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Industria y C

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-160874- -00000-0000
Fecha: 2010-12-22 12:52:32 Dep: 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 367

10-160874

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIRECCIÓN DE NUEVAS CREACIONES

INVENTARIO

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: DERIVADOS DE UREA HETEROCÍCLICOS Y MÉTODOS DE USO DE LOS MISMOS-332

SOLICITANTE: ASTRAZENECA AB

DIRECCIÓN: S-SE-151 85 Södertälje, Suecia

APODERADO: J. IAN RAISBECK

BOGOTÁ 17 Diciembre de 2010

21-01-2011

P2010/000180

NO EXC

25 F
37 S

OLARTERAISBECK
OLARTE RAISBECK MOURE &

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-160874- -00000-0000
Fecha: 2010-12-22 12:52:32 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 367

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2010/000180**
SOLICITUD DE:

(1)

[X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[X] Capítulo I. [ ] Capítulo II.

(2)

SOLICITANTE (71)

Nombre: ASTRAZENECA AB
Dirección: S-SE-151 85 Södertälje
Nacionalidad o Domicilio: Suecia
Lugar de Constitución: Suecia

Teléfono: _____ **Fax:** _____
E-mail: _____

IDENTIFICACIÓN
C.C. [ ] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual _____
Número _____

REPRESENTANTE O APODERADO

Nombre: J. IAN RAISBECK
Dirección: Diagonal 34 No. 5-28 Bogotá
Teléfono: 601-7700 **Fax:** 601-7799
E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN
C.C. [x] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual _____
Número 79.376.996
TP 135.799

INVENTOR (ES) (72)

Nombre: PAMELA HILL, JOHN IRVIN MANCHESTER, BRIAN SHERER, ALLISON LAURA CHOY
Dirección: AstraZeneca R&D Boston, 35 Gatehouse Drive, Waltham Massachusetts 02451.
Nacionalidad o Domicilio: ESTADOUNIDENSE

(5) **PCT (86)**

Solicitud Internacional No. PCT/GB2009/050611 Fecha Junio 03, 2009

Publicación Internacional No. WO 2009/147433 Fecha Diciembre 10, 2009

(6) **Título (54)** **DERIVADOS DE UREA HETEROCÍCLICOS Y MÉTODOS DE USO DE LOS MISMOS-332**

Clasificación Internacional (51) C07D 417/14, C07D 498/06, A61P 31/04, A61K 31/4709, A61K 31/4738

Prioridad

SI [X] **NO** [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Junio 04, 2008	61/058.736

(9) **Comprobante de pago No.** _____ **Fecha** _____

(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. 08-129814.
- [x] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [x] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: J. IAN RAISBECK FIRMA:

C.C. 79.376.996 Btá T.P. 135.799

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

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-160874- -00000-0000

Fecha: 2010-12-22 12:52:32 Dep. 2020 DIR.NUEVASCR
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 109,366
FECHA : DICIEMBRE 22 DE 2010

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAG	Vr. PAGO
OLARTE RAISBEY	CONSIGNACION	BANCO DE BOGOTA	062754387	387590405	22/12/2010	4,996,000.00

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

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

SON: QUINIENTOS CINCUENTA Y CUATRO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

A

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 Miniusric

5

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

6

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country : Sweden

This public document

2. has been signed by Anne-Marie Bonde

3. acting in the capacity of Notary Public

4. bears the seal/stamp of

Notary Public in Stockholm

Certified

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

7. by Björn Sandin

Notary Public

8. No 4071

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

OLARTERAISBECK
OLARTE RAISBECK & FRIERI LTDA.

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

Zayde Chahí
Simón 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

Poder

The undersigned, El suscrito,

AstraZeneca AB

domiciled in domiciliado en

Vastra Malarehamnen 9 S-151 85 Södertälje, Sweden

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

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

Signature/Firma: **Anders Burén**
Authorized Signatory

Date/Fecha: 24 OCTOBER 2007

City,Country/Ciudad,País: SODERTALJE

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BOMAN

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

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

9

MODEL OF NOTARIAL CERTIFICATION

Notarial Certification	Certificación Notarial
On this date,	En esta fecha,
The undersigned Notary Public certifies:	el Notario Público suscrito certifica:
1. That	1. Que
of legal age and domiciled in	mayor de edad y domiciliado
signed the foregoing document.	suscribió el documento que antecede.
2. That the grantor has executed the foregoing document as DULY AUTHORISED SIGNATORY of ASTRAZENECA AB	2. Que el otorgante ha suscrito el referido documento en su carácter de de
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. 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. That the grantor has the authority to execute the Power of Attorney and that his/her representation is legal.	4. Que el otorgante tiene la representación para suscribir el poder, y que ésta es legítima.
5. The foundation for my certifications contained in points 2, 3 and 4 was the exhibition of the following authentic document(s):	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):
1. CERTIFICATE OF INCORPORATION OF ASTRAZENECA AB	
2. AUTHORISATION IN FAVOUR OF SIGNATORY	

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

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

10

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

12

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

13

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. **Country :** Sweden

   This public document

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

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

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

   Notary Public in Stockholm

Certified

5. **at** Stockholm

6. **the** 26.10.2007

7. **by** Björn Sandin

   Notary Public

8. **No** 4070

9. **Seal/stamp:**

10. **Signature:**

Bolagsverket

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

Certificate of Good Standing

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

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

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

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

Anna-Karin Östin

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

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

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

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

15

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:- Crowns

Stockholm 2007-10-26

Ex officio:

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

16

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

Swedish Companies Registration Office, Sundsvall

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

Fee Stockholm this 14th day of August
Kr 60:- PAID 2007

Agneta Söderlund

MINISTRY FOR FOREIGN AFFAIRS

STOCKHOLM

SUDAN

SIGNATURE OF Agneta Söderlund
AND STAMP OF: Sec 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
10 December 2009 (10.12.2009)

PCT

(10) International Publication Number
WO 2009/147433 A1

(51) International Patent Classification:
C07D 417/14 (2006.01) *A61K 31/4709* (2006.01)
C07D 498/06 (2006.01) *A61K 31/4738* (2006.01)
A61P 31/04 (2006.01)

(21) International Application Number:
PCT/GB2009/050611

(22) International Filing Date:
3 June 2009 (03.06.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/058,736 4 June 2008 (04.06.2008) 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)*: **HILL, Pamela** [US/US]; AstraZeneca R&D Boston, 35 Gatehouse Drive, Waltham, Massachusetts 02451 (US). **MANCHESTER, John, Irvin** [US/US]; AstraZeneca R&D Boston, 35 Gatehouse Drive, Waltham, Massachusetts 02451 (US). **SHERER, Brian** [US/US]; AstraZeneca R&D Boston, 35 Gatehouse Drive, Waltham, Massachusetts 02451 (US). **CHOY, Allison, Laura** [US/US]; AstraZeneca R&D Boston, 35 Gatehouse Drive, Waltham, MA 02451 (US).

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

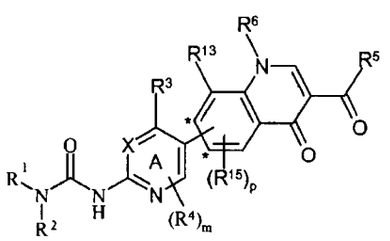
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, 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, 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, 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))*

(54) Title: HETEROCYCLIC UREA DERIVATIVES FOR THE TREATMENT OF BACTERIAL INFECTIONS



(I)

(57) Abstract: Compounds of formula (I) and their pharmaceutically acceptable salts are described. Processes for their preparation, pharmaceutical compositions containing them, their use as medicaments and their use in the treatment of bacterial infections are also described.

WO 2009/147433 A1

HETEROCYCLIC UREA DERIVATIVES FOR THE TREATMENT OF BACTERIAL INFECTIONS

Field of the Invention

The present invention relates to compounds which demonstrate antibacterial activity, processes for their preparation, pharmaceutical compositions containing them as the active ingredient, to their use as medicaments and to their use in the manufacture of medicaments for use in the treatment of bacterial infections in warm-blooded animals such as humans. In particular, this invention relates to compounds useful for the treatment of bacterial infections in warm-blooded animals such as humans, more particularly to the use of these compounds in the manufacture of medicaments for use in the treatment of bacterial infections in warm-blooded animals such as humans.

Background of the Invention

The international microbiological community continues to express serious concern that the evolution of antibiotic resistance could result in strains against which currently available antibacterial agents will be ineffective. 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. The compounds of the present invention are regarded as effective against both Gram-positive and certain Gram-negative pathogens.

Gram-positive pathogens, for example Staphylococci, Enterococci, Streptococci and mycobacteria, are particularly important because of the development of resistant strains which 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*.

The preferred clinically effective antibiotic for treatment of last resort of such resistant Gram-positive pathogens is vancomycin. Vancomycin is a glycopeptide and is associated with various toxicities, including nephrotoxicity. Furthermore, and most importantly, antibacterial resistance to vancomycin and other glycopeptides is also appearing. This resistance is increasing at a steady rate rendering these agents less and less effective in the treatment of Gram-positive pathogens. There is also now increasing resistance appearing towards agents such as β-lactams, quinolones and macrolides used for the treatment of upper respiratory tract

infections, also caused by certain Gram negative strains including *H.influenzae* and *M.catarrhalis*.

Consequently, in order to overcome the threat of widespread multi-drug resistant organisms, there is an on-going need to develop new antibiotics, particularly those with either a novel mechanism of action and/or containing new pharmacophoric groups.

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).

DNA gyrase is a well-validated target of antibacterials, including 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.

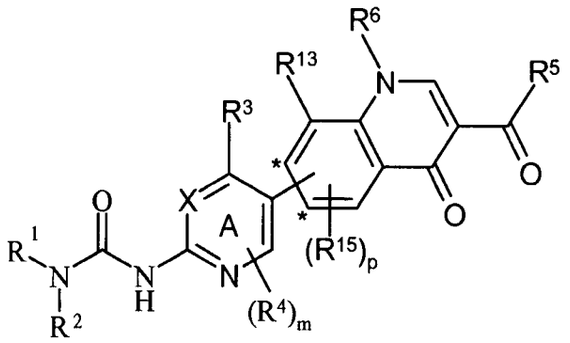
There are several known natural product inhibitors of DNA gyrase that compete with ATP for binding the GyrB subunit (Maxwell, A. and Lawson, D.M. 2003, Curr. Topics in Med. Chem. 3: 283-303). The coumarins are natural products isolated from *Streptomyces spp.*, examples of which are novobiocin, chlorobiocin 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).

Synthetic inhibitors that target the B subunit of DNA gyrase and topoisomerase IV are known in the art. For example, coumarin-containing compounds are described in patent application number WO 99/35155, 5,6-bicyclic heteroaromatic compounds are described in patent application WO 02/060879, and pyrazole compounds are described in patent application WO 01/52845 (US patent US6,608,087). AstraZeneca has also published certain applications describing anti-bacterial compounds: WO2005/026149, WO2006/087544, WO2006/087548, WO2006/087543, WO2006/092599, WO2006/092608, and WO2007/071965.

Summary of the Invention

We have discovered a new class of compounds which are useful for inhibiting DNA gyrase and / or topoisomerase IV.

In one embodiment, according to the present invention there is provided a compound of formula **(I)**:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is attached to one of the carbon atoms indicated by "*";

X is N, CH or CR^4;

R^1 is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{3-6}cycloalkyl; wherein R^1 may be optionally substituted on carbon by one or more R^7;

R^2 is selected from hydrogen or C_{1-6}alkyl; wherein said C_{1-6}alkyl may be optionally substituted by one or more groups independently selected from halo, cyano, hydroxy, nitro and amino;

or **R^1 and R^2 together** with the nitrogen to which they are attached form a heterocyclyl; wherein said heterocyclyl may be optionally substituted on one or more carbon atoms with one or more R^8; and wherein if said heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^9;

R^3 is a C_{3-14}carbocyclyl or a heterocyclyl; wherein the carbocyclyl or heterocyclyl may be optionally substituted on one or more carbon atoms by one or more R^{10}; and wherein if said heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{11};

R^4 and **R^{15}**, for each occurrence, are independently selected from the group consisting of halo, nitro, cyano, hydroxy, amino, mercapto, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, and C_{1-6}alkylsulfanyl; wherein R^4, R^{13}, and R^{15} independently of each other may be optionally substituted on one or more carbon by one or more one or more R^{12};

R^5 is –OH, -NH_2, a C_{1-6}alkoxy, an *N*-(C_{1-6}alkyl)amino, or *N,N*-(C_{1-6}alkyl)$_2$amino; wherein the C_{1-6}alkoxy, an *N*-(C_{1-6}alkyl)amino, or *N,N*-(C_{1-6}alkyl)$_2$amino may be optionally substituted on one or more carbon atoms with one or more, independently selected R^{14};

R^6, for each occurrence, is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}alkylsulfanyl, carboxy, carbamoyl, N-(C_{1-6}alkyl)carbamoyl, N,N-(C_{1-6}alkyl)$_2$carbamoyl, C_{3-14}carbocyclyl, and heterocyclyl; wherein R^6 is optionally substituted on one or more carbon atoms with one or more R^{16}; and wherein if said heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{17};

R^{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, hydroxy, amino, mercapto, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, and C_{1-6}alkylsulfanyl; wherein R^{13} may be optionally substituted on one or more carbon by one or more one or more R^{16}; or

R^6 and R^{13} together with the intervening ring atoms may form a fused heterocyclyl, wherein the fused heterocyclyl may be optionally substituted on one or more carbon atoms with one or more independently selected R^{16}; and wherein if said fused heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said fused heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{17};

m is 0 or1;

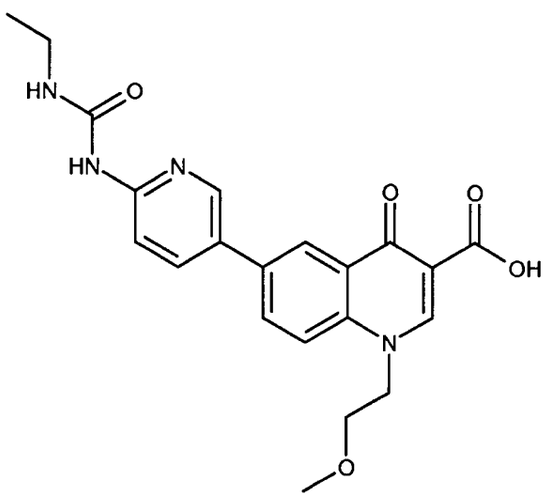
p is 0, 1, or 2;

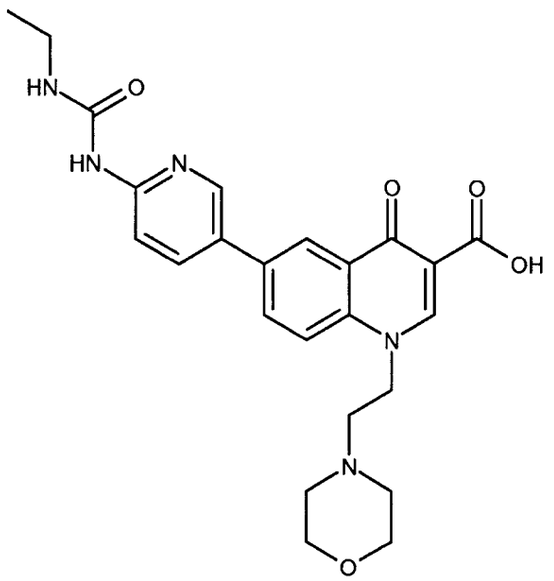
R^7, R^8, R^{10}, R^{12}, R^{14} and R^{16} are substituents on carbon which, for each occurrence, are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$- wherein a is 0, 1 or 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, C_{3-6}carbocyclyl or heterocyclyl; wherein R^7, R^8, R^{10}, R^{12}, R^{14} and R^{16} independently of each other may be optionally substituted on one or more carbon by one or more R^{19}; and wherein if said heterocyclyl

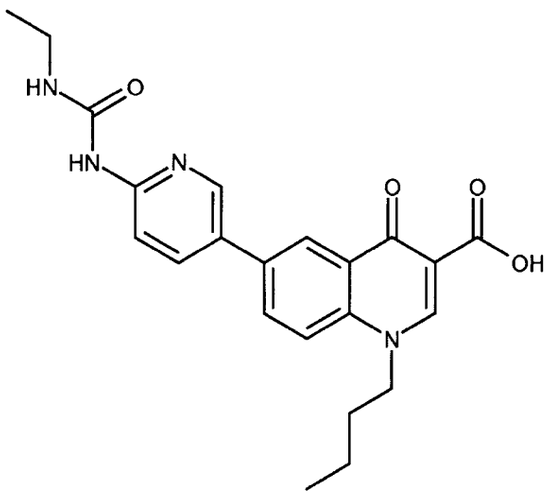
contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{20}; and wherein if said heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups

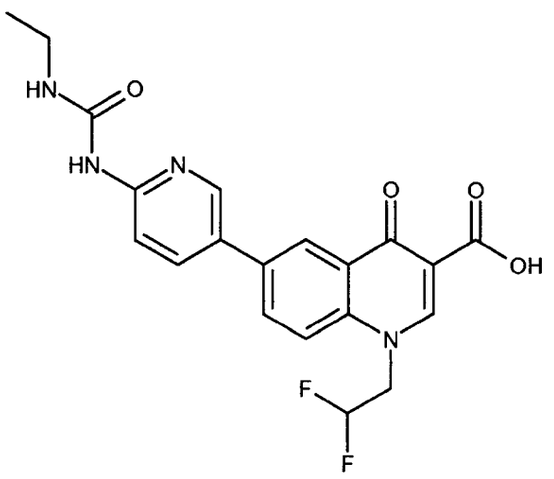
R^9, R^{11}, R^{17} and R^{20}, for each occurrence, are independently selected from C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl; wherein R^9, R^{11}, R^{17}, and R^{20} independently of each other may be optionally substituted on carbon by one or more R^{23}; and

R^{19} and R^{23}, for each occurrence, are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C1-6alkyl, C1-6alkoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl, provided that the compound is not one of the following compounds:

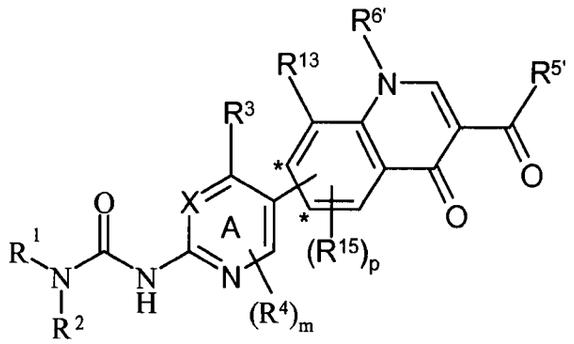








In another embodiment, the invention provides a compound of formula **(I')**:



(I')

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is attached to one of the carbon atoms indicated by "*";

X is N, CH or CR^4;

R^1 is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{3-6}cycloalkyl; wherein R^1 may be optionally substituted on carbon by one or more R^7;

R^2 is selected from hydrogen or C_{1-6}alkyl; wherein said C_{1-6}alkyl may be optionally substituted by one or more groups independently selected from halo, cyano, hydroxy, nitro and amino;

or **R^1 and R^2 together** with the nitrogen to which they are attached form a heterocyclyl; wherein said heterocyclyl may be optionally substituted on one or more carbon atoms with one or more R^8; and wherein if said heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^9;

R^3 is a C_{3-14}carbocyclyl or a heterocyclyl; wherein the carbocyclyl or heterocyclyl may be optionally substituted on one or more carbon atoms by one or more R^{10}; and wherein if said heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{11};

R^4 and **R^{15}**, for each occurrence, are independently selected from the group consisting of halo, nitro, cyano, hydroxy, amino, mercapto, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, and C_{1-6}alkylsulfanyl; wherein R^4, R^{13},

and R^{15} independently of each other may be optionally substituted on one or more carbon by one or more one or more R^{12};

$R^{5'}$ is –OH, a C_{1-6}alkoxy, C_{3-14}cycloalkoxy, or $-NR^aR^b$; wherein the C_{1-6}alkoxy group may be optionally substituted on one or more carbon atoms with one or more, independently selected R^{14}; and wherein R^a and R^b are each independently, hydrogen, a C_{1-6}alkyl, or a C_{3-14}carbocycle, or R^a and R^b, together with the nitrogen to which they are attached form a heterocycle, wherein R^a and R^b may be optionally substituted on one or more carbon atoms with one or more, independently selected R^{14}; and wherein if said heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{22};

$R^{6'}$, for each occurrence, is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}alkylsulfanyl, carboxy, carbamoyl, N-(C_{1-6}alkyl)carbamoyl, N,N-(C_{1-6}alkyl)$_2$carbamoyl, C_{3-14}carbocyclyl-L-, and heterocyclyl-L-; wherein R^6 is optionally substituted on one or more carbon atoms with one or more R^{16}; and wherein if said heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from $R^{17'}$;

R^{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, hydroxy, amino, mercapto, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, and C_{1-6}alkylsulfanyl; wherein R^{13} may be optionally substituted on one or more carbon by one or more one or more R^{16}; or

$R^{6'}$ and R^{13} together with the intervening ring atoms may form a fused heterocyclyl, wherein the fused heterocyclyl may be optionally substituted on one or more carbon atoms with one or more independently selected R^{16}; and wherein if said fused heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said fused heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from $R^{17'}$;

m is 0 or1;

p is 0, 1, or 2;

L, for each occurrence, is independently a direct bond or a C_{1-6}alkylene;

R^7, R^8, R^{10}, R^{12}, R^{14} and R^{16} are substituents on carbon which, for each occurrence, are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$- wherein a is 0, 1 or 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, C_{3-6}carbocyclyl or heterocyclyl; wherein R^7, R^8, R^{10}, R^{12}, R^{14} and R^{16} independently of each other may be optionally substituted on one or more carbon by one or more R^{19}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{20}; and wherein if said heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups;

R^9, R^{11}, and R^{20}, for each occurrence, are independently selected from C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl; wherein R^9, R^{11}, and R^{20} independently of each other may be optionally substituted on carbon by one or more R^{23};

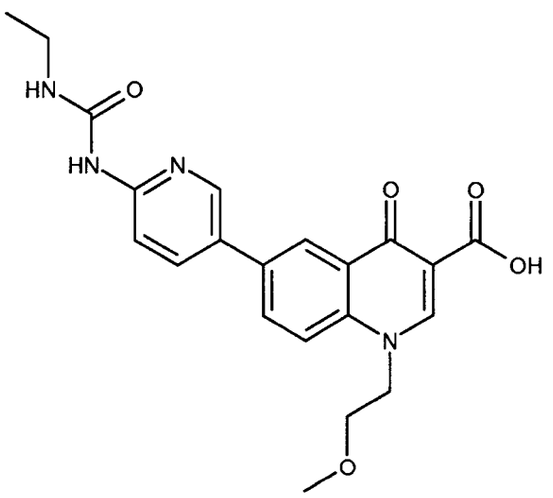
$R^{17'}$, for each occurrence, is independently selected from C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl, phenylsulphonyl, C_{3-14}carbocyclyl-L-, and heterocyclyl-L-; wherein each $R^{17'}$, independently, may be optionally substituted on carbon by one or more R^{24}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{25}; and wherein if said heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups;

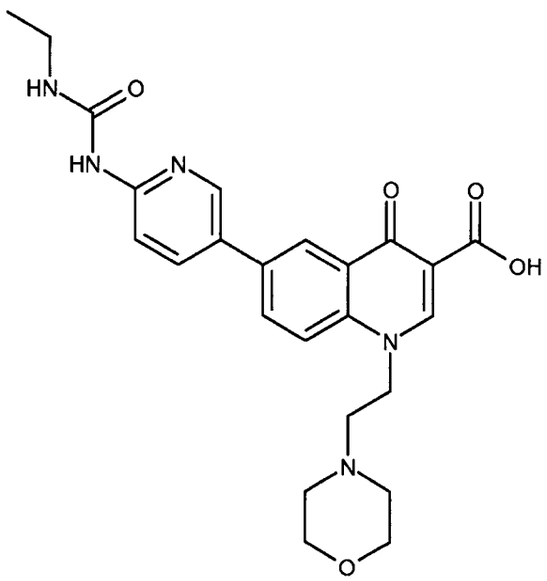
R^{22}, for each occurrence is independently selected from C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{1-6}alkoxycarbonyl, carbamoyl, N,N-(C_{1-6}alkyl)$_2$sulfamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl; wherein R^{22} for each occurrence may be independently optionally substituted on carbon by one or more R^{23};

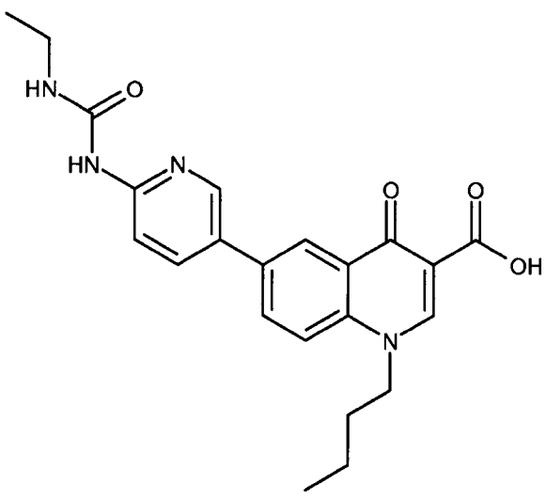
R^{19} and R^{23}, for each occurrence, are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{1-6}alkoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

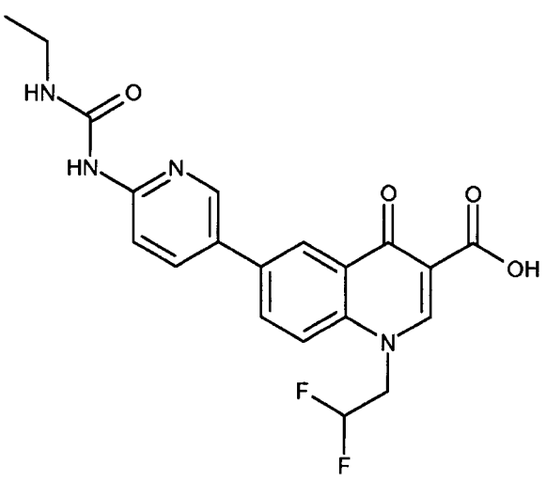
R^{24}, for each occurrence, are independently selected from halo, nitro, cyano, hydroxy, oxo, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{1-6}alkoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl; and

R^{25}, for each occurrence is independently selected from a C_{1-6}alkyl, provided that the compound is not one of the following compounds:









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In another embodiment, the invention provides pharmaceutical compositions comprising a compound represented by formula **(I)** or **(I')**, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient or carrier.

In another embodiment, the invention provides a method of inhibiting bacterial DNA gyrase and/or bacterial topoisomerase IV in a warm-blooded animal in need of such treatment, comprising administering to the animal an effective amount of a compound represented by formula **(I)** or **(I')**, or a pharmaceutically acceptable salt thereof. In a particular embodiment, the warm-blooded animal is a human.

In another embodiment, the invention provides a method of producing an antibacterial effect in a warm-blooded animal in need of such treatment, comprising administering to the animal an effective amount of a compound represented by formula **(I)** or **(I')**, or a pharmaceutically acceptable salt thereof. In a particular embodiment, the warm-blooded animal is a human.

In another embodiment, the invention provides a method of treating a bacterial infection in a warm-blooded animal in need thereof, comprising administering to the animal an effective amount of a compound represented by formula **(I)** or **(I')**, or a pharmaceutically acceptable salt thereof. In a particular embodiment, the warm-blooded animal is a human. In one embodiment, the bacterial infection is selected from the group consisting of community-acquired pneumoniae, hospital-acquired pneumoniae, skin and skin structure infections, acute exacerbation of chronic bronchitis, acute sinusitis, acute otitis media, catheter-related sepsis, febrile neutropenia, osteomyelitis, endocarditis, urinary tract infections and infections caused by drug resistant bacteria such as Penicillin-resistant Streptococcus pneumoniae, methicillin-resistant Staphylococcus aureus, methicillin-resistant Staphylococcus epidermidis and Vancomycin-Resistant Enterococci. In a particular embodiment, the warm-blooded animal is a human.

In another embodiment, the invention provides the use of a compound represented by formula **(I)** or **(I')**, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use in the production of an antibacterial effect in a warm-blooded animal. In a particular embodiment, the warm-blooded animal is a human.

In another embodiment, the invention provides the use of a compound represented by formula **(I)** or **(I')**, or a pharmaceutically acceptable salt thereof, for the manufacture of a

medicament for use in inhibition of bacterial DNA gyrase and/or topoisomerase IV in a warm-blooded animal. In a particular embodiment, the warm-blooded animal is a human.

In another embodiment, the invention provides the use of a compound represented by formula **(I)** or **(I')**, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use the treatment of a bacterial infection in a warm-blooded animal. In one embodiment, the bacterial infection is selected from the group consisting of community-acquired pneumoniae, hospital-acquired pneumoniae, skin and skin structure infections, acute exacerbation of chronic bronchitis, acute sinusitis, acute otitis media, catheter-related sepsis, febrile neutropenia, osteomyelitis, endocarditis, urinary tract infections, Penicillin-resistant Streptococcus pneumoniae, methicillin-resistant Staphylococcus aureus, methicillin-resistant Staphylococcus epidermidis and Vancomycin-Resistant Enterococci. In a particular embodiment, the warm-blooded animal is a human.

In another embodiment, the invention provides a compound represented by formula **(I)** or **(I')**, or a pharmaceutically acceptable salt thereof, for use in production of an anti-bacterial effect in a warm-blooded animal.

In another embodiment, the invention provides a compound represented by formula **(I)** or **(I')**, or a pharmaceutically acceptable salt thereof, for use in inhibition of bacterial DNA gyrase and/or topoisomerase IV in a warm-blooded animal.

In another embodiment, the invention provides a compound represented by formula **(I)** or **(I')**, or a pharmaceutically acceptable salt thereof, for use in the treatment of a bacterial infection in a warm-blooded animal.

In another embodiment, the invention provides a compound represented by formula **(I)** or **(I')**, or a pharmaceutically acceptable salt thereof, for use in the treatment of community-acquired pneumoniae, hospital-acquired pneumoniae, skin and skin structure infections, acute exacerbation of chronic bronchitis, acute sinusitis, acute otitis media, catheter-related sepsis, febrile neutropenia, osteomyelitis, endocarditis, urinary tract infections, Penicillin-resistant Streptococcus pneumoniae, methicillin-resistant Staphylococcus aureus, methicillin-resistant Staphylococcus epidermidis or Vancomycin-Resistant Enterococci.

Detailed Description of the Invention

In this specification the term alkyl includes both straight chained and branched saturated hydrocarbon groups. For example, "C_{1-6}alkyl" refers to an alkyl that has from 1 to 6 carbon atom and includes, for example, methyl, ethyl, propyl, isopropyl and *t*-butyl. However

references to individual alkyl groups such as propyl are specific for the straight chain version only unless otherwise indicated (e.g., isopropyl). An analogous convention applies to other generic terms.

As used herein, the term "alkylene" refers to an alkyl group that has two points of attachment. Examples of alkylene groups include methylene, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, and $-CH_2C(CH_3)_2CH_2-$.

As used herein, the term "halo" refers to fluoro, chloro, bromo, and iodo.

A "heterocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 4-14 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- and a ring nitrogen may be optionally substituted with one oxo to form an N-oxide and a ring sulfur may be optionally substituted with one or two oxo groups to form S-oxide(s). In one embodiment of the invention a "heterocyclyl" is a saturated, partially saturated or unsaturated, monocyclic ring containing 5 or 6 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, it may, unless otherwise specified, be carbon or nitrogen linked. In a further aspect of the invention a "heterocyclyl" is an unsaturated, carbon-linked, monocyclic ring containing 5 or 6 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen. Examples and suitable values of the term "heterocyclyl" are morpholinyl, piperidyl, pyridinyl, pyranyl, pyrrolyl, pyrazolyl, isothiazolyl, indolyl, quinolinyl, thienyl, 1,3-benzodioxolyl, benzothiazolyl, thiadiazolyl, oxadiazolyl, piperazinyl, thiazolidinyl, pyrrolidinyl, thiomorpholino, pyrrolinyl, homopiperazinyl, 3,5-dioxapiperidinyl, tetrahydropyranyl, imidazolyl, 4,5-dihydro-oxazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, isoxazolyl, thiazolyl, 1*H*-tetrazolyl, 1*H*-triazolyl, *N*-methylpyrrolyl, 4-pyridone, quinolin-4(1*H*)-one, pyridin-2(1*H*)-one, imidazo[1,2-a]pyridinyl, 1-isoquinolone, 2-pyrrolidone, 4-thiazolidone, quinoxalinyl, 5,6-dihydro[1,3]thiazolo[4,5-*d*]pyridazinyl, pyridine-*N*-oxide and quinoline-*N*-oxide. Suitable examples of "a nitrogen linked heterocyclyl" are morpholino, piperazin-1-yl, piperidin-1-yl and imidazol-1-yl. In a further aspect of the invention a "heterocyclyl" is a heteroaryl. The term "heteroaryl" refers to an unsaturated and aromatic heterocyclyl. Examples and suitable values for heteroaryl groups include pyridinyl, pyrrolyl, pyrazolyl, isothiazolyl, indolyl, quinolinyl, thienyl, benzothiazolyl, thiadiazolyl, oxadiazolyl, imidazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, isoxazolyl, thiazolyl, 1*H*-tetrazolyl, 1*H*-triazolyl, *N*-methylpyrrolyl, quinolin-4(1*H*)-one, pyridin-2(1*H*)-one, imidazo[1,2-a]pyridinyl, 1-isoquinolone,

quinoxalinyl, pyridine-*N*-oxide and quinoline-*N*-oxide. In a particular embodiment, the heteroaryl is a 5- or 6-membered heteroaryl, for example, pyridinyl, pyrrolyl, pyrazolyl, isothiazolyl, thienyl, thiadiazolyl, oxadiazolyl, imidazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, isoxazolyl, thiazolyl, 1*H*-tetrazolyl, 1*H*-triazolyl, *N*-methylpyrrolyl, and pyridine-*N*-oxide.

A "carbocyclyl" is a saturated, partially saturated or unsaturated, mono-, bi- or tricyclic carbon ring that contains 3-14 atoms; wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-. In one embodiment, "carbocyclyl" is a monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms. Examples of carbocyclyls include cyclopropyl, cyclobutyl, 1-oxocyclopentyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, phenyl, naphthyl, tetralinyl, indanyl or 1-oxoindanyl. The term carbocyclyl encompasses both cycloalkyl and aryl groups. The term cycloalkyl refers to a carbocyclyl which is completely saturated, for example cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. The term "aryl" refers to a carbocyclyl which is completely unsaturated and is aromatic. A C_{6-14}aryl is an aromatic, mono-, bi- or tricyclic carbon ring that contains 6-14 atoms, for example phenyl or naphthenyl.

An example of "C_{1-6}alkanoyloxy" is acetoxy. Examples of "C_{1-6}alkoxycarbonyl" are methoxycarbonyl, ethoxycarbonyl, *n*- and *t*-butoxycarbonyl. Examples of "C_{1-6}alkoxycarbonylamino" are methoxycarbonylamino, ethoxycarbonylamino, *n*- and *t*-butoxycarbonylamino. Examples of "C_{1-6}alkoxy" are methoxy, ethoxy and propoxy. Examples of "C_{1-6}alkanoylamino" are formamido, acetamido and propionylamino. Examples of "C_{1-6}alkyl$S(O)_a$ wherein a is 0, 1, or 2" are methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl and ethylsulphonyl. Examples of "C_{1-6}alkanoyl" are propionyl and acetyl. Examples of "*N*-(C_{1-6}alkyl)amino" are methylamino and ethylamino. Examples of "*N,N*-(C_{1-6}alkyl)$_2$amino" are di-*N*-methylamino, di-(*N*-ethyl)amino and *N*-ethyl-*N*-methylamino. Examples of "C_{2-4}alkenyl" are vinyl, allyl and 1-propenyl. Examples of "C_{2-4}alkynyl" are ethynyl, 1-propynyl and 2-propynyl. Examples of "*N*-(C_{1-6}alkyl)sulphamoyl" are *N*-(methyl)sulphamoyl and *N*-(ethyl)sulphamoyl. Examples of "*N,N*-(C_{1-6}alkyl)$_2$sulphamoyl" are *N,N*-(dimethyl)sulphamoyl and *N*-(methyl)-*N*-(ethyl)sulphamoyl. Examples of "*N*-(C_{1-6}alkyl)carbamoyl" are methylaminocarbonyl and ethylaminocarbonyl. Examples of "*N,N*-(C_{1-6}alkyl)$_2$carbamoyl" are dimethylaminocarbonyl and methylethylaminocarbonyl. Examples of "*N*-(C_{1-6}alkoxy)carbamoyl" are methoxyaminocarbonyl and isopropoxyaminocarbonyl.

Examples of "*N*-(C_{1-6}alkyl)-*N*-(C_{1-6}alkoxy)carbamoyl" are *N*-methyl-*N*-methoxyaminocarbonyl and *N*-methyl-*N*-ethoxyaminocarbonyl. Examples of "C_{3-6}cycloalkyl" are cyclopropyl, cyclobutyl, cyclopropyl and cyclohexyl. Examples of "C_{1-6}alkylsulphonylamino" are methylsulphonylamino, isopropylsulphonylamino and *t*-butylsulphonylamino. Examples of "C_{1-6}alkylsulphonylaminocarbonyl" are methylsulphonylaminocarbonyl, isopropylsulphonylaminocarbonyl and *t*-butylsulphonylaminocarbonyl. Examples of "C_{1-6}alkylsulphonyl" are methylsulphonyl, isopropylsulphonyl and *t*-butylsulphonyl.

The term "formula **(I)**", unless otherwise specified, refers to all embodiments of formula **(I)** including but not limited to formula **(Ia)**, formula **(Ib)**, and formula **(Ic)**.

The term "formula **(I')**", unless otherwise specified, refers to all embodiments of formula **(I')** including but not limited to formula **(Ia')**, formula **(Ib')**, and formula **(Ic')**.

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

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

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

Within the present invention it is to be understood that a compound of the formula **(I)** or **(I')**, or a salt thereof may exhibit the phenomenon of tautomerism and that the formulae drawings within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which inhibits DNA gyrase and / or topoisomerase IV and is not to be limited merely to any one tautomeric form utilized within the formulae drawings. The formulae drawings within this specification can

represent only one of the possible tautomeric forms and it is to be understood that the specification encompasses all possible tautomeric forms of the compounds drawn not just those forms which it has been possible to show graphically herein. The same applies to compound names.

It will be appreciated by those skilled in the art that certain compounds of formula **(I)** or **(I')** contain an asymmetrically substituted carbon and/or sulphur atom, and accordingly may exist in, and be isolated in, optically-active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic or stereoisomeric form, or mixtures thereof, which form possesses properties useful in the inhibition of DNA gyrase and / or topoisomerase IV, it being well known in the art how to prepare optically-active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, by enzymatic resolution, by biotransformation, or by chromatographic separation using a chiral stationary phase) and how to determine efficacy for the inhibition of DNA gyrase and / or topoisomerase IV by the standard tests described hereinafter.

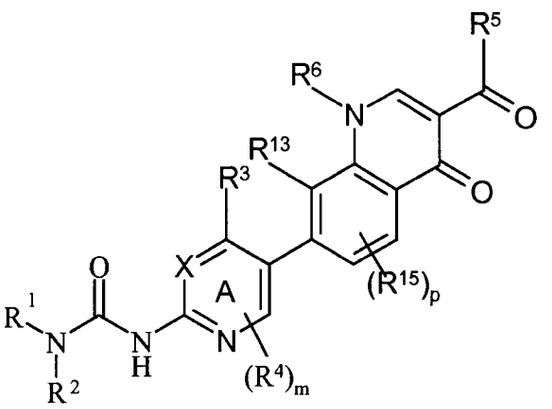
By way of clarity, compounds of the invention included all isotopes of the atoms present in formula **(I)** or **(I')** and any of the examples or embodiments disclosed herein. For example, H (or hydrogen) represents any isotopic form of hydrogen including ^{1}H, ^{2}H (D), and ^{3}H (T); C represents any isotopic form of carbon including ^{12}C, ^{13}C, and ^{14}C; O represents any isotopic form of oxygen including ^{16}O, ^{17}O and ^{18}O; N represents any isotopic form of nitrogen including ^{13}N, ^{14}N and ^{15}N; P represents any isotopic form of phosphorous including ^{31}P and ^{32}P; S represents any isotopic form of sulfur including ^{32}S and ^{35}S; F represents any isotopic form of fluorine including ^{19}F and ^{18}F; Cl represents any isotopic form of chlorine including ^{35}Cl, ^{37}Cl and ^{36}Cl; and the like. In a preferred embodiment, compounds represented by formula **(I)** or **(I')** comprises isomers of the atoms therein in their naturally occurring abundance. However, in certain instances, it is desirable to enrich one or more atom in a particular isotope which would normally be present in less abundance. For example, ^{1}H would normally be present in greater than 99.98% abundance; however, a compound of the invention can be enriched in ^{2}H or ^{3}H at one or more positions where H is present. In particular embodiments of the compounds of formula **(I)** or **(I')**, when, for example, hydrogen is enriched in the deuterium isotope, the symbol "D" is used to represent the enrichment in deuterium. In one embodiment, when a compound of the invention is

enriched in a radioactive isotope, for example ^{3}H and ^{14}C, they may be useful in drug and/or substrate tissue distribution assays. It is to be understood that the invention encompasses all such isotopic forms which inhibit DNA gyrase and / or topoisomerase IV.

It is also to be understood that certain compounds of the formula **(I)** or **(I')**, and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which inhibit DNA gyrase and / or topoisomerase IV.

There follow particular and suitable values for certain substituents and groups referred to in this specification. These values may be used where appropriate with any of the definitions and embodiments disclosed hereinbefore, or hereinafter. For the avoidance of doubt each stated species represents a particular and independent aspect of this invention.

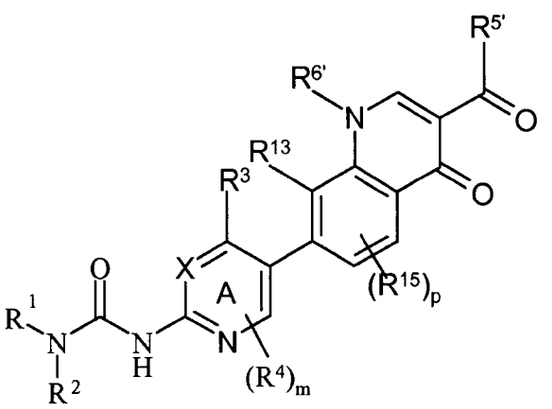
In one embodiment, compounds of the invention are represented by formula **(Ia)**:



(Ia)

or a pharmaceutically acceptable salts thereof, wherein X, R^1, R^2, R^3, R^4, R^5, R^6, R^{13}, R^{15}, m and p are defined as for formula **(I)**.

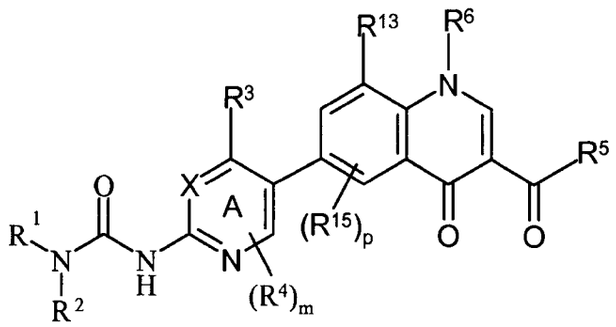
In another embodiment, compounds of the invention are represented by formula **(Ia')**:



(Ia')

or a pharmaceutically acceptable salts thereof, wherein X, R^1, R^2, R^3, R^4, $R^{5'}$, $R^{6'}$, R^{13}, R^{15}, m and p are defined as for formula **(I')**.

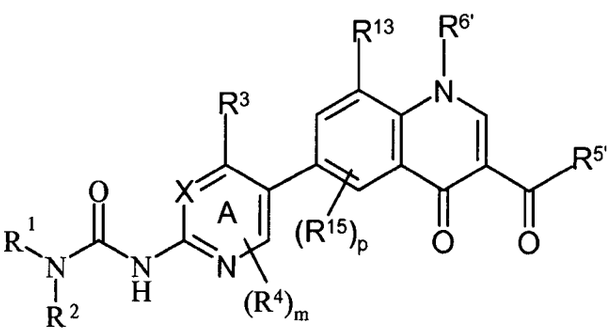
In another embodiment, the compound is represented by formula **(Ib)**:



(Ib)

or a pharmaceutically acceptable salts thereof, wherein X, R^1, R^2, R^3, R^4, R^5, R^6, R^{13}, R^{15}, m and p are defined as for formula **(I)**.

In another embodiment, the compound is represented by formula **(Ib')**:



(Ib')

or a pharmaceutically acceptable salts thereof, wherein X, R^1, R^2, R^3, R^4, $R^{5'}$, $R^{6'}$, R^{13}, R^{15}, m and p are defined as for formula **(I')**.

In another embodiment the invention provides compounds represented by formula **(I)** or **(I')** wherein X is CH.

In another embodiment the invention provides compounds represented by formula **(I)** or **(I')** wherein X is N.

In another embodiment the invention provides compounds represented by formula **(I)** or **(I')** wherein X is CR^4 and R^4 is fluoro, chloro, bromo, iodo, a C_{1-4}alkyl, or a C_{1-4}alkoxy.

In another embodiment the invention provides compounds represented by formula **(I)** or **(I')** wherein R^1 is a C_{1-6}alkyl. For example, R^1 is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, and *tert*-butyl. In a particular embodiment, R^1 is ethyl.

In another embodiment the invention provides compounds represented by formula **(I)** or **(I')** wherein R^2 is hydrogen.

In another embodiment the invention provides compounds represented by formula **(I)** or **(I')** wherein R^2 is a C_{1-6}alkyl. For example, R^2 is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, and *tert*-butyl.

In another embodiment the invention provides compounds represented by formula **(I)** or **(I')** wherein R^3 is a 5-membered heteroaryl; and wherein the heteroaryl may be optionally substituted on one or more carbon atoms by one or more R^{10}; and wherein if said heteroaryl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heteroaryl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{11}. In one aspect of this embodiment, R^{10} is selected from the group consisting of methyl, ethyl, phenyl, trifluoromethyl, and pyridinyl. In another aspect of this embodiment, R^{11} is methyl.

In another embodiment the invention provides compounds represented by formula **(I)** or **(I')** wherein R^3 is a thiazolyl; and wherein the thiazolyl may be optionally substituted on carbon by one or more R^{10}; and wherein the =N- of the thiazolyl may be optionally substituted by one oxo group; and wherein the –S- of the thiazolyl may be optionally substituted by one or two oxo groups. In one aspect of this embodiment, R^{10} is selected from the group consisting of methyl, ethyl, phenyl, trifluoromethyl, and pyridinyl. In another aspect of this embodiment, R^{11} is methyl.

In another embodiment the invention provides compounds represented by formula **(I)** or **(I')** wherein R^3 is a 1,3,4-oxadiazolyl; and wherein the 1,3,4-oxadiazolyl may be optionally substituted on one or more carbon by one or more R^{10}; and wherein each =N- of the 1,3,4-oxadiazolyl may be independently optionally substituted by one oxo group. In one aspect of this embodiment, R^{10} is selected from the group consisting of methyl, phenyl, trifluoromethyl, and pyridinyl. In another aspect of this embodiment, R^{11} is methyl.

In another embodiment the invention provides compounds represented by formula **(I)** or **(I')** wherein R^3 is a 1*H*-pyrazolyl; and wherein the 1*H*-pyrazolyl may be optionally substituted on one or more carbon by one or more R^{10}; and wherein the =N- of the 1*H*-pyrazolyl may be optionally substituted by one oxo group; and wherein the -NH- moiety of the 1*H*-pyrazolyl may be optionally substituted by a group selected from R^{11}. In one aspect of

this embodiment, R^{10} is selected from the group consisting of methyl, phenyl, trifluoromethyl, and pyridinyl. In another aspect of this embodiment, R^{11} is methyl.

In another embodiment the invention provides compounds represented by formula **(I)** or **(I')** wherein R^3 is 1,3-benzothiazolyl; and wherein the 1,3-benzothiazolyl may be optionally substituted on one or more carbon by one or more R^{10}; and wherein the =N- of the 1,3-benzothiazolyl may be optionally substituted by one oxo group; and wherein the –S- of the 1,3-benzothiazolyl may be optionally substituted by one or two oxo groups. In one aspect of this embodiment, R^{10} is selected from the group consisting of methyl, phenyl, trifluoromethyl, and pyridinyl. In another aspect of this embodiment, R^{11} is methyl.

In another embodiment the invention provides compounds represented by formula **(I)** or **(I')** wherein R^3 is a C_{6-14}aryl which may be optionally substituted on one or more carbon atoms with one or more R^{10}.

In another embodiment the invention provides compounds represented by formula **(I)** or **(I')** wherein R^3 is 4-trifluouromethyl-thiazole-2-yl, 4-ethyl-thiazole-2-yl, or 4-phenyl-thiazole-2-yl.

In another embodiment the invention provides compounds represented by formula **(I)** wherein R^5 is –OH.

In another embodiment the invention provides compounds represented by formula **(I')** wherein $R^{5'}$ is –OH.

In another embodiment the invention provides compounds represented by formula **(I)** wherein R^5 is C_{1-6}alkoxy, wherein the C_{1-6}alkoxy group may be optionally substituted on one or more carbon atoms with one or more, independently selected R^{14}. In one aspect of this embodiment, R^{14}, for each occurrence, is independently selected from hydroxy, N,N-$(C_{1-6}alkyl)_2$-amino, morpholinyl, C_{1-6}alkoxy, piperazinyl, and N-alkyl-piperizinyl. In another aspect of this embodiment, R^{14}, for each occurrence, is independently selected from hydroxy, N,N-dimethylamino, morpholino, methoxy, piperazino, and N-methyl-piperizino.

In another embodiment the invention provides compounds represented by formula **(I)** wherein R^5 is C_{1-6}alkoxy.

In another embodiment, the invention provides compounds represented by formula **(I)** wherein R^5 is ethoxy.

In another embodiment the invention provides compounds represented by formula **(I')** wherein $R^{5'}$ is C_{1-6}alkoxy, wherein the C_{1-6}alkoxy group may be optionally substituted on one or more carbon atoms with one or more, independently selected R^{14}. In one aspect of this

embodiment, R^{14}, for each occurrence, is independently selected from hydroxy, N,N-(C_{1-6}alkyl)$_2$-amino, morpholinyl, C_{1-6}alkoxy, piperazinyl, and N-alkyl-piperizinyl. In another aspect of this embodiment, R^{14}, for each occurrence, is independently selected from hydroxy, N,N-dimethylamino, morpholino, methoxy, piperazino, and N-methyl-piperizino.

In another embodiment the invention provides compounds represented by formula **(I')** wherein $R^{5'}$ is C_{1-6}alkoxy.

In another embodiment the invention provides compounds represented by formula **(I')** wherein $R^{5'}$ is ethoxy.

In another embodiment the invention provides compounds represented by formula **(I)** wherein R^5 is amino, N-(C_{1-6}alkyl)amino or N,N-(C_{1-6}alkyl)$_2$amino, wherein the each C_{1-6}alkyl group may be independently optionally substituted on one or more carbon atoms with one or more, independently selected R^{14}. In one aspect of this embodiment, R^{14}, for each occurrence, is independently selected from hydroxy, N,N-(C_{1-6}alkyl)$_2$-amino, morpholinyl, C_{1-6}alkoxy, piperazinyl, and N-alkyl-piperizinyl. In another aspect of this embodiment, R^{14}, for each occurrence, is independently selected from hydroxy, N,N-dimethylamino, morpholino, methoxy, piperazino, and N-methyl-piperizino.

In another embodiment the invention provides compounds represented by formula **(I)** wherein R^5 is amino, N-(C_{1-6}alkyl)amino or N,N-(C_{1-6}alkyl)$_2$amino.

In another embodiment the invention provides compounds represented by formula **(I')** wherein $R^{5'}$ is amino, N-(C_{1-6}alkyl)amino or N,N-(C_{1-6}alkyl)$_2$amino, wherein the each C_{1-6}alkyl group may be independently optionally substituted on one or more carbon atoms with one or more, independently selected R^{14}. In one aspect of this embodiment, R^{14}, for each occurrence, is independently selected from hydroxy, N,N-(C_{1-6}alkyl)$_2$-amino, morpholinyl, C_{1-6}alkoxy, piperazinyl, and N-alkyl-piperizinyl. In another aspect of this embodiment, R^{14}, for each occurrence, is independently selected from hydroxy, N,N-dimethylamino, morpholino, methoxy, piperazino, and N-methyl-piperizino.

In another embodiment the invention provides compounds represented by formula **(I')** wherein $R^{5'}$ is amino, N-(C_{1-6}alkyl)amino or N,N-(C_{1-6}alkyl)$_2$amino.

In another embodiment the invention provides compounds represented by formula **(I)** wherein R^5 is selected from the group consisting of –OH, ethoxy, N-methylamino, and N-ethylamino.

In another embodiment the invention provides compounds represented by formula **(I')** wherein $R^{5'}$ is selected from the group consisting of –OH, ethoxy, N-methylamino, and N-ethylamino.

In another embodiment the invention provides compounds represented by formula **(I')** wherein $R^{5'}$ is $-NR^aR^b$ and one of R^a or R^b is a C_{1-6}alkyl and the other is hydrogen, wherein the C_{1-6}alkyl may be optionally substituted on one or more carbon atoms with one or more, independently selected R^{14}. In one aspect of this embodiment, R^{14}, for each occurrence, is independently selected from hydroxy, N,N-(C_{1-6}alkyl)$_2$-amino, morpholinyl, C_{1-6}alkoxy, piperazinyl, and N-alkyl-piperizinyl. In another aspect of this embodiment, R^{14}, for each occurrence, is independently selected from hydroxy, N,N-dimethylamino, morpholino, methoxy, piperazino, and N-methyl-piperizino.

In another embodiment the invention provides compounds represented by formula **(I')** wherein $R^{5'}$ is $-NR^aR^b$ and one of R^a or R^b is a C_{3-6}cycloalkyl and the other is hydrogen, wherein the cycloalkyl may be optionally substituted on one or more carbon atoms with one or more, independently selected R^{14}.

In another embodiment, R5' is $-NR^aR^b$; wherein R^a and R^b, together with the nitrogen to which they are attached form a heterocycle, wherein R^a and R^b may be optionally substituted on one or more carbon atoms with one or more, independently selected R^{14}; and wherein if said heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{22}. In one aspect of this embodiment, R^{14}, for each occurrence, is independently selected from hydroxy, N,N-(C_{1-6}alkyl)$_2$-amino, morpholinyl, C_{1-6}alkoxy, piperazinyl, and N-alkyl-piperizinyl. In another aspect of this embodiment, R^{14}, for each occurrence, is independently selected from hydroxy, N,N-dimethylamino, morpholino, methoxy, piperazino, and N-methyl-piperizino. In another aspect of this embodiment, R^{22}, for each occurrence, is independently selected from a C_{1-6}alkyl, C_{1-6}alkylsulfonyl, N-(C_{1-6}alkyl)sufamoyl, N,N-(C_{1-6}alkyl)$_2$sufamoyl, and C_{1-6}alkanoyl. In another aspect of this embodiment, R^{22}, for each occurrence, is independently selected from methyl, methylsulfonyl, N,N-dimethylsufamoyl, and acetyl.

In another embodiment the invention provides compounds represented by formula **(I')** wherein $R^{5'}$ is selected from the group consisting of methylamino, N-cyclopropylamino, N-(2-hydroxyethyl)-amino, N-(3-hydroxypropyl)-amino, N-[2-(N,N-dimethylamino)-ethyl]-amino,

N-(2-morpholinoethyl)-amino, N-[1-(methoxymethyl)-2-methoxy-ethyl]-amino, N-[1-(hydroxymethyl)-2-hydroxy-ethyl]-amino, N-[2-(4-methyl-piperazino)-ethyl]-amino, N-(2-piperazino-ethyl)-amino, 4-acetyl-piperazino, 4-methylsulfonyl-piperazino, 4-(2-hydroxyethyl)-piperazino, and 4-(N,N-dimethylsulfamoyl)-piperazino.

In another embodiment the invention provides compounds represented by formula **(I)** wherein R^5 is selected from the group consisting of –OH, ethoxy, methylamino, N-(2-hydroxyethyl)-amino, N-(3-hydroxypropyl)-amino, N-[2-(N,N-dimethylamino)-ethyl]-amino, N-(2-morpholinoethyl)-amino, N-[1-(methoxymethyl)-2-methoxy-ethyl]-amino, N-[1-(hydroxymethyl)-2-hydroxy-ethyl]-amino, N-[2-(4-methyl-piperazino)-ethyl]-amino, and N-(2-piperazino-ethyl)-amino.

In another embodiment the invention provides compounds represented by formula **(I')** wherein $R^{5'}$ is selected from the group consisting of methylamino, N-(2-hydroxyethyl)-amino, N-(3-hydroxypropyl)-amino, N-[2-(N,N-dimethylamino)-ethyl]-amino, N-(2-morpholinoethyl)-amino, N-[1-(methoxymethyl)-2-methoxy-ethyl]-amino, N-[1-(hydroxymethyl)-2-hydroxy-ethyl]-amino, N-[2-(4-methyl-piperazino)-ethyl]-amino, and N-(2-piperazino-ethyl)-amino.

In another embodiment the invention provides compounds represented by formula **(I')** wherein $R^{5'}$ is selected from the group consisting of 4-acetyl-piperazino, 4-methylsulfonyl-piperazino, 4-(2-hydroxyethyl)-piperazino, and 4-(N,N-dimethylsulfamoyl)-piperazino.

In another embodiment the invention provides compounds represented by formula **(I)** wherein R^6 is a $C_{1\text{-}6}$alkyl which is substituted on one or more carbon atoms with one or more independently selected R^{16}. In one aspect of this embodiment, R^{16}, for each occurrence, is independently selected from the group consisting of –OH, fluoro, N-methylamino, N,N-dimethylamino, methoxy, ethoxy, methylsulfanyl, methylsulfonyl, piperidinyl, piperazinyl, morpholinyl, pyrrolidinyl, 2-oxopyrrolidinyl, pyrrolyl, imidazolyl, triazolyl, and phenyl which may be optionally substituted with one or more halo, isoxazolyl, pyridinyl, and cyclopropyl. In another aspect of this embodiment, R^{16}, for each occurrence, is independently selected from N,N-($C_{1\text{-}6}$alkyl)$_2$amino, hydroxy, $C_{1\text{-}6}$alkoxy, and carboxy. In another aspect of this embodiment, R^{16}, for each occurrence, is independently selected from N,N-dimethylamino, hydroxy, methoxy, and carboxy.

In another embodiment the invention provides compounds represented by formula **(I')** wherein $R^{6'}$ is a $C_{1\text{-}6}$alkyl which is substituted on one or more carbon atoms with one or more independently selected R^{16}. In one aspect of this embodiment, R^{16}, for each occurrence, is independently selected from the group consisting of –OH, carboxy, fluoro, N-methylamino,

N,N-dimethylamino, methoxy, ethoxy, methylsulfanyl, methylsulfonyl, cyclohexyl, piperidinyl, piperazinyl, morpholinyl, pyrrolidinyl, 2-oxopyrrolidinyl, pyrrolyl, imidazolyl, triazolyl, and phenyl. In another aspect of this embodiment, R^{16}, for each occurrence, is independently selected from N,N-(C_{1-6}alkyl)$_2$amino, hydroxy, C_{1-6}alkoxy, and carboxy. In another aspect of this embodiment, R^{16}, for each occurrence, is independently selected from N,N-dimethylamino, hydroxy, methoxy, and carboxy.

In another embodiment the invention provides compounds represented by formula **(I')** wherein $R^{6'}$ is a C_{3-6}carbocycle-C_{1-6}alkylene which is optionally substituted on one or more carbon atoms with one or more R^{16}.

In another embodiment the invention provides compounds represented by formula **(I')** wherein $R^{6'}$ is an unsubstituted C_{3-6}carbocycle-C_{1-6}alkylene.

In another embodiment the invention provides compounds represented by formula **(I')** wherein $R^{6'}$ is a cyclopropylmethyl or benzyl.

