_{18}FN_3O_4$

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.25 (d, *J*=6.78 Hz, 6H) 3.04-3.23 (m, 7H) 3.91 (br. s., 1H) 6.83-6.99 (m, 1H) 8.53 (s, 1H) 10.34 (s, 1H)

Intermediate 445

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(4-methyl-3-oxopiperazine-1-carbonyl)benzo[d]isoxazole-5-carbaldehyde

Starting material: 4-(6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)benzo[d]isoxazole-3-carbonyl)-1-methylpiperazin-2-one (**Intermediate 267**)
MS (ES) MH^+: 419 for $C_{20}H_{23}FN_4O_5$

Intermediate 446

3-(3,3-difluoroazetidine-1-carbonyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-5-carbaldehyde

Starting material: (3,3-difluoroazetidin-1-yl)(6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)benzo[d]isoxazol-3-yl)methanone (**Intermediate 268**)
MS (ES) MH^+: 398 for $C_{18}H_{18}F_3N_3O_4$
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.23 (d, *J*=6.78 Hz, 6H) 3.03-3.18 (m, 4H) 3.78-3.97 (m, 2H) 4.60 (t, *J*=12.06 Hz, 2H) 4.96 (t, *J*=11.68 Hz, 2H) 8.39-8.46 (m, 1H) 10.26-10.36 (m, 1H)

Intermediate 447

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formylbenzo[d]isoxazole-3-carboxamide

Starting material: 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)benzo[d]isoxazole-3-carboxamide (**Intermediate 269**)
MS (ES) MH^+: 322 for $C_{15}H_{16}FN_3O_4$

Intermediate 448

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formyl-*N*-(2-methoxyethyl)benzo[d]isoxazole-3-carboxamide

Starting material: 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)-*N*-(2-methoxyethyl)benzo[d]isoxazole-3-carboxamide (**Intermediate 270**)
MS (ES) MH^+: 380 for $C_{18}H_{22}FN_3O_5$
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.23 (d, *J*=6.03 Hz, 6H) 3.04-3.20 (m, 4H) 3.41 (s, 3H) 3.60 (t, *J*=4.90 Hz, 2H) 3.65-3.78 (m, 2H) 3.89 (br. s., 2H) 7.18-7.26 (m, 1H) 8.49 (s, 1H) 10.33 (s, 1H)

Intermediate 449

N-tert-butyl-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formylbenzo[d]isoxazole-3-carboxamide

Starting material: *N-tert*-butyl-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)benzo[d]isoxazole-3-carboxamide (**Intermediate 271**)

MS (ES) MH^+: 378 for $C_{19}H_{24}FN_3O_4$

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.23 (d, *J*=6.03 Hz, 6H) 1.52 (s, 9H) 3.02-3.21 (m, 4H) 3.89 (br. s., 2H) 6.73 (br. s., 1H) 8.51

(s, 1H) 10.32 (s, 1H)

Intermediate 450

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-[(1,1-dioxidothiomorpholin-4-yl)carbonyl]-7-fluoro-1,2-benzisoxazole-5-carbaldehyde

Starting material: {6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-[(1,1-dioxidothiomorpholin-4-yl)carbonyl]-7-fluoro-1,2-benzisoxazol-5-yl}methanol (**Intermediate 272**)

MS (ES) MH^+: 440 for $C_{19}H_{22}FN_3O_6S$

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.26 (d, *J*=6.03 Hz, 6H) 3.09-3.32 (m, 8H) 3.84-4.02 (m, 2H) 4.32-4.43 (m, 2H) 4.43-4.52 (m, 2H) 8.28 (s, 1H) 10.34 (s, 1H)

Intermediate 451

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formyl-*N*-(tetrahydro-2*H*-pyran-4-yl)benzo[d]isoxazole-3-carboxamide

Starting material: 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)-*N*-(tetrahydro-2*H*-pyran-4-yl)benzo[d]isoxazole-3-carboxamide (**Intermediate 273**)

MS (ES) MH^+: 406 for $C_{20}H_{24}FN_3O_5$

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.25 (d, *J*=6.03 Hz, 6H) 1.59-1.77 (m, 2H) 1.94-2.14 (m, 2H) 3.01-3.24 (m, 4H) 3.48-3.65 (m, 2H) 3.81-3.98 (m, 2H) 3.98-4.13 (m, 2H) 4.17-4.35 (m, 1H) 6.79 (br. s., 1H) 8.51 (s, 1H) 10.35 (s, 1H)

Intermediate 452

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formyl-*N*-isopropylbenzo[d]isoxazole-3-carboxamide

Starting material: 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)-*N*-isopropylbenzo[d]isoxazole-3-carboxamide (**Intermediate 274**)

MS (ES) MH^+: 364 for $C_{18}H_{22}FN_3O_4$

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.25 (d, *J*=6.78 Hz, 6H) 1.34 (d, *J*=6.78 Hz, 6H) 3.05-3.23 (m, 4H) 3.84-3.98 (m, 2H) 4.28 - 4.44 (m, 1H) 6.65-6.77 (m, 1H) 8.53 (s, 0H) 10.34 (s, 1H)

Intermediate 453

N-cyclopropyl-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formylbenzo[d]isoxazole-3-carboxamide

Starting material: *N*-cyclopropyl-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)benzo[d]isoxazole-3-carboxamide (**Intermediate 275**)

MS (ES) MH^+: 361.9 for $C_{18}H_{20}FN_3O_4$

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.74 (br. s., 2H) 0.90-1.02 (m, 2H) 1.25 (d, *J*=6.03 Hz, 6H) 2.97 (br. s., 1H) 3.07-3.21 (m, 4H) 3.80-4.00 (m, 2H) 6.98 (br. s., 1H) 8.53 (s, 1H) 10.34 (s, 1H)

Intermediate 454

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(4-methoxypiperidine-1-carbonyl)benzo[d]isoxazole-5-carbaldehyde

Starting material: (6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)benzo[d]isoxazol-3-yl)(4-methoxypiperidin-1-yl)methanone (**Intermediate 276**).

MS (ES) MH^+: 420 for $C_{21}H_{26}FN_3O_5$

^{1}H NMR (300 MHz, CHLOROFORM-*d*) d ppm 1.25 (d, *J*=6.03 Hz, 6H) 1.65-2.06 (m, 4H) 3.02-3.26 (m, 4H) 3.53-3.63 (m, 1H) 3.63-3.75 (m, 1H) 3.75-4.07 (m, 5H) 8.22 (s, 1H) 10.35 (s, 1H)

Intermediate 455

N-(cyclopropylmethyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formylbenzo[d]isoxazole-3-carboxamide

Starting material: *N*-(cyclopropylmethyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)benzo[d]isoxazole-3-carboxamide (**Intermediate 277**)

MS (ES) MH^+: 376 for $C_{19}H_{22}FN_3O_4$

Intermediate 456

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(1,2-oxazinan-2-ylcarbonyl)-1,2-benzisoxazole-5-carbaldehyde

Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(1,2-oxazinan-2-ylcarbonyl)-1,2-benzisoxazol-5-yl}methanol (**Intermediate 278**)

MS (ES) MH^+: 392 for $C_{19}H_{22}FN_3O_5$

^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.23 (d, *J*=6.03 Hz, 6H) 1.92 (br. s., 4H) 3.02-3.24 (m, 4H) 3.89 (br. s., 2H) 4.05 (br. s., 4H) 8.16 (s, 1H) 10.35 (s, 1H)

Intermediate 457

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formyl-*N*-(thiophen-2-ylmethyl)benzo[d]isoxazole-3-carboxamide

Starting material: 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)-*N*-(thiophen-2-ylmethyl)benzo[d]isoxazole-3-carboxamide (**Intermediate 279**)

MS (ES) MH^+: 418 for $C_{20}H_{20}FN_3O_4S$

Intermediate 458

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formyl-*N*-(pyridin-4-ylmethyl)benzo[d]isoxazole-3-carboxamide

Starting material: 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)-*N*-(pyridin-4-ylmethyl)benzo[d]isoxazole-3-carboxamide (**Intermediate 249**)

MS (ES) MH^+: 413 for $C_{21}H_{21}FN_4O_4$

Intermediate 459

N-(cyclohexylmethyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formylbenzo[d]isoxazole-3-carboxamide

Starting material: *N*-(cyclohexylmethyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)benzo[d]isoxazole-3-carboxamide (**Intermediate 250**)

MS (ES) MH^+: 418 for $C_{22}H_{28}FN_3O_4$

Intermediate 460

3-(4,4-difluoropiperidine-1-carbonyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-5-carbaldehyde

Starting material: (4,4-difluoropiperidin-1-yl)(6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)benzo[d]isoxazol-3-yl)methanone (**Intermediate 251**)

MS (ES) MH^+: 426 for $C_{20}H_{22}F_3N_3O_4$

Intermediate 461

3-(3,3-difluoropyrrolidine-1-carbonyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-5-carbaldehyde

Starting material: (3,3-difluoropyrrolidin-1-yl)(6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)benzo[d]isoxazol-3-yl)methanone (**Intermediate 252**)

MS (ES) MH^+: 412 for $C_{19}H_{20}F_3N_3O_4$

Intermediate 462

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formyl-*N*-(1-methylazetidin-3-yl)benzo[d]isoxazole-3-carboxamide

Starting material: 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)-*N*-(1-methylazetidin-3-yl)benzo[d]isoxazole-3-carboxamide (**Intermediate 253**)

MS (ES) MH^+: 391 for $C_{19}H_{23}FN_4O_4$

Intermediate 463

N-(1-(6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formylbenzo[d]isoxazole-3-carbonyl)azetidin-3-yl)acetamide

Starting material: *N*-(1-(6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)benzo[d]isoxazole-3-carbonyl)azetidin-3-yl)acetamide (**Intermediate 254**)
MS (ES) MH^+: 419 for $C_{20}H_{23}FN_4O_5$

Intermediate 464

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formyl-*N*-((1-methyl-1*H*-pyrazol-3-yl)methyl)benzo[d]isoxazole-3-carboxamide

Starting material: 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)-*N*-((1-methyl-1*H*-pyrazol-3-yl)methyl)benzo[d]isoxazole-3-carboxamide (**Intermediate 255**)
MS (ES) MH^+: 416 for $C_{20}H_{22}FN_5O_4$

Intermediate 465

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formyl-*N*-((1-methyl-1*H*-pyrazol-5-yl)methyl)benzo[d]isoxazole-3-carboxamide

Starting material: 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)-*N*-((1-methyl-1*H*-pyrazol-5-yl)methyl)benzo[d]isoxazole-3-carboxamide (**Intermediate 256**)
MS (ES) MH^+: 416 for $C_{20}H_{22}FN_5O_4$

Intermediate 466

N-(1,3-dimethoxy-2-(methoxymethyl)propan-2-yl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formylbenzo[d]isoxazole-3-carboxamide

Starting material: *N*-(1,3-dimethoxy-2-(methoxymethyl)propan-2-yl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)benzo[d]isoxazole-3-carboxamide (**Intermediate 257**)
MS (ES) MH^+: 468 for $C_{22}H_{30}FN_3O_7$

Intermediate 467

N-(2,2-difluoroethyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formylbenzo[d]isoxazole-3-carboxamide

Starting material: *N*-(2,2-difluoroethyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)benzo[d]isoxazole-3-carboxamide (**Intermediate 258**)

MS (ES) MH^+: 386 for $C_{17}H_{18}F_3N_3O_4$

Intermediate 468

1-(6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formylbenzo[d]isoxazole-3-carbonyl)azetidine-3-carbonitrile

Starting material: 1-(6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)benzo[d]isoxazole-3-carbonyl)azetidine-3-carbonitrile (**Intermediate 259**)

MS (ES) MH^+: 387.2 for $C_{19}H_{19}FN_4O_4$

Intermediate 469

6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-5-formylbenzo[d]isoxazole-3-carboxamide

Starting Material: 6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl) benzo[d]isoxazole-3-carboxamide (**Intermediate 281**)

MS (ES) MH^+: 322 for $C_{15}H_{16}FN_3O_4$

^1H NMR (300 MHz, DMSO-d_6) δ ppm 1.22 (d, *J*=6.78 Hz, 6H) 3.02 (m, 2H) 3.39 (d, *J*=12.06 Hz, 2H) 4.15 (m, 2H) 8.22 (s, 1H) 8.24 (s, 1H) 8.56 (s, 1H) 10.35 (s, 1H)

Intermediate 470

6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formyl-*N*,*N*-dimethylbenzo[d]isoxazole-3-carboxamide

Starting material: 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-(hydroxymethyl)-*N*,*N*-dimethylbenzo[d]isoxazole-3-carboxamide (**Intermediate 286**).

MS (ES) MH^+: 350 for $C_{17}H_{20}FN_3O_4$

Intermediate 471

7-Chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-methylisoxazolo[4,5-b]pyridine-5-carbaldehyde

(7-Chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-methylisoxazolo[4,5-b]pyridin-5-yl)methanol (**Intermediate 352**, 459 mg, 1.47 mmol) was dissolved in about 10 ml CH_2Cl_2. Manganese dioxide (1920 mg, 22.08 mmol) was added, and the slurry was stirred at room temperature for three days. The mixture was filtered through celite and concentrated. The crude was purified by

chromatography on SiO_2 using 10-30% EtOAc/hexanes. Recovered a yellow solid, 185 mg (41%).

MS (ES) MH^+: 310 for $C_{14}H_{16}ClN_3O_3$

^1H NMR (300 MHz, CD_2Cl_2) δ: 1.2 (d, 6H), 2.7 (s, 3H), 2.9-3.0 (m, 2H), 3.1-3.2 (m, 2H), 3.8-4.0 (m, 2H), 10.2 (s, 1H).

Intermediates 472 to 481 were prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 471**:

Intermediate 472

7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(pyrazin-2-yl)benzo[d]isoxazole-5-carbaldehyde

Starting material: (7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(pyrazin-2-yl)benzo[d]isoxazol-5-yl)methanol (**Intermediate 353**).

MS (ES) MH^+: 373 for $C_{18}H_{17}ClN_4O_3$

^1H NMR (DMSO-d_6) δ: 1.1 (d, 6H), 3.1-3.2 (m, 4H), 3.8-3.9 (m, 2H), 8.7 (s, 1H), 8.9 (d, 1H), 9.0 (m, 1H), 9.4 (m, 1H), 10.3 (s, 1H).

Intermediate 473

7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-formyl-*N*-methylisoxazolo[4,5-b]pyridine-3-carboxamide

Starting material: 7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-(hydroxymethyl)-*N*-methylisoxazolo[4,5-b]pyridine-3-carboxamide (**Intermediate 293**) in 20 ml CH_2Cl_2.

MS (ES) MH^+: 353 for $C_{15}H_{17}ClN_4O_4$

^1H NMR (300 MHz, CD_2Cl_2) δ: 1.2 (d, 6H), 3.0-3.2 (overlapping m, 7H), 3.9-4.0 (m, 2H), 7.9 (br s, 1H), 10.2 (s, 1H).

Intermediate 474

7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-*N*-ethyl-5-formylisoxazolo[4,5-b]pyridine-3-carboxamide

Starting material: 7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-*N*-ethyl-5-(hydroxymethyl)isoxazolo[4,5-b]pyridine-3-carboxamide (**Intermediate 294**).

MS (ES) MH^+: 367 for $C_{16}H_{19}ClN_4O_4$

^1H NMR (300 MHz, CD_2Cl_2) δ: 1.2 (d, 6H), 1.3 (t, 3H), 3.0-3.2 (m, 4H), 3.5-3.7 (m, 2H), 3.9-4.0 (m, 2H), 7.9 (br s, 1H), 10.2 (s, 1H).

Intermediate 475

7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-formyl-*N*-isopropylisoxazolo[4,5-b]pyridine-3-carboxamide

Starting material: 7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-(hydroxymethyl)-*N*-isopropylisoxazolo[4,5-b]pyridine-3-carboxamide (**Intermediate 295**)

MS (ES) MH^+: 381 for $C_{17}H_{21}ClN_4O_4$

Intermediate 476

N-tert-butyl-7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-formylisoxazolo[4,5-b]pyridine-3-carboxamide

Starting material: *N-tert*-butyl-7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-(hydroxymethyl)isoxazolo[4,5-b]pyridine-3-carboxamide (**Intermediate 296**).

MS (ES) MH^+: 395 for $C_{18}H_{23}ClN_4O_4$

^1H NMR (300 MHz, CD_2Cl_2) δ: 1.2 (d, 6H), 1.5 (s, 9H), 3.0-3.2 (m, 4H), 3.9-4.0 (m, 2H), 7.9 (br s, 1H), 10.2 (s, 1H).

Intermediate 477

7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-formyl-*N*-neopentylisoxazolo[4,5-b]pyridine-3-carboxamide

Starting material: 7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-(hydroxymethyl)-*N*-neopentylisoxazolo[4,5-b]pyridine-3-carboxamide (**Intermediate 297**).

MS (ES) MH^+: 409 for $C_{19}H_{25}ClN_4O_4$

^1H NMR (300 MHz, CD_2Cl_2) δ: 1.0 (s, 9H), 1.2 (d, 6H), 3.0-3.2 (m, 4H), 3.4 (d, 2H), 3.9-4.0 (m, 2H), 8.2 (br s, 1H), 10.2 (s, 1H).

Intermediate 478

7-chloro-3-(3,3-difluoroazetidine-1-carbonyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)isoxazolo[4,5-b]pyridine-5-carbaldehyde

Starting material: (7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-(hydroxymethyl)isoxazolo[4,5-b]pyridin-3-yl)(3,3-difluoroazetidin-1-yl)methanone (**Intermediate 298**).

MS (ES) MH^+: 415 for $C_{17}H_{17}ClF_2N_4O_4$

^1H NMR (300 MHz, CD_2Cl_2) δ: 1.2 (d, 6H), 3.0-3.1 (m, 4H), 3.9-4.0 (m, 2H), 4.6 (t, 2H), 4.9 (t, 2H), 10.2 (s, 1H).

Intermediate 479

N-benzyl-7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-formylisoxazolo[4,5-b]pyridine-3-carboxamide

Starting material: *N*-benzyl-7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-(hydroxymethyl)isoxazolo[4,5-b]pyridine-3-carboxamide (**Intermediate 299**).

MS (ES) MH^+: 429 for $C_{21}H_{21}ClN_4O_4$

^1H NMR (300 MHz, CD_2Cl_2) δ: 1.2 (d, 6H), 2.9-3.2 (m, 4H), 3.8-4.00 (m, 2H), 4.7 (d, 2H), 7.2-7.5 (m, 5H), 8.2 (br s, 1H), 10.1 (s, 1H).

Intermediate 480

7-chloro-*N*-(4-cyanobenzyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-formylisoxazolo[4,5-b]pyridine-3-carboxamide

Starting material: 7-chloro-*N*-(4-cyanobenzyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-(hydroxymethyl)isoxazolo[4,5-b]pyridine-3-carboxamide (**Intermediate 300**).

MS (ES) MH^+: 454 for $C_{22}H_{20}ClN_5O_4$

^1H NMR (300 MHz, CD_2Cl_2) δ: 1.2 (d, 6H), 3.0-3.2 (m, 4H), 3.7-4.0 (m, 2H), 4.8 (m, 2H), 7.5 (d, 2H), 7.7 (d, 2H), 8.4 (br s, 1H), 10.1 (s, 1H).

Intermediate 481

7-chloro-*N*-(3-cyanobenzyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-formylisoxazolo[4,5-b]pyridine-3-carboxamide

Starting material: 7-chloro-*N*-(3-cyanobenzyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-(hydroxymethyl)isoxazolo[4,5-b]pyridine-3-carboxamide (**Intermediate 301**).
MS (ES) MH^+: 454 for $C_{22}H_{20}ClN_5O_4$

Intermediate 482

1-benzylamino-butan-2-ol

To a solution of benzylamine (29.65 g, 277.0 mmol) in ethanol (40 mL) was added 1,2-epoxybutane (4 g, 55.47 mmol) and the mixture was heated to 150°C for 2 h in a autoclave. It was concentrated and distilled at 140-150°C/2 mm Hg to give product as color less liquid, which slowly crystallizes at room temperature after 2 days. Yield: 8.5 g (85%)

MS (ES) MH^+: 180 for $C_{11}H_{17}NO$

^1H NMR (300 MHz – $CDCl_3$) δ: 0.9 (t, 3H), 1.4 (m, 2H), 2.45 (t, 1H), 2.8 (dd, 1H), 3.55 (m, 1H), 3.8 (q, 2H), 7.2 (m, 5H).

Intermediates 483 to 485 were prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 482**:

Intermediate 483

3-(benzylamino)-1,1,1-trifluoropropan-2-ol

Starting material: benzylamine and 2-(trifluoromethyl)oxirane

MS (ES) MH^+: 220 for $C_{10}H_{12}F_3NO$

^1H NMR (300 MHz – $CDCl_3$) δ: 2.8 (m, 1H), 2.9 (m, 1H), 3.55 (m, 1H), 3.8 (s, 2H), 4.0 (m, 1H), 7.3-7.4 (m, 5H).

Intermediate 484

1-(benzylamino)-3-methoxypropan-2-ol

Starting materials: benzyl amine and 2-(methoxymethyl)oxirane

MS (ES) MH^+: 196 for $C_{11}H_{17}NO_2$

^1H NMR (300 MHz – $CDCl_3$) δ: 2.7 (m, 2H), 2.9 (s, 2H), 3.3-3.4 (m, 5H), 3.8 (d, 2H), 3.9 (m, 1H), 7.3 (m, 5H).

Intermediate 485

1-(benzyloxy)-3-[(2,4-dimethoxybenzyl)amino]propan-2-ol

Starting materials: 2,4-dimethoxy-benzylamine and 2-[(benzyloxy)methyl]oxirane

MS (ES) MH^+: 332 for $C_{19}H_{25}NO_4$

^1H NMR (300 MHz – $CDCl_3$) δ: 2.4 (m, 1H), 2.5-2.6 (m, 1H), 3.4(m, 2H), 3.6 (m, 2H), 3.75 (s, 6H), 4.5(s, 2H), 6.45 (m, 1H), 6.5 (d, 1H), 7.15 (d, 1H), 7.3-7.4 (m, 5H).

Intermediate 486

1-[Benzyl-(2-hydroxy-propyl)-amino]-butan-2-ol

To a solution of 1-benzylamino-butan-2-ol (**Intermediate 482**, 8.5 g, 47.48 mmol) in ethanol (150 mL) was added propylene oxide (8.8 g, 151 mmole) and the mixture was heated at 150°C for 2 h in autoclave. After concentration of the mixture under reduced pressure, the residue was purified by column chromatography using methanol in dichloromethane to give product as an oil. Yield: 10.2 g (93%).

MS (ES) MH^+: 238 for $C_{14}H_{23}NO_2$

^1H NMR (300 MHz – $CDCl_3$) δ: 0.9 (t, 3H), 1.2 (m, 3H), 1.9(m, 2H), 2.6 (m, 3H), 2.65 (m, 1H), 2.9 (bs, 2H), 3.8 (m, 2H), 3.9 (m, 2H), 7.2 (m, 5H).

Intermediate 487

N-benzyl-2-bromo-*N*-(3,3,3-trifluoro-2-hydroxypropyl)propanamide

To an ice cooled solution of 3-(benzylamino)-1,1,1-trifluoropropan-2-ol (**Intermediate 483,** 1.0 g, 4.5 mmol) in DCM (10 mL) was added TEA (0.8 mL, 5.7 mmol) followed by 2-bromopropanoyl chloride (0.86 g, 5.0) dropwise and the mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with DCM (10 mL), washed with 1.5 N HCl (2 x 10 mL), saturated aqueous $NaHCO_3$ (2 x 10 mL) befor drying over anhydrous Na_2SO_4, filtering and concentrating. The residue was used for next step without further purification. Yield: 1.4 g.

MS (ES) MH^+: 354 for $C_{13}H_{15}BrF_3NO_2$

Intermediates 488 and 489 were prepared from the indicated starting material, 2-bromopropanoyl chloride, and TEA, using a method similar to the one described for the synthesis of **Intermediate 487**:

Intermediate 488

N-benzyl-2-bromo-*N*-(2-hydroxy-3-methoxypropyl)propanamide

Starting material: 1-(benzylamino)-3-methoxypropan-2-ol (**Intermediate 484**)

MS (ES) MH^+: 330 for $C_{14}H_{20}BrNO_3$

Intermediate 489

N-[3-(benzyloxy)-2-hydroxypropyl]-2-bromo-*N*-(2,4-dimethoxybenzyl)propanamide

Starting material: 1-(benzyloxy)-3-[(2,4-dimethoxybenzyl)amino]propan-2-ol (**Intermediate 485**)

MS (ES) MH^+: 466 for $C_{22}H_{28}BrNO_3$

Intermediate 490

4-benzyl-6-methyl-2-(trifluoromethyl)morpholin-3-one

To an ice cooled solution of *N*-benzyl-2-bromo-*N*-(3,3,3-trifluoro-2-hydroxypropyl) propanamide (**Intermediate 487,** 1.4 g, 4.0 mmol) in THF (10 mL) was added NaH (0.188 mg, 7.8 mmol) and mixture was stirred at room temperature for 1 hour. The reaction mixture was quenched with MeOH (5 mL) and poured into 1.5 N HCl (10 mL). The aqueous layer was extracted with diethyl ether (2x 25 mL). The organic layer was washed with saturated $NaHCO_3$ (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to product as a solid. Yield: 1.0 g.

MS (ES) MH^+: 274 for $C_{13}H_{14}F_3NO_2$

Intermediates 490 and 491 were prepared from the indicated starting material and NaH using a method similar to the one described for the synthesis of **Intermediate 490**:

Intermediate 491

4-benzyl-2-(methoxymethyl)-6-methylmorpholin-3-one

Starting material: *N*-benzyl-2-bromo-*N*-(2-hydroxy-3-methoxypropyl)propanamide (**Intermediate 488**)

MS (ES) MH^+: 250 for $C_{14}H_{19}NO_3$

Intermediate 492

2-[(benzyloxy)methyl]-4-(2,4-dimethoxybenzyl)-6-methylmorpholin-3-one

Starting material: *N*-[3-(benzyloxy)-2-hydroxypropyl]-2-bromo-*N*-(2,4-dimethoxybenzyl)propanamide (**Intermediate 489**)

MS (ES) MH^+: 386 for $C_{22}H_{27}NO_5$

Intermediate 493

(2*S*,6*S*)-rel-4-benzyl-2-methyl-6-(trifluoromethyl)morpholine

To an ice cooled solution of LAH (0.291 mg, 7.6 mmol) in dry THF (10 mL) was added 4-benzyl-6-methyl-2-(trifluoromethyl)morpholin-3-one (**Intermediate 490,** 1.0 g, 3.6 mmol) in THF (10 mL) dropwise and the mixture was stirred at 60°C for 1 hour. The reaction mixture was quenched with MeOH (5 mL) and poured into 1.5 N HCl (10 mL). The aqueous layer was extracted with diethyl ether (2x 25 mL). The organic layer was washed with saturated $NaHCO_3$ (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography to afford the product as solid. Yield: 350 mg. Also isolated was the *trans*-isomer (2*S*,6*R*)-rel-4-benzyl-2-methyl-6-(trifluoromethyl)morpholine.

MS (ES) MH^+: 260 for $C_{13}H_{16}F_3NO$

^1H NMR (300 MHz – $CDCl_3$) δ: 1.2 (d, 3H), 1.9 (t, 1H), 2.1(t, 1H), 2.7(d, 1H), 2.9 (d, 1H), 3.5-3.6 (m, 2H), 3.8 (m, 1H), 4.0 (m, 1H), 7.3-7.4 (m, 5H).

Intermediates 494 and 495 were prepared from the indicated starting material and LAH using a method similar to the one described for the synthesis of **Intermediate 493**:

Intermediate 494

(2*S*,6*S*)-rel-4-benzyl-2-(methoxymethyl)-6-methylmorpholine

Starting material: 4-benzyl-2-(methoxymethyl)-6-methylmorpholin-3-one (**Intermediate 491**)

MS (ES) MH^+: 236 for $C_{14}H_{21}NO_2$

^1H NMR (300 MHz – $CDCl_3$) δ: 1.2 (d, 3H), 1.7-1.9 (m, 2H), 2.7 (t, 2H), 3.3-3.5 (m, 5H), 3.6 (s, 2H), 3.7-3.9 (m, 2H), 7.2-7.4 (m, 5H).

Intermediate 495

(2*S*,6*S*)-rel-2-[(benzyloxy)methyl]-4-(2,4-dimethoxybenzyl)-6-methylmorpholine

Starting material: 2-[(benzyloxy)methyl]-4-(2,4-dimethoxybenzyl)-6-methylmorpholin-3-one (**Intermediate 492**)

MS (ES) MH^+: 372 for $C_{22}H_{29}NO_4$

^1H NMR (300 MHz – $CDCl_3$) δ: 1.2 (d, 3H), 1.8-1.9 (m, 2H), 2.7 (t, 1H), 2.8(d, 1H), 3.4 (m, 1H), 3.5 (m, 3H), 3.7 (m, 1H), 3.8 (s, 6H), 3.9 (m, 1H), 4.5 (m, 2H), 6.5 (m, 2H), 7.2-7.4 (m, 6H).

Intermediate 496

4-Benzyl-2-ethyl-6-methyl-morpholine

A mixture of 1-[Benzyl-(2-hydroxy-propyl)-amino]-butan-2-ol (**Intermediate 486**, 10.5 g, 44.30 mmol) and sulfuric acid (70% w/w, 10 mL) was heated at 150°C for 36 hour. The reaction mixture was cooled to 0°C, basified with 10% NaHCO3 to pH ~ 10 and extracted with diethyl ether (3 x 50 mL). The organic layer was washed with brine (2 x 25 mL), water (2X 25 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by column chromatography using n-heptane in diethyl ether to give product as a light yellow oil. Yield: 2.0 g (20%)

MS (ES) MH^+: 220 for $C_{14}H_{21}NO$

^1H NMR (300 MHz – $CDCl_3$) δ: 0.9 (t, 3H), 1.2 (m, 3H), 1.5 (m, 2H), 1.8 (q, 2H), 2.8 (q, 2H), 3.5 (m, 3H), 3.7 (m, 1H), 7.3 (t, 5H).

Intermediate 497

2-Ethyl-6-methyl-morpholine

To a solution of 4-benzyl-2-ethyl-6-methyl-morpholine (**Intermediate 496,** 2.0 g, 9.13 mmol) in methanol (30 mL) was added ammonium formate (2.35 g, 10.77 mmol) followed by 10% Pd/C (1.0 g) and mixture was heated at 65°C for 1 hour. It was cooled and filtered through celite pad, washed with excess methanol and concentrated. The residue thus obtained was distilled. Yield: 1.0 g (85%)

MS (ES) MH^+: 130 for $C_7H_{15}NO$

^1H NMR (300 MHz – $CDCl_3$) δ: 0.9 (t, 3H), 1.2 (dd, 3H), 1.55 (m, 2H), 2.5 (m, 2H), 2.9 (t, 2H), 3.35 (m, 1H), 3.6 (m, 1H).

Intermediates 498 and 499 were prepared from the indicated starting material using a method similar to the one described for the synthesis of **Intermediate 497**:

Intermediate 498

(2*S*,6*S*)-rel-2-methyl-6-(trifluoromethyl)morpholine

Starting material: To a solution of (2*S*,6*S*)-rel-4-benzyl-2-methyl-6-(trifluoromethyl)morpholine (**Intermediate 493**).

MS (ES) MH^+: 170 for $C_6H_{10}F_3NO$

^1H NMR (300 MHz – $CDCl_3$) δ: 1.1 (d, 3H), 2.5 (m, 1H), 2.7 (m, 1H), 2.8 (m, 1H), 3.1 (m, 1H), 3.8 (m, 1H), 3.9 (m, 1H).

Intermediate 499

(2*S*,6*S*)-rel-2-(methoxymethyl)-6-methylmorpholine

Starting material: (2*S*,6*S*)-rel-4-benzyl-2-(methoxymethyl)-6-methylmorpholine (**Intermediate 494**)

MS (ES) MH^+: 146 for $C_7H_{15}NO_2$

^1H NMR (300 MHz – $CDCl_3$) δ: 1.1 (d, 3H), 2.4 (m, 1H), 2.6 (m, 1H), 2.9 (m, 1H), 3.3-3.5 (m, 5H), 3.6-3.7 (m, 2H).

Intermediate 500

(2*S*,6*S*)-rel-2-[(benzyloxy)methyl]-6-methylmorpholine

To a solution of (2*S*,6*S*)-rel-2-[(benzyloxy)methyl]-4-(2,4-dimethoxybenzyl)-6-methylmorpholine (**Intermediate 495,** 0.6 g, 1.6 mmol) in DCM (15 mL) was added 1-chloroethyl chloroformate (0.6 mL, 6.9 mmol) and mixture was heated at 50°C for 10 hour. To the reaction mixture methanol was added and heating was continued for 1 hour. After cooling, the mixture was concentrated give product as solid.

Yield: 0.5 g

MS (ES) MH^+: 222 for $C_{13}H_{19}NO_2$

Intermediate 501

6-(2-ethyl-6-methylmorpholin-4-yl)-7-fluoro-3-methyl-1,2-benzisoxazole-5-carbaldehyde

To an ice cooled and stirred solution of 6,7-difluoro-3-methylbenzo[d]isoxazole-5-carbaldehyde (**Intermediate 374**, 150 mg, 0.8 mmol) in anhydrous acetonitrile was added TEA (204 mg, 2.0 mmol) followed by 2-Ethyl-6-methyl-morpholine (**Intermediate 497**, 98 mg, 0.8 mmol) and the mixture heated at 80 °C for 12 hour. It was cooled to room temperature and concentrated. The residue thus obtained was purified over silica gel column using a gradient of ethyl acetate in pet. ether to give product as a solid. Yield: 75 mg (74%).

MS(ES) MH^+: 307 for $C_{16}H_{19}F_2N_2O_3$

^1H NMR (400 MHz, DMSO-d_6) δ: 0.9 (t, 3H), 1.1 (d, 3H), 1.5 (m, 2H), 2.6 (s, 3H), 3.0 (m, 2H), 3.2 (d, 2H), 3.6 (m, 1H), 3.8 (m, 1H), 8.1 (s, 1H), 10.3 (s, 1H)

Intermediates 502 and 503 were prepared from the indicated starting material, TEA, and 6,7-difluoro-3-methylbenzo[d]isoxazole-5-carbaldehyde (**Intermediate 374**), using a method similar to the one described for the synthesis of **Intermediate 501**:

Intermediate 502

7-fluoro-3-methyl-6-[(2*S*,6*S*)-rel-2-methyl-6-(trifluoromethyl) morpholin-4-yl]-1,2-benzoxazole-5-carbaldehyde

Starting material: (2*S*,6*S*)-rel-2-methyl-6-(trifluoromethyl)morpholine (**Intermediate 498**)

MS (ES) MH^+: 347 for $C_{15}H_{14}F_4N_2O_3$

Intermediate 503

7-fluoro-6-[(2*S*,6*S*)-rel-2-(methoxymethyl)-6-methylmorpholin-4-yl]-3-methyl-1,2-benzoxazole-5-carbaldehyde

Starting material: (2*S*,6*S*)-rel-2-(methoxymethyl)-6-methylmorpholine (**Intermediate 499**)

MS (ES) MH^+: 323.2 for $C_{16}H_{19}FN_2O_4$

^1H NMR (300 MHz, $CDCl_3$) δ: 1.3 (d, 3H), 2.6 (s, 3H), 3.2 (m, 2H), 3.3 (m, 2H), 3.4 (s, 3H), 4.0 (m, 2H), 8.0 (d, 1H), 10.4 (s,1H).

Intermediate 504

{3-(benzylamino)-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-1,2-benzoxazol-5-yl}methanol

To an ice cooled solution of benzaldehyde (0.08 mL, 2.54 mmol) in TFA(5 mL) was added triethylsilane (0.4 mL, 2.5 mmol) followed by {3-amino-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-1,2-benzisoxazol-5-yl}methanol (**Intermediate 7,** 250 mg, 0.84 mmol), and slowly allowed to reach room temperature and stirred for 12 hour. The reaction mixture was concentrated and the residue thus obtained was purified coloumn chromatography using EtOAc in petether to give the title compound as solid. Yield : 70 mg (21 %).

MS (ES) MH^+: 386 for $C_{21}H_{24}FN_3O_3$

Intermediates 505 to 514 were prepared from the indicated starting material, triethylsilane and {3-amino-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-1,2-benzisoxazol-5-yl}methanol (**Intermediate 7**), using a method similar to the one described for the synthesis of **Intermediate 504**:

Intermediate 505

{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[(1,3-thiazol-2-ylmethyl)amino]-1,2-benzoxazol-5-yl}methanol

Starting material: 2-thiazole carboxaldehyde.

MS (ES) MH^+: 393 for $C_{18}H_{21}FN_4O_3S$.

Intermediate 506

{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[(1*H*-imidazol-4-ylmethyl)amino]-1,2-benzoxazol-5-yl}methanol

Starting material: 4-imidazole carboxaldehyde

MS (ES) MH^+: 376.2 for $C_{18}H_{22}FN_5O_3$.

^1H NMR (400 MHz, DMSO-d_6) δ: 1.1 (d, 6H), 2.8 (m, 2H), 2.9 (d, 2H), 3.7 (m, 2H), 4.45 (d, 2H), 4.6 (s, 1H), 7.5 (s, 1H), 7.7(m, 2H), 8.75 (s, 1H).

Intermediate 507

(6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-{[(1-methyl-1*H*-pyrazol-4-yl)methyl]amino}-1,2-benzoxazol-5-yl)methanol

Starting material: 1-methyl-1*H*-pyrazole-4-carboxaldehyde

MS (ES) MH^+: 390for $C_{19}H_{24}FN_5O_3$.

Intermediate 508

(6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-{[(5-methyl-1,2-oxazol-3-yl)methyl]amino}-1,2-benzoxazol-5-yl)methanol

Starting material: 5-methylisoxazole-3-carboxaldehyde

MS (ES) MH^+: 391 for $C_{19}H_{23}FN_4O_4$.

Intermediate 509

{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[(pyridin-2-ylmethyl)amino]-1,2-benzoxazol-5-yl}methanol

Starting material: pyridine-2-carboxaldehyde

MS (ES) MH^+: 387 for $C_{20}H_{23}FN_4O_3$.

Intermediate 510

{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[(pyridin-3-ylmethyl)amino]-1,2-benzoxazol-5-yl}methanol

Starting material: pyridine-3-carboxaldehyde

MS (ES) MH^+: 387 for $C_{20}H_{23}FN_4O_3$.

Intermediate 511

{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[(pyridin-4-ylmethyl)amino]-1,2-benzoxazol-5-yl}methanol

Starting material: pyridine-4-carboxaldehyde

MS (ES) MH^+: 387 for $C_{20}H_{23}FN_4O_3$.

Intermediate 512

{3-[(cyclopropylmethyl) amino]-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-1,2-benzoxazol-5-yl}methanol

Starting material: cyclopropyl carboxaldehye

MS (ES) MH^+: 350 for $C_{18}H_{24}FN_3O_3$.

Intermediate 513

{3-[(cyclohexylmethyl) amino]-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-1,2-benzoxazol-5-yl}methanol

Starting material: cyclohexane carboxaldehyde

MS (ES) MH^+: 391 for $C_{21}H_{30}FN_3O_3$.

Intermediate 514

{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]-1,2-benzoxazol-5-yl}methanol

Starting material: Tetrahydropyran-4-carbaldehyde

MS (ES) MH^+: 394 for $C_{20}H_{28}FN_3O_4$.

Intermediate 515

3-(benzylamino)-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-1,2-benzoxazole-5-carbaldehyde

To an ice-cooled solution of {3-(benzylamino)-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-1,2-benzoxazol-5-yl}methanol (**Intermediate 504**, 160 mg, 0.41 mmol) in acetonitrile (2 mL) was added NMO (73 mg, 1.5 mmol) followed TPAP (15 mg, 0.1 mmol) and mixture stirred for 2 hours at room temperature. The reaction mixture filtered thorough silica gel bed and washed with EtOAc. The organic phase concentrated under reduced pressure to give title compound as a yellow solid. Yield: 75 mg, (47 %).

MS(ES)MH^+: 384 for $C_{21}H_{22}FN_3O_3$

Intermediates 516 to 525 were prepared from the indicated starting material, NMO, and TPAP using a method similar to the one described for the synthesis of **Intermediate 515**:

Intermediate 516

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[(1,3-thiazol-2-ylmethyl)amino]-1,2-benzoxazole-5-carbaldehyde

Starting material: {6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[(1,3-thiazol-2-ylmethyl)amino]-1,2-benzoxazol-5-yl}methanol (**Intermediate 505**)

MS (ES) MH^+: 391 for $C_{18}H_{19}FN_4O_3S$.

Intermediate 517

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[(1*H*-imidazol-4-ylmethyl)amino]-1,2-benzoxazole-5-carbaldehyde

Starting material: {6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[(1*H*-imidazol-4-ylmethyl)amino]-1,2-benzoxazol-5-yl}methanol (**Intermediate 506**)

MS (ES) MH^+: 374.2 for $C_{18}H_{20}FN_5O_3$.

Intermediate 518

(6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-{[(1-methyl-1*H*-pyrazol-4-yl)methyl]amino}-1,2-benzoxazole-5-carbaldehyde

Starting material: (6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-{[(1-methyl-1*H*-pyrazol-4-yl)methyl]amino}-1,2-benzoxazol-5-yl)methanol (**Intermediate 507**)

MS (ES) MH^+: 388 for $C_{19}H_{22}FN_5O_3$.

Intermediate 519

(6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-{[(5-methyl-1,2-oxazol-3-yl)methyl]amino}-1,2-benzoxazole-5-carbaldehyde

Starting material: (6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-{[(5-methyl-1,2-oxazol-3-yl)methyl]amino}-1,2-benzoxazol-5-yl)methanol (**Intermediate 508**)

MS (ES) MH^+: 389 for $C_{19}H_{21}FN_4O_4$.

Intermediate 520

{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[(pyridin-2-ylmethyl)amino]-1,2-benzoxazole-5-carbaldehyde

Starting material: {6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[(pyridin-2-ylmethyl)amino]-1,2-benzoxazol-5-yl}methanol (**Intermediate 509**)

MS (ES) MH^+: 385 for $C_{20}H_{21}FN_4O_3$.

Intermediate 521

{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[(pyridin-3-ylmethyl)amino]-1,2-benzoxazole-5-carbaldehyde

Starting material: {6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[(pyridin-3-ylmethyl)amino]-1,2-benzoxazol-5-yl}methanol (**Intermediate 510**)

MS (ES) MH^+: 385 for $C_{20}H_{21}FN_4O_3$.

Intermediate 522

{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[(pyridin-4-ylmethyl)amino]-1,2-benzoxazole-5-carbaldehyde

Starting material: {6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[(pyridin-4-ylmethyl)amino]-1,2-benzoxazol-5-yl}methanol (**Intermediate 511**)

MS (ES) MH^+: 385 for $C_{20}H_{21}FN_4O_3$.

Intermediate 523

{3-[(cyclopropylmethyl) amino]-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-1,2-benzoxazole-5-carbaldehyde

Starting material: {3-[(cyclopropylmethyl) amino]-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-1,2-benzoxazol-5-yl}methanol (**Intermediate 512**)

MS (ES) MH^+: 348 for $C_{18}H_{22}FN_3O_3$.

Intermediate 524

{3-[(cyclohexylmethyl) amino]-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-1,2-benzoxazole-5-carbaldehyde

Starting material: {3-[(cyclohexylmethyl) amino]-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-1,2-benzoxazol-5-yl}methanol (**Intermediate 513**)

MS (ES) MH^+: 390 for $C_{21}H_{28}FN_3O_3$

Intermediate 525

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]-1,2-benzoxazole-5-carbaldehyde

Starting material: {6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]-1,2-benzoxazol-5-yl}methanol (**Intermediate 514**)

MS (ES) MH^+: 392 for $C_{20}H_{26}FN_3O_4$

Intermediate 526

Methyl 3,4-difluoro-2-hydroxybenzoate

A solution of 3,4-difluoro-2-hydroxybenzoic acid (6.45 g, 37.05 mmol) and sulfuric acid (6 ml, 113 mmol) in MeOH (25 ml) was heated at reflux overnight. The mixture was diluted with water and extracted with ether. The ether was washed with aqueous $NaHCO_3$, water and brine. The combined aqueous layers were twice more extracted with ether, which was washed with $NaHCO_3$, water, and brine. The combined ether extracts were dried ($MgSO_4$) and concentrated to give 6.4 g of product as a white solid.

MS (ES) MH^-: 187 for $C_8H_6F_2O_3$

^1H NMR (300 MHz, DMSO-d_6) δ: 3.9 (s, 3H), 6.9-7.1 (m, 1H), 7.65 (m, 1H), 10.8 (s, 1H).

Intermediate 527

3,4-difluoro-*N*,2-dihydroxybenzamide

A solution of hydroxylamine (50% in water) (50 ml, 816 mmol) was added to a solution of methyl 3,4-difluoro-2-hydroxybenzoate (7.75 g, 41.2 mmol) (**Intermediate 526**) in dioxane (200 ml) and the mixture was stirred at room temperature for 3 days. The mixture was partitioned between water and EtOAc. The aqueous layer was acidified with concentrated HCl and extracted with EtOAc twice more. The EtOAc layers were washed with brine, combined and concentrated to give 7.9 g of a solid.

LC-MS ES MH^+ 190 for $C_7H_5F_2NO_3$.

^1H NMR (300 MHz, DMSO-d_6) δ ppm 7.0 (ddd, 1H), 7.4-7.7 (m, 1H), 9.5 (s, 1H), 11.7 (s, 1H), 13.1 (s, 1H).

Intermediate 528

6,7-difluoro-1,2-benzisoxazol-3(2*H*)-one

A mixture of 3,4-difluoro-*N*,2-dihydroxybenzamide (**Intermediate 527**, 7.91 g, 41.8 mmol) and carbonyl diimidazole (13.6 g, 83.7 mmol) in THF (200 ml) was heated at reflux for 90 min. The mixture was partitioned between EtOAC and water and acidified with conc. HCl. The solution was extracted 3 times with EtOAc, each extract being washed with water and brine. Drying ($MgSO_4$) of the combined extracts and removal of solvent gave 6.88 g of product as an off-white solid.

MS (ES) $M-H^-$: 170 for $C_7H_3F_2NO_2$;

^1H NMR (300 MHz, DMSO-d_6) δ ppm 7.3-7.5 (m, 1H), 7.6 (m, 1H), 12.9 (s, 1H).

Intermediate 529

3-chloro-6,7-difluorobenzo[d]isoxazole

TEA (5.6 ml, 40.2 mmol) was added to an ice bath cooled mixture of 6,7-difluoro-1,2-benzisoxazol-3(2*H*)-one (**Intermediate 528,** 6.88 g, 40.2 mmol) and $POCl_3$ (13.1 ml, 141 mmol) (exotherm results) in a microwave reactor vessel and the mixture was heated at 140 °C for 6 hours in a microwave reactor. The mixture was taken up in ether and washed with Na_2CO_3 (2X) and brine. The combined aqueous layers were twice more extracted with ether, which was washed with Na_2CO_3 and brine. The combined ether layers were dried ($MgSO_4$) and concentrated to give an oil that slowly solidified. The material was chromatographed on silica gel (hexanes followed by gradient elution to 50% CH_2Cl_2 in hexanes) to afford 5.64 g of product as an off-white solid.

^1H NMR ($CDCl_3$) δ 7.2-7.35 (m, 1H), 7.4-7.5 (m, 1H).

Intermediate 530

tert-butyl 6,7-difluoro-1,2-benzisoxazol-3-yl carbonate

To a solution of 6,7-difluoro-1,2-benzisoxazol-3(2*H*)-one (**Intermediate 528,** 5.0 g, 29.2 mmol) in dry THF (50 mL), was added dimethylaminopyridine (3.5 g, 29.2 mmol) followed by Boc anhydride (12.7 g, 58.4 mmol) and the mixture heated to 65 °C for 12 hours. The reaction mixture was concentrated and the residue thus obtained was purified over silica gel column using a gradient of ethyl acetate in petroleum ether to give product as yellow solid. Yield: 4.0 g (50%).

^{1}H NMR (400MHz, DMSO-d_6) δ: 1.6 (s, 9H), 7.4 (m, 1H), 7.5(m, 1H).

Intermediate 531

tert-butyl 6,7-difluoro-5-formyl-1,2-benzisoxazol-3-yl carbonate

To a solution of diisopropylamine (3.2 g, 32.4 mmol) in THF (20mL) was added n-butyl lithium (20.2 mL, 1.6N), dropwise at -10 °C and the solution stirred for 30 min. The reaction mixture was cooled to -78 °C and into this was added, *tert*-butyl 6,7-difluoro-1,2-benzisoxazol-3-yl carbonate (**Intermediate 530,** 4.0 g, 14.7 mmol) in THF (20 mL). It was stirred at -78 °C for 2 h and then treated with dimethylformamide (3.2 g, 44.2 mmol) and continued the stirring at -78 °C for 1 hour. The reaction was quenched by the addition of saturated solution of ammonium chloride and then extracted with ethyl acetate (2 X 20 mL). The combined organic layers were washed with water followed by brine and then dried over anhydrous sodium sulfate. The solution was filtered and the filtrate evaporated under vacuum, and the residue was purified over silica gel column using a gradient of ethyl acetate in pet. ether to give product as a yellow solid Yield: 3.0 g (68%).

MS (ES) MH^+: 300 for $C_{13}H_{11}F_2NO_5$;

^{1}H NMR (400MHz, DMSO-d_6) δ: 1.6 (s, 9H), 8.0 (d, 1H), 10.1(s, 1H).

Intermediate 532

3-chloro-6,7-difluorobenzo[d]isoxazole-5-carbaldehyde

A solution of n-butyllithium (2.5 M in hexanes) (16.7 ml, 42 mmol) was added slowly to a solution of 2,2,6,6-tetramethylpiperidine (7.6 ml, 45 mmol) in THF (50 ml) cooled in a dry ice-acetone bath. The solution was warmed to 0 °C and re-cooled in a dry-ice acetone bath before transferring via syringe to a solution of 3-chloro-6,7-difluorobenzo[d]isoxazole (**Intermediate 529,** 5.64 g, 30 mmol) in THF (50 ml). After 1 hour stirring, DMF (1.0 ml, 13.2 mmol) was added all at once and the mixture was stirred with cooling in a dry-ice acetone bath for 45 min.

The mixture transferred via cannula to a solution of acetic acid (6.8 ml, 119 mmol) in 100 ml Et_2O and the mixture was warmed to room temperature. The mixture was diluted with EtOAc and washed with brine. The combined aqueous layers were extracted again with EtOAc, which was washed with brine. Drying ($MgSO_4$) of the combined extracts and removal of solvent gave a brown oil that was chromatographed on silica gel (10% CH_2Cl_2 in hexanes followed by gradient elution to 100% CH_2Cl_2) to give 3.32 g of product as a white solid.
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 8.1 (dd, 1H) 10.4 (s, 1H).

Intermediate 533

tert-butyl 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-5-formyl-2,3-dihydro-1,2-benzisoxazol-3-yl carbonate

To an ice cooled and stirred solution of *tert*-butyl 6,7-difluoro-5-formyl-1,2-benzisoxazol-3-yl carbonate (**Intermediate 531,** 3.0 g, 10.0 mmol) in anhydrous acetonitrile was added DIPEA (2.56 g, 20.0 mmol) followed by *cis* 2,6-dimethylmorpholine (1.27 g, 11.0 mmol) and the mixture heated at 80 °C for 12 hours. It was cooled to room temperature and concentrated. The residue was dissolved in ethyl acetate, washed with water followed by brine and then dried over anhydrous sodium sulfate. It was filtered and the filtrate evaporated under reduced pressure. The residue was purified on a silica gel column using a gradient of ethyl acetate in pet.ether to give product as a solid. Yield: 2.9 g (74%).
MS (ES) MH^+: 395 for $C_{13}H_{11}F_2NO_5$;
^{1}H NMR (400MHz, DMSO-d_6) δ: 1.0 (d, 6H), 1.6 (s, 9H), 2.9 (t, 2H), 3.1(d, 2H), 3.8 (m, 2H), 7.7 (s,1H), 10.2(s, 1H).

Intermediate 534

3-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-1,2-benzoxazole-5-carbaldehyde

To an ice cooled and stirred solution of 3-chloro-6,7-difluorobenzo[d]isoxazole-5-carbaldehyde (**Intermediate 532,** 1.0 g, 8.75 mmol) in anhydrous acetonitrile was added DIPEA (1.8 mL, 10.5 mmol) followed by *cis* 2,6-dimethylmorpholine (1.3 mL, 10.5 mmol) and the mixture heated at 85 °C for 4 hours. It was cooled to room temperature and concentrated. The residue was dissolved in ethyl acetate, washed with water followed by brine and then dried over anhydrous sodium sulfate. It was filtered and the filtrate evaporated under reduced pressure. The residue was

purified over silica gel column using a gradient of ethylacetate in pet.ether to give title compound as solid. Yield: 2.3 g (85%).

MS (ES) MH^+: 313 for $C_{14}H_{14}ClFN_2O_3$;

^1H NMR (400MHz, DMSO-d_6) δ: 1.0 (d, 6H), 2.9 (t, 2H), 3.1 (d, 2H), 3.8 (m, 2H), 7.7 (s, 1H), 10.2 (s, 1H).

Intermediate 535

3-chloro-6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-5-carbaldehyde

A solution of 3-chloro-6,7-difluorobenzo[d]isoxazole-5-carbaldehyde (**Intermediate 532,** 3.32 g, 10.6 mmol), (2*R*,6*R*)-2,6-dimethylmorpholine (Purchased from BASF®, 2.64 g, 22.9 mmol) and DIEA (4 ml, 22.9 mmol) in acetonitrile (20 ml) was heated at reflux for 3 hours. The mixture was cooled to room temperature before being partitioned between EtOAc and 1N HCl. The EtOAc was separated and washed with brine. The combined aqueous layers were extracted with EtOAc, which was washed with brine. The combined EtOAc was dried ($MgSO_4$) and concentrated to give an oil that was chromatographed on silica gel (50% hexanes in CH_2Cl_2 followed by gradient elution to 100% CH_2Cl_2 followed by gradient elution to 5% EtOAc in CH_2Cl_2) to give 2 materials in order of elution: the first material (265 mg) is consistent with starting material and the second (3.33 g) with desired product.

LC-MS ES MH^+: 313

^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.3 (d, 6H) 3.1 (m, 2H) 3.4 (m, 2H) 4.2 (m., 2H) 8.0 (s, 1H) 10.45 (s, 1H).

Intermediates 536 to 538 were prepared from the indicated startng material using a method similar to the one described for the synthesis of **Intermediate 535**:

Intermediate 536

6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-3-methylbenzo[d]isoxazole-5-carbaldehyde

Starting materials: 6,7-difluoro-3-methylbenzo[d]isoxazole-5-carbaldehyde (Intermediate 374) and (2*R*,6*R*)-2,6-dimethylmorpholine.

MS (ES) MH^+: 293 for $C_{15}H_{17}FN_2O_3$

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.3 (d, 6H), 2.6 (s, 3H), 2.9-3.1 (m, 2H) 3.4 (m, 2H) 4.2 (m, 2H) 8.0 (s, 1H) 10.5 (s, 1H).

Intermediate 537

6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-3-(1-methyl-1*H*-1,2,4-triazol-5-yl)benzo[d]isoxazole-5-carbaldehyde

Starting materials: 6,7-difluoro-3-(1-methyl-1*H*-1,2,4-triazol-5-yl)benzo[d]isoxazole-5-carbaldehyde (**Intermediate 404**) and (2*R*,6*R*)-2,6-dimethylmorpholine.

MS (ES) MH^+: 360 for $C_{17}H_{18}FN_5O_3$

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.3 (d, 6H), 3.1 (dd, 2H), 3.5 (d, 2H) 4.3 (td, 2H), 4.4 (s, 3H), 8.1 (s, 1H), 8.7 (s, 1H), 10.5 (s, 1H).

Intermediate 538

6-((3S,5*R*)-3,5-dimethylpiperidin-1-yl)-7-fluoro-3-methylbenzo[d]isoxazole-5-carbaldehyde

Starting materials: 6,7-difluoro-3-methylbenzo[d]isoxazole-5-carbaldehyde (**Intermediate 374**) and (3S,5*R*)-3,5-dimethylpiperidine (HCl Salt).

MS (ES) MH^+: 291 for $C_{16}H_{19}FN_2O_2$

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.7-0.9 (q, 1H), 0.94 (d, 6H), 1.9 (m, 4H), 2.6 (s, 3H), 2.8-3.0 (m, 2H), 3.2-3.3 (m, 2H), 7.9 (s, 1H), 10.3 (s, 1H).

Intermediate 539

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(1*H*-1,2,4-triazol-1-yl)-1,2-benzoxazole-5-carbaldehyde

To a solution of 3-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-1,2-benzoxazole-5-carbaldehyde (**Intermediate 534,** 0.2 g, 0.68 mmol) in acetonitrile was added DBU (0.19 mL, 1.28 mmol) followed by 1,2,4-triazole (0.053 g, 0.76 mmol), and the mixture was stirred at 100° C for 12 hours.. The reaction mixture was concentrated, the residue was purified by silica gel column chromatography using EtOAc in pet. ether to give title product.

Yield: 35 mg (16 %);

MS (ES) MH^+: 346 for $C_{16}H_{16}FN_5O_3$;

^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.0 (d, 6H), 3.0 (t, 2H), 3.3 (m, 2H), 3.8 (m, 2H), 8.4 (s, 1H), 8.6 (s, 1H), 9.6 (s, 1H), 10.2(s,1H).

Intermediates 540 to 552 were prepared from the indicated starting material, DBU and 3-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-1,2-benzoxazole-5-carbaldehyde (**Intermediate 534**) using a method similar to the one described for the synthesis of **Intermediate 539**:

Intermediate 540

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(3-methyl-1*H*-1,2,4-triazol-1-yl)-1,2-benzoxazole-5-carbaldehyde

Starting material: 3-methyl-1,2,4-triazole

MS (ES) MH^+: 360 for $C_{17}H_{18}FN_5O_3$

Intermediate 541

1-{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-5-formyl-1,2-benzoxazol-3-yl}-1*H*-1,2,4-triazole-3-carbonitrile

Starting material: 3-cyano-1,2,4-triazole

MS (ES) MH^+: 371 for $C_{17}H_{15}FN_6O_3$

^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.0 (d, 6H), 3.0 (m, 2H), 3.3 (m, 2H), 3.8 (m, 2H), 8.3 (s, 1H), 10.0 (s, 1H), 10.2 (s,1H).

Intermediate 542 and Intermediate 543

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(1*H*-1,2,3-triazol-1-yl)-1,2-benzoxazole-5-carbaldehyde (**Intermediate 542**) and 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(1*H*-1,2,3-triazol-2-yl)-1,2-benzoxazole-5-carbaldehyde (**Intermediate 543**)

Starting material: 1,2,3-triazole

MS (ES) MH^+: 346 for $C_{16}H_{16}FN_5O_3$

^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.1 (d, 6H), 3.0 (m, 2H), 3.3 (m, 2H), 3.8 (m, 2H), 8.2 and 9.1 (2s, total of 1H), 8.4 (2s, total of1H), 8.5 (s, 1H), 10.3 (s, 1H).

Intermediate 544

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(1*H*-imidazol-1-yl)-1,2-benzoxazole-5-carbaldehyde

Starting material: imidazole

MS (ES) MH^+: 345.2 for $C_{17}H_{17}FN_4O_3$.

Intermediate 545

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[4-(trifluoromethyl)-1*H*-imidazol-1-yl]-1,2-benzoxazole-5-carbaldehyde

Starting material: 4-(trifluromethyl)-imidazole

MS (ES) MH^+: 359 for $C_{18}H_{19}FN_4O_3$

Intermediate 546

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(4-methyl-1*H*-pyrazol-1-yl)-1,2-benzoxazole-5-carbaldehyde

Starting material: 4-methyl-pyrazole

MS (ES) MH^+: 413.2 for $C_{18}H_{16}F_4N_4O_3$

Intermediate 547

3-(4-chloro-1*H*-pyrazol-1-yl)-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-1,2-benzoxazole-5-carbaldehyde

Starting material: 4-chloro-pyrazole

MS (ES) MH^+: 379 for $C_{17}H_{16}ClFN_4O_3$

Intermediate 548

3-amino-1-{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-5-formyl-1,2-benzoxazol-3-yl}-1*H*-pyrazole-4-carbonitrile

Starting material: 3-amino-1*H*-pyrazole-4-carbonitrile

MS (ES) MH^+: 385 for $C_{18}H_{17}FN_6O_3$

Intermediate 549

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[4-(pyrimidin-4-yl)-1*H*-pyrazol-1-yl]-1,2-benzoxazole-5-carbaldehyde

Starting material: 4-(1*H*-pyrazol-4-yl)pyrimidine

MS (ES) MH^+: 423 for $C_{21}H_{19}FN_6O_3$;

Intermediate 550

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[4-(pyrazin-2-yl)-1*H*-pyrazol-1-yl]-1,2-benzoxazole-5-carbaldehyde

Starting material: 2-(1*H*-pyrazol-4-yl)pyrazine.

MS (ES) MH^+: 423 for $C_{21}H_{19}FN_6O_3$;

Intermediate 551

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(4-iodo-1*H*-pyrazol-1-yl)-1,2-benzoxazole-5-carbaldehyde

Starting material: 4-iodo-pyrazine.

MS (ES) MH^+: 470 for $C_{17}H_{16}FIN_4O_3$

Intermediate 552

ethyl 1-{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-5-formyl-1,2-benzoxazol-3-yl}-1*H*-pyrazole-4-carboxylate

Starting material: ethyl -pyrazole-4-carboxylate.

MS (ES) MH^+: 416 for $C_{20}H_{21}FN_4O_5$

Intermediate 553

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(methylsulfanyl)-1,2-benzoxazole-5-carbaldehyde

To an ice cold solution of 3-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-1,2-benzoxazole-5-carbaldehyde (**Intermediate 534,** 0.3 g, 0.916 mmol) in dioxane was added sodium thiomethoxide (21% aq solution, 0.134 mL, 1.923 mmol) and stirred at room temperature for 12 hours. Reaction mixture was diluted with water and extracted with EtOAc (50 mL).

Organic phase washed with brine (2x 10 mL), dried over anhydrous sodium sulfate and, filtered, concentrated to give tilt product as white solid. Yield: 280 mg (90%).

MS (ES) MH^+: 325 for $C_{15}H_{17}FN_2O_3S$

^1H NMR (400 MHz, DMSO-d_6) δ: 1.1 (d, 6H), 2.7 (s, 3H), 3.0 (m, 2H), 3.2 (m, 2H), 3.8 (m, 2H), 7.9 (s, 1H), 10.2 (s,1H).

Intermediate 554

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-7-fluoro-1,2-benzoxazole-5-carbaldehyde

To a stirred and degassed solution of 3-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-1,2-benzoxazole-5-carbaldehyde (**Intermediate 534,** 0.15 g, 0.48 mmol) in toluene was added K_3PO_4 (0.51 g, 2.40 mmol), 3,5-dimethyl-1*H*-pyrazole (92 mg, 0.96 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (S-phos) (4 mg, 0.009 mmol) and tris(dibenzylideneacetone) dipalladium(0) (8 mg, 0.009 mmol), sequentially and the reaction mixture was heated to 150 °C for 2 h in microwave reactor. The reaction mixture was diluted with EtOAc (15 mL). The organic layer was washed successively with water (2x10 mL), brine (2x10 mL), dried over anhydrous Na_2SO_4 and, after filtration, concentrated. The residue was purified over silica gel column using a gradient of ethylacetate in pet.ether to give product title compound as solid. Yield: 100 mg (56 %).

MS (ES) MH^+: 373.5 for $C_{19}H_{21}FN_4O_3$;

^1H NMR (400 MHz, DMSO-d_6) δ: 1.1 (d, 6H), 2.3 (s, 3H), 2.6 (s, 3H), 3.0 (t, 2H), 3.3 (m, 2H), 3.8 (m, 2H), 6.3 (s, 1H), 8.5 (s, 1H), 10.25 (s,1H).

Intermediate 555

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(1*H*-pyrazol-4-yl)-1,2-benzoxazole-5-carbaldehyde

1*H*-pyrazole-4-boronic acid pinacolate ester, 3-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-1,2-benzoxazole-5-carbaldehyde (**Intermediate 534**), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (S-phos), and tris(dibenzylideneacetone) dipalladium(0) were reacted using a method similar to the one described for the synthesis of **Intermediate 554.**

MS (ES) MH^+: 345 for $C_{17}H_{17}FN_4O_3$

^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.25 (d, 6H), 3.2 (m, 4H), 3.9 (m, 2H), 6.6 (m, 1H), 7.9 (s, 1H), 8.3 (s, 1H), 8.7 (s, 1H), 10.35 (s,1H).

Intermediate 556

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-hydroxy-1,2-benzisoxazole-5-carbaldehyde

To a stirred solution of *tert*-butyl 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-5-formyl-2,3-dihydro-1,2-benzisoxazol-3-yl carbonate (**Intermediate 533,** 0.5 g, 1.2 mmol) in methanol (5 ml) was added 5 ml of 5% aqueous HCl before heating at 75 °C for 2 hours. The reaction mixture was quenched with 10% aqueous sodium bicarbonate solution and extracted with EtOAc. The organic layer were washed with water, dried (sodium sulfate), and concentrated. The residue purified over a silica gel flash column (elution with 50-70% EtOAc in hexanes) to give product.

Yield: 0.4 g, (100 %).

MS (ES) MH^+: 295 for $C_{14}H_{15}FN_2O_4$.

^{1}H NMR (400MHz, DMSO-d_6) δ: 1.0 (d, 6H), 2.9 (t, 2H), 3.2 (d, 2H), 3.8 (m, 2H), 7.9 (s, 1H), 10.2(s, 1H).

Intermediate 557

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-methoxy-1,2-benzisoxazole-5-carbaldehyde

To a solution of 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-hydroxy-1,2-benzisoxazole-5-carbaldehyde (**Intermediate 556,** 0.15 g, 0.5 mmol) in acetonitrile was added K_2CO_3 (0.08 g, 0.6 mmol) followed by MeI (0.07 mL, 0.5 mmol). The reaction mixture was stirred at 60°C for 2 hours. The reaction mixture was concentrated, washed with water and extracted with EtOAc (2 x 10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated to provide the title product, along with a by-product, 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-2-methyl-3-oxo-2,3-dihydro-1,2-benzoxazole-5-carbaldehyde. The mixture was used in the next step with out further purification.

Yield: 120 mg (76 %)

MS (ES) MH^+: 309.2 for $C_{15}H_{17}FN_2O_4$.

S)-)

Intermediate 558

3-(benzyloxy)-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-1,2-benzisoxazole-5-carbaldehyde

Benzyl bromide and 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-hydroxy-1,2-benzisoxazole-5-carbaldehyde (**Intermediate 556**) were reacted using a method similar to the one described for the synthesis of **Intermediate 557**, providing the title product, along with a by-product, 2-benzyl-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-oxo-2,3-dihydro-1,2-benzoxazole-5-carbaldehyde. The mixture was used in the next step with out further purification.
MS (ES) MH^+: 385 for $C_{21}H_{21}FN_2O_4$.

Intermediate 559

3-(4-acetylpiperazin-1-yl)-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-2,3-dihydro-1,2-benzisoxazole-5-carbaldehyde

To a solution of 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-hydroxy-1,2-benzisoxazole-5-carbaldehyde (**Intermediate 556,** 0.15 g, 0.5 mmol) in acetonitrile was added BOP (0.275 g, 0.66 mmol) followed by DBU (0.23 g, 1.53 mmol), and the mixture was stirred for 10 minutes at room temperature. To this mixture was added the *N*-acetyl-piperizine (0.09 g, 0.71 mmol), and the mixture was stirred for 12 h at room temperature. The reaction mixture was concentrated, diluted with water and extracted with EtOAc (2 x 10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue thus was purified by silica gel column chromatography using EtOAc in pet. ether to give product.
Yield: 25 mg (12 %);
MS (ES) MH^+: 405 for $C_{20}H_{25}FN_4O_4$.

Intermediates 560 to 573 were prepared from the indicated starting material and 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-hydroxy-1,2-benzisoxazole-5-carbaldehyde (**Intermediate 556**) using a method similar to the one described for the synthesis of **Intermediate 559**:

Intermediate 560

tert-butyl 4-{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-5-formyl-1,2-benzisoxazol-3-yl}piperazine-1-carboxylate

Starting material: *tert*-Butyl 1-piperazinecarboxylate.

MS (ES) MH^+: 463 for $C_{23}H_{31}FN_4O_5$

Intermediate 561

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(piperidin-1-yl)-1,2-benzisoxazole-5-carbaldehyde

Starting material: piperidine.

MS (ES) MH^+: 362 for $C_{19}H_{24}FN_3O_3$.

Intermediate 562

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(morpholin-4-yl)-1,2-benzisoxazole-5-carbaldehyde

Starting material: morpholine.

MS (ES) MH^+: 364 for $C_{18}H_{22}FN_3O_4$.

Intermediate 563

3-(diethylamino)-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-1,2-benzisoxazole-5-carbaldehyde

Starting material: *N,N*-diethylamine.

MS (ES) MH^+: 350 for $C_{18}H_{24}FN_3O_3$.

Intermediate 564

3-(dimethylamino)-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-1,2-benzisoxazole-5-carbaldehyde

Starting material: *N,N*-dimethyl amine.

MS (ES) MH^+: 322.2 for $C_{16}H_{20}FN_3O_3$.

Intermediate 565

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(pyrrolidin-1-yl)-1,2-benzisoxazole-5-carbaldehyde

Starting material: pyrrolidine.

MS (ES) MH^+: 348 for $C_{18}H_{22}FN_3O_3$;

^1H NMR (400 MHz, DMSO-d_6) δ: 1.0 (d, 6H), 2.0 (t, 4H), 2.9 (m, 2H), 3.2 (d, 2H), 3.6 (t, 4H), 3.8 (m, 2H), 8.0 (s, 1H), 10.2 (s,1H).

Intermediate 566

3-(azepan-1-yl)-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-1,2-benzisoxazole-5-carbaldehyde

Starting material: azepane.

MS (ES) MH^+: 350.2 for $C_{20}H_{26}FN_3O_3$.

Intermediate 567

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]-1,2-benzisoxazole-5-carbaldehyde

Starting material: 3-methyl-5-(trifluoromethyl) pyrazole.

MS (ES) MH^+: 427 for $C_{19}H_{18}F_4N_4O_3$.

Intermediate 568

N-[1-[6-[(2S,6*R*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-5-formyl-1,2-benzoxazol-3-yl]pyrazol-3-yl]acetamide

Starting material: *N*-1*H*-pyrazol-3-ylacetamide

MS (ES) MH^+: MS (ES) MH^+: 402 for $C_{19}H_{20}FN_5O_4$

Intermediate 569

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]-1,2-benzisoxazole-5-carbaldehyde

Starting material: (3-(trifluoromethyl) pyrazole.

MS (ES) MH^+: 413 for $C_{18}H_{16}F_4N_4O_3$.

Intermediate 570

3-[3-(difluoromethyl)-1*H*-pyrazol-1-yl]-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-1,2-benzisoxazole-5-carbaldehyde

Starting material: 3-(difluoromethyl)-5-methyl pyrazole.
MS (ES) MH^+: 409 for $C_{19}H_{19}F_3N_4O_3$.

Intermediate 571

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(propylamino)-1,2-benzoxazole-5-carbaldehyde

Starting material: *N*-propylamine
MS (ES) MH^+: 336 for $C_{17}H_{22}FN_3O_3$.

Intermediate 572

3-[benzyl(methyl)amino]-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-1,2-benzoxazole-5-carbaldehyde

Starting material: *N*-Methyl-1-benzylamine
MS (ES) MH^+: 463 for $C_{22}H_{24}FN_3O_3$.

Intermediate 573

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[methyl(propyl)amino]-1,2-benzoxazole-5-carbaldehyde

Starting material: *N*-Methyl-propane-1-amine
MS (ES) MH^+: 362 for $C_{18}H_{24}FN_3O_3$.

Intermediate 574

6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-3-(1*H*-1,2,4-triazol-1-yl)benzo[d]isoxazole-5-carbaldehyde

Sodium hydride (60% dispersion) (0.288 g, 7.19 mmol) was added to a solution of 1*H*-1,2,4-triazole (0.530 g, 7.67 mmol) and 3-chloro-6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-5-carbaldehyde (**Intermediate 535,** 1.5 g, 4.80 mmol) in DMF (10 ml), and the mixture was stirred at room temperature overnight. The mixture was quenched with aqueous NH_4Cl and diluted with water before being extracted with CH_2Cl_2 5 times. The combined extracts were dried ($MgSO_4$) and concentrated to give a solid that was taken up in CH_2Cl_2. Insoluble solids were filtered off and rinsed with additional CH_2Cl_2. The solids were

dried in vacuo and were consistent with desired product. The filtrate was concentrated and chromatographed on silica gel (100% CH_2Cl_2 followed by gradient elution to 50% EtOAc in CH_2Cl_2) to give additional desired product. Total of 866 mg.

MS (ES) MH^+: 345 for $C_{16}H_{16}FN_5O_3$

^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.3 (d, 6H), 3.0-3.2 (m, 2H), 3.4-3.6 (m, 2H), 4.25 (m, 2H), 8.3 (s, 1H), 8.6 (d, 1H), 9.0 (s, 1H), 10.4 (s, 1H).

Intermediate 575

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-g]quinoline-5,5'-pyrimidine]-8-carbothioamide

To a stirred solution of (2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*] quinoline-5,5'-pyrimidine]-8-carbonitrile (**Example 183**, 210 mg, 0.51 mmol) in DMF was added ammonium sulfide (0.35 mL, 1.02 mmol) and the mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated to give product as a pale yellow solid.

Yield: 215 mg (97%).

MS (ES) MH^+: 448 for $C_{19}H_{18}FN_5O_5S$;

^1H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 2.9 (d, 1H), 3.1 (m, 1H), 3.7 (m, 1H), 3.8 (m, 2H), 4.0 (d, 1H), 4.1(d, 1H), 7.6 (s, 1H), 10.0 (s, 1H), 10.35 (s, 1H), 11.5 (s, 1H), 11.8 (s, 1H).

When tested in an in-vitro assay based on the DNA gyrase supercoiling activity fluorescence polarisation assay described above, **Intermediate 575** had *E. coli* DNA gyrase supercoiling IC_{50} assay inhibitory activity measured at 1.0 μM.

Intermediate 576

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-methyl-1,2-benzothiazole-5-carbaldehyde

To an ice-cooled solution of {6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-methyl-1,2-benzothiazol-5-yl}methanol (**Intermediate 157,** 0.18 g, 0.6 mmol) in DCM/CH_3CN mixture (3 mL, 1:1 v/v) was added NMO (0.12 g, 0.7 mmol) followed TPAP (0.04, 0.2 mmol) and mixture stirred for 2 h at room temperature. The reaction mixture filtered through silica gel bed and

washed with EtOAc. The organic phase concentrated under reduced pressure to give title compound as a yellow crystalline solid. Yield: 0.12 g (67%).

MS (ES) MH^+: 309 for $C_{15}H_{17}FN_2O_2S$

^1H NMR (400 MHz, Methanol-d_4): δ 1.2 (d, 6H), 2.7 (s, 3H), 3.1 (m, 2H), 3.2 (m, 2H), 3.9 (m, 2H), 8.3 (s, 2H), 10.5 (s, 1H).

Intermediate 577 was prepared from the indicated starting material using a method similar to the one described for the synthesis of **Intermediate 576**:

Intermediate 577

6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(pyridin-2-yl)-1,2-benzothiazole-5-carbaldehyde

Starting material: {6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(pyridin-2-yl)-1,2-benzothiazol-5-yl}methanol (**Intermediate 158**)

MS (ES) MH^+: 372 for $C_{19}H_{18}FN_3O_2S$

^1H NMR (400 MHz, $CDCl_3$) δ: 1.24 (d, 6H), 3.1 (d, 4H), 3.9 (m, 2H), 7.4 (m, 1H), 7.9 (t, 1H), 8.3 (d, 1H), 8.8 (d, 1H), 9.4 (s, 1H), 10.5 (s, 1H).

Intermediate 578 was prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 62**:

Intermediate 578

{5-({[*tert*-Butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(pyrazin-2-yl)methanol

Starting material: (2*R*,6*S*)-4-[6-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-2,3-difluoro phenyl]-2,6-dimethylmorpholine (**Intermediate 3**) and pyrazine-2-carboxaldehyde.

MS (ES) MH^+: 604.8 for $C_{34}H_{39}F_2N_3O_3Si$

Intermediate 579 was prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 20**:

Intermediate 579

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(pyrazin-2-yl)methanone

Starting material: {5-({[*tert*-Butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(pyrazin-2-yl)methanol (**Intermediate 578**).

MS (ES) MH^+: 602.8 for $C_{34}H_{37}F_2N_3O_3Si$

Intermediate 580 was prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 23**:

Intermediate 580

{4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluoro-5-(hydroxymethyl)phenyl} (pyrazin-2-yl)methanone

Starting material: {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(pyrazin-2-yl)methanone (**Intermediate 579**)

MS (ES) MH^+: 364.4 for $C_{18}H_{19}F_2N_3O_3$

Intermediate 581 was prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 26**:

Intermediate 581

2-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3,4-difluoro-5-(pyrazin-2-ylcarbonyl)benzaldehyde

Starting material: {4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluoro-5-(hydroxymethyl)phenyl}(pyrazin-2-yl)methanone (**Intermediate 580**)

MS (ES) MH^+: 362.4 for $C_{18}H_{17}F_2N_3O_3$

Intermediate 582 was prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 12**:

Intermediate 582

(2*R*,4*S*,4a*S*)-rel-9,10-difluoro-2,4-dimethyl-8-(pyrazin-2-ylcarbonyl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

Starting material: 2-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3,4-difluoro-5-(pyrazin-2-ylcarbonyl)benzaldehyde (**Intermediate 581**).

MS (ES) MH^+: 472.4 for $C_{22}H_{19}F_2N_5O_5$

Intermediate 583 was prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 29**:

Intermediate 583

(2*R*,4*S*,4a*S*)-rel-9,10-difluoro-8-[(hydroxyimino)(pyrazin-2-yl)methyl]-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

Starting material: (2*R*,4*S*,4a*S*)-rel-9,10-difluoro-2,4-dimethyl-8-(pyrazin-2-ylcarbonyl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione (**Intermediate 582**).

MS (ES) MH^+: 487.4 for $C_{22}H_{20}F_2N_6O_5$

Intermediate 584 was prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 62**:

Intermediate 584

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(pyrimidin-2-yl)methanone

Starting materials: (2*R*,6*S*)-4-[6-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-2,3-difluorophenyl]-2,6-dimethylmorpholine (**Intermediate 3**) and *N*-methoxy-*N*-methylpyrimidine-2-carboxamide (prepared according to the procedure shown in PCT Pub. No. WO03/059911).

MS (ES) MH^+: 603 for $C_{34}H_{37}F_2N_3O_3Si$

Intermediate 585 was prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 336**:

Intermediate 585

{5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-fluoro-2-[(propan-2-ylideneamino)oxy]phenyl}(pyrimidin-2-yl)methanone

Starting material: {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2,3-difluorophenyl}(pyrimidin-2-yl)methanone (**Intermediate 584**)

MS (ES) MH^+: 655.8 for $C_{37}H_{43}FN_4O_4Si$

Intermediate 586 was prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 33**:

Intermediate 586

{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(pyrimidin-2-yl)-1,2-benzoxazol-5-yl}methanol

Starting material: {5-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-fluoro-2-[(propan-2-ylideneamino)oxy]phenyl}(pyrimidin-2-yl)methanone (**Intermediate 585**).

MS (ES) MH^+: 359.4 for $C_{18}H_{19}FN_4O_3$

Intermediate 587 was prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Intermediate 27**:

Intermediate 587

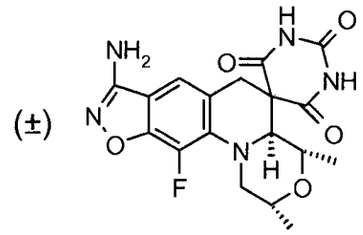
6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(pyrimidin-2-yl)-1,2-benzoxazole-5-carbaldehyde

Starting material: {6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(pyrimidin-2-yl)-1,2-benzoxazol-5-yl}methanol (**Intermediate 586**)

MS (ES) MH^+: 357.4 for $C_{18}H_{17}FN_4O_3$

Example 1

(2*R*,4*S*,4a*S*)-rel-8-amino-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione



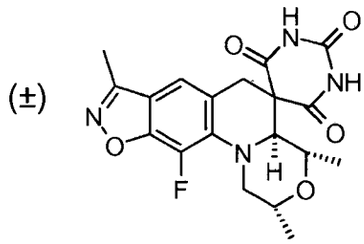
To a solution of 3-amino-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-1,2-benzisoxazole-5-carbaldehyde (**Intermediate 8**, 100 mg, 0.34 mmol) in IPA was added barbituric acid (48 mg, 0.34 mmol) and the mixture heated at 85 °C for 12 hours. Solvents were evaporated and the residue was purified over neutral alumina using a gradient of methanol in CH_2Cl_2 to give the title compound as a racemic mixture in the form of a pale yellow solid. Yield: 18 mg, (13 %).

MS (ES) $(M-H)^-$: 402.6 for $C_{18}H_{18}FN_5O_5$

^1H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 2.9 (d, 1H), 3.0 (t, 1H), 3.4 (d, 1H), 3.6 (t, 1H), 3.75 (d, 1H), 3.9 (d, 1H), 4.0 (d, 1H), 6.2 (bs, 2H), 7.1 (s, 1H), 11.4 (s, 1H), 11.8 (s, 1H).

Example 2

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4,8-trimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione



To a solution of (2*R*,4*S*,4a*S*)-rel-9,10-difluoro-8-[(1*E*)-*N*-hydroxyethanimidoyl]-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione (**Intermediate 16,** 250 mg, 0.63 mmol) in DMSO, was added K-O-*t*-Bu (47 mg, 0.636 mmol) and the mixture was heated to 120 °C for 12 hours. After cooling to room temperature and removal of solvent, the residue was purified using normal phase HPLC (95:5: Hexane:IPA) to

give the title compound as a racemic mixture in the form of a pale yellow solid. Yield: 50 mg (20%).

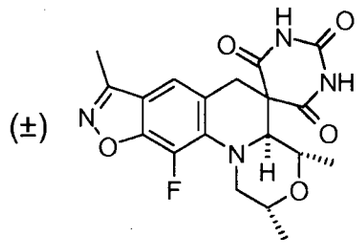
MS (ES) MH^+: 403.2 for $C_{19}H_{19}FN4O_5$

^1H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 2.4 (d, 3H), 2.5 (d, 1H), 2.9 (t, 1H), 3.5 (d, 1H), 3.6 (m, 1H), 3.8 (d, 1H), 3.9 (d, 1H), 4.0 (d, 1H), 7.2 (s, 1H), 11.4 (s, 1H), 11.8 (s, 1H).

Example 2 was also prepared using the following synthesis:

Example 2 (Alternate Preparation)

(2*R*,4*S*,4a*S*) -rel-11-fluoro-2,4,8-trimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'*H*)-trione



To a stirred solution of 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-methylbenzo[d]isoxazole-5-carbaldehyde (**Intermediate 34,** 543 mg, 1.86 mmol) in isopropanol (50 ml) was added pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (238 mg, 1.86 mmol), and the reaction mixture was stirred for 16 hours at 80° C. Solvent was removed and the residue was triturated with isopropanol. The solid was filtered, washed with isopropanol, and dried in vacuo. The filtrate was concentrated and purified on silica gel (30-50% EtOAc in hexanes). The product thus obtained was combined with the filtered solid in methanol and concentrated to give the title compound (528 mg, 71%) as a racemic mixture.

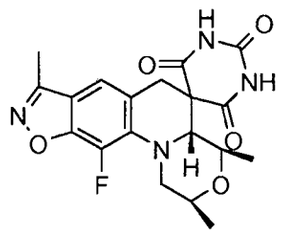
MS (ES): 403 (M+H) for $C_{19}H_{19}FN_4O_5$

^1H NMR (400 MHz, DMSO-d_6) d ppm 0.9 (d, 3H) 1.1 (d, 3H) 2.4 (s, 3H), 2.9 - 4.2 (m, 7H) 7.2 (s, 1H) 11.4 (s, 1H) 11.8 (s, 1H).

The (2*S*,4*R*,4a*R*) and (2*R*,4*S*,4a*S*) enantiomers of **Example 2** were separated by Supercritical Fluid Chromatography using a Chiralpak AD, 21 x 250mm, 5μ column (elution with 20%

MeOH, 80% CO_2 at 60 ml/min, 40°C, and 100 bar with detection at 220nm), providing **Example 2(a)** and **Example 2(b)**:

Example 2(a) - First Eluting Compound (2*S*,4*R*,4a*R*)-11-fluoro-2,4,8-trimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione



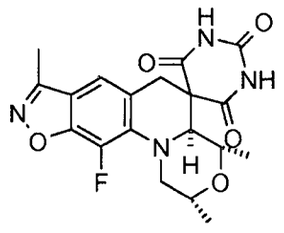
MS (ES): 403 (M+H) for $C_{19}H_{19}FN_4O_5$

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.9 (d, 3H) 1.1 (d, 3H) 2.4 (s, 3H) 2.9 - 4.2 (m, 7H) 7.2 (s, 1H) 11.6 (s, broad, 2H).

yield: (202 mg, 40%).

>98% ee by chiral HPLC; [α] = +296 (c=0.1 in MeOH).

Example 2(b) - Second Eluting Compound (2*R*,4*S*,4a*S*)-11-fluoro-2,4,8-trimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione



MS (ES): 403 (M+H) for $C_{19}H_{19}FN_4O_5$

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.9 (d, 3H) 1.1 (d, 3H) 2.4 (s, 3H) 2.9 - 4.2 (m, 7 H) 7.2 (s, 1 H) 11.6 (s, broad, 2 H).

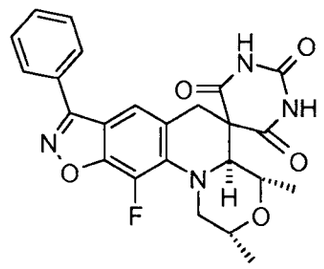
yield: (199 mg, 39%).

>98% ee by chiral HPLC; [α] = -291 (c=0.1 in MeOH).

Example 3

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-phenyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

(±)



Cs_2CO_3 (130 mg, 0.0004 mmol) was added to a solution of (2*R*,4*S*,4a*S*)-rel-9,10-difluoro-8-[(*E*)-(hydroxyimino)(phenyl)methyl]-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione (**Intermediate 29,** 100 mg, 0.0002 mmol) in DMF (1.5 mL), and the mixture was heated to 100 °C for 14h. The reaction mixture was cooled to room temperature and filtered through a Celite bed. The solvent was removed, and the residue was subjected to reverse phase prep-HPLC purification (10 mM ammonium acetate in water, CH_3CN) providing the title compound as a racemic mixture. Yield: 9.97 g (9 %).

MS (ES) MH^+: 465.2 for $C_{24}H_{21}FN_4O_5$

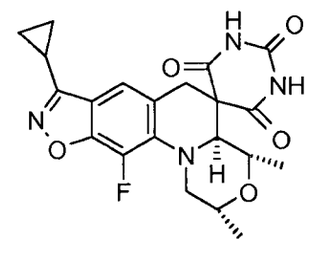
^1H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 3.0 (d, 1H), 3.1 (t, 1H), 3.6 (d, 1H), 3.7 (m, 1H), 3.75 (m, 1H), 3.9 (d, 1H), 4.1 (d, 1H), 7.6 (m, 4H), 7.9 (s, 2H), 11.5 (bs, 2H).

Examples 4 and **5** were prepared from the indicated starting materials using a method similar to the one described for the syntheses of **Example 3**. Each was obtained as a racemic mixture.

Example 4

(2*R*,4*S*,4a*S*)-rel-8-cyclopropyl-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

(±)



Starting material: (2*R*,4*S*,4a*S*)-rel-8-[(*E*)-Cyclopropyl(hydroxyimino)methyl]-9,10-difluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione (**Intermediate 31**).

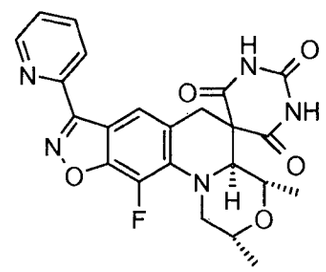
MS (ES) MH^+: 429.1 for $C_{21}H_{21}FN_4O_5$

^1H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.0 (m, 4H), 1.1 (d, 3H), 2.2 (m, 1H), 2.9 (d, 1H), 3.1 (t, 1H), 3.6 (d, 1H), 3.7 (m, 1H), 3.75 (m, 1H), 3.9 (d, 1H), 4.1 (d, 1H), 7.2 (s, 1H), 11.0 (bs, 2H).

Example 5

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-pyridin-2-yl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

(±)



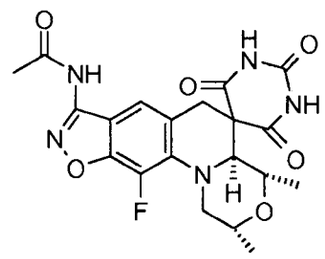
Starting material: (2*R*,4*S*,4a*S*)-rel-9,10-Difluoro-8-[(Z)-(hydroxyimino)(pyridin-2-yl)methyl]-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione (**Intermediate 30**).

MS (ES) MH^+: 466.2 for $C_{23}H_{20}FN_5O_5$

^1H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 2.9 (d, 1H), 3.1 (t, 1H), 3.6 (m, 1H), 3.7 (m, 1H), 3.75 (m, 1H), 4.0 (d, 1H), 4.1 (d, 1H), 7.6 (m, 1H), 7.8 (s, 1H), 8.0 (t, 1H), 8.1 (d, 1H), 8.8 (d, 1H), 11.4 (bs, 2H).

Example 6

N-[(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidin]-8-yl]acetamide

(±) 

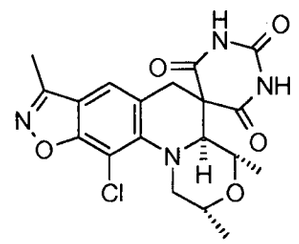
Pyridine (0.01 mL, 0.2 mmol) and acetic anhydride (0.10 mL, 0.14 mmol) were added sequentially to a solution of (2*R*,4S,4a*S*)-rel-8-amino-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6' (1'*H*, 3'*H*)-trione (**Example 1,** 54 mg, 0.13 mmol) in ethylene dichloride, and the mixture was stirred at 130 °C for 12 hours. After cooling to room temperature, solvent was removed, and the residue was purified over a silica gel flash column using a gradient of methanol in chloroform to give the title compound as a racemic mixture in the form of a yellow solid. Yield: 7.5 mg, (13 %).

MS (ES) MH^+: 446.3 for $C_{20}H_{20}FN_5O_6$

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 2.1 (s, 3H), 2.9 (d, 1H), 3.0 (t, 1H), 3.4 (d, 1H), 3.6 (t, 1H), 3.75 (d, 1H), 3.9 (d, 1H), 4.0 (d, 1H), 7.4 (s, 1H), 11.0 (s, 1H), 11.4 (s, 1H), 11.8 (s, 1H).

Example 7

(2*R*,4*S*,4a*S*)-rel-11-chloro-2,4,8-trimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

(±) 

To a solution of 7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-methyl-1,2-benzoxazole-5-carbaldehyde (**Intermediate 375,** 35 mg, 0.119 mmol) in IPA was added barbituric acid (16 mg, 0.113 mmol) and the mixture heated at 85 °C for 16 hours. Solvents were evaporated and the residue thus obtained was purified over silica column using a gradient of methanol in chloroform to give product as a solid. Yield: 10 mg (25%).

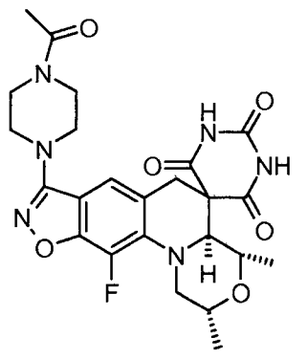
MS (ES) MH^+: 419 for $C_{19}H_{19}ClN_4O_5$;

^1H NMR (400 MHz, DMSO-D6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 2.4 (s 3H), 3.0(m, 2H), 3.5 (d, 1H), 3.6 (m, 1H), 3.9 (m, 2H), 4.5 (d, 1H), 7.3 (s, 1H), 11.45 (s, 1H), 11.85 (s,1H).

Example 8

(2*R*,4*S*,4a*S*)-rel-8-(4-acetylpiperazin-1-yl)-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

(±)



To a stirred solution of 3-(4-acetylpiperazin-1-yl)-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-2,3-dihydro-1,2-benzisoxazole-5-carbaldehyde (**Intermediate 559,** 25 mg, 0.062 mmol) in dry IPA (1 mL) was added barbituric acid (8 mg, 0.062 mmol) and the solution heated around 80 °C for 12h. Solvents were evaporated and the residue was purified over a silica gel-column to give product as white solid. Yield: 17 mg (55%).

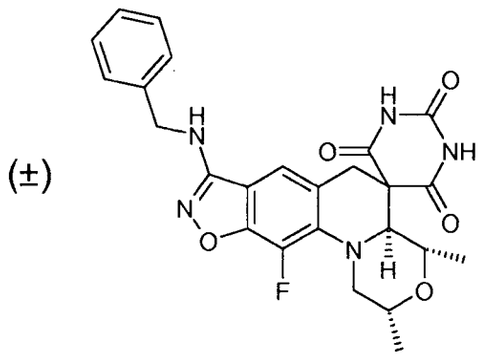
MS (ES) MH^+: 515 for $C_{24}H_{27}FN_6O_6$

^1H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.2 (d, 3H), 2.0 (s, 3H), 2.95 (d, 1H), 3.05 (t, 1H), 3.4–3.5 (m, 5H), 3.6 (d, 4H), 3.7 (m, 1H), 3.8 (m, 1H), 3.9 (d, 1H), 4.0 (d, 1H), 7.4 (s, 1H), 11.5 (s, 1H), 11.85 (s, 1H).

Examples 9 to 53 were prepared from the indicated starting material and pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione using a method similar to the one described for the synthesis of **Example 8**:

Example 9

(2*R*,4*S*,4a*S*)-rel-8-(benzylamino)-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione



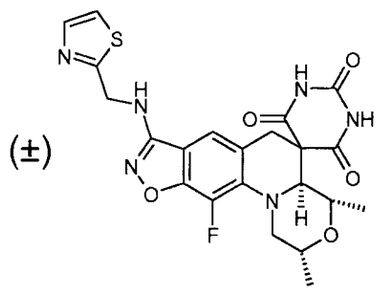
Starting material: 3-(benzylamino)-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-1,2-benzoxazole-5-carbaldehyde (**Intermediate 515**)

MS (ES) MH^+: 495 for $C_{25}H_{24}FN_5O_5$

^1H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 2.9 (d, 1H), 3.0 (m, 1H), 3.4 (d, 1H), 3.6 (t, 1H), 3.8 (d, 1H), 3.9 (d, 1H), 4.0 (d, 1H), 4.4 (d, 2H), 7.1 (s, 1H), 7.35 (q, 5H), 11.45 (s, 1H), 11.8 (s,1H).

Example 10

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-[(1,3-thiazol-2-ylmethyl)amino]-1,2,4,4a-tetrahydro-2'H,6*H*-spiro[1,4-oxazino[4,3-a][1,2]oxazolo[4,5-g]quinoline-5,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione



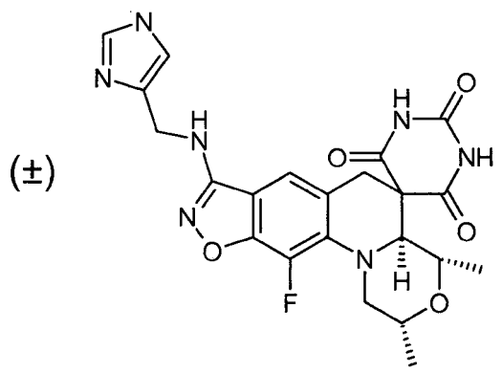
Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[(1,3-thiazol-2-ylmethyl)amino]-1,2-benzoxazole-5-carbaldehyde (**Intermediate 516**)

MS (ES) MH^+: 501 for $C_{22}H_{21}FN_6O_5S$.

^1H NMR (400 MHz, DMSO) δ: 0.9 (d, 3H), 1.1 (d, 3H), 2.9 (d, 1H), 3.0 (t, 1H), 3.5 (d, 1H), 3.6 (m, 1H), 3.75 (m, 1H), 3.9 (d, 1H), 4.0 (d, 1H), 4.7 (d, 1H), 7.1 (s, 1H), 7.6(d, 1H), 7.7 (d, 1H), 7.8 (t, 1H).

Example 11

(2*R*,4*S*,4a*S*)-rel-11-fluoro-8-[(1*H*-imidazol-4-ylmethyl)amino]-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione



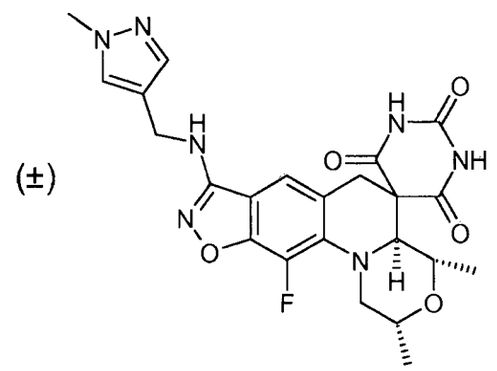
Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[(1*H*-imidazol-4-ylmethyl)amino]-1,2-benzoxazole-5-carbaldehyde (**Intermediate 517**)

MS (ES) MH^+: 484 for $C_{22}H_{22}FN_7O_5$.

^{1}H NMR (400 MHz, DMSO) δ: 0.9 (d, 3H), 1.1 (d, 3H), 2.9 (t, 1H), 3.0 (t, 1H), 3.4 (m, 1H), 3.6 (t, 1H), 3.8 (m, 1H), 3.9 (d, 1H), 4.0 (d, 1H), 4.2 (bs, 2H), 7.0(m, 1H), 7.2 (s, 1H), 7.6 (ds, 1H), 11.5 (bs, 1H), 11.9 (bs, 1H).

Example 12

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-{[(1-methyl-1*H*-pyrazol-4-yl)methyl]amino}-1,2,4,4a-tetrahydro-2'H,6*H*-spiro[1,4-oxazino[4,3-a][1,2]oxazolo[4,5-g]quinoline-5,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione



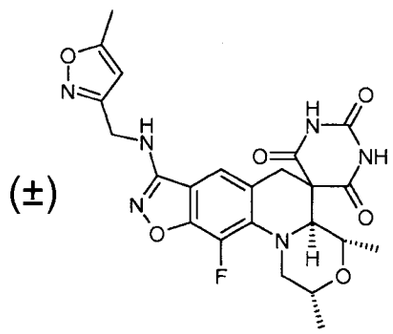
Starting material: (6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-{[(1-methyl-1*H*-pyrazol-4-yl)methyl]amino}-1,2-benzoxazole-5-carbaldehyde (**Intermediate 518**)

MS (ES) MH^+: 498 for $C_{23}H_{24}FN_7O_5$.

^1H NMR (400 MHz, DMSO) δ: 0.9 (d, 3H), 1.1 (d, 3H), 2.9 (d, 1H), 3.05 (s, 1H), 3.4 (m, 1H), 3.6 (m, 1H), 3.7 (s, 3H), 3.9 (d, 1H), 4.0 (d, 1H), 4.2 (d, 1H), 7.0 (t, 1H), 7.1 (s, 1H), 7.4 (s, 1H), 7.6(s, 1H), 11.4 (s, 1H), 11.8 (s, 1H).

Example 13

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-{[(5-methyl-1,2-oxazol-3-yl)methyl]amino}-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione



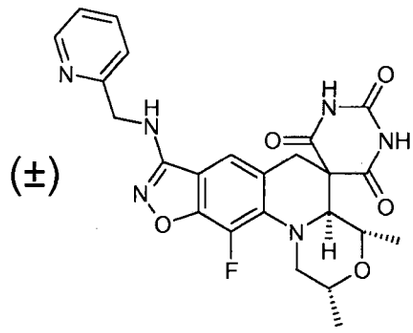
Starting material: (6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-{[(5-methyl-1,2-oxazol-3-yl)methyl]amino}-1,2-benzoxazole-5-carbaldehyde (**Intermediate 519**)

MS (ES) MH^+: 499 for $C_{23}H_{23}FN_6O_6$.

^1H NMR (400 MHz, DMSO) δ: 0.9 (d, 3H), 1.1 (d, 3H), 2.3 (s, 3H), 2.9 (d, 1H), 3.05 (t, 1H), 3.5 (d, 1H), 3.6 (m, 1H), 3.75 (t, 1H), 3.9 (d, 1H), 4.0 (d, 1H), 4.4 (d, 2H), 6.2 (s, 1H), 7.1 (s, 1H), 7.4 (t, 1H), 11.4 (s, 1H), 11.8 (s, 1H).

Example 14

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-[(pyridin-2-ylmethyl)amino]-1,2,4,4a-tetrahydro-2'H,6*H*-spiro[1,4-oxazino[4,3-a][1,2]oxazolo[4,5-g]quinoline-5,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione



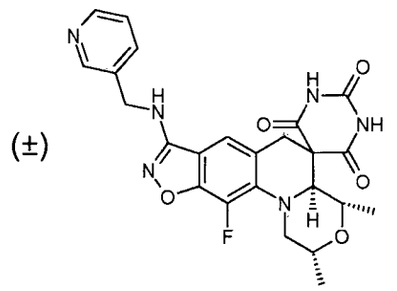
Starting material: {6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[(pyridin-2-ylmethyl)amino]-1,2-benzoxazole-5-carbaldehyde (**Intermediate 520**)

MS (ES) MH^+: 495 for $C_{24}H_{23}FN_6O_5$.

^{1}H NMR (400 MHz, DMSO) δ: 0.9 (d, 3H), 1.1 (d, 3H), 2.9 (d, 1H), 3.05 (t, 1H), 3.5 (d, 1H), 3.6 (t, 1H), 3.8 (m, 1H), 3.9 (d, 1H), 4.0 (d, 1H), 4.5 (d, 2H), 7.2 (s, 1H), 7.3 (t, 1H), 7.4 (d,1H), 7.5 (t, 1H), 7.75 (t, 1H), 8.5 (d, 1H), 11.5 (s, 1H), 11.8 (s, 1H).

Example 15

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-[(pyridin-3-ylmethyl)amino]-1,2,4,4a-tetrahydro-2'H,6*H*-spiro[1,4-oxazino[4,3-a][1,2]oxazolo[4,5-g]quinoline-5,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione



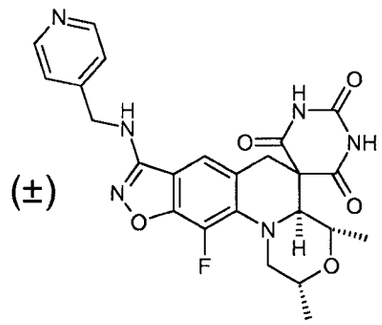
Starting material: {6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[(pyridin-3-ylmethyl)amino]-1,2-benzoxazole-5-carbaldehyde (**Intermediate 521**)

MS (ES) MH^+: 495 for $C_{24}H_{23}FN_6O_5$.

^{1}H NMR (400 MHz, DMSO) δ: 0.9 (d, 3H), 1.1 (d, 3H), 2.9 (d, 1H), 3.05 (t, 1H), 3.5 (d, 1H), 3.6 (t, 1H), 3.7 (m, 1H), 3.9 (d, 1H), 4.0 (d, 1H), 4.4 (d, 2H), 7.1 (s, 1H), 7.35 (m, 1H), 7.4 (t, 1H), 7.8 (d, 1H), 8.45 (d, 1H), 8.6 (s, 1H), 11.4 (s, 1H), 11.8 (s, 1H).

Example 16

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-[(pyridin-4-ylmethyl)amino]-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione



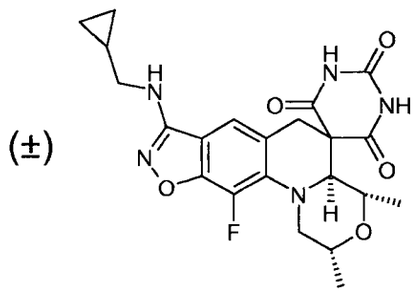
Starting material: {6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[(pyridin-4-ylmethyl)amino]-1,2-benzoxazole-5-carbaldehyde (**Intermediate 522**)

MS (ES) MH^+: 495 for $C_{24}H_{23}FN_6O_5$.

^1H NMR (400 MHz, DMSO) δ: 0.9 (d, 3H), 1.1 (d, 3H), 2.9 (d, 1H), 3.0 (t, 2H), 3.7 (m, 2H), 3.95 (d, 1H), 4.0 (d, 1H), 4.4 (d, 2H), 7.1 (s, 1H), 7.3 (d, 1H), 7.5 (t,1H), 8.5 (d, 1H).

Example 17

(2*R*,4*S*,4a*S*)-rel-8-[(cyclopropylmethyl)amino]-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione



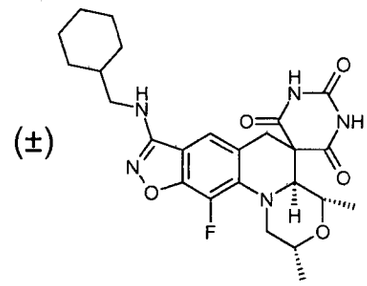
Starting material: {3-[(cyclopropylmethyl) amino]-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-1,2-benzoxazole-5-carbaldehyde (**Intermediate 523**)

MS (ES) MH^+: 458 for $C_{22}H_{24}FN_5O_5$

^{1}H NMR (400 MHz, DMSO) δ: 0.2 (m, 2H), 0.5 (m, 2H), 0.9 (d, 3H), 1.1 (d, 3H), 2.9 (d, 1H), 3.0 (m, 3H), 3.4 (d, 1H), 3.6 (m, 1H), 3.8 (m, 1H), 3.9 (d, 1H), 4.0 (d, 1H), 6.9 (t, 1H), 7.15 (s, 1H).

Example 18

(2*R*,4*S*,4a*S*)-rel-8-[(cyclohexylmethyl)amino]-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione



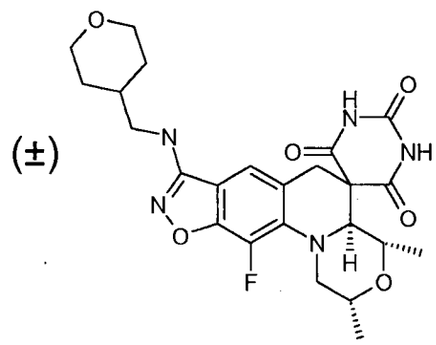
Starting material: {3-[(cyclohexylmethyl) amino]-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-1,2-benzoxazole-5-carbaldehyde (**Intermediate 524**)

MS (ES) MH^+: 500 for $C_{25}H_{30}FN_5O_5$.

^{1}H NMR (400 MHz, DMSO) δ: 0.9 (d, 3H), 0.95 (m, 2H), 1.1 (d, 3H), 1.2 (m, 3H), 1.6-1.8 (m, 6H), 2.9-3.0 (m, 4H), 3.5 (d, 1H), 3.65 (t, 1H), 3.8 (m, 1H), 3.9 (d, 1H), 4.0 (d, 2H), 6.8 (s, 1H), 7.1 (s, 1H), 11.4 (s, 1H), 11.8 (s, 1H).

Example 19

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione



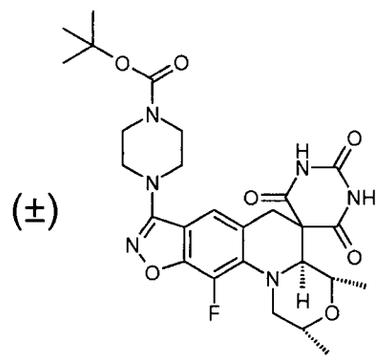
Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]-1,2-benzoxazole-5-carbaldehyde (**Intermediate 525**)

MS (ES) MH^+: 502.3 for $C_{24}H_{28}FN_5O_6$

^{1}H NMR (400 MHz, DMSO) δ: 0.9 (d, 3H), 1.1 (d, 3H), 1.2 (m, 3H), 1.6 (d, 2H), 1.9 (m, 1H), 2.9-3.0 (m, 4H), 3.5 (d, 1H), 3.65 (t, 1H), 3.8 (m, 1H), 3.9 (d, 1H), 4.0 (d, 2H), 6.8 (s, 1H), 7.1 (s, 1H), 11.4 (s, 1H), 11.8 (s, 1H).

Example 20

tert-butyl 4-[(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidin]-8-yl]piperazine-1-carboxylate



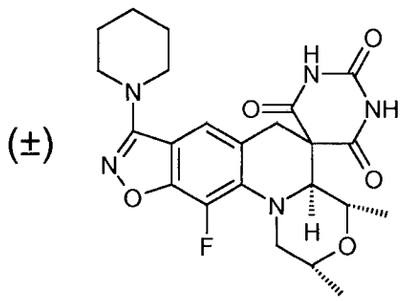
Starting material: *tert*-butyl 4-{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-5-formyl-1,2-benzisoxazol-3-yl}piperazine-1-carboxylate (**Intermediate 560**)

MS (ES) MH^+: 573 for $C_{27}H_{33}FN_6O_7$

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 1.4 (s, 9H), 2.95 (d, 1H), 3.05 (t, 1H), 3.40 (m, 4H), 3.45 (m, 5H), 3.65 (m, 1H), 3.8 (m, 1H), 3.9 (d, 1H), 4.05 (d, 1H), 7.4 (s, 1H), 11.5 (s, 1H), 11.85 (s, 1H).

Example 21

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(piperazin-1-yl)-1,2,4,4a-tetrahydro-2'H,6*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione



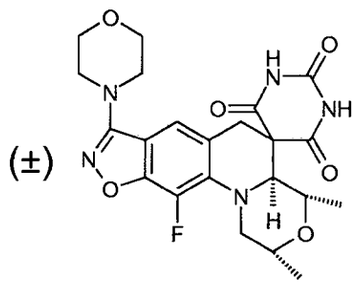
Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(piperidin-1-yl)-1,2-benzisoxazole-5-carbaldehyde (**Intermediate 561**)

MS (ES) MH^+: 472 for $C_{23}H_{26}FN_5O_5$

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 1.6 (bs, 6H), 2.9 (d, 1H), 3.0 (t, 1H), 3.35 (bs, 4H), 3.5(d, 1H), 3.7 (m, 1H), 3.8 (m, 1H), 3.9 (d, 1H), 4.05 (d, 1H), 7.1 (d, 1H).

Example 22

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(morpholin-4-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione



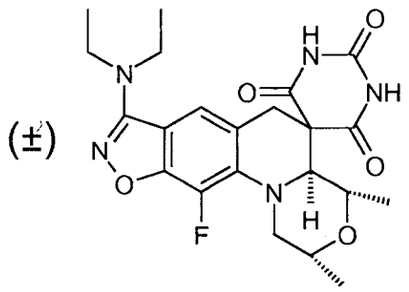
Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(morpholin-4-yl)-1,2-benzisoxazole-5-carbaldehyde (**Intermediate 562**)

MS (ES) MH^+: 474 for $C_{22}H_{24}FN_5O_6$

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 2.9 (d, 1H), 3.1 (t, 1H), 3.4 (bs, 5H), 3.45 (d, 1H), 3.7 (m, 1H), 3.75 (bs, 4H), 3.9 (d, 1H), 4.1 (d, 1H), 7.4 (s, 1H), 11.5 (s, 1H), 11.9 (s, 1H).

Example 23

(2*R*,4*S*,4a*S*)-rel-8-(diethylamino)-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione



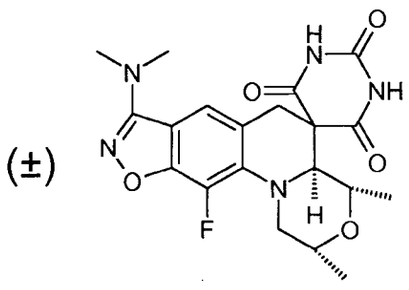
Starting material: 3-(diethylamino)-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-1,2-benzisoxazole-5-carbaldehyde (**Intermediate 563**)

MS (ES) MH^+: 460 for $C_{22}H_{26}FN_5O_5$

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (m, 9H), 2.9 (d, 1H), 3.1 (t, 1H), 3.3-3.45 (m, 4H), 3.5 (d, 1H), 3.6 (d, 1H), 3.7 (m, 1H), 3.9 (d, 1H), 4.1(d, 1H), 7.2 (s, 1H), 11.5 (s, 1H), 11.8 (s, 1H).

Example 24

(2*R*,4*S*,4a*S*)-rel-8-(dimethylamino)-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione



Starting material: 3-(dimethylamino)-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-1,2-benzisoxazole-5-carbaldehyde (**Intermediate 564**)

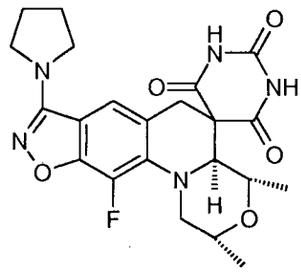
MS (ES) MH^+: 432 for $C_{20}H_{22}FN_5O_5$

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 2.95 (d, 1H), 3.0 (s, 6H), 3.05(s, 1H), 3.5 (d, 1H), 3.6 (d, 1H), 3.7 (m, 1H), 3.9 (d, 1H), 4.1 (d, 1H), 7.4 (s, 1H), 11.5 (s, 1H), 11.85 (s, 1H).

Example 25

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(pyrrolidin-1-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

(±)



Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(pyrrolidin-1-yl)-1,2-benzisoxazole-5-carbaldehyde (**Intermediate 565**)

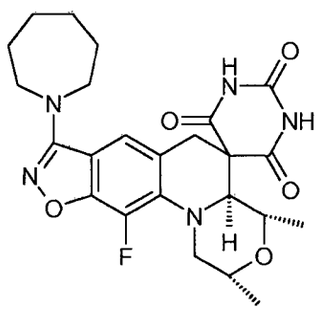
MS (ES) MH^+: 458 for $C_{22}H_{24}FN_5O_5$

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 1.9 (t, 4H), 2.9 (d, 1H), 3.0(t, 1H), 3.65 (m, 5H), 3.7 (d, 1H), 3.8 (m, 1H), 3.9 (d, 1H), 4.1 (d, 1H), 7.3 (s, 1H), 11.5 (s, 1H), 11.8 (s, 1H).

Example 26

(2*R*,4*S*,4a*S*)-rel-8-(azepan-1-yl)-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

(±)



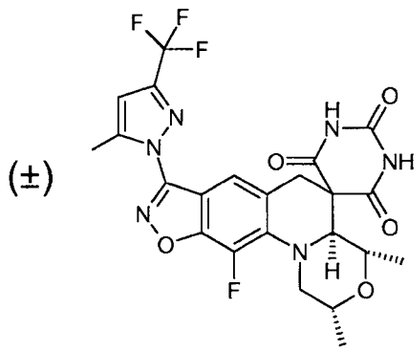
Starting material: 3-(azepan-1-yl)-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-1,2-benzisoxazole-5-carbaldehyde (**Intermediate 566**)

MS (ES) MH^+: 486 for $C_{24}H_{28}FN_5O_5$

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 1.5 (bs, 4H), 1.7(bs, 4H), 2.95 (d, 1H), 3.0 (s, 1H), 3.5 (m, 5H), 3.7 (d, 1H), 3.8 (m, 1H), 3.9 (d, 1H), 4.1(d, 1H), 7.3 (s, 1H), 11.5 (s, 1H), 11.8 (s, 1H).

Example 27

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione



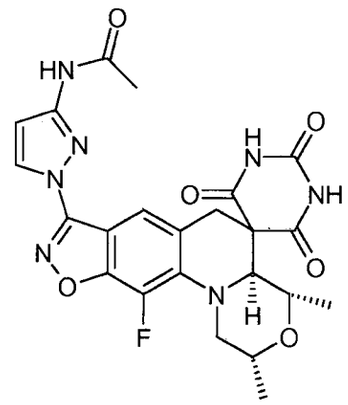
Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]-1,2-benzisoxazole-5-carbaldehyde (**Intermediate 567**)

MS (ES) MH^+: 537 for $C_{23}H_{20}F_4N_6O_5$

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 2.6(s, 3H), 2.9 (d, 1H), 3.1 (t, 1H), 3.6–3.8(m, 3H), 4.0 (d, 1H), 4.1(d, 1H), 7.0 (s, 1H), 7.5 (s, 1H), 11.5 (br, 2H).

Example 28

N-{1-[(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-1*H*-pyrazol-3-yl}acetamide

(±) 

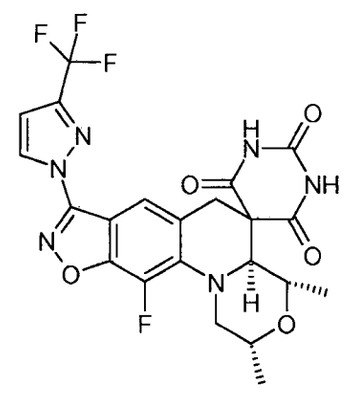
Starting material: *N*-[1-[6-[(2S,6*R*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-5-formyl-1,2-benzoxazol-3-yl]pyrazol-3-yl]acetamide (**Intermediate 568**)

MS (ES) MH^+: 512 for $C_{23}H_{22}FN_7O_6$

^1H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 2.1 (s, 3H), 3.0 (d, 1H), 3.1 (t, 1H), 3.5 (d, 1H), 3.7 (m, 1H), 3.8 (m, 1H), 4.0 (d, 1H), 4.1 (d, 1H), 7.0 (d, 1H), 7.6 (s, 1H), 8.4 (d, 1H), 10.85 (s, 1H), 11.5 (bs, 1H), 11.9 (bs, 1H).

Example 29

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

(±) 

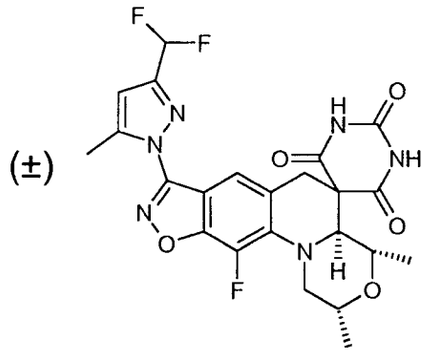
Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]-1,2-benzisoxazole-5-carbaldehyde (**Intermediate 569**)

MS (ES) MH^+: 523 for $C_{22}H_{18}F_4N_6O_5$

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 2.9 (d, 2H), 3.1 (t, 1H), 3.6 (m, 1H), 3.8 (m, 1H), 4.0 (d, 1H), 4.1 (d, 1H), 7.2 (d, 1H), 7.55 (s, 1H), 8.8 (d, 1H), 11.5 (s, 1H), 11.9 (s, 1H).

Example 30

(2*R*,4*S*,4a*S*)-rel-8-[3-(difluoromethyl)-5-methyl-1*H*-pyrazol-1-yl]-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione



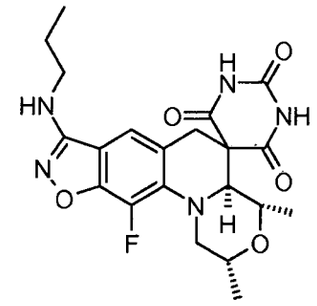
Starting material: 3-[3-(difluoromethyl)-1*H*-pyrazol-1-yl]-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-1,2-benzisoxazole-5-carbaldehyde (**Intermediate 570**)

MS (ES) MH^+: MS (ES) MH^+: 519 for $C_{23}H_{21}F_3N_6O_5$

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 2.6 (s, 3H), 2.9 (d, 2H), 3.1 (t, 1H), 3.6 (m, 1H), 3.8 (m,1H), 4.0 (d, 1H), 4.1 (d, 1H), 6.8 (s, 1H), 7.1 (t, 1H), 7.6 (s, 1H), 11.5 (s, 1H), 11.9 (s, 1H).

Example 31

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(propylamino)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

(±) 

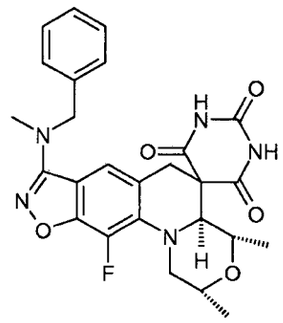
Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(propylamino)-1,2-benzoxazole-5-carbaldehyde (**Intermediate 571**)

MS (ES) MH^+: 446 for $C_{21}H_{24}FN_5O_5$

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 6H), 1.1 (d, 3H), 1.6 (t, 2H), 2.9 (d, 1H), 3.0 (m, 1H), 3.3 (m, 2H), 3.55 (d, 1H), 3.65 (m, 1H), 3.7 (m, 1H), 3.9 (d, 1H), 4.0 (d, 1H), 6.8 (m, 1H), 7.1 (s, 1H), 11.45 (bs, 1H), 11.8 (bs, 1H).

Example 32

(2*R*,4*S*,4a*S*)-rel-8-[benzyl(methyl)amino]-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

(±) 

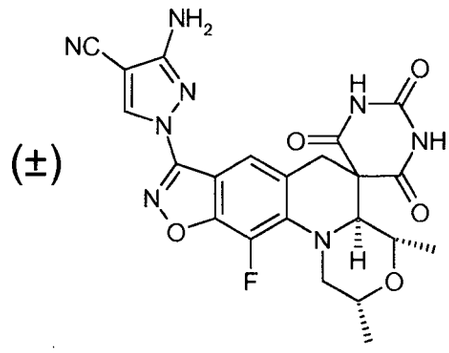
Starting material: 3-[benzyl(methyl)amino]-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-1,2-benzoxazole-5-carbaldehyde (**Intermediate 572**)

MS (ES) MH^+: 508.3 for $C_{26}H_{26}FN_5O_5$

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 2.9 (d, 1H), 3.0 (s, 3H), 3.1 (m, 1H), 3.5 (d, 1H), 3.7 (m, 1H), 3.8 (m, 1H), 3.9 (d, 1H), 4.1 (d, 1H), 4.6(d, 1H), 4.7 (d, 1H), 7.2-7.35 (m, 5H), 11.5 (s, 1H), 11.8 (s, 1H).

Example 33

3-amino-1-[(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-1*H*-pyrazole-4-carbonitrile



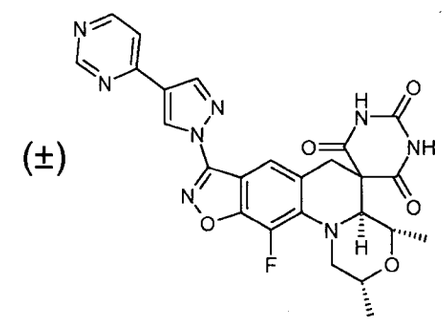
Starting material: 3-amino-1-{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-5-formyl-1,2-benzoxazol-3-yl}-1*H*-pyrazole-4-carbonitrile (**Intermediate 548**).

MS (ES) MH^+: 495 for $C_{22}H_{19}FN_8O_5$

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 2.9 (d, 1H), 3.1 (m, 1H), 3.6 (d, 1H), 3.7 (m, 1H), 3.8 (m, 1H), 4.0 (d, 1H), 4.1 (d, 1H), 6.25 (s, 2H), 7.55 (s, 1H), 9.0 (s, 1H), 11.5 (bs, 1H), 11.9 (bs, 1H).

Example 34

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-[4-(pyrimidin-4-yl)-1*H*-pyrazol-1-yl]-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione



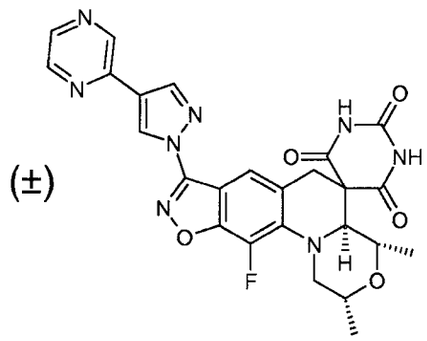
Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[4-(pyrimidin-4-yl)-1*H*-pyrazol-1-yl]-1,2-benzoxazole-5-carbaldehyde (**Intermediate 549**)

MS (ES) MH^+: 533.5 for $C_{25}H_{21}FN_8O_5$

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 2.9 (d, 1H), 3.15 (t, 1H), 3.7 (m, 1H), 3.8 (m, 2H), 4.0 (d, 1H), 4.1 (d, 1H), 7.7 (s, 1H), 8.0 (s, 1H), 8.7 (s, 1H), 8.9 (d, 1H), 9.2 (s, 1H), 9.3 (s, 1H), 11.5 (s, 1H), 11.9 (s, 1H).

Example 35

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-[4-(pyrazin-2-yl)-1*H*-pyrazol-1-yl]-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione



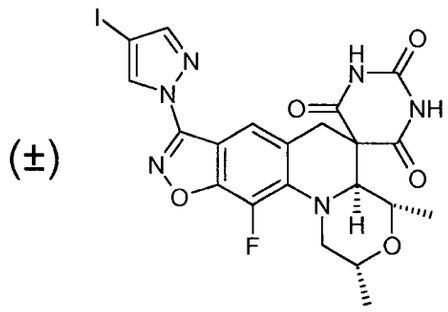
Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[4-(pyrazin-2-yl)-1*H*-pyrazol-1-yl]-1,2-benzoxazole-5-carbaldehyde (**Intermediate 550**)

MS (ES) MH^+: 533.5 for $C_{25}H_{21}FN_8O_5$

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 2.9 (d, 1H), 3.15 (t, 1H), 3.7 (m, 1H), 3.8 (m, 2H), 4.0 (d, 1H), 4.1 (d, 1H), 7.7 (s, 1H), 8.0 (s, 1H), 8.7 (s, 1H), 8.9 (d, 1H), 9.2 (s, 1H), 9.3 (s, 1H), 11.5 (s, 1H), 11.9 (s, 1H).

Example 36

(2*R*,4*S*,4a*S*)-rel-11-fluoro-8-(4-iodo-1*H*-pyrazol-1-yl)-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione



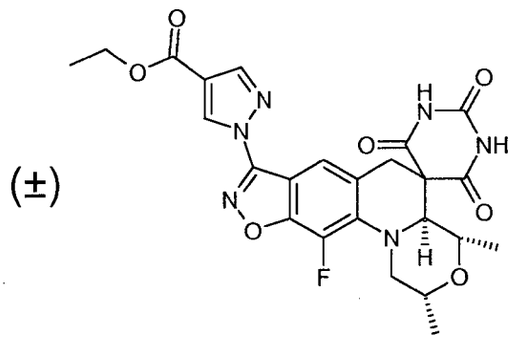
Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(4-iodo-1*H*-pyrazol-1-yl)-1,2-benzoxazole-5-carbaldehyde (**Intermediate 551**)

MS (ES) MH^+: 529.5 for $C_{21}H_{18}FIN_6O_5$;

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.15 (d, 3H), 2.9 (d, 1H), 3.1 (t, 1H), 3.7 (m, 1H), 3.8 (m, 2H), 4.0 (d, 1H), 4.1 (d, 1H), 7.6 (s, 1H), 8.1 (s, 1H), 8.7 (s, 1H), 11.5 (s, 1H), 11.9 (s, 1H).

Example 37

ethyl 1-[(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-1*H*-pyrazole-4-carboxylate



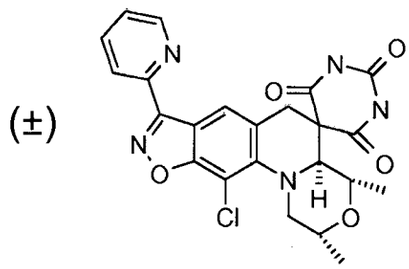
Starting material: ethyl 1-{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-5-formyl-1,2-benzoxazol-3-yl}-1*H*-pyrazole-4-carboxylate (**Intermediate 552**)

MS (ES) MH^+: 527.4 for $C_{24}H_{23}FN_6O_7$;

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.7 (d, 3H), 0.9 (d, 3H), 2.6 (d, 1H), 2.8 (m, 1H), 3.0 (d, 1H), 3.6 (m, 1H), 3.8 (d, 1H), 3.9 (d, 1H), 7.8 (s, 1H), 8.0 (s, 1H), 9.1 (s, 1H), 8.7 (s, 1H), 11.6 (s, 1H), 11.9 (s, 2H).

Example 38

(2*R*,4*S*,4a*S*)-rel-11-chloro-2,4-dimethyl-8-(pyridin-2-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione



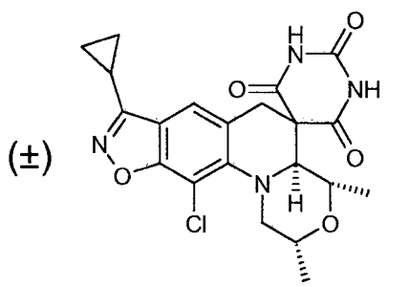
Starting material: 7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(pyridin-2-yl)-1,2-benzoxazole-5-carbaldehyde (**Intermediate 376**)

MS (ES) MH^+: 482 for $C_{23}H_{20}ClN_5O_5$

^{1}H NMR (400 MHz, DMSO-D6) δ: 0.9 (d, 3H), 1.5 (d, 3H), 2.9 (d, 1H), 3.08 (t, 1H), 3.7 (m, 1H), 3.8 (d, 1H), 4.0 (m, 2H), 4.5 (d, 1H), 7.6 (q, 1H), 7.95 (s, 1H), 8.0 (m, 1H), 8.1 (d, 1H), 8.8 (s, 1H), 11.5 (s, 1H), 11.8 (s,1H).

Example 39

(2*R*,4*S*,4a*S*)-rel-11-chloro-8-cyclopropyl-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione



Starting material: 7-chloro-3-cyclopropyl-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-1,2-benzoxazole-5-carbaldehyde (**Intermediate 377**)

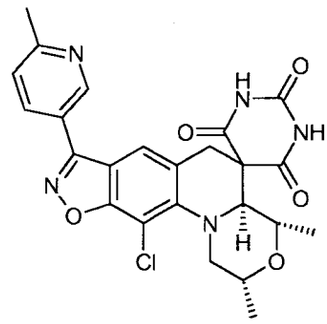
MS (ES) MH^+: 445.0 for $C_{21}H_{21}ClN_4O_5$;

^{1}H NMR (400 MHz, DMSO-D6) δ: 0.9 (d, 3H), 1.0 (m, 1H), 1.1 (m, 3H), 1.15 (d, 3H), 2.2 (m, 1H), 3.0 (m, 2H), 3.5 (d, 1H), 3.6 (m, 1H), 4.0 (m, 2H), 4.4 (d, 1H), 7.3 (s, 1H), 11.45 (s,1H), 11.8 (s, 1H).

Example 40

(2*R*,4*S*,4a*S*)-rel-11-chloro-2,4-dimethyl-8-(6-methylpyridin-3-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-g]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione isolated as the TFA salt from reverse phase HPLC purification.

(±)



Starting material: 7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(6-methylpyridin-3-yl)-1,2-benzoxazole-5-carbaldehyde (**Intermediate 378**)

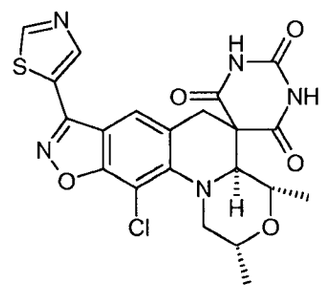
MS (ES) MH^+: 496 for $C_{24}H_{22}ClN_5O_5$

^1H NMR (400 MHz, DMSO-D6) δ: 0.9 (d,3H), 1.1 (d, 3H), 2.6 (s, 3H), 3.1 (m, 2H), 3.6 (d, 1H), 3.7 (m, 1H), 3.95 (m, 1H), 4.0 (m, 1H), 4.5 (d, 1H), 7.5 (d, 1H), 7.7 (s, 1H), 8.2 (dd, 1H), 9.0 (d, 1H), 11.5 (s, 1H), 11.9 (s, 1H)

Example 41

(2*R*,4*S*,4a*S*)-rel-11-chloro-2,4-dimethyl-8-(1,3-thiazol-5-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-g]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

(±)



Starting material: 7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(1,3-thiazol-5-yl)-7,7a-dihydro-1,2-benzoxazole-5-carbaldehyde (**Intermediate 379**)

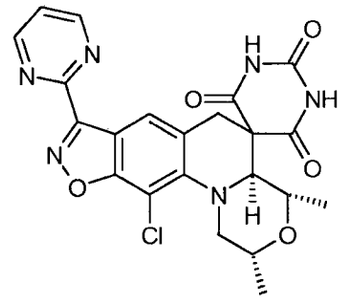
MS (ES) MH^+: 488.0 for $C_{21}H_{18}ClN_5O_5S$;

^{1}H NMR (400 MHz, DMSO-D6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 3.0 (m, 2H), 3.6 (d, 1H), 3.7 (m, 1H), 4.0 (m, 1H), 4.5 (d, 1H), 4.5 (d, 1H), 7.9 (s, 1H), 8.7 (s, 1H), 9.4 (s, 1H), 11.5 (s, 1H),11.9 (s, 1H).

Example 42

(2*R*,4*S*,4a*S*)-rel-11-chloro-2,4-dimethyl-8-(pyrimidin-2-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

(±)



Starting material: 7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(pyrimidin-2-yl)-1,2-benzoxazole-5-carbaldehyde (**Intermediate 380**)

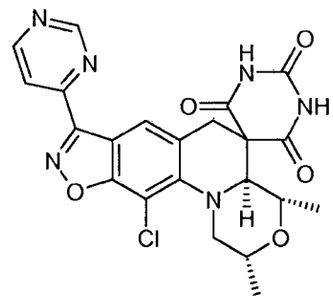
MS (ES) MH^+: 483 for $C_{22}H_{19}ClN_6O_5$

^{1}H NMR (400 MHz, DMSO-D6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 3.0 (m, 2H), 3.7(m, 1H), 3.75 (d, 1H), 4.0 (m, 2H), 4.5 (d, 1H), 7.7 (t, 1H), 7.9 (s, 1H), 9.0 (m, 2H), 11.5 (s, 1H), 11.8 (s,1H).

Example 43

(2*R*,4*S*,4a*S*)-rel-11-chloro-2,4-dimethyl-8-(pyrimidin-4-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

(±)



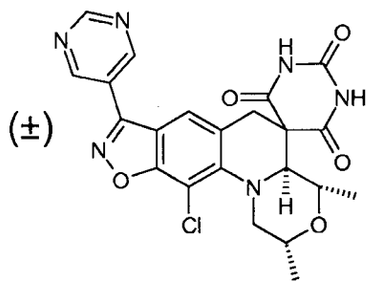
Starting material: 7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(pyrimidin-4-yl)-1,2-benzoxazole-5-carbaldehyde (**Intermediate 381**)

MS (ES) MH^+: 483 for $C_{22}H_{19}ClN_6O_5$

^{1}H NMR (400 MHz, DMSO-D6) δ 0.9 (d, 3H), 1.2 (d, 3H), 3.0 (d, 1H), 3.1 (m, 1H), 3.7 (m, 1H), 3.8 (d, 1H), 4.0 (m, 2H), 4.5 (d, 1H), 7.95 (s, 1H), 8.2 (dd, 1H), 9.0 (d, 1H), 9.4 (d, 1H), 11.5 (s, 1H), 11.85 (s,1H).

Example 44

(2*R*,4*S*,4a*S*)-rel-11-chloro-2,4-dimethyl-8-(pyrimidin-5-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione



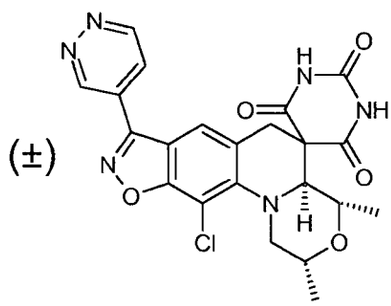
Starting material: 7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(pyrimidin-5-yl)-1,2-benzoxazole-5-carbaldehyde (**Intermediate 382**)

MS (ES) MH^+: 483 for $C_{22}H_{19}ClN_6O_5$

^{1}H NMR (400 MHz, DMSO-D6) δ 0.9 (d, 3H), 1.1 (d, 3H), 3.05 (m, 2H), 3.7 (d, 1H), 3.72 (t, 1H), 3.9 (t, 1H), 4.0 (d, 1H), 4.5 d, 1H), 7.79 (s, 1H), 9.3 (s, 1H), 9.4 (s, 1H), 11.3 (s, 1H).

Example 45

(2*R*,4*S*,4a*S*)-rel-11-chloro-2,4-dimethyl-8-(pyridazin-4-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione



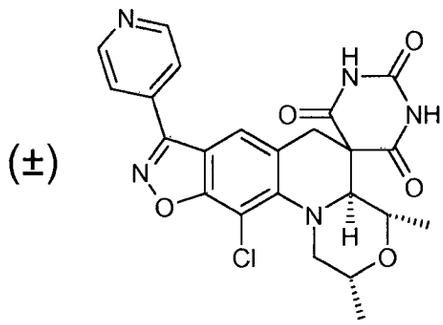
Starting material: 7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(pyridazin-4-yl)-1,2-benzoxazole-5-carbaldehyde (**Intermediate 383**)

MS (ES) MH^+: 483 for $C_{22}H_{19}ClN_6O_5$

^{1}H NMR (400 MHz, DMSO-D6) δ 0.9 (d, 3H), 1.2 (d, 3H), 3.1 (m, 1H), 3.6 (d, 1H), 3.7 (m, 1H), 4.0 (m, 1H), 4.05 (d, 1H), 4.5 (d, 1H), 7.85 (s, 1H), 8.2 (dd, 1H), 9.5 (d, 1H), 9.75 (s, 1H), 11.5 (s, 1H), 11.9 (s, 1H).

Example 46

(2*R*,4*S*,4a*S*)-rel-11-chloro-2,4-dimethyl-8-(pyridin-4-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione



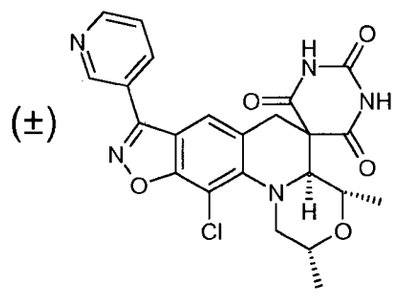
Starting material: 7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(pyridin-4-yl)-1,2-benzoxazole-5-carbaldehyde (**Intermediate 384**)

MS (ES) MH^+: 482 for $C_{23}H_{20}ClN_5O_5$;

^{1}H NMR (400 MHz, DMSO-D6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 3.1(m, 2H), 3.6 (m, 1H), 3.9 (m, 1H), 4.0 (d, 1H), 4.5 (d, 1H) 7.75 (s, 1H), 7.9 (d, 2H), 8.8 (bs, 2H), 11.5 (s, 1H), 11.9 (s, 1H)

Example 47

(2*R*,4*S*,4a*S*)-rel-11-chloro-2,4-dimethyl-8-(pyridin-3-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione (isolated as the TFA salt from reverse phase HPLC purification)



Starting material: 7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(pyridin-3-yl)-1,2-benzoxazole-5-carbaldehyde (**Intermediate 385**)

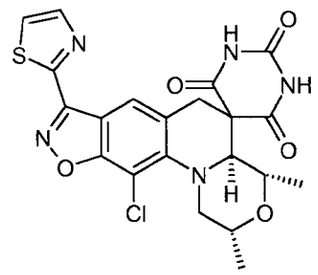
MS (ES) MH^+: 482 for $C_{23}H_{20}ClN_5O_5$

^{1}H NMR (400 MHz, DMSO-D6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 3.0 (m, 2H), 3.6 (m, 1H), 3.7 (m, 1H), 4.0 (m , 2H), 4.5 (d, 1H), 7.6 (t, 1H), 7.7 (s, 1H), 8.3 (d, 1H), 8.8 (s, 1H), 9.1 (s, 1H), 11.5 (s, 1H), 11.9 (s, 1H).

Example 48

(2*R*,4*S*,4a*S*)-rel-11-chloro-2,4-dimethyl-8-(1,3-thiazol-2-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

(±)



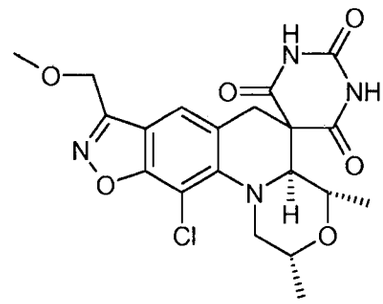
Starting material: 7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(1,3-thiazol-2-yl)-1,2-benzoxazole-5-carbaldehyde (**Intermediate 386**)

MS (ES) MH^+: 488 for $C_{21}H_{18}ClN_5O_5S$;

^{1}H NMR (400 MHz, DMSO-D6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 3.0 (d, 1H), 3.1 (m, 1H), 3.7 (m, 1H), 3.8 (d, 1H), 4.0(m, 1H), 4.5 (d, 1H), 7.8 (s, 1H), 8.1 (d, 1H), 8.2 (d, 1H), 11.5 (s, 1H), 11.8 (s, 1H).

Example 49

(2*R*,4*S*,4a*S*)-rel-11-chloro-8-(methoxymethyl)-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-g]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

(±) 

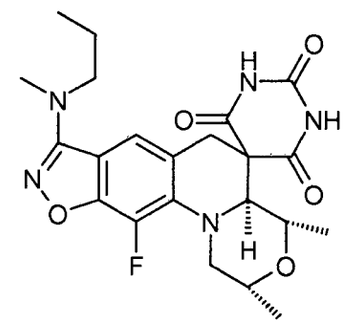
Starting material: 7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(methoxymethyl)-1,2-benzoxazole-5-carbaldehyde (**Intermediate 388**)

MS (ES) MH^+: 449 for $C_{20}H_{21}ClN_4O_6$

^1H NMR (400 MHz, DMSO-D6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 2.95-3.1 (m, 2H), 3.3 (s, 3H), 3.6-3.7 (m, 2H), 3.9-4.0 (m, 2H), 4.5 (d, 1H), 4.7 (s, 2H), 7.3 (s, 1H), 11.4 (s, 1H), 11.8 (s, 1H).

Example 50

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-[methyl(propyl)amino]-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)trione

(±) 

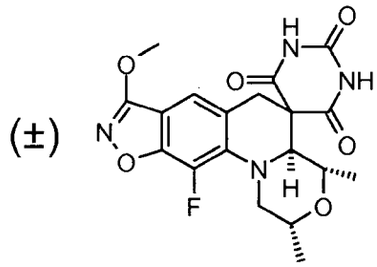
Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[methyl(propyl)amino]-1,2-benzoxazole-5-carbaldehyde (**Intermediate 573**)

MS (ES) MH^+: 460 for $C_{22}H_{26}FN_5O_5$

^1H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 6H), 1.1 (d, 3H), 1.6 (t, 2H), 2.9 (d, 1H), 3.0 (m, 5H), 3.3 (s, 1H), 3.55 (d, 1H), 3.65 (m, 1H), 3.7 (m, 1H), 3.9 (d, 1H), 4.0 (d, 1H), 7.3 (s, 1H), 11.5 (bs, 1H), 11.8 (bs, 1H).

Example 51

(2*R*,4*S*,4a*S*)-rel-11-fluoro-8-methoxy-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione



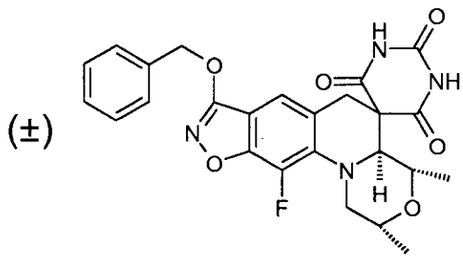
Starting material: 6-[(2*R*,6*S*)-2,6-Dimethylmorpholin-4-yl]-7-fluoro-3-methoxy-1,2-benzisoxazole-5-carbaldehyde (**Intermediate 557**)

MS (ES) MH^+: 419 for $C_{19}H_{19}FN_4O_6$

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.2 (d, 3H), 2.9 (d, 1H), 3.1 (t, 1H), 3.6 (d, 1H), 3.7 (m, 1H), 3.8 (m, 1H), 3.9 (d, 1H), 4.0 (s, 3H), 4.1(d, 1H), 7.1 (s, 1H), 11.5 (s, 1H), 11.9 (s, 1H).

Example 52

(2*R*,4S,4a*S*)-rel-8-(benzyloxy)-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'H,6*H*-spiro[1,4-oxazino[4,3-a][1,2]oxazolo[4,5-g]quinoline-5,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione



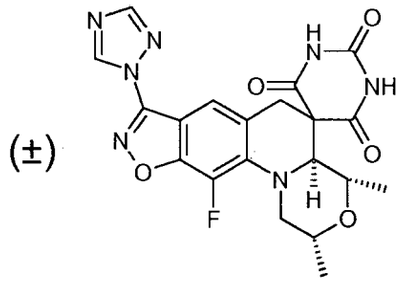
Starting material: 3-(benzyloxy)-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-1,2-benzisoxazole-5-carbaldehyde (**Intermediate 558**)

MS (ES) MH^+: 495 for $C_{25}H_{23}FN_4O_6$

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.2 (d, 3H), 2.9 (d, 1H), 3.1 (t, 1H), 3.6 (d, 1H), 3.7 (m, 1H), 3.8 (m, 1H), 3.9 (d, 1H), 4.0 (s, 1H), 5.4 (s, 2H), 7.1 (s, 1H), 7.4 (m, 3H), 7.5 (d, 2H), 11.5 (s, 1H), 11.85 (s, 1H).

Example 53

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(1*H*-1,2,4-triazol-1-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione



(±)

Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(1*H*-1,2,4-triazol-1-yl)-1,2-benzoxazole-5-carbaldehyde (**Intermediate 539**)

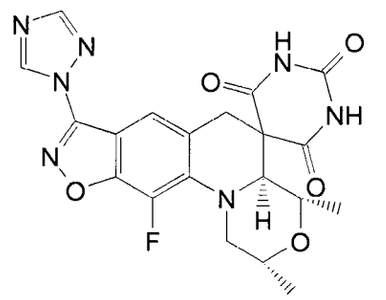
MS (ES) MH^+: 456 for $C_{20}H_{18}FN_7O_5$

^1H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 2.9 (d, 1H), 3.1 (t, 1H), 3.7 (m, 1H), 3.8 (m, 2H), 4.0 (d, 1H), 4.1(d, 1H), 7.6 (s, 1H), 8.5 (s, 1H), 9.4 (s, 1H), 11.5 (bs, 1H), 11.9 (bs, 1H).

The (2*R*,4S,4aS) enantiomer of **Example 53** was also prepared using the chiral synthesis shown below for **Example 53(a)**:

Example 53(a) – (Chiral Synthesis)

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-8-(1*H*-1,2,4-triazol-1-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione



A mixture of 6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-3-(1*H*-1,2,4-triazol-1-yl)benzo[d]isoxazole-5-carbaldehyde (**Intermediate 574,** 500 mg, 1.45 mmol) and pyrimidine-2,4,6(1H,3H,5H)-trione (185 mg, 1.45 mmol) in DMSO (6 ml) was heated at 150 °C for 2 hours

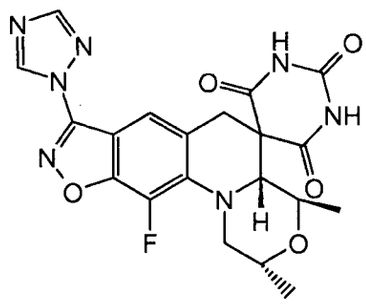
in a microwave reactor. The reaction mixture was purified by Super Critical Fluid chromatography on a Chiralpac IC column with a 35% MeOH, 65% CO_2 mobile phase to give 290 mg of product as a solid as the first eluting compound.

MS (ES) MH^+: 456 for $C_{20}H_{18}FN_7O_5$

^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.2 (d, 3H), 2.9 (d, 1H) 3.1 (t, 1H), 3.6-3.9 (m, 3H), 4. (d, 1H), 4.1 (d, 1H), 7.6 (s, 1H), 8.5 (s, 1H), 9.4 (s, 1H), 11.5 (br. s., 1H), 11.9 (br. s., 1H).

Example 53(b)

(2*R*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-(1*H*-1,2,4-triazol-1-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione



The (2*R*,4*R*,4a*R*) diastereomer was produced as a by-product of the reaction described for the synthesis of **Example 53(a)**. The chromatography described for **Example 53(a)** afforded 25 mg of the (2*R*,4*R*,4a*R*) diastereomer as the second eluting compound.

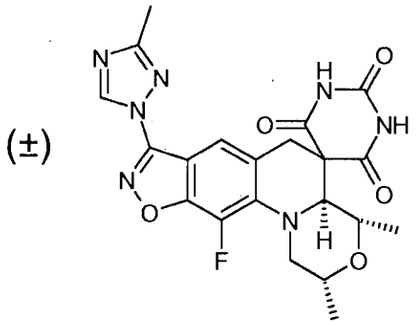
MS (ES) MH^+: 456 for $C_{20}H_{18}FN_7O_5$

^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.9 (d, 3 H), 1.3 (dd, 3 H), 3.0-3.2 (m, 1 H), 3.5-3.7 (m, 1 H), 3.7-3.8 (m, 1 H), 3.85 (s, 1 H), 3.9-4.4 (m, 2 H), 4.0-4.2 (m, 1 H), 7.6 (s, 1 H), 8.5 (s, 1 H), 9.4 (s, 1 H), 11.5 (br. s., 1 H), 11.8 (br. s., 1 H.)

Examples 54 to 83 were prepared from the indicated starting material and pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione using a method similar to the one described for the synthesis of **Example 8**:

Example 54

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(3-methyl-1*H*-1,2,4-triazol-1-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione



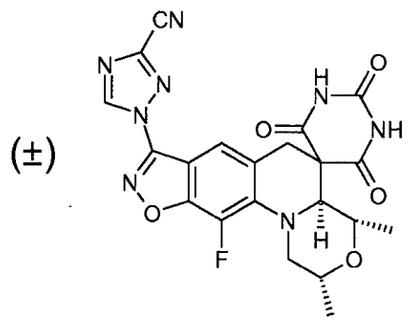
Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(3-methyl-1*H*-1,2,4-triazol-1-yl)-1,2-benzoxazole-5-carbaldehyde (**Intermediate 540**)

MS (ES) MH^+: 470 for $C_{21}H_{20}FN_7O_5$

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 2.4 (s, 3H), 2.9 (d, 1H), 3.1 (t, 1H), 3.7 (m, 1H), 3.8 (m, 2H), 4.0 (d, 1H), 4.1(d, 1H), 7.6 (s, 1H), 9.3(s, 1H), 11.5-11.9 (bs, 2H).

Example 55

1-[(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-1*H*-1,2,4-triazole-3-carbonitrile



Starting material: 1-{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-5-formyl-1,2-benzoxazol-3-yl}-1*H*-1,2,4-triazole-3-carbonitrile (**Intermediate 541**)

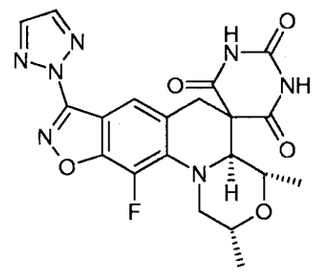
MS (ES) M*H*-: 479 for $C_{21}H_{17}FN_8O_5$

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.15 (d, 3H), 2.9 (d, 1H), 3.2 (t, 1H), 3.7 (m, 1H), 3.9 (m, 2H), 4.0 (d, 1H), 4.1(d, 1H), 7.6 (s, 1H), 9.8 (s, 1H), 11.5 (s, 1H), 11.9 (s, 1H).

Example 56

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(2*H*-1,2,3-triazol-2-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

(±)



Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(1*H*-1,2,3-triazol-2-yl)-1,2-benzoxazole-5-carbaldehyde (**Intermediate 543**), as part of a mixture that includes 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(1*H*-1,2,3-triazol-1-yl)-1,2-benzoxazole-5-carbaldehyde (**Intermediate 542**)

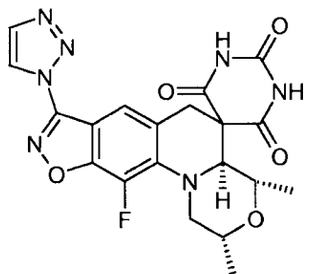
MS (ES) MH^+: 456 for $C_{20}H_{18}FN_7O_5$

^1H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.15 (d, 3H), 2.9 (d, 1H), 3.1 (m, 1H), 3.7 (m, 1H), 3.8 (m, 2H), 4.0(d, 1H), 4.1(d, 1H), 7.7 (s, 1H), 8.4 (s, 2H), 11.6 (bs, 2H).

Example 57

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(1*H*-1,2,3-triazol-1-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

(±)



Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(1*H*-1,2,3-triazol-1-yl)-1,2-benzoxazole-5-carbaldehyde (**Intermediate 542**), as part of a mixture that includes 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(1*H*-1,2,3-triazol-2-yl)-1,2-benzoxazole-5-carbaldehyde (**Intermediate 543**)

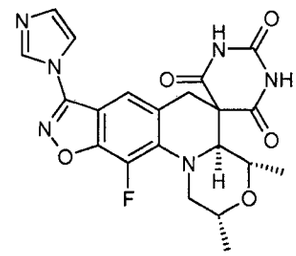
MS (ES) MH^+: 456.5 for $C_{20}H_{18}FN_7O_5$

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.15 (d, 3H), 2.9 (d, 1H), 3.1 (m, 1H), 3.7 (m, 1H), 3.8 (m, 2H), 4.0(d, 1H), 4.15(d, 1H), 7.7 (s, 1H), 8.15 (d, 1H), 9.0 (s, 1H), 11.6 (bs, 1H).

Example 58

(2*R*,4*S*,4a*S*)-rel-11-fluoro-8-(1*H*-imidazol-1-yl)-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

(±)



Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(1*H*-imidazol-1-yl)-1,2-benzoxazole-5-carbaldehyde (**Intermediate 544**)

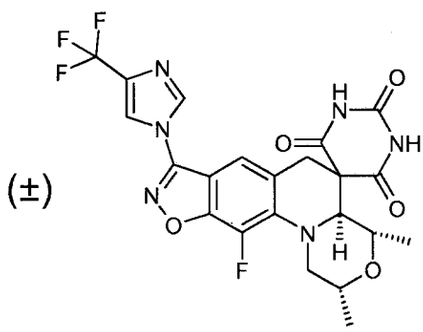
MS (ES) MH^+: 455 for $C_{21}H_{19}FN_6O_5$

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.15 (d, 3H), 3.0 (d, 1H), 3.2 (t, 1H), 3.55 (d, 1H), 3.7 (m, 1H), 3.8 (m, 1H), 4.0 (d, 1H), 4.1(d, 1H), 7.3 (s, 1H), 7.65 (s, 1H), 7.9 (s, 1H), 8.5(s, 1H), 11.6 (s, 1H), 11.9 (s, 1H).

Example 59

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-[4-(trifluoromethyl)-1*H*-imidazol-1-yl]-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

(±)



Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[4-(trifluoromethyl)-1*H*-imidazol-1-yl]-1,2-benzoxazole-5-carbaldehyde (**Intermediate 545**)

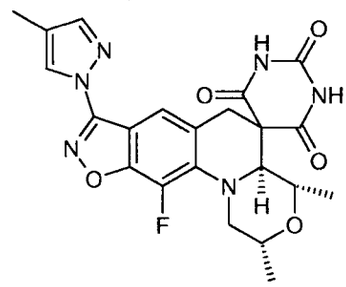
MS (ES) MH^+: 523 for $C_{22}H_{18}F_4N_6O_5$

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 3.0 (d, 1H), 3.1 (t, 1H), 3.5 (m, 1H), 3.7 (m,1H), 3.8(m, 1H), 4.0 (d, 1H), 4.1(d, 1H), 7.6 (d, 1H), 8.6 (d, 1H), 8.65 (s, 1H).

Example 60

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(4-methyl-1*H*-pyrazol-1-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

(±)



Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(4-methyl-1*H*-pyrazol-1-yl)-1,2-benzoxazole-5-carbaldehyde (**Intermediate 546**)

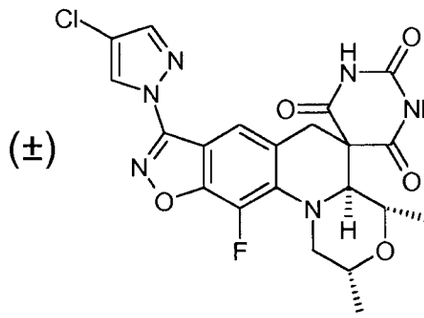
MS (ES) MH^+: 469 for $C_{22}H_{21}FN_6O_5$

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 2.1(s, 3H), 2.9 (d, 1H), 3.1 (t, 1H), 3.7 (m, 2H), 3.8 (m, 1H), 3.95 (d, 1H), 4.1(d, 1H), 7.7 (s, 1H), 7.8 (s, 1H), 8.3 (s, 1H), 11.5 (s, 1H), 11.8 (s, 1H).

Example 61

(2*R*,4*S*,4a*S*)-rel-8-(4-chloro-1*H*-pyrazol-1-yl)-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

(±)



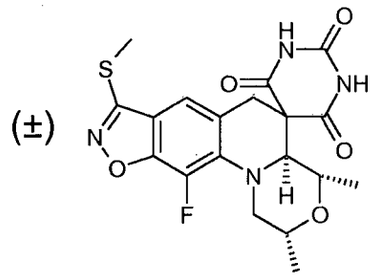
Starting material: 3-(4-chloro-1*H*-pyrazol-1-yl)-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-1,2-benzoxazole-5-carbaldehyde (**Intermediate 547**)

MS (ES) MH^+: 489 for $C_{21}H_{18}ClFN_6O_5$

^1H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 2.9 (d, 1H), 3.1 (t, 1H), 3.7 (m, 1H), 3.8 (d, 2H), 4.0 (d, 1H), 4.1(d, 1H), 7.6 (s, 1H), 8.1 (s, 1H), 8.8 (s, 1H), 11.5 (s, 1H), 11.85(s, 1H).

Example 62

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(methylsulfanyl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione



Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(methylsulfanyl)-1,2-benzoxazole-5-carbaldehyde (**Intermediate 553**)

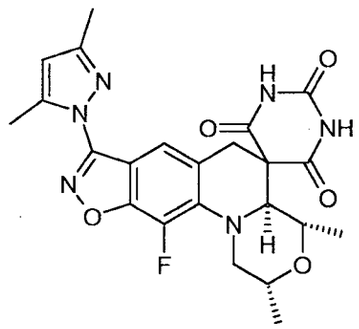
MS (ES) MH^+: 435 for $C_{19}H_{19}FN_4O_5S$

^1H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 2.7 (s, 3H), 2.9 (d, 1H), 3.1 (t, 1H), 3.6 (m, 1H), 3.7 (m,1H), 3.8 (m, 1H), 4.0 (d, 1H), 4.1(d, 1H), 7.1 (s, 1H), 11.5 (s, 1H), 11.9 (s, 1H).

Example 63

(2*R*,4*S*,4a*S*)-rel-8-(3,5-dimethyl-1*H*-pyrazol-1-yl)-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

(±)



Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-7-fluoro-1,2-benzoxazole-5-carbaldehyde (**Intermediate 554**)

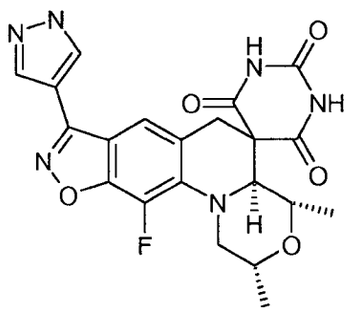
MS (ES) MH^+: 483.5 for $C_{23}H_{23}FN_6O_5$

^1H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 2.25 (s, 3H), 2.5 (s, 3H), 2.9 (d, 1H), 3.1 (t, 1H), 3.7 (m, 1H), 3.8 (m, 2H), 3.95 (d, 1H), 4.1(d, 1H), 6.25 (s, 1H), 7.6(s, 1H), 11.5 (bs, 1H), 11.9 (bs, 2H).

Example 64

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(1*H*-pyrazol-4-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

(±)



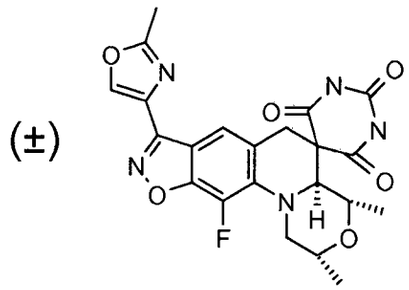
Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(1*H*-pyrazol-4-yl)-1,2-benzoxazole-5-carbaldehyde (**Intermediate 555**)

MS (ES) MH^+: 455 for $C_{21}H_{19}FN_6O_5$

^1H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.5 (d, 3H), 2.9 (d, 1H), 3.1 (t, 1H), 3.7 (m, 1H), 3.8 (m, 2H), 4.0 (d, 1H), 4.1(d, 1H), 6.7 (s, 1H), 7.7 (s, 1H), 8.0 (s, 1H), 8.5 (s, 1H), 11.5 (s, 1H), 11.8 (s, 2H).

Example 65

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(2-methyl-1,3-oxazol-4-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione



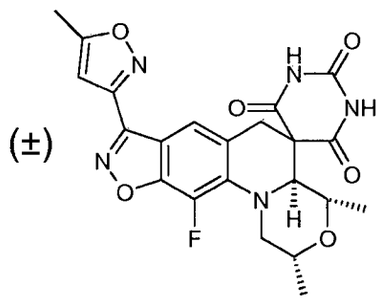
Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(2-methyl-1,3-oxazol-4-yl)-1,2-benzoxazole-5-carbaldehyde (**Intermediate 394**)

MS (ES) MH^+: 470 for $C_{22}H_{20}FN_5O_6$

^1H NMR (400 MHz, DMSO-D6) δ: 0.9 (d, 3H), 1.5 (d, 3H), 2.5 (s, 3H), 3.0 (d, 1H), 3.3 (t, 1H), 3.7 (m, 2H), 3.8 (m, 1H), 4.0 (d, 1H), 4.1 (d, 1H), 7.6 (s, 1H), 8.8 (s, 1H), 11.5 (s, 1H), 11.8 (s,1H).

Example 66

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(5-methyl-1,2-oxazol-3-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione



Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(5-methyl-1,2-oxazol-3-yl)-1,2-benzoxazole-5-carbaldehyde (**Intermediate 395**)

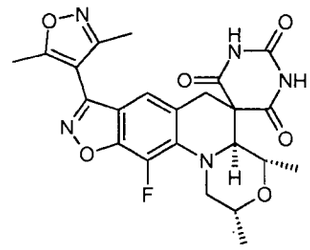
MS (ES) MH^+: 470for $C_{22}H_{20}FN_5O_6$;

^1H NMR (400 MHz, DMSO-D6) δ: 0.9 (d, 3H), 1.5 (d, 3H), 2.5(s, 3H), 3.0 (d, 1H), 3.3 (t, 1H), 3.7 (m, 1H), 3.8 (m, 2H), 4.0 (d, 1H), 4.1 (d, 1H), 6.85 (s, 1H), 7.55 (s, 1H), 11.5 (s, 1H), 11.85 (s,1H).

Example 67

(2*R*,4*S*,4a*S*)-rel-8-(3,5-dimethyl-1,2-oxazol-4-yl)-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

(±)



Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(3,5-dimethyl-1,2-oxazol-4-yl)-7-fluoro-1,2-benzoxazole-5-carbaldehyde (**Intermediate 396**).

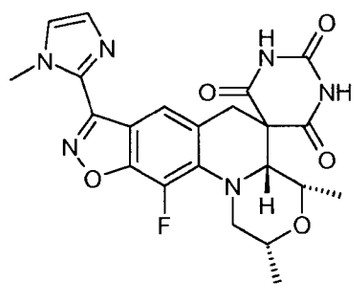
MS (ES) MH^+: 484 for $C_{23}H_{22}FN_5O_6$

^1H NMR (400 MHz, DMSO-D6) δ: 0.9 (d, 3H), 1.5 (d, 3H), 2.3 (s, 3H), 2.5 (s, 3H), 3.0 (d, 1H), 3.1 (t, 1H), 3.6 (d, 1H), 3.7 (m, 1H), 3.8 (m, 1H), 4.0 (d, 1H), 4.1 (d, 1H), 7.3 (s, 1H), 11.5 (s, 1H), 11.9 (s,1H).

Example 68

(2*R*,4*S*,4a*R*)-rel-11-fluoro-2,4-dimethyl-8-(1-methyl-1*H*-imidazol-2-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

(±)



Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(1-methyl-1*H*-imidazol-2-yl)-1,2-benzoxazole-5-carbaldehyde (**Intermediate 397**)

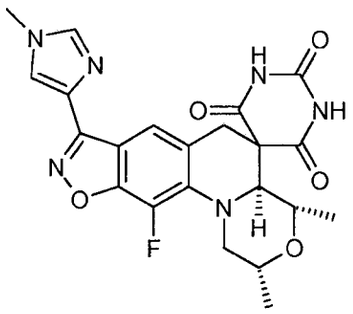
MS (ES) MH^+: 469 for $C_{22}H_{21}FN_6O_6$

^{1}H NMR (400 MHz, DMSO-D6) δ: δ: 1.1 (d, 3H), 1.2 (d, 3H), 3.2 (m, 1H), 3.4 (m, 1H), 3.5 (m, 2H), 3.6 (m, 1H), 3.9 (m, 1H), 4.1 (s, 3H), 4.15 (m, 1H), 7.2(s,1H), 7.6 (s, 1H), 7.9(d, 1H), 11.5 (s, 1H), 11.7 (s,1H).

Example 69

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(1-methyl-1*H*-imidazol-4-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

(±)



Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(1-methyl-1*H*-imidazol-4-yl)-1,2-benzoxazole-5-carbaldehyde (**Intermediate 398**)

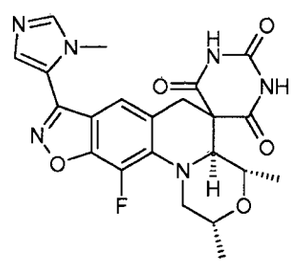
MS (ES) MH^+: 469 for $C_{22}H_{21}FN_6O_6$;

^{1}H NMR (400 MHz, DMSO-D6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 3.0 (d, 1H), 3.1 (m, 1H), 3.6 (d, 1H), 3.7 (m, 2H), 3.7 (s, 3H), 3.72 (m, 1H), 4.0 (d, 1H), 4.1 (d, 1H), 7.4 (s, 1H), 7.8 (d, 1H), 11.4 (bs, 1H), 11.8 (bs, 1H).

Example 70

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(1-methyl-1*H*-imidazol-5-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

(±)



Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(1-methyl-1*H*-imidazol-5-yl)-1,2-benzoxazole-5-carbaldehyde (**Intermediate 399**).

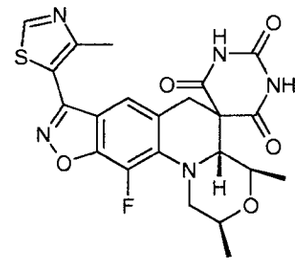
MS (ES) MH^+: 469.5 for $C_{22}H_{21}FN_6O_6$

^{1}H NMR (400 MHz, DMSO-D6) δ: 0.9 (d, 3H), 1.15 (d, 3H), 3.1 (d, 1H), 3.15 (t, 1H), 3.6 (d, 1H), 3.7 (m, 1H), 3.8 (m, 1H), 4.0 (d, 1H), 4.0 (s, 3H), 4.1 (d, 1H), 7.3 (s, 1H), 8.0(s, 1H), 8.5 (s, 1H), 11.5 (s, 1H), 11.9 (s,1H).

Example 71

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(4-methyl-1,3-thiazol-5-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

(±)



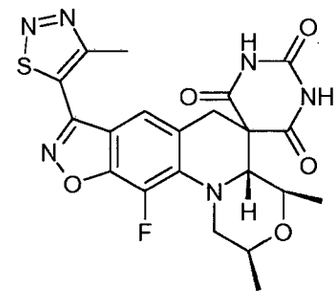
Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(4-methyl-1,3-thiazol-5-yl)-1,2-benzoxazole-5-carbaldehyde (**Intermediate 400**)

MS (ES) MH^+: 486 for $C_{22}H_{20}FN_6O_5S$;

^{1}H NMR (400 MHz, DMSO-D6) δ: 0.9 (d, 3H), 1.5 (d, 3H), 2.6 (s, 3H), 3.0 (d, 1H), 3.1 (t, 1H), 3.7 (m, 2H), 3.8 (m, 1H), 4.0 (d, 1H), 4.1 (d, 1H), 7.3 (s, 1H), 9.35 (s, 1H), 11.5 (s, 1H), 11.9 (s,1H).

Example 72

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(4-methyl-1,2,3-thiadiazol-5-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

(±) 

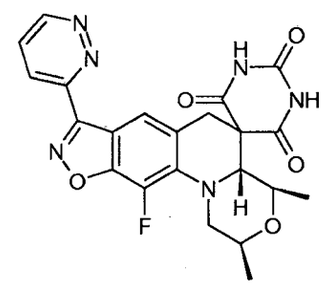
Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(4-methyl-1,2,3-thiadiazol-5-yl)-1,2-benzoxazole-5-carbaldehyde (**Intermediate 401**)

MS (ES) MH^+: 487 for $C_{21}H_{19}FN_6O_5S$

^1H NMR (400 MHz, DMSO-D6) δ: 0.9 (d, 3H), 1.15 (d, 3H), 2.9 (s, 3H), 3.0 (d, 1H), 3.1 (t, 1H), 3.6 (d, 1H), 3.7 (m, 1H), 3.8 (m, 1H), 4.0 (d, 1H), 4.1 (d, 1H), 7.4 (s, 1H), 11.5 (s, 1H), 11.9 (s,1H).

Example 73

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(pyridazin-3-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

(±) 

Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(pyridazin-3-yl)-1,2-benzoxazole-5-carbaldehyde (**Intermediate 402**)

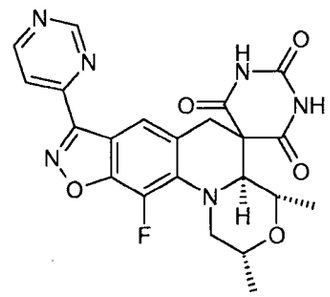
MS (ES) MH^+: 467 for $C_{22}H_{19}FN_6O_5$

^1H NMR (400 MHz, DMSO-D6): δ 0.9 (d, 3H), 1.15 (d, 3H), 3.0 (d, 1H), 3.1 (t, 1H), 3.6 (d, 1H), 3.7 (m, 1H), 3.8 (m, 1H), 4.0 (d, 1H), 4.1 (d, 1H), 7.9 (m, 2H), 8.4 (m, 1H), 9.4 (m, 1H), 11.5 (s, 1H), 11.8 (s,1H).

Example 74

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(pyrimidin-4-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

(±)



Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(pyrimidin-4-yl)-1,2-benzoxazole-5-carbaldehyde (**Intermediate 403**)

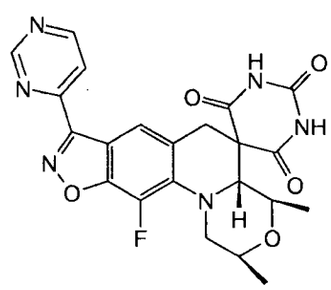
MS (ES) MH^+: 467 for $C_{22}H_{19}FN_6O_5$

^1H NMR (400 MHz, DMSO-D6) δ: 0.9 (d, 3H), 1.15 (d, 3H), 3.0 (d, 1H), 3.1 (t, 1H), 3.6 (d, 1H), 3.7 (m, 1H), 3.8 (m, 1H), 4.0 (d, 1H), 4.1 (d, 1H), 7.9 (m, 2H), 8.4 (m, 1H), 9.4 (m, 1H), 11.5 (s, 1H), 11.8 (s,1H).

The (2*S*,4*R*,4a*R*) and (2*R*,4*S*,4a*S*) enantiomers of **Example 74** separated by Supercritical Fluid Chromatography using a Chiralpak AD, 21 x 250mm, 5μ column (elution with 25% MeOH, 75% CO_2 at 60 ml/min, 40°C, and 100 bar with detection at 220nm).

Example 74(a) -First Eluting Compound

(2S,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-(pyrimidin-4-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione

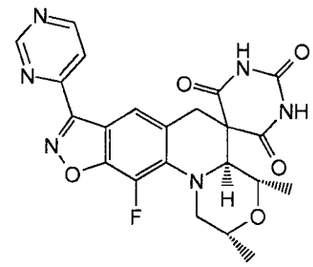


MS (ES) MH^+: 467 for $C_{22}H_{19}FN_6O_5$

^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.9 (d, 3 H) 1.2 (d, 3 H) 2.2 - 3.0 (m, 2 H) 3.6 - 4.3 (m, 5 H) 7.8 (s, 1 H) 8.1 - 8.2 (m, 1 H) 9.0 (d, 1 H) 9.4 (s, 1 H) 11.6 (s, 2 H)
>98% ee by chiral HPLC; [α] = +199 (c=0.1 in DMSO).

Example 74(b) - Second Eluting Compound

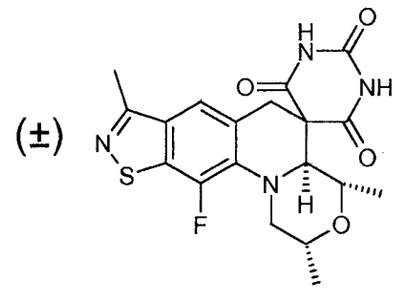
(2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-8-(pyrimidin-4-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione



MS (ES) MH^+: 467 for $C_{22}H_{19}FN_6O_5$
^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.9 (d, 3 H) 1.2 (d, 3 H) 2.8 - 3.2 (m, 2 H) 3.6 - 4.2 (m, 5 H) 7.8 (s, 1 H) 8.0 - 8.4 (m, 1 H) 9.0 (d, 1 H) 9.4 (s, 1 H) 11.5 (s, 2 H)
>98% ee by chiral HPLC; [α] = -196 (c=0.1 in DMSO).

Example 75

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4,8-trimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]thiazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

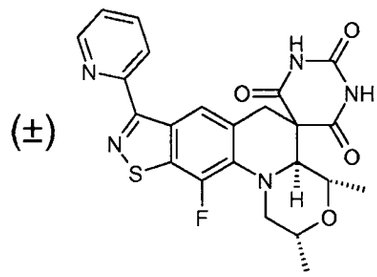


Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-methyl-1,2-benzothiazole-5-carbaldehyde (**Intermediate 576**).
MS (ES) MH^+: 419 for $C_{19}H_{19}FN_4O_4S$

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 2.5 (s, 3H), 3.0 (m, 2H), 3.6 (d, 1H), 3.7 (m, 1H), 3.8 (m, 1H), 4.0 (d, 1H), 4.1 (d, 1H), 7.5 (s, 1H), 11.5 (s, 1H), 11.9 (s, 1H).

Example 76

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(pyridin-2-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]thiazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione



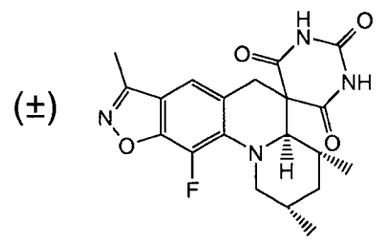
Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(pyridin-2-yl)-1,2-benzothiazole-5-carbaldehyde (**Intermediate 577**)

MS (ES) MH^+: 481 for $C_{23}H_{20}FN_5O_4S$

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.2 (d, 3H), 3.0 (d, 1H), 3.1 (t, 1H), 3.7 (m, 1H), 3.8 (m, 2H), 4.0 (d, 1H), 4.15 (d, 1H), 7.5 (m, 1H), 8.0 (t, 1H), 8.2 (d, 1H), 8.5 (s, 1H), 8.8 (d, 1H), 11.5 (s, 1H), 11.8 (s, 1H).

Example 77

(2*S*,4*R*,4a*R*)-rel-11-fluoro-2,4,8-trimethyl-1,2,3,4,4a,6-hexahydro-1'*H*-spiro[isoxazolo[4,5-g]pyrido[1,2-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione



Starting material: 6-((3*S*,5*R*)-3,5-dimethylpiperidin-1-yl)-7-fluoro-3-methylbenzo[d]isoxazole-5-carbaldehyde (**Intermediate 538**)

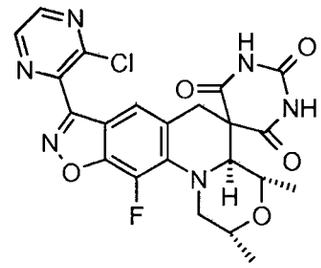
MS (ES) MH^+: 401 for $C_{20}H_{21}FN_4O_4$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.6 (d, 3H), 0.8-1.1 (m, 1H), 0.9 (d, 3H), 1.8 (m, 3H), 2.4 (s, 3H), 2.6-3.1 (m, 2H) 3.5 (d,1H), 3.8 (d, 1H) 3.9-4.0 (m, 1H) 7.1 (s, 1H) 11.4 (br. s., 2H).

Example 78

(2*R*,4*S*,4a*S*)-rel-8-(3-chloropyrazin-2-yl)-11-fluoro-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione

(±)



Starting material: 3-(3-chloropyrazin-2-yl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-5-carbaldehyde (**Intermediate 432**)

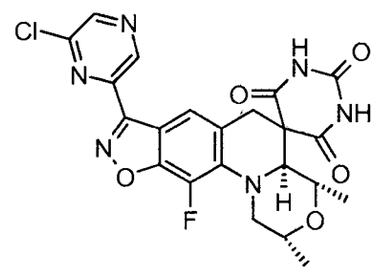
MS (ES) MH^+: 501 for $C_{22}H_{18}ClFN_6O_5$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.9 (d, 3H) 1.2 (d, 3H), 3.0 (d, 1H), 3.1 (m., 1H), 3.6-3.7 (m, 2H), 3.7 (m, 1H), 3.9 (d, 1H), 4.2 (d, 1H), 7.9 (d, 1H), 8.9 (d, 1H), 9.0 (d, 1H), 11.5 (s, 1H), 11.9 (s, 1H)

Example 79

(2*R*,4*S*,4a*S*)-rel-8-(6-chloropyrazin-2-yl)-11-fluoro-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione

(±)



Starting material: 3-(6-chloropyrazin-2-yl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-5-carbaldehyde (**Intermediate 434**)

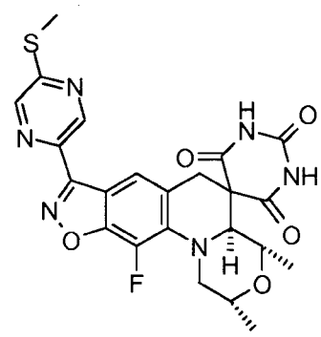
MS (ES) MH^+: 501 for $C_{22}H_{18}ClFN_6O_5$

^1H NMR (300 MHz, DMSO-d_6) δ ppm 0.9 (d, 3H), 1.2 (d, 3H), 3.0 (d, 1H), 3.1-3.2 (m, 1H), 3.7 (dd, 1H), 3.8 (m, 2H), 4.0 (d, 1H), 4.1-4.2 (m, 1H), 7.7 (s, 1H), 9.0 (s, 1H), 9.3 (s, 1H), 11.5 (s, 1H), 11.9 (s, 1H)

Example 80

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(5-(methylthio)pyrazin-2-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione

(±)



Starting material: 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(5-(methylthio)pyrazin-2-yl)benzo[d]isoxazole-5-carbaldehyde (**Intermediate 435**)

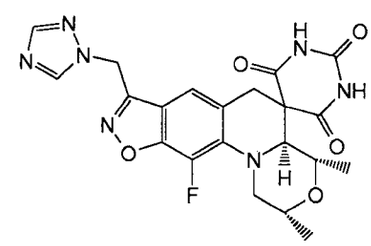
MS (ES) MH^+: 513 for $C_{23}H_{21}FN_6O_5S$

^1H NMR (300 MHz, DMSO-d_6) δ ppm 0.9 (d, 3H), 1.2 (d, 3H), 2.7 (s, 3H), 3.0 (d, 1H), 3.1-3.2 (m, 1H), 3.7 (m, 3H), 3.9-4.1 (m, 1H), 4.1 (d, 1H), 7.7 (s, 1H), 8.8 (d, 1H), 9.2 (d, 1H), 11.5 (br. s., 1H), 11.8 (br. s., 1H)

Example 81

(2*R*,4*S*,4a*S*)-rel-8-((1*H*-1,2,4-triazol-1-yl)methyl)-11-fluoro-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione

(±)



Starting material: 3-((1*H*-1,2,4-triazol-1-yl)methyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-5-carbaldehyde (**Intermediate 425**).

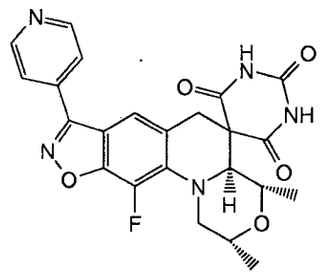
MS (ES) MH^+: 470 for $C_{21}H_{20}FN_7O_5$

^1H NMR (300 MHz, $CDCl_3$) δ: 0.87 (d, 3H), 1.12 (d, 3H), 2.85-3.19 (m, 2H), 3.46-4.15 (m, 5H), 5.68-5.93 (m, 2H), 7.01 (s, 1H), 8.00 (s, 1H), 8.76 (s, 1H), 11.45 (s, 1H), 11.81 (s, 1H).

Example 82

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(pyridin-4-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione

(±)



Starting material: 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(pyridin-4-yl)benzo[d]isoxazole-5-carbaldehyde (**Intermediate 426**).

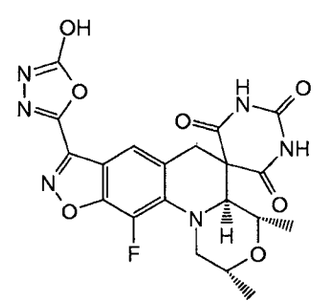
MS (ES) MH^+: 466 for $C_{23}H_{20}FN_5O_5$

^1H NMR (300 MHz, DMSO-d_6) δ: 0.89 (d, 3H), 1.15 (d, 3H), 2.90-4.23 (m, 7H), 7.63 (s, 1 H, 7.90 (d, 2H), 8.81 (d, 2H), 11.50 (s, 1H), 11.87 (s, 1H).

Example 83

(2*R*,4S,4a*S*)-rel-11-fluoro-8-(5-hydroxy-1,3,4-oxadiazol-2-yl)-2,4-dimethyl-1,2,4,4a-tetrahydro-2'H,6*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione

(±)



Starting material: 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)benzo[d]isoxazole-5-carbaldehyde (**Intermediate 405**)

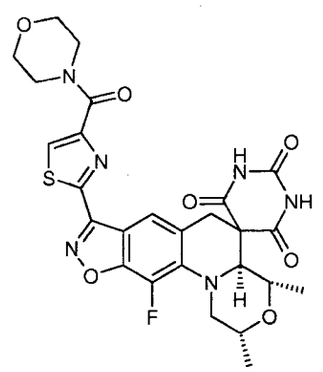
MS (ES) MH^+: 473 for $C_{20}H_{17}FN_6O_7$

^1H NMR (300 MHz, DMSO-d_6) δ: 0.9 (d, 3 H) 1.1 (d, 3 H) 2.8 - 3.2 (m, 2 H) 3.6 - 4.2 (m, 5 H) 7.5 (s, 1 H) 11.5 (br s, 1 H) 11.8 (br s, 1 H) 13.1 (br s, 1 H)

Example 84

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-[4-(morpholin-4-ylcarbonyl)-1,3-thiazol-2-yl]-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

(±)



To a solution of 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[4-(morpholin-4-ylcarbonyl)-1,3-thiazol-2-yl]-1,2-benzoxazole-5-carbaldehyde (**Intermediate 389,** 90 mg, 0.19 mmol) in IPA was added barbituric acid (24 mg, 0.103 mmol) and the mixture heated at 85 °C for 16 hours. Solvents were evaporated and the residue was purified by reverse phase HPLC to give product as solid (as a TFA salt). Yield: 16 mg (14 %).

MS (ES) MH^+: 585 for $C_{26}H_{25}FN_6O_7S$

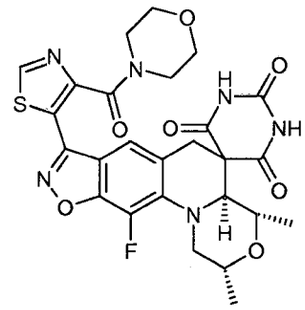
^1H NMR (400 MHz, DMSO-D6) δ: 0.9 (d, 3H), 1.5 (d, 3H), 3.0 (d, 1H), 3.1 (t, 1H), 3.6-3.8 (m, 11H), 4.0 (d, 1H), 4.1 (d, 1H), 7.6 (s, 1H), 8.4 (s, 1H).

Examples 85 to 93 were prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Example 84**:

Example 85

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-[4-(morpholin-4-ylcarbonyl)-1,3-thiazol-5-yl]-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

(±)



Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-[4-(morpholin-4-ylcarbonyl)-1,3-thiazol-5-yl]-1,2-benzoxazole-5-carbaldehyde (**Intermediate 390**)

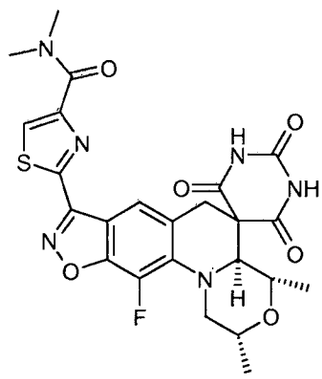
MS (ES) MH^+: 585.5 for $C_{26}H_{25}FN_6O_7S$

^1H NMR (400 MHz, DMSO-D6) δ: 0.9 (d, 3H), 1.15 (d, 3H), 2.9 (d, 1H), 3.1 (t, 1H), 3.3(m, 2H), 3.4 (m, 2H), 3.5 (m, 4H), 3.7 (m, 2H), 3.8 (m, 1H), 4.0 (d, 1H), 4.1 (d, 1H), 7.1 (s, 1H), 9.45 (s, 1H), 11.5 (s, 1H), 11.9 (s,1H).

Example 86

2-[(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-g]quinoline-5,5'-pyrimidin]-8-yl]-*N*,*N*-dimethyl-1,3-thiazole-4-carboxamide

(±)



Starting material: 2-{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-5-formyl-1,2-benzoxazol-3-yl}-*N*,*N*-dimethyl-1,3-thiazole-4-carboxamide (**Intermediate 391**)

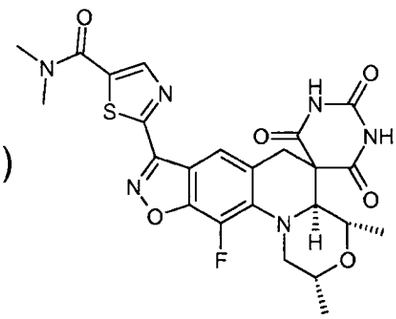
MS (ES) MH^+: 543 for $C_{24}H_{23}FN_6O_6S$.

^{1}H NMR (400 MHz, DMSO-D6) δ: 0.9 (d, 3H), 1.15 (d, 3H), 2.9(s, 3H), 3.0(s, 3H), 3.05 (d, 1H), 3.2 (t, 1H), 3.7 (m, 2H), 3.8 (m, 1H), 4.0 (d, 1H), 4.1 (d, 1H), 7.1 (s, 1H), 9.4 (s, 1H), 11.5 (bs, 1H), 11.8 (bs,1H).

Example 87

2-[(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-*N*,*N*-dimethyl-1,3-thiazole-5-carboxamide

(±)



Starting material: 2-{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-5-formyl-1,2-benzoxazol-3-yl}-*N*,*N*-dimethyl-1,3-thiazole-5-carboxamide (**Intermediate 392**)

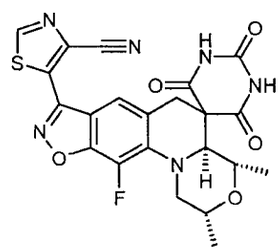
MS (ES) MH^+: 543 for $C_{24}H_{23}FN_6O_6S$.

^{1}H NMR (400 MHz, DMSO-D6) δ: 0.9 (d, 3H), 1.15 (d, 3H), 2.9 (d, 1H), 3.0(s, 3H), 3.1 (m, 1H), 3.2 (s, 3H), 3.7 (m, 1H), 3.8 (m, 2H), 4.0 (d, 1H), 4.1 (d, 1H), 7.1 (s, 1H), 9.4 (s, 1H), 11.5 (bs, 1H), 11.8 (bs,1H).

Example 88

5-[(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-1,3-thiazole-4-carbonitrile

(±)



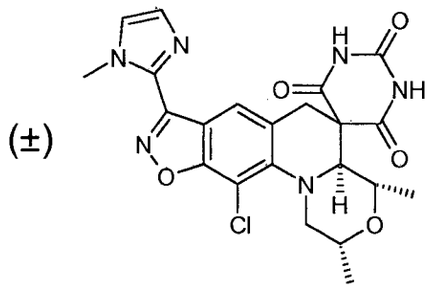
Starting material: 5-{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-5-formyl-1,2-benzoxazol-3-yl}-1,3-thiazole-4-carbonitrile (**Intermediate 393**)

MS (ES) MH^+: 497 for $C_{22}H_{17}FN_6O_5S$.

^1H NMR (400 MHz, DMSO-D6) δ: 0.9 (d, 3H), 1.15 (d, 3H), 3.0 (d, 1H), 3.1 (m, 1H), 3.6-3.8 (m, 3H), 4.0 (d, 1H), 4.1 (d, 1H), 7.4 (s, 1H), 9.6 (s, 1H), 11.5 (bs, 1H), 11.9 (bs,1H).

Example 89

(2*R*,4*S*,4a*S*)-rel-11-chloro-2,4-dimethyl-8-(1-methyl-1*H*-imidazol-2-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione isolated as the TFA salt from reverse phase HPLC purification.



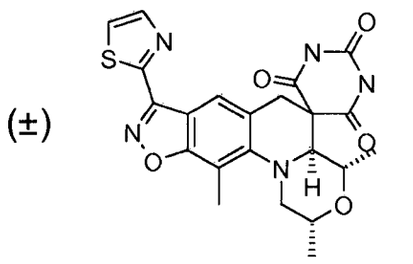
Starting material: 7-chloro-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-(1-methyl-1*H*-imidazol-2-yl)-1,2-benzoxazole-5-carbaldehyde (**Intermediate 387**).

MS (ES) MH^+: 485 for $C_{22}H_{21}ClN_6O_5$;

^1H NMR (400 MHz, DMSO-D6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 3.0 (d, 1H), 3.1 (m, 1H), 3.8 (m, 2H), 4.0 (m, 5H), 4.5 (d, 1H), 7.2 (s, 1H), 7.5 (s, 1H), 7.9 (s, 1H), 11.4 (s, 1H), 11.8 (s, 1H).

Example 90

(2*R*,4*S*,4a*S*)-rel-2,4,11-trimethyl-8-(1,3-thiazol-2-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione



Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-methyl-3-(1,3-thiazol-2-yl)-1,2-benzoxazole-5-carbaldehyde (**Intermediate 330**).

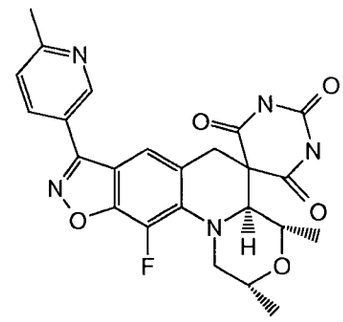
MS (ES) MH^+: 468 for $C_{22}H_{21}N_5O_5S$

^1H NMR (400 MHz, DMSO-d6) δ: 0.9 (d, 3H), 1.2 (d, 3H), 2.5 (s, 3H), 3.1 (m, 2H), 3.6 (m, 2H), 3.9 (m, 2H), 4.1 (d, 1H), 7.7 (s, 1H), 8.0 (d, 1H), 8.1(d, 1H) 11.4 (s, 1H), 11.8 (s, 1H).

Example 91

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(6-methylpyridin-3-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione

(±)



Starting material: 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(6-methylpyridin-3-yl)benzo[d]isoxazole-5-carbaldehyde (**Intermediate 421**).

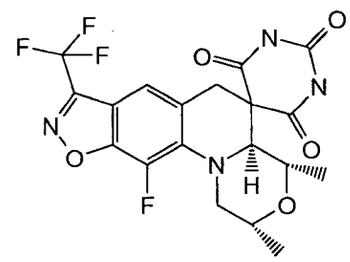
MS (ES) MH^+: 480 for $C_{24}H_{22}FN_5O_5$

^1H NMR (300 MHz, DMSO-d_6) δ: 0.89 (d, 3H), 1.15 (d, 3H), 2.57 (s, 3H), 2.88-3.24 (m, 2H), 3.51-4.22 (m, 5H), 7.49 (d, 1H), 7.59 (s, 1H), 8.19 (d, 1H), 8.97 (s, 1H), 11.48 (s, 1H), 11.86 (s, 1H).

Example 92

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(trifluoromethyl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione

(±)



Starting material: 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(trifluoromethyl)benzo[d]isoxazole-5-carbaldehyde (**Intermediate 429**).

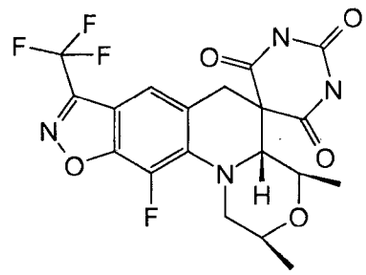
MS (ES) MH^+: 457 for $C_{19}H_{16}F_4N_4O_5$

^1H NMR (300 MHz, DMSO-d_6) δ: 0.89 (d, 3H), 1.14 (d, 3H), 2.86-3.24 (m, 2H), 3.54-4.28 (m, 5H), 7.35 (s, 1H), 11.56 (s, 1H), 11.91 (s, 1H).

The (2*S*,4*R*,4a*R*) and (2*R*,4*S*,4a*S*) enantiomers of **Example 92** were separated by Supercritical Fluid Chromatography using a Chiralpak AD, 21 x 250mm, 5μ column (elution with 25% MeOH, 75% CO_2 at 60 ml/min, 40°C, and 100 bar with detection at 220nm), providing **Example 92(a)** and **Example 92(b)**:

Example 92(a) - First Eluting Compound

(2S,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-(trifluoromethyl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione



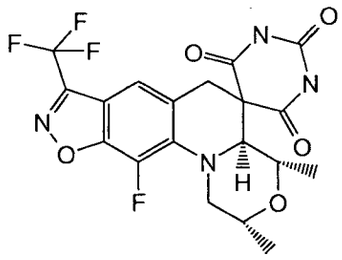
MS (ES) MH^+: 457 for $C_{19}H_{16}F_4N_4O_5$

^1H NMR (300 MHz, DMSO-d_6) δ: 0.89 (d, 3H), 1.14 (d, 3H), 2.83-3.21 (m, 2H), 3.57-4.23 (m, 5H), 7.34 (s, 1H), 11.72 (s, 2H).

>98% ee by chiral HPLC; [α] = +285 (c=0.1 in MeOH).

Example 92(b) - Second Eluting Compound

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-8-(trifluoromethyl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione



MS (ES) MH^+: 457 for $C_{19}H_{16}F_4N_4O_5$

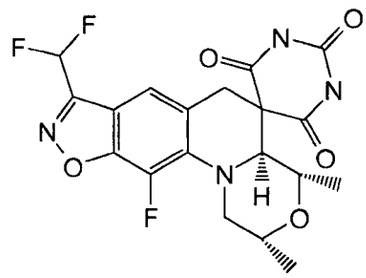
^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.89 (d, 3H), 1.14 (d, 3H), 2.89-3.25 (m, 2H), 3.56-4.30 (m, 5H), 7.34 (s, 1H), 11.72 (s, 2H).

>98% ee by chiral HPLC; [α] = -305 (c=0.1 in MeOH).

Example 93

(2*R*,4S,4a*S*)-rel-8-(difluoromethyl)-11-fluoro-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione

(±)



Starting material: 3-(difluoromethyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-5-carbaldehyde (**Intermediate 428**).

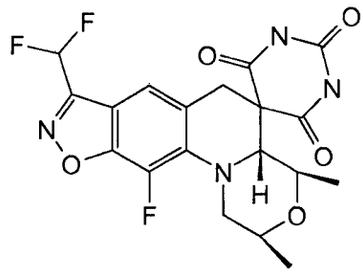
MS (ES) MH^+: 439 for $C_{19}H_{17}F_3N_4O5$

^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.88 (d, 3H), 1.14 (d, 3H), 2.82-3.24 (m, 2H), 3.55-4.20 (m, 5H), 7.30 (s, 1H), 7.52 (t, 1H), 11.52 (s, 1H), 11.87 (s, 1H).

The (2*S*,4*R*,4a*R*) and (2*R*,4*S*,4a*S*) enantiomers of **Example 93** were separated by Supercritical Fluid Chromatography using a Chiralpak AD, 21 x 250mm, 5μ column (elution with 25% MeOH, 75% CO_2 at 60 ml/min, 40°C, and 100 bar with detection at 220nm), providing **Example 93(a)** and **Example 93(b)**:

Example 93(a) - First Eluting Compound

(2S,4*R*,4a*R*)-8-(difluoromethyl)-11-fluoro-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione



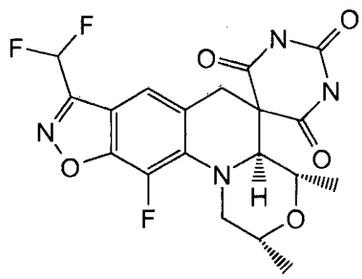
MS (ES) MH^+: 439 for $C_{19}H_{17}F_3N_4O_5$

^1H NMR (300 MHz, DMSO-d_6) δ: 0.88 (d, *J*=6.41 Hz, 3H), 1.14 (d, *J*=6.03 Hz, 3H), 2.84-3.21 (m, 2H), 3.56-4.19 (m, 5H), 7.30 (s, 1H), 7.52 (t, *J*=52.65 Hz, 1H), 11.67 (br s, 2H).

>98% ee by chiral HPLC; [α] = +276 (c=0.1 in MeOH).

Example 93(b) - Second Eluting Compound

(2*R*,4S,4a*S*)-8-(difluoromethyl)-11-fluoro-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione



MS (ES) MH^+: 439 for $C_{19}H_{17}F_3N_4O_5$

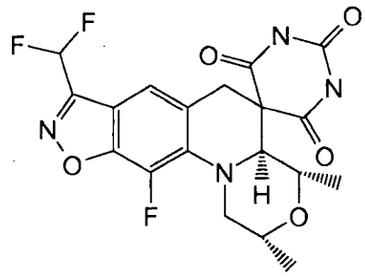
^1H NMR (300 MHz, DMSO-d_6) δ: 0.90 (d, 3H), 1.15 (d, 3H), 2.81-3.24 (m, 2H), 3.57-4.21 (m, 5H), 7.31 (s, 1H), 7.53 (t, 1H), 11.70 (br s, 2H).

>98% ee by chiral HPLC; [α] = -289 (c=0.1 in MeOH).

Using an alternate route, **Example 93(b)** was also obtained via a chiral synthesis similar to the one described for the synthesis of **Example 96**, using the indicated starting material:

Example 93(b) (Chiral Synthesis)

(2*R*,4S,4a*S*)-8-(difluoromethyl)-11-fluoro-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione



Starting material: 3-(difluoromethyl)-6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-5-carbaldehyde (**Intermediate 431**).

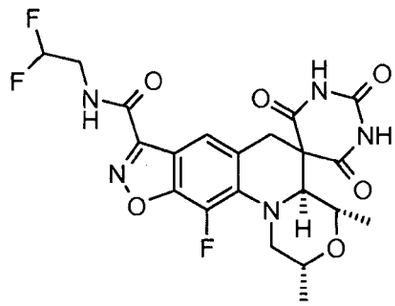
MS (ES) MH^+: 439 for $C_{19}H_{17}F_3N_4O_5$

^1H NMR (300 MHz, DMSO-d_6) δ: 0.90 (d, 3H), 1.15 (d, 3H), 2.81-3.24 (m, 2H), 3.57-4.21 (m, 5H), 7.31 (s, 1H), 7.53 (t, 1H), 11.70 (br s, 2H).

Example 94

(2*R*,4S,4a*S*)-rel-*N*-(2,2-difluoroethyl)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide

(±)



Starting material: Barbituric acid and *N*-(2,2-difluoroethyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formylbenzo[d]isoxazole-3-carboxamide were reacted (**Intermediate 467**) using a method similar to the one described for the synthesis of **Example 134**. The product was purified by reverse phase HPLC using a gradient of CH_3CN in water with 0.1% TFA.

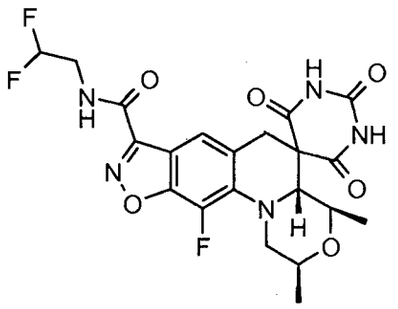
MS (ES) MH^+: 496 for $C_{21}H_{20}F_3N_5O_6$

^1H NMR (300 MHz, DMSO-d_6) δ ppm 0.9 (d, 3H), 1.2 (d, 3H), 2.9 (d, 1H), 3.1 (t, 1H), 3.6-3.9 (m, 5H), 4.0 (d, 1H), 4.1 (d, 1H), 5.9-6.4 (m, 1H), 7.4 (s, 1H), 9.3 (t, 1H), 11.6 (br. s., 2H).

The (2*S*,4*R*,4a*R*) and (2*R*,4*S*,4a*S*) enantiomers of **Example 94** were separated by Supercritical Fluid Chromatography using a Chiralpak AD, 21 x 250mm, 5μ column (elution with 25% MeOH, 75% CO_2 at 60 ml/min, 40°C, and 100 bar with detection at 220nm), providing **Example 94(a)** and **Example 94(b)**:

Example 94(a) - First Eluting Compound

(2S,4*R*,4a*R*)-*N*-(2,2-difluoroethyl)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide



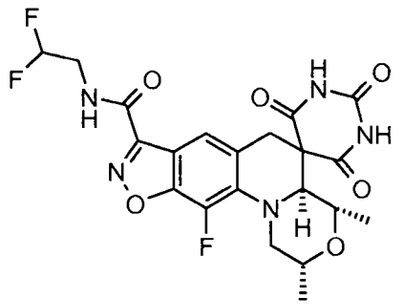
MS (ES) MH^+: 496 for $C_{21}H_{20}F_3N_5O_6$

^1H NMR (300 MHz, DMSO-d_6) δ ppm 0.9 (d, 3H), 1.2 (d, 3H), 2.9 (d, 1H), 3.1-3.2 (m, 1H), 3.6-3.9 (m, 5H), 4.0 (d, 1H), 4.1 (d, 1H), 5.9-6.4 (m, 1H), 7.5 (s, 1H), 9.3 (t, 1H), 11.5 (s, 1H), 11.8 (s, 1H).

>98% ee by chiral HPLC; [α] = +297 (c=0.1 in DMSO)

Example 94(b) - Second Eluting Compound

(2*R*,4S,4a*S*)-*N*-(2,2-difluoroethyl)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide



MS (ES) MH^+: 496 for $C_{21}H_{20}F_3N_5O_6$

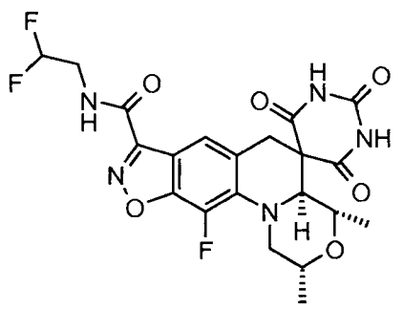
^1H NMR (300 MHz, DMSO-*d6*) δ ppm 0.9 (d, 3H), 1.2 (d, 3H), 2.9 (d, 1H), 3.1-3.2 (m, 1H), 3.6-3.9 (m, 5H), 4.0 (d, 1H), 4.1 (d, 1H), 5.9-6.4 (m, 1H), 7.5 (s, 1H), 9.3 (t, 1H), 11.5 (s, 1H), 11.8 (s, 1H).

>98% ee by chiral HPLC; [α] = -225 (c=0.1 in DMSO)

Using an alternate route, **Example 94(b)** was also obtained via a chiral synthesis similar to the one described for the synthesis of **Example 95(a)** below, using the indicated starting material:

Example 94(b) (Chiral Synthesis)

(2*R*,4S,4a*S*)-*N*-(2,2-difluoroethyl)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide



Starting Materal: *N*-(2,2-difluoroethyl)-6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-5-formylbenzo[d]isoxazole-3-carboxamide (**Intermediate 248**)

MS (ES) MH^+: 246 for $C_{21}H_{20}F_3N_5O_6$

>98% ee by chiral HPLC; [α] = -256 (c=0.1 in MeOH)

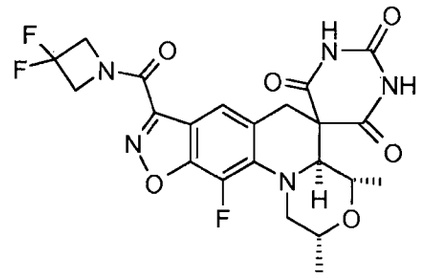
^{1}H NMR (300 MHz, DMSO-d6) δ ppm 0.9 (d, 3 H), 1.2 (d, 3 H), 2.9 (d, 1 H), 3.1 (t, 1 H), 3.6 - 3.9 (m, 4 H), 4.0 (d, 1 H), 4.1 (d, 1 H), 5.9 - 6.4 (m, 1 H), 7.4 (s, 1 H), 9.3 (t, J=6.0 Hz, 1 H), 11.5 (br. s., 1 H), 11.8 (br. s., 1 H)

Example 95 was prepared from the indicated starting material and barbituric acid using a method similar to the one described for the synthesis of **Example 134**. The compounds were purified by silica gel column chromatography using a gradient of DCM to ethyl acetate.

Example 95

(2*R*,4S,4a*S*)-rel-8-(3,3-difluoroazetidine-1-carbonyl)-11-fluoro-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione

(±)



Starting Material: 3-(3,3-difluoroazetidine-1-carbonyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-5-carbaldehyde (**Intermediate 446**)

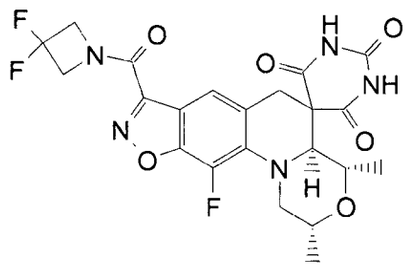
MS (ES) MH^+: 508 for $C_{22}H_{20}F_3N_5O_6$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.8 (d, 3H), 1.1 (d, 3H), 2.8 (d, 1H), 3.1 (t, 1H), 3.5-3.8 (m, 3H), 3.9 (d, 1H), 4.1 (d, 1H), 4.5 (t, 2H), 4.9 (t, 2H), 7.4 (s, 1H), 11.4 (br. s., 1H), 11.8 (br. s., 1H).

In an alternate route, the (2*R*,4S,4aS) enantiomer of **Example 95** was synthesized via a chiral synthesis, providing **Example 95(a)**:

Example 95(a)

(2*R*,4S,4a*S*)-8-(3,3-difluoroazetidine-1-carbonyl)-11-fluoro-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione



3-(3,3-difluoroazetidine-1-carbonyl)-6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-5-carbaldehyde (**Intermediate 245**, 2.08 g, 5.23 mmol) was dissolved in ~100ml of ethanol and heated with barbituric acid (0.704 g, 5.50 mmol) at 105°C (external temperature) for 6 days. The reaction was absorbed onto celite then purified on by silica gel chromatography using a gradient of DCM to ethyl acetate. Fractions were combined and concentrated. This material was then purified by Supercritical Fluid Chromatography (separation of diastereomers), using a Chiralpak AD, 21 x 250mm, 5μ column (elution with 40% isopropanol, 60% CO_2 at 60 ml/min, 40°C, and 100 bar with detection at 220nm), to give the title compound (2.16 g, 4.26 mmol, 81 %) as the first eluting compound.

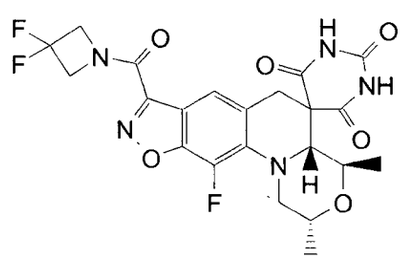
MS (ES) MH^+: 508 for $C_{22}H_{20}F_3N_5O_6$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.9 (d, 3H), 1.1 (d, 3H), 2.9 (d, 1H), 3.2 (t, 1H), 3.6-3.9 (m, 3H), 4.0 (d, 1H), 4.1 (d, 1H), 4.6 (t, 2H), 4.9 (t, 2H), 7.5 (s, 1H), 11.5 (br. s., 1H), 11.9 (br. s., 1H).

>98% ee by chiral HPLC; [α] = -296 (c=0.1 in MeOH)

Example 95(b)

(2*R*,4*R*,4a*R*)-8-(3,3-difluoroazetidine-1-carbonyl)-11-fluoro-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione



The (2*R*,4*R*,4a*R*) diastereomer was produced as a by-product of the reaction described for the synthesis of **Example 95(a)**. The chromatography described for **Example 95(a)** afforded (2*R*,4*R*,4a*R*) diastereomer as the second eluting compound.

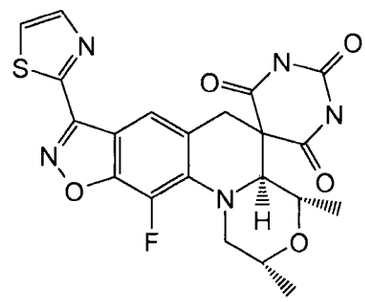
MS (ES) MH^+: 508 for $C_{22}H_{20}F_3N_5O_6$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.9 (d, 3 H), 1.3 (d, 3 H), 3.1 (d, 1 H), 3.6 (d, 1 H), 3.7 (d, 1 H), 3.8 (d, 1 H), 3.9 - 4.0 (m, 2 H), 4.0 - 4.2 (m, 1 H), 4.6 (t, 2 H), 4.9 (t, 2H), 7.5 (s, ml H), 11.5 (br. s., 1 H), 11.8 (br. s., 1 H)

[α] = +169 (c=0.1 in Methanol)

Example 96

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-8-(thiazol-2-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione



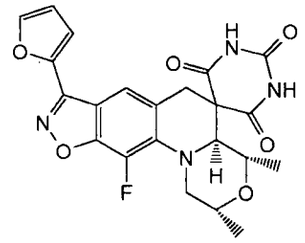
A mixture of 6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-3-(thiazol-2-yl)benzo[d]isoxazole-5-carbaldehyde (**Intermediate 430**, 1.414 g, 3.91 mmol) and pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (0.501 g, 3.91 mmol) in ethanol (200 ml) was heated at 90°C for 5 days. Solvent removed. LCMS of crude reaction indicates 9:1 mixture of two diastereomeric products. The major product was purified by reverse phase preparative HPLC to give the title compound (1.320 g, 71.6 %).

MS (ES) MH^+: 472 for $C_{21}H_{18}FN_5O_5S$

^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.89 (d, 3H), 1.15 (d, 3H), 2.85-3.23 (m, 2H), 3.60-4.22 (m, 5H), 7.72 (s, 1H), 8.08 (d, 1H), 8.17 (d, 1H), 11.48 (s, 1H), 11.84 (s, 1H).

Example 97

(2*R*,4S,4a*S*)-rel-11-fluoro-8-(furan-2-yl)-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione

(±) 

A mixture of 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(furan-2-yl)benzo[d]isoxazole-5-carbaldehyde (**Intermediate 427,** 95 mg, 0.28 mmol) and pyrimidine-2,4,6(1H,3H,5H)-trione (38.9 mg, 0.30 mmol) in isopropanol (10 ml) was heated at 90°C for 2 days. Solvent removed. Residue was triturated with methanol and the solid was filtered, washed with small amount of methanol, and dried to give title compound (107 mg, 85 %).

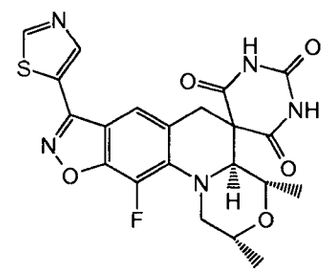
MS (ES) MH^+: 455 for $C_{22}H_{19}FN_4O_6$

^1H NMR (300 MHz, DMSO-d_6) δ: 0.89 (d, 3H), 1.14 (d, 3H), 2.89-4.23 (m, 7H), 6.79 (dd, 1H), 7.33 (d, 1H), 7.59 (s, 1H), 8.01 (d, 1H), 11.50 (s, 1H), 11.87 (s, 1H).

Examples 98 to 101 were prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Example 97**:

Example 98

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(thiazol-5-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione

(±) 

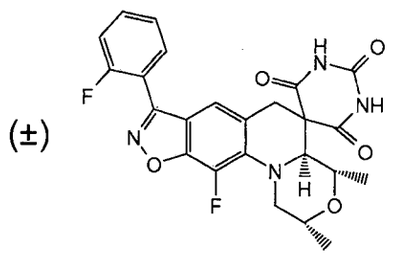
Starting material: 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(thiazol-5-yl)benzo[d]isoxazole-5-carbaldehyde (**Intermediate 422**)

MS (ES) MH^+: 472 for $C_{21}H_{18}FN_5O_5S$

^1H NMR (300 MHz, DMSO-d_6) δ: 0.89 (d, 3H), 1.15 (d, 3 H,) 2.92-3.24 (m, 2H), 3.43-4.23 (m, 5H), 7.74 (s, 1H), 8.72 (s, 1H), 9.37 (s, 1H), 11.52 (s, 1H), 11.89 (s, 1H).

Example 99

(2*R*,4S,4a*S*)-rel-11-fluoro-8-(2-fluorophenyl)-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione



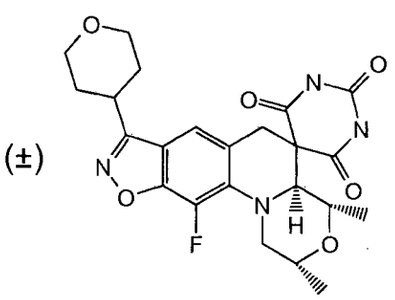
Starting material: 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(2-fluorophenyl)benzo[d]isoxazole-5-carbaldehyde (**Intermediate 423**):

MS (ES) MH^+: 483 for $C_{24}H_{20}F_2N_4O_5$

^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.88 (d, 3H), 1.15 (d, 3H), 2.86-3.21 (m, 2H), 3.50-4.21 (m, 5H), 7.22 (s, 1H), 7.30-7.88 (m, 4H), 11.46 (s, 1H), 11.82 (s, 1H).

Example 100

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(tetrahydro-2*H*-pyran-4-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione



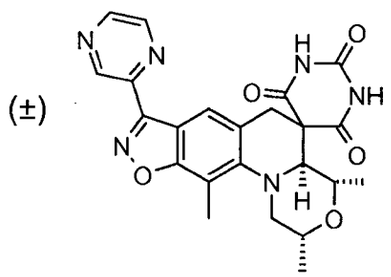
Starting material: 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(tetrahydro-2*H*-pyran-4-yl)benzo[d]isoxazole-5-carbaldehyde (**Intermediate 424**).

MS (ES) MH^+: 473 for $C_{23}H_{25}FN_4O_6$

^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.88 (d, 3H), 1.13 (d, 3H), 1.71-1.97 (m, 4H), 2.87-4.15 (m, 12H), 7.34 (s, 1H), 11.48 (s, 1H), 11.83 (s, 1H).

Example 101

(2*R*,4*S*,4a*S*)-rel-2,4,11-trimethyl-8-(pyrazin-2-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione



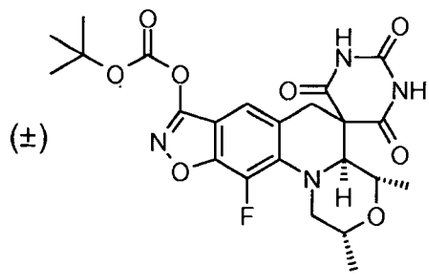
Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-methyl-3-(pyrazin-2-yl)-1,2-benzoxazole-5-carbaldehyde (**Intermediate 331**).

MS (ES) MH^+: 463 for $C_{23}H_{22}N_6O_5$

^{1}H NMR (400 MHz, DMSO-d6) δ: 0.9 (d, 3H), 1.2 (d, 3H), 2.5 (s, 3H), 3.1 (m, 2H), 3.6 (m, 2H), 3.9 (m, 2H), 4.1 (d, 1H), 7.7 (s, 1H), 8.3 (s, 1H), 8.8 (d, 1H), 8.9 (d, 1H), 9.3 (s, 1H), 11.5 (brs, 2H).

Example 102

tert-butyl (2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidin]-8-yl carbonate

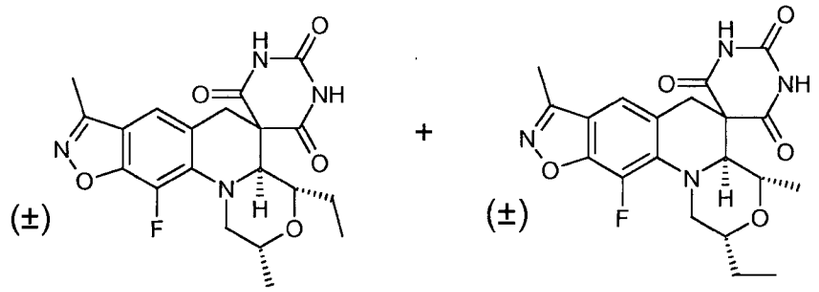


To a stirred solution of *tert*-butyl 6,7-difluoro-5-formyl-1,2-benzisoxazol-3-yl carbonate **Intermediate 531** (175 mg, 0.44 mmol) in dry IPA (10 mL) was added barbituric acid (8 mg, 0.062 mmol), and the solution heated around 80 °C for 12h. Solvents were evaporated and the residue was purified over a silica gel column to give product as a white solid. Yield: 40 mg (18%).

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 1.6 (s, 9H), 2.9 (d, 1H), 3.1 (t, 1H), 3.6 (d, 1H), 3.7 (m, 1H), 3.8 (m, 1H), 3.9 (d, 1H), 4.0 (d, 1H), 7.0 (s, 1H), 11.5 (s, 1H), 11.8 (s, 1H).

Examples 103 and 104

(2*R*,4*S*,4a*S*)-rel-8-acetyl-9,10-difluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione **(Example 103)** and (2*R*,4S,4a*S*)-rel-2-ethyl-11-fluoro-4,8-dimethyl-1,2,4,4a-tetrahydro-2'H,6*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione **(Example 104)**



To a solution of 6-(2-ethyl-6-methylmorpholin-4-yl)-7-fluoro-3-methyl-1,2-benzisoxazole-5-carbaldehyde (**Intermediate 501,** 3.0 g, 9.17 mmol) in IPA was added barbituric acid (1.4 g, 11.00 mmol) and the mixture heated at 85 °C for 12 hours. Solvents were evaporated and the residue thus obtained was purified over neutral alumina using a gradient of methanol in CH_2Cl_2 to give the product as an off white solid as a mixture of isomers. Yield: 3.0 g (75%).

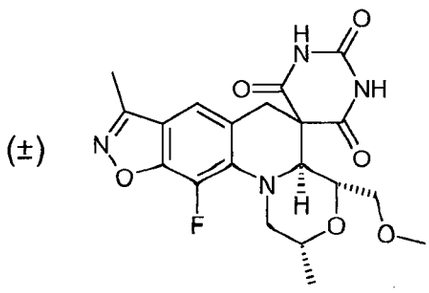
MS (ES) MH^+: 417 for $C_{20}H_{21}FN_4O_5$

^{1}H NMR (400 MHz – DMSO-D6) δ: 0.8 (t, 2H), 0.80 (d, 2H), 0.9 (t, 2H), 1.1 (t, 2H), 1.4 (m, 1H), 2.35 (s, 3H), 2.9 (m, 1H), 3.0 (m, 1H), 3.5 (m, 2H), 3.6-3.7 (m, 1H), 3.9 (m, 1H), 4.0 (m, 1H), 7.1 (d, 1H), 11.5 (br, 2H).

Examples 105 and 106 were prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Example 103 and 104.** The resulting 2 regioisomers were separated by chromatography.

Example 105 - First Eluting Compound

(2*R*,4*R*,4a*S*)-rel-11-fluoro-4-(methoxymethyl)-2,8-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione



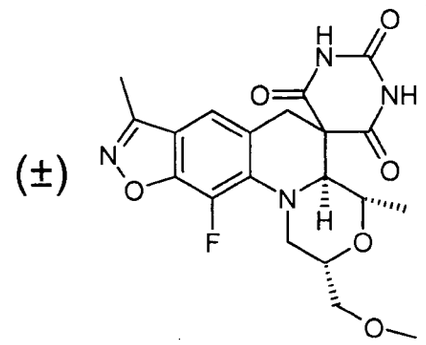
Starting material: 7-fluoro-6-[(2*S*,6*S*)-2-(methoxymethyl)-6-methylmorpholin-4-yl]-3-methyl-1,2-benzoxazole-5-carbaldehyde (**Intermediate 503**)

MS (ES) MH^+: 433 for $C_{20}H_{21}FN_4O_6$

^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.1 (d, 3H), 2.5 (s, 3H), 2.9 (d, 1H), 3.05 (s, 3H), 3.1 (m, 2H), 3.3 (m, 1H), 3.4 (m, 1H), 3.8 (m, 2H), 4.0 (m, 2H), 7.2 (s, 6H), 11.0 (s, 1H), 11.5 (s, 1H).

Example 106 - Second Eluting Compound

(2*S*,4*S*,4a*S*)-rel-11-fluoro-2-(methoxymethyl)-4,8-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione



Starting material: 7-fluoro-6-[(2*S*,6*S*)-2-(methoxymethyl)-6-methylmorpholin-4-yl]-3-methyl-1,2-benzoxazole-5-carbaldehyde (**Intermediate 503**)

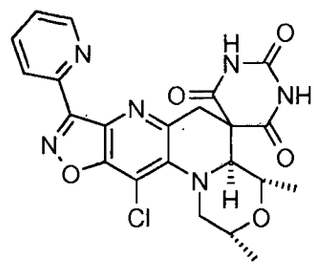
MS (ES) MH^+: 433 for $C_{20}H_{21}FN_4O_6$

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 2.5 (s, 3H), 3.0 (d, 1H), 3.25 (m, 1H), 3.3 (s, 3H), 3.3-3.4 (m, 2H), 3.5 (m, 1H), 3.7 (m, 1H), 3.8 (m, 1H), 3.9 (d, 1H), 4.1 (d, 1H), 7.2 (s, 6H), 11.4-11.8 (br, 2H).

Example 107

(2*R*,4S,4a*S*)-rel-11-chloro-2,4-dimethyl-8-(pyridyin-2-yl)-2,4,4*a*,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*) –trione (trifluoroacetic acid salt)

(±)



A mixture of 7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(pyridin-2-yl)isoxazolo[4,5-b]pyridine-5-carbaldehyde (**Intermediate 406**, 0.165 g, 0.44 mmol) and barbituric acid (0.057 g, 0.44 mmol) in 10 ml IPA was heated to 80 °C for 2 days. The mixture was concentrated, and the residue was purified by chromatography on silica gel using 10% methanol (0.1% ammonium hydroxide) in dichloromethane to give 170 mg of product as a white solid. Further purification was achieved by reverse phase HPLC on a Waters XBridge C-18 column eluting with 20-90% water/acetonitrile with trifluoroacetic acid to give 25 mg of the title compound as the mono trifluoracetic acid salt.

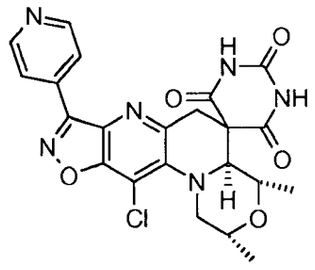
MS (ES) MH^+: 483 for $C_{22}H_{19}ClN_6O_5$ (trifluoroacetic acid salt)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.9 (d, 3H) 1.2 (br.s., 1H) 1.2 (d, 3H) 3.1 (dd, 1H) 3.3 (d, 1H) 3.5 – 3.7 (m, 1H) 3.9 – 4.0 (m, 1H) 4.4 (d, 1H) 5.7 (br.s., 1H) 7.6 (dd, 1H) 8.0 (t, 1H) 8.3 (d, 1H) 8.8 (d, 1H) 11.6 (s, 1H) 11.9 (s, 1H).

Examples 108 to 111 were prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Example 107**:

Example 108

(2*R*,4S,4a*S*)-rel-11-chloro-2,4-dimethyl-8-(pyridyin-4-yl)-2,4,4*a*,6-tetrahydro-1*H*, 1'*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)-trione (trifluoroacetic acid salt)

(±) 

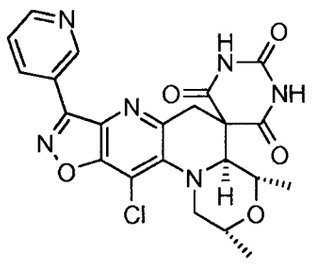
Starting material: 7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(pyridin-4-yl)isoxazolo[4,5-b]pyridine-5-carbaldehyde (**Intermediate 407**).

MS (ES) MH^+: 483 for $C_{22}H_{19}ClN_6O_5$

^1H NMR (300 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 3.1 (m, 1H), 3.3 (d, 1H), 3.6 (m, 1H), 3.7 (d, 1H), 4.0 (d, 2H), 4.4 (d, 1H), 8.3 (d, 2H), 8.8 (d, 2H), 11.6 (s, 1H), 12.0 (s, 1H).

Example 109

(2*R*,4S,4a*S*)-rel-11-chloro-2,4-dimethyl-8-(pyridyin-3-yl)-2,4,4*a*,6-tetrahydro-1*H*, 1'*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)-trione (trifluoroacetic acid salt)

(±) 

Starting material: 7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(pyridin-3-yl)isoxazolo[4,5-b]pyridine-5-carbaldehyde (**Intermediate 408**).

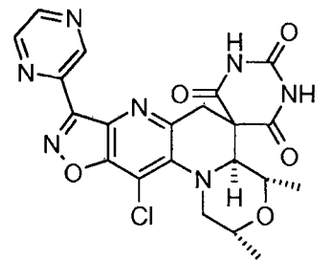
MS (ES) MH^+: 483 for $C_{22}H_{19}ClN_6O_5$

^1H NMR (300 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 4H), 3.1 (dd, 1H), 3.3 (d, 1H), 3.6 (dd, 1H), 3.7 (d, 1H), 3.9–4.0 (m, 2H), 4.4 (d, 1H), 7.6 (dd, 2H), 8.6 (dt, 1H), 8.8 (dd, 1H), 9.4 (d, 1H), 11.6 (s, 1H), 11.9 (s, 1H).

Example 110

(2*R*,4S,4a*S*)-rel-11-chloro-2,4-dimethyl-8-(pyrazin-2-yl)-2,4,4*a*,6-tetrahydro-1*H*, 1'*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)-trione (trifluoroacetic acid salt)

(±)



Starting material: 7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(pyrazin-2-yl)isoxazolo[4,5-b]pyridine-5-carbaldehyde (**Intermediate 409**).

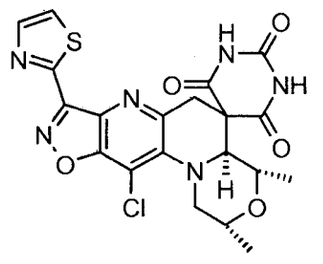
MS (ES) MH^+: 484 for $C_{21}H_{18}ClN_7O_5$

^1H NMR (300 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1-1.2 (m, 3H), 3.1 (d, 1H), 3.3 (d, 1H), 3.6 (d, 1H), 3.7 (d, 1H), 3.9–4.0 (m, 2H), 4.4 (d, 1H), 8.8–8.9 (m, 2H), 9.5 (d, 1H), 11.6 (s, 1H), 11.9 (s, 1H).

Example 111

(2*R*,4S,4a*S*)-rel-11-chloro-2,4-dimethyl-8-(thiazol-2-yl)-2,4,4*a*,6-tetrahydro-1*H*, 1'*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)-trione

(±)



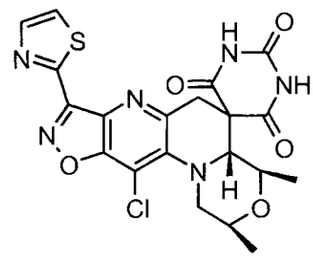
Starting material: 7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(thiazol-2-yl)isoxazolo[4,5-b]pyridine-5-carbaldehyde (**Intermediate 410**).

MS (ES) MH^+: 489 for $C_{20}H_{17}ClN_6O_5S$

^1H NMR (300 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1-.2 (m, 4H), 3.1 (dd, 1H), 3.3 (d, 1H), 3.6 (dd, 1H), 3.7 (d, 1H), 3.9 (m, 1H), 4.0 (d, 1H), 4.4 (br.s,1H), 8.1–8.2 (m, 1H), 11.6 (s, 1H), 11.9 (s, 1H).

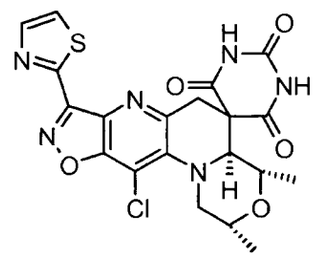
The (2*S*,4*R*,4a*R*) and (2*R*,4*S*,4a*S*) enantiomers of **Example 111** were separated by Supercritical Fluid Chromatography using a Chiralpak AD, 21 x 250mm, 5μ column (elution with 25% MeOH, 75% CO_2 at 60 ml/min, 40°C, and 100 bar with detection at 220nm), providing **Example 111(a)** and **Example 111(b)**:

Example 111(a) - First Eluting Compound
(2S,4*R*,4a*R*)-11-chloro-2,4-dimethyl-8-(thiazol-2-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'H)-trione



MS (ES) MH^+: 489 for $C_{20}H_{17}ClN_6O_5S$
^1H NMR (300 MHz, DMSO-d_6) δ: 0.9 (d, 3H) 1.0 (m, 1H) 1.1 (d, 3H) 3.1 (dd, 1H) 3.5–3.6 (m, 1H) 3.7 (d, 1H) 3.9 (m, 1H) 4.0 (d, 1H) 4.4 (d, 1H) 8.1 (m, 2H) 11.6 (s, 1H) 11.9 (s, 1H).
[α] = +130 (c=0.1 in ethanol)

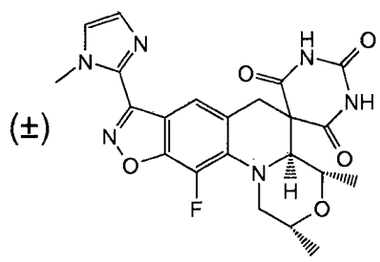
Example 111(b) – Second Eluting Compound
(2*R*,4S,4a*S*)-11-chloro-2,4-dimethyl-8-(thiazol-2-yl)-2,4,4*a*,6-tetrahydro-1*H*, 1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)-trione



MS (ES) MH^+: 489 for $C_{20}H_{17}ClN_6O_5S$
^1H NMR (300 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 3.1 (dd, 1H), 3.5–3.6 (m, 2H), 3.6–3.7 (m, 1H), 3.9 (m, 1H), 4.0 (d, 1H), 4.4 (d, 1H), 8.1–8.2 (m, 2H), 11.6 (s, 1H), 11.9 (s, 1H).
[α] = -132 (c=0.1 in ethanol)

Example 112

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(1-methyl-1*H*-imidazol-2-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione



A solution of (2*R*,4S,4a*R*)-rel-11-fluoro-2,4-dimethyl-8-(1-methyl-1*H*-imidazol-2-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'*H*)-trione (**Example 68**, 50 mg, 0.11 mmol) in ethanol (40 ml) was heated to reflux for 4 days. The solvent was removed and the residue was triturated with methanol. The resulting solid was filtered, washed with methanol, and dried to give 44 mg of product.

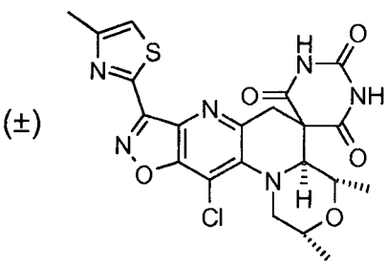
MS (ES) MH^+: 469 for $C_{22}H_{21}FN_6O_5$

^1H NMR (300 MHz, DMSO-d_6) δ: 0.9 (d, 3 H) 1.1 (d, 3 H) 7.2 (s, 1 H) 7.6 (s, 1 H) 7.8 (s, 1 H) 11.4 (s, 1 H) 11.8 (s, 1 H).

Examples 113 to 116 were prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Example 107**:

Example 113

(2*R*,4S,4a*S*)-rel-11-Chloro-2,4-dimethyl-8-(4-methylthiazol-2-yl)-2,4,4*a*,6-tetrahydro-1*H*, 1'*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)-trione



Starting material: 7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(4-methylthiazol-2-yl)isoxazolo[4,5-b]pyridine-5-carbaldehyde (**Intermediate 411**).

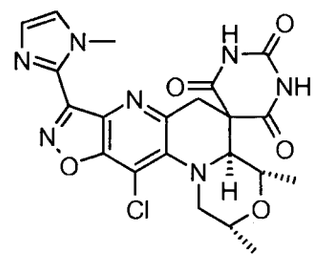
MS (ES) MH^+: 503 for $C_{21}H_{19}ClN_6O_5S$ .01[Trifluoroacetic acid]

^{1}H NMR (300 MHz, MeOD) δ: 1.0 (d, 3H) 1.2 (br.s, 1H) 1.2 (d, 3H) 2.4 – 2.6 (m, 3H) 3.16 (dd, 1H) 3.3-3.4 (m, 1H) 3.5 – 3.6 (m, 1H) 3.7 (d, 1H) 4.0 – 4.1 (m, 2H) 4.6 (dd, 1H) 4.8 (s, 2H) 7.4 (s, 1H).

Example 114

(2*R*,4S,4a*S*)-rel-11-Chloro-2,4-dimethyl-8-(1-methyl –1*H*-imidazol-2-yl)-2,4,4*a*,6-tetrahydro-1*H*, 1'*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)-trione (trifluoroacetic acid salt)

(±)



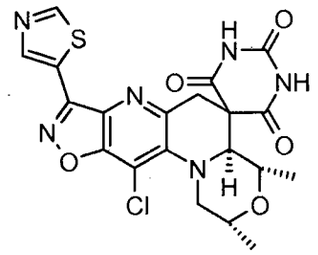
Starting material: 7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(1-methyl-1*H*-imidazol-2-yl)isoxazolo[4,5-b]pyridine-5-carbaldehyde (**Intermediate 412**).

MS (ES) MH^+: 486 for $C_{21}H_{20}ClN_7O_5$

^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.8 (d, 3H), 1.0 (m, 3H), 1.8 (s, 1H), 3.0–3.1 (m, 1H), 3.1 (d, 2H), 3.5–3.7 (m, 2H), 3.8 (m, 1H), 3.8–4.1(m, 3H), 4.0 (d, 1H), 4.4 (d, 1H), 7.1 (s, 1H), 7.4 – 7.5 (m, 1H).

Example 115

(2*R*,4S,4a*S*)-rel-11-chloro-2,4-dimethyl-8-(thiazol-5-yl)-2,4,4*a*,6-tetrahydro-1*H*, 1'*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)-trione (trifluoroacetic acid salt)

(±) 

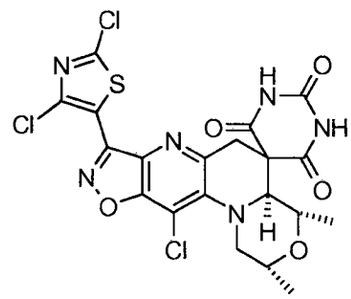
Starting material: 7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(thiazol-5-yl)isoxazolo[4,5-b]pyridine-5-carbaldehyde (**Intermediate 413**).

MS (ES) MH^+: 489 for $C_{20}H_{17}ClN_6O_5S$

^1H NMR (300 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.0-1.2 (m, 3H), 3.1 (dd, 1H), 3.3 (d, 1H) 3.5–3.6 (m, 1H), 3.8 (m, 1H), 3.9–4.0 (m, 2H), 4.4 (d, 1H), 8.9–9.0 (m, 1H), 9.3 – 9.5 (m, 1H), 11.5–11.6 (m, 1H), 11.9 (s, 1H).

Example 116

(2*R*,4S,4a*S*)-rel-11-chloro-2,4-dimethyl-8-(2,4-dichlorothiazol-5-yl)-2,4,4*a*,6-tetrahydro-1*H*, 1'*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)-trione (trifluoroacetic acid salt)

(±) 

Starting material: 7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(2,4-dichlorothiazol-5-yl)isoxazolo[4,5-b]pyridine-5-carbaldehyde (**Intermediate 420**).

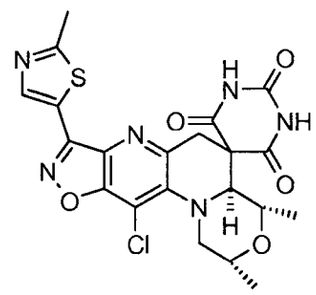
MS (ES) MH^+: 557 for $C_{20}H_{15}Cl_3N_6O_5S$

^1H NM*R* (300 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 3.1 (m, 1H), 3.1 (dd, 1H), 3.5–3.7 (m, 2H), 3.9–4.0 (m, 2H), 4.4 (d, 1H), 11.6 (s, 1H), 11.9 (s, 1H).

Example 117

(2*R*,4S,4a*S*)-rel-11-Chloro-2,4-dimethyl-8-(2-methylthiazol-5-yl)-2,4,4*a*,6-tetrahydro-1*H*, 1'*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)-trione

(±)



To isopropanol (20 ml) was added to 7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(2-methylthiazol-5-yl)isoxazolo[4,5-b]pyridine-5-carbaldehyde (**Intermediate 414**, 0.26 g, 0.66 mmol) and barbituric acid (0.085 g, 0.66 mmol), and the mixture was heated to 80 °C for about 2 days. The mixture was concentrated, and crystallization of the crude mixture from methanol gave 45 mg of the title compound.

MS (ES) MH^+: 503 for $C_{21}H_{19}ClN_6O_5S$

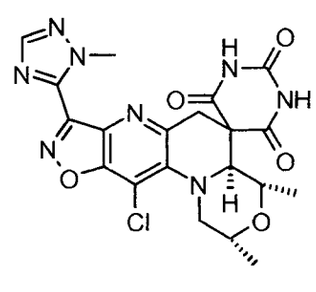
^{1}H NM*R* (300 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 2.6–2.8 (m, 3H), 3.0–3.2 (m, 1H), 3.3 (m, 1H), 3.5–3.6 (m, 1H), 3.7 (d, 1H), 4.0 (d, 2H), 4.4 (d, 1H), 8.6 (s, 1H), 11.6 (br.s, 1H), 11.9 (br.s, 1H).

Examples 118 and 119 were prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Example 117**:

Example 118

(2*R*,4S,4a*S*)-rel-11-chloro-2,4-dimethyl-8-(1-methyl-1*H*-1,2,4-triazol-5-yl)-2,4,4*a*,6-tetrahydro-1*H*, 1'*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)-trione

(±)



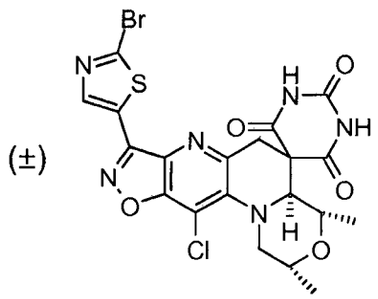
Starting material: 7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(1-methyl-1*H*-1,2,4-triazol-5-yl)isoxazolo[4,5-b]pyridine-5-carbaldehyde (**Intermediate 415**).

MS (ES) MH^+: 487 for $C_{20}H_{19}ClN_8O_5$

^1H NMR (300 MHz, DMSO-d_6) δ: 1.1 (d, 3H), 1.2 (d, 3H), 3.2 (t, 1H), 3.4–3.6 (m, 3H), 3.6–3.7 (m, 1H), 3.9 (m, 1H), 4.1 (d, 1H), 4.2 (s, 3H), 8.3 (s, 1H), 11.5 (s, 1H), 11.67 (s, 1H).

Example 119

(2*R*,4S,4a*S*)-rel-11-chloro-2,4-dimethyl-8-(2-bromothiazol-5-yl)-2,4,4*a*,6-tetrahydro-1*H*, 1'*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)-trione



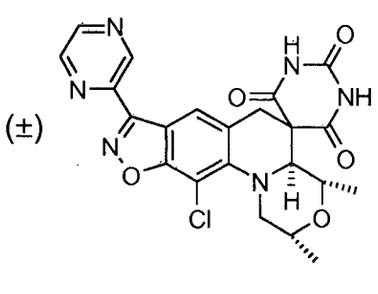
Starting material: 7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(2-bromothiazol-5-yl)isoxazolo[4,5-b]pyridine-5-carbaldehyde (**Intermediate 419**).

MS (ES) MH^+: 568 for $C_{20}H_{16}BrClN_6O_5S$

^1H NMR (300 MHz, chloroform-d) δ: 0.9 (d, 3H), 1.1 (d, 3H), 1.2 (d, 1H), 3.1 (m, 1H), 3.1 (d, 1H), 3.3 (s, 1H), 3.6 (dd, 1H), 3.7 (d, 1H), 3.9–4.0 (m, 2H), 4.4 (d, 1H), 8.6 (d, 1H).

Example 120

(2*R*,4S,4a*S*)-rel-11-chloro-2,4-dimethyl-8-(pyrazin-2-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione



Isopropanol (10ml) was added to 7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(pyrazin-2-yl)benzo[d]isoxazole-5-carbaldehyde (**Intermediate 472**, 198 mg, 0.53 mmol) to give a yellow slurry. The pyrimidine-2,4,6(1H,3H,5H)-trione (barbituric acid) (68.0 mg, 0.53 mmol) was added and the yellow mixture was heated to 80 °C. The resulting solution was stirred overnight. The resulting off-white suspension cooled to room temperature, then filtered. The filtercake was washed with MeOH/hexanes to give a white solid, 171 mg (67%).

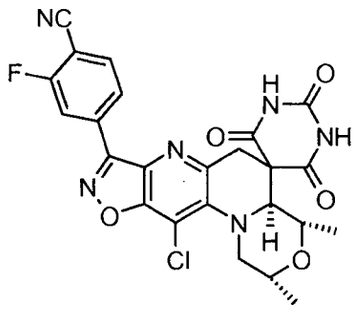
MS (ES) MH^+: 483 for $C_{22}H_{19}ClN_6O_5$

^1H NMR (300 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.2 (d, 3H), 3.0-3.1 (m, 2H), 3.6-3.8 (m, 2H), 3.9-4.1 (m, 2H), 4.5 (d, 1H). 7.9 (s, 1H), 8.8-8.9 (m, 2H), 9.3 (s, 1H), 11.4 (br s, 1H), 11.8 (br s, 1H).

Example 121

4-((2*R*,4S,4a*S*)-rel-11-chloro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4*a*,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-8-yl)-2-fluorobenzonitrile

(±)



To isopropanol (20 ml) was added to 4-(7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-formylisoxazolo[4,5-b]pyridin-3-yl)-2-fluorobenzonitrile (**Intermediate 416**, 0.126 g, 0.30 mmol) and barbituric acid (0.039 g, 0.30 mmol). The mixture was heated to 80 °C for about 2 days. The mixture was concentrated, and the residue was purified by chromatography on silica using 20% acetone in n-hexane. The solids obtained were triturated with methanol gave 41 mg of product.

MS (ES) MH^+: 525 for $C_{24}H_{18}ClFN_6O_5$

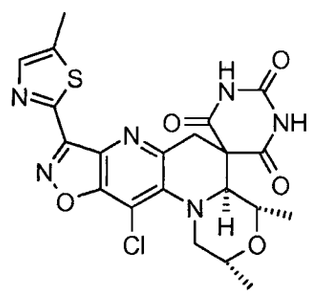
^1H NMR (300 MHz, DMSO-d_6) δ0.9 (d, 3H), 1.1 (d, 3H), 3.1 (dd, 1H), 3.3 (m, 1H), 3.6 (dd, 1H), 3.8 (d, 1H), 4.0 (d, 2H), 4.4 (m, 1H), 8.1 (t, 1H), 8.3–8.4 (m, 2H), 11.6 (s, 1H), 11.9 (s, 1H).

Examples 122 and 123 were prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Example 121**:

Example 122

(2*R*,4S,4a*S*)-rel-11-Chloro-2,4-dimethyl-8-(5-methylthiazol-2-yl)-2,4,4*a*,6-tetrahydro-1*H*, 1'*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'*H*)-trione

(±)



Starting material: 7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-(5-methylthiazol-2-yl)isoxazolo[4,5-b]pyridine-5-carbaldehyde (**Intermediate 418**).

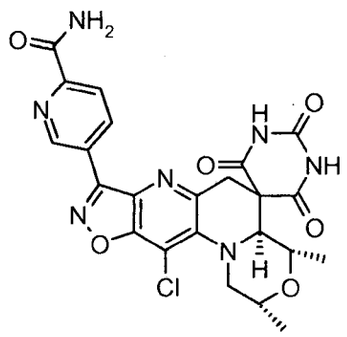
MS (ES) MH^+: 503 for $C_{21}H_{19}ClN_6O_5S$

^1H NMR (300 MHz, DMSO-d_6) δ: 1.1 (d, 3H), 1.2 (d, 3H), 2.6 (s, 3H), 3.1–3.3 (m, 2H), 3.1–3.7 (m, 1H), 3.8–4.0 (m, 1H), 4.1 (dd, 1H), 7.9 (s, 1H), 11.5 (s, 1H), 11.6 (s, 1H).

Example 123

5-((2*R*,4S,4a*S*)-rel-11-chloro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naphthyridine-5,5'-pyrimidine]-8-yl)picolinamide

(±)



Starting material: 5-(7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-formylisoxazolo[4,5-b]pyridin-3-yl)picolinonitrile (**Intermediate 417**).

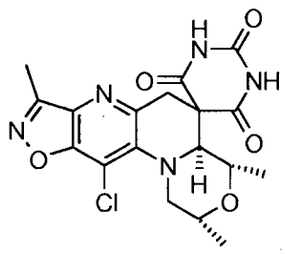
MS (ES) MH^+: 526 for $C_{23}H_{20}ClN_7O_6$

^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 3.1 (dd, 1H), 3.3–3.4 (m, 1H), 3.6 (dd, 1H), 3.7 (d, 1H), 4.0 (d, 1H), 4.4 (d, 1H), 7.8 (s, 1H), 8.1–8.3 (m, 2H), 8.8 (dd, 1H), 9.4 (d, 1H), 11.6 (s, 1H), 11.9 (s, 1H).

Example 124

(2*R*,4S,4a*S*)-rel-11-Chloro-2,4,8-trimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'H)-trione

(±)



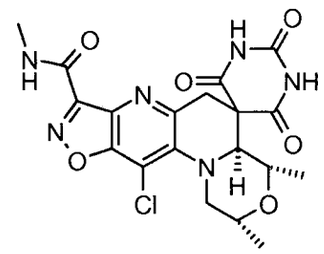
Isopropanol (12 ml) was added to 7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-3-methylisoxazolo[4,5-b]pyridine-5-carbaldehyde (**Intermediate 471**, 165 mg, 0.53 mmol) to give a yellow slurry; pyrimidine-2,4,6(1H,3H,5H)-trione (barbituric acid) (68.2 mg, 0.53 mmol) was added, and the mixture was heated to 80 °C. After about 5 days, the mixture was concentrated. The crude was purified by chromatography using 10-50% EtOAc/CH_2Cl_2 to give 95 mg yellow solid which was subsequently recrystallized from EtOAc/hexanes. A total of 57mg (19%) of the title product was obtained as a yellow solid.

MS (ES) MH^+: 420 for $C_{18}H_{18}ClN_5O_5$

^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.2 (d, 3H), 2.5 (s, 3H), 3.1 (m, 1H), 3.3 (m, under water peak, 1H), 3.5-3.7 (m 2H), 3.9-4.1 (m, 2H), 4.4 (dd, 1H), 11. 6 (br s, 1H), 11.7 (br s, 1H).

Example 125

(2*R*,4S,4a*S*)-rel-11-Chloro-*N*,2,4-trimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naphthyridine-5,5'-pyrimidine]-8-carboxamide

(±) 

7-Chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-formyl-*N*-methylisoxazolo[4,5-b]pyridine-3-carboxamide (**Intermediate 473**, 68 mg, 0.19 mmol) was dissolved in isopropanol to give a yellow solution, and pyrimidine-2,4,6(1H,3H,5H)-trione (24.69 mg, 0.19 mmol) was added to give a bright yellow slurry, which was heated to 80 °C for three days. The resulting dark orange suspension was concentrated, then purified by chromatography on SiO_2 using 20-60% $EtOAc/CH_2Cl_2$. A total of 32 mg (36%) of an off-white solid was obtained.

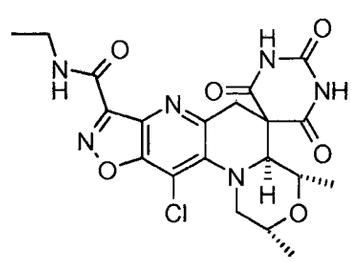
MS (ES) MH^+: 463 for $C_{19}H_{19}ClN_6O_6$

^1H NMR (300 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.2 (d, 3H), 2.8 (d, 3H), 3.1 (m, 1H), 3.3 (m under water peak, 1H), 3.5-3.7 (m, 2H), 3.9-4.1 (m, 2H), 4.4 (d, 1H). 8.8 (m, 1H), 11.6 (br s, 1H), 11.9 (br s, 1H).

Examples 126 to 133 were prepared from the indicated starting material and barbituric acid using a method similar to the one described for the syntheses of **Example 125**:

Example 126

(2*R*,4S,4a*S*)-rel-11-chloro-*N*-ethyl-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naphthyridine-5,5'-pyrimidine]-8-carboxamide

(±) 

Starting material: 7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-*N*-ethyl-5-formylisoxazolo[4,5-b]pyridine-3-carboxamide (**Intermediate 474**).

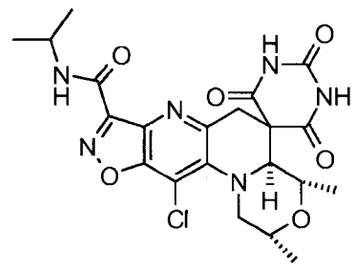
MS (ES) MH^+: 477 for $C_{20}H_{21}ClN_6O_6$

^1H NMR (300 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1-1.2 (overlapping m, 6H), 3.1 (m, 1H), 3.3 (m under water peak, 3H), 3.5-3.7 (m, 2H), 3.9-4.1 (m, 2H), 4.4 (d, 1H). 8. 8 (br t, 1H), 11.6 (br s, 1H), 11. 9 (br s, 1H).

Example 127

(2*R*,4S,4a*S*)-rel-Chloro-*N*-isopropyl-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naphthyridine-5,5'-pyrimidine]-8-carboxamide

(±)



Starting material: 7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-formyl-*N*-isopropylisoxazolo[4,5-b]pyridine-3-carboxamide (**Intermediate 475**).

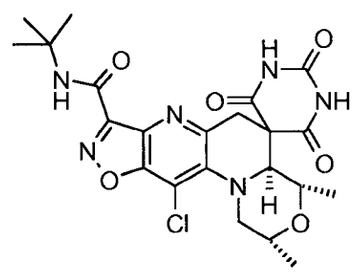
MS (ES) MH^+: 491 for $C_{21}H_{23}ClN_6O_6$

^1H NMR (300 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1-1.2 (overlapping m, 9H), 3.1 (m, 1H), 3.3 (m under water peak, 1H), 3.6 (m, 1H), 3.7 (d, 1H), 3.9 (m, 1H), 4.0 (d, 1H), 4.1 (m, 1H), 4.4 (d, 1H). 8.8 (d, 1H), 11.6 (br s, 1H), 11.9 (br s, 1H).

Example 128

(2*R*,4S,4a*S*)-rel-*N*-*tert*-butyl-11-chloro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naphthyridine-5,5'-pyrimidine]-8-carboxamide

(±)



Starting material: *N-tert*-butyl-7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-formylisoxazolo[4,5-b]pyridine-3-carboxamide (**Intermediate 476**).

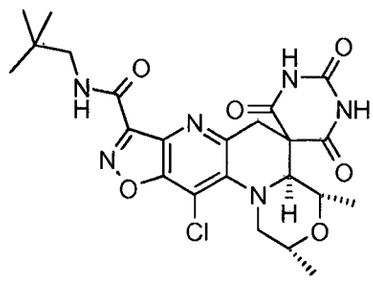
MS (ES) MH^+: 505 for $C_{22}H_{25}ClN_6O_6$

^1H NMR (300 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.2 (d, 3H), 1.4 (s, 9H), 3.1 (m, 1H), 3.3 (m under water peak, 1H), 3.6 (m, 1H), 3.7 (d, 1H), 3.9 (m, 1H), 4.0 (d, 1H), 4.4 (d, 1H). 8.4 (s, 1H), 11.6 (br s, 1H), 11.9 (br s, 1H).

Example 129

(2*R*,4S,4a*S*)-rel-11-Chloro-2,4-dimethyl-*N*-neopentyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naphthyridine-5,5'-pyrimidine]-8-carboxamide

(±)



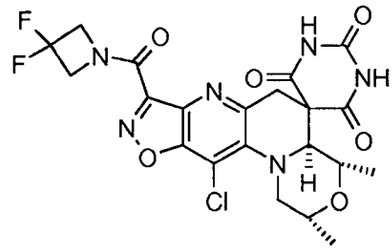
Starting material: 7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-formyl-*N*-neopentylisoxazolo[4,5-b]pyridine-3-carboxamide (**Intermediate 477**).

MS (ES) MH^+: 519 for $C_{23}H_{27}ClN_6O_6$

^1H NMR (300 MHz, DMSO-d_6) δ: 0.9-1.0 (overlapping m, 12H), 1.2 (d, 3H), 3.1-3.2 (overlapping m, 3H), 3.3 (m under water peak, 1H), 3.4-3.7 (m, 2H), 3.9-4.1 (m, 2H), 4.4 (m, 1H). 8.8 (t, 1H), 11.6 (br s, 1H), 11.9 (br s, 1H).

Example 130

(2*R*,4S,4a*S*)-rel-11-Chloro-8-(3,3-difluoroazetidine-1-carbonyl)-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naphthyridine-5,5'-pyrimidine]-2',4',6'(3'H)-trione

(±) 

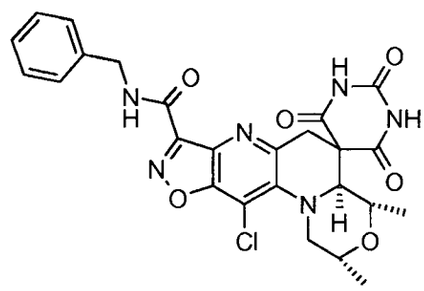
Starting material: 7-chloro-3-(3,3-difluoroazetidine-1-carbonyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)isoxazolo[4,5-b]pyridine-5-carbaldehyde (**Intermediate 478**).

MS (ES) MH^+: 525 for $C_{21}H_{19}ClF_2N_6O_6$

^1H NMR (300 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.2 (d, 3H), 3.1 (m, 1H), 3.3 (m under water peak, 1H), 3.6 (m, 1H), 3. 7 (d, 1H), 3.9 (m, 1H), 4.0 (d, 1H), 4.4 (d, 1H). 4.6 (t, 2H), 4.8 (t, 2H), 11.6 (br s, 1H), 11.9 (br s, 1H).

Example 131

(2*R*,4S,4a*S*)-rel-*N*-benzyl-11-chloro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naphthyridine-5,5'-pyrimidine]-8-carboxamide

(±) 

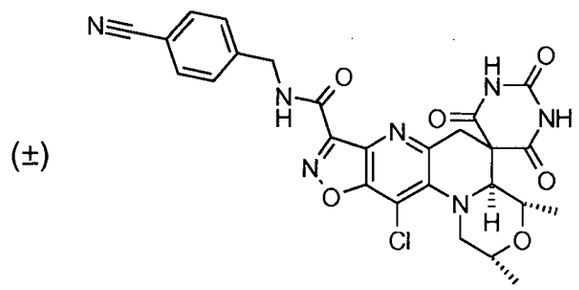
Starting material: *N*-benzyl-7-chloro-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-formylisoxazolo[4,5-b]pyridine-3-carboxamide (**Intermediate 479**).

MS (ES) MH^+: 539 for $C_{25}H_{23}ClN_6O_6$

^1H NMR (300 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.2 (d, 3H), 3.1 (m, 1H), 3.3 (m under water peak, 1H), 3.5-3.7 (m, 2H), 3.9-4.1 (m, 2H), 4.4-4. 6 (m, 3H), 7.2-7.4 (m, 5H), 9.4 (t, 1H), 11.6 (br s, 1H), 11.9 (br s, 1H).

Example 132

(2*R*,4S,4a*S*)-rel-11-chloro-*N*-(4-cyanobenzyl)-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naphthyridine-5,5'-pyrimidine]-8-carboxamide



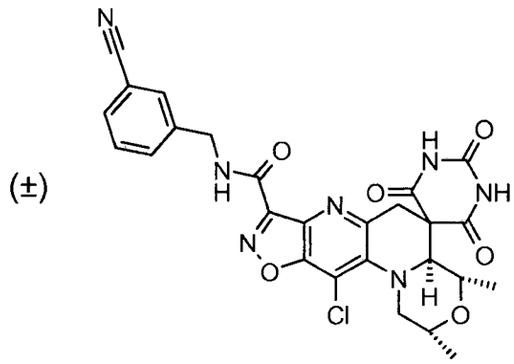
Starting material: 7-chloro-*N*-(4-cyanobenzyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-formylisoxazolo[4,5-b]pyridine-3-carboxamide (**Intermediate 480**).

MS (ES) MH^+: 564 for $C_{26}H_{22}ClN_7O_6$

^1H NMR (300 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.2 (d, 3H), 3.1 (m, 1H), 3.3 (m under water peak, 1H), 3.6-3.7 (m, 2H), 3.9 (m, 1H), 4.0 (d, 1H), 4.4 (d, 1H), 4.6 (d, 2H), 7.6 (d, 2H), 7.8 (d, 2H), 9.5 (t, 1H), 11.6 (br s, 1H), 11.9 (br s, 1H).

Example 133

(2*R*,4S,4a*S*)-rel-11-chloro-*N*-(3-cyanobenzyl)-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naphthyridine-5,5'-pyrimidine]-8-carboxamide



Starting material: 7-chloro-*N*-(3-cyanobenzyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-5-formylisoxazolo[4,5-b]pyridine-3-carboxamide (**Intermediate 481**).

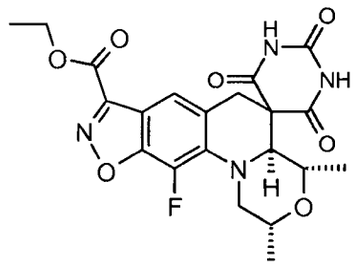
MS (ES) MH^+: 564 for $C_{26}H_{22}ClN_7O_6$

^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.2 (d, 3H), 3.1 (m, 1H), 3.3 (m under water peak, 1H), 3.5-3.7 (m, 2H), 3.9 (m, 1H), 4.0 (d, 1H), 4.4 (d, 1H), 4.6 (s, 2H), 7.6 (t, 1H), 7.7-7.8 (m, 2H), 7.8 (s, 1H), 8.5 (t, 1H), 11.6 (br s, 1H), 11.9 (br s, 1H).

Example 134

(2*R*,4S,4a*S*)-rel-ethyl 11-fluoro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxylate

(±)



Ethyl 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formylbenzo[d]isoxazole-3-carboxylate (**Intermediate 439**, 350 mg, 1.00 mmol) and barbituric acid (141 mg, 1.10 mmol) were heated to refux in ethanol (45 ml) for 64 hours. The reaction was concentrated. The residue was dissolved in DCM, absorbed onto silica and purified by silica gel column chromatography using a gradient of DCM to ethyl acetate, to give the title compound (412 mg, 76%) as a racemic mixture.

MS (ES) MH^+: 461 for $C_{21}H_{21}FN_4O_7$

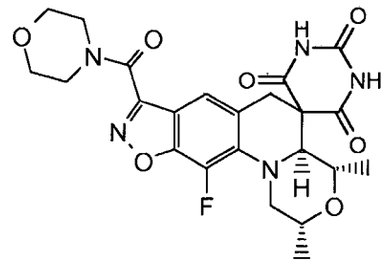
^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.89 (d, 3H) 1.04-1.25 (m, 6H) 2.93 (d, 1H) 3.13 (t, 1H) 3.60-3.71 (m, 1H) 3.72-3.87 (m, 2H) 3.97 (d, 1H) 4.12 (d, 1H) 4.44 (q, 2H) 7.43 (s, 1H) 11.49 (br. s., 1H) 11.86 (br. s., 1H)

Examples 135 to 140 were prepared from the indicated starting material and barbituric acid using a method similar to the one described for the synthesis of **Example 134**. The compounds were purified either by silica gel column chromatography using a gradient of DCM to ethyl acetate or by reverse phase HPLC using a gradient of CH_3CN in water with 0.1% TFA.

Example 135

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(morpholine-4-carbonyl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione

(±)



Starting material: 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(morpholine-4-carbonyl)benzo[d]isoxazole-5-carbaldehyde (**Intermediate 440**).

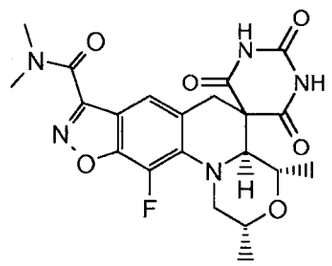
MS (ES) MH^+: 502 for $C_{23}H_{24}FN_5O_7$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.9 (d, 3H), 1.15 (d, 3H), 2.9 (d, 1H), 3.1 (t, 1H), 3.6-3.8 (m, 10H), 3.7-3.9 (m, 1H), 4.0 (d, 1H), 4.12 (d, 1H), 7.3 (s, 1H), 11.5 (br. s., 1H), 11.9 (br. s., 1H).

Example 136

(2*R*,4S,4a*S*)-rel-11-fluoro-*N*,*N*,2,4-tetramethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide

(±)



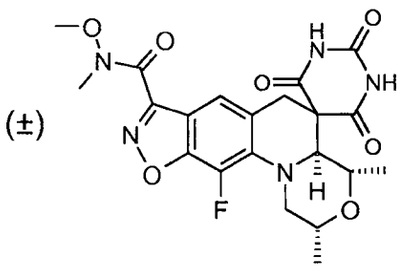
Starting material: 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formyl-*N*,*N*-dimethylbenzo[d]isoxazole-3-carboxamide (**Intermediate 470**).

MS (ES) MH^+: 460 for $C_{21}H_{22}FN_5O_6$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.9 (d, 3H), 1.1 (d, 3H), 2.9 (d, 1H), 3.1 (d, 7H), 3.6-3.7 (m, 2H), 3.7-3.9 (m, 1H), 4.0 (d, 1H), 4.1 (d, 1H), 7.2 (s, 1H), 11.5 (br. s., 1H), 11.9 (br. s., 1H).

Example 137

(2*R*,4S,4a*S*)-rel-11-fluoro-*N*-methoxy-*N*,2,4-trimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide



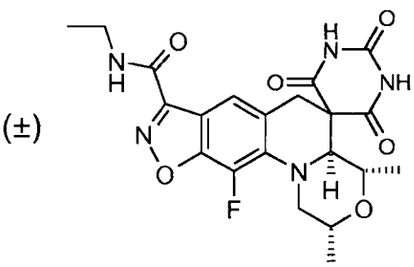
Starting material: 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formyl-*N*-methoxy-*N*-methylbenzo[d]isoxazole-3-carboxamide (**Intermediate 441**)

MS (ES) MH^+: 476 for $C_{21}H_{22}FN_5O_7$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.9 (d, 3H), 1.2 (d, 3H), 2.9 (d, 1H), 3.1 (t, 1H), 3.4 (br. s., 3H), 3.6-3.9 (m, 6H), 4.0 (d, 1H), 4.1 (d, 1H), 7.3 (s, 1H), 11.5 (s, 1H), 11.9 (s, 1H).

Example 138

(2*R*,4S,4a*S*)-rel-*N*-ethyl-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide



Starting material: 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-*N*-ethyl-7-fluoro-5-formylbenzo[d]isoxazole-3-carboxamide, (**Intermediate 442**)

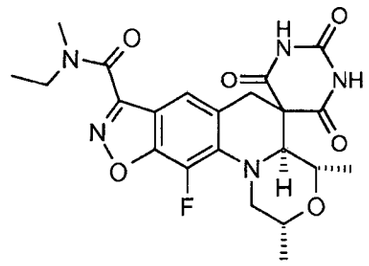
MS (ES) MH^+: 460 for $C_{21}H_{22}FN_5O_6$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.9 (d, 3H), 1.1-1.2 (m, 6H), 2.9 (d, 1H), 3.1 (t, 1H), 3.3-3.3 (m, 2H), 3.6-3.9 (m, 3H), 4.0 (d, 1H), 4.1 (d, 1H), 7.4 (s, 1H), 9.0 (t, 1H), 11.5 (s, 1H), 11.9 (s, 1H).

Example 139

(2*R*,4S,4a*S*)-rel-*N*-ethyl-11-fluoro-*N*,2,4-trimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide

(±)



Starting Material: 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-*N*-ethyl-7-fluoro-5-formyl-*N*-methylbenzo[d]isoxazole-3-carboxamide (**Intermediate 443**)

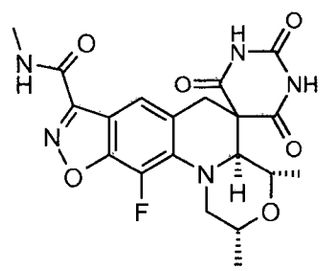
MS (ES) MH^+: 474 for $C_{22}H_{24}FN_5O_6$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.9 (d, 3H), 1.1-1.2 (m, 6H), 2.9 (d, 1H), 3.1 (d, 3H), 3.15 (d, 1H), 3.4-3.5 (m, 1H), 3.5 (d, 1H), 3.6-3.7 (m, 2H), 3.7-3.9 (m, 1H), 3.9 (d, 1H), 4.1 (d, 1H), 7.2 (d, 1H), 11.5 (br. s., 1H), 11.9 (br. s., 1H).

Example 140

(2*R*,4S,4a*S*)-rel-11-fluoro-*N*,2,4-trimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide

(±)



Starting Material:6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formyl-*N*-methylbenzo[d]isoxazole-3-carboxamide (**Intermediate 444**)

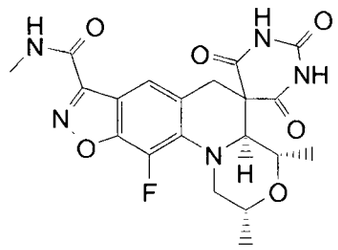
MS (ES) MH^+: 446 for $C_{20}H_{20}FN_5O_6$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.9 (d, 3H), 1.1 (d, 3H), 2.8 (d, 3H), 2.9 (d, 1H), 3.1 (t, 1H), 3.6-3.9 (m, 3H), 3.95 (d, 1H), 4.1 (d, 1H), 7.4 (s, 1H), 8.8 – 9.0 (m, 1H), 11.5 (br. s., 1H), 11.8 (br. s., 1H).

In an alternate route, the (2*R*,4S,4aS) enantiomer of **Example 140** was synthesized via a chiral synthesis similar to the one described for the synthesis of **Example 95(a)**, using barbituric acid and the indicated starting material, providing **Example 140(a)**:

Example 140(a) – (Chiral Synthesis)

(2*R*,4S,4a*S*)-11-fluoro-*N*,2,4-trimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide



Starting material: 6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-5-formyl-*N*-methylbenzo[d]isoxazole-3-carboxamide (**Intermediate 247**; purification by reverse phase HPLC using a gradient of CH_3CN in water with 0.1% TFA.

MS (ES) MH^+: 446 for $C_{20}H_{20}FN_5O_6$

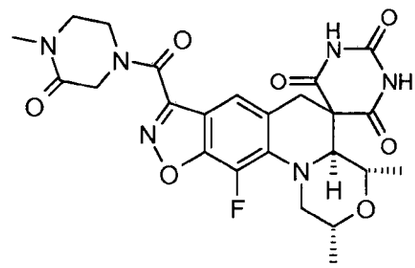
^1H NMR (300 MHz, DMSO-d_6) δ ppm 0.9 (d, 3H), 1.2 (d, 3H), 2.8 (d, 3H), 2.9 (d, 1H), 3.1 (t, 1H), 3.6-3.9 (m, 4H), 4.0 (d, 1H), 4.1 (d, 1H), 7.5 (s, 1H), 8.9 (d, 1H), 11.5 (s, 1H), 11.9 (s, 1H).

>98% ee by chiral HPLC; [α] = -263 (c=0.1 in MeOH)

Examples 141 and 142 were prepared from the indicated starting material and barbituric acid using a method similar to the one described for the synthesis of **Example 134**. The compounds were purified either by silica gel column chromatography using a gradient of DCM to ethyl acetate or by reverse phase HPLC using a gradient of CH_3CN in water with 0.1% TFA.

Example 141

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(4-methyl-3-oxopiperazine-1-carbonyl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione

(±) 

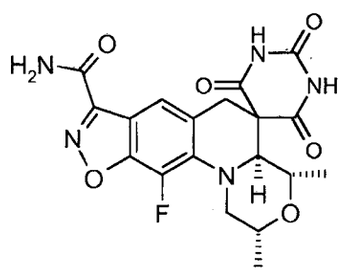
Starting Material: 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(4-methyl-3-oxopiperazine-1-carbonyl)benzo[d]isoxazole-5-carbaldehyde (**Intermediate 445**)

MS (ES) MH^+: 529 for $C_{24}H_{25}FN_6O_7$

^1H NMR (300 MHz, DMSO-d_6) δ ppm 0.8 (d, 3H), 1.1 (d, 3H), 2.8 (d, 4H), 3.1 (t, 1H), 3.3-3.4 (m, 2H), 3.7 (d, 2H), 3.9 (d, 3H), 4.0 (d, 1H), 4.1-4.4 (m, 2H), 7.2-7.3 (m, 1H), 11.5 (br. s., 1 H, 11.8 (s, 1H).

Example 142

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-^1H,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide

(±) 

Starting material: 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formylbenzo[d]isoxazole-3-carboxamide (**Intermediate 447**)

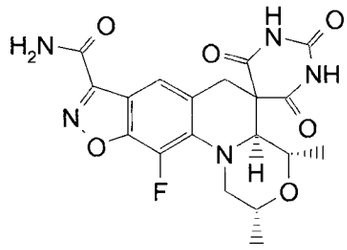
MS (ES) MH^+: 432 for $C_{19}H_{18}FN_5O_6$

^1H NMR (300 MHz, DMSO-d_6) δ ppm 0.9 (d, 3H), 1.1-1.3 (m, 3H), 2.9 (d, 1H), 3.2 m, 1H), 3.6-3.9 (m, 3H), 3.9-4.2 (m, 2H), 7.5 (s, 1H), 8.0 (s, 1H), 8.3 (s, 1H), 11.5 (br. s., 1H), 11.8 (br. s., 1H).

Using an alternate route, the (2*R*, 4S, 4aS) enantiomer of **Example 142** was also obtained via a chiral synthesis similar to the one described for the synthesis of **Example 95(a)**, using barbituric acid and the indicated starting material:

Example 142(a)

(2*R*,4S,4a*S*)-11-fluoro-2,4-diethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide



Starting material: 6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-5-formylbenzo [d]isoxazole-3-carboxamide (**Intermediate 469**); purification by reverse phase HPLC using a gradient of CH_3CN in water with 0.1% TFA.

MS (ES) MH^+: 432 for $C_{19}H_{18}FN_5O_6$

^1H NMR (300 MHz, DMSO-d_6) δ ppm 0.8 (d, 3H), 1.1 (d, 3H), 2.8 (d, 1H), 2.98-3.1 (m, 1H), 3.5-3.8 (m, 3H), 3.9 (d, 1H), 4.0 (d, 1H), 7.4 (s, 1H), 7.9 (s, 1H), 8.3 (s, 1H).

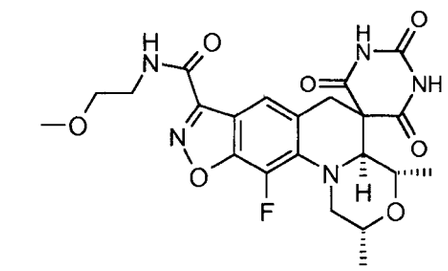
[α] = -204 (c=0.1 in MeOH)

Examples 143 to 147 were prepared from the indicated starting material and barbituric acid using a method similar to the one described for the synthesis of **Example 134**. The compounds were purified either by silica gel column chromatography using a gradient of DCM to ethyl acetate or by reverse phase HPLC using a gradient of CH_3CN in water with 0.1% TFA.

Example 143

(2*R*,4S,4a*S*)-rel-11-fluoro-*N*-(2-methoxyethyl)-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide

(±)



Starting material: 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formyl-*N*-(2-methoxyethyl)benzo[d]isoxazole-3-carboxamide (**Intermediate 448**)

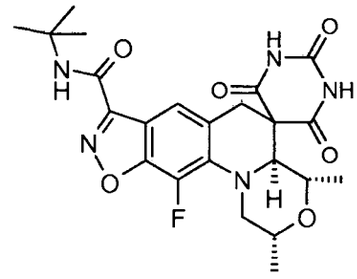
MS (ES) MH^+: 490 for $C_{22}H_{24}FN_5O_7$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.9 (d, 3H), 1.1 (d, 3H), 2.9 (d, 1H), 3.1 (t, 1H), 3.3 (s, 3H), 3.5 (br. s., 4H), 3.6-3.9 (m, 3H), 4.0 (d, 1H), 4.1 (d, 1H), 7.4 (s, 1H), 8.9 (br. s., 1H), 11.5 (br. s., 1H), 11.8 (br. s., 1H).

Example 144

(2*R*,4S,4a*S*)-rel-*N*-*tert*-butyl-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide

(±)



Starting material: *N*-*tert*-butyl-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formylbenzo[d]isoxazole-3-carboxamide (**Intermediate 449**)

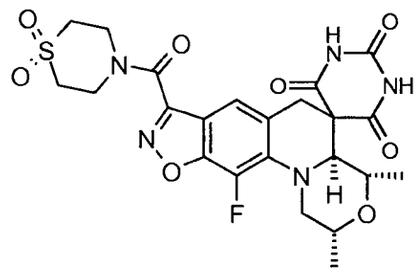
MS (ES) MH^+: 488 for $C_{23}H_{26}FN_5O_6$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.9 (d, 3H), 1.1 (d, 3H), 1.4 (s, 9H), 2.9 (d, *J*=1H), 3.1 (t, 1H), 3.6-3.9 (m, 3H), 4.0 (d, 1H), 4.1 (d, 1H), 7.4 (s, 1H), 8.3 (s, 1H), 11.3-12.0 (m, 2H).

Example 145

(2*R*,4S,4a*S*)-rel-8-[(1,1-dioxidothiomorpholin-4-yl)carbonyl]-11-fluoro-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione

(±)



Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3-[(1,1-dioxidothiomorpholin-4-yl)carbonyl]-7-fluoro-1,2-benzisoxazole-5-carbaldehyde (**Intermediate 450**)

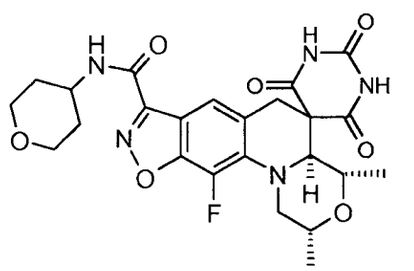
MS (ES) MH^+: 550 for $C_{23}H_{24}FN_5O_8S$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.8 (d, 3H), 1.1 (d, 3H), 2.81-2.9 (m, 2H), 2.9-3.1 (m, 2H), 3.3-3.4 (m, 2H), 3.5-3.7 (m, 2H), 3.7-3.8 (m, 1H), 3.0 (d, 1H), 4.0-4.2 (m, 5H), 7.3 (s, 1H), 11.2 – 12.0 (m, 1H).

Example 146

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-*N*-(tetrahydro-2*H*-pyran-4-yl)-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide

(±)



Starting material: 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formyl-*N*-(tetrahydro-2*H*-pyran-4-yl)benzo[d]isoxazole-3-carboxamide (**Intermediate 451**)

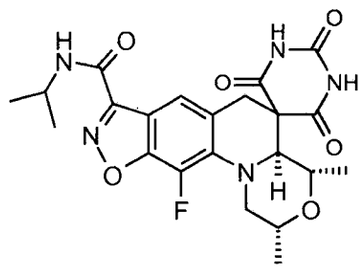
MS (ES) MH^+: 516 for $C_{24}H_{26}FN_5O_7$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.9 (d, 3H), 1.1 (d, 3H), 1.5-1.8 (m, 4H), 2.9 (d, 1H), 3.1 (t, 1H), 3.4-3.4 (m, 2H), 3.6-4.2 (m, 8H), 7.4 (s, 1H), 8.9 (d, 1H), 11.6 (br. s., 2H).

Example 147

(2*R*,4S,4a*S*)-rel-11-fluoro-*N*-isopropyl-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide

(±)



Starting material: 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formyl-*N*-isopropylbenzo[d]isoxazole-3-carboxamide (**Intermediate 452**)

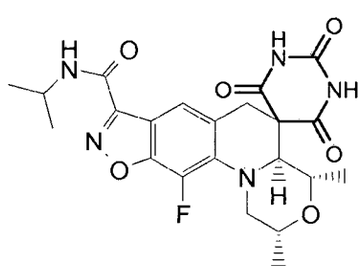
MS (ES) MH^+: 474 for $C_{22}H_{24}FN_5O6$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.9 (d, 3H), 1.1-1.3 (m, 9H), 2.9 (d, 1H), 3.1 (t, 1H), 3.6-3.9 (m, 3H), 4.0 (d, 1H), 4.0-4.2 (m, 2H), 7.4 (s, 1H), 8.8 (d, 1H).

Using an alternate route, the (2*R*, 4*S*, 4a*S*) enantiomer of **Example 147** was also obtained via a chiral synthesis similar to the one described for the synthesis of **Example 95(a)**, using barbituric acid and the indicated starting material:

Example 147(a)

(2*R*,4S,4a*S*)-11-fluoro-*N*-isopropyl-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide



Starting materials: 6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-5-formyl-*N*-isopropylbenzo[d]isoxazole-3-carboxamide (**Intermediate 246**); purification by Super Critical

Fluid chromatography on a Chiralpac IC column with a 35% MeOH, 65% CO_2 mobile phase to give product as a solid as the first eluting compound.

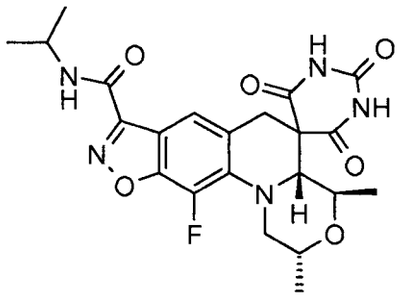
MS (ES) MH^+: 474 for $C_{22}H_{24}FN_5O_6$

^1H NMR (300 MHz, DMSO-*d*6) δ ppm 0.9 (d, 3H), 1.1-1.3 (m, 9H), 2.9 (d, 1H), 3.1 (t, 1H), 3.6-3.8 (m, 2H), 3.8-3.9 (m, 1H), 4.0 (d, 1H), 4.0-4.2 (m, 2H), 7.4 (s, 1H), 8.8 (d, 1H), 11.5 (s, 1H), 11.8 (s, 1H).

>98% ee by chiral HPLC; [α] = -259 (c=0.1 in MeOH)

Example 147(b)

(2*R*,4*R*,4a*R*)-11-fluoro-*N*-isopropyl-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide



The (2*R*,4*R*,4a*R*) diastereomer was produced as a by-product of the reaction described for the synthesis of **Example 147(a)**. The chromatography described for **Example 147(a)** afforded (2*R*,4*R*,4a*R*) diastereomer as the second eluting compound.

MS (ES) MH^+: 474 for $C_{22}H_{24}FN_5O_6$

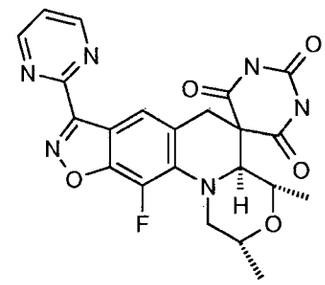
^1H NMR (300 MHz, DMSO-*d*6) δ ppm 0.9 (d, 3 H), 1.1 (d, 6 H), 1.2 (d, 3 H), 3.0 (d, 1H), 3.5 - 3.7 (m, 2 H), 3.7 (d, 1 H), 3.8 - 4.0 (m, 2 H), 4.0 - 4.2 (m, 2 H), 7.4 (s, 1 H), 8.7 (d, 1 H), 11.4 (br. s., 1 H), 11.7 (br. s., 1 H)

Example 148 was prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Example 97**:

Example 148

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(pyrimidin-2-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

(±)



Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(pyrimidin-2-yl)-1,2-benzoxazole-5-carbaldehyde (**Intermediate 587**)

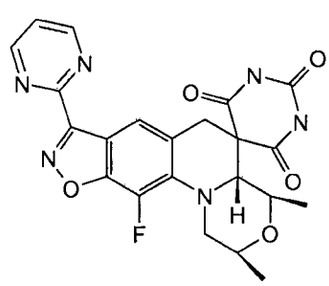
MS (ES) MH^+: 467 for $C_{22}H_{19}FN_6O_5$

^1H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.2 (d, 3H), 3.0 (d, 1H), 3.1 (t, 1H), 3.7 (m, 3H), 4.0 (d, 1H), 4.1 (d, 1H), 7.7 (m, 1H), 7.9 (s, 1H), 8.1 (d, 1H), 9.0 (s, 2H), 11.5 (s, 1H), 11.8 (s, 1H).

The (2*S*,4*R*,4a*R*) and (2*R*,4*S*,4a*S*) enantiomers of **Example 148** were separated by Supercritical Fluid Chromatography using a Chiralpak AD, 21 x 250mm, 5μ column (elution with 25% MeOH, 75% CO_2 at 60 ml/min, 40°C, and 100 bar with detection at 220nm), providing **Example 148(a)** and **Example 148(b)**:

Example 148(a) - First Eluting Compound

(2S,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-(pyrimidin-2-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione

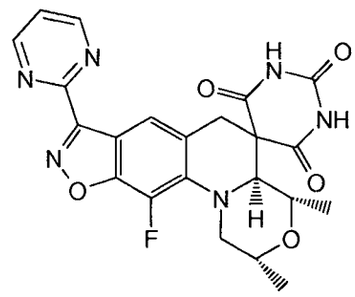


MS (ES) MH^+: 467 for $C_{22}H_{19}FN_6O_5$

^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.9 (d, 3 H) 1.2 (d, 3 H) 2.9 - 3.2 (m, 2 H) 3.6 - 4.2 (m, 5 H) 7.7 (t, 1 H) 7.8 (s, 1 H) 9.0 (d, 2 H) 11.4 (s, 1 H) 11.8 (s, 1 H)
>98% ee by chiral HPLC; [α] = +178 (c=0.1 in DMF).

Example 148(b) - Second Eluting Compound

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-8-(pyrimidin-2-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione



MS (ES) MH^+: 467 for $C_{22}H_{19}FN_6O_5$

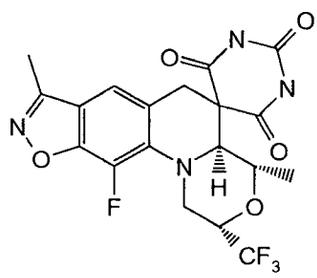
^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.9 (d, 3 H) 1.2 (d, 3 H) 2.9 - 3.2 (m, 2 H) 3.6 - 4.2 (m, 5 H) 7.7 (t, 1 H) 7.8 (s, 1 H) 9.0 (d, 2 H) 11.5 (s, 1 H) 11.8 (s, 1 H)
>98% ee by chiral HPLC; [α] = -131 (c=0.1 in DMF).

Example 149 was prepared from the indicated starting materials using a method similar to the one described for the synthesis of **Example 97**:

Example 149

(2S,4S,4a*S*)-rel-11-fluoro-4,8-dimethyl-2-(trifluoromethyl)-1,2,4,4a-tetrahydro-2'H,6*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione

(±)



Starting material: 7-fluoro-3-methyl-6-[(2*S*,6*S*)-rel-2-methyl-6-(trifluoromethyl) morpholin-4-yl]-1,2-benzoxazole-5-carbaldehyde

MS (ES) MH^+: 457 for $C_{19}H_{16}F_4N_4O_5$

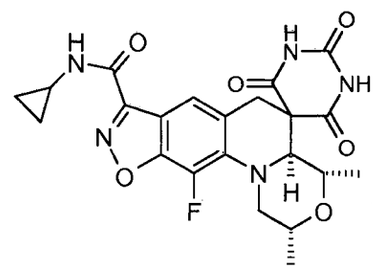
^1H NMR (300 MHz, DMSO-d_6) δ: 0.95 (d, 3H), 2.4 (s, 3H), 3.0 (d, 1H), 3.5 (t, 1H), 3.6 (d, 1H), 3.9 (m, 1H), 4.1 (d, 1H), 4.3 (d, 1H), 4.5 (m, 1H), 7.2 (s, 1H), 11.5 (s, 1H), 11.9 (s, 1H).

Examples 150 to 164 were prepared from the indicated starting material and barbituric acid using a method similar to the one described for the synthesis of **Example 134**. The compounds were purified either by silica gel column chromatography using a gradient of DCM to ethyl acetate or by reverse phase HPLC using a gradient of CH_3CN in water with 0.1% TFA.

Example 150

(2*R*,4S,4a*S*)-rel-*N*-cyclopropyl-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide

(±)



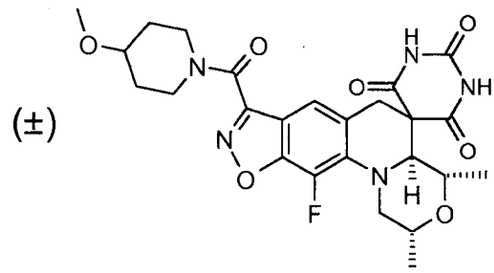
Starting material: *N*-cyclopropyl-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formylbenzo[d]isoxazole-3-carboxamide (**Intermediate 453**)

MS (ES) MH^+: 472 for $C_{22}H_{22}FN_5O_6$

^1H NMR (300 MHz, DMSO-d_6) δ ppm 0.5-0.7 (m, 4H), 0.8 (d, 3H), 1.1 (d, 3H), 2.9 (d, 2H), 3.1 (t, 1H), 3.5-3.8 (m, 3H), 3.9 (d, 1H), 4.0 (d, 1H), 7.4 (s, 1H), 9.0 (d, 1H).

Example 151

(2*R*,4S,4a*S*)-rel-11-fluoro-8-(4-methoxypiperidine-1-carbonyl)-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione



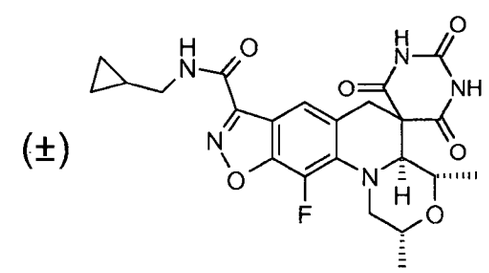
Starting material: 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-3-(4-methoxypiperidine-1-carbonyl)benzo[d]isoxazole-5-carbaldehyde (**Intermediate 454**)

MS (ES) MH^+: 530 for $C_{25}H_{28}FN_5O_7$

^1H NMR (300 MHz, DMSO-d_6) δ ppm 0.8 (d, 3H), 1.1 (d, 3H), 1.3-1.6 (m, 2H), 1.7-1.9 (m, 2H), 2.9 (d, 1H), 3.0-3.1 (m, 1H), 3.2 (s, 3H), 3.34-3.5 (m, 2H), 3.5-3.8 (m, 4H), 3.8 – 4.0 (m, 2H), 4.0 (d, 1H), 7.2 (s, 1H).

Example 152

(2*R*,4S,4a*S*)-rel-*N*-(cyclopropylmethyl)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide



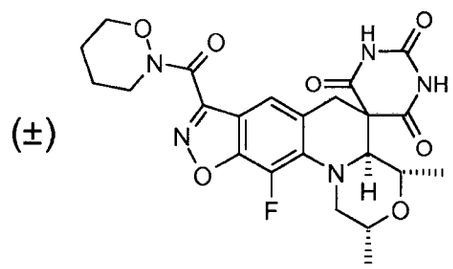
Starting material: *N*-(cyclopropylmethyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formylbenzo[d]isoxazole-3-carboxamide (**Intermediate 455**)

MS (ES) MH^+: 486 for $C_{23}H_{24}FN_5O_6$

^1H NMR (300 MHz, DMSO-d_6) δ ppm 0.01 (d, 2H), 0.2 (d, 2H), 0.6 (d, 3H), 0.7-0.9 (m, 1H), 0.9 (d, 3H), 2.7 (d, 1H), 2.8 – 3.0 (m, 3H), 3.3-3.5 (m, 2H), 3.5-3.6 (m, 1H), 3.7 (d, 1H), 3.9 (d, 1 H,) 7.2 (s, 1H), 8.8 (t, 1H), 11.3 (br. s., 2H).

Example 153

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(1,2-oxazinan-2-ylcarbonyl)-1,2,4,4a-tetrahydro-2'H,6*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione



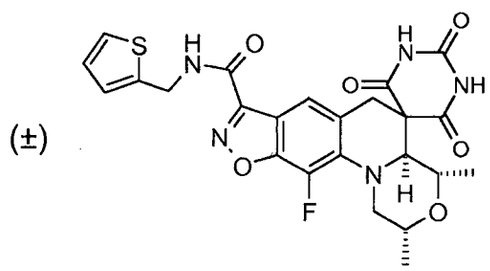
Starting material: 6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-7-fluoro-3-(1,2-oxazinan-2-ylcarbonyl)-1,2-benzisoxazole-5-carbaldehyde (**Intermediate 456**)

MS (ES) MH^+: 502. for $C_{23}H_{24}FN_5O_7$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.8 (d, 3H), 1.1 (d, 3H), 1.7 (br. s., 3H), 2.9 (d, 1H), 3.0-3.2 (m, 1H), 3.5-3.7 (m, 3H), 3.7-3.9 (m, 5H), 4.1 (d, 1H), 7.1-7.3 (m, 1H), 11.5 (s, 1H), 11.8 (s, 1H).

Example 154

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-*N*-(thiophen-2-ylmethyl)-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide



Starting material: 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formyl-*N*-(thiophen-2-ylmethyl)benzo[d]isoxazole-3-carboxamide(**Intermediate 457**)

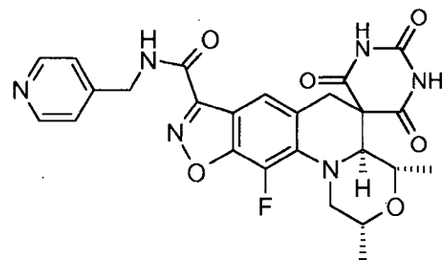
MS (ES) MH^+: 528 for $C_{24}H_{22}FN_5O_6S$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.9 (d, 3H), 1.2 (d, 3H), 2.9 (d, 1H), 3.0-3.2 (m, 1H), 3.6-3.7 (m, 2H), 3.8 (m, 1H), 4.0 (d, 1H), 4.1 (d, 1H), 4.6 (d, 2H), 6.9-7.0 (m, 1H), 7.0 (br. s., 1H), 7.4 (d, 1H), 7.4 (s, 1H), 9.6 (t, 1H).

Example 155

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-*N*-(pyridin-4-ylmethyl)-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide

(±)



Starting material: 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formyl-*N*-(pyridin-4-ylmethyl)benzo[d]isoxazole-3-carboxamide (**Intermediate 458**)

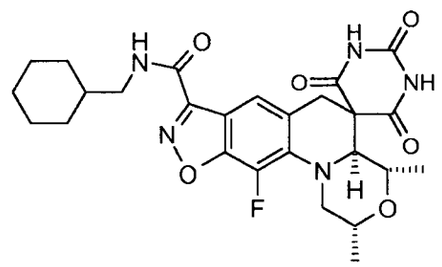
MS (ES) MH^+: 523 for $C_{25}H_{23}FN_6O_6$

^1H NMR (300 MHz, DMSO-d_6) δ ppm 0.9 (d, 3H), 1.2 (d, 3H), 2.9 (d, 1H), 3.1 (t, 1H), 3.6-3.7 (m, 2H), 3.8-3.9 (m, 1H), 4.0 (d, 1H), 4.1 (d, 1H), 4.5 (d, 2H), 7.3 (d, 2H), 7.4 (s, 1H), 8.5 (d, 2H), 9.6 (t, 1H).

Example 156

(2*R*,4S,4a*S*)-rel-*N*-(cyclohexylmethyl)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide

(±)



Starting material: *N*-(cyclohexylmethyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formylbenzo[d]isoxazole-3-carboxamide (**Intermediate 459**)

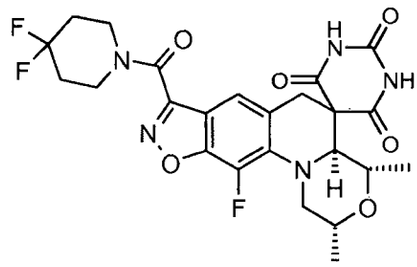
MS (ES) MH^+: 528.3 for $C_{26}H_{30}FN_5O_6$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.8-1.0 (m, 5H), 1.1-1.3 (m, 6H), 1.5-1.8 (m, 6H), 2.9 (d, 1H), 3.0-3.2 (m, 3H), 3.7 (d, 2H), 3.7-3.9 (m, 1H), 4.0 (d, 1H), 4.1 (d, 1H), 7.4 (s, 1H), 8.9 (t, 1H), 11.6 (br. s., 1H).

Example 157

(2*R*,4S,4a*S*)-rel-8-(4,4-difluoropiperidine-1-carbonyl)-11-fluoro-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione

(±)



Starting material: 3-(4,4-difluoropiperidine-1-carbonyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-5-carbaldehyde (**Intermediate 460**)

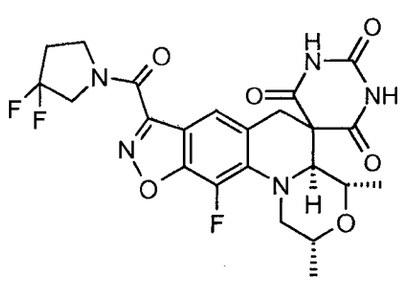
MS (ES) MH^+: 536 for $C_{24}H_{24}F_3N_5O_6$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.9 (d, 3H), 1.2 (d, 3H), 2.0-2.2 (m, 4H), 3.0 (d, 1H), 3.1-3.2 (m, 1H), 3.6-3.9 (m, 7H), 4.0 (d, 1H), 4.1 (d, 1H), 7.3 (s, 1H), 11.5 (s, 1 H,) 11.9 (s, 1H).

Example 158

(2*R*,4S,4a*S*)-rel-8-(3,3-difluoropyrrolidine-1-carbonyl)-11-fluoro-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione

(±)



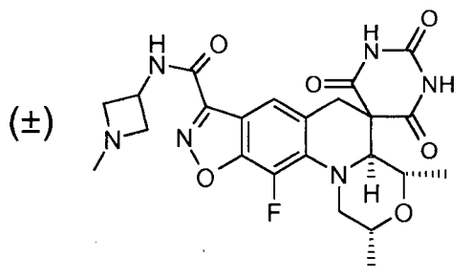
Starting material: 3-(3,3-difluoropyrrolidine-1-carbonyl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-5-carbaldehyde (**Intermediate 461**)

MS (ES) MH^+: 522 for $C_{23}H_{22}F_3N_5O_6$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.9 (d, 3H), 1.2 (d, 3H), 2.9 (d, 1H), 3.1 (t, 1H), 3.6-3.9 (m, 4H), 3.9-4.2 (m, 4H), 4.3 (t, 1H), 7.4 (d, 1H), 11.5 (s, 1H), 11.9 (s, 1H).