In another embodiment the invention provides compounds represented by formula **(I')** wherein $R^{6'}$ is a heterocyclyl-C_{1-6}alkylene which is optionally substituted on one or more carbon atoms with one or more R^{16}; wherein if said heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from $R^{17'}$. In one aspect of this embodiment, R^{16}, for each occurrence, is independently selected from oxo, C_{3-6}cycloalkyl, N,N-(C_{1-6}alkyl)$_2$amino, hydroxy, C_{1-6}alkoxy, and carboxy. In another aspect of this embodiment, R^{16}, for each occurrence, is independently selected from oxo, cyclopropyl, N,N-dimethylamino, hydroxy, methoxy, and carboxy. In another aspect of this embodiment, R^{16}, for each occurrence, is independently selected from oxo and cyclopropyl. In another aspect of this embodiment, $R^{17'}$, for each occurrence, is independently selected from C_{1-6}alkylsulfonyl(C_{1-6})alkyl, hydroxyC_{1-6}alkyl, heterocyclyl-(C_{1-6})alkylene, C_{1-6}alkyl, aminoC_{1-6}alkyl, N-(C_{1-6}alkyl)amino, and N,N-(C_{1-6}alkyl)$_2$amino. In another aspect of this embodiment, $R^{17'}$, for each occurrence, is independently selected from 2-(methylsulfonyl)-ethyl, 1-methyl-pyrrol-2-ylmethyl, 2,2-dimethyl-propyl, 2-morpholino-ethyl, 2-(N,N-diethylamino)-ethyl, 3-morpholino-2,2-dimethyl-propyl, 2-hydroxyethyl, methyl, ethyl, pyridin-4-ylmethyl, and tetrahydrofuran-2-ylmethyl. In another aspect of this embodiment, $R^{17'}$, for each occurrence, is independently selected from a C_{1-6}alkyl or heterocyclyl-C_{1-6}alkene. In another aspect of this

embodiment, $R^{17'}$, for each occurrence, is independently selected from methyl, ethyl, tetrahydrofuran-methyl, 2-hydroxyethyl, and 2-morpholino-ethyl.

In another embodiment the invention provides compounds represented by formula **(I)** wherein R^6 is a carbocyclyl which is optionally substituted on one or more carbon atoms with one or more R^{16}. In one aspect of this embodiment, R^{16}, for each occurrence is independently selected from oxo, C_{3-6}cycloalkyl, amino, N-(C_{1-6}alkyl)amino, N,N-(C_{1-6}alkyl)$_2$amino, hydroxy, C_{1-6}alkoxy, and carboxy. In another aspect of this embodiment, R^{16}, for each occurrence, is independently selected from oxo, cyclopropyl, amino, N,N-dimethylamino, hydroxy, methoxy, and carboxy. In another aspect of this embodiment, R^{16}, for each occurrence, is independently selected from hydroxy or amino.

In another embodiment the invention provides compounds represented by formula **(I')** wherein $R^{6'}$ is a carbocyclyl which is optionally substituted on one or more carbon atoms with one or more R^{16}. In one aspect of this embodiment, R^{16}, for each occurrence is independently selected from oxo, C_{3-6}cycloalkyl, amino, N-(C_{1-6}alkyl)amino, N,N-(C_{1-6}alkyl)$_2$amino, hydroxy, C_{1-6}alkoxy, and carboxy. In another aspect of this embodiment, R^{16}, for each occurrence, is independently selected from oxo, cyclopropyl, amino, N,N-dimethylamino, hydroxy, methoxy, and carboxy. In another aspect of this embodiment, R^{16}, for each occurrence, is independently selected from hydroxy or amino.

In another embodiment the invention provides compounds represented by formula **(I)** wherein R^6 is a heterocyclyl which is optionally substituted on one or more carbon atoms with one or more R^{16}; and wherein if said heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{17}. In one aspect of this embodiment, R^{16}, for each occurrence is independently selected from oxo, C_{3-6}cycloalkyl, amino, N-(C_{1-6}alkyl)amino, N,N-(C_{1-6}alkyl)$_2$amino, hydroxy, C_{1-6}alkoxy, and carboxy. In another aspect of this embodiment, R^{16}, for each occurrence, is independently selected from oxo, cyclopropyl, amino, N,N-dimethylamino, hydroxy, methoxy, and carboxy. In another aspect of this embodiment, R^{16}, for each occurrence, is independently selected from hydroxy or amino. In another aspect of this embodiment, R^{17}, for each occurrence, is independently selected from 2-(methylsulfonyl)-ethyl, 2,2-dimethyl-propyl, 2-(N,N-diethylamino)-ethyl, 2-hydroxyethyl, methyl, and ethyl. In another aspect of this embodiment, R^{17}, for each

occurrence, is independently selected from a C_{1-6}alkyl. In another aspect of this embodiment, R^{17}, for each occurrence, is independently selected from methyl, ethyl, and 2-hydroxyethyl.

In another embodiment the invention provides compounds represented by formula **(I')** wherein $R^{6'}$ is a heterocyclyl which is optionally substituted on one or more carbon atoms with one or more R^{16}; and wherein if said heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from $R^{17'}$. In one aspect of this embodiment, R^{16}, for each occurrence is independently selected from oxo, C_{3-6}cycloalkyl, amino, N-(C_{1-6}alkyl)amino, N,N-(C_{1-6}alkyl)$_2$amino, hydroxy, C_{1-6}alkoxy, and carboxy. In another aspect of this embodiment, R^{16}, for each occurrence, is independently selected from oxo, cyclopropyl, amino, N,N-dimethylamino, hydroxy, methoxy, and carboxy. In another aspect of this embodiment, R^{16}, for each occurrence, is independently selected from hydroxy or amino. In another aspect of this embodiment, $R^{17'}$, for each occurrence, is independently selected from C_{1-6}alkylsulfonyl(C_{1-6})alkyl, hydroxyC_{1-6}alkyl, heterocyclyl-(C_{1-6})alkylene, C_{1-6}alkyl, aminoC_{1-6}alkyl, N-(C_{1-6}alkyl)amino, and N,N-(C_{1-6}alkyl)$_2$amino. In another aspect of this embodiment, $R^{17'}$, for each occurrence, is independently selected from 2-(methylsulfonyl)-ethyl, 1-methyl-pyrrol-2-ylmethyl, 2,2-dimethyl-propyl, 2-morpholino-ethyl, 2-(N,N-diethylamino)-ethyl, 3-morpholino-2,2-dimethyl-propyl, 2-hydroxyethyl, methyl, ethyl, pyridin-4-ylmethyl, and tetrahydrofuran-2-ylmethyl. In another aspect of this embodiment, $R^{17'}$, for each occurrence, is independently selected from a C_{1-6}alkyl or heterocyclyl-C_{1-6}alkene. In another aspect of this embodiment, $R^{17'}$, for each occurrence, is independently selected from methyl, ethyl, tetrahydrofuran-methyl, 2-hydroxyethyl, and 2-morpholino-ethyl.

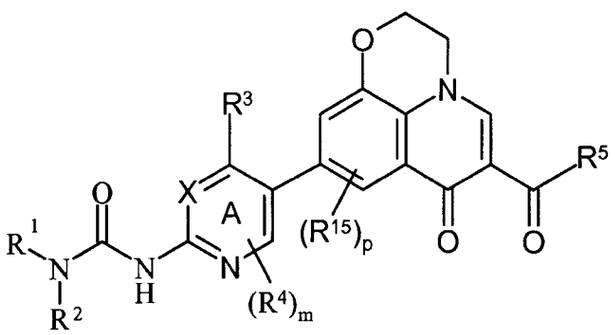
In another embodiment the invention provides compounds represented by formula **(I)** wherein R^6 is hydrogen.

In another embodiment the invention provides compounds represented by formula **(I)** wherein R^6 is C_{1-6}alkyl or a C_{3-6}cycloalkyl.

In another embodiment the invention provides compounds represented by formula **(I)** wherein R^6 is a non-aromatic heterocyclyl having 3 to 6 ring atoms; wherein said heterocyclyl is optionally substituted on one or more carbon atoms with one or more R^{16}; and wherein if said heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein

if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{17}.

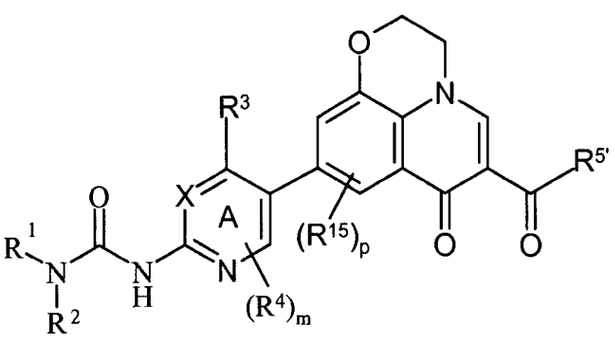
In another embodiment the invention provides compounds represented by formula **(I)** wherein R^{13} and R^6 together with the intervening ring atoms form a 5- or 6-membered fused heterocyclyl. In one aspect of this embodiment, the compounds of the invention are represented by formula **(Ic)**:



(Ic)

or a pharmaceutically acceptable salts thereof, wherein X, R^1, R^2, R^3, R^4, R^5, R^{15}, m and p are defined as for formula **(I)**.

In another embodiment the invention provides compounds represented by formula **(I')** wherein R^{13} and $R^{6'}$ together with the intervening ring atoms form a 5- or 6-membered fused heterocyclyl. In one aspect of this embodiment, the compounds of the invention are represented by formula **(Ic')**:



(Ic')

or a pharmaceutically acceptable salts thereof, wherein X, R^1, R^2, R^3, R^4, $R^{5'}$, R^{15}, m and p are defined as for formula **(I')**.

In another embodiment the invention provides compounds represented by formula **(I)** wherein R^6 is selected from hydrogen, 2-(N,N-dimethylamino)-ethyl, 1-methyl-2-hydroxy-ethyl, morpholin-3-ylmethyl, 2-(N,N-dimethylamino)-propyl, 2-hydroxycyclohexyl, 1-(2-mesyl-ethyl)-piperidin-3-yl, 1-(2,2-dimethyl-propyl)-piperidin-3-yl, 1-[2-(N,N-

dimethylamino)-ethyl]-piperidin-3-yl, 2-hydroxyethyl, ethyl, 3-methoxypropyl, methyl, cyclopropyl, isopropyl, 3-methyl-butyl, propyl, cyclopropylmethyl, 2-hydroxyethyl, 1-methoxymethyl-2-methoxy-ethyl, 1-methyl-azetidine-3-yl, benzyl, 3-hydroxy-propyl, cyclohexyl, tetrahydro-2H-pyran-4-yl, 1-methyl-piperidin-4-yl, isobutyl, 2-methoxyethyl, 1-methyl-piperidin-4-ylmethyl, 1-ethyl-2-hydroxy-ethyl, 1-hydroxymethyl-3-methyl-butyl, 1-carboxy-2-methyl-propyl, 1-methoxymethyl-2-methyl-propyl, pyrrolidin-1-ylethyl, 1-hydroxymethyl-2-methyl-butyl, pyridin-3-ylmethyl, 2-methoxy-ethyl, tetrahydro-2H-pyran-4-ylmethyl, tetrahydrofuran-2-ylmethyl, 1-hydroxymethyl-2,2-dimethyl-propyl, 5-cyclopropyl-1,2,4-oxadiazol-3-yl, 1-methyl-imidazol-4-ylmethyl, pyridin-4-ylmethyl, 1-hydroxmethy-propyl, 4-methyl-piperazin-1-ylethyl, 1-methyl-2-(N,N-dimethylamino)-ethyl, 1-methyl-piperidin-2-yl, piperidin-2-yl, 1-hydroxymethyl-2-methyl-propyl, 1-hydroxymethyl-2-hydroxy-ethyl, 1-hydroxmethyl-2-phenyl-ethyl, 1-hydroxmethyl-2-hydroxy-propyl, 1-ethyl-pyrrolidin-3-yl, 4-hydroxy-pyrrolidin-3-yl, 1-methyl-pyrrolidin-3-yl, 1-hydroxmethyl-ethyl, 1-(2-hydroxy-ethyl)-pyrrolidin-3-ylmethyl, 2-amino-cyclohexyl, tetrahydro-2H-pyran-4-ylethyl, 1-cyclohexyl-2-hydroxy-ethyl, 1-hydroxymethyl-2-(4-hydroxyphenyl)-ethyl, 1-(2-hydroxyethyl)-piperidin-3-yl, pyrrolidin-3-ylmethyl, piperidin-3-ylmethyl, piperidin-3-yl, 1-ethyl-pyrrolidin-3-yl, 1-ethyl-piperidin-3-yl, 1-methyl-pyrrolidin-3-yl, and 1-ethyl-piperidin-3-ylmethyl.

In another embodiment the invention provides compounds represented by formula **(I')** wherein $R^{6'}$ is selected from hydrogen, 2-(N,N-dimethylamino)-ethyl, 1-methyl-2-hydroxy-ethyl, morpholin-3-ylmethyl, 2-(N,N-dimethylamino)-propyl, 2-hydroxycyclohexyl, 1-(2-mesyl-ethyl)-piperidin-3-yl, 1-(1-methyl-pyrrol-2-ylmethyl)-piperidin-3-yl, 1-(2,2-dimethyl-propyl)-piperidin-3-yl, 1-(2-morpholino-ethyl)-pyrrolidin-3-ylmethyl, 1-(2-morpholinoethyl)-piperidin-3-yl, 1-[2-(N,N-dimethylamino)-ethyl]-piperidin-3-yl, 1-(2,2-dimethyl-3-morpholino-propyl)-piperidin-3-yl, 2-hydroxyethyl, ethyl, 3-methoxypropyl, methyl, cyclopropyl, 3-(2-oxo-pyrrolidin-1-yl)-propyl, isopropyl, 3-methyl-butyl, propyl, cyclopropylmethyl, 2-hydroxyethyl, 1-methoxymethyl-2-methoxy-ethyl, 1-methyl-azetidine-3-yl, benzyl, 3-hydroxy-propyl, cyclohexyl, tetrahydro-2H-pyran-4-yl, 1-methyl-piperidin-4-yl, isobutyl, 2-methoxyethyl, 1-methyl-piperidin-4-ylmethyl, 1-ethyl-2-hydroxy-ethyl, 1-hydroxymethyl-3-methyl-butyl, 1-carboxy-2-methyl-propyl, 1-methoxymethyl-2-methyl-propyl, pyrrolidin-1-ylethyl, 1-hydroxymethyl-2-methyl-butyl, pyridin-3-ylmethyl, 2-methoxy-ethyl, tetrahydro-2H-pyran-4-ylmethyl, tetrahydrofuran-2-ylmethyl, 1-hydroxymethyl-2,2-dimethyl-propyl, 5-cyclopropyl-1,2,4-oxadiazol-3-yl, 1-methyl-imidazol-4-ylmethyl, pyridin-4-ylmethyl, 1-hydroxmethy-propyl, 4-methyl-piperazin-1-ylethyl, 1-methyl-2-(N,N-dimethylamino)-ethyl, 1-methyl-

piperidin-2-yl, piperidin-2-yl, 1-hydroxymethyl-2-methyl-propyl, 1-hydroxymethyl-2-hydroxy-ethyl, 1-hydroxmethyl-2-phenyl-ethyl, 1-hydroxmethyl-2-hydroxy-propyl, 1-ethyl-pyrrolidin-3-yl, 4-hydroxy-pyrrolidin-3-yl, 1-methyl-pyrrolidin-3-yl, 1-hydroxmethyl-ethyl, 1-(pyridin-4-ylmethyl)-piperidin-3-yl, 1-(tetrahydrofuran-2-yl)-pyrrolidin-3-ylmethyl, 1-(2-hydroxy-ethyl)-pyrrolidin-3-ylmethyl, 2-amino-cyclohexyl, tetrahydro-2H-pyran-4-ylethyl, 1-cyclohexyl-2-hydroxy-ethyl, 1-hydroxymethyl-2-(4-hydroxyphenyl)-ethyl, 1-(2-hydroxyethyl)-piperidin-3-yl, pyrrolidin-3-ylmethyl, piperidin-3-ylmethyl, piperidin-3-yl, 1-ethyl-pyrrolidin-3-yl, 1-ethyl-piperidin-3-yl, 1-methyl-pyrrolidin-3-yl, 1-ethyl-piperidin-3-ylmethyl.

In another embodiment the invention provides compounds represented by formula **(I)** wherein R^6 is selected from the group consisting of methyl, ethyl, propan-1-yl, propan-2-yl, 1-hydroxy-4-methyl-pentan-2-yl, 2-methyl-propan-1-yl, 3-methyl-butan-1-yl, 2-hydroxyethyl, 2-methoxyethyl, cyclopropyl, cyclopropylmethyl, benzyl, pyridin-3-ylmethyl, 3-methoxypropan-1-yl, 2-(N,N-dimethyl)-ethyl, 3-(2-oxopyrrolidin-1-yl)-propan-1-yl, 1,3-dimethoxy-propan-2-yl, and 1-methyl-azetidine-3-yl.

In another embodiment the invention provides compounds represented by formula **(I)** or **(I')** wherein R^{13} is hydrogen.

In another embodiment the invention provides compounds represented by formula **(I)** or **(I')** wherein m is 0.

In another embodiment the invention provides compounds represented by formula **(I)** or **(I')** wherein m is 0 and X is CH.

In another embodiment the invention provides compounds represented by formula **(I)** or **(I')** wherein m is 0 and X is N.

In another embodiment the invention provides compounds represented by formula **(I)** or **(I')** wherein m is 1.

In another embodiment the invention provides compounds represented by formula **(I)** or **(I')** wherein p is 0.

In another embodiment the invention provides compounds represented by formula **(I)** or **(I')** wherein p is 1.

In a particular embodiment, the present invention provides compounds having a structural formula **(I)** as recited above wherein:

X is CH;

R^1 is C_{1-4}alkyl;

R^2 is hydrogen;

R^3 is a thiazolyl; wherein the thiazolyl may be optionally substituted on carbon by one or more R^{10};

R^5 is –OH, ethoxy, N-methylamino, or N-ethylamino;

R^6 is a C_{1-6}alkyl which is optionally substituted on one or more carbon atom with one or more R^{16};

R^{10} is trifluoromethyl, ethyl, or phenyl;

R^{13} is hydrogen;

R^{16}, for each occurrence, is independently selected from the group consisting of –OH, fluoro, N-methylamino, N,N-dimethylamino, methoxy, ethoxy, methylsulfanyl, methylsulfonyl, piperidinyl, piperazinyl, morpholinyl, pyrrolidinyl, 2-oxopyrrolidinyl, pyrrolyl, imidazolyl, triazolyl, phenyl which may be optionally substituted with one or more halo, isoxazolyl, pyridinyl, and cyclopropyl.

m is 0; and

p is 0.

In a particular embodiment, the present invention provides compounds having a structural formula **(I')** as recited above wherein:

X is CH;

R^1 is C_{1-4}alkyl;

R^2 is hydrogen;

R^3 is a thiazolyl; wherein the thiazolyl may be optionally substituted on carbon by one or more R^{10};

$R^{5'}$ is –OH, ethoxy, N-methylamino, or N-ethylamino;

$R^{6'}$ is a C_{1-6}alkyl which is optionally substituted on one or more carbon atom with one or more R^{16};

R^{10} is trifluoromethyl, ethyl, or phenyl;

R^{13} is hydrogen;

R^{16}, for each occurrence, is independently selected from the group consisting of –OH, fluoro, N-methylamino, N,N-dimethylamino, methoxy, ethoxy, methylsulfanyl, methylsulfonyl, piperidinyl, piperazinyl, morpholinyl, pyrrolidinyl, 2-oxopyrrolidinyl, pyrrolyl, imidazolyl, triazolyl, phenyl which may be optionally substituted with one or more halo, isoxazolyl, pyridinyl, and cyclopropyl;

m is 0; and

p is 0.

In a particular embodiment, the present invention provides compounds having a structural formula **(I)** as recited above wherein:

X is CH;

R^1 is ethyl;

R^2 is hydrogen;

R^3 is a thiazolyl; wherein the thiazolyl may be optionally substituted on carbon by one or more R^{10};

R^5 is –OH, ethoxy, N-methylamino, or N-ethylamino;

R^6 is a C^{1-6}alkyl which is optionally substituted on one or more carbon atom with one or more R^{16};

R^{10} is trifluoromethyl;

R^{13} is hydrogen;

R^{16}, for each occurrence, is independently selected from –OH or C_{1-6}alkoxy;

m is 0; and

p is 0.

In a particular embodiment, the present invention provides compounds having a structural formula **(I')** as recited above wherein:

X is CH;

R^1 is ethyl;

R^2 is hydrogen;

R^3 is a thiazolyl; wherein the thiazolyl may be optionally substituted on carbon by one or more R^{10};

$R^{5'}$ is –OH, ethoxy, N-methylamino, or N-ethylamino;

$R^{6'}$ is a C^{1-6}alkyl which is optionally substituted on one or more carbon atom with one or more R^{16};

R^{10} is trifluoromethyl;

R^{13} is hydrogen;

R^{16}, for each occurrence, is independently selected from –OH or C_{1-6}alkoxy;

m is 0; and

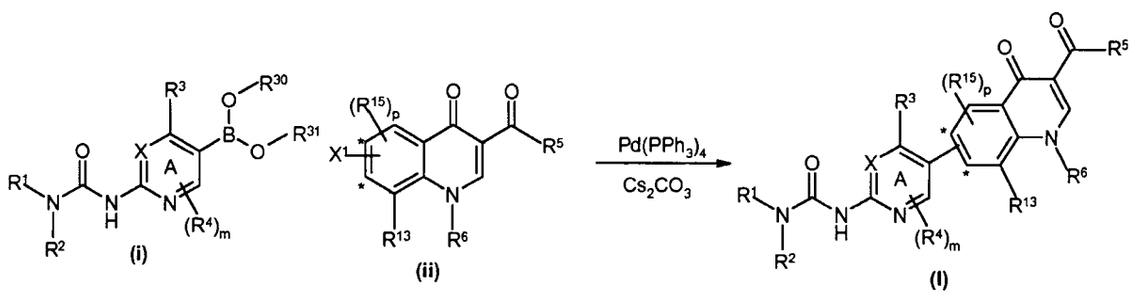
p is 0.

Particular compounds of the invention are the compounds of the Examples, and pharmaceutically acceptable salts thereof, each of which provides a further independent aspect of the invention.

In another embodiment, the invention provides pharmaceutical compositions comprising a pharmaceutically acceptable excipient or carrier and a compound represented by formula **(I)** or **(I')**, or a pharmaceutically acceptable salt thereof.

In a further aspect, the present invention provides a process for preparing a compound of formula **(I)** or **(I')**, or a pharmaceutically-acceptable salt thereof, wherein variable groups in the schemes below are as defined in formula **(I)** or **(I')** unless otherwise specified. In general, the compounds of formula **(I)** can be prepared by a palladium catalyzed Suzuki coupling reaction of a boronic ester or acid derivative **(i)** or **(iv)** and a halo derivative **(ii)** or **(iii)**, as shown in Schemes I and II. Likewise, the compounds of formula **(I')** can be prepared by a palladium catalyzed Suzuki coupling reaction of a boronic ester or acid derivative **(i)** or **(iv')** and a halo derivative **(ii')** or **(iii)**, as shown in Schemes I' and II'. Typically, the coupling reaction is heated and is carried out in the presence of a base such as Cs_2CO_3.

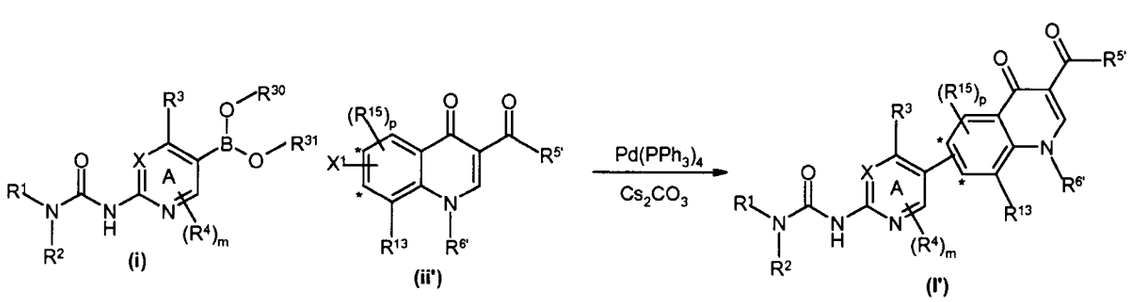
Scheme I



X^1 is a halo.

R^{30} and R^{31} are each independently hydrogen, an alkyl group or R^{30} and R^{31}, together with -O-B-O-, can form a cyclic boronic ester such as 4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl.

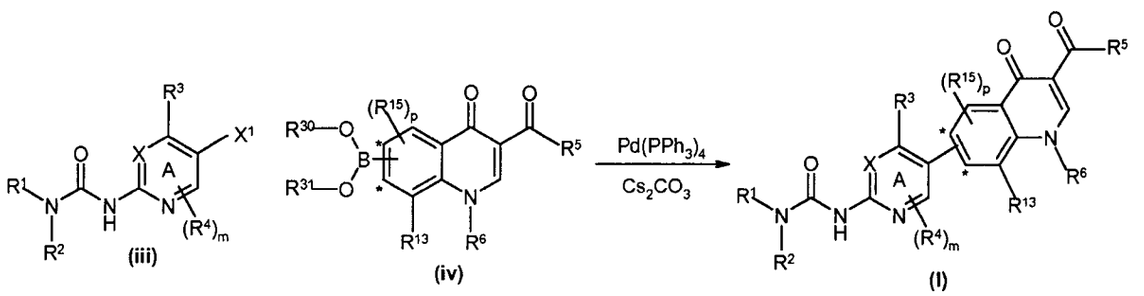
Scheme I'



X^1 is a halo.

R^{30} and R^{31} are each independently hydrogen, an alkyl group or R^{30} and R^{31}, together with -O-B-O-, can form a cyclic boronic ester such as 4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl.

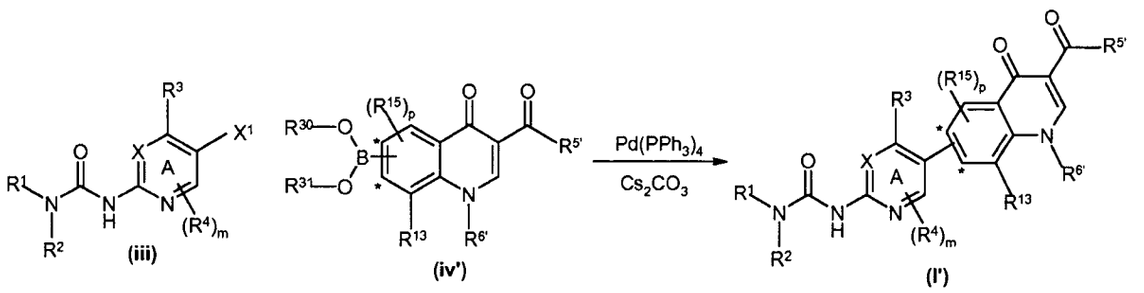
Scheme II



X^1 is a halo.

R^{30} and R^{31} are each independently hydrogen, an alkyl group or R^{21} and R^{22}, together with -O-B-O-, can form a cyclic boronic ester such as 4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl.

Scheme II'



X^1 is a halo.

R^{30} and R^{31} are each independently hydrogen, an alkyl group or R^{21} and R^{22}, together with -O-B-O-, can form a cyclic boronic ester such as 4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl.

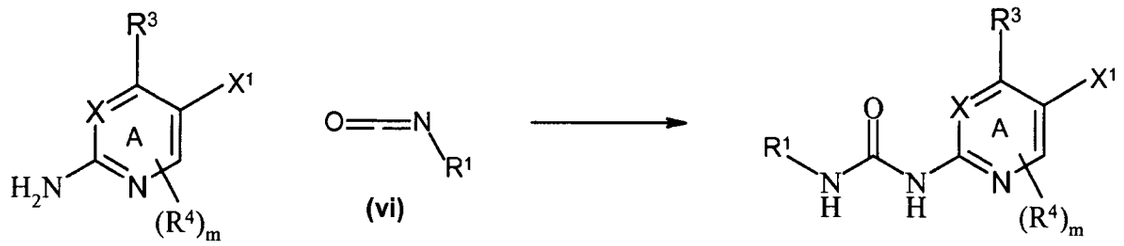
Boronic ester derivatives can be prepared by heating a halo derivative with a diboron compound such as 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) in the presence of 1,1'-bis(diphenylphosphino)ferrocene-palladium dichloride in an organic solvent.

R^5 or $R^{5'}$ in Intermediate **(ii)**, **(ii')**, **(iv)**, and **(iv')** is typically an alkoxy group which is generally stable during the Suzuki coupling reaction. R^5 or $R^{5'}$ can be converted to an –OH group after the coupling reaction by treating the product with a strong base in a protic solvent such as water, an alcohol or a mixture of an alcohol and an organic solvent (e.g. THF/MeOH). R^5 or $R^{5'}$ can be converted to an amino, an N-alkylamino or an N,N-dialkylamino by heating the ester derivative with an amino, an N-alkylamino or an N,N-dialkylamino neat or in a solvent such as an an alcohol.

The urea portion of the compounds of the invention can be prepared from an isocyanate derivative either before or after the Suzuki coupling reaction from an amine derivative. If the Suzuki coupling reaction is preformed before formation of the urea, the

amine is protected with an amine protecting group. When forming the urea derivative, an isocyanate derivative **(vi)** is typically combined with the amine derivative **(v)** in an organic solvent and heated, as shown in Scheme III. The solvent can be aqueous, organic or a mixture of an aqueous miscible organic solvent and water.

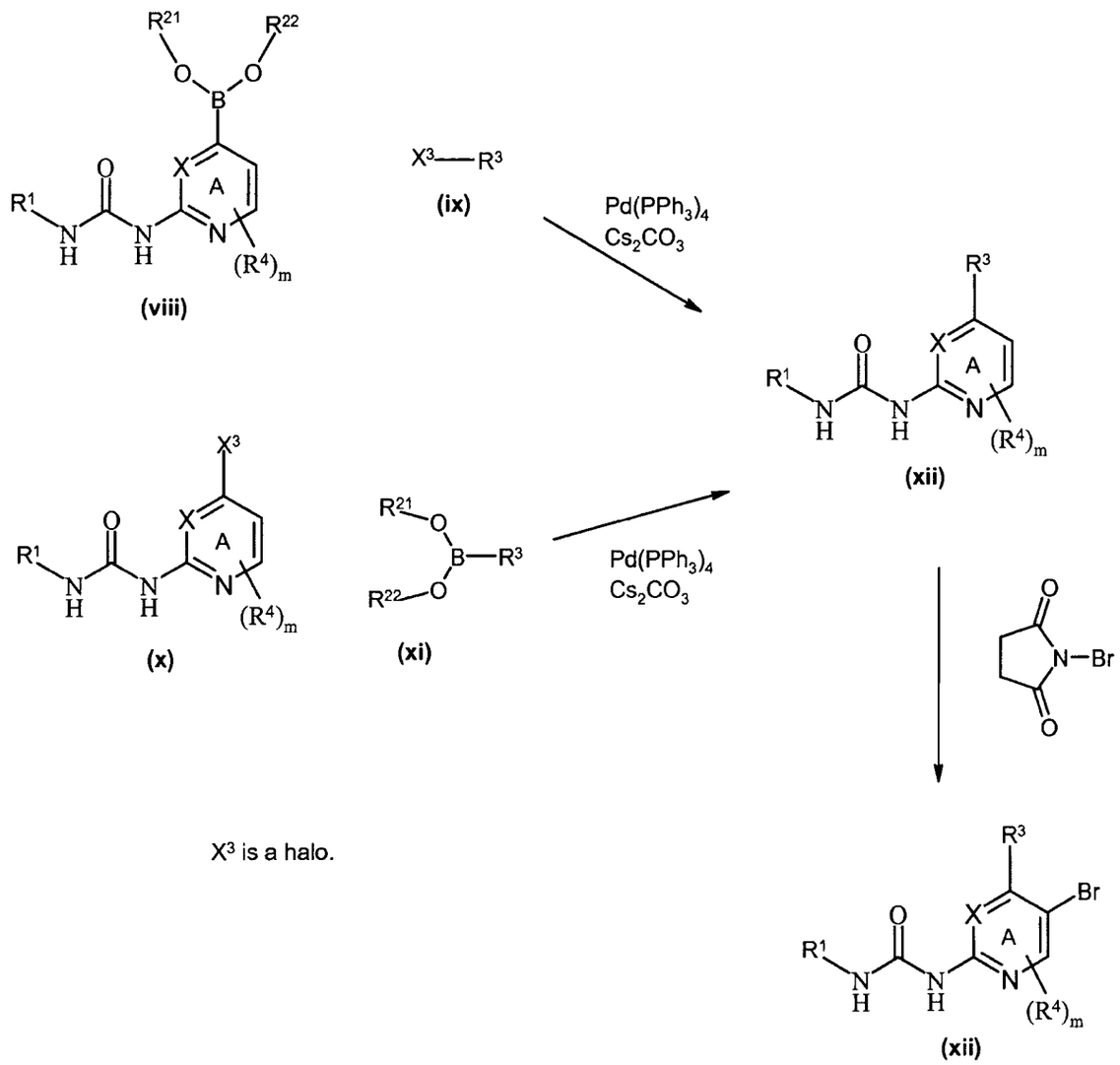
Scheme III



(v) **(vi)** **(vii)**

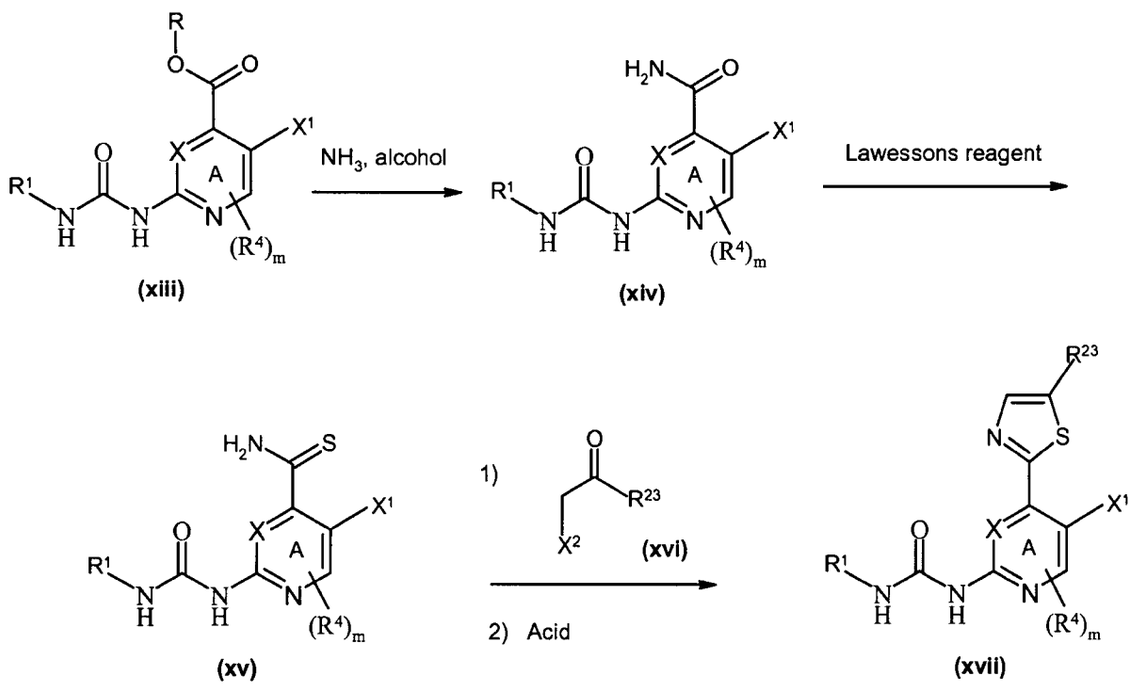
When R^3 is an aryl or a heteroaryl, a Suzuki coupling reaction can be used to attach it to ring A as shown in Scheme IV. Although Scheme IV shows the coupling reaction of R^3 occurring before the coupling reaction to link ring A to the 1,4-dihydroquinoline ring, the reactions could be preformed in the alternative order. When the R^3 group is attached before the coupling reaction to attach 1,4-dihydroquinoline ring, ring A can be brominated by heating it with 1-bromopyrrolidine-2,5-dione to form a substrate for the Suzuki coupling reaction shown in Scheme II.

Scheme IV



Alternatively, when R^3 is a heterocyclyl, it can be prepared from an ester derivative either before or after coupling of the 1,4-dihydroquinoline ring to ring A. For example, when R^3 is a thiazolyl group, an ester derivative **(xiii)** can be converted to an amide **(xiv)** by treating it with a solution of ammonia in an alcohol. The amide derivative **(xiv)** can then be converted to a thioamide **(xv)** by treating the amide with Lawessons reagent. The thioamide **(xv)** is then heated with an α-halo-ketone or an α-halo-aldehyde **(xvi)** followed by treatment with an acid such as trifluoroacetic acid to form the thiazole **(xvii)** (see Scheme V). Although the thiazole ring is prepared before the Suzuki coupling reaction to attach 1,4-dihydroquinoline ring in Scheme V, it could also be prepared after the coupling reaction of the ester derivative to the 1,4-dihydroquinoline ring.

Scheme V



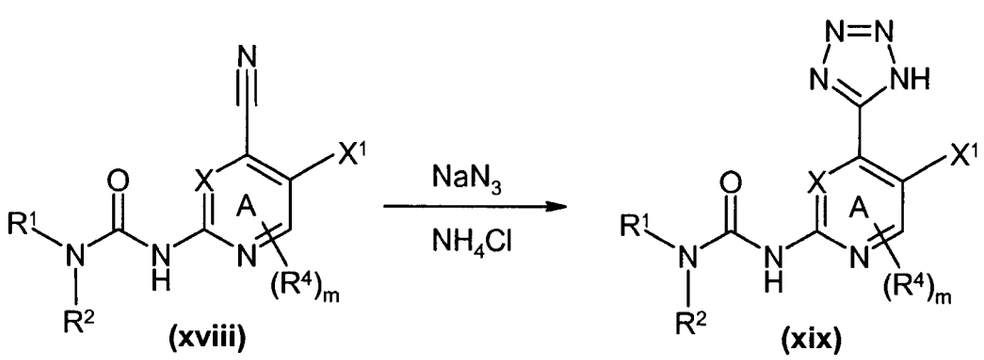
X^2 is a halo.

R is an alkyl.

R^{23} is hydrogen, an optionally substituted alkyl, a carbocyclyl or a heterocyclyl.

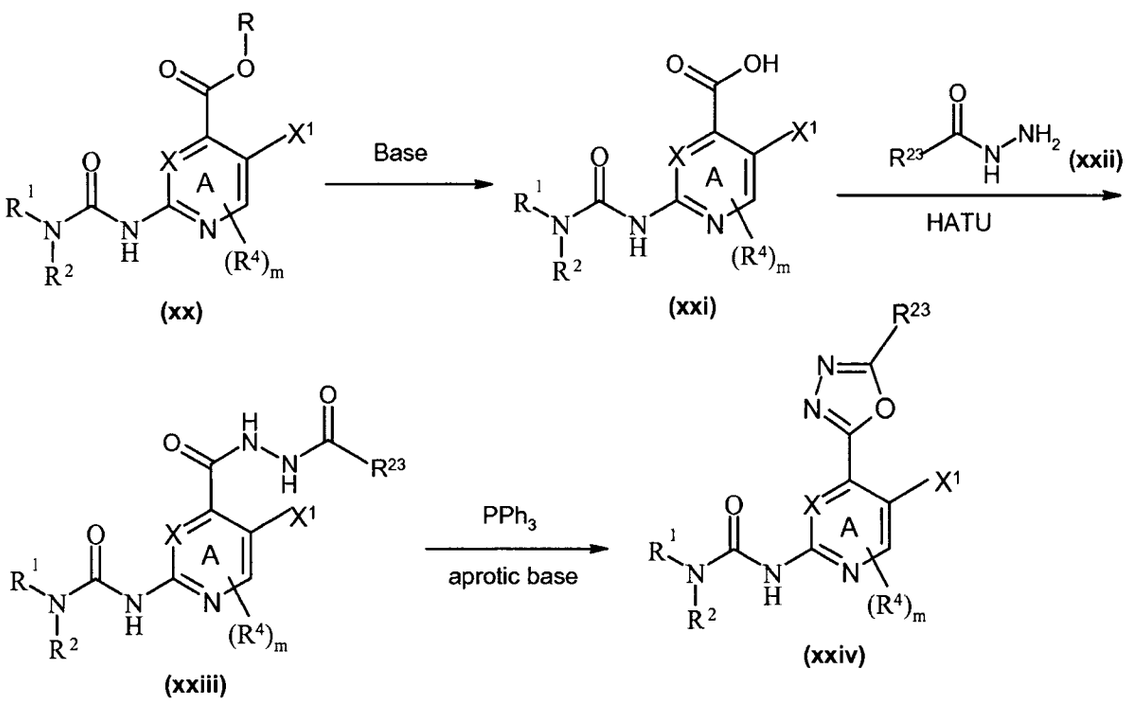
When R^3 is tetrazolyl, it can be prepared by heating a cyano derivative with sodium azide and ammonium chloride in a solvent as shown in Scheme VI. An R^3 tetrazolyl group can be prepared by the reaction shown in Scheme VI either before or after coupling of the 1,4-dihydroquinoline ring to ring A.

Scheme VI



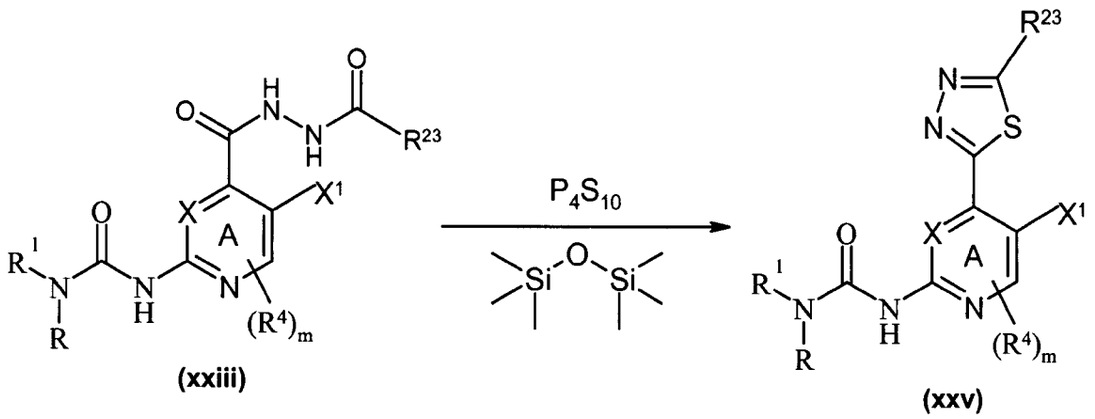
When R^3 is a 1,3,4-oxadiazolyl group, it can be prepared from an ester derivative **(xx)** by treating the ester with a base in to form a carboxylic acid **(xxi)**. The carboxylic acid **(xxi)** is then coupled to a hydrazide derivative **(xxii)** in the presence of the amide coupling reagent HATU to form a dihydrazide derivative **(xxiii)**. The dihydrazide **(xxiii)** is then treated with triphenyl phosphine in an aprotic organic solvent in the presence of an excess amount of an aprotic base to form a compound in which the R^3 group is 1,3,4-oxadiazolyl **(xxiv)** as shown in Scheme VII. An R^3 1,3,4-oxadiazolyl group can be prepared by the reaction shown in Scheme VII either before or after coupling of the 1,4-dihydroquinoline ring to ring A.

Scheme VII



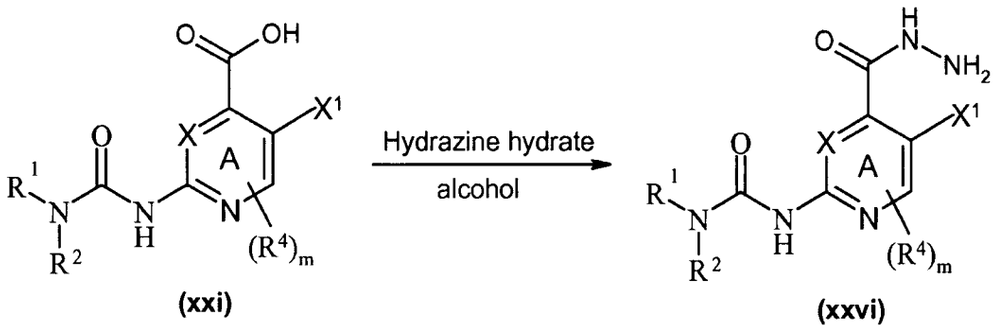
When R^3 is a 1,3,4-thiadiazolyl group, it can be prepared from a dihydrazide derivative **(xxiii)** (see Scheme VII for preparation of dihydrazide derivatives). The dihydrazide derivative **(xxiii)** is heated with phosphorous pentasulfide and hexamethyldisiloxane in an organic solvent to form a compound having an R^3 1,3,4-thiadiazolyl group **(xxv)** as shown in Scheme VIII. An R^3 1,3,4-thiadiazolyl group can be prepared by the reaction shown in Scheme VIII either before or after coupling of the 1,4-dihydroquinoline ring to ring A.

Scheme VIII

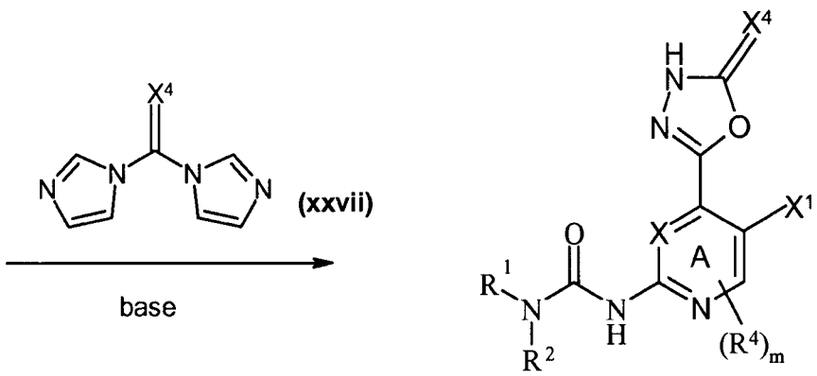


When R^3 is a 2-oxo-1,3,4-oxadiazolyl or a 2-thioxo-1,3,4-oxadiazolyl group, it can be prepared from a carboxylic acid **(xxi)** (see Scheme VII for preparation of the carboxylic acid derivative). The carboxylic acid derivative **(xxi)** is heated with hydrazine hydrate in an alcohol to form a hydrazide derivative **(xxvi)**. The hydrazide derivative **(xxvi)** is then reacted with carbonyl diimidazole or di(1-H-imidazol-2-yl)methanethione **(xxvii)** in the presence of an aprotic base in an aprotic solvent to form a compound which has an R^3 2-oxo-1,3,4-oxadiazolyl or a 2-thioxo-1,3,4-oxadiazolyl group **(xxviii)** as shown in Scheme IX. An R^3 2-oxo-1,3,4-oxadiazolyl or a 2-thioxo-1,3,4-oxadiazolyl group can be prepared by the reaction shown in Scheme IX either before or after coupling of the 1,4-dihydroquinoline ring to ring A.

Scheme IX



(xxi) (xxvi)



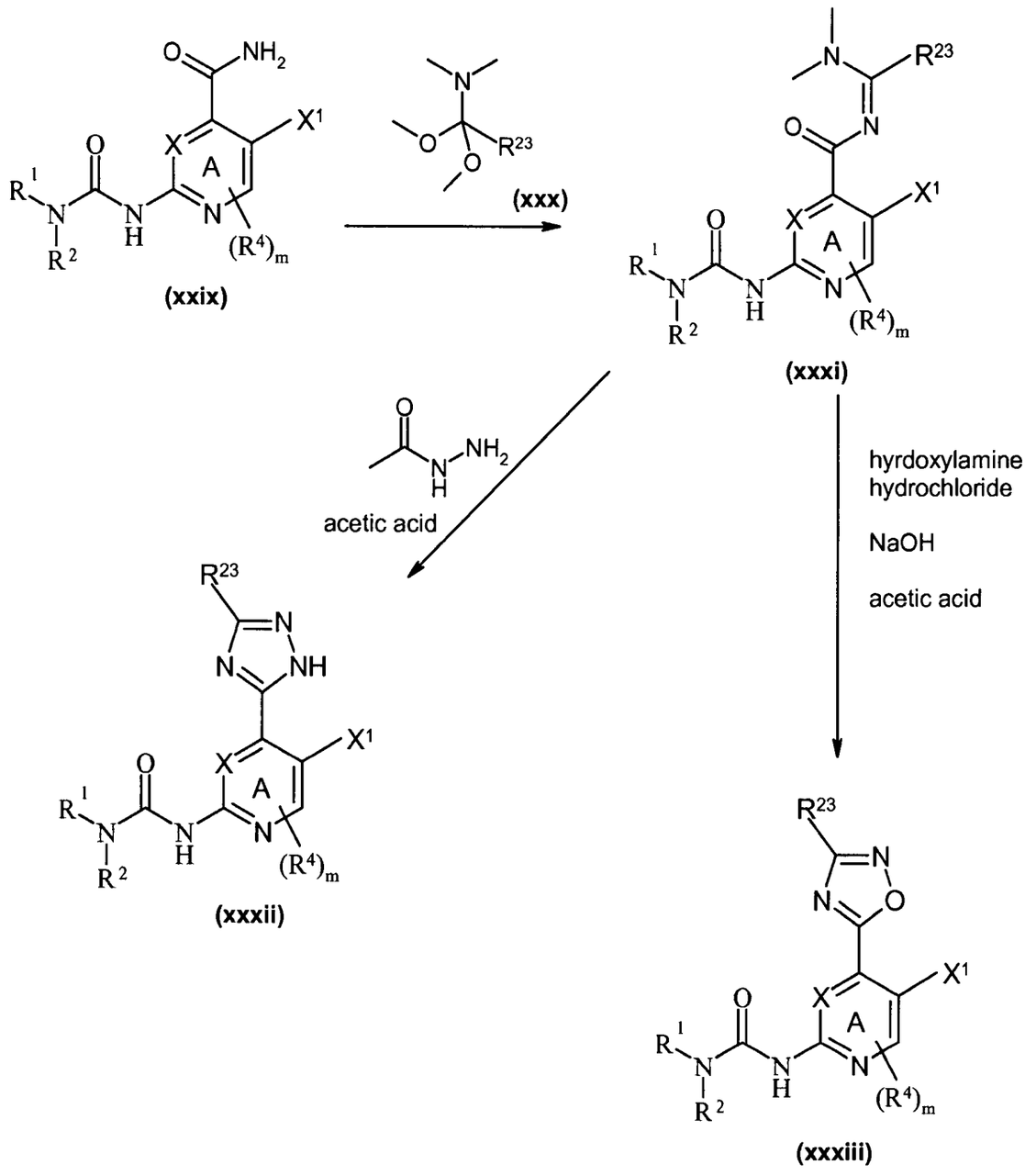
(xxviii)

X^4 is O or S.

When R^3 is a 1,2,4-triazolyl group, it can be prepared from an amide derivative **(xxix)** by heating it in 1-(N,N-dimethylamino)-1,1-dimethoxy-ethane **(xxx)** to form **(xxxi)**. **(xxxi)** is then heated with acetohydrazide in acetic acid to form a compound that has an R^3 1,2,4-triazolyl group **(xxxii)** as shown in Scheme X. An R^3 1,2,4-triazolyl group can be prepared by the reaction shown in Scheme X either before or after coupling of the 1,4-dihydroquinoline ring to ring A.

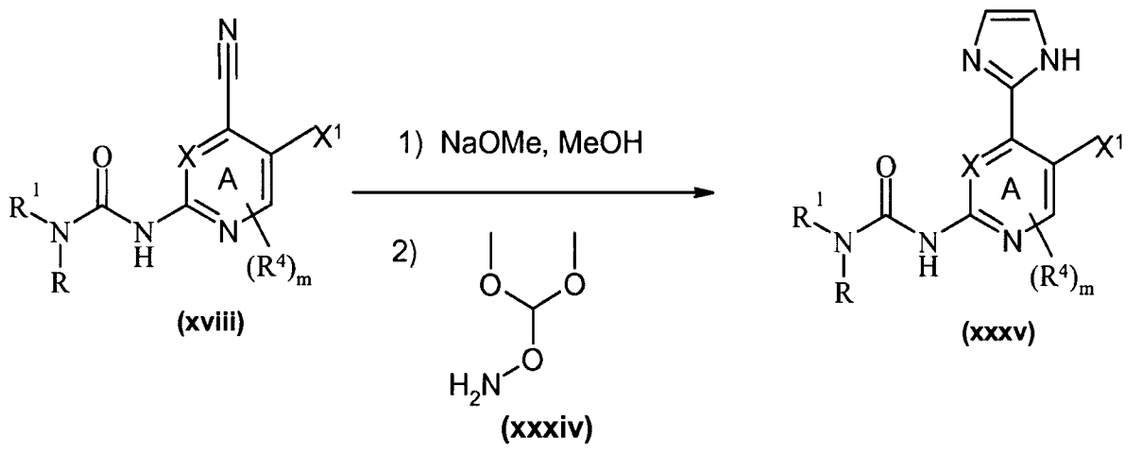
When R^3 is a 1,2,4-oxadiazolyl group, it can be prepared from **(xxxi)** by heating **(xxxi)** with hydroxyl amine hydrochloride in a solution of sodium hydroxide in 70% acetic acid in dioxane to form a compound in which R^3 is a 1,2,4-oxadiazolyl group **(xxxiii)** as shown in Scheme X. An R^3 1,2,4-oxadiazolyl group can be prepared by the reaction shown in Scheme X either before or after coupling of the 1,4-dihydroquinoline ring to ring A.

Scheme X



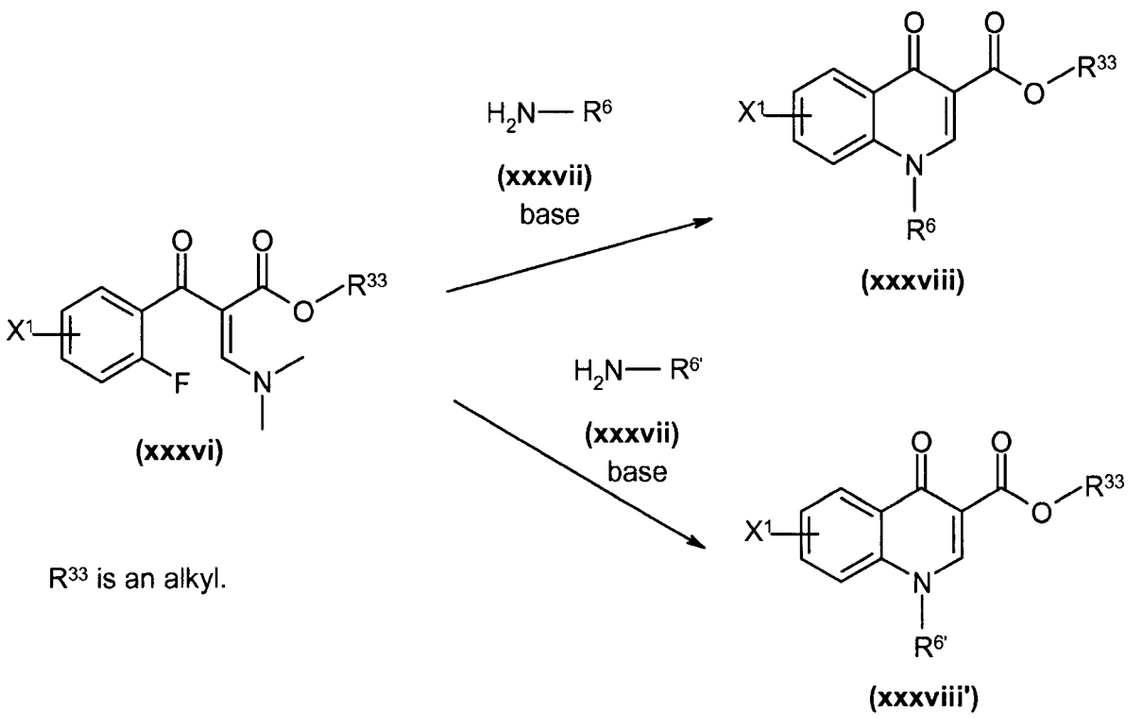
When R^3 is an imidazolyl group, it can be prepared from a cyano derivative **(xvii)** by stirring the cyano derivative **(xvii)** at room temperature in a solution of sodium methoxide in methanol for several hours. 1,1-Dimethoxy-2-aminoethane **(xxxiv)** is then added to the solution and it is heated to give a compound in which R^3 is an imidazolyl group **(xxxv)** as shown in Scheme XI. An R^3 imidazolyl group can be prepared by the reaction shown in Scheme XI either before or after coupling of the 1,4-dihydroquinoline ring to ring A.

Scheme XI



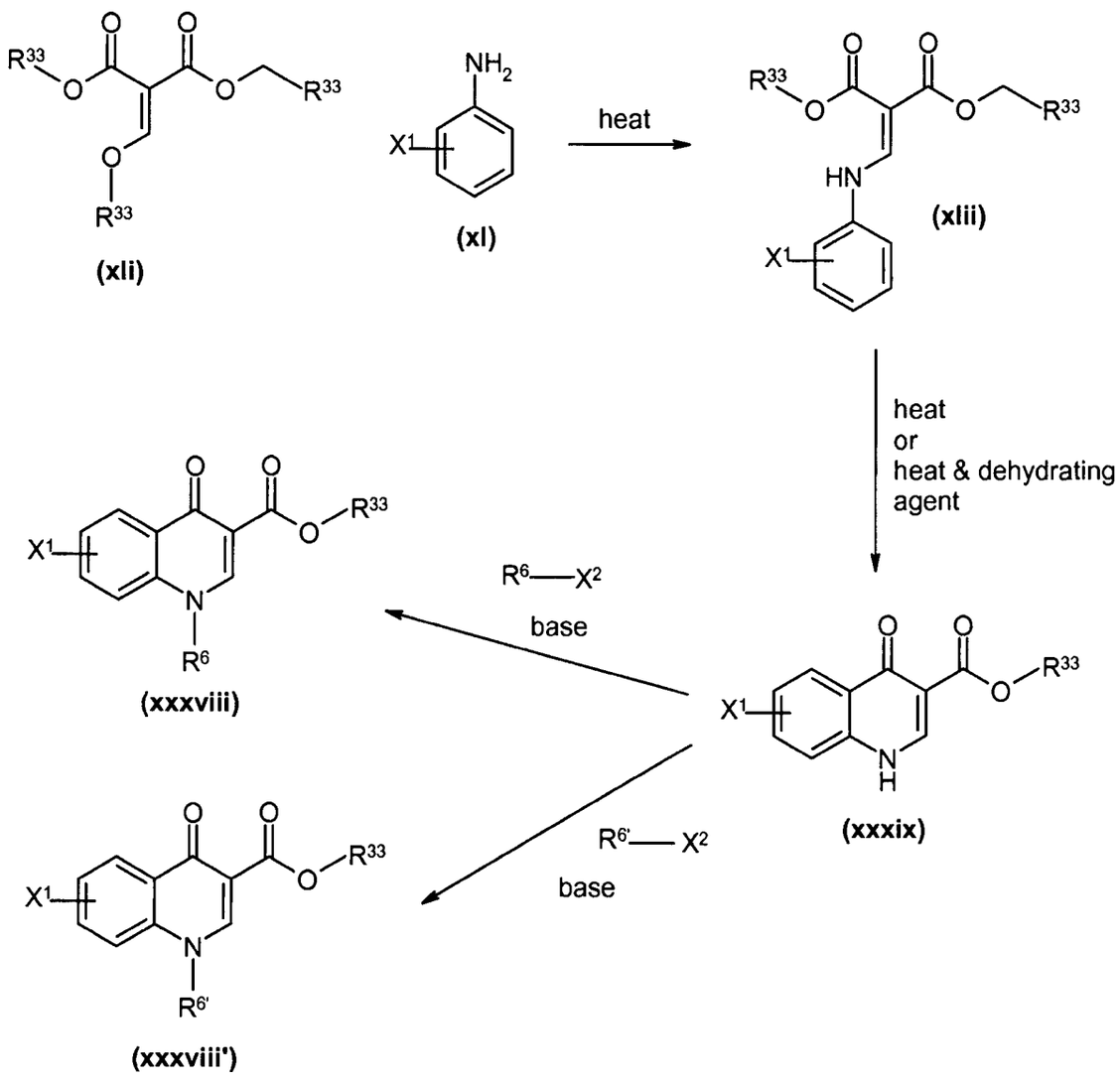
The 1,4-dihydroquinoline derivative **(xxxviii)** can be prepared from an alkyl (Z)-3-(dimethylamino)-2-(2-fluoro-5-halobenzoyl)acrylate or an alkyl (Z)-3-(dimethylamino)-2-(2-fluoro-4-halobenzoyl)acrylate **(xxxvi)** by heating it with a primary amine **(xxxvii)** in the presence of a base as shown in Scheme XII.

Scheme XII



Alternatively, 1,4-dihydroquinoline derivative **(xxxix)** can be prepared by heating an analine **(xl)** in the presence of a dialkyl(alkoxymethylidene)propanedioate **(xli)** to form

intermediate **(xlii)**. Intermediate (lxii) can either be heated in a solvent to about 200°C to 300°C or it can be heated to at a lower temperature (e.g., about 80oC-120oC) in the presence of a dehydrating reagent such as Eaton's reagent to give 1,4-dihydroquinoline derivative **(xxxix)**. 1,4-Dihydroquinoline derivative **(xxxix)** can be converted to 1,4-dihydroquinoline derivative **(xxxviii)** by heating it with an alkyl halide in the presence of a base such as potassium carbonate.



The formation of a pharmaceutically-acceptable salt is within the skill of an ordinary organic chemist using standard techniques.

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of

the invention. The reagents used to introduce such ring substituents are either commercially available or are made by processes known in the art.