Example 159

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimethyl-*N*-(1-methylazetidin-3-yl)-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide



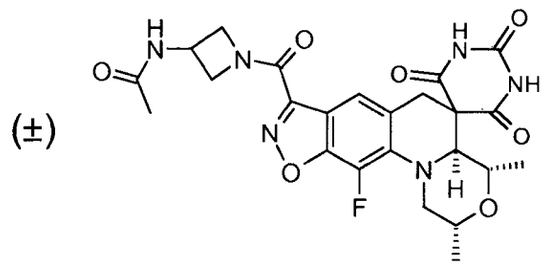
Starting material: 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formyl-*N*-(1-methylazetidin-3-yl)benzo[d]isoxazole-3-carboxamide **Intermediate 462**)

MS (ES) MH^+: 501 for $C_{23}H_{25}FN_6O_6$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.8 (d, 3H), 1.1 (d, 3H), 2.2 (s, 3H), 2.9 (d, 1H), 3.0 (t, 2H), 3.1 (d, 1H), 3.5 (t, 2H), 3.6-3.7 (m, 2H), 3.7-3.8 (m, 1H), 3.9 (d, 1H), 4.0 (d, 1H), 4.3-4.4 (m, 1H), 7.3 (s, 1H), 9.3 (d, 1H).

Example 160

N-(1-((2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-ylcarbonyl)azetidin-3-yl)acetamide



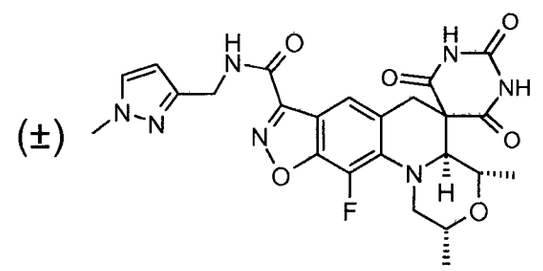
Starting material: *N*-(1-(6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formylbenzo[d]isoxazole-3-carbonyl)azetidin-3-yl)acetamide (**Intermediate 463**)

MS (ES) MH^+: 529 for $C_{24}H_{25}FN_6O_7$

^1H NMR (300 MHz, DMSO-d_6) δ ppm 0.8 (d, 3H), 1.1 (d, 3H), 1.8 (s, 3H), 2.8 (d, 1H), 3.0-3.1 (m, 1H), 3.5-3.8 (m, 3H), 3.8 -3.9 (m, 2H), 4.1 (d, 1H), 4.1-4.4 (m, 2H), 4.4-4.5 (m, 1H), 4.6-4.7 (m, 1H), 7.4 (s, 1H), 8.5 (d, 1H), 11.4 (s, 1H), 11.8 (s, 1H).

Example 161

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimethyl-*N*-((1-methyl-1*H*-pyrazol-3-yl)methyl)-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide



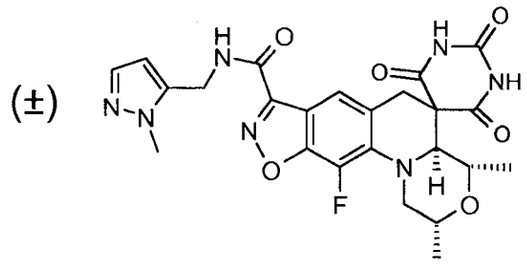
Starting material: 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formyl-*N*-((1-methyl-1*H*-pyrazol-3-yl)methyl)benzo[d]isoxazole-3-carboxamide (**Intermediate 464**)

MS (ES) MH^+: 526 for $C_{24}H_{24}FN_7O_6$

^1H NMR (300 MHz, DMSO-d_6) δ ppm 0.9 (d, 3H), 1.1 (d, 3H), 2.9 (d, 1H), 3.0-3.2 (m, 1H), 3.6-3.9 (m, 6H), 4.0 (d, 1H), 4.1 (d, 1H), 4.4 (d, 2H), 6.2 (d, 1H), 7.5 (s,1H), 7.6 (d, 1H), 9.3 (t, 1H), 11.5 (s, 1H), 11.8 (s, 1H).

Example 162

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimethyl-*N*-((1-methyl-1*H*-pyrazol-5-yl)methyl)-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide



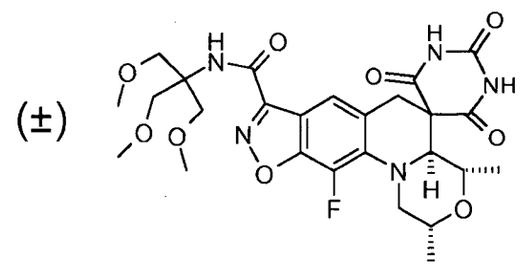
Starting material: 6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formyl-*N*-((1-methyl-1*H*-pyrazol-5-yl)methyl)benzo[d]isoxazole-3-carboxamide (**Intermediate 465**)

MS (ES) MH^+: 526 for $C_{24}H_{24}FN_7O_6$

^1H NMR (300 MHz, DMSO-d_6) δ ppm 0.9 (d, Hz, 3H), 1.1 (d, Hz, 3H), 2.9 (d, 1H), 3.1 (t, 1H), 3.6-3.8 (m, 3H), 3.8 (s, 3H), 4.0 (d, 1H), 4.1 (d, 1H), 4.4-4.6 (m, 2H), 6.2 (s, 1H), 7.3 (s, 1H), 7.4 (s, 1H), 9.5 (t, 1H), 11.5 (s, 1H), 11.8 (s, 1H).

Example 163

(2*R*,4S,4a*S*)-rel-*N*-(1,3-dimethoxy-2-(methoxymethyl)propan-2-yl)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxamide



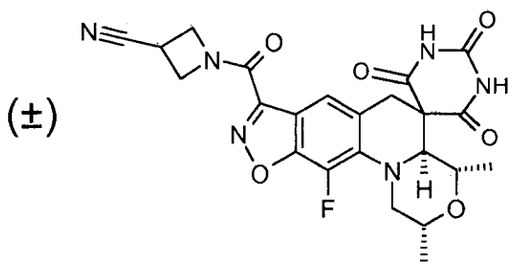
Starting material: *N*-(1,3-dimethoxy-2-(methoxymethyl)propan-2-yl)-6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formylbenzo[d]isoxazole-3-carboxamide (**Intermediate 466**)

MS (ES) MH^+: 578 for $C_{26}H_{32}FN_5O_9$

^1H NMR (300 MHz, DMSO-d_6) δ ppm 0.9 (d, 3H), 1.2 (d, 3H), 2.9 (d, 1H), 3.1-3.2 (m, 1H), 3.3 (s, 9H), 3.6-3.7 (m, 8H), 3.8-3.9 (m, 1H), 4.0 (d, 1H), 4.1 (d, 1H), 7.4 (s, 1H), 7.7 (s, 1H), 11.6 (br. s., 2H).

Example 164

1-((2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-ylcarbonyl)azetidine-3-carbonitrile



(±)

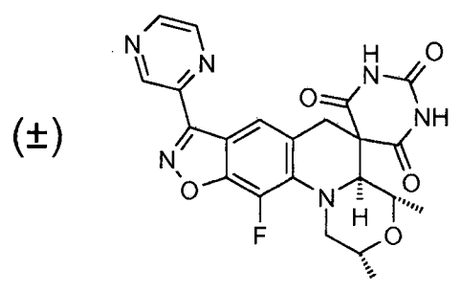
Starting material: 1-(6-((2*R*,6*S*)-2,6-dimethylmorpholino)-7-fluoro-5-formylbenzo[d]isoxazole-3-carbonyl)azetidine-3-carbonitrile (**Intermediate 468**)

MS (ES) MH^+: 497 for $C_{23}H_{21}FN_6O_6$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.9 (d, 3H), 1.2 (d, 3H), 2.9 (d, 1H), 3.0-3.2 (m, 1H), 3.6-3.8 (m, 3H), 3.9-4.0 (m, 2H), 4.1 (d, 1H), 4.3 (t, 1H), 4.3-4.5 (m, 1H), 4.6-4.9 (m, 2H), 7.5 (s, 1H).

Example 165

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(pyrazin-2-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione



(±)

Barbituric acid and (2*R*,4*S*,4a*S*)-rel-9,10-difluoro-8-[(hydroxyimino)(pyrazin-2-yl)methyl]-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-

2',4',6'(1'*H*,3'*H*)-trione (**Intermediate 583**) were reacted using a method similar to the one described for the synthesis of **Example 8**.

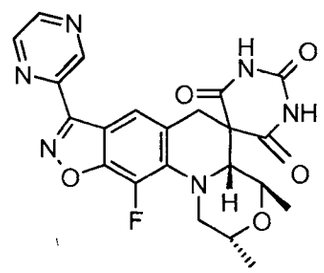
MS (ES) MH^+: 467 for $C_{22}H_{19}FN_6O_5$

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.9 (brs, 3H), 1.2 (brs, 3H), 2.9 (m, 1H), 3.1 (m, 1H), 3.8 (m, 2H), 4.0 (m, 1H), 4.2 (m, 1H), 7.6 (m, 1H), 7.8 (s, 1H), 8.9 (m, 2H), 9.3 (s, 1H), 11.5 (s, 1H), 11.8 (s, 1H).

In an alternative route, the (2*R*,4S,4aS) enantiomer of **Example 165** was synthesized using a chiral synthesis, as described below for **Example 165(b)**:

Example 165(a)

(2*R*,4S,4a*R*)-11-fluoro-2,4-dimethyl-8-(pyrazin-2-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione



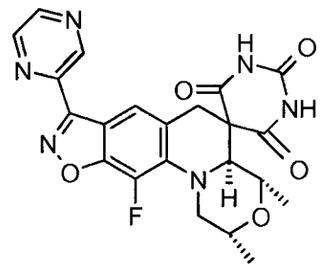
The (2*R*,4*R*,4a*R*) diastereomer was produced as a by-product of the reaction described for the synthesis of **Example 165(b)** below. The chromatography described for **Example 165(b)** afforded (2*R*,4*R*,4a*R*) diastereomer as the first eluting compound.

MS (ES) MH^+: 467 for $C_{22}H_{19}FN_6O_5$

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.9 (d, 3H), 1.3 (d, 3H), 3.1 (d, 1H), 3.55 (d, 1H), 3.65 (d, 1H), 3.75 (d, 1H), 3,8-4.0 (m, 2H), 4.0-4.1 (m, 1H), 7.7 (s, 1H), 8.8 (m, 2H), 9.3 (d, 1H), 11.4 (s, 1H), 11.7 (d, 1H)

Example 165(b)

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-8-(pyrazin-2-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione



Barbituric acid and 6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-3-(pyrazin-2-yl)benzo[d]isoxazole-5-carbaldehyde (**Intermediate 438**) were reacted using a method similar to the one described for the synthesis of **Example 53(a)**. The product was purified by reverse phase HPLC using a gradient of CH_3CN in water with 0.1% TFA, and obtained as the second eluting compound.

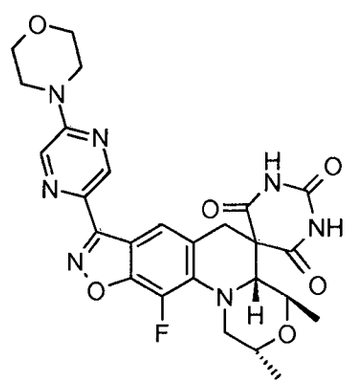
MS (ES) MH^+: 467 for $C_{22}H_{19}FN_6O_5$

^1H NMR (400 MHz, DMSO-d_6) δ ppm: 0.9 (d, 3H), 1.2 (d, 3H), 3.0 (d, 1H), 3.1 (m, 1H), 3.5-3.9 (m, 3H), 4.0 (d, 1H), 4.2 (d, 1H), 7.8 (s, 1H), 8.7-9.0 (m, 2H), 9.4 (d, 1H), 11.5 (s, 1H), 11.8 (d, 1H)

Examples 166(a) to 167 were prepared from the indicated starting material and barbituric acid using a method similar to the one described for the chiral synthesis of **Example 53(a)**:

Example 166(a)

(2*R*,4*R*,4a*R*)-11-fluoro-2,4-dimethyl-8-(5-morpholinopyrazin-2-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione



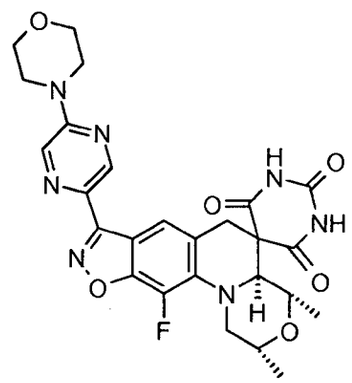
The (2*R*,4*R*,4a*R*) diastereomer was produced as a by-product of the reaction described for the synthesis of **Example 166(b)** below. The chromatography described for **Example 166(b)** afforded the (2*R*,4*R*,4a*R*) diastereomer as the first eluting compound.

MS (ES) MH^+: 552 for $C_{26}H_{26}FN_7O_6$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.0 (d, 3H), 1.3 (d, 3H), 3.2 (d, 1H), 3.6 (m, 1H), 3.6-3.8 (m, 11H), 3.9-4.0 (m,1H), 4.1 (m, 1H), 7.3 (d, 1H), 7.7 (s, 1H), 8.6 (d, 1H), 11.5 (s, 1H), 11.8 (s, 1H)

Example 166(b)

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-8-(5-morpholinopyrazin-2-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione



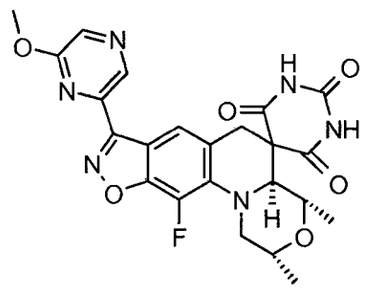
Starting material: 6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-3-(5-morpholinopyrazin-2-yl)benzo[d]isoxazole-5-carbaldehyde (**Intermediate 433**). Purification by reverse phase HPLC using a gradient of CH_3CN in water with 0.1% TFA provided the (2*R*,4S,4a*S* diastereomer as the second eluting compound.

MS (ES) MH^+: 552 for $C_{26}H_{26}FN_7O_6$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.9 (d, 3H), 1.2 (d, 3H), 3.0 (d, 1H), 3.1 (m, 1H), 3.6-3.8 (m, 11H), 4.0 (d, 1H), 4.1 (s, 1H), 7.7 (s, 1H), 8.5 (d, 1H), 8.8 (d, 1H), 11.5 (s, 1H), 11.8 (s, 1H)

Example 167

(2*R*,4S,4a*S*)-11-fluoro-8-(6-methoxypyrazin-2-yl)-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione



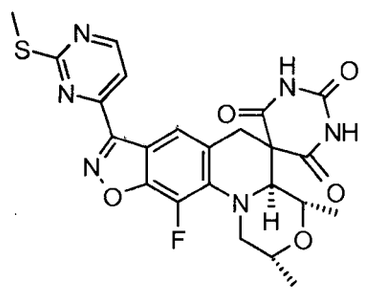
Starting material: 6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-3-(6-methoxypyrazin-2-yl)benzo[d]isoxazole-5-carbaldehyde (**Intermediate 436**); purification by reverse phase HPLC using a gradient of CH_3CN in water with 0.1% TFA.

MS (ES) MH^+: 497 for $C_{23}H_{21}FN_6O_6$

^1H NMR (300 MHz, DMSO-d_6) δ ppm: 0.9 (d, 3H), 1.2 (d, 3H), 3.0 (d, 1H), 3.1-3.2 (m, 1H), 3.6-3.7 (m, 1H), 3.8 (d, 2H), 4.0 (d, 1H), 4.1 (s, 3H), 4.2 (d, 1H), 7.7 (s, 1H), 8.5 (s, 1H), 8.9 (s, 1H), 11.5 (s, 1H), 11.9 (s, 1H).

Example 168

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-8-(2-(methylthio)pyrimidin-4-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione



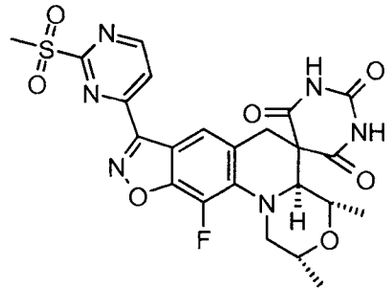
In a microwave reactor, 6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-3-(2-(methylthio)pyrimidin-4-yl)benzo[d]isoxazole-5-carbaldehyde (**Intermediate 437**, 719mg, 1.79 mmol) and 1,3,5-triazinane-2,4,6-trione (242 mg, 1.88 mmol) in EtOH (10 ml) were heated at 140 °C for 1hour. The solution was concentrated to dryness to afford 916 mg of desired product, used in subsequent reactions without further purification.

MS (ES) MH^+: 513 for $C_{23}H_{21}FN_6O_5S$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.9 (d, 3H), 1.2 (d, 3H), 2.6 (s, 3H), 3.0 (d, 1H), 3.1-3.2 (m, 1H), 3.7 (dd, 1H), 3.7-3.9 (m, 2H), 4.0 (d, 1H), 4.2 (d, 1H), 7.7 (s, 1H), 7.8 (d, 1H), 8.8 (d, 1H), 11.5 (br. s., 1H), 11.9 (br. s., 1H)

Example 169

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-8-(2-(methylsulfonyl)pyrimidin-4-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione



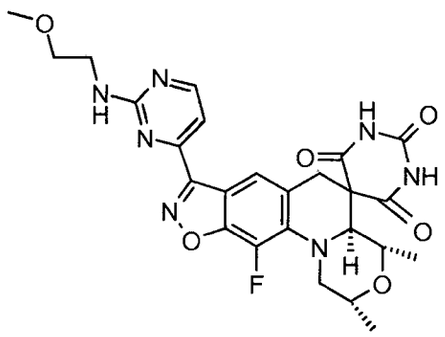
Oxone (5902 mg, 9.60 mmol) was added to a solution of (2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-8-(2-(methylthio)pyrimidin-4-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione (**Example 168,** 984 mg, 1.92 mmol) in MeOH:THF:H_2O (30 ml)(1:1:1), and the mixture was stirred at room temperature for 48 hours.The reaction mixture was diluted with DCM (50ml), stirred for 10 minutes, filtered, and the filter cake was washed with EtOH. The filtrate was washed with water and brine, concentrated under reduced presure to give the desired product used in subsequent reactions without further purification.

MS (ES) MH^+: 545 for $C_{23}H_{21}FN_6O_7S$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.9 (d, 3H), 1.2 (d, 3H), 3.0 (s, 1H), 3.2 (d, 1H) 3.7 (m, 1H), 3.8 (d, 2H), 4.0 (d,1H), 4.1 (d, 1H), 7.0 (m, 1H), 7.8 (s, 1H), 8.1 (m, 1H), 11.5 (s, 1H), 11.8 (d, 1H), 12.0-12.4 (br, s, 1H)

Example 170

(2*R*,4S,4a*S*)-11-fluoro-8-(2-(2-methoxyethylamino)pyrimidin-4-yl)-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione



2-Methoxyethanamine (8.70 μL, 0.10 mmol) was added o a solution of (2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-8-(2-(methylsulfonyl)pyrimidin-4-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione (**Example 169**, 50mg, 0.09 mmol) in THF (5 mL), and the mixture was stirred at room temperature for 3 hours, DMSO (1ml) was added followed by the addition of 2 more equivalance of methoxylethanamine, the mixture was stirred at room temperature for over night. The crude was concentrated and purified by reverse phase silica gel column chromatography (20-70% MeCN in water gradient, 0.1%TFA) to give 37 mg of product.

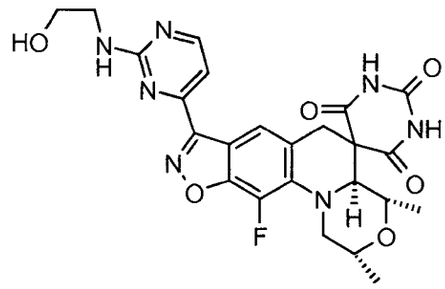
MS (ES) MH^+: 540 for $C_{25}H_{26}FN_7O_6$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.9 (d, 3H), 1.7 (d, 3H), 3.1 (m, 2H), 3.2-3.3 (m, 3H), 3.4-3.5 (m, 4H), 3.7 (m, 2H), 3.8-3.9 (m, 1H), 4.0 (d, 1H), 4.1 (d, 1H), 7.2 (d, 1H), 7.5 (br. s., 1H), 7.9 (br. s, 1H), 8.5 (d, 1H), 11.5 (s, 1H), 11.9 (s, 1H)

Examples 171 to 177 were prepared from the indicated starting materials and using a method similar to the one described for the syntheses of **Example 170**:

Example 171

(2*R*,4S,4a*S*)-11-fluoro-8-(2-(2-hydroxyethylamino)pyrimidin-4-yl)-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione



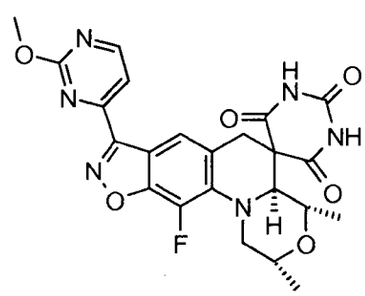
Starting material: (2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-8-(2-(methylsulfonyl)pyrimidin-4-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione (**Example 169**) and 2-aminoethanol.

MS (ES) MH^+: 526 for $C_{24}H_{24}FN_7O_6$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.9 (d, 3H), 1.2 (d, 3H), 3.1 (m, 1H), 3.5-3.7 (m, 6H), 3.7-3.8 (m, 2H), 3.8-3.9 (m, 1H), 4.0 (d, 1H), 4.1 (d, 1H), 7.2 (d, 1H), 7.4 (br. s., 1H), 7.7-8.1 (m, 1H), 8.5 (d, 1H), 11.5 (br. s., 1H) 11.9 (s, 1H).

Example 172

(2*R*,4S,4a*S*)-11-fluoro-8-(2-methoxypyrimidin-4-yl)-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione



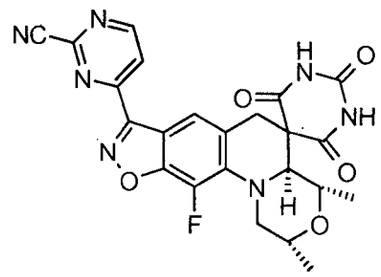
Starting material: (2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-8-(2-(methylsulfonyl)pyrimidin-4-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione (**Example 169**) and 2M ammonia in methanol.

MS (ES) MH^+: 497 for $C_{23}H_{21}FN_6O_6$

^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 0.8 (d, 3H), 1.1 (d, 3H), 2.9 (d, 1H), 3.0-3.2 (m, 1H), 3.6 (dd, 2H), 3.7-3.8 (m, 1H), 3.9 (d, 1H), 4.0 (s, 3H), 4.1 (d, 1H), 7.6-7.8 (m, 2H), 8.8 (d, 1H), 11.4 (s, 1H), 11.8 (s, 1H).

Example 173

4-((2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-yl)pyrimidine-2-carbonitrile



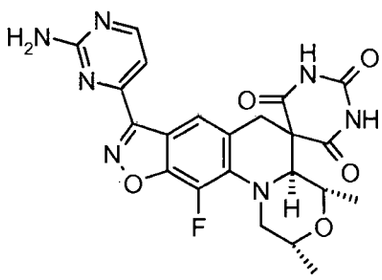
Starting material: (2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-8-(2-(methylsulfonyl)pyrimidin-4-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione (**Example 169**) and potasium cyanide.

MS (ES) MH^+: 492 (M+H) for $C_{23}H_{18}FN_7O_5$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.9 (d, 3H), 1.2 (d, 3H), 3.0 (d, 1H), 3.1-3.2 (m, 1H), 3.7 (dd, 1H), 3.8 (m, 1H), 3.9 (d, 1H), 4.0 (d, 1H), 4.2 (d, 1H), 7.7 (s, 1H), 8.5 (d, 1H), 9.2 (d, 1H), 11.5 (s, 1H), 11.8 (s, 1H).

Example 174

(2*R*,4S,4a*S*)-8-(2-aminopyrimidin-4-yl)-11-fluoro-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione



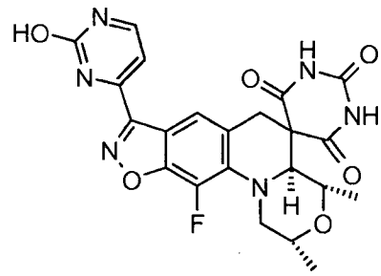
Starting materials: (2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-8-(2-(methylsulfonyl)pyrimidin-4-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione (**Example 169**) and ammonia in dioxane (0.5M)

MS (ES) MH^+: 482 (M+H) for $C_{22}H_{20}FN_7O_5$

^{1}H NMR (300 MHz, DMSO-d_6) d ppm 0.9 (d, 3H), 1.2 (d, 3H), 3.0-3.2 (m, 2H), 3.4-3.5 (m, 1H), 3.7 (dd, 1H), 3.8-3.9 (m, 1H), 4.0 (d, 1H), 4.1 (d, 1H), 7.0 (s, 2H), 7.2 (d, 1H), 7.9 (s, 1H), 8.4 (d, 1H), 11.5 (s, 1H), 11.9 (s, 1H).

Example 175

(2*R*,4*S*,4a*S*)-11-fluoro-8-(2-hydroxypyrimidin-4-yl)-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione



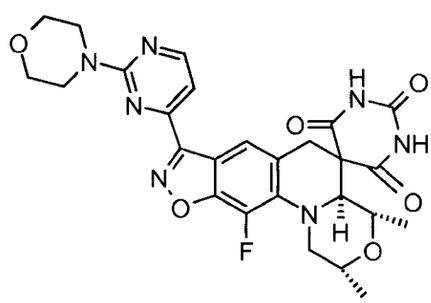
Starting materials: (2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-8-(2-(methylsulfonyl)pyrimidin-4-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione (**Example 169**) and potassium trimethylsilanolate.

MS (ES) MH^+: 483 (M+H) for $C_{22}H_{19}FN_6O_6$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.9 (d, 3H), 1.2 (d, 3H), 3.0 (s, 1H), 3.2 (d, 1H), 3.7 (m, 1H), 3.8 (d, 2H), 4.0 (d, 1H), 4.1 (d, 1H), 7.0 (br. s., 1H), 7.8 (s, 1H), 8.1 (br. s., 1H), 11.5 (s, 1H), 11.8 (d, 1H), 12.0-12.4 (m, 1H)

Example 176

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-8-(2-morpholinopyrimidin-4-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione



Starting materials: (2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-8-(2-(methylsulfonyl)pyrimidin-4-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione (**Example 169**) and morpholine.

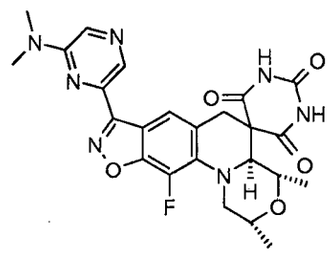
MS (ES) MH^+: 552 for $C_{26}H_{26}FN_7O_6$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 0.9 (d, 3H), 1.2 (d, 3H), 3.0 (d, 1H), 3.1-3.2 (m, 1H), 3.6-3.7 (m, 2H), 3.7 (m, 4H), 3.8-3.9 (m, 5H), 4.0 (d, 1H), 4.1 (d, 1H), 7.3 (d, 1H), 7.6 (s, 1H), 8.6 (d, 1H), 11.5 (s, 1H), 11.9 (s, 1H)

Example 177

(2*R*,4S,4a*S*)-rel-8-(6-(dimethylamino)pyrazin-2-yl)-11-fluoro-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione

(±)



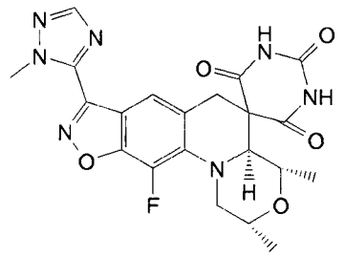
Starting materials: (2*R*,4S,4a*S*)-rel-8-(6-chloropyrazin-2-yl)-11-fluoro-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione (**Example 79**) and 2N dimethylamine in THF.

MS (ES) MH^+: 510 for $C_{24}H_{24}FN_7O_5$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.9 (d, 3H), 1.2 (d, 3H), 3.0 (d, 1H), 3.1 (m, 1H), 3.2 (s, 6H), 3.7-3.8 (m, 3H), 4.0 (d, 1H), 4.1 (d, 1H), 7.7 (s, 1H), 8.3 (s, 1H), 8.4 (s, 1H), 11.5 (br. s., 1H), 11.8 (br. s., 1H)

Example 178

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimethyl-8-(1-methyl-1*H*-1,2,4-triazol-5-yl)-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione



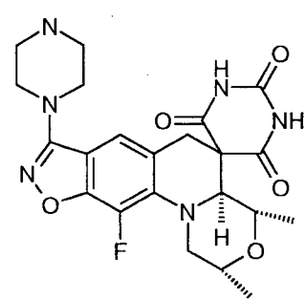
A mixture of 6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluoro-3-(1-methyl-1*H*-1,2,4-triazol-5-yl)benzo[d]isoxazole-5-carbaldehyde (**Intermediate 537,** 124 mg, 0.35 mmol) and pyrimidine-2,4,6(1H,3H,5H)-trione (44.2 mg, 0.35 mmol) in methanol (3 ml) was heated at 150 °C for 1 hour in a microwave reactor. Solvent was removed and the residue was purified by reverse phase HPLC (CH_3CN/water gradient with 0.1% TFA). The solid was taken up in 9:1 CH_2Cl_2- MeOH and washed with $NaHCO_3$ and brine. The aqueous layers were repeatedly extracted with addtional 9:1 CH_2Cl_2-MeOH with each extract being washed with brine. The combined organic layres were dried ($MgSO_4$) and concentrated and the residue was dissolved in THF. After removal of solvent, the solid residue was dried in vacuo at 50 °C overnight to afford desired product.

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.9 (d, 3H), 1.2 (d, 3H), 2.9 (d, 1H), 3.0-3.2 (m, 1H), 3.6-3.8 (m, 1H), 3.8 (d, 2H) 4.0 (d, 1H) 4.1 (d, 1H), 4.2 (s, 3H), 7.7 (s, 1H), 8.3 (s, 1H), 11.5 (s, 1H), 11.85 (s, 1H).

Example 179

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(piperazin-1-yl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione

(±)



A mixture of *tert*-butyl 4-[(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinoline-5,5'-

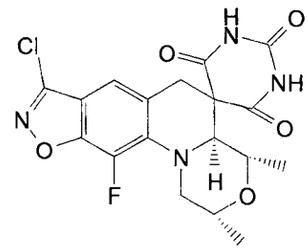
pyrimidin]-8-yl]piperazine-1-carboxylate (**Example 20**, 50 mg, 0.08 mmol) and 4N HCl in MeOH (8 mL) was stirred at room temperature for 1 hours. It was concentrated under reduced pressure and the residue was triturated with pet ether to give the title compound as brown solid. Isolated as HCl salt. Yield: 28 mg (67%)

MS (ES) MH^+: 473 for $C_{22}H_{25}FN_6O_5$

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 2.95 (d, 1H), 3.05 (t, 1H), 3.40 (m, 4H), 3.45 (m, 1H), 3.6 (m, 5H), 3.8 (m, 1H), 3.9 (d, 1H), 4.05 (d, 1H), 7.3 (s, 1H), 9.15 (bs, 2H), 11.5 (s, 1H), 11.9 (s, 1H).

Example 180

(2*R*,4S,4a*S*)-8-chloro-11-fluoro-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione



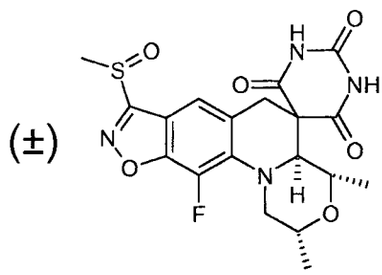
A mixture of 3-chloro-6-((2*R*,6*R*)-2,6-dimethylmorpholino)-7-fluorobenzo[d]isoxazole-5-carbaldehyde (**Intermediate 535,** 764 mg, 2.44 mmol) and pyrimidine-2,4,6(1H,3H,5H)-trione (313 mg, 2.44 mmol) in iPrOH (3 ml) was heated at reflux for 3 days. Solvent was removed and the residue was recrystallized from methanol. The solids obtained were recrystallized from 1:1 EtOH-Water to afford 273 mg of product consistent with desired product.

MS (ES) MH^+: 473 for $C_{22}H_{25}FN_6O_5$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.9 (d, 3H) 1.15 (d, 3H) 2.95 (d, 1H) 3.55-3.7 (m, 2H) 3.7-3.9 (m, 1H) 4.0 (d, 1H) 4.1 (m, 2H) 7.2 (s, 1H) 11.5 (s, 1H) 11.9 (s, 1H).

Example 181

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(methylsulfinyl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione



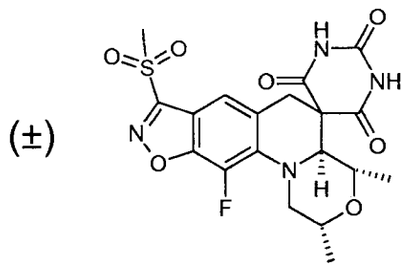
To a stirred solution of (2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(methylsulfanyl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione **Example 62,** 50 mg, 0.11 mmol) in dry DCM (1 mL) was added m-chloroperbenzoic acid (39 mg, 0.23 mmol) and stirred at room temperature for 1 hours. Solvents were evaporated and the residue thus obtained purified over a silica gel column to give product as solid. Yield: 18 mg (35 %).

MS (ES) MH^+: 451 for $C_{19}H_{19}FN_4O_6S$

^1H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.15 (d, 3H), 2.9 (d, 1H), 3.1 (t, 1H), 3.2 (m, 3H), 3.7-3.8 (m, 3H), 4.0 (d, 1H), 4.1 (d, 1H), 7.1 (t, 1H), 11.5 (s, 1H), 11.9 (s, 1H).

Example 182

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(methylsulfonyl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione



To a stirred solution of (2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(methylsulfanyl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione (**Example 62,** 50 mg, 0.11 mmol) in dry DCM (1 mL) was added m-chloroperbenzoic acid (39 mg, 0.23 mmol) and heated to 80 °C for 1 hour. Solvents were evaporated and the residue thus obtained purified over silica gel-column to give title compound as solid. Yield: 20 mg (43%).

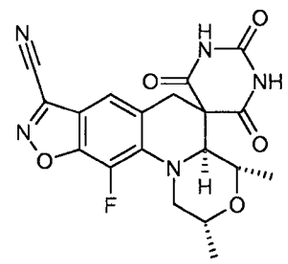
MS (ES) MH^+: 467 for $C_{19}H_{19}FN_4O_7S$;

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 2.9 (d, 1H), 3.2 (t, 1H), 3.6 (s, 3H), 3.65 (m, 1H), 3.7 (m, 1H), 3.8 (m, 1H), 4.0 (d, 1H), 4.1 (d, 1H), 7.4 (s, 1H), 11.6 (s, 1H), 11.9 (s, 1H).

Example 183

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-8-carbonitrile

(±)



To a stirred solution of (2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-8-(methylsulfonyl)-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione (**Example 182**, 1.0 g, 2.15 mmol) in DMF was added KCN (700 mg, 10.75 mmol) followed by 18-crown-6 (catalytic) and the mixture was heated at 85° C for 12 hours. The reaction mixture was cooled to room temperature and precipitated with diethyl ether (repeated twice to remove complete DMF). The precipitate was dissolved in EtOAc (50 mL) and washed with water (2X 10 mL), dried over anhydrous sodium sulfate and, filtered, concentrated. The residue was purified by 'combiflash instrument' to give product as a pale yellow solid.

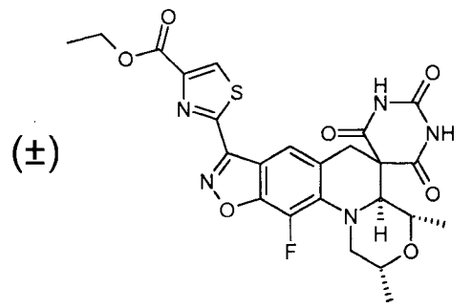
Yield: 211 mg (23%).

MS (ES) MH^+: 414.5 for $C_{19}H_{16}FN_4O_5$;

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 2.9 (d, 1H), 3.15 (m, 1H), 3.7 (m, 2H), 3.8 (m, 1H), 4.0 (d, 1H), 4.1 (d, 1H), 7.4 (s, 1H), 11.6 (bs, 1H), 11.9 (bs, 1H).

Example 184

Ethyl 2-[(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-1,3-thiazole-4-carboxylate



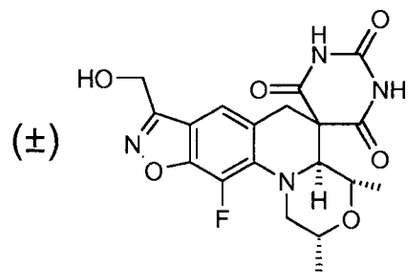
To a stirred solution of (2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-8-carbothioamide (**Intermediate 575**, 54 mg, 0.128 mmol) in mixture of EtOH:DMF(1 mL: 0.5 mL) were added ethyl bromopyruvate (47 mg, 0.24 mmol) and molecular sieves, and the mixture was stirred at 100° C for 12 hours. The reaction mixture was concentrated, the residue was purified by silca gel column chromatography to give product as solid. Yield: 13 mg (20%).

MS (ES) MH^+: 544 for $C_{24}H_{22}FN_5O_7S$

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.1 (d, 3H), 1.3 (t, 3H), 2.9 (d, 1H), 3.1 (m, 1H), 3.6 (m, 1H), 3.8 (m, 2H), 4.0 (d, 1H), 4.1(d, 1H), 4.4 (q, 2H), 7.6 (s, 1H), 8.7 (s, 1H), 11.5 (s, 1H), 11.8(s, 1H).

Example 185

(2*R*,4S,4a*S*)-rel-11-fluoro-8-(hydroxymethyl)-2,4-dimethyl-2,4,4a,6-tetrahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(3'H)-trione



Lithium borohydride (0.434 ml, 0.87 mmol) was added to an ice cooled solution of methanol (0.035 ml, 0.87 mmol) in THF (10 ml). The solution was warmed to room temperature and stirred for 1 hour. 1.5 ml of the $LiBH_4$/MeOH solution was added to a solution of (2*R*,4S,4a*S*)-rel-ethyl 11-fluoro-2,4-dimethyl-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahydro-1*H*,1'*H*-spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5,5'-pyrimidine]-8-carboxylate (**Example**

134, 30 mg, 0.07 mmol) in 5ml of THF. The reaction was stirred at room temperature of 1 hour. The reacion was diluted with water and extracted with ethyl acetate 2x. The organic layers were washed twice with brine, dried over $MgSO_4$ and concentrated. The residue was purified by HPLC (Acetonitrile (5 to 50%)/Water with a TFA modifier over 10 minutes). Freeze dried for 48 hours to give the title compound (22 mg, 0.053 mmol, 81 %).

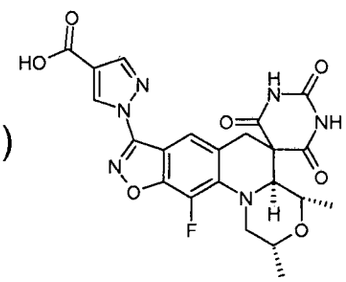
MS (ES) MH^+: 419 for $C_{19}H_{19}FN_4O_6$

^1H NMR (300 MHz, DMSO-d_6) δ ppm 0.9 (d, 3H), 1.1 (d, 3H), 2.9 (d, 1H), 3.1 (t, 1H), 3.6-3.7 (m, 3H), 3.8-3.8 (m, 1H), 3.9 (d, 1H), 4.1 (d, 1H), 4.7 (s, 2H), 7.3 (s, 1H), 11.5 (s, 1H), 11.8 (s, 1H).

Example 186

1-[(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-1*H*-pyrazole-4-carboxylic acid

(±)



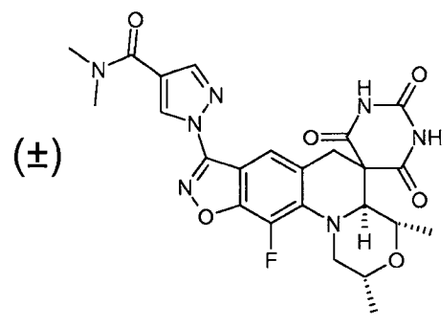
To a stirred solution of ethyl 1-[(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-1*H*-pyrazole-4-carboxylate (**Example 37,** 100 mg, 0.19 mmol) in acetonitrile (0.5 mL) was added 5% NaOH solution (14 mg, 0.11 mmol) and the mixture was stirred at room temperature for 2 hours. The reaction mixture was acidified to pH ~ 7 using 1.5 N HCl and extracted with EtOAc(5 x 10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give product as yellow solid. Yield : 45 mg

MS (ES) MH^+: 499.5 for $C_{22}H_{19}FN_6O_7$;

^1H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.15 (d, 3H), 2.9 (d, 1H), 3.2 (t, 1H), 3.7 (m, 1H), 3.8 (m, 2H), 4.0 (d, 1H), 4.1 (d, 1H), 7.65 (s, 1H), 8.3 (s, 1H), 8.9 (s, 1H), 11.5 (s, 1H), 11.9 (s, 2H).

Example 187

1-[(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-*N*,*N*-dimethyl-1*H*-pyrazole-4-carboxamide



(±)

To a an ice cooled solution of 1-[(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-1*H*-pyrazole-4-carboxylic acid (**Example 186,** 100 mg, 0.19 mmol) in THF (0.5 mL) was added dimethyl amine, (30 mg, 0.11 mmol), DIPEA (139 mg, 1.08 mmol) followed by T_3P (172 mg, 0.54 mmol) and the mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with EtOAc (15 mL). The organic layer was washed with water (2 x 10 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography using a gradient of EtOAc in pet ether to give product as yellow solid.

Yield: 25 mg

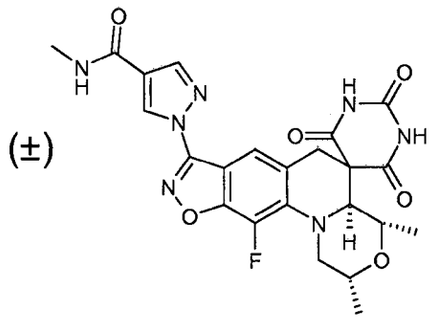
MS (ES) MH^+: 526.5 for $C_{24}H_{24}FN_7O_6$;

^1H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.15 (d, 3H), 2.90 (d, 1H), 3.0(s, 3H), 3.1(m, 1H), 3.2 (s, 3H), 3.7 (m, 1H), 3.8 (m, 2H), 4.0 (d, 1H), 4.1(d, 1H), 7.65 (s, 1H), 8.2 (s, 1H), 8.8 (s, 1H), 11.9 (br, 2H).

Examples 188 and 189 were prepared from the indicated starting material and pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione using a method similar to the one described for the synthesis of **Example 187**:

Example 188

1-[(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-*N*-methyl-1*H*-pyrazole-4-carboxamide



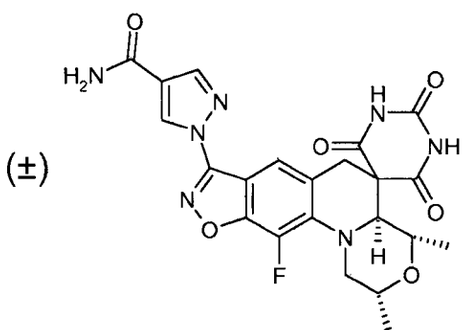
Starting material: 1-[(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-1*H*-pyrazole-4-carboxylic acid (**Example 186**) and methyl amine (0.16 mL, 2.0M in THF, 0.320 mmol).

MS (ES) MH^+: 512 for $C_{23}H_{22}FN_7O_6$

^1H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.15 (d, 3H), 2.8 (d, 3H), 2.9 (d, 1H), 3.1 (d, 1H), 3.7 (m, 1H), 3.8 (m, 2H), 4.0 (d, 1H), 4.1(d, 1H), 7.7 (s, 1H), 8.3 (s, 1H), 8.4 (d, 1H), 8.9 (s, 1H), 11.5 (s, 1H), 11.9 (s, 1H).

Example 189

1-[(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-1*H*-pyrazole-4-carboxamide



Starting materials: 1-[(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-

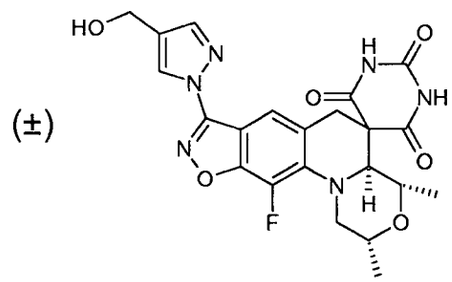
1*H*-pyrazole-4-carboxylic acid (**Example 186**) and saturated NH_3 in THF (2 mL). Purification by reverse phase HPLC.

MS (ES) MH^+: 498.5 for $C_{22}H_{20}FN_7O_6$

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.15 (d, 3H), 2.9 (d, 1H), 3.1(d, 1H), 3.7 (m, 1H), 3.8 (m, 2H), 4.0 (d, 1H), 4.1(d, 1H), 7.4 (s, 1H), 7.7 (s, 1H), 7.9 (d, 1H), 8.3 (s, 1H), 9.0(s, 1H), 11.5 (brs, 2H).

Example 190

(2*R*,4*S*,4a*S*)-rel-11-fluoro-8-[4-(hydroxymethyl)-1*H*-pyrazol-1-yl]-2,4-dimethyl-1,2,4,4a-tetrahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione



Lithium borohydride (0.434 mL, 0.87 mmol) was added to an ice cooled solution of methanol (0.035 mL, 0.87 mmol) in tetrahydrofuran (10 mL). The solution was warmed to room temp and stirred for 1 hour. 1.5 ml of this solution was added to a solution of ethyl 1-[(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimethyl-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahydro-2'*H*,6*H*-spiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinoline-5,5'-pyrimidin]-8-yl]-1*H*-pyrazole-4-carboxylate (**Example 37,** 60 mg, 0.11 mmol). The reaction was stirred at room temp for 12 hours. The reaction mixture was diluted with water and extracted twice with ethyl acetate. The organic layers were washed twice with brine, dried over MgSO4 and concentrated. The residue was purified by reverse phase HPLC to give product as a solid. Yield : 20 mg.

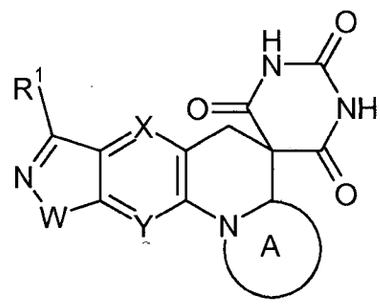
MS (ES) MH^+: 485.5 for $C_{22}H_{21}FN_6O_6$

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.9 (d, 3H), 1.15 (d, 3H), 2.9 (d, 1H), 3.1 (t, 1H), 3.7 (m, 1H), 3.8 (m, 2H), 4.0 (d, 1H), 4.1(d, 1H), 4.8 (d, 2H), 5.1 (s, 1H), 7.7 (s, 1H), 7.9 (s, 1H), 8.3 (s, 1H), 11.7 (br, 2H).

Claims

What is claimed is:

1. A compound of Formula (I),



Formula (I)

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is fused 5- to 7-membered non-aromatic heterocyclic ring, wherein said fused 5- to 7-membered non-aromatic heterocyclic ring is optionally substituted on carbon with one or more R^4, and wherein any -NH- moiety of said 5- to 7-membered heterocyclic ring is optionally substituted with R^{4*};

W is selected from -O-, -NH-, -S-, and $-S(O)_2-$;

X is selected from N and C-R^2;

Y is selected from N and C-R^3;

$\mathbf{R^1}$ is selected from H, halo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, heterocyclyl, $-OR^{1a}$, $-SR^{1a}$, $-N(R^{1a})_2$, $-N(R^{1a})C(O)R^{1b}$, $-N(R^{1a})N(R^{1a})_2$, $-NO_2$, $-N(R^{1a})OR^{1a}$, $-ON(R^{1a})_2$, -C(O)H, $-C(O)R^{1b}$, $-C(O)_2R^{1a}$, $-C(O)N(R^{1a})_2$, $-C(O)N(R^{1a})(OR^{1a})$, $-OC(O)N(R^{1a})_2$, $-N(R^{1a})C(O)_2R^{1a}$, $-N(R^{1a})C(O)N(R^{1a})_2$, $-OC(O)R^{1b}$, $-S(O)R^{1b}$, $-S(O)_2R^{1b}$, $-S(O)_2N(R^{1a})_2$, $-N(R^{1a})S(O)_2R^{1b}$, $-C(R^{1a})=N(R^{1a})$, and $-C(R^{1a})=N(OR^{1a})$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, and heterocyclyl are optionally substituted on carbon with one or more R^{10}, and wherein any -NH- moiety of said heterocyclyl is optionally substituted with R^{10*};

$\mathbf{R^{1a}}$ in each occurrence is independently selected from H, C_{1-6}alkyl, carbocyclyl, and heterocyclyl, wherein said C_{1-6}alkyl, carbocyclyl, and heterocyclyl in each occurrence are

optionally and independently substituted on carbon with one or more R^{10}, and wherein any -NH- moiety of said heterocyclyl is optionally substituted with R^{10*};

R^{1b} in each occurrence is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, and heterocyclyl, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, and heterocyclyl in each occurrence are optionally and independently substituted on carbon with one or more R^{10}, and wherein any -NH- moiety of said heterocyclyl is optionally substituted with R^{10*};

R^{2} is selected from H, halo, and -CN;

R^{3} is selected from H, halo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $-OR^{3a}$, $-SR^{3a}$, and $-N(R^{3a})_2$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, and C_{2-6}alkynyl are optionally substituted on carbon with one or more R^{30};

R^{3a} in each occurrence is independently selected from H and C_{1-6}alkyl, wherein said C_{1-6}alkyl in each occurrence is optionally and independently substituted on carbon with one or more R^{30};

R^{4} in each occurrence is independently selected from halo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, heterocyclyl, $-OR^{4a}$, $-SR^{4a}$, $-N(R^{4a})_2$, $-N(R^{4a})C(O)R^{4b}$, $-N(R^{4a})N(R^{4a})_2$, $-NO_2$, $-N(R^{4a})-OR^{4a}$, $-O-N(R^{4a})_2$, -C(O)H, $-C(O)R^{4b}$, $-C(O)_2R^{4a}$, $-C(O)N(R^{4a})_2$, $-C(O)N(R^{4a})(OR^{4a})$ $-OC(O)N(R^{4a})_2$, $-N(R^{4a})C(O)_2R^{4a}$, $-N(R^{4a})C(O)N(R^{4a})_2$, $-OC(O)R^{4b}$, $-S(O)R^{4b}$, $-S(O)_2R^{4b}$, $-S(O)_2N(R^{4a})_2$, $-N(R^{4a})S(O)_2R^{4b}$, $-C(R^{4a})=N(R^{4a})$, and $-C(R^{4a})=N(OR^{4a})$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, and heterocyclyl are optionally substituted on carbon with one or more R^{40}, and wherein any -NH- moiety of said heterocyclyl is optionally substituted with R^{40*};

R^{4*} in each occurrence is independently selected from C_{1-6}alkyl, carbocyclyl, heterocyclyl, -C(O)H, $-C(O)R^{4b}$, $-C(O)_2R^{4a}$, $-C(O)N(R^{4a})_2$, $-S(O)R^{4b}$, $-S(O)_2R^{4b}$, $-S(O)_2N(R^{4a})_2$, $-C(R^{4a})=N(R^{4a})$, and $-C(R^{4a})=N(OR^{4a})$, wherein said C_{1-6}alkyl, carbocyclyl, and heterocyclyl in each occurrence are optionally and independently substituted on carbon with one or more R^{40}, and wherein any -NH- moiety of said heterocyclyl is optionally substituted with R^{40*};

R^{4a} in each occurrence is independently selected from H, C_{1-6}alkyl, carbocyclyl, and heterocyclyl, wherein said C_{1-6}alkyl, carbocyclyl, and heterocyclyl in each occurrence are optionally and independently substituted on carbon with one or more R^{40}, and wherein

any -NH- moiety of said heterocyclyl is optionally substituted with R^{40*};

R^{4b} in each occurrence is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, and heterocyclyl, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, and heterocyclyl in each occurrence are optionally and independently substituted on carbon with one or more R^{40}, and wherein any -NH- moiety of said heterocyclyl is optionally substituted with R^{40*};

R^{10} in each occurrence is independently selected from halo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, heterocyclyl, $-OR^{10a}$, $-SR^{10a}$, $-N(R^{10a})_2$, $-N(R^{10a})C(O)R^{10b}$, $-N(R^{10a})N(R^{10a})_2$, $-NO_2$, $-N(R^{10a})$-OR^{10a}, $-O$-$N(R^{10a})_2$, -C(O)H, $-C(O)R^{10b}$, $-C(O)_2R^{10a}$, $-C(O)N(R^{10a})_2$, $-C(O)N(R^{10a})(OR^{10a})$, $-OC(O)N(R^{10a})_2$, $-N(R^{10a})C(O)_2R^{10a}$, $-N(R^{10a})C(O)N(R^{10a})_2$, $-OC(O)R^{10b}$, $-S(O)R^{10b}$, $-S(O)_2R^{10b}$, $-S(O)_2N(R^{10a})_2$, $-N(R^{10a})S(O)_2R^{10b}$, $-C(R^{10a})=N(R^{10a})$, and $-C(R^{10a})=N(OR^{10a})$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, and heterocyclyl in each occurrence are optionally and independently substituted on carbon with one or more R^a, and wherein any -NH- moiety of said heterocyclyl is optionally substituted with R^{a*};

R^{10*} in each occurrence is independently selected from C_{1-6}alkyl, carbocyclyl, heterocyclyl, -C(O)H, $-C(O)R^{10b}$, $-C(O)_2R^{10a}$, $-C(O)N(R^{10a})_2$, $-S(O)R^{10b}$, $-S(O)_2R^{10b}$, $-S(O)_2N(R^{10a})_2$, $-C(R^{10a})=N(R^{10a})$, and $-C(R^{10a})=N(OR^{10a})$, wherein said C_{1-6}alkyl, carbocyclyl, and heterocyclyl in each occurrence are optionally and independently substituted on carbon with one or more R^a, and wherein any -NH- moiety of said heterocyclyl is optionally substituted with R^{a*};

R^{10a} in each occurrence is independently selected from H, C_{1-6}alkyl, carbocyclyl, and heterocyclyl, wherein said C_{1-6}alkyl, carbocyclyl, and heterocyclyl in each occurrence are optionally and independently substituted on carbon with one or more R^a, and wherein any -NH- moiety of said heterocyclyl is optionally substituted with R^{a*};

R^{10b} in each occurrence is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, and heterocyclyl, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, and heterocyclyl in each occurrence are optionally and independently substituted on carbon with one or more R^a, and wherein any -NH- moiety of said heterocyclyl is optionally substituted with R^{a*};

R^{30} in each occurrence is independently selected from halo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl,

C_{2-6}alkynyl, $-OR^{30a}$, $-SR^{30a}$, and $-N(R^{30a})_2$;

$\mathbf{R^{30a}}$ in each occurrence is independently selected from H and C_{1-6}alkyl;

$\mathbf{R^{40}}$ in each occurrence is independently selected from halo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, heterocyclyl, $-OR^{40a}$, $-SR^{40a}$, $-N(R^{40a})_2$, $-N(R^{40a})C(O)R^{40b}$, $-N(R^{40a})N(R^{40a})_2$, $-NO_2$, $-N(R^{40a})$-OR^{40a}, -O-$N(R^{40a})_2$, -C(O)H, $-C(O)R^{40b}$, $-C(O)_2R^{40a}$, $-C(O)N(R^{40a})_2$, $-C(O)N(R^{40a})(OR^{40a})$, $-OC(O)N(R^{40a})_2$, $-N(R^{40a})C(O)_2R^{40a}$, $-N(R^{40a})C(O)N(R^{40a})_2$, $-OC(O)R^{40b}$, $-S(O)R^{40b}$, $-S(O)_2R^{40b}$, $-S(O)_2N(R^{40a})_2$, $-N(R^{40a})S(O)_2R^{40b}$, $-C(R^{40a})=N(R^{40a})$, and $-C(R^{40a})=N(OR^{40a})$;

$\mathbf{R^{40*}}$ in each occurrence is independently selected from C_{1-6}alkyl, carbocyclyl, heterocyclyl, -C(O)H, $-C(O)R^{40b}$, $-C(O)_2R^{40a}$, $-C(O)N(R^{40a})_2$, $-S(O)R^{40b}$, $-S(O)_2R^{40b}$, $-S(O)_2N(R^{40a})_2$, $-C(R^{40a})=N(R^{40a})$, and $-C(R^{40a})=N(OR^{40a})$;

$\mathbf{R^{40a}}$ in each occurrence is independently selected from H, C_{1-6}alkyl, carbocyclyl, and heterocyclyl;

$\mathbf{R^{40b}}$ in each occurrence is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, and heterocyclyl;

$\mathbf{R^{a}}$ in each occurrence is independently selected from halo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, heterocyclyl, $-OR^{m}$, $-SR^{m}$, $-N(R^{m})_2$, $-N(R^{m})C(O)R^{n}$, $-N(R^{m})N(R^{m})_2$, $-NO_2$, $-N(R^{m})$-OR^{m}, -O-$N(R^{m})_2$, -C(O)H, $-C(O)R^{n}$, $-C(O)_2R^{m}$, $-C(O)N(R^{m})_2$, $-C(O)N(R^{m})(OR^{m})$, $-OC(O)N(R^{m})_2$, $-N(R^{m})C(O)_2R^{m}$, $-N(R^{m})C(O)N(R^{m})_2$, $-OC(O)R^{n}$, $-S(O)R^{n}$, $-S(O)_2R^{n}$, $-S(O)_2N(R^{m})_2$, $-N(R^{m})S(O)_2R^{n}$, $-C(R^{m})=N(R^{m})$, and $-C(R^{m})=N(OR^{m})$;

$\mathbf{R^{a*}}$ in each occurrence is independently selected from C_{1-6}alkyl, carbocyclyl, heterocyclyl, -C(O)H, $-C(O)R^{n}$, $-C(O)_2R^{m}$, $-C(O)N(R^{m})_2$, $-S(O)R^{n}$, $-S(O)_2R^{n}$, $-S(O)_2N(R^{m})_2$, $-C(R^{m})=N(R^{m})$, and $-C(R^{m})=N(OR^{m})$;

$\mathbf{R^{m}}$ in each occurrence is independently selected from H, C_{1-6}alkyl, carbocyclyl, and heterocyclyl; and

$\mathbf{R^{n}}$ in each occurrence is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, and heterocyclyl.

2. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in claim 1, wherein

Ring A is fused morpholine, wherein said fused morpholine is optionally substituted with one or more $\mathbf{R^4}$; and

$\mathbf{R^4}$ is $C_{1\text{-}6}$alkyl.

3. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in either one of claim 1 or 2, wherein:

W is -O-;

X is C-H;

Y is C-R^3; and

$\mathbf{R^3}$ is halo.

4. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 3, wherein:

$\mathbf{R^1}$ is selected from $C_{1\text{-}6}$alkyl, 3- to 5-membered carbocyclyl, 5- or 6-membered heterocyclyl, $-OR^{1a}$, $-SR^{1a}$, $-N(R^{1a})_2$, $-N(R^{1a})C(O)R^{1b}$, $-C(O)N(R^{1a})_2$, $-C(O)R^{1b}$, $-C(O)_2R^{1a}$, $-C(O)N(R^{1a})_2$, $-C(O)N(R^{1a})(OR^{1a})$, and $-S(O)_2R^{1b}$, wherein said $C_{1\text{-}6}$alkyl, 3 to 5-membered carbocyclyl, and 5- or 6-membered heterocyclyl are optionally substituted on carbon with one or more R^{10}, and wherein any -NH- moiety of said 5- or 6-membered heterocyclyl is optionally substituted with R^{10*};

$\mathbf{R^{1a}}$ in each occurrence is independently selected from H, $C_{1\text{-}6}$alkyl, 3- to 5-membered carbocyclyl, and 5- or 6-membered heterocyclyl, wherein said $C_{1\text{-}6}$alkyl, 3- to 5-membered carbocyclyl, and 5- or 6-membered heterocyclyl in each occurrence are optionally and independently substituted with one or more R^{10}, wherein any -NH- moiety of said 5- or 6-membered heterocyclyl is optionally substituted with R^{10*};

$\mathbf{R^{1b}}$ in each occurrence is independently selected from $C_{1\text{-}6}$alkyl and 4- to 6-membered heterocyclyl, wherein said $C_{1\text{-}6}$alkyl and 4- to 6-membered heterocyclyl are optionally and independently substituted on carbon with one or more R^{10}, and wherein any -NH- moiety of said 4- to 6-membered heterocyclyl is optionally substituted with R^{10*};

$\mathbf{R^{10}}$ in each occurrence is independently selected from halo, -CN, $C_{1\text{-}6}$alkyl, 3- to 6-membered carbocyclyl, 5- or 6-membered heterocyclyl, $-OR^{10a}$, $-SR^{10a}$, $-N(R^{10a})_2$, $-N(R^{10a})C(O)R^{10b}$, $-C(O)_2R^{10a}$, $-C(O)N(R^{10a})_2$, wherein said $C_{1\text{-}6}$alkyl, 3- to 6-membered

carbocyclyl, and 5- or 6-membered heterocyclyl in each occurrence are optionally substituted with one or more R^a, and wherein any -NH- moiety of said 5- or 6-membered heterocyclyl is optionally substituted with R^{a*};

$\mathbf{R^{10*}}$ in each occurrence is independently selected from C_{1-6}alkyl and $-C(O)R^{10b}$;

$\mathbf{R^{10a}}$ in each occurrence is independently selected from H and C_{1-6}alkyl, wherein said C_{1-6}alkyl in each occurrence is optionally and independently substituted with one or more R^a;

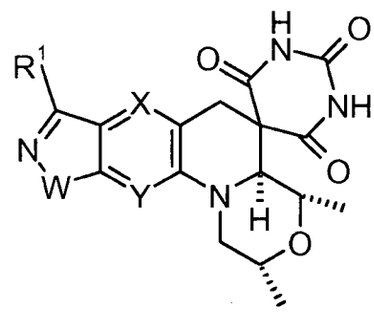
$\mathbf{R^{10b}}$ is C_{1-6}alkyl;

$\mathbf{R^a}$ in each occurrence is independently selected from halo, -CN, and $-OR^m$;

$\mathbf{R^{a*}}$ is C_{1-6}alkyl; and

$\mathbf{R^m}$ in each occurrence is independently selected from H and C_{1-6}alkyl.

5. A compound of Formula (Ia):



Formula (Ia)

or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R^1}$ is as described hereinabove, and:

W is O;

X is C-H;

Y is C-R^3;

$\mathbf{R^1}$ is selected from aminocarbonyl, 2-aminopyrimidin-4-yl, 2-cyanopyrimidin-4-yl, 3,3-difluoroazetidin-1-yl, [(2,2-difluoroethyl)amino]carbonyl, difluoromethyl, (isopropylamino)carbonyl, methyl, (methylamino)carbonyl, 2-(methylsulfanyl)pyrimidin-

4-yl, 1-methyl-1*H*-1,2,4-triazol-5-yl, pyrazin-2-yl, pyridazin-3-yl, pyrimidin-4-yl, pyrimdin-2-yl, 1,3-thiazol-2-yl, 1*H*-1,2,4-triazol-1-yl, 2*H*-1,2,3-triazol-2-yl, and trifluoromethyl.

R^3 is halo.

6. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 5, for use as a medicament.

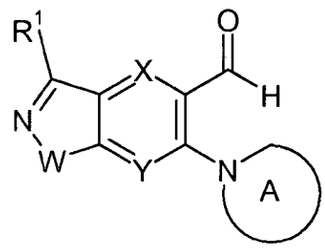
7. The use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 5, in the manufacture of a medicament for use in the treatment of a bacterial infection in a warm-blooded animal such as man.

8. A method for treating a bacterial infection in a warm-blooded animal such as man, said method comprising administering to said animal an effective amount of a compound of Formula (I), as claimed in any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof.

9. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 5, for use in treating a bacterial infection in a warm-blooded animal, such as man.

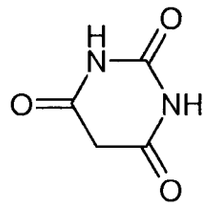
10. A pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 5, and at least one pharmaceutically acceptable carrier, diluent, or excipient.

11. A process for preparing a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 5, said process comprising reacting a compound of Formula (A1):



Formula (A1)

with barbituric acid:



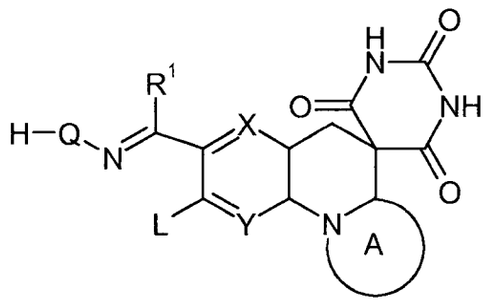
and thereafter if necessary:

i) converting a compound of Formula (I) into another compound of Formula (I);

ii) removing any protecting groups; and/or

iii) forming a pharmaceutically acceptable salt.

12. A process for preparing a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 5, said process comprising reacting a compound of Formula (A3):



Formula (A3)

with a suitable ring-forming agent,

and thereafter if necessary:

i) converting a compound of Formula (I) into another compound of Formula (I);

ii) removing any protecting groups; and/or

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Campo de la invención

La presente invención se refiere a nuevos heterociclos sustituidos, sus composiciones farmacéuticas y métodos de uso. Además, la presente invención se refiere a métodos terapéuticos para el tratamiento de infecciones bacterianas.

Antecedentes de la invención

La comunidad microbiológica y relacionada con las enfermedades infecciosas a nivel internacional continúa manifestando su preocupación con respecto a que la continua evolución de la resistencia antibacteriana podría provocar la aparición de cepas bacterianas contra las cuales los agentes antibacterianos actualmente disponibles no sean efectivos. Esto podría provocar una morbilidad y mortalidad considerables. En general, los patógenos bacterianos pueden clasificarse en patógenos Gram positivos o Gram negativos. Se considera que, generalmente, los compuestos antibióticos con actividad efectiva contra los patógenos Gram positivos y Gram negativos presentan un amplio espectro de actividad.

Los patógenos Gram positivos son objeto de especial preocupación debido al desarrollo de cepas resistentes que son difíciles de tratar y difíciles de erradicar del entorno hospitalario una vez instaladas. Algunos ejemplos de dichas cepas son el *Saphylococcus aureus* resistente a la meticilina (MRSA), estafilococos coagulasa negativos resistentes a la meticilina (MRCNS), *Streptococcus pneumoniae* resistente a la penicilina y *Enterococcus faecium* múltiplemente resistente. La resistencia está creciendo a una velocidad sostenida, lo que hace que muchos de estos agentes sean cada vez menos efectivos en el tratamiento de patógenos Gram positivos. Además, existe una resistencia creciente a agentes tales como las β-lactamas, quinolonas y macrólidos utilizados para el tratamiento de infecciones del tracto respiratorio superior causadas por cepas Gram negativas, incluidas *H. influenzae* y *M. catarrhalis*. Además, los patógenos hospitalarios Gram negativos, tales como *Pseudomonas aeruginosa*, son difíciles de tratar debido al desarrollo de resistencia. Consecuentemente, para controlar la amenaza del aumento de organismos resistentes a múltiples fármacos, existe una constante necesidad de desarrollar nuevas sustancias antibacterianas.

La ácido desoxirribonucleico (ADN) girasa es un miembro de la familia de topoisomerasas tipo II que controla el estado topológico del ADN en las células (Champoux, J. J.; 2001. Ann. Rev. Biochem. 70: 369-413). Las topoisomerasas tipo II utilizan la energía libre de la hidrólisis del trifosfato de adenosina (ATP) para alterar la topología del ADN introduciendo roturas transitorias en las dos cadenas del ADN, catalizando el pasaje de un segmento de ADN a través de la rotura y luego uniendo nuevamente el ADN. La ADN girasa es una enzima esencial y conservada en las bacterias y es única entre las topoisomerasas por su capacidad para introducir superespirales negativas en el ADN. La enzima está formada por dos subunidades, codificadas por *gyrA* y *gyrB*, que forman un complejo A_2B_2 tetramérico. La subunidad A de la girasa (GyrA) está involucrada en la rotura y sellado del ADN y contiene un residuo de tirosina conservado que forma los enlaces covalentes transitorios con el ADN durante el proceso de pasaje de segmentos. La subunidad B (GyrB) cataliza la hidrólisis del ATP e interactúa con la subunidad A para traducir la energía libre de la hidrólisis en el cambio conformacional de la enzima que permite el pasaje de segmentos y sellado del ADN.

Otra topoisomerasa tipo II conservada y esencial en las bacterias es la topoisomerasa IV, responsable principalmente de separar los cromosomas bacterianos cerrados circulares enlazados producidos en la replicación. Esta enzima está estrechamente relacionada con la ADN-girasa y posee una estructura tetramérica similar, formada por subunidades homólogas a la Gyr A y Gyr B. La identidad secuencial general entre la girasa y la topoisomerasa IV en diferentes especies bacteriales es elevada. Por lo tanto, los compuestos que actúan sobre las topoisomerasas bacterianas tipo II tienen el potencial para inhibir dos dianas en las células, la ADN-girasa y la topoisomerasa IV; este es el caso de las sustancias antibacterianas de tipo quinolona actuales (Maxwell, A. 1997, Trends Microbiol. 5: 102-109).

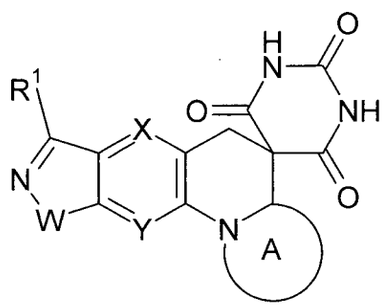
Las sustancias antibacterianas que actúan sobre la ADN girasa se conocen bien en la técnica, incluidos algunos ejemplos tales como las quinolonas y las cumarinas. Las quinolonas (por ejemplo, la ciprofloxacina) son agentes antibacterianos de amplio especto que inhiben la rotura del ADN y la actividad de reunión de la enzima y atrapan la subunidad GyrA unida covalentemente con el ADN (Drlica, K. y X. Zhao, 1997, Microbiol. Molec. Biol. Rev. 61: 377-392). Los miembros de esta clase de sustancias antibacterianas también inhiben la topoisomerasa

IV y, como resultado, la diana principal de estos compuestos varía entre las especies. Aunque las quinolonas son sustancias antibacterianas exitosas, la resistencia generada principalmente por las mutaciones en la diana (ADN girasa y topoisomerasa IV) es un problema en aumento en varios organismos, inclusive *S. aureus* y *Streptococcus pneumoniae* (Hooper, D. C., 2002, The Lancet Infectious Diseases 2: 530-538). Además, las quinolonas, como clase química, poseen efectos secundarios tóxicos, entre ellos la artropatía, lo que impide su uso en niños (Lipsky, B. A. y Baker, C. A., 1999, Clin. Infect. Dis. 28: 352-364). Más aun, su cardiotoxididad potencial, según lo predice la prolongación del intervalo QT_c, ha sido citada como una toxicidad preocupante de las quinolonas.

Se conocen varios inhibidores naturales de la ADN girasa que compiten con el ATP por la unión con la subunidad GyrB (Maxwell, A. y Lawson, D. M. 2003, Curr. Topics in Med. Chem. 3: 283-303). Las cumarinas son productos naturales aislados del *Streptomyces spp.*, algunos ejemplos de estas incluyen la novobiocina, la clorobiocina y la coumermicina A1. Aunque estos compuestos son inhibidores potentes de la ADN girasa, su utilidad terapéutica es limitada debido a su toxicidad en eucariotas y a su escasa penetración en las bacterias Gram negativas (Maxwell, A. 1997, Trends Microbiol. 5: 102-109). Otra clase de productos naturales que actúa sobre la subunidad GyrB la componen las ciclotialidinas, aisladas de *Streptomyces filipensis* (Watanabe, J. *et al* 1994, J. *Antibiot.* 47: 32-36). A pesar de su potente actividad contra la ADN girasa, la ciclotialidina es un mal agente antibacteriano, que solo muestra actividad contra algunas especies eubacterianas (Nakada, N, 1993, *Antimicrob. Agents Chemother.* 37: 2656-2661).

Compendio de la invención

La presente invención se refiere a compuestos de Fórmula (I):



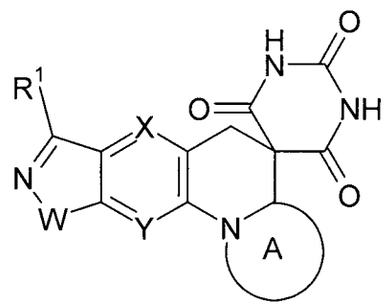
Fórmula (I)

y a sales farmacéuticamente aceptables de estos.

Se cree que los compuestos de Fórmula (I) típicos inhiben la ADN girasa bacteriana y, por lo tanto, son de interés por sus efectos antibacterianos. Se cree que los compuestos de la invención son activos contra distintos organismos bacterianos, incluidas las bacterias aeróbicas y anaeróbicas Gram positivas y Gram negativas.

Descripción detallada de la invención

La presente invención se refiere a compuestos de Fórmula (I):



Fórmula (I)

y a sales farmacéuticamente aceptables de estos, en donde:

el **Anillo A** está fusionado a un anillo heterocíclico no aromático de 5 a 7 miembros, en donde dicho anillo heterocíclico no aromático de 5 a 7 miembros fusionado está opcionalmente sustituido sobre carbono con uno o más R^4 y en donde todo resto -NH- de dicho anillo heterocíclico de 5 a 7 miembros está opcionalmente sustituido con R^{4*};

W se selecciona de -O-, -NH-, -S- y $-S(O)_2-$;

X se selecciona de N y C-R^2;

Y se selecciona de N y C-R^3;

R^1 se selecciona de H, halo, -CN, alquiloC_{1-6}, alqueniloC_{2-6}, alquiniloC_{2-6}, carbociclilo, heterociclilo, $-OR^{1a}$, $-SR^{1a}$, $-N(R^{1a})_2$, $-N(R^{1a})C(O)R^{1b}$, $-N(R^{1a})N(R^{1a})_2$, $-NO_2$, $-N(R^{1a})OR^{1a}$, $-ON(R^{1a})_2$, -C(O)H, $-C(O)R^{1b}$, $-C(O)_2R^{1a}$, $-C(O)N(R^{1a})_2$, $-C(O)N(R^{1a})(OR^{1a})$, $-OC(O)N(R^{1a})_2$, -

$N(R^{1a})C(O)_2R^{1a}$, $-N(R^{1a})C(O)N(R^{1a})_2$, $-OC(O)R^{1b}$, $-S(O)R^{1b}$, $-S(O)_2R^{1b}$, $-S(O)_2N(R^{1a})_2$, $-N(R^{1a})S(O)_2R^{1b}$, $-C(R^{1a})=N(R^{1a})$ y $-C(R^{1a})=N(OR^{1a})$, en donde dichos alquiloC_{1-6}, alqueniloC_{2-6}, alquiniloC_{2-6}, carbociclilo y heterociclilo están opcionalmente sustituidos sobre carbono con uno o más R^{10} y en donde todo resto -NH- de dicho heterociclilo está opcionalmente sustituido con R^{10*};

R^{1a} en cada caso se selecciona independientemente de H, alquiloC_{1-6}, carbociclilo y heterociclilo, en donde dichos alquiloC_{1-6}, carbociclilo y heterociclilo en cada caso se sustituyen opcionalmente e independientemente sobre carbono con uno o más R^{10} y en donde todo resto -NH- de dicho heterociclilo está opcionalmente sustituido con R^{10*};

R^{1b} en cada caso se selecciona independientemente de alquiloC_{1-6}, alqueniloC_{2-6}, alquiniloC_{2-6}, carbociclilo y heterociclilo, en donde dichos alquiloC_{1-6}, alqueniloC_{2-6}, alquiniloC_{2-6}, carbociclilo y heterociclilo en cada caso se sustituyen opcionalmente e independientemente sobre carbono con uno o más R^{10} y en donde todo resto -NH- de dicho heterociclilo está opcionalmente sustituido con R^{10*};

R^2 se selecciona de H, halo y -CN;

R^3 se selecciona de H, halo, -CN, alquiloC_{1-6}, alqueniloC_{2-6}, alquiniloC_{2-6}, $-OR^{3a}$, $-SR^{3a}$ y $-N(R^{3a})_2$, en donde dichos alquiloC_{1-6}, alqueniloC_{2-6} y alquiniloC_{2-6} están opcionalmente sustituidos sobre carbono con uno o más R^{30};

R^{3a} en cada caso se selecciona independientemente de H y alquiloC_{1-6}, en donde dicho alquiloC_{1-6} en cada caso se sustituye opcionalmente e independientemente sobre carbono con uno o más R^{30};

R^4 en cada caso se selecciona independientemente de halo, -CN, alquiloC_{1-6}, alqueniloC_{2-6}, alquiniloC_{2-6}, carbociclilo, heterociclilo, $-OR^{4a}$, $-SR^{4a}$, $-N(R^{4a})_2$, $-N(R^{4a})C(O)R^{4b}$, $-N(R^{4a})N(R^{4a})_2$, $-NO_2$, $-N(R^{4a})$-OR^{4a}, -O-$N(R^{4a})_2$, -C(O)H, $-C(O)R^{4b}$, $-C(O)_2R^{4a}$, $-C(O)N(R^{4a})_2$, $-C(O)N(R^{4a})(OR^{4a})$ $-OC(O)N(R^{4a})_2$, $-N(R^{4a})C(O)_2R^{4a}$, $-N(R^{4a})C(O)N(R^{4a})_2$, $-OC(O)R^{4b}$, $-S(O)R^{4b}$, $-S(O)_2R^{4b}$, $-S(O)_2N(R^{4a})_2$, $-N(R^{4a})S(O)_2R^{4b}$, $-C(R^{4a})=N(R^{4a})$ y $-C(R^{4a})=N(OR^{4a})$, en donde dichos alquiloC_{1-6}, alqueniloC_{2-6}, alquiniloC_{2-6}, carbociclilo y heterociclilo están opcionalmente sustituidos sobre carbono con uno o más R^{40} y en donde todo resto -NH- de dicho heterociclilo está opcionalmente sustituido con R^{40*};

R^{4*} en cada caso se selecciona independientemente de alquiloC_{1-6}, carbociclilo, heterociclilo, -C(O)H, $-C(O)R^{4b}$, $-C(O)_2R^{4a}$, $-C(O)N(R^{4a})_2$, $-S(O)R^{4b}$, $-S(O)_2R^{4b}$, $-S(O)_2N(R^{4a})_2$, $-C(R^{4a})=N(R^{4a})$

y -C(R^{4a})=N(OR^{4a}), en donde dichos alquiloC$_{1-6}$, carbociclilo y heterociclilo en cada caso se sustituyen opcionalmente e independientemente sobre carbono con uno o más R^{40} y en donde todo resto -NH- de dicho heterociclilo está opcionalmente sustituido con R^{40*};

R^{4a} en cada caso se selecciona independientemente de H, alquiloC$_{1-6}$, carbociclilo y heterociclilo, en donde dichos alquiloC$_{1-6}$, carbociclilo y heterociclilo en cada caso se sustituyen opcionalmente e independientemente sobre carbono con uno o más R^{40} y en donde todo resto -NH- de dicho heterociclilo está opcionalmente sustituido con R^{40*};

R^{4b} en cada caso se selecciona independientemente de alquiloC$_{1-6}$, alqueniloC$_{2-6}$, alquiniloC$_{2-6}$, carbociclilo y heterociclilo, en donde dichos alquiloC$_{1-6}$, alqueniloC$_{2-6}$, alquiniloC$_{2-6}$, carbociclilo y heterociclilo en cada caso se sustituyen opcionalmente e independientemente sobre carbono con uno o más R^{40} y en donde todo resto -NH- de dicho heterociclilo está opcionalmente sustituido con R^{40*};

R^{10} en cada caso se selecciona independientemente de halo, -CN, alquiloC$_{1-6}$, alqueniloC$_{2-6}$, alquiniloC$_{2-6}$, carbociclilo, heterociclilo, -OR^{10a}, -SR^{10a}, -N(R^{10a})$_2$, -N(R^{10a})C(O)R^{10b}, -N(R^{10a})N(R^{10a})$_2$, -NO_2, -N(R^{10a})-OR^{10a}, -O-N(R^{10a})$_2$, -C(O)H, -C(O)R^{10b}, -C(O)$_2R^{10a}$, -C(O)N(R^{10a})$_2$, -C(O)N(R^{10a})(OR^{10a}), -OC(O)N(R^{10a})$_2$, -N(R^{10a})C(O)$_2R^{10a}$, -N(R^{10a})C(O)N(R^{10a})$_2$, -OC(O)R^{10b}, -S(O)R^{10b}, -S(O)$_2R^{10b}$, -S(O)$_2$N(R^{10a})$_2$, -N(R^{10a})S(O)$_2R^{10b}$, -C(R^{10a})=N(R^{10a}) y -C(R^{10a})=N(OR^{10a}), en donde dichos alquiloC$_{1-6}$, alqueniloC$_{2-6}$, alquiniloC$_{2-6}$, carbociclilo y heterociclilo en cada caso se sustituyen opcionalmente e independientemente sobre carbono con uno o más R^a y en donde todo resto -NH- de dicho heterociclilo está opcionalmente sustituido con R^{a*};

R^{10*} en cada caso se selecciona independientemente de alquiloC$_{1-6}$, carbociclilo, heterociclilo, -C(O)H, -C(O)R^{10b}, -C(O)$_2R^{10a}$, -C(O)N(R^{10a})$_2$, -S(O)R^{10b}, -S(O)$_2R^{10b}$, -S(O)$_2$N(R^{10a})$_2$, -C(R^{10a})=N(R^{10a}) y -C(R^{10a})=N(OR^{10a}), en donde dichos alquiloC$_{1-6}$, carbociclilo y heterociclilo en cada caso se sustituyen opcionalmente e independientemente sobre carbono con uno o más R^a y en donde todo resto -NH- de dicho heterociclilo está opcionalmente sustituido con R^{a*};

R^{10a} en cada caso se selecciona independientemente de H, alquiloC$_{1-6}$, carbociclilo y heterociclilo, en donde dichos alquiloC$_{1-6}$, carbociclilo y heterociclilo en cada caso se sustituyen opcionalmente e independientemente sobre carbono con uno o más R^a y en donde todo resto -NH- de dicho heterociclilo está opcionalmente sustituido con R^{a*};

R^{10b} en cada caso se selecciona independientemente de alquiloC$_{1-6}$, alqueniloC$_{2-6}$, alquiniloC$_{2-6}$,

carbociclilo y heterociclilo, en donde dichos alquiloC$_{1-6}$, alqueniloC$_{2-6}$, alquiniloC$_{2-6}$, carbociclilo y heterociclilo en cada caso se sustituyen opcionalmente e independientemente sobre carbono con uno o más R^a y en donde todo resto -NH- de dicho heterociclilo está opcionalmente sustituido con R^{a*};

R^{30} en cada caso se selecciona independientemente de halo, -CN, alquiloC$_{1-6}$, alqueniloC$_{2-6}$, alquiniloC$_{2-6}$, -OR^{30a}, -SR^{30a} y -$N(R^{30a})_2$;

R^{30a} en cada caso se selecciona independientemente de H y alquiloC$_{1-6}$;

R^{40} en cada caso se selecciona independientemente de halo, -CN, alquiloC$_{1-6}$, alqueniloC$_{2-6}$, alquiniloC$_{2-6}$, carbociclilo, heterociclilo, -OR^{40a}, -SR^{40a}, -$N(R^{40a})_2$, -$N(R^{40a})C(O)R^{40b}$, -$N(R^{40a})N(R^{40a})_2$, -NO_2, -$N(R^{40a})$-OR^{40a}, -O-$N(R^{40a})_2$, -C(O)H, -$C(O)R^{40b}$, -$C(O)_2R^{40a}$, -$C(O)N(R^{40a})_2$, -$C(O)N(R^{40a})(OR^{40a})$, -$OC(O)N(R^{40a})_2$, -$N(R^{40a})C(O)_2R^{40a}$, -$N(R^{40a})C(O)N(R^{40a})_2$, -$OC(O)R^{40b}$, -$S(O)R^{40b}$, -$S(O)_2R^{40b}$, -$S(O)_2N(R^{40a})_2$, -$N(R^{40a})S(O)_2R^{40b}$, -$C(R^{40a})=N(R^{40a})$ y -$C(R^{40a})=N(OR^{40a})$;

R^{40*} en cada caso se selecciona independientemente de alquiloC$_{1-6}$, carbociclilo, heterociclilo, -C(O)H, -$C(O)R^{40b}$, -$C(O)_2R^{40a}$, -$C(O)N(R^{40a})_2$, -$S(O)R^{40b}$, -$S(O)_2R^{40b}$, -$S(O)_2N(R^{40a})_2$, -$C(R^{40a})=N(R^{40a})$ y -$C(R^{40a})=N(OR^{40a})$;

R^{40a} en cada caso se selecciona independientemente de H, alquiloC$_{1-6}$, carbociclilo y heterociclilo;

R^{40b} en cada caso se selecciona independientemente de alquiloC$_{1-6}$, alqueniloC$_{2-6}$, alquiniloC$_{2-6}$, carbociclilo y heterociclilo;

R^a en cada caso se selecciona independientemente de halo, -CN, alquiloC$_{1-6}$, alqueniloC$_{2-6}$, alquiniloC$_{2-6}$, carbociclilo, heterociclilo, -OR^m, -SR^m, -$N(R^m)_2$, -$N(R^m)C(O)R^n$, -$N(R^m)N(R^m)_2$, -NO_2, -$N(R^m)$-OR^m, -O-$N(R^m)_2$, -C(O)H, -$C(O)R^n$, -$C(O)_2R^m$, -$C(O)N(R^m)_2$, -$C(O)N(R^m)(OR^m)$, -$OC(O)N(R^m)_2$, -$N(R^m)C(O)_2R^m$, -$N(R^m)C(O)N(R^m)_2$, -$OC(O)R^n$, -$S(O)R^n$, -$S(O)_2R^n$, -$S(O)_2N(R^m)_2$, -$N(R^m)S(O)_2R^n$, -$C(R^m)=N(R^m)$ y -$C(R^m)=N(OR^m)$;

R^{a*} en cada caso se selecciona independientemente de alquiloC$_{1-6}$, carbociclilo, heterociclilo, -C(O)H, -$C(O)R^n$, -$C(O)_2R^m$, -$C(O)N(R^m)_2$, -$S(O)R^n$, -$S(O)_2R^n$, -$S(O)_2N(R^m)_2$, -$C(R^m)=N(R^m)$ y -$C(R^m)=N(OR^m)$;

R^m en cada caso se selecciona independientemente de H, alquiloC$_{1-6}$, carbociclilo y heterociclilo; y

R^n en cada caso se selecciona independientemente de alquiloC$_{1-6}$, alqueniloC$_{2-6}$, alquiniloC$_{2-6}$,

carbociclilo y heterociclilo.

Alquilo - Tal como se utiliza en la presente, el término "alquilo" se refiere a radicales hidrocarburo tanto de cadena lineal como ramificada que contienen el número especificado de átomos de carbono. Las referencias a grupos alquilo individuales tales como "propilo" son específicas para la versión de cadena lineal solamente y las referencias a grupos alquilo individuales de cadena ramificada tales como 'isopropilo' son específicas para la versión de cadena ramificada solamente. En un aspecto, "alquilo" es metilo.

Alquileno - Tal como se utiliza en la presente, el término "alquileno" se refiere a dirradicales hidrocarburo saturados tanto de cadena lineal como ramificada que contienen el número especificado de átomos de carbono. Por ejemplo, "alquilenoC$_{1-6}$" incluye grupos tales como alquilenoC$_{1-3}$, metileno, etileno, propileno, isopropileno, butileno, pentileno y hexileno.

Alquenilo – Tal como se utiliza en la presente, el término "alquenilo" se refiere a radicales hidrocarburo tanto de cadena lineal como ramificada que contienen el número especificado de átomos de carbono y que contienen al menos un doble enlace carbono-carbono. Por ejemplo, "alqueniloC_{2-6}" incluye grupos tales como alqueniloC_{2-5}, alqueniloC_{2-4}, etenilo, 2-propenilo, 2-metil-2-propenilo, 3-butenilo, 4-pentenilo, 5-hexenilo, 2-heptenilo y 2-metil-1-heptenilo.

Alquenileno – Tal como se utiliza en la presente, el término "alquenileno" se refiere a radicales hidrocarburo tanto de cadena lineal como ramificada que contienen el número especificado de átomos de carbono y que contienen al menos un doble enlace carbono-carbono. En un aspecto, "alquenileno" puede ser eteno-1,2-diilo.

Alquinilo – Tal como se utiliza en la presente, el término "alquinilo" se refiere a radicales hidrocarburo tanto de cadena lineal como ramificada que contienen el número especificado de átomos de carbono y que contienen al menos un triple enlace carbono-carbono. Por ejemplo, "alquiniloC_{2-8}" incluye grupos tales como alquiniloC_{2-6}, alquiniloC_{2-4}, etinilo, 2-propinilo, 2-metil-2-propinilo, 3-butinilo, 4-pentinilo, 5-hexinilo, 2-heptinilo y 4-metil-5- heptinilo.

Alquinileno – Tal como se utiliza en la presente, el término "alquinileno" se refiere a radicales hidrocarburo tanto de cadena lineal como ramificada que contienen el número especificado de átomos de carbono y que contienen al menos un triple enlace carbono-carbono. En un aspecto, "alquinileno" puede ser etino-1,2-diilo.

Halo – Tal como se utiliza en la presente, el término "halo" pretende incluir fluoro, cloro, bromo y yodo. En un aspecto, el término "halo" puede referirse a fluoro, cloro y bromo. En otro aspecto, el término "halo" puede referirse a fluoro y cloro. En otro aspecto adicional, el término "halo" puede referirse a fluoro. En otro aspecto adicional, el término "halo" puede referirse a cloro.

Carbociclilo – Tal como se utiliza en la presente, el término "carbociclilo" se refiere a un anillo de carbono mono o bicíclico saturado, parcialmente saturado o insaturado que contiene de 3 a 12 átomos, en donde uno o más grupos $-CH_2-$ pueden reemplazarse opcionalmente por un número correspondiente de grupos -C(O)-. En un aspecto, el término "carbociclilo" puede referirse a un anillo monocíclico que contiene 5 o 6 átomos o a un anillo bicíclico que contiene 9 o 10 átomos. Algunos ejemplos ilustrativos de "carbociclilo" incluyen adamantilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclopentenilo, ciclohexilo, ciclohexenilo, 1-oxociclopentilo, fenilo, naftilo, tetralinilo, indanilo o 1-oxoindanilo. En un aspecto, "carbociclilo" puede ser fenilo. En otro aspecto, "carbociclilo" puede seleccionarse de ciclopropilo, ciclobutilo, ciclopentilo, ciclopentenilo y ciclohexilo. En otro aspecto adicional, carbociclilo puede ser fenilo.

Carbociclilo de 3 a 6 miembros – En un aspecto, "carbociclilo" puede ser "carbociclilo de 3 a 6 miembros." El término "carbociclilo de 3 a 6 miembros" se refiere a un anillo de carbono monocíclico saturado o parcialmente saturado que contiene de 3 a 6 átomos en el anillo, de los cuales uno o más grupos $-CH_2-$ pueden reemplazarse opcionalmente por un número correspondiente de grupos -C(O)-. Algunos ejemplos ilustrativos de "carbociclilo de 3 a 6 miembros" incluyen ciclopropilo, ciclobutilo, ciclopentilo, oxociclopentilo, ciclopentenilo, ciclohexilo y fenilo. En otro aspecto, "carbociclilo de 3 a 6 miembros" puede ser ciclopropilo y fenilo. En otro aspecto adicional, "carbociclilo de 3 a 6 miembros" puede ser fenilo.

Carbociclilo de 3 a 5 miembros - En un aspecto, "carbociclilo" y "carbociclilo de 3 a 6

miembros" puede ser "carbociclilo de 3 a 5 miembros". El término "carbociclilo de 3 a 5 miembros" se refiere a un anillo de carbono monocíclico saturado o parcialmente saturado que contiene de 3 a 5 átomos en el anillo, de los cuales uno o más grupos $-CH_2-$ pueden reemplazarse opcionalmente por un número correspondiente de grupos -C(O)-. Algunos ejemplos ilustrativos de "carbociclilo de 3 a 5 miembros" incluyen ciclopropilo, ciclobutilo, ciclopentilo y ciclopentenilo. En un aspecto, "carbociclilo de 3 a 5 miembros" puede ser ciclopropilo.

Heterociclilo – Tal como se utiliza en la presente, el término "heterociclilo" se refiere a un anillo mono o bicíclico saturado, parcialmente saturado o insaturado que contiene de 4 a 12 átomos de los cuales al menos un átomo se selecciona de nitrógeno, azufre u oxígeno, que puede, a menos que se indique de otra forma, estar unido a carbono o nitrógeno, en donde uno o más grupos $-CH_2-$ pueden reemplazarse opcionalmente por un número correspondiente de grupos -C(O)-. Los átomos de azufre del anillo puede oxidarse opcionalmente para formar S-óxidos. Los átomos de nitrógeno del anillo pueden oxidarse opcionalmente para formar N-óxidos. Algunos ejemplos ilustrativos del término "heterociclilo" incluyen bencimidazolilo, 1,3-benzodioxolilo, benzofuranilo, 1-benzotiofenilo, 1,3-benzotiazolilo, 1,3-benzoxazolilo, dioxidotetrahidrotiofenilo, 3,5-dioxopiperidinilo, imidazolilo, indolilo, isoquinolona, isotiazolilo, isoxazolilo, morfolinilo, 1,2,4-oxadiazolilo, oxoimidazolidinilo, 2-oxopirrolidinilo, 2-oxotetrahidrofuranilo, 2-oxo-1,3-tiazolidinilo, piperazinilo, piperidilpiperidinilo, piranilo, pirazolilo, piridinilo, pirrolilo, pirrolidinilo, pirrolinilo, pirimidilo, pirazinilo, pirazolilo, piridazinilo, 4-piridona, quinolilo, tetrazolilo, tetrahidrofuranilo, tetrahidropiranilo, tiazolilo, 1,3,4-tiadiazolilo, tiazolidinilo, tienilo, tiomorfolino, 4*H*-1,2,4-triazolilo, *N*-óxido de piridina y *N*-óxido de quinolina. En un aspecto de la invención el término "heterociclilo" puede referirse a un anillo monocíclico saturado, parcialmente saturado o insaturado que contiene 5 o 6 átomos de los que al menos un átomo se selecciona de nitrógeno, azufre u oxígeno y puede, a menos que se indique de otra forma, estar unido a carbono o nitrógeno, y un átomo de nitrógeno del anillo puede oxidarse opcionalmente para formar un N-óxido.

Heterociclilo de 4 a 6 miembros - En un aspecto, "heterociclilo" puede ser "heterociclilo de 4 a 6 miembros". El término "heterociclilo de 4 a 6 miembros" se refiere a un anillo monocíclico saturado, parcialmente saturado o insaturado que contiene de 4 a 6 átomos en el anillo, de los

cuales al menos un átomo en el anillo se selecciona de nitrógeno, azufre y oxígeno y de los cuales un grupo -CH_2- puede reemplazarse opcionalmente por un grupo -C(O)-. A menos que se indique de otra forma, los grupos "heterociclilo de 4 a 6 miembros" pueden estar unidos a carbono o nitrógeno. Los átomos de nitrógeno del anillo pueden oxidarse opcionalmente para formar un N-óxido. Los átomos de azufre del anillo pueden oxidarse opcionalmente para formar S-óxidos. Algunos ejemplos ilustrativos de "heterociclilo de 4 a 6 miembros" incluyen, sin carácter limitante, azetidin-1-il, dioxidotetrahidrotiofenilo, 2,4-dioxoimidazolidinilo, 3,5-dioxopiperidinilo, furanilo, imidazolilo, isotiazolilo, isoxazolilo, morfolinilo, oxazolilo, oxetanilo, oxoimidazolidinilo, 3-oxo-1-piperazinilo, 2-oxopirrolidinilo, 2-oxotetrahidrofuranilo, oxo-1,3-tiazolidinilo, piperazinilo, piperidilo, 2*H*-piranilo, pirazolilo, piridinilo, pirrolilo, pirrolidinilo, pirimidinilo, pirazinilo, pirazolilo, piridazinilo, 4-piridonilo, tetrahidrofuranilo, tetrahidropiranilo, tiazolilo, 1,3,4-tiadiazolilo, tiazolidinilo, tiomorfolinilo, tiofenilo, 4*H*-1,2,4-triazolilo y *N*-oxidilo de piridina.

Heterociclilo de 5 o 6 miembros - En un aspecto, "heterociclilo" y "heterociclilo de 4 a 6 miembros" puede ser "heterociclo de 5 o 6 miembros", que se refiere a un anillo monocíclico saturado, parcialmente saturado o insaturado que contiene 5 o 6 átomos en el anillo, de los cuales al menos un átomo en el anillo se selecciona de nitrógeno, azufre y oxígeno y de los cuales uno o más grupos -CH_2- pueden reemplazarse opcionalmente por el número correspondiente de grupos -C(O)-. A menos que se indique de otra forma, los grupos "heterociclo de 5 o 6 miembros" pueden estar unidos a carbono o nitrógeno. Los átomos de nitrógeno del anillo pueden oxidarse opcionalmente para formar un N-óxido. Los átomos de azufre del anillo pueden oxidarse opcionalmente para formar S-óxidos. Algunos ejemplos ilustrativos de "heterociclo de 5 o 6 miembros" incluyen dioxidotetrahidrotiofenilo, 2,4-dioxoimidazolidinilo, 3,5-dioxopiperidinilo, furanilo, imidazolilo, isotiazolilo, isoxazolilo, morfolinilo, oxazolilo, oxoimidazolidinilo, 2-oxopirrolidinilo, 2-oxotetrahidrofuranilo, oxo-1,3-tiazolidinilo, piperazinilo, piperidinilo, 2*H*-piranilo, pirazolilo, piridinilo, pirrolilo, pirrolidinilo, pirrolidinilo, pirimidinilo, pirazinilo, pirazolilo, piridazinilo, 4-piridonilo, tetrazolilo, tetrahidrofuranilo, tetrahidropiranilo, tiazolilo, 1,3,4-tiadiazolilo, 1,3,4-tiazolidinilo, tiomorfolinilo, tiofenilo, 4*H*-1,2,4-triazolilo y *N*-oxidilo de piridina.

Heterociclilo de 6 miembros - En un aspecto, "heterociclilo", "heterociclilo de 4 a 6 miembros" y "heterociclilo de 5 o 6 miembros" pueden ser "heterociclilo de 6 miembros", que se refiere a un anillo monocíclico saturado, parcialmente saturado o insaturado que contiene 6 átomos en el anillo, de los cuales al menos un átomo en el anillo se selecciona de nitrógeno, azufre y oxígeno y de los que uno o más grupos -CH_2- pueden reemplazarse opcionalmente por un número correspondiente de grupos -C(O)-. A menos que se indique de otra forma, los grupos "heterociclilo de 6 miembros" pueden estar unidos a carbono o nitrógeno. Los átomos de nitrógeno del anillo pueden oxidarse opcionalmente para formar un N-óxido. Los átomos de azufre del anillo pueden oxidarse opcionalmente para formar S-óxidos. Algunos ejemplos ilustrativos de "heterociclilo de 6 miembros" incluyen 3,5-dioxopiperidinilo, morfolinilo, 3-oxo-1-piperazinilo, piperazinilo, piperidinilo, 2*H*-piranilo, pirazinilo, piridazinilo, piridinilo y pirimidinilo.

Heterociclilo no aromático de 5 o 6 miembros – En un aspecto, "heterociclilo" y "heterociclilo de 5 o 6 miembros" puede ser "heterociclilo no aromático de 5 o 6 miembros". El término "heterociclilo no aromático de 5 o 6 miembros" se refiere a un anillo heterociclilo no aromático monocíclico saturado o parcialmente saturado que contiene 5 o 6 átomos en el anillo, de los que al menos un átomo del anillo se selecciona de nitrógeno, azufre y oxígeno y que puede, a menos que se indique de otra forma, estar unido a carbono o nitrógeno y de los que uno o más grupos -CH_2- puede reemplazarse opcionalmente por un número correspondiente de grupos -C(O)-. Los átomos de azufre del anillo pueden oxidarse opcionalmente para formar S-óxidos. Los átomos de nitrógeno del anillo pueden oxidarse opcionalmente para formar N-óxidos. Algunos ejemplos ilustrativos de "heterociclilo no aromático de 5 o 6 miembros" incluyen dioxidotetrahidrotiofenilo, 2,4-dioxoimidazolidinilo, 3,5-dioxopiperidinilo, morfolinilo, oxoimidazolidinilo, 2-oxopirrolidinilo, 2-oxotetrahidrofuranilo, oxo-1,3-tiazolidinilo, piperazinilo, piperidinilo, 2*H*-piranilo, pirrolidinilo, tetrahidrofuranilo, tetrahidropiranilo, tiomorfolinilo y tiazolidinilo.

Heteroarilo de 5 o 6 miembros – En un aspecto, "heterociclilo" y "heterociclilo de 5 o 6 miembros" pueden ser "heteroarilo de 5 o 6 miembros". El término "heteroarilo de 5 o 6 miembros" se refiere a un anillo heterociclilo monocíclico aromático que contiene 5 o 6 átomos

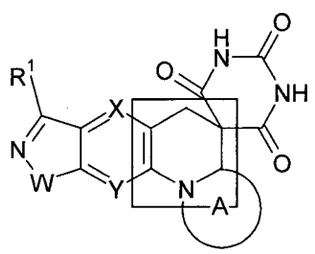
en el anillo, de los cuales al menos un átomo en el anillo se selecciona de nitrógeno, azufre y oxígeno. A menos que se indique de otra forma, los grupos "heteroarilo de 6 miembros" pueden estar unidos a carbono o nitrógeno. Los átomos de nitrógeno del anillo pueden oxidarse opcionalmente para formar un N-óxido. Los átomos de azufre del anillo pueden oxidarse opcionalmente para formar S-óxidos. Algunos ejemplos ilustrativos de "heteroarilo de 5 o 6 miembros" incluyen furanilo, imidazolilo, isotiazolilo, isoxazol, oxazolilo, pirazinilo, pirazolilo, piridazinilo, pirimidinilo, piridinilo, pirrolilo, tetrazolilo, 1,3,4-tiadiazolilo, tiazolilo, tiofenilo y 4*H*-1,2,4-triazolilo.

Heteroarilo de 6 miembros - En un aspecto, "heterociclilo", "heterociclo de 5 o 6 miembros", "heterociclilo de 6 miembros" y "heteroarilo de 5 o 6 miembros" pueden ser "heteroarilo de 6 miembros". El término "heteroarilo de 6 miembros" se refiere a un anillo heterociclilo monocíclico aromático que contiene 6 átomos en el anillo. Los átomos de nitrógeno del anillo pueden oxidarse opcionalmente para formar un N-óxido. Algunos ejemplos ilustrativos del término "heteroarilo de 6 miembros" incluyen pirazinilo, piridazinilo, pirimidinilo y piridinilo.

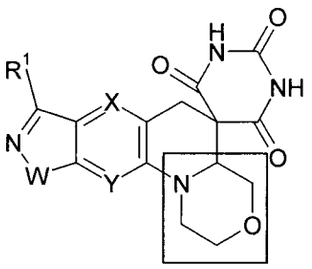
Heterociclo fusionado de 5 a 7 miembros – A los efectos del Anillo A, el término "heterociclo fusionado de 5 a 7 miembros" se refiere a un anillo monocíclico no aromático que contiene 5 o 7 átomos en el anillo, que comparte dos átomos, un carbono y un nitrógeno, con el anillo de piperidina de Fórmula (I) al cual está fusionado, formando un sistema de anillos bicíclico. El "heterociclo fusionado de 5 a 7 miembros" puede contener, además del nitrógeno que actúa como puente que se ilustra en la Fórmula (I), uno o más restos de heteroátomo en el anillo que se seleccionan de -O-, -NH- y -S-. Los átomos de azufre del anillo pueden oxidarse opcionalmente para formar S-óxidos, los átomos de nitrógeno del anillo pueden oxidarse opcionalmente para formar N-óxidos y uno o más grupos $-CH_2-$ pueden reemplazarse opcionalmente por un número correspondiente de grupos -C(O)- o $-C = N(OR^{4a})-$. Algunos ejemplos ilustrativos del término "heterociclo fusionado de 5 a 7 miembros" incluyen azepano fusionado, 3,5-dioxopiperidina fusionada, morfolina fusionada, oxopiperidina fusionada, 2-oxopirrolidina fusionada, oxo-1,3-tiazolidina fusionada, piperazina fusionada, piperidina fusionada, pirrolidina fusionada, tiazolidina fusionada y tiomorfolina fusionada. En un aspecto, "heterociclo fusionado de 5 a 7 miembros" es morfolina fusionada.

Heterociclo fusionado de 6 miembros – En un aspecto "heterociclo fusionado de 5 a 7 miembros" puede ser "heterociclo fusionado de 6 miembros". El término "heterociclo fusionado de 6 miembros" se refiere a un anillo monocíclico no aromático que contiene 6 átomos en el anillo, que comparte dos átomos, un carbono y un nitrógeno, con el anillo de piperidina al que está fusionado, formando un sistema de anillos bicíclico. El "heterociclo fusionado de 6 miembros" puede contener, además del nitrógeno que actúa como puente ilustrado en la Fórmula (I), uno o más restos de heteroátomo en el anillo que se seleccionan de -O-, -NH- y -S-. Los átomos de azufre del anillo pueden oxidarse opcionalmente para formar S-óxidos, los átomos de nitrógeno del anillo pueden oxidarse opcionalmente para formar N-óxidos y uno o más grupos $-CH_2-$ pueden reemplazarse opcionalmente por un número correspondiente de grupos -C(O)- o -C = $N(OR^{4a})$-. Algunos ejemplos ilustrativos del término "heterociclo fusionado de 6 miembros" incluyen 3,5-dioxopiperidina fusionada, morfolina fusionada, oxopiperidina fusionada, piperazina fusionada, piperidina fusionada y tiomorfolina fusionada. En un aspecto, "heterociclo fusionado de 6 miembros" es morfolina fusionada.

Para disipar cualquier posible ambigüedad en cuanto a las definiciones de "heterociclo fusionado de 5 a 7 miembros" y "heterociclo fusionado de 6 miembros" precedentes, el término "anillo de piperidina" pretende denotar el anillo de seis miembros que contiene nitrógeno delimitado por las líneas punteadas en la siguiente estructura:



Para disipar cualquier posible ambigüedad en cuanto a las definiciones de "heterociclo fusionado de 5 a 7 miembros" y "heterociclo fusionado de 6 miembros" precedentes, el término "morfolina fusionada" pretende denotar el anillo de 6 miembros que contiene oxígeno y nitrógeno delimitado por las líneas punteadas en la siguiente estructura:



El anillo de morfolina puede estar opcionalmente sustituido como se indica anteriormente y más adelante en la presente.

Opcionalmente sustituido – Tal como se utiliza en la presente, la expresión "opcionalmente sustituido" indica que la sustitución es opcional y, por lo tanto, es posible que el grupo designado esté sustituido o no sustituido. En caso de desearse una sustitución, el número adecuado de hidrógenos en el grupo designado puede reemplazarse por una selección de los sustituyentes indicados, siempre que no se exceda la valencia normal de los átomos en un sustituyente particular y que la sustitución genere un compuesto estable.

En un aspecto, cuando se dice que un grupo en particular está opcionalmente sustituido con uno o más sustituyentes, ese grupo en particular puede no estar sustituido. En otro aspecto, ese grupo en particular puede tener un sustituyente. En otro aspecto, ese grupo en particular puede tener dos sustituyentes. En otro aspecto adicional, ese grupo en particular puede tener tres sustituyentes. En otro aspecto más, ese grupo en particular puede tener cuatro sustituyentes. En un aspecto adicional, ese grupo en particular puede tener uno o dos sustituyentes. En otro aspecto adicional, ese grupo en particular puede no estar sustituido o puede tener uno o dos sustituyentes.

Farmacéuticamente aceptable - Tal como se utiliza en la presente, la expresión "farmacéuticamente aceptable" se refiere a aquellos compuestos, materiales, composiciones y/o formas de dosificación que sean, dentro del alcance de un juicio médico razonable, adecuados para su uso en contacto con los tejidos de seres humanos y animales sin excesiva toxicidad, irritación, respuestas alérgicas ni otro problema o complicación, acorde con una relación riesgo/beneficio razonable.

Cantidad efectiva – Tal como se utiliza en la presente, la expresión "cantidad efectiva" significa

una cantidad de un compuesto o composición que es suficiente como para modificar de manera significativa y positiva los síntomas y/o afecciones a tratar (por ejemplo, proporcionar una respuesta clínica positiva). La cantidad efectiva de un principio activo para su uso en una composición farmacéutica variará con la afección particular a tratar, la gravedad de la misma, la duración del tratamiento, la naturaleza de la terapia concurrente, el o los principios activos particulares que se utilicen, el o los excipientes/portadores farmacéuticamente aceptables utilizados y factores similares que forman parte de los conocimientos y la especialización del médico competente.

Grupo saliente – Tal como se utiliza en la presente, la expresión "grupo saliente" se refiere a grupos fácilmente desplazables mediante un nucleófilo tal como un nucleófilo de tipo amina y un nucleófilo de tipo alcohol o un nucleófilo de tipo tiol. Algunos ejemplos de grupos salientes adecuados incluyen halo, tal como fluoro, cloro y bromo, y grupo sulfoniloxi, tal como metanosulfoniloxi y tolueno-4-sulfoniloxi.

Grupo protector – Tal como se utiliza en la presente, el término "grupo protector" se refiere a aquellos grupos utilizados para evitar que grupos reactivos seleccionados (tales como grupos carboxi, amino, hidroxi y mercapto) sufran reacciones no deseadas.

Algunos ejemplos ilustrativos de grupos protectores adecuados para un grupo hidroxi incluyen grupos acilo; grupos alcanoilo tales como acetilo; grupos aroilo, por ejemplo benzoilo; grupos sililo tales como trimetilsililo; y grupos arilmetilo, por ejemplo bencilo. Las condiciones de desprotección para los grupos protectores de hidroxi anteriores varían necesariamente con el grupo protector elegido. Por lo tanto, por ejemplo, un grupo acilo tal como un alcanoilo o un grupo aroilo puede ser eliminado, por ejemplo, mediante hidrólisis con una base apropiada tal como un hidróxido de metal alcalino, por ejemplo hidróxido de sodio o litio. Como alternativa, un grupo sililo, tal como trimetilsililo, puede ser eliminado, por ejemplo, con fluoruro o ácido acuoso; o un grupo arilmetilo, como un grupo bencilo, puede ser eliminado, por ejemplo, mediante hidrogenación en presencia de un catalizador como paladio sobre carbón.

Algunos ejemplos ilustrativos de grupos protectores adecuados para un grupo amino incluyen

grupos acilo; grupos alcanoilo tales como acetilo; grupos alcoxicarbonilo, por ejemplo grupos metoxicarbonilo, etoxicarbonilo o *t*-butoxicarbonilo; grupos arilmetoxicarbonilo, por ejemplo benciloxicarbonilo; y grupos aroilo, por ejemplo benzoilo. Las condiciones de desprotección para los grupos protectores de amino anteriores varían necesariamente con el grupo protector elegido. Por lo tanto, por ejemplo, un grupo acilo tal como un grupo alcanoilo o alcoxicarbonilo o un grupo aroilo puede ser eliminado, por ejemplo, mediante hidrólisis con una base apropiada tal como un hidróxido de metal alcalino, por ejemplo hidróxido de sodio o litio. Como alternativa, un grupo acilo tal como un grupo *t*-butoxicarbonilo, puede ser eliminado, por ejemplo, mediante tratamiento con un ácido adecuado tal como ácido clorhídrico, sulfúrico o fosfórico, o ácido trifluoroacético y un grupo arilmetoxicarbonilo tal como un grupo benciloxicarbonilo puede ser eliminado, por ejemplo, mediante hidrogenación con un catalizador tal como paladio sobre carbón, o mediante tratamiento con un ácido de Lewis, por ejemplo tricloruro de boro. Un grupo protector alternativo adecuado para un grupo amino primario es, por ejemplo, un grupo ftaloilo, que puede ser eliminado mediante tratamiento con una alquilamina, por ejemplo, dimetilaminopropilamina o 2-hidroxietilamina, o con hidrazina. Otro grupo protector adecuado para una amina es, por ejemplo, un éter cíclico tal como tetrahidrofurano, que puede eliminarse mediante tratamiento con un ácido adecuado tal como ácido trifluoroacético.

Los grupos protectores pueden ser eliminados en cualquier etapa conveniente de la síntesis utilizando las técnicas convencionales ampliamente conocidas en la técnica química, o pueden eliminarse durante una etapa de reacción posterior o durante un tratamiento.

Los compuestos de Fórmula (I) pueden formar sales de ácido o base estables farmacéuticamente aceptables y, en estos casos, la administración de un compuesto como una sal puede ser adecuada. Algunos ejemplos de sales de adición de ácidos incluyen acetato, adipato, ascorbato, benzoato, bencenosulfonato, bicarbonato, bisulfato, butirato, camforato, camforsulfonato, colina, citrato, ciclohexilsulfamato, dietilendiamina, etanosulfonato, fumarato, glutamato, glicolato, hemisulfato, 2-hidroxietilsulfonato, heptanoato, hexanoato, clorhidrato, bromhidrato, yodhidrato, hidroximaleato, lactato, malato, maleato, metanosulfonato, meglumina, 2-naftalensulfonato, nitrato, oxalato, pamoato, persulfato, fenilacetato, fosfato, difosfato, picrato, pivalato, propionato, quinato, salicilato, estearato, succinato, sulfamato, sulfanilato, sulfato, tartrato, tosilato (p-

toluenosulfonato), trifluoroacetato y undecanoato. Algunos ejemplos de sales básicas incluyen sales de amonio; sales de metales alcalinos tales como sales de sodio, litio y potasio; sales de metales alcalinotérreos tales como sales de aluminio, calcio y magnesio; sales con bases orgánicas tales como sales de diciclohexilamina, *N*-metil-D-glucamina; y sales con aminoácidos tales como arginina, lisina, ornitina, etc. Además, los grupos básicos que contienen nitrógeno pueden cuaternizarse con agentes tales como: haluros de alquilo inferior, tales como haluros de metilo, etilo, propilo y butilo; sulfatos de dialquilo tales como sulfatos de dimetilo, dietilo y dibutilo; sulfatos de diamilo; haluros de cadena larga tales como haluros de decilo, laurilo, miristilo y estearilo; haluros de aralquilo tales como bromuro de bencilo y otros. Se prefieren las sales fisiológicamente aceptables no tóxicas, aunque otras sales también pueden ser útiles, como en el aislamiento o la purificación del producto.

Las sales pueden formarse por medios convencionales, tales como hacer reaccionar la forma de base libre del producto con uno o más equivalentes del ácido apropiado en un disolvente o medio en el que la sal es insoluble, o en un disolvente tal como agua, que se retira al vacío o mediante liofilización, o mediante intercambio de los aniones de una sal existente con otro anión en una resina de intercambio iónico adecuada.

Algunos compuestos de Fórmula (I) pueden tener centros quirales y/o centros isoméricos geométricos (isómeros E y Z) y debe entenderse que la invención abarca todos dichos isómeros ópticos, diastereoisómeros e isómeros geométricos La invención también se refiere a todas las formas tautoméricas de los compuestos de Fórmula (I).

Debe entenderse también que ciertos compuestos de Fórmula (I) pueden existir en formas solvatadas así como también en formas no solvatadas tales como, por ejemplo, formas hidratadas. Debe entenderse que la invención abarca todas las formas solvatadas.

A continuación se presentan realizaciones adicionales de la invención. Estas realizaciones adicionales se relacionan con compuestos de Fórmula (I) y sales farmacéuticamente aceptables de estos. Tales sustituyentes específicos pueden utilizarse, en donde sea adecuado, con cualquiera de las definiciones, reivindicaciones o realizaciones definidas anteriormente o posteriormente en la

presente. Todas las realizaciones descritas anteriormente y que se describen más adelante en la presente son ilustrativas y no limitan el alcance de la invención, según se define en las reivindicaciones.

Anillo A

En un aspecto, el **Anillo A** es heterociclo fusionado de 6 miembros, en donde dicho heterociclo fusionado de 6 miembros está opcionalmente sustituido sobre carbono con uno o más R^4; y
$\mathbf{R^4}$ es alquiloC_{1-6}.

En otro aspecto, el **Anillo A** es morfolina fusionada, en donde dicha morfolina fusionada está opcionalmente sustituida con uno o más $\mathbf{R^4}$; y
$\mathbf{R^4}$ es alquiloC_{1-6}.

En otro aspecto adicional, el **Anillo A** es morfolina fusionada, en donde dicha morfolina fusionada está opcionalmente sustituida con uno o más $\mathbf{R^4}$; y
$\mathbf{R^4}$ es metilo.

En otro aspecto, el **Anillo A**, junto con el anillo de piperidina al que está fusionado, forma octahidropirido[2,1-*c*][1,4]oxazina, en donde dicha octahidropirido[2,1-*c*][1,4]oxazina está opcionalmente sustituida con uno o más R^4; y
$\mathbf{R^4}$ es metilo.

En un aspecto adicional, el **Anillo A**, junto con el anillo de piperidina al que está fusionado, forma 1,3-dimetiloctahidropirido[2,1-*c*][1,4]oxazina.

En otro aspecto adicional, el **Anillo A**, junto con el anillo de piperidina al que está fusionado, forma (1*R*,3*S*)-1,3-dimetiloctahidropirido[2,1-*c*][1,4]oxazina.

W

En un aspecto, **W** es -O-.

X

En un aspecto, **X** es C-H.

Y

En un aspecto **Y** es C-R^3; y

$\mathbf{R^3}$ es halo.

En otro aspecto **Y** es C-R^3; y

$\mathbf{R^3}$ es selecciona de fluoro y cloro.

En otro aspecto adicional, **Y** es C-R^3; y

$\mathbf{R^3}$ es fluoro.

R^1

En un aspecto, $\mathbf{R^1}$ se selecciona de alquiloC_{1-6}, carbociclilo de 3 a 5 miembros, heterociclilo de 5 o 6 miembros, -OR^{1a}, -SR^{1a}, -$N(R^{1a})_2$, -$N(R^{1a})C(O)R^{1b}$, -$C(O)N(R^{1a})_2$, -$C(O)R^{1b}$, -$C(O)_2R^{1a}$, -$C(O)N(R^{1a})_2$, -$C(O)N(R^{1a})(OR^{1a})$ y -$S(O)_2R^{1b}$, en donde dichos alquiloC_{1-6}, carbociclilo de 3 a 5 miembros y heterociclilo de 5 o 6 miembros están opcionalmente sustituidos sobre carbono con uno o más R^{10} y en donde todo resto -NH- de dicho heterociclilo de 5 o 6 miembros está opcionalmente sustituido con R^{10*};

$\mathbf{R^{1a}}$ en cada caso se selecciona independientemente de H, alquiloC_{1-6}, carbociclilo de 3 a 5 miembros y heterociclilo de 5 o 6 miembros, en donde dichos alquiloC_{1-6}, carbociclilo de 3 a 5 miembros y heterociclilo de 5 o 6 miembros en cada caso se sustituyen opcionalmente e independientemente con uno o más R^{10}, en donde todo resto -NH- de dicho heterociclilo de 5 o 6 miembros está opcionalmente sustituido con R^{10*};

$\mathbf{R^{1b}}$ en cada caso se selecciona independientemente de alquiloC_{1-6} y heterociclilo de 4 a 6 miembros, en donde dichos alquiloC_{1-6} y heterociclilo de 4 a 6 miembros se sustituyen opcionalmente e independientemente sobre carbono con uno o más R^{10} y en donde todo resto -NH- de dicho heterociclilo de 4 a 6 miembros está opcionalmente sustituido con R^{10*};

$\mathbf{R^{10}}$ en cada caso se selecciona independientemente de halo, -CN, alquiloC_{1-6}, carbociclilo de 3 a

6 miembros, heterociclilo de 5 o 6 miembros, $-OR^{10a}$, $-SR^{10a}$, $-N(R^{10a})_2$, $-N(R^{10a})C(O)R^{10b}$, $-C(O)_2R^{10a}$, $-C(O)N(R^{10a})_2$, en donde dichos alquiloC$_{1-6}$, carbociclilo de 3 a 6 miembros o heterociclilo de 5 o 6 miembros en cada caso se sustituyen opcionalmente con uno o más R^a y en donde todo resto -NH- de dicho heterociclilo de 5 o 6 miembros está opcionalmente sustituido con R^{a*};

R^{10*} en cada caso se selecciona independientemente de alquiloC$_{1-6}$ y $-C(O)R^{10b}$;

R^{10a} en cada caso se selecciona independientemente de H y alquiloC$_{1-6}$, en donde dicho alquiloC$_{1-6}$ en cada caso se sustituye opcionalmente e independientemente con uno o más R^a;

R^{10b} es alquiloC$_{1-6}$;

R^a en cada caso se selecciona independientemente de halo, -CN y $-OR^m$;

R^{a*} es alquiloC$_{1-6}$; y

R^m en cada caso se selecciona independientemente de H y alquiloC$_{1-6}$.

En otro aspecto, **R^1** se selecciona de alquiloC$_{1-6}$, carbociclilo de 3 a 5 miembros, heterociclilo de 5 o 6 miembros y $-C(O)N(R^{1a})_2$, en donde dichos alquiloC$_{1-6}$, carbociclilo de 3 a 5 miembros y heterociclilo de 5 o 6 miembros están opcionalmente sustituidos sobre carbono con uno o más R^{10} y en donde todo resto -NH- de dicho heterociclilo de 5 o 6 miembros está opcionalmente sustituido con R^{10*};

R^{1a} en cada caso se selecciona independientemente de H y alquiloC$_{1-6}$, en donde dicho alquiloC$_{1-6}$ en cada caso se sustituye opcionalmente e independientemente con uno o más R^{10};

R^{10} en cada caso se selecciona independientemente de halo, -CN, alquiloC$_{1-6}$, heterociclilo de 5 o 6 miembros, $-OR^{10a}$, $-SR^{10a}$, $-N(R^{10a})_2$, $-N(R^{10a})C(O)R^{10b}$, $-C(O)_2R^{10a}$, $-C(O)N(R^{10a})_2$; en donde dicho alquiloC$_{1-6}$ en cada caso se sustituye opcionalmente e independientemente con uno o más R^a;

R^{10*} en cada caso se selecciona independientemente de alquiloC$_{1-6}$ y $-C(O)R^{10b}$;

R^{10a} en cada caso se selecciona independientemente de H y alquiloC$_{1-6}$, en donde dicho alquiloC$_{1-6}$ en cada caso se sustituye opcionalmente e independientemente con uno o más R^a;

R^{10b} es alquiloC$_{1-6}$;

R^a en cada caso se selecciona independientemente de $-OR^m$ y halo; y

R^m en cada caso se selecciona independientemente de H y alquiloC$_{1-6}$.

En otro aspecto adicional, $\mathbf{R^1}$ se selecciona de alquiloC$_{1-6}$, heterociclilo de 5 o 6 miembros y -C(O)N(R^{1a})$_2$, en donde dichos alquiloC$_{1-6}$ y heterociclilo de 5 o 6 miembros están opcionalmente sustituidos con uno o más R^{10} y en donde todo resto -NH- de dicho heterociclilo de 5 o 6 miembros está opcionalmente sustituido con R^{10*};

$\mathbf{R^{1a}}$ en cada caso se selecciona independientemente de H y alquiloC$_{1-6}$, en donde dicho alquiloC$_{1-6}$ en cada caso se sustituye opcionalmente e independientemente con uno o más R^{10};

$\mathbf{R^{10}}$ en cada caso se selecciona independientemente de halo, -CN, -SR^{10a} y -N(R^{10a})$_2$;

$\mathbf{R^{10*}}$ es alquiloC$_{1-6}$; y

$\mathbf{R^{10a}}$ en cada caso se selecciona independientemente de H y alquiloC$_{1-6}$.

En un aspecto, $\mathbf{R^1}$ se selecciona de carbociclilo de 3 a 5 miembros y heterociclilo de 5 o 6 miembros, en donde dichos carbociclilo de 3 a 5 miembros y heterociclilo de 5 o 6 miembros están opcionalmente sustituidos sobre carbono con uno o más R^{10} y en donde todo resto -NH- de dicho heterociclilo de 5 o 6 miembros está opcionalmente sustituido con R^{10*};

$\mathbf{R^{10}}$ en cada caso se selecciona independientemente de halo, -CN, alquilo C$_{1-6}$, heterociclilo de 5 o 6 miembros, -OR^{10a}, -SR^{10a}, -N(R^{10a})$_2$, -N(R^{10a})C(O)R^{10b}, -C(O)$_2R^{10a}$, -C(O)N(R^{10a})$_2$; en donde dicho alquiloC$_{1-6}$ está opcionalmente sustituido con uno o más R^a;

$\mathbf{R^{10*}}$ en cada caso se selecciona independientemente de alquiloC$_{1-6}$ y -C(O)R^{10b};

$\mathbf{R^{10a}}$ en cada caso se selecciona independientemente de H y alquiloC$_{1-6}$, en donde dicho alquiloC$_{1-6}$ en cada caso se sustituye opcionalmente e independientemente con uno o más R^a;

$\mathbf{R^{10b}}$ es alquiloC$_{1-6}$;

$\mathbf{R^a}$ en cada caso se selecciona independientemente de -OR^m y halo; y

$\mathbf{R^m}$ en cada caso se selecciona independientemente de H y alquiloC$_{1-6}$.

En otro aspecto más, $\mathbf{R^1}$ se selecciona de heterociclilo de 5 o 6 miembros, en donde dicho heterociclilo de 5 o 6 miembros está opcionalmente sustituido sobre carbono con uno o más R^{10} y en donde todo resto -NH- de dicho heterociclilo de 5 o 6 miembros está opcionalmente sustituido con R^{10*};

$\mathbf{R^{10}}$ en cada caso se selecciona independientemente de halo, -CN, alquiloC$_{1-6}$, heterociclilo de 5 o 6 miembros, -OR^{10a}, -SR^{10a}, -N(R^{10a})$_2$, -N(R^{10a})C(O)R^{10b}, -C(O)$_2R^{10a}$, -C(O)N(R^{10a})$_2$; en donde dicho alquiloC$_{1-6}$ está opcionalmente sustituido con uno o más R^a;

$\mathbf{R^{10*}}$ en cada caso se selecciona independientemente de alquiloC$_{1-6}$ y -C(O)R^{10b};
$\mathbf{R^{10a}}$ en cada caso se selecciona independientemente de H y alquiloC$_{1-6}$, en donde dicho alquiloC$_{1-6}$ en cada caso se sustituye opcionalmente e independientemente con uno o más R^a;
$\mathbf{R^{10b}}$ es alquiloC$_{1-6}$;
$\mathbf{R^a}$ en cada caso se selecciona independientemente de -OR^m y halo; y
$\mathbf{R^m}$ en cada caso se selecciona independientemente de H y alquiloC$_{1-6}$.

En un aspecto adicional, $\mathbf{R^1}$ se selecciona de -C(O)R^{1b}, -C(O)$_2R^{1a}$, -C(O)N(R^{1a})$_2$ y -C(O)N(R^{1a})(OR^{1a});
$\mathbf{R^{1a}}$ en cada caso se selecciona independientemente de H, alquiloC$_{1-6}$, carbociclilo de 3 a 5 miembros y heterociclilo de 5 o 6 miembros, en donde dicho alquiloC$_{1-6}$ está opcionalmente sustituido con uno o más R^{10} y en donde todo resto -NH- de dicho heterociclilo de 5 o 6 miembros está opcionalmente sustituido con R^{10*};
$\mathbf{R^{1b}}$ en cada caso se selecciona independientemente de alquiloC$_{1-6}$ y heterociclilo de 4 a 6 miembros, en donde dicho heterociclilo de 4 a 6 miembros se sustituye opcionalmente sobre carbono con uno o más R^{10} y en donde todo resto -NH- de dicho heterociclilo de 4 a 6 miembros está opcionalmente sustituido con R^{10*};
$\mathbf{R^{10}}$ en cada caso se selecciona independientemente de halo, -CN, carbociclilo de 3 a 6 miembros, heterociclilo de 5 o 6 miembros, -OR^{10a} y -N(R^{10a})C(O)R^{10b}, en donde dicho carbociclilo de 3 a 6 miembros se sustituye opcionalmente sobre carbono con uno o más R^a y en donde todo resto -NH- de dicho heterociclilo de 5 a 6 miembros está opcionalmente sustituido con R^{a*};
$\mathbf{R^{10*}}$ es alquiloC$_{1-6}$;
$\mathbf{R^{10a}}$ es alquiloC$_{1-6}$;
$\mathbf{R^{10b}}$ es alquiloC$_{1-6}$;
$\mathbf{R^a}$ es -CN; y
$\mathbf{R^{a*}}$ es alquiloC$_{1-6}$.

En otro aspecto adicional, $\mathbf{R^1}$ se selecciona de -C(O)N(R^{1a})$_2$;
$\mathbf{R^{1a}}$ en cada caso se selecciona independientemente de H, alquiloC$_{1-6}$ y carbociclilo de 3 a 5 miembros, en donde dicho alquiloC$_{1-6}$ está opcionalmente sustituido con uno o más R^{10};
$\mathbf{R^{10}}$ en cada caso se selecciona independientemente de halo, carbociclilo de 3 a 6 miembros,

heterociclilo de 5 o 6 miembros y -OR^{10a}, en donde dicho carbociclilo de 3 a 6 miembros se sustituye opcionalmente sobre carbono con uno o más R^a y en donde todo resto -NH- de dicho heterociclilo de 5 o 6 miembros está opcionalmente sustituido con R^{a*};

$\mathbf{R^{10a}}$ es alquiloC_{1-6};

$\mathbf{R^a}$ es -CN; y

$\mathbf{R^{a*}}$ es alquiloC_{1-6}.

En un aspecto adicional más, $\mathbf{R^1}$ se selecciona de -$C(O)N(R^{1a})_2$;

$\mathbf{R^{1a}}$ en cada caso se selecciona independientemente de H y alquiloC_{1-6}.

En un aspecto, $\mathbf{R^1}$ se selecciona de alquiloC_{1-6}, carbociclilo de 3 a 6 miembros, heterociclilo de 5 o 6 miembros, $-NH_2$ y -$N(H)C(O)R^{1b}$; y

$\mathbf{R^{1b}}$ es alquiloC_{1-6}.

En otro aspecto, $\mathbf{R^1}$ se selecciona de alquiloC_{1-6} y -$C(O)N(R^{1a})_2$;

$\mathbf{R^{1a}}$ en cada caso se selecciona independientemente de H y alquiloC_{1-6}, en donde dicho alquiloC_{1-6} en cada caso está opcionalmente sustituido con uno o más R^{10}; y

$\mathbf{R^{10}}$ es halo.

En otro aspecto, $\mathbf{R^1}$ se selecciona de alquiloC_{1-6}, carbociclilo de 3 a 6 miembros, heterociclilo de 6 miembros, $-NH_2$ y -$N(H)C(O)R^{1b}$; y

$\mathbf{R^{1b}}$ es alquiloC_{1-6}.

En un aspecto adicional, $\mathbf{R^1}$ es alquiloC_{1-6}, en donde dicho alquiloC_{1-6} está opcionalmente sustituido con uno o más R^{10}; y

$\mathbf{R^{10}}$ en cada caso se selecciona independientemente de halo y -OR^{10a};

$\mathbf{R^{10a}}$ en cada caso se selecciona independientemente de H y alquiloC_{1-6}.

En un aspecto adicional más, $\mathbf{R^1}$ es alquiloC_{1-6}, en donde dicho alquiloC_{1-6} está opcionalmente sustituido con uno o más halo.

En otro aspecto adicional, $\mathbf{R^1}$ se selecciona de aminocarbonilo, 2-aminopirimidin-4-ilo, 2-cianopirimidin-4-ilo, 3,3-difluoroazetidin-1-ilo, [(2,2-difluoroetil)amino]carbonilo, difluorometilo, (isopropilamino)carbonilo, metilo, (metilamino)carbonilo, 2-(metilsulfanil)pirimidin-4-ilo, 1-metil-1*H*-1,2,4-triazol-5-ilo, pirazin-2-ilo, piridazin-3-ilo, pirimidin-4-ilo, pirimdin-2-ilo, 1,3-tiazol-2-ilo, 1*H*-1,2,4-triazol-1-ilo, 2*H*-1,2,3-triazol-2-ilo y trifluorometilo.

En un aspecto, $\mathbf{R^1}$ se selecciona de metilo, fenilo, ciclopropilo, piridinilo, $-NH_2$ y $-N(H)C(O)R^{1b}$; y

$\mathbf{R^{1b}}$ es metilo.

En otro aspecto, $\mathbf{R^1}$ se selecciona de metilo, fenilo, ciclopropilo, piridin-2-ilo, $-NH_2$ y $-N(H)C(O)R^{1b}$; y

$\mathbf{R^{1b}}$ es metilo.

En otro aspecto, $\mathbf{R^1}$ se selecciona de metilo, (metilamino)carbonilo y [(2,2-difluoroetil)amino]carbonilo.

Anillo A, W, X, Y y $\mathbf{R^1}$

En un aspecto, el **Anillo A** es heterociclo fusionado de 6 miembros, en donde dicho heterociclo fusionado de 6 miembros está opcionalmente sustituido sobre carbono con uno o más R^4;

W es -O-;

X es C-H;

Y es C-R^3;

$\mathbf{R^1}$ se selecciona de alquiloC_{1-6}, carbociclilo de 3 a 6 miembros, heterociclilo de 5 o 6 miembros, $-NH_2$ y $-N(H)C(O)R^{1b}$;

$\mathbf{R^{1b}}$ es alquiloC_{1-6};

$\mathbf{R^3}$ es halo; y

$\mathbf{R^4}$ es alquiloC_{1-6}.

En otro aspecto, el **Anillo A** es morfolina fusionada, en donde dicha morfolina fusionada está

opcionalmente sustituida con uno o más $\mathbf{R^4}$;

W es -O-;

X es C-H;

Y es C-R^3;

$\mathbf{R^1}$ se selecciona de alquiloC_{1-6}, carbociclilo de 3 a 6 miembros, heterociclilo de 6 miembros, -NH_2 y -N(H)C(O)R^{1b};

$\mathbf{R^{1b}}$ es alquiloC_{1-6};

$\mathbf{R^3}$ es halo; y

$\mathbf{R^4}$ es alquiloC_{1-6}.

En otro aspecto adicional, el **Anillo A**, junto con el anillo de piperidina al que está fusionado, forma 1,3-dimetiloctahidropirido[2,1-*c*][1,4]oxazina;

W es -O-;

X es C-H;

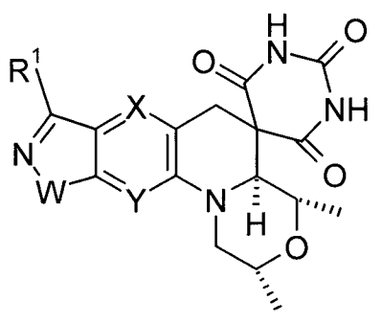
Y es C-R^3;

$\mathbf{R^1}$ se selecciona de metilo, fenilo, ciclopropilo, piridin-2-ilo, -NH_2 y -N(H)C(O)R^{1b};

$\mathbf{R^{1b}}$ es metilo; y

$\mathbf{R^3}$ es fluoro.

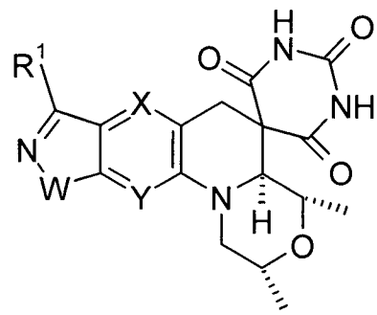
En otro aspecto, el compuesto de Fórmula (I) es un compuesto de Fórmula (Ia):



Fórmula (Ia)

o una sal farmacéuticamente aceptable de este, en donde **W**, **X**, **Y** y $\mathbf{R^1}$ son como se describe anteriormente.

En otro aspecto más, el compuesto de Fórmula (I) es un compuesto de Fórmula (Ia):



Fórmula (Ia)

o una sal farmacéuticamente aceptable de este, en donde $\mathbf{R^1}$ es como se describe anteriormente y en donde:

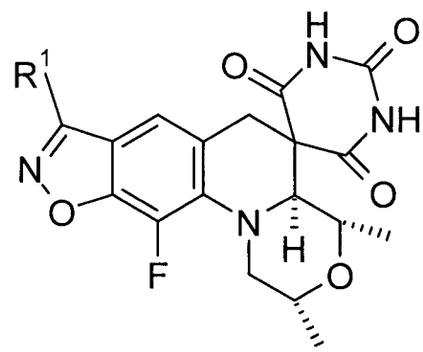
W es -O-;

X es C-H;

Y es C-R^3; y

$\mathbf{R^3}$ es halo.

En un aspecto adicional, el compuesto de Fórmula (I) es un compuesto de Fórmula (Ib):



Fórmula (Ib)

o una sal farmacéuticamente aceptable de este, en donde **R1** es como se describe anteriormente.

En otro aspecto adicional, la presente invención proporciona un compuesto de Fórmula (I) que se

selecciona de los ejemplos, bases libres de este y sales farmacéuticamente aceptables de este.

En un aspecto adicional más, la presente invención proporciona un compuesto que se selecciona de:
(2*R*,4*S*,4a*S*)-8-amino-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*R*,4*S*,4a*S*)-11-fluoro-2,4,8-trimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-fenil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*R*,4*S*,4a*S*)-8-ciclopropil-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-piridin-2-il-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
N-[(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-il]acetamida;
(2*R*,4*S*,4a*S*)-11-cloro-2,4,8-trimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*R*,4*S*,4a*S*)-8-(4-acetilpiperazin-1-il)-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*R*,4*S*,4a*S*)-8-(bencilamino)-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-[(1,3-tiazol-2-ilmetil)amino]-1,2,4,4a-tetrahidro-2'H,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'H,3'H)-triona;
(2*R*,4*S*,4a*S*)-11-fluoro-8-[(1*H*-imidazol-4-ilmetil)amino]-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-{[(1-metil-1*H*-pirazol-4-il)metil]amino}-1,2,4,4a-tetrahidro-2'H,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'H,3'H)-triona;
(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-{[(5-metil-1,2-oxazol-3-il)metil]amino}-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-

triona;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-[(piridin-2-ilmetil)amino]-1,2,4,4a-tetrahidro-2'H,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'H,3'H)-triona;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-[(piridin-3-ilmetil)amino]-1,2,4,4a-tetrahidro-2'H,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'H,3'H)-triona;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-[(piridin-4-ilmetil)amino]-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*S*)-8-[(ciclopropilmetil)amino]-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*S*)-8-[(ciclohexilmetil)amino]-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-[(tetrahidro-2*H*-piran-4-ilmetil)amino]-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

4-[(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-il]piperazin-1-carboxilato de *terc*-butilo;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(piperazin-1-il)-1,2,4,4a-tetrahidro-2'H,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'H,3'H)-triona;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(morfolin-4-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*S*)-8-(dietilamino)-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*S*)-8-(dimetilamino)-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(pirrolidin-1-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*S*)-8-(azepan-1-il)-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-[5-metil-3-(trifluorometil)-1*H*-pirazol-1-il]-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-

2',4',6'(1'*H*,3'*H*)-triona;
N-{1-[(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-1*H*-pirazol-3-il}acetamida;
(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-[3-(trifluorometil)-1*H*-pirazol-1-il]-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*R*,4*S*,4a*S*)-8-[3-(difluorometil)-5-metil-1*H*-pirazol-1-il]-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(propilamino)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*R*,4*S*,4a*S*)-8-[bencil(metil)amino]-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
3-amino-1-[(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-1*H*-pirazol-4-carbonitrilo;
(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-[4-(pirimidin-4-il)-1*H*-pirazol-1-il]-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-[4-(pirazin-2-il)-1*H*-pirazol-1-il]-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*R*,4*S*,4a*S*)-11-fluoro-8-(4-yodo-1*H*-pirazol-1-il)-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
1-[(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-1*H*-pirazol-4-carboxilato de etilo;
(2*R*,4*S*,4a*S*)-11-cloro-2,4-dimetil-8-(piridin-2-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*R*,4*S*,4a*S*)-11-cloro-8-ciclopropil-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*S*)-11-cloro-2,4-dimetil-8-(6-metilpiridin-3-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*S*)-11-cloro-2,4-dimetil-8-(1,3-tiazol-5-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*S*)-11-cloro-2,4-dimetil-8-(pirimidin-2-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*S*)-11-cloro-2,4-dimetil-8-(pirimidin-4-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*S*)-11-cloro-2,4-dimetil-8-(pirimidin-5-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*S*)-11-cloro-2,4-dimetil-8-(piridazin-4-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*S*)-11-cloro-2,4-dimetil-8-(piridin-4-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*S*)-11-cloro-2,4-dimetil-8-(piridin-3-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*S*)-11-cloro-2,4-dimetil-8-(1,3-tiazol-2-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*S*)-11-cloro-8-(metoximetil)-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-[metil(propil)amino]-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*S*)-11-fluoro-8-metoxi-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*S*)-8-(benciloxi)-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'H,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'H,3'H)-triona;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(1*H*-1,2,4-triazol-1-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(3-metil-1*H*-1,2,4-triazol-1-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

1-[(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-

espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-1*H*-1,2,4-triazol-3-carbonitrilo;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(2*H*-1,2,3-triazol-2-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(1*H*-1,2,3-triazol-1-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*S*)-11-fluoro-8-(1*H*-imidazol-1-il)-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-[4-(trifluorometil)-1*H*-imidazol-1-il]-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(4-metil-1*H*-pirazol-1-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*S*)-8-(4-cloro-1*H*-pirazol-1-il)-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(metilsulfanil)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*S*)-8-(3,5-dimetil-1*H*-pirazol-1-il)-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(1*H*-pirazol-4-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(2-metil-1,3-oxazol-4-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(5-metil-1,2-oxazol-3-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*S*)-8-(3,5-dimetil-1,2-oxazol-4-il)-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*R*)-11-fluoro-2,4-dimetil-8-(1-metil-1*H*-imidazol-2-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(1-metil-1*H*-imidazol-4-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(1-metil-1*H*-imidazol-5-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(4-metil-1,3-tiazol-5-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(4-metil-1,2,3-tiadiazol-5-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(piridazin-3-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(pirimidin-4-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*R*,4*S*,4a*S*)-11-fluoro-2,4,8-trimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]thiazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(piridin-2-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]tiazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4,8-trimetil-1,2,3,4,4a,6-hexahidro-1'*H*-espiro[isoxazolo[4,5-*g*]pirido[1,2-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;
(2*R*,4*S*,4a*S*)-8-(3-cloropirazin-2-il)-11-fluoro-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;
(2*R*,4*S*,4a*S*)-8-(6-cloropirazin-2-il)-11-fluoro-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;
(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(5-(metiltio)pirazin-2-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;
(2*R*,4*S*,4a*S*)-8-((1*H*-1,2,4-triazol-1-il)metil)-11-fluoro-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;
(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(piridin-4-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;
(2*R*,4*S*,4a*S*)-11-fluoro-8-(5-hidroxi-1,3,4-oxadiazol-2-il)-2,4-dimetil-1,2,4,4a-tetrahidro-2'H,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'H,3'H)-triona;
(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-[4-(morfolin-4-ilcarbonil)-1,3-tiazol-2-il]-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-[4-(morfolin-4-ilcarbonil)-1,3-tiazol-5-il]-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

2-[(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-*N*,*N*-dimetil-1,3-thiazol-4-carboxamida;

2-[(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-*N*,*N*-dimetil-1,3-tiazol-5-carboxamida;

5-[(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-1,3-tiazol-4-carbonitrilo;

(2*R*,4*S*,4a*S*)-11-cloro-2,4-dimetil-8-(1-metil-1*H*-imidazol-2-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*S*)-2,4,11-trimetil-8-(1,3-tiazol-2-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(6-metilpiridin-3-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(trifluorometil)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;

(2*R*,4*S*,4a*S*)-8-(difluorometil)-11-fluoro-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;

(2*R*,4*S*,4a*S*)-*N*-(2,2-difluoroetil)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxamida;

(2*R*,4*S*,4a*S*)-8-(3,3-difluoroazetidin-1-carbonil)-11-fluoro-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(tiazol-2-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;

(2*R*,4*S*,4a*S*)-11-fluoro-8-(furan-2-il)-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(tiazol-5-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-

g][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;
(2*R*,4*S*,4a*S*)-11-fluoro-8-(2-fluorofenil)-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;
(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(tetrahidro-2*H*-piran-4-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;
(2*R*,4*S*,4a*S*)-2,4,11-trimetil-8-(pirazin-2-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-ilcarbonato de *terc*-butilo;
(2*R*,4*S*,4a*S*)-8-acetil-9,10-difluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*R*,4*S*,4a*S*)-2-etil-11-fluoro-4,8-dimetil-1,2,4,4a-tetrahidro-2'H,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'H,3'H)-triona;
(2*R*,4*R*,4a*S*)-11-fluoro-4-(metoximetil)-2,8-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*S*,4a*S*)-11-fluoro-2-(metoximetil)-4,8-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*R*,4*S*,4a*S*)-11-cloro-2,4-dimetil-8-(piridin-2-il)-2,4,4*a*,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona;
(2*R*,4*S*,4a*S*)-11-cloro-2,4-dimetil-8-(piridin-4-il)-2,4,4*a*,6-tetrahidro-1*H*, 1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona;
(2*R*,4*S*,4a*S*)-11-cloro-2,4-dimetil-8-(piridin-3-il)-2,4,4*a*,6-tetrahidro-1*H*, 1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona;
(2*R*,4*S*,4a*S*)-11-cloro-2,4-dimetil-8-(pirazin-2-il)-2,4,4*a*,6-tetrahidro-1*H*, 1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona;
(2*R*,4*S*,4a*S*)-11-cloro-2,4-dimetil-8-(tiazol-2-il)-2,4,4*a*,6-tetrahidro-1*H*, 1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona;
(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(1-metil-1*H*-imidazol-2-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;
(2*R*,4*S*,4a*S*)-11-cloro-2,4-dimetil-8-(4-metiltiazol-2-il)-2,4,4*a*,6-tetrahidro-1*H*, 1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona;

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(2*R*,4*S*,4a*S*)-11-cloro-2,4-dimetil-8-(1-metil –1*H*-imidazol-2-il)-2,4,4*a*,6-tetrahidro-1*H*, 1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona;

(2*R*,4*S*,4a*S*)-11-cloro-2,4-dimetil-8-(tiazol-5-il)-2,4,4*a*,6-tetrahidro-1*H*, 1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona;

(2*R*,4*S*,4a*S*)-11-cloro-2,4-dimetil-8-(2,4-diclorotiazol-5-il)-2,4,4*a*,6-tetrahidro-1*H*, 1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona;

(2*R*,4*S*,4a*S*)-11-cloro-2,4-dimetil-8-(2-metiltiazol-5-il)-2,4,4*a*,6-tetrahidro-1*H*, 1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona;

(2*R*,4*S*,4a*S*)-11-cloro-2,4-dimetil-8-(1-metil-1*H*-1,2,4-triazol-5-il)-2,4,4*a*,6-tetrahidro-1*H*, 1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona;

(2*R*,4*S*,4a*S*)-11-cloro-2,4-dimetil-8-(2-bromotiazol-5-il)-2,4,4*a*,6-tetrahidro-1*H*, 1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona;

(2*R*,4*S*,4a*S*)-11-cloro-2,4-dimetil-8-(pirazin-2-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;

4-((2*R*,4S,4a*S*)-11-cloro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4*a*,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-8-il)-2-fluorobenzonitrilo;

(2*R*,4*S*,4a*S*)-11-cloro-2,4-dimetil-8-(5-metiltiazol-2-il)-2,4,4*a*,6-tetrahidro-1*H*, 1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona;

5-((2*R*,4*S*,4a*S*)-11-cloro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-8-il)picolinamida;

(2*R*,4*S*,4a*S*)-11-cloro-2,4,8-trimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'H)-triona;

(2*R*,4*S*,4a*S*)-11-cloro-*N*,2,4-trimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-8-carboxamida;

(2*R*,4*S*,4a*S*)-11-cloro-*N*-etil-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-8-carboxamida;

(2*R*,4*S*,4a*S*)-cloro-*N*-isopropil-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-8-carboxamida;

(2*R*,4*S*,4a*S*)-*N*-*terc*-butil-11-cloro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-8-carboxamida;

(2*R*,4*S*,4a*S*)-11-cloro-2,4-dimetil-*N*-neopentil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-8-carboxamida;

(2*R*,4*S*,4a*S*)-11-cloro-8-(3,3-difluoroazetidin-1-carbonil)-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'H)-triona;

(2*R*,4*S*,4a*S*)-*N*-bencil-11-cloro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-8-carboxamida;

(2*R*,4*S*,4a*S*)-11-cloro-*N*-(4-cianobencil)-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-8-carboxamida;

(2*R*,4*S*,4a*S*)-11-cloro-*N*-(3-cianobencil)-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-8-carboxamida;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxilato de etilo;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(morfolin-4-carbonil)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;

(2*R*,4*S*,4a*S*)-11-fluoro-*N*,*N*,2,4-tetrametil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxamida;

(2*R*,4*S*,4a*S*)-11-fluoro-*N*-metoxi-*N*,2,4-trimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxamida;

(2*R*,4*S*,4a*S*)-*N*-etil-11-fluoro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxamida;

(2*R*,4*S*,4a*S*)-*N*-etil-11-fluoro-*N*,2,4-trimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxamida;

(2*R*,4*S*,4a*S*)-11-fluoro-*N*,2,4-trimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxamida;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(4-metil-3-oxopiperazin-1-carbonil)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-^{1}*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxamida;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dietil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxamida;

(2*R*,4*S*,4a*S*)-11-fluoro-*N*-(2-metoxietil)-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-

1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxamida;
(2*R*,4*S*,4a*S*)-*N*-*terc*-butil-11-fluoro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxamida;
(2*R*,4*S*,4a*S*)-8-[(1,1-dioxidothiomorfolin-4-il)carbonil]-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'H,3'H)-triona;
(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-*N*-(tetrahidro-2*H*-piran-4-il)-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxamida;
(2*R*,4*S*,4a*S*)-11-fluoro-*N*-isopropil-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxamida;
(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(pirimidin-2-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2S,4*S*,4a*S*)-11-fluoro-4,8-dimetil-2-(trifluorometil)-1,2,4,4a-tetrahidro-2'H,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'H,3'H)-triona;
(2*R*,4*S*,4a*S*)-*N*-ciclopropil-11-fluoro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxamida;
(2*R*,4*S*,4a*S*)-11-fluoro-8-(4-metoxipiperidin-1-carbonil)-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;
(2*R*,4*S*,4a*S*)-*N*-(ciclopropilmetil)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxamida;
(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(1,2-oxazinan-2-ilcarbonil)-1,2,4,4a-tetrahidro-2'H,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'H,3'H)-triona;
(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-*N*-(tiofen-2-ilmetil)-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxamida;
(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-*N*-(piridin-4-ilmetil)-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxamida;
(2*R*,4*S*,4a*S*)-*N*-(ciclohexilmetil)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxamida;

(2*R*,4*S*,4a*S*)-8-(4,4-difluoropiperidin-1-carbonil)-11-fluoro-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;

(2*R*,4*S*,4a*S*)-8-(3,3-difluoropirrolidin-1-carbonil)-11-fluoro-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-*N*-(1-metilazetidin-3-il)-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxamida;

N-(1-((2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-ilcarbonil)azetidin-3-il)acetamida;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-*N*-((1-metil-1*H*-pirazol-3-il)metil)-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxamida;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-*N*-((1-metil-1*H*-pirazol-5-il)metil)-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxamida;

(2*R*,4*S*,4a*S*)-*N*-(1,3-dimetoxi-2-(metoximetil)propan-2-il)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxamida;

1-((2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-ilcarbonil)azetidin-3-carbonitrilo;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(pirazin-2-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(5-morfolinopirazin-2-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;

(2*R*,4*S*,4a*S*)-11-fluoro-8-(6-metoxipirazin-2-il)-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(2-(metiltio)pirimidin-4-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;

(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(2-(metilsulfonil)pirimidin-4-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-

espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;
(2*R*,4*S*,4a*S*)-11-fluoro-8-(2-(2-metoxietilamino)pirimidin-4-il)-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;
(2*R*,4*S*,4a*S*)-11-fluoro-8-(2-(2-hidroxietilamino)pirimidin-4-il)-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;
(2*R*,4*S*,4a*S*)-11-fluoro-8-(2-metoxipirimidin-4-il)-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;
4-((2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-il)pirimidin-2-carbonitrilo;
(2*R*,4*S*,4a*S*)-8-(2-aminopirimidin-4-il)-11-fluoro-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;
(2*R*,4*S*,4a*S*)-11-fluoro-8-(2-hidroxipirimidin-4-il)-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(2-morfolinopirimidin-4-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;
(2*R*,4*S*,4a*S*)-8-(6-(dimetilamino)pirazin-2-il)-11-fluoro-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;
(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(1-metil-1*H*-1,2,4-triazol-5-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;
(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(piperazin-1-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*R*,4*S*,4a*S*)-8-cloro-11-fluoro-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;
(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(metilsulfinil)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-8-(metilsulfonil)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-carbonitrilo;
2-[(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-1,3-tiazol-4-

carboxilato de etilo;
(2*R*,4*S*,4a*S*)-11-fluoro-8-(hidroximetil)-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;
ácido 1-[(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-1*H*-pirazol-4-carboxílico;
1-[(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-*N*,*N*-dimetil-1*H*-pirazol-4-carboxamida;
1-[(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-*N*-metil-1*H*-pirazol-4-carboxamida;
1-[(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-1*H*-pirazol-4-carboxamida;
(2*R*,4*S*,4a*S*)-11-fluoro-8-[4-(hidroximetil)-1*H*-pirazol-1-il]-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona,
o una sal farmacéuticamente aceptable de estos.

En un aspecto adicional más, la presente invención proporciona un compuesto que se selecciona de:
(2*S*,4*R*,4a*R*)-8-amino-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4,8-trimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-fenil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-8-ciclopropil-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-piridin-2-il-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-

g][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-il]acetamida;
(2*S*,4*R*,4a*R*)-11-cloro-2,4,8-trimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-8-(4-acetilpiperazin-1-il)-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-8-(bencilamino)-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-[(1,3-tiazol-2-ilmetil)amino]-1,2,4,4a-tetrahidro-2'H,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'H,3'H)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-8-[(1*H*-imidazol-4-ilmetil)amino]-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-{[(1-metil-1*H*-pirazol-4-il)metil]amino}-1,2,4,4a-tetrahidro-2'H,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'H,3'H)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-{[(5-metil-1,2-oxazol-3-il)metil]amino}-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-[(piridin-2-ilmetil)amino]-1,2,4,4a-tetrahidro-2'H,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'H,3'H)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-[(piridin-3-ilmetil)amino]-1,2,4,4a-tetrahidro-2'H,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'H,3'H)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-[(piridin-4-ilmetil)amino]-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-8-[(ciclopropilmetil)amino]-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-8-[(ciclohexilmetil)amino]-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-[(tetrahidro-2*H*-piran-4-ilmetil)amino]-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-

triona;

4-[(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-il]piperazin-1-carboxilato de *terc*-butilo;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(piperazin-1-il)-1,2,4,4a-tetrahidro-2'H,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'H,3'H)-triona;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(morfolin-4-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*S*,4*R*,4a*R*)-8-(dietilamino)-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*S*,4*R*,4a*R*)-8-(dimetilamino)-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(pirrolidin-1-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*S*,4*R*,4a*R*)-8-(azepan-1-il)-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-[5-metil-3-(trifluorometil)-1*H*-pirazol-1-il]-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

N-{1-[(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-1*H*-pirazol-3-il}acetamida;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-[3-(trifluorometil)-1*H*-pirazol-1-il]-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*S*,4*R*,4a*R*)-8-[3-(difluorometil)-5-metil-1*H*-pirazol-1-il]-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(propilamino)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*S*,4*R*,4a*R*)-8-[bencil(metil)amino]-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-

oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
3-amino-1-[(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-1*H*-pirazol-4-carbonitrilo;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-[4-(pirimidin-4-il)-1*H*-pirazol-1-il]-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-[4-(pirazin-2-il)-1*H*-pirazol-1-il]-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-8-(4-yodo-1*H*-pirazol-1-il)-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
1-[(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-1*H*-pirazol-4-carboxilato de etilo;
(2*S*,4*R*,4a*R*)-11-cloro-2,4-dimetil-8-(piridin-2-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-cloro-8-ciclopropil-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-cloro-2,4-dimetil-8-(6-metilpiridin-3-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-cloro-2,4-dimetil-8-(1,3-tiazol-5-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-cloro-2,4-dimetil-8-(pirimidin-2-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-cloro-2,4-dimetil-8-(pirimidin-4-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-cloro-2,4-dimetil-8-(pirimidin-5-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-cloro-2,4-dimetil-8-(piridazin-4-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*S*,4*R*,4a*R*)-11-cloro-2,4-dimetil-8-(piridin-4-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-cloro-2,4-dimetil-8-(piridin-3-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-cloro-2,4-dimetil-8-(1,3-tiazol-2-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-cloro-8-(metoximetil)-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-[metil(propil)amino]-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-8-metoxi-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)l-8-(benciloxi)-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'H,6*H*-espiro[1,4-oxazino[4,3-a][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'H,3'H)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(1*H*-1,2,4-triazol-1-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(3-metil-1*H*-1,2,4-triazol-1-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-1*H*-1,2,4-triazol-3-carbonitrilo;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(2*H*-1,2,3-triazol-2-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(1*H*-1,2,3-triazol-1-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-8-(1*H*-imidazol-1-il)-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-[4-(trifluorometil)-1*H*-imidazol-1-il]-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(4-metil-1*H*-pirazol-1-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*S*,4*R*,4a*R*)-8-(4-cloro-1*H*-pirazol-1-il)-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(metilsulfanil)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-8-(3,5-dimetil-1*H*-pirazol-1-il)-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(1*H*-pirazol-4-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(2-metil-1,3-oxazol-4-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(5-metil-1,2-oxazol-3-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-8-(3,5-dimetil-1,2-oxazol-4-il)-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(1-metil-1*H*-imidazol-2-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(1-metil-1*H*-imidazol-4-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(1-metil-1*H*-imidazol-5-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(4-metil-1,3-tiazol-5-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(4-metil-1,2,3-tiadiazol-5-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(piridazin-3-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(pirimidin-4-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4,8-trimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]tiazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(piridin-2-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-

oxazino[4,3-*a*][1,2]tiazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4,8-trimetil-1,2,3,4,4a,6-hexahidro-1'*H*-espiro[isoxazolo[4,5-*g*]pirido[1,2-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;

(2*S*,4*R*,4a*R*)-8-(3-cloropirazin-2-il)-11-fluoro-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;

(2*S*,4*R*,4a*R*)-8-(6-cloropirazin-2-il)-11-fluoro-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(5-(metiltio)pirazin-2-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;

(2*S*,4*R*,4a*R*)-8-((1*H*-1,2,4-triazol-1-il)metil)-11-fluoro-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(piridin-4-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;

(2*S*,4*R*,4a*R*)-11-fluoro-8-(5-hidroxi-1,3,4-oxadiazol-2-il)-2,4-dimetil-1,2,4,4a-tetrahidro-2'H,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'H,3'H)-triona;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-[4-(morfolin-4-ilcarbonil)-1,3-tiazol-2-il]-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-[4-(morfolin-4-ilcarbonil)-1,3-tiazol-5-il]-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-*N*,*N*-dimetil-1,3-tiazol-4-carboxamida;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-*N*,*N*-dimetil-1,3-tiazol-5-carboxamida;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-1,3-tiazol-4-carbonitrilo;

(2*S*,4*R*,4a*R*)-11-cloro-2,4-dimetil-8-(1-metil-1*H*-imidazol-2-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*S*,4*R*,4a*R*)-2,4,11-trimetil-8-(1,3-tiazol-2-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(6-metilpiridin-3-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(trifluorometil)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;

(2*S*,4*R*,4a*R*)-8-(difluorometil)-11-fluoro-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;

(2*S*,4*R*,4a*R*)-*N*-(2,2-difluoroetil)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxamida;

(2*S*,4*R*,4a*R*)-8-(3,3-difluoroazetidin-1-carbonil)-11-fluoro-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;

(2*S*,4*R*,4a*R*)-11-fluoro-8-(furan-2-il)-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(tiazol-5-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;

(2*S*,4*R*,4a*R*)-11-fluoro-8-(2-fluorofenil)-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(tetrahidro-2*H*-piran-4-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;

(2*S*,4*R*,4a*R*)-2,4,11-trimetil-8-(pirazin-2-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-il carbonato de *terc*-butilo;

(2*S*,4*R*,4a*R*)-8-acetil-9,10-difluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*S*,4*R*,4a*R*)-2-etil-11-fluoro-4,8-dimetil-1,2,4,4a-tetrahidro-2'H,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'H,3'H)-triona;

(2*S*,4*S*,4a*R*)-11-fluoro-4-(metoximetil)-2,8-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*R*,4*R*,4a*R*)-11-fluoro-2-(metoximetil)-4,8-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-

oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-cloro-2,4-dimetil-8-(piridin-2-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-cloro-2,4-dimetil-8-(piridin-4-il)-2,4,4a,6-tetrahidro-1*H*, 1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-cloro-2,4-dimetil-8-(piridin-3-il)-2,4,4a,6-tetrahidro-1*H*, 1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-cloro-2,4-dimetil-8-(pirazin-2-il)-2,4,4a,6-tetrahidro-1*H*, 1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-cloro-2,4-dimetil-8-(tiazol-2-il)-2,4,4a,6-tetrahidro-1*H*, 1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(1-metil-1*H*-imidazol-2-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;
(2*S*,4*R*,4a*R*)-11-cloro-2,4-dimetil-8-(4-metiltiazol-2-il)-2,4,4a,6-tetrahidro-1*H*, 1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-cloro-2,4-dimetil-8-(1-metil –1*H*-imidazol-2-il)-2,4,4a,6-tetrahidro-1*H*, 1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-cloro-2,4-dimetil-8-(tiazol-5-il)-2,4,4a,6-tetrahidro-1*H*, 1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-cloro-2,4-dimetil-8-(2,4-diclorotiazol-5-il)-2,4,4a,6-tetrahidro-1*H*, 1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-cloro-2,4-dimetil-8-(2-metiltiazol-5-il)-2,4,4a,6-tetrahidro-1*H*, 1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-cloro-2,4-dimetil-8-(1-metil-1*H*-1,2,4-triazol-5-il)-2,4,4a,6-tetrahidro-1*H*, 1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-cloro-2,4-dimetil-8-(2-bromotiazol-5-il)-2,4,4a,6-tetrahidro-1*H*, 1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-cloro-2,4-dimetil-8-(pirazin-2-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;
4-((2*S*,4*R*,4a*R*)-11-cloro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-8-il)-2-

fluorobenzonitrilo;
(2*S*,4*R*,4a*R*)-11-cloro-2,4-dimetil-8-(5-metiltiazol-2-il)-2,4,4a,6-tetrahidro-1*H*, 1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona;
5-((2*S*,4*R*,4a*R*)-11-cloro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-8-il)picolinamida;
(2*S*,4*R*,4a*R*)-11-cloro-2,4,8-trimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'H)-triona;
(2*S*,4*R*,4a*R*)-11-cloro-*N*,2,4-trimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-8-carboxamida;
(2*S*,4*R*,4a*R*)-11-cloro-*N*-etil-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-8-carboxamida;
(2*S*,4*R*,4a*R*)-cloro-*N*-isopropil-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-8-carboxamida;
(2*S*,4*R*,4a*R*)-*N*-*terc*-butil-11-cloro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-8-carboxamida;
(2*S*,4*R*,4a*R*)-11-cloro-2,4-dimetil-*N*-neopentil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-8-carboxamida;
(2*S*,4*R*,4a*R*)-11-cloro-8-(3,3-difluoroazetidin-1-carbonil)-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'H)-triona;
(2*S*,4*R*,4a*R*)-*N*-bencil-11-cloro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-a][1,5]naftiridin-5,5'-pirimidin]-8-carboxamida;
(2*S*,4*R*,4a*R*)-11-cloro-*N*-(4-cianobencil)-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-a][1,5]naftiridin-5,5'-pirimidin]-8-carboxamida;
(2*S*,4*R*,4a*R*)-11-cloro-*N*-(3-cianobencil)-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-a][1,5]naftiridin-5,5'-pirimidin]-8-carboxamida;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxilato de etilo;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(morfolin-4-carbonil)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-*N*,*N*,2,4-tetrametil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxamida;

(2*S*,4*R*,4a*R*)-11-fluoro-*N*-metoxi-*N*,2,4-trimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxamida;

(2*S*,4*R*,4a*R*)-*N*-etil-11-fluoro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxamida;

(2*S*,4*R*,4a*R*)-*N*-etil-11-fluoro-*N*,2,4-trimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxamida;

(2*S*,4*R*,4a*R*)-11-fluoro-*N*,2,4-trimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxamida;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(4-metil-3-oxopiperazin-1-carbonil)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxamida;

(2*S*,4*R*,4a*R*)-11-fluoro-*N*-(2-metoxietil)-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxamida;

(2*S*,4*R*,4a*R*)-*N*-*terc*-butil-11-fluoro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxamida;

(2*S*,4*R*,4a*R*)-8-[(1,1-dioxidotiomorfolin-4-il)carbonil]-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'H,3'H)-triona;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-*N*-(tetrahidro-2*H*-piran-4-il)-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxamida;

(2*S*,4*R*,4a*R*)-11-fluoro-*N*-isopropil-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxamida;

(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(pirimidin-2-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;

(2*S*,4*R*,4a*R*)-11-fluoro-4,8-dimetil-2-(trifluorometil)-1,2,4,4a-tetrahidro-2'H,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'H,3'H)-triona;

(2*S*,4*R*,4a*R*)-*N*-ciclopropil-11-fluoro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxamida;

(2*S*,4*R*,4a*R*)-11-fluoro-8-(4-metoxipiperidin-1-carbonil)-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-

espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;
(2*S*,4*R*,4a*R*)-*N*-(ciclopropilmetil)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-8-carboxamida;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(1,2-oxazinan-2-ilcarbonil)-1,2,4,4a-tetrahidro-2'H,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'H,3'H)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-*N*-(tiofen-2-ilmetil)-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxamida;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-*N*-(piridin-4-ilmetil)-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxamida;
(2*S*,4*R*,4a*R*)-*N*-(ciclohexilmetil)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxamida;
(2*S*,4*R*,4a*R*)-8-(4,4-difluoropiperidin-1-carbonil)-11-fluoro-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;
(2*S*,4*R*,4a*R*)-8-(3,3-difluoropirrolidin-1-carbonil)-11-fluoro-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-*N*-(1-metilazetidin-3-il)-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-8-carboxamida;
N-(1-((2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-ilcarbonil)azetidin-3-il)acetamida;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-*N*-((1-metil-1*H*-pirazol-3-il)metil)-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxamida;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-*N*-((1-metil-1*H*-pirazol-5-il)metil)-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxamida;
(2*S*,4*R*,4a*R*)-*N*-(1,3-dimetoxi-2-(metoximetil)propan-2-il)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-

pirimidin]-8-carboxamida;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-ilcarbonil)azetidin-3-carbonitrilo;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(pirazin-2-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-8-(6-(dimetilamino)pirazin-2-il)-11-fluoro-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(piperazin-1-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(metilsulfinil)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(metilsulfonil)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-carbonitrilo;
2-[(2*S*,4*R*,4a*R*)11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-1,3-tiazol-4-carboxilato de etilo;
(2*S*,4*R*,4a*R*)-11-fluoro-8-(hidroximetil)-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona;
ácido (2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-1*H*-pirazol-4-carboxílico;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-*N*,*N*-dimetil-1*H*-pirazol-4-carboxamida;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-*N*-metil-1*H*-pirazol-4-carboxamida;
(2*S*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-

oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-1*H*-pirazol-4-carboxamida; (2*S*,4*R*,4a*R*)-11-fluoro-8-[4-(hidroximetil)-1*H*-pirazol-1-il]-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona,
o una sal farmacéuticamente aceptable de estos.

Actividad biológica

Se cree que los compuestos de Fórmula (I) típicos inhiben la ADN girasa bacteriana y, por lo tanto, son de interés por sus efectos antibacterianos. Se cree que los compuestos de la invención son activos contra distintos organismos bacterianos, incluidas las bacterias aeróbicas y anaeróbicas Gram positivas y Gram negativas.

Estas propiedades pueden evaluarse utilizando, por ejemplo, el ensayo que se describe a continuación.

Ensayo de polarización de fluorescencia de la actividad de superenrollamiento de la ADN girasa

En una placa de ensayo de poliestireno negra de 384 pocillos, 30 microlitros/pocillo de tetrámero A/B de ADN girasa de *Escherichia coli* 5 nM y 130 microgramos/mL de plásmido topológicamente relajado que contiene la secuencia formadora de tríplex TTCTTCTTCTTCTTCTTCTTCTTC en una solución amortiguadora de ensayo que consiste en Tris-HCl 35 mM (pH 7,5), KCl 24 mM, $MgCl_2$ 4 mM, ditiotreitol 2 mM, espermidina 1,8 mM, 5% (v/v) glicerol, albúmina de suero bovino 200 nM, dimetilsulfóxido al 0,8% y ATP 0,3 mM pueden incubarse a temperatura ambiente (normalmente durante 30 minutos) en ausencia o presencia de 5 -10 concentraciones de compuesto de prueba diferentes. Las reacciones de superenrollamiento pueden detenerse mediante la adición de 10 microlitros/pocillo de sonda de oligodesoxinucleótido 40 nM en solución amortiguadora formadora de tríplex 3X que consiste en NaCl 150 mM y acetato de sodio 150 mM a pH 3,5. La sonda de oligodesoxinucleótido puede ser TTCTTCTTC marcada con 5'-BODIPY-FL. Después de 60 minutos, la aniostropía de fluorescencia de BODIPY-FL puede medirse en un lector de placas Tecan Ultra, utilizando fitros de excitación de 485 nm y de emisión de 535 nm equipados con polarizadores. El valor de CI_{50} puede determinarse mediante regresión no lineal utilizando dos reacciones de control. La primera

no contiene compuesto de prueba, sino DMSO al 0,8% (100% de actividad), mientras que la segunda reacción de control contiene Ciprofloxacina 5μM y DMSO al 0,8% (0% de actividad).

Cuando se evaluó en un ensayo *in vitro* basado en el ensayo de polarización de fluorescencia de la actividad de superenrollamiento de la ADN girasa descrito anteriormente, la actividad inhibitoria del ensayo de CI_{50} del superenrollamiento de la ADN girasa de *E. coli* de los siguientes ejemplos se midió en la CI_{50} indicada. Un guión indica que no se proporciona una medición de CI_{50} para ese compuesto en particular, aunque esto no quiere decir que ese compuesto en particular no posea actividad de CI_{50}.

Ejemplo	**CI_{50} (μM)**
1	0,5
2	0,4
2(a)	83
2(b)	0,3
3	0,4
4	0,3
5	0,2
6	0,8
7	0,4
8	8,3
9	1,7
10	1,9
11	0,8
12	1,2
13	1,7
14	2,0
15	1,0
16	2,4

17	1,4
18	2,9
19	2,9
20	20
21	2,4
22	2,6
23	4,3
24	0,3
25	1,5
26	3,7
27	7,1
28	3,1
29	-
30	5,4
31	2,2
32	0,6
33	1,0
34	16,3
35	30
36	2,1
37	8,5
38	0,8
39	0,6
40	1,6
41	0,8
42	1,2
43	0,5
44	1,0

45	1,6
46	1,0
47	0,3
48	1,0
49	1,7
50	0,5
51	1,0
52	2,4
53	2,8
53(a)	0,2
53(b)	20
54	2,0
55	2,6
56	0,7
57	1,5
58	0,5
59	6,6
60	1,2
61	9,3
62	0,9
63	2,7
64	0,8
65	1,1
66	0,4
67	3,2
68	0,7
69	17
70	0,5

71	0,9
72	0,9
73	0,5
74	-
74(a)	27
74(b)	0,3
75	0,2
76	-
77	0,3
78	0,8
79	0,8
80	1,7
81	3,0
82	0,2
83	-
84	-
85	17
86	5,0
87	6,7
88	1,2
89	1,3
90	-
91	1,9
92	1,4
92(a)	65
92(b)	0,6
93	0,7
93(a)	56

93(b)	0,4
94	1,6
94(a)	51
94(b)	0,8
95	0,3
95(a)	1,0
95(b)	-
96	0,7
97	0,7
98	0,4
99	0,4
100	4,1
101	1,4
102	2,7
103 + 104	0,2
105	0,7
106	1,1
107	1,4
108	0,8
109	0,5
110	3,0
111	0,7
111(a)	83
111(b)	1,1
112	-
113	2,5
114	5,2
115	1,1

116	2,0
117	2,0
118	-
119	3,1
120	0,2
121	0,6
122	0,5
123	5,8
124	1,8
125	0,7
126	0,5
127	19
128	19
129	31
130	30
131	4,4
132	7,7
133	13
134	1,0
135	3,3
136	2,8
137	2,3
138	1,7
139	7,6
140	1,1
140(a)	0,9
141	4,9
142	0,3

142(a)	1,7
143	1,0
144	2,9
145	5,2
146	4,9
147	3,9
147(a)	0,9
147(b)	-
148	0,9
148(a)	83
148(b)	0,4
149	4,4
150	1,3
151	5,5
152	2,1
153	3,7
154	1,5
155	1,2
156	1,5
157	6,4
158	1,4
159	1,4
160	1,0
161	1,3
162	2,1
163	17
164	1,2
165	0,4

165(a)	7,8
165(b)	0,2
166(a)	83
166(b)	6,9
167	1,1
168	0,6
169	-
170	0,7
171	0,3
172	0,9
173	0,1
174	0,5
175	0,9
176	3,2
177	5,0
178	1,3
179	2,0
180	0,2
181	3,3
182	2,4
183	12
184	-
185	1,4
186	7,6
187	3,3
188	2,7
189	2,2
190	2,1

En un aspecto se proporciona un compuesto de Fórmula (I), o una sal farmacéuticamente aceptable de este, para su uso como un medicamento.

En un aspecto, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Acinetobacter baumanii*. En otro aspecto, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Aeromis hydrophila*. En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Bacillus anthracis*. En otro aspecto más, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Bacteroides fragilis*. En un aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Bordatella pertussis*. En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Burkholderia cepacia*. En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Chlamyida pneumoniae*. En un aspecto, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Citrobacter freundii*. En otro aspecto, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Clostridium difficile*. En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Enterobacter cloacae*. En otro aspecto más, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Enterococcus faecalis*. En un aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Enterococcus faecium*. En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Enterobacter aerogenes*. En otro aspecto más adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Escherichia coli*. En un aspecto, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Fusobacterium necrophorum*. En otro aspecto, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Haemophilus influenzae*. En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Haemophilus parainfluenzae*. En otro aspecto más, los términos "infección" e "infección

bacteriana" pueden referirse a una infección bacteriana causada por *Haemophilus somnus*. En un aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Klebsiella oxytoca*. En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Klebsiella pneumoniae*. En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Legionella pneumophila*. En un aspecto, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Listeria monocytogenes*. En otro aspecto, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Moraxella catarrhalis*. En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Morganella morganii*. En otro aspecto más, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Mycoplasma pneumoniae*. En un aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Neisseria gonorrhoeae*. En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Neisseria meningitidis*. En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Pasteurella multocida*. En un aspecto, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Proteus mirabilis*. En otro aspecto, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Proteus vulgaris*. En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Pseudomonas aeruginosa*. En otro aspecto más, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Salmonella typhi*. En un aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Salmonella typhimurium*. En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Serratia marcesens*. En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Shigella flexneria*. En un aspecto, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Shigella dysenteriae*. En otro aspecto, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada

por *Staphylococcus aureus*. En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Staphylococcus epidermidis*. En otro aspecto más, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Staphylococcus haemolyticus*. En un aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Staphylococcus intermedius*. En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Staphylococcus saprophyticus*. En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Stenotrophomonas maltophila*. En un aspecto, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Streptococcus agalactiae*. En otro aspecto, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Streptococcus mutans*. En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Streptococcus pneumoniae*. En otro aspecto más, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por *Streptococcus pyrogenes*.

En un aspecto, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por una bacteria del género *Aeromonas*. En otro aspecto, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por una bacteria del género *Acinetobacter*. En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por una bacteria del género *Bacillus*. En otro aspecto más, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por una bacteria del género *Bacteroides*. En un aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por una bacteria del género *Bordetella*. En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por una bacteria del género *Burkholderia*. En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por una bacteria del género *Chlamydophila*. En un aspecto, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por una bacteria del género

Citrobacter. En otro aspecto, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por una bacteria del género *Clostridium*. En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por una bacteria del género *Enterobacter*. En otro aspecto más, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por una bacteria del género *Enterococcus*. En un aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por una bacteria del género *Escherichia*. En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por una bacteria del género *Flavobacterium*. En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por una bacteria del género *Fusobacterium*. En un aspecto, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por una bacteria del género *Haemophilus*. En un aspecto, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por una bacteria del género *Klebsiella*. En otro aspecto, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por una bacteria del género *Legionella*. En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por una bacteria del género *Listeria*. En otro aspecto más, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por una bacteria del género *Morganella*. En un aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por una bacteria del género *Moraxella*. En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por una bacteria del género *Mycoplasma*. En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por una bacteria del género *Neisseria*. En un aspecto, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por una bacteria del género *Pasteurella*. En otro aspecto, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por una bacteria del género *Peptococci*. En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por una bacteria del género *Peptostreptococci*. En otro aspecto más, los términos "infección" e "infección bacteriana" pueden referirse a una

infección bacteriana causada por una bacteria del género *Prevotella*. En un aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por una bacteria del género *Proteus*. En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por una bacteria del género *Pseudomonas*. En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por una bacteria del género *Salmonella*. En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por una bacteria del género *Serratia*. En un aspecto, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por una bacteria del género *Shigella*. En otro aspecto más, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por una bacteria del género *Staphylococcus*. En otro aspecto, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por una bacteria del género *Stenotrophomonas*. En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección bacteriana causada por una bacteria del género *Streptococcus*.

En un aspecto, los términos "infección" e "infección bacteriana" pueden referirse a una infección ginecológica. En otro aspecto, los términos "infección" e "infección bacteriana" pueden referirse a una infección del tracto respiratorio (ITR). En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una enfermedad de transmisión sexual. En otro aspecto más, los términos "infección" e "infección bacteriana" pueden referirse a una infección del tracto urinario. En un aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a la exacerbación aguda de la bronquitis crónica (EPOC). En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a otitis media aguda. En un aspecto, los términos "infección" e "infección bacteriana" pueden referirse a sinusitis aguda. En otro aspecto, los términos "infección" e "infección bacteriana" pueden referirse a una infección causada por bacterias resistentes a los fármacos. En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a sepsis relacionada con catéteres. En otro aspecto más, los términos "infección" e "infección bacteriana" pueden referirse a chancroide. En un aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a clamidia. En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden

referirse a neumonía adquirida en la comunidad (NAC). En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a una infección complicada de la piel y de la estructura de la piel. En un aspecto, los términos "infección" e "infección bacteriana" pueden referirse a una infección no complicada de la piel y de la estructura de la piel. En otro aspecto, los términos "infección" e "infección bacteriana" pueden referirse a endocarditis. En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a neutropenia febril. En otro aspecto más, los términos "infección" e "infección bacteriana" pueden referirse a cervicitis gonocócica. En un aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a uretritis gonocócica. En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a neumonía adquirida en el hospital (NAH). En otro aspecto, los términos "infección" e "infección bacteriana" pueden referirse a osteomielitis. En un aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a sepsis. En otro aspecto adicional, los términos "infección" e "infección bacteriana" pueden referirse a sífilis.

En un aspecto, se proporciona el uso de un compuesto de Fórmula (I), o una sal farmacéuticamente aceptable de este, en la fabricación de un medicamento para la producción de un efecto inhibitorio de la ADN girasa bacteriana en un animal de sangre caliente tal como el hombre.

En otro aspecto, se proporciona el uso de un compuesto de Fórmula (I), o una sal farmacéuticamente aceptable de este, en la fabricación de un medicamento para el tratamiento de una infección bacteriana en un animal de sangre caliente tal como el hombre.

En otro aspecto adicional, se proporciona el uso de un compuesto de Fórmula (I), o una sal farmacéuticamente aceptable de este, en la fabricación de un medicamento para el tratamiento de infecciones del tracto urinario, neumonía, prostatitis, infecciones de la piel y tejidos blandos e infecciones intra-abdominales, en un animal de sangre caliente tal como el hombre.

En otro aspecto, se proporciona un método para producir un efecto inhibitorio de la ADN girasa bacteriana en un animal de sangre caliente tal como el hombre, comprendiendo dicho método administrar a dicho animal una cantidad efectiva de un compuesto de Fórmula (I) o una sal

farmacéuticamente aceptable de este.

En un aspecto adicional, se proporciona un método para el tratamiento de una infección bacteriana en un animal de sangre caliente tal como el hombre, comprendiendo dicho método administrar a dicho animal una cantidad efectiva de un compuesto de Fórmula (I) o una sal farmacéuticamente aceptable de este.

En otro aspecto adicional, se proporciona un método para el tratamiento de infecciones del tracto urinario, neumonía, prostatitis, infecciones de la piel y tejidos blandos e infecciones intra-abdominales, en un animal de sangre caliente tal como el hombre, comprendiendo dicho método administrar a dicho animal una cantidad efectiva de un compuesto de Fórmula (I) o una sal farmacéuticamente aceptable de este.

En otro aspecto adicional, se proporciona un compuesto de Fórmula (I) o una sal farmacéuticamente aceptable de este, para su uso en la producción de un efecto inhibitorio de la ADN girasa bacteriana en un animal de sangre caliente tal como el hombre.

En un aspecto, se proporciona un compuesto de Fórmula (I) o una sal farmacéuticamente aceptable de este, para su uso en el tratamiento de una infección bacteriana en un animal de sangre caliente, tal como el hombre.

En otro aspecto, se proporciona un compuesto de Fórmula (I) o una sal farmacéuticamente aceptable del mismo, para su uso en el tratamiento de infecciones del tracto urinario, neumonía, prostatitis, infecciones de la piel y tejidos blandos e infecciones intra-abdominales, en un animal de sangre caliente tal como el hombre.

En otro aspecto adicional, se proporciona una composición farmacéutica que comprende un compuesto de Fórmula (I) o una sal farmacéuticamente aceptable de este y al menos un portador, diluyente o excipiente farmacéuticamente aceptable.

Las composiciones de la invención pueden presentarse en formas adecuadas para uso oral (por

ejemplo, como comprimidos, grageas, cápsulas duras o blandas, suspensiones acuosas u oleosas, emulsiones, gránulos o polvos dispersables, jarabes o elixires), para uso tópico (por ejemplo, como cremas, ungüentos, geles o soluciones o suspensiones acuosas u oleosas), para administración mediante inhalación (por ejemplo, como un polvo dividido finamente o un aerosol líquido), para administración mediante insuflación (por ejemplo, como un polvo dividido finamente) o para administración parenteral (por ejemplo, como una solución acuosa u oleosa estéril para dosificación intravenosa, subcutánea, intramuscular o intramuscular o como un supositorio para dosificación rectal).

Las composiciones de la invención pueden obtenerse mediante procedimientos convencionales, utilizando excipientes farmacéuticos convencionales, ampliamente conocidos en la técnica. Es así que las composiciones para uso oral pueden contener, por ejemplo, uno o más agentes colorantes, edulcorantes, saborizantes y/o conservantes.

Los excipientes farmacéuticamente aceptables apropiados para una formulación en comprimidos incluyen, por ejemplo, diluyentes inertes como lactosa, carbonato de sodio, fosfato de calcio o carbonato de calcio; agentes granulantes y desintegrantes como almidón de maíz o ácido algénico; agentes aglutinantes, como almidón; agentes lubricantes como estearato de magnesio, ácido esteárico o talco; agentes conservantes como p-hidroxibenzoato de etilo o propilo; y antioxidantes, como ácido ascórbico. Las formulaciones en comprimidos pueden estar recubiertas o no ya sea para modificar su desintegración y posterior absorción del principio activo dentro del tracto gastrointestinal, como para mejorar su estabilidad y/o apariencia, utilizando en ambos casos, agentes y procedimientos de recubrimiento convencionales ampliamente conocidos en la técnica.

Las composiciones para uso oral pueden estar en forma de cápsulas de gelatina dura, en donde el principio activo está mezclado con un diluyente sólido inerte, por ejemplo, carbonato de calcio, fosfato de calcio o caolina, o como cápsulas de gelatina blanda, en donde el principio activo está mezclado con agua o con un aceite tal como aceite de maní, parafina líquida o aceite de oliva.

Las suspensiones acuosas contienen generalmente el principio activo en forma de polvo

finamente molido o en forma de partículas nano o micronizadas conjuntamente con uno o más agentes de suspensión, tales como carboximetilcelulosa de sodio, metilcelulosa, hidroxipropilmetilcelulosa, alginato de sodio, polivinilpirrolidona, goma tragacanto y goma acacia; agentes dispersantes o humectantes, tales como lecitina o productos de condensación de un óxido de alquileno con ácidos grasos (por ejemplo, estearato de polioxetileno), o productos de condensación de óxido de etileno con alcoholes alifáticos de cadena larga, por ejemplo heptadecaetilenooxicetanol, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y un hexitol tal como monooleato de polioxietileno sorbitol, o productos de condensación de óxido de etileno con alcoholes alifáticos de cadena larga, por ejemplo heptadecaetilenooxicetanol, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y un hexitol tal como monooleato de polioxietileno sorbitol, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y anhídridos de hexitol, por ejemplo monooleato de polietileno sorbitán. Las suspensiones acuosas también pueden contener uno o más conservantes tales como p-hidroxibenzoato de propilo o etilo; antioxidantes tales como ácido ascórbico; agentes colorantes; agentes saborizantes y/o agentes edulcorantes tales como sacarosa, sacarina o aspartamo.

Las suspensiones oleosas pueden formularse mediante la suspensión del principio activo en un aceite vegetal tal como aceite de maní, aceite de oliva, aceite de sésamo o aceite de coco, o en un aceite mineral tal como parafina líquida. Las suspensiones oleosas también pueden contener un agente espesante tal como cera de abeja, parafina dura o alcohol cetílico. Los agentes edulcorantes como los mencionados anteriormente y los agentes saborizantes pueden agregarse para proporcionar una preparación oral agradable al paladar. Estas composiciones pueden conservarse agregando un antioxidante tal como ácido ascórbico.

Los polvos y gránulos dispersables adecuados para la preparación de una suspensión acuosa mediante la adición de agua, contienen generalmente el principio activo junto con un agente dispersante o humectante, un agente de suspensión y uno o más conservantes. Los agentes dispersantes o humectantes y agentes de suspensión adecuados quedan ejemplificados por los ya mencionados anteriormente. También pueden estar presentes excipientes adicionales tales como agentes edulcorantes, saborizantes y colorantes.

Las composiciones farmacéuticas de la invención también pueden estar en forma de emulsiones de aceite en agua. La fase oleosa puede ser un aceite vegetal, tal como aceite de oliva o aceite de maní, o un aceite mineral, tal como por ejemplo, parafina líquida, o una mezcla de cualquiera de estos aceites. Los agentes emulsionantes adecuados pueden ser, por ejemplo, gomas naturales, como por ejemplo, goma acacia o goma tragacanto, fosfátidos naturales tales como soja, lecitina, ésteres o ésteres parciales derivados de ácidos grasos y anhídridos de hexitol (por ejemplo, monooleato de sorbitán) y productos de condensación de dichos ésteres parciales con óxido de etileno, tales como monooleato de polioxietileno sorbitán. Las emulsiones también pueden contener agentes edulcorantes, saborizantes y conservantes.

Los jarabes y elíxires pueden formularse con agentes edulcorantes tales como glicerol, propilenglicol, sorbitol, aspartamo o sacarosa y también pueden contener un agente demulcente, conservante, saborizante y/o colorante.

Las composiciones farmacéuticas también pueden estar en forma de una suspensión oleosa o acuosa inyectable estéril, que puede formularse de acuerdo con los procedimientos conocidos, utilizando uno o más de los agentes dispersantes o humectantes y agentes de suspensión adecuados mencionados anteriormente. Un preparado inyectable estéril también puede ser una solución o suspensión inyectable estéril en un diluyente o disolvente parenteral aceptable no tóxico, como por ejemplo, una solución en 1,3-butanodiol.

Las composiciones para la administración por inhalación pueden estar en forma de un aerosol presurizado convencional diseñado para dispensar el principio activo como un aerosol que contiene microgotas líquidas o sólidas finamente divididas. Se pueden utilizar los propelentes para aerosoles convencionales tales como hidrocarburos o hidrocarburos fluorados volátiles y el dispositivo de aerosol puede diseñarse convenientemente para dispensar una cantidad cuantificada del principio activo.

Para obtener más información sobre la formulación, se remite al lector al capítulo 25.2 del volumen 5 de Comprehensive Medicinal Chemistry (Corwin Hansch; Presidente del Comité

Editorial), Pergamon Pres 1990.

La cantidad de principio activo que se combina con uno o más excipientes para producir una forma de dosificación única variará necesariamente según el huésped tratado y la vía de administración particular. Por ejemplo, una formulación para la administración oral en humanos contendrá generalmente, por ejemplo, entre 0,5 mg y 4 g de agente activo compuesto por una cantidad apropiada y conveniente de excipientes que pueden variar de aproximadamente 5 a aproximadamente 98 por ciento en peso de la composición total. Las formas de dosificación unitaria generalmente contendrán de aproximadamente 1 mg a aproximadamente 500 mg de un principio activo. Para obtener más información sobre las vías de administración y regímenes de dosis, se remite al lector al capítulo 25.3 del volumen 5 de Comprehensive Medicinal Chemistry (Corwin Hansch; Presidente del Comité Editorial), Pergamon Press 1990.

Además de los compuestos de la presente invención, la composición farmacéutica de esta invención también puede contener o administrarse conjuntamente (simultáneamente, secuencialmente o separadamente) con uno o más fármacos conocidos que se seleccionan de otras clases clínicamente útiles de agentes antibacterianos (por ejemplo, macrólidos, quinolonas, ß-lactamas o aminoglucósidos) y/u otros agentes antiinfecciosos (por ejemplo, un triazol o amfotericina antifúngicos). Estos pueden incluir carbapenemas, por ejemplo meropenema o imipenema, para ampliar la eficacia terapéutica. Los compuestos de esta invención también pueden contener o administrarse conjuntamente con productos proteicos bactericidas/incrementadores de la permeabilidad (BPI) o inhibidores de la bomba de eflujo para mejorar la actividad contra bacterias gram negativas y bacterias resistentes a los agentes antimicrobianos.

Como se estableció anteriormente, el tamaño de la dosis requerida para el tratamiento terapéutico o profiláctico de un estado de enfermedad en particular variará necesariamente dependiendo del huésped tratado, la vía de administración y la gravedad de la enfermedad tratada. Preferiblemente se emplea una dosis diaria en el rango de 1-50 mg/kg. Por lo tanto, el facultativo que esté tratando a un paciente en particular podrá determinar la dosis óptima.

Además de su uso en la medicina terapéutica, el compuesto de Fórmula (I) y sus sales farmacéuticamente aceptables, son también útiles como herramientas farmacológicas en el desarrollo y la estandarización de sistemas de prueba *in vitro* e *en vivo* para la evaluación de los efectos de inhibidores de la ADN girasa en animales de laboratorio, tales como gatos, perros, conejos, monos, ratas y ratones, como parte de la búsqueda de nuevos agentes terapéuticos.

Si no se encuentran comercialmente disponibles, los materiales de partida necesarios para los procedimientos tales como los descritos anteriormente pueden elaborarse mediante procedimientos que se seleccionan de técnicas de la química orgánica convencionales, técnicas que son análogas a la síntesis de compuestos conocidos estructuralmente similares, o técnicas que son análogas a las del procedimiento descrito anteriormente o los procedimientos descritos en los ejemplos.

Muchos de los materiales de partida para los métodos sintéticos como se describe en la presente se encuentran comercialmente disponibles y/o ampliamente descritos en la bibliografía científica, o pueden elaborarse a partir de compuestos comercialmente disponibles utilizando adaptaciones de procesos descritos en la bibliografía científica. Se recomienda que el lector consulte *Advanced Organic Chemistry*, 5.ª edición, de Jerry March y Michael Smith, publicada por John Wiley & Sons **2001**, para obtener una guía general con respecto a las condiciones de reacción y los reactivos.

Los compuestos de Fórmula (I) pueden prepararse de distintas maneras. Los procesos que se muestran a continuación ilustran un método para sintetizar los compuestos de Fórmula (I) (en donde el **Anillo A, W, X, Y** y $\mathbf{R^1}$, a menos que se definan de otra forma, son tal como se definen anteriormente). Las reacciones se llevan a cabo en disolventes adecuados para los reactivos y los materiales empleados y son adecuadas para las transformaciones que se realizan. Además, se comprenderá que en la descripción de los métodos sintéticos descritos a continuación, todas las condiciones de reacción propuestas, incluida la elección del disolvente, la atmósfera de la reacción, la temperatura de la reacción, la duración del experimento y los procedimientos para tratar la reacción, se seleccionan de forma tal que sean condiciones convencionales para la reacción en cuestión, las cuales serán fácilmente reconocidas por cualquier experto en la técnica.

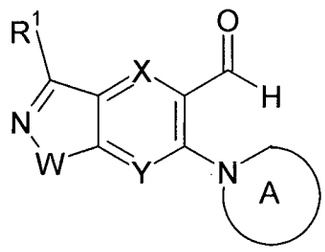
Los expertos en la técnica de la síntesis orgánica comprenderán que la funcionalidad presente en varias porciones de la molécula debe ser compatible con los reactivos y las reacciones propuestos. Estas restricciones de los sustituyentes, que son compatibles con las condiciones de la reacción, serán fácilmente evidentes para el experto en la técnica y luego podrán utilizarse métodos alternativos. Los Esquemas y Procesos no pretenden presentar una lista exhaustiva de métodos para preparar los compuestos de Fórmula (I). Por el contrario, también pueden utilizarse técnicas adicionales conocidas por el químico experto para la síntesis de los compuestos. Las reivindicaciones no pretenden limitarse a las estructuras que se muestran en los Esquemas y Procesos.

También se apreciará que, en algunas de las reacciones que se muestran en los Esquemas y Procesos mencionados en la presente, puede ser necesario/deseable proteger los grupos sensibles en los compuestos. Los casos en los que la protección es necesaria o deseable y los métodos adecuados para la protección son conocidos por los expertos en la técnica. Pueden utilizarse grupos protectores convencionales de acuerdo con la práctica estándar (para más detalles, remítase a T. W. Green, *Protective Groups in Organic Synthesis*, publicado por John Wiley & Sons, **1991**) y como se describió anteriormente en la presente.

El químico especializado podrá utilizar y adaptar la información incluida y a la cual se hace referencia en la referencias precedentes y en los ejemplos que se encuentran en ellas y también en los ejemplos y el Esquema de la presente para obtener los materiales de partida y los productos necesarios.

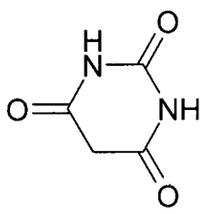
En un aspecto, los compuestos de Fórmula (I) o las sales farmacéuticamente aceptables de estos, pueden prepararse mediante:

Proceso A - hacer reaccionar un compuesto de Fórmula (A1):



Fórmula (A1)

con ácido barbitúrico:



,

y luego, si es necesario:

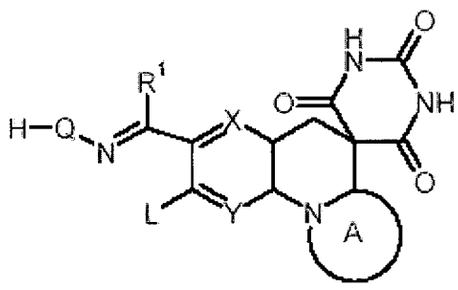
i) convertir un compuesto de Fórmula (I) en otro compuesto de Fórmula (I);

ii) eliminar todo grupo protector; y/o

iii) formar una sal farmacéuticamente aceptable.

En otro aspecto, los compuestos de Fórmula (Ib), que son compuestos de Fórmula (I) en los que **W** es -O- o -NH-, o sales farmacéuticamente aceptables de estos, pueden prepararse mediante:

Proceso B – hacer reaccionar un compuesto de Fórmula (A3):



Fórmula (A3)

con un agente formador de anillos adecuado,

y luego, si es necesario:

i) convertir un compuesto de Fórmula (I) en otro compuesto de Fórmula (I);

ii) eliminar todo grupo protector; y/o

iii) formar una sal farmacéuticamente aceptable,

en donde

L es un grupo saliente, como se describió anteriormente; y

Q se selecciona de -O- y -NH-.

Proceso A

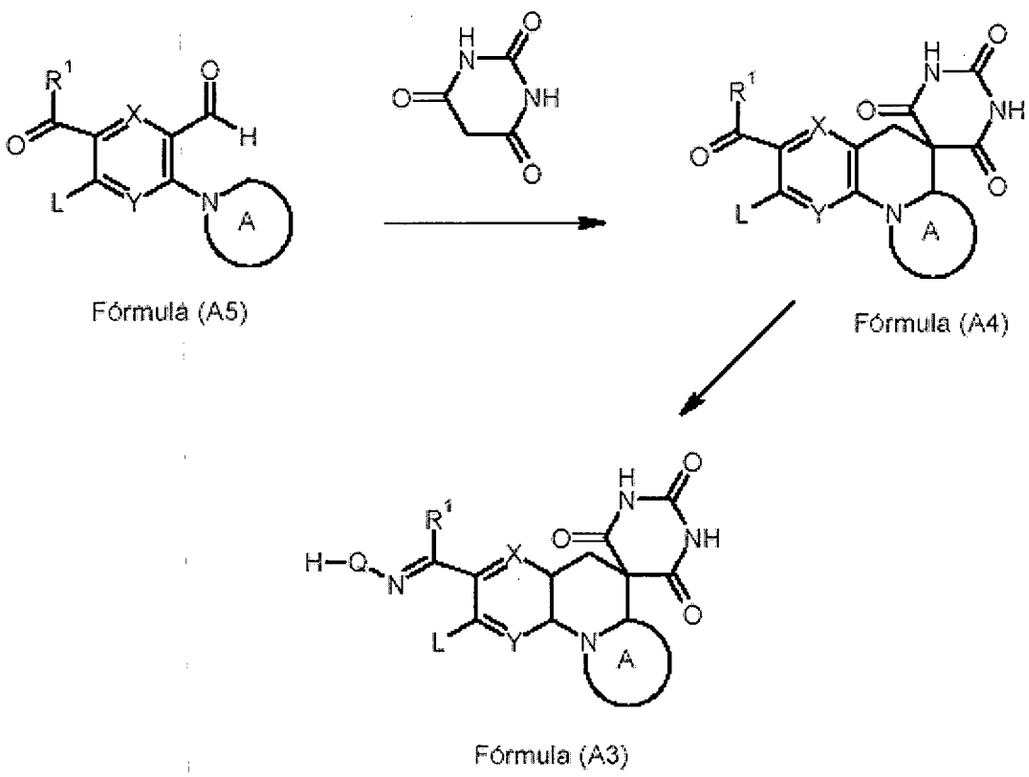
La reacción del **Proceso A** puede llevarse a cabo en una o dos etapas de reacción separadas haciendo reaccionar un compuesto de Fórmula (A1) con un compuesto de Fórmula (A2) en condiciones de reacción de Knoevenagel convencionales para formar una olefina intermedia. Los disolventes adecuados para dicha reacción incluyen alcoholes tales como metanol, isopropanol y butanol, disolventes hidrocarburo tales como tolueno y benceno, y disolventes etéreos tales como dioxano y dimetoxietano. Las temperaturas típicas pueden encontrarse en el rango de entre aproximadamente 60 °C y aproximadamente 120 °C. La reacción de Knoevenagel puede catalizarse con una base tal como trietilamina o pirrolidina o una sal orgánica sal tal como acetato de piperidinio. A menudo, en las condiciones de reacción, la olefina intermedia (aducto de Knoevenagel) se reordena para convertirse en un compuesto de Fórmula (A1). Este reordenamiento se debe a lo que a veces se denomina el "efecto amina terciaria". Si el reordenamiento no se produce, la temperatura de la reacción puede aumentarse y/o los disolventes pueden intercambiarse por disolventes más polares tales como dimetilformamida y dimetilsulfóxido. La temperatura de reacción aumentada puede variar entonces entre aproximadamente 70 °C y aproximadamente 180 °C.

Proceso B

La reacción que se muestra para el **Proceso B** puede llevarse a cabo en disolventes próticos tales como MeOH, EtOH o IPA, disolventes etéreos tales como THF y dioxano o disolventes apróticos tales como DMF o acetonitrilo, dependiendo de la naturaleza de la base. Las temperaturas de la reacción pueden variar entre la temperatura ambiente y 130 °C. Algunos ejemplos ilustrativos del "agente formador de anillos" incluyen bases carbonato tales como $CsCO_3$ y Na_2CO_3, alcóxidos tales como NaOMe y NaOEt, aminas tales como trietilamina y DBU y bases hidruro tales como NaH.

El Esquema 1 ilustra un procedimiento mediante el cual pueden prepararse compuestos de Fórmula (A3).

Esquema 1

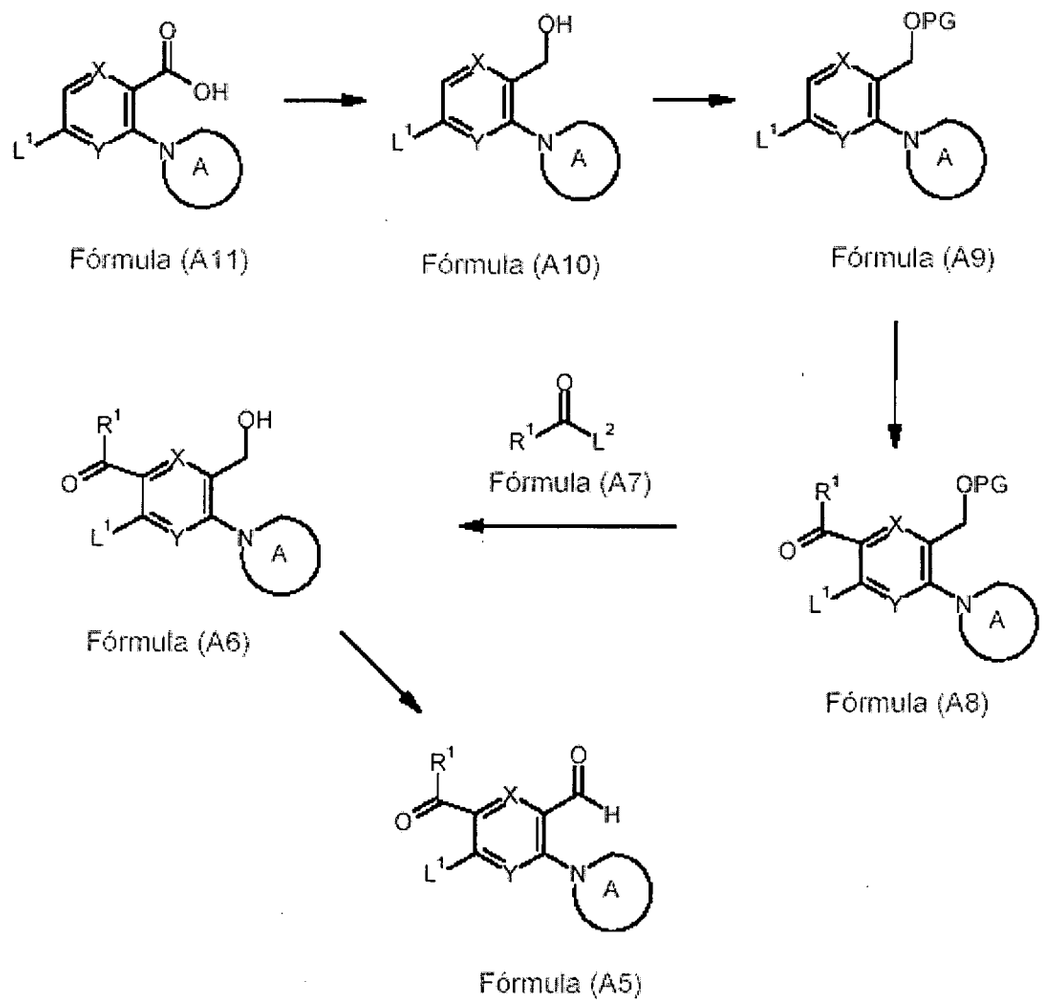


Los compuestos de Fórmula (A5) pueden hacerse reaccionar con ácido barbitúrico en las condiciones descritas para la reacción del **Proceso A**, para proporcionar un compuesto de Fórmula (A4). El compuesto de Fórmula (A3) puede obtenerse mediante reacción del compuesto de Fórmula (A4) con clorhidrato de hidroxilamina o hidrazina opcionalmente en presencia de un catalizador o reactivo tal como acetato de sodio, bicarbonato de sodio o piridina a temperaturas que van desde la temperatura ambiente hasta 130 °C en disolventes adecuados, incluidos disolventes próticos tales como metanol o etanol, disolventes polares tales como DMF o DMSO, etéreos tales como THF o dioxano y disolventes aromáticos tales como tolueno o piridina. A

menudo, en las condiciones de reacción, los compuestos intermedios A3 se ciclizan para convertirse en compuestos de Fórmula A (W es O o NH).

El Esquema 2 ilustra un proceso mediante el cual se preparan los compuestos de Fórmula (A5). El grupo saliente $\mathbf{L^1}$ habitualmente incluye halógenos tales como flúor, cloro o bromo o ésteres sulfónicos tales como trifluometanosulfoniloxi.

Esquema 2



Los compuestos de Fórmula (A5) pueden prepararse a partir de compuestos de Fórmula (A11) utilizando la síntesis ilustrada en el Esquema 2. La reducción del grupo ácido del compuesto de Fórmula (A11) a un alcohol puede lograrse utilizando agentes reductores típicos tales como

borano, borohidruro de sodio y yodo, y cloroformiato de etilo y borohidruro de litio en condiciones de reducción estándar, para proporcionar el compuesto de Fórmula (A10). La protección del compuesto de Fórmula (A10) en condiciones típicas con grupos protectores de alcohol estándar, incluidos grupos protectores de sililo tales como TBMS, proporciona el compuesto de Fórmula (A9). El resto R^1-(CO)- puede agregarse mediante la reacción del compuesto de Fórmula (A9) con un compuesto de Fórmula (A7) en condiciones básicas, para proporcionar el compuesto de Fórmula (A6). Los grupos salientes típicos (designados por L^2) adecuados para dicha reacción incluyen aminas tales como dimetilamina y (N-metoxi)-metilamina, alcoholes tales como metanol o etanol o haluros tales como cloruro o bromuro. Las bases adecuadas para dicha reacción incluyen alquillitios tales como *s*-butillitio y *n*-butillitio y aminas tales como una diisopropilamina de litio, hexametildisilazina de litio y tetrametilpiperidina de litio. La oxidación del alcohol del compuesto de Fórmula (A6) utilizando un agente de oxidación tal como MnO_2, clorocromato de pirdinio, el periodinano de Dess-Martin y DMF/cloruro de oxalilo.DMSO proporciona el compuesto de Fórmula (A5).

En cualquiera de las características de las composiciones farmacéuticas, procesos, métodos, usos, medicamentos y fabricación de la presente invención mencionadas anteriormente, también se aplican cualquiera de las realizaciones alternativas de los compuestos de la invención descritas en la presente.

Ejemplos

La invención se describirá ahora adicionalmente a través de los siguientes ejemplos ilustrativos, en los que, a menos que se indique de otra forma:

(i) las temperaturas se citan en grados Celsius (°C); las operaciones se llevaron a cabo a temperatura ambiente, esto es, en el rango de 18-25 °C;

(ii) las soluciones orgánicas se secaron con sulfato de magnesio anhidro; la evaporación del disolvente orgánico se llevó a cabo utilizando un evaporador rotativo a presión reducida (4,5 - 30 mmHg) con una temperatura de baño de hasta 60 °C;

(iii) cromatografía significa cromatografía instantánea sobre gel de sílice; la cromatografía en capa fina (TLC) se llevó a cabo en placas de gel de sílice;

(iv) en general, las reacciones se siguieron mediante TLC, o cromatografía

líquida/espectroscopía de masas (LC/MS) y los tiempos de reacción se proporcionan a modo ilustrativo solamente;

(v) los productos finales tienen datos satisfactorios de espectros de resonancia magnética nuclear protónica (RMN) y/o espectros de masas;

(vi) los rendimientos se proporcionan a modo ilustrativo solamente y no son necesariamente los que se pueden obtener mediante un desarrollo del proceso cuidadoso; las preparaciones se repitieron cuando fue necesario más material;

(vii) cuando se proporcionan, los datos de RMN se encuentran en forma de valores delta para los principales protones de diagnóstico, proporcionados en partes por millón (ppm) con relación a tetrametisilano (TMS) como estándar interno, determinados a 300 MHz en DMSO-d_6 a menos que se indique de otra forma;

(viii) los símbolos químicos tienen su significado habitual;

(ix) las relaciones entre disolventes se proporcionan en términos de volumen:volumen (v/v);

(x) Combiflash de ISCO se refiere a cromatografía instantánea en gel de sílice utilizando un sistema de separación Combiflash® de ISCO: columna instantánea en fase normal RediSep, velocidad de flujo, 30-40 mL/min;

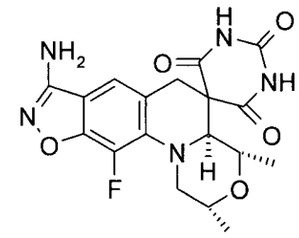
(xi) se utilizaron las siguientes abreviaturas:

BINAP	2,2'-bis(difenilfosfino)-1,1'-binaftilo
Boc_2O	anhídrido de *terc*-butiloxicarbonilo
DAST	Trifluoruro de dietilaminosulfuro
DCM	diclorometano
DIPEA	*N, N*-diisopropiletilamina
DMAc	*N,N*-dimetilacetamida
DMF	*N,N*-dimetilformamida
dppf	1,1'-bis(difenilfosfino)ferroceno
DMAP	4-dimetilaminopiridina
DMSO	dimetilsulfóxido
ee	exceso enantiomérico
EtOAc	acetato de etilo
Et_2O	éter dietílico

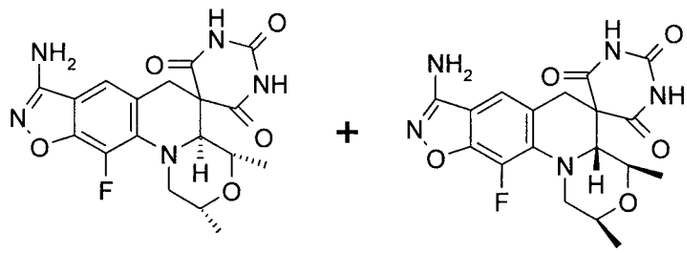
GC	cromatografía de gases
HATU	Hexafluorofosfato de O-(7-azabenzotriazol-1-il)-*N*,*N*,*N*',*N*'-tetrametiluronio
HPLC	cromatografía líquida de alta resolución
h	horas
LDA	Diisopropilamida de litio
min	minutos
NMO	N-óxido de 4-metilmorfolina
NMP	*N*-metilpirrolidona
d/n	durante toda la noche
$Pd_2(dba)_3$	Tris(dibencilidenoacetona)dipalladio(0)
*i*PrOH	*i*-propanol
rac.	racémico
SEM	1-((2-(trimetilsilil)etoxi)metilo
TBME	éter *terc*-butil metílico
TEA	trietilamina
TFA	ácido trifluoroacético
TFAA	anhídrido trifluoroacético
THF	tetrahidrofurano
TMS	trimetilsililo
Tosilo, Ts	para-toluenosulfonilo
TPAP	perrutenato de tetrapropilamonio
Xantphos	9,9-dimetil-4,5-bis(difenilfosfino)xanteno

En los casos en los que el nombre de un compuesto incluye "rel", como en, por ejemplo, "(2*R*,4*S*,4a*S*)-rel-8-amino-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona", debe entenderse que dicha designación implica que el compuesto indicado se encuentra en forma de una mezcla racémica. En el ejemplo indicado, el nombre indica que el compuesto se encuentra en forma de una mezcla racémica de dos enantiómeros: el enantiómero (2*R*,4*S*,4a*S*) y el enantiómero (2*S*,4*R*,4a*R*).

De manera adicional, la descripción estructural de un enantiómero (2*R*, 4*S*, 4a*S*) precedida por un signo "(±)" indica que el compuesto está presente en forma de una mezcla racémica que contiene el enantiómero (2*R*,4*S*,4a*S*) y el enantiómero (2*S*,4*R*,4a*R*) del compuesto. Por ejemplo, la estructura mostrada en el **Ejemplo 1**:

(±) 

indica que el compuesto del título está presente como una mezcla racémica de los dos enantiómeros siguientes:



Los ejemplos son ilustrativos y no debe interpretarse que limitan el alcance de la invención, tal como se define en las reivindicaciones.

Intermedio 1

Ácido 2-((2*R*,6*S*)-2,6-dimetilmorfolin-4-il)-3,4-difluorobenzoico

A una solución agitada de ácido 2,3,4-trifluorobenzoico (25,0 g, 142 mmol) en THF (250 mL), se agregó bis(trimetilsilil)amida de litio (1M en THF, 156 mL, 156 mmol) a -78 °C en atmósfera de nitrógeno y la solución se agitó durante 45 min. A esto se agregó una solución mezclada previamente de cis-2,6-dimetilmorfolina (17,4 mL, 142 mmol) y bis(trimetilsilil)amida de litio (1M en THF, 156 mL, 156 mmol) (que se agitó durante 45 minutos a -78 °C, antes de la adición) y se continuó agitando durante 1 h a -78 °C. Se llevó hasta temperatura ambiente y se continuó agitando durante 12 horas más. Los disolventes se evaporaron y el residuo se disolvió en acetato de etilo, que se lavó con HCl 1N, agua y salmuera. La capa orgánica se secó y se concentró para proporcionar el compuesto del título como un semi-sólido. Rendimiento: 27,5 g, (72 %).

MS (ES) $M+H^+$: 271,2 para $C_{13}H_{15}F_2NO_3$

^1H RMN (400 MHz – $CDCl_3$) δ: 1,2 (s, 6H), 2,9 (d, 2H), 3,1 (d, 2H), 3,9 (m, 2H), 7,2 (s, 1H), 7,3 (t, 1H), 8,1 (m, 1H).

Intermedio 2

[2-((2*R*,6*S*)-2,6-dimetilmorfolin-4-il)-3,4-difluorofenil]metanol

A una solución agitada y enfriada con un baño de hielo de ácido 2-((2*R*,6*S*)-2,6-dimetilmorfolin-4-il)-3,4-difluorobenzoico (**Intermedio 1,** 27,0 g, 99,6 mmol) en THF (250 mL) se agregó borohidruro de sodio (12,56 g, 358,6 mmol) en pequeñas porciones, seguido por yodo (32,5 g, 139,4 mmol) en THF (250 mL). La adición se llevó a cabo de forma tal que la temperatura se mantuvo por debajo de 10 °C. La mezcla se llevó hasta temperatura ambiente y se sometió a reflujo durante 12 horas. Se enfrió y luego se detuvo con metanol (250 mL). Los disolventes se evaporaron y el residuo se trató con NaOH 2M (500 mL) durante 2 horas. La capa acuosa se extrajo con acetato de etilo (3x 150 mL) y las fases orgánicas combinadas se lavaron con agua y salmuera antes de secarse (Na_2SO_4) y concentrarse para proporcionar el compuesto del título como un sólido gomoso. MS (ES) MH^+: 257,2 para $C_{13}H_{17}F_2NO_2$

^1H RMN (400 MHz, $CDCl_3$) δ: 1,24 (s, 6H), 3,0 (d, 3H), 3,1 (d, 2H), 3,9 (m, 2H), 4,78 (s, 2H), 6,9 (d, 1H), 7,0 (t, 1H).

Intermedio 3

(2*R*,6*S*)-4-[6-({[*terc*-butil(difenil)silil]oxi}metil)-2,3-difluorofenil]-2,6-dimetilmorfolina

A una solución enfriada con hielo y agitada de [2-((2*R*,6*S*)-2,6-dimetilmorfolin-4-il)-3,4-difluorofenil]metanol (**Intermedio 2,** 27,0 g, 105 mmol) en CH_2Cl_2 se agregó imidazol (8,5 g, 126 mmol) y luego *t*-butil clorodifenilsilano (30 mL, 115 mmol) durante un período de 15 min. La mezcla se llevó hasta temperatura ambiente y se agitó durante 12 h, en este período de tiempo la TLC mostró la desaparición del material de partida. La mezcla de reacción se diluyó con CH_2Cl_2 y se lavó sucesivamente con HCl 1 N (1x 250mL), agua y salmuera. La capa orgánica se secó (Na_2SO_4), se filtró y se concentró. El residuo se purificó en una columna instantánea de gel de sílice utilizando un gradiente de acetato de etilo en éter de pet. para proporcionar el compuesto del título como un sólido blanco. Rendimiento: 45 g (94 %).

MS (ES) MH^+: 495,6 para $C_{29}H_{35}F_2NO_2Si$

^{1}H RMN (400 MHz, $CDCl_3$) δ: 1,1 (s, 15H), 2,6 (d, 2H), 2,8 (m, 2H), 3,5 (t, 2H), 4,7 (s, 2H), 7,0 (c, 1H); 7,3 (t, 1H), 7,4 (m, 10H).

Intermedio 4

5-(*terc*-butildifenilsilaniloximetil)-4-((2*R*,6*S*)-2,6-dimetilmorfolin-4-il)-2,3-difluoro-benzaldehído

A una solución agitada de (2*R*,6*S*)-4-[6-({[*terc*-butil(difenil)silil]oxi}metil)-2,3-difluorofenil]-2,6-dimetilmorfolina (**Intermedio 3,** 15,0 g, 30,0 mmol) en THF (150 mL) se agregó *sec*-butillitio (1,4 M en ciclohexano, 66,4 mL, 93 mmol) a -78 °C en una atmósfera de nitrógeno. Después de agitar durante 1 h a esta temperatura, se agregó gota a gota DMF (3,4 mL, 45 mmol) de forma tal que la temperatura se mantuvo por debajo de -60 °C. Después de agitar durante ½ h, la mezcla de reacción se trató con solución acuosa saturada de NH_4Cl y la capa acuosa se extrajo con EtOAc (2 X 100 mL). Las fases orgánicas combinadas se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo se purificó en una columna instantánea de gel de sílice utilizando un gradiente de acetato de etilo en éter de pet. para proporcionar el compuesto del título como un sólido amarillo.

MS (ES) MH^+: 523,6 para $C_{30}H_{35}F_2NO_3Si$

^{1}H RMN (400 MHz – $CDCl_3$) δ: 1,1 (s, 15H), 2,8 (m, 4H), 3,4 (m, 2H), 4,6 (s, 2H), 7,3 (t, 4H), 7,4 (t, 2H), 7,6 (d, 4H), 7,8 (s, 1H), 10,2 (s, 1H).

Intermedio 5

1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}-*N*-hidroximetanimina

A una solución enfriada con baño de hielo y agitada de 5-(*terc*-butildifenilsilaniloximetil)-4-((2*R*,6*S*)-2,6-dimetilmorfolin-4-il)-2,3-difluorobenzaldehído (**Intermedio 4,** 9,1 g, 17 mmol) en THF se agregó DIPEA (4,5 mL, 26 mmol) y luego clorhidrato de hidroxilamina (1,3 g, 19 mmol) durante un período de 15 min. La mezcla se llevó hasta temperatura ambiente y se agitó durante 12 horas. La mezcla de reacción se diluyó con CH_2Cl_2 y se lavó sucesivamente con HCl 1 N (1x 250mL), agua y salmuera. La capa orgánica se secó (Na_2SO_4), se filtró y se concentró. El residuo se purificó en una columna instantánea de gel de sílice utilizando un gradiente de acetato de etilo

en éter de pet. para proporcionar el compuesto del título como un sólido blanco. Rendimiento: 8,9 g, (86 %).

MS (ES) MH^+: 539,6 para $C_{30}H_{36}F_2N_2O_3Si$

Intermedio 6

5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorobenzonitrilo

Una mezcla de (*E*)-1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}-*N*-hidroximetanimina (**Intermedio 5**, 8,0 g, 14,8 mmol) y anhídrido acético (10 mL) se agitó a 130 °C durante 12 horas. La mezcla de reacción se enfrió hasta alcanzar temperatura ambiente y se concentró y el residuo se purificó en una columna instantánea de gel de sílice utilizando un gradiente de acetato de etilo en éter de pet. para proporcionar el compuesto del título como un sólido amarillo. Rendimiento: 6,5 g (85 %).

MS (ES) MH^+: 521,2 para $C_{30}H_{34}F_2N_2O_2Si$

^1H RMN (300 MHz,$CDCl_3$) δ: 1,1 (s, 6H), 1,3 (s, 9H), 2,8 (d, 2H), 2,9 (m, 2H), 3,5 (d, 2H), 4,7 (s, 2H), 7,3 (s, 1H), 7,4 (s, 1H), 7,6 (d, 1H).

Intermedio 7

{3-amino-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-1,2-bencisoxazol-5-il}metanol

A una solución enfriada con baño de hielo y agitada de 5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorobenzonitrilo (**Intermedio 6,** 500 mg, 0,96 mmol) en DMF se agregó *t*-BuOK (161 mg, 1,4 mmol) y luego ácido acetohidroxámico (108 mg, 1,4 mmol). La mezcla se llevó hasta temperatura ambiente y se agitó durante 12 horas. La mezcla de reacción se diluyó con EtOAc y se lavó sucesivamente con HCl 1 N (1x 250mL), agua y salmuera. La capa orgánica se secó (Na_2SO_4), se filtró y se concentró. El residuo se purificó en columna instantánea de gel de sílice utilizando un gradiente de acetato de etilo en éter de pet. para proporcionar el compuesto del título como un sólido blanco. Rendimiento: 200 mg (70 %).

MS (ES) MH^+: 296,6 para $C_{14}H_{18}FN_3O_3$

^1H RMN (400 MHz, $CDCl_3$) δ: 1,1 (s, 6H), 2,8 (d, 2H), 2,9 (m, 2H), 3,6 (t, 2H), 4,7 (s, 2H), 5,3 (t, 1H), 6,5 (s, 2H), 7,8 (d, 1H).

Intermedio 8

3-amino-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-1,2-bencisoxazol-5-carbaldehído

A una solución enfriada con hielo de {3-amino-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-1,2-bencisoxazol-5-il}metanol (**Intermedio 7**, 200 mg, 0,67 mmol) en una mezcla de CH_2Cl_2/CH_3CN (4 mL, 1:1 v/v) se agregó NMO (119 mg, 1,0 mmol) y luego TPAP (23 mg, 0,06 mmol) y la mezcla se agitó durante 2 h a temperatura ambiente. La mezcla de reacción se filtró a través de un lecho de sílice y se lavó con EtOAc. La fase orgánica se concentró a presión reducida para proporcionar el compuesto del título como un sólido amarillo. Rendimiento: 100 mg (50 %).

MS (ES) MH^+: 294,6 para $C_{14}H_{16}FN_3O_3$

Intermedio 9

1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}etanona

A una solución agitada de (2*R*,6*S*)-4-[6-({[*terc*-butil(difenil)silil]oxi}metil)-2,3-difluorofenil]-2,6-dimetilmorfolina (**Intermedio 3,** 15,0 g, 30,0 mmol) en THF (150 mL) se agregó *sec*-butillitio (1,4 M en ciclohexano, 66,4 mL, 93 mmol) a -78 °C en una atmósfera de nitrógeno. Después de agitar durante 1 h, se agregó *N*-metoxi-*N*-metilacetamida (3,4 mL, 45 mmol) y, después de agitar durante ½ h a -78 °C, se dejó que la solución alcanzara la temperatura ambiente y la agitación continuó durante 12 horas. La mezcla de reacción se trató con solución acuosa saturada de NH_4Cl y la capa acuosa se extrajo con EtOAc (2 X 100 mL). Las fases orgánicas se combinaron, se secaron (Na_2SO_4) y se concentraron. El residuo se purificó en una columna instantánea de gel de sílice utilizando un gradiente de acetato de etilo en éter de pet. para proporcionar el compuesto del título como un sólido amarillo. Rendimiento: 13,2 g (82%)

MS (ES) MH^+: 538,6 para $C_{31}H_{37}F_2NO_3Si$

^1H RMN (400 MHz, $CDCl_3$) δ: 1,1 (s, 15H), 2,8 (m, 4H), 3,4 (m, 2H), 4,6 (s, 2H), 7,3 (t, 4H), 7,4 (t, 2H), 7,6 (d, 4H), 7,8 (s, 1H), 10,2 (s, 1H).

Intermedio 10

1-[4-((2*R*,6*S*)-2,6-dimetilmorfolin-4-il)-2,3-difluoro-5-hidroximetilfenil]etanona

Una mezcla de 1-[5-(*terc*-butildifenilsilaniloximetil)-4-((2*R*,6*S*)-2,6-dimetilmorfolin-4-il)-2,3-difluorofenil]etanona (**Intermedio 9,** 7,2 g, 28 mmol) y HCl 4N en dioxano seco (75 mL) se agitó a temperatura ambiente durante 12 horas. La mezcla de reacción se trató con agua fría (20 mL) y se extrajo con acetato de etilo (3 x 50 mL). Las fases orgánicas combinadas se secaron (Na_2SO_4) y se concentraron. El residuo se purificó en una columna instantánea de gel de sílice utilizando un gradiente de acetato de etilo en éter de pet. para proporcionar el compuesto del título como un sólido amarillo. Rendimiento: 3,4 g (42%).

MS (ES) MH^+: 300 para $C_{15}H_{19}F_2NO_3$

^{1}H RMN (400 MHz, $CDCl_3$) δ: 1,1 (s, 15H), 2,5 (d, 2H), 2,7 (t, 2H), 2,8 (s, 2H), 4,7 (s, 2H), 5,2 (t, 1H), 7,3 (t, 1H), 7,4 (s, 10H).

Intermedio 11

5-acetil-2-((2*R*,6*S*)-2,6-dimetilmorfolin-4-il)-3,4-difluorobenzaldehído

A una solución enfriada con hielo de 1-[4-((2*R*,6*S*)-2,6-dimetilmorfolin-4-il)-2,3-difluoro-5-hidroximetilfenil]etanona (**Intermedio 10,** 3,2 g, 9,72 mmol) en una mezcla de CH_2Cl_2/CH_3CN (20 mL, 1:1 v/v) se agregó NMO (2,2 g, 19,44 mmol) y luego TPAP (340 mg, 0,97 mmol) y la mezcla se agitó durante 2 horas a temperatura ambiente. La mezcla de reacción se filtró a través de un lecho de sílice y se lavó con EtOAc. La fase orgánica se concentró a presión reducida para proporcionar el compuesto del título como un sólido cristalino amarillo. Rendimiento: 3,0 g (94%).

MS(ES) MH^+: 298,2 para $C_{15}H_{17}F_2NO_3$

^{1}H RMN (400 MHz, $CDCl_3$): δ 1,2 (d, 6H), 2,1 (s, 3H), 3,0 (d, 2H), 3,1 (t, 2H), 3,8 (s, 2H), 5,1 (s, 2H), 7,6 (t, 1H), 10,2 (s, 1H).

Intermedio 12

(2*R*,4*S*,4a*S*)-rel-8-acetil-9,10-difluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

A una solución de 5-acetil-2-((2*R*,6*S*)-2,6-dimetilmorfolin-4-il)-3,4-difluorobenzaldehído (**Intermedio 11,** 3,0 g, 9,17 mmol) en IPA se agregó ácido barbitúrico (1,4 g, 11,00 mmol) y la mezcla se calentó a 85°C durante 12 horas. Los disolventes se evaporaron y el residuo se purificó sobre alúmina neutra utilizando un gradiente de metanol en CH_2Cl_2 para proporcionar el

compuesto del título como una mezcla racémica en forma de un sólido blanquecino.
Rendimiento: 3,0 g (75%).
MS (ES) MH^+: 408,2 para $C_{19}H_{19}F_2N_3O_5$
^1H RMN (400 MHz – DMSO-d_6) δ: 0,8 (d, 3H), 1,1 (d, 3H), 2,1 (s, 3H), 2,8 (d, 1H), 3,0 (t, 1H), 3,5 (d, 1H), 3,6 (m, 1H), 3,7 (d, 1H), 3,9 (d, 1H), 4,1 (d, 1H), 7,2 (d, 1H), 11,5 (s, 1H), 11,8 (s, 1H).

Los **Intermedios 13** a **15** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 12**. Cada uno se obtuvo como una mezcla racémica.

Intermedio 13

(2*R*,4*S*,4a*S*)-rel-9,10-difluoro-2,4-dimetil-8-(fenilcarbonil)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

Material de partida: 2-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3,4-difluoro-5-(fenilcarbonil)benzaldehído (**Intermedio 26**).
MS(ES)MH^+: 470,2 para $C_{24}H_{21}F_2N_3O_5$
^1H RMN (400 MHz, DMSO-d_6) δ: 0,8 (d, 3H), 1,1 (d, 3H), 2,9 (d, 1H), 3,1 (t, 1H), 3,6 (m, 2H), 3,8 (m, 1H), 3,9 (d, 1H), 4,1 (d, 1H), 7,1 (d, 1H), 7,5 (m, 2H), 7,6 (m, 3H), 11,5 (s, 1H), 11,8 (s, 1H).

Intermedio 14

(2*R*,4*S*,4a*S*)-rel-9,10-difluoro-2,4-dimetil-8-(piridin-2-ilcarbonil)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

Material de partida: 2-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3,4-difluoro-5-(piridin-2-ilcarbonil)benzaldehído (**Intermedio 27**).
MS (ES) MH^+: 471,2 para $C_{23}H_{20}F_2N_4O_5$

Intermedio 15

(2*R*,4*S*,4a*S*)-rel-8-(ciclopropilcarbonil)-9,10-difluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

Material de partida: 5-(Ciclopropilcarbonil)-2-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3,4-difluorobenzaldehído (**Intermedio 28**).

MS (ES) MH^+: 434,1 para $C_{21}H_{21}F_2N_3O_5$

Intermedio 16

(2*R*,4*S*,4a*S*)-rel-9,10-difluoro-8-[(1*E*)-*N*-hidroxietanimidoil]-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

A una solución de (2*R*,4*S*,4a*S*)-rel-8-acetil-9,10-difluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona (**Intermedio 12,** 250 mg, 0,63 mmol) en MeOH, se agregó clorhidrato de hidroxilamina (88 mg, 1,3 mmol) y la mezcla se calentó hasta alcanzar 85 °C durante 12 horas. Después de enfriar hasta alcanzar temperatura ambiente, el disolvente se eliminó y el residuo se purificó mediante HPLC de fase normal (95:5: Hexano:IPA) para proporcionar el compuesto del título como una mezcla racémica en forma de un sólido amarillo claro. Rendimiento: 50 mg (20%).

MS (ES) MH^+: 423,2 para $C_{19}H_{20}F_2N_4O_5$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 2,0 (d, 3H), 2,8 (d, 1H), 3,0 (t, 1H), 3,3 (d, 1H), 3,6 (d, 1H), 3,7 (t, 1H), 3,8 (t, 1H), 4,0 (d, 1H), 4,1 (d, 2H), 6,8 (d, 1H), 11,1 (s, 1H), 11,4 (s, 1H), 11,8 (s, 1H).

Intermedio 17

{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(fenil)metanol

A una solución agitada de (2*R*,6*S*)-4-[6-({[*terc*-butil(difenil)silil]oxi}metil)-2,3-difluorofenil]-2,6-dimetilmorfolina (**Intermedio 3,** 1 g, 2,0 mmol) en THF anhidro (10 mL), se agregó *s*-butillitio (4,5 mL, 1,4 M en ciclohexano, 6,3 mmol) y se agitó durante 2 h a -78 °C. Se agregó gota a gota benzaldehído (685 mg, 0,0064 mmol) en THF (5 mL) y la solución se agitó durante 1 h más. La mezcla de reacción se detuvo con una solución de cloruro de amonio saturado y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se secó (Na_2SO_4) y el disolvente se eliminó. El residuo se purificó en una columna de cromatografía en gel sílice utilizando un gradiente de acetato de etilo-éter de pet. para proporcionar el compuesto del título. Rendimiento: 1,1 g (92%)

MS (ES) MH^+: 602,2 para $C_{36}H_{41}F_2NO_3Si$

Los **Intermedios 18** a **19** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 17**. Cada uno se obtuvo como una mezcla racémica.

Intermedio 18

{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(piridin-2-il)metanol

Material de partida: (2*R*,6*S*)-4-[6-({[*terc*-butil(difenil)silil]oxi}metil)-2,3-difluorofenil]-2,6-dimetilmorfolina (**Intermedio 3**) y piridin-2-carboxaldehído.

MS (ES) MH^+: 603,2 para $C_{35}H_{40}F_2N_2O_3Si$

Intermedio 19

{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(ciclopropil)metanol

Material de partida: (2*R*,6*S*)-4-[6-({[*terc*-butil(difenil)silil]oxi}metil)-2,3-difluorofenil]-2,6-dimetilmorfolina (**Intermedio 3**) y ciclopropilcarboxaldehído.

MS (ES) MH^+: 566,2 para $C_{33}H_{41}F_2NO_3Si$

Intermedio 20

{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(fenil)metanona

Se agregaron NMO (428 mg, 0,0037 mmol) y TPAP (65 mg, 0,0002 mmol) a una solución agitada de {5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(fenil)metanol (**Intermedio 17,** 1,1 g, 0,002 mmol) en CH_2Cl_2:CH_3CN (1:1, 10 mL) 0 °C. La mezcla se dejó entibiar hasta alcanzar la temperatura ambiente agitando durante 12 horas. Los disolventes se eliminaron y el residuo se purificó en una columna de cromatografía en gel sílice utilizando un gradiente de acetato de etilo-éter de pet., para proporcionar el compuesto del título. Rendimiento: 1 g (92 %)

MS (ES) MH^+: 600,2 para $C_{36}H_{39}F_2NO_3Si$

Intermedio 21

{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(piridin-2-il)metanona

Se agregó PCC (1,07 g, 0,005 mmol) a una solución de {5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(piridin-2-il)metanol (**Intermedio 18**, 1,8 g, 0,002 mmol) en DMC anhidro (15 mL) a 0 °C y la mezcla se dejó agitar durante 1h a temperatura ambiente. La mezcla de reacción se filtró y los disolventes se eliminaron al vacío y el residuo se purificó en una columna de cromatografía en gel de sílice utilizando un gradiente de acetato de etilo-éter de pet., para proporcionar el compuesto del título. Rendimiento: 1,5 g (83 %). MS (ES) MH^+: 603,2 para $C_{35}H_{40}F_2N_2O_3Si$

El **Intermedio 22** se preparó a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 21**.

Intermedio 22

{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(ciclopropil)metanona

Material de partida: {5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(ciclopropil)metanol (**Intermedio 19**).

MS (ES) MH^+: 564,2 para $C_{33}H_{39}F_2NO_3Si$

Intermedio 23

{4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluoro-5-(hidroximetil)fenil}(fenil)metanona

Se agregó en pequeñas porciones fluoruro de *terc*-butilamonio (435 mg, 0,002 mmol) a una solución agitada de {5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(fenil)metanona (**Intermedio 20,** 1 g, 0,002 mmol) en THF anhidro (10 mL) a 0 °C y se continuó agitando durante 1h entibiando hasta alcanzar la temperatura ambiente. El disolvente se eliminó y el residuo se purificó en una columna de cromatografía en gel sílice

utilizando un gradiente de acetato de etilo-éter de pet., para proporcionar el compuesto del título.
Rendimiento: 450 mg (75%)
MS (ES) MH^+: 362,2 para $C_{20}H_{21}F_2NO_3$

Los **Intermedios 24** y **25** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 23**.

Intermedio 24

{4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluoro-5-(hidroximetil)fenil}(piridin-2-il)metanona

Material de partida: {5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(piridin-2-il)metanol (**Intermedio 18**).
MS (ES) MH^+: 363,2 para $C_{19}H_{20}F_2N_2O_3$

Intermedio 25

ciclopropil{4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluoro-5-(hidroximetil)fenil}metanona

Material de partida: {5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(ciclopropil)metanona (**Intermedio 22**).
MS (ES) MH^+: 326,2 para $C_{17}H_{21}F_2NO_3$

Intermedio 26

2-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3,4-difluoro-5-(fenilcarbonil)benzaldehído

Se agregaron NMO (295 mg, 0,0025 mmol) y TPAP (44 mg, 0,0001 mmol) a una solución agitada de {4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluoro-5-(hidroximetil)fenil}(fenil)metanona (**Intermedio 23,** 450 mg, 0,001 mmol) en CH_2Cl_2:CH_3CN anhidro (1:1, 10 mL) a 0 °C y la mezcla se agitó durante 12 horas entibiando hasta alcanzar temperatura ambiente. Los disolventes se eliminaron y el residuo se purificó en una columna de cromatografía en gel sílice utilizando un gradiente de acetato de etilo-éter de pet., para proporcionar el compuesto del título. Rendimiento: 340 mg (76 %)
MS (ES) MH^+: 360,2 para $C_{20}H_{19}F_2NO_3$

Intermedio 27

2-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3,4-difluoro-5-(piridin-2-ilcarbonil)benzaldehído

Se agregó PCC (297 mg, 0,002 mmol) a una solución de {4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluoro-5-(hidroximetil)fenil}(piridin-2-il)metanona (**Intermedio 24**, 500 mg, 0,001 mmol) en CH_2Cl_2 anhidro (5 mL), a 0 °C y la mezcla se agitó entibiando hasta alcanzar temperatura ambiente durante 1h. La mezcla de reacción se filtró, los disolventes se eliminaron y el residuo se purificó en una columna de cromatografía en gel de sílice utilizando un gradiente de acetato de etilo-éter de pet., para proporcionar el compuesto del título. Rendimiento: 350 mg (70 %).

MS (ES) MH^+: 361,2 para $C_{19}H_{18}F_2N_2O_3$

El **Intermedio 28** se preparó a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 27**.

Intermedio 28

5-(ciclopropilcarbonil)-2-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3,4-difluorobenzaldehído

Material de partida: ciclopropil{4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluoro-5-(hidroximetil)fenil}metanona (**Intermedio 25**).

MS (ES) MH^+: 324,2 para $C_{17}H_{19}F_2NO_3$

Intermedio 29

(2*R*,4*S*,4a*S*)-rel-9,10-difluoro-8-[(*E*)-(hidroxiimino)(fenil)metil]-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

Se agregó clorhidrato de hidroxilamina (77 mg, 0,001 mmol) a una solución de (2*R*,4*S*,4a*S*)-rel-9,10-difluoro-2,4-dimetil-8-(fenilcarbonil)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona (**Intermedio 13,** 280 mg, 0,6 mmol) en metanol:piridina (1:1, 3 mL) y la solución se calentó hasta alcanzar 90 °C durante 12 horas. Los disolventes se eliminaron y el residuo se sometió a cromatografía en columna de gel de sílice utilizando un gradiente de acetato de etilo en éter de pet. para proporcionar el compuesto del título como una mezcla racémica. Rendimiento: 120 mg (42 %).

MS (ES) MH^+: 485,2 para $C_{24}H_{22}F_2N_4O_5$

^{1}H RMN (400 MHz – DMSO-d_6) δ: 0,8 (d, 3H), 1,2 (d, 3H), 2,8 (d, 1H), 3,0 (m, 1H), 3,4 (d, 1H), 3,6 (m, 1H), 3,7 (m, 1H), 3,8 (d, 1H), 4,0 (d, 1H), 6,6 (d, 1H), 7,4 (s, 5H), 11,5 (s, 2H).

Los **Intermedios 30** y **31** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 29**. Cada uno se obtuvo como una mezcla racémica.

Intermedio 30

(2*R*,4*S*,4a*S*)-rel-9,10-difluoro-8-[(*Z*)-(hidroxiimino)(piridin-2-il)metil]-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

Material de partida: (2*R*,4*S*,4a*S*)-rel-9,10-Difluoro-2,4-dimetil-8-(piridin-2-ilcarbonil)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona (**Intermedio 1H**).

MS (ES) MH^+: 486,3 para $C_{23}H_{21}F_2N_5O_5$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,8 (d, 3H), 1,1 (d, 3H), 2,9 (d, 1H), 3,0 (m, 1H), 3,4 (d, 1H), 3,6 (m, 1H), 3,7 (m, 1H), 3,8 (d, 1H), 4,0 (d, 1H), 6,65 (d, 1H), 7,3 (m, 1H), 7,8 (m, 2H), 8,4 (d, 1H), 11,5 (s, 1H), 11,8 (s, 1H), 11,8 (d, 1H).

Intermedio 31

(2*R*,4*S*,4a*S*)-rel-8-[(*E*)-ciclopropil(hidroxiimino)metil]-9,10-difluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

Material de partida: (2*R*,4*S*,4a*S*)-rel-8-(Ciclopropilcarbonil)-9,10-difluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona (**Intermedio 15**).

MS (ES) MH^+: 449,1 para $C_{21}H_{22}F_2N_4O_5$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,3 (m, 1H), 0,8 (d, 2H), 0,85 (d, 3H), 1,1 (d, 3H), 2,3 (m, 1H), 2,9 (d, 1H), 3,0 (m, 1H), 3,3 (m, 1H), 3,6 (m, 1H), 3,7 (m, 1H), 3,8 (d, 1H), 4,0 (d, 1H), 6,55 (d, 1H), 11,1 (s, 3H).

Intermedio 32

1-(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoro-2-(propan-2-ilidenoaminooxi)fenil)etanona

A una solución agitada de oxima de propan-2-ona (913 mg, 12,50 mmol) en THF (15 mL) se agregó KOtBu (935 mg, 8,33 mmol) a temperatura ambiente. Después de agitar durante 45 minutos se agregó 1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}etanona (**Intermedio 9,** 2240 mg, 4,17 mmol) disuelta en 10 mL de THF. Después de agitar durante 3 horas la reacción se detuvo con una solución saturada acuosa de cloruro de amonio y se extrajo con EtOAc. La capa orgánica se secó (Na_2SO_4), se filtró y se concentró para proporcionar el compuesto bruto del título (2,5 g). La LCMS y la RMN indicaron >90% de pureza. Se utilizó en la siguiente etapa sin purificación adicional.

MS (ES): 591 (M+H) para $C_{34}H_{43}FN_2O_4Si$

1H RMN (300 MHz, $CDCl_3$) δ ppm 1,0-1,1 (s y d, 15H), 2,0 (s, 3H), 2,1 (s, 3H), 2,5-2,95 (m, 7H), 3,3-3,6 (m, 2H), 4,7 (s, 2H), 7,3-7,5 (m, 6H), 7,55 - 7,8 (m, 5H).

Intermedio 33

(6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-metilbenzo[d]isoxazol-5-il)metanol

Una solución agitada de 1-(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoro-2-(propan-2-ilidenoaminooxi)fenil)etanona (**Intermedio 32**, 77 mg, 0,13 mmol, producto bruto de la reacción anterior) disuelta en etanol (5 mL) se trató con 5 mL de HCl acuoso al 5% a 75 °C durante 2 horas. La reacción se detuvo con una solución acuosa de bicarbonato de sodio al 10% y se extrajo con EtOAc. La capa orgánica se lavó con agua, se secó y se concentró. El residuo se purificó sobre una columna instantánea de gel de sílice (elución con 50-70% de EtOAc en hexanos) para proporcionar el compuesto del título (15 mg, 39 %).

MS (ES): 295 (M+H) para $C_{15}H_{19}FN_2O_3$

^{1}H RMN (300 MHz, $CDCl_3$) δ ppm 1,2 (d, 6H), 2,5 (s, 3H), 2,8-3,2 (m, 5H), 3,7- 3,95 (m, 2H), 4,8 (s, 2H), 7,3 (s, 1H).

Intermedio 34

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-metilbenzo[d]isoxazol-5-carbaldehído

A una solución agitada de (6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-metilbenzo[d]isoxazol-5-il)metanol (**Intermedio 33,** 0,65 g, 2,21 mmol) en CH_2Cl_2 (30 mL) se agregó MnO_2 (3,84 g, 44,17 mmol). Después de agitar durante 3 días a temperatura ambiente el MnO_2 se filtró y se lavó con CH_2Cl_2. El filtrado se concentró y se secó para proporcionar el compuesto del título (0,547 g, 85 %).

MS (ES): 293 (M+H) para $C_{15}H_{17}FN_2O_3$

^{1}H RMN (300 MHz, $CDCl_3$) δ ppm 1,2 (d, 6H) 2,6 (s, 3H) 2,9 - 3,2 (m, 4H) 3,7-4,0 (m, 2H), 7,9 (s, 1H), 10,4 (s, 1H).

Los **Intermedios 35** y **36** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 1**.

Intermedio 35

Ácido 3-cloro-2-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-4-fluorobenzoico

Materiales de partida: ácido 3-cloro-2,4-difluorobenzoico y cis-2,6-dimetilmorfolina.

MS (ES) MH^+: 288 para $C_{13}H_{15}ClFNO_3$

^{1}H RMN (400 MHz, $CDCl_3$) δ: 1,1 (d, 6H), 2,5 (d, 2H), 3,1(t, 2H), 3,4 (m, 2H), 6,9 (d, 1H), 7,0 (t, 1H), 13,2 (a, 1H).

Intermedio 36

Ácido 2-((2*R*,6*R*)-2,6-dimetilmorfolino)-3,4-difluorobenzoico

Materiales de partida: ácido 2,3,4-trifluorobenzoico y (2*R*,6*R*)-2,6-dimetilmorfolina (BASF).

MS (ES) MH^+: 272 para $C_{13}H_{15}F_2NO_3$

^{1}H RMN (300 MHz, $CDCl_3$) δ: 1,17 (d, 6H), 2,84 (dd, 2H), 3,20 (d, 2H), 3,86-4,19 (m, 2H), 7,14-7,40 (m, 1H), 7,44-7,61 (m, 1H), 14,14 (s, 1H).

Los **Intermedios 37** y **38** se prepararon a partir de los materiales de partida, I_2 y $NaBH_4$ utilizando un método similar al descrito para la síntesis del **Intermedio 2**.

Intermedio 37

{3-cloro-2-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-4-fluorofenil}metanol

Material de partida: ácido 3-cloro-2-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-4-fluorobenzoico (**Intermedio 35**).

MS (ES) MH^+: 274 para $C_{13}H_{17}ClFNO_2$

^1H RMN (400 MHz, $CDCl_3$) δ: 1,1 (d, 6H), 2,5 (d, 2H), 3,1(t, 2H), 3,4 (m, 2H), 4,78 (s, 2H), 6,9 (d, 1H), 7,0 (t, 1H).

Intermedio 38

(2-((2*R*,6*R*)-2,6-dimetilmorfolino)-3,4-difluorofenil)metanol

Material de partida: ácido 2-((2*R*,6*R*)-2,6-dimetilmorfolino)-3,4-difluorobenzoico (**Intermedio 36**).

MS (ES) MH^+: 258 para $C_{13}H_{17}F_2NO_2$

^1H RMN (300 MHz, $CDCl_3$) δ: ppm 1,32 (d, 6H), 2,73-3,41 (m, 4H), 4,00-4,29 (m, 2H), 4,60-4,89 (m, 2H), 6,78-7,19 (m, 2H).

Intermedio 39

1-(dimetoximetil)-2,3,4-trifluorobenceno

Una solución de 2,3,4-trifluorobenzaldehído (25 g, 156,16 mmol), 2,2-dimetoxipropano (58,1 mL, 468,48 mmol) y ácido 4-metilbencenosulfónico (0,269 g, 1,56 mmol) se agitó a temperatura ambiente durante toda la noche. La mezcla de reacción se diluyó con éter y se lavó sucesivamente con solución de bicarbonato de sodio ac., agua y salmuera. La capa orgánica se secó sobre sulfato de sodio y se concentró. El residuo se destiló al alto vacío para proporcionar el compuesto del título (23,07 g, 71,7 %).

^1H RMN (300 MHz, $CDCl_3$) δ: 3,36 (s, 6H), 5,54 (s, 1H), 6,8-7,1 (m, 1H), 7,1-7,4 (m, 1H).

Intermedio 40

Ácido 3-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-fluoropicolínico

Una solución de ácido 3,5-difluoropicolínico (20,5 g, 128,86 mmol), cis-2,6-dimetilmorfolina (63,5 mL, 515,43 mmol) y DIEA (45,0 mL, 257,72 mmol) en THF (200 mL) se agitó a temperatura ambiente durante 3 días. La mezcla se diluyó con EtOAc y se extrajo 3 veces con Na_2CO_3 acuoso. La capa acuosa se acidificó con HCl 1N para llevar el pH a aproximadamente 3 y luego se saturó con NaCl antes de extraerse 10 veces con EtOAc. Las capas de EtOAc se

secaron ($MgSO_4$) y el disolvente se eliminó para proporcionar 33,5 g del producto como un sólido.

MS (ES) $(M-H)^-$: 253 para $C_{12}H_{15}FN_2O_3$

^1H RMN (DMSO-d^6): 1,1 (d, 6H), 2,5 (m, 2H), 3,2 (d, 2H), 3,7 (m, 2H), 7,5 (d, 1H), 8,1 (s, 1H), 13,3 (s, ancho, 1H).

Intermedio 41

(3-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-fluoropiridin-2-il)metanol

Se agregó cloroformiato de etilo (4,04 mL, 42,05 mmol) a una solución de ácido 3-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-fluoropicolínico (**Intermedio 40,** 8,91 g, 35,04 mmol) y TEA (5,86 mL, 42,05 mmol) enfriado en un baño de agua helada. Después de completar la adición, la mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente con agitación durante 1 hora. Se agregó en porciones borohidruro de litio (1,985 g, 91,11 mmol) y la mezcla se agitó durante 1 hora. La mezcla se detuvo primero con agua y luego con HCl 1N. Luego se recogió con EtOAc y Na_2CO_3 acuoso. La capa orgánica se separó y se lavó con salmuera. Las capas acuosas combinadas se extrajeron con EtOAc 3 veces, y cada extracto se lavó con salmuera. Las capas de EtOAc combinadas se secaron ($MgSO_4$) y se concentraron para proporcionar un aceite que solidificó lentamente. El residuo se recristalizó a partir de ciclohexano para proporcionar un producto como un sólido blanco. Las aguas madres se concentraron y el residuo se cromatografió en gel de sílice (100% de CH_2Cl_2 seguido por elución en gradiente a 50% de EtOAc en CH_2Cl_2) para proporcionar un producto adicional como un sólido blanco. Rendimiento total de 5,6 g.

MS (ES) MH^+: 241 para $C_{12}H_{17}FN_2O_2$

^1H RMN (DMSO-d^6): 1,1 (d, 6H), 2,4 (t, 2H), 3,1 (d, 2H), 3,7-3,8 (m, 2H), 4,5 (d, 2H), 5,1 (t, 1H), 7,4 (d, 1H), 8,2 (s, 1H).

Los **Intermedios 42** a **44** se prepararon a partir del material de partida indicado y difenilsilano de *t*-butil cloro utilizando un método similar al descrito para la síntesis del **Intermedio 3**:

Intermedio 42

(2*R*,6*S*)-4-[6-({[*terc*-butil(difenil)silil]oxi}metil)-2-cloro-3-fluorofenil]-2,6-dimetilmorfolina

Material de partida: {3-cloro-2-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-4-fluorofenil}metanol (**Intermedio 37**).

MS (ES) MH^+: 496 para $C_{29}H_{35}F_2NO_2Si$

^1H RMN (400 MHz, $CDCl_3$) δ: 1,0 (s, 15H), 1,1(s, 9H), 2,5 (d, 2H), 3,1 (t, 2H), 3,4 (m, 2H); 4,7 (s, 2H), 7,0 (t, 1H), 7,3 (t, 1H), 7,4 (m, 10H).

Intermedio 43

(2*R*,6*R*)-4-(6-((*terc*-butildifenilsililoxi)metil)-2,3-difluorofenil)-2,6-dimetilmorfolina

Material de partida: (2-((2*R*,6*R*)-2,6-dimetilmorfolino)-3,4-difluorofenil)metanol (**Intermedio 38**).

MS (ES) MH^+: 496 para $C_{29}H_{35}F_2NO_2Si$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,04 (d, 6H) 1,09 (s, 9H), 2,44-2,77 (m, 2H), 2,82-3,15 (m, 2H), 3,72-4,03 (m, 2H), 4,62-4,93 (m, 2H), 6,91-7,12 (m, 1H), 7,29-7,52 (m, 7H), 7,57-7,76 (m, 4H).

Intermedio 44

(2*R*,6*S*)-4-(2-((*terc*-butildifenilsililoxi)metil)-5-fluoropiridin-3-il)-2,6-dimetilmorfolina

Material de partida: (3-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-fluoropiridin-2-il)metanol (**Intermedio 41**).

MS (ES) MH^+: 479 para $C_{28}H_{35}FNO_2Si$

^1H RMN ($CDCl_3$): δ 1,0 (s, 9H), 1,15 (d, 6H, 2,4 (t, 2H), 3,0 (d, 2H), 3,6-3,7 (m, 2H), 4,8 (s, 2H), 7,0 (d, 1H), 7,4 (m, 6H), 7,7 (m, 4H), 8,2 (s, 1H).

Intermedio 45

(2*R*,6*S*)-4-(2-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-fluoropiridin-3-il)-2,6-dimetilmorfolina

Una solución de diisopropilamina (3,51 mL, 24,65 mmol) en THF (30 mL) se enfrió en un baño de hielo seco-acetona. Una solución de n-butillitio (2,5 M en hexanos, 9,28 mL, 23,20 mmol) se agregó y la mezcla se entibió hasta alcanzar 0 °C y se enfrió nuevamente en un baño de hielo seco-acetona. La solución se agregó a una segunda solución de (2*R*,6*S*)-4-(2-((*terc*-butildifenilsililoxi)metil)-5-fluoropiridin-3-il)-2,6-dimetilmorfolina (**Intermedio 44**, 6,94 g, 14,50 mmol) en THF (30 mL) enfriada en un baño de hielo seco-acetona. La mezcla se agitó durante 45 minutos antes de que la solución se transfiriera a través de una cánula a una solución

de hexacloroetano (2,79 mL, 24,65 mmol) en 60 mL de THF también enfriada en un baño de hielo seco-acetona. La mezcla se dejó entibiar hasta alcanzar la temperatura ambiente antes de diluirse con EtOAc y lavarse con agua y salmuera. Las capas acuosas combinadas se extrajeron nuevamente con EtOAc, que se lavó con salmuera. El secado ($MgSO_4$) de los extractos combinados de EtOAc y la eliminación del disolvente proporcionó una un sólido gomoso que se cromatografió en gel de sílice (50% de hexanos en CH_2Cl_2 seguido por elución en gradiente a 100% de CH_2Cl_2) para proporcionar un producto como un aceite que solidificó lentamente (5,26 g de rendimiento). MS (ES) MH^+: 513 para $C_{28}H_{34}ClFN_2O_2Si$.

^1H RMN ($CDCl_3$): δ 1,0 (s, 9H), 1,15 (d, 6H, 2,4 (t, 2H), 3,0 (d, 2H), 3,6-3,7 (m, 2H), 4,8 (s, 2H), 7,0 (d, 1H), 7,4 (m, 6H), 7,7 (m, 4H), 8,2 (s, 1H).

Intermedio 46

Ácido 2,4-difluoro-3-metilbenzoico

A una solución agitada de diisopropilamina (1,7 g, 16,4 mmol) en THF se agregó solución de n-BuLi 2,6 M (1,1 g, 16,4 mmol) a -30 °C y la mezcla se agitó durante una hora a la misma temperatura. A esta mezcla se agregó lentamente una solución de ácido 2,4-difluorobenzoico (1,0 g, 6,3 mmol) en THF a -78 °C, seguido por yoduro de metilo (2,2 g, 15,7 mmol) y se agitó durante otras 2 h a la misma temperatura y se dejó alcanzar la temperatura ambiente. La mezcla de reacción se trató con solución acuosa saturada de NH_4Cl y la capa acuosa se extrajo con etilacetato (3 x 25 mL). Las fases orgánicas se combinaron y se secaron sobre sulfato de sodio anhidro. Después de la eliminación del disolvente, el residuo se purificó en una columna instantánea de gel de sílice utilizando un gradiente de acetato de etilo en éter de pet. para proporcionar un producto como un sólido blanco. Rendimiento: 0,77 g (70%)

MS (ES) MH^+: 172 para $C_8H_6F_2O_2$

^1H RMN (400 MHz, $CDCl_3$) δ: 2,2 (s, 3H), 7,0 (m, 1H), 7,9 (m, 1H).

Intermedio 47

3-cloro-2-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-4-fluorobenzoato de metilo

A una solución agitada de ácido 3-cloro-2-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-4-fluorobenzoico (**Intermedio 35,** 10,0 g, 34,8 mmol) en metanol (50 mL) se agregó H_2SO_4 (1 mL) concentrado y la solución se sometió a reflujo durante 12 horas. La mezcla de reacción se concentró y se diluyó

con EtOAc (100 mL). La capa orgánica se lavó con H_2O (2x 20 mL), se secó sobre sulfato de sodio anhidro y se concentró. El residuo se purificó mediante cromatografía en columna con acetato de etilo- éter de pet. para proporcionar un producto como un sólido. Rendimiento: 9,0 g (86%)

MS (ES) MH^+: 303 para $C_{14}H_{17}ClFNO_3$

Intermedio 48

terc-butildifenil(2,3,4-trifluorobenciloxi)silano

Se agregó lentamente *terc*-butilclorodifenilsilano (8,86 mL, 34 mmol) con una jeringa a una solución de (2,3,4-trifluorofenil)metanol (5,0 g, 31 mmol) e imidazol (2,53 g, 37,2 mmol) en CH_2Cl_2 (30 mL) enfriado en un baño de agua helada. La mezcla se entibió hasta alcanzar la temperatura ambiente y se agitó durante toda la noche. El disolvente se eliminó y el residuo se dividió entre Et_2O y agua. El Et_2O se separó y se lavó con salmuera y las capas acuosas combinadas se extrajeron dos veces más con Et_2O, que se lavó con salmuera. El secado ($MgSO_4$) y la eliminación del disolvente proporcionó un aceite que se cromatografió en gel de sílice (50% de CH_2Cl_2 en hexanos seguido por elución en gradiente a 100% de CH_2Cl_2) para aislar un aceite que solidificó lentamente para proporcionar 11,9 g (96%) de un sólido blanco.

^1H RMN: δ 7,7 (m, 4H), 7,4 (m, 6H), 7,3 (m, 1H), 7,0 (m, 1H), 4,8 (s, 1H), 1,1 (s, 9H).

Intermedio 49

N-metoxi-*N*,1-dimetil-1*H*-1,2,4-triazol-5-carboxamida

Una mezcla de 1-metil-1*H*-1,2,4-triazol (3,15 mL, 55,56 mmol) y cloruro metoxi(metil)carbámico (7,55 g, 61,11 mmol) en acetonitrilo (60 mL) se enfrió en un baño de agua helada antes de agregar TEA (8,52 mL, 61,11 mmol). La mezcla se dejó entibiar lentamente hasta alcanzar la temperatura ambiente y luego se agitó durante toda la noche. El material se diluyó con éter y los sólidos se filtraron y se enjuagaron bien con éter. El filtrado se concentró y el residuo se recogió con éter. Los sólidos no solubles se eliminaron por filtración y se enjuagaron bien con éter adicional. El filtrado se concentró para proporcionar un aceite que se cromatografió en gel de sílice (100% de CH_2Cl_2 seguido por elución en gradiente a 40% de

EtOAc en CH_2Cl_2) para proporcionar un producto como un aceite que solidificó lentamente. 6,13 g (65% de rendimiento).

MS ES^+ (MH): 171

^1H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 3,4 (s a, 3H) 3,9 (s, 3H) 4,1 (s a, 3H) 7,9 (s, 1H).

Intermedio 50

N-metoxi-*N*-metilpirazina-2-carboxamida

En un matraz de fondo redondo de 500 mL, se suspendió ácido pirazina-2-carboxílico (58 g, 467,37 mmol) en CH_2Cl_2 seco (250 mL): se agregó cloruro de oxalilo (50,1 mL, 560,85 mmol) junto con unas gotas de DMF y la mezcla se agitó a temperatura ambiente durante 12 horas. Se agregó N, O-dimetilclorhidrato de hidroxilamina (54,7 g, 560,85 mmol) y la mezcla resultante se enfrió hasta alcanzar 5 °C. Se agregó trietilamina (195 mL, 1402,12 mmol) mediante un embudo de goteo y la mezcla de reacción se agitó a temperatura ambiente durante 30 minutos antes de filtrarse. La torta de filtrado se lavó con EtOAc y el filtrado combinado se lavó con bicarbonato de sodio saturado y salmuera, se concentró hasta proporcionar un aceite y se secó al alto vacío para proporcionar el producto deseado (72g).

MS (ES) MH^+: 168 para $C_7H_9N_3O_2$

Intermedio 51

6-cloro-*N*-metoxi-*N*-metilpirazina-2-carboxamida

En un matraz de fondo redondo de 100 mL, ácido 6-cloropirazina-2-carboxílico (1g, 6,31 mmol) se suspendió en CH_2Cl_2 seco (30 mL). Se agregó cloruro de oxalilo (3,78 mL, 7,57 mmol) junto con unas gotas de DMF, la mezcla se agitó a temperatura ambiente durante 12 h, se agregó N, O-dimetilclorhidrato de hidroxilamina (0,800 g, 8,20 mmol), la mezcla resultante se enfrió hasta alcanzar 5 °C, se agregó TEA (2,64 mL, 18,92 mmol) mediante un embudo de goteo, la mezcla de reacción se agitó a temperatura ambiente durante 30 minutos, se filtró y la torta de filtrado se lavó con EtOAc, el filtrado combinado se lavó con bicarbonato de sodio saturado y salmuera, se concentró hasta proporcionar un aceite, se purificó en gel de sílice con Hexanos/EtOAc como disolventes para proporcionar un producto (1,06 g).

MS (ES) MH^+: 202 para $C_7H_8ClN_3O_2$

Los **Intermedios 52** a **55** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 50**:

Intermedio 52

N-metoxi-*N*-metil-5-morfolinopirazina-2-carboxamida

Material de partida: ácido 5-morfolinopirazina-2-carboxílico

MS (ES) MH^+: 253 para $C_{11}H_{16}N_4O_3$

Intermedio 53

3-cloro-*N*-metoxi-*N*-metilpirazina-2-carboxamida

Material de partida: ácido 3-cloropirazina-2-carboxílico

MS (ES) MH^+: 202 para $C_7H_8ClN_3O_2$

Intermedio 54

5-cloro-*N*-metoxi-*N*-metilpirazina-2-carboxamida

Material de partida: ácido 5-cloropirazina-2-carboxílico

Intermedio 55

N,6-dimetoxi-*N*-metilpirazina-2-carboxamida

Material de partida: ácido 6-metoxipirazina-2-carboxílico

MS (ES) MH^+: 198 para $C_8H_{11}N_3O_3$

Intermedio 56

2-(metoxi(metil)amino)-2-oxoacetato de etilo

A una solución de N,O-dimetilclorhidrato de hidroxilamina (10 g, 102,52 mmol) y etil clorooxoacetato (13,77 mL, 123,02 mmol) en diclorometano (163 mL) a 0 °C se agregó trietilamina (28,6 mL, 205,04 mmol) gota a gota. La reacción se agitó a temperatura ambiente durante 1,5 h. La reacción se detuvo con 20 mL de metanol y luego se concentró. El sólido resultante se lavó con THF y se eliminó por filtración. El filtrado se concentró. El residuo se destiló al vacío de un matraz a otro. A aproximadamente 85 °C se recogieron impurezas y luego

se descartaron. El compuesto del título se recogió a aproximadamente 120 °C como un aceite puro (11,6 g, 72,0 mmol, 70,2 %).

MS (ES) MH^+: 162 para $C_6H_{11}NO_4$

^1H RMN (300 MHz, DMSO-d_6) δ ppm 1,27 (t, 3H) 3,17 (s, 3H) 3,70 (s, 3H) 4,29 (c, 2H)

Intermedio 57

Ácido 2,4-difluoro-5-[hidroxi(1,3-tiazol-2-il)metil]-3-metilbenzoico

Una solución de n-BuLi 1,9 M (3,8 mL, 7,2 mmol) en hexanos se agregó a -30 °C a una solución agitada de 2,2,6,6-tetrametilpiperidina (1,2 g, 9,0 mmol) en THF y la mezcla se agitó durante una hora a la misma temperatura. Después de enfriar hasta alcanzar -78 °C, una solución de ácido 2,4-difluoro-3-metilbenzoico (**Intermedio 46**, 0,5 g, 3,0 mmol) en THF se agregó lentamente y la mezcla se agitó durante otras 2 h a la misma temperatura. A esta mezcla, se agregó gota a gota una solución de tiazol-2-carboxaldehído (0,8 g, 7,2 mmol) en THF durante un período de 10 minutos y la mezcla se llevó hasta la temperatura ambiente. La mezcla de reacción se detuvo con ácido clorhídrico 1,5N y la capa orgánica se separó, la capa acuosa se extrajo con acetato de etilo (3 x 10 mL) y la capa orgánica combinada se secó sobre sulfato de sodio. La eliminación del disolvente proporcionó el compuesto del título como un producto incoloro. Rendimiento: 0,42 g (51%).

MS (ES) MH^+: 285 para $C_{12}H_9F_2NO_3S$

El **Intermedio 58** se preparó a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis de ácido 2,4-difluoro-5-[hidroxi(1,3-tiazol-2-il)metil]-3-metilbenzoico (**Intermedio 57**):

Intermedio 58

Ácido 2,4-difluoro-3-metil-5-(pirazin-2-ilcarbonil)benzoico

Materiales de partida: ácido 2,4-difluoro-3-metilbenzoico (**Intermedio 46**) y *N*-metoxi-*N*-metilpirazina-2-carboxamida.

MS (ES) MH^+: 278 para $C_{13}H_8F_2N_2O_3$

^1H RMN (400 MHz, $CDCl_3$) δ: 2,1 (s, 3H), 7,8 (t, 1H), 8,8 (s, 1H), 8,9 (t, 1H), 9,3 (d, 1H), 13,6 (s, 1H).

Intermedio 59

Ácido 2,4-difluoro-3-metil-5-(1,3-tiazol-2-ilcarbonil)benzoico

Una mezcla agitada de ácido 2,4-difluoro-5-[hidroxi(pirazin-2-il)metil]-3-metilbenzoico (**Intermedio 57**, 0,43 g, 1,5 mmol) en 1,4-dioxano (10 mL), MnO_2 (0,65 g, 7,4 mmol) se sometió a reflujo durante 5 horas. La mezcla de reacción se enfrió hasta alcanzar la temperatura ambiente y se filtró a través de celite y el disolvente se eliminó al vacío para proporcionar un producto. Rendimiento: 0,4 g (95%).

MS (ES) MH^+: 283 para $C_{12}H_7F_2NO_3S$

Intermedio 60

Ácido 2-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-4-fluoro-3-metil-5-(1,3-tiazol-2-ilcarbonil)benzoico

En un tubo sellado, una mezcla de ácido 2,4-difluoro-3-metil-5-(1,3-tiazol-2-ilcarbonil)benzoico (**Intermedio 59**, 0,4 g, 1,4 mmol), cis-2,6-dimetilmorfolina (0,25 g, 2,1 mmol) y diisopropiletilamina (0,55 g, 4,2 mmol) en acetonitrilo (1 mL) se calentaron a 90 °C durante toda la noche. Los disolventes se eliminaron al vacío y el residuo se recogió con acetato de etilo, que se lavó con ácido clorhídrico 1,5N y se secó sobre sulfato de sodio. La eliminación del acetato de etilo proporcionó el producto bruto que se purificó mediante cromatografía en columna de gel de sílice (eluyente: 3% de metanol en cloroformo) para proporcionar un producto. Rendimiento: 0,31 g (58 %).

MS (ES) MH^+: 378,2 para $C_{18}H_{19}FN_2O_4S$

El **Intermedio 61** se preparó a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis de ácido 2-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-4-fluoro-3-metil-5-(1,3-tiazol-2-ilcarbonil)benzoico (**Intermedio 60**):

Intermedio 61

Ácido 2-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-4-fluoro-3-metil-5-(pirazin-2-ilcarbonil)benzoico

Material de partida: ácido 2,4-difluoro-3-metil-5-(pirazin-2-ilcarbonil)benzoico (**Intermedio 58**).

MS (ES) MH^+: 383 para $C_{19}H_{20}FN_3O_4$

^{1}H RMN (400 MHz, DMSO-d6) δ: 1,2 (d, 6H), 2,5 (s, 3H), 3,0 (d, 2H), 3,2 (t, 2H), 3,9 (m, 2H), 8,5 (d, 1H), 8,6 (t, 1H), 8,8 (d, 1H), 9,3 (s, 1H).

Intermedio 62

{5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}(piridin-2-il)metanol

A una solución agitada de (2*R*,6*S*)-4-[6-({[*terc*-butil(difenil)silil]oxi}metil)-2-cloro-3-fluorofenil]-2,6-dimetilmorfolina (**Intermedio 42,** 2,0 g, 3,9 mmol) en THF anhidro (10 mL), se agregó *sec*-butillitio (1,4 M en ciclohexano, 2,1 eq) y la solución se agitó durante ½ h a -78 °C. Se agregó gota a gota piridina-2-carbaldehído (0,74 mL, 7,8 mmol) en THF (5 mL) y la solución se agitó durante 1 h más. La mezcla de reacción se detuvo con solución de cloruro de amonio saturado y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se secó sobre sulfato de sodio anhidro. El disolvente se eliminó al vacío y el residuo se purificó en una columna de cromatografía en gel de sílice utilizando un gradiente de acetato de etilo-éter de pet. para obtener un producto. Rendimiento: 900 mg, (37%)

MS (ES) MH^+: 619 para $C_{35}H_{40}ClFN_2O_3Si$

Los **Intermedios 63** a **70** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 62**:

Intermedio 63

{5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}(1,3-tiazol-5-il)metanol

Materiales de partida: (2*R*,6*S*)-4-[6-({[*terc*-butil(difenil)silil]oxi}metil)-2-cloro-3-fluorofenil]-2,6-dimetilmorfolina (**Intermedio 42**), 1,3-tiazol-5-carbaldehído y 2,2,6,6-tetrametilpiperidina de litio.

MS (ES) MH^+: 625 para $C_{33}H_{38}ClFN_2O_3Si$

Intermedio 64

{5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}(piridin-4-il)metanol

Materiales de partida: (2*R*,6*S*)-4-[6-({[*terc*-butil(difenil)silil]oxi}metil)-2-cloro-3-fluorofenil]-2,6-dimetilmorfolina (**Intermedio 42**), 4-piridina-carboaldehído y 2,2,6,6-tetrametilpiperidina de litio.

MS (ES) MH^+: 619 para $C_{35}H_{40}ClFN_2O_3Si$

Intermedio 65

{5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}(piridin-3-il)metanol

Material de partida: (2*R*,6*S*)-4-[6-({[*terc*-butil(difenil)silil]oxi}metil)-2-cloro-3-fluorofenil]-2,6-dimetilmorfolina (**Intermedio 42**), piridina-3-carboaldehído y LDA

MS (ES) MH^+: 619 para $C_{35}H_{40}ClFN_2O_3Si$

Intermedio 66

{5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}(1,3-tiazol-2-il)metanol

Material de partida: (2*R*,6*S*)-4-[6-({[*terc*-butil(difenil)silil]oxi}metil)-2-cloro-3-fluorofenil]-2,6-dimetilmorfolina (**Intermedio 42**), 1,3-tiazol-2-carbaldehído y 2,2,6,6-tetrametilpiperidina de litio.

MS (ES) MH^+: 626 para $C_{33}H_{38}ClFN_2O_3Si$

Intermedio 67

{5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}(1-metil-1*H*-imidazol-2-il)metanol

Material de partida: (2*R*,6*S*)-4-[6-({[*terc*-butil(difenil)silil]oxi}metil)-2-cloro-3-fluorofenil]-2,6-dimetilmorfolina (**Intermedio 42**), 1-metil-imidazol-2-carbaldehído y *n*-BuLi

MS (ES) MH^+: 622 para $C_{34}H_{41}ClFN_3O_3Si$

Intermedio 68

3-cloro-5-[ciclopropil(hidroxi)metil]-2-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-4-fluorobenzoato de metilo

Materiales de partida: Metil 3-cloro-2-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-4-fluorobenzoato (**Intermedio 47**), ciclopropilo carbaldehído y LDA.

MS (ES) MH^+: 372 para $C_{18}H_{23}ClFNO_4$

Intermedio 69

{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(1-metil-1*H*-imidazol-5-il)metanol

Materiales de partida: (2*R*,6*S*)-4-[6-({[*terc*-butil(difenil)silil]oxi}metil)-2,3-difluorofenil]-2,6-dimetilmorfolina (**Intermedio 3**), 1-metil-imidazol-5-carbaldehído (116 mg, 1,06 mmol) y *sec*-butillitio.

MS (ES) MH^+: 605 para $C_{34}H_{41}F_2N_3O_3Si$

Intermedio 70

{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(4-metil-1,3-tiazol-5-il)metanol

Materiales de partida: (2*R*,6*S*)-4-[6-({[*terc*-butil(difenil)silil]oxi}metil)-2,3-difluorofenil]-2,6-dimetilmorfolina (**Intermedio 3**, 1,0 g, 2,02 mmol), 4-metil-1,3-tiazol-5-carbaldehído y *sec*-butillitio

MS (ES) MH^+: 623 para $C_{34}H_{40}F_2N_2$-O_3SSi

Intermedio 71

(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*R*)-2,6-dimetilmorfolino)-2,3-difluorofenil)(2-(metiltio)pirimidin-4-il)metanol

Materiales de partida: (2*R*,6*R*)-4-(6-((*terc*-butildifenilsililoxi)metil)-2,3-difluorofenil)-2,6-dimetilmorfolina (**Intermedio 43,** 7,36 g, 14,84 mmol) en t-BuOMe (20 mL) se agregó s-BuLi (12,45 mL, 16,19 mmol) a -75 °C en atmósfera de nitrógeno. Después de agitar durante 20 minutos a esta temperatura, se transfirió mediante una cánula a una solución de 2-(metiltio)pirimidin-4-carbaldehído (2,08 g, 13,49 mmol) en t-BuOMe (20 mL) (previamente enfriado hasta -70 °C), la mezcla luego se agitó durante 0,5 hora a -70 °C, se detuvo con solución de cloruro de amonio saturada acuosa y se extrajo con acetato de etilo, se secó y se concentró, se

purificó mediante cromatografía instantánea en columna en gel de sílice con Hex/EtOAc para proporcionar el producto deseado(3,024 g).
MS (ES) MH^+: 650 para $C_{35}H_{41}F_2N_3O_3SSi$

Intermedio 72

(5-((*terc*-butildifenilsililoxi)metil)-3-cloro-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2-fluorofenil)(pirazin-2-il)metanona

Una solución de butillitio, 2,5M en hexanos (1,718 mL, 4,30 mmol) se agregó gota a gota a una solución de 2,2,6,6-tetrametilpiperidina (0,802 mL, 4,73 mmol) en 15 mL de THF a -78 °C. El matraz se retiró del baño a -78 °C y se agitó a aproximadamente 0 °C durante 10 min, luego se enfrió nuevamente hasta alcanzar -78 °C para proporcionar una solución amarilla clara de LiTMP. Una solución de (2*R*,6*S*)-4-[6-({[*terc*-butil(difenil)silil]oxi}metil)-2-cloro-3-fluorofenil]-2,6-dimetilmorfolina (**Intermedio 42**, 1,1 g, 2,15 mmol) 20 mL de THF se introdujo mediante una cánula en la solución LiTMP para proporcionar una solución amarilla que se agitó a -78 °C durante aproximadamente 1 h; luego se agregó *N*-metoxi-*N*-metilpirazina-2-carboxamida (1,077 g, 6,44 mmol). La mezcla se agitó a -78 °C. La reacción se trató después de 5 h agregando NH_4Cl saturado a la solución a -78 °C y extraeyendo con EtOAc (3X). Tras el secado sobre $MgSO_4$, la concentración de la mezcla proporcionó material que se purificó en SiO_2 utilizando 0-10% de acetona/hexanos para recuperar 891 mg (67%) del compuesto del título como un aceite amarillo.
MS (ES) MH^+: 618 para $C_{34}H_{37}ClFN_3O_3Si$
^1H RMN (CD_2Cl_2) δ: 1,0-1,1 (superposición de m, 15H), 2,5-2,7 (m, 2H), 3,0-3,2 (m, 2H), 3,3-3,4 (m, 2H), 4,8 (s, 2H), 7,3-7,5 (m, 6H), 7,6-7,7 (m, 4H), 7,9 (s a, 1H), 8,6 (m, 1H), 8,7 (d, 1H), 9,2 (s a, 1H).

Intermedio 73

(6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)(1-metil-1*H*-imidazol-2-il)metanol

Se agregó gota a gota diisopropilamina (0,868 mL, 6,14 mmol) a una solución agitada de butillitio 2,5M en hexanos (2,339 mL, 5,85 mmol) en THF (20 mL) a -78 °C. La solución se entibió hasta alcanzar 0 °C durante 10 minutos y luego se enfrió nuevamente hasta -78 °C. Se agregó LDA mediante una cánula a -78 °C a (2*R*,6*S*)-4-(2-((*terc*-butildifenilsililoxi)metil)-4-

cloro-5-fluoropiridin-3-il)-2,6-dimetilmorfolina (**Intermedio 45,** 1,5 g, 2,92 mmol) en THF (10 mL) a -78 °C. Se dejó agitar la solución oscura durante 20 minutos, luego se introdujo mediante una cánula en una solución agitada de 1-metil-1*H*-imidazol-2-carbaldehído (0,644 g, 5,85 mmol) en THF (10 mL) a -78 °C. Se dejó entibiar a la solución hasta –50 °C, luego se detuvo con solución de cloruro de amonio saturado. Se extrajo la mezcla con acetato de etilo y los orgánicos resultantes se lavaron con salmuera. Tras secar los orgánicos sobre sulfato de sodio, se filtraron y el filtrado se evacuó al vacío para proporcionar un aceite amarillo bruto. El aceite bruto se purificó sobre sílice utilizando 40% de acetato de etilo en n-hexano para proporcionar 1,2 g (66%) del compuesto del título como un aceite.

MS (ES) MH^+: 623 para $C_{33}H_{40}ClFN_4O_3Si$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,0 (s, 9H), 1,1 (d, 6H), 2,8 (s a, 2H), 3,1 (s a, 2H), 3,6 (s a, 2H), 3,7 (s, 3H), 5,0 (s a, 2H), 6,0 (s a, 1H), 6,8 (s a, 1H), 6,9 (d, 1H) 7,3–7,4 (m, 6H), 7,6 – 7,7 (m, 4H), 9,1(s, 1H).

Los **Intermedios 74** a **79** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 73:**

Intermedio 74

(6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)(tiazol-5-il)metanol

Materiales de partida: (2*R*,6*S*)-4-(2-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-fluoropiridin-3-il)-2,6-dimetilmorfolina (**Intermedio 45**) y tiazol-5-carbaldehído.

MS (ES) MH^+: 626 para $C_{32}H_{37}ClFN_3O_3SiS$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,0 (s, 9H), 1,1–1,2 (m, 6H), 2,7 – 2,8 (m, 2H), 3,1 (s a, 2H), 3,7 (s a, 2H), 4,8 (s a, 2H), 6,2 (s, 1H), 7,2 (s a, 1H), 7,3–7,4 (m, 6H), 7,6–7,7 (m, 4H), 8,5 (s, 1H), 9,1(s, 1H).

Intermedio 75

(6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)(2-metiltiazol-5-il)metanol

Materiales de partida: (2*R*,6*S*)-4-(2-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-fluoropiridin-3-il)-2,6-dimetilmorfolina (**Intermedio 45**) y 2-metiltiazol-5-carbaldehído.

MS (ES) MH^+: 640 para $C_{33}H_{39}ClFN_3O_3SiS$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,0 (s, 9H), 1,1–1,2 (m, 6H), 2,6 (s, 3H), 2,7–2,8 (m, 2H), 3,1 (s a, 2H), 3,7 (s a, 2H), 4,8 (s a, 2H), 6,1 (s, 1H), 7,2 (s a, 1H), 7,3–7,5 (m, 6H), 7,6–7,7 (m, 4H), 8,2 (s, 1H).

Intermedio 76

4-((6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)(hidroxi)metil)-2-fluorobenzonitrilo

Materiales de partida: (2*R*,6*S*)-4-(2-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-fluoropiridin-3-il)-2,6-dimetilmorfolina (**Intermedio 45**) y 2-fluoro-4-formilbenzonitrilo.

MS (ES) MH^+: 662 para $C_{36}H_{38}ClF_2N_3O_3Si$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,0 (s, 9H), 1,1–1,2 (m, 6H), 2,7 (s a, 2H), 3,1 (s a, 2H), 3,6 (s a, 2H), 4,8 (s a, 2H), 5,9 (s, 1H), 6,1 (s, 1H), 7,2–7,5 (m, 6H), 7,5 (dd, 1H), 7,6 (s a, 2H), 7,6–7,7 (m, 4H).

Intermedio 77

(6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)(5-metiltiazol-2-il)metanol

Materiales de partida: (2*R*,6*S*)-4-(2-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-fluoropiridin-3-il)-2,6-dimetilmorfolina (**Intermedio 45**) y 5-metiltiazol-2-carbaldehído.

MS (ES) MH^+: 640 para $C_{33}H_{39}ClFN_3O_3SiS$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,0 (s, 9H), 1,1–1,2 (m, 6H), 2,4 (d, 3H), 2,7 (s a, 2H), 3,1 (s a, 2H), 3,6 (s a, 2H), 4,8 (s a, 2H), 5,0 (s, 1H), 6,1 (s, 1H), 7,2 (s, 1H), 7,3–7,5 (m, 6H), 7,6–7,7 (m, 4H).

Intermedio 78

(2-bromotiazol-5-il)(6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)metanol

Materiales de partida: 2*R*,6*S*)-4-(2-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-fluoropiridin-3-il)-2,6-dimetilmorfolina (**Intermedio 45**) y 2-bromotiazol-5-carbaldehído.

MS (ES) MH^+: 705 para $C_{32}H_{36}ClFBrN_3O_3SiS$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,0 (s, 9H), 1,1–1,2 (m, 6H), 2,7 (s a, 2H), 3,1 (s a, 2H), 3,7 (s a, 2H), 4,8 (s a, 2H), 6,1 (d, 1H,) 7,3–7,5 (m, 6H), 7,6–7,7 (m, 4H), 8,1(s, 1H), 9,9 (m, 1H).

Intermedio 79

(6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)(2,4-diclorotiazol-5-il)metanol

Materiales de partida: (2*R*,6*S*)-4-(2-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-fluoropiridin-3-il)-2,6-dimetilmorfolina (**Intermedio 45**) y 2,4-diclorotiazol-5-carbaldehído.

MS (ES) MH^+: 694 para $C_{32}H_{35}Cl_3FN_3O_3SiS$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,0 (s, 9H), 1,1–1,2 (m, 6H), 2,8 (s a, 2H), 3,1 (s a, 2H), 3,7 (s a, 2H), 4,8 (s a, 2H), 6,2 (d, 1H), 7,3–7,5 (m, 6H), 7,6–7,7 (m, 4H).

Intermedio 80 e Intermedio 81

{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}[4-(morfolin-4-ilcarbonil)-1,3-tiazol-2-il]metanol (**Intermedio 80**) y {5-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}[4-(morfolin-4-ilcarbonil)-1,3-tiazol-5-il]metanol (**Intermedio 81**).

Se agregó morfolin-4-il(1,3-tiazol-4-il)metanona (1,0 g, 5,05 mmol) en THF anhidro (10 mL) a una solución agitada de LiTMP (3,2 eq, generados a partir de n-butillitio y 2,2,6,6-tetrametilpiperidina en 10 mL THF) a -78 °C y la mezcla se agitó durante 2 horas a -78 °C. Una solución de 5-(*terc*-butil-difenil-silaniloximetil)-4-((2*R*,6*S*)-2,6-dimetil-morfolin-4-il)-2,3-difluoro-benzaldehído (**Intermedio 4,** 2,6 g, 5,05 mmol) en THF (10 mL) se agregó gota a gota y la mezcla se agitó durante 1 hora más a -78 °C. La mezcla de reacción se detuvo con solución de cloruro de amonio saturado y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se secó sobre sulfato de sodio anhidro. El disolvente se eliminó al vacío y el residuo se purificó en columna de gel de sílice utilizando un gradiente de acetato de etilo-éter de pet. para proporcionar dos productos: **Intermedio 80** e **Intermedio 81**. Rendimiento: 600 mg (17%).

Intermedio 80 MS (ES) MH^+: 722 para $C_{38}H_{45}F_2N_3O_5SSi$.

Intermedio 81 MS (ES) MH^+: 722 para $C_{38}H_{45}F_2N_3O_5SSi$;

Los **Intermedios 82** a **84** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 80** e **Intermedio 81**:

Intermedio 82

2-[{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(hidroxi)metil]-*N*,*N*-dimetil-1,3-tiazol-4-carboxamida

Material de partida: 5-(*terc*-butil-difenil-silaniloximetil)-4-((2*R*,6*S*)-2,6-dimetil-morfolin-4-il)-2,3-difluoro-benzaldehído (**Intermedio 4**) y *N*,*N*-dimetil-1,3-tiazol-4-carboxamida.

MS (ES) MH^+: 680 para $C_{36}H_{43}F_2N_3$-O_4SSi

Intermedio 83

2-[{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(hidroxi)metil]-*N*,*N*-dimetil-1,3-tiazol-5-carboxamida

Material de partida: 5-(*terc*-butil-difenil-silaniloximetil)-4-((2*R*,6*S*)-2,6-dimetil-morfolin-4-il)-2,3-difluoro-benzaldehído (**Intermedio 4**) y *N*,*N*-dimetil-1,3-tiazol-5-carboxamida

MS (ES) MH^+: 680 para $C_{36}H_{43}F_2N_3$-O_4SSi

Intermedio 84

5-[{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(hidroxi)metil]-1,3-tiazol-4-carbonitrilo

Material de partida: 5-(*terc*-Butil-difenil-silaniloximetil)-4-((2*R*,6*S*)-2,6-dimetil-morfolin-4-il)-2,3-difluoro-benzaldehído (**Intermedio 4**) y 4-ciano-1,3-tiazol.

MS (ES) MH^+: 634 para $C_{34}H_{37}F_2N_23O_3SSi$

Intermedio 85

{5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}(piridin-2-il)metanona

A la solución de {5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}(piridin-2-il)metanol (**Intermedio 62**, 100 mg, 0,165 mmol) en DCM anhidro

(5 mL) se agregó NMO (37 mg, 0,323 mmol) y TPAP (0,1 eq) a 0 °C y la mezcla se dejó agitar durante 1 hora a temperatura ambiente. La mezcla de reacción se filtró y los disolventes se eliminaron al vacío y el residuo se purificó en una columna de cromatografía en gel de sílice utilizando un gradiente de acetato de etilo-éter de pet. para proporcionar un producto como un sólido. Rendimiento: 90 mg, (90 %).

MS (ES) MH^+: 617 para $C_{35}H_{38}ClFN_2O_3Si$

Los **Intermedios 86** a **96** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 85**:

Intermedio 86

{5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}(1,3-tiazol-5-il)metanona

Material de partida: {5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}(1,3-tiazol-5-il)metanol (**Intermedio 63**).

MS (ES) MH^+: 623 para $C_{33}H_{36}ClFN_2O_3Si$

Intermedio 87

{5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}(piridin-4-il)metanona

Material de partida: {5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}(piridin-4-il)metanol (**Intermedio 64**).

MS (ES) MH^+: 617 para $C_{35}H_{38}ClFN_2O_3Si$

Intermedio 88

{5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}(piridin-3-il)metanona

Material de partida: {5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}(piridin-3-il)metanol (**Intermedio 65**).

MS (ES) MH^+: 617 para $C_{35}H_{38}ClFN_2O_3Si$

Intermedio 89

{5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}(1,3-tiazol-2-il)metanona

Material de partida: {5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}(1,3-tiazol-2-il)metanol (**Intermedio 66**).

MS (ES) MH^+: 623 para $C_{33}H_{36}ClFN_2O_3Si$

Intermedio 90

{5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}(1-metil-1*H*-imidazol-2-il)metanona

Material de partida: {5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}(1-metil-1*H*-imidazol-2-il)metanol (**Intermedio 67**).

MS (ES) MH^+: 620 para $C_{34}H_{39}ClFN_3O_3Si$

Intermedio 91

3-cloro-5-(ciclopropilcarbonil)-2-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-4-fluorobenzoato de metilo

Material de partida: Metil 3-cloro-5-[ciclopropil(hidroxi)metil]-2-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-4-fluorobenzoato (**Intermedio 68**).

MS (ES) MH^+: 370 para $C_{18}H_{21}ClFNO_4$

Intermedio 92

{2-[{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(hidroxi)metil]-1,3-tiazol-4-il}(morfolin-4-il)metanona

Material de partida: {5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}[4-(morfolin-4-ilcarbonil)-1,3-tiazol-2-il]metanol (**Intermedio 80**).

MS (ES) MH^+: 720 para $C_{38}H_{43}F_2N_3O_5SSi$

Intermedio 93

{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}{4-[hidroxi(morfolin-4-il)metil]-1,3-tiazol-5-il}metanona

Material de partida: {5-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}[4-(morfolin-4-ilcarbonil)-1,3-tiazol-5-il]metanol (**Intermedio 81**).
MS (ES) MH^+: 720 para $C_{38}H_{43}F_2N_3O_5SSi$

Intermedio 94

2-({5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}carbonil)-*N*,*N*-dimetil-1,3-tiazol-4-carboxamida
Material de partida: 2-[{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(hidroxi)metil]-*N*,*N*-dimetil-1,3-tiazol-4-carboxamida (**Intermedio 82**).
MS (ES) MH^+: 678 para $C_{36}H_{41}F_2N_3O_4SSi$

Intermedio 95

2-({5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}carbonil)-*N*,*N*-dimetil-1,3-tiazol-5-carboxamida
Material de partida: 2-[{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(hidroxi)metil]-*N*,*N*-dimetil-1,3-tiazol-5-carboxamida (**Intermedio 83**).
MS (ES) MH^+: 678 para $C_{36}H_{41}F_2N_3O_4SSi$

Intermedio 96

5-({5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}carbonil)-1,3-tiazol-4-carbonitrilo
Material de partida: 5-[{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(hidroxi)metil]-1,3-tiazol-4-carbonitrilo (**Intermedio 84**).
MS (ES) MH^+: 632 para $C_{34}H_{35}F_2N_23O_3SSi$

Intermedio 97

{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(1-metil-1*H*-imidazol-5-il)metanona
A la solución de {5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(1-metil-1*H*-imidazol-5-il)metanol (**Intermedio 69**, 50 mg, 0,08 mmol) en DCM anhidro (5 mL), MnO_2 (143 mg, 1,65 mmol) se agregó a 0 °C y se dejó agitar durante 1 hora a

temperatura ambiente. La mezcla de reacción se filtró y los disolventes se eliminaron al vacío y el residuo se purificó en una columna de cromatografía en gel de sílice utilizando un gradiente de acetato de etilo-éter de pet. para proporcionar un sólido. Rendimiento: 37 mg, (75 %).
MS (ES) MH^+: 604 para $C_{34}H_{39}F_2N_3O_3Si$

El **Intermedio 98** se preparó a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 97**:

Intermedio 98

{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(4-metil-1,3-tiazol-5-il)metanona

Material de partida: {5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(4-metil-1,3-tiazol-5-il)metanol e (**Intermedio 70**).
MS (ES) MH^+: 621 para $C_{34}H_{38}F_2N_2$-O_3SSi

Intermedio 99

(6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)(1-metil-1*H*-imidazol-2-il)metanona

A una solución agitada de (6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)(1-metil-1*H*-imidazol-2-il)metanol (1,2 g, 1,93 mmol, **Intermedio 73**) en diclorometano (20 mL) se agregó óxido de manganeso (IV) (0,670 g, 7,70 mmol). La mezcla se dejó agitar durante toda la noche a temperatura ambiente. La reacción se filtró a través de Celite® y el filtrado se concentró al vacío para proporcionar un aceite claro. El aceite se purificó en un lecho corto de sílice utilizando 20-30% de acetato de etilo en n-hexano para proporcionar 1,0 g (84%) del compuesto del título como un aceite.
MS (ES) MH^+: 621 para $C_{33}H_{38}ClFN_4O_3Si$
^1H RMN (300 MHz, $CDCl_3$) δ: 1,1 (s, 9H), 1,2 (d, 6H), 2,9 (s a, 2H), 3,2 (m, 2H), 3,8 (s a, 2H), 4,2 (s, 2H), 4,9 (s, 2H), 7,3–7,4 (m, 4H), 7,4–7,5 (m, 5H), 7,8 (d, 4H).

Los **Intermedios 100** a **106** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 99:**

Intermedio 100

(6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)(tiazol-5-il)metanona

Material de partida: (6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)(tiazol-5-il)metanol (**Intermedio 74**).

MS (ES) MH^+: 624 para $C_{32}H_{35}ClFN_3O_3SiS$

^1H RMN (300 MHz, $CDCl_3$) δ: 0,9-1,0 (s, 9H), 1,1 (d, 6H), 3,0–3,1 (m, 4H), 3,7 (s a, 2H), 4,9 (s, 2H), 7,3–7,4 (m, 6H), 7,5 – 7,7 (m, 4H), 8,8–8,9 (m, 2H).

Intermedio 101

(6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)(2-metiltiazol-5-il)metanona

Material de partida: (6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)(2-metiltiazol-5-il)metanol (**Intermedio 75**).

MS (ES) MH^+: 638 para $C_{33}H_{37}ClFN_3O_3SiS$

^1H RMN (300 MHz, $CDCl_3$) δ: 0,9-1,0 (m, 9H), 1,1 (d, 6H), 2,7 (s, 3H), 3,0 (s a, 2H), 3,0–3,1 (m, 2H), 3,7 (s a, 2H), 4,9 (s, 2H), 7,3–7,4 (m, 6H), 7,5–7,7 (m, 4H), 8,6 (s, 1H).

Intermedio 102

4-(6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropicolinoil)-2-fluorobenzonitrilo

Material de partida: 4-((6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)(hidroxi)metil)-2-fluorobenzonitrilo (**Intermedio 76**).

MS (ES) MH^+: 660 para $C_{36}H_{36}ClF_2N_3O_3Si$

^1H RMN (300 MHz, $CDCl_3$) δ: 0,9–1,1 (m, 9H), 1,2 (d, 6H), 1,8 (td, 3H), 3,1 (d, 2H), 3,6–3,7 (m, 4H), 4,8 (s, 2H), 7,2–7,3 (m, 2H), 7,3–7,5 (m, 2H), 7,5–7,6 (m, 5H), 7,7 (d, 2H).

Intermedio 103

(6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)(5-metiltiazol-2-il)metanona

Material de partida: (6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)(5-metiltiazol-2-il)metanol (**Intermedio 77**).

MS (ES) MH^+: 638 para $C_{33}H_{37}ClFN_3O_3SiS$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,0 (s, 9H), 1,1–1,2 (m, 6H), 2,5 (s, 3H), 2,9–3,0 (m, 2H), 3,0–3,1 (m, 2H), 3,7 (d, 2H), 4,9 (s, 2H), 7,3–7,5 (m, 6H), 7,6–7,7 (m, 4H), 7,8 (d, 1H).

Intermedio 104

(2-bromotiazol-5-il)(6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)metanona

Material de partida: (2-bromotiazol-5-il)(6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)metanol (**Intermedio 78**).

MS (ES) MH^+: 703 para $C_{32}H_{34}ClFBrN_3O_3SiS$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,0 (s, 9H), 1,1–1,2 (m, 6H), 2,9–3,0 (m, 2H), 3,0–3,1 (m, 2H), 3,7 (d, 2H), 4,9 (s, 2H), 7,3–7,5 (m, 6H), 7,6–7,7 (m, 4H), 8,4 (s, 1H).

Intermedio 105

(6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)(2,4-diclorotiazol-5-il)metanona

Material de partida: (6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)(2,4-diclorotiazol-5-il)metanol (**Intermedio 79**).