Introduction of substituents into a ring may convert one compound of the formula **(I)** into another compound of the formula **(I)**. Likewise, introduction of substituents into a ring may convert one compound of the formula **(I')** into another compound of the formula **(I')**. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents, oxidation of substituents, esterification of substituents, amidation of substituents, formation of heteroaryl rings. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of alkoxides, diazotization reactions followed by introduction of thiol group, alcohol group, halogen group. Examples of modifications include oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

The skilled organic chemist will be able to use and adapt the information contained and referenced within the above references, and accompanying Examples therein and also the Examples herein, to obtain necessary starting materials, and products. If not commercially available, the necessary starting materials for the procedures such as those described above may be made by procedures which are selected from standard organic chemical techniques, techniques which are analogous to the synthesis of known, structurally similar compounds, or techniques which are analogous to the above described procedure or the procedures described in the Examples. It is noted that many of the starting materials for synthetic methods as described above 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, 4th Edition, by Jerry March, published by John Wiley & Sons 1992, for general guidance on reaction conditions and reagents.

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

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

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

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

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

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

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

Enzyme Potency Testing Methods

E.coli GyrB ATPase Inhibition Activity: Compounds can be tested for inhibition of *E. coli* GyrB ATPase activity using an ammonium molybdate/malachite green-based phosphate detection assay (Lanzetta, P. A., L. J. Alvarez, P. S. Reinach, and O. A. Candia, 1979, 100: 95-97). Assays can be performed in multiwell plates in 30µl reactions containing: 50 mM Hepes buffer pH 7.5, 75 mM ammonium acetate, 8.0 mM magnesium chloride, 0.5 mM ethylenediaminetetraacetic acid, 5% glycerol, 1 mM 1,4-Dithio-DL-threitol, 200 nM bovine serum albumin, 1.6 µg/ml sheared salmon sperm DNA, 400 pM *E. coli* GyrA, 400 pM *E. coli* GyrB, 250 µM ATP, and compound in dimethylsulfoxide. Reactions can be quenched with 30 µl of ammonium molybdate/malachite green detection reagent containing 1.2 mM malachite green hydrochloride, 8.5 mM ammonium molybdate tetrahydrate, and 1 M hydrochloric acid. Plates can be read in an absorbance plate reader at 650 nm and percent inhibition values are calculated using dimethylsulfoxide (2%)-containing reactions as 0% inhibition and EDTA-containing (2.4 µM) reactions as 100% inhibition controls. An IC_{50} measurement of compound potency for each compound can be determined from reactions performed in the presence of 10 different compound concentrations.

E. coli Topoisomerase IV ATPase Inhibition Activity: Compounds can be tested for inhibition of *E. coli* topoisomerase IV ATPase activity as described above for *E. coli* GyrB except the

30µl reactions contained the following: 20 mM TRIS buffer pH 8, 50 mM ammonium acetate, 8 mM magnesium chloride, 5% glycerol, 5 mM 1,4-Dithio-DL-threitol, 0.005% Brij-35, 5 µg/ml sheared salmon sperm DNA, 500 pM *E. coli* ParC, 500 pM *E. coli* ParE, 160 µM ATP, and compound in dimethylsulfoxide. An IC_{50} measurement of compound potency for each compound can be determined from reactions performed in the presence of 10 different compound concentrations.

Many of the compounds of the invention were tested in an assay substantially similar to the assays described above for measuring the inhibition of *E.coli* GyrB ATPase and *E. coli* Topoisomerase IV ATPase and had IC_{50} values of <200µM in one or both assays.

S. *aureus* GyrB ATPase Inhibition Activity: Compounds may be tested for inhibition of *S. aureus* GyrB ATPase activity using an ammonium molybdate/malachite green-based phosphate detection assay (Lanzetta, P. A., L. J. Alvarez, P. S. Reinach, and O. A. Candia, 1979, 100: 95-97). Assays can be performed in multiwell plates in 30µl reactions containing: 50 mM Hepes buffer pH 7.5, 75 mM ammonium acetate, 8.0 mM magnesium chloride, 0.5 mM ethylenediaminetetraacetic acid, 5% glycerol, 1.0 mM 1,4-Dithio-DL-threitol, 200 nM bovine serum albumin, 1.0 µg/ml sheared salmon sperm DNA, 250 pM *E. coli* GyrA, 250 pM *S. aureus* GyrB, 250 µM ATP, and compound in dimethylsulfoxide. Reactions can be quenched with 30 µl of ammonium molybdate/malachite green detection reagent containing 1.2 mM malachite green hydrochloride, 8.5 mM ammonium molybdate tetrahydrate, and 1 M hydrochloric acid. Plates can be read in an absorbance plate reader at 650 nm and percent inhibition values can be calculated using dimethylsulfoxide (2%)-containing reactions as 0% inhibition and EDTA-containing (2.4 µM) reactions as 100% inhibition controls. An IC_{50} measurement of compound potency for each compound can be determined from reactions performed in the presence of 10 different compound concentrations.

The compounds in the table below were tested in an assay substantially similar to the assay described above for measuring the inhibition of *S. aureus* GyrB ATPase and were found to have a percent inhibition of *S. aureus* GyrB ATPase a 1 µM as shown in the table. If a compound was tested more than once, a percent inhibition value for each test is shown in the table.

Example	% Inhibition	Example	% Inhibition	Example	% Inhibition
1	100 104	128	92	255	No data
2	100	129	93	256	No data
3	No data	130	101	257	No data
4	98	131	No data	258	No data
5	No data	132	No data	259	No data
6	No data	133	No data	260	No data
7	100	134	No data	261	No data
8	No data	135	No data	262	No data
9	106	136	No data	263	No data
10	99	137	No data	264	No data
11	102	138	No data	265	No data
12	93	139	No data	266	No data
13	98	140	95	267	No data
14	No data	141	97	268	No data
15	101	142	97	269	No data
16	101	143	95	270	No data
17	103	144	94	271	No data
18	98	145	92	272	No data
19	98	146	No data	273	No data
20	96	147	102	274	No data
21	98	148	93	275	No data
22	99	149	93	276	106
23	101	150	No data	277	103
24	99	151	No data	278	101
25	99	152	95 106	279	103
26		153	105	280	103
27	99	154	107	281	106
28	97	155	94	282	105
29	No data	156	105	283	102

Example	% Inhibition	Example	% Inhibition	Example	% Inhibition
30	95	157	103	284	107
31	No data	158	106	285	105
32	98	159	105	286	102
33	97 109	160	103	287	100
34	100	161	101	288	99
35	No data	162	106	289	103
36	64	163	106	290	100
37	96	164	107	291	107
38	99	165	109	292	102
39	101	166	104	293	106
40	No data	167	109	294	109
41	105	168	102	295	No data
42	113	169	105	296	No data
43	No data	170	102	297	No data
44	98	171	112	298	No data
45	No data	172	107	299	No data
46	No data	173	No data	300	No data
47	No data	174	No data	301	No data
48	106	175	No data	302	No data
49	No data	176	No data	302	No data
50	No data	177	No data	304	No data
51	No data	178	No data	305	103
52	No data	179	No data	306	105 100 102
53	No data	180	No data	307	105
54	No data	181	No data	308	111
55	No data	182	No data	309	109
56	No data	183	No data	310	106
57	No data	184	No data	311	100

Example	% Inhibition	Example	% Inhibition	Example	% Inhibition
58	No data	185	No data	312	105
59	No data	186	No data	313	103
60	No data	187	No data	314	114
61	No data	188	No data	315	No data
62	No data	189	100	316	No data
63	No data	190	No data	317	No data
64	No data	191	94	318	No data
65	No data	192	92	319	No data
66	No data	193	93	320	98
67	No data	194	93	321	100
68	No data	195	98	322	96
69	No data	196	97	323	106
70	No data	197	116	324	No data
71	107	198	108	325	96
72	103	199	103	326	97
73	105	200	111	327	100
74	103	201	No data	328	109
75	102	202	103	329	97
76	110	203	87	330	109
77	110	204	No data	331	109
78	102	205	94	332	109
79	97	206	92	333	106
80	96	207	93	334	95
81	96	208	97	335	107
82	111	209	No data	336	109
83	96	210	93	337	106
84	95	211	97	338	99
85	96	212	94	339	109
86	98	213	94	340	93
87	96	214	118	341	99
88	90	215	120	342	99

Example	% Inhibition	Example	% Inhibition	Example	% Inhibition
89	91	216	109	343	98
90	97	217	105	344	95
91	No data	218	97	345	98
92	No data	219	86	346	87
93	95	220	97	347	100
94	95	221	72	348	98
95	109	222	106	349	108
96	95	223	98	350	96
97	No data	224	96	351	95
98	No data	225	95	352	88
99	No data	226	94	353	99
100	No data	227	91	354	98
101	No data	228	104	355	87
102	No data	229	106	356	85
103	No data	230	102	357	87
104	No data	231	No data	358	95
105	No data	232	98	359	92
106	No data	233	No data	360	No data
107	No data	234	No data	361	97
108	No data	235	No data	362	94
109	No data	236	No data	363	95
110	No data	237	103	364	97
111	No data	238	97	365	99
112	No data	239	No data	366	99
113	No data	240	No data	367	100
114	No data	241	105 100 102	368	87
115	No data	242	104	369	97
116	No data	243	116	370	98
117	No data	244	111	371	98

Example	% Inhibition	Example	% Inhibition	Example	% Inhibition
118	No data	245	105	372	98
119	No data	246	104	373	94
120	No data	247	115	374	86
121	No data	248	103	375	99
122	95	249	113	376	108
123	95	250	112	377	106
124	87	251	113	378	107
125	93	252	105	379	97
126	117	253	No data	380	No data
127	117	254	No data		

Bacterial Susceptibility Testing Methods

Compounds may be tested for antimicrobial activity by susceptibility testing in liquid media. Compounds may be dissolved in dimethylsulfoxide and tested in 10 doubling dilutions in the susceptibility assays. The organisms used in the assay may be grown overnight on suitable agar media and then suspended in a liquid medium appropriate for the growth of the organism. The suspension can be a 0.5 McFarland and a further 1 in 10 dilution can be made into the same liquid medium to prepare the final organism suspension in 100 μL. Plates can be incubated under appropriate conditions at 37 °C for 24 hrs prior to reading. The Minimum Inhibitory Concentration (MIC) may be determined as the lowest drug concentration able to reduce growth by 80% or more.

In an assay comparable to the above, Example 9 had an MIC of 0.02 μM against *Streptococcus pneumoniae*.

According to a further feature of the invention there is provided a compound of the formula **(I)** or **(I')**, or a pharmaceutically-acceptable salt thereof, for use in a method of treatment of the human or animal body by therapy.

In one embodiment, the invention provides a method of treating a bacterial infection in an animal, such as a human, comprising administering to the animal or human an effective amount of a compound of any one of formulas **(I)** or **(I')**, or a pharmaceutically acceptable salt thereof.

We have found that compounds of the present invention inhibit bacterial DNA gyrase and / or topoisomerase IV and are therefore of interest for their antibacterial effects. In one aspect of the invention the compounds of the invention inhibit bacterial DNA gyrase and are therefore of interest for their antibacterial effects. In one aspect of the invention, the compounds of the invention inhibit topoisomerase IV and are therefore of interest for their antibacterial effects. In one aspect of the invention, the compounds of the invention inhibit both DNA gyrase and topoisomerase IV and are therefore of interest for their antibacterial effects. Thus, the compounds of the invention are useful in treating or preventing bacterial infections.

In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Acinetobacter baumanii*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Acinetobacter haemolyticus*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Acinetobacter junii*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Acinetobacter johnsonii*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Acinetobacter lwoffi*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Bacteroides bivius*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Bacteroides fragilis*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Burkholderia cepacia*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Campylobacter jejuni*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Chlamydia pneumoniae*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Chlamydia urealyticus*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Chlamydophila pneumoniae*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Clostridium difficile*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Enterobacter aerogenes*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Enterobacter cloacae*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Enterococcus faecalis*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Enterococcus faecium*. In one aspect of the invention an "infection" or "bacterial infection"

refers to an infection caused by *Escherichia coli*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Gardnerella vaginalis*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Haemophilus parainfluenzae*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Haemophilus influenzae*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Helicobacter pylori*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Klebsiella pneumoniae*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Legionella pneumophila*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Methicillin-resistant *Staphylococcus aureus*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Methicillin-susceptible *Staphylococcus aureus*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Moraxella catarrhalis*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Morganella morganii*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Mycoplasma pneumoniae*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Neisseria gonorrhoeae*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Penicillin-resistant *Streptococcus pneumoniae*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Penicillin-susceptible *Streptococcus pneumoniae*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Peptostreptococcus magnus*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Peptostreptococcus micros*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Peptostreptococcus anaerobius*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Peptostreptococcus asaccharolyticus*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Peptostreptococcus prevotii*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Peptostreptococcus tetradius*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Peptostreptococcus vaginalis*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Proteus mirabilis*. In one aspect of the invention an

"infection" or "bacterial infection" refers to an infection caused by *Pseudomonas aeruginosa*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Quinolone-Resistant *Staphylococcus aureus*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Quinolone-Resistant *Staphylococcus epidermis*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Salmonella typhi*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Salmonella paratyphi*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Salmonella enteritidis*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Salmonella typhimurium*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Serratia marcescens*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Staphylococcus aureus*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Staphylococcus epidermidis*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Staphylococcus saprophyticus*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Streptoccocus agalactiae*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Streptococcus pneumoniae*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Streptococcus pyogenes*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Stenotrophomonas maltophilia*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Ureaplasma urealyticum*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Vancomycin-Resistant *Enterococcus faecium*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Vancomycin-Resistant *Enterococcus faecalis*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Vancomycin-Resistant *Staphylococcus aureus*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Vancomycin-Resistant *Staphylococcus epidermis*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Mycobacterium tuberculosis. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Clostridium perfringens. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Klebsiella

oxytoca. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Neisseria miningitidis. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Fusobacterium spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Peptococcus spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Proteus vulgaris. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Coagulase-negative Staphylococcus (including Staphylococcus lugdunensis, Staphylococcus capitis, Staphylococcus hominis, and Staphylococcus saprophyticus).

In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Acinetobacter spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Bacteroides spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Burkholderia spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Campylobacter spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Chlamydia spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Chlamydophila spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Clostridium spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Enterobacter spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Enterococcus spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Escherichia spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Gardnerella spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Haemophilus spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Helicobacter spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Klebsiella spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Legionella spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Moraxella spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Morganella spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Mycoplasma spp. In one aspect of the invention an "infection" or "bacterial

infection" refers to an infection caused by Neisseria spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Peptostreptococcus spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Proteus spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Pseudomonas spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Salmonella spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Serratia spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Staphylococcus spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Streptoccocus spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Stenotrophomonas spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Ureaplasma spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by aerobes. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by obligate anaerobes. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by facultative anaerobes. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by gram-positive bacteria. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by gram-negative bacteria. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by gram-variable bacteria. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by atypical respiratory pathogens. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Enterics. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Shigella spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Citrobacter.

In one aspect of the invention "infection" or "bacterial infection" refers to a gynecological infection. In one aspect of the invention "infection" or "bacterial infection" refers to a respiratory tract infection (RTI). In one aspect of the invention "infection" or "bacterial infection" refers to a sexually transmitted disease. In one aspect of the invention "infection" or "bacterial infection" refers to a urinary tract infection. In one aspect of the invention "infection" or "bacterial infection" refers to acute exacerbation of chronic bronchitis (ACEB). In one aspect of the invention "infection" or "bacterial infection" refers to acute

otitis media. In one aspect of the invention "infection" or "bacterial infection" refers to acute sinusitis. In one aspect of the invention "infection" or "bacterial infection" refers to an infection caused by drug resistant bacteria. In one aspect of the invention "infection" or "bacterial infection" refers to catheter-related sepsis. In one aspect of the invention "infection" or "bacterial infection" refers to chancroid. In one aspect of the invention "infection" or "bacterial infection" refers to chlamydia. In one aspect of the invention "infection" or "bacterial infection" refers to community-acquired pneumonia (CAP). In one aspect of the invention "infection" or "bacterial infection" refers to complicated skin and skin structure infection. In one aspect of the invention "infection" or "bacterial infection" refers to uncomplicated skin and skin structure infection. In one aspect of the invention "infection" or "bacterial infection" refers to endocarditis. In one aspect of the invention "infection" or "bacterial infection" refers to febrile neutropenia. In one aspect of the invention "infection" or "bacterial infection" refers to gonococcal cervicitis. In one aspect of the invention "infection" or "bacterial infection" refers to gonococcal urethritis. In one aspect of the invention "infection" or "bacterial infection" refers to hospital-acquired pneumonia (HAP). In one aspect of the invention "infection" or "bacterial infection" refers to osteomyelitis. In one aspect of the invention "infection" or "bacterial infection" refers to sepsis. In one aspect of the invention "infection" or "bacterial infection" refers to syphilis. In one aspect of the invention "infection" or "bacterial infection" refers to ventilator-associated pneumonia. In one aspect of the invention "infection" or "bacterial infection" refers to intraabdominal infections. In one aspect of the invention "infection" or "bacterial infection" refers to gonorrhoeae. In one aspect of the invention "infection" or "bacterial infection" refers to meningitis. In one aspect of the invention "infection" or "bacterial infection" refers to tetanus. In one aspect of the invention "infection" or "bacterial infection" refers to tuberculosis.

In one embodiment, it is expected that the compounds of the present invention will be useful in treating bacterial infections including, but not limited to community-acquired pneumoniae, hospital-acquired pneumoniae, skin & skin structure infections, acute exacerbation of chronic bronchitis, acute sinusitis, acute otitis media, catheter-related sepsis, febrile neutropenia, osteomyelitis, endocarditis, urinary tract infections and infections caused by drug resistant bacteria such as Penicillin-resistant Streptococcus pneumoniae, methicillin-resistant Staphylococcus aureus, methicillin-resistant Staphylococcus epidermidis and Vancomycin-Resistant Enterococci.

According to a further feature of the present invention there is provided a method for producing an antibacterial effect in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the present invention, or a pharmaceutically-acceptable salt thereof.

According to a further feature of the invention there is provided a method for inhibition of bacterial DNA gyrase and / or topoisomerase IV in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula **(I)** or **(I')**, or a pharmaceutically acceptable salt thereof as defined hereinbefore.

According to a further feature of the invention there is provided a method of treating a bacterial infection in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula **(I)** or **(I')**, or a pharmaceutically acceptable salt thereof as defined hereinbefore.

According to a further feature of the invention there is provided a method of treating a bacterial infection selected from community-acquired pneumoniae, hospital-acquired pneumoniae, skin & skin structure infections, acute exacerbation of chronic bronchitis, acute sinusitis, acute otitis media, catheter-related sepsis, febrile neutropenia, osteomyelitis, endocarditis, urinary tract infections and infections caused by drug resistant bacteria such as Penicillin-resistant Streptococcus pneumoniae, methicillin-resistant Staphylococcus aureus, methicillin-resistant Staphylococcus epidermidis and Vancomycin-Resistant Enterococciin a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula **(I)** or **(I')**, or a pharmaceutically acceptable salt thereof as defined hereinbefore.

A further feature of the present invention is a compound of formula **(I)** or **(I')**, and pharmaceutically acceptable salts thereof for use as a medicament. Suitably the medicament is an antibacterial agent.

According to a further aspect of the invention there is provided the use of a compound of formula **(I)** or **(I')**, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the production of an anti-bacterial effect in a warm-blooded animal such as a human being.

According to a further aspect of the invention there is provided the use of a compound of formula **(I)** or **(I')**, or a pharmaceutically acceptable salt thereof, in the manufacture of a

medicament for use in inhibition of bacterial DNA gyrase and / or topoisomerase IV in a warm-blooded animal such as a human being.

Thus according to a further aspect of the invention there is provided the use of a compound of formula **(I)** or **(I')**, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of a bacterial infection in a warm-blooded animal such as a human being.

Thus according to a further aspect of the invention there is provided the use of a compound of formula **(I)** or **(I')**, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of a bacterial infection selected from community-acquired pneumoniae, hospital-acquired pneumoniae, skin & skin structure infections, acute exacerbation of chronic bronchitis, acute sinusitis, acute otitis media, catheter-related sepsis, febrile neutropenia, osteomyelitis, endocarditis, urinary tract infections and infections caused by drug resistant bacteria such as Penicillin-resistant Streptococcus pneumoniae, methicillin-resistant Staphylococcus aureus, methicillin-resistant Staphylococcus epidermidis and Vancomycin-Resistant Enterococci in a warm-blooded animal such as a human being.

According to a further aspect of the invention there is provided a compound of formula **(I)** or **(I')**, or a pharmaceutically acceptable salt thereof, for use in the production of an anti-bacterial effect in a warm-blooded animal such as a human being.

According to a further aspect of the invention there is provided a compound of formula **(I)** or **(I')**, or a pharmaceutically acceptable salt thereof, for use in inhibition of bacterial DNA gyrase and / or topoisomerase IV in a warm-blooded animal such as a human being.

Thus according to a further aspect of the invention there is provided a compound of formula **(I)** or **(I')**, or a pharmaceutically acceptable salt thereof, for use in the treatment of a bacterial infection in a warm-blooded animal such as a human being.

Thus according to a further aspect of the invention there is provided a compound of formula **(I)** or **(I')**, or a pharmaceutically acceptable salt thereof, for use in the treatment of a bacterial infection selected from community-acquired pneumoniae, hospital-acquired pneumoniae, skin & skin structure infections, acute exacerbation of chronic bronchitis, acute sinusitis, acute otitis media, catheter-related sepsis, febrile neutropenia, osteomyelitis, endocarditis, urinary tract infections and infections caused by drug resistant bacteria such as Penicillin-resistant Streptococcus pneumoniae, methicillin-resistant Staphylococcus aureus,

methicillin-resistant Staphylococcus epidermidis and Vancomycin-Resistant Enterococci in a warm-blooded animal such as a human being.

In order to use a compound of the formula **(I)** or **(I')**, or a pharmaceutically-acceptable salt thereof, (hereinafter in this section relating to pharmaceutical composition "a compound of this invention") for the therapeutic (including prophylactic) treatment of mammals including humans, in particular in treating infection, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the formula **(I)** or **(I')**, or a pharmaceutically-acceptable salt thereof, and a pharmaceutically-acceptable diluent or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula **(I)** or **(I')**, as defined hereinbefore or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable excipient or carrier for use in producing an anti-bacterial effect in an warm-blooded animal, such as a human being.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula **(I)** or **(I')**, as defined hereinbefore or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable excipient or carrier for use in inhibition of bacterial DNA gyrase and / or topoisomerase IV in an warm-blooded animal, such as a human being.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula **(I)** or **(I')**, as defined hereinbefore or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable excipient or carrier for use in the treatment of a bacterial infection in an warm-blooded animal, such as a human being.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula **(I)** or **(I')**, as defined hereinbefore or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable excipient or carrier for use in the treatment of a bacterial infection selected from community-acquired pneumoniae, hospital-acquired pneumoniae, skin & skin structure infections, acute exacerbation of chronic bronchitis, acute sinusitis, acute otitis media, catheter-related sepsis, febrile neutropenia, osteomyelitis, endocarditis, urinary tract infections and infections caused by drug resistant bacteria such as Penicillin-resistant Streptococcus pneumoniae, methicillin-

resistant Staphylococcus aureus, methicillin-resistant Staphylococcus epidermidis and Vancomycin-Resistant Enterococci in an warm-blooded animal, such as a human being.

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 together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example

heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

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

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, 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 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The compounds of the invention described herein may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. Where the administration is sequential or separate, the delay in administering the second component should not be such as to lose the beneficial effect of the combination. Suitable classes and substances may be selected from one or more of the following:

i) other antibacterial agents for example macrolides e.g. erythromycin, azithromycin or clarithromycin; quinolones e.g. ciprofloxacin or levofloxacin; ß-lactams e.g. penicillins e.g.

amoxicillin or piperacillin; cephalosporins e.g. ceftriaxone or ceftazidime; carbapenems, e.g. meropenem or imipenem etc; aminoglycosides e.g. gentamicin or tobramycin; or oxazolidinones; and/or

ii) anti-infective agents for example, an antifungal triazole e.g. or amphotericin; and/or

iii) biological protein therapeutics for example antibodies, cytokines, bactericidal/permeability-increasing protein (BPI) products; and/or

iv) efflux pump inhibitors.

Therefore, in a further aspect of the invention there is provided a compound of the formula **(I)** or **(I')**, or a pharmaceutically acceptable salt thereof, and a chemotherapeutic agent selected from:

i) one or more additional antibacterial agents; and/or

ii) one or more anti-infective agents; and/or

iii) biological protein therapeutics for example antibodies, cytokines, bactericidal/permeability-increasing protein (BPI) products; and/or

iv) one or more efflux pump inhibitors.

In another embodiment, the invention relates to a method of treating a bacterial infection in an animal, such as a human, comprising administering to the animal an effective amount of a compound of formula **(I)** or **(I')**, or a pharmaceutically acceptable salt thereof, and a chemotherapeutic agent selected from:

i) one or more additional antibacterial agents; and/or

ii) one or more anti-infective agents; and/or

iii) biological protein therapeutics for example antibodies, cytokines, bactericidal/permeability-increasing protein (BPI) products; and/or

iv) one or more efflux pump inhibitors.

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, the severity of the illness being treated, and whether or not an additional chemotherapeutic agent is administered in combination with a compound of the invention. Preferably a daily dose in the range of 1-50 mg/kg is employed. However the daily

dose will necessarily be varied depending upon the host treated, the particular route of administration, the severity of the illness being treated, and whether or not an additional chemotherapeutic agent is administered in combination with a compound of the invention. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

As noted above, one embodiment of the present invention is directed to treating or preventing diseases caused by bacterial infections, wherein the bacteria comprise a GyrB ATPase or topoisomerase IV ATPase enzyme. "Treating a subject with a disease caused by a bacterial infection" includes achieving, partially or substantially, one or more of the following: the reducing or amelioration of the progression, severity and/or duration of the infection, arresting the spread of an infection, ameliorating or improving a clinical symptom or indicator associated with a the infection (such as tissue or serum components), and preventing the reoccurrence of the infection.

As used herein, the terms "preventing a bacterial infection" refer to the reduction in the risk of acquiring the infection, or the reduction or inhibition of the recurrence of the infection. In a preferred embodiment, a compound of the invention is administered as a preventative measure to a patient, preferably a human, before a surgical procedure is preformed on the patient to prevent infection.

As used herein, the term "effective amount" refers to an amount of a compound of this invention for treating or preventing a bacterial infection is an amount which is sufficient to prevent the onset of an infection, reduce or ameliorate the severity, duration, or progression, of an infection, prevent the advancement of an infection, cause the regression of an infection, prevent the recurrence, development, onset or progression of a symptom associated with an infection, or enhance or improve the prophylactic or therapeutic effect(s) of another therapy.

In addition to its use in therapeutic medicine, compounds of formula **(I)**, and their 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 and / or topoisomerase IV in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

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

Example

The invention is now illustrated but not limited by the following Example in which unless otherwise stated :-

(i) evaporations were carried out by rotary evaporation *in-vacuo* and work-up procedures were carried out after removal of residual solids by filtration;

(ii) operations were generally carried out at ambient temperature, that is typically in the range 18-26 °C and without exclusion of air unless otherwise stated, or unless the skilled person would otherwise work under an inert atmosphere;

(iii) column chromatography (by the flash procedure) was used to purify compounds and was performed on Merck Kieselgel silica (Art. 9385) unless otherwise stated;

(iv) yields are given for illustration only and are not necessarily the maximum attainable; the structure of the end-products of the invention were generally confirmed by NMR and mass spectral techniques; proton magnetic resonance spectra is quoted and was generally determined in DMSO-d_6 unless otherwise stated using a Bruker DRX-300 spectrometer operating at a field strength of 300 MHz. Chemical shifts are reported in parts per million downfield from tetramethysilane as an internal standard (δ scale) and peak multiplicities are shown thus: s, singlet; d, doublet; AB or dd, doublet of doublets; dt, doublet of triplets; dm, doublet of multiplets; t, triplet, m, multiplet; br, broad; fast-atom bombardment (FAB) mass spectral data were generally obtained using a Platform spectrometer (supplied by Micromass) run in electrospray and, where appropriate, either positive ion data or negative ion data were collected or using Agilent 1100series LC/MSD equipped with Sedex 75ELSD, run in atmospheric pressure chemical ionization mode and, where appropriate, either positive ion data or negative ion data were collected; mass spectra were run with an electron energy of 70 electron volts in the chemical ionization (CI) mode using a direct exposure probe; where indicated ionization was effected by electron impact (EI), fast atom bombardment (FAB) or electrospray (ESP); values for m/z are given; generally, only ions which indicate the parent mass are reported;

(vi) each intermediate was purified to the standard required for the subsequent stage and was characterized in sufficient detail to confirm that the assigned structure was correct; purity was assessed by high pressure liquid chromatography, thin layer chromatography, or NMR and identity was determined by infra-red spectroscopy (IR), mass spectroscopy or NMR spectroscopy as appropriate;

(vii) the following abbreviations may be used:

ACN is acetonitrile;

$CDCl_3$ is deuterated chloroform;

DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene;

DCM is dichloromethane;

DIEA is diisopropyl ethylamine;

DMF is *N,N*-dimethylformamide;

DMSO is dimethylsulfoxide;

EDC is 1-ethyl-3-(3-dimethyllaminopropyl)carbodiimide;

EtOAc is ethyl acetate;

EtOH is ethanol;

HATU is N-[(dimethylamino)-1H,2,3-triazolo[4,5-b-]pyridin-1-ylmethylene]-N-methylmethanaminium hexafluorophosphate N-oxide;

HOBT is 1-hydroxybenzotriazole;

MeOH is methanol;

MS is mass spectroscopy;

RT or rt is room temperature;

SM is starting material;

TFA is trifluoroacetic acid;

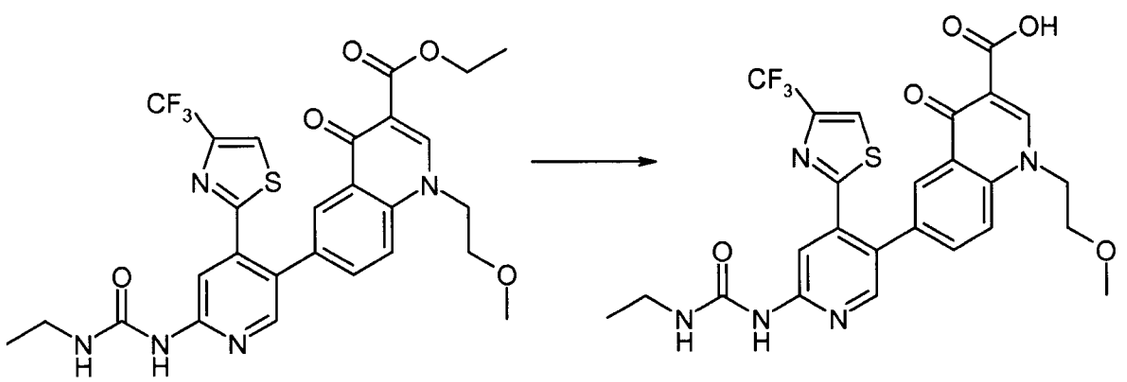
TFAA is trifluoroacetic anhydride;

THF is tetrahydrofuran; and

(viii) temperatures are quoted as °C.

Example 1

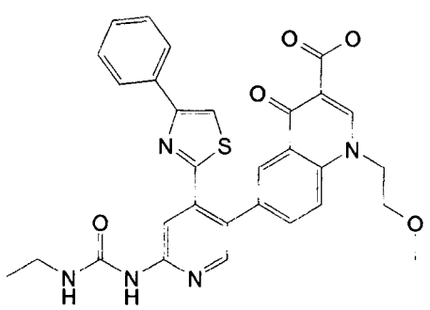
6-(6-(3-Ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(2-methoxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

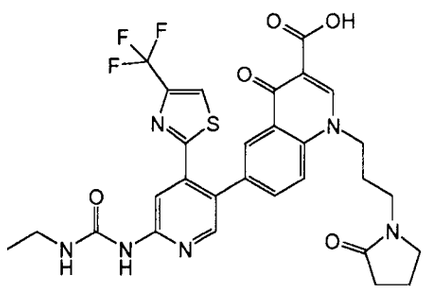
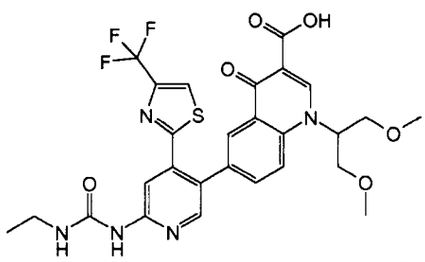


Ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(2-methoxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (Example 51, 0.090 g, 0.15 mmol) and LiOH (0.092 mL, 0.18 mmol) were combined in MeOH (1 mL)/THF (1 mL) and heated to 100 °C in the microwave for 15 min. The reaction mixture was cooled to room temperature, diluted with water (1.000 mL) and heated until the compound dissolved. The resulting solution was filtered and the filtrate was then concentrated under reduced pressure to remove methanol. HCl (1 N) was added and the resulting precipitate was collected by filtration, washed with water and dried overnight to yield a white solid (0.063g).
MS (ES) $(M+H)^+$: 562 for $C_{25}H_{22}F_3N_5O_5S$;
NMR: 1.11 (t, 3H), 3.19-3.23 (m, 5H), 3.71 (d, 2H), 4.81 (q, 2H), 7.60 (dd, 1H), 7.86 (d, 1H), 8.12 (d, 1H), 8.22 (s, 1H), 8.31 (s, 1H), 8.38 (s, 1H), 8.52 (s, 1H), 8.96 (s, 1H), 8.49 (s, 1H).

Examples 2-4

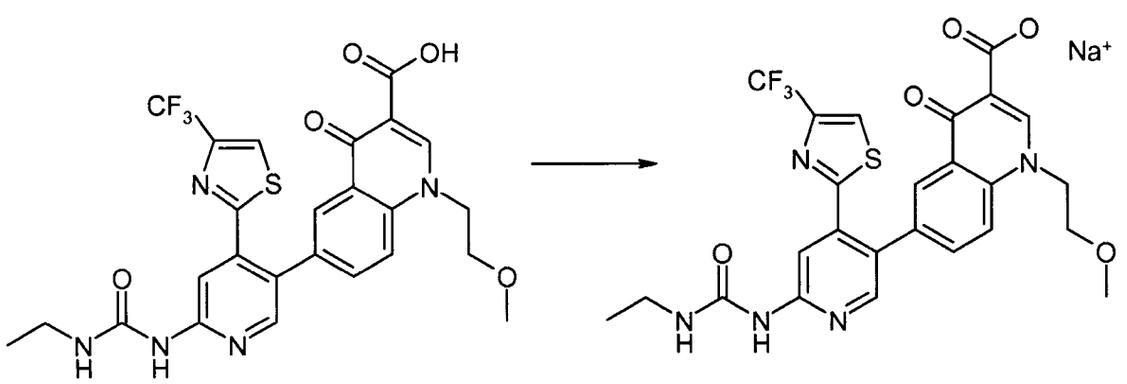
The following Examples were prepared by the procedure described in Example 1 from the starting materials (SM) indicated.

Ex	Compound	Data	SM
2	6-(6-(3-ethylureido)-4-(4-phenylthiazol-2-yl)pyridin-3-yl)-1-(2-methoxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ES) $(M+H)^+$: 570 for $C_{30}H_{27}N_5O_5S$ NMR: 1.12 (t, 3H), 3.18-3.21 (m, 5H), 3.69 (t, 2H), 4.63 (q, 2H), 7.31-7.39 (m, 3H), 7.75-7.83 (m, 4H), 7.88 (d, 1H), 8.14 (s, 1H), 8.29 (s, 3H), 8.81 (s, 1H), 9.47 (s, 1H).	Example 52

Ex	Compound	Data	SM
3	6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(3-(2-oxopyrrolidin-1-yl)propyl)-1,4-dihydroquinoline-3-carboxylic acid 	MS (ES) $(M+H)^+$: 629 for $C_{29}H_{27}F_3N_6O_5S$	Example 53
4	1-(1,3-dimethoxypropan-2-yl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ES) $(M+H)^+$: 606 for $C_{27}H_{26}F_3N_5O_6S$	Example 54

Example 5

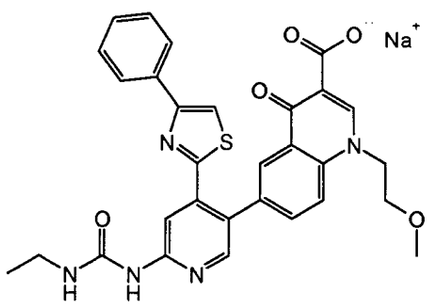
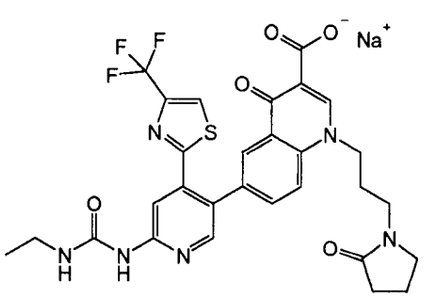
Sodium 6-(6-(3-Ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(2-methoxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate

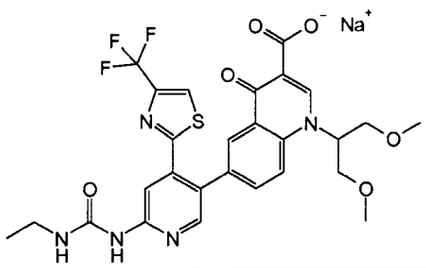


6-(6-(3-Ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(2-methoxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (0.032 g, 0.06 mmol, Example 1) was suspended in MeOH (1.0 mL)/THF (1.0 mL). 1N NaOH (0.057 mL, 0.06 mmol) was added. Once in solution, the reaction mixture was concentrated under reduced pressure and dried for several hours to yield a white solid (0.030g).

Examples 6-8

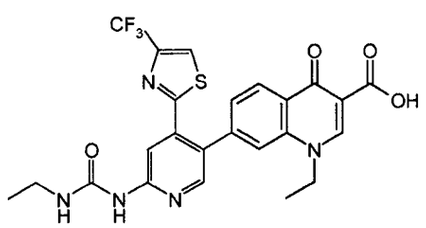
The following Examples were prepared by the procedure described in Example 5 from the starting materials (SM) indicated.

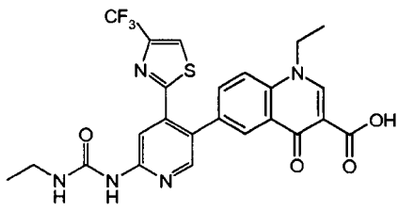
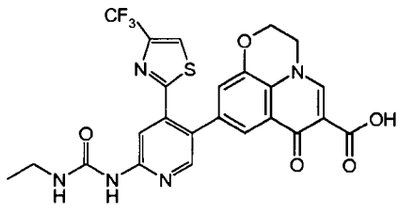
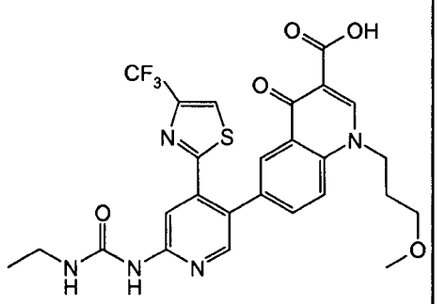
Ex	Compound	Data	SM
6	sodium 6-(6-(3-ethylureido)-4-(4-phenylthiazol-2-yl)pyridin-3-yl)-1-(2-methoxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ES) $(M+H)^+$: 570 for $C_{30}H_{27}N_5O_5S$[Na+] NMR: 1.12 (t, 3H), 3.18-3.21 (m, 5H), 3.69 (t, 2H), 4.60 (q, 2H), 7.31-7.39 (m, 3H), 7.75-7.83 (m, 4H), 7.88 (d, 1H), 8.14 (s, 1H), 8.29 (s, 3H), 8.81 (s, 1H), 9.49 (s, 1H).	Example 2
7	6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(3-(2-oxopyrrolidin-1-yl)propyl)-1,4-dihydroquinoline-3-carboxylic acid sodium 	MS (ES) $(M+H)^+$: 629 for $C_{29}H_{27}F_3N_6O_5S$ [Na+] NMR: 1.11 (t, 3H), 1.94 (m, 5H), 2.22 (t, 3H), 3.31-3.36 (m, 4H), 4.35 (q, 2H), 7.60 (d, 1H), 7.80 (d, 1H), 8.20 (m, 1H), 8.25 (s, 1H), 8.32 (s, 1H), 8.38 (s, 1H), 8.44 (s, 1H), 8.66 (s, 1H), 10.18 (s, 1H).	Example 3

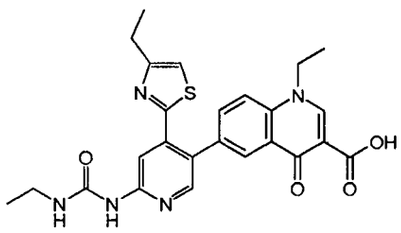
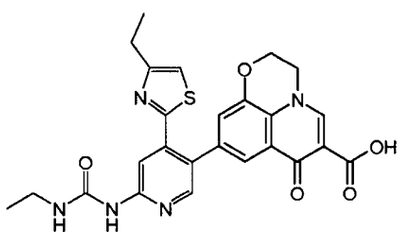
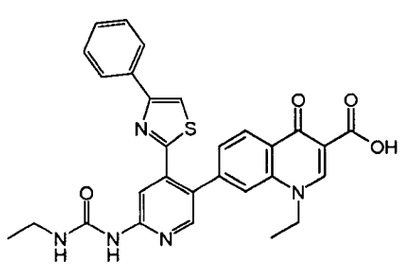
Ex	Compound	Data	SM
8	1-(1,3-dimethoxypropan-2-yl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ES) $(M+H)^+$: 570 for $C_{27}H_{26}F_3N_5O_6S \cdot [Na+]$	Example 4

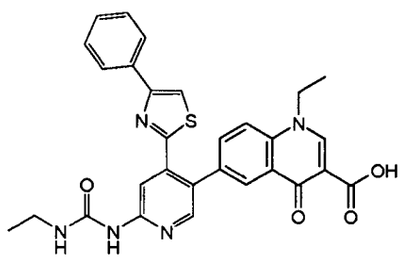
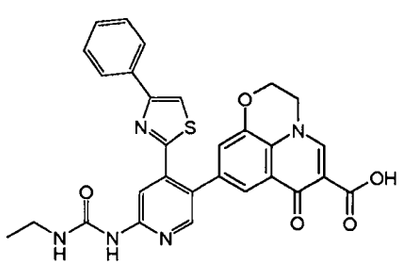
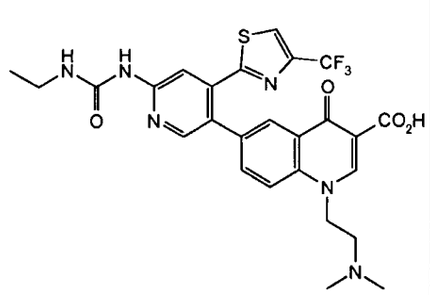
Examples 9-32

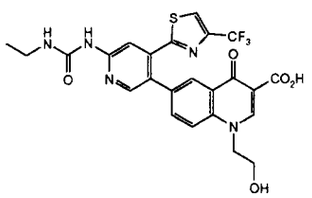
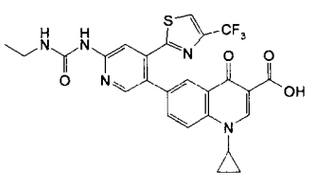
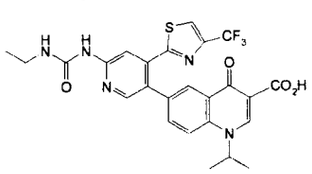
The following Examples were prepared by the procedure described in Example 1 from the starting materials (SM) indicated.

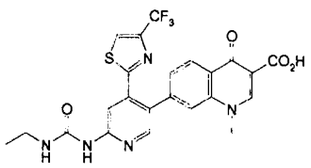
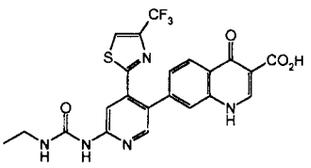
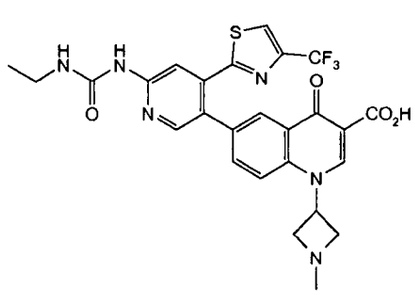
Ex	Compound	Data	SM
9	1-ethyl-7-(6-(3-ethylureido)-4-(4-trifluoromethylthiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 532 (MH^+) for $C_{24}H_{20}F_3N_5O_4S$ ^1H NMR (d_6-DMSO): δ 1.11 (t, 3H), 1.24 (t, 3H), 3.21 (m, 2H), 4.58 (q, 2H), 7.56-7.61 (m, 2H), 8.07 (d, 1H), 8.24 (s, 1H), 8.38-8.42 (m, 2H), 8.51 (d, 1H), 9.09 (s, 1H), 9.55 (s, 1H)	Example 42

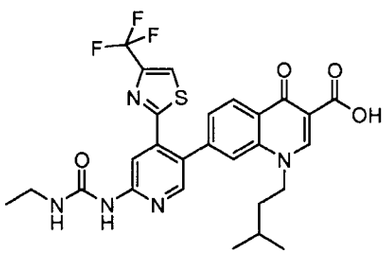
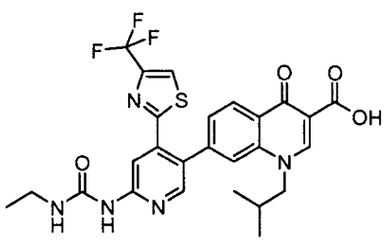
Ex	Compound	Data	SM
10	1-ethyl-6-(6-(3-ethylureido)-4-(4-trifluoromethylthiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 532 (MH^+) for $C_{24}H_{20}F_3N_5O_4S$ ^1H NMR (d_6-DMSO): δ 1.11 (t, 3H), 1.40 (t, 3H), 3.20 (m, 2H), 4.64 (q, 2H), 7.63 (bt, 1H), 7.85 (d, 1H), 8.11 (d, 1H), 8.23 (s, 1H), 8.32 (d, 1H), 8.37 (s, 1H), 8.51 (d, 1H), 9.11 (s, 1H), 9.51 (s, 1H)	Example 45
11	9-(6-(3-ethylureido)-4-(4-trifluoromethylthiazol-2-yl)pyridin-3-yl)-7-oxo-3,7-dihydro-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acid 	MS (ESP): 546 (MH^+) for $C_{24}H_{18}F_3N_5O_5S$ ^1H NMR (d_6-DMSO): δ 1.11 (t, 3H), 3.17-3.24 (m, 2H), 4.51-4.69 (m, 4H), 7.45 (d, 1H), 7.62 (bt, 1H), 7.80 (d, 1H), 8.22 (s, 1H), 8.32 (s, 1H), 8.53 (d, 1H), 8.99 (s, 1H), 9.48 (s, 1H).	Example 48
12	6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(3-methoxypropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 576 (MH^+) for $C_{26}H_{24}F_3N_5O_5S$ ^1H NMR (300 MHz, DMSO-d6) δ 1.11 t, J = 7 Hz, 3H), 2.05 (m, 2H), 3.18 (m, 4H), 3.20 (s, 3H), 4.65 (m, 2H), 7.61 (m, 1H), 7.88 (m, 1H), 8.05 (m, 1H), 8.22 (s, 1H), 8.34 (m, 1H), 8.37 (s, 1H), 8.52 (s, 1H), 9.02 (s, 1H), 9.49 (s, 1H), 15.06 (br s, 1H).	Example 55

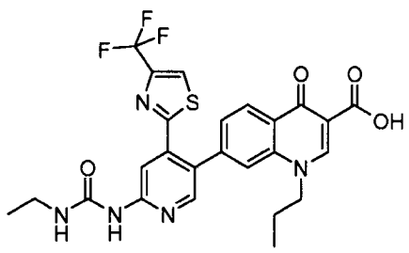
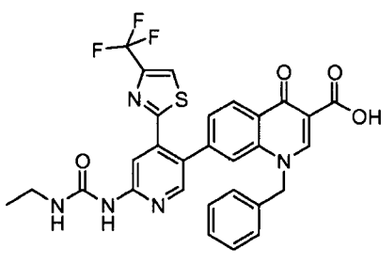
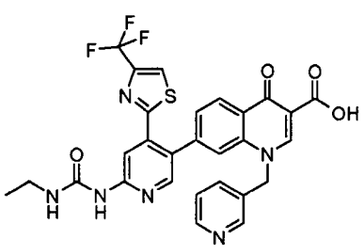
Ex	Compound	Data	SM
13	1-ethyl-6-(6-(3-ethylureido)-4-(4-ethylthiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 492 (MH^+) for $C_{25}H_{25}N_5O_4S$ ^1H NMR (d_6-DMSO): δ 1.02-1.14 (m, 6H), 1.43 (t, 3H), 2.64 (q, 2H), 3.23 (m, 2H), 4.63 (q, 2H), 7.35 (s, 1H), 7.72 (bt, 1H), 7.82 (d, 1H), 8.07 (d, 1H), 8.13 (s, 1H), 8.26-8.30 (m, 2H), 9.10 (s, 1H), 9.43 (s, 1H)	Example 46
14	9-(6-(3-ethylureido)-4-(4-ethylthiazol-2-yl)pyridin-3-yl)-7-oxo-3,7-dihydro-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acid 	MS (ESP): 506 (MH^+) for $C_{25}H_{23}N_5O_5S$ ^1H NMR (d_6-DMSO): δ 1.11 (t, 6H), 2.67 (q, 2H), 3.21 (m, 2H), 4.58 (m, 4H), 7.37 (m, 2H), 7.73 (bt, 1H), 7.76 (d, 1H), 8.12 (s, 1H), 8.26 (s, 1H), 8.98 (s, 1H), 9.42 (s, 1H)	Example 49
15	1-ethyl-7-(6-(3-ethylureido)-4-(4-phenylthiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 540 (MH^+) for $C_{29}H_{25}N_5O_4S$ ^1H NMR (d_6-DMSO): δ 1.08-1.27 (m, 6H), 3.15-3.24 (m, 2H), 4.58 (bq, 2H), 7.26-7.35 (m, 3H), 7.59 (d, 1H), 7.61-7.70 (m, 3H), 8.08 (s, 1H), 8.18 (s, 1H), 8.27 (s, 1H), 8.35-8.41 (m, 2H), 9.08 (s, 1H), 9.51 (s, 1H)	Example 44

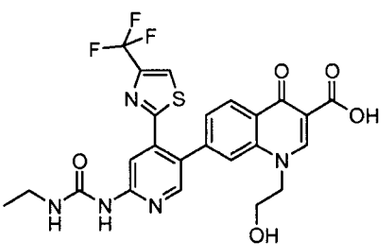
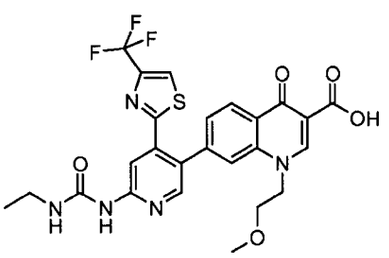
Ex	Compound	Data	SM
16	1-ethyl-6-(6-(3-ethylureido)-4-(4-phenylthiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 540 (MH^+) for $C_{29}H_{25}N_5O_4S$ ^{1}H NMR (d_6-DMSO): δ 1.12 (t, 3H), 1.41 (t, 3H), 3.16-3.28 (m, 2H), 4.60 (bq, 2H), 7.31-7.39 (m, 3H), 7.71-7.81 (m, 4H), 8.05 (d, 1H), 8.17 (s, 1H), 8.29-8.36 (m, 2H), 9.05 (s, 1H), 9.61 (br s, 1H)	Example 47
17	9-(6-(3-ethylureido)-4-(4-phenylthiazol-2-yl)pyridin-3-yl)-7-oxo-3,7-dihydro-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acid 	MS (ESP): 554 (MH^+) for $C_{29}H_{23}N_5O_5S$ ^{1}H NMR (d_6-DMSO): δ 1.09 (t, 3H), 3.19-3.26 (m, 2H), 4.59 (m, 4H), 7.34-7.38 (m, 3H), 7.43 (d, 1H), 7.70 (bt, 1H), 7.80 (d, 1H), 7.83 (d, 1H), 7.87 (d, 1H), 8.18 (s, 1H), 8.26 (s, 1H), 8.29 (s, 1H), 8.99 (s, 1H), 9.45 (s, 1H)	Example 50
18	1-(2-(dimethylamino)ethyl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 575 (M+1) for $C_{26}H_{25}F_3N_6O_4S$ ^{1}H-NMR (DMSO-d_6): 1.11 (t, J=7.20 Hz, 3H); 2.87 (br. s., 6H); 3.13 - 3.28 (m, 2H); 3.57 (br. s., 2H); 5.01 (br. s., 2H); 7.64 (br. s., 1H); 7.92 (dd, J=8.72, 1.64 Hz, 1H); 8.14 - 8.28 (m, 2H); 8.28 - 8.41 (m, 2H); 8.54 (s, 1H); 9.17 (s, 1H); 9.51 (s, 1H); 10.74 (br. s., 1H); 14.91 (br. s., 1H)	Example 56

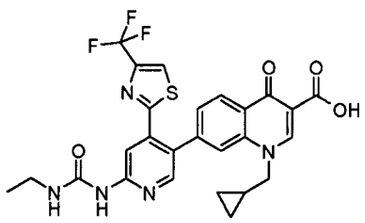
Ex	Compound	Data	SM
19	6-(6-(3-Ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 548 (M+1) for $C_{24}H_{20}F_3N_5O_5S$ ^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, *J*=7.20 Hz, 3H); 3.15 - 3.28 (m, 2H); 3.73 - 3.83 (m, 2H); 4.59 - 4.72 (m, 2H); 5.10 (t, *J*=5.56 Hz, 1H); 7.62 (br. s., 1H); 7.86 (dd, *J*=8.97, 2.15 Hz, 1H); 8.13 (d, *J*=8.84 Hz, 1 H); 8.23 (s, 1H); 8.33 (d, *J*=2.27 Hz, 1H); 8.37 (s, 1 H); 8.52 (s, 1H); 8.94 (s, 1 H)	Example 57
20	1-Cyclopropyl-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 544 (M+1) for $C_{25}H_{20}F_3N_5O_4S$ ^{1}H-NMR (DMSO-d_6): 1.11 (t, *J*=7.20 Hz, 3H); 1.16 - 1.25 (m, 2H); 1.29 - 1.38 (m, 2H); 3.15 - 3.28 (m, 2H); 3.83 - 3.93 (m, 2H); 7.56 - 7.66 (m, 1H); 7.92 (dd, *J*=8.84, 2.02 Hz, 1 H); 8.23 (s, 1H); 8.27 - 8.39 (m, 2H); 8.52 (s, 1H); 8.80 (s, 1H); 9.48 (s, 1H)	Example 58
21	6-(6-(3-Ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-isopropyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 546 (M+1) for $C_{25}H_{22}F_3N_5O_4S$ ^{1}H-NMR (DMSO-d_6): 1.11 (t, *J*=7.20 Hz, 3H); 1.54 (d, *J*=5.81 Hz, 6H); 3.14 - 3.26 (m, 2H); 5.10 - 5.29 (m, 1H); 7.51 - 7.82 (m, 2H); 8.09 (br. s., 1H); 8.25 (s, 1H); 8.28 - 8.39 (m, 2H); 8.45 (br. s., 1H); 8.95 (s, 1H); 9.46 (s, 1H)	Example 59

Ex	Compound	Data	SM
22	7-(6-(3-Ethylureido)-4(4-(trifluoromethyl) thiazol-2-yl)pyridin-3-yl)-1-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 518 (M+1) $C_{23}H_{18}F_3N_5O_4S$ ^{1}H-NMR (DMSO-d_6): 1.11 (t, *J*=7.20 Hz, 3H); 3.15 - 3.26 (m, 2H); 4.08 (s, 3H); 7.51 (d, *J*=7.83 Hz, 1H); 7.55 - 7.63 (m, 1H); 8.04 (s, 1 H); 8.24 (s, 1H); 8.34 (d, *J*=8.34 Hz, 1H); 8.45 (s, 1 H); 8.53 (s, 1H); 9.08 (s, 1 H); 9.53 (s, 1H); 15.18 (s, 1H)	Example 60
23	7-(6-(3-Ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 504 (M+1) $C_{22}H_{16}F_3N_5O_4S$ ^{1}H-NMR (DMSO-d_6): 1.11 (t, *J*=7.07 Hz, 3H); 3.09 - 3.28 (m, 2H); 7.50 (d, *J*=8.34 Hz, 1H); 7.53 - 7.64 (m, 1H); 7.76 (s, 1H); 8.24 (s, 1H); 8.30 (d, *J*=8.34 Hz, 1H); 8.37 (s, 1H); 8.52 (s, 1H); 8.89 -9.00 (m, 1H); 9.51 (s, 1H); 13.43 (br. s., 1H)	Example 61
24	6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-methylazetidin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 573 (M+1) for $C_{26}H_{23}F_3N_6O_4S$ ^{1}H NMR (DMSO-d_6): 1.11 (t, J=7.07 Hz, 3H); 2.33 (s, 3H); 3.14 - 3.27 (m, 2H); 3.35 - 3.46 (m, 2H); 3.90 (t, J=6.69 Hz, 2H); 5.19 - 5.33 (m, 1H); 7.64 - 7.92 (m, 3H); 8.23 - 8.40 (m, 3H); 8.49 (s, 1H); 8.87 (s, 1H); 9.80 (br s, 1H)	Example 62

Ex	Compound	Data	SM
25	7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-1-(3-methylbutyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	^{1}H NMR (400 MHz, DMSO-d_6): 0.83 (d, 6H), 1.13 (t, 3H), 1.44 (q, 2H), 1.55 (m, 1H), 3.21 (q, 2H), 4.52 (t, 2H), 7.56 (m, 1H), 7.63 (d, 1H), 7.93 (s, 1H), 8.25 (s, 1H), 8.40 (s, 1H), 8.43 (d, 1H), 8.51 (s, 1H), 9.06 (s, 1H), 9.48 (s, 1H).	Example 63
26	7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-1-(2-methylpropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	^{1}H NMR (400 MHz, DMSO-d_6): 0.75 (d, 6H), 1.13 (t, 3H), 1.64 (m, 1H), 3.21 (q, 2H), 4.33 (d, 2H), 7.59 (m, 4H), 7.94 (s, 1H), 8.19 (s, 1H), 8.40 (s, 1H), 8.43 (d, 1H), 8.53 (s, 1H), 9.00 (s, 1H), 9.49 (s, 1H).	Example 64

Ex	Compound	Data	SM
27	7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-4-oxo-1-propyl-1,4-dihydroquinoline-3-carboxylic acid 	^{1}H NMR (400 MHz, DMSO-d_6): 0.79 (t, 3H), 1.11 (t, 3H), 1.55 (q, 2H), 3.21 (q, 2H), 4.48 (t, 2H), 7.60 (m, 2H), 8.00 (s, 1H), 8.21 (s, 1H), 8.41 (t, 2H), 8.51 (s, 1H), 9.06 (s, 1H), 9.49 (s, 1H).	Example 65
28	1-benzyl-7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	^{1}H NMR (400 MHz, DMSO-d_6): 1.10 (t, 3H), 3.20 (q, 2H), 5.84 (s, 2H), 7.15 (t, 2H), 7.23 (m, 3H), 7.53 (d, 2H), 7.92 (s, 1H), 8.15 (s, 1H), 8.24 (s, 1H), 8.34 (s, 1H), 8.41 (d, 1H), 9.29 (s, 1H), 9.48 (s, 1H).	Example 66
29	7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-4-oxo-1-(pyridin-3-ylmethyl)-1,4-dihydroquinoline-3-carboxylic acid 	^{1}H NMR (400 MHz, DMSO-d_6): 0.85 (m, 3H), 1.10 (t, 3H), 3.19 (q, 2H), 5.92 (s, 2H), 7.39 (m, 1H), 7.54 (m, 2H), 7.67 (d, 1H), 7.96 (s, 1H), 8.17 (s, 1H), 8.25 (s, 1H), 8.36 (s, 1H), 8.41 (d, 1H), 8.50 (d, 1H), 8.57 (br s, 1H), 9.34 (s, 1H), 9.50 (s, 1H).	Example 67

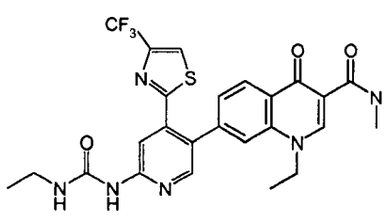
Ex	Compound	Data	SM
30	7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	^{1}H NMR (400 MHz, DMSO-d_6): 1.11 (t, 3H), 3.22 (q, 2H), 3.61 (q, 2H), 4.62 (s, 2H), 5.02 (s, 1H), 7.51 (d, 1H), 7.63 (s, 1H), 8.14 (s, 1H), 8.26 (s, 1H), 8.41 (d, 2H), 8.51 (s, 1H), 8.91 (s, 1H), 9.56 (s, 1H).	Example 68
31	7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-1-(2-methoxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	^{1}H NMR (400 MHz, DMSO-d_6): 1.11 (t, 3H), 3.21 (m, 5H), 3.50 (t, 2H), 4.75 (m, 2H), 7.58 (d, 2H), 8.12 (s, 1H), 8.24 (s, 1H), 8.40 (m, 2H), 8.52 (s, 1H), 8.92 (s, 1H), 9.49 (s, 1H).	Example 69

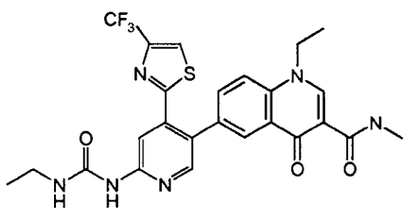
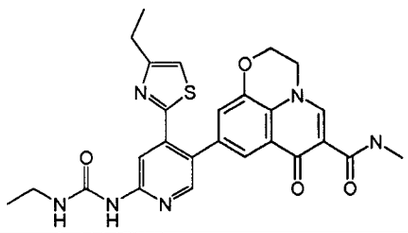
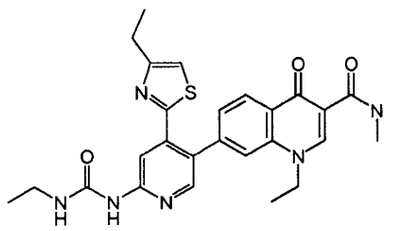
Ex	Compound	Data	SM
32	1-(cyclopropylmethyl)-7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	^{1}H NMR (400 MHz, DMSO-d_6): 0.44 (m, 4H), 1.09 (m, 1H), 1.11 (t, 3H), 3.22 (m, 3H), 4.42 (d, 2H), 7.61 (m, 2H), 8.13 (s, 1H), 8.21 (s, 1H), 8.40(s, 1H), 8.42 (s, 1H), 9.08 (s, 1H), 9.50 (s, 1H).	Example 70

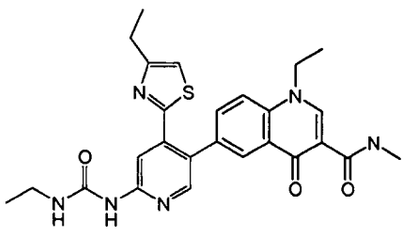
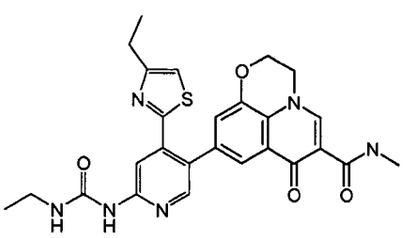
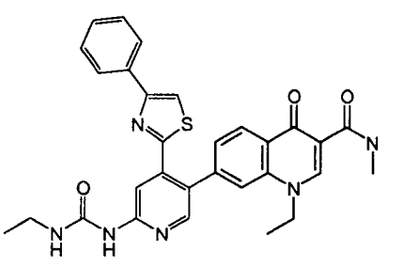
Examples 33-41

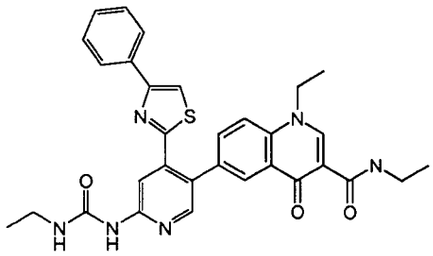
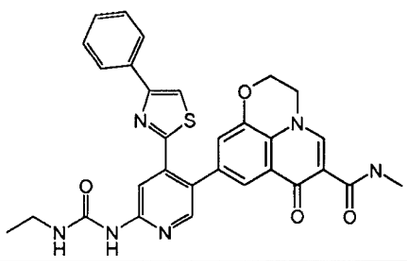
The following compounds were synthesized by the general procedure described below.