MS (ES) MH^+: 692 para $C_{32}H_{33}Cl_3FN_3O_3SiS$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,0 (s, 9H), 1,1–1,2 (m, 6H), 2,8 (s a, 2H), 3,1 (s a, 2H), 3,7 (s a, 2H), 4,8 (s, 2H), 7,3–7,5 (m, 6H), 7,6 – 7,7 (m, 4H).

Intermedio 106

(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*R*)-2,6-dimetilmorfolino)-2,3-difluorofenil)(2-(metiltio)pirimidin-4-il)metanona

Material de partida: (5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*R*)-2,6-dimetilmorfolino)-2,3-difluorofenil)(2-(metiltio)pirimidin-4-il)metanol (**Intermedio 71**).

MS (ES) MH^+: 648 (M+H) para $C_{35}H_{39}F_2N_3O_3SSi$

Intermedio 107

5-acetil-3-cloro-2-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-4-fluorobenzoato de metilo

A una solución agitada de LDA (3,1 eq) a -50 °C en THF se agregó metil 3-cloro-2-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-4-fluorobenzoato (**Intermedio 47,** 1,5 g, 4,96 mmol) en THF anhidro (10 mL) gota a gota y la solución se agitó durante 1 h a -50 °C. Se agregó gota a gota *N*-metoxi-*N*-metilacetamida (1,66 g, 14,9 mmol) en THF (5 mL) y se continuó agitando durante 1 h más. La mezcla de reacción se detuvo con cloruro de amonio acuoso saturado y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se secó sobre sulfato de sodio anhidro. El disolvente se eliminó al vacío y el residuo se purificó en una columna de cromatografía en gel de sílice utilizando un gradiente de acetato de etilo-éter de pet. para obtener el compuesto del título.

Rendimiento: 800 mg, (47%)

MS (ES) MH^+: 344 para $C_{16}H_{19}ClFNO_4$

Los **Intermedios 108** a **113** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 107**:

Intermedio 108

{5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}(6-metilpiridin-3-il)metanona

Materiales de partida: (2*R*,6*S*)-4-[6-({[*terc*-butil(difenil)silil]oxi}metil)-2-cloro-3-fluorofenil]-2,6-dimetilmorfolina (**Intermedio 42**) y *N*-metoxi-6,*N*-dimetilnicotinamida.

MS (ES) MH^+: 631 para $C_{36}H_{40}ClFN_2O_3Si$

Intermedio 109

{5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}(pirimidin-2-il)metanona

Materiales de partida: (2*R*,6*S*)-4-[6-({[*terc*-butil(difenil)silil]oxi}metil)-2-cloro-3-fluorofenil]-2,6-dimetilmorfolina (**Intermedio 42**) y *N*-metoxi-*N*-metilpirimidina-2-carboxamida.

MS (ES) MH^+: 618 para $C_{34}H_{37}ClFN_3O_3Si$

Intermedio 110

{5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}(pirimidin-4-il)metanona

Materiales de partida: (2*R*,6*S*)-4-[6-({[*terc*-butil(difenil)silil]oxi}metil)-2-cloro-3-fluorofenil]-2,6-dimetilmorfolina (**Intermedio 42**) y *N*-metoxi-*N*-metilpirimidina-4-carboxamida

MS (ES) MH^+: 618 para $C_{34}H_{37}ClFN_3O_3Si$

Intermedio 111

{5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}(pirimidin-5-il)metanona

Material de partida: (2*R*,6*S*)-4-[6-({[*terc*-butil(difenil)silil]oxi}metil)-2-cloro-3-fluorofenil]-2,6-dimetilmorfolina (**Intermedio 42**) y *N*-metoxi-*N*-metilpirimidina-5-carboxamida.

MS (ES) MH^+: 618 para $C_{34}H_{37}ClFN_3O_3Si$

Intermedio 112

{5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}(piridazin-4-il)metanona

Materiales de partida: (2*R*,6*S*)-4-[6-({[*terc*-butil(difenil)silil]oxi}metil)-2-cloro-3-fluorofenil]-2,6-dimetilmorfolina (**Intermedio 42**) y *N*-metoxi-*N*-metilpiridazina-4-carboxamida

MS (ES) MH^+: 618 para $C_{34}H_{37}ClFN_3O_3Si$

Intermedio 113

1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}-2-metoxietanona

Material de partida: (2*R*,6*S*)-4-[6-({[*terc*-butil(difenil)silil]oxi}metil)-2-cloro-3-fluorofenil]-2,6-dimetilmorfolina (**Intermedio 42**) y *N*,2-dimetoxi-*N*-metilacetamida.

MS (ES) MH^+: 583 para $C_{32}H_{39}ClFNO_4Si$

Intermedio 114 y **Intermedio 115**

2-(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)-2-oxoacetato de etilo (**Intermedio 114**) y 2-(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)-*N*-metoxi-*N*-metil-2-oxoacetamida (**Intermedio 115**)

Se disolvió (2*R*,6*S*)-4-(6-((*terc*-butildifenilsililoxi)metil)-2,3-difluorofenil)-2,6-dimetilmorfolina (**Intermedio 3**, 0,5 g, 1,01 mmol) en THF (10 mL) y se enfrió hasta alcanzar -78 °C. Se agregó gota a gota sec-butillitio (1,552 mL, 2,02 mmol) durante ~20 minutos y se agitó a -78 °C durante 1 h. Una solución de etil 2-(metoxi(metil)amino)-2-oxoacetato (**Intermedio 56**) (0,406 g, 2,52 mmol) en 10 mL de THF se agregó gota a gota durante 15 minutos. La reacción se agitó a –78 °C durante 30 minutos y luego se detuvo en frío con 3 mL de NH_4Cl sat. La reacción se dejó entibiar hasta alcanzar la temperatura ambiente, se diluyó con agua y se extrajo tres veces con acetato de etilo. Se combinaron las capas orgánicas, se lavaron con salmuera, se secaron con $MgSO_4$ y se concentraron. El residuo se purificó mediante cromatografía en columna de gel de sílice utilizando un gradiente de hexanos a acetato de etilo para proporcionar el compuesto que eluyó en primer lugar, **Intermedio 114** (2,38 g, 3,99 mmol, 39,6 %):

MS (ES) MH^+: 596 para $C_{33}H_{39}F_2NO_5Si$

^1H RMN (300 MHz, DMSO-d_6) δ ppm 1,0 (d, 6H), 1,04 (s, 9H), 1,3 (t, 3H), 2,6-2,75 (m, 2H), 2,9 (d, 2H), 3,3 (m, 2H), 4,4 (c, 2H), 4,7 (s, 2H), 7,4-7,6 (m, 10H) 7,85 (d, 1H).

y el compuesto que eluyó en segundo lugar, **Intermedio 115** (1,8 g, 2,95 mmol, 29,2 %):

(1,8 g, 2,95 mmol, 29,2 %):

MS (ES) MH^+: 611 para $C_{33}H_{40}F_2N_2O_5Si$

^1H RMN (300 MHz, DMSO-d_6) δ ppm 1,0 (d, 6H), 1,04 (s, 9H), 2,7 (t, 2H), 2,9 (d, 2H), 3,25 (s, 3H), 3,3 (m, 2H), 3,33 (s, 3H), 3,6 (s, 2H), 7,4-7,5 (m, 6H), 7,6 (d, 4H), 7,87 (d, 1H).

El **Intermedio 114** también se preparó de acuerdo con el siguiente método:

Intermedio 114 (Síntesis alternativa)

2-(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)-2-oxoacetato de etilo

Se disolvió 2*R*,6*S*)-4-[6-({[*terc*-butil(difenil)silil]oxi}metil)-2,3-difluorofenil]-2,6-dimetilmorfolina (**Intermedio 3**, 0,5 g, 1,01 mmol) en 10 mL de THF y se enfrió hasta alcanzar -78 °C. Se agregó gota a gota sec-butillitio (1,358 mL, 1,77 mmol) durante 5 minutos. La reacción se agitó a -78 °C durante 1,5 horas. La mezcla de reacción se introdujo mediante una cánula en un matraz enfriado a -78 °C que contenía oxalato de dietilo (1,370 mL, 10,09 mmol) en 10 mL de THF. La reacción se dejó agitar a -78 °C durante 30 minutos; se detuvo en frío con 1 mL de NH_4Cl sat. y se dejó entibiar hasta alcanzar la temperatura ambiente. La reacción se diluyó con agua y se extrajo dos veces con acetato de etilo. Se combinaron las capas orgánicas y se lavaron dos veces con salmuera, se secaron con $MgSO_4$ y se concentraron. El residuo se purificó mediante cromatografía en columna de gel de sílice utilizando un gradiente de hexanos a acetato de etilo para proporcionar el compuesto del título (486 mg, 81% de rendimiento) contaminado con oxalato de dietilo. Este material se utilizó en la siguiente etapa sin purificación adicional.
MS (ES) MH^+: 596 para $C_{33}H_{39}F_2NO_5Si$

Los **Intermedios 116** y **117** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 114** (Síntesis alternativa):

Intermedio 116

2-(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*R*)-2,6-dimetilmorfolino)-2,3-difluorofenil)-2-oxoacetato de etilo

Materiales de partida: (2*R*,6*R*)-4-(6-((*terc*-butildifenilsililoxi)metil)-2,3-difluorofenil)-2,6-dimetilmorfolina (11,96 g, 24,13 mmol) (**Intermedio 43**) y oxalato de dietilo.
MS (ES) MH^+: 596 para $C_{33}H_{39}F_2NO_5Si$

Intermedio 117

2-(5-(dimetoximetil)-2,3,4-trifluorofenil)-2-oxoacetato de etilo

Materiales de partida: 1-(dimetoximetil)-2,3,4-trifluorobenceno (**Intermedio 39**) y oxalato de dietilo.
^1H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1,4-1,5 (m, 3H), 3,35-3,4 (m, 6H), 4,5 (c, 2H), 7,3 (s, 1H), 7,9-8,0 (m, 1H).

Intermedio 118

Ácido 2-(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)-2-oxoacético

Se disolvió etil 2-(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)-2-oxoacetato (**Intermedio 114**, 0,785 g, 3,00 mmol) en etanol (60 mL) y se agitó a temperatura ambiente con 1 mL de KOH al 10%. Después de 3 horas, la LCMS indicó que aproximadamente 40-50% de la reacción había desaparecido. Se agregó 1 mL adicional de KOH al 10% y la reacción se agitó a temperatura ambiente durante 30 minutos. La reacción tenía un 70-80% según la LCMS. Se agregó 1 mL adicional de KOH al 10% y la reacción se agitó a temperatura ambiente durante 60 minutos. La reacción se volvió ácida con ácido acético, se diluyó con agua y se extrajo tres veces con acetato de etilo. Las capas orgánicas se lavaron dos veces con salmuera, se secaron con $MgSO_4$ y se concentraron. El aceite resultante pegajoso se disolvió en acetato de etilo, se lavó con $NaHCO_3$ sat., se secó con $MgSO_4$ y se concentró. El aceite resultante se secó al vacío durante 2 horas para proporcionar el compuesto del título como un sólido amarillo.

MS (ES) MH^+: 568 para $C_{31}H_{35}F_2NO_5Si$

^1H RMN (300 MHz, DMSO-d_6) δ ppm 0,96 (d, 6H), 1,02 (s, 9H), 2,6-2,7 (m, 2H), 2,7-2,8 (m, 2H), 3,2-3,3 (m, 2H), 4,7 (s, 2H), 7,4-7,5 (m, 6H), 7,6 (d, 4H), 7,87 (d, 1H).

Intermedio 119

1-(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)-2-morfolinoetano-1,2-diona

Se agitaron ácido 2-(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)-2-oxoacético (**Intermedio 118,** 150 mg, 0,26 mmol), HATU (121 mg, 0,32 mmol), morfolina (0,025 mL, 0,29 mmol) y trietilamina (0,055 mL, 0,40 mmol) en DMF (5 mL) a temperatura ambiente durante 1 hora. La reacción se diluyó con agua y se extrajo dos veces con acetato de etilo. Las capas orgánicas se lavaron tres veces con salmuera, se secaron con $MgSO_4$ y se concentraron para proporcionar un aceite. El aceite se purificó mediante cromatografía en columna de gel de sílice utilizando un gradiente de hexanos a acetato de etilo para proporcionar el compuesto del título (130 mg, 0,204 mmol, 77 %)

MS (ES) MH^+: 637 para $C_{35}H_{42}F_2N_2O_5Si$

^{1}H RMN (300 MHz, CLOROFORMO-d) δ ppm 1,0-1,2 (m, 15H), 2,7-2,9 (m, 4H), 3,5 (m, 4H), 3,7-3,9 (m, 6H), 4,7 (s, 2H), 7,4-7,5 (m, 6H), 7,7 (d, 4H), 7,95 (d, 1H).

Intermedio 120

2-(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)-*N*,*N*-dimetil-2-oxoacetamida

Se agitaron ácido 2-(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)-2-oxoacético (**Intermedio 118**, 250 mg, 0,44 mmol), HATU (335 mg, 0,88 mmol), trietilamina (0,184 mL, 1,32 mmol) y dimetilamina 2,0M (0,440 mL, 0,88 mmol) en THF en DMF (5 mL) en un vial cerrado durante 16 horas. La reacción se diluyó con agua y se extrajo 3x con acetato de etilo. Las capas orgánicas se lavaron 3x con salmuera, se secaron con $MgSO_4$ y se concentraron para proporcionar un aceite. El aceite se purificó mediante cromatografía en columna de gel de sílice utilizando un gradiente de hexanos a acetato de etilo. Las fracciones se combinaron y se concentraron para proporcionar el compuesto del título (195 mg, 0,328 mmol, 74,5 %)

MS (ES) MH^+: 595 para $C_{33}H_{40}F_2N_2O_4Si$

^{1}H RMN (300 MHz, CLOROFORMO-d) δ ppm 1,0-1,1 (m, 15H), 2,7-2,9 (m, 4H), 3,0 (s, 3H), 3,1 (s, 3H), 3,45 (m, 2H), 4,65 (s, 2H), 7,3-7,5 (m, 6H), 7,7 (d, 4H), 7,9 (d, 1H).

Intermedio 121

2-(6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)-2-oxoacetato de etilo

Una solución de n-butillitio, 2,5M en hexanos (3,43 mL, 8,58 mmol) se agregó gota a gota a una solución de diisopropilamina (1,333 mL, 9,35 mmol) en 15 mL de THF a -78 °C. El matraz se retiró del baño a -78 grados y se colocó en un baño de hielo. Se agitó a aprox. 0 °C durante 10 minutos, luego se enfrió nuevamente hasta alcanzar -78 °C para proporcionar una solución amarilla clara de LDA. La LDA se agregó mediante canulación (durante menos de 5 min) a una solución enfriada previamente a -78 °C de (2*R*,6*S*)-4-(2-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-fluoropiridin-3-il)-2,6-dimetilmorfolina (**Intermedio 45**, 2 g, 3,90 mmol) en THF, 20 mL, para proporcionar una solución marrón. La solución se agitó a -78 durante aprox. 1 hora, luego se agregó mediante una cánula durante aprox. 5 minutos a una solución a -78 °C de oxalato de

dietilo (1,588 mL, 11,69 mmol) en 20 mL de THF para proporcionar una solución amarilla. La solución se agitó a -78 °C. Después de aproximadamente 2,5 horas, la solución amarilla se trató mediante la adición de NH_4Cl saturado a la solución a -78 °C y se extrajo con EtOAc (3X). La fase orgánica se secó con $MgSO_4$ y se concentró hasta proporcionar un aceite amarillo. El bruto se purificó mediante cromatografía en SiO_2 utilizando 0-25% de EtOAc/hexanos para proporcionar 2,3 g (96%) de un sólido amarillo, una porción se recristalizó a partir de EtOAc/hexanos.

MS (ES) MH^+: 613 para $C_{32}H_{38}ClFN_2O_5Si$

^1H RMN (300 MHz, DMSO-d_6) δ: 0,9-1,1 (superposición de multiplete, 15H), 1,2 (t, 3H), 2,9-3,0 (m, 2H), 3,1-3,2 (m, 2H), 3,5-3,7 (m, 2H), 4,2 (q, 2H), 4,8 (s, 2H), 7,4-7,6 (m, 10H).

Intermedio 122

(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)(furan-2-il)metanona

A una solución agitada de (2*R*,6*S*)-4-(6-((*terc*-butildifenilsililoxi)metil)-2,3-difluorofenil)-2,6-dimetilmorfolina (**Intermedio 3,** 1 g, 2,02 mmol) en THF (8 mL) se agregó sBuLi (1,3 M en ciclohexano/hexanos, 3,1 mL, 4,03 mmol) a -70 °C en atmósfera de nitrógeno. Después de agitar durante 1 h a esta temperatura, *N*-metoxi-*N*-metilfuran-2-carboxamida (0,939 g, 6,05 mmol) se agregó en 3 mL de THF. Después de agitar durante 1½ h a -70 °C, la reacción se detuvo con solución sat. de cloruro de amonio y la capa acuosa se extrajo con acetato de etilo (2 X 100 mL). Las fases orgánicas se combinaron, se secaron (Na_2SO_4) y se concentraron. El residuo se purificó en una columna instantánea de gel de sílice utilizando un gradiente de acetato de etilo en hexanos para proporcionar el compuesto del título (0,90 g, 76%).

MS (ES) MH^+: 590 para $C_{34}H_{37}F_2NO_4Si$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,05 (s, 9H), 1,08 (d, 6H), 2,59-2,93 (m, 4H), 3,35-3,58 (m, 2H), 4,71 (s, 2H), 6,58 (dd, 1H), 7,18 (d, 1H), 7,32-7,48 (m, 6H), 7,57-7,74 (m, 6H).

Los **Intermedios 123** a **138** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 122:**

Intermedio 123

(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)(tiazol-5-il)metanona

Materiales de partida: (2*R*,6*S*)-4-(6-((*terc*-butildifenilsililoxi)metil)-2,3-difluorofenil)-2,6-dimetilmorfolina (**Intermedio 3**) y *N*-metoxi-*N*-metiltiazol-5-carboxamida.

MS (ES) MH^+: 607 para $C_{33}H_{36}F_2N_2O_3SSi$

^1H RMN (300 MHz, $CDCl_3$) δ: 0,99-1,14 (superposición de doblete y singlete, 15H), 2,67-2,94 (m, 4H), 3,38-3,57 (m, 2H), 4,70 (s, 2H), 7,28-7,51 (m, 6H), 7,54-7,74 (m, 5H), 8,26 (d, 1H), 9,08 (s, 1H).

Intermedio 124

(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)(6-metilpiridin-3-il)metanona

Materiales de partida (2*R*,6*S*)-4-(6-((*terc*-butildifenilsililoxi)metil)-2,3-difluorofenil)-2,6-dimetilmorfolina (**Intermedio 3** y *N*-metoxi-*N*,6-dimetilnicotinamida.

MS (ES) MH^+: 615 para $C_{36}H_{40}F_2N_2O_3Si$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,00-1,12 (superposición de doblete y singlete,15H), 2,67 (s, 3H), 2,69-2,93 (m, 4H), 3,32-3,61 (m, 2H), 4,70 (s, 2H), 7,25-7,71 (m, 12H), 8,02 (d, 1H), 8,88 (s, 1H).

Intermedio 125

(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)(2-fluorofenil)metanona

Materiales de partida: (2*R*,6*S*)-4-(6-((*terc*-butildifenilsililoxi)metil)-2,3-difluorofenil)-2,6-dimetilmorfolina (**Intermedio 3**) y 2-fluoro-*N*-metoxi-*N*-metilbenzamida.

MS (ES) MH^+: 618 para $C_{36}H_{38}F_3NO_3Si$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,01 (s, 9H), 1,07 (d, 6H), 2,59-2,93 (m, 4H), 3,30-3,59 (m, 2H), 4,67 (s, 2H), 6,99-7,81 (m, 15H).

Intermedio 126

(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)(tetrahidro-2*H*-piran-4-il)metanona

Materiales de partida: (2*R*,6*S*)-4-(6-((*terc*-butildifenilsililoxi)metil)-2,3-difluorofenil)-2,6-dimetilmorfolina (**Intermedio 3**) y *N*-metoxi-*N*-metiltetrahidro-2*H*-piran-4-carboxamida.

MS (ES) MH^+: 608 para $C_{35}H_{43}F_2NO_4Si$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,04-1,11 (superposición de singlete y doblete, 15H), 1,73-1,90 (m, 4H), 2,62-2,93 (m, 4H), 3,19-3,36 (m, 1H), 3,39-3,59 (m, 4H), 3,95-4,08 (m, 2H), 4,67 (s, 2H), 7,30-7,52 (m, 6H), 7,58-7,72 (m, 4H), 7,78 (d, 1H).

Intermedio 127

1-(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)-2-cloroetanona

Materiales de partida (2*R*,6*S*)-4-(6-((*terc*-butildifenilsililoxi)metil)-2,3-difluorofenil)-2,6-dimetilmorfolina (**Intermedio 3**) y 2-cloro-*N*-metoxi-*N*-metilacetamida.

MS (ES) MH^+: 572 para $C_{31}H_{36}ClF_2NO_3Si$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,05-1,16 (superposición de doblete y singlete, 15H), 2,70-2,92 (m, 4H), 3,34-3,61 (m, 2H), 4,67 (s, 2H) 4,71 (d, 2H), 7,35-7,53 (m, 6H), 7,60-7,74 (m, 4H) 7,97 (dd, 1,98 Hz, 1H).

Intermedio 128

(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)(piridin-4-il)metanona

Materiales de partida: (2*R*,6*S*)-4-(6-((*terc*-butildifenilsililoxi)metil)-2,3-difluorofenil)-2,6-dimetilmorfolina (**Intermedio 3**) y *N*-metoxi-*N*-metilisonicotinamida.

MS (ES) MH^+: 601 para $C_{35}H_{38}F_2N_2O_3Si$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,03 (s, 9H), 1,09 (d, 6H), 2,65-2,95 (m, 4H), 3,38-3,59 (m, 2H), 4,68 (s, 2H), 7,28-7,47 (m, 6H), 7,52-7,68 (m, 7H), 8,80 (d, 2H).

Intermedio 129

1-(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)-2,2-difluoroetanona

Materiales de partida: (2*R*,6*S*)-4-(6-((*terc*-butildifenilsililoxi)metil)-2,3-difluorofenil)-2,6-dimetilmorfolina (**Intermedio 3**) y 2,2-difluoro-*N*-metoxi-*N*-metilacetamida.

MS (ES) MH^+: 574 para $C_{31}H_{35}F_4NO_3Si$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,05-1,10 (superposición de doblete y singlete, 15H), 2,71-2,92 (m, 4H), 3,37-3,55 (m, 2H), 4,63 (s, 2H), 6,12-6,57 (m, 1H), 7,31-7,49 (m, 6H), 7,58-7,70 (m, 4H), 7,93 (dd, 1,79 Hz, 1H).

Intermedio 130

1-(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)-2,2,2-trifluoroetanona

Materiales de partida (2*R*,6*S*)-4-(6-((*terc*-butildifenilsililoxi)metil)-2,3-difluorofenil)-2,6-dimetilmorfolina (**Intermedio 3**) y 2,2,2-trifluoro-*N*-metoxi-*N*-metilacetamida. El compuesto existe en forma hidratada.

MS (ES) MH^+: 610 para $C_{31}H_{34}F_5NO_3Si.H_2O$

Intermedio 131

(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*R*)-2,6-dimetilmorfolino)-2,3-difluorofenil)(tiazol-2-il)metanona

Materiales de partida (2*R*,6*R*)-4-(6-((*terc*-butildifenilsililoxi)metil)-2,3-difluorofenil)-2,6-dimetilmorfolina (**Intermedio 43**) y *N*-metoxi-*N*-metiltiazol-2-carboxamida (MTBE se utilizó como disolvente en lugar de THF).

MS (ES) MH^+: 607 para $C_{33}H_{36}F_2N_2O_3SSi$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,05 (d, 6H) 1,07 (s, 9H), 2,58-2,80 (m, 2H), 2,91-3,21 (m, 2H), 3,78-3,96 (m, 2H), 4,64-4,94 (m, 2 H, 7,30-8,20 (m, 13H).

Intermedio 132

1-(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*R*)-2,6-dimetilmorfolino)-2,3-difluorofenil)-2,2-difluoroetanona

Materiales de partida (2*R*,6*R*)-4-(6-((*terc*-butildifenilsililoxi)metil)-2,3-difluorofenil)-2,6-dimetilmorfolina (**Intermedio 43**) y 2,2-difluoro-*N*-metoxi-*N*-metilacetamida (MTBE se utilizó como disolvente en lugar de THF).

MS (ES) MH^+: 574 para $C_{31}H_{35}F_4NO_3Si$

^1H RMN (300 MHz, $CDCl_3$) δ: 0,99-1,17 (superposición de doblete y singlete, 15H), 2,58-2,85 (m, 2H), 2,97-3,20 (m, 2H), 3,76-3,99 (m, 2H), 4,57-4,82 (m, 2H), 6,36 (t, 1H), 7,30-8,10 (m, 11H).

Intermedio 133

(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*R*)-2,6-dimetilmorfolino)-2,3-difluorofenil)(pirazin-2-il)metanona

Material de partida: *N*-metoxi-*N*-metilpirazina-2-carboxamida (**Intermedio 50**).

MS (ES) MH^+: 602 para $C_{34}H_{37}F_2N_3O_3Si$

Intermedio 134

(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*R*)-2,6-dimetilmorfolino)-2,3-difluorofenil)(5-morfolinopirazin-2-il)metanona

Material de partida: *N*-metoxi-*N*-metil-5-morfolinopirazina-2-carboxamida (**Intermedio 52**).

MS (ES) MH^+: 740 para $C_{41}H_{50}FN_5O_5Si$

Intermedio 135

(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)(3-cloropirazin-2-il)metanona

Material de partida: 3-cloro-*N*-metoxi-*N*-metilpirazina-2-carboxamida (**Intermedio 53**).

MS (ES) MH^+: 637 para $C_{34}H_{36}ClF_2N_3O_3Si$

Intermedio 136

(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)(6-cloropirazin-2-il)metanona

Material de partida: 6-cloro-*N*-metoxi-*N*-metilpirazina-2-carboxamida (**Intermedio 51**).

MS (ES) MH^+: 637 para $C_{34}H_{36}ClF_2N_3O_3Si$

Intermedio 137

(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)(5-cloropirazin-2-il)metanona

Material de partida: 5-cloro-*N*-metoxi-*N*-metilpirazina-2-carboxamida (**Intermedio 54**).

MS (ES) MH^+: 637 para $C_{34}H_{36}ClF_2N_3O_3Si$

Intermedio 138

(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*R*)-2,6-dimetilmorfolino)-2,3-difluorofenil)(6-metoxipirazin-2-il)metanona

Material de partida: *N*,6-dimetoxi-*N*-metilpirazina-2-carboxamida (**Intermedio 55**).

MS (ES) MH^+: 632 para $C_{35}H_{39}F_2N_3O_4Si$

Intermedio 139

1-(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)-2-(1*H*-1,2,4-triazol-1-il)etanona

Se agregó carbonato de potasio (1208 mg, 8,74 mmol) a una mezcla de 1-(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)-2-cloroetanona (**Intermedio 127**, 500 mg, 0,87 mmol) y 1*H*-1,2,4-triazol (66,4 mg, 0,96 mmol) disuelto en 15 mL de acetonitrilo. La mezcla se agitó a temperatura ambiente durante 3 horas. Carbonato de potasio se filtró de la mezcla y el filtrado se diluyó con agua y se extrajo con acetato de etilo (2 X 100 mL). Las fases orgánicas se combinaron, se secaron (Na_2SO_4) y se concentraron. El residuo bruto (482 mg, 91%) contenía principalmente el compuesto del título deseado y se utilizó en la siguiente etapa sin purificación adicional.

MS (ES) MH^+: 605 para $C_{33}H_{38}F_2N_4O_3Si$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,02-1,12 (superposición de singlete y doblete, 15H), 2,67-2,91 (m, 4H), 3,35-3,54 (m, 2H), 4,63 (s, 2H), 5,56 (d, 2H), 7,29-8,32 (m, 13H).

Intermedio 140

(6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)(piridin-2-il)metanona

Se agregó gota a gota diisopropilamina (0,925 mL, 6,55 mmol) a una solución agitada de 2,5M n-butillitio en hexano (2,495 mL, 6,24 mmol) en THF (10 mL) a -78 °C. Se dejó entibiar la solución hasta 0 °C durante 10 minutos y posteriormente se enfrió nuevamente hasta -78 °C. Se introdujo mediante una cánula la LDA preparada a -78 °C en (2*R*,6*S*)-4-(2-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-fluoropiridin-3-il)-2,6-dimetilmorfolina (**Intermedio 45,** 1,6 g, 3,12 mmol) en THF (10 mL) a -78 °C . Se dejó agitar la solución oscura durante 20 minutos y luego se introdujo mediante una cánula en una solución agitada de *N*-metoxi-*N*-metilpicolinamida (1,05 g, 6,24 mmol) en THF (10 mL) a -78 °C. Se dejó entibiar la solución hasta –50 °C y luego se detuvo con solución de cloruro de amonio saturado. Se extrajo la mezcla con acetato de etilo y las fases orgánicas resultantes se lavaron con salmuera. Las fases orgánicas se secaron sobre sulfato de sodio, se filtraron y el filtrado se evacuó al vacío para proporcionar un aceite amarillo bruto. El aceite bruto se purificó sobre sílice utilizando 10-30% de acetona en n-hexano como eluyente para proporcionar 1,3 g (67%) del compuesto del título como un aceite.
MS (ES) MH^+: 618 para $C_{34}H_{37}ClFN_3O_3Si$
^1H RMN (300 MHz, $CDCl_3$) δ: 0,9 (s, 9H), 1,0 (d, 6H), 2,7–2,9 (m, 2H), 2,9–3,1 (m, 2H), 3,6 (s a, 2H), 4,8 (s, 2H), 7,1–7,3 (m, 4H), 7,3-7,4 (m, 2H), 7,5-7,6 (m, 5H), 7,9–8,1 (m, 2H), 8,5–8,6 (m, 1H).

Los **Intermedios 141** a **148** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 140:**

Intermedio 141

(6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)(piridin-4-il)metanona

Material de partida: (2*R*, 6*S*)-4-(2-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-fluoropiridin-3-il)-2,6-dimetilmorfolina (1,5 g, 2,92 mmol) (**Intermedio 45**) y *N*-metoxi-*N*-metilisonicotinamida.
MS (ES) MH^+: 621 para $C_{34}H_{37}ClFN_3O_3Si$

Intermedio 142

(6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)(piridin-3-il)metanona

Material de partida: (2*R*, 6*S*)-4-(2-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-fluoropiridin-3-il)-2,6-dimetilmorfolina (**Intermedio 45**) y *N*-metoxi-*N*-metilnicotinamida.

MS (ES) MH^+: 618 para $C_{34}H_{37}ClFN_3O_3Si$:

^1H RMN (300 MHz, $CDCl_3$) δ: 0,9-1,0 (m, 9H), 1,2 (dd, 6H), 3,0-3,1 (m, 4H), 3,7 (d, 2H), 4,8 (m, 2H), 7,2–7,3 (m, 4H), 7,4 (td, 3H), 7,6 (m, 3H), 7,7 (dd, 2H), 8,6–8,7 (m, 2H).

Intermedio 143

(6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)(pirazin-2-il)metanona

Material de partida: (2-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-fluoropiridin-3-il)-2,6-dimetilmorfolina (**Intermedio 45**) y *N*-metoxi-*N*-metilpirazina-2-carboxamida.

MS (ES) MH^+: 619 para $C_{33}H_{36}ClFN_4O_3Si$

^1H RMN (300 MHz, $CDCl_3$) δ: 0,9-1,0 (m, 9H), 1,1–1,2 (m, 6H,) 2,9-3,1 (m, 2H), 3,2 (t, 2H), 3,7 (s a, 2H), 4,8 (s, 2H), 7,2–7,3 (m, 4H), 7,3–7,4 (m, 2H), 7,6–7,7 (m, 4H), 8,2 (m, 1H), 8,8 (m, 1H), 9,1 (d, 1H).

Intermedio 144

(6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)(tiazol-2-il)metanona

Material de partida: (2-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-fluoropiridin-3-il)-2,6-dimetilmorfolina (**Intermedio 45**) y *N*-metoxi-*N*-metiltiazol-2-carboxamida.

MS (ES) MH^+: 624 para $C_{32}H_{35}ClFN_3O_3SiS$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,0 (s, 9H), 1,1 (d, 6H), 3,0 (s a, 2H), 3,1–3,2 (m, 2H), 3,7 (s a, 2H), 4,9 (s, 2H), 7,2–7,5 (m, 6H), 7,5–7,6 (m, 4H), 8,1 (s, 1H).

Intermedio 145

(6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)(4-metiltiazol-2-il)metanona

Material de partida: (2-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-fluoropiridin-3-il)-2,6-dimetilmorfolina (**Intermedio 45**) y *N*-metoxi-*N*,4-dimetiltiazol-2-carboxamida.

MS (ES) MH^+: 638 para $C_{33}H_{37}ClFN_3O_3SiS$

^{1}H RMN (300 MHz, $CDCl_3$) δ: 1,0 (s, 9H), 1,1 (d, 6H), 2,5 (s, 3H), 3,0 (s a, 2H), 3,1– 3,2 (m, 2H), 3,7 (dd, 2H), 4,9 (s, 2H), 7,2–7,5 (m, 6H), 7,5–7,6 (m, 4H), 7,6 (s, 1H).

Intermedio 146

(6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)(1-metil-1*H*-1,2,4-triazol-5-il)metanona

Material de partida: (2*R*,6*S*)-4-(2-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-fluoropiridin-3-il)-2,6-dimetilmorfolina (**Intermedio 45**) y *N*-metoxi-*N*,1-dimetil-1*H*-1,2,4-triazol-5-carboxamida (**Intermedio 49**).

MS (ES) MH^+: 622 para $C_{32}H_{37}ClFN_5O_3Si$

^{1}H RMN (300 MHz, $CDCl_3$) δ: 0,9 -1,0 (m, 9H) 1,2 (d, 6H) 2,8–3,0 (m, 2H) 3,0 (d, 2H) 3,7 (d, 2H) 4,3 (s, 2H) 4,8 (s, 2H) 7,2–7,3 (m, 4H) 7,3–7,6 (m, 3H) 7,7 (d, 4H) 7,9 (s, 1H).

Intermedio 147

5-(6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropicolinoil)picolinonitrilo

Material de partida: (2*R*,6*S*)-4-(2-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-fluoropiridin-3-il)-2,6-dimetilmorfolina (**Intermedio 45**) y 6-ciano-*N*-metoxi-*N*-metilnicotinamida.

MS (ES) MH^+: 643 para $C_{35}H_{36}ClFN_4O_3Si$

^{1}H RMN (300 MHz, $CDCl_3$) δ: 0,9–1,1 (m, 9H), 1,2 (d, 6H), 3,0–3,1 (m, 2H), 3,6–3,7 (m, 2H), 3,6–3,7 (m, 2H), 4,7–4,8 (m, 2H), 7,2–7,3 (m, 4H), 7,5–7,6 (m, 5H), 7,6–7,7 (m, 2H), 8,3 (dd, 1H), 9,1 (d, 1H).

Intermedio 148

1-(6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)etanona

Materiales de partida: (2*R*,6*S*)-4-(2-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-fluoropiridin-3-il)-2,6-dimetilmorfolina (**Intermedio 45**) y *N*-metoxi-*N*-metilacetamida.

MS (ES) MH^+: 555 para $C_{30}H_{36}ClFN_2O_3Si$

^{1}H RMN (300 MHz, CD_2Cl_2) δ: 1,05 (s, 9H), 1,1 (d, 6H), 2,6 (s, 3H), 3,0-3,2 (m, 4H), 3,7-3,8 (m, 2H), 4,9 (s, 2H), 7,4-7,5 (m 6H), 7,7-7,8 (m, 4H).

Intermedio 149

{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(2-metil-1,3-oxazol-4-il)metanona

Se agregó *sec*-butillitio (1,4 M en ciclohexano, 3,2 eq) a una solución agitada de (2*R*,6*S*)-4-[6-({[*terc*-butil(difenil)silil]oxi}metil)-2,3-difluorofenil]-2,6-dimetilmorfolina (**Intermedio 3,** 1,0 g, 2,02 mmol) en THF anhidro (10 mL) a -78 °C y la mezcla se agitó durante 2 h. Se agregó gota a gota *N*-metoxi-*N*,2-dimetil-1,3-oxazol-4-carboxamida (1,0 g, 6,46 mmol) en THF (5 mL) y se continuó agitando durante una 1 h más. La mezcla de reacción se detuvo con solución de cloruro de amonio saturado y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se secó sobre sulfato de sodio anhidro. El disolvente se eliminó al vacío y el residuo se purificó mediante cromatografía en gel de sílice utilizando un gradiente de acetato de etilo-éter de pet. para obtener un producto. Rendimiento: 600 mg, (50%)

MS (ES) MH^+: 605 para $C_{34}H_{38}F_2N_2O_4Si$

^1H RMN (400 MHz, DMSO-d_6) δ: 1,0 (m, 15H), 2,5 (s, 3H), 2,7 (m, 2H), 2,8 (d, 2H), 4,8 (s, 2H), 7,4 (m, 6H), 7,6 (t, 4H), 7,7 (d, 1H), 8,8 (s, 1H).

Los **Intermedios 150** a **156** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 149**:

Intermedio 150

{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(5-metil-1,2-oxazol-3-il)metanona

Materiales de partida: (2*R*,6*S*)-4-[6-({[*terc*-butil(difenil)silil]oxi}metil)-2,3-difluorofenil]-2,6-dimetilmorfolina (**Intermedio 3**) y *N*-metoxi-*N*,5-dimetil-1,2-oxazol-3-carboxamida.

MS (ES) MH^+: 605 para $C_{34}H_{38}F_2N_2O_4Si$

Intermedio 151

{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(3,5-dimetil-1,2-oxazol-4-il)metanona

Materiales de partida: (2*R*,6*S*)-4-[6-({[*terc*-butil(difenil)silil]oxi}metil)-2,3-difluorofenil]-2,6-dimetilmorfolina (**Intermedio 3**) y *N*-metoxi-*N*,3,5-trimetil-1,2-oxazol-4-carboxamida.
MS (ES) MH^+: 619,5 para $C_{35}H_{40}F_2N_2O_4Si$

Intermedio 152

{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(1-metil-1*H*-imidazol-2-il)metanona

Materiales de partida: (2*R*,6*S*)-4-[6-({[*terc*-butil(difenil)silil]oxi}metil)-2,3-difluorofenil]-2,6-dimetilmorfolina (**Intermedio 3**) y *N*-metoxi-*N*,1-dimetil-1*H*-imidazol-2-carboxamida.
MS (ES) MH^+: 604 para $C_{34}H_{39}F_2N_3O_3Si$

Intermedio 153

{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(1-metil-1*H*-imidazol-4-il)metanona

Materiales de partida: (2*R*,6*S*)-4-[6-({[*terc*-butil(difenil)silil]oxi}metil)-2,3-difluorofenil]-2,6-dimetilmorfolina (**Intermedio 3**) y *N*-metoxi-*N*,1-dimetil-1*H*-imidazol-4-carboxamida.
MS (ES) MH^+: 604,2 para $C_{34}H_{39}F_2N_3O_3Si$

Intermedio 154

{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(4-metil-1,2,3-tiadiazol-5-il)metanona

Materiales de partida: (2*R*,6*S*)-4-[6-({[*terc*-butil(difenil)silil]oxi}metil)-2,3-difluorofenil]-2,6-dimetilmorfolina (**Intermedio 3**) y *N*-metoxi-*N*,4-dimetil-1,2,3-tiadiazol-5-carboxamida
MS (ES) MH^+: 622 para $C_{33}H_{37}F_2N_3O_3SSi$

Intermedio 155

{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(piridazin-3-il)metanona

Material de partida: (2*R*,6*S*)-4-[6-({[*terc*-butil(difenil)silil]oxi}metil)-2,3-difluorofenil]-2,6-dimetilmorfolina (**Intermedio 3**) y *N*-metoxi-*N*-metilpiridazina-3-carboxamida
MS (ES) MH^+: 602 para $C_{34}H_{37}F_2N_3O_3Si$

Intermedio 156

{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(pirimidin-4-il)metanona

Material de partida: (2*R*,6*S*)-4-[6-({[*terc*-butil(difenil)silil]oxi}metil)-2,3-difluorofenil]-2,6-dimetilmorfolina (**Intermedio 3**) y *N*-metoxi-*N*-metilpirimidina-4-carboxamida

MS (ES) MH^+: 602 para $C_{34}H_{37}F_2N_3O_3Si$

Intermedio 157

{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-metil-1,2-benzotiazol-5-il}metanol

Una mezcla de 1-[5-(*terc*-butildifenilsilaniloximetil)-4-[(2*R*,6*S*)-2,6-dimetil-morfolin-4-il]-2,3-difluorofenil]etanona (**Intermedio 9**, 0,5 g, 0,92 mmol), polvo de azufre (0,06 g, 1,8 mmol), yoduro de potasio (0,08 g, 0,4 mmol) y solución de amoníaco acuoso al 25% (10 mL) en DMSO (10 mL) se calentó en un tubo sellado a 100 °C durante 4 horas. La mezcla de reacción se enfrió y se agregó agua. La mezcla se extrajo con acetato de etilo, que se secó (Na_2SO_4) y se concentró. El residuo se purificó mediante cromatografía en columna (1:9 acetato de etilo:hexanos) para proporcionar un producto como un sólido amarillo. Rendimiento: 0,18 g (63%).

MS (ES) MH^+: 311 para $C_{15}H_{19}FN_2O_2S$

^{1}H RMN (400 MHz, metanol-d_4): δ 1,2 (d, 6H), 2,5 (s, 3H), 3,0 (m, 4H), 3,8 (m, 2H), 4,8 (s, 2H), 8,0 (s, 1H).

El **Intermedio 158** se preparó a partir del material de partida indicado utilizando un método similar al descrito para la síntesis del **Intermedio 157:**

Intermedio 158

{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(piridin-2-il)-1,2-benzotiazol-5-il}metanol

Material de partida: {5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(piridin-2-il)metanona (**Intermedio 21**).

MS (ES) MH^+: 374 para $C_{19}H_{20}FN_3O_2S$

^{1}H RMN (400 MHz, $CDCl_3$) δ: 1,25 (d, 6H), 2,7 (m, 2H), 3,0 (d, 2H), 3,1 (t, 2H), 3,8 (m, 2H), 4,9 (s, 2H), 7,5 (m, 1H), 7,9 (t, 1H), 8,3 (d, 1H), 8,8 (d, 1H), 8,9 (s, 1H).

Intermedio 159

1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}-2,2,2-trifluoro-*N*-hidroxietanimina

Se agregó piridina (2597 µl, 32,11 mmol) a una mezcla de 1-(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)-2,2,2-trifluoroetanona (**Intermedio 130,** 1900 mg, 3,21 mmol) y clorhidrato de hidroxilamina (223 mg, 3,21 mmol) en 50 mL de etanol y la solución se calentó a 80 °C durante 40 horas. La mezcla de reacción se concentró, se diluyó con agua y se extrajo con acetato de etilo. Las fases orgánicas se combinaron, se secaron (Na_2SO_4) y se concentraron para proporcionar el compuesto bruto del título (1,95 g, 98%), que se utilizó en la siguiente etapa sin purificación adicional.

MS (ES) MH^+: 607 para $C_{31}H_{35}F_5N_2O_3Si$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,03-1,15 (m, 15H), 2,56-2,91 (m, 4H), 3,33-3,59 (m, 2H), 4,58-4,80 (m, 2H), 7,27-7,51 (m, 7H), 7,57-7,74 (m, 4H).

Los **Intermedios 160** a **164** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 159:**

Intermedio 160

1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}-2,2-difluoro-*N*-hidroxietanimina

Material de partida: 1-(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)-2,2-difluoroetanona (**Intermedio 129**).

MS (ES) MH^+: 589 para $C_{31}H_{36}F_4N_2O_3Si$

Intermedio 161

1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}-*N*-hidroxi-1-piridin-4-ilmetanimina

Material de partida: (5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)(piridin-4-il)metanona (**Intermedio 128**).

MS (ES) MH^+: 616 para $C_{35}H_{39}F_2N_3O_3Si$

Intermedio 162

1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}-1-furan-2-il-*N*-hidroximetanimina

Material de partida: (5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)(furan-2-il)metanona (**Intermedio 122**).

MS (ES) MH^+: 605 para $C_{34}H_{38}F_2N_2O_4Si$

Intermedio 163

1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}-*N*-hidroxi-2-(1*H*-1,2,4-triazol-1-il)etanimina

Material de partida: 1-(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)-2-(1*H*-1,2,4-triazol-1-il)etanona (**Intermedio 139**).

MS (ES) MH^+: 620 para $C_{33}H_{39}F_2N_5O_3Si$

Intermedio 164

1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*R*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}-2,2-difluoro-*N*-hidroxietanimina

Material de partida: 1-(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*R*)-2,6-dimetilmorfolino)-2,3-difluorofenil)-2,2-difluoroetanona (**Intermedio 132**).

MS (ES) MH^+: 589 para $C_{31}H_{36}F_4N_2O_3Si$

Intermedio 165

2-(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)-2-(hidroxiimino)acetato de etilo

Se disolvió 2-(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)-2-oxoacetato de etilo (**Intermedio 114**, 2,808 g, 4,71 mmol) y clorhidrato de hidroxilamina (0,360 g, 5,18 mmol) en piridina (40 mL) y se agitó a 115 °C durante 16 horas. La reacción se concentró para eliminar el exceso de piridina. El residuo se disolvió en acetato de etilo y se lavó con agua y salmuera 3x. La capa orgánica se secó con $MgSO_4$ y se concentró. El residuo se purificó mediante cromatografía en columna de gel de sílice utilizando un gradiente de

hexanos a acetato de etilo para proporcionar el compuesto del título como una mezcla de isómeros de oxima (1,924 g, 3,15 mmol, 66,8 %).

MS (ES) MH^+: 611 para $C_{33}H_{40}F_2N_2O_5Si$ (2 picos mediante LCMS).

^1H RMN (300 MHz, DMSO-d_6) δ ppm 0,9-1,1 (m, 15H), 1,15-1,3 (m, 3H), 2,6-2,8 (m, 4H), 4,2-4,35 (m, 2H), 4,7-4,8 (m, 2H), 7,3-7,65 (m, 11H).

Los **Intermedios 166** y **167** se prepararon a partir del material de partida indicado utilizando un método similar al descrito para la síntesis del **Intermedio 165:**

Intermedio 166

2-(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*R*)-2,6-dimetilmorfolino)-2,3-difluorofenil)-2-(hidroxiimino)acetato de etilo

Material de partida: 2-(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*R*)-2,6-dimetilmorfolino)-2,3-difluorofenil)-2-oxoacetato de etilo (**Intermedio 116**).

MS (ES) MH^+: 611 para $C_{33}H_{40}F_2N_2O_5Si$

Intermedio 167

2-(5-(dimetoximetil)-2,3,4-trifluorofenil)-2-(hidroxiimino)acetato de etilo

Material de partida: 2-(5-(dimetoximetil)-2,3,4-trifluorofenil)-2-oxoacetato de etilo (**Intermedio 117**).

MS (ES) $M^+(-CH_3O)$: 290

Intermedio 168

2-(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)-2-(hidroxiimino)-1-morfolinoetanona

Se agitó 1-(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)-2-morfolinoetano-1,2-diona (**Intermedio 119**, 130 mg, 0,20 mmol) en piridina a 115 °C durante 16 horas. La reacción se dejó enfriar hasta alcanzar la temperatura ambiente y luego se concentró. El residuo se disolvió en acetato de etilo, se diluyó con agua y se volvió ácido con HCl 1N. La mezcla se extrajo dos veces con acetato de etilo. Las capas orgánicas se lavaron dos veces con salmuera, se secaron sobre $MgSO_4$ y se concentraron para proporcionar el

compuesto del título como un aceite que se secó al vacío. El residuo se utilizó más adelante sin purificación adicional.
MS (ES) MH^+: 652 para $C_{35}H_{43}F_2N_3O_5Si$

Los **Intermedios 169** y **170** se prepararon a partir del material de partida indicado utilizando un método similar al descrito para la síntesis del **Intermedio 168**:

Intermedio 169

2-(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)-2-(hidroxiimino)-*N*,*N*-dimetilacetamida

Material de partida: 2-(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)-*N*,*N*-dimetil-2-oxoacetamida (**Intermedio 120**).
MS (ES) MH^+: 610 para $C_{33}H_{41}F_2N_3O_4Si$

Intermedio 170

2-(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)-2-(hidroxiimino)-*N*-metoxi-*N*-metilacetamida

Material de partida: 2-(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)-*N*-metoxi-*N*-metil-2-oxoacetamida (**Intermedio 115**).
MS (ES) MH^+: 626 para $C_{33}H_{41}F_2N_3O_5Si$

Intermedio 171

3-cloro-2-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-4-fluoro-5-[*N*-hidroxietanimidoil]benzoato de metilo

A una solución de 5-acetil-3-cloro-2-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-4-fluorobenzoato de metilo (**Intermedio 107,** 800 mg, 2,32 mmol) en metanol:piridina (1:1, 6 mL) se agregó clorhidrato de hidroxilamina (223 mg, 3,48 mmol) y la mezcla se agitó a temperatura ambiente durante 12 horas. Los disolventes se retiraron al vacío y el residuo se sometió a cromatografía en columna de gel de sílice utilizando un gradiente de acetato de etilo en éter de pet. para proporcionar el compuesto del título. Rendimiento: 700 mg (87%).
MS (ES) MH^+: MS (ES) MH^+: 359 para $C_{16}H_{20}ClFN_2O_4$

Los **Intermedios 172** a **196** se prepararon a partir del material de partida indicado y clorhidrato de hidroxilamina utilizando un método similar al descrito para la síntesis del **Intermedio 171**:

Intermedio 172

1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}-*N*-hidroxi-1-(piridin-2-il)metanimina

Material de partida: {5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}(piridin-2-il)metanona (**Intermedio 85**).

MS (ES) MH^+: 632 para $C_{35}H_{39}ClFN_3O_3Si$

Intermedio 173

1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}-*N*-hidroxi-1-(6-metilpiridin-3-il)metanimina

Material de partida: {5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}(6-metilpiridin-3-il)metanona (**Intermedio 108**).

MS (ES) MH^+: 646 para $C_{36}H_{41}ClFN_3O_3Si$.

Intermedio 174

1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}-*N*-hidroxi-1-(1,3-tiazol-5-il)metanimina

Material de partida: {5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}(1,3-tiazol-5-il)metanona (**Intermedio 86**).

MS (ES) MH^+: 638 para $C_{33}H_{37}ClFN_3O_3SSi$

Intermedio 175

1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}-*N*-hidroxi-1-(piridin-4-il)metanimina

Material de partida: {5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}(piridin-4-il)metanona (**Intermedio 87**).

MS (ES) MH^+: 632 para $C_{35}H_{39}ClFN_3O_3Si$

Intermedio 176

1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}-*N*-hidroxi-1-(piridin-3-il)metanimina

Material de partida: {5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}(piridin-3-il)metanona (**Intermedio 88**).

MS (ES) MH^+: 632 para $C_{35}H_{39}ClFN_3O_3Si$

Intermedio 177

1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}-*N*-hidroxi-1-(1,3-tiazol-2-il)metanimina

Material de partida: {5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}(1,3-tiazol-2-il)metanona (**Intermedio 89**).

MS (ES) MH^+: 638 para $C_{33}H_{37}ClFN_3O_3SSi$

Intermedio 178

1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}-*N*-hidroxi-1-(1-metil-1*H*-imidazol-2-il)metanimina

Material de partida: {5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}(1-metil-1*H*-imidazol-2-il)metanona (**Intermedio 90**).

MS (ES) MH^+: 635 para $C_{34}H_{40}ClFN_4O_3Si$

Intermedio 179

1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}-*N*-hidroxi-2-metoxietanimina

Material de partida: 1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}-2-metoxietanona (**Intermedio 113**).

MS (ES) MH^+: 599 para $C_{32}H_{40}ClFN_2O_4Si$

Intermedio 180

{2-[{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(hidroxiimino)metil]-1,3-tiazol-4-il}(morfolin-4-il)metanona

Material de partida: {2-[{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(hidroxi)metil]-1,3-tiazol-4-il}(morfolin-4-il)metanona (**Intermedio 92**).

MS (ES) MH^+: MS (ES) MH^+: 620 para $C_{34}H_{39}F_2N_3O_4Si$

Intermedio 181

{5-[{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(hidroxiimino)metil]-1,3-tiazol-4-il}(morfolin-4-il)metanona

Material de partida: {5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}{4-[hidroxi(morfolin-4-il)metil]-1,3-tiazol-5-il}metanona (**Intermedio 93**).

MS (ES) MH^+: 735 para $C_{38}H_{44}F_2N_4O_5SSi$

Intermedio 182

2-[{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(hidroxiimino)metil]-*N*,*N*-dimetil-1,3-tiazol-4-carboxamida

Material de partida: 2-({5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}carbonil)-*N*,*N*-dimetil-1,3-tiazol-4-carboxamida (**Intermedio 94**).

MS (ES) MH^+: 693 para $C_{36}H_{42}F_2N_4O_4SSi$

Intermedio 183

2-[{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(hidroxiimino)metil]-*N*,*N*-dimetil-1,3-tiazol-5-carboxamida

Material de partida: 2-({5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}carbonil)-*N*,*N*-dimetil-1,3-tiazol-5-carboxamida (**Intermedio 95**).

MS (ES) MH^+: 693 para $C_{36}H_{42}F_2N_4O_4SSi$

Intermedio 184

5-[{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(hidroxiimino)metil]-1,3-tiazol-4-carbonitrilo

Material de partida: 5-({5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}carbonil)-1,3-tiazol-4-carbonitrilo (**Intermedio 96**).

MS (ES) MH^+: 647 para $C_{34}H_{36}F_2N_4O_3SSi$

Intermedio 185

1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}-*N*-hidroxi-1-(2-metil-1,3-oxazol-4-il)metanimina

Material de partida: {5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(2-metil-1,3-oxazol-4-il)metanona (**Intermedio 149**).

MS (ES) MH^+: MS (ES) MH^+: 620 para $C_{34}H_{39}F_2N_3O_4Si$

Intermedio 186

1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}-*N*-hidroxi-1-(5-metil-1,2-oxazol-3-il)metanimina

Material de partida: {5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(5-metil-1,2-oxazol-3-il)metanona (**Intermedio 150**).

MS (ES) MH^+: 620 para $C_{34}H_{39}F_2N_3O_4Si$

Intermedio 187

1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}-1-(3,5-dimetil-1,2-oxazol-4-il)-*N*-hidroximetanimina

Material de partida: {5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(3,5-dimetil-1,2-oxazol-4-il)metanona (**Intermedio 151**).

MS (ES) MH^+: 634 para $C_{35}H_{41}F_2N_3O_4Si$

Intermedio 188

1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}-*N*-hidroxi-1-(1-metil-1*H*-imidazol-2-il)metanimina

Material de partida: {5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(1-metil-1*H*-imidazol-2-il)metanona (**Intermedio 152**).

MS (ES) MH^+: 618 para $C_{34}H_{40}F_2N_4O_3Si$

Intermedio 189

1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}-*N*-hidroxi-1-(1-metil-1*H*-imidazol-4-il)metanimina

Material de partida: {5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(1-metil-1*H*-imidazol-4-il)metanona (**Intermedio 153**).

MS (ES) MH^+: 618 para $C_{34}H_{40}F_2N_4O_3Si$

Intermedio 190

1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}-*N*-hidroxi-1-(1-metil-1*H*-imidazol-5-il)metanimina

Material de partida: {5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(1-metil-1*H*-imidazol-5-il)metanona (**Intermedio 97**).

MS (ES) MH^+: 618 para $C_{34}H_{40}F_2N_4O_3Si$

Intermedio 191

1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}-*N*-hidroxi-1-(4-metil-1,3-tiazol-5-il)metanimina

Material de partida: {5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(4-metil-1,3-tiazol-5-il)metanona (**Intermedio 98**).

MS (ES) MH^+: 636 para $C_{34}H_{39}F_2N_3O_3Si$

Intermedio 192

1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}-*N*-hidroxi-1-(4-metil-1,2,3-tiadiazol-5-il)metanimina

Material de partida: {5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(4-metil-1,2,3-tiadiazol-5-il)metanona (**Intermedio 154**).

MS (ES) MH^+: 637 para $C_{33}H_{38}F_2N_4O_3SSi$

Intermedio 193

1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}-*N*-hidroxi-1-(piridazin-3-il)metanimina

Material de partida: {5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(piridazin-3-il)metanona (**Intermedio 155**).

MS (ES) MH^+: 617,2 para $C_{34}H_{38}F_2N_4O_3Si$

Intermedio 194

1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}-*N*-hidroxi-1-(pirimidin-4-il)metanimina

Material de partida: {5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(pirimidin-4-il)metanona (**Intermedio 156**).

MS (ES) MH^+: 617 para $C_{34}H_{38}F_2N_4O_3Si$

Intermedio 195

Ácido 2-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-4-fluoro-5-[(hidroxiimino)(1,3-tiazol-2-il)metil]-3-metilbenzoico

Material de partida: ácido 2-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-4-fluoro-3-metil-5-(1,3-tiazol-2-ilcarbonil)benzoico (**Intermedio 60**).

MS (ES) MH^+: 393 para $C_{18}H_{20}FN_3O_4S$

Intermedio 196

Ácido 2-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-4-fluoro-5-[(hidroxiimino)(pirazin-2-il)metil]-3-metilbenzoico

Material de partida: ácido 2-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-4-fluoro-3-metil-5-(pirazin-2-ilcarbonil)benzoico (**Intermedio 61**).

MS (ES) MH^+: 388 para $C_{19}H_{21}FN_4O_4$

Intermedio 197

2-(6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)-2-(hidroxiimino)acetato de etilo

Se suspendió etil 2-(6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)-2-oxoacetato (**Intermedio 121**, 13,4 g, 21,85 mmol) en isopropanol (150 mL) y se agregó piridina (124 mL, 1529,70 mmol) para proporcionar una solución amarilla. Se agregó clorhidrato de hidroxilamina (1,670 g, 24,04 mmol) y la suspensión se agitó a temperatura ambiente durante aproximadamente 16 horas. La solución resultante se concentró hasta proporcionar un aceite. El residuo se purificó mediante cromatografía en SiO_2 utilizando 5-40 % de EtOAc/hexano. Un total de 11,93 g (87%) del producto del título como una mezcla de isómeros de oxima se obtuvo como un aceite amarillo.

MS (ES) MH^+: 628 para $C_{32}H_{39}CFN_3O_5Si$

Intermedio 198

{5-[(3-cloropirazin-2-il)(hidroxiimino)metil]-2-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3,4-difluorofenil}metanol

Una mezcla de (5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)(3-cloropirazin-2-il)metanona (**Intermedio 135,** ~150 mg) y $NH_2OH.HCl$ en 10 mL de MeOH se agitó durante 72 horas a temperatura ambiente. La mezcla de reacción se diluyó con EtOAc y se lavó con agua y salmuera. Después de secarse con sulfato de sodio anhidro, filtrarse y concentrarse, el residuo resultante se purificó mediante cromatografía en columna de gel de sílice (Hexanos/EtOAc) para proporcionar el producto (106 mg).

MS (ES) MH^+: 413 para $C_{18}H_{19}ClF_2N_4O_3$

Los **Intermedios 199** y **200** se prepararon a partir del material de partida indicado y clorhidrato de hidroxilamina utilizando un método similar al descrito para la síntesis del **Intermedio 198**:

Intermedio 199

1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}-1-(6-cloropirazin-2-il)-*N*-hidroximetanimina

Material de partida: (5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)(6-cloropirazin-2-il)metanona (**Intermedio 136**).

MS (ES) MH^+: 652 para $C_{34}H_{37}ClF_2N_4O_3Si$

Intermedio 200

1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}-1-(5-cloropirazin-2-il)-*N*-hidroximetanimina

Material de partida: (5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)(5-cloropirazin-2-il)metanona (**Intermedio 137**).

MS (ES) MH^+: 652 para $C_{34}H_{37}ClF_2N_4O_3Si$

Intermedio 201

(7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(piridin-2-il)isoxazolo[4,5-b]piridin-5-il)metanol

Una solución de (6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)(piridin-2-il)metanona (**Intermedio 140**, 1,3 g, 2,10 mmol) y clorhidrato de hidroxilamina (0,146 g, 2,10 mmol) en una mezcla de piridina (10 mL) / metanol (20 mL) se calentó durante 2 horas a 40 °C y posteriormente se enfrió y se concentró al vacío para proporcionar un aceite amarillo bruto que pesó 1,3 g.

Al aceite anterior se agregó DMF (30 mL) y carbonato de cesio (0,801 g, 2,46 mmol). La suspensión se calentó a 40 °C durante 4 horas y luego se enfrió. La mezcla de reacción se detuvo con agua y se extrajo con acetato de etilo. Las fases orgánicas se lavaron con salmuera luego las fases orgánicas se secaron con sulfato de sodio, se filtraron y el filtrado se evacuó al vacío para proporcionar un aceite amarillo bruto. El aceite bruto se purificó sobre sílice utilizando 20-40% de acetona en n-hexano para proporcionar 0,39 g (51%) del compuesto del título como un aceite.

MS (ES) MH^+: 375 para $C_{18}H_{19}ClN_4O_3$

^1H RMN (300 MHz, DMSO-d_6) δ: 1,0–1,1 (m, 6H), 3,0 (d, 4H), 3,7–3,9 (m, 2H), 4,8 (td, 2H), 5,2 (s a, 1H), 7,6 (td, 1H), 8,1 (td, 1H), 8,6 (d, 1H), 8,8 (dd, 1H).

Los **Intermedios 202** y **203** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 201:**

Intermedio 202

(7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(piridin-4-il)isoxazolo[4,5-b]piridin-5-il)metanol

Material de partida: (6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)(piridin-4-il)metanona (**Intermedio 141**).

MS (ES) MH^+: 375 para $C_{18}H_{19}ClN_4O_3$

^1H RMN (300 MHz, DMSO-d_6) δ: 1,0–1,1 (m, 6H), 3,0 (d, 4H), 3,7–3,8 (m, 2H), 4,8 (td, 2H), 5,3 (s a, 1H), 8,4 (dd, 2H), 8,8 (dd, 2H).

Intermedio 203

(7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(piridin-3-il)isoxazolo[4,5-b]piridin-5-il)metanol

Material de partida: (6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)(piridin-3-il)metanona (**Intermedio 142**).

MS (ES) MH^+: 375 para $C_{18}H_{19}ClN_4O_3$

^1H RMN (300 MHz, DMSO-d_6) δ: 1,0–1,1 (m, 6H), 3,0 (d, 4H), 3,7–3,9 (m, 2H), 4,8 (td, 2H), 5,2 (s a, 1H), 7,9 (dd, 1H), 8,7-8,8 (m, 2H).

Intermedio 204

5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxilato de etilo

Se suspendió hidruro de sodio (0,159 g, 3,97 mmol) en 20 mL de DMF y se enfrió en un baño de hielo. 2-(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)-2-(hidroxiimino)acetato de etilo (**Intermedio 165**, 1,94 g, 3,18 mmol) se disolvió en 20 mL de DMF y se agregó al matraz de reacción. El baño de hielo se retiró y la reacción se agitó a temperatura ambiente durante 2 horas. La reacción se detuvo con NH_4Cl sat.(5 mL), se diluyó con agua y se extrajo tres veces con acetato de etilo. Se combinaron las capas orgánicas, se lavaron con agua y salmuera 5x, se secaron con $MgSO_4$ y se concentraron. El residuo se purificó mediante cromatografía en columna de gel de sílice utilizando un gradiente de hexanos a acetato de etilo para proporcionar el compuesto del título (1,250 g, 66,6 %).

MS (ES) MH^+: 591 para $C_{33}H_{39}FN_2O_5Si$

^1H RMN (300 MHz, DMSO-d_6) δ ppm 1,0 (d, 6H), 1,1 (s, 9H), 1,4 (t, 3H), 2,6-2,8 (m, 4H), 4,5 (c, 2H), 4,9 (s, 2H), 7,4-7,5 (m, 6H), 7,6 (d, 4H), 8,1 (s, 1H).

Los **Intermedios 205** y **206** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 204**:

Intermedio 205

5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-*N*-metoxi-*N*-metilbenzo[d]isoxazol-3-carboxamida

Material de partida: 2-(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)-2-(hidroxiimino)-*N*-metoxi-*N*-metilacetamida (**Intermedio 170**).

MS (ES) MH^+: 606 para $C_{33}H_{40}FN_3O_5Si$

^1H RMN (300 MHz, CLOROFORMO-d) δ ppm 1,0-1,2 (m, 15H), 2,7 (d, 2H), 2,8-3,0 (m, 2H), 3,4-3,6 (m, 5H), 3,8 (s, 3H), 4,8 (s, 2H), 7,3-7,5 (m, 6H), 7,7 (d, 4H), 7,9 (s a, 1H).

Intermedio 206

5-(dimetoximetil)-6,7-difluorobenzo[d]isoxazol-3-carboxilato de etilo

Material de partida: 2-(5-(dimetoximetil)-2,3,4-trifluorofenil)-2-(hidroxiimino)acetato de etilo (**Intermedio 167**).

MS (ES) $M^+(-CH_3O)$: 270

^1H RMN (300 MHz, CLOROFORMO-d) δ ppm 1,5 (t, 3H), 3,4 (s, 6H), 4,6 (c, 2H), 5,7 (s, 1H), 8,1 (d, 1H).

Intermedio 207

5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carbohidrazida

Se trató etil 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxilato (**Intermedio 204**, 0,5 g, 0,85 mmol) en 4,5 mL de etanol con hidrazina anhidra (0,490 mL, 15,60 mmol) a temperatura ambiente durante 2 horas. La reacción se diluyó con diclorometano y salmuera. La capa orgánica se lavó con agua, se secó con sulfato de sodio y se concentró. El residuo se purificó en una columna de gel de sílice (elución 40% de EtOAc en hexanos) para proporcionar 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carbohidrazida (0,354 g, 72,5%).

MS (ES) MH^+:577 para $C_{31}H_{37}FN_4O_4Si$

Intermedio 208

5-(5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-il)-1,3,4-oxadiazol-2(3H)-ona

Se disolvió 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carbohidrazida (**Intermedio 207**, 490 mg, 0,85 mmol) y di(1*H*-imidazol-1-il)metanona (207 mg, 1,27 mmol) en 8 mL de THF y se trató con DIEA (297 µl, 1,70 mmol) a temperatura ambiente durante 16 horas. La reacción se diluyó con acetato de etilo y se detuvo con solución ac. de cloruro de amonio. La capa orgánica se separó y se lavó con agua, se secó con sulfato de sodio y se concentró para proporcionar 5-(5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-il)-1,3,4-oxadiazol-2(3H)-ona (495 mg, 97 %).

MS (ES) MH^+: 603 para $C_{32}H_{35}FN_4O_5Si$

^1H RMN (300 MHz, DMSO-d_6) δ : 1,1 (d, 6 H) 1,1 (s, 9 H) 2,5 - 3,0 (m, 4 H) 3,3 - 3,6 (m, 2 H) 4,8 (s, 2 H) 7,3 - 7,7 (m, 10 H) 8,1 (s, 1 H) 9,0 (s, 1 H).

Intermedio 209

5-(6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)benzo[d]isoxazol-3-il)-1,3,4-oxadiazol-2(3H)-ona

Se trató 5-(5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-il)-1,3,4-oxadiazol-2(3H)-ona (**Intermedio 208,** 490 mg, 0,81 mmol) en 10 mL de THF con TBAF (1M en THF;1626 µl, 1,63 mmol) a temperatura ambiente durante 16 horas. La reacción se detuvo con solución ac. de cloruro de amonio y se extrajo con acetato de etilo. El producto bruto se purificó en columna (50-80% de EtOAc en hexanos) para proporcionar 5-(6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)benzo[d]isoxazol-3-il)-1,3,4-oxadiazol-2(3H)-ona (235 mg, 79%)

MS (ES) MH^+: 365 para $C_{16}H_{17}FN_4O_5$

^1H RMN (300 MHz, DMSO-d_6) δ: 1,1 (d, 6 H) 2,9 - 3,3 (m, 4 H) 3,7 - 3,9 (m, 2 H) 8,2 (s, 1 H) 10,3 (s, 1 H) 13,4 (s, 1 H)

Intermedio 210

5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxilato de etilo

Se suspendió hidruro de sodio (0,723 g, 18,07 mmol) en 60 mL de DMF y se enfrió en un baño de hielo. Se disolvió 2-(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*R*)-2,6-dimetilmorfolino)-2,3-difluorofenil)-2-(hidroxiimino)acetato de etilo (**Intermedio 166**, 8,827 g, 14,45 mmol) en 30 mL de DMF y se agregó al matraz de reacción. El baño de hielo se retiró y la reacción se agitó a temperatura ambiente durante 2 horas. El análisis por LCMS indicó que la reacción fue incompleta, por lo que se agregaron 100 mg adicionales de NaH y la reacción se agitó durante 30 minutos. El análisis por LCMS indicó que la reacción fue incompleta, por lo que se agregaron 100 mg adicionales de NaH y la reacción se agitó durante 30 minutos. La reacción se enfrió en un baño de hielo y se detuvo gota a gota con 5 mL de NH_4Cl saturado. La reacción se diluyó con agua y se extrajo tres veces con acetato de etilo. Se combinaron las capas orgánicas, se lavaron 5x con salmuera, se secaron con $MgSO_4$ y se concentraron para proporcionar un aceite. El aceite se purificó mediante cromatografía en columna de gel de sílice utilizando un gradiente de hexanos a acetato de etilo. Las fracciones se combinaron y se concentraron para proporcionar el compuesto del título (5,156 g, 8,73 mmol, 60,4 %).

MS (ES) MH^+: 591 para $C_{33}H_{39}FN_2O_5Si$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,94 (d, 6H) 1,10 (s, 9H) 1,38 (t, 3H) 2,59-2,73 (m, 2H) 2,91-3,10 (m, 2H) 3,77 (s a, 2H) 4,49 (c, J = 7,03 Hz, 2H) 4,84-5,03 (m, 2H) 7,36-7,54 (m, 6H) 7,63 (d, 4H) 8,14 (s, 1H)

También se aisló durante la purificación (2Z)-(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*R*)-2,6-dimetilmorfolino)-2,3-difluorofenil)-2-(hidroxiimino)acetato de etilo (1,22 g, 14%) como un solo isómero de oxima.

MS (ES) MH^+: 611 para $C_{33}H_{40}F_2N_2O_5Si$

Intermedio 211

5-((*terc*-butildifenilsililoxi)metil)-7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)isoxazolo[4,5-b]piridina-3-carboxilato de etilo

Se agregó hidruro de sodio, dispersión al 60% en aceite mineral (0,063 g, 1,56 mmol) a un matraz y DMF, 5 mL, se agregó para proporcionar una suspensión blanca. La mezcla se enfrió en un baño de hielo. Se agregó 2-(6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)-2-(hidroxiimino)acetato de etilo (**Intermedio 197,** 0,786 g, 1,25 mmol) en 5 mL de DMF a la suspensión de hidruro de sodio. Se produjo cierto desprendimiento de gas y la mezcla se volvió una solución naranja. La reacción se trató después de 1 hora. Luego se agregó solución de NH_4Cl saturada; la mezcla se extrajo con EtOAc y se lavó con agua (3x). La fase orgánica combinada se secó con $MgSO_4$ y se concentró. El residuo se purificó mediante cromatografía sobre SiO_2 utilizando 0-40% de EtOAc/hexanos para recuperar 544 mg (71%) del compuesto del título como una espuma amarilla.

MS (ES) MH^+: 608 para $C_{32}H_{38}ClN_3O_5Si$

^1H RMN (300 MHz, CD_2Cl_2) δ: 1,0-1,2 (superposición de multiplete, 15H), 1,5 (t, 3H), 2,8-2,9 (m, 2H), 3,1 (t, 2H), 3,7 (s a, 2H), 4. 6 (c, 2H), 5,0 (s, 2H), 7,3-7,8 (m, 10H).

Intermedio 212

5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-*N*-etil-7-fluorobenzo[d]isoxazol-3-carboxamida

En una atmósfera de nitrógeno, trimetilaluminio (2M en tolueno, 1206 µl, 2,41 mmol) se agregó lentamente (desprendimiento de gas) a una solución enfriada con hielo de etilamina (2M en THF) (1206 µl, 2,41 mmol) en 7 mL de tolueno. La reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó durante 2 horas. Se agregó 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxilato de etilo, (**Intermedio 204**, 190 mg, 0,32 mmol) como una solución en tolueno (3 mL). La reacción se agitó a 45 °C durante 18 horas. La reacción se detuvo gota a gota (fuerte desprendimiento de gas) con 2 mL de HCl 1N. La reacción bruta se filtró para eliminar los sólidos, se diluyó con agua y se extrajo dos veces con acetato de etilo. Se combinaron las capas orgánicas, se lavaron dos veces con salmuera, se secaron con $MgSO_4$ y se concentraron para proporcionar un aceite. El aceite se purificó mediante cromatografía en columna de gel de sílice utilizando un gradiente de hexanos a acetato de etilo. Las fracciones se combinaron y se concentraron para proporcionar el compuesto del título. (170 mg, 0,288 mmol, 90%).

MS (ES) MH^+: 590 para $C_{33}H_{40}FN_3O_4Si$

^{1}H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1,0-1,2 (m, 15H), 1,3 (t, 3H), 2,7 (d, 2H), 2,88 (t, 2H), 3,45 (m, 2H), 3,5-3,7 (m, 2H), 4,8 (s, 2H), 6,9 (m, 1H), 7,35-7,5 (m, 6H), 7,0 (d, 4H), 8,3 (s, 1H).

Los **Intermedios 213** a **240** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 212**:

Intermedio 213

5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-*N*-etil-7-fluoro-*N*-metilbenzo[d]isoxazol-3-carboxamida

Materiales de partida: 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxilato de etilo (**Intermedio 204**) y clorhidrato de *N*-metiletanamina.

MS (ES) MH^+: 604 para $C_{34}H_{42}FN_3O_4Si$

^{1}H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1,0-1,2 (m, 15H), 1,2-1,4 (m, 3H), 2,7 (d, 2H), 2,9 (t, 2H), 3,2 (d, 3H), 3,4-3,6 (m, 2H), 3,6-3,8 (m, 2H), 4,8 (s, 2H), 7,3-7,5 (m, 6H), 7,7 (d, 4H), 7,9 (s a, 1H).

Intermedio 214

5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-*N*-metilbenzo[d]isoxazol-3-carboxamida

Materiales de partida: 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxilato de etilo (**Intermedio 204**) y metilamina (2M en THF)

MS (ES) MH^+: 576 para $C_{32}H_{38}FN_3O_4Si$

^{1}H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1,0-1,2 (m, 15H), 2,7 (d, 2H), 2,8-3,0 (m, 2H), 3,12 (d, 3H), 3,5 (m, 2H), 4,8 (s, 2H), 6,9-7,1 (m, 1H), 7,3-7,5 (m, 6H), 7,7 (d, 4H), 8,3 (s, 1H).

Intermedio 215

4-(5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carbonil)-1-metilpiperazin-2-ona

Materiales de partida: 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxilato de etilo (**Intermedio 204**) y clorhidrato de 1-metilpiperazin-2-ona.

MS (ES) MH^+: 659 para $C_{36}H_{43}FN_4O_5Si$

Intermedio 216

(5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-il)(3,3-difluoroazetidin-1-il)metanona

Materiales de partida: 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxilatode etilo (**Intermedio 204**) y clorhidrato de 3,3-difluoroazetidina.

MS (ES) MH^+: 638 para $C_{34}H_{38}F_3N_3O_4Si$

^{1}H RMN (300 MHz, CLOROFORMO-*d*) d ppm 1,0-1,2 (m, 15H), 2,67 (d, 2H), 2,8-3,0 (m, 2H), 3,4 (d, 2H), 4,6 (t, 2H), 5,0 (t, 2H), 7,3-7,5 (m, 6H), 7,7 (d, 4H), 8,2 (s, 1H).

Intermedio 217

5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxamida

Materiales de partida: 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxilato de etilo (**Intermedio 204**) y cloruro de amonio.

MS (ES) MH^+: 562 para $C_{31}H_{36}FN_3O_4Si$

Intermedio 218

5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-*N*-(2-metoxietil)benzo[d]isoxazol-3-carboxamida

Materiales de partida: 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxilato de etilo (**Intermedio 204**) y 2-metoxietanamina.

MS (ES) MH^+: 620 para $C_{34}H_{42}FN_3O_5Si$

^{1}H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1,0-1,2 (m, 15H), 2,7 (d, 2H), 2,8-2,95 (m, 2H), 3,4-3,5 (m, 5H), 3,6 (t, 2H), 3,7 (t, 2H), 4,8 (s, 2H), 7,35 – 7,5 (m, 6H), 7,7-7,8 (m, 4H), 8,26 (s, 1H).

Intermedio 219

N-terc-butil-5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxamida

Materiales de partida: 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxilato de etilo (**Intermedio 204**) y 2-metilpropan-2-amina.

MS (ES) MH^+: 618 para $C_{35}H_{44}FN_3O_4Si$

^{1}H RMN (300 MHz, CLOROFORMO-*d*) d ppm 1,0-1,2 (m, 15H), 1,55 (s, 9H), 2,7 (d, 2H), 2,8–3,0 (m, 2H), 3,4-3,55 (m, 2H), 4,8 (s, 2H), 6,75 (s a, 1H), 7,3-7. (m, 6H), 7,7 (d, 4H), 8,2 (s, 1H).

Intermedio 220

5-({[*terc*-butil(difenil)silil]oxi}metil)-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-[(1,1-dioxidotiomorfolin-4-il)carbonil]-7-fluoro-1,2-bencisoxazol

Materiales de partida: 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxilato de etilo (**Intermedio 204**) y 1,1-dióxido de tiomorfolina.

MS (ES) MH^+: 680 para $C_{35}H_{42}FN_3O_6SSi$

Intermedio 221

5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-*N*-(tetrahidro-2*H*-piran-4-il)benzo[d]isoxazol-3-carboxamida

Materiales de partida: 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxilato de etilo (**Intermedio 204**) y tetrahidro-2*H*-piran-4-amina.

MS (ES) MH^+: 646 para $C_{36}H_{44}FN_3O_5Si$

^{1}H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1,0-1,2 (m, 1H), 1,6-1,8 (m, 2H), 2,0-2,1 (m, 2H), 2,7 (d, 2H), 2,8–3,0 (m, 2H), 3,4-3,5 (m, 2H), 3,6 (t, 2H), 4,1 (d, 2H), 4,2-4,4 (m, 1H), 4,8 (s, 2H), 6,85 (d, 1H), 7,3-7,5 (m, 6H), 7,7 (d, 4H), 8,3 (s, 1H).

Intermedio 222

5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-*N*-isopropilbenzo[d]isoxazol-3-carboxamida

Materiales de partida: 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxilato de etilo (**Intermedio 204**) y propan-2-amina.

MS (ES) MH^+: 604,2 para $C_{34}H_{42}FN_3O_4Si$

^1H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1,0-1,2 (m, 15H), 1,35 (d, 6H), 2,7 (d, 2H), 2,8-3,0 (m, 2H), 3,45 (m, 2H), 4,3-4,5 (m, 1H), 4,8 (s, 2H), 6,8 (d, 1H), 7,3-7,5 (m, 6H), 7,7 (d, 4H), 8,3 (s, 1H).

Intermedio 223

5-((*terc*-butildifenilsililoxi)metil)-*N*-ciclopropil-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxamida

Materiales de partida: 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxilato de etilo (**Intermedio 204**) y ciclopropanamina.

MS (ES) MH^+: 602 para $C_{34}H_{40}FN_3O_4Si$

^1H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 0,7-0,8 (m, 2H), 0,9–1,0 (m, 2H), 1,1 (d, 6H), 1,1 (s, 9H), 2,7 (d, 2H), 2,8-2,95 (m, 2H), 2,95-3,1 (m, 1H), 3,4-3,55 (m, 2H), 4,8 (s, 2H), 7,0 (s a, 1H), 7,3-7,5 (m, 6H), 7,7 (d, 4H), 8,3 (s, 1H).

Intermedio 224

(5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-il)(4-metoxipiperidin-1-il)metanona

Materiales de partida: 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxilato de etilo (**Intermedio 204**) y 4-metoxipiperidina.

MS (ES) MH^+: 660 para $C_{37}H_{46}FN_3O_5Si$

^1H RMN (300 MHz, CLOROFORMO-*d*) d ppm 1,02-1,17 (m, 15H) 1,64-2,05 (m, 4H) 2,69 (d, *J* = 11,30 Hz, 2H) 2,81-3,00 (m, 2H) 3,41 (s, 3H) 3,43-3,66 (m, 4H) 3,72-3,86 (m, 1H) 3,86-4,08 (m, 2H) 4,82 (s, 2H) 7,33-7,52 (m, 6H) 7,69 (d, *J* = 6,78 Hz, 4H) 7,83 (s, 1H).

Intermedio 225

5-((*terc*-butildifenilsililoxi)metil)-*N*-(ciclopropilmetil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxamida

Materiales de partida: 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxilato de etilo (**Intermedio 204**) y ciclopropilmetanamina.
MS (ES) MH^+: 616 para $C_{35}H_{42}FN_3O_4Si$

Intermedio 226

5-({[*terc*-butil(difenil)silil]oxi}metil)-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(1,2-oxazinan-2-ilcarbonil)-1,2-bencisoxazol

Materiales de partida: 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxilato de etilo (**Intermedio 204**) y [1,2]oxazinano.
MS (ES) MH^+: 632 para $C_{35}H_{42}FN_3O_5Si$
^1H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1,06-1,19 (m, 15H) 1,92 (s a, 4H) 2,69 (d, *J* = 10,55 Hz, 2H) 2,90 (t, *J* = 9,42 Hz, 2H) 3,41-3,56 (m, 2H) 4,06 (s a, 4H) 4,83 (s, 2H) 7,34-7,51 (m, 6H) 7,69 (d, *J* = 6,78 Hz, 4H) 7,84 (s a, 1H)

Intermedio 227

5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-*N*-(tiofen-2-ilmetil)benzo[d]isoxazol-3-carboxamida

Materiales de partida: 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxilato de etilo (**Intermedio 204**) y tiofen-2-ilmetanamina.
MS (ES) MH^+: 658 para $C_{36}H_{40}FN_3O_4SSi$
^1H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1,11 (d, *J* = 6,03 Hz, 6H) 1,16 (s, 9H) 2,71 (d, *J* = 10,55 Hz, 2H) 2,83-3,00 (m, 2H) 3,39-3,56 (m, 2H) 4,85 (s, 2H) 4,92 (d, *J* = 5,27 Hz, 2H) 6,98-7,06 (m, 1H) 7,08-7,16 (m, 1H) 7,25-7,36 (m, 2H) 7,36-7,52 (m, 6H) 7,73 (d, *J* = 6,03 Hz, 4H) 8,29 (s, 1H)

Intermedio 228

(3,3-difluoroazetidin-1-il)(5-(dimetoximetil)-6,7-difluorobenzo[d]isoxazol-3-il)metanona

Materiales de partida: 5-(dimetoximetil)-6,7-difluorobenzo[d]isoxazol-3-carboxilato de etilo (**Intermedio 206**) y clorhidrato de 3,3-difluoroazetidina.
^1H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 3,4 (s, 6H) 4,6 (t, 2H) 5,0 (t, 2H) 5,7 (s, 1H) 8,2 (d, 1H).

Intermedio 229

5-(dimetoximetil)-6,7-difluoro-*N*-isopropilbenzo[d]isoxazol-3-carboxamida

Materiales de partida: 5-(dimetoximetil)-6,7-difluorobenzo[d]isoxazol-3-carboxilato de etilo (**Intermedio 206**) e isopropilamina.

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 1,2 (d, 6H), 3,3 (s, 6H), 4,2 (dc, 1H), 5,7 (s, 1H), 8,0 (d, 1H), 9,1 (d, 1H).

Intermedio 230

5-((*terc*-butildifenilsililoxi)metil)-7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-*N*-metilisoxazolo[4,5-b]piridin-3-carboxamida

Materiales de partida: 5-((*terc*-butildifenilsililoxi)metil)-7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)isoxazolo[4,5-b]piridin-3-carboxilato de etilo (**Intermedio 211**) y metilamina, 2M en THF.

MS (ES) MH^+: 593 para $C_{31}H_{37}ClN_4O_4Si$

^{1}H RMN (300 MHz, CD_2Cl_2) δ: 1,0-1,2 (superposición de multiplete, 15H), 2,7-2,9 (m, 2H), 3,0 (d, 3H), 3,1-3,2 (m, 2H), 3,6-3,7 (m, 2H), 5,0 (s, 2H). 7,3-7,5 (m, 6H), 7,6-7,7 (m, 4H), 8,3 (s a, 1H).

Intermedio 231

5-((*terc*-butildifenilsililoxi)metil)-7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-*N*-etilisoxazolo[4,5-b]piridin-3-carboxamida

Material de partida: 5-((*terc*-butildifenilsililoxi)metil)-7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)isoxazolo[4,5-b]piridin-3-carboxilato de etilo (**Intermedio 211**) y etilamina.

MS (ES) MH^+: 607 para $C_{32}H_{39}ClN_4O_4Si$

^{1}H RMN (300 MHz, CD_2Cl_2) δ: 1,0-1,1 (superposición de multiplete, 15H), 1,2 (t, 3H), 2,7-2,9 (m, 2H), 3,1-3,2 (m, 2H), 3,4-3,5 (m, 2H), 3,6-3,7 (m, 2H), 5,0 (s, 2H), 7,3-7,5 (m, 6H), 7,6-7,7 (m, 4H), 8,4 (s a, 1H).

Intermedio 232

5-((*terc*-butildifenilsililoxi)metil)-7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-*N*-isopropilisoxazolo[4,5-b]piridin-3-carboxamida

Material de partida: 5-((*terc*-butildifenilsililoxi)metil)-7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)isoxazolo[4,5-b]piridin-3-carboxilato de etilo (**Intermedio 211**) e isopropilamina.

MS (ES) MH^+: 621 para $C_{33}H_{41}ClN_4O_4Si$

^1H RMN (300 MHz, CD_2Cl_2) δ: 1,0-1,1 (superposición de multiplete, 15H), 1,2 (d, 6H), 2,7-2,8 (m, 2H), 3,1-3,2 (m, 2H), 3,5-3,7 (m, 2H), 4,3 (m, 1H), 5,0 (s, 2H), 7,3-7,5 (m, 6H), 7,6-7,7 (m, 4H), 8,15 (s a, 1H).

Intermedio 233

N-*terc*-butil-5-((*terc*-butildifenilsililoxi)metil)-7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)isoxazolo[4,5-b]piridin-3-carboxamida

Material de partida: 5-((*terc*-butildifenilsililoxi)metil)-7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)isoxazolo[4,5-b]piridin-3-carboxilato de etilo (**Intermedio 211**) y *t*-butilamina.

MS (ES) MH^+: 635 para $C_{34}H_{43}ClN_4O_4Si$

^1H RMN (300 MHz, CD_2Cl_2) δ: 1,0 (s, 9H), 1,1 (d, 6H),1,4 (s, 9H), 2,7-2,8 (m, 2H), 3,1-3,2 (m, 2H), 3,5-3,7 (m, 2H), 5,0 (s, 2H), 7,3-7,5 (m, 6H), 7,6-7,9 (m, 4H), 8,1 (s a, 1H).

Intermedio 234

5-((*terc*-butildifenilsililoxi)metil)-7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-*N*-neopentilisoxazolo[4,5-b]piridin-3-carboxamida

Material de partida: 5-((*terc*-butildifenilsililoxi)metil)-7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)isoxazolo[4,5-b]piridin-3-carboxilato de etilo (**Intermedio 211**) y 2,2-dimetilpropan-1-amina.

MS (ES) MH^+: 649 para $C_{35}H_{45}ClN_4O_4Si$

Intermedio 235

(5-((*terc*-butildifenilsililoxi)metil)-7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)isoxazolo[4,5-b]piridin-3-il)(3,3-difluoroazetidin-1-il)metanona

Material de partida: 5-((*terc*-butildifenilsililoxi)metil)-7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)isoxazolo[4,5-b]piridin-3-carboxilato de etilo (**Intermedio 211**) y 3,3-difluoroazetidina-HCl.

MS (ES) MH^+: 655 para $C_{33}H_{37}ClF_2N_4O_4Si$

^1H RMN (300 MHz, CD_2Cl_2) δ: 1,0 (s, 9H), 1,1 (d, 6H), 2,8-2,9 (m, 2H), 3,2 (t, 2H), 3,6-3,7 (m, 2H), 4,6 (t, 2H), 4,8 (t, 2H), 5,0 (s, 2H), 7,3-7,5 (m, 6H), 7,7-7,8 (m, 4H).

Intermedio 236

N-bencil-5-((*terc*-butildifenilsililoxi)metil)-7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)isoxazolo[4,5-b]piridin-3-carboxamida

Material de partida: 5-((*terc*-butildifenilsililoxi)metil)-7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)isoxazolo[4,5-b]piridin-3-carboxilato de etilo (**Intermedio 211**) y bencilamina.

MS (ES) MH^+: 669 para $C_{37}H_{41}ClN_4O_4Si$

^1H RMN (300 MHz, CD_2Cl_2) δ: 1,0 (s, 9H), 1,1 (d, 6H), 2,7-2,8 (m, 2H), 3,1-3,2 (m, 2H), 3,5-3,7 (m, 2H), 4,6 (d, 2H), 5,0 (s, 2H), 7,2-7,5 (m, 11H), 7,6-7,7 (m, 4H), 8,7 (s a, 1H).

Intermedio 237

5-((*terc*-butildifenilsililoxi)metil)-7-cloro-*N*-(4-cianobencil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)isoxazolo[4,5-b]piridin-3-carboxamida

Material de partida: 5-((*terc*-butildifenilsililoxi)metil)-7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)isoxazolo[4,5-b]piridin-3-carboxilato de etilo (**Intermedio 211**) y 4-(aminometil)benzonitrilo.

MS (ES) MH^+: 694 para $C_{38}H_{40}ClN_5O_4Si$

^1H RMN (300 MHz, CD_2Cl_2) δ: 1,0 (s, 9H), 1,1 (d, 6H), 2,7-2,8 (m, 2H), 3,1-3,2 (m, 2H), 3,5-3,7 (m, 2H), 4,7 (d, 2H), 5,0 (s a, 2H), 7,2-7,4 (m, 8H), 7,5-7,6 (m, 6H), 8. 9 (s a).

Intermedio 238

5-((*terc*-butildifenilsililoxi)metil)-7-cloro-*N*-(3-cianobencil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)isoxazolo[4,5-b]piridin-3-carboxamida

Materiales de partida: 5-((*terc*-butildifenilsililoxi)metil)-7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)isoxazolo[4,5-b]piridin-3-carboxilato de etilo (**Intermedio 211**) y 3-(aminometil)benzonitrilo-HCl.

MS (ES) MH^+: 694 para $C_{38}H_{40}ClN_5O_4Si$

^1H RMN (300 MHz, CD_2Cl_2) δ: 1,0 (s, 9H), 1,1 (d, 6H), 2,7-2,8 (m, 2H), 3,1-3,2 (m, 2H), 3,5-3,7 (m, 2H), 4,6 (d, 2H), 5,0 (s a, 2H), 7,2-7,7 (m, 14H), 8,9 (s a).

Intermedio 239

N-(2,2-difluoroetil)-5-(dimetoximetil)-6,7-difluorobenzo[d]isoxazol-3-carboxamida

Material de partida: 5-(dimetoximetil)-6,7-difluorobenzo[d]isoxazol-3-carboxilato de etilo (**Intermedio 206**).

MS (ES) $M^+(-CH_3O)$: 305

^1H RMN (300 MHz, DMSO-d_6) δ ppm 3,3 (s, 6H), 3,6 - 3,9 (m, 2H), 5,7 (s, 1H), 6,0 - 6,5 (m, 1H), 8,0 (d, 1H), 9,6 (t, 1H)

Intermedio 240

5-(dimetoximetil)-6,7-difluoro-*N*-metilbenzo[d]isoxazol-3-carboxamida

Material de partida: 5-(dimetoximetil)-6,7-difluorobenzo[d]isoxazol-3-carboxilato de etilo (**Intermedio 206**).

MS (ES) $M^+(-CH_3O)$: 255

^1H RMN (300 MHz, DMSO-d_6) δ ppm 2,9 (d, 3H) 3,3 (s, 6H) 5,7 (s, 1H) 8,0 (d, 1H) 9,1 (d, 1H)

Intermedio 241

3-(3,3-difluoroazetidin-1-carbonil)-6,7-difluorobenzo[d]isoxazol-5-carbaldehído

(3,3-difluoroazetidin-1-il)(5-(dimetoximetil)-6,7-difluorobenzo[d]isoxazol-3-il)metanona (**Intermedio 228,** 3,336 g, 9,58 mmol) se disolvió en una mezcla 4:1 THF:agua (62,5 mL) y se calentó a 75 °C con monohidrato de ácido tósico (0,911 g, 4,79 mmol) durante tres horas. La reacción se dejó enfriar hasta alcanzar la temperatura ambiente, se diluyó con acetato de etilo, se lavó 3x con $NaHCO_3$ saturado, se secó con $MgSO_4$ y se concentró. El residuo se purificó mediante cromatografía en columna de gel de sílice utilizando un gradiente de hexanos a acetato

de etilo. Las fracciones se combinaron y se concentraron para proporcionar el compuesto del título (2,66 g, 8,83 mmol).

MS (ES) MH^+ 303 para $C_{12}H_6F_4N_2O_3$

^1H RMN (300 MHz, CLOROFORMO-d) δ ppm 4,64 (t, 2H) 5,0 (t, 2H) 8,61 (d, 1H) 10,36 (s, 1H).

Los **Intermedios 242** a **244** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 241**:

Intermedio 242

6,7-difluoro-5-formil-*N*-isopropilbenzo[d]isoxazol-3-carboxamida

Material de partida: 5-(dimetoximetil)-6,7-difluoro-*N*-isopropilbenzo[d]isoxazol-3-carboxamida (**Intermedio 229**).

MS (ES) MH^+ 269 para $C_{12}H_{10}F_2N_2O_3$

^1H RMN (300 MHz, DMSO-d_6) δ ppm 1,23 (d, 6H) 4,09-4,28 (m, 1H) 8,41 (d, 1H) 9,16 (d, 1H) 10,23 (s, 1H).

Intermedio 243

N-(2,2-difluoroetil)-6,7-difluoro-5-formilbenzo[d]isoxazol-3-carboxamida

Material de partida: *N*-(2,2-difluoroetil)-5-(dimetoximetil)-6,7-difluorobenzo[d]isoxazol-3-carboxamida (**Intermedio 239**).

MS (ES) MH^-: 289 para $C_{11}H_6F_4N_2O_3$

^1H RMN (300 MHz, DMSO-d_6) δ ppm 3,7 - 3,9 (m, 2 H), 5,9 - 6,5 (m, 1 H), 8,4 (d, 1 H), 9,6 - 9,7 (m, 1 H), 10,2 (s, 1 H).

Intermedio 244

6,7-difluoro-5-formil-*N*-metilbenzo[d]isoxazol-3-carboxamida

Material de partida: 5-(dimetoximetil)-6,7-difluoro-*N*-metilbenzo[d]isoxazol-3-carboxamida (**Intermedio 240**).

MS (ES) MH^+: 241 para $C_{10}H_6F_2N_2O_3$

^1H RMN (300 MHz, DMSO-d_6) δ ppm 2,9 (d, 3H), 8,4 (d, 1H), 9,2 (d, 1H), 10,2 (s, 1H).

Intermedio 245

3-(3,3-difluoroazetidin-1-carbonil)-6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-5-carbaldehído

Diisopropiletilamina (1,432 mL, 8,20 mmol) y (2*R*,6*R*)-2,6-dimetilmorfolina (1,027 mL, 8,20 mmol) se agregaron a una solución de 3-(3,3-difluoroazetidin-1-carbonil)-6,7-difluorobenzo[d]isoxazol-5-carbaldehído (**Intermedio 241,** 1,906 g, 6,31 mmol) en acetonitrilo (50 mL). La reacción se agitó a reflujo durante 20 horas. La reacción se enfrió hasta alcanzar la temperatura ambiente, se diluyó con agua y salmuera y se extrajo dos veces con acetato de etilo. Se combinaron las capas orgánicas, se secaron con $MgSO_4$ y se concentraron. El residuo se purificó mediante cromatografía en columna de gel de sílice utilizando un gradiente de DCM a acetato de etilo. Las fracciones se combinaron y se concentraron para proporcionar el compuesto del título.

MS (ES) MH^+ 398,1 para $C_{18}H_{18}F_3N_3O_4$

^{1}H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1,35 (d, 6H) 3,07 (dd, 5,65 Hz, 2H) 3,45 (d, 2H) 4,26 (m, 2H) 4,62 (t, 2H) 4,99 (t, 2H) 8,50 (s, 1H) 10,44 (s, 1H).

Los **Intermedios 246** y **247** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 245:**

Intermedio 246

6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-5-formil-*N*-isopropilbenzo[d]isoxazol-3-carboxamida

El compuesto del título se preparó a partir de 6,7-difluoro-5-formil-*N*-isopropilbenzo[d]isoxazol-3-carboxamida (**Intermedio 242**) y (2*R*,6*R*)-2,6-dimetilmorfolina.

MS (ES) MH^+ 364 para $C_{18}H_{22}FN_3O_4$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 1,14-1,29 (m, 12H) 3,02 (dd, J = 10,93, 2H) 3,40 (d, 2H) 4,05-4,26 (m, 3H) 8,22 (s, 1H) 9,05 (d, 1H) 10,35 (s, 1H).

Intermedio 247

6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-5-formil-*N*-metilbenzo[d]isoxazol-3-carboxamida

Material de partida: 6,7-difluoro-5-formil-*N*-metilbenzo[d]isoxazol-3-carboxamida. (**Intermedio 244**).

MS (ES) MH^+: 336 para $C_{16}H_{18}FN_3O_4$

^1H RMN (300 MHz, DMSO-d_6) δ ppm 1,2 (d, 6 H), 2,9 (d, 3 H), 2,9 - 3,1 (m, 2 H), 3,4 (d, 2 H), 4,1 - 4,2 (m, 2 H), 8,2 (s, 1 H), 9,1 (d, 1 H), 10,4 (s, 1 H).

El Intermedio 247 también se preparó de acuerdo con el siguiente procedimiento:

Intermedio 247 (Síntesis alternativa)

6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-5-formil-*N*-metilbenzo[d]isoxazol-3-carboxamida

Material de partida: 6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)-*N*-metilbenzo[d]isoxazol-3-carboxamida (**Intermedio 280**).

MS (ES) MH^+: 336 para $C_{16}H_{18}FN_3O_4$

^1H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1,35 (d, *J* = 6,78 Hz, 6H) 2,99-3,16 (m, 5H) 3,45 (d, *J* = 12,06 Hz, 2H) 4,20-4,35 (m, 2H) 6,83 -6,96 (m, 1H) 8,54 (s, 1H) 10,44 (s, 1H).

Intermedio 248

N-(2,2-difluoroetil)-6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-5-formilbenzo[d]isoxazol-3-carboxamida

N-(2,2-difluoroetil)-6,7-difluoro-5-formilbenzo[d]isoxazol-3-carboxamida (**Intermedio 243**, 2,86 g, 9,86 mmol) se disolvió en butironitrilo (50 mL) y agua (2,5 mL). Carbonato de potasio (1,362 g, 9,86 mmol) y (2*R*,6*R*)-2,6-dimetilmorfolina (1,481 mL, 11,83 mmol) se agregaron y la reacción se agitó a 90 °C durante 4 horas. La mezcla de reacción bruta se diluyó con agua, salmuera y acetato de etilo. La mezcla se lavó 2x con salmuera. La capa acuosa se retroextrajo con acetato de etilo. Las capas orgánicas se combinaron, se secaron con $MgSO_4$ y se concentraron. El residuo se disolvió en DCM y se purificó mediante cromatografía en columna de gel de sílice utilizando un gradiente de DCM a acetato de etilo. Las fracciones se combinaron y se concentraron para proporcionar el compuesto del título.

MS (ES) MH^+: 286 para $C_{17}H_{18}F_3N_3O_4$

^1H RMN (300 MHz, DMSO-d_6) δ ppm 1,2 (d, 6 H), 3,0 (m, 2 H), 3,4 (d, 2 H), 3,8 (m, 2 H), 4,1 - 4,2 (m, 2 H), 6,0 - 6,4 (m, 1 H), 8,2 (s, 1 H), 9,5 (t, *J* = 5,7 Hz, 1 H), 10,3 (s, 1 H).

Intermedio 249

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)-*N*-(piridin-4-ilmetil)benzo[d]isoxazol-3-carboxamida

Trimetilaluminio (2M en tolueno, 2116 µl, 4,23 mmol) se agregó lentamente (desprendimiento de gas) a una solución de piridin-4-ilmetanamina (458 mg, 4,23 mmol) en tolueno (10 mL) a temperatura ambiente y en una atmósfera de nitrógeno. La reacción se agitó durante 2 horas a temperatura ambiente. 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxilato de etilo (**Intermedio 204,** 500 mg, 0,85 mmol) se agregó como una solución en 5 mL de tolueno. La reacción se agitó a 45 °C durante tres días. La reacción se enfrió hasta alcanzar la temperatura ambiente y luego se detuvo gota a gota con 3 mL de HCl 1N (fuerte desprendimiento de gas). La reacción bruta se vertió en un tubo Biotage Isolute® HM-N (10 mL de capacidad) con una pequeña cantidad de lana de vidrio para prevenir obstrucciones. Una columna de sulfato de sodio Biotage (2,5 g) se ajustó al fondo del tubo Isolute®. La mezcla de reacción se dejó eluir por gravedad a través del tubo y se lavó con 2-3 volúmenes de columna de acetato de etilo. El eluyente se concentró. El residuo se disolvió en THF (10 mL) y se agitó a temperatura ambiente con ácido acético (0,097 mL, 1,70 mmol) y TBAF (1N en THF, 0,935 mL, 0,94 mmol) durante 16 horas. Las reacciones se diluyeron con 1 mL de agua y se agitaron vigorosamente. La muestra se agregó a un tubo Varian Chem Elute® CE 1003 con una columna de sulfato de sodio Biotage (2,5 g) en el fondo. La muestra se eluyó por gravedad con 2-3 volúmenes de columna de acetato de etilo y se concentró. El residuo se purificó mediante cromatografía en columna de gel de sílice. Las fracciones se combinaron y se concentraron para proporcionar el compuesto del título (241 mg, 0,552 mmol, 65%).

MS (ES) MH^+: 415 para $C_{21}H_{23}FN_4O_4$

^{1}H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1,26 (d, *J* = 6,03 Hz, 6H) 2,91-3,17 (m, 4H) 3,72-3,95 (m, 2H) 4,70-4,91 (m, 4H) 7,46 (d, *J* = 5,27 Hz, 2H) 7,51 (s a, 1H) 7,97 (s, 1H) 8,55-8,77 (m, 2H).

Los **Intermedios 250** a **261** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 249:**

Intermedio 250

N-(ciclohexilmetil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)benzo[d]isoxazol-3-carboxamida

Materiales de partida: 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxilato de etilo (**Intermedio 204**) y ciclohexilmetanamina.

MS (ES) MH^+: 420,3 para $C_{22}H_{30}FN_3O_4$

Intermedio 251

(4,4-difluoropiperidin-1-il)(6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)benzo[d]isoxazol-3-il)metanona

Materiales de partida: 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxilato de etilo (**Intermedio 204**) y 4,4-difluoropiperidina.

MS (ES) MH^+: 428 para $C_{20}H_{24}F_3N_3O_4$

Intermedio 252

(3,3-difluoropirrolidin-1-il)(6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)benzo[d]isoxazol-3-il)metanona

Material de partida: 3,3-difluoropirrolidina.

MS (ES) MH^+: 414 para $C_{19}H_{22}F_3N_3O_4$

Intermedio 253

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)-*N*-(1-metilazetidin-3-il)benzo[d]isoxazol-3-carboxamida

Materiales de partida: 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxilato de etilo (**Intermedio 204**) y 1-metilazetidin-3-amina.

MS (ES) MH^+: 393 para $C_{19}H_{25}FN_4O_4$

Intermedio 254

N-(1-(6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)benzo[d]isoxazol-3-carbonil)azetidin-3-il)acetamida

Materiales de partida: 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxilato de etilo (**Intermedio 204**) y *N*-(azetidin-3-il)acetamida.
MS (ES) MH^+: 421 para $C_{20}H_{25}FN_4O_5$

Intermedio 255

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)-*N*-((1-metil-1*H*-pirazol-3-il)metil)benzo[d]isoxazol-3-carboxamida

Materiales de partida: 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxilato de etilo (**Intermedio 204**) y (1-metil-1*H*-pirazol-3-il)metanamina.
MS (ES) MH^+: 318 para $C_{20}H_{24}FN_5O_4$

Intermedio 256

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)-*N*-((1-metil-1*H*-pirazol-5-il)metil)benzo[d]isoxazol-3-carboxamida

Materiales de partida: 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxilato de etilo (**Intermedio 204**) y (1-metil-1*H*-pirazol-5-il)metanamina.
MS (ES) MH^+: 418 para $C_{20}H_{24}FN_5O_4$

Intermedio 257

N-(1,3-dimetoxi-2-(metoximetil)propan-2-il)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)benzo[d]isoxazol-3-carboxamida

Materiales de partida: 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxilato de etilo (**Intermedio 204**) y 1,3-dimetoxi-2-(metoximetil)propan-2-amina.
MS (ES) MH^+: 470 para $C_{22}H_{32}FN_3O_7$

Intermedio 258

N-(2,2-difluoroetil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)benzo[d]isoxazol-3-carboxamida

Materiales de partida: 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxilato de etilo (**Intermedio 204**) y 2,2-difluoroetanamina.
MS (ES) MH^+: 388 para $C_{17}H_{20}F_3N_3O_4$

Intermedio 259

1-(6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)benzo[d]isoxazol-3-carbonil)azetidin-3-carbonitrilo

Materiales de partida: 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxilato de etilo (**Intermedio 204**) y azetidina-3-carbonitrilo.
MS (ES) MH^+: 389 para $C_{19}H_{21}FN_4O_4$

Intermedio 260

5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-*N*-metilbenzo[d]isoxazol-3-carboxamida

Materiales de partida: 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxilato de etilo (**Intermedio 210**, 5,16 g, 8,73 mmol) y metilamina (2M en THF).
MS (ES) MH^+: 576 para $C_{32}H_{38}FN_3O_4Si$
^1H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1,06 (d, 6H) 1,17 (s, 9H) 2,64-2,80 (m, 2H) 3,04-3,15 (m, 5H) 3,82-3,96 (m, 2H) 4,80-4,98 (m, 2H) 6,93 (s a, 1H) 7,33-7,50 (m, 6H) 7,66-7,76 (m, 4H) 8,35 (s, 1H)

Intermedio 261

5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxamida

Materiales de partida: 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxilato de etilo (**Intermedio 210**) y amoníaco (0,5 M en dioxano).
MS (ES) MH^+: 362,2 para $C_{31}H_{36}FN_3O_4Si$

Intermedio 262

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)benzo[d]isoxazol-3-carboxilato de etilo 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxilato de etilo (**Intermedio 204**, 693 mg, 1,17 mmol) se disolvió en THF (3 mL) junto con ácido acético (0,134 mL, 2,35 mmol). TBAF (1N en THF, 1,290 mL, 1,29 mmol) se agregó y la reacción se agitó a temperatura ambiente durante 30 minutos. La reacción se diluyó con agua y se extrajo 2x con acetato de etilo. Se combinaron las capas orgánicas, se lavaron con salmuera, se secaron con $MgSO_4$ y se concentraron. El residuo se purificó mediante cromatografía en columna de gel de sílice para proporcionar el compuesto del título.

MS (ES) MH^+: 353 para $C_{17}H_{21}FN_2O_5$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 1,1 (d, 6H) 1,4 (t, 3H) 2,8 (t, 2H) 3,0 (d, 2H) 3,6-3,8 (m, 2H) 4,5 (c, 2H) 4,7 (d, 2H) 5,45 (t, 1H) 7,95 (s, 1H).

Los **Intermedios 263** a **281** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para las síntesis del **Intermedio 262**:

Intermedio 263

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)-*N*-metoxi-*N*-metilbenzo[d]isoxazol-3-carboxamida

Material de partida: 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-*N*-metoxi-*N*-metilbenzo[d]isoxazol-3-carboxamida (**Intermedio 205**).

MS (ES) MH^+: 368 para $C_{17}H_{22}FN_3O_5$

^{1}H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1,26 (d, J = 6,78 Hz, 6H) 2,93-3,04 (m, 2H) 3,04-3,16 (m, 2H) 3,49 (s a, 3H) 3,87 (s a, 5H) 4,83 (s, 2H) 7,70 (s a, 1H)

Intermedio 264

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-*N*-etil-7-fluoro-5-(hidroximetil)benzo[d]isoxazol-3-carboxamida

Material de partida: 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-*N*-etil-7-fluorobenzo[d]isoxazol-3-carboxamida (**Intermedio 212**).

MS (ES) MH^+: 352 para $C_{17}H_{22}FN_3O_4$

^1H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1,15-1,37 (m, 9H) 2,91-3,17 (m, 4H) 3,48-3,65 (m, 2H) 3,75-3,94 (m, 2H) 4,82 (s, 2H) 6,92 (s a, 1H) 7,95 (s, 1H)

Intermedio 265

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-*N*-etil-7-fluoro-5-(hidroximetil)-*N*-metilbenzo[d]isoxazol-3-carboxamida

Material de partida: 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-*N*-etil-7-fluoro-*N*-metilbenzo[d]isoxazol-3-carboxamida (**Intermedio 213**).

MS (ES) MH^+: 366 para $C_{18}H_{24}FN_3O_4$

^1H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1,24 (d, *J* = 6,40 Hz, 6H) 1,26-1,34 (m, 3H) 2,89-3,01 (m, 2H) 3,01-3,14 (m, 2H) 3,15-3,34 (m, 3H) 3,68 (c, *J* = 7,16 Hz, 2H) 3,76-3,91 (m, 2H) 4,79 (s, 2H) 7,68 (d, *J* = 7,16 Hz, 1H).

Intermedio 266

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)-*N*-metilbenzo[d]isoxazol-3-carboxamida

Material de partida: 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-*N*-metilbenzo[d]isoxazol-3-carboxamida (**Intermedio 21H**).

MS (ES) MH^+: 338 para $C_{16}H_{20}FN_3O_4$

^1H RMN (300 MHz, CLOROFORMO-d) δ ppm 1,23 (d, J = 6,78 Hz, 6H) 2,93-3,13 (m, 7H) 3,76-3,93 (m, 2H) 4,81 (s, 2H) 6,99 (s a, 1H) 7,94 (s, 1H)

Intermedio 267

4-(6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)benzo[d]isoxazol-3-carbonil)-1-metilpiperazin-2-ona

Material de partida: 4-(5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carbonil)-1-metilpiperazin-2-ona (**Intermedio 215**).

MS (ES) MH^+: 421 para $C_{20}H_{25}FN_4O_5$

Intermedio 268

(3,3-difluoroazetidin-1-il)(6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)benzo[d]isoxazol-3-il)metanona

Material de partida: (5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-il)(3,3-difluoroazetidin-1-il)metanona (**Intermedio 216**).

MS (ES) MH^+: 400 para $C_{18}H_{20}F_3N_3O_4$

^1H RMN (300 MHz, CLOROFORMO-d) δ ppm 1,17 (d, *J* = 6,03 Hz, 6H) 2,81-3,09 (m, 4H) 3,76 (s a, 2H) 4,52 (t, *J* = 12,06 Hz, 2H) 4,74 (s, 2H) 4,90 (t, *J* = 11,68 Hz, 2H) 7,85 (s, 1H)

Intermedio 269

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)benzo[d]isoxazol-3-carboxamida

Material de partida: 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxamida (**Intermedio 217**).

MS (ES) MH^+: 324 para $C_{15}H_{18}FN_3O_4$

^1H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1,25 (d, *J* = 6,03 Hz, 6H) 2,93-3,19 (m, 4H) 3,78-3,94 (m, 2H) 4,84 (s, 2H) 5,72 (s a, 1H) 6,83 (s a, 1H) 7,96 (s, 1H)

Intermedio 270

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)-*N*-(2-metoxietil)benzo[d]isoxazol-3-carboxamida

Material de partida: 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-*N*-(2-metoxietil)benzo[d]isoxazol-3-carboxamida (**Intermedio 218**).

MS (ES) MH^+: 382 para $C_{18}H_{24}FN_3O_5$

^1H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1,23 (d, *J* = 6,03 Hz, 6H) 2,89-3,15 (m, 4H) 3,41 (s, 3H) 3,60 (t, *J* = 4,90 Hz, 2H) 3,70 (c, *J* = 5,27 Hz, 2H) 3,83 (m, 2H) 4,81 (s, 2H) 7,93 (s, 1H).

Intermedio 271

N-*terc*-butil-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)benzo[d]isoxazol-3-carboxamida

Material de partida: *N*-*terc*-butil-5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxamida (**Intermedio 219**).

MS (ES) MH^+: 380 para $C_{19}H_{26}FN_3O_4$

^1H RMN (300 MHz, CLOROFORMO-*d*) d ppm 1,23 (d, *J* = 6,03 Hz, 6H) 1,51 (s, 9H) 2,90-3,15 (m, 4H) 3,83 (s a, 2H) 4,80 (s, 2H) 6,78 (s a, 1H) 7,95 (s, 1H).

Intermedio 272

{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-[(1,1-dioxidotiomorfolin-4-il)carbonil]-7-fluoro-1,2-bencisoxazol-5-il}metanol

Material de partida: 5-({[*terc*-butil(difenil)silil]oxi}metil)-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-[(1,1-dioxidotiomorfolin-4-il)carbonil]-7-fluoro-1,2-bencisoxazol (**Intermedio 220**).

MS (ES) MH^+: 442,0 para $C_{19}H_{24}FN_3O_6S$

^1H RMN (300 MHz, CLOROFORMO-d) δ ppm 1,26 (d, *J* = 6,03 Hz, 6H) 2,91-3,03 (m, 2H) 3,03-3,16 (m, 2H) 3,19-3,33 (m, 4H) 3,79-3,91 (m, 2H) 4,32-4,42 (m, 2H) 4,42-4,52 (m, 2H) 4,84 (s, 4H) 7,74 (s, 1H).

Intermedio 273

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)-*N*-(tetrahidro-2*H*-piran-4-il)benzo[d]isoxazol-3-carboxamida

Material de partida: 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-*N*-(tetrahidro-2*H*-piran-4-il)benzo[d]isoxazol-3-carboxamida (**Intermedio 221**).

MS (ES) MH^+: 408 para $C_{20}H_{26}FN_3O_5$

^1H RMN (300 MHz, CLOROFORMO-d) δ ppm 1,26 (d, *J* = 6,78 Hz, 6H) 1,57-1,77 (m, *J* = 11,77, 11,77, 11,49, 4,14 Hz, 2H) 2,05 (d, *J* = 10,55 Hz, 2H) 2,98-3,18 (m, 4H) 3,57 (t, *J* = 11,68 Hz, 2H) 3,90 (s a, 2H) 4,05 (d, *J* = 10,55 Hz, 2H) 4,19-4,34 (m, 1H) 4,87 (s, 2H) 6,84 (d, *J* = 7,54 Hz, 1H) 7,96 (s, 1H).

Intermedio 274

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)-*N*-isopropilbenzo[d]isoxazol-3-carboxamida

Material de partida: 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-*N*-isopropilbenzo[d]isoxazol-3-carboxamida (**Intermedio 222**).

MS (ES) MH^+: 366 para $C_{18}H_{24}FN_3O_4$

^{1}H RMN (300 MHz, CLOROFORMO-d) δ ppm 1,26 (d, *J* = 6,78 Hz, 6H) 1,29-1,38 (m, 6H) 2,93-3,17 (m, 4H) 3,86 (m 2H) 4,26-4,41 (m, 1H) 4,84 (s, 2H) 6,76 (d, *J* = 6,78 Hz, 1H) 7,97 (s, 1H).

Intermedio 275

N-ciclopropil-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)benzo[d]isoxazol-3-carboxamida

Material de partida: 5-((*terc*-butildifenilsililoxi)metil)-*N*-ciclopropil-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxamida (**Intermedio 223**).

MS (ES) MH^+: 364 para $C_{18}H_{22}FN_3O_4$

^{1}H RMN (300 MHz, CLOROFORMO-d) δ ppm 0,64-0,79 (m, 2H) 0,85-1,02 (m, 2H) 1,25 (d, *J* = 6,78 Hz, 6H) 2,88-3,18 (m, 5H) 3,85 (m, 2H) 4,84 (s, 2H) 7,02 (s a, 1H) 7,97 (s, 1H).

Intermedio 276

(6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)benzo[d]isoxazol-3-il)(4-metoxipiperidin-1-il)metanona

Material de partida: (5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-il)(4-metoxipiperidin-1-il)metanona (**Intermedio 224**).

MS (ES) MH^+: 422 para $C_{21}H_{28}FN_3O_5$

^{1}H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1,23 (d, *J* = 6,03 Hz, 6H) 1,62-2,04 (m, 4H) 2,84-2,97 (m, 2H) 3,04 (t, *J* = 9,80 Hz, 2H) 3,49-3,88 (m, 6H) 3,88-4,06 (m, 2H) 4,75 (d, *J* = 6,03 Hz, 2H) 7,62 (s, 1H).

Intermedio 277

N-(ciclopropilmetil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)benzo[d]isoxazol-3-carboxamida

Material de partida: 5-((*terc*-butildifenilsililoxi)metil)-*N*-(ciclopropilmetil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxamida (**Intermedio 225**).

MS (ES) MH^+: 378 para $C_{19}H_{24}FN_3O_4$

^{1}H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 0,25 (d, *J* = 5,27 Hz, 2H) 0,45-0,60 (m, 2H) 0,94-1,09 (m, 1H) 1,17 (d, *J* = 6,03 Hz, 6H) 2,84-2,96 (m, 2H) 2,96-3,10 (m, 2H) 3,20-3,39 (m, 2H) 3,65-3,88 (m, 2H) 4,75 (s, 2H) 6,95 (s a, 1H) 7,88 (s, 1H)

Intermedio 278

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(1,2-oxazinan-2-ilcarbonil)-1,2-bencisoxazol-5-il}metanol

Material de partida: 5-({[*terc*-butil(difenil)silil]oxi}metil)-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(1,2-oxazinan-2-ilcarbonil)-1,2-bencisoxazol (**Intermedio 226**).

MS (ES) MH^+: 394 para $C_{19}H_{24}FN_3O_5$

^{1}H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1,25 (d, *J* = 6,03 Hz, 6H) 1,92 (s a, 4H) 2,83-3,18 (m, 4H) 3,83 (s a, 2H) 3,96-4,38 (m, 4H) 4,80 (s, 2H) 7,61 (s a, 1H).

Intermedio 279

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)-*N*-(tiofen-2-ilmetil)benzo[d]isoxazol-3-carboxamida

Materiales de partida: 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-*N*-(tiofen-2-ilmetil)benzo[d]isoxazol-3-carboxamida (**Intermedio 227**).

MS (ES) MH^+: 420 para $C_{20}H_{22}FN_3O_4S$

Intermedio 280

6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)-*N*-metilbenzo[d]isoxazol-3-carboxamida

Material de partida: 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-*N*-metilbenzo[d]isoxazol-3-carboxamida (**Intermedio 260**).

MS (ES) MH^+: 338 para $C_{16}H_{20}FN_3O_4$

^{1}H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1,29-1,48 (m, 6H) 2,90-3,03 (m, 2H) 3,09 (d, *J* = 5,27 Hz, 3H) 3,31 (s a, 2H) 4,18 (m, 2H) 4,78-4,94 (m, 2H) 6,92 (s a, 1H) 8,01 (s, 1H).

Intermedio 281

6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)benzo[d]isoxazol-3-carboxamida

Material de partida: 5-((*terc*-butildifenilsililoxi)metil)-6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-3-carboxamida (**Intermedio 261**).

MS (ES) MH^+: 324 para $C_{15}H_{18}FN_3O_4$

^1H RMN (300 MHz, DMSO-d_6) δ ppm 1,23 (d, *J* = 6,03 Hz, 6H) 2,82 (m, 2H) 3,19 (d, *J* = 11,30 Hz, 2H) 3,95-4,13 (m, 2H) 4,64-4,80 (m, 2H) 5,43 (t, *J* = 5,27 Hz, 1H) 7,97 (s, 1H) 8,10 (s, 1H) 8,45 (s, 1H).

Intermedio 282

(3-(6-cloropirazin-2-il)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-5-il)metanol

5-((*terc*-butildifenilsililoxi)metil)-3-(6-cloropirazin-2-il)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol (**Intermedio 329**, 320 mg, 0,51 mmol) se disolvió en etanol (10 mL) y se trató con 15 mL de HCl ac al 10%, la mezcla se calentó a 70 °C durante 1 hora. La reacción se enfrió y se diluyó con EtOAc antes de aplacarse con solución acuosa de bicarbonato de sodio. La mezcla se extrajo con EtOAc, que se lavó con salmuera, se secó ($MgSO_4$) y se concentró.

MS (ES) MH^+: 393 para $C_{18}H_{18}ClFN_4O_3$

Intermedio 283

(6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(5-(metiltio)pirazin-2-il)benzo[d]isoxazol-5-il)metanol

Se trató 1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}-1-(5-cloropirazin-2-il)-*N*-hidroximetanimina (**Intermedio 200,** 400 mg, 0,61 mmol) en DMF (5 mL) con tiometóxido de sodio (45,3 mg, 0,61 mmol) a temperatura ambiente, la mezcla se agitó a temperatura ambiente durante 10 min. Se agregó K_2CO_3 (5 eq) y la mezcla se calentó hasta alcanzar 100 °C durante 1 hora. La mezcla de reacción se diluyó con acetato de etilo (20 mL). La capa orgánica se lavó con agua y salmuera, luego se secó con sulfato de sodio, se filtró y el filtrado se concentró, se purificó mediante cromatografía en columna de gel de sílice (gradiente de Hexanos/EtOAc) para proporcionar el producto deseado (97 mg, 39,0%).

MS (ES) MH^+: 405 para $C_{19}H_{21}FN_4O_3S$

El **Intermedio 284** se preparó a partir de los materiales de partida indicados utilizando un método similar al descrito para las síntesis del **Intermedio 283**:

Intermedio 284

(6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-3-(2-(metiltio)pirimidin-4-il)benzo[d]isoxazol-5-il)metanol

Material de partida: (5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*R*)-2,6-dimetilmorfolino)-2,3-difluorofenil)(2-(metiltio)pirimidin-4-il)metanona (**Intermedio 106**).

MS (ES) MH^+: 405 (M+H) para $C_{19}H_{21}FN_4O_3S$

Intermedio 285

(6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)benzo[d]isoxazol-3-il)(morfolino)metanona

Se disolvió 2-(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)-2-(hidroxiimino)-1-morfolinoetanona, (**Intermedio 168,** 133 mg, 0,20 mmol) en DMF y se agitó a 60 °C con carbonato de cesio (332 mg, 1,02 mmol) durante 6 horas. La reacción se agitó a temperatura ambiente durante 2 días. La reacción se diluyó con agua y se extrajo tres veces con acetato de etilo. Se combinaron las capas orgánicas y se lavaron 5x con salmuera, se secaron con $MgSO_4$ y se concentraron para proporcionar un aceite. El aceite se purificó mediante cromatografía en columna de gel de sílice utilizando un gradiente de hexanos a acetato de etilo para proporcionar el compuesto del título (34 mg, 0,086 mmol).

MS (ES) MH^+: 394 para $C_{19}H_{24}FN_3O_5$

^1H RMN (300 MHz, CLOROFORMO-d) δ ppm 1,25 (d, 6H), 2,9-3,0 (m, 2H), 3,0-3,2 (m, 2H), 3,7-3,9 (m, 8H), 3,9-4,0 (m, 2H), 4,8 (s, 2H), 7,7 (s, 1H).

Los **Intermedios 286** a **301** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 285**:

Intermedio 286

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)-*N*,*N*-dimetilbenzo[d]isoxazol-3-carboxamida

2-(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)-2-(hidroxiimino)-*N*,*N*-dimetilacetamida (**Intermedio 169**).

MS (ES) MH^+: 352 para $C_{17}H_{22}FN_3O_4$

^1H RMN (300 MHz, CLOROFORMO-d) δ ppm 1,25 (d, 6H), 3,0-3,05 (m, 2H), 3,1 (m, 2H), 3,2 (s, 3H), 3,35 (s, 3H), 3,9 (m, 2H), 4,8 (s, 2H), 7,7 (s, 1H).

Intermedio 287

(6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(piridin-4-il)benzo[d]isoxazol-5-il)metanol

Material de partida: 1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}-*N*-hidroxi-1-piridin-4-ilmetanimina (**Intermedio 161**).

MS (ES) MH^+: 358 para $C_{19}H_{20}FN_3O_3$

^1H RMN (300 MHz, $CDCl_3$) δ: ppm 1,23 (d, 6H), 2,87-3,17 (m, 4H), 3,37 (s, 1H), 3,71-3,92 (m, 2H), 4,85 (s, 2H), 7,64 (s, 1H), 7,86 (d, 2H), 8,84 (d, 2H).

Intermedio 288

(3-((1*H*-1,2,4-triazol-1-il)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-5-il)metanol

Material de partida: 1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}-*N*-hidroxi-2-(1*H*-1,2,4-triazol-1-il)etanimina (**Intermedio 163**).

MS (ES) MH^+: 362 para $C_{17}H_{20}FN_5O_3$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,21 (d, 6H), 2,76-3,13 (m, 5H), 3,60-3,93 (m, 2H), 4,75 (s, 2H) 5,72 (s, 2H), 7,36 (s, 1H), 7,99 (s, 1H), 8,23 (s, 1H).

Intermedio 289

(6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(furan-2-il)benzo[d]isoxazol-5-il)metanol

Material de partida: 1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}-1-furan-2-il-*N*-hidroximetanimina (**Intermedio 162**).

MS (ES) MH^+: 347 para $C_{18}H_{19}FN_2O_4$

^1H RMN (300 MHz, $CDCl_3$) δ:1,23 (d, 6H), 2,89-3,17 (m, 4H), 3,72-3,92 (m, 2H), 4,84 (s, 2H) 6,63 (d, 1H), 7,19 (d, 1H), 7,70 (s, 1H), 7,78 (s, 1H).

Intermedio 290

(6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(trifluorometil)benzo[d]isoxazol-5-il)metanol

Material de partida: 1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}-2,2,2-trifluoro-*N*-hidroxietanimina (**Intermedio 159**).

MS (ES) MH^+: 349 para $C_{15}H_{16}F_4N_2O_3$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,22 (d, 6H), 1,97 (pico ancho, 1H), 2,85-3,15 (m, 4H), 3,66-3,93 (m, 2H), 4,82 (s, 2H) 7,55 (s, 1H).

Intermedio 291

(3-(difluorometil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-5-il)metanol

Material de partida: 1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}-2,2-difluoro-*N*-hidroxietanimina (**Intermedio 160**).

MS (ES) MH^+: 331 para $C_{15}H_{17}F_3N_2O_3$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,23 (d, 6H), 2,88-3,16 (m, 4H), 3,72-3,95 (m, 2H), 4,83 (s, 2H), 7,00 (t, 1H), 7,61 (s, 1H).

Intermedio 292

(3-(difluorometil)-6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-5-il)metanol

Materiales de partida 1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*R*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}-2,2-difluoro-*N*-hidroxietanimina (**Intermedio 164**).

MS (ES) MH^+: 331 para $C_{15}H_{17}F_3N_2O_3$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,34 (d, 6H) 2,79-3,41 (m, 4H) 4,02-4,28 (m, 2H) 4,68-5,07 (m, 2H) 7,00 (t, 1H) 7,66 (s, 1H).

Intermedio 293

7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-(hidroximetil)-*N*-metilisoxazolo[4,5-b]piridin-3-carboxamida

Material de partida: 5-((*terc*-butildifenilsililoxi)metil)-7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-*N*-metilisoxazolo[4,5-b]piridin-3-carboxamida (**Intermedio 230**).

MS (ES) MH^+: 355 para $C_{15}H_{19}ClN_4O_4$

^1H RMN (300 MHz, DMSO-d_6) δ: 1,1 (d, 6H), 2,9 (d, 3H), 2,9-3,1 (m, 4H), 3,7-3,9 (m, 2H), 4,8 (d, 2H), 5,4 (t a, 1H), 8,9 (m, 1H).

Intermedio 294

7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-*N*-etil-5-(hidroximetil)isoxazolo[4,5-b]piridin-3-carboxamida

Material de partida: 5-((*terc*-butildifenilsililoxi)metil)-7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-*N*-etilisoxazolo[4,5-b]piridin-3-carboxamida (**Intermedio 231**).

MS (ES) MH^+: 369 para $C_{16}H_{21}ClN_4O_4$

^1H RMN (300 MHz, DMSO-d_6) δ: 1,1 (d, 6H), 1,2 (t, 3H), 2,9-3,1 (m, 4H), 3,3-3,5 (m, 2H), 3,7-3,9 (m, 2H), 4,8 (d, 2H), 5,3 (t a, 1H), 9,0 (m, 1H).

Intermedio 295

7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-(hidroximetil)-*N*-isopropilisoxazolo[4,5-b]piridin-3-carboxamida

Material de partida: 5-((*terc*-butildifenilsililoxi)metil)-7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-*N*-isopropilisoxazolo[4,5-b]piridin-3-carboxamida (**Intermedio 232**).

MS (ES) MH^+: 383 para $C_{17}H_{23}ClN_4O_4$

^1H RMN (300 MHz CD_2Cl_2) δ: 1,2 (d, 6H), 1,3 (d, 6H), 2,8-2,9 (m, 2H), 3,1-3,3 (m, 2H), 3,5 (s a, 1H), 3,8-3,9 (m, 2H), 4,3 (m, 1H), 4,9 (s a, 2H), 7,5 (s a, 1H).

Intermedio 296

N-*terc*-butil-7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-(hidroximetil)isoxazolo[4,5-b]piridin-3-carboxamida

Material de partida: *N*-*terc*-butil-5-((*terc*-butildifenilsililoxi)metil)-7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)isoxazolo[4,5-b]piridin-3-carboxamida (**Intermedio 233**).

MS (ES) MH^+: 397 para $C_{18}H_{25}ClN_4O_4$

^1H RMN (300 MHz, CD_2Cl_2) δ: 1,2 (d, 6H), 1,5 (s, 9H), 2,7-2,9 (m, 2H), 3,2-3,3 (m, 2H), 3,4 (m, 1H), 3,7-3,9 (m, 2H), 4,9 (d, 2H), 7,6 (s a, 1H).

Intermedio 297

7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-(hidroximetil)-*N*-neopentilisoxazolo[4,5-b]piridin-3-carboxamida

Material de partida: 5-((*terc*-butildifenilsililoxi)metil)-7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-*N*-neopentilisoxazolo[4,5-b]piridin-3-carboxamida (**Intermedio 234**).

MS (ES) MH^+: 411 para $C_{19}H_{27}ClN_4O_4$

^1H RMN (300 MHz, CD_2Cl_2) δ: 1,0 (s, 9H), 1,2 (d, 6H), 2,8-2,9 (m, 2H), 3,2-3,3 (m, 2H), 3,3-3,4 (superposición de m, 3H), 3,8-3,9 (m, 2H), 4,9 (d, 2H), 7,9 (s a 1H).

Intermedio 298

(7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-(hidroximetil)isoxazolo[4,5-b]piridin-3-il)(3,3-difluoroazetidin-1-il)metanona

Material de partida: (5-((*terc*-butildifenilsililoxi)metil)-7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)isoxazolo[4,5-b]piridin-3-il)(3,3-difluoroazetidin-1-il)metanona (**Intermedio 235**).

MS (ES) MH^+: 417 para $C_{17}H_{19}ClF_2N_4O_4$

^1H RMN (300 MHz, CD_2Cl_2) δ: 1,2 (d, 6H), 2,8-2,9 (m, 2H), 3,1-3,3 (m, 2H), 3,8-3,9 (m, 2H), 3,9 (s a, 1H), 4,6 (t, 2H), 4,8-4,9 (m, 4H).

Intermedio 299

N-bencil-7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-(hidroximetil)isoxazolo[4,5-b]piridin-3-carboxamida

Material de partida: *N*-bencil-5-((*terc*-butildifenilsililoxi)metil)-7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)isoxazolo[4,5-b]piridin-3-carboxamida (**Intermedio 236**).

MS (ES) MH^+: 431 para $C_{21}H_{23}ClN_4O_4$

^1H RMN (300 MHz, CD_2Cl_2) δ: 1,2 (d, 6H), 2,8-2,9 (m, 2H), 3,2-3,3 (m, 2H), 3,8-3,9 (m, 2H), 4,7 (d, 2H), 4. 9 (s, 2H), 7,3-7,4 (m, 5H), 8,0 (s a, 1H).

Intermedio 300

7-cloro-*N*-(4-cianobencil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-(hidroximetil)isoxazolo[4,5-b]piridin-3-carboxamida

Material de partida: 5-((*terc*-butildifenilsililoxi)metil)-7-cloro-*N*-(4-cianobencil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)isoxazolo[4,5-b]piridin-3-carboxamida (**Intermedio 237**).

MS (ES) MH^+: 456 para $C_{22}H_{22}ClN_5O_4$

^{1}H RMN (300 MHz, CD_2Cl_2) δ: 1,2 (d, 6H), 2,8-2,9 (m, 2H), 3,1-3,3 (m, 2H), 3,4 (m, 1H), 3,8-3,9 (m, 2H), 4,8, (d, 2H), 4,9 (d, 2H), 7,5 (d, 2H), 7,7 (d, 2H), 8,1 (s a, 1H).

Intermedio 301

7-cloro-*N*-(3-cianobencil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-(hidroximetil)isoxazolo[4,5-b]piridin-3-carboxamida

Material de partida: 5-((*terc*-butildifenilsililoxi)metil)-7-cloro-*N*-(3-cianobencil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)isoxazolo[4,5-b]piridin-3-carboxamida (**Intermedio 238**).

MS (ES) MH^+: 456 para $C_{22}H_{22}ClN_5O_4$

^{1}H RMN (300 MHz, CD_2Cl_2) δ: 1,2 (d, 6H), 2,8-2,9 (m, 2H), 3,1-3,3 (m, 2H), 3,4 (m, 1H), 3,7-3,9 (m, 2H), 4,8, (d, 2H), 4,9 (m, 2H), 7,5 (t, 1H), 7,6-7,7 (m, 3H), 8,2 (m, 1H).

Intermedio 302

Ácido 7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-metil-1,2-benzoxazol-5-carboxílico

A una solución de 3-cloro-2-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-4-fluoro-5-[*N*-hidroxietanimidoil]benzoato de metilo (**Intermedio 171**, 700 mg, 1,94 mmol) en DMF (4 mL) se agregó Cs_2CO_3 (1,9 g, 5,84 mmol) y la mezcla se calentó hasta alcanzar 130 °C durante 14 horas. La mezcla de reacción se enfrió hasta alcanzar la temperatura ambiente y se filtró a través de un lecho de celite. El disolvente se eliminó al vacío y el residuo se purificó mediante cromatografía en columna de gel de sílice utilizando un gradiente de acetato de etilo-éter de pet. para obtener el producto. Rendimiento: 250 mg, (41%).

MS (ES) MH^+: 335 para $C_{15}H_{17}ClN_2O_4$

Los **Intermedios 303** a **325** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 302**:

Intermedio 303

{7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(piridin-2-il)-1,2-benzoxazol-5-il}metanol

Material de partida: 1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}-*N*-hidroxi-1-(piridin-2-il)metanimina (**Intermedio 172**).

MS (ES) MH^+: 374 para $C_{19}H_{20}ClN_3O_3$

Intermedio 304

{7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(6-metilpiridin-3-il)-1,2-benzoxazol-5-il}metanol

Material de partida: 1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}-*N*-hidroxi-1-(6-metilpiridin-3-il)metanimina (**Intermedio 173**).

MS (ES) MH^+: 388,4 para $C_{20}H_{22}ClN_3O_3$.

Intermedio 305

{7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(1,3-tiazol-5-il)-7,7a-dihidro-1,2-benzoxazol-5-il}metanol

Material de partida: 1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}-*N*-hidroxi-1-(1,3-tiazol-5-il)metanimina (**Intermedio 174**).

MS (ES) MH^+: 382,2 para $C_{17}H_{20}ClN_3O_3S$

Intermedio 306

{7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(piridin-4-il)-1,2-benzoxazol-5-il}metanol

Material de partida: 1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}-*N*-hidroxi-1-(piridin-4-il)metanimina (**Intermedio 175**).

MS (ES) MH^+: 374 para $C_{19}H_{20}ClN_3O_3$

Intermedio 307

{7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(piridin-3-il)-1,2-benzoxazol-5-il}metanol

Material de partida: 1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}-*N*-hidroxi-1-(piridin-3-il)metanimina (**Intermedio 176**).

MS (ES) MH^+: 374 para $C_{19}H_{20}ClN_3O_3$

Intermedio 308

{7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(1,3-tiazol-2-il)-1,2-benzoxazol-5-il}metanol

Material de partida: 1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}-*N*-hidroxi-1-(1,3-tiazol-2-il)metanimina (**Intermedio 177**).
MS (ES) MH^+: 380 para $C_{17}H_{18}ClN_3O_3S$

Intermedio 309

{7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(1-metil-1*H*-imidazol-2-il)-1,2-benzoxazol-5-il}metanol

Material de partida: 1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}-*N*-hidroxi-1-(1-metil-1*H*-imidazol-2-il)metanimina (**Intermedio 178**).
MS (ES) MH^+: 377 para $C_{18}H_{21}ClN_4O_3$

Intermedio 310

{7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(metoximetil)-1,2-benzoxazol-5-il}metanol

Material de partida: (1*E*)-1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}-*N*-hidroxi-2-metoxietanimina (**Intermedio 179**).
MS (ES) MH^+: 341 para $C_{16}H_{21}ClN_2O_4$

Intermedio 311

{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(2-metil-1,3-oxazol-4-il)-1,2-benzoxazol-5-il}metanol

Material de partida: 1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}-*N*-hidroxi-1-(2-metil-1,3-oxazol-4-il)metanimina (**Intermedio 185**).
MS (ES) MH^+: 362 para $C_{18}H_{20}FN_2O_4$

Intermedio 312

{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(5-metil-1,2-oxazol-3-il)-1,2-benzoxazol-5-il}metanol

Material de partida: 1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}-*N*-hidroxi-1-(5-metil-1,2-oxazol-3-il)metanimina (**Intermedio 186**).
MS (ES) MH^+: 362 para $C_{18}H_{20}FN_3O_4$

Intermedio 313

{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(3,5-dimetil-1,2-oxazol-4-il)-7-fluoro-1,2-benzoxazol-5-il}metanol

Material de partida: 1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}-1-(3,5-dimetil-1,2-oxazol-4-il)-*N*-hidroximetanimina (**Intermedio 187**).

MS (ES) MH^+: 376 para $C_{19}H_{22}FN_3O_4$

Intermedio 314

{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(1-metil-1*H*-imidazol-2-il)-1,2-benzoxazol-5-il}metanol

Material de partida: 1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}-*N*-hidroxi-1-(1-metil-1*H*-imidazol-2-il)metanimina (**Intermedio 188**).

MS (ES) MH^+: 361 para $C_{18}H_{21}FN_4O_3$

Intermedio 315

{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(1-metil-1*H*-imidazol-4-il)-1,2-benzoxazol-5-il}metanol

Material de partida: 1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}-*N*-hidroxi-1-(1-metil-1*H*-imidazol-4-il)metanimina (**Intermedio 189**).

MS (ES) MH^+: 361,2 para $C_{18}H_{21}FN_4O_3$

Intermedio 316

{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(1-metil-1*H*-imidazol-5-il)-1,2-benzoxazol-5-il}metanol

Material de partida: 1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}-*N*-hidroxi-1-(1-metil-1*H*-imidazol-5-il)metanimina (**Intermedio 190**).

MS (ES) MH^+: 361 para $C_{18}H_{21}FN_4O_3$

Intermedio 317

{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(4-metil-1,3-tiazol-5-il)-1,2-benzoxazol-5-il}metanol

Material de partida: 1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}-*N*-hidroxi-1-(4-metil-1,3-tiazol-5-il)metanimina (**Intermedio 191**).

MS (ES) MH^+: 378 para $C_{18}H_{20}FN_3O_3S$

Intermedio 318

{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(4-metil-1,2,3-tiadiazol-5-il)-1,2-benzoxazol-5-il}metanol

Material de partida: 1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}-*N*-hidroxi-1-(4-metil-1,2,3-tiadiazol-5-il)metanimina (**Intermedio 192**).

MS (ES) MH^+: 379 para $C_{17}H_{19}FN_4O_3S$

Intermedio 319

{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(piridazin-3-il)-1,2-benzoxazol-5-il}metanol

Material de partida: 1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}-*N*-hidroxi-1-(piridazin-3-il)metanimina (**Intermedio 193**).

MS (ES) MH^+: 359 para $C_{18}H_{19}FN_4O_3$

Intermedio 320

{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(pirimidin-4-il)-1,2-benzoxazol-5-il}metanol

Material de partida: 1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}-*N*-hidroxi-1-(pirimidin-4-il)metanimina (**Intermedio 194**).

MS (ES) MH^+: 359 para $C_{18}H_{19}FN_4O_3$

Intermedio 321

(2-{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-5-(hidroximetil)-1,2-benzoxazol-3-il}-1,3-tiazol-4-il)(morfolin-4-il)metanona

Material de partida: {2-[{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(hidroxiimino)metil]-1,3-tiazol-4-il}(morfolin-4-il)metanona (**Intermedio 180**).

MS (ES) MH^+: 477 para $C_{22}H_{25}FN_4O_4S$

Intermedio 322

(5-{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-5-(hidroximetil)-1,2-benzoxazol-3-il}-1,3-tiazol-4-il)(morfolin-4-il)metanona

Material de partida: {5-[{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(hidroxiimino)metil]-1,3-tiazol-4-il}(morfolin-4-il)metanona (**Intermedio 181**).

MS (ES) MH^+: 477 para $C_{22}H_{25}FN_4O_4S$

Intermedio 323

2-{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-5-(hidroximetil)-1,2-benzoxazol-3-il}-*N*,*N*-dimetil-1,3-tiazol-4-carboxamida

Material de partida: 2-[{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(hidroxiimino)metil]-*N*,*N*-dimetil-1,3-tiazol-4-carboxamida (**Intermedio 182**).

MS (ES) MH^+: 435,2 para $C_{20}H_{23}FN_4O_4S$

Intermedio 324

2-{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-5-(hidroximetil)-1,2-benzoxazol-3-il}-*N*,*N*-dimetil-1,3-tiazol-5-carboxamida

Material de partida: 2-[{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(hidroxiimino)metil]-*N*,*N*-dimetil-1,3-tiazol-5-carboxamida (**Intermedio 183**).

MS (ES) MH^+: 435 para $C_{20}H_{23}FN_4O_4S$

Intermedio 325

5-{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-5-(hidroximetil)-1,2-benzoxazol-3-il}-1,3-tiazol-4-carbonitrilo

Material de partida: 5-[{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(hidroxiimino)metil]-1,3-tiazol-4-carbonitrilo (**Intermedio 184**).

MS (ES) MH^+: 388 para $C_{18}H_{17}FN_4O_3S$

Intermedio 326

Ácido 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-metil-3-(1,3-tiazol-2-il)-1,2-benzoxazol-5-carboxílico

Una solución de ácido 2-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-4-fluoro-5-[(hidroxiimino)(1,3-tiazol-2-il)metil]-3-metilbenzoico de metilo (**Intermedio 195**, 0,31 g, 0,8 mmol), K_2CO_3 (0,4 g, 2,3 mmol) y yoduro de potasio (0,03 g, 0,2 mmol) en DMF (10 mL) se calentó a 130 °C durante 12 horas. Los disolventes se eliminaron al vacío y el residuo se trató con ácido clorhídrico 1,5N y se extrajo con acetato de etilo, que se secó con sulfato de sodio. La eliminación del disolvente al vacío proporcionó el producto. Rendimiento: 0,18 g (62%).

MS (ES) MH^+: 373 para $C_{18}H_{19}N_3O_4S$

El Intermedio 327 se preparó a partir del material de partida indicado utilizando un método similar al descrito para la síntesis del **Intermedio 326:**

Intermedio 327

Ácido 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-metil-3-(pirazin-2-il)-1,2-benzoxazol-5-carboxílico

Material de partida: ácido 2-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-4-fluoro-5-[(hidroxiimino)(pirazin-2-il)metil]-3-metilbenzoico (**Intermedio 196**).

MS (ES) MH^+: 368 para $C_{19}H_{20}N_4O_4$

Intermedio 328

(3-(3-cloropirazin-2-il)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-5-il)metanol

{5-[(3-cloropirazin-2-il)(hidroxiimino)metil]-2-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3,4-difluorofenil}metanol (**Intermedio 198,** 106 mg, 0,26 mmol) en MeCN (4 mL) se trató con

K_2CO_3 (53,2 mg, 0,39 mmol) a 120 °C durante 1 hora. La mezcla se diluyó con EtOAc y se lavó con agua y salmuera. La solución de EtOAc se secó con sulfato de sodio anhidro, se filtró y se concentró para proporcionar 90 mg del producto.
MS (ES) MH^+: 393 para $C_{18}H_{18}ClFN_4O_3$

El **Intermedio 329** se preparó a partir del material de partida indicado utilizando un método similar al descrito para la síntesis del **Intermedio 328:**

Intermedio 329
5-((*terc*-butildifenilsililoxi)metil)-3-(6-cloropirazin-2-il)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol
Material de partida: 1-{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}-1-(6-cloropirazin-2-il)-*N*-hidroximetanimina (**Intermedio 199**).
MS (ES) MH^+: 632 para $C_{34}H_{36}ClFN_4O_3Si$

Intermedio 330
6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-metil-3-(1,3-tiazol-2-il)-1,2-benzoxazol-5-carbaldehído
Cloruro de oxalilo (0,31 g, 2,4 mmol) se agregó a una solución agitada de ácido 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-metil-3-(1,3-tiazol-2-il)-1,2-benzoxazol-5-carboxílico (**Intermedio 326**, 0,18 g, 0,4 mmol) y dos gotas de DMF en diclorometano (5 mL) a 0 °C y la mezcla se agitó a temperatura ambiente durante 2 horas. El disolvente se eliminó a presión reducida y el residuo se disolvió en THF (10 mL) y la solución se enfrió hasta alcanzar -78 °C y solución de hidruro de tri(t-butoxi)aluminio y litio 1M (0,28 g, 1,1 mmol) se agregó lentamente y se agitó durante 30 min a la misma temperatura. La reacción se detuvo con ácido clorhídrico 1,5N y se extrajo con acetato de etilo, las capas orgánicas combinadas se secaron con sulfato de sodio y el disolvente se eliminó. El aceite viscoso marrón obtenido de esta forma se purificó mediante cromatografía en columna de gel de sílice (20% de acetato de etilo en hexano) para proporcionar el producto como un sólido amarillo. Rendimiento: 0,06 g (35%).
MS (ES) MH^+: 357 para $C_{18}H_{19}N_3O_3S$

El **Intermedio 331** se preparó a partir del material de partida indicado utilizando un método similar al descrito para la síntesis del **Intermedio 330:**

Intermedio 331

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-metil-3-(pirazin-2-il)-1,2-benzoxazol-5-carbaldehído

Material de partida: ácido 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-metil-3-(pirazin-2-il)-1,2-benzoxazol-5-carboxílico (**Intermedio 327**).

MS (ES) MH^+: 352 para $C_{19}H_{20}N_4O_3$

^{1}H RMN (400 MHz, $CDCl_3$) δ: 1,2 (d, 6H), 2,7 (s, 3H), 3,0 (d, 2H), 3,2 (t, 2H), 3,9 (m, 2H), 8,7 (s, 1H), 8,8 (s, 2H), 9,4 (s, 1H), 10,5 (s, 1H).