The ethyl ester starting material (SM) (0.09 mmol) was suspended in 33% methylamine in ethanol (3.5 ml). The resulting suspension was heated at 90°C in a microwave for 1.5 h. When the reaction was complete, the solution was cooled to room temperature, and methyl tert-butyl ether (4 ml) was added. The reaction mixture was allowed to stand for 1 h then filtered. The solid was washed with methyl *tert*-butyl ether (4 ml) and dried in a vacuum oven at 50°C for 4 hours.

Ex	Compound	Data	SM
33	1-ethyl-7-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-N-methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 545.1 (MH^+) for $C_{25}H_{23}F_3N_6O_3S$ ^{1}H NMR (d_6-DMSO): 1.11 (t, 3H), 1.24 (t, 3H), 3.21 (m, 2H), 4.58 (q, 2H), 7.45 (dd, 1H), 7.62 (br t, 1H), 7.91 (d, 1H), 8.22 (d, 1H), 8.34-8.40 (m, 2H), 8.48 (d, 1H), 8.89 (s, 1H), 9.50 (s, 1H), 9.78 (m, 1H)	Example 42

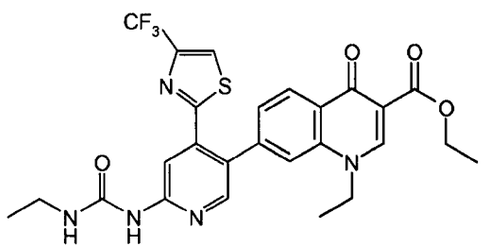
Ex	Compound	Data	SM
34	1-ethyl-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-N-methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 545.1 (MH^+) for $C_{25}H_{23}F_3N_6O_3S$ ^{1}H NMR (d_6-DMSO): 1.11 (t, 3H), 1.40 (t, 3H), 2.85 (d, 3H), 3.20 (m, 2H), 4.54 (q, 2H), 7.64 (br t, 1H), 7.68 (dd, 1H), 7.98 (d, 1H), 8.23-8.26 (m, 2H), 8.34 (d, 1H), 8.48 (d, 1H), 8.92 (s, 1H), 9.46 (s, 1H), 9.73 (d, 1H)	Example 45
35	N-methyl-9-(6-(3-ethylureido)-4-(4-trifluoromethylthiazol-2-yl)pyridin-3-yl)-7-oxo-3,7-dihydro-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide 	MS (ESP): 559.2 (MH^+) for $C_{25}H_{21}F_3N_6O_4S$ ^{1}H NMR (d_6-DMSO): 1.11 (t, 3H), 2.49 (d, 3H), 3.19-3.28 (m, 2H), 4.51-4.58 (br s, 4H), 7.32 (d, 1H), 7.63 (br t, 1H), 7.73 (d, 1H), 8.22 (s, 1H), 8.29 (s, 1H), 8.50 (d, 1H), 8.79 (s, 1H), 9.45 (s, 1H), 9.72 (d, 1H)	Example 48
36	1-ethyl-7-(4-(4-ethylthiazol-2-yl)-6-(3-ethylureido)pyridin-3-yl)-N-methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 505.2 (MH^+) for $C_{26}H_{28}N_6O_3S$ ^{1}H NMR (d_6-DMSO): 1.00-1.16 (m, 9H), 2.64 (q, 2H), 2.87 (d, 3H), 3.24 (q, 2H), 4.46 (q, 2H), 7.34 (s, 1H), 7.39 (d, 1H), 7.73 (m, 1H), 7.82 (s, 1H), 8.11 (s, 1H), 8.33-8.36 (m, 2H), 8.87 (s, 1H), 9.44 (s, 1H), 9.80 (d, 1H)	Example 43

Ex	Compound	Data	SM
37	1-ethyl-6-(4-(4-ethylthiazol-2-yl)-6-(3-ethylureido)pyridin-3-yl)-N-methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 505.2 (MH^+) $C_{26}H_{28}N_6O_3S$ ^{1}H NMR (d_6-DMSO): 1.00-1.14 (m, 6H), 1.40 (t, 3H), 2.65 (q, 2H), 2.85 (d, 3H), 3.21 (m, 2H), 4.53 (q, 2H), 7.33 (s, 1H), 7.68-7.72 (m, 2H), 7.93 (d, 1H), 8.13 (s, 1H), 8.21 (d, 1H), 8.26 (s, 2H), 8.90 (s, 1H), 9.43 (s, 1H), 9.76 (m, 1H)	Example 46
38	9-(4-(4-ethylthiazol-2-yl)-6-(3-ethylureido)pyridin-3-yl)-N-methyl-7-oxo-3,7-dihydro-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide 	MS (ESP): 518.3 (MH^+) for $C_{26}H_{26}N_6O_4S$ ^{1}H NMR (d_6-DMSO): 1.06-1.16 (m, 6H), 2.50 (q, 2H), 2.85 (d, 3H), 3.16-3.22 (m, 2H), 4.52 (br s, 4H), 7.24 (d, 1H), 7.33 (s, 1H), 7.70 (d, 1H), 7.76 (br t, 1H), 8.12 (s, 1H), 8.23 (s, 1H), 8.78 (s, 1H), 9.40 (s, 1H), 9.74 (m, 1H)	Example 49
39	1-ethyl-7-(6-(3-ethylureido)-4-(4-phenylthiazol-2-yl)pyridin-3-yl)-N-methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 553.2 (MH^+) for $C_{30}H_{28}N_6O_3S$ ^{1}H NMR (d_6-DMSO): 1.08-1.22 (m, 6H), 2.87 (d, 3H), 3.15-3.24 (m, 2H), 4.47 (br q, 2H), 7.26-7.42 (m, 3H), 7.47 (d, 1H), 7.72-7.76 (m, 3H), 7.93 (s, 1H), 8.16 (s, 1H), 8.26 (s, 1H), 8.33-8.37 (m, 2H), 8.88 (s, 1H), 9.48 (s, 1H), 9.81 (m, 1H)	Example 44

Ex	Compound	Data	SM
40	1-ethyl-6-(6-(3-ethylureido)-4-(4-phenylthiazol-2-yl)pyridin-3-yl)-N-methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 553.2 (MH^+) for $C_{30}H_{28}N_6O_3S$ ^{1}H NMR (d_6-DMSO): 1.12 (t, 3H), 1.41 (t, 3H), 3.16-3.28 (m, 2H), 4.60 (br q, 2H), 7.31-7.39 (m, 3H), 7.71-7.81 (m, 4H), 8.05 (d, 1H), 8.17 (s, 1H), 8.29-8.36 (m, 2H), 9.05 (s, 1H), 9.61 (br s, 1H)	Example 47
41	9-(6-(3-ethylureido)-4-(4-phenylthiazol-2-yl)pyridin-3-yl)-N-methyl-7-oxo-3,7-dihydro-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide 	MS (ESP): 567.3 (MH^+) for $C_{30}H_{26}N_6O_4S$ ^{1}H NMR (d_6-DMSO): 1.12 (t, 3H), 2.84 (d, 3H), 3.16-3.28 (m, 2H), 4.53 (br s, 4H), 7.35-7.44 (m, 4H), 7.77-7.85 (m, 4H), 8.17 (s, 1H), 8.26 (m, 2H), 8.79 (s, 1H), 9.47 (s, 1H), 9.75 (m, 1H)	Example 50

Example 42

Ethyl 1-ethyl-7-(6-(3-ethylureido)-4-(4-trifluoromethylthiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate



To a slurry of 6-(3-ethylureido)-4-(4-trifluoromethylthiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 17, 330 mg, 0.91mmol), ethyl 1-ethyl-7-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate (Intermediate 9, 281 mg, 0.75 mmol) and trans-

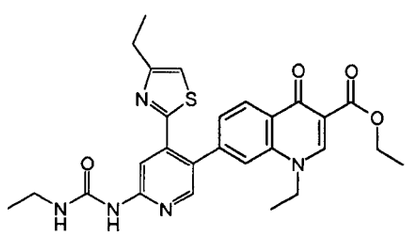
dichlorobis(triphenylphosphine)palladium (II) (53 mg, 0.075 mmol) in 1,4-dioxane (8 ml) was added a solution of potassium carbonate (210 mg, 1.52 mmol) in water (3 ml). The reaction was stirred for 1.5 hours at 70°C. The reaction was cooled to room temperature, and ethyl acetate (8 mL) was added to help separate the layers. The water was removed, and the organic phase was washed with water (3 mL). The reaction was then concentrated and ethanol (5 mL) was added. The suspension was filtered, and the solid washed with methyl *tert*-butyl ether (2 ×, 5 ml). The solid was dried in a vacuum oven at 50°C for 4 hours to give 195 mg (60%) of ethyl 1-ethyl-7-(6-(3-ethylureido)-4-(4-trifluoromethylthiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate as an off white solid.

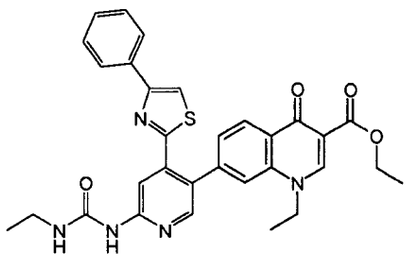
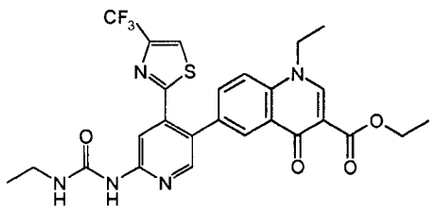
MS (ESP): 560 (MH^+) for $C_{26}H_{24}F_3N_5O_4S$

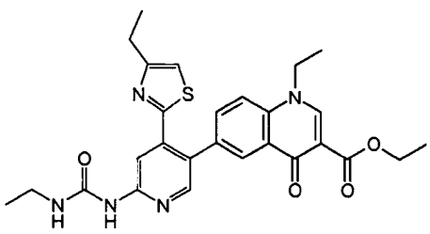
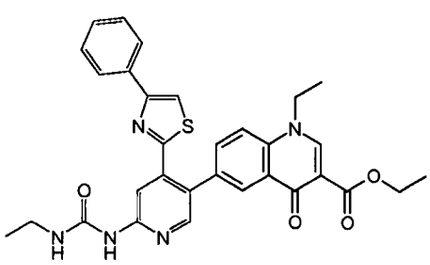
^1H NMR ($CDCl_3$): δ 1.24 (m, 3H), 1.28 9 (m, 6H), 3.50 (m, 2H), 4.20 (m, 2H), 4.42 (m, 2H), 7.34 (m, 2H), 7.53 (s, 1H), 7.72 (s, 1H), 8.29 (s, 1H), 8.53 (s, 1H) 8.59 (m, 1H), 9.03 (m, 1H).

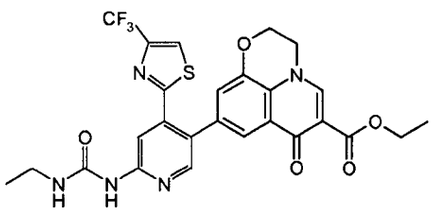
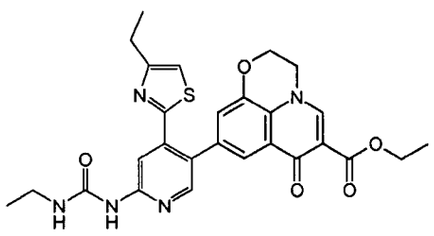
Examples 43-50

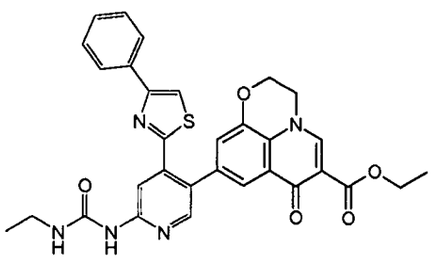
The following Examples were prepared by the procedure described in Example 42 from the starting materials (SM) indicated.

Ex	Compound	Data	SM
43	ethyl 1-ethyl-7-(6-(3-ethylureido)-4-(4-ethylthiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 520.2 (MH^+) for $C_{27}H_{29}N_5O_4S$	Intermediate 18 and Intermediate 9

Ex	Compound	Data	SM
44	ethyl 1-ethyl-7-(6-(3-ethylureido)-4-(4-phenylthiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 568.2 (MH^+) for $C_{31}H_{29}N_5O_4S$ ^1H NMR ($CDCl_3$): δ 1.22-1.35 (m, 6H), 1.42 (t, 3H), 3.40-3.52 (m, 2 H), 4.09 (q, 2H), 4.41 (q, 2 H), 7.27-7.41 (m, 5H), 7.61 (s, 1 H), 7.72 (m, 2H), 8.29 (s, 1H), 8.46 (s, 1H), 8.52-8.61 (m, 2H), 9.04 (br s, 1H)	Intermediate 19 and Intermediate 9
45	ethyl 1-ethyl-6-(6-(3-ethylureido)-4-(4-trifluoromethylthiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 560.1 (MH^+) for $C_{26}H_{24}F_3N_5O_4S$ ^1H NMR (d_6-DMSO): δ 1.12 (t, 3H), 1.26 (t, 3H), 1.39 (t, 3 H), 3.15-3.21 (m, 2 H), 4.24 (q, 3H), 4.44 (q, 2H), 7.64 (bt, 1H), 7.71 (d, 1H), 7.91 (d, 1 H), 8.18 (d, 1H), 8.23 (s, 1H), 8.33 (s, 1H), 8.42 (s, 1H), 8.72 (s, 1H), 9.42 (s, 1H)	Intermediate 17 and Intermediate 6

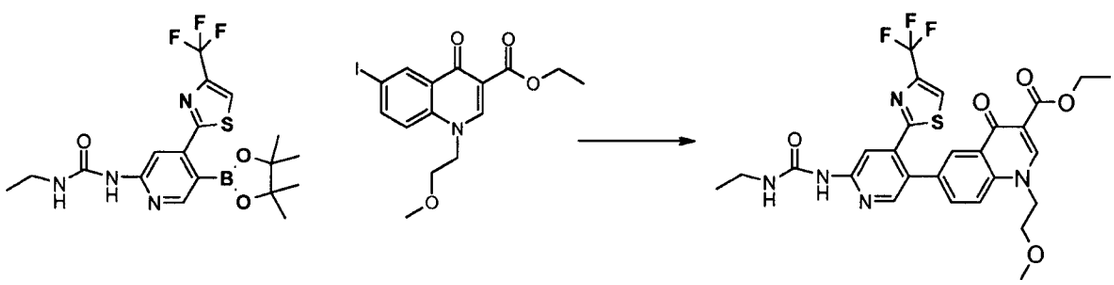
Ex	Compound	Data	SM
46	ethyl 1-ethyl-6-(6-(3-ethylureido)-4-(4-ethylthiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 520.1 (MH^+) for $C_{27}H_{29}N_5O_4S$ ^1H NMR (d_6-DMSO): δ 1.10 (m, 6H), 1.28 (t, 3H), 1.37 (t, 3 H), 2.68 (q, 2H), 3.14-3.21 (m, 2 H), 4.22 (q, 3H), 4.45 (q, 2H), 7.35 (s, 1H), 7.66 (d, 1H), 7.79 (bt, 1H), 7.84 (d, 1H), 8.15 (d, 1 H), 8.23 (s, 1H), 8.74 (s, 1H), 9.41 (s, 1H)	Intermediate 18 and Intermediate 6
47	ethyl 1-ethyl-6-(6-(3-ethylureido)-4-(4-phenylthiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 568.2 (MH^+) for $C_{31}H_{29}N_5O_4S$ ^1H NMR (d_6-DMSO): δ 1.11 (t, 3H), 1.28 (t, 3H), 1.35 (t, 3H), 3.18-3.23 (m, 2 H), 4.19 (q, 2H), 4.46 (q, 2 H), 7.28-7.41 (m, 4H), 62-7.80 (m, 5 H), 7.85 (d, 1H), 8.14 (d, 1H), 8.19 (d, 1H), 8.24 (m, 2H), 8.75 (s, 1H), 9.41 (bs, 1H)	Intermediate 19 and Intermediate 6

Ex	Compound	Data	SM
48	ethyl 9-(6-(3-ethylureido)-4-(4-trifluoromethylthiazol-2-yl)pyridin-3-yl)-7-oxo-3,7-dihydro-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylate 	MS (ESP): 574.2 (MH^+) for $C_{26}H_{22}F_3N_5O_3S$ ^1H NMR (d_6-DMSO): δ 1.11 (t, 3H), 1.28 (t, 3H), 3.18-3.22 (m, 2H), 4.23 (q, 2H), 4.45 (m, 2H), 4.51 (m, 2H), 7.28 (s, 1H), 7.63-7.70 (m, 2H), 8.22 (s, 1H), 8.28 (s, 1H), 8.51 (s, 1H), 8.62 (s, 1H), 9.44 (s, 1H)	Intermediate 17 and Intermediate 13
49	ethyl 9-(6-(3-ethylureido)-4-(4-ethylthiazol-2-yl)pyridin-3-yl)-7-oxo-3,7-dihydro-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylate 	MS (ESP): 534.1 (MH^+) for $C_{27}H_{27}N_5O_5S$	Intermedaite 18 and Interemediate 13

Ex	Compound	Data	SM
50	ethyl 9-(6-(3-ethylureido)-4-(4-phenylthiazol-2-yl)pyridin-3-yl)-7-oxo-3,7-dihydro-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylate 	MS (ESP): 581.9 (MH^+) for $C_{31}H_{27}N_5O_5S$ ^1H NMR (d_6-DMSO): δ 1.08-1.18 (m, 6H), 1.27 (t, 3H), 3.17-3.24 (m, 2 H), 4.22 (q, 2H), 4.44 (m, 4 H), 7.23-7.55 (m, 5H), 7.71-7.82 (m, 2 H), 8.00-8.29 (m, 2H), 8.61 (m, 1H), 9.51 (bs, 1H)	Intermediate 19 and Intermediate 13

Example 51

Ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(2-methoxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate



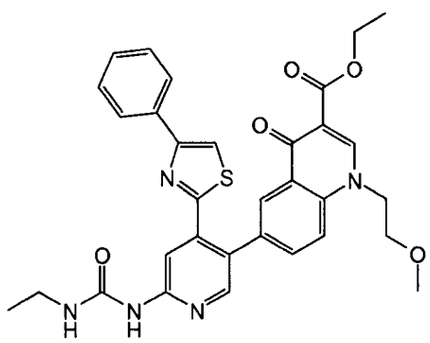
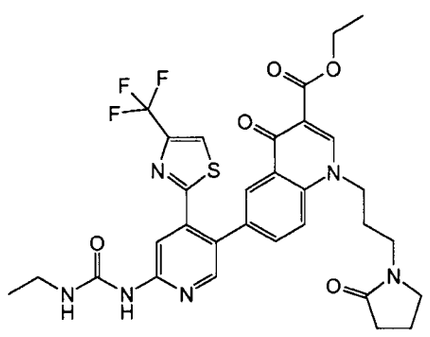
1-Ethyl-3-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)urea (0.171 g, 0.39 mmol, Intermediate 17), ethyl 6-iodo-1-(2-methoxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (0.155 g, 0.39 mmol, Intermediate 20), cesium carbonate (0.214 g, 0.66 mmol, Aldrich) and tris(dibenzylideneacetaone)palladium (0) (0.035 g, 0.04 mmol, Aldrich) or tetrakis(triphenylphosphine)palladium (0) (5 mol%, Strem) were combined in dioxane (2 mL)/water (0 mL) and heated to 100 °C. The reaction mixture was stirred for 1 h. The reaction mixture was cooled to room temperature and then placed in an ice-bath. The resulting precipitate was collected by filtration and dried under vacuum to provide the desired product (0.090g).

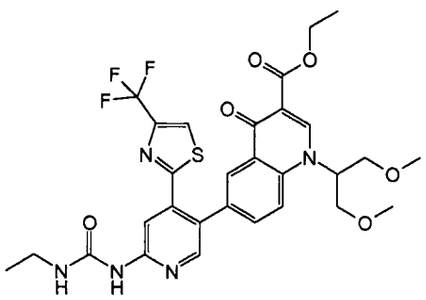
MS (ES) $(M+H)^+$: 590 for $C_{27}H_{26}F_3N_5O_5S$;

NMR: 1.11 (t, 3H), 1.28 (t, 3H), 3.24 (m, 5H), 3.66 (d, 2H), 4.24 (q, 2H), 4.61 (q, 2H), 7.70 (m, 2H), 7.91 (d, 1H), 8.14 (s, 1H), 8.22 (s, 1H), 8.33 (s, 1H), 8.49 (s, 1H), 8.62 (s, 1H), 9.46 (s, 1H).

Examples 52-54

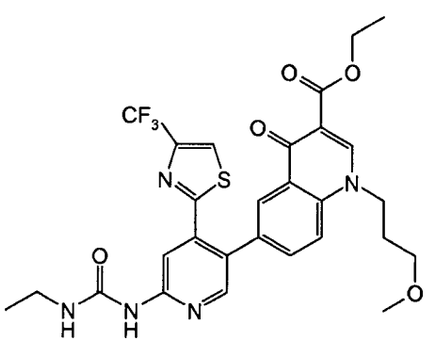
The following Examples were prepared by the procedure described in Example 51 from the starting materials (SM) indicated.

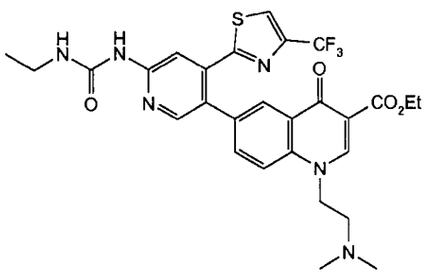
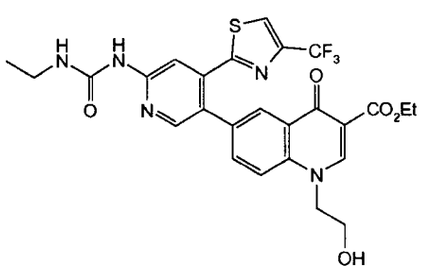
Ex	Compound	Data	SM
52	ethyl 6-(6-(3-ethylureido)-4-(4-phenylthiazol-2-yl)pyridin-3-yl)-1-(2-methoxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ES) $(M+H)^+$: 598 for $C_{32}H_{31}N_5O_5S$ NMR: 1.12 (t, 3H), 1.28 (t, 3H), 3.18-3.22 (m, 5H), 3.66 (d, 2H), 4.22 (q, 2H), 4.61 (q, 2H), 7.32-7.38 (m, 3H), 7.70-7.77 (m, 4H), 7.89 (d, 1H), 8.16 (s, 1H), 8.20 (s, 1H), 8.26 (d, 1H), 8.62 (s, 1H), 9.44 (s, 1H).	Intermediate 19 and Intermediate 20
53	ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(3-(2-oxopyrrolidin-1-yl)propyl)-1,4-dihydroquinoline-3-carboxylate 	MS (ES) $(M+H)^+$: 657 for $C_{31}H_{31}F_3N_6O_5S$ NMR: 1.11 (t, 3H), 1.29 (t, 3H), 2.22 (m, 4H), 2.73 (d, 1H), 3.31 (s, 6H), 4.22 (q, 2H), 4.39 (q, 2H), 7.70 (s, 1H), 7.73 (d, 1H), 7.87 (d, 1H), 8.15 (s, 1H), 8.23 (s, 1H), 8.33 (s, 1H), 8.49 (s, 1H), 8.75 (s, 1H), 9.49 (s, 1H).	Intermediate 17 and Intermediate 21

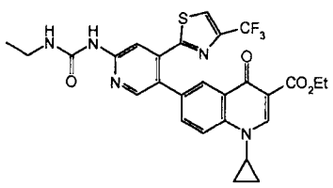
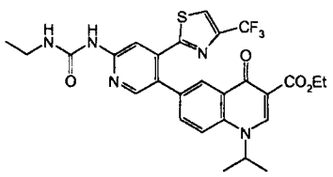
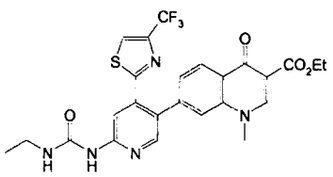
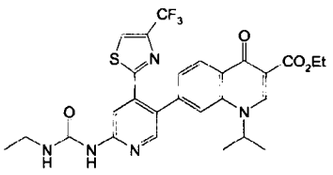
Ex	Compound	Data	SM
54	ethyl 1-(1,3-dimethoxypropan-2-yl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ES) $(M+H)^+$: 634 for $C_{29}H_{30}F_3N_5O_6S$	Intermediate 17 and Intermediate 22

Examples 55-61

The following Examples were prepared by the procedure described in Example 51 from the starting materials (SM) indicated.

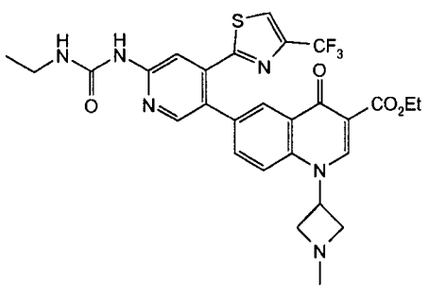
Ex	Compound	Data	SM
55	ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(3-methoxypropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ES) $(M+H)^+$: 604 for $C_{28}H_{28}F_3N_5O_5S$	Intermediate 17 and Intermediate 23

Ex	Compound	Data	SM
56	Ethyl 1-(2-(dimethylamino)ethyl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 603 (M+1) for $C_{28}H_{29}F_3N_6O_4S$ ^{1}H-NMR (DMSO-d_6) 1.11 (t, *J*=7.07 Hz, 3H); 1.29 (t, *J*=7.07 Hz, 3H); 2.21 (br. s., 6H); 2.57 - 2.69 (m, 2H); 3.16 - 3.27 (m, 2H); 4.24 (q, *J*=7.07 Hz, 2H); 4.51 (br. s., 2H); 7.59 - 7.66 (m, 1H); 7.69 (dd, *J*=8.59, 2.02 Hz, 1H); 7.88 (d, *J*=9.09 Hz, 1H); 8.15 (d, *J*=2.02 Hz, 1H); 8.22 (s, 1H); 8.33 (s, 1H); 8.51 (s, 1H); 8.66 (s, 1H); 9.45 (s, 1H)	Interemediate 17 and Interemdiate 29
57	Ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 576 (M+1) for $C_{26}H_{24}F_3N_5O_5S$ ^{1}H-NMR (DMSO-d_6) : 1.11 (t, *J*=7.20 Hz, 3H); 1.28 (t, *J*=7.07 Hz, 3H); 3.16 - 3.26 (m, 2H); 3.71 - 3.78 (m, 2H); 4.24 (q, *J*=7.07 Hz, 2H); 4.41 - 4.51 (m, 2H); 5.07 (t, *J*=5.43 Hz, 1H); 7.60 - 7.67(m, 1H); 7.69 (dd, *J*=8.84, 2.27 Hz, 1H); 7.91 (d, *J*=8.84 Hz, 1 H); 8.16 (d, *J*=2.27 Hz, 1H); 8.23 (s, 1H); 8.31 (s, 1H); 8.49 (s, 1H); 8.61 (s, 1H); 9.45 (s, 1 H)	Intermediate 17 and Intermediate 30

Ex	Compound	Data	SM
58	Ethyl 1-cyclopropyl-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 572 (M+1) for $C_{27}H_{24}F_3N_5O_4S$	Intermediate 17 and Intermediate 27
59	Ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-isopropyl-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 574 (M+1) for $C_{27}H_{26}F_3N_5O_4S$	Intermediate 17 and Intermediate 28
60	Ethyl 7-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 546 (M+1) for $C_{25}H_{22}F_3N_5O_4S$	Interemedaite 17 and Interemdiate 25
61	Ethyl 7-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-isopropyl-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 574 (M+1) for $C_{27}H_{26}F_3N_5O_4S$	Intermediate 17 and Intermediate 26

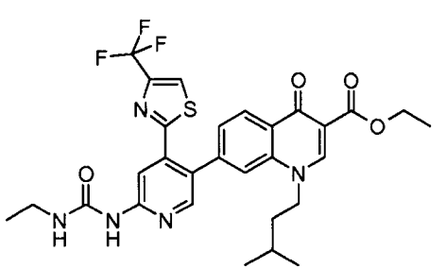
Example 62

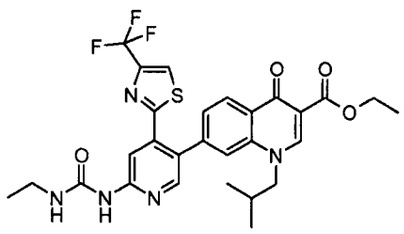
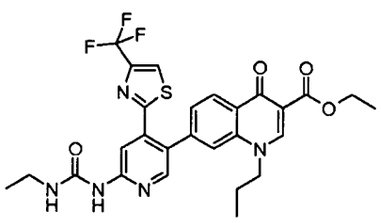
The following Intermediate was prepared by the procedure described in Example 51 from the starting materials (SM) indicated.

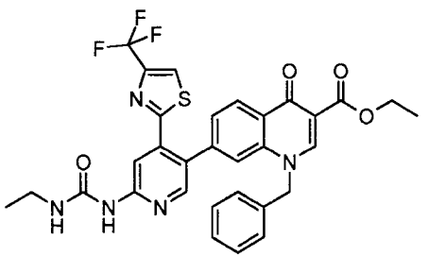
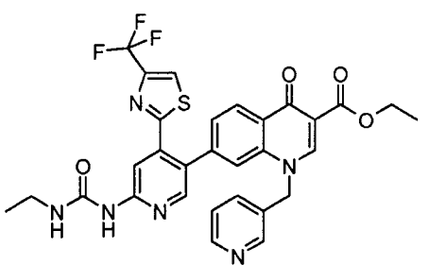
Ex	Compound	Data	SM
62	Ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-methylazetidin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 601 (M+1) for $C_{28}H_{27}F_3N_6O_4S$	Intermediate 17 and Intermediate 31

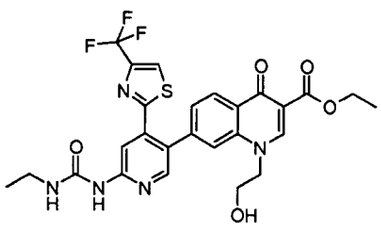
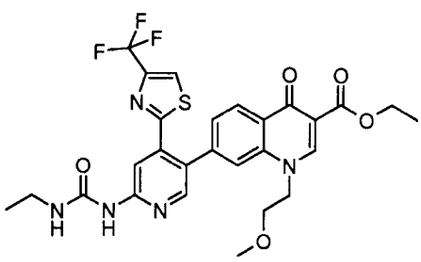
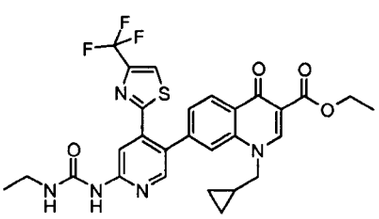
Examples 63-70

The following Intermediates were prepared by the procedure described in Example 42 from the starting materials (SM) indicated.

Ex	Compound	Data	SM
63	Ethyl 7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-1-(3-methylbutyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	^{1}H NMR (400 MHz, DMSO-d_6): 0.91 (d, 6H), 1.12 (t, 3H), 1.31 (t, 3H), 1.39 (d, 2H), 1.56 (m, 1H), 3.21 (q, 2H), 4.21 (q, 2H), 4.31 (t, 2H), 7.48 (d, 1H), 7.58 (t, 2H), 7.68 (s, 1H), 8.24 (s, 1H), 8.30 (d, 1H), 8.38 (s, 1H), 8.51 (s, 1H), 8.68 (s, 1H).	Intermediate 17 and Intermediate 34

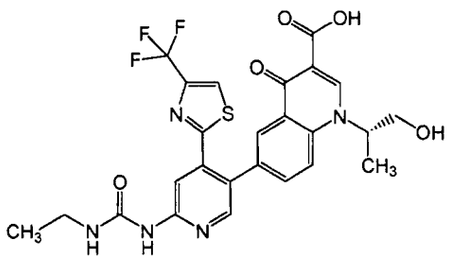
Ex	Compound	Data	SM
64	Ethyl 7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-1-(2-methylpropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	^{1}H NMR (400 MHz, DMSO-d_6): 0.78 (d, 6H), 1.15 (t, 3H), 1.32 (t, 3H), 1.61 (m, 1H), 3.38 (q, 2H), 4.12 (d, 2H), 4.36 (q, 2H), 7.48 (d, 1H), 7.61 (d, 2H), 7.71 (s, 1H), 8.18 (s, 1H), 8.31 (d, 1H), 8.39 (s, 1H), 8.52 (s, 1H), 8.64 (s, 1H), 9.52 (s, 1H).	Intermediate 17 and Intermediate 35
65	Ethyl 7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-4-oxo-1-propyl-1,4-dihydroquinoline-3-carboxylate 	^{1}H NMR (400 MHz, DMSO-d_6): 0.91 (t, 3H), 1.16 (t, 3H), 1.56 (m, 2H), 3.21 (q, 2H), 3.34 (s, 2H), 4.26 (q, 2H), 7.41 (d, 1H), 7.60 (s, 1H), 7.78 (s, 1H), 8.21 (s, 1H), 8.28 (d, 1H), 8.52 (s, 2H), 8.68 (s, 1H), 9.42 (s, 1H).	Intermediate 17 and Intermediate 36

Ex	Compound	Data	SM
66	Ethyl 1-benzyl-7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-4-oxo-1,4-dihydroquinoline-3-carboxylate 	^{1}H NMR (400 MHz, DMSO-d_6): 1.10 (t, 3H), 1.31 (t, 3H), 3.21 (q, 2H), 4.24 (q, 2H), 5.63 (s, 1H), 7.14 (d, 2H), 7.22 (d, 3H), 7.36 (d, 1H), 7.56 (s, 1H), 7.77 (s, 1H), 8.14 (s, 1H), 8.24 (s, 1H), 8.31 (s, 2H), 8.89 (s, 1H), 9.41 (s, 1H).	Intermediate 17 and Intermediate 37
67	Ethyl 7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-4-oxo-1-(pyridin-3-ylmethyl)-1,4-dihydroquinoline-3-carboxylate 	^{1}H NMR (400 MHz, DMSO-d_6): 1.08 (t, 3H), 1.36 (t, 3H), 3.21 (q, 2H), 4.21 (q, 2H), 5.68 (s, 2H), 7.38 (d, 2H), 7.61 (d, 2H), 7.71 (s, 1H), 8.18 (s, 1H), 8.22 (s, 1H), 8.31 (d, 1H), 8.34 (s, 1H), 8.51 (s, 2H).	Intermediate 17 and Intermediate 38

Ex	Compound	Data	SM
68	Ethyl 7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	^{1}H NMR (400 MHz, DMSO-d_6): δ 1.16 (t, 3H), 1.29 (t, 3H), 3.21 (t, 2H), 3.61 (t, 2H), 4.21 (q, 2H), 4.41 (s, 2H), 5.01 (s, 1H), 7.26 (s, 1H), 7.38 (d, 2H), 7.65 (s, 1H), 7.89 (s, 1H), 8.26 (d, 2H), 8.36 (s, 1H), 8.48 (s, 1H), 8.58 (s, 1H), 9.52 (s, 1H).	Intermediate 17 and Intermediate 39
69	Ethyl 7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-1-(2-methoxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	^{1}H NMR (400 MHz, DMSO-d_6): 1.14 (t, 3H), 1.32 (t, 3H), 3.11 (s, 3H), 3.30 (s, 2H), 3.46 (s, 1H), 4.21 (q, 2H), 4.58 (s, 2H), 7.41 (d, 1H), 7.64 (s, 1H), 7.86 (s, 1H), 8.24 (d, 2H), 8.38 (s, 1H), 8.50 (s, 1H), 8.58 (s, 1H).	Intermediate 17 and Intermediate 40
70	Ethyl 1-(cyclopropylmethyl)-7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-4-oxo-1,4-dihydroquinoline-3-carboxylate 	^{1}H NMR (400 MHz, DMSO-d_6): 0.38 (m, 4H), 0.98 (m, 1H), 1.10 (t, 3H), 1.29 (t, 3H), 3.19 (q, 2H), 4.29 (q, 2H), 7.40 (d, 1H), 7.61 (s, 1H), 7.91 (s, 1H), 8.21 (s, 1H),. 8.23 (d, 1H), 8.38 (s, 1H), 8.48 (s, 1H), 8.71 (s, 1H), 9.42 (s, 1H).	Intermediate 17 and Intermediate 41

Example 71

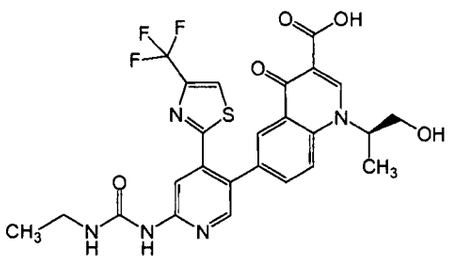
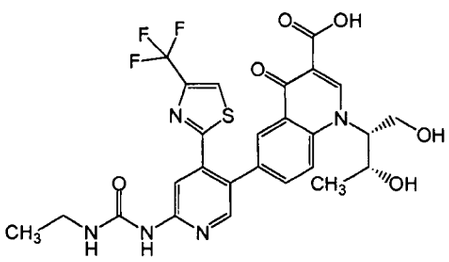
(*S*)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-hydroxypropan-2-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

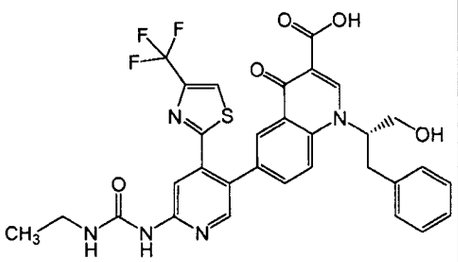
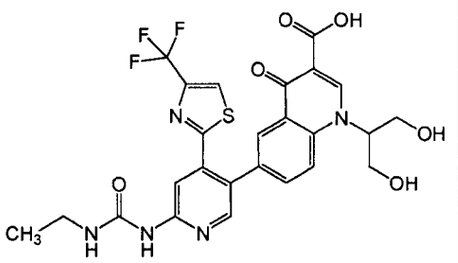
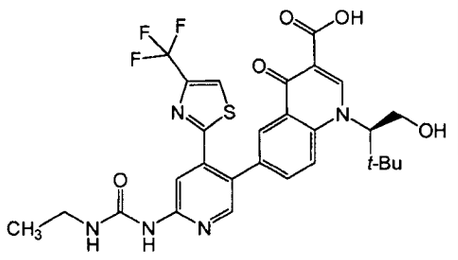


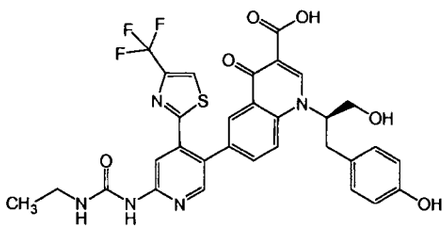
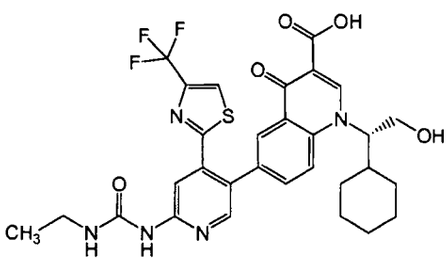
To a solution of (*S*)- ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-hydroxypropan-2-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (Example 97, 200 mg, 0.34 mmol, 1 equiv.) in tetrahydrofuran (1 mL) and methanol (1 mL) was added 2 M lithium hydroxide (0.339 mL). The mixture was stirred in the microwave at 100 °C for 15 min. The reaction mixture was cooled to room temperature and diluted with water. 1 N HCl was added until pH 3-4 was reached. The reaction mixture was partitioned between ethyl acetate (5 mL) and water (5 mL). The aqueous layer was extracted with ethyl acetate (2x5 mL), and the organics were washed with brine (10 mL), dried over sodium sulfate, and concentrated under reduced pressure. Purification via reverse phase HPLC (C18 column, acetonitrile/water 0-95% gradient) and concentrated under reduced pressure to provide (*S*)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-hydroxypropan-2-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid as a light yellow solid (92 mg, 48%).
MS (ESP) $[M + H]^+$: 562 for $C_{25}H_{22}F_3N_5O_5S$.
H^1NMR (d_6-DMSO) δ 14.98 (s, 1H), 9.53 (s, 1H), 8.93 (s, 1H), 8.51 (s, 1H), 8.36 (s, 1H), 8.34 (d, 1H), 8.25 (d, 1H), 8.23 (s, 1H), 7.87-7.83 (dd, 1H), 7.65 (t, 1H), 5.28 (s, 2H), 3.81 (s, 2H), 3.25-3.16 (m, 3H), 1.56 (d, 3H), 1.11 (t, 3H).

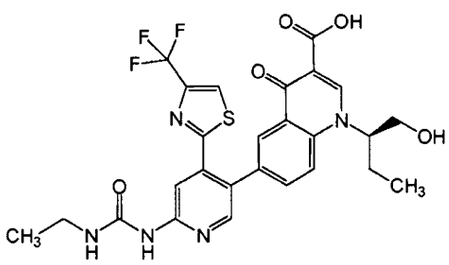
Examples 72-79

The following examples were prepared by the procedure described in Example 71 from the indicated starting material

Ex	Compound	Data	SM
72	(*R*)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-hydroxypropan-2-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 562 (M + 1) for $C_{25}H_{22}F_3N_5O_5S$ NMR (d_6-DMSO) δ 15.09 (s, 1H), 9.51 (s, 1H), 8.94 (s, 1H), 8.51 (s, 1H), 8.36 (d, 2H), 8.24 (s, 2H), 7.87 (d, 1H), 7.65 (s, 1H), 5.3 (s, 2H), 3.82 (s, 2H), 3.21 (m, 3H), 1.56 (d, 3H), 1.11 (t, 3H)	Example 98
73	1-((2*R*,3*R*)-1,3-dihydroxybutan-2-yl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 592 (M + 1) for $C_{26}H_{24}F_3N_5O_6S$ NMR (d_6-DMSO) δ 15.1 (s, 1H), 9.48 (s, 1H), 9.12 (s, 1H), 8.53 (s, 1H), 8.38, (s, 1H), 8.33 (d, 1H), 8.29 (d, 1H), 8.22 (s, 1H), 7.84 (dd, 1H), 7.61 (t, 1H), 5.3-5.1 (m, 2H), 4.26 (t, 1H), 4.04-3.97 (m, 1H), 3.87 (d, 1H), 3.23-3.17 (m, 2), 1.14 (d, 3H), 1.11 (t, 3H)	Example 99

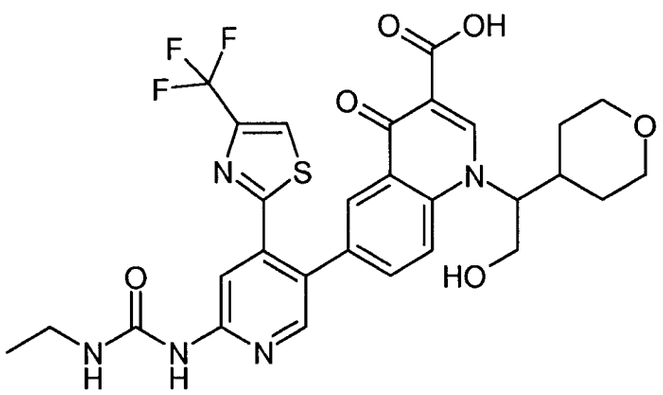
Ex	Compound	Data	SM
74	(*S*)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-hydroxy-3-phenylpropan-2-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 638 (M + 1) for $C_{31}H_{26}F_3N_5O_5S$ NMR (d_6-DMSO) δ 14.47 (s, 1H), 9.47 (s, 1H), 9.05 (s, 1H), 8.58 (s, 1H), 8.32 (s, 1H), 8.24 (d, 1H), 8.22 (s, 1H), 8.19 (d, 1H), 7.77 (dd, 1H), 7.6 (t, 1H), 7.2-7.15 (m, 5H), 5.55 (s, 1H), 5.36 (t, 1H), 3.99-3.82 (m, 2H), 3.22-3.16 (m, 2H), 1.11 (t, 3H)	Example 109
75	1-(1,3-dihydroxypropan-2-yl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 578 (M + 1) for $C_{25}H_{22}F_3N_5O_6S$ NMR (d_6-DMSO) δ 9.5 (s, 1H), 8.96 (s, 1H), 8.51 (d, 1H), 8.36 (s, 1H), 8.35 (d, 1H), 8.26 (d, 1H), 8.23 (s, 1H), 7.87 (dd, 1H), 7.63 (t, 1H), 5.28-5.19 (m, 2H), 3.99-3.84 (m, 4H), 3.25-3.16 (2H), 1.11 (t, 3H)	Example 100
76	(*R*)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-hydroxy-3,3-dimethylbutan-2-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 604 (M + 1) for $C_{28}H_{28}F_3N_5O_5S$ NMR (d_6-DMSO) δ 9.59 (s, 1H), 8.87 (s, 1H), 8.55 (s, 1H), 8.47 (d, 1H), 8.39 (s, 1H), 8.33 (d, 1H), 8.23 (s, 1H), 7.8 (dd, 1H), 7.67 (t, 1H), 5.21-5.17 (m, 1H), 4.16-4.03 (m, 2H), 3.25-3.16 (m, 2H), 1.11 (t, 3H), 0.97 (s, 9H)	Example 108

Ex	Compound	Data	SM
77	(*R*)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-hydroxy-3-(4-hydroxyphenyl)propan-2-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 604 (M + 1) for $C_{31}H_{26}F_3N_5O_6S$ NMR (d_6-DMSO) δ 14.99 (s, 1H), 9.46 (s, 1H), 89.25 (s, 1H), 9.01 (s, 1H), 8.51 (s, 1H), 8.32 (s, 1H), 8.24 (s, 1H), 8.19 (d, 1H), 7.79 (d, 1H), 7.6 (t, 1H), 6.98 (d, 2H), 6.56 (d, 2H), 5.51-5.44 (m 1H), 5.33 (t, 1H), 3.99-3.79 (m, 2H), 3.26-3.09 (m, 3H), 1.11 (t, 3H), 0.07 (s, 1H)	Example 117
78	(*S*)-1-(1-cyclohexyl-2-hydroxyethyl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 630 (M + 1) for $C_{30}H_{30}F_3N_5O_5S$ NMR (d_6-DMSO) δ 15.03 (s, 1H), 9.48 (s, 1H), 9.01 (s, 1H), 8.54 (s, 1H), 8.39 (s, 1H), 8.34 (d, 1H), 8.32 (d, 1H), 8.2 (s, 1H), 7.82 (dd, 1H), 7.59 (t, 1H), 5.27 (t, 1H), 5.02-4.95 (m, 1H), 4.07-3.97 (m, 1H), 3.81-3.75 (m, 1H), 3.26-3.18 (m, 2H), 2.15-2.01 (m, 1H), 1.97-1.9 (m 1H), 1.81-1.73 (m, 1H), 1.61-1.55 (m , 2H), 1.3-1.17 (m, 2H), 1.11 (t, 3H)	Example 118

Ex	Compound	Data	SM
79	(*R*)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-hydroxybutan-2-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 576 (M + 1) for $C_{26}H_{24}F_3N_5O_5S$ NMR (d_6-DMSO) δ 15.1 (s, 1H), 9.48 (s, 1H), 8.93 (s, 1H), 8.53 (s, 1H), 8.38 (s, 1H), 8.34 (d, 1H), 8.3 (d, 1H), 8.22 (s, 1H), 7.86 (dd, 1H), 7.6 (t, 1H), 5.13 (m, 2H), 3.92-3.84 (m, 2H), 3.26-3.17 (m, 2H), 2.06-1.92 (m, 2H), 1.11 (t, 3H), 0.89 (t, 3H)	Example 102

Example 80

6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(2-hydroxy-1-(tetrahydro-2H-pyran-4-yl)ethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



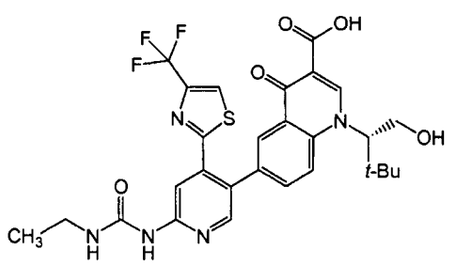
To a solution of ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(2-hydroxy-1-(tetrahydro-2H-pyran-4-yl)ethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (Example 103, 107 mg, 0.16 mmol, 1 equiv.) in tetrahydrofuran (1 mL) and methanol (1 mL) was added 2 M lithium hydroxide (0.162 mL, 0.32 mmol). The reaction mixture was heated to 100 °C for 15 min in a micriowave. The reaction mixture was cooled to room temperature and diluted with water. The reaction mixture was filtered, and the filtrate was dried. Purification via reverse phase HPLC (C18, acetonitrile/water 0-95% gradient) and concentrated under reduced pressure to provide 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(2-hydroxy-1-(tetrahydro-2H-pyran-4-yl)ethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid as a light yellow solid (26.5 mg, 26%).

MS (ESP): 632 (M + 1) for $C_{29}H_{28}F_3N_5O_6S$.

NMR (d_6-DMSO) δ 15.03 (s, 1H), 9.39 (s, 1H), 8.98 (s, 1H), 8.46 (s, 1H), 8.32 (s, 1H), 8.29 (d, 1H), 8.25 (d, 1H), 8.13 (s, 1H), 7.76 (dd, 1H), 7.51 (t, 1H), 4.97 (m, 1H), 3.98 (dd, 1H), 3.83 (dd, 1H), 3.73-3.63 (3H), 3.19-3.10 (m, 2H), 2.31-2.2 (m, 1H), 1.73-1.68 (m, 1H), 1.59-1.5 (m, 1H), 1.16-1.09 (m, 1H), 1.04 (t, 3H), 1.0-0.94 (m, 1H).

Example 81

6-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-1-[(1*S*)-1-(hydroxymethyl)-2,2-dimethylpropyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



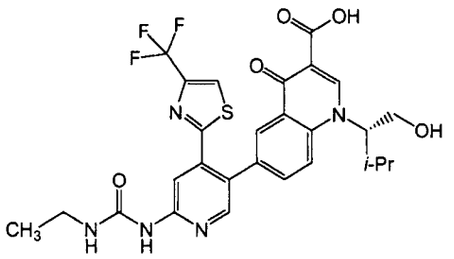
To a solution of (*S*)- ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-hydroxy-3,3-dimethylbutan-2-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (Example 104, 212.7 mg, 0.34 mmol) in tetrahydrofuran (1 mL) and methanol (1 mL) was added 2 M lithium hydroxide (0.253 mL, 0.51 mmol). The reaction mixture was heated at 100 °C for 15 min in a microwave reactor. The reaction mixture was cooled to room temperature and diluted with water. 1 N HCl was added until pH 3-4 was reached. The precipitate that formed was collected by filtration, washed with water and hexanes. Purification via column chromatography (silica, 95:5 methylene chloride/methanol) provided (*S*)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-hydroxy-3,3-dimethylbutan-2-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid as a light yellow solid (72.3 mg, 35%).

MS (ESP): 604 (M + 1) for $C_{28}H_{28}F_3N_5O_5S$.

NMR (d_6-DMSO) δ 15.01 (s, 1H), 9.4 (s, 1H), 8.78 (s, 1H), 8.46 (s, 1H), 8.37 (d, 1H), 8.31 (s, 1H), 8.25 (d, 1H), 8.11 (s, 1H), 7.72 (dd, 1H), 7.5 (t, 1H), 5.12-5.08 (m, 1H), 4.09-3.96 (m, 2H), 3.17-3.08 (m, 2H), 1.02 (t, 3H), 0.89 (s, 9H).

Example 82

6-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-1-[(1*S*)-1-(hydroxymethyl)-2-methylpropyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



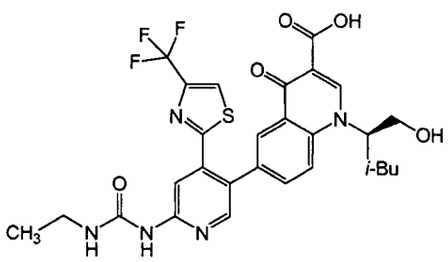
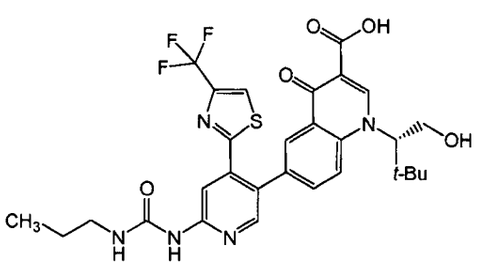
To a solution of (*S*)- ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-hydroxy-3-methylbutan-2-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (Example 110, 213 mg, 0.35 mmol) in tetrahydrofuran (1 mL) and methanol (1 mL) was added 2 M lithium hydroxide (0.259 mL, 0.52 mmol). The reaction mixture was heated at 100 °C for 15 min in a microwave reactor. The reaction mixture was cooled to room temperature, diluted with water, and treated with 1 N HCl until pH 3-4. The precipitate that formed was collected by filtration, washed with water and hexanes. Purification via reverse phase HPLC (C18, acetonitrile/water 0-95% gradient) provided (*S*)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-hydroxy-3-methylbutan-2-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid as a light yellow solid (146.4 mg, 72%).

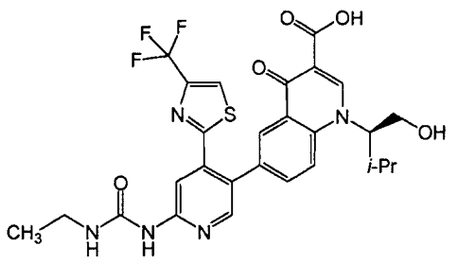
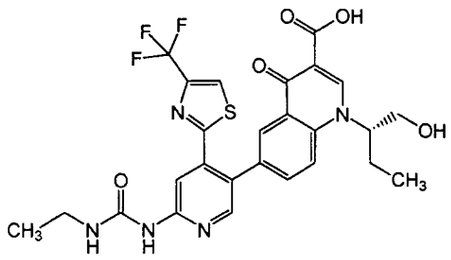
MS (ESP): 590 for $C_{27}H_{26}F_3N_5O_5S$.

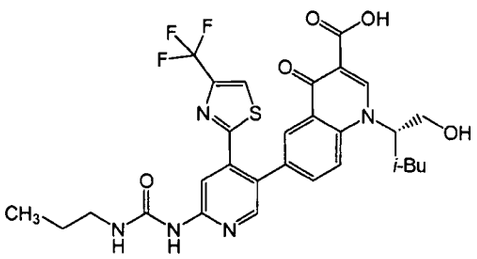
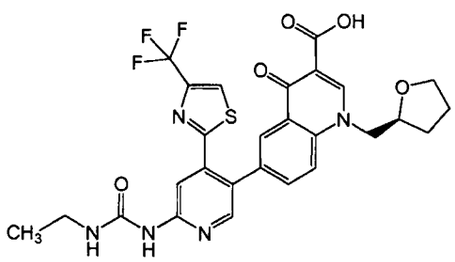
NMR (d_6-DMSO) δ 14.98 (s, 1H), 9.5 (s, 1H), 9.0 (s, 1H), 8.53 (s, 1H), 8.39 (s, 1H), 8.33 (d, 1H), 8.21 (s, 1H), 7.83 (dd, 1H), 7.62 (t, 1H), 5.26 (s, 1H), 4.92 (s, 1H), 4.0 (d, 1H), 3.81 (d, 1H), 3.22-3.19 (m, 2H), 2.38 (m, 1H), 1.11 (t, 3H), 1.09 (d, 3H), 0.74 (d, 3H).

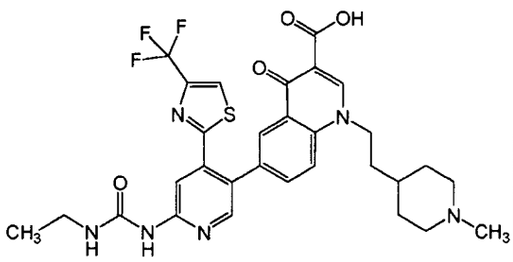
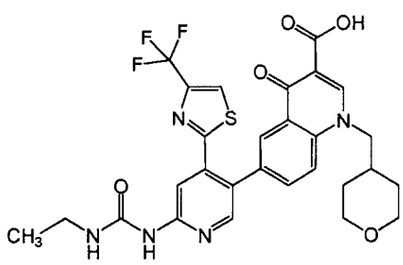
Examples 83-95

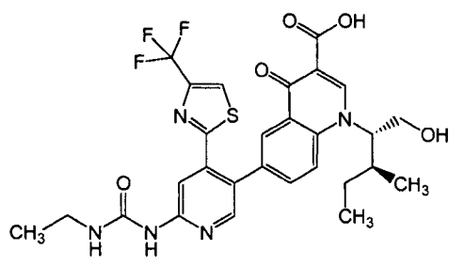
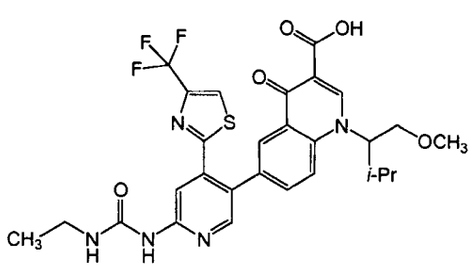
The following examples were prepared by the procedure described in Example 83 from the indicated starting material.

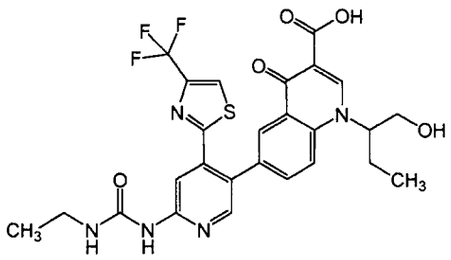
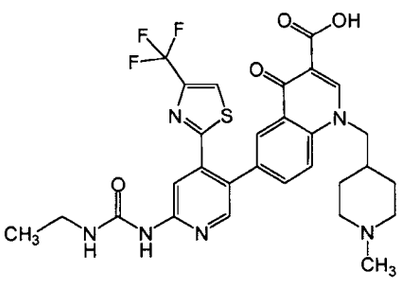
Ex	Compound	Data	SM
83	(*S*)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-hydroxy-4-methylpentan-2-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 604 for $C_{28}H_{28}F_3N_5O_5S$ NMR (d_6-DMSO) δ 14.88 (s, 1H), 9.53 (s, 1H), 8.9 (s, 1H), 8.54 (s, 1H), 8.39 (s, 1H), 8.34 (d, 1H), 8.32 (d, 1H), 8.22 (s, 1H), 7.85 (dd, 1H), 7.63 (t, 1H), 5.24 (s, 2H), 3.83-3.73 (m, 2H), 3.22-3.17 (m, 3H), 1.97-1.81 (m, 2H), 1.48-1.4 (m, 1H), 1.11 (t, 3H), 0.92 (d, 3H), 0.86 (d, 3H)	Example 111
84	(*S*)-1-(1-hydroxy-3,3-dimethylbutan-2-yl)-4-oxo-6-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 618 for $C_{29}H_{30}F_3N_5O_5S$ NMR (d_6-DMSO) δ 15.09 (s, 1H), 9.48 (s, 1H0, 8.91 (s, 1H), 8.54 (s, 1H), 8.39 (s, 1H), 8.34 (d, 1H), 8.3 (s, 1H), 8.22 (s, 1H), 7.87 (dd, 1H), 7.65 (t, 1H), 5.26-5.23 (m, 2H), 3.85-3.73 (m, 2H), 3.19-3.12 (m, 2H), 1.55-1.42 (m, 2H), 0.92 (t, 3H), 0.91 (s, 9H)	Example 101

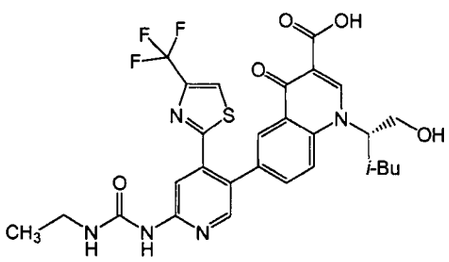
Ex	Compound	Data	SM
85	(*R*)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-hydroxy-3-methylbutan-2-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 590 for $C_{27}H_{26}F_3N_5O_5S$ H^1NMR (d_6-DMSO) δ 9.56 (s, 1H), 8.99 (s, 1H), 8.53 (s, 1H), 8.39 (s, 1H) 8.33 (d, 1H), 8.3 (s, 1H), 8.22 (s, 1H), 7.82 (dd, 1H), 7.67 (t, 1H), 4.91 (s, 1H), 4.04-3.98 (m, 1H), 3.8 (d, 1H), 3.25-3.16 (m, 2H), 2.42-2.35 (m, 1H), 1.11 (t, 3H), 1.09 (d, 3H), 0.73 (d, 3H)	Example 112
86	(*S*)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-hydroxybutan-2-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 576 for $C_{30}H_{24}F_3N_5O_5S$ NMR (d_6-DMSO) δ 15.08 (s, 1H), 9.48 (s, 1H), 8.93 (s, 1H), 8.53 (s, 1H), 8.38 (s, 1H) 8.34 (d, 1H), 8.3 (d, 1H), 8.22 (s, 1H), 7.86 (dd, 1H), 7.6 (t, 1H), 5.13 (m, 2H), 3.89-3.75 (m, 2H), 3.26-3.17 (m, 2H), 2.09-1.92 (m, 2H), 1.11 (t, 3H), 0.89 (t, 3H)	Example 113

Ex	Compound	Data	SM
87	(*S*)-1-(1-hydroxy-4-methylpentan-2-yl)-4-oxo-6-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 618 for $C_{29}H_{30}F_3N_5O_5S$ H^1NMR (d_6-DMSO) δ 14.61 (s, 1H), 9.04 (s, 1H), 8.47 (s, 1H), 8.1 (s, 1H), 7.96 (s, 1H), 7.9 (s, 1H), 7.89 (d, 1H), 7.78 (s, 1H), 7.42 (dd, 1H), 7.2 (t, 1H), 4.79 (m, 1H), 3.3 (m, 2H), 2.74-2.69 (m, 2H), 1.54-1.47 (m, 1H), 1.44-1.39 (m, 1H), 1.1-.79 (m, 3H), 0.48 (t, 3H), 0.47 (d, 3H), 0.43 (d, 3H)	Example 114
88	(*S*)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-((tetrahydrofuran-2-yl)methyl)-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 588 for $C_{27}H_{24}F_3N_5O_5S$ H^1NMR (d_6-DMSO) δ 15.06 (s, 1H), 9.48 (s, 1H), 8.98 (s, 1H), 8.51 (s, 1H), 8.37 (s, 1H), 8.32 (d, 1H), 8.23 (s, 1H), 8.19 (d, 1H), 7.86 (dd, 1H), 7.61 (t, 1H), 4.88 (d, 1h), 4.55-4.46 (m, 1H), 4.21-4.16 (m, 1H), 3.86-3.78 (m, 1H), 3.78-3.62 (m, 1H), 3.24-3.18 (m, 2H), 2.11-2.07 (m, 1H), 1.94-1.87 (m, 1H), 1.87-1.81 (m, 1H), 1.67-1.61 (m 1H), 1.11 (t, 3H)	Example 105

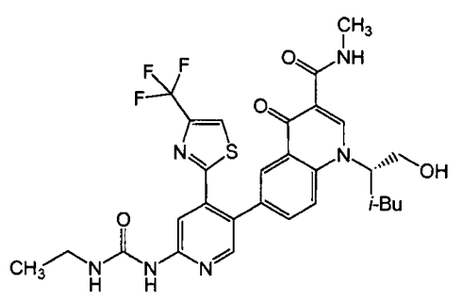
Ex	Compound	Data	SM
89	6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(2-(1-methylpiperidin-4-yl)ethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 629 for $C_{30}H_{31}F_3N_6O_4S$ NMR (d_6-DMSO) δ 15.02 (s, 1H), 9.44 (s, 1H), 9.1 (s, 1H), 8.49 (s, 1H), 8.33 (s, 1H), 8.28 (d, 1H), 8.18 (s, 1H), 8.02 (s, 1H), 7.83 (dd, 1H), 7.54 (t, 1H), 4.62-4.55 (m, 2H), 3.21-3.12 (m, 2H), 2.93-2.81 (m, 2H), 2.72 (d, 3H), 1.95 (d, 2H), 1.77-1.69 (m, 3H), 1.37-1.25(m, 2H), 1.07 (t, 3H)	Example 106
90	6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-((tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 602 for $C_{28}H_{26}F_3N_5O_5S$ NMR (d_6-DMSO) δ 15.08 (s, 1H), 9.48 (s, 1H), 9.06 (s, 1H), 8.54 (s, 1H), 8.39 (s, 1H), 8.31 (d, 1H), 8.21 (s, 1H), 8.17 (d, 1H), 7.84 (dd, 1H), 7.59 (t, 1H), 4.54 (dd, 2H), 3.86 (dd, 2H), 3.26-3.14 (m, 4H), 2.15-2.04 (m, 1H), 1.47-1.3 (m, 4H), 1.11 (t, 3H)	Example 107

Ex	Compound	Data	SM
91	1-((2*S*,3*S*)-1,3-dihydroxypentan-2-yl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 604 for $C_{28}H_{28}F_3N_5O_5S$ NMR (d_6-DMSO) δ 15.03 (s, 1H), 9.52 (s, 1H), 8.97 (s, 1H), 8.59 (s, 1H), 8.38 (s, 1H), 8.32 (d, 1H), 8.26 (d, 1H), 8.21 (s, 1H), 7.8 (m, 1H), 7.64 (t, 1H), 5.3-5.2 (m, 1H), 5.0-4.86 (m, 1H), 4.14-3.95 (m, 1H), 3.85-3.72 (m, 1H), 3.24-3.16 (m, 2H), 2.23-2.11 (m, 1H), 1.11 (t, 3H), 0.76-0.7 (m, 2H), 0.06 (t, 3H)	Example 115
92	6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-methoxy-3-methylbutan-2-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 604 for $C_{28}H_{28}F_3N_5O_5S$ H^1NMR (d_6-DMSO) δ 15.06 (s, 1H), 9.48 (s, 1H), 8.98 (s, 1H), 8.55 (s, 1H), 8.4 (s, 1H), 8.37 (d, 1H), 8.32 (s, 1H), 8.2 (s, 1H), 7.83 (dd, 1H), 7.59 (t, 1H), 5.19-5.05 (m, 1H), 4.06-3.93 (m, 1H), 3.8-3.73 (m, 1H), 3.63-3.59 (m, 1H), 3.3-3.23 (m, 2H), 3.24 (s, 3H), 1.81-1.73 (m, 1H), 1.11 (t, 3H), 1.09 (d, 3H), 0.72 (d, 3H)	Example 116

Ex	Compound	Data	SM
93	6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-hydroxybutan-2-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 576 for $C_{26}H_{24}F_3N_5O_5S$ NMR (d_6-DMSO) δ 15.13 (s, 1H), 9.48 (s, 1H), 8.93 (s, 1H), 8.53 (s, 1H), 8.38 (s, 1H), 8.34 (s, 1H), 8.3 (d, 1H), 8.21 (d, 1H), 8.21 (d, 1H), 7.86 (dd, 1H), 7.61 (t, 1H), 5.28-2.21 (m, 1H), 5.17-5.06 (m, 1H), 3.95-3.88 (m, 1H), 3.8-3.75 (m, 1H), 3.26-3.19 (m, 2H), 2.09-1.88 (m, 2H), 1.11 (t, 3H), 0.89 (t, 3H)	Example 120
94	6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-((1-methylpiperidin-4-yl)methyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 615 for $C_{29}H_{29}F_3N_6O_4S$ NMR (d_6-DMSO) δ 9.53 (s, 1H), 8.82 (s, 1H), 8.46 (s, 1H), 8.34 (s, 1H), 8.26 (s, 1H), 8.25 (s, 1H), 7.95 (dd, 1H), 7.72 (t, 1H), 7.65 (d, 1H), 4.35-4.3 (m, 2H), 3.26-3.18 (m, 2H), 2.76-2.71 (m, 2H), 2.1 (s, 3H), 1.75-1.67 (m, 2H), 1.48-1.4 (m, 2H), 1.37-1.31 (m, 2H), 1.25-1.22 (m, 1H), 1.1 (t, 3H)	Example 121

Ex	Compound	Data	SM
95	(*S*)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-hydroxy-4-methylpentan-2-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 604 for $C_{28}H_{28}F_3N_5O_5S$ NMR (d_6-DMSO) δ 15.08 (s, 1H), 9.47 (s, 1H), 8.89 (s, 1H), 8.53 (s, 1H), 8.37 (s, 1H), 8.32 (d, 1H), 8.2 (s, 1H), 7.85 (dd, 1H), 7.58 (t, 1H), 5.23 (s, 2H), 3.84-3.75 (m, 2H), 3.24-3.17 (m, 2H), 1.92-1.82 (m, 2H), 1.48-1.42 (m, 1H), 1.09 (t, 3H), 0.91 (d, 3H), 0.85 (d, 3H)	Example 119

Example 96

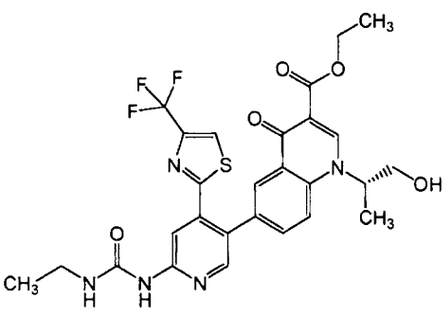


A solution of (*S*)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-hydroxy-4-methylpentan-2-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (Example 119, 280 mg, 0.44 mmol) in 33 wt. % methylamine solution in absolute ethanol (4 mL, 32.13 mmol) was heated in the microwave at 80 °C for 30 min. The reaction mixture was concentrated under reduced pressure. Purification via column chromatography to provide (silica, 95:5 methylene chloride/methanol) gave (*S*)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-hydroxy-4-methylpentan-2-yl)-N-methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide as a light yellow solid (219.2 mg, 80 %).
MS (ESP): 617 for $C_{29}H_{31}F_3N_6O_4S$.
NMR (d_6-DMSO) δ 9.75-9.7 (m, 1H), 9.46 (s, 1H), 8.86 (s, 1H), 8.52 (s, 1H), 8.36 (s, 1H), 8.27 (d, 1H), 8.21 (s, 1H), 8.19 (d, 1H), 7.75 (dd, 1H), 7.62 (t, 1H), 5.19 (t, 1H), 5.12 (s, 1H),

3.79-3.7 (m, 2H), 3.25-3.17 (m, 2H), 2.86 (d, 3H), 1.96-1.85 (m, 1H), 1.85-1.74 (m, 1H), 1.48-1.34 (m, 1H), 1.11 (t, 3H), 0.91 (d, 3H), 0.85 (d, 3H).

Example 97

ethyl 6-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-1-[(1*S*)-2-hydroxy-1-methylethyl]-4-oxo-1,4-dihydroquinoline-3-carboxylate



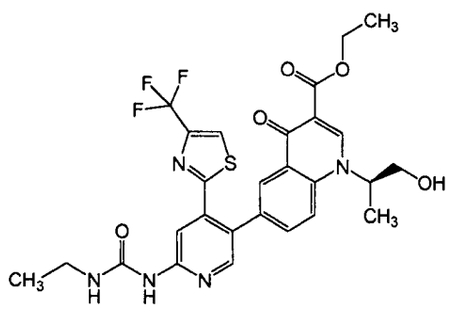
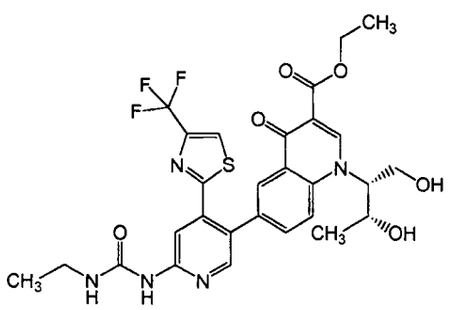
To a solution of palladium (II) acetate (28.0 mg, 0.12 mmol, 0.1 equiv.) and 1,1'-bis(di-*t*-butylphosphino)ferrocene (59.1 mg, 0.12 mmol, 0.1 equiv.) in acetonitrile (3 mL) was added (*S*)-ethyl 1-(1-hydroxypropan-2-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate (Intermediate 49, 500 mg, 1.25 mmol), followed by 6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazole-2-yl)pyridine-3-ylboronic acid (Intermediate 17, 453 mg, 1.26 mmol) and a solution of potassium carbonate (258 mg, 1.87 mmol, 1.5 equiv.) in water (1 mL). The reaction mixture was stirred at 60 °C for 2 h, cooled to room temperature, and diluted with water (2 mL). The precipitate that formed was collected by filtration, washed with water and hexanes and dried to provide (*S*)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-hydroxypropan-2-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate as a grey solid (583 mg, 79%).

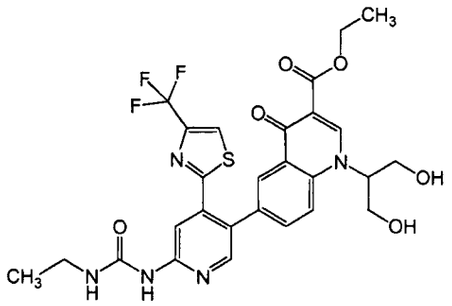
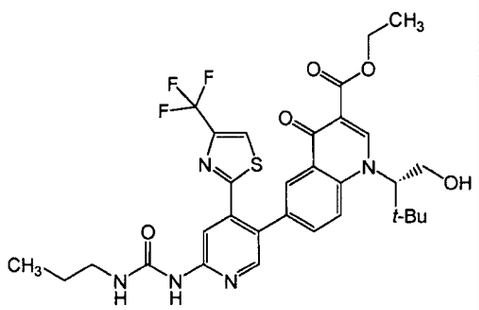
MS (ESP): 590 for $C_{27}H_{26}F_3N_5O_5S$.

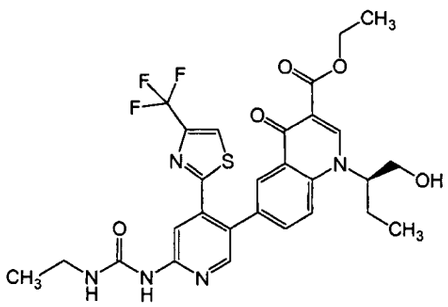
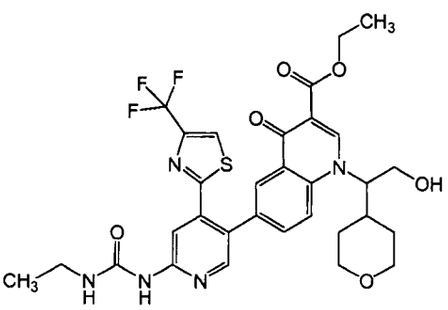
NMR (d_6-DMSO) δ 9.47 (s, 1H), 8.68 (s, 1H), 8.49 (s, 1H), 8.31 (s, 1H), 8.24 (s, 1H), 8.19 (d, 1h), 8.106 (d, 1H), 7.72 (dd, 1H), 7.66 (t, 1H), 5.26 (s, 1H), 5.11-5.06 (m, 1H), 4.28 (m, 2H), 3.79 (d, 2H), 3.25-3.17 (m, 2H), 1.51 (d, 3H), 1.29 (t, 3H), 1.11 (t, 3H).

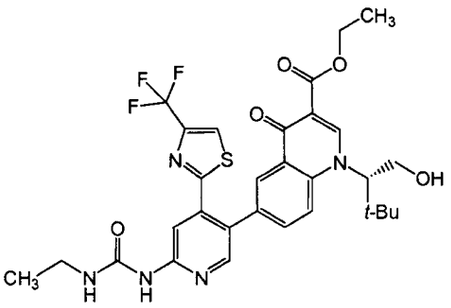
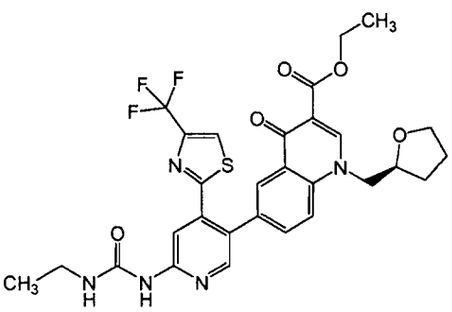
Examples 98-108

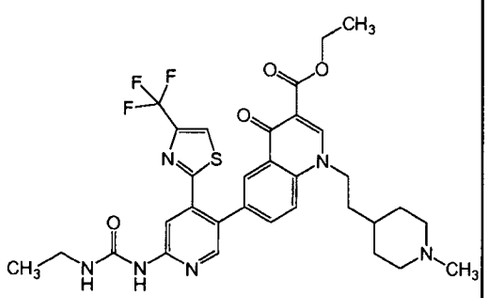
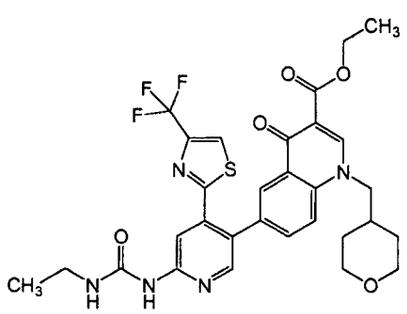
The following examples were prepared by the procedure described in Example 97 from the indicated starting material.

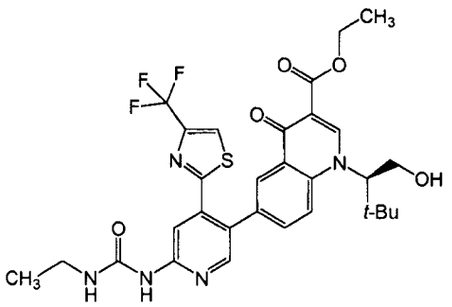
Ex	Compound	Data	SM
98	(*R*)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-hydroxypropan-2-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 590 for $C_{27}H_{26}F_3N_5O_5S$ NMR (d_6-DMSO) δ 9.48 (s, 1H), 8.68 (s, 1H), 8.49 (s, 1H), 8.31 (s, 1H),l 8.24 (s, 1h), 8.19 (d, 1H), 8.06 (d, 1H), 7.71 (dd, 2H), 5.35-5.25 (m, 1H), 5.11-5.06 (m, 1H), 4.28-4.21 (m, 2H), 3.79 (d, 2H), 3.25-3.19 (m, 2H), 1.51 (d, 3H), 1.29 (t, 3H), 1.11 (t, 3H)	Intermediate 48 and Intermediate 17
99	Ethyl 1-((2*R*,3*R*)-1,3-dihydroxybutan-2-yl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 620 for $C_{28}H_{28}F_3N_5O_6S$ NMR (d_6-DMSO) δ 9.47 (s, 1H), 8.89 (s, 1H), 8.51 (s, 1H), 8.32 (s, 1H), 8.23 (s, 1H), 8.17 (s, 1H), 8.07 (d, 1H), 7.7-7.65 (m, 2H), 5.22 (s, 1H), 4.87 (s, 1H), 4.25-4.22 (m, 3H), 3.97-3.82 (m, 2H), 3.25-3.18 (m, 2H), 1.28 (t, 3H), 1.13 (d, 3H), 1.11 (t, 3H)	Intermediate 50 and Intermediate 17

Ex	Compound	Data	SM
100	Ethyl 1-(1,3-dihydroxypropan-2-yl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 606 for $C_{27}H_{26}F_3N_5O_6S$ NMR (d_6-DMSO) δ 9.47 (s, 1H), 8.72 (s, 1H), 8.49 (s, 1H), 8.31(s, 1H), 8.24 (s, 1H), 8.19 (d, 1H0, 8.13 (s, 1H), 7.71 (dd, 1H), 5.3 (s, 1H), 4.54-4.36 (m, 2H), 4.25-4.14 (m, 2H), 4.04-3.86 (m, 2H), 3.24-3.14 (m, 4H), 1.27 (t, 3H), 1.11 (t, 3H)	Intermediate 52 and Intermediate 17
101	(*S*)-ethyl 6-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-hydroxy-3,3-dimethylbutan-2-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 646 for $C_{31}H_{34}F_3N_5O_5S$	Intermediate 55 anmd Intermediate 47

Ex	Compound	Data	SM
102	(*R*)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-hydroxybutan-2-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 604 for $C_{28}H_{28}F_3N_5O_5S$ NMR (d_6-DMSO) δ 9.45 (s, 1H), 8.66 (s, 1H), 8.51 (s, 1H), 8.33 (s, 1H), 8.22 (s, 1H), 8.19 (d, 1H), 8.06 (d, 1H), 7.7-7.65 (m, 2H), 5.23-5.18 (m, 1H), 4.91 (s, 1H), 4.28-4.21 (m, 2H), 3.85-3.73 (m, 2H), 3.25-3.17 (m, 2H), 2.0-1.9 (m, 2H), 1.28 (t, 3H), 1.11 (t, 3H), 0.89 (t, 3H)	Intermediate 57 and Intermediate 17
103	Ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(2-hydroxy-1-(tetrahydro-2H-pyran-4-yl)ethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 660 for $C_{31}H_{32}F_3N_5O_6S$ NMR (d_6-DMSO) δ 9.44 (s, 1H), 8.79 (s, 1H), 8.53 (s, 1H), 8.35 (s, 1H), 8.22 (s, 1H), 8.19 (d, 1H), 8.15 (d, 1H), 7.68-7.6 (m, 2H), 5.27-5.23 (m, 1H), 4.83 (s, 1H), 4.29-4.22 (m, 2H), 4.0-3.92 (m, 2H), 3.81-3.75 (m, 2H), 3.25-3.2 (m, 2H), 2.3-2.25 (m, 1H), 1.83-1.76 (m, 2H), 1.3 (t, 3H), 1.23-1.17 (m, 2H), 1.13 (t, 3H)	Intermediate 59 and Intermediate 17

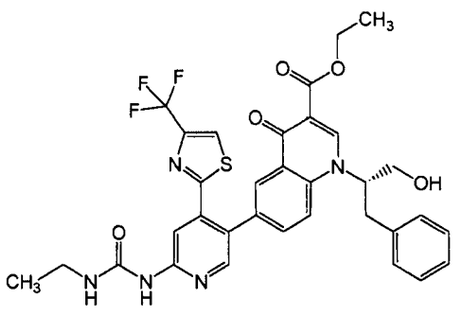
Ex	Compound	Data	SM
104	(*S*)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-hydroxy-3,3-dimethylbutan-2-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 632 for $C_{30}H_{32}F_3N_5O_5S$ NMR (d_6-DMSO) δ 9.45 (s, 1H), 8.65 (s, 1H), 8.53 (s, 1H), 8.34 (s, 1H), 8.21-8.17 (m, 3H), 7.63 (d, 2H), 5.12-5.09 (m, 1H), 4.97-4.92 (m, 1H), 4.29-4.2 (m, 2H), 4.05-4.0 (m, 2H), 3.26-3.18 (m, 2H), 1.28 (t, 3H), 1.11 (t, 3H), 0.97 (s, 9H)	Intermediate 55 and Intermediate 17
105	(*S*)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-((tetrahydrofuran-2-yl)methyl)-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 616 for $C_{29}H_{28}F_3N_5O_5S$ NMR (d_6-DMSO) δ 9.45 (s, 1H), 8.63 (s, 1H), 8.49 (s, 1H), 8.32 (s, 1H), 8.23 (s, 1H), 8.15 (d, 1H), 7.98 (d, 1H), 7.7 (dd, 1H), 7.67 (t, 1H), 4.67 (d, 1H), 4.35-4.3 (m, 1H), 4.27-4.21 (m, 2H), 4.2-4.18 (m, 1H), 3.83-3.79 (m, 1H), 3.67-3.62 (m, 1H), 3.25-3.19 (m, 2H), 2.1-2.04 (m, 1H), 1.92-1.8 (m, 2H), 1.64-1.55 (m, 2H), 1.28 (t, 3H), 1.11 (t, 3H)	Intermediate 61 and Intermediate 17

Ex	Compound	Data	SM
106	Ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(2-(1-methylpiperidin-4-yl)ethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 657 for $C_{32}H_{35}F_3N_6O_4S$ NMR (d_6-DMSO) δ 9.45 (s, 1H), 8.72 (s, 1H), 8.49 (s, 1H), 8.32 (s, 1H), 8.22 (s, 1H), 8.14 (s, 1H), 7.84 (d, 1H), 7.7 (dd, 1H), 7.62 (t, 1H), 4.48-4.4 (m, 1H), 4.27-4.19 (m, 2H), 3.25-3.19 (m, 2H), 2.82-2.72 (m, 2H), 2.15 (s, 3H), 1.86-1.82 (m, 2H), 1.75-1.68 (m, 2H), 1.28 (t, 3H), 1.11 (t, 3H)	Intermediate 69 and Intermediate 17
107	Ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-((tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 630 for $C_{30}H_{30}F_3N_5O_5S$ NMR (d_6-DMSO) δ 9.45 (s, 1H), 8.68 (s, 1H), 8.51 (s, 1H), 8.33 (s, 1H), 8.21 (s, 1H), 8.14 (s, 1H), 7.96 (d, 1H), 7.68 (dd, 1H), 7.62 (t, 1H), 4.34 (d, 1H), 4.24-4.2 (m, 2H), 3.86 (d, 2H), 3.24-3.17 (m, 4H), 2.1-2.06 (m, 1H), 1.46-1.42 (m, 4H), 1.28 (t, 3H), 1.11 (t, 3H)	Intermediate 62 and Intermediate 17

Ex	Compound	Data	SM
108	(*R*)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-hydroxy-3,3-dimethylbutan-2-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 632 for $C_{30}H_{32}F_3N_5O_5S$	Intermediate 66 and Intermediate 17

Example 109

ethyl 1-[(1*S*)-1-benzyl-2-hydroxyethyl]-6-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-4-oxo-1,4-dihydroquinoline-3-carboxylate



To a solution of palladium (II) acetate (23.52 mg, 0.10 mmol, 0.1 equiv.) and 1,1'-bis(di-*t*-butylphosphino)ferrocene (49.7 mg, 0.10 mmol, 0.1 equiv.) in acetonitrile (3 mL) was added (*S*)-ethyl 1-(1-hydroxy-3-phenylpropan-2-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate (Intermediate 51, 500 mg, 1.05 mmol), followed by 6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazole-2-yl)pyridine-3-ylboronic acid (Intermediate 17, 381 mg, 1.06 mmol) and a solution of potassium carbonate (217 mg, 1.57 mmol) in water (1 mL). The reaction mixture was stirred at 60 °C for 2 h, cooled to room temperature, and diluted with water (2 mL). The reaction mixture was partitioned between water (10 mL) and ethyl acetate (10 mL). The aqueous layer was extracted with ethyl acetate (2x10 mL), and the organics were dried over sodium sulfate and concentrated to provide (*S*)-ethyl 6-(6-(3-ethylureido)-4-

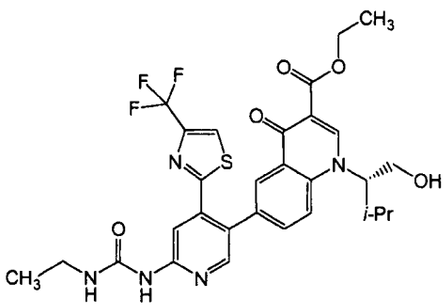
(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-hydroxy-3-phenylpropan-2-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate as a grey solid (619 mg, 89%).

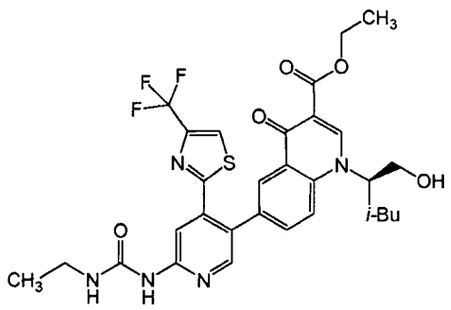
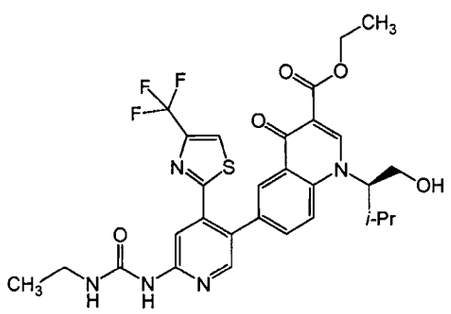
MS (ESP): 620 for $C_{28}H_{28}F_3N_5O_6S$.

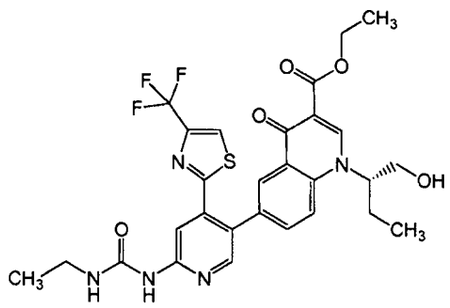
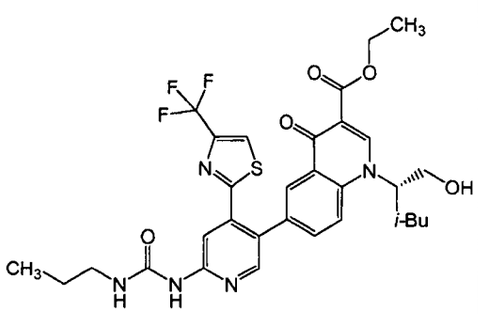
NMR (d_6-DMSO) δ 9.43 (s, 1H), 8.75 (s, 1H), 8.56 (s, 1H), 8.26 (s, 1H), 8.22 (s, 1H), 8.08 (d, 1H), 7.97 (d, 1H), 7.64-7.56 (m, 2H), 5.35-5.29 (m, 2H), 4.29-4.19 (m, 2H), 3.85 (s, 2H), 3.25-3.16 (m, 3H), 1.3 (t, 3H), 1.1 (t, 3H).

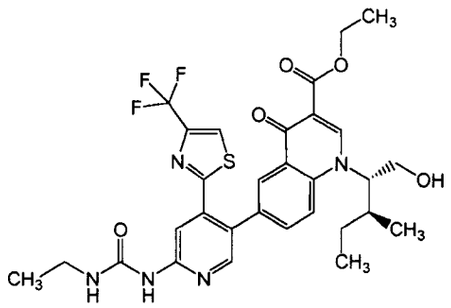
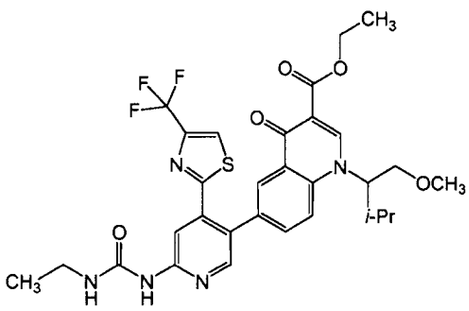
Examples 110-119

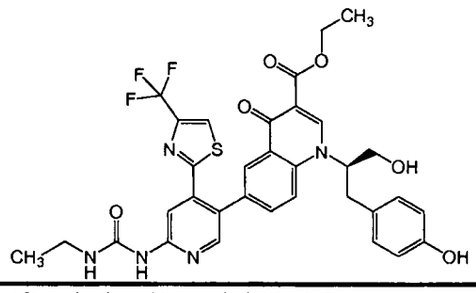
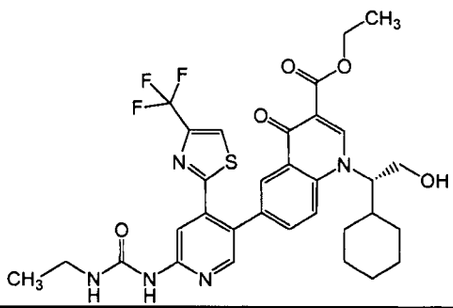
The following examples were prepared by the procedure described in Example 109 from the indicated starting material.

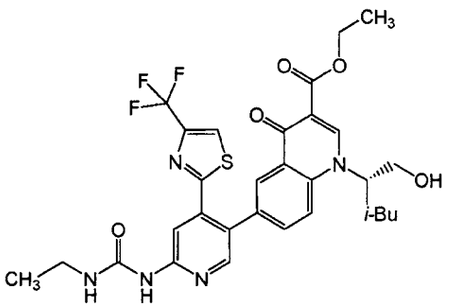
Ex	Compound	Data	SM
110	(*S*)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-hydroxy-3-methylbutan-2-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 618 for $C_{29}H_{30}F_3N_5O_5S$ NMR (d_6-DMSO) δ 9.44 (s, 1H), 8.72 (s, 1H), 8.51 (s, 1H), 8.33 (s, 1H), 8.2 (s, 1H), 8.17 (d, 1H), 8.11 (d, 1H), 7.62 (t, 2H), 5.22-5.17 (m, 1H), 4.68 (s, 1H), 4.27-4.2 (m, 2H), 3.95-3.91 (m, 1H), 3.8-3.74 (m, 1H), 3.24-3.15 (m 4H), 2.4-2.3 (m, 1H), 1.27 (t, 3H), 1.1 (t, 3H), 1.08 (d, 3H), 0.75 (d, 3H)	Intermediate 53 and Intermediate 17

Ex	Compound	Data	SM
111	(*R*)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-hydroxy-4-methylpentan-2-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 632 for $C_{30}H_{32}F_3N_5O_5S$ NMR (d_6-DMSO) δ 9.45 (s, 1H), 8.64 (s, 1H), 8.52 (s, 1H), 8.33 (s, 1H), 8.21 (s, 1H), 8.17 (d, 1H), 8.14 (d, 1H), 7.64 (t, 1H), 7.47 (dd, 1H), 5.19 (t, 1H), 5.02 (s, 1H), 4.27-4.2 (m, 3H), 3.76-3.72 (m, 2H), 3.25-3.15 (m, 4H), 1.9-1.78 (m, 1H), 1.76-1.72 (m, 1H), 1.56-1.45 (m, 2H), 1.28 (t, 3H), 1.11 (t, 3H), 0.92 (d, 3H), 0.86 (d, 3H)	Intermediate 54 and Intermediate 17
112	(*R*)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-hydroxy-3-methylbutan-2-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 618 for $C_{29}H_{30}F_3N_5O_5S$ NMR (d_6-DMSO) δ 9.45 (s, 1H), 8.73 (s, 1H), 8.51 (s, 1H), 8.34 (s, 1H), 8.21 (s, 1H), 8.17 (d, 1H), 8.12 (d, 1H), 7.63 (t, 2H), 5.22-5.17 (m, 1H), 4.7 (s, 1H), 4.27-4.2 (m, 2H), 3.98-3.91 (m, 1H), 3.81-3.76 (m, 1H), 3.25-3.15 (m, 2H), 2.34-3.27 (m, 1H), 1.28 (t, 3H), 1.11 (t, 3H), 1.08 (d, 3H), 0.75 (d, 3H)	Intermediate 56 and Intermediate 17

Ex	Compound	Data	SM
113	(*S*)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-hydroxybutan-2-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 604 for $C_{28}H_{28}F_3N_5O_5S$ NMR (d_6-DMSO) δ 9.45 (s, 1H), 8.66 (s, 1H), 8.51 (s, 1H), 8.33 (s, 1H), 8.22 (s, 1H), 8.18 (d, 1H), 8.08 (d, 1H), 7.69 (dd, 1H), 7.66 (t, 1H), 5.23-5.18 (m, 1H), 4.91 (s, 1H), 4.27-4.2 (m, 2H), 3.83-3.75 (m, 2H), 3.25-3.17 (m, 2H), 2.07-1.9 (m, 2H), 1.28 (t, 3H), 1.11 (t, 3H), 0.88 (t, 3H)	Intermediate 58 and Intermediate 17
114	(*S*)-ethyl 1-(1-hydroxy-3,3-dimethylbutan-2-yl)-4-oxo-6-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 646 for $C_{31}H_{34}F_3N_5O_5S$ NMR (d_6-DMSO) δ 9.44 (s, 1H), 8.64 (s, 1H), 8.52 (s, 1H), 8.33 (s, 1H), 8.22 (s, 1H), 8.17 (d, 1H), 8.1 (d, 1H), 7.7-7.66 (m, 2H), 5.22-5.18 (m, 1H), 5.02 (s, 1H), 4.27-4.2 (m, 2H), 3.76-3.73 (m, 2H), 3.18-3.12 (m, 2H), 1.99-94 (m, 1H), 1.93-1.88 (s, 1H), 1.54-1.44 (m, 2H), 1.28 (t, 3H), 0.92 (d, 3H), 0.9 (s, 9H), 0.88 (d, 3H)	Intermediate 60 and Intermediate 47

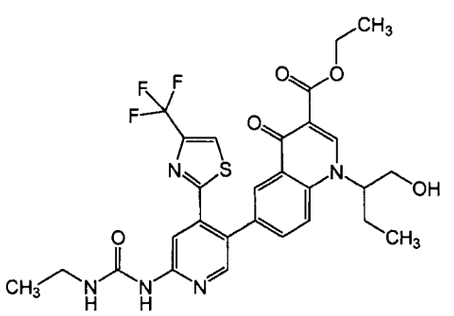
Ex	Compound	Data	SM
115	Ethyl 1-((2*S*,3*S*)-1,3-dihydroxypentan-2-yl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 632 for $C_{30}H_{32}F_3N_5O_5S$ NMR (d_6-DMSO) δ 9.45 (s, 1H), 8.72 (s, 1H), 8.52 (s, 1H), 8.34 (s, 1H), 8.2 (d, 1H), 8.09 (d, 1H), 7.68-7.60 (m, 2H), 5.2-5.17 (m, 1H), 4.76 (s, 1H), 4.27-4.2 (m, 2H), 4.01-3.94 (m, 1H), 3.8-3.75 (m, 1H), 3.24-3.16 (m, 2H), 2.13 (s, 1H), 1.27 (t, 3H), 1.11 (t, 3H), 0.77-0.73 (m, 4H)	Intermediate 63 and Intermediate 17
116	Ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-methoxy-3-methylbutan-2-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 632 for $C_{30}H_{32}F_3N_5O_5S$ NMR (d_6-DMSO) δ 9.45 (s, 1H), 8.71 (s, 1H), 8.52 (s, 1H), 8.35 (s, 1H), 8.2-8.12 (m, 3H), 7.65-7.62 (m, 2H), 4.89 (s, 1H), 4.27-4.2 (m, 2H), 3.91 (s, 1H0, 3.74-3.71 (m, 1H), 3.26-3.21 (m, 2H), 3.25 (s, 3H), 2.3-2.27 (m, 2H), 1.28 (t, 3H), 1.11 (t, 3H), 0.75 (d, 3H)	Intermediate 70 and Intermediate 17

Ex	Compound	Data	SM
117	(*R*)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-hydroxy-3-(4-hydroxyphenyl)propan-2-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 682 for $C_{33}H_{30}F_3N_5O_6S$	Intermediate 67 and Intermediate 17
118	(*S*)-ethyl 1-(1-cyclohexyl-2-hydroxyethyl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 658 for $C_{32}H_{34}F_3N_5O_5S$	Intermediate 68 and Intermediate 17

Ex	Compound	Data	SM
119	(*S*)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-hydroxy-4-methylpentan-2-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 632 for $C_{30}H_{32}F_3N_5O_5S$ NMR (d_6-DMSO) δ 9.45 (s, 1H), 8.64 (s, 1H), 8.52 (s, 1H), 8.33 (s, 1H), 8.21 (s, 1H), 8.18 (d, 1H), 8.1 (d, 1H), 7.69-7.61 (m, 2H), 5.21-5.18 (m, 1H), 5.02 (s, 1H), 4.27-4.21 (m, 2H), 3.78-3.71 (m, 2H), 3.25-3.17 (m, 2H), 1.92-1.84 (m, 1H), 1.78-1.74 (m, 1H), 1.49-1.42 (m, 1H), 1.28 (t, 3H), 1.11 (t, 3H), 0.92 (d, 3H), 0.86 (d, 3H)	Intermediate 60 and Intermediate 17

Example 120

ethyl 6-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-1-[1-(hydroxymethyl)propyl]-4-oxo-1,4-dihydroquinoline-3-carboxylate



To a suspension of ethyl 1-(1-hydroxybutan-2-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate (Intermediate 64, 282 mg, 0.78 mmol) and 6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazole-2-yl)pyridine-3-ylboronic acid (Intermediate 17, 350 mg, 0.84 mmol) in 1,4-dioxane (3 mL) was added a solution of cesium carbonate (467 mg, 1.43 mmol) in water (1 mL) followed by tetrakis(triphenylphosphino)palladium(0) (48.7 mg, 0.04 mmol). The reaction mixture was stirred at 100 °C for 2 h, cooled to room temperature, and diluted with water (2 mL). The precipitate that formed was collected by filtration, washed with water and hexanes. Purification via column chromatography (silica, 95:5 methylene

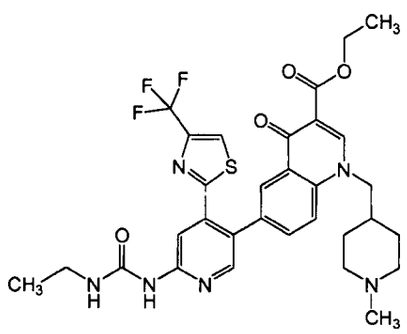
chloride/methanol) provided ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-hydroxybutan-2-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate as a yellow/orange solid (136 mg, 27%).

MS (ESP): 604 for $C_{28}H_{28}F_3N_5O_5S$.

NMR (d_6-DMSO) δ 9.44 (s, 1H), 8.66 (s, 1H), 8.5 (s, 1H), 8.32 (s, 1H), 8.22 (s, 1H), 8.18 (d, 1H), 8.08 (d, 1H), 7.69-7.65 (m, 2H), 5.23-5.18 (m, 1H), 4.9 (s, 1H), 4.27-4.2 (m, 2H), 3.82-3.76 (m, 2H), 3.26-3.16 (m, 2H), 2.0-1.93 (m, 2H), 1.28 (t, 3H), 1.11 (t, 3H), 0.88 (t, 3H).

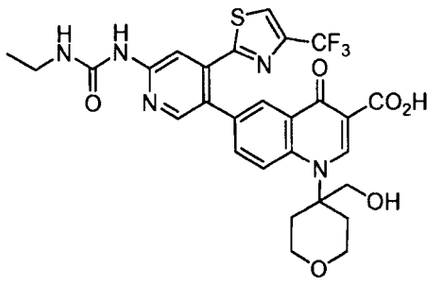
Example 121

The following example was prepared by the procedure described in Example 120 with the indicated starting material.

Ex	Compound	Data	SM
121	Ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-((1-methylpiperidin-4-yl)methyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 643 for $C_{31}H_{33}F_3N_6O_4S$ NMR (d_6-DMSO) δ 9.47 (s, 1H), 8.72 (s, 1H), 8.5 (s, 1H), 8.23 (s, 1H), 8.31 (s, 1H), 8.15 (d, 1H), 7.97 (d, 1H), 7.72 (dd, 1H), 7.66 (t, 1H), 4.4-4.36 (m, 1H), 4.26-4.21 (m, 2H), 3.39-3.35 (m, 2H), 3.25-3.19 (m, 2H), 2.85-2.8 (m, 2H), 2.69 (d, 3H), 1.8-1.76 (m, 2H), 1.63-1.5 (m, 2H), 1.28 (t, 3H), 1.11 (t, 3H)	Intermediate 65 and Intermediate 17

Example 122

6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(4-(hydroxymethyl)tetrahydro-2*H*-pyran-4-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



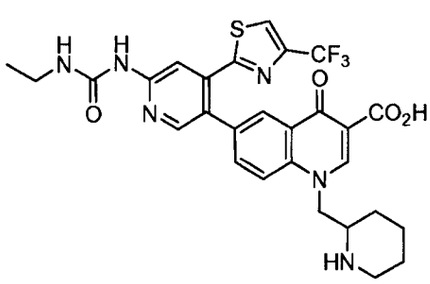
Ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(4-(hydroxymethyl)tetrahydro-2*H*-pyran-4-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (Example 132, 0.225 g, 0.35 mmol) was diluted with 2:1 MeOH:THF (3 mL). A 2 M aq solution of LiOH (0.35 mL, 0.7 mmol) was added and the reaction mixture was heated in the microwave to 100 °C for 15 min. The mixture was conc *in vacuo* and acidified to approx. pH 3 with 1 N aq HCl. The resultant solid was collected and purified by column chromatography (silica 95:5 methylene chloride/methanol) followed by purification by reverse phase HPLC (C18, 0-95% acetonitrile/water gradient).

LC/MS (ES^+)[$(M+H)^+$]: 618 for $C_{28}H_{26}F_3N_5O_6S$

^1H NMR (DMSO-d_6): δ14.93 (br s, 1H); 9.52 (s, 1H); 8.96 (s, 1H); 8.55 (s, 1H); 8.49 (m, 1H); 8.37 (m, 2H); 8.22 (s, 1H); 7.73 (m, 1H); 7.63 (m, 1H); 5.48 (t, 1H); 4.29 (m, 2H); 3.75 (m, 4 H); 3.21 (m, 2H); 2.54 –2.32 (br m, 4 H); 1.11 (t, 3H).

Example 123

6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(piperidin-2-ylmethyl)-1,4-dihydroquinoline-3-carboxylic acid



A solution of 1-((1-(tert-butoxycarbonyl)piperidin-2-yl)methyl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 138, 0.888 g, 1.27 mmol) in THF (10 mL) and anisole (0.208 mL, 1.90 mmol) was cooled to 0 °C. A 4 M solution of HCl in dioxane (9.5 mL, 38 mmol) was added dropwise. After the addition was complete, the ice bath was removed and the reaction was stirred at room

temperature for 1.5 h. An additional 40 mL of 4 M HCl in dioxane was added and the reaction mixture was stirred for 5 days. The volume of the reaction mixture was then reduced by two-thirds *in vacuo*. Diethyl ether (15 mL) was added to the reaction mixture under N_2 and it was stirred for 1 h. The resultant solid was collected and rinsed with ether. Purification was performed by reverse phase HPLC (C18, 0-95% acetonotrile/water gradient) to provide the desired product.

LC/MS (ES^+)[$(M+H)^+$]: 601 for $C_{28}H_{27}F_3N_6O_4S$

^1H NMR (DMSO-d_6): δ9.48 (s, 1H); 8.94 (s, 1H); 8.53 (s, 1H); 8.37 (s, 1H); 8.31 (d, 1H); 8.21 (s, 1H); 8.13 (d, 1H); 7.82 (dd, 1H); 7.60 (m, 1H); 4.60 (dd, 1H); 4.34 (m, 1H); 3.21 (m, 2H); 2.86 (m, 2H); 2.30 (m, 1H); 1.73 (m, 2H); 1.47 (m, 1H); 1.27 (m, 2H); 1.11 (m, 1H); 1.11 (t, 3H).

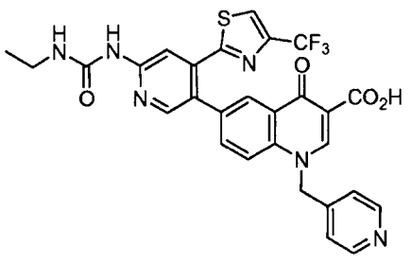
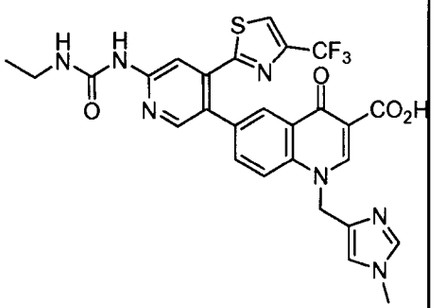
Examples 124-127

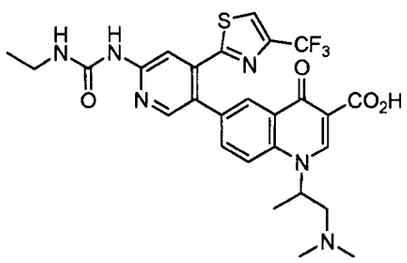
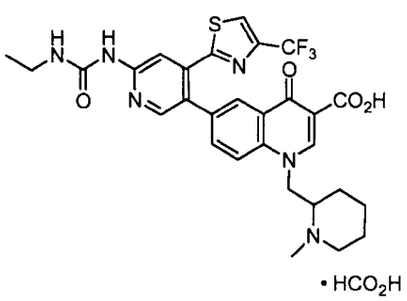
General Procedures

The following compounds were prepared by either of the procedures described below from the starting materials indicated in the table.

Procedure A: The appropriate ethyl ester (1 eq) was diluted with 2:1 MeOH:THF. A 2 M aq solution of LiOH (2 eq) was added and the reaction mixture was heated in the microwave to 100 °C for 15 min. The mixture was conc *in vacuo* and then diluted with CH_2Cl_2 and cooled to 0 °C. The mixture was acidified to approximately pH 4 with 1 N aq HCl. The layers were separated and the organic layer was conconcentrated *in vacuo*. Purification was performed by column chromatography (silica, 95:5 methylene choride/methanol) to provide the desired product.

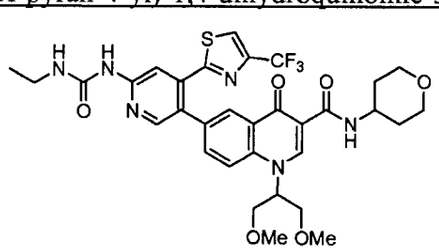
Procedure B: The appropriate ethyl ester (1 eq) was diluted with 2:1 MeOH:THF. A 2 M aq solution of LiOH (2 eq) was added and the reaction mixture was heated in the microwave to 100 °C for 15 min. The mixture was cooled to 0 °C, acidified with 1 N aq HCl and conconcentrated *in vacuo*. Purification was performed by reverse phase HPLC (C18, 0-95% acetonitrile/water gradient) to provide the desired product.

Ex	Compound	Data	SM
124	6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(pyridin-4-ylmethyl)-1,4-dihydroquinoline-3-carboxylic acid 	LC/MS (ES^+)[$(M+H)^+$]: 595 for $C_{28}H_{21}F_3N_6O_4S$ ^1H NMR (DMSO-d_6): δ14.96 (s, 1H); 9.46 (s, 1H); 9.33 (s, 1H); 8.53 (m, 3H); 8.33 (m, 2H); 8.19 (s, 1H); 7.74 (s, 2H); 7.57 (m, 1H); 7.22 (m, 2H); 5.97 (s, 2H); 3.20 (m, 2H); 1.10 (t, 3H).	Example 133
125	6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-((1-methyl-1H-imidazol-4-yl)methyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	LC/MS (ES^+)[$(M+H)^+$]: 598 for $C_{27}H_{22}F_3N_7O_4S$ ^1H NMR (DMSO-d_6): δ15.04 (br s, 1H); 9.48 (s, 1H); 9.19 (s, 1H); 8.49 (s, 1H); 8.33 (s, 1H); 8.27 (m, 2H); 8.21 (s, 1H); 7.82 (m, 1H); 7.61 (m, 1H); 7.54 (s, 1H); 7.31 (s, 1H); 5.66 (s, 2H); 3.59 (s, 3H); 3.20 (m, 2H); 1.10 (t, 3H).	Example 136

Ex	Compound	Data	SM
126	1-(1-(dimethylamino)propan-2-yl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	LC/MS (ES^+)[$(M+H)^+$]: 589 for $C_{27}H_{27}F_3N_6O_4S$ ^1H NMR (DMSO-d_6): δ15.07 (s, 1H); 9.47 (s, 1H); 8.88 (s, 1H); 8.53 (s, 1H); 8.39 (s, 1H); 8.34 (d, 1H); 8.29 (d, 1H); 8.22 (s, 1H); 7.84 (m, 1H); 7.59 (m, 1H); 5.35 (br s, 1H); 3.22 (m, 2H); 3.10 (m, 1H); 2.62 (m, 1H); 2.14 (br s, 6H); 1.54 (m, 3H); 1.11 (t, 3H).	Example 134
127	6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-((1-methylpiperidin-2-yl)methyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, formic acid salt 	LC/MS (ES^+)[$(M+H)^+$]: 615 for $C_{29}H_{29}F_3N_6O_4S$ ^1H NMR (DMSO-d_6): δ15.00 (br s, 1H); 9.46 (s, 1H); 9.01 (s, 1H); 8.53 (s, 1H); 8.39 (s, 1H); 8.30 (d, 1H); 8.21 (s, 1H); 8.14 (s, 1H); 8.05 (d, 1H); 7.84 (dd, 1H); 7.57 (m, 1H); 5.02 (m, 1H); 4.47 (m, 1H): 3.22 (m, 2H): 2.95 (m, 1H); 2.57 (m, 2H); 2.42 (s, 3H); 2.18 (m, 1H); 1.62 (m, 1H); 1.47 (m, 2H); 1.21 (m, 2H); 1.11 (t, 3H).	Example 135

Example 128

1-(1,3-dimethoxypropan-2-yl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-N-(tetrahydro-2H-pyran-4-yl)-1,4-dihydroquinoline-3-carboxamide



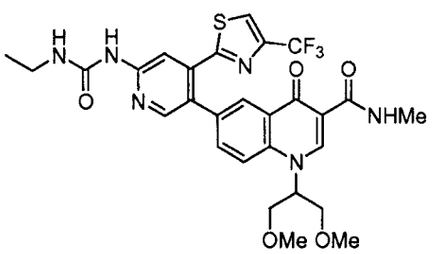
1-(1,3-Dimethoxypropan-2-yl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4, 0.112 g, 0.18 mmol) was suspended in DMF (1 mL). O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) (0.105 g, 0.28 mmol) was added, followed by diisopropylethylamine (0.193 mL, 1.11 mmol). The reaction mixture was stirred for 15 min at RT. The 4-aminotetrahydropyran hydrochloride (0.038 g, 0.28 mmol) was added in one portion and the mixture was stirred at RT for 2 days. Water was added and the resultant solid was purified by column chromatography (silica, 95:5 methylene chloride/methanol) to provide the product as a solid. The solid was further purified by trituration with CH_2Cl_2 and hexanes.

LC/MS (ES^+)[$(M+H)^+$]: 689 for $C_{32}H_{35}F_3N_6O_6S$

^1H NMR (DMSO-d_6): δ9.99 (m, 1H); 9.46 (s, 1H); 8.93 (s, 1H); 8.50 (s, 1H); 8.32 (d, 2H); 8.24 (s, 1H); 8.15 (d, 1H); 7.73 (m, 1H); 7.61 (m, 1H); 5.45 (br s, 1H); 3.92 (m, 7H); 3.45 (m, 2H); 3.25 (m, 8H); 1.87 (m, 2H); 1.50 (m, 2H); 1.11 (t, 3H).

Example 129

1-(1,3-dimethoxypropan-2-yl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-N-methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide



1-(1,3-Dimethoxypropan-2-yl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4, 0.112 g, 0.18 mmol) was suspended in DMF (1 mL). O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) (0.105 g, 0.28 mmol) was added, followed by diisopropylethylamine (0.097 mL, 0.55 mmol). The reaction mixture was stirred for 15 min at RT. A 2.0 M solution of methylamine in THF (0.2 mL, 0.40 mmol) was added and the mixture was stirred at RT for 2 d. Water was added and the solid precipitate was purified by column chromatography (silica, 95:5 methylene chloride/methanol). The solid was further

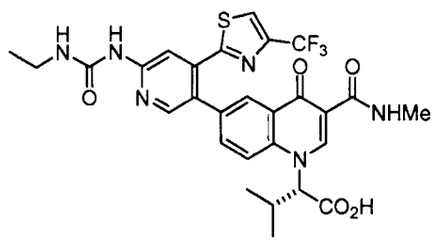
purified by trituration with CH_2Cl_2 and hexanes.

LC/MS (ES^+)[$(M+H)^+$]: 619 for $C_{28}H_{29}F_3N_6O_5S$

^1H NMR (DMSO-d_6): δ9.69 (m, 1H); 9.46 (s, 1H); 8.92 (s, 1H); 8.50 (s, 1H); 8.29 (m, 3H); 8.14 (d, 1H); 7.74 (m, 1H); 7.63 (m, 1H); 5.44 (br s, 1H); 3.84 (m, 4H); 3.25 (m, 8H); 2.86 (m, 3H); 1.11 (t, 3H).

Example 130

(S)-2-(6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-3-(methylcarbamoyl)-4-oxoquinolin-1(4*H*)-yl)-3-methylbutanoic acid



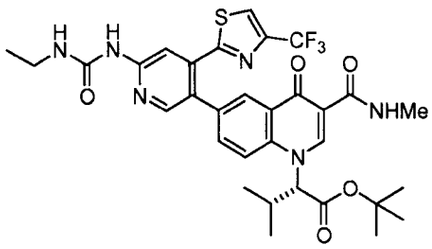
(S)-*Tert*-butyl 2-(6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-3-(methylcarbamoyl)-4-oxoquinolin-1(4H)-yl)-3-methylbutanoate (Example 131, 0.079 g, 0.12 mmol) was diluted with CH_2Cl_2 (4 mL). Triethylsilane (0.047 mL, 0.29 mmol) was added, followed immediately by the addition of trifluoroacetic acid (0.118 mL, 1.53 mmol). The solution was stirred at RT overnight. An additional 26 eq of TFA (0.24 mL) and 5 eq of triethylsilane (0.1 mL) were added and the mixture was stirred for 2 d. The mixture was conconcentrated *in vacuo*, then diluted with ether and conconcentrated *in vacuo* again. Ether was added to the residue and the resultant solid was collected and washed with ether. The solid was purified by trituration with EtOAc.

LC/MS (ES^+)[$(M+H)^+$]: 617 for $C_{28}H_{27}F_3N_6O_5S$

^1H NMR (DMSO-d_6): δ9.64 (s, 1H); 9.46 (s, 1H); 8.91 (s, 1H); 8.50 (s, 1H); 8.36 (s, 1H); 8.23 (m, 2H); 7.76 (m, 1H); 7.62 (s, 1H); 5.43 (s, 1H); 3.21 (m, 3H); 2.86 (m, 3H); 1.13 (m, 6H); 0.81 (br s, 3H).

Example 131

(S)-tert-butyl 2-(6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-3-(methylcarbamoyl)-4-oxoquinolin-1(4*H*)-yl)-3-methylbutanoate



A solution of (S)-ethyl 1-(1-*tert*-butoxy-3-methyl-1-oxobutan-2-yl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (Example 137, 0.100 g, 0.15 mmol) in 33 wt.% methylamine solution in absolute ethanol (3 mL, 24.1 mmol) was heated in the microwave to 80 °C for 15 min. The mixture was conconcentrated *in vacuo* and purified by column chromatography (silica, 95:5 methylene chloride/methanol) to provide the desired product.