Intermedio 332

1-(5-((*terc*-butildifenilsililoxi)metil)-2,3,4-trifluorofenil)etanona

Una solución de *s*-butillitio (1,4 M en ciclohexano) (6,42 mL, 8,99 mmol) se agregó lentamente a una solución de *terc*-butildifenil(2,3,4-trifluorobenciloxi)silano (**Intermedio 48,** 3 g, 7,49 mmol) en THF (30 mL) se enfrió en un baño de hielo seco-acetona para mantener una temperatura por debajo de -60 °C. Después de agitar en el baño de hielo seco-acetona durante 20 minutos, se agregó gota a gota *N*-metoxi-*N*-metilacetamida (1,035 mL, 9,74 mmol) manteniendo una temperatura por debajo de -60 °C. La mezcla se agitó fría durante 40 minutos antes de aplacarse con NH_4Cl (acuoso) y se entibió hasta alcanzar la temperatura ambiente. La solución se repartió entre EtOAc y agua. El EtOAc se separó y se lavó con salmuera. Las capas acuosas combinadas se extrajeron con EtOAc, que se lavó con salmuera. El EtOAc combinado se secó ($MgSO_4$) y se concentró para proporcionar un aceite que se cromatografió en gel de sílice (10% de CH_2Cl_2 en hexanos seguido por elución en gradiente a 70% de CH_2Cl_2 en hexanos) para proporcionar 2 materiales, el componente que eluyó en primer lugar (0,76 g) consistente con el material de partida y el componente que eluyó en segundo lugar (2,05 g) consistente con el producto.

^{1}H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1,1 (s, 9H), 2,6 (d, 3H), 4,8 (s, 2H), 7,3-7,5 (m, 6H) 7,6-7,7 (m, 4H), 7,8-7,95 (m, 1H).

El **Intermedio 333** se preparó a partir del material de partida indicado y *terc*-butildifenil(2,3,4-trifluorobenciloxi)silano (**Intermedio 48**) utilizando un método similar al descrito para la síntesis del **Intermedio 332:**

Intermedio 333

(5-((*terc*-butildifenilsililoxi)metil)-2,3,4-trifluorofenil)(1-metil-1*H*-1,2,4-triazol-5-il)metanona

Material de partida: *N*-metoxi-*N*,1-dimetil-1*H*-1,2,4-triazol-5-carboxamida (**Intermedio 49**).

MS ES$^+$ MH$^+$ 510 para $C_{27}H_{26}F_3N_3O_2Si$

^{1}H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1,1 (s, 9H), 4,3 (s, 3H), 4,8 (s, 2H), 7,3-7,5 (m, 5H), 7,6-7,7 (m, 4H), 7,95 (s, 1H), 8,0 (m, 1H).

Intermedio 334

(6,7-difluoro-3-metil-1,2-bencisoxazol-5-il)metanol

A una solución agitada de oxima de propan-2-ona (1,73 g, 23,7 mmol) en THF (25 mL) se agregó *t*-butóxido de potasio (solución 1M en THF, 23,8 mL) a 0 °C en atmósfera de nitrógeno y la mezcla se agitó entibiando hasta alcanzar la temperatura ambiente durante 1 hora. La mezcla se enfrió hasta alcanzar – 78 °C y se agregó a la mezcla una solución de 1-(5-((*terc*-butildifenilsililoxi)metil)-2,3,4-trifluorofenil)etanona (**Intermedio 332**, 3,0 g, 6,8 mmol) en THF (15 mL), se agitó durante 20 minutos a -78 °C luego a -20 °C durante 2 horas. La reacción se detuvo con una solución acuosa saturada de NH_4Cl y se extrajo con EtOAc. La capa orgánica se secó (Na_2SO_4), se filtró y se concentró para proporcionar material que se utilizó para la siguiente etapa sin purificación adicional. Una solución agitada del material disuelto en etanol (130 mL) se trató con 5 mL de HCl acuoso al 5% a 45 °C durante 8 horas. La reacción se detuvo con solución acuosa de bicarbonato de sodio al 10% y se extrajo con EtOAc. La capa orgánica se lavó con agua, se secó y se concentró. El residuo se purificó en una columna instantánea de gel de sílice (elución con 15-20% de EtOAc en hexanos) para proporcionar el compuesto del título como un sólido amarillo. Rendimiento: 600 mg, (46%).

MS (ES) MH$^+$: 200 para $C_9H_7F_2NO_2$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 2,6 (s, 3H), 4,6 (d, 2H), 5,55 (s, 1H), 7,7 (d, 1H).

El **Intermedio 335** se preparó a partir del material de partida indicado y oxima de propan-2-ona utilizando un método similar al descrito para la síntesis del **Intermedio 334**:

Intermedio 335

(6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-3-(5-morfolinopirazin-2-il)benzo[d]isoxazol-5-il)metanol

Material de partida: (5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*R*)-2,6-dimetilmorfolino)-2,3-difluorofenil)(5-morfolinopirazin-2-il)metanona (**Intermedio 134**).

MS (ES) MH^+: 444 (M+H) para $C_{22}H_{26}FN_5O_4$

Intermedio 336

1-(6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(propan-2-ilidenoaminooxi)piridin-2-il)etanona

Se disolvió oxima de propan-2-ona (104 mg, 1,43 mmol) en 2 mL de THF y se agregó *terc*-butóxido de potasio, 1M en THF (1,427 mL, 1,43 mmol), para proporcionar una mezcla blanca que se agitó a temperatura ambiente durante 45 min. La mezcla se enfrió en un baño de hielo y una solución de 1-(6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)etanona (**Intermedio 148**, 660 mg, 1,19 mmol) en 3 mL de THF se agregó para proporcionar una solución amarilla. Se agitó a 0 °C. Después de aproximadamente 30 minutos, se agregó NH_4Cl saturado para detener la reacción, a lo que siguió la extracción con EtOAc. Las fases se separaron y la fase orgánica combinada se secó con $MgSO_4$ antes de concentrarse hasta proporcionar un aceite amarillo claro, 635 mg (88%).

MS (ES) MH^+: 608 para $C_{33}H_{42}ClN_3O_4Si$

Los **Intermedios 337** a **344** se prepararon a partir del material de partida indicado y oxima de propan-2-ona utilizando un método similar al descrito para la síntesis del **Intermedio 336**:

Intermedio 337

(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoro-2-(propan-2-ilidenoaminooxi)fenil)(tiazol-5-il)metanona

Materiales de partida: (5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)(tiazol-5-il)metanona (**Intermedio 123**).

MS (ES) MH^+: 660 para $C_{36}H_{42}FN_3O_4SSi$

^1H RMN (300 MHz, $CDCl_3$) δ: 0,84-1,10 (superposición de doblete y singlete, 15H), 1,58-1,92 (6H), 2,43-2,97 (m, 4H), 3,24-3,60 (m, 2H) 4,68 (s, 2H), 7,23-7,45 (m, 7H), 7,47-7,71 (m, 4H), 8,11 (s, 1H) 8,93 (s, 1H).

Intermedio 338

(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoro-2-(propan-2-ilidenoaminooxi)fenil)(6-metilpiridin-3-il)metanona

Material de partida: (5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)(6-metilpiridin-3-il)metanona (**Intermedio 124**).

MS (ES) MH^+: 660 para $C_{39}H_{46}FN_3O_4Si$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,01-1,11 (superposición de doblete y singlete, 15H), 1,62 (3H), 1,68(3H), 2,64 (s, 3H), 2,66-2,90 (m, 4H), 3,39-3,55 (m, 2H), 4,74 (s, 2H), 7,22 (d, 1H), 7,31-7,46 (m, 7H), 7,59-7,68 (m, 4H), 7,96 (d, 1H), 8,86 (s, 1H).

Intermedio 339

(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoro-2-(propan-2-ilidenoaminooxi)fenil)(2-fluorofenil)metanona

Materiales de partida: (5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)(2-fluorofenil)metanona (**Intermedio 125**).

MS (ES) MH^+: 671 para $C_{39}H_{44}F_2N_2O_4Si$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,03 (s, 9H), 1,07 (d, 6H), 1,53 (s, 3H), 1,73 (s, 3H), 2,55-2,91 (m, 4H), 3,30-3,64 (m, 2H), 4,73 (s, 2H), 6,94-7,74 (m, 15H).

Intermedio 340

(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoro-2-(propan-2-ilidenoaminooxi)fenil)(tetrahidro-2*H*-piran-4-il)metanona

Materiales de partida: (5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2,3-difluorofenil)(tetrahidro-2*H*-piran-4-il)metanona (**Intermedio 126**).

MS (ES) MH^+: 661 para $C_{38}H_{49}FN_2O_5Si$

Intermedio 341

(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*R*)-2,6-dimetilmorfolino)-3-fluoro-2-(propan-2-ilidenoaminooxi)fenil)(tiazol-2-il)metanona

Materiales de partida: (5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*R*)-2,6-dimetilmorfolino)-2,3-difluorofenil)(tiazol-2-il)metanona (**Intermedio 131**).

MS (ES) MH^+: $C_{36}H_{42}FN_3O_4SSi$

Intermedio 342

(5-((*terc*-butildifenilsililoxi)metil)-3-cloro-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2-(propan-2-ilidenoaminooxi)fenil)(pirazin-2-il)metanona

Material de partida: (5-((*terc*-butildifenilsililoxi)metil)-3-cloro-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2-fluorofenil)(pirazin-2-il)metanona (**Intermedio 72**, 847 mg, 1,37 mmol).

MS (ES) MH^+: 671 para $C_{37}H_{43}ClN_4O_4Si$

Intermedio 343

(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*R*)-2,6-dimetilmorfolino)-3-fluoro-2-(propan-2-ilidenoaminooxi)fenil)(pirazin-2-il)metanona

Material de partida: (5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*R*)-2,6-dimetilmorfolino)-2,3-difluorofenil)(pirazin-2-il)metanona (**Intermedio 133**).

MS (ES) MH^+: 655 para $C_{37}H_{43}FN_4O_4Si$

Intermedio 344

(5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*R*)-2,6-dimetilmorfolino)-3-fluoro-2-(propan-2-ilidenoaminooxi)fenil)(6-metoxipirazin-2-il)metanona

Material de partida: (5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*R*)-2,6-dimetilmorfolino)-2,3-difluorofenil)(6-metoxipirazin-2-il)metanona (**Intermedio 138**).

MS (ES) MH^+: 685 para $C_{38}H_{45}FN_4O_5Si$

Los **Intermedios 345** a **351** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 33**:

Intermedio 345

(6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(tiazol-5-il)benzo[d]isoxazol-5-il)metanol

Material de partida: (5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoro-2-(propan-2-ilidenoaminooxi)fenil)(tiazol-5-il)metanona (**Intermedio 337**).

MS (ES) MH^+: 364 para $C_{17}H_{18}FN_3O_3S$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,23 (d, 6H), 2,85-3,20 (m, 4H), 3,70-3,94 (m, 2H), 4,80 (s, 2H), 7,66 (s, 1H), 8,57 (s, 1H), 9,00 (s, 1H).

Intermedio 346

(6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(6-metilpiridin-3-il)benzo[d]isoxazol-5-il)metanol

Material de partida: (5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoro-2-(propan-2-ilidenoaminooxi)fenil)(6-metilpiridin-3-il)metanona (**Intermedio 338**).

MS (ES) MH^+: 372 para $C_{20}H_{22}FN_3O_3$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,22 (s, 3H), 1,24 (s, 3H), 2,68 (s, 3H), 2,82-3,22 (m, 4H), 3,29-3,55 (pico ancho, 1H), 3,67-4,00 (m, 2H), 4,82 (s, 2H), 7,37 (d, 1H), 7,60 (s, 1H), 8,15 (d, 1H), 9,06 (s, 1H).

Intermedio 347

(6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(2-fluorofenil)benzo[d]isoxazol-5-il)metanol

Material de partida: (5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoro-2-(propan-2-ilidenoaminooxi)fenil)(2-fluorofenil)metanona (**Intermedio 339**).

MS (ES) MH^+: 375 para $C_{20}H_{20}F_2N_2O_3$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,23 (d, 6H), 2,90-3,18 (m, 4H), 3,69-3,94 (m, 2H), 4,81 (s, 2H), 7,25-7,88 (m, 5H).

Intermedio 348

(6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(tetrahidro-2*H*-piran-4-il)benzo[d]isoxazol-5-il)metanol

Material de partida: (5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoro-2-(propan-2-ilidenoaminooxi)fenil)(tetrahidro-2*H*-piran-4-il)metanona (**Intermedio 340**).
MS (ES) MH^+: 365 para $C_{19}H_{25}FN_2O_4$
^1H RMN (300 MHz, $CDCl_3$) δ: 1,22 (d, 6H), 1,87-2,24 (m, 4H), 2,84-2,99 (m, 2H), 3,07 (t, 2H), 3,24-3,39 (m, 1H), 3,59 (t, 2H), 3,71-3,94 (m, 2H), 4,00-4,21 (m, 2H), 4,80 (s, 2H), 7,40 (s, 1H).

Intermedio 349

(6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-3-(tiazol-2-il)benzo[d]isoxazol-5-il)metanol

Material de partida: (5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*R*)-2,6-dimetilmorfolino)-3-fluoro-2-(propan-2-ilidenoaminooxi)fenil)(tiazol-2-il)metanona (**Intermedio 341**).
MS (ES) MH^+: 364 para $C_{17}H_{18}FN_3O_3S$
^1H RMN (300 MHz, $CDCl_3$) δ: 1,35 (d, 6H), 2,90-3,08 (m, 2H), 3,20-3,47 (m, 2H), 4,04-4,29 (m, 2H), 4,76-4,99 (m, 2H), 7,57 (d, 1H), 8,09 (d, 1H), 8,18 (s, 1H).

Intermedio 350

(6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-3-(pirazin-2-il)benzo[d]isoxazol-5-il)metanol

Material de partida: (5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*R*)-2,6-dimetilmorfolino)-3-fluoro-2-(propan-2-ilidenoaminooxi)fenil)(pirazin-2-il)metanona (**Intermedio 343**).
MS (ES) MH^+: 359 para $C_{18}H_{19}FN_4O_3$

Intermedio 351

(6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-3-(6-metoxipirazin-2-il)benzo[d]isoxazol-5-il)metanol

Material de partida: (5-((*terc*-butildifenilsililoxi)metil)-4-((2*R*,6*R*)-2,6-dimetilmorfolino)-3-fluoro-2-(propan-2-ilidenoaminooxi)fenil)(6-metoxipirazin-2-il)metanona (**Intermedio 344**).
MS (ES) MH^+: 389 para $C_{19}H_{21}FN_4O_4$

Intermedio 352

(7-Cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-metilisoxazolo[4,5-b]piridin-5-il)metanol

Se disolvió 1-(6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(propan-2-ilidenoaminooxi)piridin-2-il)etanona (**Intermedio 336**, 821 mg, 1,35 mmol) en 13 mL

de EtOH. Se agregó HCl 1M acuoso, (4,33 mL, 4,33 mmol) para proporcionar un precipitado inmediato, que se disolvió para proporcionar una solución amarilla brumosa. La mezcla se calentó a 75 °C. Después de 1 hora, 15 minutos, la reacción se enfrió y se diluyó con EtOAc. Se agregó $NaHCO_3$ saturado para detener y luego se extrajo 2X con EtOAc. La fase orgánica combinada se secó con $MgSO_4$ y se concentró. El bruto se purificó con SiO_2 utilizando 15-40% de EtOAc/hexanos. Se recuperaron 389 mg (88%) del compuesto del título como un sólido blanco.

MS (ES) MH^+: 312 para $C_{14}H_{18}ClN_3O_3$

^1H RMN (300 MHz, CD_2Cl_2) δ: 1,2 (d, 6H), 2,6 (s, 3H), 2,7-2,8 (m, 2H), 3,2-3,3 (m, 2H), 3,7-3,9 (m, 2H), 4,0 (s a, 1H), 4,9 (d, 2H).

El **Intermedio 353** se preparó a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 352**:

Intermedio 353

(7-Cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(pirazin-2-il)benzo[d]isoxazol-5-il)metanol

Material de partida: (5-((*terc*-butildifenilsililoxi)metil)-3-cloro-4-((2*R*,6*S*)-2,6-dimetilmorfolino)-2-(propan-2-ilidenoaminooxi)fenil)(pirazin-2-il)metanona (**Intermedio 342**).

MS (ES) MH^+: 375 para $C_{18}H_{19}ClN_4O_3$

^1H RMN (DMSO-d_6) δ: 1,1 (d, 6H), 2,8-3,0 (m, 2H), 3,1-3,2 (m, 2H), 3,7-3,8 (m, 2H), 4,7-4,8 (m, 2H), 5,4 (m, 1H), 8,4 (s a, 1H), 8,9 (d, 1H), 9,0 (m, 1H), 9,4 (m, 1H).

Intermedio 354

Ácido 7-cloro-3-ciclopropil-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-1,2-benzoxazol-5-carboxílico

A una solución agitada de oxima de propan-2-ona (80 mg, 1,10 mmol) en THF (10 mL) se agregó *t*-butóxido de potasio (solución 1M en THF, 2,0 mL, 2,0 mmol) a -20 °C. Después de agitar durante 45 minutos se agregó una solución de metil 3-cloro-5-(ciclopropilcarbonil)-2-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-4-fluorobenzoato (**Intermedio 91**) (370 mg, 1,0 mmol) en THF (5 mL) y la mezcla se agitó durante 20 minutos a -20 °C antes de entibiarse hasta alcanzar la temperatura ambiente durante 1 hora. La reacción se detuvo con solución de cloruro de amonio saturado acuoso y se extrajo con EtOAc. La capa orgánica se secó (Na_2SO_4), se filtró y se

concentró para proporcionar el material bruto, que se utilizó para la siguiente etapa sin purificación adicional. Una solución agitada de material bruto (500 mg) de la reacción anterior disuelto en etanol (20 mL) se trató con 5 mL de HCl acuoso al 5% a 50 °C durante 12 horas. La reacción se detuvo con solución acuosa de bicarbonato de sodio al 10% y se extrajo con EtOAc. La capa orgánica se lavó con agua, se secó y se concentró. El residuo se purificó en una columna instantánea de gel de sílice (elución con 50-70% de EtOAc en hexanos) para proporcionar el producto. Rendimiento: 100 mg (28%).
MS (ES): 295,4 para $C_{15}H_{19}FN_2O_3$

Los **Intermedios 355** a **371** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 354**:

Intermedio 355
{7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(pirimidin-2-il)-1,2-benzoxazol-5-il}metanol
Material de partida: {5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}(pirimidin-2-il)metanona (**Intermedio 109**).
MS (ES) MH^+: 375,2 para $C_{18}H_{19}ClN_4O_3$

Intermedio 356
{7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(pirimidin-4-il)-1,2-benzoxazol-5-il}metanol
Material de partida: {5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}(pirimidin-4-il)metanona (**Intermedio 110**).
MS (ES) MH^+: 375,2 para $C_{18}H_{19}ClN_4O_3$

Intermedio 357
{7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(pirimidin-5-il)-1,2-benzoxazol-5-il}metanol
Material de partida: {5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}(pirimidin-5-il)metanona (**Intermedio 111**).
MS (ES) MH^+: 375,2 para $C_{18}H_{19}ClN_4O_3$

Intermedio 358

{7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(piridazin-4-il)-1,2-benzoxazol-5-il}metanol

Material de partida: {5-({[*terc*-butil(difenil)silil]oxi}metil)-3-cloro-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2-fluorofenil}(piridazin-4-il)metanona (**Intermedio 112**).

MS (ES) MH^+: 375,2 para $C_{18}H_{19}ClN_4O_3$

Intermedio 359

(6,7-difluoro-3-(1-metil-1*H*-1,2,4-triazol-5-il)benzo[d]isoxazol-5-il)metanol

Material de partida: (5-((*terc*-butildifenilsililoxi)metil)-2,3,4-trifluorofenil)(1-metil-1*H*-1,2,4-triazol-5-il)metanona (**Intermedio 333**).

MS (ES) MH^+: 267 para $C_{11}H_8F_2N_4O_2$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 4,3 (s, 3H), 4,7 (d, 2H), 5,7 (t, 1H), 8,3 (d, 1H), 8,4 (s, 1H).

Intermedio 360

(7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(pirazin-2-il)isoxazolo[4,5-b]piridin-5-il)metanol

Material de partida: (6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)(pirazin-2-il)metanona (1,1 g, 1,78 mmol) (**Intermedio 143**).

MS (ES) MH^+: 376 para $C_{17}H_{18}ClN_5O_3$

^{1}H RMN (300 MHz, DMSO-d_6) δ: 1,0–1,1 (m, 6H), 3,0 (d, 4H), 3,7–3,9 (m, 2H), 4,8 (td, 2H), 5,2 (s a, 1H), 8,7-8,8 (m, 2H), 9,5 (d, 1H).

Intermedio 361

(7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(tiazol-2-il)isoxazolo[4,5-b]piridin-5-il)metanol

Material de partida: (6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)(tiazol-2-il)metanona (**Intermedio 144**).

MS (ES) MH^+: 381 para $C_{16}H_{17}ClN_4O_3S$

^{1}H RMN (300 MHz, $CDCl_3$) δ: 1,1–1,2 (m, 6H), 2,8 (s a, 4H), 3,3 (s a, 2H), 3,8 (s a, 2H), 4,9 (s, 1H), 7,7 (d, 1H), 8,2 (d, 1H).

Intermedio 362

(7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(4-metiltiazol-2-il)isoxazolo[4,5-b]piridin-5-il)metanol

Material de partida: (6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)(4-metiltiazol-2-il)metanona (**Intermedio 145**).

MS (ES) MH^+: 395 para $C_{17}H_{19}ClN_4O_3S$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,1–1,2 (m, 6H), 2,7 (s a, 4H), 2,8 (s, 3H), 3,3 (s a, 2H), 3,8 (s a, 2H), 4,9 (s, 1H), 7,5 (s, 1H).

Intermedio 363

(7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(1-metil-1*H*-imidazol-2-il)isoxazolo[4,5-b]piridin-5-il)metanol

Material de partida: (6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)(1-metil-1*H*-imidazol-2-il)metanona (**Intermedio 99**).

MS (ES) MH^+: 378 para $C_{17}H_{20}ClN_5O_3$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,1–1,2 (m, 6H), 2,8 (s a, 4H), 3,2 (s a, 2H), 3,8 (s a, 2H), 4,0 (s, 3H), 4,9 (s a, 1H), 7,1 (s, 1H), 7,3 (s a, 1H).

Intermedio 364

(7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(tiazol-5-il)isoxazolo[4,5-b]piridin-5-il)metanol

Material de partida: (6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)(tiazol-5-il)metanona (**Intermedio 100**).

MS (ES) MH^+: 381 para $C_{16}H_{17}ClN_4O_3S$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,1–1,2 (m, 6H), 2,8 (s a, 2H), 3,3 (s a, 2H), 3,8 (s a, 2H), 4,9 (s, 2H), 9,0 (2s, 2H).

Intermedio 365

(7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(2-metiltiazol-5-il)isoxazolo[4,5-b]piridin-5-il)metanol

Material de partida: (6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)(2-metiltiazol-5-il)metanona (**Intermedio 101**).

MS (ES) MH^+: 395 para $C_{16}H_{17}ClN_4O_3S$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,1–1,2 (m, 6H) 2,7–2,9 (m, 5H), 3,3 (s a, 2H), 3,8 (s a, 2H), 4,9 (s, 2H), 8,7 (s, 1H).

Intermedio 366

(7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(1-metil-1*H*-1,2,4-triazol-5-il)isoxazolo[4,5-b]piridin-5-il)metanol

Material de partida: (6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)(1-metil-1*H*-1,2,4-triazol-5-il)metanona (**Intermedio 146**).

MS (ES) MH^+: 379 para $C_{16}H_{19}ClN_6O_3$

Intermedio 367

4-(7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-(hidroximetil)isoxazolo[4,5-b]piridin-3-il)-2-fluorobenzonitrilo

Material de partida: 4-(6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropicolinoil)-2-fluorobenzonitrilo (**Intermedio 102**).

MS (ES) MH^+: 417 para $C_{20}H_{18}ClN_4O_3$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,1–1,3 (m, 6H), 2,8 (s a, 2H), 3,3 (s a, 2H), 3,8 (s a, 2H), 4,9 (s, 2H), 7,8 (dd, 1H), 8,2 – 8,4 (m, 2H).

Intermedio 368

(7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(5-metiltiazol-2-il)isoxazolo[4,5-b]piridin-5-il)metanol

Material de partida: (6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)(5-metiltiazol-2-il)metanona (**Intermedio 103**).

MS (ES) MH^+: 395 para $C_{17}H_{19}ClN_4O_3S$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,1–1,2 (m, 6H), 2,5–2,7 (m, 3H), 2,8 (s a, 2H), 3,3 (s a, 2H), 3,8 (s a, 2H), 4,9 (s, 2H), 7,8 (d, 1H).

Intermedio 369

5-(7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-(hidroximetil)isoxazolo[4,5-b]piridin-3-il)picolinonitrilo

Material de partida: 5-(6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropicolinoil)picolinonitrilo (**Intermedio 147**).

MS (ES) MH^+: 400 para $C_{19}H_{18}ClN_5O_3$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,1–1,2 (m, 6H), 2,8 (s a, 2H), 3,3 (s a, 2H), 3,8 (s a, 2H), 4,9 (s, 2H), 8,8 (dd, 1H), 9,7 (d, 1H).

Intermedio 370

(3-(2-bromotiazol-5-il)-7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)isoxazolo[4,5-b]piridin-5-il)metanol

Material de partida: (2-bromotiazol-5-il)(6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)metanona (**Intermedio 104**).

MS (ES) MH^+: 460 para $C_{16}H_{16}ClBrN_4O_3S$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,1–1,2 (m, 6H), 2,7–2,9 (m, 2H), 3,3 (s a, 2H), 3,8 (s a, 2H), 4,9 (s, 2H), 8,6 (s, 1H).

Intermedio 371

(7-cloro-3-(2,4-diclorotiazol-5-il)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)isoxazolo[4,5-b]piridin-5-il)metanol

Material de partida: (6-((*terc*-butildifenilsililoxi)metil)-4-cloro-5-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-fluoropiridin-2-il)(2,4-diclorotiazol-5-il)metanona (**Intermedio 105**).

MS (ES) MH^+: 449 para $C_{16}H_{15}Cl_3N_4O_3S$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,1–1,2 (m, 6H), 2,7 – 2,9 (m, 2H), 3,3 (s a, 2H), 3,8 (s a, 2H), 4,9 (s, 2H).

Intermedio 372

{7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-metil-1,2-benzoxazol-5-il}metanol

A una solución agitada de $NaBH_4$ (78 mg, 2,43 mmol) en diglima (1 mL) se agregó BF_3 (1,6 mL, 2,59 mmol) y el gas diborano generado de esta forma se purgó en una solución de ácido 7-cloro-

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-metil-1,2-benzoxazol-5-carboxílico (**Intermedio 302,** 250 mg, 0,8 mmol) en THF (1 mL). La mezcla se agitó a temperatura ambiente durante 30 minutos antes de detenerse con metanol (1 mL) y se concentró. El residuo se purificó mediante cromatografía en columna para proporcionar el producto como un sólido. Rendimiento: 130 mg (52%).

MS (ES) MH^+: 311 para $C_{15}H_{19}ClN_2O_3$

El **Intermedio 373** se preparó a partir del material de partida indicado utilizando un método similar al descrito para la síntesis del **Intermedio 372**:

Intermedio 373

{7-cloro-3-ciclopropil-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-1,2-benzoxazol-5-il}metanol

Material de partida: ácido 7-cloro-3-ciclopropil-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-1,2-benzoxazol-5-carboxílico (**Intermedio 354**).

MS (ES) MH^+: 337 para $C_{17}H_{21}ClN_2O_3$

Intermedio 374

6,7-difluoro-3-metilbenzo[d]isoxazol-5-carbaldehído

A una solución enfriada con hielo de (6,7-difluoro-3-metil-1,2-bencisoxazol-5-il)metanol (**Intermedio 334,** 200 mg, 1,0 mmol) en CH_2Cl_2 (10 mL) se agregó NMO (235 mg, 2,0 mmol) y luego TPAP (35 mg, 0,1 mmol) y la mezcla se agitó durante 2 horas a temperatura ambiente. La mezcla de reacción se filtró a través de un lecho de gel de sílice y se lavó con EtOAc. La fase orgánica se concentró a presión reducida para proporcionar el producto como un sólido amarillo. Rendimiento: 150 mg (76%).

MS (ES) MH^+: 198 para $C_9H_5F_2NO_2$

^1H RMN (400 MHz, DMSO-d_6) δ: 2,5 (s, 3H), 8,3 (dd, 1H), 10,2 (s, 1H).

Intermedio 374 (Método alternativo)

6,7-difluoro-3-metilbenzo[d]isoxazol-5-carbaldehído

Una mezcla de (6,7-difluoro-3-metil-1,2-bencisoxazol-5-il)metanol (**Intermedio 334**, 0,7 g, 3,51 mmol) y dióxido de manganeso (6,11 g, 70,30 mmol) en CH_2Cl_2 (70 mL) se agitó a temperatura

ambiente durante 3 días. La TLC muestra una conversión a un punto más alto de Rf con material de partida. Se agregó más MnO_2 (5 g) y la mezcla se calentó hasta alcanzar reflujo durante 24 horas. La mezcla se filtró a través de celite y se enjuagó bien con CH_2Cl_2. El disolvente se eliminó del filtrado para proporcionar 640 mg del producto como un sólido de color tostado.
MS (ES) MH^+: 198 para $C_9H_5F_2NO_2$
^1H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 2,6 (s, 3H), 8,0 (d, 1H), 10,4 (s, 1H).

Intermedio 375
7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-metil-1,2-benzoxazol-5-carbaldehído
A la solución de {7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-metil-1,2-benzoxazol-5-il}metanol (**Intermedio 372**, 130 mg, 4,4 mmol) en DCM anhidro (5 mL), se agregó NMO (103 mg, 8,8 mmol) y TPAP (31 mg, 0,88 mmol) a 0 °C y se dejó agitar durante 1 h a temperatura ambiente. La mezcla de reacción se filtró y los disolventes se eliminaron al vacío y el residuo se purificó en una columna de cromatografía en gel de sílice utilizando un gradiente de acetato de etilo-éter de pet. para proporcionar un sólido. Rendimiento: 35 mg, (27%).
MS (ES) MH^+: 309 para $C_{15}H_{17}ClN_2O_3$

Los **Intermedios 376** a **393** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 375**:

Intermedio 376
7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(piridin-2-il)-1,2-benzoxazol-5-carbaldehído
Material de partida: {7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(piridin-2-il)-1,2-benzoxazol-5-il}metanol (**Intermedio 303**).
MS (ES) MH^+: 372 para $C_{19}H_{18}ClN_3O_3$

Intermedio 377
7-cloro-3-ciclopropil-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-1,2-benzoxazol-5-carbaldehído
Material de partida: {7-cloro-3-ciclopropil-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-1,2-benzoxazol-5-il}metanol (**Intermedio 373**).
MS (ES) MH^+: 335 para $C_{17}H_{19}ClN_2O_3$

Intermedio 378

7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(6-metilpiridin-3-il)-1,2-benzoxazol-5-carbaldehído

Material de partida: {7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(6-metilpiridin-3-il)-1,2-benzoxazol-5-il}metanol (**Intermedio 304**).

MS (ES) MH^+: 386,4 para $C_{20}H_{20}ClN_3O_3$

Intermedio 379

7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(1,3-tiazol-5-il)-7,7a-dihidro-1,2-benzoxazol-5-carbaldehído

Material de partida: {7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(1,3-tiazol-5-il)-7,7a-dihidro-1,2-benzoxazol-5-il}metanol (**Intermedio 305**).

MS (ES) MH^+: 380 para $C_{17}H_{19}ClN_3O_3S$

Intermedio 380

7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(pirimidin-2-il)-1,2-benzoxazol-5-carbaldehído

Material de partida: {7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(pirimidin-2-il)-1,2-benzoxazol-5-il}metanol (**Intermedio 355**).

MS (ES) MH^+: 373 para $C_{18}H_{17}ClN_4O_3$

Intermedio 381

7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(pirimidin-4-il)-1,2-benzoxazol-5-carbaldehído

Material de partida: {7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(pirimidin-4-il)-1,2-benzoxazol-5-il}metanol (**Intermedio 356**).

MS (ES) MH^+: 375,2 para $C_{18}H_{19}ClN_4O_3$

Intermedio 382

7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(pirimidin-5-il)-1,2-benzoxazol-5-carbaldehído

Material de partida: {7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(pirimidin-5-il)-1,2-benzoxazol-5-il}metanol (**Intermedio 357**).

MS (ES) MH^+: 373 para $C_{18}H_{17}ClN_4O_3$

Intermedio 383

7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(piridazin-4-il)-1,2-benzoxazol-5-carbaldehído

Material de partida: {7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(piridazin-4-il)-1,2-benzoxazol-5-il}metanol (**Intermedio 358**).

MS (ES) MH^+: 373,2 para $C_{18}H_{17}ClN_4O_3$

Intermedio 384

7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(piridin-4-il)-1,2-benzoxazol-5-carbaldehído

Material de partida: {7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(piridin-4-il)-1,2-benzoxazol-5-il}metanol (**Intermedio 306**).

MS (ES) MH^+: 372 para $C_{19}H_{18}ClN_3O_3$

Intermedio 385

7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(piridin-3-il)-1,2-benzoxazol-5-carbaldehído

Material de partida: {7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(piridin-3-il)-1,2-benzoxazol-5-il}metanol (**Intermedio 307**).

MS (ES) MH^+: 372 para $C_{19}H_{18}ClN_3O_3$

Intermedio 386

7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(1,3-tiazol-2-il)-1,2-benzoxazol-5-carbaldehído

Material de partida: {7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(1,3-tiazol-2-il)-1,2-benzoxazol-5-il}metanol (**Intermedio 308**).

MS (ES) MH^+: 380 para $C_{17}H_{18}ClN_3O_3S$

Intermedio 387

7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(1-metil-1*H*-imidazol-2-il)-1,2-benzoxazol-5-carbaldehído

Material de partida: {7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(1-metil-1*H*-imidazol-2-il)-1,2-benzoxazol-5-il}metanol (**Intermedio 309**).

MS (ES) MH^+: 375,4 para $C_{18}H_{19}ClN_4O$

Intermedio 388

7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(metoximetil)-1,2-benzoxazol-5-carbaldehído

Material de partida: {7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(metoximetil)-1,2-benzoxazol-5-il}metanol (**Intermedio 310**).

MS (ES) MH^+: 339 para $C_{16}H_{19}ClN_2O_4$

Intermedio 389

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[4-(morfolin-4-ilcarbonil)-1,3-tiazol-2-il]-1,2-benzoxazol-5-carbaldehído

Material de partida: (2-{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-5-(hidroximetil)-1,2-benzoxazol-3-il}-1,3-tiazol-4-il)(morfolin-4-il)metanona (**Intermedio 321**).

MS (ES) MH^+: 475 para $C_{22}H_{23}FN_4O_4S$

Intermedio 390

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[4-(morfolin-4-ilcarbonil)-1,3-tiazol-5-il]-1,2-benzoxazol-5-carbaldehído

Material de partida: (5-{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-5-(hidroximetil)-1,2-benzoxazol-3-il}-1,3-tiazol-4-il)(morfolin-4-il)metanona (**Intermedio 322**).

MS (ES) MH^+: 475 para $C_{22}H_{23}FN_4O_4S$

Intermedio 391

2-{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-5-formil-1,2-benzoxazol-3-il}-*N*,*N*-dimetil-1,3-tiazol-4-carboxamida

Material de partida: 2-{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-5-(hidroximetil)-1,2-benzoxazol-3-il}-*N*,*N*-dimetil-1,3-tiazol-4-carboxamida (**Intermedio 323**).

MS (ES) MH^+: 433 para $C_{20}H_{21}FN_4O_4S$

Intermedio 392

2-{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-5-formil-1,2-benzoxazol-3-il}-*N*,*N*-dimetil-1,3-tiazol-5-carboxamida

Material de partida: 2-{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-5-(hidroximetil)-1,2-benzoxazol-3-il}-*N*,*N*-dimetil-1,3-tiazol-5-carboxamida (**Intermedio 324**).

MS (ES) MH^+: 433,2 para $C_{20}H_{21}FN_4O_4S$

Intermedio 393

5-{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-5-formil-1,2-benzoxazol-3-il}-1,3-tiazol-4-carbonitrilo

Material de partida: 5-{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-5-(hidroximetil)-1,2-benzoxazol-3-il}-1,3-tiazol-4-carbonitrilo (**Intermedio 325**).

MS (ES) MH^+: 386,4 para $C_{18}H_{15}FN_4O_3S$

Intermedio 394

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(2-metil-1,3-oxazol-4-il)-1,2-benzoxazol-5-carbaldehído

Se agregó MnO_2 (227 mg, 2,8 mmol) a 0 °C a una solución de {6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(2-metil-1,3-oxazol-4-il)-1,2-benzoxazol-5-il}metanol **Intermedio 311**, 50 mg, 0,13 mmol) en DCM anhidro (5 mL) y la mezcla se dejó agitar durante 1 h a temperatura ambiente. La mezcla de reacción se filtró y los disolventes se eliminaron al vacío y el residuo se purificó mediante cromatografía en gel de sílice utilizando un gradiente de acetato de etilo-éter de pet. para proporcionar el producto como un sólido. Rendimiento: 37 mg, (75%).

MS (ES) MH^+: 360 para $C_{18}H_{18}FN_3O_4$

Los **Intermedios 395** a **403** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 394**:

Intermedio 395

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(5-metil-1,2-oxazol-3-il)-1,2-benzoxazol-5-carbaldehído

Material de partida: {6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(5-metil-1,2-oxazol-3-il)-1,2-benzoxazol-5-il}metanol (**Intermedio 312**).

MS (ES) MH^+: 360 para $C_{18}H_{18}FN_3O_4$

Intermedio 396

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(3,5-dimetil-1,2-oxazol-4-il)-7-fluoro-1,2-benzoxazol-5-carbaldehído

Material de partida: {6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(3,5-dimetil-1,2-oxazol-4-il)-7-fluoro-1,2-benzoxazol-5-il}metanol (**Intermedio 313**).

MS (ES) MH^+: 374 para $C_{19}H_{20}FN_3O_4$

Intermedio 397

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(1-metil-1*H*-imidazol-2-il)-1,2-benzoxazol-5-carbaldehído

Material de partida: {6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(1-metil-1*H*-imidazol-2-il)-1,2-benzoxazol-5-il}metanol (**Intermedio 314).**

MS (ES) MH^+: 359 para $C_{18}H_{19}FN_4O_3$

Intermedio 398

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(1-metil-1*H*-imidazol-4-il)-1,2-benzoxazol-5-carbaldehído

Material de partida: {6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(1-metil-1*H*-imidazol-4-il)-1,2-benzoxazol-5-il}metanol (**Intermedio 315**).

MS (ES) MH^+: 359 para $C_{18}H_{19}FN_4O_3$

Intermedio 399

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(1-metil-1*H*-imidazol-5-il)-1,2-benzoxazol-5-carbaldehído

Material de partida: {6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(1-metil-1*H*-imidazol-5-il)-1,2-benzoxazol-5-il}metanol (**Intermedio 316**).

MS (ES) MH^+: 359 para $C_{18}H_{19}FN_4O_3$

Intermedio 400

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(4-metil-1,3-tiazol-5-il)-1,2-benzoxazol-5-carbaldehído

Material de partida: {6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(4-metil-1,3-tiazol-5-il)-1,2-benzoxazol-5-il}metanol (**Intermedio 317**).

MS (ES) MH^+: 377 para $C_{18}H_{20}FN_3O_3S$

Intermedio 401

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(4-metil-1,2,3-tiadiazol-5-il)-1,2-benzoxazol-5-carbaldehído

Material de partida: {6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(4-metil-1,2,3-tiadiazol-5-il)-1,2-benzoxazol-5-il}metanol (**Intermedio 318**).

MS (ES) MH^+: 377,2 para $C_{17}H_{17}FN_4O_3S$

Intermedio 402

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(piridazin-3-il)-1,2-benzoxazol-5-carbaldehído

Material de partida: {6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(piridazin-3-il)-1,2-benzoxazol-5-il}metanol (**Intermedio 319**).

MS (ES) MH^+: 357 para $C_{18}H_{17}FN_4O_3$

Intermedio 403

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(pirimidin-4-il)-1,2-benzoxazol-5-carbaldehído

Material de partida: {6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(pirimidin-4-il)-1,2-benzoxazol-5-il}metanol (**Intermedio 320**).

MS (ES) MH^+: 357 para $C_{18}H_{17}FN_4O_3$

Los **Intermedios 404** y **405** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 374** (Método alternativo):

Intermedio 404

6,7-difluoro-3-(1-metil-1*H*-1,2,4-triazol-5-il)benzo[d]isoxazol-5-carbaldehído

Material de partida: (6,7-difluoro-3-(1-metil-1*H*-1,2,4-triazol-5-il)benzo[d]isoxazol-5-il)metanol (**Intermedio 359**).

MS (ES) MH^+: 266 para $C_{11}H_6F_2N_2O_4$

^1H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 4,4 (s, 3H), 8,1 (s, 1H), 8,8 (d, 1H), 10,4 (s, 1).

Intermedio 405

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(5-oxo-4,5-dihidro-1,3,4-oxadiazol-2-il)benzo[d]isoxazol-5-carbaldehído

Material de partida: 5-(6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)benzo[d]isoxazol-3-il)-1,3,4-oxadiazol-2(3H)-ona (**Intermedio 209**).

MS (ES) MH^+: 363 para $C_{16}H_{15}FN_4O_5$

Intermedio 406

7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(piridin-2-il)isoxazolo[4,5-b]piridin-5-carbaldehído

A una solución agitada de (7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(piridin-2-il)isoxazolo[4,5-b]piridin-5-il)metanol (**Intermedio 201**, 0,39 g, 1,04 mmol) en diclorometano (20 mL) se agregó dióxido de manganeso (0,543 g, 6,24 mmol). La mezcla se dejó agitar 2 días a temperatura ambiente. La reacción se filtró con Celite® y el filtrado se concentró al vacío para proporcionar un aceite claro. El aceite se purificó en un lecho corto de sílice utilizando un 20-30% de acetona en n-hexano para proporcionar 0,16 g (42%) del compuesto del título como un sólido amarillo.

^1H RMN (300 MHz, DMSO-d_6) δ: 1,1 (m, 6H), 3,0–3,1 (m, 2H), 3,1–3,2 (m, 2H), 3,9 (td, 2H), 7,5 (dd, 1H), 7,9 (t, 1H), 8,6 (d, 1H), 8,9 (d, 1H), 10,2 (s, 1H).

Los **Intermedios 407** a **438** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 406:**

Intermedio 407

7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(piridin-4-il)isoxazolo[4,5-b]piridin-5-carbaldehído

Material de partida: (7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(piridin-4-il)isoxazolo[4,5-b]piridin-5-il)metanol (**Intermedio 202**).

^{1}H RMN (300 MHz, DMSO-d_6) δ: 1,1 (m, 6H), 3,0–3,1 (m, 2H), 3,1–3,2 (m, 2H), 3,9 (td, 2H), 8,3–8,4 (m, 2H), 8,8 (dd, 2H), 10,2 (s, 1H).

Intermedio 408

7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(piridin-3-il)isoxazolo[4,5-b]piridin-5-carbaldehído

Material de partida: (7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(piridin-3-il)isoxazolo[4,5-b]piridin-5-il)metanol (**Intermedio 203**).

^{1}H RMN (300 MHz, DMSO-d_6) δ: 1,1 (m, 6H), 3,0–3,1 (m, 2H), 3,1–3,2 (m, 2H), 3,9 (td, 2H), 7,5 (dd, 1H), 8,7–8,8 (m, 2H), 9,7 (d, 1H), 10,2 (s, 1H).

Intermedio 409

7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(pirazin-2-il)isoxazolo[4,5-b]piridin-5-carbaldehído

Material de partida: (7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(pirazin-2-il)isoxazolo[4,5-b]piridin-5-il)metanol (**Intermedio 360**).

^{1}H RMN (300 MHz, DMSO-d_6) δ: 1,1 (m, 6H), 3,0–3,1 (m, 2H), 3,1–3,2 (m, 2H), 3,9 (td, 2H), 8,7–8,9 (m, 2H), 9,8 (d, 1H), 10,2 (s, 1H).

Intermedio 410

7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(tiazol-2-il)isoxazolo[4,5-b]piridin-5-carbaldehído

Material de partida: (7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(tiazol-2-il)isoxazolo[4,5-b]piridin-5-il)metanol (**Intermedio 361**).

^{1}H RMN (300 MHz, DMSO-d_6) δ: 1,1 (m, 6H), 2,9–3,0 (m, 2H), 3,1–3,2 (m, 2H), 3,9 (td, 2H), 7,7 (d, 1H), 8,2 (d, 1H), 10,2 (s, 1H).

Intermedio 411

7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(4-metiltiazol-2-il)isoxazolo[4,5-b]piridin-5-carbaldehído

Material de partida: (7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(4-metiltiazol-2-il)isoxazolo[4,5-b]piridin-5-il)metanol (**Intermedio 362**).

^{1}H RMN (300 MHz, DMSO-d_6) δ: 1,1 (m, 6H), 2,5 (s, 3H), 2,8–3,0 (m, 2H), 3,1 – 3,2 (m, 2H), 3,8 (d, 2H), 7,8 (s, 1H), 10,2 (s, 1H).

Intermedio 412

7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(1-metil-1*H*-imidazol-2-il)isoxazolo[4,5-b]piridin-5-carbaldehído

Material de partida: (7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(1-metil-1*H*-imidazol-2-il)isoxazolo[4,5-b]piridin-5-il)metanol (**Intermedio 363**).

^{1}H RMN (300 MHz, DMSO-d_6) δ: 1,1 (m, 6H), 2,9–3,0 (m, 2H), 3,1–3,2 (m, 2H), 3,9 (m, 2H), 4,1 (s, 3H), 7,1 (s, 1H), 7,4 (1H), 10,2 (s, 1H).

Intermedio 413

7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(tiazol-5-il)isoxazolo[4,5-b]piridin-5-carbaldehído

Material de partida: (7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(tiazol-5-il)isoxazolo[4,5-b]piridin-5-il)metanol (**Intermedio 364**).

^{1}H RMN (300 MHz, DMSO-d_6) δ: 1,0 (m, 6H), 3,0–3,1 (m, 2H), 3,2 (m, 2H), 3,9–4,0 (m, 2H), 9,1 (s, 1H), 9,3 (s, 1H), 10,2 (s, 1H).

Intermedio 414

7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(2-metiltiazol-5-il)isoxazolo[4,5-b]piridin-5-carbaldehído

Material de partida: (7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(2-metiltiazol-5-il)isoxazolo[4,5-b]piridin-5-il)metanol (**Intermedio 365**).

^{1}H RMN (300 MHz, DMSO-d_6) δ: 1,0 (m, 6H), 2,8 (s, 3H), 3,0–3,1 (m, 2H), 3,2 (m, 2H), 3,9–4,0 (m, 2H), 8,9 (s, 1H), 10,2 (s, 1H).

Intermedio 415

7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(1-metil-1*H*-1,2,4-triazol-5-il)isoxazolo[4,5-b]piridin-5-carbaldehído

Material de partida: (7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(1-metil-1*H*-1,2,4-triazol-5-il)isoxazolo[4,5-b]piridin-5-il)metanol (**Intermedio 366**).

^{1}H RMN (300 MHz, DMSO-d_6) δ: 1,2 (m, 6H), 2,8–2,9 (m, 2H), 3,0–3,1 (m, 2H), 3,9 (td, 2H), 4,3 (s, 3H), 8,2 (s, 1H), 10,2 (s, 1H).

Intermedio 416

4-(7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-formilisoxazolo[4,5-b]piridin-3-il)-2-fluorobenzonitrilo

Material de partida: 4-(7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-(hidroximetil)isoxazolo[4,5-b]piridin-3-il)-2-fluorobenzonitrilo (**Intermedio 367**).

^{1}H RMN (300 MHz, DMSO-d_6) δ: 1,1 – 1,3 (m, 6H), 2,9–3,1 (m, 2H), 3,1–3,2 (m, 2H), 3,9 (td, 2H), 7,8 (dd, 1H), 8,4–8,5 (m, 2H), 10,2 (s, 1H).

Intermedio 417

5-(7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-formilisoxazolo[4,5-b]piridin-3-il)picolinonitrilo

Material de partida: 5-(7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-(hidroximetil)isoxazolo[4,5-b]piridin-3-il)picolinonitrilo (**Intermedio 369**).

^{1}H RMN (300 MHz, DMSO-d_6) δ: 1,2 (d, 6H), 3,1–3,2 (m, 4H), 3,9–4,1 (m, 2H), 7,9 (dd, 1H), 8,3–8,5 (m, 1H), 8,9–9,0 (m, 1H), 10,2 (s, 1H).

Intermedio 418

7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(5-metiltiazol-2-il)isoxazolo[4,5-b]piridin-5-carbaldehído

Material de partida: (7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(5-metiltiazol-2-il)isoxazolo[4,5-b]piridin-5-il)metanol (0,49 g, 1,24 mmol, **Intermedio 368**).

^{1}H RMN (300 MHz, DMSO-d_6) δ: 1,2 (d, 6H), 2,6 (s, 3H), 3,0–3,1 (m, 2H), 3,1–3,2 (m, 2H), 3,8–4,0 (m, 2H), 7,8 (d, 1H), 10,2 (s, 1H).

Intermedio 419

7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(2-bromotiazol-5-il)isoxazolo[4,5-b]piridin-5-carbaldehído

Material de partida: (3-(2-bromotiazol-5-il)-7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)isoxazolo[4,5-b]piridin-5-il)metanol (**Intermedio 370**).

^{1}H RMN (300 MHz, DMSO-d_6) δ: 1,0 (m, 6H), 3,0–3,1 (m, 2H), 3,2 (m, 2H), 3,9–4,0 (m, 2H), 8,9 (s, 1H), 10,2 (s, 1H).

Intermedio 420

7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(2,4-diclorotiazol-5-il)isoxazolo[4,5-b]piridin-5-carbaldehído

Material de partida: (7-cloro-3-(2,4-diclorotiazol-5-il)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)isoxazolo[4,5-b]piridin-5-il)metanol (**Intermedio 371**).

^{1}H RMN (300 MHz, DMSO-d_6) δ: 1,0 (m, 6H), 3,0–3,1 (m, 2H), 3,2 (m, 2H), 3,9–4,0 (m, 2H), 10,2 (s, 1H).

Intermedio 421

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(6-metilpiridin-3-il)benzo[d]isoxazol-5-carbaldehído

Material de partida: (6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(6-metilpiridin-3-il)benzo[d]isoxazol-5-il)metanol (**Intermedio 346**).

MS (ES) MH^+: 370 para $C_{20}H_{20}FN_3O_3$

^{1}H RMN (300 MHz, $CDCl_3$) δ: 1,23 (d, 6H), 2,70 (s, 3H), 2,98-3,28 (m, 4H), 3,74-4,00 (m, 2H), 7,40 (d, 1H), 8,03-8,33 (m, 2H), 9,09 (d, 1H), 10,38 (s, 1H).

Intermedio 422

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(tiazol-5-il)benzo[d]isoxazol-5-carbaldehído

Material de partida: (6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(tiazol-5-il)benzo[d]isoxazol-5-il)metanol (**Intermedio 345**).

MS (ES) MH^+: 362 para $C_{17}H_{16}FN_3O_3S$

^{1}H RMN (300 MHz, $CDCl_3$) δ: 1,23 (d, 6H), 2,44-3,23 (m, 4H), 3,75-4,03 (m, 2H), 8,21 (s, 1H), 8,62 (s, 1H), 9,04 (s, 1H), 10,38 (s, 1H).

Intermedio 423

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(2-fluorofenil)benzo[d]isoxazol-5-carbaldehído

Material de partida: (6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(2-fluorofenil)benzo[d]isoxazol-5-il)metanol (**Intermedio 347**).

MS (ES) MH^+: 373 para $C_{17}H_{16}FN_3O_3S$

^1H RMN (400 MHz, $CDCl_3$) δ: 1,23 (d, 6H), 2,94-3,30 (m, 4H), 3,79-3,97 (m, 2H), 7,27-7,86 (m, 4H), 8,09 (d, 1H), 10,37 (s, 1H).

Intermedio 424

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(tetrahidro-2*H*-piran-4-il)benzo[d]isoxazol-5-carbaldehído

Material de partida: (6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(tetrahidro-2*H*-piran-4-il)benzo[d]isoxazol-5-il)metanol (**Intermedio 348**).

MS (ES) MH^+: 363 para $C_{19}H_{23}FN_2O_4$

^1H RMN (400 MHz, $CDCl_3$) δ: 1,22 (d, 6H), 1,91-2,19 (m, 4H), 2,98-3,21 (m, 4H), 3,25-3,41 (m, 1H), 3,53-3,67 (m, 2H), 3,75-3,97 (m, 2H), 4,06-4,16 (m, 2H), 8,00 (s, 1H), 10,37 (s, 1H).

Intermedio 425

3-((1*H*-1,2,4-triazol-1-il)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-5-carbaldehído

Material de partida: (3-((1*H*-1,2,4-triazol-1-il)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-5-il)metanol (**Intermedio 288**).

MS (ES) MH^+: 360 para $C_{17}H_{18}FN_5O_3$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,08 (d, 6H), 2,81-3,24 (m, 4H), 3,67-3,94 (m, 2H), 6,00 (s, 2H), 7,93 (s, 1 H, 8,04 (s, 1H), 8,83 (s, 1H), 10,22 (s, 1H).

Intermedio 426

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(piridin-4-il)benzo[d]isoxazol-5-carbaldehído

Material de partida: (6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(piridin-4-il)benzo[d]isoxazol-5-il)metanol (**Intermedio 287**).

MS (ES) MH^+: 356 para $C_{19}H_{18}FN_3O_3$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,24 (d, 6H), 3,03-3,27 (m, 4H), 3,77-4,01 (m, 2H), 7,87 (d, 2H), 8,20 (s, 1H), 8,86 (d, 2H), 10,38 (s, 1H).

Intermedio 427

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(furan-2-il)benzo[d]isoxazol-5-carbaldehído

Material de partida: (6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(furan-2-il)benzo[d]isoxazol-5-il)metanol (**Intermedio 289**).

MS (ES) MH^+: 345 para $C_{18}H_{17}FN_2O_4$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,23 (d, 6H), 2,99-3,26 (m, 4H), 3,77-3,98 (m, 2H), 6,65 (dd, 1H), 7,24 (s, 1H), 7,73 (d, 1H), 8,38 (d, 1H), 10,39 (s, 1H).

Intermedio 428

3-(difluorometil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-5-carbaldehído

Material de partida: (3-(difluorometil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-5-il)metanol (**Intermedio 291**).

MS (ES) MH^+: 329 para $C_{15}H_{15}F_3N_2O_3$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,22 (d, 6H), 3,04-3,23 (m, 4H), 3,80-3,99 (m, 2H), 7,00 (t, 1H), 8,15 (s, 1H), 10,34 (s, 1H).

Intermedio 429

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(trifluorometil)benzo[d]isoxazol-5-carbaldehído

Material de partida: (6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(trifluorometil)benzo[d]isoxazol-5-il)metanol (**Intermedio 290**).

MS (ES) MH^+: 347 para $C_{15}H_{14}F_4N_2O_3$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,23 (d, 6H), 2,96-3,29 (m, 4H), 3,74-4,03 (m, 2H), 8,06 (s, 1H), 10,32 (s, 1H).

Intermedio 430

6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-3-(tiazol-2-il)benzo[d]isoxazol-5-carbaldehído

Material de partida: (6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-3-(tiazol-2-il)benzo[d]isoxazol-5-il)metanol (**Intermedio 349**).

MS (ES) MH^+: 362 para $C_{17}H_{16}FN_3O_3S$

^{1}H RMN (300 MHz, $CDCl_3$) δ: 1,33 (d, 6H), 2,89-3,22 (m, 2H), 3,31-3,52 (m, 2H), 4,07-4,36 (m, 2H), 7,59 (d, 1H), 8,12 (d, 1H), 8,55-8,72 (s, 1H), 10,48 (s, 1H).

Intermedio 431

3-(difluorometil)-6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-5-carbaldehído

Material de partida: (3-(difluorometil)-6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-5-il)metanol (**Intermedio 292**).

MS (ES) MH^+: 329 para $C_{15}H_{15}F_3N_2O_3$

^{1}H RMN (300 MHz, $CDCl_3$) δ: 1,32 (d, 6H), 2,93-3,52 (m, 4H), 4,07-4,36 (m, 2H), 7,01 (t, 1H), 8,16 (s, 1H), 10,44 (s, 1H).

Intermedio 432

3-(3-cloropirazin-2-il)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-5-carbaldehído

Material de partida: (3-(3-cloropirazin-2-il)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-5-il)metanol (**Intermedio 328**).

MS (ES) MH^+: 391 para $C_{18}H_{16}ClFN_4O_3$

Intermedio 433

6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-3-(5-morfolinopirazin-2-il)benzo[d]isoxazol-5-carbaldehído

Material de partida: (6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-3-(5-morfolinopirazin-2-il)benzo[d]isoxazol-5-il)metanol (**Intermedio 335**).

MS (ES) MH^+: 442 (M+H) para $C_{22}H_{24}FN_5O_4$

Intermedio 434

3-(6-cloropirazin-2-il)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-5-carbaldehído

Material de partida: (3-(6-cloropirazin-2-il)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-5-il)metanol (**Intermedio 282**).

MS (ES) MH^+: 391 para $C_{18}H_{16}ClFN_4O_3$

Intermedio 435

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(5-(metiltio)pirazin-2-il)benzo[d]isoxazol-5-carbaldehído

Material de partida: (6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(5-(metiltio)pirazin-2-il)benzo[d]isoxazol-5-il)metanol (**Intermedio 283**).

MS (ES) MH^+: 403 para $C_{19}H_{19}FN_4O_3S$

Intermedio 436

6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-3-(6-metoxipirazin-2-il)benzo[d]isoxazol-5-carbaldehído

Material de partida: (6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-3-(6-metoxipirazin-2-il)benzo[d]isoxazol-5-il)metanol (**Intermedio 351**).

MS (ES) MH^+: 387 para $C_{19}H_{19}FN_4O_4$

Intermedio 437

6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-3-(2-(metiltio)pirimidin-4-il)benzo[d]isoxazol-5-carbaldehído

Material de partida: (6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-3-(2-(metiltio)pirimidin-4-il)benzo[d]isoxazol-5-il)metanol (**Intermedio 284**).

MS (ES) MH^+: 403 (M+H) para $C_{19}H_{19}FN_4O_3S$

Intermedio 438

6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-3-(pirazin-2-il)benzo[d]isoxazol-5-carbaldehído

Material de partida: (6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-3-(pirazin-2-il)benzo[d]isoxazol-5-il)metanol (**Intermedio 350).**

MS (ES) MH^+: 357 para $C_{18}H_{17}FN_4O_3$

Intermedio 439

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formilbenzo[d]isoxazol-3-carboxilato de etilo

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)benzo[d]isoxazol-3-carboxilato de etilo (**Intermedio 262**, 430 mg, 1,22 mmol) se disolvió en diclorometano (100 mL). Se agregó dióxido de manganeso (2122 mg, 24,41 mmol) y la reacción se agitó vigorosamente durante toda la noche. La reacción fue incompleta por lo que se agregaron 2 g adicionales de MnO_2 y la reacción se agitó durante 4 horas. La reacción aún estaba incompleta por lo que se agregaron 2 g adicionales de MnO_2 y la reacción se agitó durante toda la noche. La reacción se filtró a través de celite y se lavó con DCM y acetato de etilo. El filtrado se concentró para proporcionar el compuesto del título (350 mg, 0,999 mmol, 82%).

MS (ES) MH^+: 351 para $C_{17}H_{19}FN_2O_5$

^{1}H RMN (300 MHz, CLOROFORMO-d) δ ppm 1,3 (d, 6H), 1,5 (t, 3H), 3,0-3,3 (m, 4H), 3,9 (s a, 2H), 4,6 (q, 2H), 8,4 (s, 1H), 10,4 (s, 1H).

Los **Intermedios 440** a **470** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 439:**

Intermedio 440

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(morfolin-4-carbonil)benzo[d]isoxazol-5-carbaldehído

Material de partida: (6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)benzo[d]isoxazol-3-il)(morfolino)metanona (**Intermedio 285**).

MS (ES) MH^+: 392 para $C_{19}H_{22}FN_3O_5$

^{1}H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1,2 (d, 6H), 3,0-3,2 (m, 4H), 3,6-3,7 (m, 2H), 3,7-3,9 (m, 8H), 8,2 (s, 1H), 10,25 (s, 1H).

Intermedio 441

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formil-*N*-metoxi-*N*-metilbenzo[d]isoxazol-3-carboxamida

Material de partida: 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)-*N*-metoxi-*N*-metilbenzo[d]isoxazol-3-carboxamida (**Intermedio 263**).

MS (ES) MH^+: 366 para $C_{17}H_{20}FN_3O_5$

Intermedio 442

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-*N*-etil-7-fluoro-5-formilbenzo[d]isoxazol-3-carboxamida

Material de partida: 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-*N*-etil-7-fluoro-5-(hidroximetil)benzo [d]isoxazol-3-carboxamida (**Intermedio 264**).

MS (ES) MH^+: 350 para $C_{17}H_{20}FN_3O_4$

^1H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1,23 (d, *J* = 6,03 Hz, 6H) 1,31 (t, *J* = 7,16 Hz, 3H) 3,02-3,22 (m, 4H) 3,48-3,65 (m, 2H) 3,82 -3,98 (m, 2H) 6,81-6,96 (s a, 1H) 8,51 (s, 1H) 10,33 (s, 1H).

Intermedio 443

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-*N*-etil-7-fluoro-5-formil-*N*-metilbenzo[d]isoxazol-3-carboxamida

Material de partida: 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-*N*-etil-7-fluoro-5-(hidroximetil)-*N*-metilbenzo[d]isoxazol-3-carboxamida (**Intermedio 265**).

MS (ES) MH^+: 364 para $C_{18}H_{22}FN_3O_4$

Intermedio 444

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formil-*N*-metilbenzo[d]isoxazol-3-carboxamida

Material de partida: 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)-*N*-metilbenzo[d]isoxazol-3-carboxamida (**Intermedio 266**).

MS (ES) MH^+: 336 para $C_{16}H_{18}FN_3O_4$

^1H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1,25 (d, *J* = 6,78 Hz, 6H) 3,04-3,23 (m, 7H) 3,91 (s a, 1H) 6,83-6,99 (m, 1H) 8,53 (s, 1H) 10,34 (s, 1H).

Intermedio 445

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(4-metil-3-oxopiperazin-1-carbonil)benzo[d]isoxazol-5-carbaldehído

Material de partida: 4-(6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)benzo[d]isoxazol-3-carbonil)-1-metilpiperazin-2-ona (**Intermedio 267**).

MS (ES) MH^+: 419 para $C_{20}H_{23}FN_4O_5$

Intermedio 446

3-(3,3-difluoroazetidin-1-carbonil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-5-carbaldehído

Material de partida: (3,3-difluoroazetidin-1-il)(6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)benzo[d]isoxazol-3-il)metanona (**Intermedio 268**).

MS (ES) MH^+: 398 para $C_{18}H_{18}F_3N_3O_4$

^{1}H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1,23 (d, *J* = 6,78 Hz, 6H) 3,03-3,18 (m, 4H) 3,78-3,97 (m, 2H) 4,60 (t, *J* = 12,06 Hz, 2H) 4,96 (t, *J* = 11,68 Hz, 2H) 8,39-8,46 (m, 1H) 10,26-10,36 (m, 1H).

Intermedio 447

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formilbenzo[d]isoxazol-3-carboxamida

Material de partida: 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)benzo[d]isoxazol-3-carboxamida (**Intermedio 269**).

MS (ES) MH^+: 322 para $C_{15}H_{16}FN_3O_4$

Intermedio 448

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formil-*N*-(2-metoxietil)benzo[d]isoxazol-3-carboxamida

Material de partida: 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)-*N*-(2-metoxietil)benzo[d]isoxazol-3-carboxamida (**Intermedio 270**).

MS (ES) MH^+: 380 para $C_{18}H_{22}FN_3O_5$

^{1}H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1,23 (d, *J* = 6,03 Hz, 6H) 3,04-3,20 (m, 4H) 3,41 (s, 3H) 3,60 (t, *J* = 4,90 Hz, 2H) 3,65-3,78 (m, 2H) 3,89 (s a, 2H) 7,18-7,26 (m, 1H) 8,49 (s, 1H) 10,33 (s, 1H).

Intermedio 449

N-terc-butil-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formilbenzo[d]isoxazol-3-carboxamida

Material de partida: *N-terc*-butil-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)benzo[d]isoxazol-3-carboxamida (**Intermedio 271**).

MS (ES) MH^+: 378 para $C_{19}H_{24}FN_3O_4$

^{1}H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1,23 (d, *J* = 6,03 Hz, 6H) 1,52 (s, 9H) 3,02-3,21 (m, 4H) 3,89 (s a, 2H) 6,73 (s a, 1H) 8,51 (s, 1H) 10,32 (s, 1H).

Intermedio 450

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-[(1,1-dioxidotiomorfolin-4-il)carbonil]-7-fluoro-1,2-bencisoxazol-5-carbaldehído

Material de partida: {6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-[(1,1-dioxidotiomorfolin-4-il)carbonil]-7-fluoro-1,2-bencisoxazol-5-il}metanol (**Intermedio 272**).

MS (ES) MH^+: 440 para $C_{19}H_{22}FN_3O_6S$

^{1}H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1,26 (d, *J* = 6,03 Hz, 6H) 3,09-3,32 (m, 8H) 3,84-4,02 (m, 2H) 4,32-4,43 (m, 2H) 4,43-4,52 (m, 2H) 8,28 (s, 1H) 10,34 (s, 1H).

Intermedio 451

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formil-*N*-(tetrahidro-2*H*-piran-4-il)benzo[d]isoxazol-3-carboxamida

Material de partida: 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)-*N*-(tetrahidro-2*H*-piran-4-il)benzo[d]isoxazol-3-carboxamida (**Intermedio 273**).

MS (ES) MH^+: 406 para $C_{20}H_{24}FN_3O_5$

^{1}H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1,25 (d, *J* = 6,03 Hz, 6H) 1,59-1,77 (m, 2H) 1,94-2,14 (m, 2H) 3,01-3,24 (m, 4H) 3,48-3,65 (m, 2H) 3,81-3,98 (m, 2H) 3,98-4,13 (m, 2H) 4,17-4,35 (m, 1H) 6,79 (s a, 1H) 8,51 (s, 1H) 10,35 (s, 1H).

Intermedio 452

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formil-*N*-isopropilbenzo[d]isoxazol-3-carboxamida

Material de partida: 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)-*N*-isopropilbenzo[d]isoxazol-3-carboxamida (**Intermedio 274**).

MS (ES) MH^+: 364 para $C_{18}H_{22}FN_3O_4$

^{1}H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1,25 (d, *J* = 6,78 Hz, 6H) 1,34 (d, *J* = 6,78 Hz, 6H) 3,05-3,23 (m, 4H) 3,84-3,98 (m, 2H) 4,28 -4,44 (m, 1H) 6,65-6,77 (m, 1H) 8,53 (s, 0H) 10,34 (s, 1H).

Intermedio 453

N-ciclopropil-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formilbenzo[d]isoxazol-3-carboxamida

Material de partida: *N*-ciclopropil-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)benzo[d]isoxazol-3-carboxamida (**Intermedio 275**).

MS (ES) MH^+: 361,9 para $C_{18}H_{20}FN_3O_4$

^1H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 0,74 (s a, 2H) 0,90-1,02 (m, 2H) 1,25 (d, *J* = 6,03 Hz, 6H) 2,97 (s a, 1H) 3,07-3,21 (m, 4H) 3,80-4,00 (m, 2H) 6,98 (s a, 1H) 8,53 (s, 1H) 10,34 (s, 1H).

Intermedio 454

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(4-metoxipiperidin-1-carbonil)benzo[d]isoxazol-5-carbaldehído

Material de partida: (6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)benzo[d]isoxazol-3-il)(4-metoxipiperidin-1-il)metanona (**Intermedio 276**).

MS (ES) MH^+: 420 para $C_{21}H_{26}FN_3O_5$

^1H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1,25 (d, *J* = 6,03 Hz, 6H) 1,65-2,06 (m, 4H) 3,02-3,26 (m, 4H) 3,53-3,63 (m, 1H) 3,63-3,75 (m, 1H) 3,75-4,07 (m, 5H) 8,22 (s, 1H) 10,35 (s, 1H).

Intermedio 455

N-(ciclopropilmetil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formilbenzo[d]isoxazol-3-carboxamida

Material de partida: *N*-(ciclopropilmetil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)benzo[d]isoxazol-3-carboxamida (**Intermedio 277**).

MS (ES) MH^+: 376 para $C_{19}H_{22}FN_3O_4$

Intermedio 456

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(1,2-oxazinan-2-ilcarbonil)-1,2-bencisoxazol-5-carbaldehído

Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(1,2-oxazinan-2-ilcarbonil)-1,2-bencisoxazol-5-il}metanol (**Intermedio 278**).

MS (ES) MH^+: 392 para $C_{19}H_{22}FN_3O_5$

^1H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1,23 (d, *J* = 6,03 Hz, 6H) 1,92 (s a, 4H) 3,02-3,24 (m, 4H) 3,89 (s a, 2H) 4,05 (s a, 4H) 8,16 (s, 1H) 10,35 (s, 1H).

Intermedio 457

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formil-*N*-(tiofen-2-ilmetil)benzo[d]isoxazol-3-carboxamida

Material de partida: 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)-*N*-(tiofen-2-ilmetil)benzo[d]isoxazol-3-carboxamida (**Intermedio 279**).

MS (ES) MH^+: 418 para $C_{20}H_{20}FN_3O_4S$

Intermedio 458

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formil-*N*-(piridin-4-ilmetil)benzo[d]isoxazol-3-carboxamida

Material de partida: 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)-*N*-(piridin-4-ilmetil)benzo[d]isoxazol-3-carboxamida (**Intermedio 249**).

MS (ES) MH^+: 413 para $C_{21}H_{21}FN_4O_4$

Intermedio 459

N-(ciclohexilmetil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formilbenzo[d]isoxazol-3-carboxamida

Material de partida: *N*-(ciclohexilmetil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)benzo[d]isoxazol-3-carboxamida (**Intermedio 250**).

MS (ES) MH^+: 418 para $C_{22}H_{28}FN_3O_4$

Intermedio 460

3-(4,4-difluoropiperidin-1-carbonil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-5-carbaldehído

Material de partida: (4,4-difluoropiperidin-1-il)(6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)benzo[d]isoxazol-3-il)metanona (**Intermedio 251**).
MS (ES) MH^+: 426 para $C_{20}H_{22}F_3N_3O_4$

Intermedio 461

3-(3,3-difluoropirrolidin-1-carbonil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-5-carbaldehído

Material de partida: (3,3-difluoropirrolidin-1-il)(6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)benzo[d]isoxazol-3-il)metanona (**Intermedio 252**).
MS (ES) MH^+: 412 para $C_{19}H_{20}F_3N_3O_4$

Intermedio 462

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formil-*N*-(1-metilazetidin-3-il)benzo[d]isoxazol-3-carboxamida

Material de partida: 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)-*N*-(1-metilazetidin-3-il)benzo[d]isoxazol-3-carboxamida (**Intermedio 253**).
MS (ES) MH^+: 391 para $C_{19}H_{23}FN_4O_4$

Intermedio 463

N-(1-(6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formilbenzo[d]isoxazol-3-carbonil)azetidin-3-il)acetamida

Material de partida: *N*-(1-(6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)benzo[d]isoxazol-3-carbonil)azetidin-3-il)acetamida (**Intermedio 254**).
MS (ES) MH^+: 419 para $C_{20}H_{23}FN_4O_5$

Intermedio 464

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formil-*N*-((1-metil-1*H*-pirazol-3-il)metil)benzo[d]isoxazol-3-carboxamida

Material de partida: 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)-*N*-((1-metil-1*H*-pirazol-3-il)metil)benzo[d]isoxazol-3-carboxamida (**Intermedio 255**).
MS (ES) MH^+: 416 para $C_{20}H_{22}FN_5O_4$

Intermedio 465

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formil-*N*-((1-metil-1*H*-pirazol-5-il)metil)benzo[d]isoxazol-3-carboxamida

Material de partida: 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)-*N*-((1-metil-1*H*-pirazol-5-il)metil)benzo[d]isoxazol-3-carboxamida (**Intermedio 256**).

MS (ES) MH^+: 416 para $C_{20}H_{22}FN_5O_4$

Intermedio 466

N-(1,3-dimetoxi-2-(metoximetil)propan-2-il)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formilbenzo[d]isoxazol-3-carboxamida

Material de partida: *N*-(1,3-dimetoxi-2-(metoximetil)propan-2-il)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)benzo[d]isoxazol-3-carboxamida (**Intermedio 257**).

MS (ES) MH^+: 468 para $C_{22}H_{30}FN_3O_7$

Intermedio 467

N-(2,2-difluoroetil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formilbenzo[d]isoxazol-3-carboxamida

Material de partida: *N*-(2,2-difluoroetil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)benzo[d]isoxazol-3-carboxamida (**Intermedio 258**).

MS (ES) MH^+: 386 para $C_{17}H_{18}F_3N_3O_4$

Intermedio 468

1-(6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formilbenzo[d]isoxazol-3-carbonil)azetidin-3-carbonitrilo

Material de partida: 1-(6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)benzo[d]isoxazol-3-carbonil)azetidin-3-carbonitrilo (Intermedio **259**).

MS (ES) MH^+: 387,2 para $C_{19}H_{19}FN_4O_4$

Intermedio 469

6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-5-formilbenzo[d]isoxazol-3-carboxamida

Material de partida: 6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil) benzo[d]isoxazol-3-carboxamida (**Intermedio 281**).

MS (ES) MH^+: 322 para $C_{15}H_{16}FN_3O_4$

^1H RMN (300 MHz, DMSO-d_6) δ ppm 1,22 (d, J = 6,78 Hz, 6H) 3,02 (m, 2H) 3,39 (d, J = 12,06 Hz, 2H) 4,15 (m, 2H) 8,22 (s, 1H) 8,24 (s, 1H) 8,56 (s, 1H) 10,35 (s, 1H).

Intermedio 470

6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formil-*N*,*N*-dimetilbenzo[d]isoxazol-3-carboxamida

Material de partida: 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-(hidroximetil)-*N*,*N*-dimetilbenzo[d]isoxazol-3-carboxamida (**Intermedio 286**).

MS (ES) MH^+: 350 para $C_{17}H_{20}FN_3O_4$

Intermedio 471

7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-metilisoxazolo[4,5-b]piridin-5-carbaldehído

(7-Cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-metilisoxazolo[4,5-b]piridin-5-il)metanol (**Intermedio 352**, 459 mg, 1,47 mmol) se disolvió en aproximadamente 10 mL de CH_2Cl_2. Se agregó dióxido de manganeso (1920 mg, 22,08 mmol) y la suspensión se agitó a temperatura ambiente durante tres días. La mezcla se filtró a través de celite y se concentró. El bruto se purificó mediante cromatografía en SiO_2 utilizando 10-30% de EtOAc/hexanos. Se recuperó un sólido amarillo, 185 mg (41%).

MS (ES) MH^+: 310 para $C_{14}H_{16}ClN_3O_3$

^1H RMN (300 MHz, CD_2Cl_2) δ: 1,2 (d, 6H), 2,7 (s, 3H), 2,9-3,0 (m, 2H), 3,1-3,2 (m, 2H), 3,8-4,0 (m, 2H), 10,2 (s, 1H).

Los **Intermedios 472** a **481** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 471**:

Intermedio 472

7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(pirazin-2-il)benzo[d]isoxazol-5-carbaldehído

Material de partida: (7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(pirazin-2-il)benzo[d]isoxazol-5-il)metanol (**Intermedio 353**).

MS (ES) MH^+: 373 para $C_{18}H_{17}ClN_4O_3$

^1H RMN ($DMSO-d_6$) δ: 1,1 (d, 6H), 3,1-3,2 (m, 4H), 3,8-3,9 (m, 2H), 8,7 (s, 1H), 8,9 (d, 1H), 9,0 (m, 1H), 9,4 (m, 1H), 10,3 (s, 1H).

Intermedio 473

7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-formil-*N*-metilisoxazolo[4,5-b]piridin-3-carboxamida

Material de partida: 7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-(hidroximetil)-*N*-metilisoxazolo[4,5-b]piridin-3-carboxamida (**Intermedio 293**) en 20 mL de CH_2Cl_2.

MS (ES) MH^+: 353 para $C_{15}H_{17}ClN_4O_4$

^1H RMN (300 MHz, CD_2Cl_2) δ: 1,2 (d, 6H), 3,0-3,2 (superposición de m, 7H), 3,9-4,0 (m, 2H), 7,9 (s a, 1H), 10,2 (s, 1H).

Intermedio 474

7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-*N*-etil-5-formilisoxazolo[4,5-b]piridin-3-carboxamida

Material de partida: 7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-*N*-etil-5-(hidroximetil)isoxazolo[4,5-b]piridin-3-carboxamida (**Intermedio 294**).

MS (ES) MH^+: 367 para $C_{16}H_{19}ClN_4O_4$

^1H RMN (300 MHz, CD_2Cl_2) δ: 1,2 (d, 6H), 1,3 (t, 3H), 3,0-3,2 (m, 4H), 3,5-3,7 (m, 2H), 3,9-4,0 (m, 2H), 7,9 (s a, 1H), 10,2 (s, 1H).

Intermedio 475

7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-formil-*N*-isopropilisoxazolo[4,5-b]piridin-3-carboxamida

Material de partida: 7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-(hidroximetil)-*N*-isopropilisoxazolo[4,5-b]piridin-3-carboxamida (**Intermedio 295**).

MS (ES) MH^+: 381 para $C_{17}H_{21}ClN_4O_4$

Intermedio 476

N-terc-butil-7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-formilisoxazolo[4,5-b]piridin-3-carboxamida

Material de partida: *N-terc*-butil-7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-(hidroximetil)isoxazolo[4,5-b]piridin-3-carboxamida (**Intermedio 296**).
MS (ES) MH^+: 395 para $C_{18}H_{23}ClN_4O_4$
^1H RMN (300 MHz, CD_2Cl_2) δ: 1,2 (d, 6H), 1,5 (s, 9H), 3,0-3,2 (m, 4H), 3,9-4,0 (m, 2H), 7,9 (s a, 1H), 10,2 (s, 1H).

Intermedio 477

7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-formil-*N*-neopentilisoxazolo[4,5-b]piridin-3-carboxamida

Material de partida: 7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-(hidroximetil)-*N*-neopentilisoxazolo[4,5-b]piridin-3-carboxamida (**Intermedio 297**).
MS (ES) MH^+: 409 para $C_{19}H_{25}ClN_4O_4$
^1H RMN (300 MHz, CD_2Cl_2) δ: 1,0 (s, 9H), 1,2 (d, 6H), 3,0-3,2 (m, 4H), 3,4 (d, 2H), 3,9-4,0 (m, 2H), 8,2 (s a, 1H), 10,2 (s, 1H).

Intermedio 478

7-cloro-3-(3,3-difluoroazetidin-1-carbonil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)isoxazolo[4,5-b]piridin-5-carbaldehído

Material de partida: (7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-(hidroximetil)isoxazolo[4,5-b]piridin-3-il)(3,3-difluoroazetidin-1-il)metanona (**Intermedio 298**).
MS (ES) MH^+: 415 para $C_{17}H_{17}ClF_2N_4O_4$
^1H RMN (300 MHz, CD_2Cl_2) δ: 1,2 (d, 6H), 3,0-3,1 (m, 4H), 3,9-4,0 (m, 2H), 4,6 (t, 2H), 4,9 (t, 2H), 10,2 (s, 1H).

Intermedio 479

N-bencil-7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-formilisoxazolo[4,5-b]piridin-3-carboxamida

Material de partida: *N*-bencil-7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-(hidroximetil)isoxazolo[4,5-b]piridin-3-carboxamida (**Intermedio 299**).
MS (ES) MH^+: 429 para $C_{21}H_{21}ClN_4O_4$

^{1}H RMN (300 MHz, CD_2Cl_2) δ: 1,2 (d, 6H), 2,9-3,2 (m, 4H), 3,8-4,00 (m, 2H), 4,7 (d, 2H), 7,2-7,5 (m, 5H), 8,2 (s a, 1H), 10,1 (s, 1H).

Intermedio 480

7-cloro-*N*-(4-cianobencil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-formilisoxazolo[4,5-b]piridin-3-carboxamida

Material de partida: 7-cloro-*N*-(4-cianobencil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-(hidroximetil)isoxazolo[4,5-b]piridin-3-carboxamida (**Intermedio 300**).

MS (ES) MH^+: 454 para $C_{22}H_{20}ClN_5O_4$

^{1}H RMN (300 MHz, CD_2Cl_2) δ: 1,2 (d, 6H), 3,0-3,2 (m, 4H), 3,7-4,0 (m, 2H), 4,8 (m, 2H), 7,5 (d, 2H), 7,7 (d, 2H), 8,4 (s a, 1H), 10,1 (s, 1H).

Intermedio 481

7-cloro-*N*-(3-cianobencil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-formilisoxazolo[4,5-b]piridin-3-carboxamida

Material de partida: 7-cloro-*N*-(3-cianobencil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-(hidroximetil)isoxazolo[4,5-b]piridin-3-carboxamida (**Intermedio 301**).

MS (ES) MH^+: 454 para $C_{22}H_{20}ClN_5O_4$

Intermedio 482

1-bencilamino-butan-2-ol

A una solución de bencilamina (29,65 g, 277,0 mmol) en etanol (40 mL) se agregó 1,2-epoxibutano (4 g, 55,47 mmol) y la mezcla se calentó hasta alcanzar 150 °C durante 2 h en un autoclave. Se concentró y destiló a 140-150 °C/2 mm Hg para proporcionar el producto como un líquido incoloro, que lentamente cristalizó a temperatura ambiente después de 2 días.

Rendimiento: 8,5 g (85%)

MS (ES) MH^+: 180 para $C_{11}H_{17}NO$

^{1}H RMN (300 MHz – $CDCl_3$) δ: 0,9 (t, 3H), 1,4 (m, 2H), 2,45 (t, 1H), 2,8 (dd, 1H), 3,55 (m, 1H), 3,8 (c, 2H), 7,2 (m, 5H).

Los **Intermedios 483** a **485** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 482:**

Intermedio 483

3-(bencilamino)-1,1,1-trifluoropropan-2-ol

Material de partida: bencilamina y 2-(trifluorometil)oxirano.

MS (ES) MH^+: 220 para $C_{10}H_{12}F_3NO$

^1H RMN (300 MHz – $CDCl_3$) δ: 2,8 (m, 1H), 2,9 (m, 1H), 3,55 (m, 1H), 3,8 (s, 2H), 4,0 (m, 1H), 7,3-7,4 (m, 5H).

Intermedio 484

1-(bencilamino)-3-metoxipropan-2-ol

Materiales de partida: bencilamina y 2-(metoximetil)oxirano.

MS (ES) MH^+: 196 para $C_{11}H_{17}NO_2$

^1H RMN (300 MHz – $CDCl_3$) δ: 2,7 (m, 2H), 2,9 (s, 2H), 3,3-3,4 (m, 5H), 3,8 (d, 2H), 3,9 (m, 1H), 7,3 (m, 5H).

Intermedio 485

1-(benciloxi)-3-[(2,4-dimetoxibencil)amino]propan-2-ol

Materiales de partida: 2,4-dimetoxibencilamina y 2-[(benciloxi)metil]oxirano.

MS (ES) MH^+: 332 para $C_{19}H_{25}NO_4$

^1H RMN (300 MHz – $CDCl_3$) δ: 2,4 (m, 1H), 2,5-2,6 (m, 1H), 3,4(m, 2H), 3,6 (m, 2H), 3,75 (s, 6H), 4,5 (s, 2H), 6,45 (m, 1H), 6,5 (d, 1H), 7,15 (d, 1H), 7,3-7,4 (m, 5H).

Intermedio 486

1-[bencil-(2-hidroxipropil)amino]butan-2-ol

A una solución de 1-bencilaminobutan-2-ol (**Intermedio 482**, 8,5 g, 47,48 mmol) en etanol (150 mL) se agregó óxido de propileno (8,8 g, 151 mmol) y la mezcla se calentó a 150 °C durante 2 h en un autoclave. Después de la concentración de la mezcla a presión reducida, el residuo se purificó mediante cromatografía en columna utilizando metanol en diclorometano para proporcionar el producto como un aceite. Rendimiento: 10,2 g (93%).

MS (ES) MH^+: 238 para $C_{14}H_{23}NO_2$

^1H RMN (300 MHz – $CDCl_3$) δ: 0,9 (t, 3H), 1,2 (m, 3H), 1,9 (m, 2H), 2,6 (m, 3H), 2,65 (m, 1H), 2,9 (s a, 2H), 3,8 (m, 2H), 3,9 (m, 2H), 7,2 (m, 5H).

Intermedio 487

N-bencil-2-bromo-*N*-(3,3,3-trifluoro-2-hidroxipropil)propanamida

A una solución enfriada con hielo de 3-(bencilamino)-1,1,1-trifluoropropan-2-ol (**Intermedio 483,** 1,0 g, 4,5 mmol) en DCM (10 mL) se agregó TEA (0,8 mL, 5,7 mmol) y luego cloruro de 2-bromopropanoilo (0,86 g, 5,0) gota a gota y la mezcla se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se diluyó con DCM (10 mL), se lavó con HCl 1,5 N (2 x 10 mL) y $NaHCO_3$ acuoso saturado (2 x 10 mL) antes de secarse con Na_2SO_4 anhidro, filtrarse y concentrarse. El residuo se utilizó para la siguiente etapa sin purificación adicional. Rendimiento: 1,4 g.

MS (ES) MH^+: 354 para $C_{13}H_{15}BrF_3NO_2$

Los **Intermedios 488** y **489** se prepararon a partir del material de partida indicado, cloruro de 2-bromopropanoilo y TEA, utilizando un método similar al descrito para la síntesis del **Intermedio 487**:

Intermedio 488

N-bencil-2-bromo-*N*-(2-hidroxi-3-metoxipropil)propanamida

Material de partida: 1-(bencilamino)-3-metoxipropan-2-ol (**Intermedio 484**).

MS (ES) MH^+: 330 para $C_{14}H_{20}BrNO_3$

Intermedio 489

N-[3-(benciloxi)-2-hidroxipropil]-2-bromo-*N*-(2,4-dimetoxibencil)propanamida

Material de partida: 1-(benciloxi)-3-[(2,4-dimetoxibencil)amino]propan-2-ol (**Intermedio 485**).

MS (ES) MH^+: 466 para $C_{22}H_{28}BrNO_3$

Intermedio 490

4-bencil-6-metil-2-(trifluorometil)morfolin-3-ona

A una solución enfriada con hielo de *N*-bencil-2-bromo-*N*-(3,3,3-trifluoro-2-hidroxipropil) propanamida (**Intermedio 487,** 1,4 g, 4,0 mmol) en THF (10 mL) se agregó NaH (0,188 mg, 7,8 mmol) y la mezcla se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se detuvo con MeOH (5 mL) y se vertió en HCl 1,5 N (10 mL). La capa acuosa se extrajo con éter dietílico (2x 25 mL). La capa orgánica se lavó con $NaHCO_3$ saturado (2 x 10 mL), se secó con Na_2SO_4 anhidro, se filtró y se concentró para proporcionar el producto como un sólido. Rendimiento: 1,0 g.
MS (ES) MH^+: 274 para $C_{13}H_{14}F_3NO_2$

Los **Intermedios 490** y **491** se prepararon a partir del material de partida indicado y NaH utilizando un método similar al descrito para la síntesis de **Intermedio 490**:

Intermedio 491

4-bencil-2-(metoximetil)-6-metilmorfolin-3-ona

Material de partida: *N*-bencil-2-bromo-*N*-(2-hidroxi-3-metoxipropil)propanamida (**Intermedio 488**).
MS (ES) MH^+: 250 para $C_{14}H_{19}NO_3$

Intermedio 492

2-[(benciloxi)metil]-4-(2,4-dimetoxibencil)-6-metilmorfolin-3-ona

Material de partida: *N*-[3-(benciloxi)-2-hidroxipropil]-2-bromo-*N*-(2,4-dimetoxibencil)propanamida (**Intermedio 489**).
MS (ES) MH^+: 386 para $C_{22}H_{27}NO_5$

Intermedio 493

(2*S*,6*S*)-rel-4-bencil-2-metil-6-(trifluorometil)morfolina

A una solución enfriada con hielo de LAH (0,291 mg, 7,6 mmol) en THF seco (10 mL) se agregó 4-bencil-6-metil-2-(trifluorometil)morfolin-3-ona (**Intermedio 490,** 1,0 g, 3,6 mmol) en THF (10 mL) gota a gota y la mezcla se agitó a 60 °C durante 1 hora. La mezcla de reacción se detuvo con MeOH (5 mL) y se vertió en HCl 1,5 N (10 mL). La capa acuosa se extrajo con éter dietílico (2x 25 mL). La capa orgánica se lavó con $NaHCO_3$ saturado (2 x 10 mL), se secó con Na_2SO_4

anhidro, se filtró y se concentró. El residuo se purificó mediante cromatografía en columna de gel de sílice para proporcionar el producto como un sólido. Rendimiento: 350 mg. También se aisló el isómero *trans* (2*S*,6*R*)-rel-4-bencil-2-metil-6-(trifluorometil)morfolina.

MS (ES) MH^+: 260 para $C_{13}H_{16}F_3NO$

^1H RMN (300 MHz – $CDCl_3$) δ: 1,2 (d, 3H), 1,9 (t, 1H), 2,1(t, 1H), 2,7 (d, 1H), 2,9 (d, 1H), 3,5-3,6 (m, 2H), 3,8 (m, 1H), 4,0 (m, 1H), 7,3-7,4 (m, 5H).

Los **Intermedios 494** y **495** se prepararon a partir del material de partida indicado y LAH utilizando un método similar al descrito para la síntesis del **Intermedio 493**:

Intermedio 494

(2*S*,6*S*)-rel-4-bencil-2-(metoximetil)-6-metilmorfolina

Material de partida: 4-bencil-2-(metoximetil)-6-metilmorfolin-3-ona (**Intermedio 491**).

MS (ES) MH^+: 236 para $C_{14}H_{21}NO_2$

^1H RMN (300 MHz – $CDCl_3$) δ: 1,2 (d, 3H), 1,7-1,9 (m, 2H), 2,7 (t, 2H), 3,3-3,5 (m, 5H), 3,6 (s, 2H), 3,7-3,9 (m, 2H), 7,2-7,4 (m, 5H).

Intermedio 495

(2*S*,6*S*)-rel-2-[(benciloxi)metil]-4-(2,4-dimetoxibencil)-6-metilmorfolina

Material de partida: 2-[(benciloxi)metil]-4-(2,4-dimetoxibencil)-6-metilmorfolin-3-ona (**Intermedio 492**).

MS (ES) MH^+: 372 para $C_{22}H_{29}NO_4$

^1H RMN (300 MHz – $CDCl_3$) δ: 1,2 (d, 3H), 1,8-1,9 (m, 2H), 2,7 (t, 1H), 2,8(d, 1H), 3,4 (m, 1H), 3,5 (m, 3H), 3,7 (m, 1H), 3,8 (s, 6H), 3,9 (m, 1H), 4,5 (m, 2H), 6,5 (m, 2H), 7,2-7,4 (m, 6H).

Intermedio 496

4-bencil-2-etil-6-metilmorfolina

Una mezcla de 1-[bencil-(2-hidroxipropil)amino]butan-2-ol (**Intermedio 486**, 10,5 g, 44,30 mmol) y ácido sulfúrico (70% p/p, 10 mL) se calentó a 150 °C durante 36 h. La mezcla de reacción se enfrió hasta alcanzar 0 °C, se basificó con $NaHCO_3$ al 10% hasta alcanzar pH ~ 10 y se extrajo con éter dietílico (3 x 50 mL). La capa orgánica se lavó con salmuera (2 x 25 mL),

agua (2 x 25 mL), se secó con sulfato de sodio, se filtró y se concentró. El residuo se purificó mediante cromatografía en columna utilizando n-heptano en éter dietílico para proporcionar el producto como un aceite amarillo claro. Rendimiento: 2,0 g (20%).

MS (ES) MH^+: 220 para $C_{14}H_{21}NO$

^1H RMN (300 MHz – $CDCl_3$) δ: 0,9 (t, 3H), 1,2 (m, 3H), 1,5 (m, 2H), 1,8 (c, 2H), 2,8 (c, 2H), 3,5 (m, 3H), 3,7 (m, 1H), 7,3 (t, 5H).

Intermedio 497

2-etil-6-metilmorfolina

A una solución de 4-bencil-2-etil-6-metilmorfolina (**Intermedio 496,** 2,0 g, 9,13 mmol) en metanol (30 mL) se agregó formiato de amonio (2,35 g, 10,77 mmol) y luego Pd/C al 10% (1,0 g) y la mezcla se calentó a 65 °C durante 1 hora. Se enfrió y se filtró a través de una almohadilla de celite, se lavó con exceso de metanol y se concentró. El residuo obtenido de esta forma se destiló. Rendimiento: 1,0 g (85%).

MS (ES) MH^+: 130 para $C_7H_{15}NO$

^1H RMN (300 MHz – $CDCl_3$) δ: 0,9 (t, 3H), 1,2 (dd, 3H), 1,55 (m, 2H), 2,5 (m, 2H), 2,9 (t, 2H), 3,35 (m, 1H), 3,6 (m, 1H).

Los **Intermedios 498** y **499** se prepararon a partir del material de partida indicado utilizando un método similar al descrito para la síntesis del **Intermedio 497:**

Intermedio 498

(2*S*,6*S*)-rel-2-metil-6-(trifluorometil)morfolina

Material de partida: a una solución de (2*S*,6*S*)-rel-4-bencil-2-metil-6-(trifluorometil)morfolina (**Intermedio 493**).

MS (ES) MH^+: 170 para $C_6H_{10}F_3NO$

^1H RMN (300 MHz – $CDCl_3$) δ: 1,1 (d, 3H), 2,5 (m, 1H), 2,7 (m, 1H), 2,8 (m, 1H), 3,1 (m, 1H), 3,8 (m, 1H), 3,9 (m, 1H).

Intermedio 499

(2*S*,6*S*)-rel-2-(metoximetil)-6-metilmorfolina

Material de partida: (2*S*,6*S*)-rel-4-bencil-2-(metoximetil)-6-metilmorfolina (**Intermedio 494**).

MS (ES) MH^+: 146 para $C_7H_{15}NO_2$

^1H RMN (300 MHz – $CDCl_3$) δ: 1,1 (d, 3H), 2,4 (m, 1H), 2,6 (m, 1H), 2,9 (m, 1H), 3,3-3,5 (m, 5H), 3,6-3,7 (m, 2H).

Intermedio 500

(2*S*,6*S*)-rel-2-[(benciloxi)metil]-6-metilmorfolina

A una solución de (2*S*,6*S*)-rel-2-[(benciloxi)metil]-4-(2,4-dimetoxibencil)-6-metilmorfolina (**Intermedio 495,** 0,6 g, 1,6 mmol) en DCM (15 mL) se agregó cloroformiato de 1-cloroetilo (0,6 mL, 6,9 mmol) y mezcla se calentó a 50 °C durante 10 horas. A la mezcla de reacción se agregó metanol y se continuó calentando durante 1 hora. Después de enfriar, la mezcla se concentró para proporcionar el producto como un sólido.

Rendimiento: 0,5 g

MS (ES) MH^+: 222 para $C_{13}H_{19}NO_2$

Intermedio 501

6-(2-etil-6-metilmorfolin-4-il)-7-fluoro-3-metil-1,2-bencisoxazol-5-carbaldehído

A una solución enfriada con hielo y agitada de 6,7-difluoro-3-metilbenzo[d]isoxazol-5-carbaldehído (**Intermedio 374**, 150 mg, 0,8 mmol) en acetonitrilo anhidro se agregó TEA (204 mg, 2,0 mmol) y luego 2-etil-6-metil-morfolina (**Intermedio 497**, 98 mg, 0,8 mmol) y la mezcla se calentó a 80 °C durante 12 h. Se enfrió hasta alcanzar la temperatura ambiente y se concentró. El residuo obtenido de esta forma se purificó sobre columna de gel de sílice utilizando un gradiente de acetato de etilo en éter de pet. para proporcionar el producto como un sólido.

Rendimiento: 75 mg (74%).

MS(ES) MH^+: 307 para $C_{16}H_{19}F_2N_2O_3$

^1H RMN (400 MHz, DMSO-d_6) δ: 0,9 (t, 3H), 1,1 (d, 3H), 1,5 (m, 2H), 2,6 (s, 3H), 3,0 (m, 2H), 3,2 (d, 2H), 3,6 (m, 1H), 3,8 (m, 1H), 8,1 (s, 1H), 10,3 (s, 1H).

Los **Intermedios 502** y **503** se prepararon a partir del material de partida indicado, TEA y 6,7-difluoro-3-metilbenzo[d]isoxazol-5-carbaldehído (**Intermedio 374**), utilizando un método similar al descrito para la síntesis del **Intermedio 501**:

Intermedio 502

7-fluoro-3-metil-6-[(2*S*,6*S*)-rel-2-metil-6-(trifluorometil)morfolin-4-il]-1,2-benzoxazol-5-carbaldehído

Material de partida: (2*S*,6*S*)-rel-2-metil-6-(trifluorometil)morfolina (**Intermedio 498**).

MS (ES) MH^+: 347 para $C_{15}H_{14}F_4N_2O_3$

Intermedio 503

7-fluoro-6-[(2*S*,6*S*)-rel-2-(metoximetil)-6-metilmorfolin-4-il]-3-metil-1,2-benzoxazol-5-carbaldehído

Material de partida: (2*S*,6*S*)-rel-2-(metoximetil)-6-metilmorfolina (**Intermedio 499**).

MS (ES) MH^+: 323,2 para $C_{16}H_{19}FN_2O_4$

^1H RMN (300 MHz, $CDCl_3$) δ: 1,3 (d, 3H), 2,6 (s, 3H), 3,2 (m, 2H), 3,3 (m, 2H), 3,4 (s, 3H), 4,0 (m, 2H), 8,0 (d, 1H), 10,4 (s, 1H).

Intermedio 504

{3-(bencilamino)-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-1,2-benzoxazol-5-il}metanol

A una solución enfriada con hielo de benzaldehído (0,08 mL, 2,54 mmol) en TFA (5 mL) se agregó trietilsilano (0,4 mL, 2,5 mmol) y luego {3-amino-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-1,2-bencisoxazol-5-il}metanol (**Intermedio 7,** 250 mg, 0,84 mmol) y lentamente se dejó alcanzar la temperatura ambiente y se agitó durante 12 horas. La mezcla de reacción se concentró y el residuo obtenido de esta forma se purificó mediante cromatografía en columna utilizando EtOAc en éter de pet. para proporcionar el compuesto del título como un sólido. Rendimiento: 70 mg (21%).

MS (ES) MH^+: 386 para $C_{21}H_{24}FN_3O_3$

Los **Intermedios 505** a **514** se prepararon a partir del material de partida indicado, trietilsilano y {3-amino-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-1,2-bencisoxazol-5-il}metanol (**Intermedio 7**), utilizando un método similar al descrito para la síntesis del **Intermedio 504**:

Intermedio 505

{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[(1,3-tiazol-2-ilmetil)amino]-1,2-benzoxazol-5-il}metanol

Material de partida: 2-tiazol carboxaldehído.

MS (ES) MH^+: 393 para $C_{18}H_{21}FN_4O_3S$

Intermedio 506

{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[(1*H*-imidazol-4-ilmetil)amino]-1,2-benzoxazol-5-il}metanol

Material de partida: 4-imidazolcarboxaldehído.

MS (ES) MH^+: 376,2 para $C_{18}H_{22}FN_5O_3$

^1H RMN (400 MHz, DMSO-d_6) δ: 1,1 (d, 6H), 2,8 (m, 2H), 2,9 (d, 2H), 3,7 (m, 2H), 4,45 (d, 2H), 4,6 (s, 1H), 7,5 (s, 1H), 7,7 (m, 2H), 8,75 (s, 1H).

Intermedio 507

(6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-{[(1-metil-1*H*-pirazol-4-il)metil]amino}-1,2-benzoxazol-5-il)metanol

Material de partida: 1-metil-1*H*-pirazol-4-carboxaldehído.

MS (ES) MH^+: 390 para $C_{19}H_{24}FN_5O_3$

Intermedio 508

(6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-{[(5-metil-1,2-oxazol-3-il)metil]amino}-1,2-benzoxazol-5-il)metanol

Material de partida: 5-metilisoxazol-3-carboxaldehído.

MS (ES) MH^+: 391 para $C_{19}H_{23}FN_4O_4$

Intermedio 509

{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[(piridin-2-ilmetil)amino]-1,2-benzoxazol-5-il}metanol

Material de partida: piridin-2-carboxaldehído.

MS (ES) MH^+: 387 para $C_{20}H_{23}FN_4O_3$

Intermedio 510

{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[(piridin-3-ilmetil)amino]-1,2-benzoxazol-5-il}metanol

Material de partida: piridin-3-carboxaldehído

MS (ES) MH^+: 387 para $C_{20}H_{23}FN_4O_3$

Intermedio 511

{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[(piridin-4-ilmetil)amino]-1,2-benzoxazol-5-il}metanol

Material de partida: piridin-4-carboxaldehído.

MS (ES) MH^+: 387 para $C_{20}H_{23}FN_4O_3$

Intermedio 512

{3-[(ciclopropilmetil)amino]-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-1,2-benzoxazol-5-il}metanol

Material de partida: ciclopropilcarboxaldehído.

MS (ES) MH^+: 350 para $C_{18}H_{24}FN_3O_3$

Intermedio 513

{3-[(ciclohexilmetil)amino]-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-1,2-benzoxazol-5-il}metanol

Material de partida: ciclohexanocarboxaldehído.

MS (ES) MH^+: 391 para $C_{21}H_{30}FN_3O_3$

Intermedio 514

{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[(tetrahidro-2*H*-piran-4-ilmetil)amino]-1,2-benzoxazol-5-il}metanol

Material de partida: Tetrahidropiran-4-carbaldehído.

MS (ES) MH^+: 394 para $C_{20}H_{28}FN_3O_4$

Intermedio 515

3-(bencilamino)-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-1,2-benzoxazol-5-carbaldehído

A una solución enfriada con hielo de {3-(bencilamino)-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-1,2-benzoxazol-5-il}metanol (**Intermedio 504**, 160 mg, 0,41 mmol) en acetonitrilo (2 mL) se agregó NMO (73 mg, 1,5 mmol) y luego TPAP (15 mg, 0,1 mmol) y la mezcla se agitó durante 2 horas a temperatura ambiente. La mezcla de reacción se filtró a través de un lecho de sílice y se lavó con EtOAc. La fase orgánica se concentró a presión reducida para proporcionar compuesto del título como un sólido amarillo. Rendimiento: 75 mg (47%).

MS (ES) MH^+: 384 para $C_{21}H_{22}FN_3O_3$

Los **Intermedios 516** a **525** se prepararon a partir del material de partida indicado, NMO y TPAP utilizando un método similar al descrito para la síntesis del **Intermedio 515**:

Intermedio 516

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[(1,3-tiazol-2-ilmetil)amino]-1,2-benzoxazol-5-carbaldehído

Material de partida: {6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[(1,3-tiazol-2-ilmetil)amino]-1,2-benzoxazol-5-il}metanol (**Intermedio 505**).

MS (ES) MH^+: 391 para $C_{18}H_{19}FN_4O_3S$

Intermedio 517

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[(1*H*-imidazol-4-ilmetil)amino]-1,2-benzoxazol-5-carbaldehído

Material de partida: {6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[(1*H*-imidazol-4-ilmetil)amino]-1,2-benzoxazol-5-il}metanol (**Intermedio 506**).

MS (ES) MH^+: 374,2 para $C_{18}H_{20}FN_5O_3$

Intermedio 518

(6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-{[(1-metil-1*H*-pirazol-4-il)metil]amino}-1,2-benzoxazol-5-carbaldehído

Material de partida: (6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-{[(1-metil-1*H*-pirazol-4-il)metil]amino}-1,2-benzoxazol-5-il)metanol (**Intermedio 507**).

MS (ES) MH^+: 388 para $C_{19}H_{22}FN_5O_3$

Intermedio 519

(6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-{[(5-metil-1,2-oxazol-3-il)metil]amino}-1,2-benzoxazol-5-carbaldehído

Material de partida: (6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-{[(5-metil-1,2-oxazol-3-il)metil]amino}-1,2-benzoxazol-5-il)metanol (**Intermedio 508**).

MS (ES) MH^+: 389 para $C_{19}H_{21}FN_4O_4$

Intermedio 520

{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[(piridin-2-ilmetil)amino]-1,2-benzoxazol-5-carbaldehído

Material de partida: {6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[(piridin-2-ilmetil)amino]-1,2-benzoxazol-5-il}metanol (**Intermedio 509**).

MS (ES) MH^+: 385 para $C_{20}H_{21}FN_4O_3$

Intermedio 521

{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[(piridin-3-ilmetil)amino]-1,2-benzoxazol-5-carbaldehído

Material de partida: {6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[(piridin-3-ilmetil)amino]-1,2-benzoxazol-5-il}metanol (**Intermedio 510**).

MS (ES) MH^+: 385 para $C_{20}H_{21}FN_4O_3$

Intermedio 522

{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[(piridin-4-ilmetil)amino]-1,2-benzoxazol-5-carbaldehído

Material de partida: {6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[(piridin-4-ilmetil)amino]-1,2-benzoxazol-5-il}metanol (**Intermedio 511**).

MS (ES) MH^+: 385 para $C_{20}H_{21}FN_4O_3$

Intermedio 523

{3-[(ciclopropilmetil)amino]-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-1,2-benzoxazol-5-carbaldehído

Material de partida: {3-[(ciclopropilmetil)amino]-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-1,2-benzoxazol-5-il}metanol (**Intermedio 512**).

MS (ES) MH^+: 348 para $C_{18}H_{22}FN_3O_3$

Intermedio 524

{3-[(ciclohexilmetil)amino]-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-1,2-benzoxazol-5-carbaldehído

Material de partida: {3-[(ciclohexilmetil)amino]-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-1,2-benzoxazol-5-il}metanol (**Intermedio 513**).

MS (ES) MH^+: 390 para $C_{21}H_{28}FN_3O_3$

Intermedio 525

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[(tetrahidro-2*H*-piran-4-ilmetil)amino]-1,2-benzoxazol-5-carbaldehído

Material de partida: {6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[(tetrahidro-2*H*-piran-4-ilmetil)amino]-1,2-benzoxazol-5-il}metanol (**Intermedio 514).**

MS (ES) MH^+: 392 para $C_{20}H_{26}FN_3O_4$

Intermedio 526

3,4-difluoro-2-hidroxibenzoato de metilo

Una solución de ácido 3,4-difluoro-2-hidroxibenzoico (6,45 g, 37,05 mmol) y ácido sulfúrico (6 mL, 113 mmol) en MeOH (25 mL) se calentó a reflujo durante toda la noche. La mezcla se diluyó con agua y se extrajo con éter. El éter se lavó con $NaHCO_3$ acuoso, agua y salmuera. Las capas acuosas combinadas se extrajeron dos veces más con éter, que se lavó con $NaHCO_3$, agua y salmuera. Los extractos de éter combinados se secaron ($MgSO_4$) y se concentraron para proporcionar 6,4 g del producto como un sólido blanco.

MS (ES) MH^-: 187 para $C_8H_6F_2O_3$

^{1}H RMN (300 MHz, DMSO-d_6) δ: 3,9 (s, 3H), 6,9-7,1 (m, 1H), 7,65 (m, 1H), 10,8 (s, 1H).

Intermedio 527

3,4-difluoro-*N*,2-dihidroxibenzamida

Una solución de hidroxilamina (50% en agua) (50 mL, 816 mmol) se agregó a una solución de 3,4-difluoro-2-hidroxibenzoato de metilo (7,75 g, 41,2 mmol) (**Intermedio 526**) en dioxano (200 mL) y la mezcla se agitó a temperatura ambiente durante 3 días. La mezcla se repartió entre agua y EtOAc. La capa acuosa se acidificó con HCl concentrado y se extrajo con EtOAc dos veces más. Las capas de EtOAc se lavaron con salmuera, se combinaron y se concentraron para proporcionar 7,9 g de un sólido.

LC-MS ES MH^+ 190 para $C_7H_5F_2NO_3$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 7,0 (ddd, 1H), 7,4-7,7 (m, 1H), 9,5 (s, 1H), 11,7 (s, 1H), 13,1 (s, 1H).

Intermedio 528

6,7-difluoro-1,2-bencisoxazol-3(2*H*)-ona

Una mezcla de 3,4-difluoro-*N*,2-dihidroxibenzamida (**Intermedio 527**, 7,91 g, 41,8 mmol) y carbonildiimidazol (13,6 g, 83,7 mmol) en THF (200 mL) se calentó a reflujo durante 90 min. La mezcla se repartió entre EtOAc y agua y se acidificó con HCl conc. La solución se extrajo 3 veces con EtOAc, cada extracto se lavó con agua y salmuera. El secado ($MgSO_4$) de los extractos combinados y la eliminación del disolvente proporcionaron 6,88 g del producto como un sólido blanquecino.

MS (ES) $M-H^-$: 170 para $C_7H_3F_2NO_2$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 7,3-7,5 (m, 1H), 7,6 (m, 1H), 12,9 (s, 1H).

Intermedio 529

3-cloro-6,7-difluorobenzo[d]isoxazol

Se agregó TEA (5,6 mL, 40,2 mmol) a una mezcla enfriada con un baño de hielo de 6,7-difluoro-1,2-bencisoxazol-3(2*H*)-ona (**Intermedio 528,** 6,88 g, 40,2 mmol) y $POCl_3$ (13,1 mL, 141 mmol) (reacción exotérmica) en un recipiente de reactor de microondas y la mezcla se calentó a 140 °C durante 6 horas en un reactor de microondas. La mezcla se recogió con éter y se lavó con Na_2CO_3

(2X) y salmuera. Las capas acuosas combinadas se extrajeron dos veces más con éter, que se lavó con Na_2CO_3 y salmuera. Las capas de éter combinadas se secaron ($MgSO_4$) y se concentraron para proporcionar un aceite que solidificó lentamente. El material se cromatografió en gel de sílice (hexanos seguido por elución en gradiente a 50% de CH_2Cl_2 en hexanos) para proporcionar 5,64 g del producto como un sólido blanquecino.

^{1}H RMN ($CDCl_3$) δ: 7,2-7,35 (m, 1H), 7,4-7,5 (m, 1H).

Intermedio 530

6,7-difluoro-1,2-bencisoxazol-3-il carbonato de *terc*-butilo

A una solución de 6,7-difluoro-1,2-bencisoxazol-3(2*H*)-ona (**Intermedio 528,** 5,0 g, 29,2 mmol) en THF seco (50 mL), se agregó dimetilaminopiridina (3,5 g, 29,2 mmol) y luego anhídrido de Boc (12,7 g, 58,4 mmol) y la mezcla se calentó hasta alcanzar 65 °C durante 12 horas. La mezcla de reacción se concentró y el residuo obtenido de esta forma se purificó en columna de gel de sílice utilizando un gradiente de acetato de etilo en éter de petróleo para proporcionar el producto como un sólido amarillo. Rendimiento: 4,0 g (50%).

^{1}H RMN (400 MHz, DMSO-d_6) δ: 1,6 (s, 9H), 7,4 (m, 1H), 7,5 (m, 1H).

Intermedio 531

6,7-difluoro-5-formil-1,2-bencisoxazol-3-ilcarbonato de *terc*-butilo

A una solución de diisopropilamina (3,2 g, 32,4 mmol) en THF (20 mL) se agregó n-butillitio (20,2 mL, 1,6N), gota a gota a -10 °C y la solución se agitó durante 30 min. La mezcla de reacción se enfrió hasta alcanzar -78 °C y a esto se agregó, 6,7-difluoro-1,2-bencisoxazol-3-ilcarbonato de *terc*-butilo (**Intermedio 530,** 4,0 g, 14,7 mmol) en THF (20 mL). Se agitó a -78 °C durante 2 h y luego se trató con dimetilformamida (3,2 g, 44,2 mmol) y se continuó agitando a -78 °C durante 1 hora. La reacción se detuvo mediante la adición de solución saturada de cloruro de amonio y luego se extrajo con acetato de etilo (2 X 20 mL). Las capas orgánicas combinadas se lavaron con agua seguido por salmuera y luego se secaron con sulfato de sodio anhidro. La solución se filtró y el filtrado se evaporó al vacío y el residuo se purificó en columna de gel de sílice utilizando un gradiente de acetato de etilo en éter de pet. para proporcionar el producto como un sólido amarillo. Rendimiento: 3,0 g (68%).

MS (ES) MH^+: 300 para $C_{13}H_{11}F_2NO_5$

^{1}H RMN (400MHz, DMSO-d_6) δ: 1,6 (s, 9H), 8,0 (d, 1H), 10,1(s, 1H).

Intermedio 532

3-cloro-6,7-difluorobenzo[d]isoxazol-5-carbaldehído

Una solución de n-butillitio (2,5 M en hexanos) (16,7 mL, 42 mmol) se agregó lentamente a una solución de 2,2,6,6-tetrametilpiperidina (7,6 mL, 45 mmol) en THF (50 mL) enfriada en un baño de hielo seco-acetona. La solución se entibió hasta alcanzar 0 °C y se enfrió nuevamente en un baño de hielo seco-acetona antes de transferirse mediante una jeringa a una solución de 3-cloro-6,7-difluorobenzo[d]isoxazol (**Intermedio 529,** 5,64 g, 30 mmol) en THF (50 mL). Después de 1 hora agitando, se agregó DMF (1,0 mL, 13,2 mmol) todo de una vez y la mezcla se agitó con enfriamiento en un baño de hielo seco-acetona durante 45 min. La mezcla se transfirió mediante una cánula a una solución de ácido acético (6,8 mL, 119 mmol) en 100 mL de Et_2O y la mezcla se entibió hasta alcanzar la temperatura ambiente. La mezcla se diluyó con EtOAc y se lavó con salmuera. Las capas acuosas combinadas se extrajeron nuevamente con EtOAc, que se lavó con salmuera. El secado ($MgSO_4$) de los extractos combinados y la eliminación del disolvente proporcionaron un aceite marrón que se cromatografió en gel de sílice (10% de CH_2Cl_2 en hexanos seguido por elución en gradiente a 100% de CH_2Cl_2) para proporcionar 3,32 g del producto como un sólido blanco.

^{1}H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 8,1 (dd, 1H) 10,4 (s, 1H).

Intermedio 533

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-5-formil-2,3-dihidro-1,2-bencisoxazol-3-ilcarbonato de *terc*-butilo

A una solución enfriada con hielo y agitada de 6,7-difluoro-5-formil-1,2-bencisoxazol-3-ilcarbonato de *terc*-butilo (**Intermedio 531,** 3,0 g, 10,0 mmol) en acetonitrilo anhidro se agregó DIPEA (2,56 g, 20,0 mmol) y luego *cis* 2,6-dimetilmorfolina (1,27 g, 11,0 mmol) y la mezcla se calentó a 80 °C durante 12 horas. Se enfrió hasta alcanzar la temperatura ambiente y se concentró. El residuo se disolvió en acetato de etilo, se lavó con agua seguido por salmuera y luego se secó con sulfato de sodio anhidro. Se filtró y el filtrado se evaporó a presión reducida. El

residuo se purificó en columna de gel de sílice utilizando un gradiente de acetato de etilo en éter de pet. para proporcionar el producto como un sólido. Rendimiento: 2,9 g (74%).

MS (ES) MH^+: 395 para $C_{13}H_{11}F_2NO_5$

^1H RMN (400MHz, DMSO-d_6) δ: 1,0 (d, 6H), 1,6 (s, 9H), 2,9 (t, 2H), 3,1(d, 2H), 3,8 (m, 2H), 7,7 (s,1H), 10,2 (s, 1H).

Intermedio 534

3-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-1,2-benzoxazol-5-carbaldehído

A una solución enfriada con hielo y agitada de 3-cloro-6,7-difluorobenzo[d]isoxazol-5-carbaldehído (**Intermedio 532,** 1,0 g, 8,75 mmol) en acetonitrilo anhidro se agregó DIPEA (1,8 mL, 10,5 mmol) y luego *cis* 2,6-dimetilmorfolina (1,3 mL, 10,5 mmol) y la mezcla se calentó a 85 °C durante 4 horas. Se enfrió hasta alcanzar la temperatura ambiente y se concentró. El residuo se disolvió en acetato de etilo, se lavó con agua seguido por salmuera y luego se secó con sulfato de sodio anhidro. Se filtró y el filtrado se evaporó a presión reducida. El residuo se purificó en columna de gel de sílice utilizando un gradiente de acetato de etilo en éter de pet. para proporcionar compuesto del título como un sólido. Rendimiento: 2,3 g (85%).

MS (ES) MH^+: 313 para $C_{14}H_{14}ClFN_2O_3$

^1H RMN (400MHz, DMSO-d_6) δ: 1,0 (d, 6H), 2,9 (t, 2H), 3,1 (d, 2H), 3,8 (m, 2H), 7,7 (s, 1H), 10,2 (s, 1H).

Intermedio 535

3-cloro-6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-5-carbaldehído

Una solución de 3-cloro-6,7-difluorobenzo[d]isoxazol-5-carbaldehído (**Intermedio 532,** 3,32 g, 10,6 mmol), (2*R*,6*R*)-2,6-dimetilmorfolina (adquirida de BASF®, 2,64 g, 22,9 mmol) y DIEA (4 mL, 22,9 mmol) en acetonitrilo (20 mL) se calentó a reflujo durante 3 horas. La mezcla se enfrió hasta alcanzar la temperatura ambiente antes de repartirse entre EtOAc y HCl 1N. El EtOAc se separó y se lavó con salmuera. Las capas acuosas combinadas se extrajeron con EtOAc, que se lavó con salmuera. El EtOAc combinado se secó ($MgSO_4$) y se concentró para proporcionar un aceite que se cromatografió en gel de sílice (50% de hexanos en CH_2Cl_2 seguido por elución en gradiente a 100% de CH_2Cl_2 seguido por elución en gradiente a 5% de EtOAc en CH_2Cl_2) para

proporcionar 2 materiales en orden de elución: el primer material (265 mg) consistente con el material de partida y el segundo (3,33 g) con el producto deseado.

LC-MS ES MH^+: 313

^{1}H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1,3 (d, 6H) 3,1 (m, 2H) 3,4 (m, 2H) 4,2 (m, 2H) 8,0 (s, 1H) 10,45 (s, 1H).

Los **Intermedios 536** a **538** se prepararon a partir del material de partida indicado utilizando un método similar al descrito para la síntesis del **Intermedio 535:**

Intermedio 536

6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-3-metilbenzo[d]isoxazol-5-carbaldehído

Materiales de partida: 6,7-difluoro-3-metilbenzo[d]isoxazol-5-carbaldehído (Intermedio 374) y (2*R*,6*R*)-2,6-dimetilmorfolina.

MS (ES) MH^+: 293 para $C_{15}H_{17}FN_2O_3$

^{1}H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1,3 (d, 6H), 2,6 (s, 3H), 2,9-3,1 (m, 2H), 3,4 (m, 2H), 4,2 (m, 2H), 8,0 (s, 1H), 10,5 (s, 1H).

Intermedio 537

6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-3-(1-metil-1*H*-1,2,4-triazol-5-il)benzo[d]isoxazol-5-carbaldehído

Materiales de partida: 6,7-difluoro-3-(1-metil-1*H*-1,2,4-triazol-5-il)benzo[d]isoxazol-5-carbaldehído (**Intermedio 404**) y (2*R*,6*R*)-2,6-dimetilmorfolina.

MS (ES) MH^+: 360 para $C_{17}H_{18}FN_5O_3$

^{1}H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1,3 (d, 6H), 3,1 (dd, 2H), 3,5 (d, 2H), 4,3 (td, 2H), 4,4 (s, 3H), 8,1 (s, 1H), 8,7 (s, 1H), 10,5 (s, 1H).

Intermedio 538

6-((3S,5*R*)-3,5-dimetilpiperidin-1-il)-7-fluoro-3-metilbenzo[d]isoxazol-5-carbaldehído

Materiales de partida: 6,7-difluoro-3-metilbenzo[d]isoxazol-5-carbaldehído (**Intermedio 374**) y (3S,5*R*)-3,5-dimetilpiperidina (sal de HCl).

MS (ES) MH^+: 291 para $C_{16}H_{19}FN_2O_2$

^{1}H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 0,7-0,9 (c, 1H), 0,94 (d, 6H), 1,9 (m, 4H), 2,6 (s, 3H), 2,8-3,0 (m, 2H), 3,2-3,3 (m, 2H), 7,9 (s, 1H), 10,3 (s, 1H).

Intermedio 539

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(1*H*-1,2,4-triazol-1-il)-1,2-benzoxazol-5-carbaldehído

A una solución de 3-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-1,2-benzoxazol-5-carbaldehído (**Intermedio 534,** 0,2 g, 0,68 mmol) en acetonitrilo se agregó DBU (0,19 mL, 1,28 mmol) y luego 1,2,4-triazol (0,053 g, 0,76 mmol) y la mezcla se agitó a 100 °C durante 12 horas. La mezcla de reacción se concentró, el residuo se purificó mediante cromatografía en columna de gel de sílice utilizando EtOAc en éter de pet. para proporcionar el producto del título.

Rendimiento: 35 mg (16 %).

MS (ES) MH^+: 346 para $C_{16}H_{16}FN_5O_3$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 1,0 (d, 6H), 3,0 (t, 2H), 3,3 (m, 2H), 3,8 (m, 2H), 8,4 (s, 1H), 8,6 (s, 1H), 9,6 (s, 1H), 10,2 (s,1H).

Los **Intermedios 540** a **552** se prepararon a partir del material de partida indicado, DBU y 3-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-1,2-benzoxazol-5-carbaldehído (**Intermedio 534**) utilizando un método similar al descrito para la síntesis del **Intermedio 539:**

Intermedio 540

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(3-metil-1*H*-1,2,4-triazol-1-il)-1,2-benzoxazol-5-carbaldehído

Material de partida: 3-metil-1,2,4-triazol.

MS (ES) MH^+: 360 para $C_{17}H_{18}FN_5O_3$

Intermedio 541

1-{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-5-formil-1,2-benzoxazol-3-il}-1*H*-1,2,4-triazol-3-carbonitrilo

Material de partida: 3-ciano-1,2,4-triazol.

MS (ES) MH^+: 371 para $C_{17}H_{15}FN_6O_3$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 1,0 (d, 6H), 3,0 (m, 2H), 3,3 (m, 2H), 3,8 (m, 2H), 8,3 (s, 1H), 10,0 (s, 1H), 10,2 (s, 1H).

Intermedio 542 e **Intermedio 543**

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(1*H*-1,2,3-triazol-1-il)-1,2-benzoxazol-5-carbaldehído (**Intermedio 542**) y 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(1*H*-1,2,3-triazol-2-il)-1,2-benzoxazol-5-carbaldehído (**Intermedio 543**)

Material de partida: 1,2,3-triazol.

MS (ES) MH^+: 346 para $C_{16}H_{16}FN_5O_3$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 1,1 (d, 6H), 3,0 (m, 2H), 3,3 (m, 2H), 3,8 (m, 2H), 8,2 y 9,1 (2s, total de 1H), 8,4 (2s, total de 1H), 8,5 (s, 1H), 10,3 (s, 1H).

Intermedio 544

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(1*H*-imidazol-1-il)-1,2-benzoxazol-5-carbaldehído

Material de partida: imidazol.

MS (ES) MH^+: 345,2 para $C_{17}H_{17}FN_4O_3$

Intermedio 545

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[4-(trifluorometil)-1*H*-imidazol-1-il]-1,2-benzoxazol-5-carbaldehído

Material de partida: 4-(triflurometil)imidazol.

MS (ES) MH^+: 359 para $C_{18}H_{19}FN_4O_3$

Intermedio 546

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(4-metil-1*H*-pirazol-1-il)-1,2-benzoxazol-5-carbaldehído

Material de partida: 4-metilpirazol.

MS (ES) MH^+: 413,2 para $C_{18}H_{16}F_4N_4O_3$

Intermedio 547

3-(4-cloro-1*H*-pirazol-1-il)-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-1,2-benzoxazol-5-carbaldehído

Material de partida: 4-cloropirazol.

MS (ES) MH^+: 379 para $C_{17}H_{16}ClFN_4O_3$

Intermedio 548

3-amino-1-{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-5-formil-1,2-benzoxazol-3-il}-1*H*-pirazol-4-carbonitrilo

Material de partida: 3-amino-1*H*-pirazol-4-carbonitrilo.

MS (ES) MH^+: 385 para $C_{18}H_{17}FN_6O_3$

Intermedio 549

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[4-(pirimidin-4-il)-1*H*-pirazol-1-il]-1,2-benzoxazol-5-carbaldehído

Material de partida: 4-(1*H*-pirazol-4-il)pirimidina.

MS (ES) MH^+: 423 para $C_{21}H_{19}FN_6O_3$

Intermedio 550

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[4-(pirazin-2-il)-1*H*-pirazol-1-il]-1,2-benzoxazol-5-carbaldehído

Material de partida: 2-(1*H*-pirazol-4-il)pirazina.

MS (ES) MH^+: 423 para $C_{21}H_{19}FN_6O_3$

Intermedio 551

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(4-yodo-1*H*-pirazol-1-il)-1,2-benzoxazol-5-carbaldehído

Material de partida: 4-yodopirazina.

MS (ES) MH^+: 470 para $C_{17}H_{16}FIN_4O_3$

Intermedio 552

1-{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-5-formil-1,2-benzoxazol-3-il}-1*H*-pirazol-4-carboxilato de etilo

Material de partida: pirazol-4-carboxilato de etilo.

MS (ES) MH^+: 416 para $C_{20}H_{21}FN_4O_5$

Intermedio 553

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(metilsulfanil)-1,2-benzoxazol-5-carbaldehído

A una solución helada de 3-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-1,2-benzoxazol-5-carbaldehído (**Intermedio 534,** 0,3 g, 0,916 mmol) en dioxano se agregó tiometóxido de sodio (solución ac. al 21%, 0,134 mL, 1,923 mmol) y se agitó a temperatura ambiente durante 12 horas. La mezcla de reacción se diluyó con agua y se extrajo con EtOAc (50 mL). La fase orgánica se lavó con salmuera (2x 10 mL), se secó con sulfato de sodio anhidro, se filtró y se concentró para proporcionar el producto del título como un sólido blanco. Rendimiento: 280 mg (90%).

MS (ES) MH^+: 325 para $C_{15}H_{17}FN_2O_3S$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 1,1 (d, 6H), 2,7 (s, 3H), 3,0 (m, 2H), 3,2 (m, 2H), 3,8 (m, 2H), 7,9 (s, 1H), 10,2 (s,1H).

Intermedio 554

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(3,5-dimetil-1*H*-pirazol-1-il)-7-fluoro-1,2-benzoxazol-5-carbaldehído

A una solución agitada y desgasificada de 3-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-1,2-benzoxazol-5-carbaldehído (**Intermedio 534,** 0,15 g, 0,48 mmol) en tolueno se agregó K_3PO_4 (0,51 g, 2,40 mmol), 3,5-dimetil-1*H*-pirazol (92 mg, 0,96 mmol), 2-diciclohexilfosfino-2',6'-dimetoxibifenilo (S-phos) (4 mg, 0,009 mmol) y tris(dibencilidenoacetona)dipaladio(0) (8 mg, 0,009 mmol) secuencialmente y la mezcla de reacción se calentó hasta alcanzar 150 °C durante 2 h en un reactor de microondas. La mezcla de reacción se diluyó con EtOAc (15 mL). La capa orgánica se lavó sucesivamente con agua (2x10 mL), salmuera (2x10 mL), se secó con Na_2SO_4 anhidro y, después de la filtración, se concentró. El residuo se purificó en columna de gel de sílice utilizando un gradiente de acetato de etilo en éter de pet. para proporcionar el producto compuesto del título como un sólido. Rendimiento: 100 mg (56 %).

MS (ES) MH^+: 373,5 para $C_{19}H_{21}FN_4O_3$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 1,1 (d, 6H), 2,3 (s, 3H), 2,6 (s, 3H), 3,0 (t, 2H), 3,3 (m, 2H), 3,8 (m, 2H), 6,3 (s, 1H), 8,5 (s, 1H), 10,25 (s,1H).

Intermedio 555

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(1*H*-pirazol-4-il)-1,2-benzoxazol-5-carbaldehído

Se hicieron reaccionar 1*H*-pirazol-4-boronato de pinacol, 3-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-1,2-benzoxazol-5-carbaldehído (**Intermedio 534**), 2-diciclohexilfosfino-2',6'-dimetoxibifenilo (S-phos) y tris(dibencilidenoacetona)dipaladio(0) utilizando un método similar al descrito para la síntesis del **Intermedio 554.**

MS (ES) MH^+: 345 para $C_{17}H_{17}FN_4O_3$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 1,25 (d, 6H), 3,2 (m, 4H), 3,9 (m, 2H), 6,6 (m, 1H), 7,9 (s, 1H), 8,3 (s, 1H), 8,7 (s, 1H), 10,35 (s,1H).

Intermedio 556

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-hidroxi-1,2-bencisoxazol-5-carbaldehído

A una solución agitada de 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-5-formil-2,3-dihidro-1,2-bencisoxazol-3-il carbonato de *terc*-butilo (**Intermedio 533,** 0,5 g, 1,2 mmol) en metanol (5 mL) se agregaron 5 mL de HCl acuoso al 5% antes de calentar a 75 °C durante 2 horas. La mezcla de reacción se detuvo con solución acuosa de bicarbonato de sodio al 10% y se extrajo con EtOAc. La capa orgánica se lavó con agua, se secó (sulfato de sodio) y se concentró. El residuo se purificó en una columna instantánea de gel de sílice (elución con 50-70% de EtOAc en hexanos) para proporcionar el producto. Rendimiento: 0,4 g (100 %).

MS (ES) MH^+: 295 para $C_{14}H_{15}FN_2O_4$

^{1}H RMN (400MHz, DMSO-d_6) δ: 1,0 (d, 6H), 2,9 (t, 2H), 3,2 (d, 2H), 3,8 (m, 2H), 7,9 (s, 1H), 10,2 (s, 1H).

Intermedio 557

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-metoxi-1,2-bencisoxazol-5-carbaldehído

A una solución de 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-hidroxi-1,2-bencisoxazol-5-carbaldehído (**Intermedio 556,** 0,15 g, 0,5 mmol) en acetonitrilo se agregó K_2CO_3 (0,08 g, 0,6 mmol) y luego MeI (0,07 mL, 0,5 mmol) y la mezcla de reacción se agitó a 60 °C durante 2

horas. La mezcla de reacción se concentró, se lavó con agua y se extrajo con EtOAc (2 x 10 mL). La capa orgánica se secó con Na_2SO_4, se filtró y se concentró para proporcionar el producto del título, junto con un producto secundario, 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-2-metil-3-oxo-2,3-dihidro-1,2-benzoxazol-5-carbaldehído. La mezcla se utilizó en la siguiente etapa sin purificación adicional.

Rendimiento: 120 mg (76 %)

MS (ES) MH^+: 309,2 para $C_{15}H_{17}FN_2O_4$

Intermedio 558

3-(benciloxi)-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-1,2-bencisoxazol-5-carbaldehído

Se hicieron reaccionar bromuro de bencilo y 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-hidroxi-1,2-bencisoxazol-5-carbaldehído (**Intermedio 556**) utilizando un método similar al descrito para la síntesis del **Intermedio 557**, para proporcionar el producto del título, junto con un producto secundario, 2-bencil-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-oxo-2,3-dihidro-1,2-benzoxazol-5-carbaldehído. La mezcla se utilizó en la siguiente etapa sin purificación adicional.

MS (ES) MH^+: 385 para $C_{21}H_{21}FN_2O_4$

Intermedio 559

3-(4-acetilpiperazin-1-il)-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-2,3-dihidro-1,2-bencisoxazol-5-carbaldehído

A una solución de 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-hidroxi-1,2-bencisoxazol-5-carbaldehído (**Intermedio 556,** 0,15 g, 0,5 mmol) en acetonitrilo se agregó BOP (0,275 g, 0,66 mmol) y luego DBU (0,23 g, 1,53 mmol) y la mezcla se agitó durante 10 minutos a temperatura ambiente. A esta mezcla se agregó la *N*-acetil-piperizina (0,09 g, 0,71 mmol) y la mezcla se agitó durante 12 h a temperatura ambiente. La mezcla de reacción se concentró, se diluyó con agua y se extrajo con EtOAc (2 x 10 mL). La capa orgánica se secó con Na_2SO_4, se filtró y se concentró. De esta forma el residuo se purificó mediante cromatografía en columna de gel de sílice utilizando EtOAc en éter de pet. para proporcionar el producto.

Rendimiento: 25 mg (12 %);

MS (ES) MH^+: 405 para $C_{20}H_{25}FN_4O_4$

Los **Intermedios 560** a **573** se prepararon a partir del material de partida indicado y 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-hidroxi-1,2-bencisoxazol-5-carbaldehído (**Intermedio 556**) utilizando un método similar al descrito para la síntesis del **Intermedio 559**:

Intermedio 560

4-{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-5-formil-1,2-bencisoxazol-3-il}piperazin-1-carboxilato de *terc*-butilo

Material de partida: 1-piperazinocarboxilato de *terc*-butilo.

MS (ES) MH^+: 463 para $C_{23}H_{31}FN_4O_5$

Intermedio 561

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(piperidin-1-il)-1,2-bencisoxazol-5-carbaldehído

Material de partida: piperidina.

MS (ES) MH^+: 362 para $C_{19}H_{24}FN_3O_3$

Intermedio 562

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(morfolin-4-il)-1,2-bencisoxazol-5-carbaldehído

Material de partida: morfolina.

MS (ES) MH^+: 364 para $C_{18}H_{22}FN_3O_4$

Intermedio 563

3-(dietilamino)-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-1,2-bencisoxazol-5-carbaldehído

Material de partida: *N*,*N*-dietilamina.

MS (ES) MH^+: 350 para $C_{18}H_{24}FN_3O_3$

Intermedio 564

3-(dimetilamino)-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-1,2-bencisoxazol-5-carbaldehído

Material de partida: *N*,*N*-dimetilamina.

MS (ES) MH^+: 322,2 para $C_{16}H_{20}FN_3O_3$

Intermedio 565

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(pirrolidin-1-il)-1,2-bencisoxazol-5-carbaldehído

Material de partida: pirrolidina.

MS (ES) MH^+: 348 para $C_{18}H_{22}FN_3O_3$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 1,0 (d, 6H), 2,0 (t, 4H), 2,9 (m, 2H), 3,2 (d, 2H), 3,6 (t, 4H), 3,8 (m, 2H), 8,0 (s, 1H), 10,2 (s,1H).

Intermedio 566

3-(azepan-1-il)-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-1,2-bencisoxazol-5-carbaldehído

Material de partida: azepano.

MS (ES) MH^+: 350,2 para $C_{20}H_{26}FN_3O_3$

Intermedio 567

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[5-metil-3-(trifluorometil)-1*H*-pirazol-1-il]-1,2-bencisoxazol-5-carbaldehído

Material de partida: 3-metil-5-(trifluorometil)pirazol.

MS (ES) MH^+: 427 para $C_{19}H_{18}F_4N_4O_3$

Intermedio 568

N-[1-[6-[(2S,6*R*)-2,6-dimetilmorfolin-4-il]-7-fluoro-5-formil-1,2-benzoxazol-3-il]pirazol-3-il]acetamida

Material de partida: *N*-1*H*-pirazol-3-ilacetamida.

MS (ES) MH^+: 402 para $C_{19}H_{20}FN_5O_4$

Intermedio 569

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[3-(trifluorometil)-1*H*-pirazol-1-il]-1,2-bencisoxazol-5-carbaldehído

Material de partida: (3-(trifluorometil) pirazol.

MS (ES) MH^+: 413 para $C_{18}H_{16}F_4N_4O_3$

Intermedio 570

3-[3-(difluorometil)-1*H*-pirazol-1-il]-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-1,2-bencisoxazol-5-carbaldehído

Material de partida: 3-(difluorometil)-5-metilpirazol.

MS (ES) MH^+: 409 para $C_{19}H_{19}F_3N_4O_3$

Intermedio 571

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(propilamino)-1,2-benzoxazol-5-carbaldehído

Material de partida: *N*-propilamina.

MS (ES) MH^+: 336 para $C_{17}H_{22}FN_3O_3$

Intermedio 572

3-[bencil(metil)amino]-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-1,2-benzoxazol-5-carbaldehído

Material de partida: *N*-metil-1-bencilamina.

MS (ES) MH^+: 463 para $C_{22}H_{24}FN_3O_3$

Intermedio 573

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[metil(propil)amino]-1,2-benzoxazol-5-carbaldehído

Material de partida: *N*-metil-propano-1-amina.

MS (ES) MH^+: 362 para $C_{18}H_{24}FN_3O_3$

Intermedio 574

6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-3-(1*H*-1,2,4-triazol-1-il)benzo[d]isoxazol-5-carbaldehído

Se agregó hidruro de sodio (dispersión del 60%) (0,288 g, 7,19 mmol) a una solución de 1*H*-1,2,4-triazol (0,530 g, 7,67 mmol) y 3-cloro-6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-5-carbaldehído (**Intermedio 535,** 1,5 g, 4,80 mmol) en DMF (10 mL) y la mezcla se agitó a temperatura ambiente durante toda la noche. La mezcla se detuvo con NH_4Cl acuoso y se diluyó con agua antes de extraerse con CH_2Cl_2 5 veces. Los extractos combinados se

secaron ($MgSO_4$) y se concentraron para proporcionar un sólido que se recogió con CH_2Cl_2. Los sólidos insolubles se separaron por filtración y se enjuagaron con más CH_2Cl_2. Los sólidos se secaron al vacío y fueron consistentes con el producto deseado. El filtrado se concentró y se cromatografió en gel de sílice (100% de CH_2Cl_2 seguido por elución en gradiente hasta 50% de EtOAc en CH_2Cl_2) para proporcionar más producto deseado. Total de 866 mg.

MS (ES) MH^+: 345 para $C_{16}H_{16}FN_5O_3$

^{1}H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1,3 (d, 6H), 3,0-3,2 (m, 2H), 3,4-3,6 (m, 2H), 4,25 (m, 2H), 8,3 (s, 1H), 8,6 (d, 1H), 9,0 (s, 1H), 10,4 (s, 1H).

Intermedio 575

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-carbotioamida

A una solución agitada de (2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*] quinolin-5,5'-pirimidin]-8-carbonitrilo (**Ejemplo 183**, 210 mg, 0,51 mmol) en DMF se agregó sulfuro de amonio (0,35 mL, 1,02 mmol) y la mezcla se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se concentró para proporcionar el producto como un sólido amarillo claro.

Rendimiento: 215 mg (97%).

MS (ES) MH^+: 448 para $C_{19}H_{18}FN_5O_5S$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 2,9 (d, 1H), 3,1 (m, 1H), 3,7 (m, 1H), 3,8 (m, 2H), 4,0 (d, 1H), 4,1(d, 1H), 7,6 (s, 1H), 10,0 (s, 1H), 10,35 (s, 1H), 11,5 (s, 1H), 11,8 (s, 1H).

Cuando se evaluó en un ensayo *in vitro* basado en el ensayo de polarización de fluorescencia de la actividad de superenrollamiento de la ADN girasa descrito anteriormente, la actividad inhibitoria del ensayo de CI_{50} del superenrollamiento de la ADN girasa de *E. coli* del **Intermedio 575** se midió en 1,0 μM.

Intermedio 576

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-metil-1,2-benzotiazol-5-carbaldehído

A una solución enfriada con hielo de {6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-metil-1,2-benzotiazol-5-il}metanol (**Intermedio 157,** 0,18 g, 0,6 mmol) en una mezcla de DCM/CH_3CN (3 mL, 1:1 v/v) se agregó NMO (0,12 g, 0,7 mmol) y luego TPAP (0,04, 0,2 mmol) y la mezcla se agitó durante 2 h a temperatura ambiente. La mezcla de reacción se filtró a través de un lecho de sílice y se lavó con EtOAc. La fase orgánica se concentró a presión reducida para proporcionar el compuesto del título como un sólido cristalino amarillo. Rendimiento: 0,12 g (67%).

MS (ES) MH^+: 309 para $C_{15}H_{17}FN_2O_2S$

^1H RMN (400 MHz, Metanol-*d*-$_4$): δ 1,2 (d, 6H), 2,7 (s, 3H), 3,1 (m, 2H), 3,2 (m, 2H), 3,9 (m, 2H), 8,3 (s, 2H), 10,5 (s, 1H).

El **Intermedio 577** se preparó a partir del material de partida indicado utilizando un método similar al descrito para la síntesis del **Intermedio 576**:

Intermedio 577

6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(piridin-2-il)-1,2-benzotiazol-5-carbaldehído

Material de partida: {6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(piridin-2-il)-1,2-benzotiazol-5-il}metanol (**Intermedio 158**).

MS (ES) MH^+: 372 para $C_{19}H_{18}FN_3O_2S$

^1H RMN (400 MHz, $CDCl_3$) δ: 1,24 (d, 6H), 3,1 (d, 4H), 3,9 (m, 2H), 7,4 (m, 1H), 7,9 (t, 1H), 8,3 (d, 1H), 8,8 (d, 1H), 9,4 (s, 1H), 10,5 (s, 1H).

El **Intermedio 578** se preparó a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 62:**

Intermedio 578

{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(pirazin-2-il)metanol

Material de partida: (2*R*,6*S*)-4-[6-({[*terc*-butil(difenil)silil]oxi}metil)-2,3-difluorofenil]-2,6-dimetilmorfolina (**Intermedio 3**) y pirazina-2-carboxaldehído.

MS (ES) MH^+: 604,8 para $C_{34}H_{39}F_2N_3O_3Si$

El **Intermedio 579** se preparó a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 20:**

Intermedio 579

{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(pirazin-2-il)metanona

Material de partida: {5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(pirazin-2-il)metanol (**Intermedio 578**).

MS (ES) MH^+: 602,8 para $C_{34}H_{37}F_2N_3O_3Si$

El **Intermedio 580** se preparó a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 23:**

Intermedio 580

{4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluoro-5-(hidroximetil)fenil}(pirazin-2-il)metanona

Material de partida: {5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(pirazin-2-il)metanona (**Intermedio 579**).

MS (ES) MH^+: 364,4 para $C_{18}H_{19}F_2N_3O_3$

El **Intermedio 581** se preparó a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 26:**

Intermedio 581

2-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3,4-difluoro-5-(pirazin-2-ilcarbonil)benzaldehído

Material de partida: {4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluoro-5-(hidroximetil)fenil}(pirazin-2-il)metanona (**Intermedio 580**).

MS (ES) MH^+: 362,4 para $C_{18}H_{17}F_2N_3O_3$

El **Intermedio 582** se preparó a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 12:**

Intermedio 582

(2*R*,4*S*,4a*S*)-rel-9,10-difluoro-2,4-dimetil-8-(pirazin-2-ilcarbonil)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

Material de partida: 2-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3,4-difluoro-5-(pirazin-2-ilcarbonil)benzaldehído (**Intermedio 581**).

MS (ES) MH^+: 472,4 para $C_{22}H_{19}F_2N_5O_5$

El **Intermedio 583** se preparó a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 29:**

Intermedio 583

(2*R*,4*S*,4a*S*)-rel-9,10-difluoro-8-[(hidroxiimino)(pirazin-2-il)metil]-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

Material de partida: (2*R*,4*S*,4a*S*)-rel-9,10-difluoro-2,4-dimetil-8-(pirazin-2-ilcarbonil)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona (**Intermedio 582**).

MS (ES) MH^+: 487,4 para $C_{22}H_{20}F_2N_6O_5$

El **Intermedio 584** se preparó a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 62:**

Intermedio 584

{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(pirimidin-2-il)metanona

Materiales de partida: (2*R*,6*S*)-4-[6-({[*terc*-butil(difenil)silil]oxi}metil)-2,3-difluorofenil]-2,6-dimetilmorfolina (**Intermedio 3**) y *N*-metoxi-*N*-metilpirimidina-2-carboxamida (preparada de acuerdo con el procedimiento mostrado en la publicación PCT N.° WO03/059911).

MS (ES) MH^+: 603 para $C_{34}H_{37}F_2N_3O_3Si$

El **Intermedio 585** se preparó a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 336:**

Intermedio 585

{5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-fluoro-2-[(propan-2-ilidenoamino)oxi]fenil}(pirimidin-2-il)metanona

Material de partida: {5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-2,3-difluorofenil}(pirimidin-2-il)metanona (**Intermedio 584**).

MS (ES) MH^+: 655,8 para $C_{37}H_{43}FN_4O_4Si$

El **Intermedio 586** se preparó a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 33:**

Intermedio 586

{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(pirimidin-2-il)-1,2-benzoxazol-5-il}metanol

Material de partida: {5-({[*terc*-butil(difenil)silil]oxi}metil)-4-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-fluoro-2-[(propan-2-ilidenoamino)oxi]fenil}(pirimidin-2-il)metanona (**Intermedio 585**).

MS (ES) MH^+: 359,4 para $C_{18}H_{19}FN_4O_3$

El **Intermedio 587** se preparó a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Intermedio 27:**

Intermedio 587

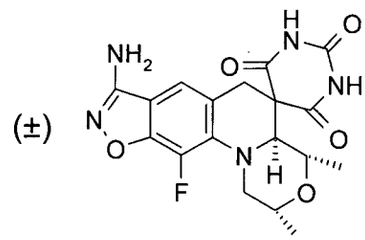
6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(pirimidin-2-il)-1,2-benzoxazol-5-carbaldehído

Material de partida: {6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(pirimidin-2-il)-1,2-benzoxazol-5-il}metanol (**Intermedio 586**).

MS (ES) MH^+: 357,4 para $C_{18}H_{17}FN_4O_3$

Ejemplo 1

(2*R*,4*S*,4a*S*)-rel-8-amino-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona



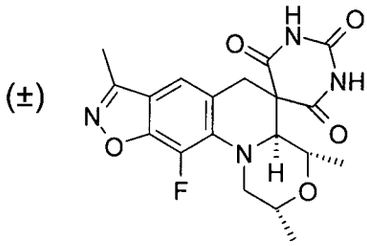
A una solución de 3-amino-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-1,2-bencisoxazol-5-carbaldehído (**Intermedio 8**, 100 mg, 0,34 mmol) en IPA se agregó ácido barbitúrico (48 mg, 0,34 mmol) y la mezcla se calentó a 85 °C durante 12 horas. Los disolventes se evaporaron y el residuo se purificó en alúmina neutra utilizando un gradiente de metanol en CH_2Cl_2 para proporcionar el compuesto del título como una mezcla racémica en forma de un sólido amarillo claro. Rendimiento: 18 mg (13 %).

MS (ES) $(M-H)^-$: 402,6 para $C_{18}H_{18}FN_5O_5$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 2,9 (d, 1H), 3,0 (t, 1H), 3,4 (d, 1H), 3,6 (t, 1H), 3,75 (d, 1H), 3,9 (d, 1H), 4,0 (d, 1H), 6,2 (s a, 2H), 7,1 (s, 1H), 11,4 (s, 1H), 11,8 (s, 1H).

Ejemplo 2

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4,8-trimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona



A una solución de (2*R*,4*S*,4a*S*)-rel-9,10-difluoro-8-[(1*E*)-*N*-hidroxietanimidoil]-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona (**Intermedio 16,** 250 mg, 0,63 mmol) en DMSO, se agregó K-O-*t*-Bu (47 mg, 0,636 mmol) y la mezcla se calentó hasta alcanzar 120 °C durante 12 horas. Después de enfriar hasta alcanzar temperatura ambiente y eliminar el disolvente, el residuo se purificó utilizando HPLC de fase normal (95:5: Hexano:IPA) para proporcionar el compuesto del título como una mezcla racémica en forma de un sólido amarillo claro. Rendimiento: 50 mg (20%).

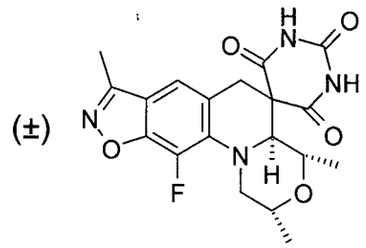
MS (ES) MH^+: 403,2 para $C_{19}H_{19}FN_4O_5$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 2,4 (d, 3H), 2,5 (d, 1H), 2,9 (t, 1H), 3,5 (d, 1H), 3,6 (m, 1H), 3,8 (d, 1H), 3,9 (d, 1H), 4,0 (d, 1H), 7,2 (s, 1H), 11,4 (s, 1H), 11,8 (s, 1H).