LC/MS (ES^+)[$(M+H)^+$]: 673 for $C_{32}H_{35}F_3N_6O_5S$

^1H NMR (DMSO-d_6): δ9.62 (m, 1H); 9.46 (s, 1H); 8.90 (br s, 1H); 8.53 (s, 1H); 8.37 (s, 1H); 8.25 (d, 1H); 8.18 (s, 1H); 7.75 (m, 1H); 7.60 (m, 2H); 5.43 (m, 1H); 3.21 (m, 2H); 2.86 (d, 3H); 2.59 (m, 1H); 1.36 (br s, 9H); 1.17 (br s, 3H); 1.11 (t, 3H); 0.82 (br s, 3H).

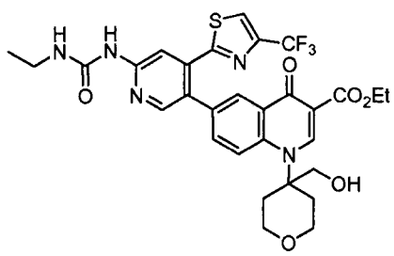
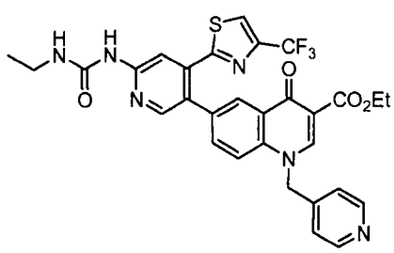
Examples 132-137

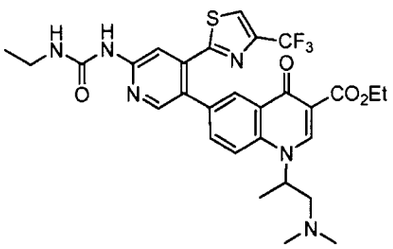
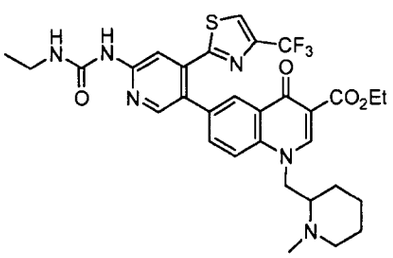
The following compounds were synthesized by either of the procedures described below from the starting material in the table.

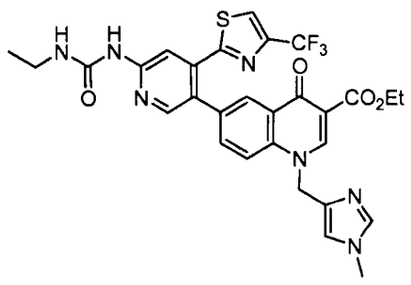
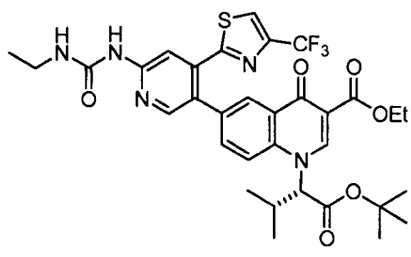
Procedure A: 6-(3-Ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 17) (1 eq) and the appropriate aryl iodide (1 eq) were combined and diluted with dioxane. A solution of Cs_2CO_3 (1.7 eq) in water was added (used a 4:1 ratio of dioxane to water in the reaction). Tetrakis(triphenylphosphine)palladium(0) (0.1 eq) was added and the reaction mixture was heated at 100 °C. After cooling to RT, water was added and the resultant solid was collected. In some cases, purification was performed by column chromatography.

Procedure B: 6-(3-Ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 17) (1 eq) and the appropriate aryl iodide (1 eq) were combined and diluted with dioxane. A solution of Cs_2CO_3 (3 eq) in water was added (used a 4:1 ratio of dioxane to water in the reaction). Tetrakis(triphenylphosphine)palladium(0) (0.1 eq) was added and the

reaction mixture was heated at 100 °C. After cooling to RT, water was added and the resultant solid was collected. The solid was purified by column chromatography.

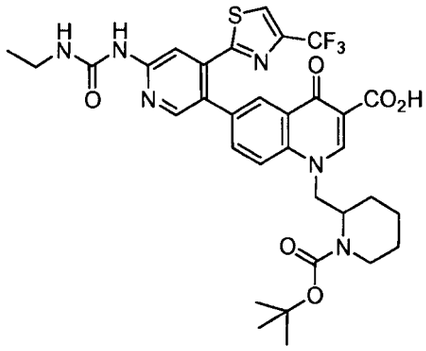
Ex	Compound	Data	SM
132	ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 646 for $C_{30}H_{30}F_3N_5O_6S$	Intermediate 71
133	ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(pyridin-4-ylmethyl)-1,4-dihydroquinoline-3-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 623 for $C_{30}H_{25}F_3N_6O_4S$	Intermediate 73

Ex	Compound	Data	SM
134	ethyl 1-(1-(dimethylamino)propan-2-yl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 617 for $C_{29}H_{31}F_3N_6O_4S$ ^1H NMR (DMSO-d_6): δ9.45 (s, 1H); 8.58 (s, 1H); 8.51 (d, 1H); 8.33 (s, 1H); 8.22 (s, 1H); 8.18 (d, 1H); 8.09 (d, 1H); 7.67 (dd, 1H); 7.63 (m, 1H); 5.12 (m, 1H); 4.22 (m, 2H); 3.21 (m, 2H); 2.99 (m, 1H); 2.57 (m, 1H); 2.15 (br s, 6H); 1.44 (d, 3H); 1.28 (t, 3H); 1.11 (t, 3H).	Intermediate 74
135	ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-((1-methylpiperidin-2-yl)methyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 643 for $C_{31}H_{33}F_3N_6O_4S$ ^1H NMR (DMSO-d_6): δ9.45 (s, 1H); 8.68 (s, 1H); 8.51 (d, 1H); 8.34 (s, 1H); 8.21 (s, 1H); 8.14 (d, 1H); 7.84 (d, 1H); 7.68 (dd, 1H); 7.61 (m, 1H); 4.86 (m, 1H); 4.23 (q, 2H); 4.22 (m, 1H); 3.21 (m, 2H); 2.85 (m, 1H); 2.45 (m, 1H); 2.38 (s, 3H); 2.10 (m, 1H); 1.63 (m, 1H); 1.46 (m, 2H); 1.28 (t, 3H); 1.26 (m, 2H); 1.11 (t, 3H); 1.11 (m, 1H).	Intermediate 75

Ex	Compound	Data	SM
136	ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-((1-methyl-1H-imidazol-4-yl)methyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 626 for $C_{29}H_{26}F_3N_7O_4S$	Intermediate 76
137	(S)-ethyl 1-(1-tert-butoxy-3-methyl-1-oxobutan-2-yl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 688 for $C_{33}H_{36}F_3N_5O_6S$ ^{1}H NMR (DMSO-d_6): δ9.46 (s, 1H); 8.70 (br m , 1H); 8.53 (s, 1H); 8.35 (m, 1H); 8.17 (m, 2H); 7.64 (m, 3H); 5.32 (m, 1H); 4.25 (q, 2H); 3.21 (m, 2H); 2.59 (m, 1H); 1.37 (br s, 9H); 1.28 (t, 3H); 1.17 (br s, 3H); 1.11 (t, 3H); 0.83 (br s, 3H).	Intermediate 77

Example 138

1-((1-(tert-butoxycarbonyl)piperidin-2-yl)methyl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

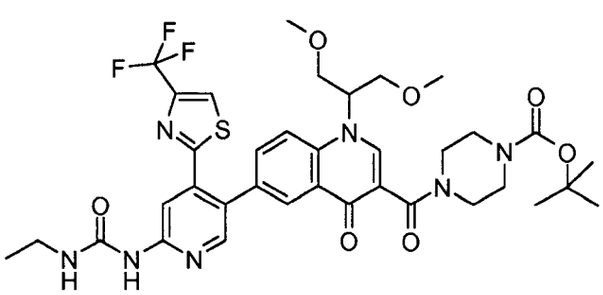


6-(3-Ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 17, 0.448 g, 1.24 mmol) and ethyl 1-((1-(tert-butoxycarbonyl)piperidin-2-yl)methyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate (Intermediate 72, 0.672 g, 1.24 mmol) were combined and diluted with dioxane (6 mL). A solution of Cs_2CO_3 (0.689 g, 2.11 mmol) in water (1.5 mL) was added. Tetrakis(triphenylphosphine)palladium(0) (0.144 g, 0.12 mmol) was added. The mixture was heated at 100 °C overnight. After cooling to RT, water and MeOH were added and the mixture was conconcentrated *in vacuo*. The residue was acidified with 1 N aq HCl and then dried on a lyophilizer. The resultant solid with diluted with EtOAc and water and the layers were separated. The organic layer was washed with water, brine, dried over Na_2SO_4 and conconcentrated *in vacuo* to give the title compound which was used without further purification.

LC/MS (ES^+)[$(M+H)^+$]: 701 for $C_{33}H_{35}F_3N_6O_6S$

Example 139

Tert-butyl 4-{[1-(1,3-dimethoxypropan-2-yl)-6-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-4-oxo-1,4-dihydroquinolin-3-yl]carbonyl}piperazine-1-carboxylate



A solution of tert-butyl 4-{[1-(1,3-dimethoxypropan-2-yl)-6-iodo-4-oxo-1,4-dihydroquinolin-3-yl]carbonyl}piperazine-1-carboxylate (Intermediate 79, 400 mg, 0.68 mmol) in dimethylformamide (15 mL) was purged argon gas, then tetrakis(triphenylphosphine) palladium (69.25 mg, 0.06 mmol) followed by 1-ethyl-3-{5-(4,4,5,5-tetramethyl-1,3,2-

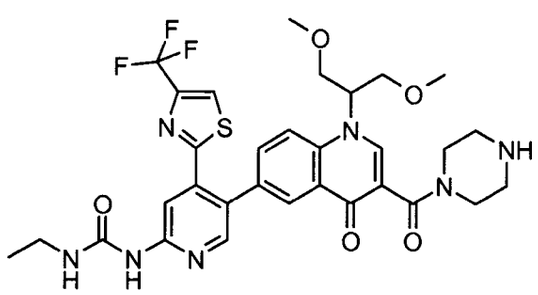
dioxaborolan-2-yl)-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-2-yl}urea (Intermediate 17, 360 mg, 0.82 mmol) was added. The mixture was stirred at room temperature and sodium carbonate (217 mg, 2.05 mmol) which was dissolved in minimum amount of water was added and the reaction mixture was heated to 95 °C for 3 h. After completion of the reaction, the reaction mixture was cooled to room temperature, filtered through celite, and the filtrate was poured into water (200 mL) and stirred for 30 min. The obtained solid was filtered and dried to give the crude compound. The crude was purified by column chromatography eluting with a gradient of 30% ethyl acetate / petroleum ether to 60% ethyl acetate / petroleum ether to afford 260 mg (49%) of tert-butyl 4-{[1-(1,3-dimethoxypropan-2-yl)-6-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-4-oxo-1,4-dihydroquinolin-3-yl]carbonyl}piperazine-1-carboxylate.

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.13 (t, 3H), 1.41 (s, 9H), 3.02 (s, 3H), 3.18 – 3.29 (m, 8H), 3.31 – 3.72 (m, 8H), 3.79 (m, 1H), 4.48 (m, 1H), 7.63 (d, 1H), 7.74 (d, 1H), 8.06 (d, 1H), 8.37 (2s, 2H), 8.39 (s, 1H), 8.47 (s, 1H), 8.75 (s, 1H), 9.47 (s, 1H).

MASS (APCI +ve Scan): m/z 774 (M+H).

Example 140

1-{5-[1-(1,3-dimethoxypropan-2-yl)-4-oxo-3-(piperazin-1-ylcarbonyl)-1,4-dihydroquinolin-6-yl]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-2-yl}-3-ethylurea



Tert-butyl 4-{[1-(1,3-dimethoxypropan-2-yl)-6-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-4-oxo-1,4-dihydroquinolin-3-yl]carbonyl}piperazine-1-carboxylate (Example 139, 260 mg, 0.33 mmol) was dissolved in dichloromethane (15 mL). Trifluoroacetic acid (195 mg, 1.68 mmol) was added to the mixture and it was stirred for 30 h at room temperature. The reaction mixture was concentrated, and the pH was adjusted to 8 with saturated sodium bicarbonate solution to give solid compound which was filtered and dried to afford 160 mg (72%) of 1-{5-[1-(1,3-dimethoxypropan-2-yl)-4-oxo-3-

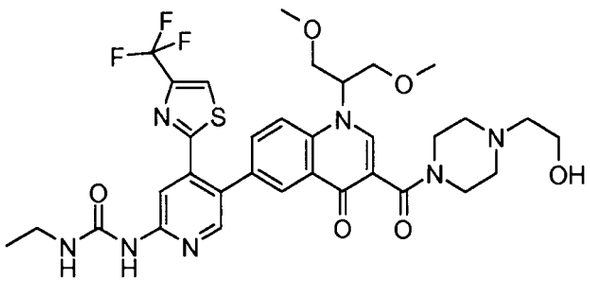
(piperazin-1-ylcarbonyl)-1,4-dihydroquinolin-6-yl]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-2-yl}-3-ethylurea.

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.13 (t, 3H), 2.4-2-82 (m, 3H), 3.02 (s, 3H), 3.18 – 3.29 (m, 7H), 3.31 – 3.72 (m, 8H), 3.79 (m, 1H), 4.48 (m, 1H), 7.63 (d, 1H), 7.74 (d, 1H), 8.06 (d, 1H), 8.37 (2s, 2H), 8.39 (s, 1H), 8.47 (s, 1H), 8.75 (s, 1H), 9.47 (s, 1H).

LC-MS: m/z 674 (M+H).

Example 141

1-{5-[1-(1,3-dimethoxypropan-2-yl)-3-{[4-(2-hydroxyethyl)piperazin-1-yl]carbonyl}-4-oxo-1,4-dihydroquinolin-6-yl]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-2-yl}-3-ethylurea



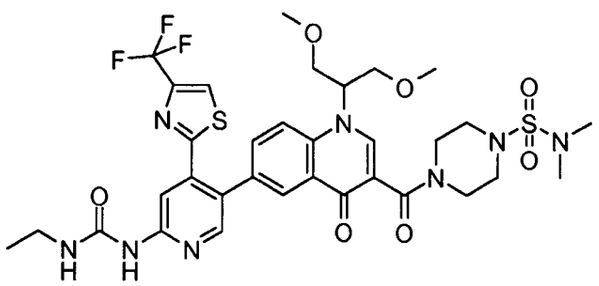
1-{5-[1-(1,3-Dimethoxypropan-2-yl)-4-oxo-3-(piperazin-1-ylcarbonyl)-1,4-dihydroquinolin-6-yl]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-2-yl}-3-ethylurea (Example 140, 180 mg, 0.267 mmol) was dissolved in acetonitrile (15 mL). Potassium carbonate (73.7 mg, 0.53 mmol) was added, followed by the addition of 2-bromoethanol (40 mg, 0.32 mmol) and the mixture was heated to 55 °C for 16 h. The reaction mixture was filtered, and the filtrate was concentrated and dried to give the crude compound. The crude was dissolved in water (10 mL) and the pH was adjusted to 2. The aqueous solution was washed with ethyl acetate, then basified to pH~8 with saturated sodium bicarbonate solution, then extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford 65 mg (34%) of 1-{5-[1-(1,3-dimethoxypropan-2-yl)-3-{[4-(2-hydroxyethyl)piperazin-1-yl]carbonyl}-4-oxo-1,4-dihydroquinolin-6-yl]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-2-yl}-3-ethylurea as an off-white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.09 (t, 3H), 2.41 – 2.44 (m, 5H), 2.66 (m, 1H), 3.04 (s, 3H), 3.21 – 3.24 (m, 7H), 3.49 – 3.60 (m, 7H), 3.77 (br s, 1H), 4.39 (t, 1H), 4.53 (t, 1H), 7.60 (s, 1H), 7.70 (d, 1H), 8.03 (d, 1H), 8.26 (s, 2H), 8.43 (d, 2H), 8.70 (s, 1H), 9.44 (s, 1H).

LC-MS: m/z 718.5 (M+H).

Example 142

4-{[1-(1,3-dimethoxypropan-2-yl)-6-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-4-oxo-1,4-dihydroquinolin-3-yl]carbonyl}-N,N-dimethylpiperazine-1-sulfonamide



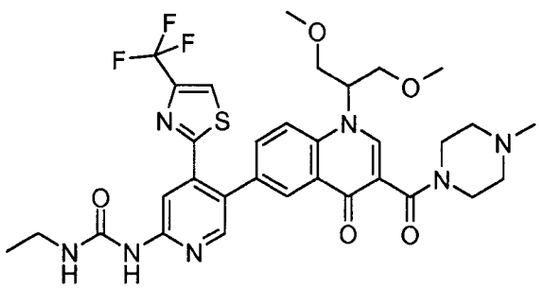
1-{5-[1-(1,3-Dimethoxypropan-2-yl)-4-oxo-3-(piperazin-1-ylcarbonyl)-1,4-dihydroquinolin-6-yl]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-2-yl}-3-ethylurea (Example 140, 250 mg, 0.37 mmol) was dissolved in acetonitrile (25 mL) and potassium carbonate 204.7 mg, 1.48 mmol) was added, followed by addition of dimethylsulfamyl chloride (133 mg, 0.92 mmol). The reaction mixture was stirred for 16 h at 70 °C, then filtered. The filtrate was concentrated to give the crude compound. The crude compound was dissolved in ethyl acetate (60 mL) and washed with water (2 x 60 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford 118 mg, of 4-{[1-(1,3-dimethoxypropan-2-yl)-6-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-4-oxo-1,4-dihydroquinolin-3-yl]carbonyl}-N,N-dimethylpiperazine-1-sulfonamide.

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.07 – 1.13 (m, 4H), 2.74 – 2.78 (m, 6H), 3.04 (s, 3H), 3.13 – 3.20 (m, 1H), 3.25 – 3.37 (m, 6H), 3.42 (m, 3H), 3.51 (d, 3H), 3.68 – 3.69 (br d, 1H), 3.85 (br d, 1H), 4.47 – 4.50 (t, 1H), 7.59 (s, 1H), 7.69 – 7.72 (d, 1H), 8.04 – 8.08 (m, 1H),

LC-MS: m/z 781 (M+H).

Example 143

1-(5-{1-(1,3-dimethoxypropan-2-yl)-3-[(4-methylpiperazin-1-yl)carbonyl]-4-oxo-1,4-dihydroquinolin-6-yl}-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-2-yl)-3-ethylurea



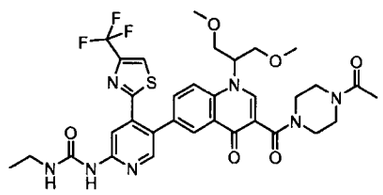
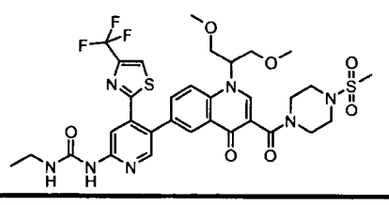
A solution of 1-(1,3-dimethoxypropan-2-yl)-6-iodo-3-[(4-methylpiperazin-1-yl)carbonyl]quinolin-4(1H)-one (Intermediate 80, 300 mg, 0.6012 mmol) in dimethylformamide (10 mL) was prepared. The solution was purged with argon gas and tetrakis(triphenylphosphine) palladium (69.25 mg, 0.060 mmol) followed by 1-ethyl-3-{5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-2-yl}urea (Intermediate 17, 398 mg, 0.90mmol) were added and the mixture was stirred at room temperature. Sodium carbonate (125 mg, 1.18 mmol) was dissolved in minimum amount of water and the solution was added to the reaction mixture. The reaction mixture was heated to 95 °C for 3 h. After completion of the reaction, the reaction mixture was cooled to room temperature, filtered through celite, and the filtrate was poured into water (200 mL) and stirred for ½ h. The obtained solid was filtered and dried to get crude product which was purified by column chromatography eluting with a gradient of 100% ethyl acetate to 55 Methanol / ethyl acetate to afford 150 mg (48%) of 1-(5-{1-(1,3-dimethoxypropan-2-yl)-3-[(4-methylpiperazin-1-yl)carbonyl]-4-oxo-1,4-dihydroquinolin-6-yl}-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-2-yl)-3-ethylurea.

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.14 (t, 3H), 2.22 (s, 4H), 2.34 (d, 2H), 2.37 (d, 2H), 3.04 (s, 3H), 3.18 – 3.33 (m, 7H), 3.42 (m, 1H), 3.44 – 3.56(m, 4H), 4.83 (s, 1H), 4.51 (m, 1H), 7.64 (d, 1H), 7.72 (d, 1H), 8.06 (d, 1H), 8.28 (d, 2H), 8.37 (s, 1H), 8.46 (s, 1H), 8.72 (s, 1H), 9.48 (s, 1H).

LC-MS: m/z 688.5 (M+H) at 98.23%

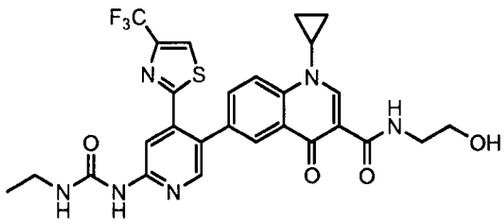
Examples 144-145

The following compounds were prepared according to the procedure described for Example 143 from the starting materials indicated in the table.

Ex	Compound	Data	SM
144	1-(5-{3-[(4-acetylpiperazin-1-yl)carbonyl]-1-(1,3-dimethoxypropan-2-yl)-4-oxo-1,4-dihydroquinolin-6-yl}-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-2-yl)-3-ethylurea 	^{1}H NMR (400 MHz, DMSO-d_6): δ 1.14 (t, 3H), 2.19 (d, 3H), 3.05 (s, 3H), 3.11 – 3.33 (m, 6H), 3.38 (m, 2H), 3.32 – 3.84 (m, 8H), 4.52 (m, 1H), 7.63 (d, 1H), 7.74 (d, 1H), 8.06 (d, 1H), 8.21 (s, 1H), 8.24 (d, 1H), 8.37 (s, 1H), 8.46 (s, 1H), 8.77 (d, 1H), 9.48 (s, 1H). LC-MS: m/z 716.5 (M+H) .	Intermediate 81 and Intermediate 17
145	1-{5-[1-(1,3-dimethoxypropan-2-yl)-3-{[4-(methylsulfonyl)piperazin-1-yl]carbonyl}-4-oxo-1,4-dihydroquinolin-6-yl]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-2-yl}-3-ethylurea 	^{1}H NMR (400 MHz, DMSO-d_6): δ 1.14 (t, 3H), 2.92 (s, 3H), 3.06 (s, 3H), 3.11 – 3.24 (m, 6H), 3.33 – 3.46 (m, 4H), 3.52 (m, 3H), 3.64 (m, 1H), 4.04 (m, 1H), 4.48 (m, 1H), 7.62 (d, 1H), 7.74 (d, 1H), 8.06 (d, 1H), 8.26 (s, 1H), 8.32 (s, 1H), 8.38 (s, 3H), 8.46 (s, 1H), 8.76 (s, 1H), 9.46 (s, 1H). LC-MS: m/z 752 (M+H).	Intermediate 82 and Intermediate 17

Example 146

1-cyclopropyl-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-N-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide



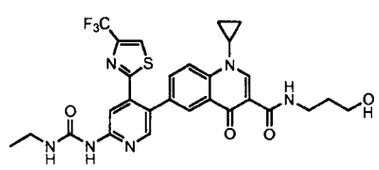
A suspension of ethyl 1-cyclopropyl-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-N-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (Example 58, 50 mg, 0.09 mmol) in ethanolamine (0.5 mL) was heated to 100°C in a microwave for 30 min. The reaction mixture was cooled to room temperature. The precipitate that formed was isolated by filtration and washed with methyl tert-butyl ether and water then dried to give 20 mg of white solid.

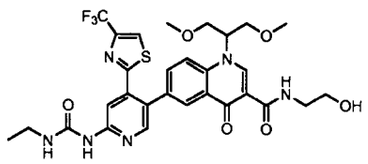
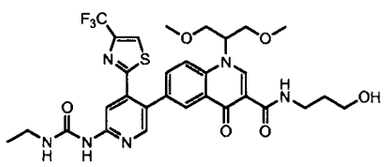
MS (ESP): 587 (MH^+) for $C_{27}H_{25}F_3N_6O_4S$

^1H NMR (300 MHz, DMSO-d_6): δ 1.11 (m, 4H), 1.32 (m, 3H), 3.21 (q, 2H), 3.42 (q, 2H), 3.50 (q, 2H), 3.79 (brs, 1H), 4.82 (t, 1H), 7.65 (t, 1H), 7.79 (d, 1H), 8.20 (s, 1H), 8.25 (m, 2H), 8.32 (s, 1H), 8.48 (s, 1H), 8.75 (s, 1H), 9.47 (s, 1H), 9.91 (s, 1H).

Examples 147-149

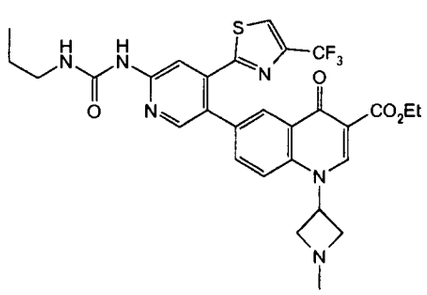
The following compounds were prepared according to the procedure described for Example 146 from the indicated starting materials.

Ex	Compound	Data	SM
147	1-cyclopropyl-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-N-(3-hydroxypropyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 601 (MH^+) for $C_{28}H_{27}F_3N_6O_4S$ ^1H NMR (300 MHz, CD_3OD): δ 1.23 (m, 4H), 1.38 (m, 3H), 1.83 (m, 2H), 3.34 (q, 2H), 3.53 (q, 2H), 3.65 (q, 2H), 3.76 (brs, 1H), 7.77 (d, 1H), 7.89 (s, 1H), 8.14 (s, 1H), 8.25 (d, 1H), 8.35 (s, 1H), 8.36 (s, 1H), 8.9 (s, 1H).	Example 59 and propanol-amine

Ex	Compound	Data	SM
148	1-(1,3-dimethoxypropan-2-yl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-N-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 649 (MH^+) for $C_{30}H_{31}F_3N_6O_5S$ ^1H NMR (300 MHz, CD_3OD): δ 1.19 (t, 3H), 3.55 (brs, 2H), 3.71 (brs, 2H), 3.86 (brs 2H), 3.95 (brs, 2H), 5.34 (brs, 1H), 7.67 (d, 1H), 7.85 (s, 1H), 7.99 (d, 1H), 8.12 (s, 1H), 8.32 (s, 1H), 8.39 (s, 1H), 9.06 (s, 1H)	Example 54 and ethanolamine
149	1-(1,3-dimethoxypropan-2-yl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-N-(3-hydroxypropyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 663.3 (MH^+) for $C_{31}H_{35}F_3N_6O_8S$ ^1H NMR (300 MHz, DMSO-d_6): δ 1.11 (t, 3H), 1.62-1.71 (m, 2H), 3.16-3.33 (m, 2H), 3.26 (s, 6H), 3.40-3.51 (m, 2H), 3.77-3.82 (m, 2H), 3.84-3.93 (m, 2H), 4.56, (t, 1H), 5.46 (m, 1H), 7.64 (bt, 1H), 7.73 (dd, 1H), 8.14 (d, 1H), 8.23 (s, 1H), 8.29 (d, 1H), 8.35 (s, 1H), 8.51 (d, 1H), 8.92 (s, 1H), 9.49 (s, 1H), 9.89 (bt, 1H)	Example 54 and propanol-amine

Example 150

Ethyl 1-(1-methylazetidin-3-yl)-4-oxo-6-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1,4-dihydroquinoline-3-carboxylate

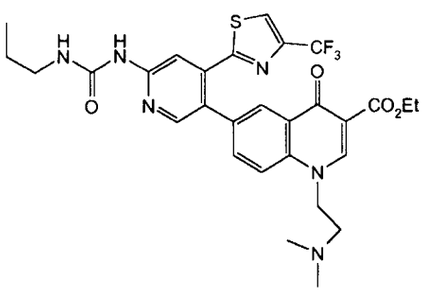


A suspension of ethyl 6-iodo-1-(1-methylazetidin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (Intermediate 31, 500 mg, 1.21 mmol) in dimethoxyethane (9.7 mL) in a vial was stirred with heating to obtain solution. The solution was cooled to 30 °C and trans dichlorobis(triphenylphosphine)palladium (II) (111 mg, 0.16 mmol) was added. The mixture was stirred for ~10 min at room temperature, then 6-(3-propylureido)-4-(4-trifluoromethylthiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 47, 1.3 eq) was added to the mixture followed by an aqueous solution of sodium bicarbonate (252 mg in 2.4 mL of water) and the vial was sealed. The mixture was stirred at 75°C for 1 h and then cooled to 0 °C. The solid that formed was isolated by filtration, washed with a small amount of dimethoxyethane, then methyl tert-butyl ether to give 735 mg of yellow solid, which was used without further purification.

MS (ESP): 615 (MH^+) for $C_{29}H_{29}F_3N_6O_4S$

Example 151

Ethyl 1-(1-methylazetidin-3-yl)-4-oxo-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1,4-dihydroquinoline-3-carboxylate

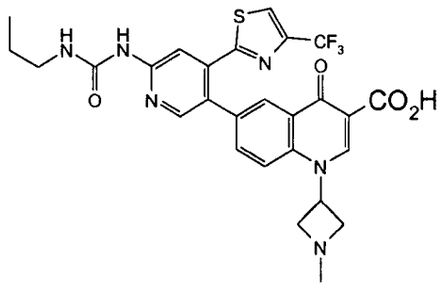


The following compound was prepared according to the procedure described for Example 150 from Intermediate 29 and Intermediate 47.

MS (ESP): 617 (MH^+) for $C_{29}H_{31}F_3N_6O_4S$.

Example 152

1-(2-(dimethylamino)ethyl)-4-oxo-6-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1,4-dihydroquinoline-3-carboxylic acid



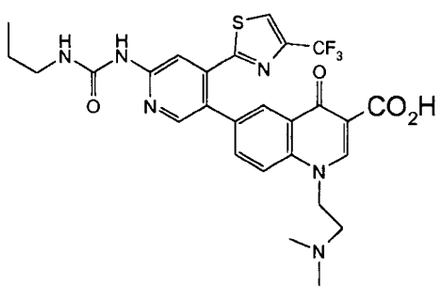
To a solution of ethyl 1-(2-(dimethylamino)ethyl)-4-oxo-6-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1,4-dihydroquinoline-3-carboxylate (Example 150, 100 mg, 0.16 mmol) in tetrahydrofuran (2 mL) was added lithium hydroxide (1 M, 650 μL) and the mixture was stirred for 1 h at room temperature. The organics were removed under a stream of nitrogen and the precipitate that formed was isolated by filtration, washed with water (1 mL), and dried in a vacuum oven overnight at 40 °C to give 70 mg of yellowish solid.

MS (ESP): 589 (MH^+) for $C_{27}H_{27}F_3N_6O_4S$.

^1H NMR (300 MHz, CD_3OD): δ 1.11 (t, 3H), 1.63 (m, 3H), 2.32 (s, 6H), 2.87 (q, 2H), 4.50 (q, 2H), 4.39 (t, 2H), 7.65 (d, 1H), 7.82 (d, 1H), 7.87(s, 1H), 8.33 (s, 1H), 8.44 (s, 1H), 8.78 (s, 1H)

Example 153

1-(1-methylazetidin-3-yl)-4-oxo-6-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1,4-dihydroquinoline-3-carboxylic acid



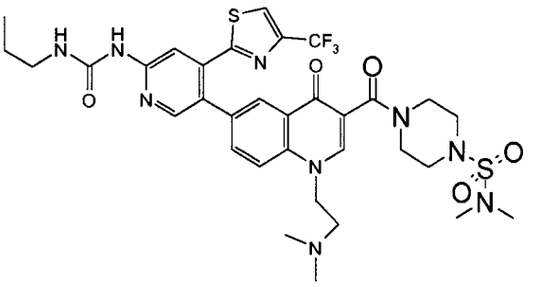
The following compound was prepared according to the procedure described for Example 152 using Example 151 as the starting material.

MS (ESP): 587 (MH^+) for $C_{27}H_{24}F_3N_6NaO_4S$.

^1H NMR (300 MHz, CD_3OD): δ 1.00 (t, 3H), 1.63 (m, 2H), 2.46 (s, 3H), 3.51 (m, 2H), 4.09 (t, 2H), 5.17 (m, 1H), 7.60 (s, 3H), 7.89 (s, 1H), 8.31 (s, 1H), 8.43(s, 1H), 8.66 (s, 1H).

Example 154

4-(1-(2-(dimethylamino)ethyl)-4-oxo-6-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1,4-dihydroquinoline-3-carbonyl)-N,N-dimethylpiperazine-1-sulfonamide



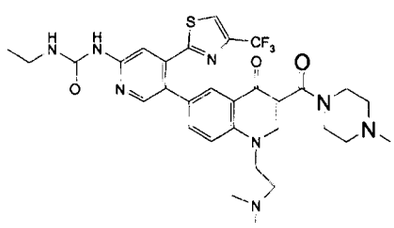
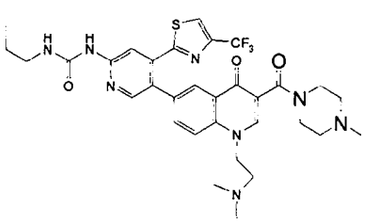
To a solution of 1-(2-(dimethylamino)ethyl)-4-oxo-6-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1,4-dihydroquinoline-3-carboxylic acid (Example 153, 80 mg, 0.14 mmol) in dimethylformamide (0.5 mL) was added HATU (78.4 mg, 0.20 mmol) then diisopropylethylamine (95.2 uL, 0.55 mmol). This was followed by N,N-dimethylpiperazine-1-sulfonamide (52.7 mg, 0.27 mmol) and the reaction was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the residue purified by prep HPLC (Water-methanol-0.1% Formic acid).

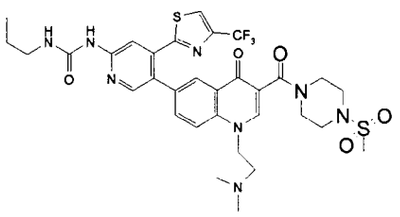
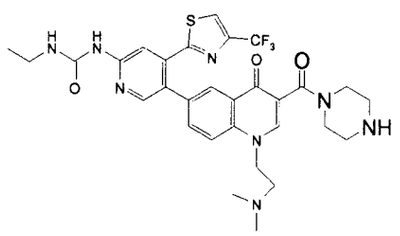
MS (ESP): 764.4 (MH^+) for $C_{34}H_{42}F_3N_9O_7S_2$

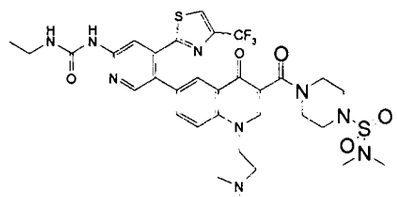
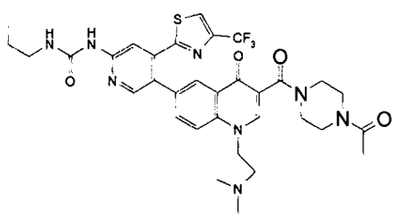
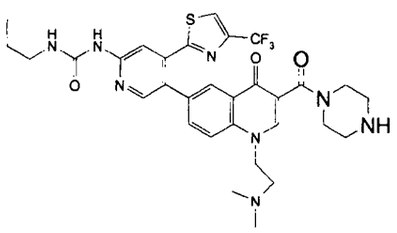
^1H NMR (300 MHz, CD_3OD): δ 0.99 (t, 3H), 1.63 (m, 2H), 2.43 (s, 6H), 2.85 (s, 6H), 2.92 (t, 2H), 3.32 (brs, 6H), 3.47 (brs, 2H), 3.81 (brs, 2H), 4.55 (t, 2H), 7.67 (d, 1H), 7.84 (s, 1H), 7.87 (d, 1H), 8.18 (s, 1H), 8.29 (s, 1H), 8.32 (s, 2H).

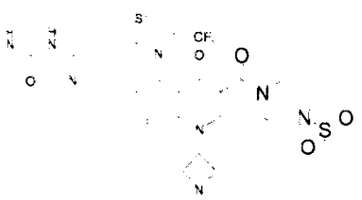
Examples 155-172

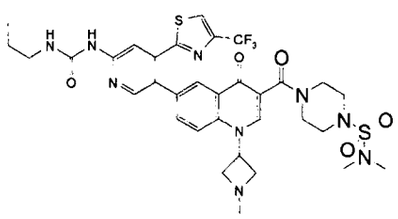
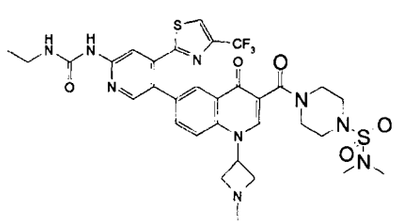
The following compounds were prepared according to the procedure described for Example 154 from the starting materials indicated in the table.

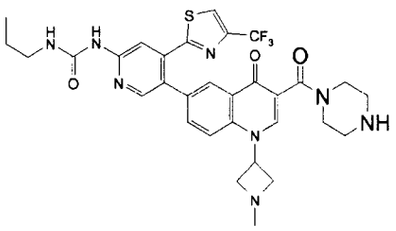
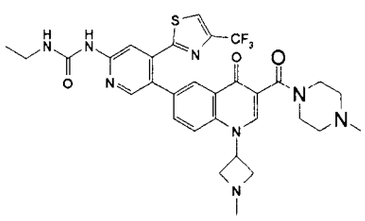
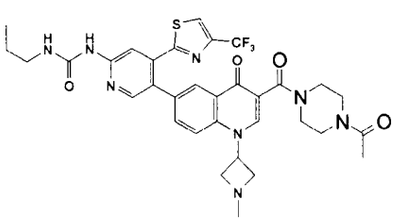
Ex	Compound	Data	SM
155	1-(5-(1-(2-(dimethylamino)ethyl)-3-(4-methylpiperazine-1-carbonyl)-4-oxo-1,4-dihydroquinolin-6-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea 	MS (ESP): 657 (MH^+) for $C_{32}H_{37}F_3N_8O_5S$ ^1H NMR (300 MHz, CD_3OD): δ 1.22 (t, 3H), 2.44 (s, 6H), 2.62 (s, 3H), 2.93 (brs, 6H), 3.34 (q, 2H), 3.54 (brs, 2H), 3.89 (brs, 2H), 4.55 (t, 2H), 7.70 (d, 1H), 7.85 (s, 1H), 7.88 (d, 1H), 8.19 (s, 1H), 8.28 (s, 1H), 8.32 (s, 1H), 8.35 (s, 1H)	Example 18 and 4-methyl-piperazine
156	1-(5-(1-(2-(dimethylamino)ethyl)-3-(4-methylpiperazine-1-carbonyl)-4-oxo-1,4-dihydroquinolin-6-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-propylurea 	MS (ESP): 671 (MH^+) for $C_{32}H_{37}F_3N_8O_3S$ ^1H NMR (300 MHz, CD_3OD): δ 0.99 (t, 3H), 1.64 (m, 2H), 2.32 (s, 6H), 2.54 (brs, 4H), 2.77 (t, 2H), 3.45 (brs, 2H), 3.79 (brs, 2H), 4.49 (brs, 2H), 7.70 (d, 1H), 7.85 (m, 2H), 8.18 (s, 1H), 8.25 (s, 1H), 8.32 (s, 1H), 8.35 (s, 1H)	Example 153 and 4-methyl-piperzine

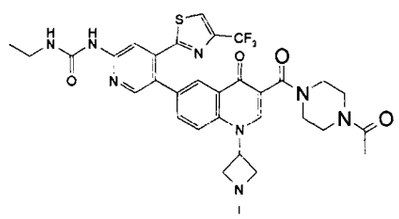
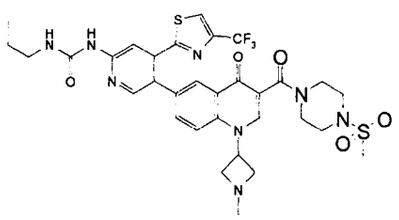
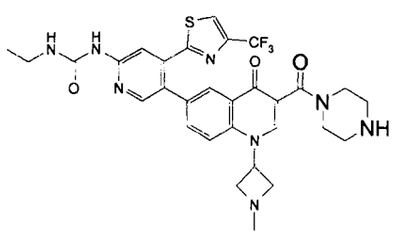
Ex	Compound	Data	SM
157	1-(5-(1-(2-(dimethylamino)ethyl)-3-(4-(methylsulfonyl)piperazine-1-carbonyl)-4-oxo-1,4-dihydroquinolin-6-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-propylurea 	MS (ESP): 735 (MH^+) for $C_{33}H_{39}F_3N_8O_7S_2$ ^1H NMR (300 MHz, CD_3OD): δ 1.02 (t, 3H), 1.63 (m, 2H), 2.49 (s, 6H), 2.87 (s, 3H), 3.01 (t, 2H), 3.52 (brs, 2H), 3.86 (brs, 2H), 4.59 (t, 2H), 7.70 (d, 1H), 7.85 (m, 2H), 8.19 (s, 1H), 8.28 (s, 1H), 8.32 (d, 1H), 8.35 (s, 1H)	Example 153 and 4-methyl-sulfonyl piperazine
158	1-(5-(1-(2-(dimethylamino)ethyl)-4-oxo-3-(piperazine-1-carbonyl)-1,4-dihydroquinolin-6-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea 	MS (ESP): 643 (MH^+) for $C_{31}H_{35}F_3N_8O_5S$ ^1H NMR (300 MHz, CD_3OD): δ 1.22 (t, 3H), 3.04 (s, 6H), 3.31 (m, 8), 3.68 (m, 4H), 4.0 (brs, 2H), 7.80 (d, 1H), 7.90 (s, 1H), 7.96 (d, 1H), 8.22 (s, 1H), 8.34 (s, 1H), 8.35 (s, 1H), 8.46 (s, 1H)	Example 18 and piperazine

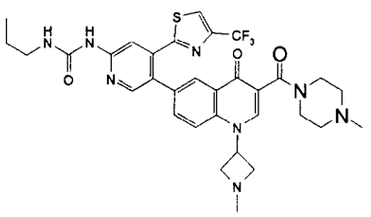
Ex	Compound	Data	SM
159	4-(1-(2-(dimethylamino)ethyl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carbonyl)-N,N-dimethylpiperazine-1-sulfonamide 	MS (ESP): 750 (MH^+) for $C_{33}H_{40}F_3N_9O_7S_2$ ^1H NMR (300 MHz, CD_3OD): δ 1.22 (t, 3H), 2.40 (s, 6H), 2.84 (s, 6H), 2.86 (t, 2H), 3.36 (m, 6H), 3.47 (brs, 2H), 3.82 (brs, 2H), 4.53 (t, 2H), 7.72 (d, 1H), 7.85 (s, 2H), 7.87 (d, 1H), 8.19 (s, 1H), 8.29 (s, 1H), 8.32 (s, 1H), 8.35 (s, 1H)	Example 18 and N,N-dimethyl-piperazine-1-sulfonamide
160	1-(5-(3-(4-acetylpiperazine-1-carbonyl)-1-(2-(dimethylamino)ethyl)-4-oxo-1,4-dihydroquinolin-6-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-propylurea 	MS (ESP): 699 (MH^+) for $C_{34}H_{39}F_3N_8O_6S$ ^1H NMR (300 MHz, CD_3OD): δ 0.99 (t, 3H), 1.61 (m, 2H), 2.15 (br s, 3H), 2.34 (s, 6H), 2.80 (t, 2H), 3.66 (brm, 8H), 4.51 (t, 2H), 7.68 (d, 1H), 7.85 (s, 2H), 7.88 (d, 1H), 8.19 (s, 1H), 8.28 (s, 1H), 8.32 (s, 1H), 8.36 (s, 1H)	Example 153 and 4-acetyl-piperazine
161	1-(5-(1-(2-(dimethylamino)ethyl)-4-oxo-3-(piperazine-1-carbonyl)-1,4-dihydroquinolin-6-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-propylurea 	MS (ESP): 657 (MH^+) for $C_{31}H_{36}ClF_3N_8O_3S$ ^1H NMR (300 MHz, CD_3OD): δ 0.99 (t, 3H), 1.62 (m, 2H), 3.05 (s, 6H), 3.31 (m, 4H), 3.72 (m, 6H), 3.99 (brs, 2H), 7.86 (d, 1H), 8.08 (s, 1H), 8.11 (d, 1H), 8.32 (s, 1H), 8.34 (s, 1H), 8.45 (s, 1H), 8.51 (1H).	Example 153 and piperazine

Ex	Compound	Data	SM
162	1-(5-(3-(4-acetylpiperazine-1-carbonyl)-1-(2-(dimethylamino)ethyl)-4-oxo-1,4-dihydroquinolin-6-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea	MS (ESP): 685 (MH^+) for $C_{32}H_{35}F_3N_8O_4S$ ^1H NMR (300 MHz, CD_3OD): δ 1.20 (t, 3H), 2.11&2.15 (s, 3H), 2.36 (s, 6H), 2.83 (t, 2H), 3.39 (q, 2H), 3.65 (m, 8H), 4.54 (t, 2H), 7.69 (d, 1H), 7.85 (s, 1H), 7.88 (d, 1H), 8.19 (s, 1H), 8.29 (s, 1H), 8.32 (s, 1H), 8.36 (s, 1H)	Example 18 and 4-acetyl-piperazine
163	1-ethyl-3-(5-(1-(1-methylazetidin-3-yl)-3-(4-(methylsulfonyl)piperazine-1-carbonyl)-4-oxo-1,4-dihydroquinolin-6-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)urea 	MS (ESP): 719 (MH^+) for $C_{32}H_{35}F_3N_8O_7S_2$ ^1H NMR (300 MHz, CD_3OD): δ 1.22 (t, 3H), 2.57 (s, 3H), 2.87 (s, 3H), 3.32 (m, 6H), 3.52 (brs, 2H), 3.73 (t, 2H), 3.88 (brs, 2H), 4.18 (t, 2H), 5.31 (m, 1H), 7.65 (d, 1H), 7.68 (d, 1H), 7.85 (s, 1H), 8.19 (s, 1H), 8.22 (brs, 1H), 8.32 (s, 1H), 8.34 (s, 2H)	Example 24 and 4-(methyl-sulfonyl)-piperazine

Ex	Compound	Data	SM
164	N,N-dimethyl-4-(1-(1-methylazetidin-3-yl)-4-oxo-6-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1,4-dihydroquinoline-3-carbonyl)piperazine-1-sulfonamide 	MS (ESP): 762 (MH^+) for $C_{34}H_{40}F_3N_9O_7S_2$ ^1H NMR (300 MHz, CD_3OD): δ 0.99 (t, 3H), 1.61 (m, 2H), 2.54 (s, 3H), 2.84 (s, 6H), 3.35 (brs, 6H), 3.47 (brs, 2H), 3.67 (brs, 2H), 3.84 (brs, 2H), 4.16 (t, 2H), 5.29 (brs, 1H), 7.66 (d, 1H), 7.69 (d, 1H), 7.84 (s, 1H), 8.18 (s, 1H), 8.33 (m, 3H).	Example 152 and N,N-dimethylpiperazine-1-sulfonamide
165	4-(6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-methylazetidin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carbonyl)-N,N-dimethylpiperazine-1-sulfonamide 	MS (ESP): 748 (MH^+)) for $C_{33}H_{38}F_3N_9O_7S_2$ ^1H NMR (300 MHz, CD_3OD): δ 1.22 (t, 3H), 2.59 (s, 3H), 2.84 (s, 6H), 3.31 (m, 6H), 3.47 (brs, 2H), 3.84 (m, 4H), 4.22 (t, 2H), 5.33 (m, 1H), 7.62 (d, 1H), 7.68 (d, 1H), 7.84 (s, 1H), 8.19 (s, 2H), 8.35 (m, 3H).	Example 24 and N,N-dimethyl-piperazine-1-sulfonamide

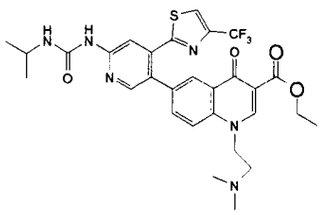
Ex	Compound	Data	SM
166	1-(5-(1-(1-methylazetidin-3-yl)-4-oxo-3-(piperazine-1-carbonyl)-1,4-dihydroquinolin-6-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-propylurea 	MS (ESP): 655 (MH^+) for $C_{31}H_{34}ClF_3N_8O_3S$ ^{1}H NMR (300 MHz, CD_3OD): δ 0.99 (t, 3H), 1.62 (m, 2H), 3.12 & 3.18 (s, 3H), 3.36 (brs, 4H), 3.72 (m, 4H), 4.01 (br, 2H), 4.89 (m, 2H), 5.01 (m, 2H), 5.86 & 6.0 (brs, 1H), 7.68 (d, 1H), 7.81 (d, 1H), 8.02 (s, 1H), 8.31 (s, 1H), 8.33 (s, 1H), 8.40 & 8.61 (s, 1H), 8.43 (s, 1H).	Example 152 and piperazine
167	1-ethyl-3-(5-(1-(1-methylazetidin-3-yl)-3-(4-methylpiperazine-1-carbonyl)-4-oxo-1,4-dihydroquinolin-6-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)urea 	MS (ESP): 655 (MH^+) for $C_{32}H_{35}F_3N_8O_5S$ ^{1}H NMR (300 MHz, CD_3OD): δ 1.22 (t, 3H), 2.33 (s, 3H), 2.46 (s, 3H), 2.50 (brs, 4H), 3.31 (q, 2H), 3.44 (brs, 2H), 3.51 (t, 2H), 3.80 (brs, 2H), 4.05 (t, 2H), 5.21 (m, 1H), 7.66 (d, 1H), 7.67 (d, 1H), 7.85 (s, 2H), 8.17 (s, 1H), 8.32 (m, 2H), 8.34 (s, 1H).	Example 24 and 4-methyl-piperazine
168	1-(5-(3-(4-acetylpiperazine-1-carbonyl)-1-(1-methylazetidin-3-yl)-4-oxo-1,4-dihydroquinolin-6-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-propylurea 	MS (ESP): 697 (MH^+) for $C_{33}H_{35}F_3N_8O_4S$ ^{1}H NMR (300 MHz, CD_3OD): δ 0.99 (t, 3H), 1.61 (m, 2H), 2.11 & 2.16 (s, 3H), 2.47 (s, 3H), 3.52 (m, 7H), 4.07 (t, 2H), 5.23 (m, 1H), 7.67 (d, 1H), 7.69 (d, 1H), 7.85 (s, 2H), 8.19 (s, 1H), 8.35 (m, 3H).	Example 152 and 4-acetyl-piperazine

Ex	Compound	Data	SM
169	1-(5-(3-(4-acetylpiperazine-1-carbonyl)-1-(1-methylazetidin-3-yl)-4-oxo-1,4-dihydroquinolin-6-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea 	MS (ESP): 683 (MH^+) for $C_{33}H_{35}F_3N_8O_6S$ ^1H NMR (300 MHz, CD_3OD): δ 1.22 (t, 3H), 2.11 & 2,16 (s, 3H), 2.63 (s, 3H), 3.31 (m, 2H), 3.67 (brm, 8H), 3.81 (m, 2H), 4.25 (t, 2H), 5.36 (m, 1H), 7.64 (d, 1H), 7.69 (d, 1H), 7.85 (s, 2H), 8.18 (s, 1H), 8.34 (m, 3H).	Example 24 and 4-acetyl-piperazine
170	1-(5-(1-(1-methylazetidin-3-yl)-3-(4-(methylsulfonyl)piperazine-1-carbonyl)-4-oxo-1,4-dihydroquinolin-6-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-propylurea 	MS (ESP): 733 (MH^+) for $C_{33}H_{37}F_3N_8O_7S_2$ ^1H NMR (300 MHz, CD_3OD): δ 0.99 (t, 3H), 1.61 (m, 2H), 2.57 (s, 3H), 2.88 (s, 3H), 3.52 (brs, 2H), 3.74 (t, 2H), 3.88 (brs, 2H), 4.19 (t, 2H), 5.31 (m, 1H), 7.65 (d, 1H), 7.69 (d, 1H), 7.85 (s, 2H), 8.19 (s, 1H), 8.35 (m, 3H).	Example 152 and 4-(methyl-sulfonyl)-piperazine
171	1-ethyl-3-(5-(1-(1-methylazetidin-3-yl)-4-oxo-3-(piperazine-1-carbonyl)-1,4-dihydroquinolin-6-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)urea 	MS (ESP): 641.1 (MH^+) for $C_{30}H_{32}ClF_3N_8O_3S$ ^1H NMR (300 MHz, CD_3OD): δ 1.22 (t, 3H), 3.12 & 3.18 (s, 3H), 3.39 (m, 4H), 3.67 (m, 4H), 4.02 (brs, 2H), 4.80 (m, 2H), 4.99 (m, 2H), 5.75 & 6.0 (brs, 1H), 7.71 (d, 1H), 7.86 (d, 1H), 8.07 (s, 1H), 8.33 (s, 2H), 8.41 & 8.64 (s, 1H), 8.45 (s, 1H).	Example 24 and piperazine

Ex	Compound	Data	SM
172	1-(5-(1-(1-methylazetidin-3-yl)-3-(4-methylpiperazine-1-carbonyl)-4-oxo-1,4-dihydroquinolin-6-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-propylurea 	MS (ESP): 669.3 (MH^+) for $C_{33}H_{37}F_3N_8O_5S_2$ ^1H NMR (300 MHz, CD_3OD): δ 1.02 (t, 3H), 1.64 (m, 2H), 2.52 (s, 3H), 2.54 (s, 3H), 2.81 (brs, 4H), 3.53 (brs, 2H), 3.66 (t, 2H), 3.87 (brs, 2H), 4.12 (t, 2H), 5.27 (m, 1H), 7.65 (d, 1H), 7.68 (d, 1H), 7.85 (s, 1H), 8.17 (s, 1H), 8.29 (brs, 1H), 8.32 (s, 1H), 8.34 (s, 1H)	Example 152 and 4-methyl-piperazine

Example 173

ethyl 1-(2-(dimethylamino)ethyl)-6-(6-(3-isopropylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate

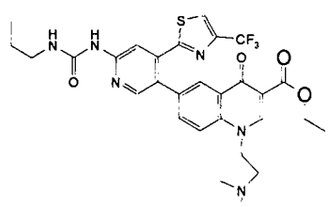
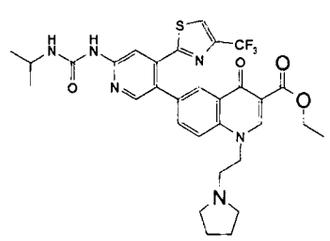


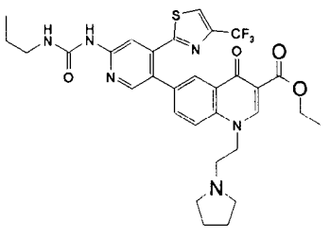
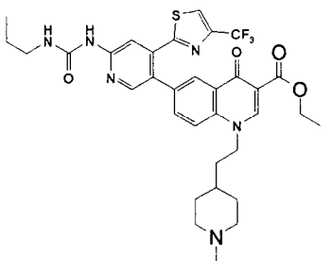
A suspension of ethyl 1-(2-(dimethylamino)ethyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate (Intermediate 29, 250 mg, 0.60 mmol) in dimethoxyethane (4.8 mL) in a microwave vial was stirred with heating to obtain a solution . The solution was then cooled to 30°C, trans-dichlorobis(triphenylphosphine)palladium (II) (55 mg, 0.08 mmol) was added and the mixture was stirred for 10 min at room temperature. 6-(3-isopropylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 89, 294 mg, 0.79 mmol) was added to the mixture followed by an aqueous solution of sodium bicarbonate (163 mg in 1.2 mL of water) and the vial was sealed. The mixture was stirred at 65 °C for 30 min in a heating block then cooled to room temperature. The crude reaction mixture was placed into fridge for a 2 h. The solid precipitate that formed was colected by filtration, washed with a small amount of dimethoxyethane, methyl tert-butyl ether and dried to give ~270 mg yellowish solid.

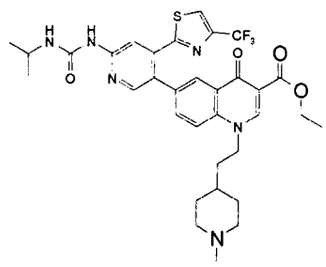
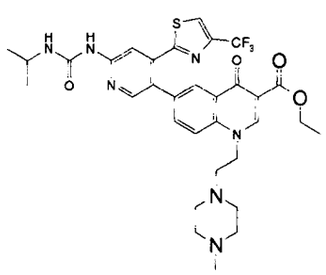
MS (ESP): 634 ($M+H^+$) for $C_{29}H_{30}F_3N_5O_6S$.

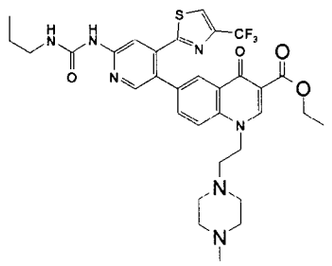
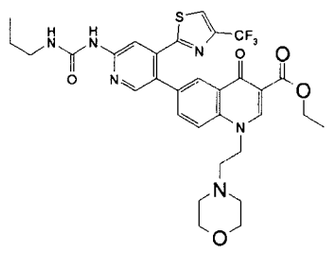
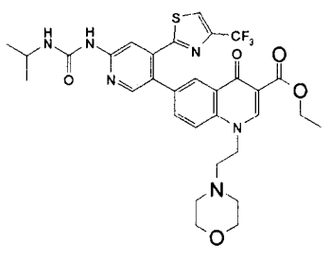
Examples 174-188

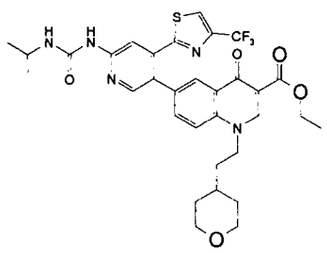
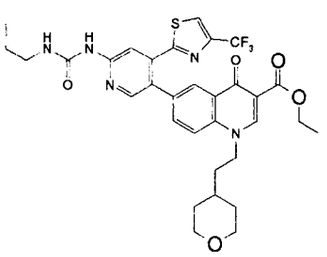
The following compounds were prepared according to the procedure described for Example 173 from the indicated starting material.

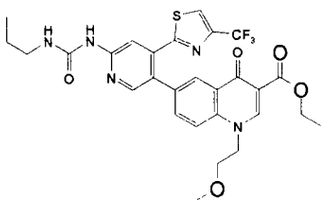
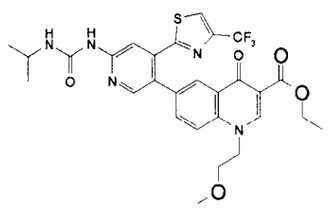
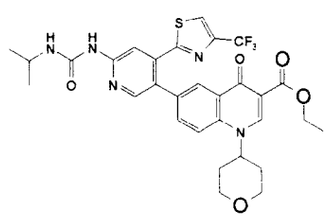
Ex	Compound	Data	SM
174	ethyl 1-(2-(dimethylamino)ethyl)-4-oxo-6-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 634 ($M+H^+$) for $C_{29}H_{30}F_3N_5O_6S$	Intermediate 29 and Intermediate 47
175	ethyl 6-(6-(3-isopropylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(2-(pyrrolidin-1-yl)ethyl)-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 643.2 ($M+H^+$) for $C_{31}H_{33}F_3N_6O_4S$	Intermediate 89 and Intermediate 93

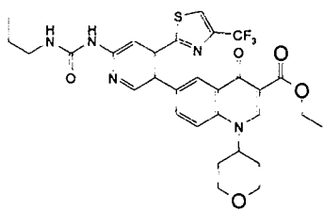
Ex	Compound	Data	SM
176	ethyl 4-oxo-6-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(2-(pyrrolidin-1-yl)ethyl)-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 643.2 ($M+H^+$) for $C_{31}H_{33}F_3N_6O_4S$	Intermediate 47 and Intermediate 93
177	ethyl 1-(2-(1-methylpiperidin-4-yl)ethyl)-4-oxo-6-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 671.1 ($M+H^+$) for $C_{33}H_{37}F_3N_6O_4S$	Intermediate 47 and Intermediate 69

Ex	Compound	Data	SM
178	ethyl 6-(6-(3-isopropylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(2-(1-methylpiperidin-4-yl)ethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 671.1 ($M+H^+$) for $C_{33}H_{37}F_3N_6O_4S$	Intermediate 89 and Intermediate 69
179	ethyl 6-(6-(3-isopropylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(2-(4-methylpiperazin-1-yl)ethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 673 ($M+H^+$) for $C_{32}H_{36}F_3N_7O_4S$	Intermediate 89 and Intermediate 92

Ex	Compound	Data	SM
180	ethyl 1-(2-(4-methylpiperazin-1-yl)ethyl)-4-oxo-6-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 673 ($M+H^+$) for $C_{32}H_{36}F_3N_7O_4S$	Intermediate 47 and Intermediate 92
181	ethyl 1-(2-morpholinoethyl)-4-oxo-6-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 660.1 ($M+H^+$) for $C_{31}H_{33}F_3N_6O_5S$	Intermediate 47 and Intermediate 90
182	ethyl 6-(6-(3-isopropylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(2-morpholinoethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 660.1 ($M+H^+$) for $C_{31}H_{33}F_3N_6O_5S$	Intermediate 89 and Intermediate 90

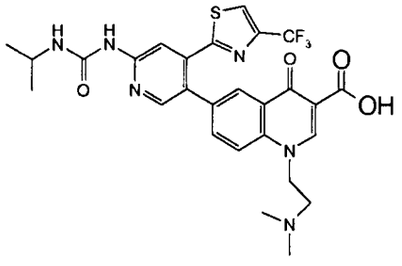
Ex	Compound	Data	SM
183	ethyl 6-(6-(3-isopropylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 659 ($M+H^+$) for $C_{32}H_{34}F_3N_5O_5S$	Intermediate 89 and Intermediate 94
184	ethyl 4-oxo-6-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 659 ($M+H^+$) for $C_{32}H_{34}F_3N_5O_5S$	Intermediate 47 and Intermediate 94

Ex	Compound	Data	SM
185	ethyl 1-(2-methoxyethyl)-4-oxo-6-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 604.6 ($M+H^+$) for $C_{28}H_{28}F_3N_5O_5S$	Intermediate 47 and Intermediate 20
186	ethyl 6-(6-(3-isopropylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(2-methoxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 604.6 ($M+H^+$) for $C_{28}H_{28}F_3N_5O_5S$	Intermediate 89 and Intermediate 20
187	ethyl 6-(6-(3-isopropylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(tetrahydro-2H-pyran-4-yl)-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 631 ($M+H^+$) for $C_{30}H_{30}F_3N_5O_5S$	Intermediate 89 and Intermediate 91

Ex	Compound	Data	SM
188	ethyl 4-oxo-6-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(tetrahydro-2H-pyran-4-yl)-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 631 ($M+H^+$) for $C_{30}H_{30}F_3N_5O_5S$	Intermediate 47 and Intermediate 91

Example 189

1-(2-(dimethylamino)ethyl)-7-(6-(3-isopropylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate



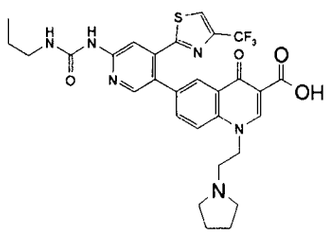
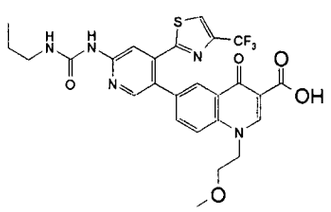
A solution of ethyl 1-(2-(dimethylamino)ethyl)-6-(6-(3-isopropylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (Example 173, 100 mg, 0.16 mmol) was dissolved in tetrahydrofuran (4 mL) and treated with 1M lithium hydroxide (1 mL) and the mixture stirred at room temperature for 24 h. The reaction mixture was concentrated under reduced pressure, diluted with water, and acidified to pH 4 with 1 N HCl. The solid that formed was collected by filtration and washed with ethyl acetate to give 60 mg of product after drying.

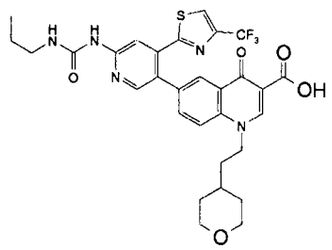
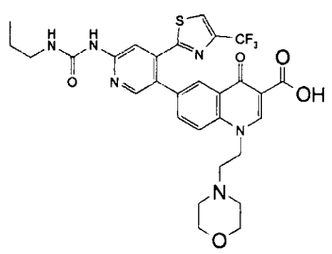
MS (ESP): 589.2 ($M+H^+$) for $C_{27}H_{26}F_3N_6NaO_4S$.

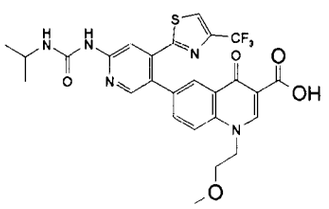
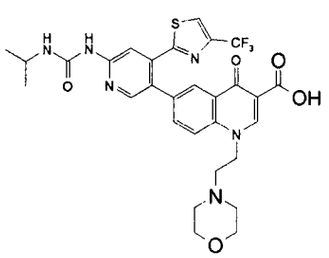
^{1}H NMR (300 MHz, DMSO-d_6): δ 1.07 (d, 6H), 2.19 (s, 6H), 2.58 (t, 2H), 3.35-3.80 (m, 1H), 4.38 (t, 2H), 7.41 (d, 1H), 7.67 (d, 1H), 8.02-8.05 (m, 2H), 8.14 (d, 1H), 8.39 (s, 1H), 8.54 (d, 1H)

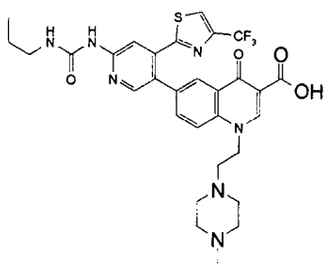
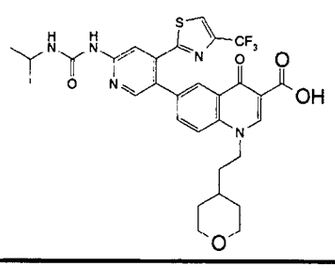
Examples 190-202

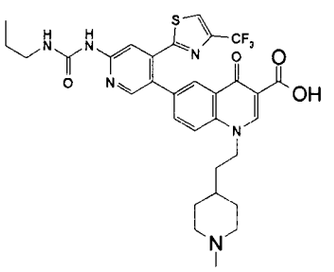
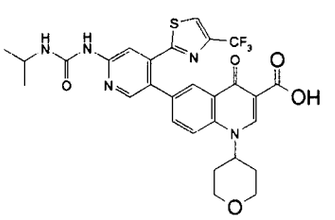
The following compounds were according to the procedure described for Example 189 from the starting materials indicated in the table.

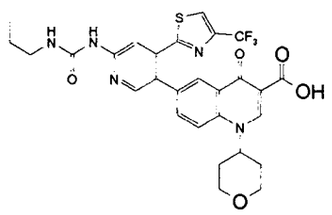
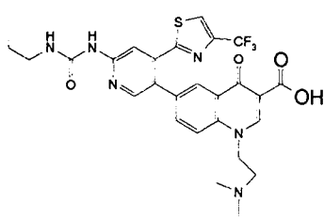
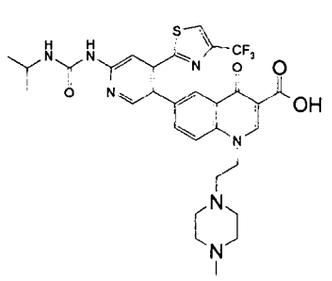
Ex	Compound	Data	SM
190	4-oxo-6-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(2-(pyrrolidin-1-yl)ethyl)-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 614 ($M+H^+$) for $C_{29}H_{29}F_3N_6O_4S$ ^1H NMR (300 MHz, CD_3OD): δ 0.99 (t, 3H), 1.63 (m, 2H), 1.81 (m, 4H), 2.63 (m, 4H), 2.97 (m, 2H), 4.51 (m, 2H), 7.68 (d, 1H), 7.85 (d, 1H), 7.87 (s, 1H), 8.15 (s, 1H), 8.33 (s, 1H), 8.43 (s, 1H), 8.77 (s, 1H)	Example 176
191	1-(2-methoxyethyl)-4-oxo-6-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 576 ($M+H^+$) for $C_{26}H_{23}F_3N_5NaO_5S$ ^1H NMR (300 MHz, DMSO-d_6): δ 0.90 (t, 3H), 1.50 (m, 2H), 3.15 (s, 2H), 3.23 (s, 3H), 3.69 (brs, 2H), 4.61 (brs, 2H), 7.66 (d, 1H), 7.82 (s, 1H), 7.92 (d, 1H), 8.25 (s, 1H), 8.28 (s, 1H), 8.32 (s, 1H), 8.45 (s, 1H), 8.78 (s, 1H), 9.61(s, 1H).	Example 185

Ex	Compound	Data	SM
192	4-oxo-6-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(tetrahydro-2H-pyran-4-yl)-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 603 ($M+H^+$) for $C_{28}H_{25}F_3N_5NaO_5S$ ^1H NMR (300 MHz, DMSO-d_6): δ 0.90 (t, 3H), 1.50 (m, 2H), 2.02 (m, 4H), 3.13 (m, 2H), 3.64 (m, 2H), 4.02 (m, 2H), 5.05 (brs, 1H), 7.62 (d, 1H), 7.80 (brs, 1H), 8.19 (d, 1H), 8.28 (s, 1H), 8.31 (s, 1H), 8.44 (s, 2H), 8.94 (s, 1H), 9.5 (s, 1H)	Example 184
193	1-(2-morpholinoethyl)-4-oxo-6-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 631 ($M+H^+$) for $C_{29}H_{28}F_3LiN_6O_5S$ ^1H NMR (300 MHz, DMSO-d_6): δ 0.90 (t, 3H), 1.49 (m, 2H), 2.49 (brs, 4H), 2.73 (m, 2H), 3.16 (m, 2H), 3.46 (m, 2H), 4.52 (brs, 2H), 7.61 (d, 1H), 7.75 (brs, 1H), 7.90 (d, 1H), 8.25 (s, 2H), 8.31 (s, 1H), 8.44 (s, 1H), 8.78 (s, 1H), 9.53 (s, 1H), 9.46 (s, 1H)	Example 181

Ex	Compound	Data	SM
194	6-(6-(3-isopropylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(2-methoxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 576 ($M+H^+$) for $C_{26}H_{24}F_3N_5O_5S$ ^1H NMR (300 MHz, CD_3OD): δ 1.24 (d, 6H), 3.81 (t, 2H), 3.99 (m, 1H), 4.71 (t, 2H), 7.78 (d, 1H), 7.90 (s, 1H), 8.00 (d, 1H), 8.18 (s, 1H), 8.37 (s, 1H), 8.42 (s, 1H), 8.89 (s, 1H)	Example 186
195	6-(6-(3-isopropylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(2-morpholinoethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 631 ($M+H^+$) for $C_{29}H_{29}F_3N_6O_5S$ ^1H NMR (300 MHz, CD_3OD): δ 1.24 (d, 6H), 3.4 (brs, 2H), 3.63 (brs, 2H), 3.99 (brs, 5H), 4.97 (brs (2H), 7.86 (d, 1H), 7.90 (s, 1H), 8.03 (d, 1H), 8.21 (s, 2H), 8.34 (s, 1H), 8.41 (s, 1H), 9.04 (s, 1H).	Example 182

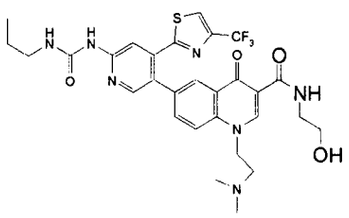
Ex	Compound	Data	SM
196	1-(2-(4-methylpiperazin-1-yl)ethyl)-4-oxo-7-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 644.1 ($M+H^+$) for $C_{30}H_{32}F_3N_7O_4S$ ^1H NMR (300 MHz, DMSO-d_6): δ 0.91 (t, 3H), 1.50 (m, 2H), 2.10 (s, 3H), 2.22-2.73 (m, 10H), 3.16 (q, 2H), 4.69 (t, 2H), 7.65 (s, 1H), 7.85 (dd, 1H), 8.11 (d, 1H), 8.22 (s, 1H), 8.28 (s, 1H), 8.30 (d, 1H), 8.39 (s, 1H), 8.52 (d, 1H), 8.92 (d, 1H), 9.48 (s, 1H)	Example 180
197	7-(6-(3-isopropylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 630.3 ($M+H^+$) for $C_{30}H_{29}F_3N_5NaO_5S$ ^1H NMR (300 MHz, CD_3OD): δ 1.25 (d, 6H), 1.35-1.40 (m, 2H), 1.71-1.87 (m, 4H), 3.43 (t, 2H), 3.72 (m, 1H), 3.90-4.05 (m, 3H), 4.40 (t, 2H), 7.55-7.65 (m, 3H), 7.77 (d, 1H), 7.92 (s, 1H), 8.14 (d, 1H), 8.33 (s, 1H), 8.41 (d, 1H), 8.51 (s, 1H)	Example 183

Ex	Compound	Data	SM
198	1-(2-(1-methylpiperidin-4-yl)ethyl)-4-oxo-6-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 643 ($M+H^+$) for $C_{31}H_{33}F_3N_6O_4S$ ^1H NMR (300 MHz, CD_3OD): δ 0.99 (t, 3H), 1.37 (m, 2H), 1.63 (m, 2H), 1.84 (m, 3H), 2.03 (t, 2H), 2.25 (s, 3H), 2.99 (m, 2H), 4.40 (t, 2H), 7.61 (d, 1H), 7.76 (d, 1H), 7.90 (s, 1H), 8.32 (s, 1H), 8.44 (s, 1H), 8.61 (s, 1H)	Example 177
199	6-(6-(3-isopropylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(tetrahydro-2H-pyran-4-yl)-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 602 ($M+H^+$) for $C_{28}H_{26}F_3N_5O_5S$ ^1H NMR (300 MHz, CD_3OD): δ 1.26 (d, 6H), 2.16 (m, 4H), 3.75 (m, 2H), 3.99 (m, 1H), 4.15 (m, 2H), 5.15 (brs, 1H), 7.82 (d, 1H), 7.90 (s, 1H), 8.18 (s, 1H), 8.22 (d, 1H), 8.38 (s, 1H), 8.47 (s, 1H), 9.01 (s, 1H).	Example 187

Ex	Compound	Data	SM
200	4-oxo-6-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 630 ($M+H^+$) for $C_{30}H_{30}F_3N_5O_5S$ ^1H NMR (300 MHz, CD_3OD): δ 0.99 (t, 3H), 1.38 (m, 2H), 1.71 (m, 7H), 3.43 (m, 2H), 3.92 (m, 1H), 4.40 (m, 2H), 7.60 (d, 1H), 7.75 (d, 1H), 7.90 (s, 1H), 8.30 (s, 1H), 8.43 (s, 1H), 8.54 (s, 1H), 8.59 (s, 1H).	Exqmple 188
201	6-(6-(3-isopropylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(2-(1-methylpiperidin-4-yl)ethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 589.2 ($M+H^+$) for $C_{27}H_{27}F_3N_6O_4S$ ^1H NMR (300 MHz, CD_3OD): δ 1.00 (t, 3H), 1.88 (m, 2H), 2.34 (s, 6H), 2.79 (t, 2H), 4.46 (t, 2H), 7.62 (d, 1H), 7.79 (d, 1H), 7.89 (s, 1H), 8.14 (s, 1H), 8.34 (s, 1H), 8.43 (s, 1H), 8.55 (s, 1H).	Example 174
202	6-(6-(3-isopropylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(2-(1-methylpiperidin-4-yl)ethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 643.2 ($M+H^+$) for $C_{31}H_{33}F_3N_6O_4S$ ^1H NMR (300 MHz, CD_3OD): δ 1.25 (d, 6H), 1.52 (m, 2H), 1.93 (m, 3H), 2.13 (brd, 2H), 2.87 (s, 3H), 3.02 (m, 2H), 3.53 (m, 2H), 4.02 (m, 1H), 4.60 (t, 2H), 7.81 (d, 1H), 7.92 (s, 1H), 7.96 (d, 1H), 8.21 (s, 1H), 8.38 (s, 1H), 8.43 (s, 1H), 9.00 (s, 1H).	Example 179

Example 203

1-(2-(dimethylamino)ethyl)-N-(2-hydroxyethyl)-4-oxo-6-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1,4-dihydroquinoline-3-carboxamide



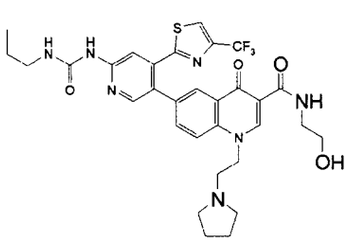
A suspension of ethyl 1-(2-(dimethylamino)ethyl)-4-oxo-6-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1,4-dihydroquinoline-3-carboxylate (Example 174, 50 mg, 0.09 mmol) in ethanolamine (0.5 mL) was heated to 85-90°C for 3 h. The reaction mixture was cooled to room temperature and the precipitate that formed was isolated by filtration and washed with acetonitrile and water then dried overnight under high vacuum.

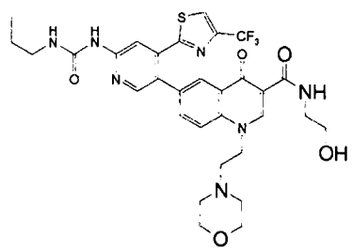
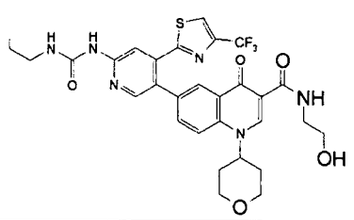
MS (ESP): 589 ($M+H^+$) for $C_{29}H_{32}F_3N_7O_4S$

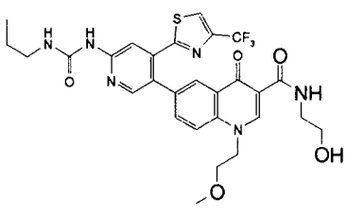
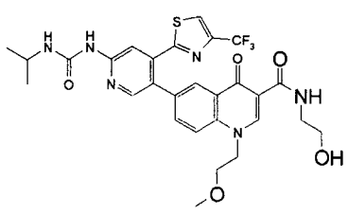
^1H NMR (300 MHz, CD_3OD): δ 1.00 (t, 3H), 1.64 (m, 2H), 2.33 (s, 6H), 2.78 (t, 2H), 3.37 (q, 2H), 3.66 (m, 2H), 3.83 (brs, 2H), 4.37 (t, 2H), 7.60 (m, 4H), 8.01 (s, 1H), 8.24 (s, 1H), 8.59 (s, 1H), 8.84 (s, 1H), 9.1 (brs, 1H), 10.25 (brs, 1H).

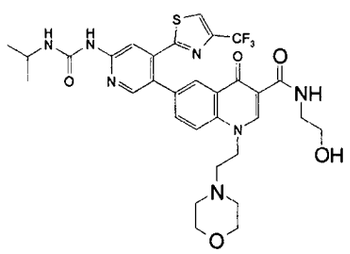
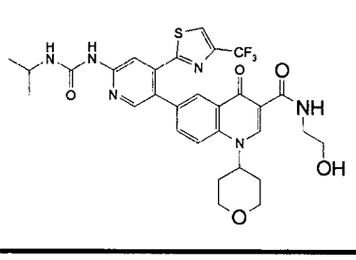
Examples 204-232

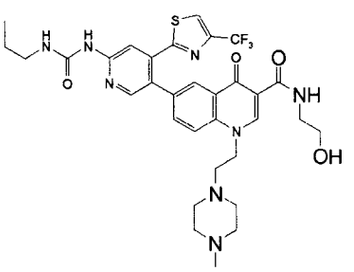
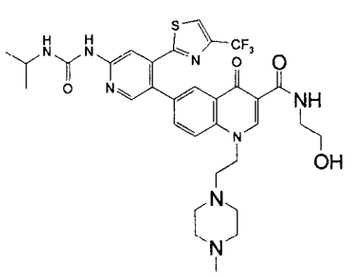
The following compounds were prepared according to the procedure described for Example 203 from the starting materials indicated in the table.

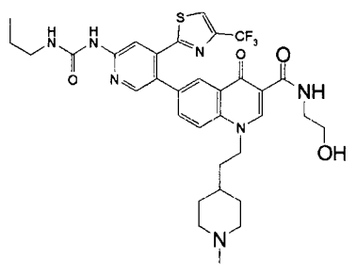
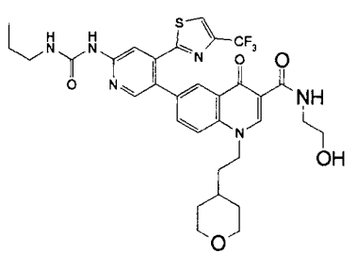
Ex	Compound	Data	SM
204	N-(2-hydroxyethyl)-4-oxo-6-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(2-(pyrrolidin-1-yl)ethyl)-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 658 ($M+H^+$) for $C_{31}H_{34}F_3N_7O_4S$ ^1H NMR (300 MHz, CD_3OD): δ 1.00 (t, 3H), 1.62 (m, 2H), 1.80 (m, 4H), 2.62 (m, 4H), 2.98 (m, 2H), 3.56 (m, 2H), 3.72 (m, 2H), 4.59 (m, 2H) 7.73 (d, 1H), 7.86 (s, 1H), 7.89 (d, 1H), 8.15 (s, 1H), 8.35 (s, 1H), 8.39 (s, 1H), 8.88 (s, 1H)	Example 176 and ethanolamine

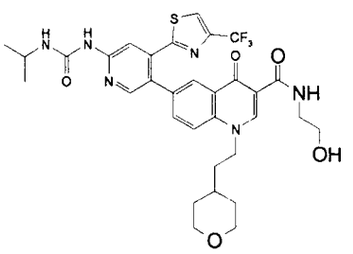
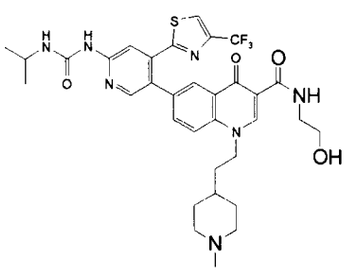
Ex	Compound	Data	SM
205	N-(2-hydroxyethyl)-1-(2-morpholinoethyl)-4-oxo-6-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 675 ($M+H^+$) for $C_{31}H_{34}F_3N_7O_5S$ ^1H NMR (300 MHz, CD_3OD): δ 0.90 (t, 3H), 1.49 (m, 2H), 2.4 (brs, 4H), 2.67 (m, 2H), 3.16 (m, 2H), 3.41 (m, 2H), 3.50 (brs, 6H), 4.60 (brs, 2H), 7.70 (s, 1H), 7.73 (d, 1H), 7.96 (d, 1H), 8.23 (s, 1H), 8.25 (s, 1H), 8.34 (s, 1H), 8.48 (s, 1H), 8.84 (s, 1H), 9.46 (s, 1H), 9.97 (s, 1H)	Example 181 and ethanolamine
206	N-(2-hydroxyethyl)-4-oxo-6-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(tetrahydro-2H-pyran-4-yl)-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 645 ($M+H^+$) for $C_{30}H_{31}F_3N_6O_5S$ ^1H NMR (300 MHz, CD_3OD): δ 0.99 (t, 3H), 2.18 (m, 4H), 3.55 (m, 2H), 3.74 (m, 4H), 4.17 (m, 2H), 5.10 (m, 1H), 7.72 (d, 1H), 7.86 (s, 1H), 8.09 (d, 1H), 8.14 (s, 1H), 8.34 (s, 1H), 8.42 (s, 1H), 8.99 (s, 1H)	Example 188 and ethanolamine

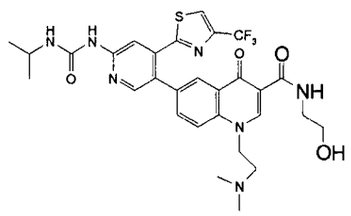
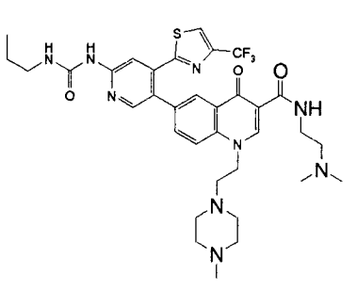
Ex	Compound	Data	SM
207	N-(2-hydroxyethyl)-1-(2-methoxyethyl)-4-oxo-6-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 619 ($M+H^+$) for $C_{29}H_{31}F_3N_6O_7S$ ^1H NMR (300 MHz, dmso-d_6): δ 0.91 (t, 3H), 1.49 (m, 2H), 3.16 (q, 2H), 3.23 (s, 3H), 3.40 (m, 2H), 3.50 (m, 2H), 3.69 (m, 2H), 4.70 (brs, 2H), 4.82 (t, 1H), 7.67 (t, 1H), 7.72 (d, 1H), 7.99 (d, 1H), 8.26 (s, 1H), 8.24 (s, 1H), 8.34 (s, 1H), 8.79 (s, 1H), 9.47 (s, 1H), 9.98 (t, 1H)	Example 185 and ethanolamine
208	N-(2-hydroxyethyl)-6-(6-(3-isopropylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(2-methoxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 619 ($M+H^+$) for $C_{28}H_{29}F_3N_6O_5S$ ^1H NMR (300 MHz, DMSO-d_6): δ 1.15(d, 6H), 3.34(s, 3H), 3.41 (m, 2H), 3.51 (m, 2H), 3.69 (m, 3H), 3.83 (m, 1H), 4.70 (brs, 2H), 4.82 (t, 1H), 7.71 (d, 1H), 7.74 (d, 1H), 8.02 (d, 1H), 8.26 (s, 1H), 8.28 (s, 1H), 8.35 (s, 1H), 8.49 (s, 1H), 8.80 (s, 1H), 9.34 (s, 1H), 9.98 (t, 1H)	Example 186 and ethanolamine

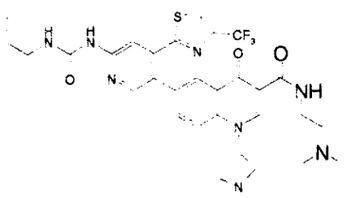
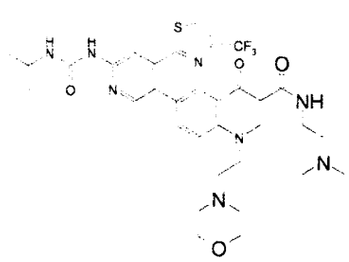
Ex	Compound	Data	SM
209	N-(2-hydroxyethyl)-6-(6-(3-isopropylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(2-morpholinoethyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 674 ($M+H^+$) for $C_{31}H_{34}F_3N_7O_5S$ ^1H NMR (300 MHz, dmso-d_6): δ 1.15 (d, 6H), 2.44 (brs, 4H), 2.67 (brs, 2H), 3.42 (m, 2H), 3.53 (brs, 6H), 3.82 (m, 1H), 4.61 (brs,2H), 4.82 (t, 1H), 7.48 (d, 1H), 7.73 (d, 1H), 7.98 (d, 1H), 8.25 (s, 1H), 8.27 (s, 1H), 8.35 (s, 1H), 8.49 (s, 1H), 8.84 (s, 1H), 9.46 (s, 1H), 9.97 (s, 1H)	Example 182 and ethanolamine
210	N-(2-hydroxyethyl)-6-(6-(3-isopropylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(tetrahydro-2H-pyran-4-yl)-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 645 ($M+H^+$) for $C_{30}H_{31}F_3N_6O_5S$ ^1H NMR (300 MHz, CD_3OD): δ 1.22 (d, 6H), 2.18 (m, 4H), 2.72 (m, 1H), 3.57 (t, 2H), 3.72 (m, 4H), 3.99 (m, 1H), 4.14 (m, 2H), 5.10 (m, 1H), 7.73 (d, 1H), 7.91 (s, 1H), 8.10 (d, 1H), 8.14 (s, 1H), 8.35 (s, 1H), 8.43 (s, 1H), 9.00 (s, 1H)	Example 187 and ethanolamine

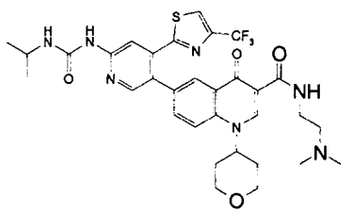
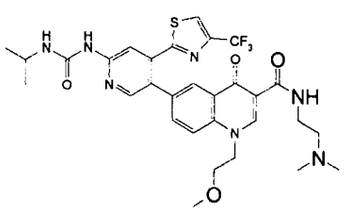
Ex	Compound	Data	SM
211	N-(2-hydroxyethyl)-1-(2-(4-methylpiperazin-1-yl)ethyl)-4-oxo-7-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 687.3 ($M+H^+$) for $C_{32}H_{37}F_3N_8O_4S$ ^1H NMR (300 MHz, dmso-d_6): δ 0.91 (t, 3H), 1.46-1.53 (m, 2H), 2.09 (s, br, 3H), 2.14-2.45 (m, 5H), 2.66 (t, 2H), 3.16 (q, 2H), 3.37-3.40 (m, 4H), 3.51 (q, 3H), 4.60 (t, br, 2H), 4.83 (t, 1H), 7.68-7.74 (m, 2H), 7.97 (d, 1H), 8.23 (s, 1H), 8.25 (d, 1H), 8.35 (s, 1H), 8.50 (t, 1H), 8.82 (d, 1H), 9.47 (s, 1H), 9.99 (t, 1H)	Example 180 and ethanolamine
212	N-(2-hydroxyethyl)-6-(4-(3-isopropylureido)-2-(4-(trifluoromethyl)thiazol-2-yl)phenyl)-1-(2-(4-methylpiperazin-1-yl)ethyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 687 ($M+H^+$) for $C_{33}H_{37}F_3N_8O_4S$ ^1H NMR (300 MHz, dmso-d_6): δ 1.17 (d, 6H), 2.10 (s, 3H), 2.43 (brs, 2H), 2.49 (brs, 2H), 2.66 (brs, 2H), 3.31 (m, 2H), 3.52 (m, 2H), 3.85 (m, 1H), 4.58 (m, 2H), 4.58 (t, 1H), 7.43 (d, 1H), 7.69 (d, 1H), 7.69 (d, 1H), 7.94 (d, 1H), 8.24 (s, 1H), 8.26 (s, 1H), 8.34 (s, 1H), 8.48 (s, 1H), 9.91 (s, 1H), 9.99 (t, 1H)	Example 179 and ethanolamine

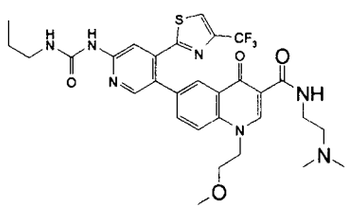
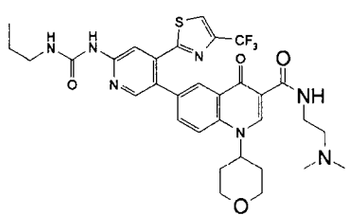
Ex	Compound	Data	SM
213	N-(2-hydroxyethyl)-1-(2-(1-methylpiperidin-4-yl)ethyl)-4-oxo-6-(4-(3-propylureido)-2-(4-(trifluoromethyl)thiazol-2-yl)phenyl)-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 686 ($M+H^+$) for $C_{33}H_{38}F_3N_7O_4S$ ^1H NMR (300 MHz, dmso-d_6): δ 0.91 (t, 3H), 1.23 (m, 3H), 1.59 (m, 2H), 1.76 (m, 4H), 2.12 (s, 3H), 2.75 (m, 2H), 3.18 (m, 2H), 3.37 (m, 1H), 3.50 (m, 2H), 4.49 (brs, 2H), 4.80 (brs, 1H), 7.72 (d, 1H), 7.89 (d, 1H), 7.69 (d, 1H), 7.82 (s, 2H), 8.31 (s, 1H), 8.48 (s, 1H), 8.89 (s, 1H), 9.53 (s, 1H), 9.95 (t, 1H)	Example 177 and ethanolamine
214	N-(2-hydroxyethyl)-4-oxo-6-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 673 ($M+H^+$) for $C_{32}H_{35}F_3N_6O_5S$ ^1H NMR (300 MHz, dmso-d_6): δ 0.90 (t, 3H), 1.27 (m, 2H), 1.48 (m, 2H), 1.64 (m, 4H), 2.92 (m, 1H), 3.24 (m, 2H), 3. 28 (m, 2H), 3.39 (m, 2H), 3.86 (m, 2H), 4.51 (t, 2H), 4.81 (s, 1H), 7.75 (d, 1H), 7.93 (d, 1H), 8.25 (s, 2H), 8.34 (s, 1H), 8.49 (s, 2H), 8.91 (s, 1H), 9.57 (s, 1H), 9.98 (t, 1H)	Example 184 and ethanolamine

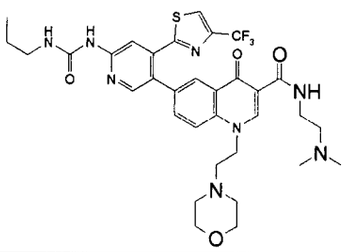
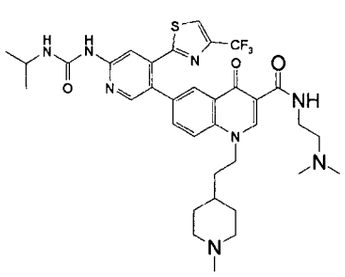
Ex	Compound	Data	SM
215	N-(2-hydroxyethyl)-7-(6-(3-isopropylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 673.2 ($M+H^+$) for $C_{32}H_{35}F_3N_6O_5S$ ^1H NMR (300 MHz, dmso-d_6): δ 1.15 (d, 6H), 1.23-1.35 (m, 3H), 1.64-1.79 (m, 6H), 3.05-3.12 (m, 2H), 3.49-3.53 (m, 2H), 3.83-3.87 (m, 3H), 4.54 (br, 2H), 4.64 (t, 1H), 4.80 (t, 1H), 7.45 (dd, 1H), 7.74 (dd, 1H), 7.92 (d, 1H), 8.25 (d, 1H), 8.27 (d, 1H), 8.34 (d, 1H), 8.49 (d, 1H), 8.91 (s, 1H), 9.32 (s, 1H), 9.98 (t, 1H)	Example 183 and ethanolamine
216	N-(2-hydroxyethyl)-6-(6-(3-isopropylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(2-(1-methylpiperidin-4-yl)ethyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 686 ($M+H^+$) for $C_{33}H_{38}F_3N_7O_4S$ ^1H NMR (300 MHz, dmso-d_6): δ 1.20 (d, 3H), 1.24 (m, 2H), 1.68 (m, 3H), 1.83 (m, 2H), 2.08 (s, 3H), 2.75 (brs, 2H), 3.41 (m, 2H), 3.50 (m, 2H), 3.83 (m, 1H), 4.53 (t, 2H), 4.81 (t, 1H), 7.46 (d, 1H), 7.76 (d, 1H), 7.89 (d, 1H), 8.25 (s, 1H), 8.27 (s, 1H), 8.34 (s, 1H), 8.49 (s, 1H), 8.89 (s, 1H), 9.32 (s, 1H), 9.98 (t, 1H)	Example 178 and ethanolamine

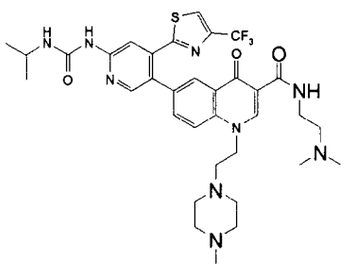
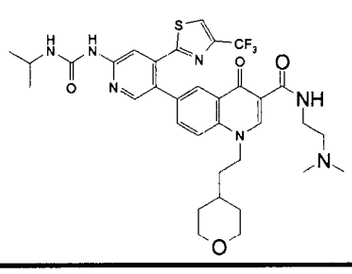
Ex	Compound	Data	SM
217	1-(2-(dimethylamino)ethyl)-N-(2-hydroxyethyl)-7-(6-(3-isopropylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 632.1 ($M+H^+$) for $C_{29}H_{32}F_3N_7O_4S$ ^1H NMR (300 MHz, dmso-d_6): δ 1.15 (d, 6H), 2.19 (s, 6H), 2.62 (t, 2H), 3.40 (q, 2H), 3.43-3.51 (m, 2H), 3.81-3.88 (m, 1H), 4.59 (t, br, 2H), 4.81 (br, 1H), 7.46 (d, 1H), 7.72 (dd, 1H), 7.95 (d, 1H), 8.25 (d, 1H), 8.27 (s, 1H), 8.34 (d, 1H), 8.49 (d, 1H), 8.82 (s, 1H), 9.33 (s, 1H), 9.99 (t, 1H)	Example 173 and ethanolamine
218	N-(2-(dimethylamino)ethyl)-1-(2-(4-methylpiperazin-1-yl)ethyl)-4-oxo-7-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 714.3 ($M+H^+$) for $C_{34}H_{42}F_3N_9O_3S$ ^1H NMR (300 MHz, dmso-d_6): δ 0.91 (t, 3H), 1.47-1.54 (m, 2H), 2.11 (s, 3H), 2.18 (s, 6H), 2.19-2.38 (m, 2H), 2.40-2.50 (m, 4H), 2.66 (t, 2H), 3.15 (q, 2H), 3.42 (q, 2H), 4.58 (t, 2H), 7.66-7.72 (m, 2H), 7.96 (d, 1H), 8.24 (s, 1H), 8.27 (d, 1H), 8.34 (d, 1H), 8.49 (d, 1H), 8.80 (s, 1H), 9.44 (s, 1H), 9.92 (t, 1H)	Example 180 and N^1,N^1-dimethyl-ethane-1,2-diamine

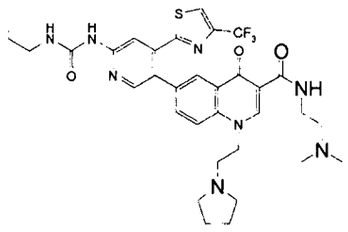
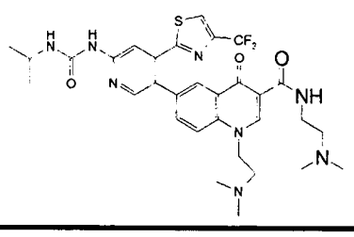
Ex	Compound	Data	SM
219	N,1-bis(2-(dimethylamino)ethyl)-4-oxo-6-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 659 ($M+H^+$) for $C_{31}H_{37}F_3N_8O_3S$ ^1H NMR (300 MHz, dmso-d_6): δ 0.91 (t, 3H), 1.51 (m, 2H), 2.17 (s, 6H), 2.39 (t, 2H), 2.61 (brs, 2H), 3.16 (m, 2H), 3.42 (m, 2H), 4.57 (t, 2H), 7.69 (s, 1H), 7.71 (d, 1H), 7.96 (d, 1H), 8.24 (s, 1H), 8.27 (s, 1H), 8.33 (s, 1H), 8.48 (s, 1H), 8.80 (s, 1H), 9.4 (s, 1H), 9.93 (brs, 1H)	Example 174 and N^1,N^1-dimethyl-ethane-1,2-diamine
220	N-(2-(dimethylamino)ethyl)-7-(6-(3-isopropylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(2-morpholinoethyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 701.4 ($M+H^+$) for $C_{33}H_{39}F_3N_8O_4S$ ^1H NMR (300 MHz, dmso-d_6): δ 1.15 (d, 6H), 2.12 (d, 1H), 2.18 (s, 6H), 2.27 (t, 1H), 2.37-2.51 (m, 8H), 2.65 (t, 1H), 2.73 (t, 1H), 3.42 (q, 1H), 3.50 (t, 2H), 3.8 (q, 1H), 4.60 (t, 1H), 7.45 (d, 1H), 7.70 (dd, 1H), 7.96 (d, 1H), 8.27 (m, 2H), 8.34 (s, 1H), 8.48 (d, 1H), 8.83 (s, 1H), 9.34 (s, 1H), 9.91 (m, 1H)	Example 182 and N^1,N^1-dimethyl-ethane-1,2-diamine

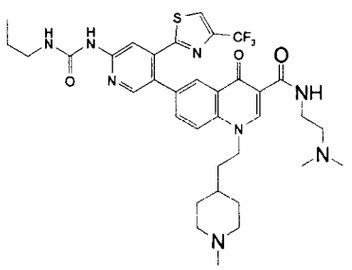
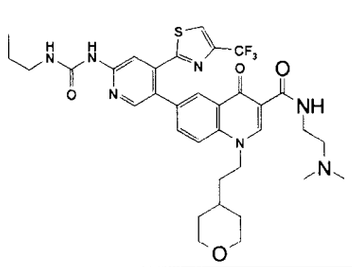
Ex	Compound	Data	SM
221	N-(2-(dimethylamino)ethyl)-7-(6-(3-isopropylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(tetrahydro-2H-pyran-4-yl)-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 672.3 ($M+H^+$) for $C_{32}H_{36}F_3N_7O_4S$ ^1H NMR (300 MHz, dmso-d_6): δ 1.15 (d, 6H), 2.03-2.16 (m, 4H), 2.16 (s, 6H), 3.60-3.70 (m, 1H), 3.80-3.90 (m, 1H), 4.0-4.1 (m, 1H), 5.05-5.10 (m, 1H), 7.50 (d, 1H), 7.72 (dd, 1H), 8.20-8.32 (m, 3H), 8.46 (s, 1H), 8.84 (s, 1H), 9.32 (d, 1H), 9.88 (m, 1H)	Example 187 and N^1,N^1-dimethyl-ethane-1,2-diamine
222	N-(2-(dimethylamino)ethyl)-7-(6-(3-isopropylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(2-methoxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 646.2 ($M+H^+$) for $C_{30}H_{34}F_3N_7O_4S$ ^1H NMR (300 MHz, $CDCl_3$): δ 1.29 (d, 6H), 2.32 (s, 6H), 2.56 (t, 2H), 3.34 (s, 3H), 3.60 (q, 2H), 3.80 (t, 2H), 4.11 (q, 1H), 4.46 (t, 2H), 7.22 (d, 1H), 7.42 (s, 1H), 7.51-7.61 (m, 2H), 7.68 (s, 1H), 8.28 (s, 1H), 8.57 (d, 1H), 8.84 (s, 1H), 8.91 (d, 1H), 10.02 (br, 1H)	Example 186 and N^1,N^1-dimethyl-ethane-1,2-diamine

Ex	Compound	Data	SM
223	N-(2-(dimethylamino)ethyl)-1-(2-methoxyethyl)-4-oxo-7-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 646.2 ($M+H^+$) for $C_{30}H_{34}F_3N_7O_4S$ ^1H NMR (300 MHz, $CDCl_3$): δ 1.01 (t, 3H), 1.67 (q, 2H), 2.18 (s, 6H), 2.32 (t, 2H), 3.34 (s, 3H), 3.39 (q, 2H), 3.60 (q, 2H), 3.80 (t, 2H), 4.46 (t, 2H), 7.44 (s, 1H), 7.48 (s, 1H), 7.52-7.61 (m, 2H), 7.68 (d, 1H), 8.27 (s, 1H), 8.57 (d, 1H), 8.85 (s, 1H), 9.11 (br, 1H), 10.02 (br, 1H)	Example 185 and N^1,N^1-dimethyl-ethane-1,2-diamine
224	N-(2-(dimethylamino)ethyl)-4-oxo-7-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(tetrahydro-2H-pyran-4-yl)-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 672.3 ($M+H^+$) for $C_{32}H_{36}F_3N_7O_4S$ ^1H NMR (300 MHz, $CDCl_3$): δ 1.01 (t, 3H), 1.67 (q, 2H), 2.10-2.30 (m, 4H), 2.31 (s, 6H), 2.56 (t, 2H), 3.41 (q, 2H), 3.57-3.70 (m, 4H), 4.25 (dd, 2H), 4.73 (m, 1H), 7.44 (s, 1H), 7.50 (s, 1H), 7.54-7.66 (m, 2H), 7.68 (d, 1H), 8.27 (d, 1H), 8.62 (d, 1H), 9.03 (s, 1H), 9.09 (br, 1H), 10.01 (t, br, 1H)	Example 188 and N^1,N^1-dimethyl-ethane-1,2-diamine

Ex	Compound	Data	SM
225	N-(2-(dimethylamino)ethyl)-1-(2-morpholinoethyl)-4-oxo-7-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 701.4 ($M+H^+$) for $C_{33}H_{39}F_3N_8O_4S$ ^1H NMR (300 MHz, $CDCl_3$): δ 1.01 (t, 3H), 1.64 (q, 2H), 2.32 (s, 6H), 2.52-2.56 (m, 6H), 2.81 (t, 2H), 3.38 (q, 2H), 3.59-3.70 (m, 6H), 4.37 (t, 2H), 7.40 (s, 1H), 7.55 (d, 2H), 7.69 (s, 1H), 8.27 (s, 1H), 8.58 (s, 1H), 8.82 (s, 1H), 9.05 (br, 1H), 10.01 (br, 1H)	Example 181 and N^1,N^1-dimethyl-ethane-1,2-diamine
226	N-(2-(dimethylamino)ethyl)-6-(4-(3-isopropylureido)-2-(4-(trifluoromethyl)thiazol-2-yl)phenyl)-1-(2-(1-methylpiperidin-4-yl)ethyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 686 ($M+H^+$) for $C_{35}H_{43}F_3N_8O_3S$ ^1H NMR (300 MHz, dmso-d_6): δ 1.17 (d, 6H), 1.23 (m, 3H), 1.72 (m, 4H), 1.80 (m, 2H), 2.12 (s, 3H), 2.17 (s, 6H), 2.39 (t, 2H), 2.71 (m, 2H), 3.41 (m, 2H), 3.85 (m, 1H), 4.52 (brs, 1H), 7.45 (d, 1H), 7.73 (d, 1H), 7.89 (d, 1H), 8.27 (s, 2H), 8.34 (s, 1H), 8.48 (s, 1H), 8.89 (s, 1H), 9.33 (s, 1H), 9.92 (t, 1H)	Example 178 and N^1,N^1-dimethyl-ethane-1,2-diamine

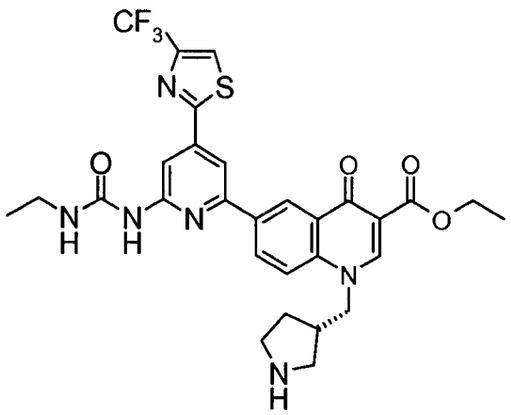
Ex	Compound	Data	SM
227	N-(2-(dimethylamino)ethyl)-6-(6-(3-isopropylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(2-(4-methylpiperazin-1-yl)ethyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 714 ($M+H^+$) for $C_{34}H_{42}F_3N_9O_3S$ ^{1}H NMR (300 MHz, dmso-d_6): δ 1.14 (d, 6H), 2.12 (s, 3H), 2.18 (s, 6H), 2.27 (brs, 2H), 2.36 (m, 6H), 2.66 (t, 2H), 3.41 (m, 2H), 3.87 (m, 1H), 4.58 (t, 2H), 7.48 (d, 1H), 7.71 (d, 1H), 7.97 (d, 1H), 8.26 (s, 2H), 8.34 (s, 1H), 8.48 (s, 1H), 8.80 (s, 1H), 9.34 (s, 1H), 9.92 (t, 1H)	Example 179 and N^1,N^1-dimethyl-ethane-1,2-diamine
228	N-(2-(dimethylamino)ethyl)-7-(6-(3-isopropylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 700.2 ($M+H^+$) for $C_{34}H_{40}F_3N_7O_4S$ ^{1}H NMR (300 MHz, dmso-d_6): δ 1.15 (d, 6H), 1.23-1.35 (m, 3H), 1.64-1.79 (m, 6H), 2.22 (s, 6H), 3.20-3.40 (m, 2H), 3.43-3.53 (m, 2H), 3.83-3.87 (m, 3H), 4.54 (br, 2H), 7.45 (d, 1H), 7.73 (dd, 1H), 7.91 (d, 1H), 8.27 (d, 2H), 8.34 (d, 1H), 8.49 (d, 1H), 8.91 (s, 1H), 9.32 (s, 1H), 9.94 (t, 1H)	Example 183 and N^1,N^1-dimethyl-ethane-1,2-diamine

Ex	Compound	Data	SM
229	N-(2-(dimethylamino)ethyl)-4-oxo-7-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(2-(pyrrolidin-1-yl)ethyl)-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 685.2 ($M+H^+$) for $C_{34}H_{41}F_3N_8O_5S$ ^1H NMR (300 MHz, dmso-d_6): δ 0.83-0.88 (m, 2H), 0.91 (t, 3H), 1.47-1.54 (m, 2H), 1.65 (br, 4H), 2.18 (s, 6H), 2.39 (t, 2H), 2.82 (t, 2H), 3.15 (q, 2H), 3.34-3.50 (m, 4H), 4.60 (t, 2H), 7.67-7.73 (m, 2H), 7.95 (d, 1H), 8.24 (s, 1H), 8.27 (d, 1H), 8.35 (s, 1H), 8.48 (d, 1H), 8.82 (s, 1H), 9.46 (s, 1H), 9.92 (t, 1H)	Example 176 and N^1,N^1-dimethyl-ethane-1,2-diamine
230	N,1-bis(2-(dimethylamino)ethyl)-7-(6-(3-isopropylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 659.4 ($M+H^+$) for $C_{31}H_{37}F_3N_8O_3S$ ^1H NMR (300 MHz, dmso-d_6): δ 1.16 (d, 6H), 2.19 (s, 6H), 2.21 (s, 6H), 2.44 (t, 2H), 2.62 (t, 2H), 3.43 (q, 2H), 3.80-3.86 (m, 1H), 4.58 (t, br, 2H), 7.44 (d, 1H), 7.71 (dd, 1H), 7.95 (d, 1H), 8.27 (d, 2H), 8.35 (d, 1H), 8.49 (d, 1H), 8.81 (s, 1H), 9.32 (s, 1H), 9.95 (t, 1H)	Example 173 and N^1,N^1-dimethyl-ethane-1,2-diamine

Ex	Compound	Data	SM
231	N-(2-(dimethylamino)ethyl)-1-(2-(1-methylpiperidin-4-yl)ethyl)-4-oxo-6-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 713 ($M+H^+$) for $C_{36}H_{45}F_3N_8O_5S$ ^1H NMR (300 MHz, dmso-d_6): δ 0.91 (t, 3H), 1.25 (brs, 4H), 1.51 (m, 2H), 1.72 (m, 3H), 1.89 (t, 2H), 2.40 (t, 2H), 2.80 (m, 2H), 2.50 (s, 9H), 3.16 (q, 2H), 3.43 (m, 2H), 4.52 (t, 2H), 7.67 (t, 1H), 7.74 (d, 1H), 7.89 (d, 1H), 8.24 (s, 1H), 8.27 (s, 1H), 8.34 (s, 1H), 8.48 (s, 1H), 8.89 (s, 1H), 9.45 (s, 1H), 9.92 (s, 1H)	Example 177 and N^1,N^1-dimethyl-ethane-1,2-diamine
232	N-(2-(dimethylamino)ethyl)-4-oxo-6-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 700 ($M+H^+$) for $C_{35}H_{42}F_3N_7O_6S$ ^1H NMR (300 MHz, CD_3OD): δ 1.00 (t, 3H), 1.36 (m, 2H), 1.59 (m, 2H), 1.64 (m, 3H), 1.84 (m, 2H), 2.60 (s, 6H), 2.93 (t, 2H), 3.43 (t, 2H), 3. 68 (t, 2H), 3.97 (m, 2H), 4.53 (t, 2H), 7.75 (d, 1H), 7.87 (s, 1H), 7.90 (d, 1H), 8.17 (s, 1H), 8.35 (s, 1H), 8.39 (s, 1H), 8.51 (brs, 1H), 8.89 (s, 1H)	Example 184 and N^1,N^1-dimethyl-ethane-1,2-diamine

Example 233

(R)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(pyrrolidin-3-ylmethyl)-1,4-dihydroquinoline-3-carboxylate

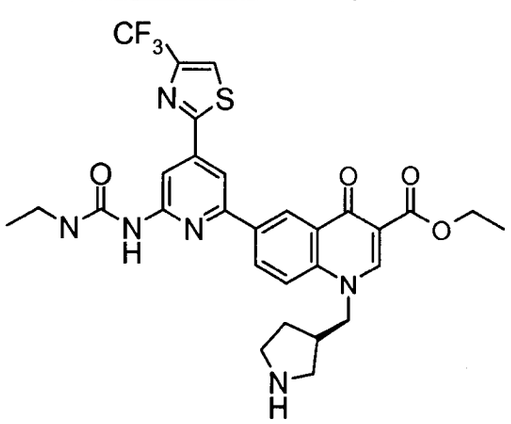


A vial was charged with (R)-ethyl 6-iodo-4-oxo-1-(pyrrolidin-3-ylmethyl)-1,4-dihydroquinoline-3-carboxylate hydrochloride (Intermediate 97, 1.0 g, 2.16 mmol), 6-(3-ethylureido)-4-(4-trifluoromethylthiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 17, 940 mg, 2.61 mmol), and sodium bicarbonate (730 mg, 8.65 mmol) in dimethoxyethane (10 mL) and water (2 mL). The reaction mixture was purged with N_2 for about 5 min, then trans-dichlorobis(triphenylphosphine)palladium (II) (160 mg, 0.228 mmol) was added. The reaction mixture was heated for 3 h at 80-85°C, then cooled to room temperature and water (10 mL) was added. The precipitated solid was collected by filtration to give (R)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(pyrrolidin-3-ylmethyl)-1,4-dihydroquinoline-3-carboxylate (1.1 g, 82.7%) as a light brown solid after drying under vacuum at 40°C overnight.

MS (ESP): 615.3 ($M+H^+$) for $C_{29}H_{29}F_3N_6O_4S$.

Example 234

(S)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(pyrrolidin-3-ylmethyl)-1,4-dihydroquinoline-3-carboxylate

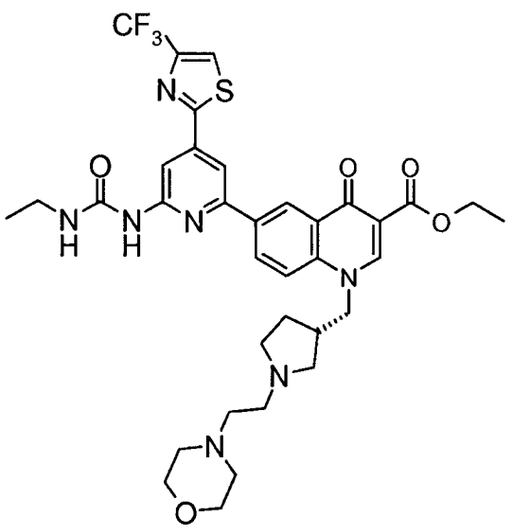


A vial was charged with (S)-ethyl 6-iodo-4-oxo-1-(pyrrolidin-3-ylmethyl)-1,4-dihydroquinoline-3-carboxylate hydrochloride (Intermediate 98, 1.0 g, 2.16 mmol), 6-(3-ethylureido)-4-(4-trifluoromethylthiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 17, 940 mg, 2.61 mmol), and sodium bicarbonate (730 mg, 8.65 mmol) in dimethoxyethane (10 mL) and water (2 mL). The reaction mixture was purged by N_2 for about 5 min, then trans-dichlorobis(triphenylphosphine)palladium (II) (160 mg, 0.228 mmol) was added. The reaction was heated for 1 hour at 80-85°C, then cooled to room temperature, and water (10 mL) was added. The precipitate that formed was collected by filtration to give (S)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(pyrrolidin-3-ylmethyl)-1,4-dihydroquinoline-3-carboxylate (1.16 g, 87.2%) as a light brown solid after drying under vacuum at 40°C overnight.

MS (ESP): 615.3 ($M+H^+$) for $C_{29}H_{29}F_3N_6O_4S$.

Example 235

(R)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-((1-(2-morpholinoethyl)pyrrolidin-3-yl)methyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate



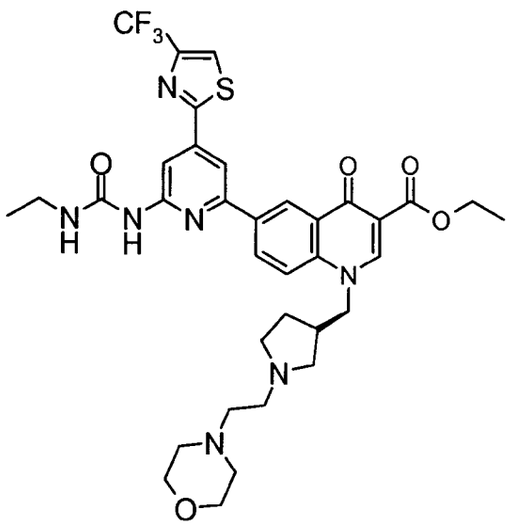
A vial was chargedwith (R)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(pyrrolidin-3-ylmethyl)-1,4-dihydroquinoline-3-carboxylate (Example 233, 700 mg, 1.14 mmol) and morpholin-4-yl-acetaldehyde monohydrate hydrochloride (250 mg, 1.37 mmol) in methanol (10 mL). MP-cyanoborohydride (730 mg, 1.71 mmol) beads were added and the resulting mixture was allowed to stir at room temperature overnight. The reaction mixture was filtered and the beads were washed with more methanol. The filtrate was concentrated under reduced pressure and purified by

Analogix SF15-24 g in dichloromethane/ methanol system to give a light yellow solid (320 mg, 38.6%).

MS (ESP): 728.1 (MH^+) for $C_{35}H_{40}F_3N_7O_5S$.

Example 236

(S)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-((1-(2-morpholinoethyl)pyrrolidin-3-yl)methyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate

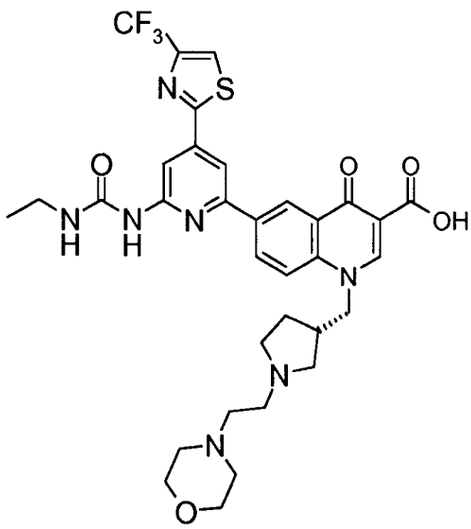


A vial was charged with (S)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(pyrrolidin-3-ylmethyl)-1,4-dihydroquinoline-3-carboxylate (Example 234, 800 mg, 1.3 mmol) and morpholin-4-yl-acetaldehyde monohydrate hydrochloride (270 mg, 1.47 mmol) in methanol (10 mL). MP-cyanoborohydride (850 mg, 2.0 mmol) beads were added and the resulting mixture was allowed to stir at room temperature overnight. The mixture was filtered and the beads were washed with more methanol. The filtrate was concentrated and purified by Analogix SF15-24 g in DCM/ methanol system to give a light yellow solid (380 mg, 45.8%).

MS (ESP): 728.1 (MH^+) for $C_{35}H_{40}F_3N_7O_5S$

Example 237

(R)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-((1-(2-morpholinoethyl)pyrrolidin-3-yl)methyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



(R)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-((1-(2-morpholinoethyl)pyrrolidin-3-yl)methyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (Example 235, 320 mg) was dissolved in methanol (3 mL) and tetrahydrofuran (3 mL). To this solution was added 24 wt% sodium hydroxide (1 mL) and the reaction mixture was stirred at room temperature overnight. The reaction mixture was then concentrated to remove the organic solvents. Water (10 mL) was added and the aqueous layer was acidified to pH 6~7 with 1N hydrochloric acid. The solution was centrifuged to help isolate the solid that precipitated, and the precipitate was washed with cold water once to give a light yellow solid (260 mg, 86.9%) after drying.

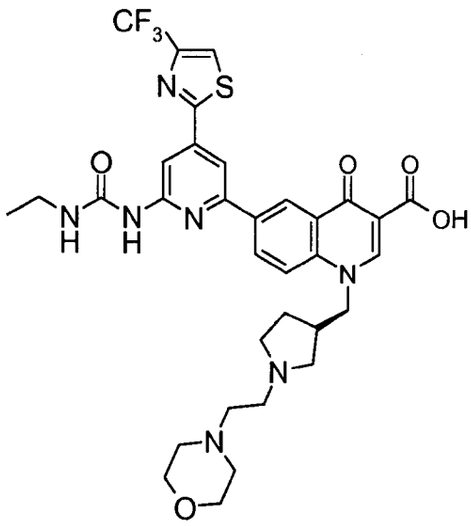
MS (ESP): 700.2 (MH^+) for $C_{33}H_{36}F_3N_7O_5S$

^1H NMR (300 MHz, DMSO-d_6):1.11 (t, 3H), 2.38-2.50 (bm, 4H), 3.18-3.25 (bm, 8H), 3.50-3.62 (bm, 6H), 4.13 (br, 1H), 4.75 (br, 2H), 7.67 (bt, 1H), 7.86 (dd, 1H), 8.23-8.25 (b, 1H), 8.25 (s, 1H), 8.31 (d, 1H), 8.37 (s, 1H), 8.54 (s, 1H), 9.11 (s, 1H), 9.55 (s, 1H)

^{19}F NMR Spectrum (DMSO-d_6) -62.79

Example 238

(S)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-((1-(2-morpholinoethyl)pyrrolidin-3-yl)methyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



(S)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-((1-(2-morpholinoethyl)pyrrolidin-3-yl)methyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (Example 236, 380 mg) was dissolved in methanol (3 mL) and tetrahydrofuran (3 mL). To this solution was added 24 wt% sodium hydroxide (1 mL) and the reaction was stirred at room temperature overnight. The solution was then concentrated to remove the organic solvents. Water (10 mL) was added and the aqueous layer was carefully acidified to pH 6~7 with 1N hydrochloric acid. The solution was centrifuged to help isolate the solid that precipitated which was washed with cold water once to give a light yellow solid (300 mg, 82.1%) after drying.