El **Ejemplo 2** también se preparó utilizando la siguiente síntesis:

Ejemplo 2 (Preparación Alternativa)

(2*R*,4*S*,4a*S*) -rel-11-fluoro-2,4,8-trimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona



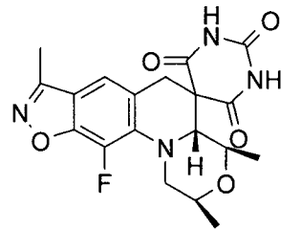
A una solución agitada de 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-metilbenzo[d]isoxazol-5-carbaldehído (**Intermedio 34,** 543 mg, 1,86 mmol) en isopropanol (50 mL) se agregó pirimidina-2,4,6(1*H*,3*H*,5*H*)-triona (238 mg, 1,86 mmol) y la mezcla de reacción se agitó durante 16 horas a 80 °C. El disolvente se eliminó y el residuo se lavó con isopropanol. El sólido se filtró, se lavó con isopropanol y se secó al vacío. El filtrado se concentró y purificó en gel de sílice (30-50% de EtOAc en hexanos). El producto obtenido de esta forma se combinó con el sólido filtrado en metanol y se concentró para proporcionar el compuesto del título (528 mg, 71%) como una mezcla racémica.

MS (ES): 403 (M+H) para $C_{19}H_{19}FN_4O_5$

^{1}H RMN (400 MHz, DMSO-d_6) d ppm 0,9 (d, 3H) 1,1 (d, 3H) 2,4 (s, 3H), 2,9 - 4,2 (m, 7H) 7,2 (s, 1H) 11,4 (s, 1H) 11,8 (s, 1H).

Los enantiómeros (2*S*,4*R*,4a*R*) y (2*R*,4*S*,4a*S*) del **Ejemplo 2** se separaron mediante Cromatografía de Fluidos Supercríticos utilizando una columna Chiralpak AD, 21 x 250 mm, 5 µ (elución con 20% de MeOH, 80% de CO_2 a 60 mL/min, 40 °C y 100 bar con detección a 220 nm), para proporcionar el **Ejemplo 2(a)** y el **Ejemplo 2(b)**:

Ejemplo 2(a) - Compuesto que eluyó en primer lugar (2*S*,4*R*,4a*R*)-11-fluoro-2,4,8-trimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona



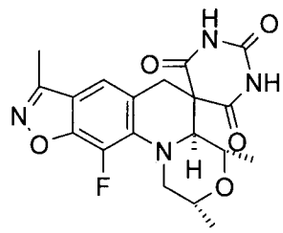
MS (ES): 403 (M+H) para $C_{19}H_{19}FN_4O_5$

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 0,9 (d, 3H) 1,1 (d, 3H) 2,4 (s, 3H) 2,9 - 4,2 (m, 7H) 7,2 (s, 1H) 11,6 (s a, 2H).

Rendimiento: (202 mg, 40%).

>98% ee mediante HPLC quiral; [α] = +296 (c = 0,1 en MeOH).

Ejemplo 2(b) - Compuesto que eluyó en segundo lugar (2*R*,4*S*,4a*S*)-11-fluoro-2,4,8-trimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona



MS (ES): 403 (M+H) para $C_{19}H_{19}FN_4O_5$

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 0,9 (d, 3H) 1,1 (d, 3H) 2,4 (s, 3H) 2,9 - 4,2 (m, 7 H) 7,2 (s, 1 H) 11,6 (s a, 2 H).

Rendimiento: (199 mg, 39%).

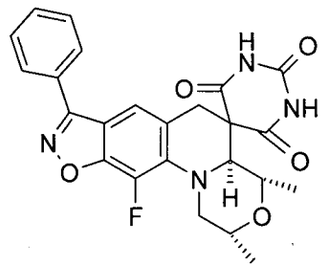
>98% ee mediante HPLC quiral; [α] = -291 (c = 0,1 en MeOH).

Ejemplo 3

103542-1P

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-fenil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±)



Se agregó Cs_2CO_3 (130 mg, 0,0004 mmol) a una solución de (2*R*,4*S*,4a*S*)-rel-9,10-difluoro-8-[(*E*)-(hidroxiimino)(fenil)metil]-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona (**Intermedio 29,** 100 mg, 0,0002 mmol) en DMF (1,5 mL) y la mezcla se calentó hasta alcanzar 100 °C durante 14 h. La mezcla de reacción se enfrió hasta alcanzar la temperatura ambiente y se filtró a través de un lecho de celite. El disolvente se eliminó y el residuo se sometió a purificación mediante HPLC prep de fase inversa (acetato de amonio 10 mM en agua, CH_3CN) para proporcionar el compuesto del título como una mezcla racémica. Rendimiento: 9,97 g (9 %).

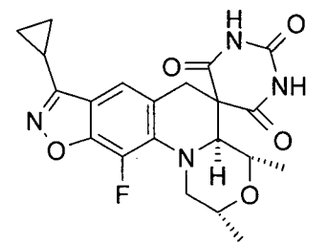
MS (ES) MH^+: 465,2 para $C_{24}H_{21}FN_4O_5$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 3,0 (d, 1H), 3,1 (t, 1H), 3,6 (d, 1H), 3,7 (m, 1H), 3,75 (m, 1H), 3,9 (d, 1H), 4,1 (d, 1H), 7,6 (m, 4H), 7,9 (s, 2H), 11,5 (s a, 2H).

Los **Ejemplos 4** y **5** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Ejemplo 3**. Cada uno se obtuvo como una mezcla racémica.

Ejemplo 4

(2*R*,4*S*,4a*S*)-rel-8-ciclopropil-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±) 

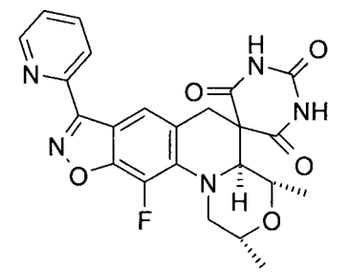
Material de partida: (2*R*,4*S*,4a*S*)-rel-8-[(*E*)-ciclopropil(hidroxiimino)metil]-9,10-difluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona (**Intermedio 31**)

MS (ES) MH^+: 429,1 para $C_{21}H_{21}FN_4O_5$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,0 (m, 4H), 1,1 (d, 3H), 2,2 (m, 1H), 2,9 (d, 1H), 3,1 (t, 1H), 3,6 (d, 1H), 3,7 (m, 1H), 3,75 (m, 1H), 3,9 (d, 1H), 4,1 (d, 1H), 7,2 (s, 1H), 11,0 (bs, 2H).

Ejemplo 5

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-piridin-2-il-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±) 

Material de partida: (2*R*,4*S*,4a*S*)-rel-9,10-difluoro-8-[(Z)-(hidroxiimino)(piridin-2-il)metil]-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona (**Intermedio 30**)

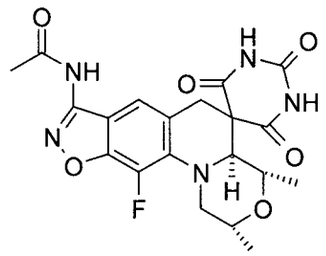
MS (ES) MH^+: 466,2 para $C_{23}H_{20}FN_5O_5$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 2,9 (d, 1H), 3,1 (t, 1H), 3,6 (m, 1H), 3,7 (m, 1H), 3,75 (m, 1H), 4,0 (d, 1H), 4,1 (d, 1H), 7,6 (m, 1H), 7,8 (s, 1H), 8,0 (t, 1H), 8,1 (d, 1H), 8,8 (d, 1H), 11,4 (s a, 2H).

Ejemplo 6

103542-1P

N-[(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-il]acetamida

(±) 

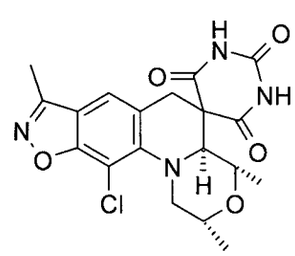
Se agregaron secuencialmente piridina (0,01 mL, 0,2 mmol) y anhídrido acético (0,10 mL, 0,14 mmol) a una solución de (2*R*,4S,4a*S*)-rel-8-amino-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6' (1'*H*, 3'*H*)-triona (**Ejemplo 1,** 54 mg, 0,13 mmol) en dicloruro de etileno y la mezcla se agitó a 130 °C durante 12 horas. Después de enfriar hasta alcanzar temperatura ambiente, el disolvente se eliminó y el residuo se purificó en una columna instantánea de gel de sílice utilizando un gradiente de metanol en cloroformo para proporcionar el compuesto del título como una mezcla racémica en forma de un sólido amarillo. Rendimiento: 7,5 mg (13 %).

MS (ES) MH^+: 446,3 para $C_{20}H_{20}FN_5O_6$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 2,1 (s, 3H), 2,9 (d, 1H), 3,0 (t, 1H), 3,4 (d, 1H), 3,6 (t, 1H), 3,75 (d, 1H), 3,9 (d, 1H), 4,0 (d, 1H), 7,4 (s, 1H), 11,0 (s, 1H), 11,4 (s, 1H), 11,8 (s, 1H).

Ejemplo 7

(2*R*,4*S*,4a*S*)-rel-11-cloro-2,4,8-trimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±) 

A una solución de 7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-metil-1,2-benzoxazol-5-carbaldehído (**Intermedio 375,** 35 mg, 0,119 mmol) en IPA se agregó ácido barbitúrico (16 mg,

0,113 mmol) y la mezcla se calentó a 85 °C durante 16 horas. Los disolventes se evaporaron y el residuo obtenido de esta forma se purificó en columna de sílice utilizando un gradiente de metanol en cloroformo para proporcionar el producto como un sólido. Rendimiento: 10 mg (25%).

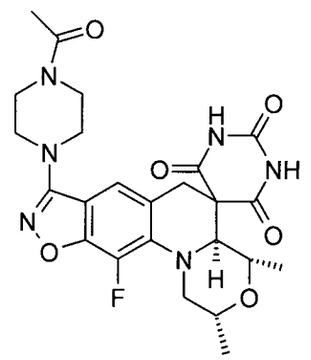
MS (ES) MH^+: 419 para $C_{19}H_{19}ClN_4O_5$

^{1}H RMN (400 MHz, DMSO-D6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 2,4 (s, 3H), 3,0 (m, 2H), 3,5 (d, 1H), 3,6 (m, 1H), 3,9 (m, 2H), 4,5 (d, 1H), 7,3 (s, 1H), 11,45 (s, 1H), 11,85 (s,1H).

Ejemplo 8

(2*R*,4*S*,4a*S*)-rel-8-(4-acetilpiperazin-1-il)-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±)



A una solución agitada de 3-(4-acetilpiperazin-1-il)-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-2,3-dihidro-1,2-bencisoxazol-5-carbaldehído (**Intermedio 559,** 25 mg, 0,062 mmol) en IPA seco (1 mL) se agregó ácido barbitúrico (8 mg, 0,062 mmol) y la solución se calentó a aproximadamente 80 °C durante 12 h. Los disolventes se evaporaron y el residuo se purificó en una columna de gel de sílice para proporcionar el producto como un sólido blanco. Rendimiento: 17 mg (55%).

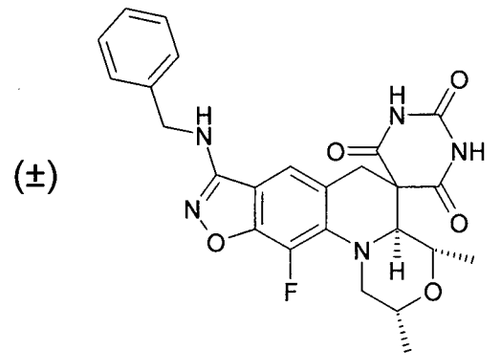
MS (ES) MH^+: 515 para $C_{24}H_{27}FN_6O_6$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,2 (d, 3H), 2,0 (s, 3H), 2,95 (d, 1H), 3,05 (t, 1H), 3,4–3,5 (m, 5H), 3,6 (d, 4H), 3,7 (m, 1H), 3,8 (m, 1H), 3,9 (d, 1H), 4,0 (d, 1H), 7,4 (s, 1H), 11,5 (s, 1H), 11,85 (s, 1H).

Los **Ejemplos 9** a **53** se prepararon a partir de los materiales de partida y pirimidin-2,4,6(1*H*,3*H*,5*H*)-triona utilizando un método similar al descrito para la síntesis del **Ejemplo 8**:

Ejemplo 9

(2*R*,4*S*,4a*S*)-rel-8-(bencilamino)-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona



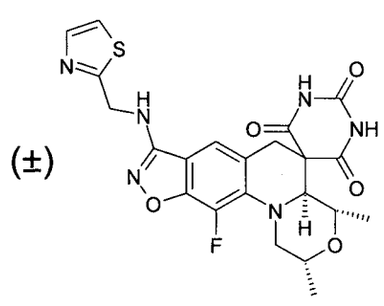
Material de partida: 3-(bencilamino)-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-1,2-benzoxazol-5-carbaldehído (**Intermedio 515**)

MS (ES) MH^+: 495 para $C_{25}H_{24}FN_5O_5$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 2,9 (d, 1H), 3,0 (m, 1H), 3,4 (d, 1H), 3,6 (t, 1H), 3,8 (d, 1H), 3,9 (d, 1H), 4,0 (d, 1H), 4,4 (d, 2H), 7,1 (s, 1H), 7,35 (c, 5H), 11,45 (s, 1H), 11,8 (s,1H).

Ejemplo 10

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimetil-8-[(1,3-tiazol-2-ilmetil)amino]-1,2,4,4a-tetrahidro-2'H,6*H*-espiro[1,4-oxazino[4,3-a][1,2]oxazolo[4,5-g]quinolin-5,5'-pirimidin]-2',4',6'(1'H,3'H)-triona



Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[(1,3-tiazol-2-ilmetil)amino]-1,2-benzoxazol-5-carbaldehído (**Intermedio 516**)

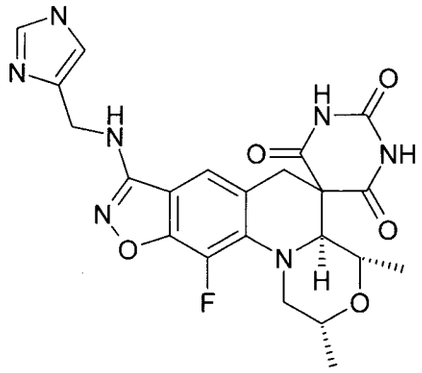
MS (ES) MH^+: 501 para $C_{22}H_{21}FN_6O_5S$

^{1}H RMN (400 MHz, DMSO) δ: 0,9 (d, 3H), 1,1 (d, 3H), 2,9 (d, 1H), 3,0 (t, 1H), 3,5 (d, 1H), 3,6 (m, 1H), 3,75 (m, 1H), 3,9 (d, 1H), 4,0 (d, 1H), 4,7 (d, 1H), 7,1 (s, 1H), 7,6 (d, 1H), 7,7 (d, 1H), 7,8 (t, 1H).

Ejemplo 11

(2*R*,4*S*,4a*S*)-rel-11-fluoro-8-[(1*H*-imidazol-4-ilmetil)amino]-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-g]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±)



Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[(1*H*-imidazol-4-ilmetil)amino]-1,2-benzoxazol-5-carbaldehído (**Intermedio 517**)

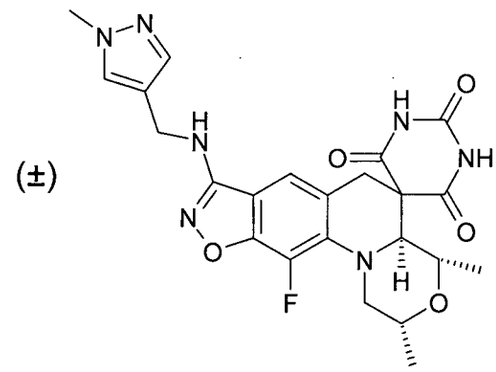
MS (ES) MH^+: 484 para $C_{22}H_{22}FN_7O_5$

^{1}H RMN (400 MHz, DMSO) δ: 0,9 (d, 3H), 1,1 (d, 3H), 2,9 (t, 1H), 3,0 (t, 1H), 3,4 (m, 1H), 3,6 (t, 1H), 3,8 (m, 1H), 3,9 (d, 1H), 4,0 (d, 1H), 4,2 (s a, 2H), 7,0 (m, 1H), 7,2 (s, 1H), 7,6 (ds, 1H), 11,5 (s a, 1H), 11,9 (s a, 1H).

Ejemplo 12

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimetil-8-{[(1-metil-1*H*-pirazol-4-il)metil]amino}-1,2,4,4a-tetrahidro-2'H,6*H*-espiro[1,4-oxazino[4,3-a][1,2]oxazolo[4,5-g]quinolin-5,5'-pirimidin]-2',4',6'(1'H,3'H)-triona

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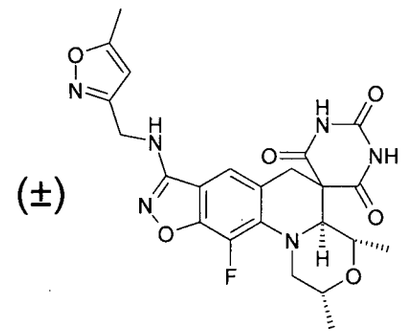
Material de partida: (6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-{[(1-metil-1*H*-pirazol-4-il)metil]amino}-1,2-benzoxazol-5-carbaldehído (**Intermedio 518**)

MS (ES) MH^+: 498 para $C_{23}H_{24}FN_7O_5$

^1H RMN (400 MHz, DMSO) δ: 0,9 (d, 3H), 1,1 (d, 3H), 2,9 (d, 1H), 3,05 (s, 1H), 3,4 (m, 1H), 3,6 (m, 1H), 3,7 (s, 3H), 3,9 (d, 1H), 4,0 (d, 1H), 4,2 (d, 1H), 7,0 (t, 1H), 7,1 (s, 1H), 7,4 (s, 1H), 7,6 (s, 1H), 11,4 (s, 1H), 11,8 (s, 1H).

Ejemplo 13

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-{[(5-metil-1,2-oxazol-3-il)metil]amino}-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona



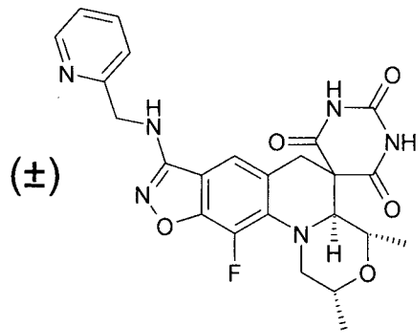
Material de partida: (6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-{[(5-metil-1,2-oxazol-3-il)metil]amino}-1,2-benzoxazol-5-carbaldehído (**Intermedio 519**)

MS (ES) MH^+: 499 para $C_{23}H_{23}FN_6O_6$

^1H RMN (400 MHz, DMSO) δ: 0,9 (d, 3H), 1,1 (d, 3H), 2,3 (s, 3H), 2,9 (d, 1H), 3,05 (t, 1H), 3,5 (d, 1H), 3,6 (m, 1H), 3,75 (t, 1H), 3,9 (d, 1H), 4,0 (d, 1H), 4,4 (d, 2H), 6,2 (s, 1H), 7,1 (s, 1H), 7,4 (t, 1H), 11,4 (s, 1H), 11,8 (s, 1H).

Ejemplo 14

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimetil-8-[(piridin-2-ilmetil)amino]-1,2,4,4a-tetrahidro-2'H,6*H*-espiro[1,4-oxazino[4,3-a][1,2]oxazolo[4,5-g]quinolin-5,5'-pirimidin]-2',4',6'(1'H,3'H)-triona



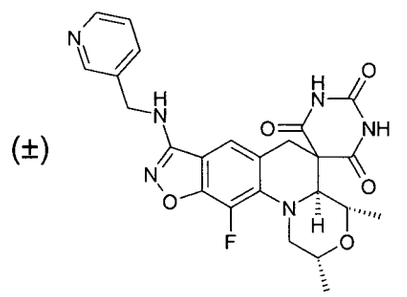
Material de partida: {6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[(piridin-2-ilmetil)amino]-1,2-benzoxazol-5-carbaldehído (**Intermedio 520**)

MS (ES) MH^+: 495 para $C_{24}H_{23}FN_6O_5$

^{1}H RMN (400 MHz, DMSO) δ: 0,9 (d, 3H), 1,1 (d, 3H), 2,9 (d, 1H), 3,05 (t, 1H), 3,5 (d, 1H), 3,6 (t, 1H), 3,8 (m, 1H), 3,9 (d, 1H), 4,0 (d, 1H), 4,5 (d, 2H), 7,2 (s, 1H), 7,3 (t, 1H), 7,4 (d, 1H), 7,5 (t, 1H), 7,75 (t, 1H), 8,5 (d, 1H), 11,5 (s, 1H), 11,8 (s, 1H).

Ejemplo 15

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimetil-8-[(piridin-3-ilmetil)amino]-1,2,4,4a-tetrahidro-2'H,6*H*-espiro[1,4-oxazino[4,3-a][1,2]oxazolo[4,5-g]quinolin-5,5'-pirimidin]-2',4',6'(1'H,3'H)-triona



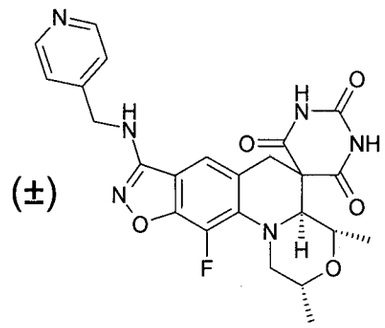
Material de partida: {6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[(piridin-3-ilmetil)amino]-1,2-benzoxazol-5-carbaldehído (**Intermedio 521**)

MS (ES) MH^+: 495 para $C_{24}H_{23}FN_6O_5$

^{1}H RMN (400 MHz, DMSO) δ: 0,9 (d, 3H), 1,1 (d, 3H), 2,9 (d, 1H), 3,05 (t, 1H), 3,5 (d, 1H), 3,6 (t, 1H), 3,7 (m, 1H), 3,9 (d, 1H), 4,0 (d, 1H), 4,4 (d, 2H), 7,1 (s, 1H), 7,35 (m, 1H), 7,4 (t, 1H), 7,8 (d, 1H), 8,45 (d, 1H), 8,6 (s, 1H), 11,4 (s, 1H), 11,8 (s, 1H).

Ejemplo 16

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-[(piridin-4-ilmetil)amino]-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona



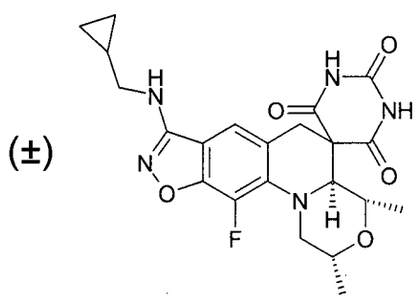
Material de partida: {6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[(piridin-4-ilmetil)amino]-1,2-benzoxazol-5-carbaldehído (**Intermedio 522**)

MS (ES) MH^+: 495 para $C_{24}H_{23}FN_6O_5$

^{1}H RMN (400 MHz, DMSO) δ: 0,9 (d, 3H), 1,1 (d, 3H), 2,9 (d, 1H), 3,0 (t, 2H), 3,7 (m, 2H), 3,95 (d, 1H), 4,0 (d, 1H), 4,4 (d, 2H), 7,1 (s, 1H), 7,3 (d, 1H), 7,5 (t,1H), 8,5 (d, 1H).

Ejemplo 17

(2*R*,4*S*,4a*S*)-rel-8-[(ciclopropilmetil)amino]-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona



Material de partida: {3-[(ciclopropilmetil)amino]-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-1,2-benzoxazol-5-carbaldehído (**Intermedio 523**)

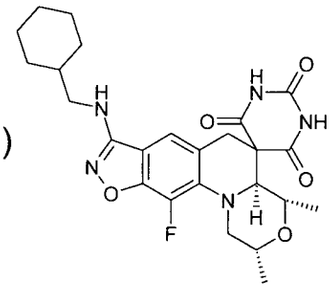
MS (ES) MH^+: 458 para $C_{22}H_{24}FN_5O_5$

^1H RMN (400 MHz, DMSO) δ: 0,2 (m, 2H), 0,5 (m, 2H), 0,9 (d, 3H), 1,1 (d, 3H), 2,9 (d, 1H), 3,0 (m, 3H), 3,4 (d, 1H), 3,6 (m, 1H), 3,8 (m, 1H), 3,9 (d, 1H), 4,0 (d, 1H), 6,9 (t, 1H), 7,15 (s, 1H).

Ejemplo 18

(2*R*,4*S*,4a*S*)-rel-8-[(ciclohexilmetil)amino]-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±)



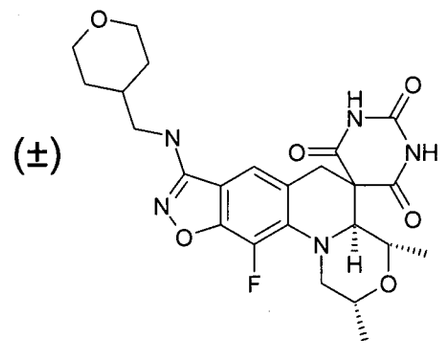
Material de partida: {3-[(ciclohexilmetil)amino]-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-1,2-benzoxazol-5-carbaldehído (**Intermedio 524**)

MS (ES) MH^+: 500 para $C_{25}H_{30}FN_5O_5$

^1H RMN (400 MHz, DMSO) δ: 0,9 (d, 3H), 0,95 (m, 2H), 1,1 (d, 3H), 1,2 (m, 3H), 1,6-1,8 (m, 6H), 2,9-3,0 (m, 4H), 3,5 (d, 1H), 3,65 (t, 1H), 3,8 (m, 1H), 3,9 (d, 1H), 4,0 (d, 2H), 6,8 (s, 1H), 7,1 (s, 1H), 11,4 (s, 1H), 11,8 (s, 1H).

Ejemplo 19

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-[(tetrahidro-2*H*-piran-4-ilmetil)amino]-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona



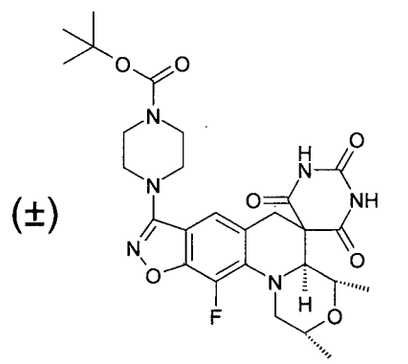
Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[(tetrahidro-2*H*-piran-4-ilmetil)amino]-1,2-benzoxazol-5-carbaldehído (**Intermedio 525**)

MS (ES) MH^+: 502,3 para $C_{24}H_{28}FN_5O_6$

^{1}H RMN (400 MHz, DMSO) δ: 0,9 (d, 3H), 1,1 (d, 3H), 1,2 (m, 3H), 1,6 (d, 2H), 1,9 (m, 1H), 2,9-3,0 (m, 4H), 3,5 (d, 1H), 3,65 (t, 1H), 3,8 (m, 1H), 3,9 (d, 1H), 4,0 (d, 2H), 6,8 (s, 1H), 7,1 (s, 1H), 11,4 (s, 1H), 11,8 (s, 1H).

Ejemplo 20

4-[(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-il]piperazina-1-carboxilato de *terc*-butilo



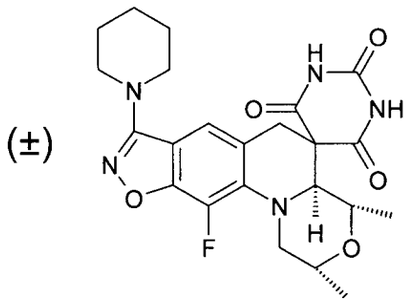
Material de partida: 4-{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-5-formil-1,2-bencisoxazol-3-il}piperazina-1-carboxilato de *terc*-butilo (**Intermedio 560**)

MS (ES) MH^+: 573 para $C_{27}H_{33}FN_6O_7$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 1,4 (s, 9H), 2,95 (d, 1H), 3,05 (t, 1H), 3,40 (m, 4H), 3,45 (m, 5H), 3,65 (m, 1H), 3,8 (m, 1H), 3,9 (d, 1H), 4,05 (d, 1H), 7,4 (s, 1H), 11,5 (s, 1H), 11,85 (s, 1H).

Ejemplo 21

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(piperazin-1-il)-1,2,4,4a-tetrahidro-2'H,6*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(1'H,3'H)-triona



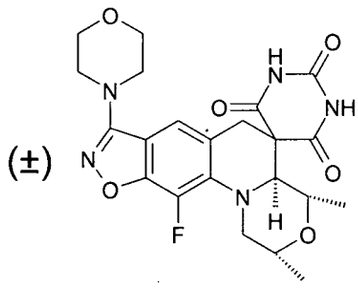
Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(piperidin-1-il)-1,2-bencisoxazol-5-carbaldehído (**Intermedio 561**)

MS (ES) MH^+: 472 para $C_{23}H_{26}FN_5O_5$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 1,6 (s a, 6H), 2,9 (d, 1H), 3,0 (t, 1H), 3,35 (s a, 4H), 3,5 (d, 1H), 3,7 (m, 1H), 3,8 (m, 1H), 3,9 (d, 1H), 4,05 (d, 1H), 7,1 (d, 1H).

Ejemplo 22

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(morfolin-4-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona



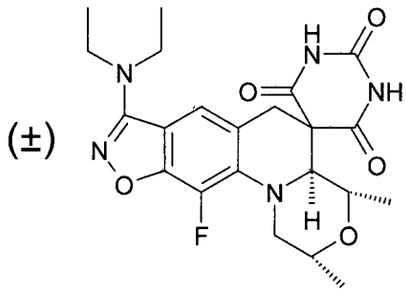
Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(morfolin-4-il)-1,2-bencisoxazol-5-carbaldehído (**Intermedio 562**)

MS (ES) MH^+: 474 para $C_{22}H_{24}FN_5O_6$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 2,9 (d, 1H), 3,1 (t, 1H), 3,4 (s a, 5H), 3,45 (d, 1H), 3,7 (m, 1H), 3,75 (s a, 4H), 3,9 (d, 1H), 4,1 (d, 1H), 7,4 (s, 1H), 11,5 (s, 1H), 11,9 (s, 1H).

Ejemplo 23

(2*R*,4*S*,4a*S*)-rel-8-(dietilamino)-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona



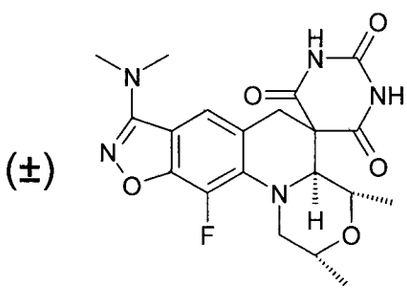
Material de partida: 3-(dietilamino)-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-1,2-bencisoxazol-5-carbaldehído (**Intermedio 563**)

MS (ES) MH^+: 460 para $C_{22}H_{26}FN_5O_5$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (m, 9H), 2,9 (d, 1H), 3,1 (t, 1H), 3,3-3,45 (m, 4H), 3,5 (d, 1H), 3,6 (d, 1H), 3,7 (m, 1H), 3,9 (d, 1H), 4,1 (d, 1H), 7,2 (s, 1H), 11,5 (s, 1H), 11,8 (s, 1H).

Ejemplo 24

(2*R*,4*S*,4a*S*)-rel-8-(dimetilamino)-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona



Material de partida: 3-(dimetilamino)-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-1,2-bencisoxazol-5-carbaldehído (**Intermedio 564**)

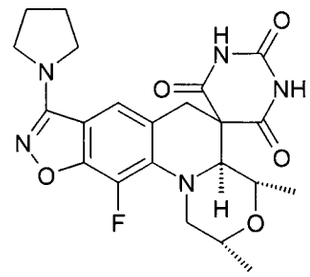
MS (ES) MH^+: 432 para $C_{20}H_{22}FN_5O_5$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 2,95 (d, 1H), 3,0 (s, 6H), 3,05 (s, 1H), 3,5 (d, 1H), 3,6 (d, 1H), 3,7 (m, 1H), 3,9 (d, 1H), 4,1 (d, 1H), 7,4 (s, 1H), 11,5 (s, 1H), 11,85 (s, 1H).

Ejemplo 25

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(pirrolidin-1-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±)



Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(pirrolidin-1-il)-1,2-bencisoxazol-5-carbaldehído (**Intermedio 565**)

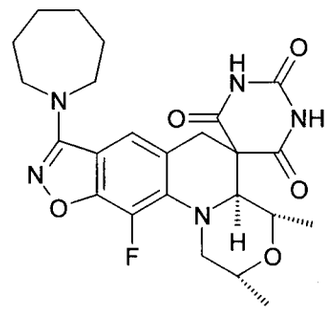
MS (ES) MH^+: 458 para $C_{22}H_{24}FN_5O_5$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 1,9 (t, 4H), 2,9 (d, 1H), 3,0 (t, 1H), 3,65 (m, 5H), 3,7 (d, 1H), 3,8 (m, 1H), 3,9 (d, 1H), 4,1 (d, 1H), 7,3 (s, 1H), 11,5 (s, 1H), 11,8 (s, 1H).

Ejemplo 26

(2*R*,4*S*,4a*S*)-rel-8-(azepan-1-il)-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±)



Material de partida: 3-(azepan-1-il)-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-1,2-bencisoxazol-5-carbaldehído (**Intermedio 566**)

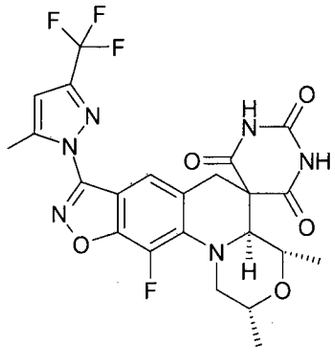
MS (ES) MH^+: 486 para $C_{24}H_{28}FN_5O_5$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 1,5 (s a, 4H), 1,7 (s a, 4H), 2,95 (d, 1H), 3,0 (s, 1H), 3,5 (m, 5H), 3,7 (d, 1H), 3,8 (m, 1H), 3,9 (d, 1H), 4,1(d, 1H), 7,3 (s, 1H), 11,5 (s, 1H), 11,8 (s, 1H).

Ejemplo 27

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-[5-metil-3-(trifluorometil)-1*H*-pirazol-1-il]-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±)



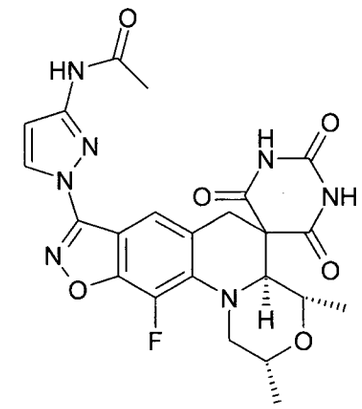
Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[5-metil-3-(trifluorometil)-1*H*-pirazol-1-il]-1,2-bencisoxazol-5-carbaldehído (**Intermedio 567**)

MS (ES) MH^+: 537 para $C_{23}H_{20}F_4N_6O_5$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 2,6 (s, 3H), 2,9 (d, 1H), 3,1 (t, 1H), 3,6–3,8(m, 3H), 4,0 (d, 1H), 4,1 (d, 1H), 7,0 (s, 1H), 7,5 (s, 1H), 11,5 (s a, 2H).

Ejemplo 28

N-{1-[(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-1*H*-pirazol-3-il}acetamida

(±) 

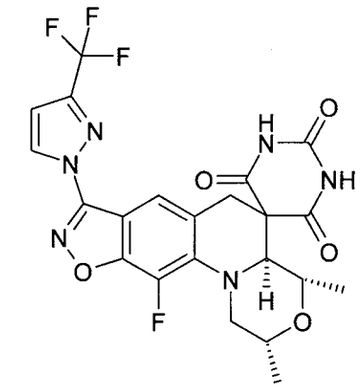
Material de partida: *N*-[1-[6-[(2S,6*R*)-2,6-dimetilmorfolin-4-il]-7-fluoro-5-formil-1,2-benzoxazol-3-il]pirazol-3-il]acetamida (**Intermedio 568**)

MS (ES) MH^+: 512 para $C_{23}H_{22}FN_7O_6$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 2,1 (s, 3H), 3,0 (d, 1H), 3,1 (t, 1H), 3,5 (d, 1H), 3,7 (m, 1H), 3,8 (m, 1H), 4,0 (d, 1H), 4,1 (d, 1H), 7,0 (d, 1H), 7,6 (s, 1H), 8,4 (d, 1H), 10,85 (s, 1H), 11,5 (s a, 1H), 11,9 (s a, 1H).

Ejemplo 29

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-[3-(trifluorometil)-1*H*-pirazol-1-il]-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±) 

Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[3-(trifluorometil)-1*H*-pirazol-1-il]-1,2-bencisoxazol-5-carbaldehído (**Intermedio 569**)

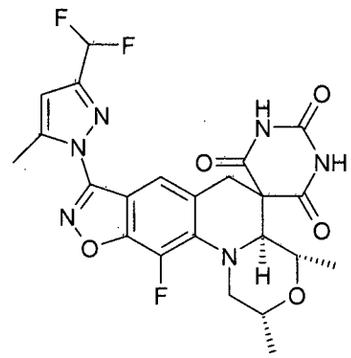
MS (ES) MH^+: 523 para $C_{22}H_{18}F_4N_6O_5$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 2,9 (d, 2H), 3,1 (t, 1H), 3,6 (m, 1H), 3,8 (m, 1H), 4,0 (d, 1H), 4,1 (d, 1H), 7,2 (d, 1H), 7,55 (s, 1H), 8,8 (d, 1H), 11,5 (s, 1H), 11,9 (s, 1H).

Ejemplo 30

(2*R*,4*S*,4a*S*)-rel-8-[3-(difluorometil)-5-metil-1*H*-pirazol-1-il]-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±)



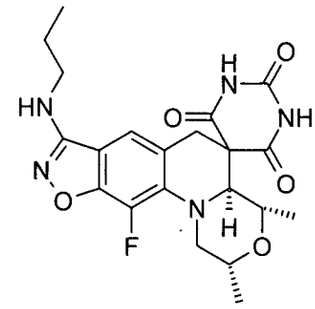
Material de partida: 3-[3-(difluorometil)-1*H*-pirazol-1-il]-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-1,2-bencisoxazol-5-carbaldehído (**Intermedio 570**)

MS (ES) MH^+: 519 para $C_{23}H_{21}F_3N_6O_5$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 2,6 (s, 3H), 2,9 (d, 2H), 3,1 (t, 1H), 3,6 (m, 1H), 3,8 (m,1H), 4,0 (d, 1H), 4,1 (d, 1H), 6,8 (s, 1H), 7,1 (t, 1H), 7,6 (s, 1H), 11,5 (s, 1H), 11,9 (s, 1H).

Ejemplo 31

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(propilamino)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±) 

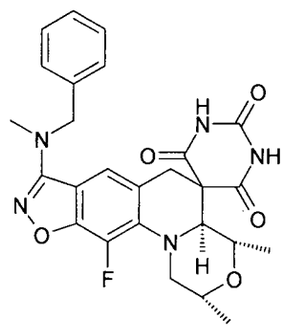
Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(propilamino)-1,2-benzoxazol-5-carbaldehído (**Intermedio 571**)

MS (ES) MH^+: 446 para $C_{21}H_{24}FN_5O_5$

^1H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 6H), 1,1 (d, 3H), 1,6 (t, 2H), 2,9 (d, 1H), 3,0 (m, 1H), 3,3 (m, 2H), 3,55 (d, 1H), 3,65 (m, 1H), 3,7 (m, 1H), 3,9 (d, 1H), 4,0 (d, 1H), 6,8 (m, 1H), 7,1 (s, 1H), 11,45 (s a, 1H), 11,8 (s a, 1H).

Ejemplo 32

(2*R*,4*S*,4a*S*)-rel-8-[bencil(metil)amino]-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±) 

Material de partida: 3-[bencil(metil)amino]-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-1,2-benzoxazol-5-carbaldehído (**Intermedio 572**)

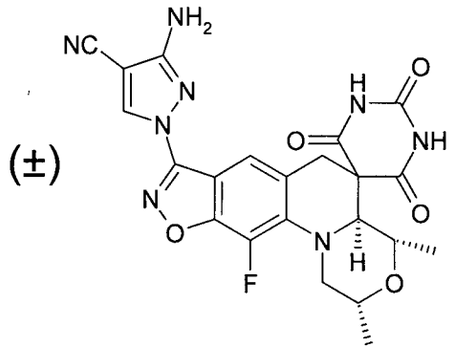
MS (ES) MH^+: 508,3 para $C_{26}H_{26}FN_5O_5$

^1H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 2,9 (d, 1H), 3,0 (s, 3H), 3,1 (m, 1H), 3,5 (d, 1H), 3,7 (m, 1H), 3,8 (m, 1H), 3,9 (d, 1H), 4,1 (d, 1H), 4,6 (d, 1H), 4,7 (d, 1H), 7,2-7,35 (m, 5H), 11,5 (s, 1H), 11,8 (s, 1H).

Ejemplo 33

103542-1P

3-amino-1-[(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-1*H*-pirazol-4-carbonitrilo



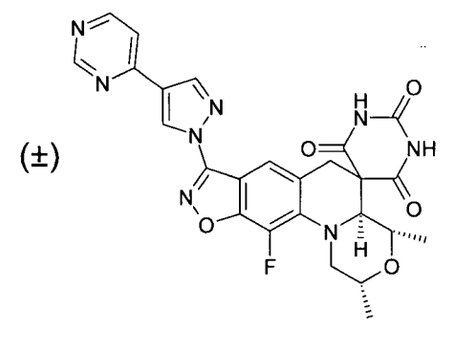
Material de partida: 3-amino-1-{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-5-formil-1,2-benzoxazol-3-il}-1*H*-pirazol-4-carbonitrilo (**Intermedio 548**)

MS (ES) MH^+: 495 para $C_{22}H_{19}FN_8O_5$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 2,9 (d, 1H), 3,1 (m, 1H), 3,6 (d, 1H), 3,7 (m, 1H), 3,8 (m, 1H), 4,0 (d, 1H), 4,1 (d, 1H), 6,25 (s, 2H), 7,55 (s, 1H), 9,0 (s, 1H), 11,5 (s a, 1H), 11,9 (s a, 1H).

Ejemplo 34

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-[4-(pirimidin-4-il)-1*H*-pirazol-1-il]-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona



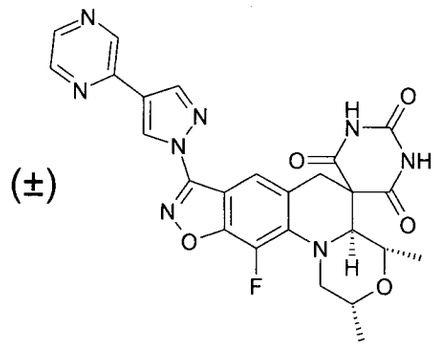
Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[4-(pirimidin-4-il)-1*H*-pirazol-1-il]-1,2-benzoxazol-5-carbaldehído (**Intermedio 549**)

MS (ES) MH^+: 533,5 para $C_{25}H_{21}FN_8O_5$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 2,9 (d, 1H), 3,15 (t, 1H), 3,7 (m, 1H), 3,8 (m, 2H), 4,0 (d, 1H), 4,1 (d, 1H), 7,7 (s, 1H), 8,0 (s, 1H), 8,7 (s, 1H), 8,9 (d, 1H), 9,2 (s, 1H), 9,3 (s, 1H), 11,5 (s, 1H), 11,9 (s, 1H).

Ejemplo 35

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-[4-(pirazin-2-il)-1*H*-pirazol-1-il]-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona



Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[4-(pirazin-2-il)-1*H*-pirazol-1-il]-1,2-benzoxazol-5-carbaldehído (**Intermedio 550**)

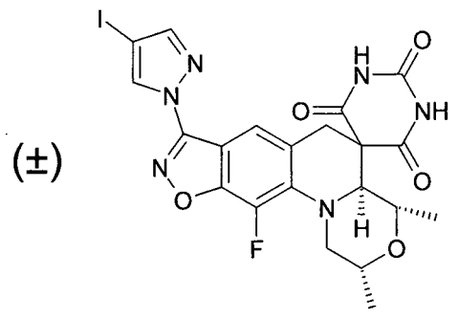
MS (ES) MH^+: 533,5 para $C_{25}H_{21}FN_8O_5$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 2,9 (d, 1H), 3,15 (t, 1H), 3,7 (m, 1H), 3,8 (m, 2H), 4,0 (d, 1H), 4,1 (d, 1H), 7,7 (s, 1H), 8,0 (s, 1H), 8,7 (s, 1H), 8,9 (d, 1H), 9,2 (s, 1H), 9,3 (s, 1H), 11,5 (s, 1H), 11,9 (s, 1H).

Ejemplo 36

(2*R*,4*S*,4a*S*)-rel-11-fluoro-8-(4-yodo-1*H*-pirazol-1-il)-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

103542-1P



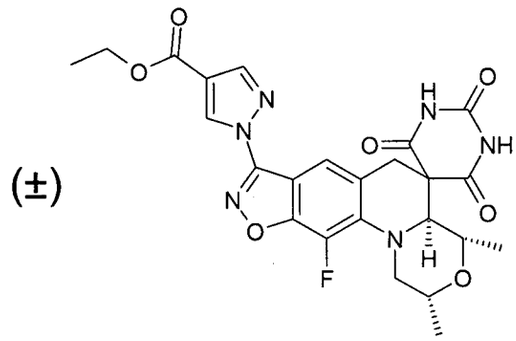
Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(4-yodo-1*H*-pirazol-1-il)-1,2-benzoxazol-5-carbaldehído (**Intermedio 551**)

MS (ES) MH^+: 529,5 para $C_{21}H_{18}FIN_6O_5$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,15 (d, 3H), 2,9 (d, 1H), 3,1 (t, 1H), 3,7 (m, 1H), 3,8 (m, 2H), 4,0 (d, 1H), 4,1 (d, 1H), 7,6 (s, 1H), 8,1 (s, 1H), 8,7 (s, 1H), 11,5 (s, 1H), 11,9 (s, 1H).

Ejemplo 37

1-[(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-1*H*-pirazol-4-carboxilato de etilo



Material de partida: 1-{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-5-formil-1,2-benzoxazol-3-il}-1*H*-pirazol-4-carboxilato de etilo (**Intermedio 552**)

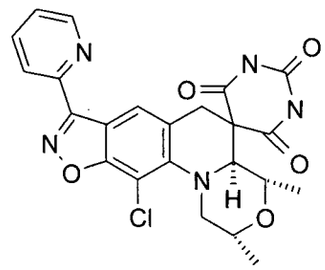
MS (ES) MH^+: 527,4 para $C_{24}H_{23}FN_6O_7$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,7 (d, 3H), 0,9 (d, 3H), 2,6 (d, 1H), 2,8 (m, 1H), 3,0 (d, 1H), 3,6 (m, 1H), 3,8 (d, 1H), 3,9 (d, 1H), 7,8 (s, 1H), 8,0 (s, 1H), 9,1 (s, 1H), 8,7 (s, 1H), 11,6 (s, 1H), 11,9 (s, 2H).

Ejemplo 38

(2*R*,4*S*,4a*S*)-rel-11-cloro-2,4-dimetil-8-(piridin-2-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±)



Material de partida: 7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(piridin-2-il)-1,2-benzoxazol-5-carbaldehído (**Intermedio 376**)

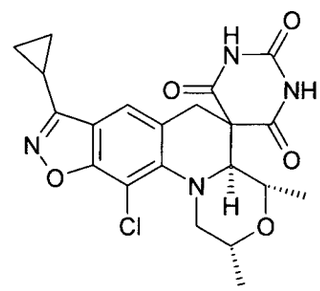
MS (ES) MH^+: 482 para $C_{23}H_{20}ClN_5O_5$

^1H RMN (400 MHz, DMSO-D6) δ: 0,9 (d, 3H), 1,5 (d, 3H), 2,9 (d, 1H), 3,08 (t, 1H), 3,7 (m, 1H), 3,8 (d, 1H), 4,0 (m, 2H), 4,5 (d, 1H), 7,6 (c, 1H), 7,95 (s, 1H), 8,0 (m, 1H), 8,1 (d, 1H), 8,8 (s, 1H), 11,5 (s, 1H), 11,8 (s,1H).

Ejemplo 39

(2*R*,4*S*,4a*S*)-rel-11-cloro-8-ciclopropil-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±)



Material de partida: 7-cloro-3-ciclopropil-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-1,2-benzoxazol-5-carbaldehído (**Intermedio 377**)

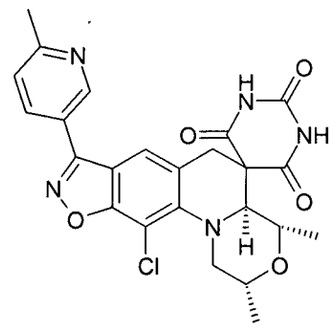
MS (ES) MH^+: 445,0 para $C_{21}H_{21}ClN_4O_5$

^1H RMN (400 MHz, DMSO-D6) δ: 0,9 (d, 3H), 1,0 (m, 1H), 1,1 (m, 3H), 1,15 (d, 3H), 2,2 (m, 1H), 3,0 (m, 2H), 3,5 (d, 1H), 3,6 (m, 1H), 4,0 (m, 2H), 4,4 (d, 1H), 7,3 (s, 1H), 11,45 (s,1H), 11,8 (s, 1H).

Ejemplo 40

(2*R*,4*S*,4a*S*)-rel-11-cloro-2,4-dimetil-8-(6-metilpiridin-3-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona aislada como la sal de TFA a partir de la purificación mediante HPLC de fase inversa.

(±)



Material de partida: 7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(6-metilpiridin-3-il)-1,2-benzoxazol-5-carbaldehído (**Intermedio 378**)

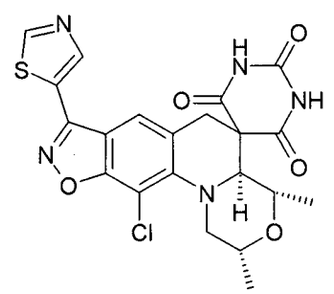
MS (ES) MH^+: 496 para $C_{24}H_{22}ClN_5O_5$

^1H RMN (400 MHz, DMSO-D6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 2,6 (s, 3H), 3,1 (m, 2H), 3,6 (d, 1H), 3,7 (m, 1H), 3,95 (m, 1H), 4,0 (m, 1H), 4,5 (d, 1H), 7,5 (d, 1H), 7,7 (s, 1H), 8,2 (dd, 1H), 9,0 (d, 1H), 11,5 (s, 1H), 11,9 (s, 1H)

Ejemplo 41

(2*R*,4*S*,4a*S*)-rel-11-cloro-2,4-dimetil-8-(1,3-tiazol-5-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±)



Material de partida: 7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(1,3-tiazol-5-il)-7,7a-dihidro-1,2-benzoxazol-5-carbaldehído (**Intermedio 379**)

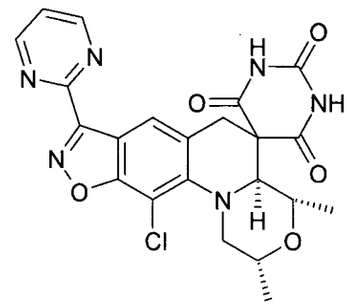
MS (ES) MH^+: 488,0 para $C_{21}H_{18}ClN_5O_5S$

^{1}H RMN (400 MHz, DMSO-D6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 3,0 (m, 2H), 3,6 (d, 1H), 3,7 (m, 1H), 4,0 (m, 1H), 4,5 (d, 1H), 4,5 (d, 1H), 7,9 (s, 1H), 8,7 (s, 1H), 9,4 (s, 1H), 11,5 (s, 1H),11,9 (s, 1H).

Ejemplo 42

(2*R*,4*S*,4a*S*)-rel-11-cloro-2,4-dimetil-8-(pirimidin-2-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±)



Material de partida: 7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(pirimidin-2-il)-1,2-benzoxazol-5-carbaldehído (**Intermedio 380**)

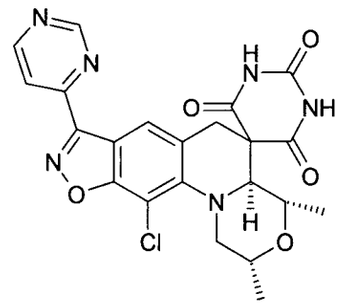
MS (ES) MH^+: 483 para $C_{22}H_{19}ClN_6O_5$

^{1}H RMN (400 MHz, DMSO-D6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 3,0 (m, 2H), 3,7 (m, 1H), 3,75 (d, 1H), 4,0 (m, 2H), 4,5 (d, 1H), 7,7 (t, 1H), 7,9 (s, 1H), 9,0 (m, 2H), 11,5 (s, 1H), 11,8 (s, 1H).

Ejemplo 43

(2*R*,4*S*,4a*S*)-rel-11-cloro-2,4-dimetil-8-(pirimidin-4-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±)



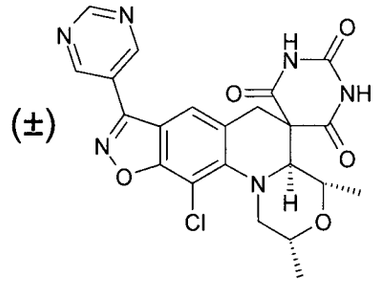
Material de partida: 7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(pirimidin-4-il)-1,2-benzoxazol-5-carbaldehído (**Intermedio 381**)

MS (ES) MH^+: 483 para $C_{22}H_{19}ClN_6O_5$

^{1}H RMN (400 MHz, DMSO-D6) δ 0,9 (d, 3H), 1,2 (d, 3H), 3,0 (d, 1H), 3,1 (m, 1H), 3,7 (m, 1H), 3,8 (d, 1H), 4,0 (m, 2H), 4,5 (d, 1H), 7,95 (s, 1H), 8,2 (dd, 1H), 9,0 (d, 1H), 9,4 (d, 1H), 11,5 (s, 1H), 11,85 (s,1H).

Ejemplo 44

(2*R*,4*S*,4a*S*)-rel-11-cloro-2,4-dimetil-8-(pirimidin-5-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona



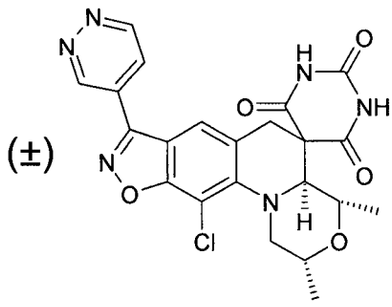
Material de partida: 7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(pirimidin-5-il)-1,2-benzoxazol-5-carbaldehído (**Intermedio 382**)

MS (ES) MH^+: 483 para $C_{22}H_{19}ClN_6O_5$

^{1}H RMN (400 MHz, DMSO-D6) δ 0,9 (d, 3H), 1,1 (d, 3H), 3,05 (m, 2H), 3,7 (d, 1H), 3,72 (t, 1H), 3,9 (t, 1H), 4,0 (d, 1H), 4,5 (d, 1H), 7,79 (s, 1H), 9,3 (s, 1H), 9,4 (s, 1H), 11,3 (s, 1H).

Ejemplo 45

(2*R*,4*S*,4a*S*)-rel-11-cloro-2,4-dimetil-8-(piridazin-4-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona



Material de partida: 7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(piridazin-4-il)-1,2-benzoxazol-5-carbaldehído (**Intermedio 383**)

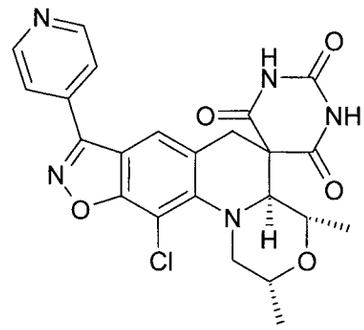
MS (ES) MH^+: 483 para $C_{22}H_{19}ClN_6O_5$

^{1}H RMN (400 MHz, DMSO-D6) δ 0,9 (d, 3H), 1,2 (d, 3H), 3,1 (m, 1H), 3,6 (d, 1H), 3,7 (m, 1H), 4,0 (m, 1H), 4,05 (d, 1H), 4,5 (d, 1H), 7,85 (s, 1H), 8,2 (dd, 1H), 9,5 (d, 1H), 9,75 (s, 1H), 11,5 (s, 1H), 11,9 (s, 1H).

Ejemplo 46

(2*R*,4*S*,4a*S*)-rel-11-cloro-2,4-dimetil-8-(piridin-4-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±)



Material de partida: 7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(piridin-4-il)-1,2-benzoxazol-5-carbaldehído (**Intermedio 384**)

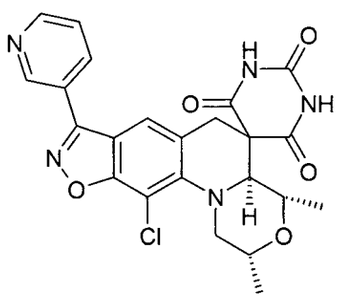
MS (ES) MH^+: 482 para $C_{23}H_{20}ClN_5O_5$

^{1}H RMN (400 MHz, DMSO-D6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 3,1 (m, 2H), 3,6 (m, 1H), 3,9 (m, 1H), 4,0 (d, 1H), 4,5 (d, 1H), 7,75 (s, 1H), 7,9 (d, 2H), 8,8 (s a, 2H), 11,5 (s, 1H), 11,9 (s, 1H).

Ejemplo 47

(2*R*,4*S*,4a*S*)-rel-11-cloro-2,4-dimetil-8-(piridin-3-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona (aislada como la sal de TFA a partir de la purificación mediante HPLC de fase inversa).

(±)



103542-1P

Material de partida: 7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(piridin-3-il)-1,2-benzoxazol-5-carbaldehído (**Intermedio 385**)

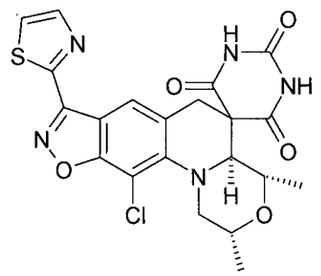
MS (ES) MH^+: 482 para $C_{23}H_{20}ClN_5O_5$

^{1}H RMN (400 MHz, DMSO-D6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 3,0 (m, 2H), 3,6 (m, 1H), 3,7 (m, 1H), 4,0 (m, 2H), 4,5 (d, 1H), 7,6 (t, 1H), 7,7 (s, 1H), 8,3 (d, 1H), 8,8 (s, 1H), 9,1 (s, 1H), 11,5 (s, 1H), 11,9 (s, 1H).

Ejemplo 48

(2*R*,4*S*,4a*S*)-rel-11-cloro-2,4-dimetil-8-(1,3-tiazol-2-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±)



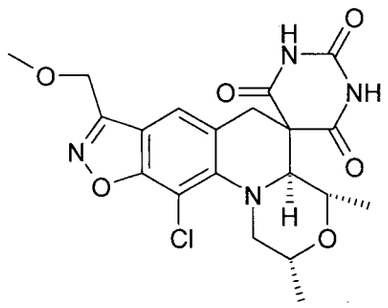
Material de partida: 7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(1,3-tiazol-2-il)-1,2-benzoxazol-5-carbaldehído (**Intermedio 386**)

MS (ES) MH^+: 488 para $C_{21}H_{18}ClN_5O_5S$

^{1}H RMN (400 MHz, DMSO-D6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 3,0 (d, 1H), 3,1 (m, 1H), 3,7 (m, 1H), 3,8 (d, 1H), 4,0 (m, 1H), 4,5 (d, 1H), 7,8 (s, 1H), 8,1 (d, 1H), 8,2 (d, 1H), 11,5 (s, 1H), 11,8 (s, 1H).

Ejemplo 49

(2*R*,4*S*,4a*S*)-rel-11-cloro-8-(metoximetil)-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±) 

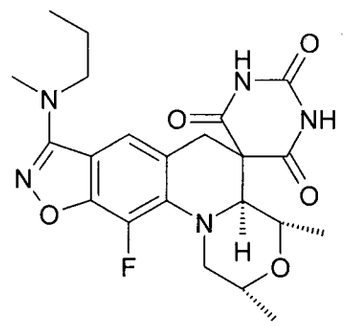
Material de partida: 7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(metoximetil)-1,2-benzoxazol-5-carbaldehído (**Intermedio 388**)

MS (ES) MH^+: 449 para $C_{20}H_{21}ClN_4O_6$

^{1}H RMN (400 MHz, DMSO-D6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 2,95-3,1 (m, 2H), 3,3 (s, 3H), 3,6-3,7 (m, 2H), 3,9-4,0 (m, 2H), 4,5 (d, 1H), 4,7 (s, 2H), 7,3 (s, 1H), 11,4 (s, 1H), 11,8 (s, 1H).

Ejemplo 50

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-[metil(propil)amino]-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±) 

Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[metil(propil)amino]-1,2-benzoxazol-5-carbaldehído (**Intermedio 573**)

MS (ES) MH^+: 460 para $C_{22}H_{26}FN_5O_5$

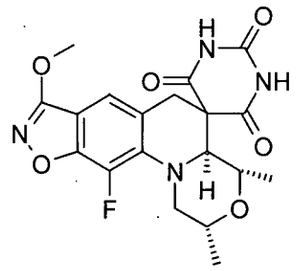
^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 6H), 1,1 (d, 3H), 1,6 (t, 2H), 2,9 (d, 1H), 3,0 (m, 5H), 3,3 (s, 1H), 3,55 (d, 1H), 3,65 (m, 1H), 3,7 (m, 1H), 3,9 (d, 1H), 4,0 (d, 1H), 7,3 (s, 1H), 11,5 (s a, 1H), 11,8 (s a, 1H).

103542-1P

Ejemplo 51

(2*R*,4*S*,4a*S*)-rel-11-fluoro-8-metoxi-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±)



Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-metoxi-1,2-bencisoxazol-5-carbaldehído (**Intermedio 557**)

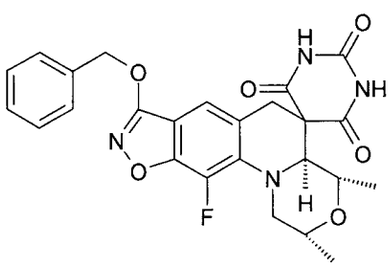
MS (ES) MH^+: 419 para $C_{19}H_{19}FN_4O_6$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,2 (d, 3H), 2,9 (d, 1H), 3,1 (t, 1H), 3,6 (d, 1H), 3,7 (m, 1H), 3,8 (m, 1H), 3,9 (d, 1H), 4,0 (s, 3H), 4,1 (d, 1H), 7,1 (s, 1H), 11,5 (s, 1H), 11,9 (s, 1H).

Ejemplo 52

(2*R*,4S,4a*S*)-rel-8-(benciloxi)-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'H,6*H*-espiro[1,4-oxazino[4,3-a][1,2]oxazolo[4,5-g]quinolin-5,5'-pirimidin]-2',4',6'(1'H,3'H)-triona

(±)



Material de partida: 3-(benciloxi)-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-1,2-bencisoxazol-5-carbaldehído (**Intermedio 558**)

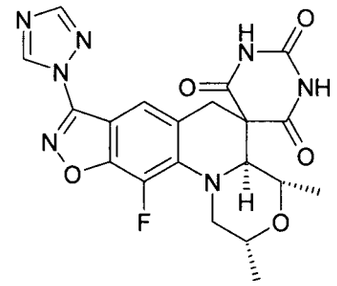
MS (ES) MH^+: 495 para $C_{25}H_{23}FN_4O_6$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,2 (d, 3H), 2,9 (d, 1H), 3,1 (t, 1H), 3,6 (d, 1H), 3,7 (m, 1H), 3,8 (m, 1H), 3,9 (d, 1H), 4,0 (s, 1H), 5,4 (s, 2H), 7,1 (s, 1H), 7,4 (m, 3H), 7,5 (d, 2H), 11,5 (s, 1H), 11,85 (s, 1H).

Ejemplo 53

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(1*H*-1,2,4-triazol-1-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±)



Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(1*H*-1,2,4-triazol-1-il)-1,2-benzoxazol-5-carbaldehído (**Intermedio 539**)

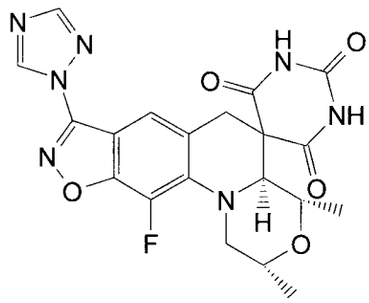
MS (ES) MH^+: 456 para $C_{20}H_{18}FN_7O_5$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 2,9 (d, 1H), 3,1 (t, 1H), 3,7 (m, 1H), 3,8 (m, 2H), 4,0 (d, 1H), 4,1 (d, 1H), 7,6 (s, 1H), 8,5 (s, 1H), 9,4 (s, 1H), 11,5 (s a, 1H), 11,9 (s a, 1H).

El enantiómero (2*R*,4S,4aS) del **Ejemplo 53** también se preparó utilizando la síntesis quiral descrita a continuación para el **Ejemplo 53(a):**

Ejemplo 53(a) – (Síntesis Quiral)

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimetil-8-(1*H*-1,2,4-triazol-1-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona



Una mezcla de 6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-3-(1*H*-1,2,4-triazol-1-il)benzo[d]isoxazol-5-carbaldehído (**Intermedio 574,** 500 mg, 1,45 mmol) y pirimidin-2,4,6(1H,3H,5H)-triona (185 mg, 1,45 mmol) en DMSO (6 mL) se calentó a 150 °C durante 2

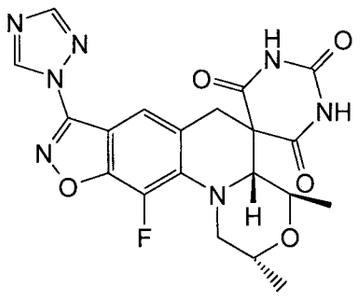
horas en un reactor de microondas. La mezcla de reacción se purificó mediante Cromatografía de Fluidos Supercríticos en una columna Chiralpac IC con una fase móvil de 35% de MeOH, 65% de CO_2 para proporcionar 290 mg del producto como un sólido como el compuesto que eluyó en primer lugar.

MS (ES) MH^+: 456 para $C_{20}H_{18}FN_7O_5$

^{1}H RMN (300 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,2 (d, 3H), 2,9 (d, 1H) 3,1 (t, 1H), 3,6-3,9 (m, 3H), 4, (d, 1H), 4,1 (d, 1H), 7,6 (s, 1H), 8,5 (s, 1H), 9,4 (s, 1H), 11,5 (s a, 1H), 11,9 (s a, 1H).

Ejemplo 53(b)

(2*R*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(1*H*-1,2,4-triazol-1-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona



El diastereómero (2*R*,4*R*,4a*R*) se produjo como un producto secundario de la reacción descrito para la síntesis del **Ejemplo 53(a)**. La cromatografía descrita para el **Ejemplo 53(a)** proporcionó 25 mg del diastereómero (2*R*,4*R*,4a*R*) como el compuesto que eluyó en segundo lugar.

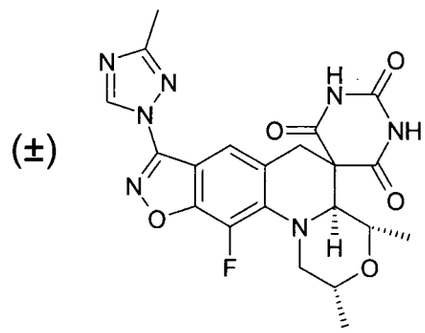
MS (ES) MH^+: 456 para $C_{20}H_{18}FN_7O_5$

^{1}H RMN (300 MHz, DMSO-d_6) δ: 0,9 (d, 3 H), 1,3 (dd, 3 H), 3,0-3,2 (m, 1 H), 3,5-3,7 (m, 1 H), 3,7-3,8 (m, 1 H), 3,85 (s, 1 H), 3,9-4,4 (m, 2 H), 4,0-4,2 (m, 1 H), 7,6 (s, 1 H), 8,5 (s, 1 H), 9,4 (s, 1 H), 11,5 (s a, 1 H), 11,8 (s a, 1 H).

Los **Ejemplos 54** a **83** se prepararon a partir del material de partida indicado y pirimidin-2,4,6(1*H*,3*H*,5*H*)-triona utilizando un método similar al descrito para la síntesis del **Ejemplo 8**:

Ejemplo 54

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(3-metil-1*H*-1,2,4-triazol-1-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona



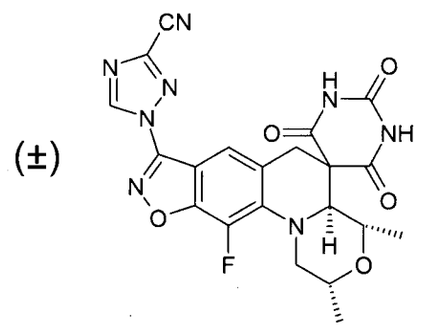
Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(3-metil-1*H*-1,2,4-triazol-1-il)-1,2-benzoxazol-5-carbaldehído (**Intermedio 540**)

MS (ES) MH^+: 470 para $C_{21}H_{20}FN_7O_5$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 2,4 (s, 3H), 2,9 (d, 1H), 3,1 (t, 1H), 3,7 (m, 1H), 3,8 (m, 2H), 4,0 (d, 1H), 4,1 (d, 1H), 7,6 (s, 1H), 9,3 (s, 1H), 11,5-11,9 (s a, 2H).

Ejemplo 55

1-[(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-1*H*-1,2,4-triazol-3-carbonitrilo



Material de partida: 1-{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-5-formil-1,2-benzoxazol-3-il}-1*H*-1,2,4-triazol-3-carbonitrilo (**Intermedio 541**)

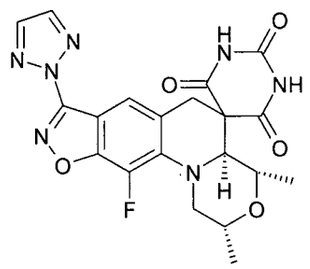
MS (ES) M*H*-: 479 para $C_{21}H_{17}FN_8O_5$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,15 (d, 3H), 2,9 (d, 1H), 3,2 (t, 1H), 3,7 (m, 1H), 3,9 (m, 2H), 4,0 (d, 1H), 4,1 (d, 1H), 7,6 (s, 1H), 9,8 (s, 1H), 11,5 (s, 1H), 11,9 (s, 1H).

Ejemplo 56

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(2*H*-1,2,3-triazol-2-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±)



Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(1*H*-1,2,3-triazol-2-il)-1,2-benzoxazol-5-carbaldehído (**Intermedio 543**), como parte de una mezcla que incluye 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(1*H*-1,2,3-triazol-1-il)-1,2-benzoxazol-5-carbaldehído (**Intermedio 542**)

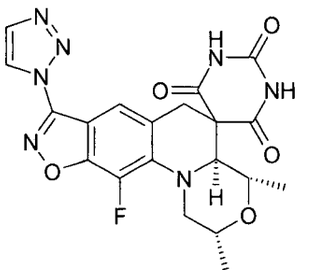
MS (ES) MH^+: 456 para $C_{20}H_{18}FN_7O_5$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,15 (d, 3H), 2,9 (d, 1H), 3,1 (m, 1H), 3,7 (m, 1H), 3,8 (m, 2H), 4,0 (d, 1H), 4,1 (d, 1H), 7,7 (s, 1H), 8,4 (s, 2H), 11,6 (s a, 2H).

Ejemplo 57

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(1*H*-1,2,3-triazol-1-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±)



Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(1*H*-1,2,3-triazol-1-il)-1,2-benzoxazol-5-carbaldehído (**Intermedio 542**), como parte de una mezcla que incluye 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(1*H*-1,2,3-triazol-2-il)-1,2-benzoxazol-5-carbaldehído (**Intermedio 543**)

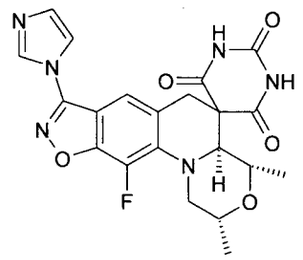
MS (ES) MH^+: 456,5 para $C_{20}H_{18}FN_7O_5$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,15 (d, 3H), 2,9 (d, 1H), 3,1 (m, 1H), 3,7 (m, 1H), 3,8 (m, 2H), 4,0 (d, 1H), 4,15 (d, 1H), 7,7 (s, 1H), 8,15 (d, 1H), 9,0 (s, 1H), 11,6 (s a, 1H).

Ejemplo 58

(2*R*,4*S*,4a*S*)-rel-11-fluoro-8-(1*H*-imidazol-1-il)-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±)



Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(1*H*-imidazol-1-il)-1,2-benzoxazol-5-carbaldehído (**Intermedio 544**)

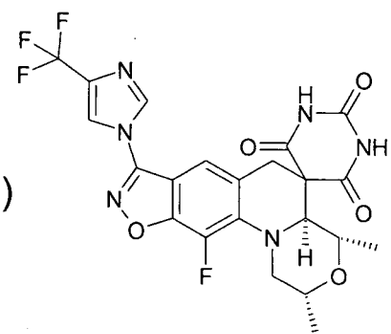
MS (ES) MH^+: 455 para $C_{21}H_{19}FN_6O_5$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,15 (d, 3H), 3,0 (d, 1H), 3,2 (t, 1H), 3,55 (d, 1H), 3,7 (m, 1H), 3,8 (m, 1H), 4,0 (d, 1H), 4,1 (d, 1H), 7,3 (s, 1H), 7,65 (s, 1H), 7,9 (s, 1H), 8,5 (s, 1H), 11,6 (s, 1H), 11,9 (s, 1H).

Ejemplo 59

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-[4-(trifluorometil)-1*H*-imidazol-1-il]-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±)



Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[4-(trifluorometil)-1*H*-imidazol-1-il]-1,2-benzoxazol-5-carbaldehído (**Intermedio 545**)

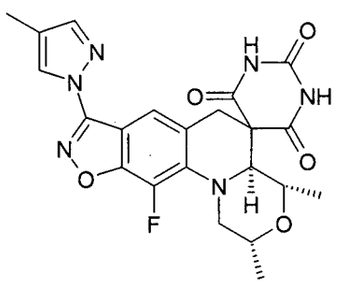
MS (ES) MH^+: 523 para $C_{22}H_{18}F_4N_6O_5$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 3,0 (d, 1H), 3,1 (t, 1H), 3,5 (m, 1H), 3,7 (m,1H), 3,8 (m, 1H), 4,0 (d, 1H), 4,1 (d, 1H), 7,6 (d, 1H), 8,6 (d, 1H), 8,65 (s, 1H).

Ejemplo 60

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(4-metil-1*H*-pirazol-1-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±)



Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(4-metil-1*H*-pirazol-1-il)-1,2-benzoxazol-5-carbaldehído (**Intermedio 546**)

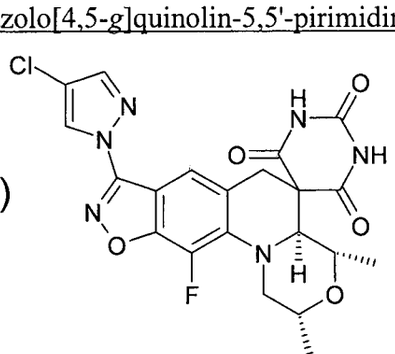
MS (ES) MH^+: 469 para $C_{22}H_{21}FN_6O_5$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 2,1 (s, 3H), 2,9 (d, 1H), 3,1 (t, 1H), 3,7 (m, 2H), 3,8 (m, 1H), 3,95 (d, 1H), 4,1 (d, 1H), 7,7 (s, 1H), 7,8 (s, 1H), 8,3 (s, 1H), 11,5 (s, 1H), 11,8 (s, 1H).

Ejemplo 61

(2*R*,4*S*,4a*S*)-rel-8-(4-cloro-1*H*-pirazol-1-il)-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±)



Material de partida: 3-(4-cloro-1*H*-pirazol-1-il)-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-1,2-benzoxazol-5-carbaldehído (**Intermedio 547**)

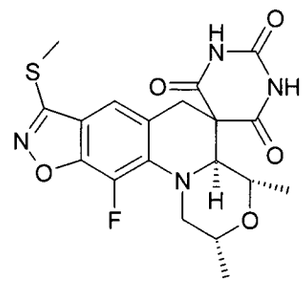
MS (ES) MH^+: 489 para $C_{21}H_{18}ClFN_6O_5$

^1H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 2,9 (d, 1H), 3,1 (t, 1H), 3,7 (m, 1H), 3,8 (d, 2H), 4,0 (d, 1H), 4,1(d, 1H), 7,6 (s, 1H), 8,1 (s, 1H), 8,8 (s, 1H), 11,5 (s, 1H), 11,85 (s, 1H).

Ejemplo 62

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(metilsulfanil)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±)



Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(metilsulfanil)-1,2-benzoxazol-5-carbaldehído (**Intermedio 553**)

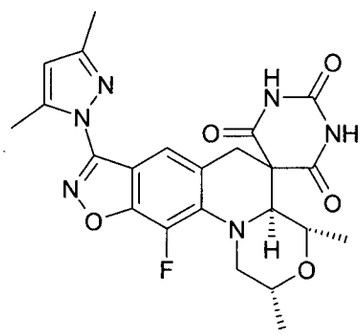
MS (ES) MH^+: 435 para $C_{19}H_{19}FN_4O_5S$

^1H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 2,7 (s, 3H), 2,9 (d, 1H), 3,1 (t, 1H), 3,6 (m, 1H), 3,7 (m,1H), 3,8 (m, 1H), 4,0 (d, 1H), 4,1(d, 1H), 7,1 (s, 1H), 11,5 (s, 1H), 11,9 (s, 1H).

Ejemplo 63

(2*R*,4*S*,4a*S*)-rel-8-(3,5-dimetil-1*H*-pirazol-1-il)-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±)



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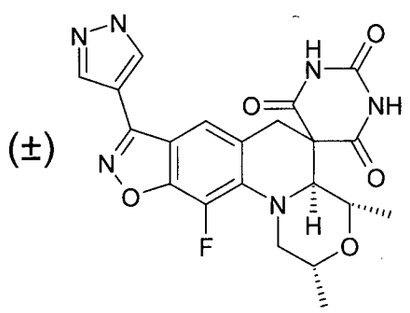
Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(3,5-dimetil-1*H*-pirazol-1-il)-7-fluoro-1,2-benzoxazol-5-carbaldehído (**Intermedio 554**)

MS (ES) MH^+: 483,5 para $C_{23}H_{23}FN_6O_5$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 2,25 (s, 3H), 2,5 (s, 3H), 2,9 (d, 1H), 3,1 (t, 1H), 3,7 (m, 1H), 3,8 (m, 2H), 3,95 (d, 1H), 4,1 (d, 1H), 6,25 (s, 1H), 7,6 (s, 1H), 11,5 (s a, 1H), 11,9 (s a, 2H).

Ejemplo 64

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(1*H*-pirazol-4-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona



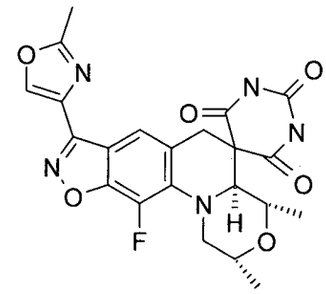
Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(1*H*-pirazol-4-il)-1,2-benzoxazol-5-carbaldehído (**Intermedio 555**)

MS (ES) MH^+: 455 para $C_{21}H_{19}FN_6O_5$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,5 (d, 3H), 2,9 (d, 1H), 3,1 (t, 1H), 3,7 (m, 1H), 3,8 (m, 2H), 4,0 (d, 1H), 4,1(d, 1H), 6,7 (s, 1H), 7,7 (s, 1H), 8,0 (s, 1H), 8,5 (s, 1H), 11,5 (s, 1H), 11,8 (s, 2H).

Ejemplo 65

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(2-metil-1,3-oxazol-4-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±) 

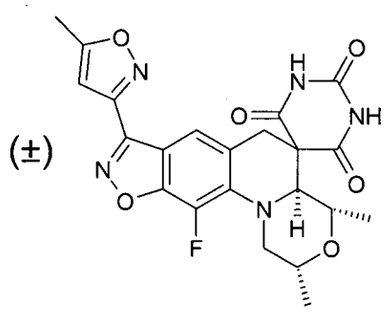
Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(2-metil-1,3-oxazol-4-il)-1,2-benzoxazol-5-carbaldehído (**Intermedio 394**)

MS (ES) MH^+: 470 para $C_{22}H_{20}FN_5O_6$

^{1}H RMN (400 MHz, DMSO-D6) δ: 0,9 (d, 3H), 1,5 (d, 3H), 2,5 (s, 3H), 3,0 (d, 1H), 3,3 (t, 1H), 3,7 (m, 2H), 3,8 (m, 1H), 4,0 (d, 1H), 4,1 (d, 1H), 7,6 (s, 1H), 8,8 (s, 1H), 11,5 (s, 1H), 11,8 (s, 1H).

Ejemplo 66

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(5-metil-1,2-oxazol-3-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±) 

Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(5-metil-1,2-oxazol-3-il)-1,2-benzoxazol-5-carbaldehído (**Intermedio 395**)

MS (ES) MH^+: 470 para $C_{22}H_{20}FN_5O_6$

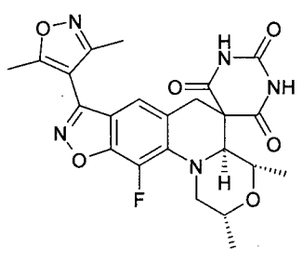
^{1}H RMN (400 MHz, DMSO-D6) δ: 0,9 (d, 3H), 1,5 (d, 3H), 2,5 (s, 3H), 3,0 (d, 1H), 3,3 (t, 1H), 3,7 (m, 1H), 3,8 (m, 2H), 4,0 (d, 1H), 4,1 (d, 1H), 6,85 (s, 1H), 7,55 (s, 1H), 11,5 (s, 1H), 11,85 (s, 1H).

Ejemplo 67

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(2*R*,4*S*,4a*S*)-rel-8-(3,5-dimetil-1,2-oxazol-4-il)-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±)



Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(3,5-dimetil-1,2-oxazol-4-il)-7-fluoro-1,2-benzoxazol-5-carbaldehído (**Intermedio 396**)

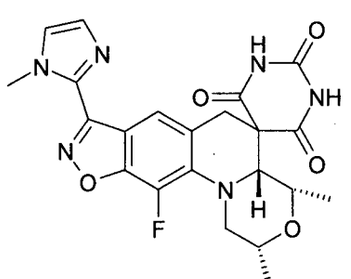
MS (ES) MH^+: 484 para $C_{23}H_{22}FN_5O_6$

^{1}H RMN (400 MHz, DMSO-D6) δ: 0,9 (d, 3H), 1,5 (d, 3H), 2,3 (s, 3H), 2,5 (s, 3H), 3,0 (d, 1H), 3,1 (t, 1H), 3,6 (d, 1H), 3,7 (m, 1H), 3,8 (m, 1H), 4,0 (d, 1H), 4,1 (d, 1H), 7,3 (s, 1H), 11,5 (s, 1H), 11,9 (s,1H).

Ejemplo 68

(2*R*,4*S*,4a*R*)-rel-11-fluoro-2,4-dimetil-8-(1-metil-1*H*-imidazol-2-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±)



Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(1-metil-1*H*-imidazol-2-il)-1,2-benzoxazol-5-carbaldehído (**Intermedio 397**)

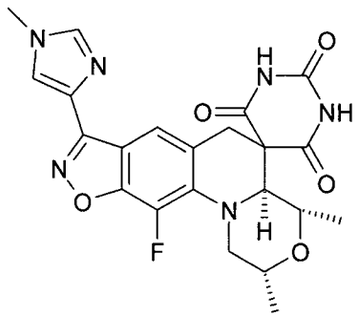
MS (ES) MH^+: 469 para $C_{22}H_{21}FN_6O_6$

^{1}H RMN (400 MHz, DMSO-D6) δ: 1,1 (d, 3H), 1,2 (d, 3H), 3,2 (m, 1H), 3,4 (m, 1H), 3,5 (m, 2H), 3,6 (m, 1H), 3,9 (m, 1H), 4,1 (s, 3H), 4,15 (m, 1H), 7,2 (s,1H), 7,6 (s, 1H), 7,9 (d, 1H), 11,5 (s, 1H), 11,7 (s,1H).

Ejemplo 69

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(1-metil-1*H*-imidazol-4-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±)



Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(1-metil-1*H*-imidazol-4-il)-1,2-benzoxazol-5-carbaldehído (**Intermedio 398**)

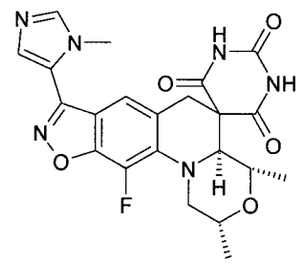
MS (ES) MH^+: 469 para $C_{22}H_{21}FN_6O_6$

^{1}H RMN (400 MHz, DMSO-D6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 3,0 (d, 1H), 3,1 (m, 1H), 3,6 (d, 1H), 3,7 (m, 2H), 3,7 (s, 3H), 3,72 (m, 1H), 4,0 (d, 1H), 4,1 (d, 1H), 7,4 (s, 1H), 7,8 (d, 1H), 11,4 (s a, 1H), 11,8 (s a, 1H).

Ejemplo 70

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(1-metil-1*H*-imidazol-5-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±)



Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(1-metil-1*H*-imidazol-5-il)-1,2-benzoxazol-5-carbaldehído (**Intermedio 399**)

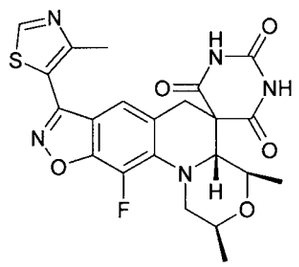
MS (ES) MH^+: 469,5 para $C_{22}H_{21}FN_6O_6$

^{1}H RMN (400 MHz, DMSO-D6) δ: 0,9 (d, 3H), 1,15 (d, 3H), 3,1 (d, 1H), 3,15 (t, 1H), 3,6 (d, 1H), 3,7 (m, 1H), 3,8 (m, 1H), 4,0 (d, 1H), 4,0 (s, 3H), 4,1 (d, 1H), 7,3 (s, 1H), 8,0 (s, 1H), 8,5 (s, 1H), 11,5 (s, 1H), 11,9 (s,1H).

Ejemplo 71

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(4-metil-1,3-tiazol-5-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±)



Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(4-metil-1,3-tiazol-5-il)-1,2-benzoxazol-5-carbaldehído (**Intermedio 400**)

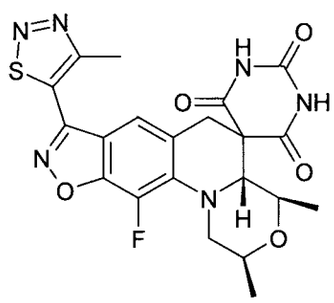
MS (ES) MH^+: 486 para $C_{22}H_{20}FN_6O_5S$

^{1}H RMN (400 MHz, DMSO-D6) δ: 0,9 (d, 3H), 1,5 (d, 3H), 2,6 (s, 3H), 3,0 (d, 1H), 3,1 (t, 1H), 3,7 (m, 2H), 3,8 (m, 1H), 4,0 (d, 1H), 4,1 (d, 1H), 7,3 (s, 1H), 9,35 (s, 1H), 11,5 (s, 1H), 11,9 (s, 1H).

Ejemplo 72

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(4-metil-1,2,3-tiadiazol-5-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±)



Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(4-metil-1,2,3-tiadiazol-5-il)-1,2-benzoxazol-5-carbaldehído (**Intermedio 401**)

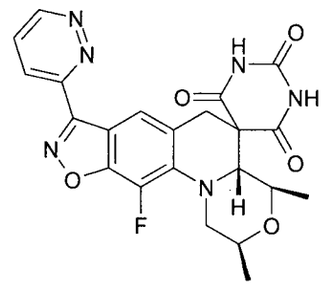
MS (ES) MH^+: 487 para $C_{21}H_{19}FN_6O_5S$

^{1}H RMN (400 MHz, DMSO-D6) δ: 0,9 (d, 3H), 1,15 (d, 3H), 2,9 (s, 3H), 3,0 (d, 1H), 3,1 (t, 1H), 3,6 (d, 1H), 3,7 (m, 1H), 3,8 (m, 1H), 4,0 (d, 1H), 4,1 (d, 1H), 7,4 (s, 1H), 11,5 (s, 1H), 11,9 (s, 1H).

Ejemplo 73

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(piridazin-3-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±)



Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(piridazin-3-il)-1,2-benzoxazol-5-carbaldehído (**Intermedio 402**)

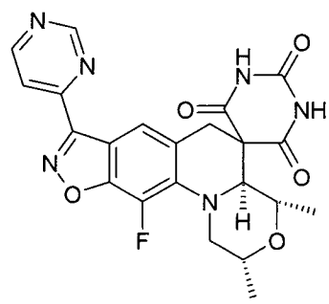
MS (ES) MH^+: 467 para $C_{22}H_{19}FN_6O_5$

^1H RMN (400 MHz, DMSO-D6) δ: 0,9 (d, 3H), 1,15 (d, 3H), 3,0 (d, 1H), 3,1 (t, 1H), 3,6 (d, 1H), 3,7 (m, 1H), 3,8 (m, 1H), 4,0 (d, 1H), 4,1 (d, 1H), 7,9 (m, 2H), 8,4 (m, 1H), 9,4 (m, 1H), 11,5 (s, 1H), 11,8 (s,1H).

Ejemplo 74

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(pirimidin-4-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±)



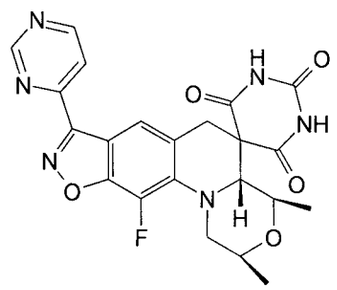
Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(pirimidin-4-il)-1,2-benzoxazol-5-carbaldehído (**Intermedio 403**)

MS (ES) MH^+: 467 para $C_{22}H_{19}FN_6O_5$

^{1}H RMN (400 MHz, DMSO-D6) δ: 0,9 (d, 3H), 1,15 (d, 3H), 3,0 (d, 1H), 3,1 (t, 1H), 3,6 (d, 1H), 3,7 (m, 1H), 3,8 (m, 1H), 4,0 (d, 1H), 4,1 (d, 1H), 7,9 (m, 2H), 8,4 (m, 1H), 9,4 (m, 1H), 11,5 (s, 1H), 11,8 (s,1H).

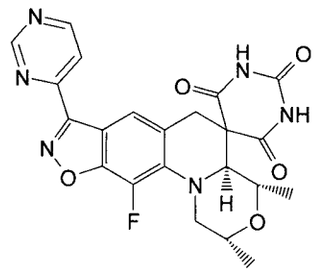
Los enantiómeros (2*S*,4*R*,4a*R*) y (2*R*,4*S*,4a*S*) del **Ejemplo 74** se separaron mediante Cromatografía de Fluidos Supercríticos utilizando una columna Chiralpak AD, 21 x 250 mm, 5 µ (elución con 25% de MeOH, 75% de CO_2 a 60 mL/min, 40 °C y 100 bar con detección a 220 nm).

Ejemplo 74(a) -Compuesto que eluyó en primer lugar
(2S,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(pirimidin-4-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona



MS (ES) MH^+: 467 para $C_{22}H_{19}FN_6O_5$
^{1}H RMN (300 MHz, DMSO-d_6) δ: 0,9 (d, 3H) 1,2 (d, 3H) 2,2 - 3,0 (m, 2H) 3,6 - 4,3 (m, 5H) 7,8 (s, 1H) 8,1 - 8,2 (m, 1H) 9,0 (d, 1H) 9,4 (s, 1H) 11,6 (s, 2H)
>98% ee mediante HPLC quiral; [α] = +199 (c = 0,1 en DMSO).

Ejemplo 74(b) - Compuesto que eluyó en segundo lugar
(2*R*,4S,4a*S*)-11-fluoro-2,4-dimetil-8-(pirimidin-4-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona



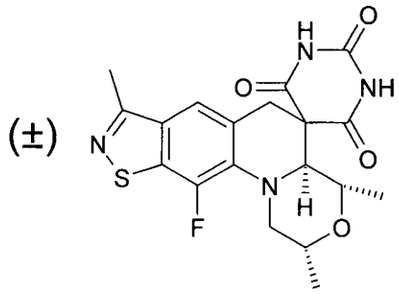
MS (ES) MH^+: 467 para $C_{22}H_{19}FN_6O_5$

^1H RMN (300 MHz, DMSO-d_6) δ: 0,9 (d, 3H) 1,2 (d, 3H) 2,8 - 3,2 (m, 2H) 3,6 - 4,2 (m, 5H) 7,8 (s, 1H) 8,0 - 8,4 (m, 1H) 9,0 (d, 1H) 9,4 (s, 1H) 11,5 (s, 2H)

>98% ee mediante HPLC quiral; [α] = -196 (c = 0,1 en DMSO).

Ejemplo 75

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4,8-trimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]tiazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona



Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-metil-1,2-benzotiazol-5-carbaldehído (**Intermedio 576**)

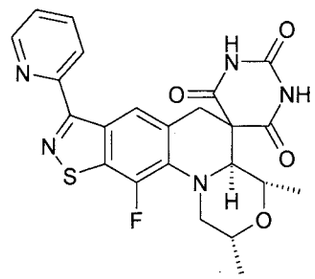
MS (ES) MH^+: 419 para $C_{19}H_{19}FN_4O_4S$

^1H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 2,5 (s, 3H), 3,0 (m, 2H), 3,6 (d, 1H), 3,7 (m, 1H), 3,8 (m, 1H), 4,0 (d, 1H), 4,1 (d, 1H), 7,5 (s, 1H), 11,5 (s, 1H), 11,9 (s, 1H).

Ejemplo 76

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(piridin-2-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]tiazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

103542-1P

(±) 

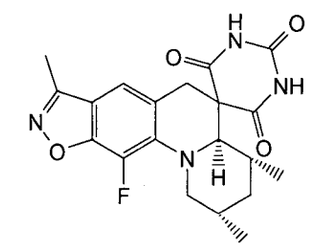
Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(piridin-2-il)-1,2-benzotiazol-5-carbaldehído (**Intermedio 577**)

MS (ES) MH^+: 481 para $C_{23}H_{20}FN_5O_4S$

^1H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,2 (d, 3H), 3,0 (d, 1H), 3,1 (t, 1H), 3,7 (m, 1H), 3,8 (m, 2H), 4,0 (d, 1H), 4,15 (d, 1H), 7,5 (m, 1H), 8,0 (t, 1H), 8,2 (d, 1H), 8,5 (s, 1H), 8,8 (d, 1H), 11,5 (s, 1H), 11,8 (s, 1H).

Ejemplo 77

(2*S*,4*R*,4a*R*)-rel-11-fluoro-2,4,8-trimetil-1,2,3,4,4a,6-hexahidro-1'*H*-espiro[isoxazolo[4,5-g]pirido[1,2-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona

(±) 

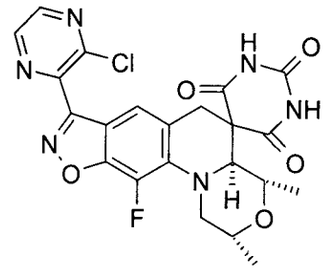
Material de partida: 6-((3*S*,5*R*)-3,5-dimetilpiperidin-1-il)-7-fluoro-3-metilbenzo[d]isoxazol-5-carbaldehído (**Intermedio 538**)

MS (ES) MH^+: 401 para $C_{20}H_{21}FN_4O_4$

^1H RMN (300 MHz, DMSO-d_6) δ ppm 0,6 (d, 3H), 0,8-1,1 (m, 1H), 0,9 (d, 3H), 1,8 (m, 3H), 2,4 (s, 3H), 2,6-3,1 (m, 2H), 3,5 (d, 1H), 3,8 (d, 1H), 3,9-4,0 (m, 1H), 7,1 (s, 1H), 11,4 (s a, 2H).

Ejemplo 78

(2*R*,4*S*,4a*S*)-rel-8-(3-cloropirazin-2-il)-11-fluoro-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona

(±) 

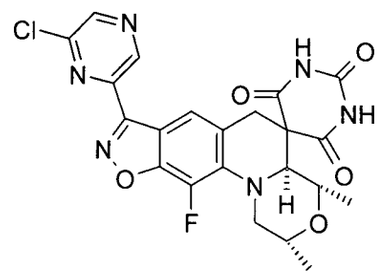
Material de partida: 3-(3-cloropirazin-2-il)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-5-carbaldehído (**Intermedio 432**)

MS (ES) MH^+: 501 para $C_{22}H_{18}ClFN_6O_5$

^1H RMN (300 MHz, DMSO-d_6) δ ppm 0,9 (d, 3H), 1,2 (d, 3H), 3,0 (d, 1H), 3,1 (m, 1H), 3,6-3,7 (m, 2H), 3,7 (m, 1H), 3,9 (d, 1H), 4,2 (d, 1H), 7,9 (d, 1H), 8,9 (d, 1H), 9,0 (d, 1H), 11,5 (s, 1H), 11,9 (s, 1H).

Ejemplo 79

(2*R*,4*S*,4a*S*)-rel-8-(6-cloropirazin-2-il)-11-fluoro-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona

(±) 

Material de partida: 3-(6-cloropirazin-2-il)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-5-carbaldehído (**Intermedio 434**)

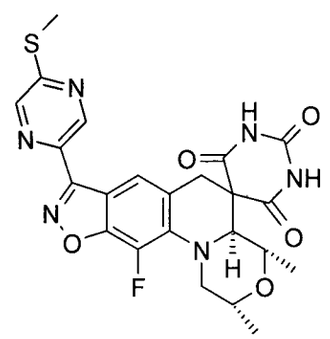
MS (ES) MH^+: 501 para $C_{22}H_{18}ClFN_6O_5$

^1H RMN (300 MHz, DMSO-d_6) δ ppm 0,9 (d, 3H), 1,2 (d, 3H), 3,0 (d, 1H), 3,1-3,2 (m, 1H), 3,7 (dd, 1H), 3,8 (m, 2H), 4,0 (d, 1H), 4,1-4,2 (m, 1H), 7,7 (s, 1H), 9,0 (s, 1H), 9,3 (s, 1H), 11,5 (s, 1H), 11,9 (s, 1H).

Ejemplo 80

103542-1P

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(5-(metiltio)pirazin-2-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona

(±) 

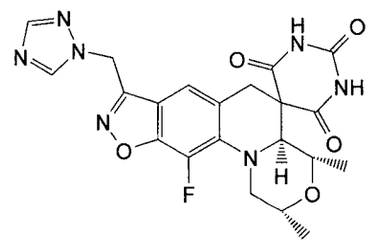
Material de partida: 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(5-(metiltio)pirazin-2-il)benzo[d]isoxazol-5-carbaldehído (**Intermedio 435**)

MS (ES) MH^+: 513 para $C_{23}H_{21}FN_6O_5S$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,9 (d, 3H), 1,2 (d, 3H), 2,7 (s, 3H), 3,0 (d, 1H), 3,1-3,2 (m, 1H), 3,7 (m, 3H), 3,9-4,1 (m, 1H), 4,1 (d, 1H), 7,7 (s, 1H), 8,8 (d, 1H), 9,2 (d, 1H), 11,5 (s a, 1H), 11,8 (s a, 1H).

Ejemplo 81

(2*R*,4*S*,4a*S*)-rel-8-((1*H*-1,2,4-triazol-1-il)metil)-11-fluoro-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona

(±) 

Material de partida: 3-((1*H*-1,2,4-triazol-1-il)metil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-5-carbaldehído (**Intermedio 425**)

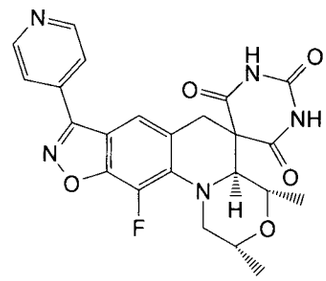
MS (ES) MH^+: 470 para $C_{21}H_{20}FN_7O_5$

^{1}H RMN (300 MHz, $CDCl_3$) δ: 0,87 (d, 3H), 1,12 (d, 3H), 2,85-3,19 (m, 2H), 3,46-4,15 (m, 5H), 5,68-5,93 (m, 2H), 7,01 (s, 1H), 8,00 (s, 1H), 8,76 (s, 1H), 11,45 (s, 1H), 11,81 (s, 1H).

Ejemplo 82

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(piridin-4-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona

(±)



Material de partida: 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(piridin-4-il)benzo[d]isoxazol-5-carbaldehído (**Intermedio 426**)

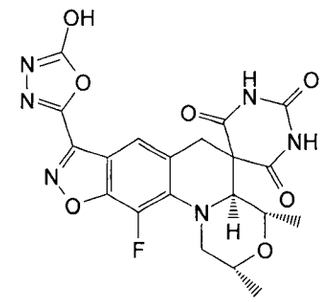
MS (ES) MH^+: 466 para $C_{23}H_{20}FN_5O_5$

^1H RMN (300 MHz, DMSO-d_6) δ: 0,89 (d, 3H), 1,15 (d, 3H), 2,90-4,23 (m, 7H), 7,63 (s, 1H, 7,90 (d, 2H), 8,81 (d, 2H), 11,50 (s, 1H), 11,87 (s, 1H).

Ejemplo 83

(2*R*,4S,4a*S*)-rel-11-fluoro-8-(5-hidroxi-1,3,4-oxadiazol-2-il)-2,4-dimetil-1,2,4,4a-tetrahidro-2'H,6*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(1'H,3'H)-triona

(±)



Material de partida: 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(5-oxo-4,5-dihidro-1,3,4-oxadiazol-2-il)benzo[d]isoxazol-5-carbaldehído (**Intermedio 405**)

MS (ES) MH^+: 473 para $C_{20}H_{17}FN_6O_7$

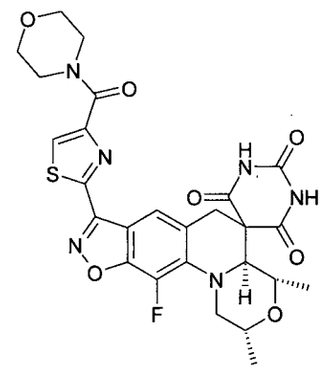
^1H RMN (300 MHz, DMSO-d_6) δ: 0,9 (d, 3H) 1,1 (d, 3H) 2,8 - 3,2 (m, 2H) 3,6 - 4,2 (m, 5H) 7,5 (s, 1H) 11,5 (s a, 1H) 11,8 (s a, 1H) 13,1 (s a, 1H).

Ejemplo 84

103542-1P

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-[4-(morfolin-4-ilcarbonil)-1,3-tiazol-2-il]-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±)

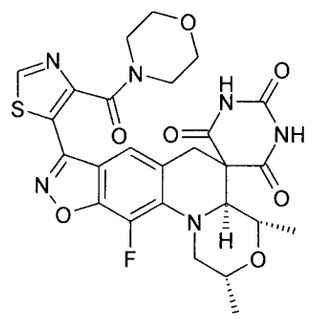


A una solución de 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[4-(morfolin-4-ilcarbonil)-1,3-tiazol-2-il]-1,2-benzoxazol-5-carbaldehído (**Intermedio 389,** 90 mg, 0,19 mmol) en IPA se agregó ácido barbitúrico (24 mg, 0,103 mmol) y la mezcla se calentó a 85 °C durante 16 horas. Los disolventes se evaporaron y el residuo se purificó mediante HPLC de fase inversa para proporcionar el producto como un sólido (como una sal de TFA). Rendimiento: 16 mg (14 %).
MS (ES) MH^+: 585 para $C_{26}H_{25}FN_6O_7S$
^{1}H RMN (400 MHz, DMSO-D6) δ: 0,9 (d, 3H), 1,5 (d, 3H), 3,0 (d, 1H), 3,1 (t, 1H), 3,6-3,8 (m, 11H), 4,0 (d, 1H), 4,1 (d, 1H), 7,6 (s, 1H), 8,4 (s, 1H).

Los **Ejemplos 85** a **93** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Ejemplo 84**:

Ejemplo 85

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-[4-(morfolin-4-ilcarbonil)-1,3-tiazol-5-il]-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±) 

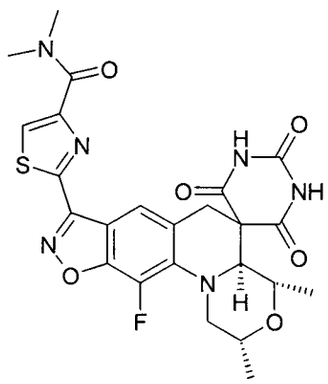
Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-[4-(morfolin-4-ilcarbonil)-1,3-tiazol-5-il]-1,2-benzoxazol-5-carbaldehído (**Intermedio 390**)

MS (ES) MH^+: 585,5 para $C_{26}H_{25}FN_6O_7S$

^{1}H RMN (400 MHz, DMSO-D6) δ: 0,9 (d, 3H), 1,15 (d, 3H), 2,9 (d, 1H), 3,1 (t, 1H), 3,3 (m, 2H), 3,4 (m, 2H), 3,5 (m, 4H), 3,7 (m, 2H), 3,8 (m, 1H), 4,0 (d, 1H), 4,1 (d, 1H), 7,1 (s, 1H), 9,45 (s, 1H), 11,5 (s, 1H), 11,9 (s,1H).

Ejemplo 86

2-[(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-*N*,*N*-dimetil-1,3-tiazol-4-carboxamida

(±) 

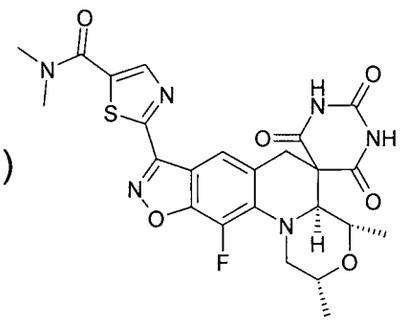
Material de partida: 2-{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-5-formil-1,2-benzoxazol-3-il}-*N*,*N*-dimetil-1,3-tiazol-4-carboxamida (**Intermedio 391**)

MS (ES) MH^+: 543 para $C_{24}H_{23}FN_6$-O_6S

^{1}H RMN (400 MHz, DMSO-D6) δ: 0,9 (d, 3H), 1,15 (d, 3H), 2,9 (s, 3H), 3,0 (s, 3H), 3,05 (d, 1H), 3,2 (t, 1H), 3,7 (m, 2H), 3,8 (m, 1H), 4,0 (d, 1H), 4,1 (d, 1H), 7,1 (s, 1H), 9,4 (s, 1H), 11,5 (s a, 1H), 11,8 (s a,1H).

Ejemplo 87

2-[(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-*N*,*N*-dimetil-1,3-tiazol-5-carboxamida

(±) 

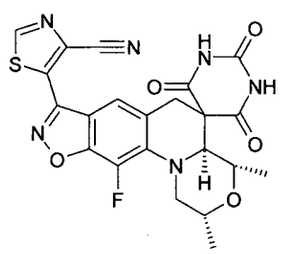
Material de partida: 2-{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-5-formil-1,2-benzoxazol-3-il}-*N*,*N*-dimetil-1,3-tiazol-5-carboxamida (**Intermedio 392**)

MS (ES) MH^+: 543 para $C_{24}H_{23}FN_6O_6S$

^{1}H RMN (400 MHz, DMSO-D6) δ: 0,9 (d, 3H), 1,15 (d, 3H), 2,9 (d, 1H), 3,0 (s, 3H), 3,1 (m, 1H), 3,2 (s, 3H), 3,7 (m, 1H), 3,8 (m, 2H), 4,0 (d, 1H), 4,1 (d, 1H), 7,1 (s, 1H), 9,4 (s, 1H), 11,5 (s a, 1H), 11,8 (s a,1H).

Ejemplo 88

5-[(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-1,3-tiazol-4-carbonitrilo

(±) 

Material de partida: 5-{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-5-formil-1,2-benzoxazol-3-il}-1,3-tiazol-4-carbonitrilo (**Intermedio 393**)

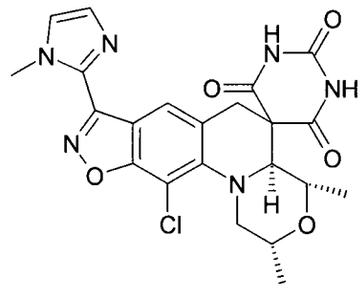
MS (ES) MH^+: 497 para $C_{22}H_{17}FN_6O_5S$

^{1}H RMN (400 MHz, DMSO-D6) δ: 0,9 (d, 3H), 1,15 (d, 3H), 3,0 (d, 1H), 3,1 (m, 1H), 3,6-3,8 (m, 3H), 4,0 (d, 1H), 4,1 (d, 1H), 7,4 (s, 1H), 9,6 (s, 1H), 11,5 (s a, 1H), 11,9 (s a,1H).

Ejemplo 89

(2*R*,4*S*,4a*S*)-rel-11-cloro-2,4-dimetil-8-(1-metil-1*H*-imidazol-2-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona aislada como la sal de TFA a partir de la purificación mediante HPLC de fase inversa.

(±)



Material de partida: 7-cloro-6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-(1-metil-1*H*-imidazol-2-il)-1,2-benzoxazol-5-carbaldehído (**Intermedio 387**)

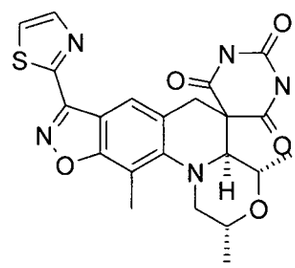
MS (ES) MH^+: 485 para $C_{22}H_{21}ClN_6O_5$

^{1}H RMN (400 MHz, DMSO-D6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 3,0 (d, 1H), 3,1 (m, 1H), 3,8 (m, 2H), 4,0 (m, 5H), 4,5 (d, 1H), 7,2 (s, 1H), 7,5 (s, 1H), 7,9 (s, 1H), 11,4 (s, 1H), 11,8 (s, 1H).

Ejemplo 90

(2*R*,4*S*,4a*S*)-rel-2,4,11-trimetil-8-(1,3-tiazol-2-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±)



Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-metil-3-(1,3-tiazol-2-il)-1,2-benzoxazol-5-carbaldehído (**Intermedio 330**)

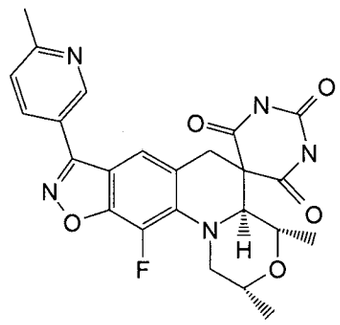
MS (ES) MH^+: 468 para $C_{22}H_{21}N_5O_5S$

^{1}H RMN (400 MHz, DMSO-d6) δ: 0,9 (d, 3H), 1,2 (d, 3H), 2,5 (s, 3H), 3,1 (m, 2H), 3,6 (m, 2H), 3,9 (m, 2H), 4,1 (d, 1H), 7,7 (s, 1H), 8,0 (d, 1H), 8,1 (d, 1H), 11,4 (s, 1H), 11,8 (s, 1H).

Ejemplo 91

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(6-metilpiridin-3-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona

(±)



Material de partida: 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(6-metilpiridin-3-il)benzo[d]isoxazol-5-carbaldehído (**Intermedio 421**)

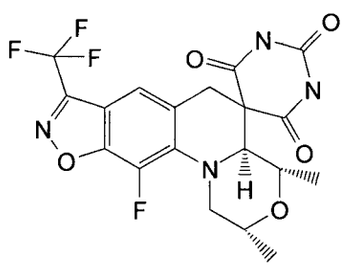
MS (ES) MH^+: 480 para $C_{24}H_{22}FN_5O_5$

^{1}H RMN (300 MHz, DMSO-d_6) δ: 0,89 (d, 3H), 1,15 (d, 3H), 2,57 (s, 3H), 2,88-3,24 (m, 2H), 3,51-4,22 (m, 5H), 7,49 (d, 1H), 7,59 (s, 1H), 8,19 (d, 1H), 8,97 (s, 1H), 11,48 (s, 1H), 11,86 (s, 1H).

Ejemplo 92

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(trifluorometil)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona

(±)



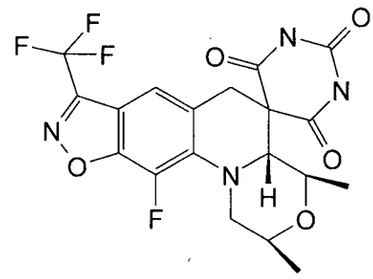
Material de partida: 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(trifluorometil)benzo[d]isoxazol-5-carbaldehído (**Intermedio 429**)

MS (ES) MH^+: 457 para $C_{19}H_{16}F_4N_4O_5$

^{1}H RMN (300 MHz, DMSO-d_6) δ: 0,89 (d, 3H), 1,14 (d, 3H), 2,86-3,24 (m, 2H), 3,54-4,28 (m, 5H), 7,35 (s, 1H), 11,56 (s, 1H), 11,91 (s, 1H).

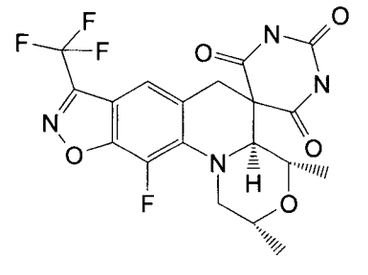
Los enantiómeros (2*S*,4*R*,4a*R*) y (2*R*,4*S*,4a*S*) del **Ejemplo 92** se separaron mediante Cromatografía de Fluidos Supercríticos utilizando una columna Chiralpak AD, 21 x 250 mm, 5 µ (elución con 25% de MeOH, 75% de CO_2 a 60 mL/min, 40 °C y 100 bar con detección a 220 nm), para proporcionar el **Ejemplo 92(a)** y el **Ejemplo 92(b)**:

Ejemplo 92(a) - Compuesto que eluyó en primer lugar
(2S,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(trifluorometil)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona



MS (ES) MH^+: 457 para $C_{19}H_{16}F_4N_4O_5$
^{1}H RMN (300 MHz, DMSO-d_6) δ: 0,89 (d, 3H), 1,14 (d, 3H), 2,83-3,21 (m, 2H), 3,57-4,23 (m, 5H), 7,34 (s, 1H), 11,72 (s, 2H).
>98% ee mediante HPLC quiral; [α] = +285 (c = 0,1 en MeOH).

Ejemplo 92(b) - Compuesto que eluyó en segundo lugar
(2*R*,4S,4a*S*)-11-fluoro-2,4-dimetil-8-(trifluorometil)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona

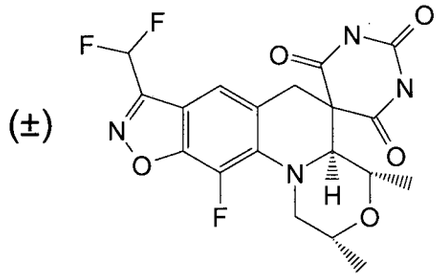


MS (ES) MH^+: 457 para $C_{19}H_{16}F_4N_4O_5$

^{1}H RMN (300 MHz, DMSO-d_6) δ: 0,89 (d, 3H), 1,14 (d, 3H), 2,89-3,25 (m, 2H), 3,56-4,30 (m, 5H), 7,34 (s, 1H), 11,72 (s, 2H).
>98% ee mediante HPLC quiral; [α] = -305 (c = 0,1 en MeOH).

Ejemplo 93

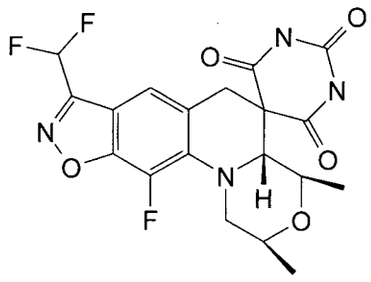
(2*R*,4S,4a*S*)-rel-8-(difluorometil)-11-fluoro-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona



Material de partida: 3-(difluorometil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-5-carbaldehído (**Intermedio 428**)
MS (ES) MH^+: 439 para $C_{19}H_{17}F_3N_4O_5$
^{1}H RMN (300 MHz, DMSO-d_6) δ: 0,88 (d, 3H), 1,14 (d, 3H), 2,82-3,24 (m, 2H), 3,55-4,20 (m, 5H), 7,30 (s, 1H), 7,52 (t, 1H), 11,52 (s, 1H), 11,87 (s, 1H).

Los enantiómeros (2*S*,4*R*,4a*R*) y (2*R*,4*S*,4a*S*) del **Ejemplo 93** se separaron mediante Cromatografía de Fluidos Supercríticos utilizando una columna Chiralpak AD, 21 x 250 mm, 5 µ (elución con 25% de MeOH, 75% de CO_2 a 60 mL/min, 40 °C y 100 bar con detección a 220 nm), para proporcionar el **Ejemplo 93(a)** y el **Ejemplo 93(b)**:

Ejemplo 93(a) - Compuesto que eluyó en primer lugar
(2S,4*R*,4a*R*)-8-(difluorometil)-11-fluoro-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona



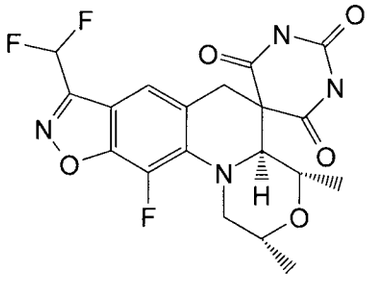
MS (ES) MH^+: 439 para $C_{19}H_{17}F_3N_4O_5$

^1H RMN (300 MHz, DMSO-d_6) δ: 0,88 (d, J = 6,41 Hz, 3H), 1,14 (d, J = 6,03 Hz, 3H), 2,84-3,21 (m, 2H), 3,56-4,19 (m, 5H), 7,30 (s, 1H), 7,52 (t, J = 52,65 Hz, 1H), 11,67 (s a, 2H).

>98% ee mediante HPLC quiral; [δ] = +276 (c = 0,1 en MeOH).

Ejemplo 93(b) - Compuesto que eluyó en segundo lugar

(2*R*,4S,4a*S*)-8-(difluorometil)-11-fluoro-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona



MS (ES) MH^+: 439 para $C_{19}H_{17}F_3N_4O_5$

^1H RMN (300 MHz, DMSO-d_6) δ: 0,90 (d, 3H), 1,15 (d, 3H), 2,81-3,24 (m, 2H), 3,57-4,21 (m, 5H), 7,31 (s, 1H), 7,53 (t, 1H), 11,70 (s a, 2H).

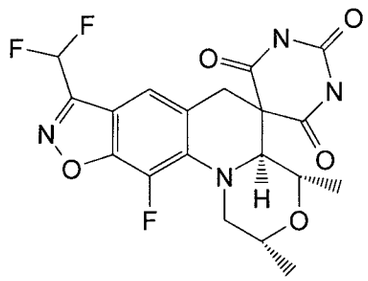
>98% ee mediante HPLC quiral; [α] = -289 (c = 0,1 en MeOH).

Utilizando una ruta alternativa, el **Ejemplo 93(b)** también se obtuvo mediante una síntesis quiral similar a la descrita para la síntesis del **Ejemplo 96**, utilizando el material de partida indicado:

Ejemplo 93(b) (Síntesis Quiral)

(2*R*,4S,4a*S*)-8-(difluorometil)-11-fluoro-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona

103542-1P



Material de partida: 3-(difluorometil)-6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-5-carbaldehído (**Intermedio 431**)

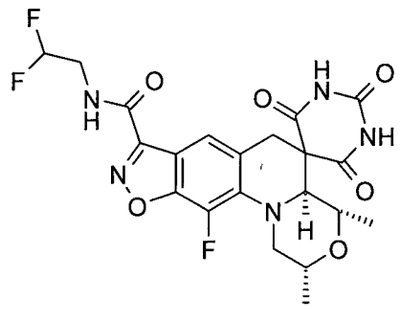
MS (ES) MH^+: 439 para $C_{19}H_{17}F_3N_4O_5$

^{1}H RMN (300 MHz, DMSO-d_6) δ: 0,90 (d, 3H), 1,15 (d, 3H), 2,81-3,24 (m, 2H), 3,57-4,21 (m, 5H), 7,31 (s, 1H), 7,53 (t, 1H), 11,70 (s a, 2H).

Ejemplo 94

(2*R*,4S,4a*S*)-rel-*N*-(2,2-difluoroetil)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-8-carboxamida

(±)



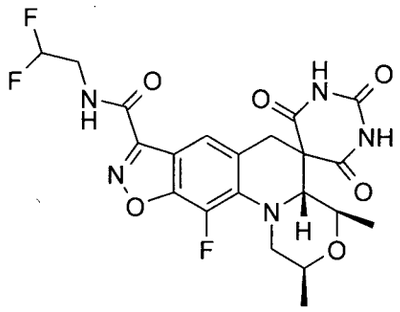
Material de partida: se hicieron reaccionar ácido barbitúrico y *N*-(2,2-difluoroetil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formilbenzo[d]isoxazol-3-carboxamida (**Intermedio 467**) utilizando un método similar al descrito para la síntesis del **Ejemplo 134**. El producto se purificó mediante HPLC de fase inversa utilizando un gradiente de CH_3CN en agua con 0,1% de TFA.

MS (ES) MH^+: 496 para $C_{21}H_{20}F_3N_5O_6$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,9 (d, 3H), 1,2 (d, 3H), 2,9 (d, 1H), 3,1 (t, 1H), 3,6-3,9 (m, 5H), 4,0 (d, 1H), 4,1 (d, 1H), 5,9-6,4 (m, 1H), 7,4 (s, 1H), 9,3 (t, 1H), 11,6 (s a, 2H).

Los enantiómeros (2*S*,4*R*,4a*R*) y (2*R*,4*S*,4a*S*) del **Ejemplo 94** se separaron mediante Cromatografía de Fluidos Supercríticos utilizando una columna Chiralpak AD, 21 x 250 mm, 5 µ (elución con 25% de MeOH, 75% de CO_2 a 60 mL/min, 40 °C y 100 bar con detección a 220 nm), para proporcionar el **Ejemplo 94(a)** y el **Ejemplo 94(b)**:

Ejemplo 94(a) - Compuesto que eluyó en primer lugar (2S,4*R*,4a*R*)-*N*-(2,2-difluoroetil)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-8-carboxamida

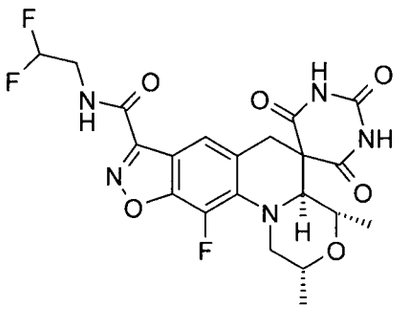


MS (ES) MH^+: 496 para $C_{21}H_{20}F_3N_5O_6$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,9 (d, 3H), 1,2 (d, 3H), 2,9 (d, 1H), 3,1-3,2 (m, 1H), 3,6-3,9 (m, 5H), 4,0 (d, 1H), 4,1 (d, 1H), 5,9-6,4 (m, 1H), 7,5 (s, 1H), 9,3 (t, 1H), 11,5 (s, 1H), 11,8 (s, 1H).

>98% ee mediante HPLC quiral; [α] = +297 (c = 0,1 en DMSO)

Ejemplo 94(b) - Compuesto que eluyó en segundo lugar (2*R*,4S,4a*S*)-*N*-(2,2-difluoroetil)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-8-carboxamida



MS (ES) MH^+: 496 para $C_{21}H_{20}F_3N_5O_6$

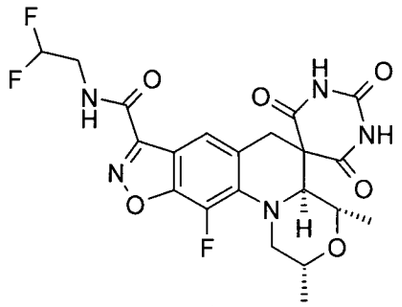
^{1}H RMN (300 MHz, DMSO-*d6*) δ ppm 0,9 (d, 3H), 1,2 (d, 3H), 2,9 (d, 1H), 3,1-3,2 (m, 1H), 3,6-3,9 (m, 5H), 4,0 (d, 1H), 4,1 (d, 1H), 5,9-6,4 (m, 1H), 7,5 (s, 1H), 9,3 (t, 1H), 11,5 (s, 1H), 11,8 (s, 1H).

>98% ee mediante HPLC quiral; [α] = -225 (c = 0,1 en DMSO)

Utilizando una ruta alternativa, el **Ejemplo 94(b)** también se obtuvo mediante una síntesis quiral similar a la descrita para la síntesis del **Ejemplo 95(a)** a continuación, utilizando el material de partida indicado:

Ejemplo 94(b) (Síntesis Quiral)

(2*R*,4S,4a*S*)-*N*-(2,2-difluoroetil)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-8-carboxamida



Material de partida: *N*-(2,2-difluoroetil)-6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-5-formilbenzo[d]isoxazol-3-carboxamida (**Intermedio 248**)

MS (ES) MH^+: 246 para $C_{21}H_{20}F_3N_5O_6$

>98% ee mediante HPLC quiral; [α] = -256 (c = 0,1 en MeOH)

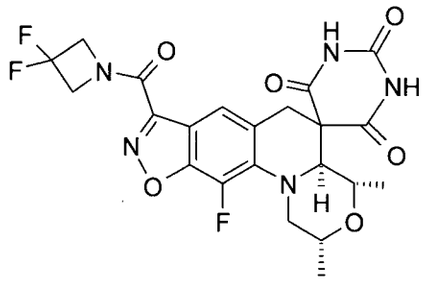
^{1}H RMN (300 MHz, DMSO-d6) δ ppm 0,9 (d, 3H), 1,2 (d, 3H), 2,9 (d, 1H), 3,1 (t, 1H), 3,6 - 3,9 (m, 4H), 4,0 (d, 1H), 4,1 (d, 1H), 5,9 - 6,4 (m, 1H), 7,4 (s, 1H), 9,3 (t, *J* = 6,0 Hz, 1H), 11,5 (s a, 1H), 11,8 (s a, 1H).

El **Ejemplo 95** se preparó a partir del material de partida indicado y ácido barbitúrico utilizando un método similar al descrito para la síntesis del **Ejemplo 134**. Los compuestos se purificaron mediante cromatografía en columna de gel de sílice utilizando un gradiente de DCM a acetato de etilo.

Ejemplo 95

(2*R*,4S,4a*S*)-rel-8-(3,3-difluoroazetidin-1-carbonil)-11-fluoro-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona

(±)



Material de partida: 3-(3,3-difluoroazetidin-1-carbonil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-5-carbaldehído (**Intermedio 446**)

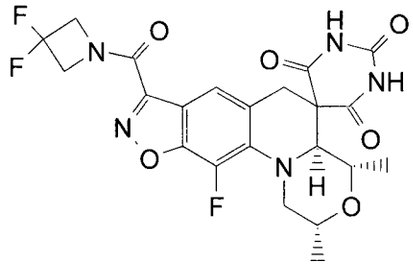
MS (ES) MH^+: 508 para $C_{22}H_{20}F_3N_5O_6$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,8 (d, 3H), 1,1 (d, 3H), 2,8 (d, 1H), 3,1 (t, 1H), 3,5-3,8 (m, 3H), 3,9 (d, 1H), 4,1 (d, 1H), 4,5 (t, 2H), 4,9 (t, 2H), 7,4 (s, 1H), 11,4 (s a, 1H), 11,8 (s a, 1H).

En una ruta alternativa, el enantiómero (2*R*,4S,4aS) del **Ejemplo 95** se sintetizó mediante síntesis quiral, para proporcionar el **Ejemplo 95(a)**:

Ejemplo 95(a)

(2*R*,4S,4a*S*)-8-(3,3-difluoroazetidin-1-carbonil)-11-fluoro-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona



Se disolvió 3-(3,3-difluoroazetidina-1-carbonil)-6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-5-carbaldehído (**Intermedio 245**, 2,08 g, 5,23 mmol) en ~100 mL de

etanol y se calentó con ácido barbitúrico (0,704 g, 5,50 mmol) a 105 °C (temperatura externa) durante 6 días. La reacción se adsorbió en celite luego se purificó mediante cromatografía en gel de sílice utilizando un gradiente de DCM a acetato de etilo. Las fracciones se combinaron y se concentraron. Este material luego se purificó mediante Cromatografía de Fluidos Supercríticos (separación de diastereómeros), utilizando una columna Chiralpak AD, 21 x 250 mm, 5 µ (elución con 40% de isopropanol, 60% de CO_2 a 60 mL/min, 40 °C y 100 bar con detección a 220 nm), para proporcionar el compuesto del título (2,16 g, 4,26 mmol, 81 %) como el compuesto que eluyó en primer lugar.

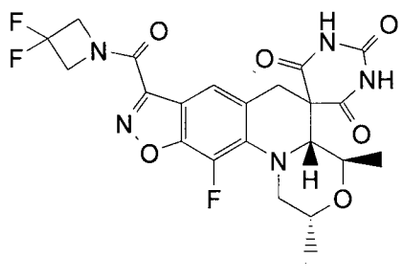
MS (ES) MH^+: 508 para $C_{22}H_{20}F_3N_5O_6$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,9 (d, 3H), 1,1 (d, 3H), 2,9 (d, 1H), 3,2 (t, 1H), 3,6-3,9 (m, 3H), 4,0 (d, 1H), 4,1 (d, 1H), 4,6 (t, 2H), 4,9 (t, 2H), 7,5 (s, 1H), 11,5 (s a, 1H), 11,9 (s a, 1H).

>98% ee mediante HPLC quiral; [α] = -296 (c = 0,1 en MeOH)

Ejemplo 95(b)

(2*R*,4*R*,4a*R*)-8-(3,3-difluoroazetidin-1-carbonil)-11-fluoro-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-trione



El diastereómero (2*R*,4*R*,4a*R*) se generó como un producto secundario de la reacción descrita para la síntesis del **Ejemplo 95(a)**. La cromatografía descrita para el **Ejemplo 95(a)** proporcionó el diastereómero (2*R*,4*R*,4a*R*) como el compuesto que eluyó en segundo lugar.

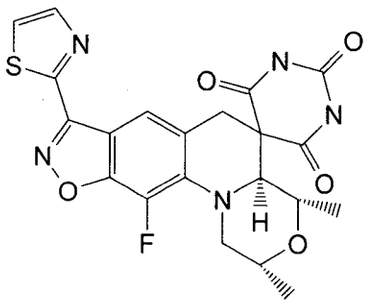
MS (ES) MH^+: 508 para $C_{22}H_{20}F_3N_5O_6$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,9 (d, 3H), 1,3 (d, 3H), 3,1 (d, 1H), 3,6 (d, 1H), 3,7 (d, 1H), 3,8 (d, 1H), 3,9 - 4,0 (m, 2H), 4,0 - 4,2 (m, 1H), 4,6 (t, 2H), 4,9 (t, 2H), 7,5 (s, m 1H), 11,5 (s a, 1H), 11,8 (s a, 1H).

[α] = +169 (c=0,1 en metanol)

Ejemplo 96

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimetil-8-(tiazol-2-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona



Una mezcla de 6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-3-(tiazol-2-il)benzo[d]isoxazol-5-carbaldehído (**Intermedio 430**, 1,414 g, 3,91 mmol) y pirimidina-2,4,6(1H,3H,5H)-triona (0,501 g, 3,91 mmol) en etanol (200 mL) se calentó a 90 °C durante 5 días. El disolvente se eliminó. La LCMS de la reacción bruta indicó una mezcla 9:1 de dos productos diastereoméricos. El producto principal se purificó mediante HPLC de fase inversa preparativa para proporcionar el compuesto del título (1,320 g, 71,6 %).

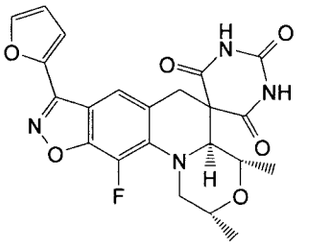
MS (ES) MH^+: 472 para $C_{21}H_{18}FN_5O_5S$

^{1}H RMN (300 MHz, DMSO-d_6) δ: 0,89 (d, 3H), 1,15 (d, 3H), 2,85-3,23 (m, 2H), 3,60-4,22 (m, 5H), 7,72 (s, 1H), 8,08 (d, 1H), 8,17 (d, 1H), 11,48 (s, 1H), 11,84 (s, 1H).

Ejemplo 97

(2*R*,4S,4a*S*)-rel-11-fluoro-8-(furan-2-il)-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona

(±)



Una mezcla de 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(furan-2-il)benzo[d]isoxazol-5-carbaldehído (**Intermedio 427,** 95 mg, 0,28 mmol) y pirimidina-2,4,6(1H,3H,5H)-triona (38,9

mg, 0,30 mmol) en isopropanol (10 mL) se calentó a 90 °C durante 2 días. El disolvente se eliminó. El residuo se lavó con metanol y el sólido se filtró, se lavó con una pequeña cantidad de metanol y se secó para proporcionar compuesto del título (107 mg, 85 %).

MS (ES) MH^+: 455 para $C_{22}H_{19}FN_4O_6$

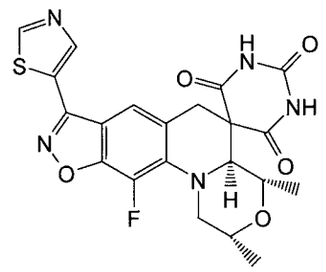
^1H RMN (300 MHz, DMSO-d_6) δ: 0,89 (d, 3H), 1,14 (d, 3H), 2,89-4,23 (m, 7H), 6,79 (dd, 1H), 7,33 (d, 1H), 7,59 (s, 1H), 8,01 (d, 1H), 11,50 (s, 1H), 11,87 (s, 1H).

Los **Ejemplos 98** a **101** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Ejemplo 97:**

Ejemplo 98

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(tiazol-5-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona

(±)



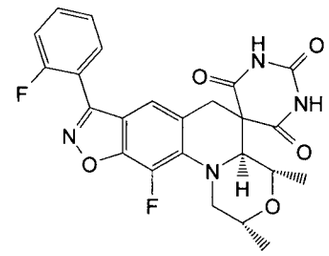
Material de partida: 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(tiazol-5-il)benzo[d]isoxazol-5-carbaldehído (**Intermedio 422**)

MS (ES) MH^+: 472 para $C_{21}H_{18}FN_5O_5S$

^1H RMN (300 MHz, DMSO-d_6) δ: 0,89 (d, 3H), 1,15 (d, 3H,) 2,92-3,24 (m, 2H), 3,43-4,23 (m, 5H), 7,74 (s, 1H), 8,72 (s, 1H), 9,37 (s, 1H), 11,52 (s, 1H), 11,89 (s, 1H).

Ejemplo 99

(2*R*,4S,4a*S*)-rel-11-fluoro-8-(2-fluorofenil)-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona

(±) 

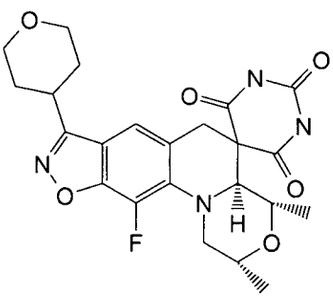
Material de partida: 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(2-fluorofenil)benzo[d]isoxazol-5-carbaldehído (**Intermedio 423**)

MS (ES) MH^+: 483 para $C_{24}H_{20}F_2N_4O_5$

^1H RMN (300 MHz, DMSO-d_6) δ: 0,88 (d, 3H), 1,15 (d, 3H), 2,86-3,21 (m, 2H), 3,50-4,21 (m, 5H), 7,22 (s, 1H), 7,30-7,88 (m, 4H), 11,46 (s, 1H), 11,82 (s, 1H).

Ejemplo 100

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(tetrahidro-2*H*-piran-4-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona

(±) 

Material de partida: 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(tetrahidro-2*H*-piran-4-il)benzo[d]isoxazol-5-carbaldehído (**Intermedio 424**)

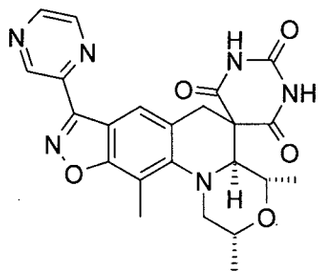
MS (ES) MH^+: 473 para $C_{23}H_{25}FN_4O_6$

^1H RMN (300 MHz, DMSO-d_6) δ: 0,88 (d, 3H), 1,13 (d, 3H), 1,71-1,97 (m, 4H), 2,87-4,15 (m, 12H), 7,34 (s, 1H), 11,48 (s, 1H), 11,83 (s, 1H).

Ejemplo 101

(2*R*,4*S*,4a*S*)-rel-2,4,11-trimetil-8-(pirazin-2-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

103542-1P

(±) 

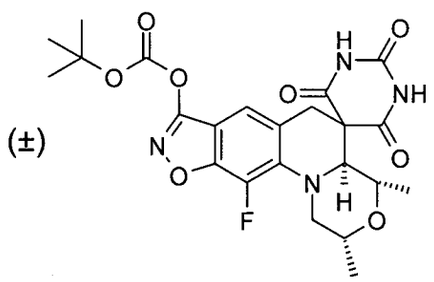
Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-metil-3-(pirazin-2-il)-1,2-benzoxazol-5-carbaldehído (**Intermedio 331**)

MS (ES) MH^+: 463 para $C_{23}H_{22}N_6O_5$

^{1}H RMN (400 MHz, DMSO-d6) δ: 0,9 (d, 3H), 1,2 (d, 3H), 2,5 (s, 3H), 3,1 (m, 2H), 3,6 (m, 2H), 3,9 (m, 2H), 4,1 (d, 1H), 7,7 (s, 1H), 8,3 (s, 1H), 8,8 (d, 1H), 8,9 (d, 1H), 9,3 (s, 1H), 11,5 (s a, 2H).

Ejemplo 102

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidi]-8-ilcarbonato de *terc*-butilo

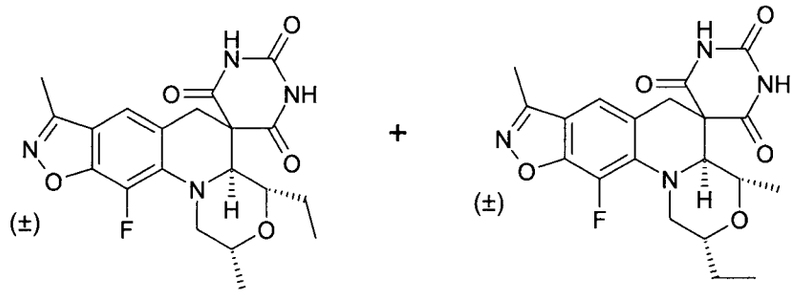
(±) 

A una solución agitada de 6,7-difluoro-5-formil-1,2-bencisoxazol-3-ilcarbonato de *terc*-butilo **Intermedio 531** (175 mg, 0,44 mmol) en IPA seco (10 mL) se agregó ácido barbitúrico (8 mg, 0,062 mmol) y la solución se calentó a aproximadamente 80 °C durante 12 h. Los disolventes se evaporaron y el residuo se purificó sobre una columna de gel de sílice para proporcionar un producto como un sólido blanco. Rendimiento: 40 mg (18%).

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 1,6 (s, 9H), 2,9 (d, 1H), 3,1 (t, 1H), 3,6 (d, 1H), 3,7 (m, 1H), 3,8 (m, 1H), 3,9 (d, 1H), 4,0 (d, 1H), 7,0 (s, 1H), 11,5 (s, 1H), 11,8 (s, 1H).

Ejemplos 103 y 104

(2*R*,4*S*,4a*S*)-rel-8-acetil-9,10-difluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona **(Ejemplo 103)** y (2*R*,4S,4a*S*)-rel-2-etil-11-fluoro-4,8-dimetil-1,2,4,4a-tetrahidro-2'H,6*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(1'H,3'H)-triona **(Ejemplo 104)**



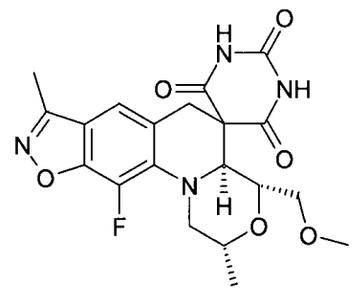
A una solución de 6-(2-etil-6-metilmorfolin-4-il)-7-fluoro-3-metil-1,2-bencisoxazol-5-carbaldehído (**Intermedio 501,** 3,0 g, 9,17 mmol) en IPA se agregó ácido barbitúrico (1,4 g, 11,00 mmol) y la mezcla se calentó a 85 °C durante 12 horas. Los disolventes se evaporaron y el residuo obtenido de esta forma se purificó sobre alúmina neutra utilizando un gradiente de metanol en CH_2Cl_2 para proporcionar el producto como un sólido blanquecino como una mezcla de isómeros. Rendimiento: 3,0 g (75%).

MS (ES) MH^+: 417 para $C_{20}H_{21}FN_4O_5$

^{1}H RMN (400 MHz – DMSO-D6) δ: 0,8 (t, 2H), 0,80 (d, 2H), 0,9 (t, 2H), 1,1 (t, 2H), 1,4 (m, 1H), 2,35 (s, 3H), 2,9 (m, 1H), 3,0 (m, 1H), 3,5 (m, 2H), 3,6-3,7 (m, 1H), 3,9 (m, 1H), 4,0 (m, 1H), 7,1 (d, 1H), 11,5 (a, 2H).

Los **Ejemplos 105 y 106** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Ejemplo 103 y 104.** Los 2 regioisómeros resultantes se separaron se separaron mediante cromatografía.

Ejemplo 105 - Compuesto que eluyó en primer lugar (2*R*,4*R*,4a*S*)-rel-11-fluoro-4-(metoximetil)-2,8-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

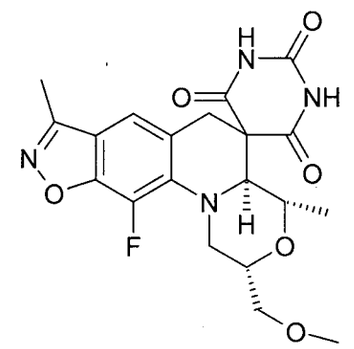
(±) 

Material de partida: 7-fluoro-6-[(2*S*,6*S*)-2-(metoximetil)-6-metilmorfolin-4-il]-3-metil-1,2-benzoxazol-5-carbaldehído (**Intermedio 503**)

MS (ES) MH^+: 433 para $C_{20}H_{21}FN_4O_6$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 1,1 (d, 3H), 2,5 (s, 3H), 2,9 (d, 1H), 3,05 (s, 3H), 3,1 (m, 2H), 3,3 (m, 1H), 3,4 (m, 1H), 3,8 (m, 2H), 4,0 (m, 2H), 7,2 (s, 6H), 11,0 (s, 1H), 11,5 (s, 1H).

Ejemplo 106 - Compuesto que eluyó en segundo lugar (2*S*,4*S*,4a*S*)-rel-11-fluoro-2-(metoximetil)-4,8-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±) 

Material de partida: 7-fluoro-6-[(2*S*,6*S*)-2-(metoximetil)-6-metilmorfolin-4-il]-3-metil-1,2-benzoxazol-5-carbaldehído (**Intermedio 503**)

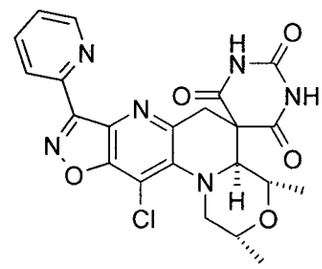
MS (ES) MH^+: 433 para $C_{20}H_{21}FN_4O_6$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 2,5 (s, 3H), 3,0 (d, 1H), 3,25 (m, 1H), 3,3 (s, 3H), 3,3-3,4 (m, 2H), 3,5 (m, 1H), 3,7 (m, 1H), 3,8 (m, 1H), 3,9 (d, 1H), 4,1 (d, 1H), 7,2 (s, 6H), 11,4-11,8 (a, 2H).

Ejemplo 107

(2*R*,4S,4a*S*)-rel-11-cloro-2,4-dimetil-8-(piridin-2-il)-2,4,4*a*,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*) –triona (sal de ácido trifluoroacético)

(±)



Una mezcla de 7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(piridin-2-il)isoxazolo[4,5-b]piridin-5-carbaldehído (**Intermedio 406**, 0,165 g, 0,44 mmol) y ácido barbitúrico (0,057 g, 0,44 mmol) en 10 mL de IPA se calentó hasta alcanzar 80 °C durante 2 días. La mezcla se concentró y el residuo se purificó mediante cromatografía sobre gel de sílice utilizando 10% de metanol (0,1% de hidróxido de amonio) en diclorometano para proporcionar 170 mg de un producto como un sólido blanco. La purificación adicional se realizó mediante HPLC de fase inversa en una columna Waters XBridge C-18 eluyendo con el 20-90% de agua/acetonitrilo con ácido trifluoroacético para proporcionar 25 mg del compuesto del título como la sal de ácido mono trifluoroacético.

MS (ES) MH^+: 483 para $C_{22}H_{19}ClN_6O_5$ (sal de ácido trifluoroacético)

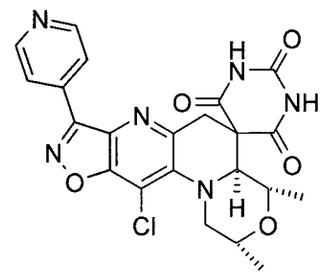
^{1}H RMN (300 MHz, DMSO-d_6) δ: 0,9 (d, 3H) 1,2 (s a, 1H) 1,2 (d, 3H) 3,1 (dd, 1H) 3,3 (d, 1H) 3,5 – 3,7 (m, 1H) 3,9 – 4,0 (m, 1H) 4,4 (d, 1H) 5,7 (s a, 1H) 7,6 (dd, 1H) 8,0 (t, 1H) 8,3 (d, 1H) 8,8 (d, 1H) 11,6 (s, 1H) 11,9 (s, 1H).

Los **Ejemplos 108** a **111** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Ejemplo 107:**

Ejemplo 108

(2*R*,4S,4a*S*)-rel-11-cloro-2,4-dimetil-8-(piridin-4-il)-2,4,4*a*,6-tetrahidro-1*H*, 1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona (sal de ácido trifluoroacético)

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(±) 

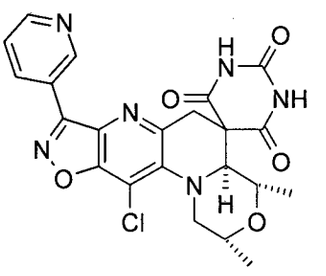
Material de partida: 7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(piridin-4-il)isoxazolo[4,5-b]piridin-5-carbaldehído (**Intermedio 407**)

MS (ES) MH^+: 483 para $C_{22}H_{19}ClN_6O_5$

^1H RMN (300 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 3,1 (m, 1H), 3,3 (d, 1H), 3,6 (m, 1H), 3,7 (d, 1H), 4,0 (d, 2H), 4,4 (d, 1H), 8,3 (d, 2H), 8,8 (d, 2H), 11,6 (s, 1H), 12,0 (s, 1H).

Ejemplo 109

(2*R*,4S,4a*S*)-rel-11-cloro-2,4-dimetil-8-(piridin-3-il)-2,4,4*a*,6-tetrahidro-1*H*, 1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona (sal de ácido trifluoroacético)

(±) 

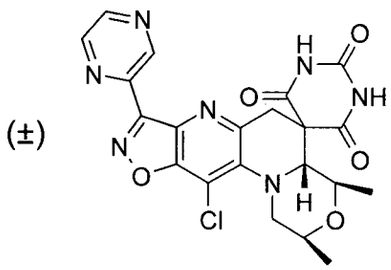
Material de partida: 7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(piridin-3-il)isoxazolo[4,5-b]piridin-5-carbaldehído (**Intermedio 408**)

MS (ES) MH^+: 483 para $C_{22}H_{19}ClN_6O_5$

^1H RMN (300 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 4H), 3,1 (dd, 1H), 3,3 (d, 1H), 3,6 (dd, 1H), 3,7 (d, 1H), 3,9–4,0 (m, 2H), 4,4 (d, 1H), 7,6 (dd, 2H), 8,6 (dt, 1H), 8,8 (dd, 1H), 9,4 (d, 1H), 11,6 (s, 1H), 11,9 (s, 1H).

Ejemplo 110

(2*R*,4S,4a*S*)-rel-11-cloro-2,4-dimetil-8-(pirazin-2-il)-2,4,4*a*,6-tetrahidro-1*H*, 1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona (sal de ácido trifluoroacético)



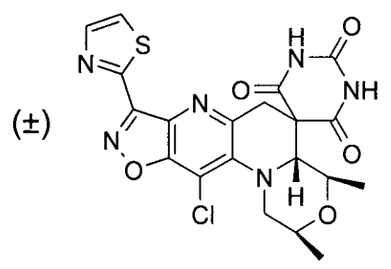
Material de partida: 7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(pirazin-2-il)isoxazolo[4,5-b]piridin-5-carbaldehído (**Intermedio 409**)

MS (ES) MH^+: 484 para $C_{21}H_{18}ClN_7O_5$

^1H RMN (300 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1-1,2 (m, 3H), 3,1 (d, 1H), 3,3 (d, 1H), 3,6 (d, 1H), 3,7 (d, 1H), 3,9–4,0 (m, 2H), 4,4 (d, 1H), 8,8–8,9 (m, 2H), 9,5 (d, 1H), 11,6 (s, 1H), 11,9 (s, 1H).

Ejemplo 111

(2*R*,4S,4a*S*)-rel-11-cloro-2,4-dimetil-8-(tiazol-2-il)-2,4,4*a*,6-tetrahidro-1*H*, 1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona



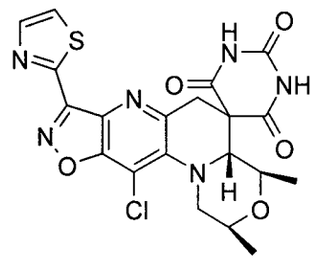
Material de partida: 7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(tiazol-2-il)isoxazolo[4,5-b]piridin-5-carbaldehído (**Intermedio 410**)

MS (ES) MH^+: 489 para $C_{20}H_{17}ClN_6O_5S$

^1H RMN (300 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1-,2 (m, 4H), 3,1 (dd, 1H), 3,3 (d, 1H), 3,6 (dd, 1H), 3,7 (d, 1H), 3,9 (m, 1H), 4,0 (d, 1H), 4,4 (s a,1H), 8,1–8,2 (m, 1H), 11,6 (s, 1H), 11,9 (s, 1H).

Los enantiómeros (2*S*,4*R*,4a*R*) y (2*R*,4*S*,4a*S*) del **Ejemplo 111** se separaron mediante Cromatografía de Fluidos Supercríticos utilizando una columna Chiralpak AD, 21 x 250 mm, 5 µ (elución con 25% de MeOH, 75% de CO_2 a 60 mL/min, 40 °C y 100 bar con detección a 220 nm) para proporcionar el **Ejemplo 111(a)** y el **Ejemplo 111(b)**:

Ejemplo 111(a) - Compuesto que eluyó en primer lugar (2S,4*R*,4a*R*)-11-cloro-2,4-dimetil-8-(tiazol-2-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'H)-triona

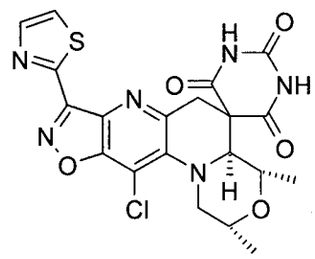


MS (ES) MH^+: 489 para $C_{20}H_{17}ClN_6O_5S$

^{1}H RMN (300 MHz, DMSO-d_6) δ: 0,9 (d, 3H) 1,0 (m, 1H) 1,1 (d, 3H) 3,1 (dd, 1H) 3,5–3,6 (m, 1H) 3,7 (d, 1H) 3,9 (m, 1H) 4,0 (d, 1H) 4,4 (d, 1H) 8,1 (m, 2H) 11,6 (s, 1H) 11,9 (s, 1H).

[α] = +130 (c = 0,1 en etanol)

Ejemplo 111(b) – Compuesto que eluyó en segundo lugar (2*R*,4S,4a*S*)-11-cloro-2,4-dimetil-8-(tiazol-2-il)-2,4,4*a*,6-tetrahidro-1*H*, 1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona



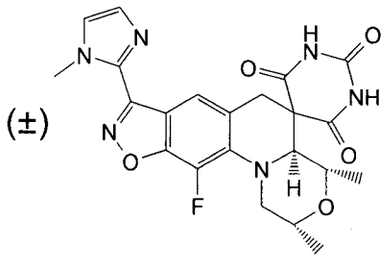
MS (ES) MH^+: 489 para $C_{20}H_{17}ClN_6O_5S$

^{1}H RMN (300 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 3,1 (dd, 1H), 3,5–3,6 (m, 2H), 3,6–3,7 (m, 1H), 3,9 (m, 1H), 4,0 (d, 1H), 4,4 (d, 1H), 8,1–8,2 (m, 2H), 11,6 (s, 1H), 11,9 (s, 1H).

[α] = -132 (c = 0,1 en etanol)

Ejemplo 112

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(1-metil-1*H*-imidazol-2-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona



Una solución de (2*R*,4S,4a*R*)-rel-11-fluoro-2,4-dimetil-8-(1-metil-1*H*-imidazol-2-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona (**Ejemplo 68**, 50 mg, 0,11 mmol) en etanol (40 mL) se calentó hasta alcanzar reflujo durante 4 días. El disolvente se eliminó y el residuo se lavó con metanol. El sólido resultante se filtró, se lavó con metanol y se secó para proporcionar 44 mg de producto.

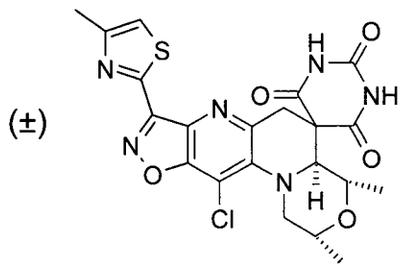
MS (ES) MH^+: 469 para $C_{22}H_{21}FN_6O_5$

^{1}H RMN (300 MHz, DMSO-d_6) δ: 0,9 (d, 3 H) 1,1 (d, 3 H) 7,2 (s, 1 H) 7,6 (s, 1 H) 7,8 (s, 1 H) 11,4 (s, 1 H) 11,8 (s, 1 H).

Los **Ejemplos 113** a **116** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Ejemplo 107:**

Ejemplo 113

(2*R*,4S,4a*S*)-rel-11-cloro-2,4-dimetil-8-(4-metiltiazol-2-il)-2,4,4*a*,6-tetrahidro-1*H*, 1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona



Material de partida: 7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(4-metiltiazol-2-il)isoxazolo[4,5-b]piridina-5-carbaldehído (**Intermedio 411**)

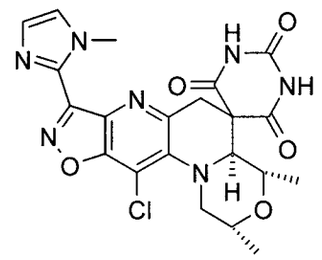
MS (ES) MH^+: 503 para $C_{21}H_{19}ClN_6O_5S.01$[Ácido trifluoroacético]

^{1}H RMN (300 MHz, MeOD) δ: 1,0 (d, 3H) 1,2 (s a, 1H) 1,2 (d, 3H) 2,4 – 2,6 (m, 3H) 3,16 (dd, 1H) 3,3-3,4 (m, 1H) 3,5 – 3,6 (m, 1H) 3,7 (d, 1H) 4,0 – 4,1 (m, 2H) 4,6 (dd, 1H) 4,8 (s, 2H) 7,4 (s, 1H).

Ejemplo 114

(2*R*,4S,4a*S*)-rel-11-cloro-2,4-dimetil-8-(1-metil –1*H*-imidazol-2-il)-2,4,4*a*,6-tetrahidro-1*H*, 1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona (sal de ácido trifluoroacético)

(±)



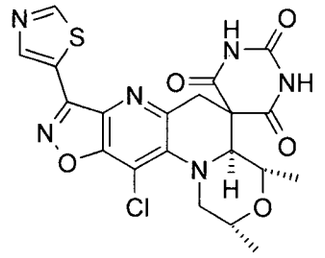
Material de partida: 7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(1-metil-1*H*-imidazol-2-il)isoxazolo[4,5-b]piridin-5-carbaldehído (**Intermedio 412**)

MS (ES) MH^+: 486 para $C_{21}H_{20}ClN_7O_5$

^{1}H RMN (300 MHz, DMSO-d_6) δ: 0,8 (d, 3H), 1,0 (m, 3H), 1,8 (s, 1H), 3,0–3,1 (m, 1H), 3,1 (d, 2H), 3,5–3,7 (m, 2H), 3,8 (m, 1H), 3,8–4,1 (m, 3H), 4,0 (d, 1H), 4,4 (d, 1H), 7,1 (s, 1H), 7,4 – 7,5 (m, 1H).

Ejemplo 115

(2*R*,4S,4a*S*)-rel-11-cloro-2,4-dimetil-8-(tiazol-5-il)-2,4,4*a*,6-tetrahidro-1*H*, 1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona (sal de ácido trifluoroacético)

(±) 

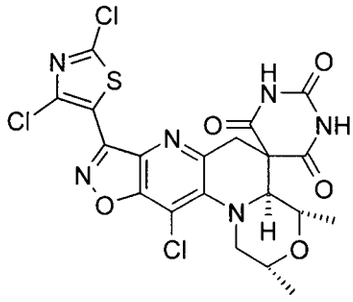
Material de partida: 7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(tiazol-5-il)isoxazolo[4,5-b]piridin-5-carbaldehído (**Intermedio 413**)

MS (ES) MH^+: 489 para $C_{20}H_{17}ClN_6O_5S$

^1H RMN (300 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,0-1,2 (m, 3H), 3,1 (dd, 1H), 3,3 (d, 1H) 3,5–3,6 (m, 1H), 3,8 (m, 1H), 3,9–4,0 (m, 2H), 4,4 (d, 1H), 8,9–9,0 (m, 1H), 9,3 – 9,5 (m, 1H), 11,5–11,6 (m, 1H), 11,9 (s, 1H).

Ejemplo 116

(2*R*,4S,4a*S*)-rel-11-cloro-2,4-dimetil-8-(2,4-diclorotiazol-5-il)-2,4,4*a*,6-tetrahidro-1*H*, 1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona (sal de ácido trifluoroacético)

(±) 

Material de partida: 7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(2,4-diclorotiazol-5-il)isoxazolo[4,5-b]piridin-5-carbaldehído (**Intermedio 420**)

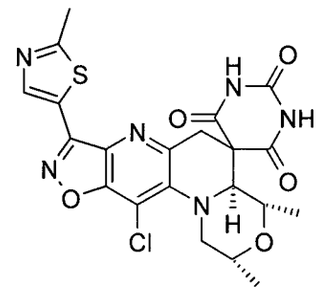
MS (ES) MH^+: 557 para $C_{20}H_{15}Cl_3N_6O_5S$

^1H RMN (300 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 3,1 (m, 1H), 3,1 (dd, 1H), 3,5–3,7 (m, 2H), 3,9–4,0 (m, 2H), 4,4 (d, 1H), 11,6 (s, 1H), 11,9 (s, 1H).

Ejemplo 117

(2*R*,4S,4a*S*)-rel-11-cloro-2,4-dimetil-8-(2-metiltiazol-5-il)-2,4,4*a*,6-tetrahidro-1*H*, 1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona

(±)



Se agregó isopropanol (20 mL) a 7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(2-metiltiazol-5-il)isoxazolo[4,5-b]piridin-5-carbaldehído (**Intermedio 414**, 0,26 g, 0,66 mmol) y ácido barbitúrico (0,085 g, 0,66 mmol) y la mezcla se calentó hasta alcanzar 80 °C durante aproximadamente 2 días. La mezcla se concentró y la cristalización de la mezcla bruta en metanol proporcionó 45 mg del compuesto del título.

MS (ES) MH^+: 503 para $C_{21}H_{19}ClN_6O_5S$

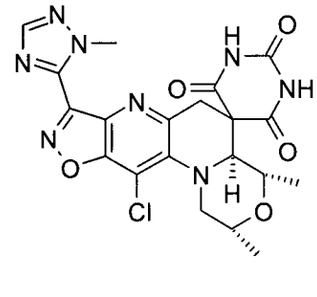
^1H RMN (300 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 2,6–2,8 (m, 3H), 3,0–3,2 (m, 1H), 3,3 (m, 1H), 3,5–3,6 (m, 1H), 3,7 (d, 1H), 4,0 (d, 2H), 4,4 (d, 1H), 8,6 (s, 1H), 11,6 (s a, 1H), 11,9 (s a, 1H).

Los **Ejemplos 118** y **119** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Ejemplo 117:**

Ejemplo 118

(2*R*,4S,4a*S*)-rel-11-cloro-2,4-dimetil-8-(1-metil-1*H*-1,2,4-triazol-5-il)-2,4,4*a*,6-tetrahidro-1*H*, 1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona

(±)



Material de partida: 7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(1-metil-1*H*-1,2,4-triazol-5-il)isoxazolo[4,5-b]piridin-5-carbaldehído (**Intermedio 415**)

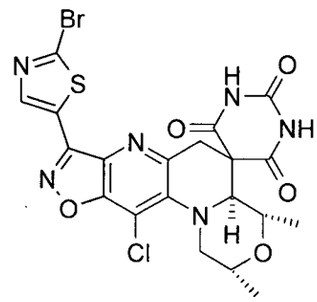
MS (ES) MH^+: 487 para $C_{20}H_{19}ClN_8O_5$

^{1}H RMN (300 MHz, DMSO-d_6) δ: 1,1 (d, 3H), 1,2 (d, 3H), 3,2 (t, 1H), 3,4–3,6 (m, 3H), 3,6–3,7 (m, 1H), 3,9 (m, 1H), 4,1 (d, 1H), 4,2 (s, 3H), 8,3 (s, 1H), 11,5 (s, 1H), 11,67 (s, 1H).

Ejemplo 119

(2*R*,4S,4a*S*)-rel-11-cloro-2,4-dimetil-8-(2-bromotiazol-5-il)-2,4,4*a*,6-tetrahidro-1*H*, 1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona

(±)



Material de partida: 7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(2-bromotiazol-5-il)isoxazolo[4,5-b]piridin-5-carbaldehído (**Intermedio 419**)

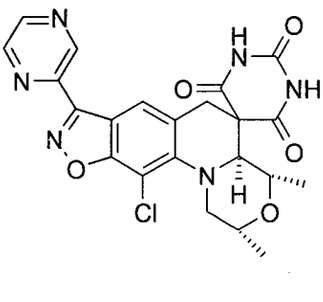
MS (ES) MH^+: 568 para $C_{20}H_{16}BrClN_6O_5S$

^{1}H RMN (300 MHz, cloroformo-d) δ: 0,9 (d, 3H), 1,1 (d, 3H), 1,2 (d, 1H), 3,1 (m, 1H), 3,1 (d, 1H), 3,3 (s, 1H), 3,6 (dd, 1H), 3,7 (d, 1H), 3,9–4,0 (m, 2H), 4,4 (d, 1H), 8,6 (d, 1H).

Ejemplo 120

(2*R*,4S,4a*S*)-rel-11-cloro-2,4-dimetil-8-(pirazin-2-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona

(±)



Se agregó isopropanol (10 mL) a 7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(pirazin-2-il)benzo[d]isoxazol-5-carbaldehído (**Intermedio 472**, 198 mg, 0,53 mmol) para proporcionar una suspensión amarilla. Se agregó pirimidin-2,4,6(1H,3H,5H)-triona (ácido barbitúrico) (68,0 mg, 0,53 mmol) y la mezcla amarilla se calentó hasta alcanzar 80 °C. La solución resultante se agitó durante toda la noche. La suspensión blanquecina resultante se enfrió hasta alcanzar temperatura ambiente, luego se filtró. La torta del filtrado se lavó con MeOH/hexanos para proporcionar un sólido blanco, 171 mg (67%).

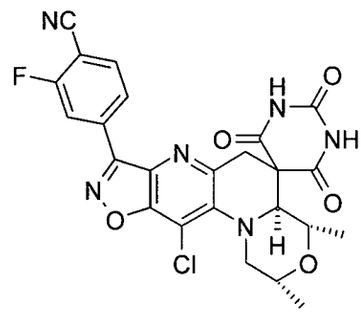
MS (ES) MH^+: 483 para $C_{22}H_{19}ClN_6O_5$

^1H RMN (300 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,2 (d, 3H), 3,0-3,1 (m, 2H), 3,6-3,8 (m, 2H), 3,9-4,1 (m, 2H), 4,5 (d, 1H), 7,9 (s, 1H), 8,8-8,9 (m, 2H), 9,3 (s, 1H), 11,4 (s a, 1H), 11,8 (s a, 1H).

Ejemplo 121

4-((2*R*,4S,4a*S*)-rel-11-cloro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4*a*,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-8-il)-2-fluorobenzonitrilo

(±)



Se agregó isopropanol (20 mL) a 4-(7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-formilisoxazolo[4,5-b]piridin-3-il)-2-fluorobenzonitrilo (**Intermedio 416**, 0,126 g, 0,30 mmol) y ácido barbitúrico (0,039 g, 0,30 mmol). La mezcla se calentó hasta alcanzar 80 °C durante aproximadamente 2 días. La mezcla se concentró y el residuo se purificó mediante cromatografía en gel de sílice utilizando acetona al 20% en n-hexano. Los sólidos obtenidos se lavaron con metanol lo que proporcionó 41 mg de producto.

MS (ES) MH^+: 525 para $C_{24}H_{18}ClFN_6O_5$

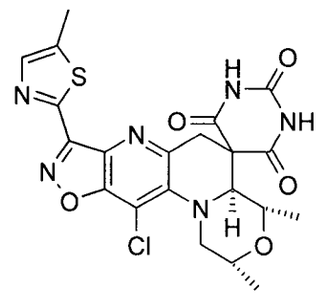
^1H RMN (300 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 3,1 (dd, 1H), 3,3 (m, 1H), 3,6 (dd, 1H), 3,8 (d, 1H), 4,0 (d, 2H), 4,4 (m, 1H), 8,1 (t, 1H), 8,3–8,4 (m, 2H), 11,6 (s, 1H), 11,9 (s, 1H).

Los **Ejemplos 122** y **123** se prepararon a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Ejemplo 121:**

Ejemplo 122

(2*R*,4S,4a*S*)-rel-11-cloro-2,4-dimetil-8-(5-metiltiazol-2-il)-2,4,4*a*,6-tetrahidro-1*H*, 1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'*H*)-triona

(±)



Material de partida: 7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-(5-metiltiazol-2-il)isoxazolo[4,5-b]piridin-5-carbaldehído (**Intermedio 418**)

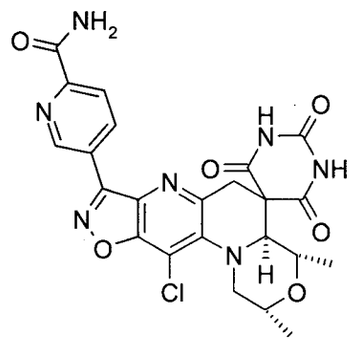
MS (ES) MH^+: 503 para $C_{21}H_{19}ClN_6O_5S$

^1H RMN (300 MHz, DMSO-d_6) δ: 1,1 (d, 3H), 1,2 (d, 3H), 2,6 (s, 3H), 3,1–3,3 (m, 2H), 3,1–3,7 (m, 1H), 3,8–4,0 (m, 1H), 4,1 (dd, 1H), 7,9 (s, 1H), 11,5 (s, 1H), 11,6 (s, 1H).

Ejemplo 123

5-((2*R*,4S,4a*S*)-rel-11-cloro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naftiridin-5,5'-pirimidin]-8-il)picolinamida

(±)



Material de partida: 5-(7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-formilisoxazolo[4,5-b]piridin-3-il)picolinonitrilo (**Intermedio 417**)

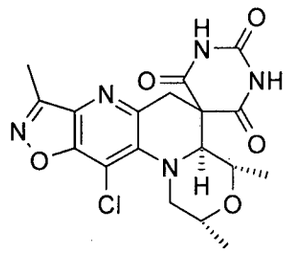
MS (ES) MH^+: 526 para $C_{23}H_{20}ClN_7O_6$

^{1}H RMN (300 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 3,1 (dd, 1H), 3,3–3,4 (m, 1H), 3,6 (dd, 1H), 3,7 (d, 1H), 4,0 (d, 1H), 4,4 (d, 1H), 7,8 (s, 1H), 8,1–8,3 (m, 2H), 8,8 (dd, 1H), 9,4 (d, 1H), 11,6 (s, 1H), 11,9 (s, 1H).

Ejemplo 124

(2*R*,4S,4a*S*)-rel-11-cloro-2,4,8-trimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'H)-triona

(±)



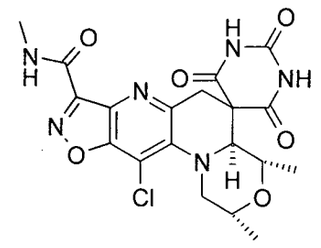
Se agregó isopropanol (12 mL) a 7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-3-metilisoxazolo[4,5-b]piridin-5-carbaldehído (**Intermedio 471**, 165 mg, 0,53 mmol) para proporcionar una suspensión amarilla; se agregó pirimidin-2,4,6(1H,3H,5H)-triona (ácido barbitúrico) (68,2 mg, 0,53 mmol) y la mezcla se calentó hasta alcanzar 80 °C. Después de aproximadamente 5 días, la mezcla se concentró. El bruto se purificó mediante cromatografía utilizando el 10-50% de EtOAc/CH_2Cl_2 para proporcionar 95 mg de un sólido amarillo que a continuación se recristalizó en EtOAc/hexanos. Se obtuvo un total de 57 mg (19%) del producto del título como un sólido amarillo.

MS (ES) MH^+: 420 para $C_{18}H_{18}ClN_5O_5$

^{1}H RMN (300 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,2 (d, 3H), 2,5 (s, 3H), 3,1 (m, 1H), 3,3 (m, bajo pico de agua, 1H), 3,5-3,7 (m, 2H), 3,9-4,1 (m, 2H), 4,4 (dd, 1H), 11. 6 (s a, 1H), 11,7 (s a, 1H).

Ejemplo 125

(2*R*,4S,4a*S*)-rel-11-cloro-*N*,2,4-trimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naftiridin-5,5'-pirimidin]-8-carboxamida

(±) 

Se disolvió 7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-formil-*N*-metilisoxazolo[4,5-b]piridin-3-carboxamida (**Intermedio 473**, 68 mg, 0,19 mmol) en isopropanol para proporcionar una solución amarilla y se agregó pirimidin-2,4,6(1H,3H,5H)-triona (24,69 mg, 0,19 mmol) para proporcionar una suspensión amarilla brillante, que se calentó hasta alcanzar 80 °C durante tres días. La suspensión naranja oscuro resultante se concentró, luego se purificó mediante cromatografía en SiO_2 utilizando 20-60% de $EtOAc/CH_2Cl_2$. Se obtuvo un total de 32 mg (36%) de un sólido blanquecino.

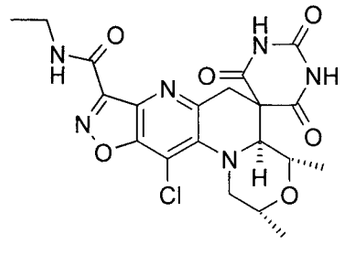
MS (ES) MH^+: 463 para $C_{19}H_{19}ClN_6O_6$

^1H RMN (300 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,2 (d, 3H), 2,8 (d, 3H), 3,1 (m, 1H), 3,3 (m bajo pico de agua, 1H), 3,5-3,7 (m, 2H), 3,9-4,1 (m, 2H), 4,4 (d, 1H). 8,8 (m, 1H), 11,6 (s a, 1H), 11,9 (s a, 1H).

Los **Ejemplos 126** a **133** se prepararon a partir de los materiales de partida y ácido barbitúrico utilizando un método similar al descrito para la síntesis del **Ejemplo 125**:

Ejemplo 126

(2*R*,4S,4a*S*)-rel-11-cloro-*N*-etil-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naftiridin-5,5'-pirimidin]-8-carboxamida

(±) 

Material de partida: 7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-*N*-etil-5-formilisoxazolo[4,5-b]piridin-3-carboxamida (**Intermedio 474**)

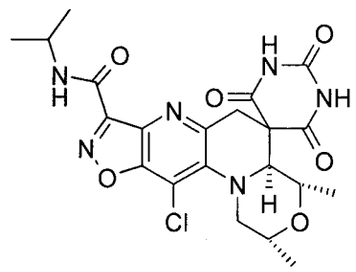
MS (ES) MH^+: 477 para $C_{20}H_{21}ClN_6O_6$

^1H RMN (300 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1-1,2 (superposición de m, 6H), 3,1 (m, 1H), 3,3 (m bajo pico de agua, 3H), 3,5-3,7 (m, 2H), 3,9-4,1 (m, 2H), 4,4 (d, 1H). 8. 8 (t a, 1H), 11,6 (s a, 1H), 11. 9 (s a, 1H).

Ejemplo 127

(2*R*,4S,4a*S*)-rel-cloro-*N*-isopropil-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naftiridin-5,5'-pirimidin]-8-carboxamida

(±)



Material de partida: 7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-formil-*N*-isopropilisoxazolo[4,5-b]piridin-3-carboxamida (**Intermedio 475**)

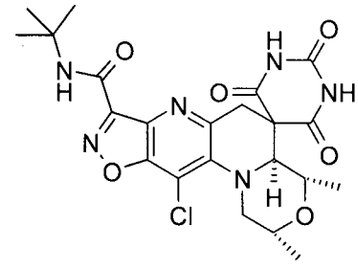
MS (ES) MH^+: 491 para $C_{21}H_{23}ClN_6O_6$

^1H RMN (300 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1-1,2 (superposición de m, 9H), 3,1 (m, 1H), 3,3 (m bajo pico de agua, 1H), 3,6 (m, 1H), 3,7 (d, 1H), 3,9 (m, 1H), 4,0 (d, 1H), 4,1 (m, 1H), 4,4 (d, 1H). 8,8 (d, 1H), 11,6 (s a, 1H), 11,9 (s a, 1H).

Ejemplo 128

(2*R*,4S,4a*S*)-rel-*N*-*terc*-butil-11-cloro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naftiridin-5,5'-pirimidin]-8-carboxamida

(±)



Material de partida: *N*-*terc*-butil-7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-formilisoxazolo[4,5-b]piridin-3-carboxamida (**Intermedio 476**)

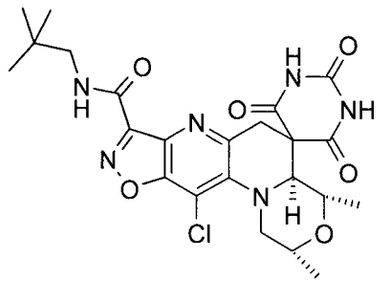
MS (ES) MH^+: 505 para $C_{22}H_{25}ClN_6O_6$

^1H RMN (300 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,2 (d, 3H), 1,4 (s, 9H), 3,1 (m, 1H), 3,3 (m bajo pico de agua, 1H), 3,6 (m, 1H), 3,7 (d, 1H), 3,9 (m, 1H), 4,0 (d, 1H), 4,4 (d, 1H). 8,4 (s, 1H), 11,6 (s a, 1H), 11,9 (s a, 1H).

Ejemplo 129

(2*R*,4S,4a*S*)-rel-11-cloro-2,4-dimetil-*N*-neopentil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naftiridin-5,5'-pirimidin]-8-carboxamida

(±)



Material de partida: 7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-formil-*N*-neopentilisoxazolo[4,5-b]piridin-3-carboxamida (**Intermedio 477**)

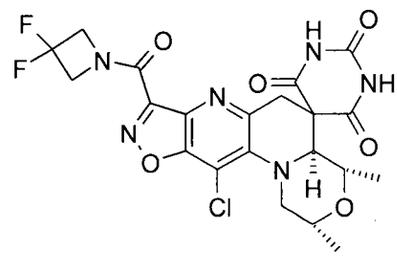
MS (ES) MH^+: 519 para $C_{23}H_{27}ClN_6O_6$

^1H RMN (300 MHz, DMSO-d_6) δ: 0,9-1,0 (superposición de m, 12H), 1,2 (d, 3H), 3,1-3,2 (superposición de m, 3H), 3,3 (m bajo pico de agua, 1H), 3,4-3,7 (m, 2H), 3,9-4,1 (m, 2H), 4,4 (m, 1H), 8,8 (t, 1H), 11,6 (s a, 1H), 11,9 (s a, 1H).

Ejemplo 130

(2*R*,4S,4a*S*)-rel-11-cloro-8-(3,3-difluoroazetidina-1-carbonil)-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naftiridin-5,5'-pirimidin]-2',4',6'(3'H)-triona

(±)



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Material de partida: 7-cloro-3-(3,3-difluoroazetidina-1-carbonil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)isoxazolo[4,5-b]piridin-5-carbaldehído (**Intermedio 478**)

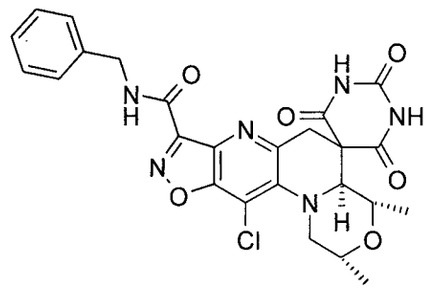
MS (ES) MH^+: 525 para $C_{21}H_{19}ClF_2N_6O_6$

^{1}H RMN (300 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,2 (d, 3H), 3,1 (m, 1H), 3,3 (m bajo pico de agua, 1H), 3,6 (m, 1H), 3,7 (d, 1H), 3,9 (m, 1H), 4,0 (d, 1H), 4,4 (d, 1H). 4,6 (t, 2H), 4,8 (t, 2H), 11,6 (s a, 1H), 11,9 (s a, 1H).

Ejemplo 131

(2*R*,4S,4a*S*)-rel-*N*-bencil-11-cloro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naftiridin-5,5'-pirimidin]-8-carboxamida

(±)



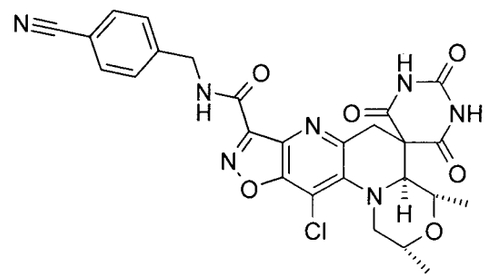
Material de partida: *N*-bencil-7-cloro-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-formilisoxazolo[4,5-b]piridin-3-carboxamida (**Intermedio 479**)

MS (ES) MH^+: 539 para $C_{25}H_{23}ClN_6O_6$

^{1}H RMN (300 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,2 (d, 3H), 3,1 (m, 1H), 3,3 (m bajo pico de agua, 1H), 3,5-3,7 (m, 2H), 3,9-4,1 (m, 2H), 4,4-4,6 (m, 3H), 7,2-7,4 (m, 5H), 9,4 (t, 1H), 11,6 (s a, 1H), 11,9 (s a, 1H).

Ejemplo 132

(2*R*,4S,4a*S*)-rel-11-cloro-*N*-(4-cianobencil)-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naftiridin-5,5'-pirimidin]-8-carboxamida

(±) 

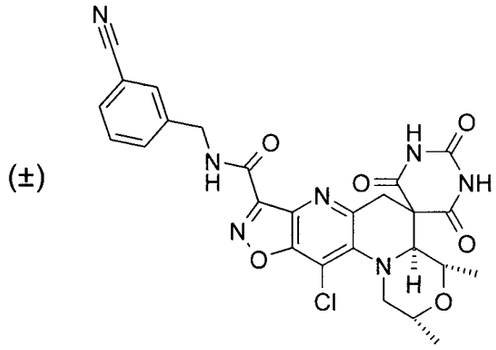
Material de partida: 7-cloro-*N*-(4-cianobencil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-formilisoxazolo[4,5-b]piridin-3-carboxamida (**Intermedio 480**)

MS (ES) MH^+: 564 para $C_{26}H_{22}ClN_7O_6$

^1H RMN (300 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,2 (d, 3H), 3,1 (m, 1H), 3,3 (m bajo pico de agua, 1H), 3,6-3,7 (m, 2H), 3,9 (m, 1H), 4,0 (d, 1H), 4,4 (d, 1H), 4,6 (d, 2H), 7,6 (d, 2H), 7,8 (d, 2H), 9,5 (t, 1H), 11,6 (s a, 1H), 11,9 (s a, 1H).

Ejemplo 133

(2*R*,4S,4a*S*)-rel-11-cloro-*N*-(3-cianobencil)-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a][1,5]naftiridin-5,5'-pirimidin]-8-carboxamida

(±) 

Material de partida: 7-cloro-*N*-(3-cianobencil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-5-formilisoxazolo[4,5-b]piridin-3-carboxamida (**Intermedio 481**)

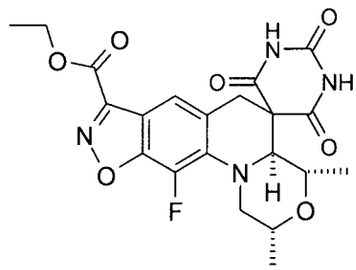
MS (ES) MH^+: 564 para $C_{26}H_{22}ClN_7O_6$

^1H RMN (300 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,2 (d, 3H), 3,1 (m, 1H), 3,3 (m bajo pico de agua, 1H), 3,5-3,7 (m, 2H), 3,9 (m, 1H), 4,0 (d, 1H), 4,4 (d, 1H), 4,6 (s, 2H), 7,6 (t, 1H), 7,7-7,8 (m, 2H), 7,8 (s, 1H), 8,5 (t, 1H), 11,6 (s a, 1H), 11,9 (s a, 1H).

Ejemplo 134

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-8-carboxilato de etilo

(±)



Se calentaron a reflujo 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formilbenzo[d]isoxazol-3-carboxilato de etilo (**Intermedio 439**, 350 mg, 1,00 mmol) y ácido barbitúrico (141 mg, 1,10 mmol) en etanol (45 mL) durante 64 horas. La reacción se concentró. El residuo se disolvió en DCM, se absorbió en sílice y se purificó mediante cromatografía en columna de gel de sílice utilizando un gradiente de DCM a acetato de etilo, para proporcionar el compuesto del título (412 mg, 76%) como una mezcla racémica.

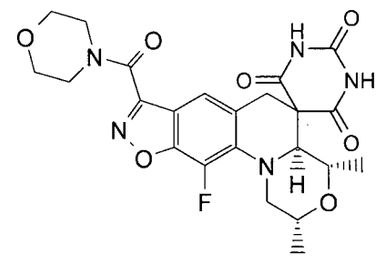
MS (ES) MH^+: 461 para $C_{21}H_{21}FN_4O_7$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,89 (d, 3H) 1,04-1,25 (m, 6H) 2,93 (d, 1H) 3,13 (t, 1H) 3,60-3,71 (m, 1H) 3,72-3,87 (m, 2H) 3,97 (d, 1H) 4,12 (d, 1H) 4,44 (c, 2H) 7,43 (s, 1H) 11,49 (s a, 1H) 11,86 (s a, 1H).

Los **Ejemplos 135** a **140** se prepararon a partir del material de partida indicado y ácido barbitúrico utilizando un método similar al descrito para la síntesis del **Ejemplo 134**. Los compuestos se purificaron mediante cromatografía en columna de gel de sílice utilizando un gradiente de DCM a acetato de etilo o mediante HPLC de fase inversa utilizando un gradiente de CH_3CN en agua con 0,1% de TFA.

Ejemplo 135

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(morfolin-4-carbonil)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona

(±) 

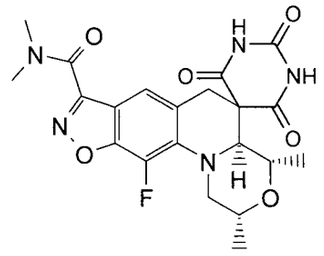
Material de partida: 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(morfolin-4-carbonil)benzo[d]isoxazol-5-carbaldehído (**Intermedio 440**)

MS (ES) MH^+: 502 para $C_{23}H_{24}FN_5O_7$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,9 (d, 3H), 1,15 (d, 3H), 2,9 (d, 1H), 3,1 (t, 1H), 3,6-3,8 (m, 10H), 3,7-3,9 (m, 1H), 4,0 (d, 1H), 4,12 (d, 1H), 7,3 (s, 1H), 11,5 (s a, 1H), 11,9 (s a, 1H).

Ejemplo 136

(2*R*,4S,4a*S*)-rel-11-fluoro-*N*,*N*,2,4-tetrametil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-8-carboxamida

(±) 

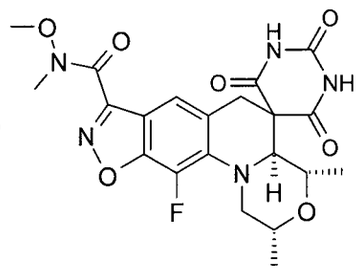
Material de partida: 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formil-*N*,*N*-dimetilbenzo[d]isoxazol-3-carboxamida (**Intermedio 470**)

MS (ES) MH^+: 460 para $C_{21}H_{22}FN_5O_6$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,9 (d, 3H), 1,1 (d, 3H), 2,9 (d, 1H), 3,1 (d, 7H), 3,6-3,7 (m, 2H), 3,7-3,9 (m, 1H), 4,0 (d, 1H), 4,1 (d, 1H), 7,2 (s, 1H), 11,5 (s a, 1H), 11,9 (s a, 1H).

Ejemplo 137

(2*R*,4S,4a*S*)-rel-11-fluoro-*N*-metoxi-*N*,2,4-trimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-8-carboxamida

(±) 

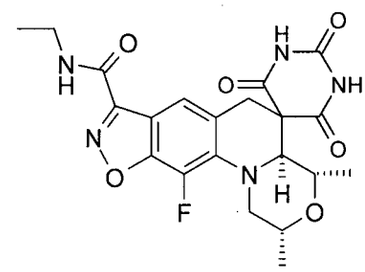
Material de partida: 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formil-*N*-metoxi-*N*-metilbenzo[d]isoxazol-3-carboxamida (**Intermedio 441**)

MS (ES) MH^+: 476 para $C_{21}H_{22}FN_5O_7$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,9 (d, 3H), 1,2 (d, 3H), 2,9 (d, 1H), 3,1 (t, 1H), 3,4 (s a, 3H), 3,6-3,9 (m, 6H), 4,0 (d, 1H), 4,1 (d, 1H), 7,3 (s, 1H), 11,5 (s, 1H), 11,9 (s, 1H).

Ejemplo 138

(2*R*,4S,4a*S*)-rel-*N*-etil-11-fluoro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-8-carboxamida

(±) 

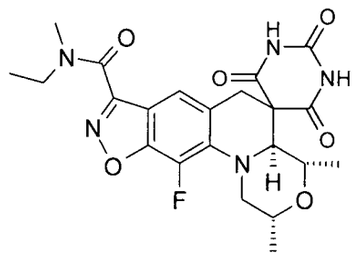
Material de partida: 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-*N*-etil-7-fluoro-5-formilbenzo[d]isoxazol-3-carboxamida, (**Intermedio 442**)

MS (ES) MH^+: 460 para $C_{21}H_{22}FN_5O_6$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,9 (d, 3H), 1,1-1,2 (m, 6H), 2,9 (d, 1H), 3,1 (t, 1H), 3,3-3,3 (m, 2H), 3,6-3,9 (m, 3H), 4,0 (d, 1H), 4,1 (d, 1H), 7,4 (s, 1H), 9,0 (t, 1H), 11,5 (s, 1H), 11,9 (s, 1H).

Ejemplo 139

(2*R*,4S,4a*S*)-rel-*N*-etil-11-fluoro-*N*,2,4-trimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-8-carboxamida

(±) 

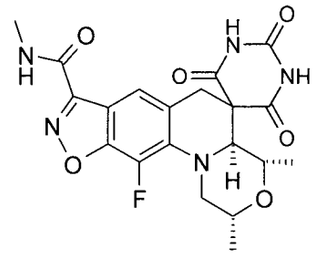
Material de partida: 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-*N*-etil-7-fluoro-5-formil-*N*-metilbenzo[d]isoxazol-3-carboxamida (**Intermedio 443**)

MS (ES) MH^+: 474 para $C_{22}H_{24}FN_5O_6$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,9 (d, 3H), 1,1-1,2 (m, 6H), 2,9 (d, 1H), 3,1 (d, 3H), 3,15 (d, 1H), 3,4-3,5 (m, 1H), 3,5 (d, 1H), 3,6-3,7 (m, 2H), 3,7-3,9 (m, 1H), 3,9 (d, 1H), 4,1 (d, 1H), 7,2 (d, 1H), 11,5 (s a, 1H), 11,9 (s a, 1H).

Ejemplo 140

(2*R*,4S,4a*S*)-rel-11-fluoro-*N*,2,4-trimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-8-carboxamida

(±) 

Material de partida: 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formil-*N*-metilbenzo[d]isoxazol-3-carboxamida (**Intermedio 444**)

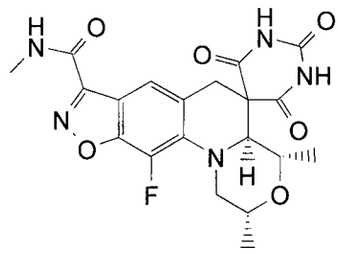
MS (ES) MH^+: 446 para $C_{20}H_{20}FN_5O_6$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,9 (d, 3H), 1,1 (d, 3H), 2,8 (d, 3H), 2,9 (d, 1H), 3,1 (t, 1H), 3,6-3,9 (m, 3H), 3,95 (d, 1H), 4,1 (d, 1H), 7,4 (s, 1H), 8,8 – 9,0 (m, 1H), 11,5 (s a, 1H), 11,8 (s a, 1H).

En una ruta alternativa, el enantiómero (2*R*,4S,4aS) del **Ejemplo 140** se sintetizó mediante una síntesis quiral similar a la descrita para la síntesis del **Ejemplo 95(a)**, utilizando ácido barbitúrico y el material de partida indicado, para proporcionar el **Ejemplo 140(a)**:

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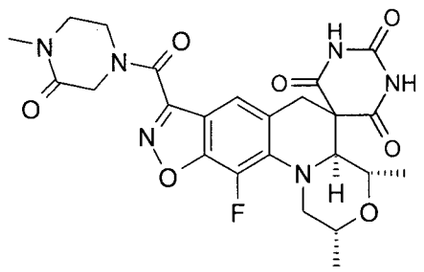
Ejemplo 140(a) – (Síntesis quiral)
(2*R*,4S,4a*S*)-11-fluoro-*N*,2,4-trimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-8-carboxamida



Material de partida: 6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-5-formil-*N*-metilbenzo[d]isoxazol-3-carboxamida (**Intermedio 247**; purificación mediante HPLC de fase inversa utilizando un gradiente de CH_3CN en agua con 0,1% de TFA.
MS (ES) MH^+: 446 para $C_{20}H_{20}FN_5O_6$
^1H RMN (300 MHz, DMSO-d_6) δ ppm 0,9 (d, 3H), 1,2 (d, 3H), 2,8 (d, 3H), 2,9 (d, 1H), 3,1 (t, 1H), 3,6-3,9 (m, 4H), 4,0 (d, 1H), 4,1 (d, 1H), 7,5 (s, 1H), 8,9 (d, 1H), 11,5 (s, 1H), 11,9 (s, 1H).
>98% ee mediante HPLC quiral; [α] = -263 (c = 0,1 en MeOH)

Los **Ejemplos 141** y **142** se prepararon a partir del material de partida indicado y ácido barbitúrico utilizando un método similar al descrito para la síntesis del **Ejemplo 134**. Los compuestos se purificaron mediante cromatografía en columna de gel de sílice utilizando un gradiente de DCM a acetato de etilo o mediante HPLC de fase inversa utilizando un gradiente de CH_3CN en agua con 0,1% de TFA.

Ejemplo 141
(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(4-metil-3-oxopiperazina-1-carbonil)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona

(±) 

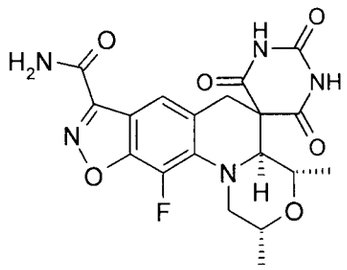
Material de partida: 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(4-metil-3-oxopiperazina-1-carbonil)benzo[d]isoxazol-5-carbaldehído (**Intermedio 445**)

MS (ES) MH^+: 529 para $C_{24}H_{25}FN_6O_7$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,8 (d, 3H), 1,1 (d, 3H), 2,8 (d, 4H), 3,1 (t, 1H), 3,3-3,4 (m, 2H), 3,7 (d, 2H), 3,9 (d, 3H), 4,0 (d, 1H), 4,1-4,4 (m, 2H), 7,2-7,3 (m, 1H), 11,5 (s a, 1 H, 11,8 (s, 1H).

Ejemplo 142

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-^{1}*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-8-carboxamida

(±) 

Material de partida: 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formilbenzo[d]isoxazol-3-carboxamida (**Intermedio 447**)

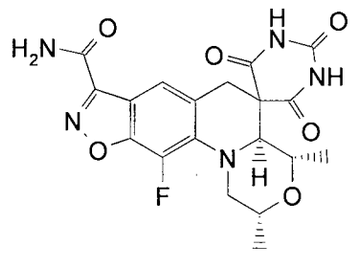
MS (ES) MH^+: 432 para $C_{19}H_{18}FN_5O_6$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,9 (d, 3H), 1,1-1,3 (m, 3H), 2,9 (d, 1H), 3,2 m, 1H), 3,6-3,9 (m, 3H), 3,9-4,2 (m, 2H), 7,5 (s, 1H), 8,0 (s, 1H), 8,3 (s, 1H), 11,5 (s a, 1H), 11,8 (s a, 1H).

Utilizando una ruta alternativa, el enantiómero (2*R*, 4S, 4aS) del **Ejemplo 142** también se obtuvo mediante una síntesis quiral similar a la descrita para la síntesis del **Ejemplo 95(a)**, utilizando ácido barbitúrico y el material de partida indicado:

Ejemplo 142(a)

(2*R*,4S,4a*S*)-11-fluoro-2,4-dietil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-8-carboxamida



Material de partida: 6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-5-formilbenzo[d]isoxazol-3-carboxamida (**Intermedio 469**); purificación mediante HPLC de fase inversa utilizando un gradiente de CH_3CN en agua con 0,1% de TFA.

MS (ES) MH^+: 432 para $C_{19}H_{18}FN_5O_6$

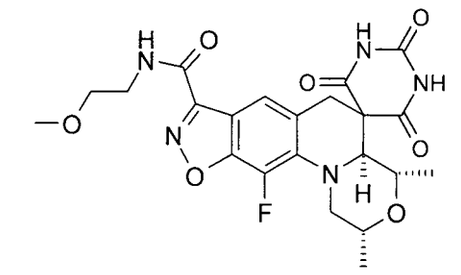
^1H RMN (300 MHz, DMSO-d_6) δ ppm 0,8 (d, 3H), 1,1 (d, 3H), 2,8 (d, 1H), 2,98-3,1 (m, 1H), 3,5-3,8 (m, 3H), 3,9 (d, 1H), 4,0 (d, 1H), 7,4 (s, 1H), 7,9 (s, 1H), 8,3 (s, 1H).

[α] = -204 (c = 0,1 en MeOH)

Los **Ejemplos 143** a **147** se prepararon a partir del material de partida indicado y ácido barbitúrico utilizando un método similar al descrito para la síntesis del **Ejemplo 134**. Los compuestos se purificaron mediante cromatografía en columna de gel de sílice utilizando un gradiente de DCM a acetato de etilo o mediante HPLC de fase inversa utilizando un gradiente de CH_3CN en agua con 0,1% de TFA.

Ejemplo 143

(2*R*,4S,4a*S*)-rel-11-fluoro-*N*-(2-metoxietil)-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-8-carboxamida

(±) 

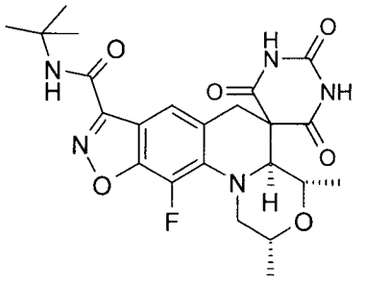
Material de partida: 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formil-*N*-(2-metoxietil)benzo[d]isoxazol-3-carboxamida (**Intermedio 448**)

MS (ES) MH^+: 490 para $C_{22}H_{24}FN_5O_7$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,9 (d, 3H), 1,1 (d, 3H), 2,9 (d, 1H), 3,1 (t, 1H), 3,3 (s, 3H), 3,5 (s a, 4H), 3,6-3,9 (m, 3H), 4,0 (d, 1H), 4,1 (d, 1H), 7,4 (s, 1H), 8,9 (s a, 1H), 11,5 (s a, 1H), 11,8 (s a, 1H).

Ejemplo 144

(2*R*,4S,4a*S*)-rel-*N*-*terc*-butil-11-fluoro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-8-carboxamida

(±) 

Material de partida: *N*-*terc*-butil-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formilbenzo[d]isoxazol-3-carboxamida (**Intermedio 449**)

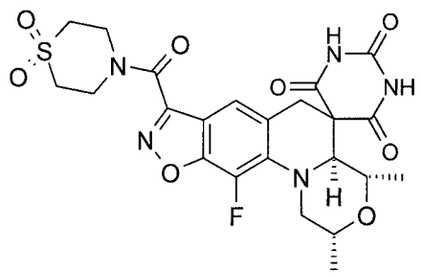
MS (ES) MH^+: 488 para $C_{23}H_{26}FN_5O_6$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,9 (d, 3H), 1,1 (d, 3H), 1,4 (s, 9H), 2,9 (d, J = 1H), 3,1 (t, 1H), 3,6-3,9 (m, 3H), 4,0 (d, 1H), 4,1 (d, 1H), 7,4 (s, 1H), 8,3 (s, 1H), 11,3-12,0 (m, 2H).

Ejemplo 145

(2*R*,4S,4a*S*)-rel-8-[(1,1-dioxidotiomorfolin-4-il)carbonil]-11-fluoro-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(1'H,3'H)-triona

(±)



Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-3-[(1,1-dioxidotiomorfolin-4-il)carbonil]-7-fluoro-1,2-bencisoxazol-5-carbaldehído (**Intermedio 450**)

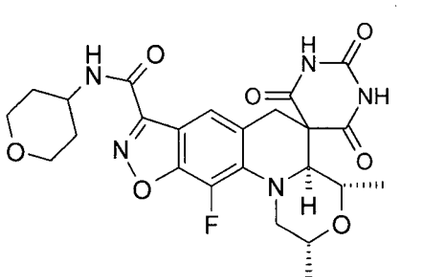
MS (ES) MH^+: 550 para $C_{23}H_{24}FN_5O_8S$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,8 (d, 3H), 1,1 (d, 3H), 2,81-2,9 (m, 2H), 2,9-3,1 (m, 2H), 3,3-3,4 (m, 2H), 3,5-3,7 (m, 2H), 3,7-3,8 (m, 1H), 3,0 (d, 1H), 4,0-4,2 (m, 5H), 7,3 (s, 1H), 11,2 – 12,0 (m, 1H).

Ejemplo 146

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimetil-2',4',6'-trioxo-*N*-(tetrahidro-2*H*-piran-4-il)-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-8-carboxamida

(±)



Material de partida: 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formil-*N*-(tetrahidro-2*H*-piran-4-il)benzo[d]isoxazol-3-carboxamida (**Intermedio 451**)

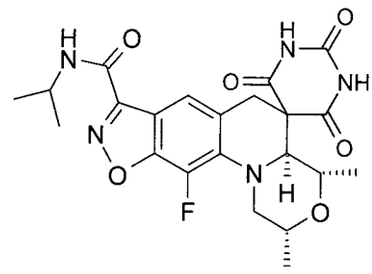
MS (ES) MH^+: 516 para $C_{24}H_{26}FN_5O_7$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,9 (d, 3H), 1,1 (d, 3H), 1,5-1,8 (m, 4H), 2,9 (d, 1H), 3,1 (t, 1H), 3,4-3,4 (m, 2H), 3,6-4,2 (m, 8H), 7,4 (s, 1H), 8,9 (d, 1H), 11,6 (s a, 2H).

Ejemplo 147

(2*R*,4S,4a*S*)-rel-11-fluoro-*N*-isopropil-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-8-carboxamida

(±)



Material de partida: 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formil-*N*-isopropilbenzo[d]isoxazol-3-carboxamida (**Intermedio 452**)

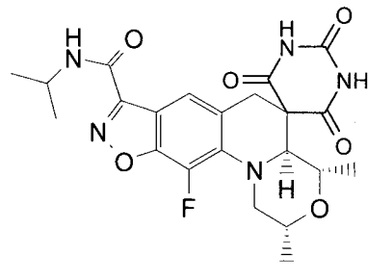
MS (ES) MH^+: 474 para $C_{22}H_{24}FN_5O_6$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,9 (d, 3H), 1,1-1,3 (m, 9H), 2,9 (d, 1H), 3,1 (t, 1H), 3,6-3,9 (m, 3H), 4,0 (d, 1H), 4,0-4,2 (m, 2H), 7,4 (s, 1H), 8,8 (d, 1H).

Utilizando una ruta alternativa, el enantiómero (2*R*, 4*S*, 4a*S*) del **Ejemplo 147** también se obtuvo mediante una síntesis quiral similar a la descrita para la síntesis del **Ejemplo 95(a)**, utilizando ácido barbitúrico y el material de partida indicado:

Ejemplo 147(a)

(2*R*,4S,4a*S*)-11-fluoro-*N*-isopropil-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-8-carboxamida



Materiales de partida: 6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-5-formil-*N*-isopropilbenzo[d]isoxazol-3-carboxamida (**Intermedio 246**); purificación mediante Cromatografía de Fluidos Supercríticos en una columna Chiralpac IC con una fase móvil de 35%

de MeOH, 65% de CO_2 para proporcionar el producto como un sólido como el compuesto que eluyó en primer lugar.

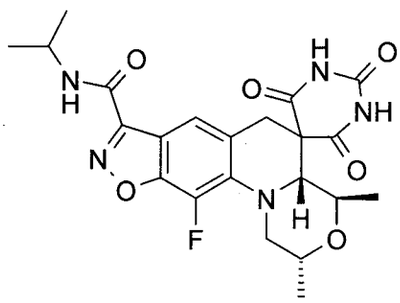
MS (ES) MH^+: 474 para $C_{22}H_{24}FN_5O_6$

^{1}H RMN (300 MHz, DMSO-*d6*) δ ppm 0,9 (d, 3H), 1,1-1,3 (m, 9H), 2,9 (d, 1H), 3,1 (t, 1H), 3,6-3,8 (m, 2H), 3,8-3,9 (m, 1H), 4,0 (d, 1H), 4,0-4,2 (m, 2H), 7,4 (s, 1H), 8,8 (d, 1H), 11,5 (s, 1H), 11,8 (s, 1H).

>98% ee mediante HPLC quiral; [α] = -259 (c = 0,1 en MeOH)

Ejemplo 147(b)

(2*R*,4*R*,4a*R*)-11-fluoro-*N*-isopropil-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-carboxamida



El diastereómero (2*R*,4*R*,4a*R*) se generó como un producto secundario de la reacción descrita para la síntesis del **Ejemplo 147(a)**. La cromatografía descrita para el **Ejemplo 147(a)** proporcionó el diastereómero (2*R*,4*R*,4a*R*) como el compuesto que eluyó en segundo lugar.

MS (ES) MH^+: 474 para $C_{22}H_{24}FN_5O_6$

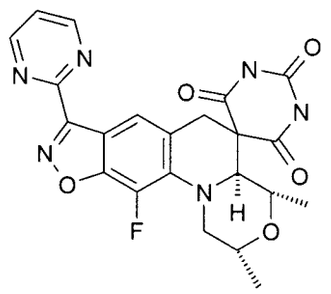
^{1}H RMN (300 MHz, DMSO-*d6*) δ ppm 0,9 (d, 3H), 1,1 (d, 6H), 1,2 (d, 3H), 3,0 (d, 1H), 3,5 - 3,7 (m, 2H), 3,7 (d, 1H), 3,8 - 4,0 (m, 2H), 4,0 - 4,2 (m, 2H), 7,4 (s, 1H), 8,7 (d, 1H), 11,4 (s a, 1H), 11,7 (s a, 1H).

El **Ejemplo 148** se preparó a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Ejemplo 97:**

Ejemplo 148

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(pirimidin-2-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±)



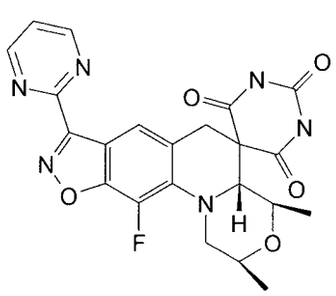
Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(pirimidin-2-il)-1,2-benzoxazol-5-carbaldehído (**Intermedio 587**)

MS (ES) MH^+: 467 para $C_{22}H_{19}FN_6O_5$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,2 (d, 3H), 3,0 (d, 1H), 3,1 (t, 1H), 3,7 (m, 3H), 4,0 (d, 1H), 4,1 (d, 1H), 7,7 (m, 1H), 7,9 (s, 1H), 8,1 (d, 1H), 9,0 (s, 2H), 11,5 (s, 1H), 11,8 (s, 1H).

Los enantiómeros (2*S*,4*R*,4a*R*) y (2*R*,4*S*,4a*S*) del **Ejemplo 148** se separaron mediante Cromatografía de Fluidos Supercríticos utilizando una columna Chiralpak AD, 21 x 250 mm, 5 µ (elución con 25% de MeOH, 75% de CO_2 a 60 mL/min, 40 °C y 100 bar con detección a 220 nm), para proporcionar el **Ejemplo 148(a)** y el **Ejemplo 148(b)**:

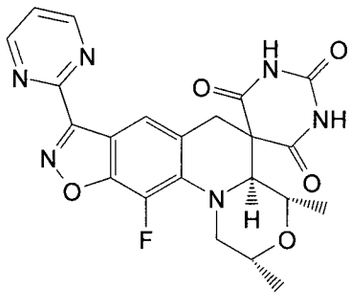
Ejemplo 148(a) - Compuesto que eluyó en primer lugar (2S,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(pirimidin-2-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona



MS (ES) MH^+: 467 para $C_{22}H_{19}FN_6O_5$

^{1}H RMN (300 MHz, DMSO-d_6) δ: 0,9 (d, 3H) 1,2 (d, 3H) 2,9 - 3,2 (m, 2H) 3,6 - 4,2 (m, 5H) 7,7 (t, 1H) 7,8 (s, 1H) 9,0 (d, 2H) 11,4 (s, 1H) 11,8 (s, 1H)
>98% ee mediante HPLC quiral; [α] = +178 (c = 0,1 en DMF).

Ejemplo 148(b) - Compuesto que eluyó en segundo lugar
(2*R*,4S,4a*S*)-11-fluoro-2,4-dimetil-8-(pirimidin-2-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona

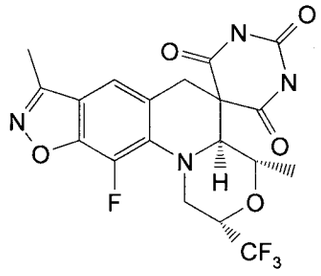


MS (ES) MH^+: 467 para $C_{22}H_{19}FN_6O_5$
^{1}H RMN (300 MHz, DMSO-d_6) δ: 0,9 (d, 3H) 1,2 (d, 3H) 2,9 - 3,2 (m, 2H) 3,6 - 4,2 (m, 5H) 7,7 (t, 1H) 7,8 (s, 1H) 9,0 (d, 2H) 11,5 (s, 1H) 11,8 (s, 1H).
>98% ee mediante HPLC quiral; [α] = -131 (c = 0,1 en DMF).

El **Ejemplo 149** se preparó a partir de los materiales de partida indicados utilizando un método similar al descrito para la síntesis del **Ejemplo 97:**

Ejemplo 149
(2S,4S,4a*S*)-rel-11-fluoro-4,8-dimetil-2-(trifluorometil)-1,2,4,4a-tetrahidro-2'H,6*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(1'H,3'H)-triona

(±)



Material de partida: 7-fluoro-3-metil-6-[(2*S*,6*S*)-rel-2-metil-6-(trifluorometil) morfolin-4-il]-1,2-benzoxazol-5-carbaldehído

MS (ES) MH^+: 457 para $C_{19}H_{16}F_4N_4O_5$

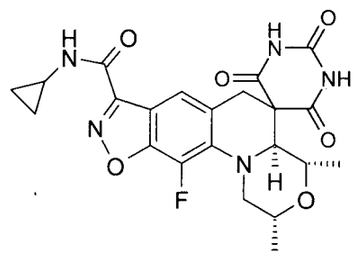
^{1}H RMN (300 MHz, DMSO-d_6) δ: 0,95 (d, 3H), 2,4 (s, 3H), 3,0 (d, 1H), 3,5 (t, 1H), 3,6 (d, 1H), 3,9 (m, 1H), 4,1 (d, 1H), 4,3 (d, 1H), 4,5 (m, 1H), 7,2 (s, 1H), 11,5 (s, 1H), 11,9 (s, 1H).

Los **Ejemplos 150** a **164** se prepararon a partir del material de partida indicado y ácido barbitúrico utilizando un método similar al descrito para la síntesis del **Ejemplo 134**. Los compuestos se purificaron mediante cromatografía en columna de gel de sílice utilizando un gradiente de DCM a acetato de etilo o mediante HPLC de fase inversa utilizando un gradiente de CH_3CN en agua con 0,1% de TFA.

Ejemplo 150

(2*R*,4S,4a*S*)-rel-*N*-ciclopropil-11-fluoro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-8-carboxamida

(±)



Material de partida: *N*-ciclopropil-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formilbenzo[d]isoxazol-3-carboxamida (**Intermedio 453**)

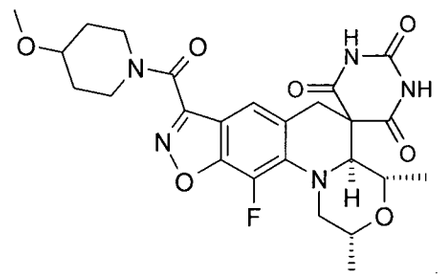
MS (ES) MH^+: 472 para $C_{22}H_{22}FN_5O_6$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,5-0,7 (m, 4H), 0,8 (d, 3H), 1,1 (d, 3H), 2,9 (d, 2H), 3,1 (t, 1H), 3,5-3,8 (m, 3H), 3,9 (d, 1H), 4,0 (d, 1H), 7,4 (s, 1H), 9,0 (d, 1H).

Ejemplo 151

(2*R*,4S,4a*S*)-rel-11-fluoro-8-(4-metoxipiperidin-1-carbonil)-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona

103542-1P

(±) 

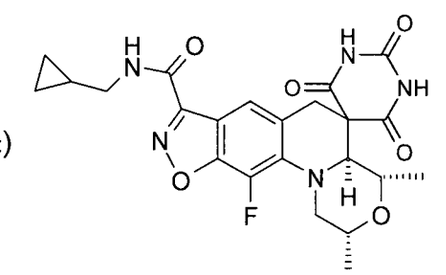
Material de partida: 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-3-(4-metoxipiperidina-1-carbonil)benzo[d]isoxazol-5-carbaldehído (**Intermedio 454**)

MS (ES) MH^+: 530 para $C_{25}H_{28}FN_5O_7$

^1H RMN (300 MHz, DMSO-d_6) δ ppm 0,8 (d, 3H), 1,1 (d, 3H), 1,3-1,6 (m, 2H), 1,7-1,9 (m, 2H), 2,9 (d, 1H), 3,0-3,1 (m, 1H), 3,2 (s, 3H), 3,34-3,5 (m, 2H), 3,5-3,8 (m, 4H), 3,8 – 4,0 (m, 2H), 4,0 (d, 1H), 7,2 (s, 1H).

Ejemplo 152

(2*R*,4S,4a*S*)-rel-*N*-(ciclopropilmetil)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-8-carboxamida

(±) 

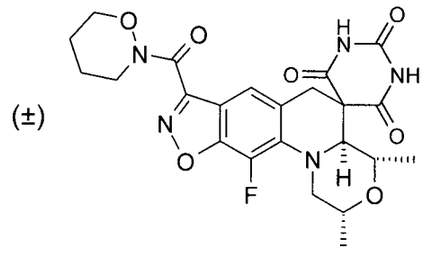
Material de partida: *N*-(ciclopropilmetil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formilbenzo[d]isoxazol-3-carboxamida (**Intermedio 455**)

MS (ES) MH^+: 486 para $C_{23}H_{24}FN_5O_6$

^1H RMN (300 MHz, DMSO-d_6) δ ppm 0,01 (d, 2H), 0,2 (d, 2H), 0,6 (d, 3H), 0,7-0,9 (m, 1H), 0,9 (d, 3H), 2,7 (d, 1H), 2,8 – 3,0 (m, 3H), 3,3-3,5 (m, 2H), 3,5-3,6 (m, 1H), 3,7 (d, 1H), 3,9 (d, 1 H), 7,2 (s, 1H), 8,8 (t, 1H), 11,3 (s a, 2H).

Ejemplo 153

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(1,2-oxazinan-2-ilcarbonil)-1,2,4,4a-tetrahidro-2'H,6*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(1'H,3'H)-triona



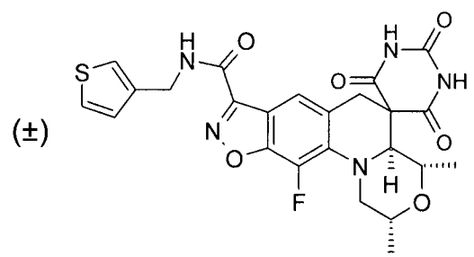
Material de partida: 6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]-7-fluoro-3-(1,2-oxazinan-2-ilcarbonil)-1,2-bencisoxazol-5-carbaldehído (**Intermedio 456**)

MS (ES) MH^+: 502 para $C_{23}H_{24}FN_5O_7$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,8 (d, 3H), 1,1 (d, 3H), 1,7 (s a, 3H), 2,9 (d, 1H), 3,0-3,2 (m, 1H), 3,5-3,7 (m, 3H), 3,7-3,9 (m, 5H), 4,1 (d, 1H), 7,1-7,3 (m, 1H), 11,5 (s, 1H), 11,8 (s, 1H).

Ejemplo 154

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimetil-2',4',6'-trioxo-*N*-(tiofen-2-ilmetil)-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-8-carboxamida



Material de partida: 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formil-*N*-(tiofen-2-ilmetil)benzo[d]isoxazol-3-carboxamida (**Intermedio 457**)

MS (ES) MH^+: 528 para $C_{24}H_{22}FN_5O_6S$

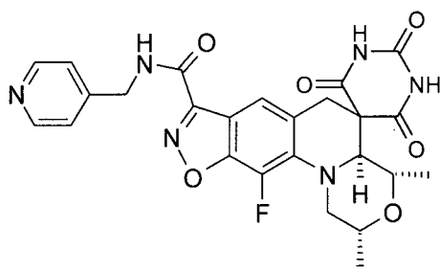
^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,9 (d, 3H), 1,2 (d, 3H), 2,9 (d, 1H), 3,0-3,2 (m, 1H), 3,6-3,7 (m, 2H), 3,8 (m, 1H), 4,0 (d, 1H), 4,1 (d, 1H), 4,6 (d, 2H), 6,9-7,0 (m, 1H), 7,0 (s a, 1H), 7,4 (d, 1H), 7,4 (s, 1H), 9,6 (t, 1H).

Ejemplo 155

103542-1P

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimetil-2',4',6'-trioxo-*N*-(piridin-4-ilmetil)-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-8-carboxamida

(±)



Material de partida: 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formil-*N*-(piridin-4-ilmetil)benzo[d]isoxazol-3-carboxamida (**Intermedio 458**)

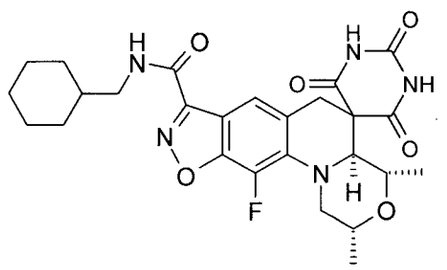
MS (ES) MH^+: 523 para $C_{25}H_{23}FN_6O_6$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,9 (d, 3H), 1,2 (d, 3H), 2,9 (d, 1H), 3,1 (t, 1H), 3,6-3,7 (m, 2H), 3,8-3,9 (m, 1H), 4,0 (d, 1H), 4,1 (d, 1H), 4,5 (d, 2H), 7,3 (d, 2H), 7,4 (s, 1H), 8,5 (d, 2H), 9,6 (t, 1H).

Ejemplo 156

(2*R*,4S,4a*S*)-rel-*N*-(ciclohexilmetil)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-8-carboxamida

(±)



Material de partida: *N*-(ciclohexilmetil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formilbenzo[d]isoxazol-3-carboxamida (**Intermedio 459**)

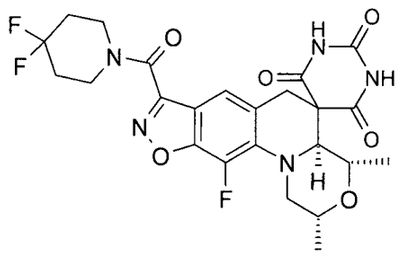
MS (ES) MH^+: 528,3 para $C_{26}H_{30}FN_5O_6$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,8-1,0 (m, 5H), 1,1-1,3 (m, 6H), 1,5-1,8 (m, 6H), 2,9 (d, 1H), 3,0-3,2 (m, 3H), 3,7 (d, 2H), 3,7-3,9 (m, 1H), 4,0 (d, 1H), 4,1 (d, 1H), 7,4 (s, 1H), 8,9 (t, 1H), 11,6 (s a, 1H).

Ejemplo 157

(2*R*,4S,4a*S*)-rel-8-(4,4-difluoropiperidin-1-carbonil)-11-fluoro-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona

(±)



Material de partida: 3-(4,4-difluoropiperidin-1-carbonil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-5-carbaldehído (**Intermedio 460**)

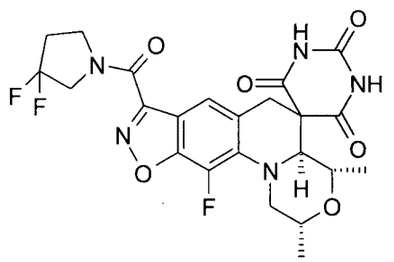
MS (ES) MH^+: 536 para $C_{24}H_{24}F_3N_5O_6$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,9 (d, 3H), 1,2 (d, 3H), 2,0-2,2 (m, 4H), 3,0 (d, 1H), 3,1-3,2 (m, 1H), 3,6-3,9 (m, 7H), 4,0 (d, 1H), 4,1 (d, 1H), 7,3 (s, 1H), 11,5 (s, 1 H,) 11,9 (s, 1H).

Ejemplo 158

(2*R*,4S,4a*S*)-rel-8-(3,3-difluoropirrolidin-1-carbonil)-11-fluoro-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona

(±)



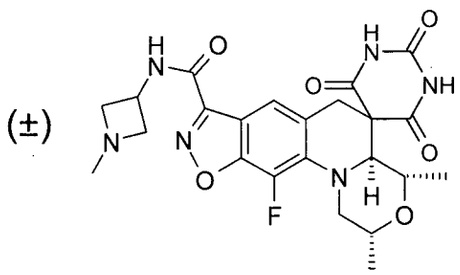
Material de partida: 3-(3,3-difluoropirrolidin-1-carbonil)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-5-carbaldehído (**Intermedio 461**)

MS (ES) MH^+: 522 para $C_{23}H_{22}F_3N_5O_6$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,9 (d, 3H), 1,2 (d, 3H), 2,9 (d, 1H), 3,1 (t, 1H), 3,6-3,9 (m, 4H), 3,9-4,2 (m, 4H), 4,3 (t, 1H), 7,4 (d, 1H), 11,5 (s, 1H), 11,9 (s, 1H).

Ejemplo 159

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimetil-*N*-(1-metilazetidin-3-il)-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-8-carboxamida



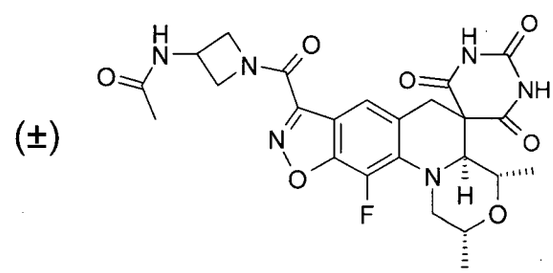
Material de partida: 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formil-*N*-(1-metilazetidin-3-il)benzo[d]isoxazol-3-carboxamida (**Intermedio 462**)

MS (ES) MH^+: 501 para $C_{23}H_{25}FN_6O_6$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,8 (d, 3H), 1,1 (d, 3H), 2,2 (s, 3H), 2,9 (d, 1H), 3,0 (t, 2H), 3,1 (d, 1H), 3,5 (t, 2H), 3,6-3,7 (m, 2H), 3,7-3,8 (m, 1H), 3,9 (d, 1H), 4,0 (d, 1H), 4,3-4,4 (m, 1H), 7,3 (s, 1H), 9,3 (d, 1H).

Ejemplo 160

N-(1-((2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-8-ilcarbonil)azetidin-3-il)acetamida



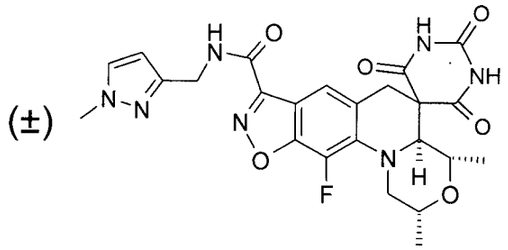
Material de partida: *N*-(1-(6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formilbenzo[d]isoxazol-3-carbonil)azetidin-3-il)acetamida (**Intermedio 463**)

MS (ES) MH^+: 529 para $C_{24}H_{25}FN_6O_7$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,8 (d, 3H), 1,1 (d, 3H), 1,8 (s, 3H), 2,8 (d, 1H), 3,0-3,1 (m, 1H), 3,5-3,8 (m, 3H), 3,8 -3,9 (m, 2H), 4,1 (d, 1H), 4,1-4,4 (m, 2H), 4,4-4,5 (m, 1H), 4,6-4,7 (m, 1H), 7,4 (s, 1H), 8,5 (d, 1H), 11,4 (s, 1H), 11,8 (s, 1H).

Ejemplo 161

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimetil-*N*-((1-metil-1*H*-pirazol-3-il)metil)-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-8-carboxamida



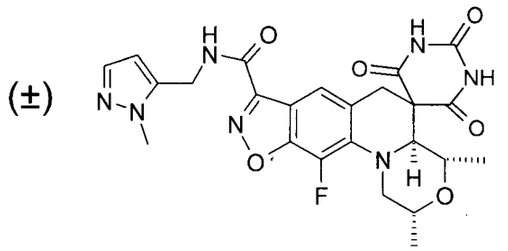
Material de partida: 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formil-*N*-((1-metil-1*H*-pirazol-3-il)metil)benzo[d]isoxazol-3-carboxamida (**Intermedio 464**)

MS (ES) MH^+: 526 para $C_{24}H_{24}FN_7O_6$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,9 (d, 3H), 1,1 (d, 3H), 2,9 (d, 1H), 3,0-3,2 (m, 1H), 3,6-3,9 (m, 6H), 4,0 (d, 1H), 4,1 (d, 1H), 4,4 (d, 2H), 6,2 (d, 1H), 7,5 (s,1H), 7,6 (d, 1H), 9,3 (t, 1H), 11,5 (s, 1H), 11,8 (s, 1H).

Ejemplo 162

(2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimetil-*N*-((1-metil-1*H*-pirazol-5-il)metil)-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-8-carboxamida



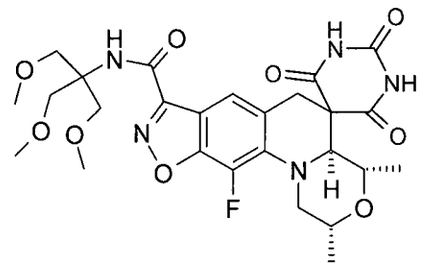
Material de partida: 6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formil-*N*-((1-metil-1*H*-pirazol-5-il)metil)benzo[d]isoxazol-3-carboxamida (**Intermedio 465**)

MS (ES) MH^+: 526 para $C_{24}H_{24}FN_7O_6$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,9 (d, Hz, 3H), 1,1 (d, Hz, 3H), 2,9 (d, 1H), 3,1 (t, 1H), 3,6-3,8 (m, 3H), 3,8 (s, 3H), 4,0 (d, 1H), 4,1 (d, 1H), 4,4-4,6 (m, 2H), 6,2 (s, 1H), 7,3 (s, 1H), 7,4 (s, 1H), 9,5 (t, 1H), 11,5 (s, 1H), 11,8 (s, 1H).

Ejemplo 163

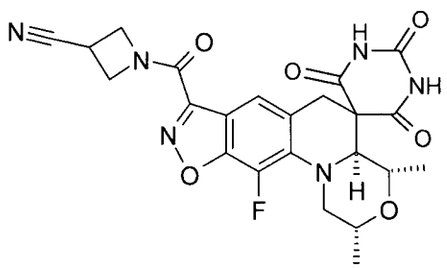
(2*R*,4S,4a*S*)-rel-*N*-(1,3-dimetoxi-2-(metoximetil)propan-2-il)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-8-carboxamida

(±) 

Material de partida: *N*-(1,3-dimetoxi-2-(metoximetil)propan-2-il)-6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formilbenzo[d]isoxazol-3-carboxamida (**Intermedio 466**)
MS (ES) MH^+: 578 para $C_{26}H_{32}FN_5O_9$
^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,9 (d, 3H), 1,2 (d, 3H), 2,9 (d, 1H), 3,1-3,2 (m, 1H), 3,3 (s, 9H), 3,6-3,7 (m, 8H), 3,8-3,9 (m, 1H), 4,0 (d, 1H), 4,1 (d, 1H), 7,4 (s, 1H), 7,7 (s, 1H), 11,6 (s a, 2H).

Ejemplo 164

1-((2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-8-ilcarbonil)azetidin-3-carbonitrilo

(±) 

Material de partida: 1-(6-((2*R*,6*S*)-2,6-dimetilmorfolino)-7-fluoro-5-formilbenzo[d]isoxazol-3-carbonil)azetidin-3-carbonitrilo (**Intermedio 468**)

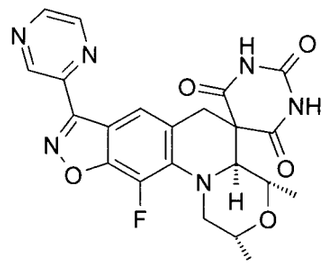
MS (ES) MH^+: 497 para $C_{23}H_{21}FN_6O_6$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,9 (d, 3H), 1,2 (d, 3H), 2,9 (d, 1H), 3,0-3,2 (m, 1H), 3,6-3,8 (m, 3H), 3,9-4,0 (m, 2H), 4,1 (d, 1H), 4,3 (t, 1H), 4,3-4,5 (m, 1H), 4,6-4,9 (m, 2H), 7,5 (s, 1H).

Ejemplo 165

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(pirazin-2-il)-1',2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±)



Se hicieron reaccionar ácido barbitúrico y (2*R*,4*S*,4a*S*)-rel-9,10-difluoro-8-[(hidroxiimino)(pirazin-2-il)metil]-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona (**Intermedio 583**) utilizando un método similar al descrito para la síntesis del **Ejemplo 8**.

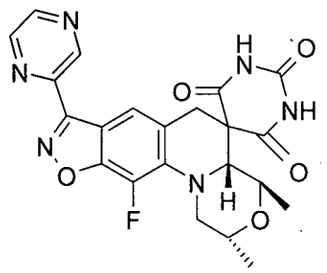
MS (ES) MH^+: 467 para $C_{22}H_{19}FN_6O_5$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (s a, 3H), 1,2 (s a, 3H), 2,9 (m, 1H), 3,1 (m, 1H), 3,8 (m, 2H), 4,0 (m, 1H), 4,2 (m, 1H), 7,6 (m, 1H), 7,8 (s, 1H), 8,9 (m, 2H), 9,3 (s, 1H), 11,5 (s, 1H), 11,8 (s, 1H).

En una ruta alternativa, el enantiómero (2*R*,4S,4aS) del **Ejemplo 165** se sintetizó utilizando una síntesis quiral, como se describe a continuación para el **Ejemplo 165(a)**:

Ejemplo 165(a)

(2*R*,4*S*,4a*R*)-11-fluoro-2,4-dimetil-8-(pirazin-2-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona



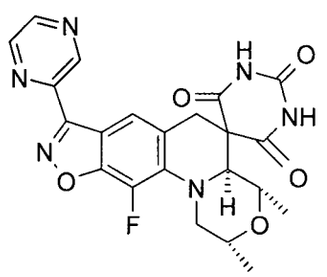
El diastereómero (2*R*,4*R*,4a*R*) se generó como un producto secundario de la reacción descrita para la síntesis del **Ejemplo 165(b)** a continuación. La cromatografía descrita para el **Ejemplo 165(b)** proporcionó el diastereómero (2*R*,4*R*,4a*R*) como el compuesto que eluyó en primer lugar.

MS (ES) MH^+: 467 para $C_{22}H_{19}FN_6O_5$

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm: 0,9 (d, 3H), 1,3 (d, 3H), 3,1 (d, 1H), 3,55 (d, 1H), 3,65 (d, 1H), 3,75 (d, 1H), 3,8-4,0 (m, 2H), 4,0-4,1 (m, 1H), 7,7 (s, 1H), 8,8 (m, 2H), 9,3 (d, 1H), 11,4 (s, 1H), 11,7 (d, 1H).

Ejemplo 165(b)

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimetil-8-(pirazin-2-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona



Se hicieron reaccionar ácido barbitúrico y 6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-3-(pirazin-2-il)benzo[d]isoxazol-5-carbaldehído (**Intermedio 438**) utilizando un método similar al descrito para la síntesis del **Ejemplo 53(a)**. El producto se purificó mediante HPLC de fase inversa utilizando un gradiente de CH_3CN en agua con 0,1% de TFA y se obtuvo como el compuesto que eluyó en segundo lugar.

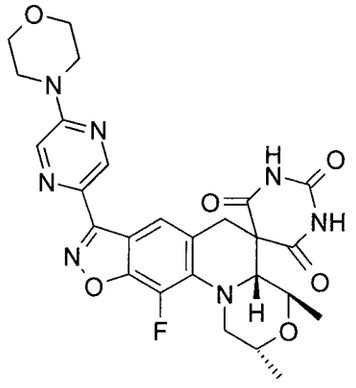
MS (ES) MH^+: 467 para $C_{22}H_{19}FN_6O_5$

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm: 0,9 (d, 3H), 1,2 (d, 3H), 3,0 (d, 1H), 3,1 (m, 1H), 3,5-3,9 (m, 3H), 4,0 (d, 1H), 4,2 (d, 1H), 7,8 (s, 1H), 8,7-9,0 (m, 2H), 9,4 (d, 1H), 11,5 (s, 1H), 11,8 (d, 1H).

Los **Ejemplos 166(a)** a **167** se prepararon a partir del material de partida indicado y ácido barbitúrico utilizando un método similar al descrito para la síntesis del **Ejemplo 53(a):**

Ejemplo 166(a)

(2*R*,4*R*,4a*R*)-11-fluoro-2,4-dimetil-8-(5-morfolinopirazin-2-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona



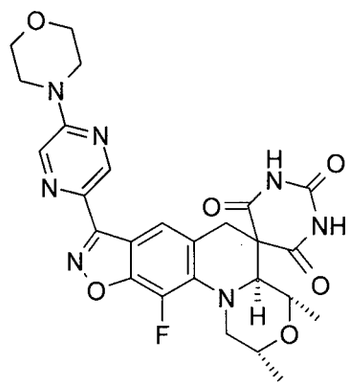
El diastereómero (2*R*,4*R*,4a*R*) se generó como un producto secundario de la reacción descrita para la síntesis del **Ejemplo 166(b)** a continuación. La cromatografía descrita para el **Ejemplo 166(b)** proporcionó el diastereómero (2*R*,4*R*,4a*R*) como el compuesto que eluyó en primer lugar. MS (ES) MH^+: 552 para $C_{26}H_{26}FN_7O_6$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 1,0 (d, 3H), 1,3 (d, 3H), 3,2 (d, 1H), 3,6 (m, 1H), 3,6-3,8 (m, 11H), 3,9-4,0 (m, 1H), 4,1 (m, 1H), 7,3 (d, 1H), 7,7 (s, 1H), 8,6 (d, 1H), 11,5 (s, 1H), 11,8 (s, 1H).

Ejemplo 166(b)

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimetil-8-(5-morfolinopirazin-2-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona

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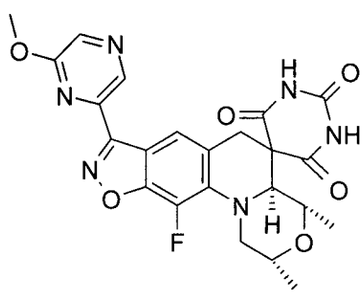
Material de partida: 6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-3-(5-morfolinopirazin-2-il)benzo[d]isoxazol-5-carbaldehído (**Intermedio 433**). La purificación mediante HPLC de fase inversa utilizando un gradiente de CH_3CN en agua con 0,1% de TFA proporcionó el diastereómero (2*R*, 4*S*, 4a*S*) como el compuesto que eluyó en segundo lugar.

MS (ES) MH^+: 552 para $C_{26}H_{26}FN_7O_6$

^1H RMN (300 MHz, DMSO-d_6) δ ppm 0,9 (d, 3H), 1,2 (d, 3H), 3,0 (d, 1H), 3,1 (m, 1H), 3,6-3,8 (m, 11H), 4,0 (d, 1H), 4,1 (s, 1H), 7,7 (s, 1H), 8,5 (d, 1H), 8,8 (d, 1H), 11,5 (s, 1H), 11,8 (s, 1H)

Ejemplo 167

(2*R*,4S,4a*S*)-11-fluoro-8-(6-metoxipirazin-2-il)-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona



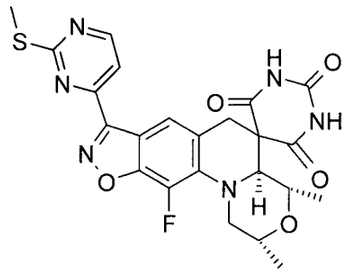
Material de partida: 6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-3-(6-metoxipirazin-2-il)benzo[d]isoxazol-5-carbaldehído (**Intermedio 436**); purificación mediante HPLC de fase inversa utilizando un gradiente de CH_3CN en agua con 0,1% de TFA.

MS (ES) MH^+: 497 para $C_{23}H_{21}FN_6O_6$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm: 0,9 (d, 3H), 1,2 (d, 3H), 3,0 (d, 1H), 3,1-3,2 (m, 1H), 3,6-3,7 (m, 1H), 3,8 (d, 2H), 4,0 (d, 1H), 4,1 (s, 3H), 4,2 (d, 1H), 7,7 (s, 1H), 8,5 (s, 1H), 8,9 (s, 1H), 11,5 (s, 1H), 11,9 (s, 1H).

Ejemplo 168

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimetil-8-(2-(metiltio)pirimidin-4-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona



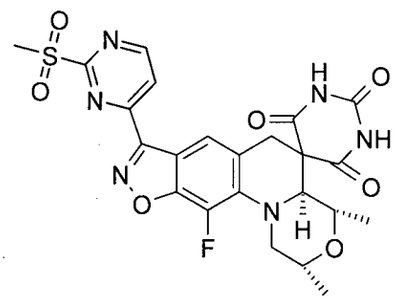
En un reactor de microondas, 6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-3-(2-(metiltio)pirimidin-4-il)benzo[d]isoxazol-5-carbaldehído (**Intermedio 437**, 719 mg, 1,79 mmol) y 1,3,5-triazinano-2,4,6-triona (242 mg, 1,88 mmol) en EtOH (10 mL) se calentaron a 140 °C durante 1 hora. La solución se concentró hasta secarse para proporcionar 916 mg del producto deseado, utilizado en reacciones subsiguientes sin purificación adicional.

MS (ES) MH^+: 513 para $C_{23}H_{21}FN_6O_5S$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,9 (d, 3H), 1,2 (d, 3H), 2,6 (s, 3H), 3,0 (d, 1H), 3,1-3,2 (m, 1H), 3,7 (dd, 1H), 3,7-3,9 (m, 2H), 4,0 (d, 1H), 4,2 (d, 1H), 7,7 (s, 1H), 7,8 (d, 1H), 8,8 (d, 1H), 11,5 (s a, 1H), 11,9 (s a, 1H).

Ejemplo 169

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimetil-8-(2-(metilsulfonil)pirimidin-4-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona



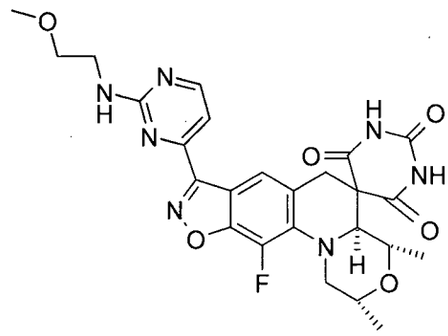
Se agregó oxono (5902 mg, 9,60 mmol) a una solución de (2*R*,4S,4a*S*)-11-fluoro-2,4-dimetil-8-(2-(metiltio)pirimidin-4-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona (**Ejemplo 168,** 984 mg, 1,92 mmol) en MeOH:THF:H_2O (30 mL)(1:1:1) y la mezcla se agitó a temperatura ambiente durante 48 horas.La mezcla de reacción se diluyó con DCM (50 mL), se agitó durante 10 minutos, se filtró y la torta de filtrado se lavó con EtOH. El filtrado se lavó con agua y salmuera, se concentró a presión reducida para proporcionar el producto deseado utilizado en reacciones subsiguientes sin purificación adicional.

MS (ES) MH^+: 545 para $C_{23}H_{21}FN_6O_7S$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,9 (d, 3H), 1,2 (d, 3H), 3,0 (s, 1H), 3,2 (d, 1H) 3,7 (m, 1H), 3,8 (d, 2H), 4,0 (d,1H), 4,1 (d, 1H), 7,0 (m, 1H), 7,8 (s, 1H), 8,1 (m, 1H), 11,5 (s, 1H), 11,8 (d, 1H), 12,0-12,4 (s a, 1H)

Ejemplo 170

(2*R*,4S,4a*S*)-11-fluoro-8-(2-(2-metoxietilamino)pirimidin-4-il)-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona



Se agregó 2-metoxietanamina (8,70 µL, 0,10 mmol) a una solución de (2*R*,4S,4a*S*)-11-fluoro-2,4-dimetil-8-(2-(metilsulfonil)pirimidin-4-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-

g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona (**Ejemplo 169**, 50 mg, 0,09 mmol) en THF (5 mL) y la mezcla se agitó a temperatura ambiente durante 3 horas, se agregó DMSO (1 mL) seguido por la adición de 2 equivalentes más de metoxiletanamina, la mezcla se agitó a temperatura ambiente durante toda la noche. El bruto se concentró y se purificó mediante cromatografía en columna de gel de sílice de fase inversa (gradiente de 20-70% de MeCN en agua, 0,1% de TFA) para proporcionar 37 mg de producto.

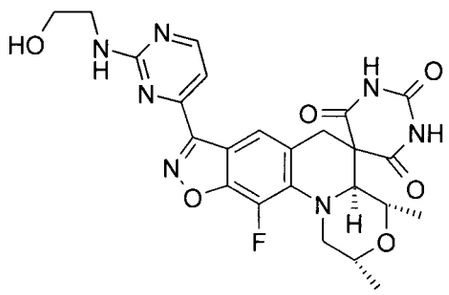
MS (ES) MH^+: 540 para $C_{25}H_{26}FN_7O_6$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,9 (d, 3H), 1,7 (d, 3H), 3,1 (m, 2H), 3,2-3,3 (m, 3H), 3,4-3,5 (m, 4H), 3,7 (m, 2H), 3,8-3,9 (m, 1H), 4,0 (d, 1H), 4,1 (d, 1H), 7,2 (d, 1H), 7,5 (s a, 1H), 7,9 (br. s, 1H), 8,5 (d, 1H), 11,5 (s, 1H), 11,9 (s, 1H).

Los **Ejemplos 171** a **177** se prepararon a partir de los materiales de partida indicados y utilizando un método similar al descrito para la síntesis del **Ejemplo 170**:

Ejemplo 171

(2*R*,4S,4a*S*)-11-fluoro-8-(2-(2-hidroxietilamino)pirimidin-4-il)-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona



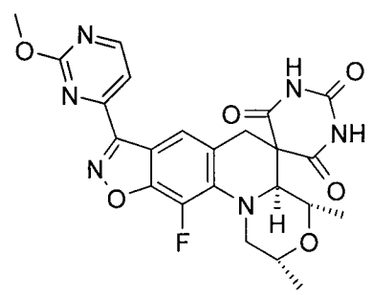
Material de partida: (2*R*,4S,4a*S*)-11-fluoro-2,4-dimetil-8-(2-(metilsulfonil)pirimidin-4-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona (**Ejemplo 169**) y 2-aminoetanol

MS (ES) MH^+: 526 para $C_{24}H_{24}FN_7O_6$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,9 (d, 3H), 1,2 (d, 3H), 3,1 (m, 1H), 3,5-3,7 (m, 6H), 3,7-3,8 (m, 2H), 3,8-3,9 (m, 1H), 4,0 (d, 1H), 4,1 (d, 1H), 7,2 (d, 1H), 7,4 (s a, 1H), 7,7-8,1 (m, 1H), 8,5 (d, 1H), 11,5 (s a, 1H) 11,9 (s, 1H).

Ejemplo 172

(2*R*,4S,4a*S*)-11-fluoro-8-(2-metoxipirimidin-4-il)-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona



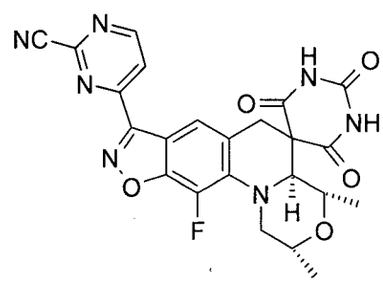
Material de partida: (2*R*,4S,4a*S*)-11-fluoro-2,4-dimetil-8-(2-(metilsulfonil)pirimidin-4-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona (**Ejemplo 169**) y amoníaco 2M en metanol

MS (ES) MH^+: 497 para $C_{23}H_{21}FN_6O_6$

^{1}H RMN (300 MHz, DMSO-d_6): δ ppm 0,8 (d, 3H), 1,1 (d, 3H), 2,9 (d, 1H), 3,0-3,2 (m, 1H), 3,6 (dd, 2H), 3,7-3,8 (m, 1H), 3,9 (d, 1H), 4,0 (s, 3H), 4,1 (d, 1H), 7,6-7,8 (m, 2H), 8,8 (d, 1H), 11,4 (s, 1H), 11,8 (s, 1H).

Ejemplo 173

4-((2*R*,4S,4a*S*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-8-il)pirimidin-2-carbonitrilo



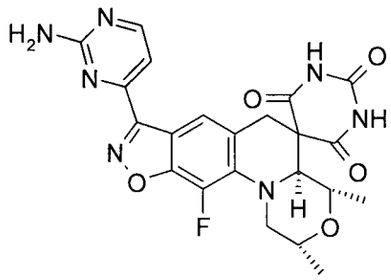
Material de partida: (2*R*,4S,4a*S*)-11-fluoro-2,4-dimetil-8-(2-(metilsulfonil)pirimidin-4-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona (**Ejemplo 169**) y cianuro de potasio

MS (ES) MH^+: 492 (M+H) para $C_{23}H_{18}FN_7O_5$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,9 (d, 3H), 1,2 (d, 3H), 3,0 (d, 1H), 3,1-3,2 (m, 1H), 3,7 (dd, 1H), 3,8 (m, 1H), 3,9 (d, 1H), 4,0 (d, 1H), 4,2 (d, 1H), 7,7 (s, 1H), 8,5 (d, 1H), 9,2 (d, 1H), 11,5 (s, 1H), 11,8 (s, 1H).

Ejemplo 174

(2*R*,4S,4a*S*)-8-(2-aminopirimidin-4-il)-11-fluoro-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona



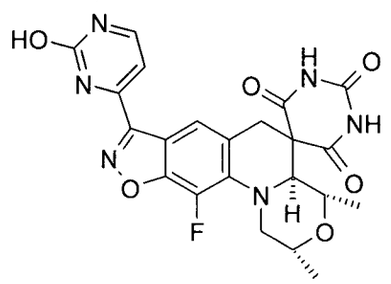
Materiales de partida: (2*R*,4S,4a*S*)-11-fluoro-2,4-dimetil-8-(2-(metilsulfonil)pirimidin-4-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona (**Ejemplo 169**) y amoníaco en dioxano (0,5M)

MS (ES) MH^+: 482 (M+H) para $C_{22}H_{20}FN_7O_5$

^{1}H RMN (300 MHz, DMSO-d_6) d ppm 0,9 (d, 3H), 1,2 (d, 3H), 3,0-3,2 (m, 2H), 3,4-3,5 (m, 1H), 3,7 (dd, 1H), 3,8-3,9 (m, 1H), 4,0 (d, 1H), 4,1 (d, 1H), 7,0 (s, 2H), 7,2 (d, 1H), 7,9 (s, 1H), 8,4 (d, 1H), 11,5 (s, 1H), 11,9 (s, 1H).

Ejemplo 175

(2*R*,4*S*,4a*S*)-11-fluoro-8-(2-hidroxipirimidin-4-il)-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona



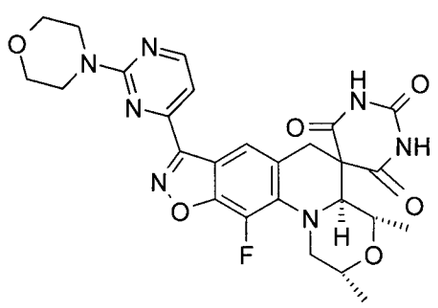
Materiales de partida: (2*R*,4S,4a*S*)-11-fluoro-2,4-dimetil-8-(2-(metilsulfonil)pirimidin-4-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona (**Ejemplo 169**) y trimetilsilanolato de potasio

MS (ES) MH^+: 483 (M+H) para $C_{22}H_{19}FN_6O_6$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,9 (d, 3H), 1,2 (d, 3H), 3,0 (s, 1H), 3,2 (d, 1H), 3,7 (m, 1H), 3,8 (d, 2H), 4,0 (d, 1H), 4,1 (d, 1H), 7,0 (s a, 1H), 7,8 (s, 1H), 8,1 (s a, 1H), 11,5 (s, 1H), 11,8 (d, 1H), 12,0-12,4 (m, 1H)

Ejemplo 176

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimetil-8-(2-morfolinopirimidin-4-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona



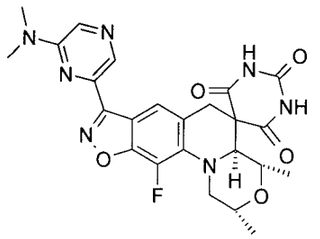
Materiales de partida: (2*R*,4S,4a*S*)-11-fluoro-2,4-dimetil-8-(2-(metilsulfonil)pirimidin-4-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona (**Ejemplo 169**) y morfolina

MS (ES) MH^+: 552 para $C_{26}H_{26}FN_7O_6$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm: 0,9 (d, 3H), 1,2 (d, 3H), 3,0 (d, 1H), 3,1-3,2 (m, 1H), 3,6-3,7 (m, 2H), 3,7 (m, 4H), 3,8-3,9 (m, 5H), 4,0 (d, 1H), 4,1 (d, 1H), 7,3 (d, 1H), 7,6 (s, 1H), 8,6 (d, 1H), 11,5 (s, 1H), 11,9 (s, 1H)

Ejemplo 177

(2*R*,4S,4a*S*)-rel-8-(6-(dimetilamino)pirazin-2-il)-11-fluoro-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona

(±) 

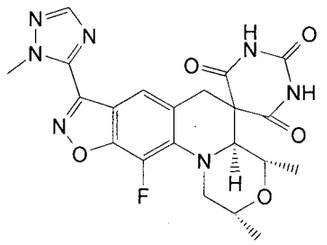
Materiales de partida: (2*R*,4S,4a*S*)-rel-8-(6-cloropirazin-2-il)-11-fluoro-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona (**Ejemplo 79**) y dimetilamina 2N en THF

MS (ES) MH^+: 510 para $C_{24}H_{24}FN_7O_5$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,9 (d, 3H), 1,2 (d, 3H), 3,0 (d, 1H), 3,1 (m, 1H), 3,2 (s, 6H), 3,7-3,8 (m, 3H), 4,0 (d, 1H), 4,1 (d, 1H), 7,7 (s, 1H), 8,3 (s, 1H), 8,4 (s, 1H), 11,5 (s a, 1H), 11,8 (s a, 1H).

Ejemplo 178

(2*R*,4S,4a*S*)-11-fluoro-2,4-dimetil-8-(1-metil-1*H*-1,2,4-triazol-5-il)-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona



Una mezcla de 6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluoro-3-(1-metil-1*H*-1,2,4-triazol-5-il)benzo[d]isoxazol-5-carbaldehído (**Intermedio 537,** 124 mg, 0,35 mmol) y pirimidin-2,4,6(1H,3H,5H)-triona (44,2 mg, 0,35 mmol) en metanol (3 mL) se calentó a 150 °C durante 1 hora en un reactor de microondas. El disolvente se eliminó y el residuo se purificó mediante HPLC de fase inversa (gradiente de CH_3CN/agua con 0,1% de TFA). El sólido se recogió con CH_2Cl_2- MeOH 9:1 y se lavó con $NaHCO_3$ y salmuera. Las capas acuosas se extrajeron repetidamente con CH_2Cl_2-MeOH 9:1 adicional y cada extracto se lavó con salmuera. Las capas orgánicas combinadas se secaron ($MgSO_4$) y se concentraron y el residuo se disolvió en THF.

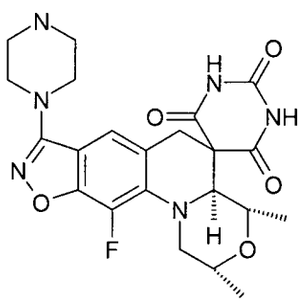
Después de eliminar del disolvente, el residuo sólido se secó al vacío a 50 °C durante toda la noche para proporcionar el producto deseado.

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,9 (d, 3H), 1,2 (d, 3H), 2,9 (d, 1H), 3,0-3,2 (m, 1H), 3,6-3,8 (m, 1H), 3,8 (d, 2H) 4,0 (d, 1H) 4,1 (d, 1H), 4,2 (s, 3H), 7,7 (s, 1H), 8,3 (s, 1H), 11,5 (s, 1H), 11,85 (s, 1H).

Ejemplo 179

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(piperazin-1-il)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±)



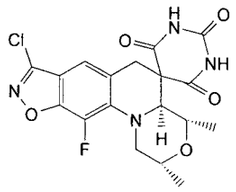
Una mezcla de 4-[(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[isoxazolo[4,5-*g*][1,4]oxazino[4,3-*a*]quinolin-5,5'-pirimidin]-8-il]piperazin-1-carboxilato de *terc*-butilo (**Ejemplo 20**, 50 mg, 0,08 mmol) y HCl 4N en MeOH (8 mL) se agitó a temperatura ambiente durante 1 hora. Se concentró a presión reducida y el residuo se lavó con éter de pet para proporcionar el compuesto del título como un sólido marrón. Se aisló como la sal HCl. Rendimiento: 28 mg (67%)

MS (ES) MH^+: 473 para $C_{22}H_{25}FN_6O_5$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 2,95 (d, 1H), 3,05 (t, 1H), 3,40 (m, 4H), 3,45 (m, 1H), 3,6 (m, 5H), 3,8 (m, 1H), 3,9 (d, 1H), 4,05 (d, 1H), 7,3 (s, 1H), 9,15 (s a, 2H), 11,5 (s, 1H), 11,9 (s, 1H).

Ejemplo 180

(2*R*,4S,4a*S*)-8-cloro-11-fluoro-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona



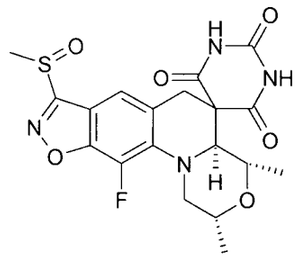
Una mezcla de 3-cloro-6-((2*R*,6*R*)-2,6-dimetilmorfolino)-7-fluorobenzo[d]isoxazol-5-carbaldehído (**Intermedio 535,** 764 mg, 2,44 mmol) y pirimidin-2,4,6(1H,3H,5H)-triona (313 mg, 2,44 mmol) en iPrOH (3 mL) se calentó a reflujo durante 3 días. El disolvente se eliminó y el residuo se recristalizó en metanol. Los sólidos obtenidos se recristalizaron en EtOH-Agua 1:1 para proporcionar 273 mg de un producto consistente con el producto deseado.

MS (ES) MH^+: 473 para $C_{22}H_{25}FN_6O_5$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,9 (d, 3H) 1,15 (d, 3H) 2,95 (d, 1H) 3,55-3,7 (m, 2H) 3,7-3,9 (m, 1H) 4,0 (d, 1H) 4,1 (m, 2H) 7,2 (s, 1H) 11,5 (s, 1H) 11,9 (s, 1H).

Ejemplo 181

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(metilsulfinil)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±) 

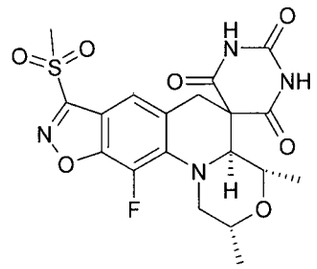
A una solución agitada de (2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(metilsulfanil)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona (**Ejemplo 62,** 50 mg, 0,11 mmol) en DCM seco (1 mL) se agregó ácido m-cloroperbenzoico (39 mg, 0,23 mmol) y se agitó a temperatura ambiente durante 1 hora. Los disolventes se evaporaron y el residuo obtenido de esta forma se purificó en una columna de gel de sílice para proporcionar el producto como un sólido. Rendimiento: 18 mg (35 %).

MS (ES) MH^+: 451 para $C_{19}H_{19}FN_4O_6S$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,15 (d, 3H), 2,9 (d, 1H), 3,1 (t, 1H), 3,2 (m, 3H), 3,7-3,8 (m, 3H), 4,0 (d, 1H), 4,1 (d, 1H), 7,1 (t, 1H), 11,5 (s, 1H), 11,9 (s, 1H).

Ejemplo 182

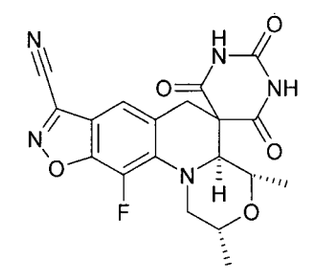
(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(metilsulfonil)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±) 

A una solución agitada de (2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(metilsulfanil)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona (**Ejemplo 62,** 50 mg, 0,11 mmol) en DCM seco (1 mL) se agregó ácido m-cloroperbenzoico (39 mg, 0,23 mmol) y se calentó hasta alcanzar 80 °C durante 1 hora. Los disolventes se evaporaron y el residuo obtenido de esta forma se purificó en una columna de gel de sílice para proporcionar el compuesto del título como un sólido. Rendimiento: 20 mg (43%).
MS (ES) MH^+: 467 para $C_{19}H_{19}FN_4O_7S$;
^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 2,9 (d, 1H), 3,2 (t, 1H), 3,6 (s, 3H), 3,65 (m, 1H), 3,7 (m, 1H), 3,8 (m, 1H), 4,0 (d, 1H), 4,1 (d, 1H), 7,4 (s, 1H), 11,6 (s, 1H), 11,9 (s, 1H).

Ejemplo 183

(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-carbonitrilo

(±) 

A una solución agitada de (2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-8-(metilsulfonil)-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-

2',4',6'(1'*H*,3'*H*)-triona (**Ejemplo 182**, 1,0 g, 2,15 mmol) en DMF se agregó KCN (700 mg, 10,75 mmol) y luego 18-corona-6 (cantidad catalítica) y la mezcla se calentó a 85 °C durante 12 horas. La mezcla de reacción se enfrió hasta alcanzar temperatura ambiente y se precipitó con éter dietílico (se repitió dos veces para eliminar totalmente el DMF). El precipitado se disolvió en EtOAc (50 mL) y se lavó con agua (2X 10 mL), se secó con sulfato de sodio anhidro, se filtró y se concentró. El residuo se purificó con un instrumento Combiflash para proporcionar el producto como un sólido amarillo claro. Rendimiento: 211 mg (23%).

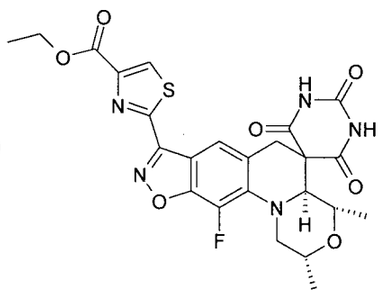
MS (ES) MH^+: 414,5 para $C_{19}H_{16}FN_4O_5$

^1H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 2,9 (d, 1H), 3,15 (m, 1H), 3,7 (m, 2H), 3,8 (m, 1H), 4,0 (d, 1H), 4,1 (d, 1H), 7,4 (s, 1H), 11,6 (s a, 1H), 11,9 (s a, 1H).

Ejemplo 184

2-[(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-1,3-tiazol-4-carboxilato de etilo

(±)



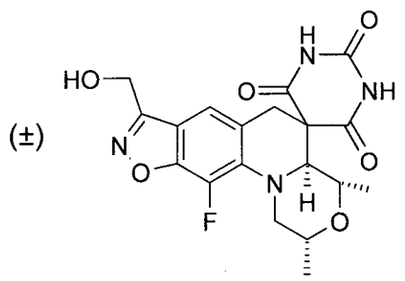
A una solución agitada de (2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-carbotioamida (**Intermedio 575**, 54 mg, 0,128 mmol) en una mezcla de EtOH:DMF (1 mL: 0,5 mL) se agregaron bromopiruvato de etilo (47 mg, 0,24 mmol) y tamices moleculares y la mezcla se agitó a 100 °C durante 12 horas. La mezcla de reacción se concentró, el residuo se purificó mediante cromatografía en columna de gel de sílice para proporcionar el producto como un sólido. Rendimiento: 13 mg (20%).

MS (ES) MH^+: 544 para $C_{24}H_{22}FN_5O_7S$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,1 (d, 3H), 1,3 (t, 3H), 2,9 (d, 1H), 3,1 (m, 1H), 3,6 (m, 1H), 3,8 (m, 2H), 4,0 (d, 1H), 4,1 (d, 1H), 4,4 (c, 2H), 7,6 (s, 1H), 8,7 (s, 1H), 11,5 (s, 1H), 11,8 (s, 1H).

Ejemplo 185

(2*R*,4S,4a*S*)-rel-11-fluoro-8-(hidroximetil)-2,4-dimetil-2,4,4a,6-tetrahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-2',4',6'(3'H)-triona



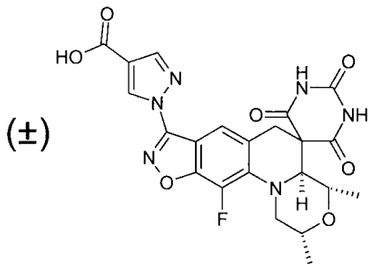
Se agregó borohidruro de litio (0,434 mL, 0,87 mmol) a una solución enfriada con hielo de metanol (0,035 mL, 0,87 mmol) en THF (10 mL). La solución se entibió hasta alcanzar la temperatura ambiente y se agitó durante 1 hora. Se agregó 1,5 mL de la solución de $LiBH_4$/MeOH a una solución de (2*R*,4S,4a*S*)-rel-11-fluoro-2,4-dimetil-2',4',6'-trioxo-2,2',3',4,4a,4',6,6'-octahidro-1*H*,1'*H*-espiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinolin-5,5'-pirimidin]-8-carboxilato de etilo (**Ejemplo 134**, 30 mg, 0,07 mmol) en 5 mL de THF. La reacción se agitó a temperatura ambiente durante 1 hora. La reacción se diluyó con agua y se extrajo con acetato de etilo 2x. Las capas orgánicas se lavaron dos veces con salmuera, se secaron con $MgSO_4$ y se concentraron. El residuo se purificó mediante HPLC (acetonitrilo (5 a 50%)/agua con un modificador de TFA durante 10 minutos). Se liofilizó durante 48 horas para proporcionar el compuesto del título (22 mg, 0,053 mmol, 81%).

MS (ES) MH^+: 419 para $C_{19}H_{19}FN_4O_6$

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 0,9 (d, 3H), 1,1 (d, 3H), 2,9 (d, 1H), 3,1 (t, 1H), 3,6-3,7 (m, 3H), 3,8-3,8 (m, 1H), 3,9 (d, 1H), 4,1 (d, 1H), 4,7 (s, 2H), 7,3 (s, 1H), 11,5 (s, 1H), 11,8 (s, 1H).

Ejemplo 186

Ácido 1-[(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-1*H*-pirazol-4-carboxílico



A una solución agitada de 1-[(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-1*H*-pirazol-4-carboxilato de etilo (**Ejemplo 37,** 100 mg, 0,19 mmol) en acetonitrilo (0,5 mL) se agregó una solución de NaOH al 5% (14 mg, 0,11 mmol) y la mezcla se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se acidificó hasta alcanzar pH ~ 7 utilizando HCl 1,5 N y se extrajo con EtOAc (5 x 10 mL). La capa orgánica se secó con Na_2SO_4 anhidro y se concentró para proporcionar el producto como un sólido amarillo. Rendimiento : 45 mg

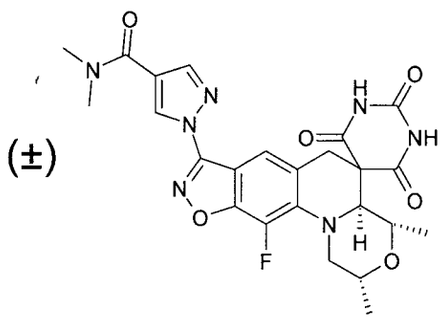
MS (ES) MH^+: 499,5 para $C_{22}H_{19}FN_6O_7$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,15 (d, 3H), 2,9 (d, 1H), 3,2 (t, 1H), 3,7 (m, 1H), 3,8 (m, 2H), 4,0 (d, 1H), 4,1 (d, 1H), 7,65 (s, 1H), 8,3 (s, 1H), 8,9 (s, 1H), 11,5 (s, 1H), 11,9 (s, 2H).

Ejemplo 187

1-[(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-*N*,*N*-dimetil-1*H*-pirazol-4-carboxamida

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A una solución enfriada con hielo de ácido 1-[(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-1*H*-pirazol-4-carboxílico (**Ejemplo 186,** 100 mg, 0,19 mmol) en THF (0,5 mL) se agregó dimetilamina (30 mg, 0,11 mmol), DIPEA (139 mg, 1,08 mmol) y luego T_3P (172 mg, 0,54 mmol) y la mezcla se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se diluyó con EtOAc (15 mL). La capa orgánica se lavó con agua (2 x 10 mL), se secó con Na_2SO_4 anhidro y se concentró. El residuo se purificó mediante cromatografía en columna de gel de sílice utilizando un gradiente de EtOAc en éter de pet para proporcionar el producto como un sólido amarillo. Rendimiento: 25 mg

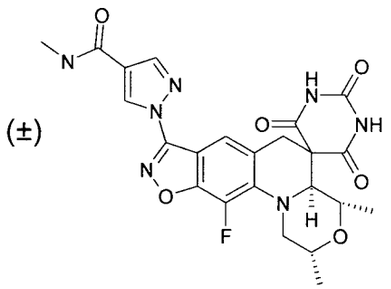
MS (ES) MH^+: 526,5 para $C_{24}H_{24}FN_7O_6$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,15 (d, 3H), 2,90 (d, 1H), 3,0 (s, 3H), 3,1 (m, 1H), 3,2 (s, 3H), 3,7 (m, 1H), 3,8 (m, 2H), 4,0 (d, 1H), 4,1 (d, 1H), 7,65 (s, 1H), 8,2 (s, 1H), 8,8 (s, 1H), 11,9 (s a, 2H).

Los **Ejemplos 188** y **189** se prepararon a partir del material de partida indicado y pirimidin-2,4,6(1*H*,3*H*,5*H*)-triona utilizando un método similar al descrito para la síntesis del **Ejemplo 187**:

Ejemplo 188

1-[(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-*N*-metil-1*H*-pirazol-4-carboxamida



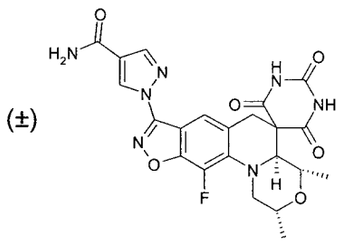
Material de partida: ácido 1-[(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-1*H*-pirazol-4-carboxílico (**Ejemplo 186**) y metilamina (0,16 mL, 2,0M en THF, 0,320 mmol).

MS (ES) MH^+: 512 para $C_{23}H_{22}FN_7O_6$

^1H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,15 (d, 3H), 2,8 (d, 3H), 2,9 (d, 1H), 3,1 (d, 1H), 3,7 (m, 1H), 3,8 (m, 2H), 4,0 (d, 1H), 4,1 (d, 1H), 7,7 (s, 1H), 8,3 (s, 1H), 8,4 (d, 1H), 8,9 (s, 1H), 11,5 (s, 1H), 11,9 (s, 1H).

Ejemplo 189

1-[(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-1*H*-pirazol-4-carboxamida



Materiales de partida: ácido 1-[(2*R*,4*S*,4a*S*)-rel-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-1*H*-pirazol-4-carboxílico (**Ejemplo 186**) y NH_3 saturado en THF (2 mL). Purificación mediante HPLC de fase inversa.

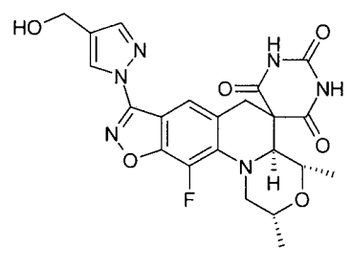
MS (ES) MH^+: 498,5 para $C_{22}H_{20}FN_7O_6$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,15 (d, 3H), 2,9 (d, 1H), 3,1(d, 1H), 3,7 (m, 1H), 3,8 (m, 2H), 4,0 (d, 1H), 4,1(d, 1H), 7,4 (s, 1H), 7,7 (s, 1H), 7,9 (d, 1H), 8,3 (s, 1H), 9,0 (s, 1H), 11,5 (s a, 2H).

Ejemplo 190

(2*R*,4*S*,4a*S*)-rel-11-fluoro-8-[4-(hidroximetil)-1*H*-pirazol-1-il]-2,4-dimetil-1,2,4,4a-tetrahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-2',4',6'(1'*H*,3'*H*)-triona

(±)



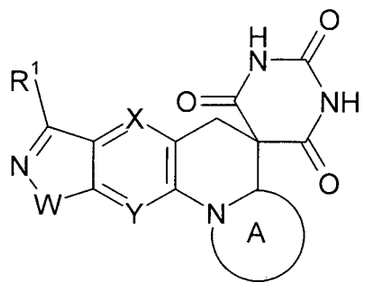
Se agregó borohidruro de litio (0,434 mL, 0,87 mmol) a una solución enfriada con hielo de metanol (0,035 mL, 0,87 mmol) en tetrahidrofurano (10 mL). La solución se entibió hasta alcanzar la temperatura ambiente y se agitó durante 1 hora. Se agregaron 1,5 mL de esta solución a una solución de 1-[(2*R*,4*S*,4a*S*)-11-fluoro-2,4-dimetil-2',4',6'-trioxo-1,1',2,3',4,4',4a,6'-octahidro-2'*H*,6*H*-espiro[1,4-oxazino[4,3-*a*][1,2]oxazolo[4,5-*g*]quinolin-5,5'-pirimidin]-8-il]-1*H*-pirazol-4-carboxilato de etilo (**Ejemplo 37,** 60 mg, 0,11 mmol). La reacción se agitó a temperatura ambiente durante 12 horas. La mezcla de reacción se diluyó con agua y se extrajo dos veces con acetato de etilo. Las capas orgánicas se lavaron dos veces con salmuera, se secaron con $MgSO_4$ y se concentraron. El residuo se purificó mediante HPLC de fase inversa para proporcionar el producto como un sólido. Rendimiento : 20 mg.

MS (ES) MH^+: 485,5 para $C_{22}H_{21}FN_6O_6$

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,9 (d, 3H), 1,15 (d, 3H), 2,9 (d, 1H), 3,1 (t, 1H), 3,7 (m, 1H), 3,8 (m, 2H), 4,0 (d, 1H), 4,1(d, 1H), 4,8 (d, 2H), 5,1 (s, 1H), 7,7 (s, 1H), 7,9 (s, 1H), 8,3 (s, 1H), 11,7 (s a, 2H).

Reivindicaciones

1. Un compuesto de Fórmula (I),



Fórmula (I)

o una sal farmacéuticamente aceptable de este, en donde:

el **Anillo A** está fusionado a un anillo heterocíclico no aromático de 5 a 7 miembros, en donde dicho anillo heterocíclico no aromático de 5 a 7 miembros fusionado está opcionalmente sustituido sobre carbono con uno o más R^4, y en donde todo resto -NH- de dicho anillo heterocíclico de 5 a 7 miembros está opcionalmente sustituido con R^{4*};

W se selecciona de -O-, -NH-, -S- y $-S(O)_2-$;

X se selecciona de N y C-R^2;

Y se selecciona de N y C-R^3;

$\mathbf{R^1}$ se selecciona de H, halo, -CN, alquiloC_{1-6}, alqueniloC_{2-6}, alquiniloC_{2-6}, carbociclilo, heterociclilo, $-OR^{1a}$, $-SR^{1a}$, $-N(R^{1a})_2$, $-N(R^{1a})C(O)R^{1b}$, $-N(R^{1a})N(R^{1a})_2$, $-NO_2$, $-N(R^{1a})OR^{1a}$, $-ON(R^{1a})_2$, -C(O)H, $-C(O)R^{1b}$, $-C(O)_2R^{1a}$, $-C(O)N(R^{1a})_2$, $-C(O)N(R^{1a})(OR^{1a})$, $-OC(O)N(R^{1a})_2$, $-N(R^{1a})C(O)_2R^{1a}$, $-N(R^{1a})C(O)N(R^{1a})_2$, $-OC(O)R^{1b}$, $-S(O)R^{1b}$, $-S(O)_2R^{1b}$, $-S(O)_2N(R^{1a})_2$, $-N(R^{1a})S(O)_2R^{1b}$, $-C(R^{1a})=N(R^{1a})$ y $-C(R^{1a})=N(OR^{1a})$, en donde dichos alquiloC_{1-6}, alqueniloC_{2-6}, alquiniloC_{2-6}, carbociclilo y heterociclilo están opcionalmente sustituidos sobre carbono con uno o más R^{10} y en donde todo resto -NH- de dicho heterociclilo está opcionalmente sustituido con R^{10*};

$\mathbf{R^{1a}}$ en cada caso se selecciona independientemente de H, alquiloC_{1-6}, carbociclilo y heterociclilo, en donde dichos alquiloC_{1-6}, carbociclilo y heterociclilo en cada caso se sustituyen opcionalmente e independientemente sobre carbono con uno o más R^{10} y en donde todo resto -NH- de dicho heterociclilo está opcionalmente sustituido con R^{10*};

R^{1b} en cada caso se selecciona independientemente de alquiloC_{1-6}, alqueniloC_{2-6}, alquiniloC_{2-6}, carbociclilo y heterociclilo, en donde dichos alquiloC_{1-6}, alqueniloC_{2-6}, alquiniloC_{2-6}, carbociclilo y heterociclilo en cada caso se sustituyen opcionalmente e independientemente sobre carbono con uno o más R^{10} y en donde todo resto -NH- de dicho heterociclilo está opcionalmente sustituido con R^{10*};

R^{2} se selecciona de H, halo y -CN;

R^{3} se selecciona de H, halo, -CN, alquiloC_{1-6}, alqueniloC_{2-6}, alquiniloC_{2-6}, $-OR^{3a}$, $-SR^{3a}$ y $-N(R^{3a})_2$, en donde dichos alquiloC_{1-6}, alqueniloC_{2-6} y alquiniloC_{2-6} están opcionalmente sustituidos sobre carbono con uno o más R^{30};

R^{3a} en cada caso se selecciona independientemente de H y alquiloC_{1-6}, en donde dicho alquiloC_{1-6} en cada caso se sustituye opcionalmente e independientemente sobre carbono con uno o más R^{30};

R^{4} en cada caso se selecciona independientemente de halo, -CN, alquiloC_{1-6}, alqueniloC_{2-6}, alquiniloC_{2-6}, carbociclilo, heterociclilo, $-OR^{4a}$, $-SR^{4a}$, $-N(R^{4a})_2$, $-N(R^{4a})C(O)R^{4b}$, $-N(R^{4a})N(R^{4a})_2$, $-NO_2$, $-N(R^{4a})$-OR^{4a}, -O-$N(R^{4a})_2$, -C(O)H, $-C(O)R^{4b}$, $-C(O)_2R^{4a}$, $-C(O)N(R^{4a})_2$, $-C(O)N(R^{4a})(OR^{4a})$ $-OC(O)N(R^{4a})_2$, $-N(R^{4a})C(O)_2R^{4a}$, $-N(R^{4a})C(O)N(R^{4a})_2$, $-OC(O)R^{4b}$, $-S(O)R^{4b}$, $-S(O)_2R^{4b}$, $-S(O)_2N(R^{4a})_2$, $-N(R^{4a})S(O)_2R^{4b}$, $-C(R^{4a})=N(R^{4a})$ y $-C(R^{4a})=N(OR^{4a})$, en donde dichos alquiloC_{1-6}, alqueniloC_{2-6}, alquiniloC_{2-6}, carbociclilo y heterociclilo están opcionalmente sustituidos sobre carbono con uno o más R^{40} y en donde todo resto -NH- de dicho heterociclilo está opcionalmente sustituido con R^{40*};

R^{4*} en cada caso se selecciona independientemente de alquiloC_{1-6}, carbociclilo, heterociclilo, -C(O)H, $-C(O)R^{4b}$, $-C(O)_2R^{4a}$, $-C(O)N(R^{4a})_2$, $-S(O)R^{4b}$, $-S(O)_2R^{4b}$, $-S(O)_2N(R^{4a})_2$, $-C(R^{4a})=N(R^{4a})$ y $-C(R^{4a})=N(OR^{4a})$, en donde dichos alquiloC_{1-6}, carbociclilo y heterociclilo en cada caso se sustituyen opcionalmente e independientemente sobre carbono con uno o más R^{40} y en donde todo resto -NH- de dicho heterociclilo está opcionalmente sustituido con R^{40*};

R^{4a} en cada caso se selecciona independientemente de H, alquiloC_{1-6}, carbociclilo y heterociclilo, en donde dichos alquiloC_{1-6}, carbociclilo y heterociclilo en cada caso se sustituyen opcionalmente e independientemente sobre carbono con uno o más R^{40} y en donde todo resto -NH- de dicho heterociclilo está opcionalmente sustituido con R^{40*};

R^{4b} en cada caso se selecciona independientemente de alquiloC_{1-6}, alqueniloC_{2-6},

alquiniloC$_{2-6}$, carbociclilo y heterociclilo, en donde dichos alquiloC$_{1-6}$, alqueniloC$_{2-6}$, alquiniloC$_{2-6}$, carbociclilo y heterociclilo en cada caso se sustituyen opcionalmente e independientemente sobre carbono con uno o más R^{40} y en donde todo resto -NH- de dicho heterociclilo está opcionalmente sustituido con R^{40*};

R^{10} en cada caso se selecciona independientemente de halo, -CN, alquiloC$_{1-6}$, alqueniloC$_{2-6}$, alquiniloC$_{2-6}$, carbociclilo, heterociclilo, -OR^{10a}, -SR^{10a}, -$N(R^{10a})_2$, -$N(R^{10a})C(O)R^{10b}$, -$N(R^{10a})N(R^{10a})_2$, -NO_2, -$N(R^{10a})$-OR^{10a}, -O-$N(R^{10a})_2$, -C(O)H, -$C(O)R^{10b}$, -$C(O)_2R^{10a}$, -$C(O)N(R^{10a})_2$, -$C(O)N(R^{10a})(OR^{10a})$, -$OC(O)N(R^{10a})_2$, -$N(R^{10a})C(O)_2R^{10a}$, -$N(R^{10a})C(O)N(R^{10a})_2$, -$OC(O)R^{10b}$, -$S(O)R^{10b}$, -$S(O)_2R^{10b}$, -$S(O)_2N(R^{10a})_2$, -$N(R^{10a})S(O)_2R^{10b}$, -$C(R^{10a})=N(R^{10a})$ y -$C(R^{10a})=N(OR^{10a})$, en donde dichos alquiloC$_{1-6}$, alqueniloC$_{2-6}$, alquiniloC$_{2-6}$, carbociclilo y heterociclilo en cada caso se sustituyen opcionalmente e independientemente sobre carbono con uno o más R^a y en donde todo resto -NH- de dicho heterociclilo está opcionalmente sustituido con R^{a*};

R^{10*} en cada caso se selecciona independientemente de alquiloC$_{1-6}$, carbociclilo, heterociclilo, -C(O)H, -$C(O)R^{10b}$, -$C(O)_2R^{10a}$, -$C(O)N(R^{10a})_2$, -$S(O)R^{10b}$, -$S(O)_2R^{10b}$, -$S(O)_2N(R^{10a})_2$, -$C(R^{10a})=N(R^{10a})$ y -$C(R^{10a})=N(OR^{10a})$, en donde dichos alquiloC$_{1-6}$, carbociclilo y heterociclilo en cada caso se sustituyen opcionalmente e independientemente sobre carbono con uno o más R^a y en donde todo resto -NH- de dicho heterociclilo está opcionalmente sustituido con R^{a*};

R^{10a} en cada caso se selecciona independientemente de H, alquiloC$_{1-6}$, carbociclilo y heterociclilo, en donde dichos alquiloC$_{1-6}$, carbociclilo y heterociclilo en cada caso se sustituyen opcionalmente e independientemente sobre carbono con uno o más R^a y en donde todo resto -NH- de dicho heterociclilo está opcionalmente sustituido con R^{a*};

R^{10b} en cada caso se selecciona independientemente de alquiloC$_{1-6}$, alqueniloC$_{2-6}$, alquiniloC$_{2-6}$, carbociclilo y heterociclilo, en donde dichos alquiloC$_{1-6}$, alqueniloC$_{2-6}$, alquiniloC$_{2-6}$, carbociclilo y heterociclilo en cada caso se sustituyen opcionalmente e independientemente sobre carbono con uno o más R^a y en donde todo resto -NH- de dicho heterociclilo está opcionalmente sustituido con R^{a*};

R^{30} en cada caso se selecciona independientemente de halo, -CN, alquiloC$_{1-6}$, alqueniloC$_{2-6}$, alquiniloC$_{2-6}$, -OR^{30a}, -SR^{30a} y -$N(R^{30a})_2$;

R^{30a} en cada caso se selecciona independientemente de H y alquiloC$_{1-6}$;

$\mathbf{R^{40}}$ en cada caso se selecciona independientemente de halo, -CN, alquiloC$_{1-6}$, alqueniloC$_{2-6}$, alquiniloC$_{2-6}$, carbociclilo, heterociclilo, -OR^{40a}, -SR^{40a}, -N(R^{40a})$_2$, -N(R^{40a})C(O)R^{40b}, -N(R^{40a})N(R^{40a})$_2$, -NO$_2$, -N(R^{40a})-OR^{40a}, -O-N(R^{40a})$_2$, -C(O)H, -C(O)R^{40b}, -C(O)$_2$R^{40a}, -C(O)N(R^{40a})$_2$, -C(O)N(R^{40a})(OR^{40a}), -OC(O)N(R^{40a})$_2$, -N(R^{40a})C(O)$_2$R^{40a}, -N(R^{40a})C(O)N(R^{40a})$_2$, -OC(O)R^{40b}, -S(O)R^{40b}, -S(O)$_2$R^{40b}, -S(O)$_2$N(R^{40a})$_2$, -N(R^{40a})S(O)$_2$R^{40b}, -C(R^{40a})=N(R^{40a}) y -C(R^{40a})=N(OR^{40a});

$\mathbf{R^{40*}}$ en cada caso se selecciona independientemente de alquiloC$_{1-6}$, carbociclilo, heterociclilo, -C(O)H, -C(O)R^{40b}, -C(O)$_2$R^{40a}, -C(O)N(R^{40a})$_2$, -S(O)R^{40b}, -S(O)$_2$R^{40b}, -S(O)$_2$N(R^{40a})$_2$, -C(R^{40a})=N(R^{40a}) y -C(R^{40a})=N(OR^{40a});

$\mathbf{R^{40a}}$ en cada caso se selecciona independientemente de H, alquiloC$_{1-6}$, carbociclilo y heterociclilo;

$\mathbf{R^{40b}}$ en cada caso se selecciona independientemente de alquiloC$_{1-6}$, alqueniloC$_{2-6}$, alquiniloC$_{2-6}$, carbociclilo y heterociclilo;

$\mathbf{R^{a}}$ en cada caso se selecciona independientemente de halo, -CN, alquiloC$_{1-6}$, alqueniloC$_{2-6}$, alquiniloC$_{2-6}$, carbociclilo, heterociclilo, -OR^{m}, -SR^{m}, -N(R^{m})$_2$, -N(R^{m})C(O)R^{n}, -N(R^{m})N(R^{m})$_2$, -NO$_2$, -N(R^{m})-OR^{m}, -O-N(R^{m})$_2$, -C(O)H, -C(O)R^{n}, -C(O)$_2$R^{m}, -C(O)N(R^{m})$_2$, -C(O)N(R^{m})(OR^{m}), -OC(O)N(R^{m})$_2$, -N(R^{m})C(O)$_2$R^{m}, -N(R^{m})C(O)N(R^{m})$_2$, -OC(O)R^{n}, -S(O)R^{n}, -S(O)$_2$R^{n}, -S(O)$_2$N(R^{m})$_2$, -N(R^{m})S(O)$_2$R^{n}, -C(R^{m})=N(R^{m}) y -C(R^{m})=N(OR^{m});

$\mathbf{R^{a*}}$ en cada caso se selecciona independientemente de alquiloC$_{1-6}$, carbociclilo, heterociclilo, -C(O)H, -C(O)R^{n}, -C(O)$_2$R^{m}, -C(O)N(R^{m})$_2$, -S(O)R^{n}, -S(O)$_2$R^{n}, -S(O)$_2$N(R^{m})$_2$, -C(R^{m})=N(R^{m}) y -C(R^{m})=N(OR^{m});

$\mathbf{R^{m}}$ en cada caso se selecciona independientemente de H, alquiloC$_{1-6}$, carbociclilo y heterociclilo; y

$\mathbf{R^{n}}$ en cada caso se selecciona independientemente de alquiloC$_{1-6}$, alqueniloC$_{2-6}$, alquiniloC$_{2-6}$, carbociclilo y heterociclilo.

2. Un compuesto de Fórmula (I), o una sal farmacéuticamente aceptable de este, como se reivindica en la reivindicación 1, en donde

el **Anillo A** es morfolina fusionada, en donde dicha morfolina fusionada está opcionalmente sustituida con uno o más $\mathbf{R^4}$; y

R^4 es alquiloC$_{1-6}$.

3. Un compuesto de Fórmula (I), o una sal farmacéuticamente aceptable de este, como se reivindica en cualquiera de las reivindicaciones 1 o 2, en donde:

W es -O-;

X es C-H;

Y es C-R^3; y

R^3 es halo.

4. Un compuesto de Fórmula (I), o una sal farmacéuticamente aceptable de este, como se reivindica en cualquiera de las reivindicaciones 1 a 3, en donde:

R^1 se selecciona de alquiloC$_{1-6}$, carbociclilo de 3 a 5 miembros, heterociclilo de 5 o 6 miembros, -OR^{1a}, -SR^{1a}, -N(R^{1a})$_2$, -N(R^{1a})C(O)R^{1b}, -C(O)N(R^{1a})$_2$, -C(O)R^{1b}, -C(O)$_2$R^{1a}, -C(O)N(R^{1a})$_2$, -C(O)N(R^{1a})(OR^{1a}) y -S(O)$_2$R^{1b}, en donde dichos alquiloC$_{1-6}$, carbocicliclo de 3 a 5 miembros y heterociclilo de 5 o 6 miembros están opcionalmente sustituidos sobre carbono con uno o más R^{10} y en donde todo resto -NH- de dicho heterociclilo de 5 o 6 miembros está opcionalmente sustituido con R^{10*};

R^{1a} en cada caso se selecciona independientemente de H, alquiloC$_{1-6}$, carbociclilo de 3 a 5 miembros y heterociclilo de 5 o 6 miembros, en donde dichos alquiloC$_{1-6}$, carbociclilo de 3 a 5 miembros y heterociclilo de 5 o 6 miembros en cada caso se sustituyen opcionalmente e independientemente con uno o más R^{10}, en donde todo resto -NH- de dicho heterociclilo de 5 o 6 miembros está opcionalmente sustituido con R^{10*};

R^{1b} en cada caso se selecciona independientemente de alquiloC$_{1-6}$ y heterociclilo de 4 a 6 miembros, en donde dichos alquiloC$_{1-6}$ y heterociclilo de 4 a 6 miembros se sustituyen opcionalmente e independientemente sobre carbono con uno o más R^{10} y en donde todo resto -NH- de dicho heterociclilo de 4 a 6 miembros está opcionalmente sustituido con R^{10*};

R^{10} en cada caso se selecciona independientemente de halo, -CN, alquiloC$_{1-6}$, carbociclilo de 3 a 6 miembros, heterociclilo de 5 o 6 miembros, -OR^{10a}, -SR^{10a}, -N(R^{10a})$_2$, -N(R^{10a})C(O)R^{10b}, -C(O)$_2$R^{10a}, -C(O)N(R^{10a})$_2$, en donde dichos alquiloC$_{1-6}$, carbociclilo de 3 a 6 miembros y heterociclilo de 5 o 6 miembros en cada caso se sustituyen

opcionalmente con uno o más R^a y en donde todo resto -NH- de dicho heterociclilo de 5 o 6 miembros está opcionalmente sustituido con R^{a*};

$\mathbf{R^{10*}}$ en cada caso se selecciona independientemente de alquiloC_{1-6} y -C(O)R^{10b};

$\mathbf{R^{10a}}$ en cada caso se selecciona independientemente de H y alquiloC_{1-6}, en donde dicho alquiloC_{1-6} en cada caso se sustituye opcionalmente e independientemente con uno o más R^a;

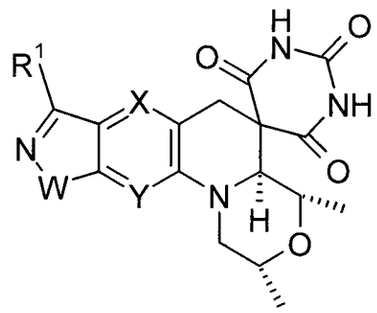
$\mathbf{R^{10b}}$ es alquiloC_{1-6};

$\mathbf{R^a}$ en cada caso se selecciona independientemente de halo, -CN y -OR^m;

$\mathbf{R^{a*}}$ es alquiloC_{1-6}; y

$\mathbf{R^m}$ en cada caso se selecciona independientemente de H y alquiloC_{1-6}.

5. Un compuesto de Fórmula (Ia):



Fórmula (Ia)

o una sal farmacéuticamente aceptable de este, en donde $\mathbf{R^1}$ es como se describe anteriormente en la presente y:

W es O;

X es C-H;

Y es C-R^3;

$\mathbf{R^1}$ se selecciona de aminocarbonilo, 2-aminopirimidin-4-ilo, 2-cianopirimidin-4-ilo, 3,3-difluoroazetidin-1-ilo, [(2,2-difluoroetil)amino]carbonilo, difluorometilo, (isopropilamino)carbonilo, metilo, (metilamino)carbonilo, 2-(metilsulfanil)pirimidin-4-ilo, 1-metil-1*H*-1,2,4-triazol-5-ilo, pirazin-2-ilo, piridazin-3-ilo, pirimidin-4-ilo, pirimdin-2-ilo, 1,3-tiazol-2-ilo, 1*H*-1,2,4-triazol-1-ilo, 2*H*-1,2,3-triazol-2-ilo y trifluorometilo.

R^3 es halo.

6. Un compuesto de Fórmula (I), o una sal farmacéuticamente aceptable de este, como se reivindica en cualquiera de las reivindicaciones 1 a 5, para su uso como un medicamento.

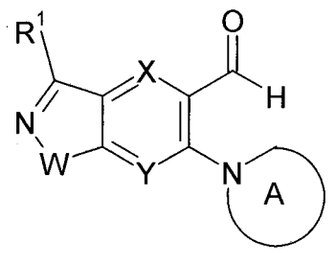
7. El uso de un compuesto de Fórmula (I), o una sal farmacéuticamente aceptable de este, como se reivindica en cualquiera de las reivindicaciones 1 a 5, en la fabricación de un medicamento para su uso en el tratamiento de una infección bacteriana en un animal de sangre caliente tal como el hombre.

8. Un método para el tratamiento de una infección bacteriana en un animal de sangre caliente tal como el hombre, comprendiendo dicho método administrar a dicho animal una cantidad efectiva de un compuesto de Fórmula (I), como se reivindica en cualquiera de las reivindicaciones 1 a 5, o una sal farmacéuticamente aceptable de este.

9. Un compuesto de Fórmula (I), o una sal farmacéuticamente aceptable de este, como se reivindica en cualquiera de las reivindicaciones 1 a 5, para su uso en el tratamiento de una infección bacteriana en un animal de sangre caliente, tal como el hombre.

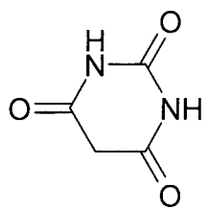
10. Una composición farmacéutica que comprende un compuesto de Fórmula (I), o una sal farmacéuticamente aceptable de este, como se reivindica en cualquiera de las reivindicaciones 1 a 5, y al menos un portador, diluyente o excipiente farmacéuticamente aceptable.

11. Un proceso para preparar un compuesto de Fórmula (I), o una sal farmacéuticamente aceptable de este, como se reivindica en cualquiera de las reivindicaciones 1 a 5, comprendiendo dicho proceso hacer reaccionar un compuesto de Fórmula (A1):



Fórmula (A1)

con ácido barbitúrico:



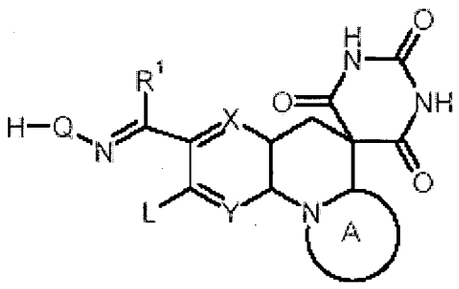
y luego, si es necesario:

i) convertir un compuesto de Fórmula (I) en otro compuesto de Fórmula (I);

ii) eliminar todo grupo protector; y/o

iii) formar una sal farmacéuticamente aceptable.

12. Un proceso para preparar un compuesto de Fórmula (I), o una sal farmacéuticamente aceptable de este, como se reivindica en cualquiera de las reivindicaciones 1 a 5, comprendiendo dicho proceso hacer reaccionar un compuesto de Fórmula (A3):



Fórmula (A3)

con un agente formador de anillos adecuado,

y luego, si es necesario:

i) convertir un compuesto de Fórmula (I) en otro compuesto de Fórmula (I);

ii) eliminar todo grupo protector; y/o

iii) formar una sal farmacéuticamente aceptable,

en donde:

L es un grupo saliente; y

Q se selecciona de -O- y -NH-.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2009/051363

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/22 C07D498/22 C07D513/22 A61P31/04 A61K31/535

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/031195 A1 (UPJOHN CO [US]; BARBACHYN MICHEL ROBERT [US]; DOBROWOLSKI PAUL JOSEPH) 15 April 2004 (2004-04-15) pages 101, 69	1-12
A	WO 2006/120563 A2 (WARNER LAMBERT CO [US]; BARBACHYN MICHAEL ROBERT [US]; DOBROWOLSKI PAU) 16 November 2006 (2006-11-16) claim 1	1-12
A	WO 2007/072151 A1 (PFIZER PROD INC [US]; JOHNSON TIMOTHY ALLEN [US]; SHERRY DEBRA ANN [US) 28 June 2007 (2007-06-28) claim 1	1-12

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such 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
19 February 2010	26/02/2010

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Fax: (+31–70) 340–3016	Duval, Eric

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2009/051363

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004031195 A1	15-04-2004	AU 2003264768 A1	23-04-2004
		BR 0315139 A	09-08-2005
		CA 2500824 A1	15-04-2004
		EP 1551849 A1	13-07-2005
		JP 4009652 B2	21-11-2007
		JP 2006511595 T	06-04-2006
		MX PA05002701 A	19-08-2005
WO 2006120563 A2	16-11-2006	CA 2606847 A1	16-11-2006
		EP 1888597 A2	20-02-2008
		JP 2008543739 T	04-12-2008
WO 2007072151 A1	28-06-2007	AR 058701 A1	20-02-2008
		CA 2634644 A1	28-06-2007
		EP 1971612 A1	24-09-2008
		GT 200600520 A	17-07-2007
		JP 2009520804 T	28-05-2009
		NL 2000373 A1	26-06-2007
		US 2009275536 A1	05-11-2009
		US 2007197518 A1	23-08-2007
		UY 30030 A1	31-07-2007

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

414

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 0032494

Bogotá D.C., Abril 07 de 2011 - 16:23:54

RECIBIDO DE : OLARTERAISBECK NI 830.122.870

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	418332692	07/04/2011	4.492.000.00

*** 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. 11-043260- -00000-0000
Fecha: 2011-04-07 17:02:53 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 414

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-043260- -00000-0000

Fecha: 2011-04-07 17:02:53 Dep: 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 414

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PATENTE DE INVENCIÓN ☐ MOD

- ☐ 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 ☐

Bogotá D.C.,
2020

Doctor(a)
OLARTE GARCIA CARLOS REINALDO
Apoderado(a) y/o Representante de
ASTRAZENECA AB

REFERENCIA		
	Radicación No.	11 043260
	Solicitud internacional	PCT/GB2009/51363
	Fecha inicio fase nacional	14/05/2011
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	

08245

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. Con respecto al resumen y de conformidad con lo dispuesto en el artículo 31 D. 486 en el cual se establece que el resumen consiste en una síntesis de la divulgación técnica contenida en la solicitud de patente, debe adecuar el resumen a los dispuesto en dicha norma, teniendo en cuenta que el extracto permitirá precisar el objeto de la invención, sus elemnentos característicos y el campo de aplicación.

2. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se consideraró abandonada y perderá su prelación.

Continua en la página siguiente...

Sede Centro: Carrera 13 No. 27-00 Pisos 2, 5 , 7 y 10 PBX: 5870000
Sede CAN: Av. Cra 50 No. 26-55 int. 2 Tel: 5880070
Call Center 6513240. Línea 01800-910165
Web: www.sic.gov.co e-mail: info@sic.gov.co
Bogotá D.C. - Colombia

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

JOSE LUIS SALAZAR LOPEZ
Director de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 20 MAYO 2011
adpa11

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Web: www.sic.gov.co e-mail: info@sic.gov.co
Bogotá D.C. - Colombia

Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

Doctor(a)
OLARTE GARCIA CARLOS REINALDO
Apoderado(a) y/o Representante de
ASTRAZENECA AB

REFERENCIA	Radicación No.	11 043260
	Solicitud internacional	PCT/GB2009/51363
	Fecha inicio fase nacional	14/05/2011
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	0 8 2 4 6

Teniendo en cuenta que el capítulo reivindicatorio presentado excede de diez reivindicaciones, es necesario que cancele la tasa establecida por cada reivindicación adicional presentada, de conformidad con lo dispuesto en la resolución de tasas vigente para la fecha de presentación de la solicitud, so pena de que no sean tenidas en cuenta dentro del presente trámite administrativo.

En consecuencia, con fundamento en lo previsto por el artículo 12 del Código Contencioso Administrativo, se le requiere para que dentro del término de dos (2) meses siguientes a la fecha de notificación del presente oficio atienda el requerimiento aquí señalado. Lo anterior, con el alcance que para tal efecto establece el artículo 13 de la misma codificación, respecto de las reivindicaciones adicionales.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del titulo primero de la Circular Única N° 10 de 2001.

JOSE LUIS SALAZAR LOPEZ
Director de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 20 MAYO 2011.

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