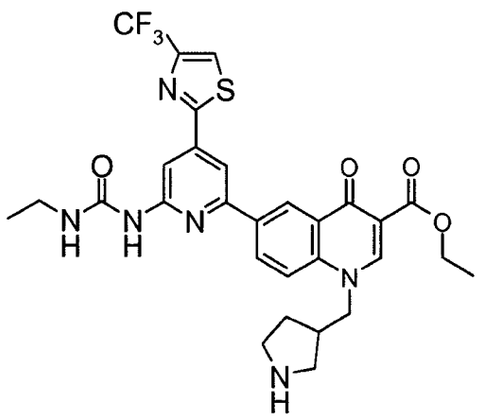
MS (ESP): 700.2 (MH^+) for $C_{33}H_{36}F_3N_7O_5S$

^1H NMR (300 MHz, CD_3OD): 1.23 (m, 3H), 1.99-2.1 (br, 1H), 2.25-2.4 (br, 2H), 3.2-3.3 (m, 4H), 3.30-3.5 (m, 6H), 3.6-3.7 (m, 4H), 3.9-4.0 (m, 4H), 4.70-4.8 (br, 2H), 7.85 (d, 1H), 7.88 (s, 1H), 8.11 (d, 1H), 8.22 (s, 1H), 8.37 (s, 1H), 8.46 (d, 1H), 9.09 (s, 1H)

^{19}F NMR Spectrum (CD_3OD) -65.78.

Example 239

ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(pyrrolidin-3-ylmethyl)-1,4-dihydroquinoline-3-carboxylate

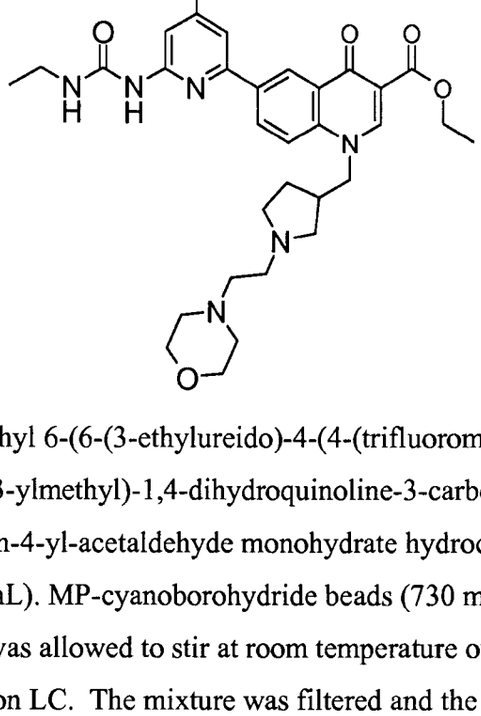


A tall vial was charged with ethyl 6-iodo-4-oxo-1-(pyrrolidin-3-ylmethyl)-1,4-dihydroquinoline-3-carboxylate hydrochloride (Intermediate 126, 1.5 g, 3.24 mmol), 6-(3-ethylureido)-4-(4-trifluoromethylthiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 17, 1.41 g, 3.9 mmol) and sodium bicarbonate (1.1 g, 12.9 mmol) in dimethoxyethane (10 mL) and water (2 mL). The reaction mixture was purged by N_2 for about 5 minutes, then trans-dichlorobis(triphenylphosphine)palladium (II) (228 mg, 0.324 mmol) was added. The reaction was stirred for 1 h at 75°C. The reaction mixture was cooled to room temperature, and water (10 mL) was added. A solid precipitated and was collected to give ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(pyrrolidin-3-ylmethyl)-1,4-dihydroquinoline-3-carboxylate (1.6 g, 80.4%) as a light brown solid after drying in a vacuum oven at 40°C overnight.

MS (ESP): 615.0 ($M+H^+$) for $C_{29}H_{29}F_3N_6O_4S$.

Example 240

ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-((1-(2-morpholinoethyl)pyrrolidin-3-yl)methyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate

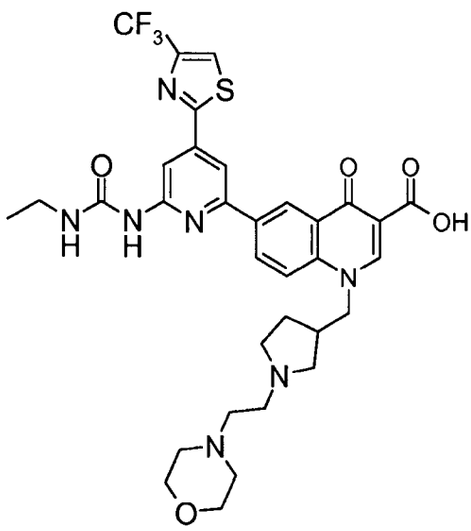


A vial was charged with ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(pyrrolidin-3-ylmethyl)-1,4-dihydroquinoline-3-carboxylate (Example 239, 700 mg, 1.14 mmol), morpholin-4-yl-acetaldehyde monohydrate hydrochloride (260 mg, 1.39 mmol) and methanol (10 mL). MP-cyanoborohydride beads (730 mg, 1.71 mmol) were added and the resulting mixture was allowed to stir at room temperature overnight. The reaction went to completion based on LC. The mixture was filtered and the beads were washed with methanol. The filtrate was concentrated under reduced pressure and purified by Analogix SF15-24 g column eluting with dichloromethane/ methanol system to give a light yellow solid (310 mg, 37.4%).

MS (ESP): 728.1 (MH^+) for $C_{35}H_{40}F_3N_7O_5S$.

Example 241

6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-((1-(2-morpholinoethyl)pyrrolidin-3-yl)methyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



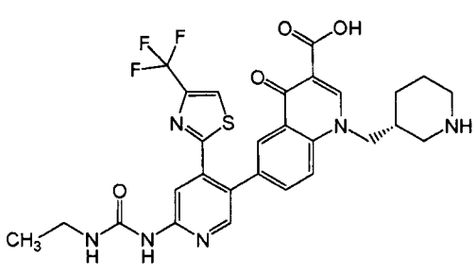
Ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-((1-(2-morpholinoethyl)pyrrolidin-3-yl)methyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (Example 240, 340 mg) was dissolved in methanol (3 mL) and tetrahydrofuran (3 mL). To this solution was added 24 wt% sodium hydroxide (1 mL) and the reaction mixture was stirred at room temperature for 3 h. The solution was concentrated under reduced pressure to remove the organics. Water (7 mL) was added and the aqueous layer was carefully acidified to pH~3 with 1N hydrochloric acid. A solid precipitated, and the mixture was centrifuged to help collect the solid which was then washed with cold water once and dried to give a light yellow solid (270 mg, 81.2%).

MS (ESP): 700.2 (MH^+) for $C_{33}H_{36}F_3N_7O_5S$

^1H NMR (CD_3OD): 1.23 (m, 3H), 1.99-2.1 (br, 1H), 2.25-2.4 (br, 2H), 3.3-3.4 (m, 6H), 3.45-3.6 (m, 4H), 3.7-3.8 (m, 4H), 3.9-4.0 (m, 4H), 4.85-4.9 (br, 2H), 7.85 (d, 1H), 7.90 (s, 1H), 8.12 (d, 1H), 8.23 (s, 1H), 8.37 (s, 1H), 8.47 (s, 1H), 9.11 (s, 1H).

Example 242

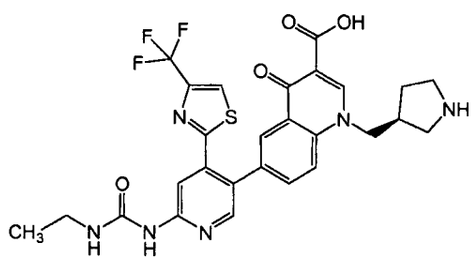
(*R*)-1-((1-piperidin-3-yl)methyl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

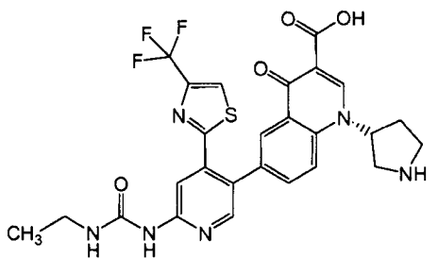
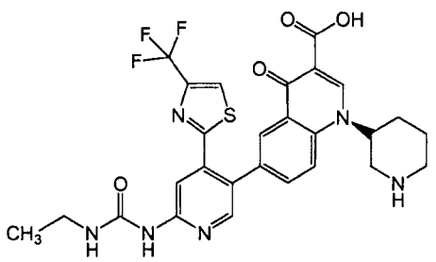
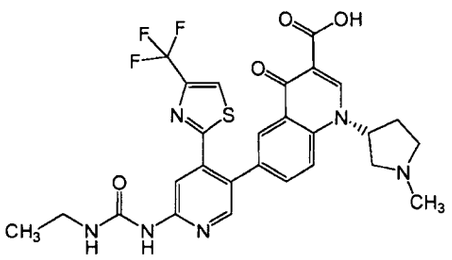


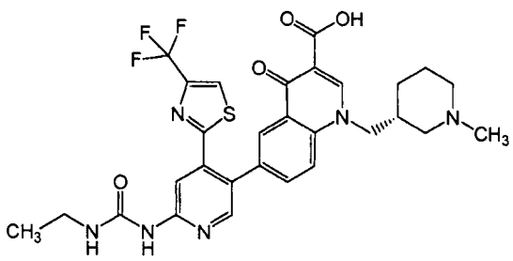
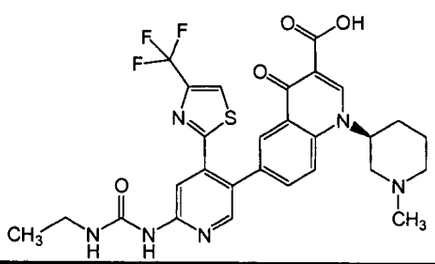
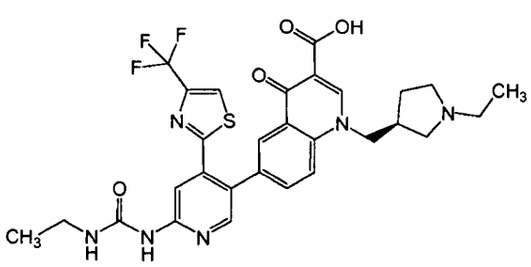
To a solution of (*R*)-ethyl 6-iodo-4-oxo-1-(piperidin-3-ylmethyl)-1,4-dihydroquinoline-3-carboxylate (Intermediate 108, 200 mg, 0.42 mmol, 1 equiv.) and 6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 17, 151 mg, 0.42 mmol, 1 equiv.) in 1,4-dioxane (4.5 mL) was added tetrakis(triphenylphosphine)palladium(0) (48.5 mg, 0.04 mmol, 0.1 equiv.) followed by a solution of cesium carbonate (205 mg, 0.63 mmol, 1.5 equiv.) in water (1.5 mL). This was stirred at 100 °C for 2 h. 2 M lithium hydroxide (0.629 mL, 1.26 mmol, 3 equiv.) was then added and the mixture was stirred at 100 °C for 12 h. The reaction mixture was diluted with water, and the precipitate that formed was collected by filtration, washed with water and hexanes and dried under vacuum. Purification via reverse phase HPLC (C18, 0-95% acteonitirile/water gradient) gave (*R*)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(piperidin-3-ylmethyl)-1,4-dihydroquinoline-3-carboxylic acid as a light yellow solid (92.5 mg, 36 %).
Calcd for $C_{28}H_{27}F_3N_6O_4S$ $[M + H]^+$: 601.06.

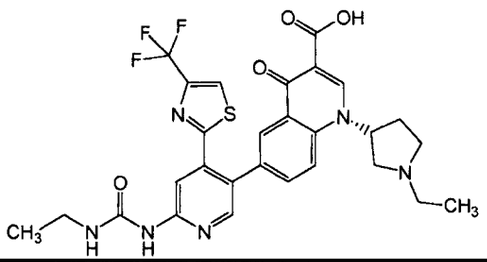
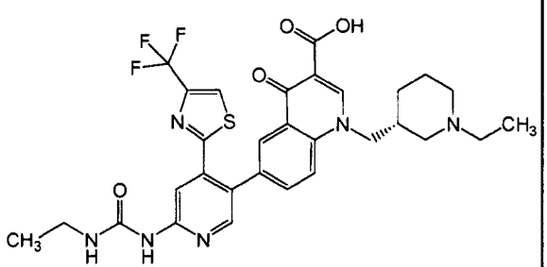
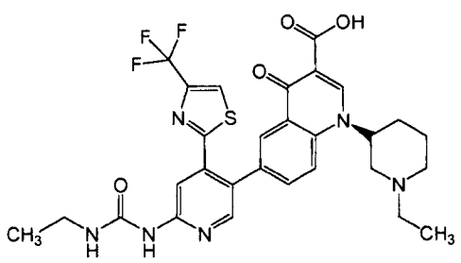
Examples 243-252

The following examples were prepared according to the procedure described in Example 242 from the indicated starting materials.

Ex	Compound	Data	SM
243	(*S*)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(pyrrolidin-3-ylmethyl)-1,4-dihydroquinoline-3-carboxylic acid 	Calcd for $C_{27}H_{25}F_3N_6O_4S$ $[M + H]^+$: 587.02	Intermediate 109 & Intermediate 17

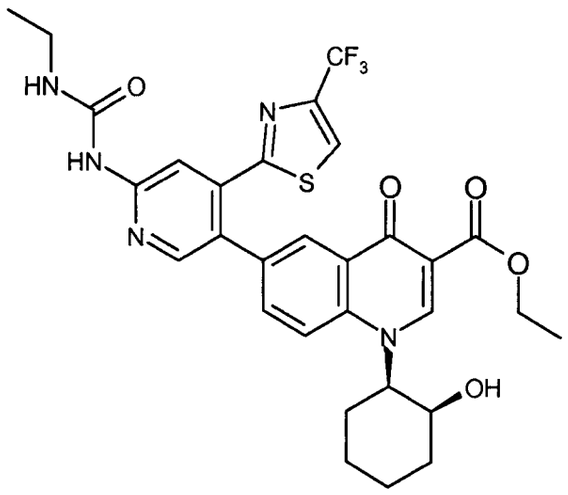
Ex	Compound	Data	SM
244	(*R*)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(pyrrolidin-3-yl)-1,4-dihydroquinoline-3-carboxylic acid 	Calcd for $C_{26}H_{23}F_3N_6O_4S$ $[M + H]^+$: 573.01	Intermediate 110 & Intermediate 17
245	(*S*)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(piperidin-3-yl)-1,4-dihydroquinoline-3-carboxylic acid 	Calcd for $C_{27}H_{25}F_3N_6O_4S$ $[M + H]^+$: 587.02	Intermediate 111 & Intermediate 17
246	(*R*)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-methylpyrrolidin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	Calcd for $C_{27}H_{25}F_3N_6O_4S$ $[M + H]^+$: 587.02	Intermediate 101 & Intermediate 17

Ex	Compound	Data	SM
247	(*R*)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-((1-methylpiperidin-3-yl)methyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	Calcd for $C_{29}H_{29}F_3N_6O_4S$ $[M + H]^+$: 615.02	Intermediate 102 & Intermediate 17
248	(*S*)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-methylpiperidin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	Calcd for $C_{28}H_{27}F_3N_6O_4S$ $[M + H]^+$: 601.04	Intermediate 103 & Intermediate 17
249	(*S*)-1-((1-ethylpyrrolidin-3-yl)methyl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	Calcd for $C_{29}H_{29}F_3N_6O_4S$ $[M + H]^+$: 615.04	Intermediate 104 & Intermediate 17

Ex	Compound	Data	SM
250	(*R*)-1-(1-ethylpyrrolidin-3-yl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	Calcd for $C_{28}H_{27}F_3N_6O_4S$ $[M + H]^+$: 615.04	Intermediate 105 & Intermediate 17
251	(*R*)-1-((1-ethylpiperidin-3-yl)methyl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	Calcd for $C_{30}H_{31}F_3N_6O_4S$ $[M + H]^+$: 629.06	Intermediate 106 & Intermediate 17
252	(*R*)-1-(1-ethylpiperidin-3-yl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	Calcd for $C_{29}H_{29}F_3N_6O_4S$ $[M + H]^+$: 615.04	Intermediate 107 & Intermediate 17

Example 253

Ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(*cis*-2-hydroxycyclohexyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate

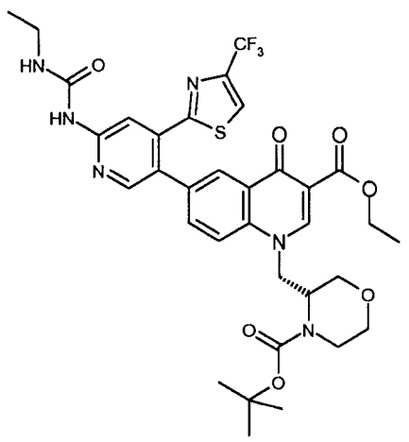


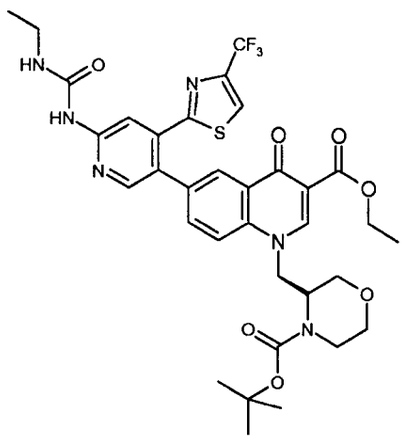
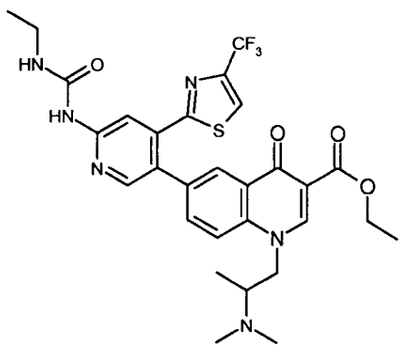
Palladium (II) acetate (0.027 g, 0.12 mmol) and1,1'-bis(di-t-butylphosphino)ferrocene (0.058 g, 0.12 mmol) were dissolved in 1 ml of acetonitrile. Ethyl 1-(*cis*-2-hydroxycyclohexyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate (Intermediate 121, 0.539 g, 1.22 mmol) and 6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 17, 0.444 g, 1.23 mmol) were added along with an additional 2 ml of acetonitrile. Potassium carbonate (0.253 g, 1.83 mmol) was dissolved in water (1.333 mL) then added to the mixture. The reaction was stirred at 100°C for 30 min, then cooled to room temperature and quenched with water (2ml). The precipitate was filtered off and washed with water, ethyl acetate and hexanes, then dried in a vacuum oven at 50°C for 18 h to give 0.606g (78%) of ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(cis-2-hydroxycyclohexyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate as a light brown solid.

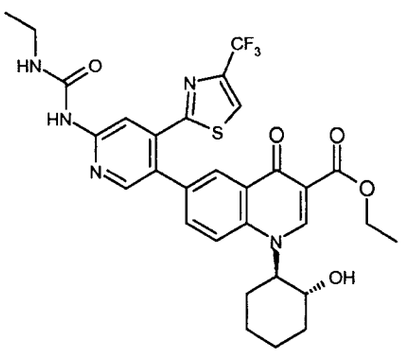
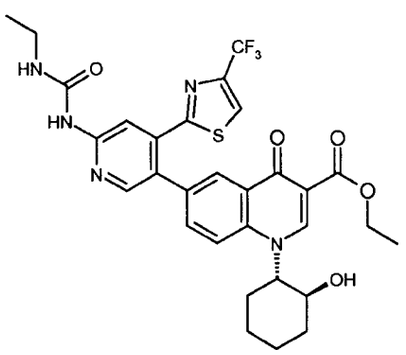
MS (ES) $(M+H)^+$: 630 for $C_{30}H_{30}F_3N_5O_5S$.

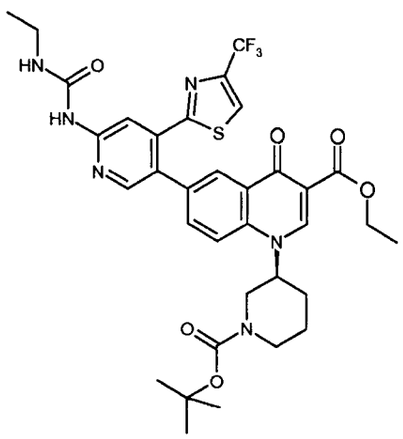
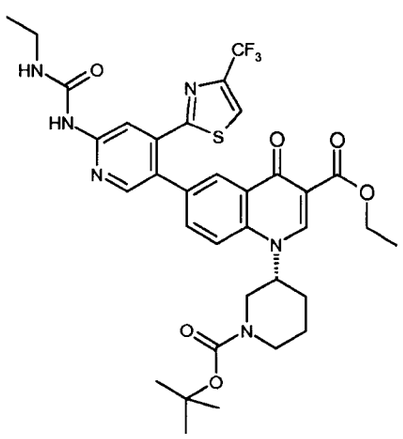
Examples 254-260

The following Examples were prepared by the procedure described in Example 253 from the starting materials (SM) indicated.

Ex	Compound	Data	SM
254	(R)-tert-butyl 3-((3-(ethoxycarbonyl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxoquinolin-1(4H)-yl)methyl)morpholine-4-carboxylate 	MS (ES) $(M+H)^+$: 731 for $C_{34}H_{37}F_3N_6O_7S$ NMR: (300 MHz, *DMSO-d_6*) δ 9.45 (br. s., 1 H), 8.53 (s, 2 H), 8.31 - 8.44 (m, 1 H), 8.15 - 8.26 (m, 2 H), 7.97 - 8.14 (m, 1 H), 7.61 - 7.75 (m, 2 H), 4.61 - 4.81 (m, 2 H), 4.14 - 4.32 (m, 2 H), 3.96 - 4.06 (m, 1 H), 3.60 - 3.94 (m, 2 H), 3.49 - 3.60 (m, 1 H), 3.38 (d, *J*=7.54 Hz, 2 H), 3.15 - 3.27 (m, 2 H), 1.21 - 1.33 (m, 4 H), 1.05 - 1.20 (m, 6 H), 0.79 - 0.90 (m, 6 H).	Intermediate 17 and Intermediate 117

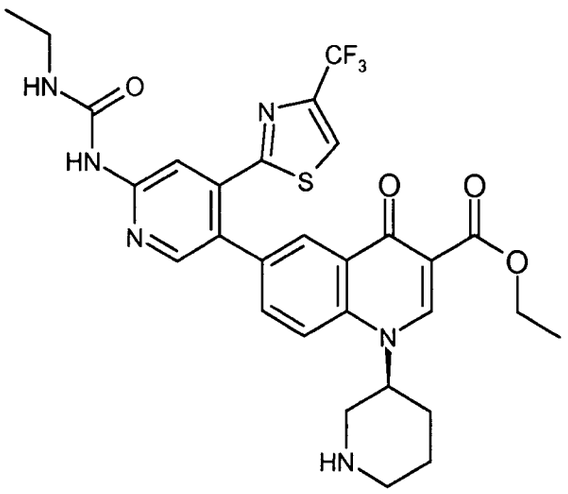
Ex	Compound	Data	SM
255	(S)-tert-butyl 3-((3-(ethoxycarbonyl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxoquinolin-1(4H)-yl)methyl)morpholine-4-carboxylate 	MS (ES) $(M+H)^+$: 731 for $C_{34}H_{37}F_3N_6O_7S$ NMR: (300 MHz, *DMSO-d_6*) δ 9.46 (br. s., 1 H), 8.53 (s, 1 H), 8.32 - 8.45 (m, 1 H), 8.15 - 8.27 (m, 2 H), 7.98 - 8.14 (m, 1 H), 7.61 - 7.75 (m, 2 H), 4.64 - 4.76 (m, 2 H), 4.15 - 4.33 (m, 3 H), 3.95 - 4.14 (m, 2 H), 3.73 - 3.95 (m, 2 H), 3.36 - 3.61 (m, 2 H), 3.10 - 3.29 (m, 2 H), 1.21 - 1.34 (m, 4 H), 1.03 - 1.20 (m, 6 H), 0.76 - 0.90 (m, 6 H).	Intermediate 17 and Intermediate 118
256	ethyl 1-(2-(dimethylamino)propyl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ES) $(M+H)^+$: 617 for $C_{29}H_{31}F_3N_6O_4S$ NMR: (300 MHz, *DMSO-d_6*) δ 9.44 (s, 1 H), 8.56 (s, 1 H), 8.51 (s, 1 H), 8.33 (s, 1 H), 8.22 (s, 1 H), 8.14 (d, *J*=2.26 Hz, 1 H), 7.86 (d, *J*=9.04 Hz, 1 H), 7.58 - 7.68 (m, 2 H), 4.17 - 4.42 (m, 4 H), 3.15 - 3.27 (m, 2 H), 2.92 - 3.05 (m, 1 H), 2.16 (s, 5 H), 1.28 (t, *J*=6.78 Hz, 3 H), 1.11(t, *J*=7.16 Hz, 3 H), 0.96 (d, 3 H).	Intermediate 17 and Intermediate 116

Ex	Compound	Data	SM
257	ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-((1R,2R)-2-hydroxycyclohexyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ES) $(M+H)^+$: 630 for $C_{30}H_{30}F_3N_5O_5S$ NMR: (300 MHz, *DMSO-d_6*) δ 9.43 (s, 1 H), 8.59 - 8.70 (m, 1 H), 8.46 - 8.55 (m, 1 H), 8.31 (s, 1 H), 8.05 - 8.25 (m, 3 H), 7.56 - 7.74 (m, 2H), 5.15 (d, *J*=5.27 Hz, 1 H), 4.50 - 4.69 (m, 1 H), 4.25 (q, *J*=6.78 Hz, 2 H), 3.94 (br. s., 1 H), 3.38 (q, *J*=7.28 Hz, 1 H), 3.21 (dq, *J*=6.78, 6.53 Hz, 2H), 1.89 - 2.11 (m, 1 H), 1.73 (d, *J*=9.04 Hz, 2 H), 1.39 - 1.63 (m, 3 H), 1.29 (t, *J*=7.16 Hz, 3 H), 1.10 (q, *J*=6.78 Hz, 4 H).	Intermediate 17 and Intermediate 119
258	ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-((1R,2R)-2-hydroxycyclohexyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ES) $(M+H)^+$: 630 for $C_{30}H_{30}F_3N_5O_5S$ NMR: (300 MHz, *DMSO-d_6*) δ 9.43 (s, 1 H), 8.65 (s, 1 H), 8.48 (s, 1 H), 8.29 - 8.38 (m, 1 H), 8.04 - 8.26 (m, 2 H), 7.60 - 7.71 (m, 1 H), 5.15 (d, *J*=5.27 Hz, 1 H), 4.59 (br. s., 1 H), 4.25 (q, *J*=6.78 Hz, 1 H), 4.08 (q, *J*=5.27 Hz, 1 H), 3.86 - 3.98 (m, 1 H), 3.15 - 3.26 (m, 6 H), 1.99 (s, 2 H), 1.71 (br. s., 2 H), 1.48 (d, *J*=9.80 Hz, 2 H), 1.29 (t, *J*=7.16 Hz, 2 H), 1.03 - 1.18 (m, 3 H).	Intermediate 17 and Intermediate 120

Ex	Compound	Data	SM
259	(S)-ethyl 1-(1-(tert-butoxycarbonyl)piperidin-3-yl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ES) $(M+H)^+$: 630 for $C_{34}H_{37}F_3N_6O_6S$	Intermediate 17 and Intermediate 122
260	(R)-ethyl 1-(1-(tert-butoxycarbonyl)piperidin-3-yl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ES) $(M+H)^+$: 630 for $C_{34}H_{37}F_3N_6O_6S$	Intermediate 17 and Intermediate 123

Example 261

(S)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(piperidin-3-yl)-1,4-dihydroquinoline-3-carboxylate

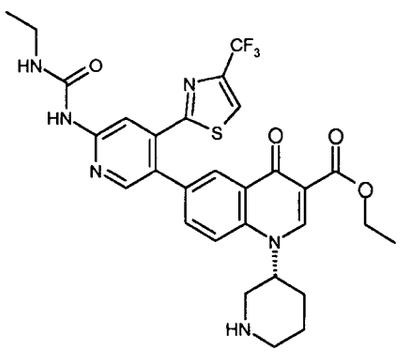


(S)-ethyl 1-(1-(*tert*-butoxycarbonyl)piperidin-3-yl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (Example 259, 5.00 g, 7.00 mmol) was taken up in dichloromethane (10 mL) and 4M HCl in dioxane (0.486 mL, 13.99 mmol) was added while stirring at RT for 1h. Removed solvent in vaccuo and residue was taken back up in methanol and water. The reaction was neutralized using $NaHCO_3$ and a precipitate was collected, washed with ether and dried under high vacuum overnight to give (S)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(piperidin-3-yl)-1,4-dihydroquinoline-3-carboxylate (3.10 g, 72.1 %).

MS (ES) $(M+H)^+$: 615 for $C_{29}H_{29}F_3N_6O_4S$.

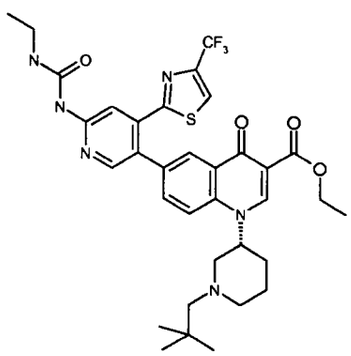
Example 262

The following Example was prepared by the procedure described in Example 261 from the starting materials (SM) indicated.

Int	Compound	Data	SM
262	(R)-ethyl 1-(1-(tert-butoxycarbonyl)piperidin-3-yl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ES) $(M+H)^+$: 615 for $C_{29}H_{29}F_3N_6O_4S$	Example 260

Example 263

(R)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(piperidin-3-yl)-1,4-dihydroquinoline-3-carboxylate



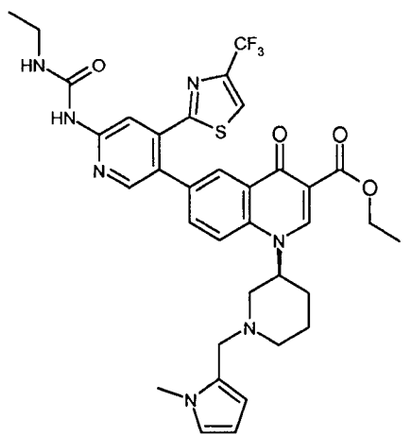
(R)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(piperidin-3-yl)-1,4-dihydroquinoline-3-carboxylate (Example 262, 0.150 g, 0.24 mmol) was taken up in dichloromethane (5 mL) and added pivalaldehyde (0.030 ml, 0.27 mmol) and stirred at RT for 15 min. Sodium triacetoxyborohydride (0.078 g, 0.37 mmol) was added and reaction was stired at 60°C for 18 h. The reaction was then quenched with $NaHCO_3$ and extracted with DCM 3 times. The organics were combined and dried over Na_2SO_4 then the solvent was removed *in vaccuo*. The residue was purified by flash column chromatography

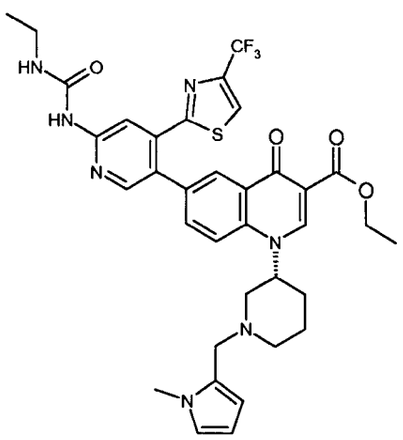
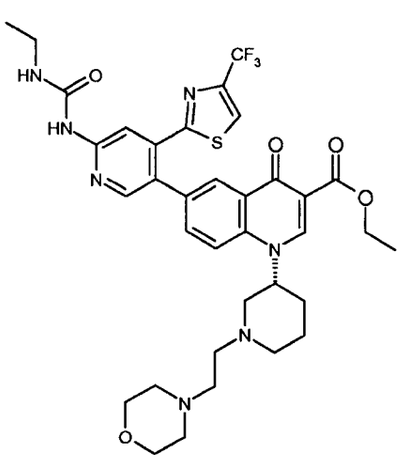
on silica gel using (dichloromethane-methanol) to give (R)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(piperidin-3-yl)-1,4-dihydroquinoline-3-carboxylate (0.060g, 38%).

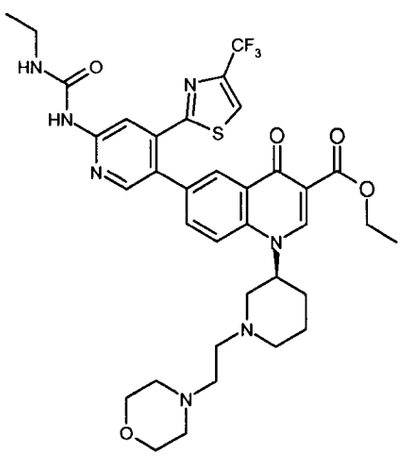
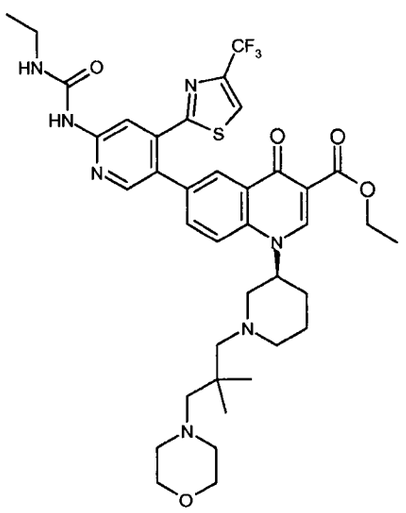
MS (ES) $(M+H)^+$: 685 for $C_{34}H_{39}F_3N_6O_4S$

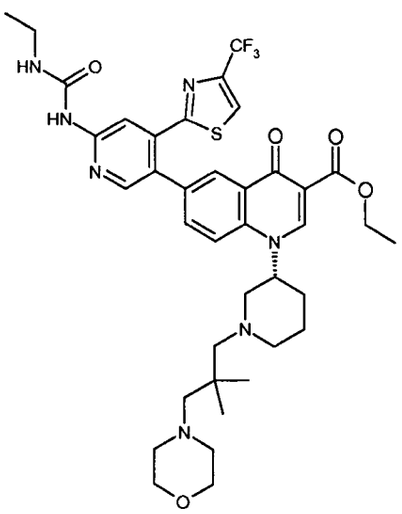
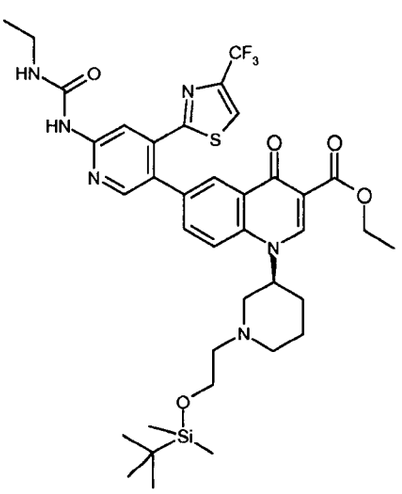
Examples 264-272

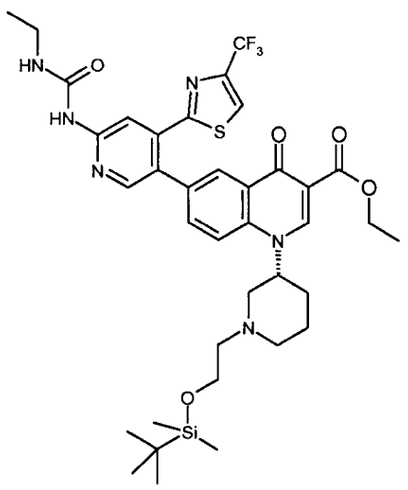
The following Examples were prepared by the procedure described in Example 263 from the starting materials (SM) indicated.

Ex	Compound	Data	SM
264	(S)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-((1-methyl-1H-pyrrol-2-yl)methyl)piperidin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ES) $(M+H)^+$: 708 for $C_{35}H_{36}F_3N_7O_4S$	Example 261 and 1-methyl-1H-pyrrole-2-carbaldehyde

Ex	Compound	Data	SM
265	(R)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-((1-methyl-1H-pyrrol-2-yl)methyl)piperidin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ES) $(M+H)^+$: 708 for $C_{35}H_{36}F_3N_7O_4S$	Example 262 and 1-methyl-1H-pyrrole-2-carbaldehyde
266	(R)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-(2-morpholinoethyl)piperidin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ES) $(M+H)^+$: 728 for $C_{35}H_{40}F_3N_7O_5S$	Example 262 and 2-morpholino-acetaldehyde 2,2,2-trifluoro-acetate

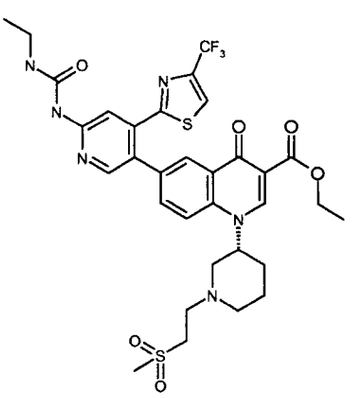
Ex	Compound	Data	SM
267	(S)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-(2-morpholinoethyl)piperidin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ES) $(M+H)^+$: 728 for $C_{35}H_{40}F_3N_7O_5S$	Example 261 and 2-morpholino-acetaldehyde 2,2,2-trifluoro-acetate
268	(S)-ethyl 1-(1-(2,2-dimethyl-3-morpholinopropyl)piperidin-3-yl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ES) $(M+H)^+$: 770 for $C_{38}H_{46}F_3N_7O_5S$	Example 261 and 2,2-dimethyl-3-morpholino-propanal

Ex	Compound	Data	SM
269	(R)-ethyl 1-(1-(2,2-dimethyl-3-morpholinopropyl)piperidin-3-yl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ES) $(M+H)^+$: 770 for $C_{38}H_{46}F_3N_7O_5S$	Example 262 and 2,2-dimethyl-3-morpholino-propanal
270	(S)-ethyl 1-(1-(2-(tert-butyldimethylsilyloxy)ethyl)piperidin-3-yl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ES) $(M+H)^+$: 773 for $C_{37}H_{47}F_3N_6O_5SSi$	Example 261 and 2-(tert-butyl-dimethylsilyl oxy)acet-aldehyde

Ex	Compound	Data	SM
271	(R)-ethyl 1-(1-(2-(tert-butyldimethylsilyloxy)ethyl)piperidin-3-yl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ES) $(M+H)^+$: 773 for $C_{37}H_{47}F_3N_6O_5SSi$	Example 262 and 2-(tert-butyl-dimethylsilyloxy)acet-aldehyde

Example 272

(R)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-(2-(methylsulfonyl)ethyl)piperidin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate



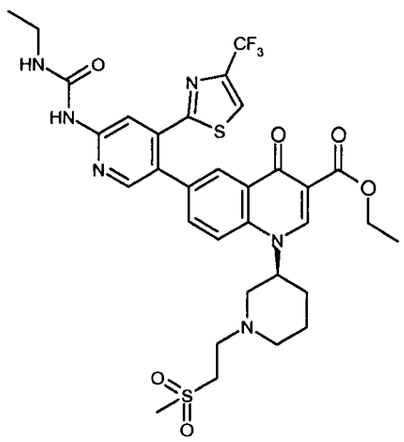
(R)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(piperidin-3-yl)-1,4-dihydroquinoline-3-carboxylate (Example 262, 0.150 g, 0.24 mmol) was taken up in isopropanol (2 mL) and methyl vinyl sulfone (0.026 mL, 0.29 mmol) was added. The reaction mixture was stirred at 100 °C for 18 h in a sealed vessel, then cooled to room temperature and the solvent was removed *in vacuo* and loaded directly onto silica. Purified

by flash column chromatography on silica gel using (dichloromethane-methanol) gave (R)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-(2-(methylsulfonyl)ethyl)piperidin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (0.110 g, 62.5 %).

MS (ES) $(M+H)^+$: 721 for $C_{32}H_{35}F_3N_6O_6S_2$

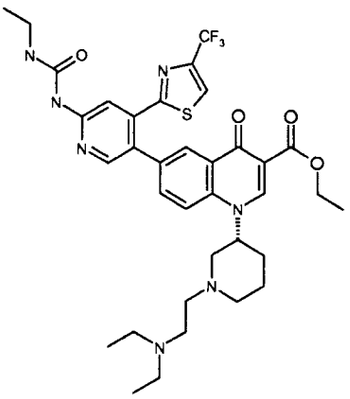
Example 273

The following Example was prepared according to the procedure described in Example 272 from the starting materials indicated.

Int	Compound	Data	SM
273	(S)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-(2-(methylsulfonyl)ethyl)piperidin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ES) $(M+H)^+$: 721 for $C_{32}H_{35}F_3N_6O_6S_2$	Example 261 and methyl vinyl sulfone

Example 274

(R)-ethyl 1-(1-(2-(diethylamino)ethyl)piperidin-3-yl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate

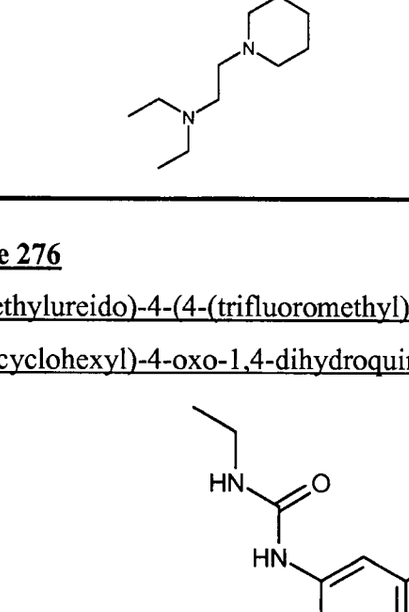


(R)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(piperidin-3-yl)-1,4-dihydroquinoline-3-carboxylate (Example 262, 0.100 g, 0.16 mmol) was taken up in in DMF (2 mL), K_2CO_3 (0.112 g, 0.81 mmol) and 2-chloro-N,N-diethylethanamine hydrochloride (0.031 g, 0.18 mmol) were added. The mixture was heated to 100 °C overnight then the reaction was cooled to room temperature and diluted with EtOAc. The organic layer was washed with brine twice and water twice, then the solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel using (dichloromethane-methanol) to give (R)-ethyl 1-(1-(2-(diethylamino)ethyl)piperidin-3-yl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (0.020 g, 17 %).

MS (ES) $(M+H)^+$: 714 for $C_{35}H_{42}F_3N_7O_4S$

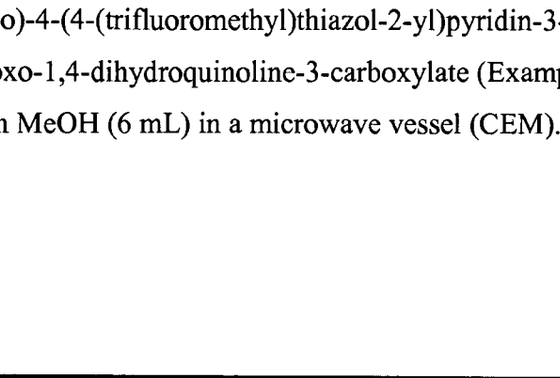
Example 275

The following Example was prepared according to the procedure described for Example 274 from the starting material indicated.

Ex	Compound	Data	SM
275	(S)-ethyl 1-(1-(2-(diethylamino)ethyl)piperidin-3-yl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ES) $(M+H)^+$: 714 for $C_{35}H_{42}F_3N_7O_4S$	Example 261 and 2-chloro-N,N-diethyl-ethanamine hydrochloride

Example 276

6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(*cis*-2-hydroxycyclohexyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



Ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(*cis*-2-hydroxycyclohexyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (Example 253, 0.240 g, 0.38 mmol) was suspended in MeOH (6 mL) in a microwave vessel (CEM). THF (3.00 mL) was

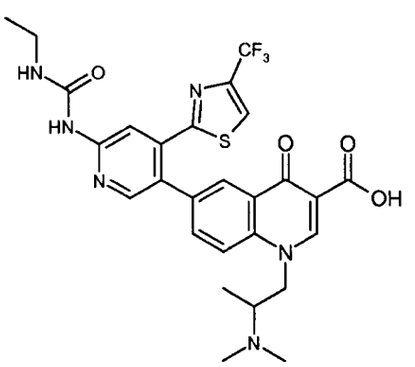
added. A 2.0 M aq solution of LiOH (0.381 mL, 0.76 mmol) was added. The microwave vessel was heated in the microwave at 100 °C for 15 min. After cooling to room temperature, the solvent was removed *in vacuo* to give a residue which was purified by flash column chromatography on silica gel using (dichloromethane-methanol) to give 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(*cis*-2-hydroxycyclohexyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (0.113g, 49%).

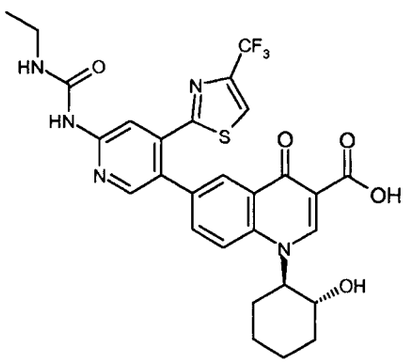
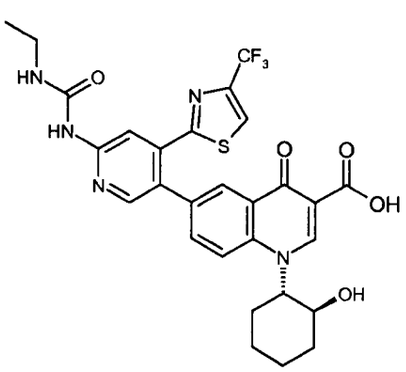
MS (ES) $(M+H)^+$: 602 for $C_{28}H_{26}F_3N_5O_5S$.

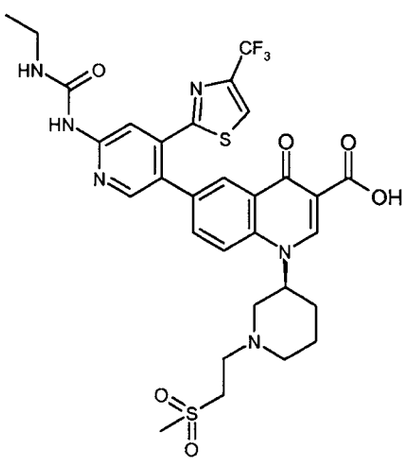
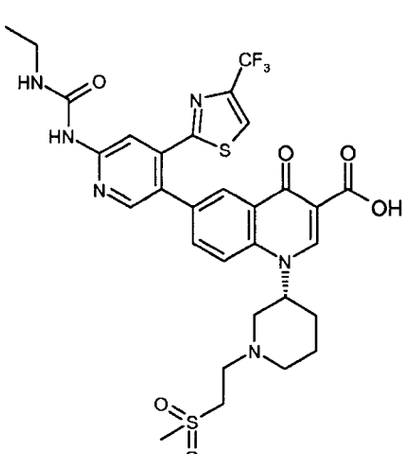
^{1}H NMR (300 MHz, *DMSO-d$_6$*) δ 15.10 (s, 1 H), 9.48 (s, 1 H), 8.87 (s, 1 H), 8.53 (s, 1 H), 8.36 (s, 2 H), 8.29 (d, *J*=9.80 Hz, 1 H), 8.22 (s, 1 H), 7.85 (d, *J*=7.54 Hz, 1 H), 7.57 - 7.65 (m, 1 H), 5.20 (d, *J*=4.52 Hz, 1 H), 5.09 (d, *J*=10.55 Hz, 1 H), 3.96 (br. s., 1 H), 3.15 - 3.27 (m, 2 H), 2.29 (d, *J*=11.30 Hz, 1 H), 1.74 - 1.96 (m, 4 H), 1.62 (d, *J*=7.54 Hz, 2 H), 1.48 (d, 1 H), 1.11 (t, *J*=7.16 Hz, 3 H).

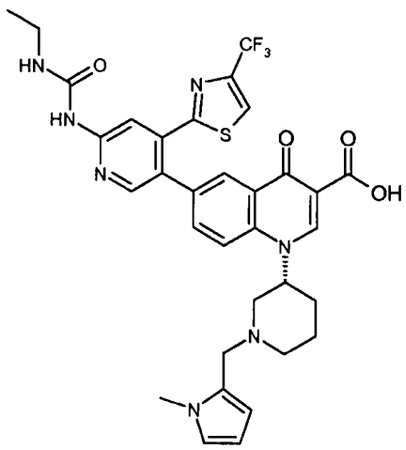
Examples 277-286

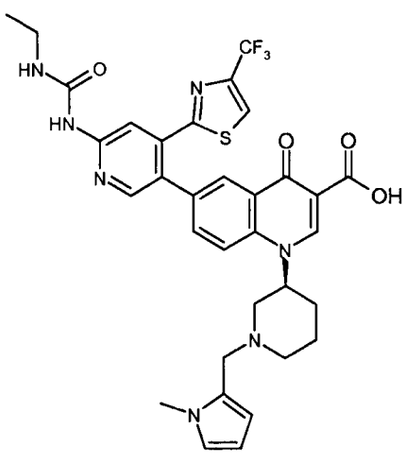
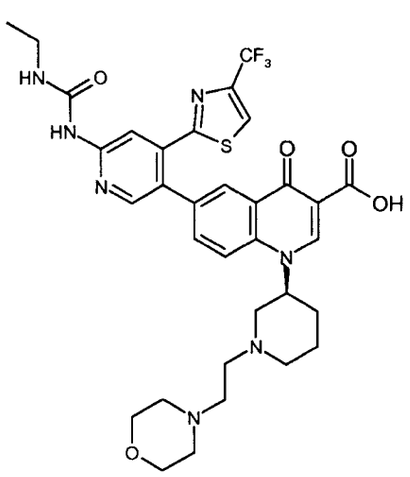
The following Examples were prepared according to the procedure described for Example 276 from the indicated starting materials.

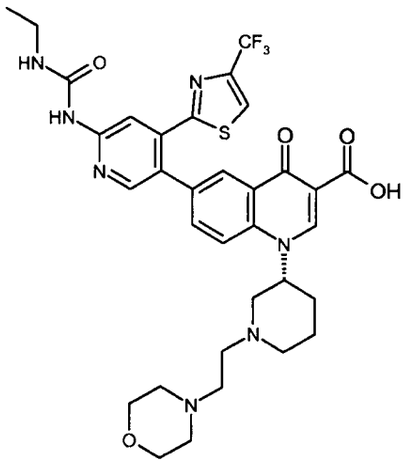
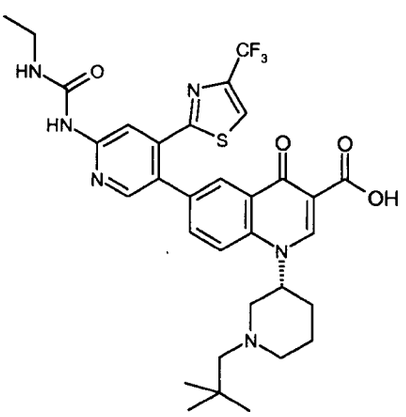
Ex	Compound	Data	SM
277	1-(2-(dimethylamino)propyl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ES) $(M+H)^+$: 589 for $C_{27}H_{27}F_3N_6O_4S$ ^{1}H NMR (300 MHz, *DMSO-d$_6$*) δ 14.87 (br. s., 1 H), 10.57 (br. s., 1 H), 9.48 (s, 1 H), 9.16 (s, 1 H), 8.55 (s, 1 H), 8.34 (d, *J*=12.81 Hz, 2 H), 8.23 (s, 2 H), 7.89 (d, *J*=8.29 Hz, 1 H), 7.60 (br. s., 1 H), 5.06 (br. s., 1 H), 4.86 (d, *J*=11.30 Hz, 1 H), 3.93 (br. s., 1 H), 3.17 - 3.25 (m, 1 H), 2.84 (br. s., 6 H), 1.05 - 1.26 (m, 6 H).	Example 256

Ex	Compound	Data	SM
278	6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-((1R,2R)-2-hydroxycyclohexyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ES) $(M+H)^+$: 602 for $C_{28}H_{26}F_3N_5O_5S$ ^{1}H NMR (300 MHz, *DMSO-d*$_6$) δ 15.15 (s, 1 H), 9.47 (s, 1 H), 8.98 (s, 1 H), 8.51 (s, 1 H), 8.35 (d, *J*=9.80 Hz, 3 H), 8.22 (s, 1 H), 7.85 (d, *J*=10.55 Hz, 1 H), 7.61 (t, *J*=4.90 Hz, 1 H), 5.21 (d, *J*=5.27 Hz, 1 H), 4.80 (t, *J*=9.04 Hz, 1 H), 4.00 - 4.11 (m, 1 H), 3.15 - 3.27 (m, 2 H), 2.01 (d, *J*=14.32 Hz, 2 H), 1.80 - 1.94 (m, 1 H), 1.72 (br. s., 2 H), 1.45 - 1.64 (m, 3 H), 1.11 (t, *J*=7.16 Hz, 3 H).	Example 257
279	6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-((1S,2S)-2-hydroxycyclohexyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ES) $(M+H)^+$: 602 for $C_{28}H_{26}F_3N_5O_5S$ ^{1}H NMR (300 MHz, *DMSO-d*$_6$) δ 15.15 (s, 1 H), 9.47 (s, 1 H), 8.98 (s, 1 H), 8.51 (s, 1 H), 8.35 (d, *J*=9.80 Hz, 3 H), 8.22 (s, 1 H), 7.85 (dd, *J*=9.04, 2.26 Hz, 1 H), 7.61 (t, *J*=5.27 Hz, 1 H), 5.21 (d, *J*=5.27 Hz, 1 H), 4.75 - 4.85 (m, 1 H), 4.04 - 4.13 (m, 2 H), 3.23 (d, *J*=6.78 Hz, 1 H), 2.02 (d, *J*=13.56 Hz, 2 H), 1.85 (d, *J*=11.30 Hz, 1 H), 1.72 (br. s., 2 H), 1.44 - 1.64 (m, 3 H), 1.11 (t, *J*=7.16 Hz, 3 H).	Example 258

Ex	Compound	Data	SM
280	(S)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-(2-(methylsulfonyl)ethyl)piperidin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ES) $(M+H)^+$: 693 for $C_{30}H_{31}F_3N_6O_5S_2$ ^{1}H NMR (300 MHz, *DMSO-d*$_6$) δ 15.01 (br. s., 1 H), 9.48 (s, 1 H), 9.40 (br. s., 1 H), 8.52 (s, 1 H), 8.36 (br. s., 2 H), 8.13 - 8.28 (m, 2 H), 7.88 (d, *J*=9.04 Hz, 1 H), 7.60 (d, *J*=5.27 Hz, 1 H), 5.03 (br. s., 1 H), 3.28 - 3.45 (m, 3 H), 3.14 - 3.28 (m, 3 H), 2.99 - 3.12 (m, 3 H), 2.87 (t, *J*=6.78 Hz, 3 H), 2.70 (d, *J*=15.82 Hz, 1 H), 1.90 - 2.14 (m, 2 H), 1.72 (br. s., 2 H), 1.11 (t, *J*=6.78 Hz, 3 H).	Example 273
281	(R)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-(2-(methylsulfonyl)ethyl)piperidin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ES) $(M+H)^+$: 693 for $C_{30}H_{31}F_3N_6O_5S_2$ ^{1}H NMR (300 MHz, *DMSO-d*$_6$) δ 14.99 (br. s., 1 H), 9.48 (s, 1 H), 9.30 - 9.45 (m, 1 H), 8.53 (s, 1 H), 8.35 (br. s., 2 H), 8.23 (s, 2 H), 7.91 (br. s., 1 H), 7.55 - 7.69 (m, 1 H), 5.04 (br. s., 1 H), 3.21 (dq, *J*=6.78, 6.53 Hz, 3 H), 3.06 (br. s., 5 H), 2.87 (br. s., 2 H), 2.72 (br. s., 1 H), 2.06 (br. s., 3 H), 1.72 (d, *J*=7.54 Hz, 2 H), 1.11 (t, *J*=7.16 Hz, 3 H).	Example 272

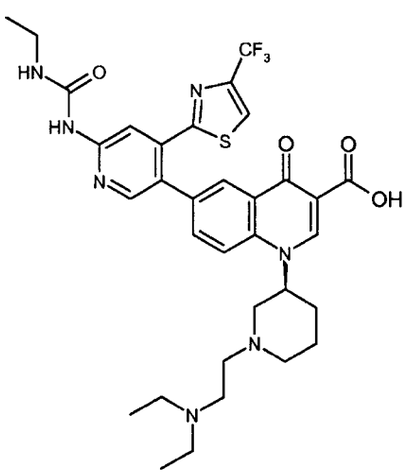
Ex	Compound	Data	SM
282	(R)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-((1-methyl-1H-pyrrol-2-yl)methyl)piperidin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ES) $(M+H)^+$: 680 for $C_{33}H_{32}F_3N_7O_4S$ ^1H NMR (300 MHz, *DMSO- d_6*) δ 15.04 (br. s., 1 H), 9.55 (br. s., 2 H), 8.50 (s, 1 H), 8.34 (br. s., 2 H), 8.24 (s, 1 H), 8.08 (d, *J*=9.04 Hz, 1 H), 7.82 (d, *J*=8.29 Hz, 1 H), 7.66 (br. s., 1 H), 6.67 (br. s., 1 H), 5.96 (br. s., 1 H), 5.86 (br. s., 1 H), 5.08 (br. s., 1 H), 3.68 (s, 3 H), 3.57 (d, *J*=13.56 Hz, 1 H), 3.43 (d, *J*=13.56 Hz, 1 H), 3.12 - 3.25 (m, 2 H), 2.92 - 3.07 (m, 1 H), 2.89 (br. s., 1 H), 2.38 (br. s., 1 H), 1.96 (d, *J*=15.82 Hz, 2 H), 1.66 (br. s., 2 H), 1.19 - 1.39 (m, 1 H), 1.11 (t, *J*=7.16 Hz, 3 H).	Example 265

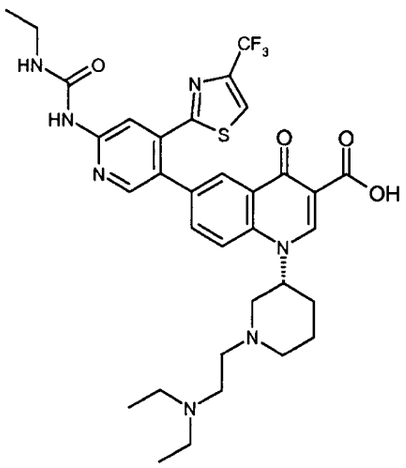
Ex	Compound	Data	SM
283	(S)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-((1-methyl-1H-pyrrol-2-yl)methyl)piperidin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ES) $(M+H)^+$: 680 for $C_{33}H_{32}F_3N_7O_4S$ ^1H NMR (300 MHz, *DMSO- d_6*) δ 14.89 (br. s., 1 H), 10.60 (br. s., 1 H), 9.49 (s, 1 H), 8.97 (s, 1 H), 8.55 (s, 2 H), 8.35 (br. s., 3 H), 8.24 (s, 1 H), 7.97 (d, *J*=9.04 Hz, 1 H), 7.62 (br. s., 1 H), 6.88 (br. s., 1 H), 6.33 (br. s., 1 H), 6.04 (br. s., 1 H), 4.37 (br. s., 2 H), 3.70 (s, 5 H), 3.48 - 3.57 (m, 1 H), 3.22 (ddd, 3 H), 1.99 - 2.34 (m, 3 H), 1.12 (t, *J*=7.16 Hz, 3 H).	Example 264
284	(S)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-(2-morpholinoethyl)piperidin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ES) $(M+H)^+$: 700 for $C_{33}H_{36}F_3N_7O_5S$ ^1H NMR (300 MHz, *DMSO- d_6*) δ 15.01 (br. s., 1 H), 9.75 (br. s., 1 H), 9.48 (s, 1 H), 8.52 (s, 1 H), 8.35 (br. s., 2 H), 8.22 (s, 1 H), 8.12 (d, *J*=9.04 Hz, 1 H), 7.86 (d, *J*=8.29 Hz, 1 H), 7.61 (br. s., 1 H), 5.04 (br. s., 1 H), 3.53 (d, *J*=4.52 Hz, 4 H), 3.06 - 3.26 (m, 3 H), 2.94 (d, *J*=9.80 Hz, 1 H), 2.66 (br. s., 1 H), 2.38 (br. s., 4 H), 1.98 (br. s., 2 H), 1.65 (br. s., 2 H), 1.11 (t, *J*=7.16 Hz, 3 H), 0.96 (t, *J*=6.78 Hz, 1 H).	Example 267

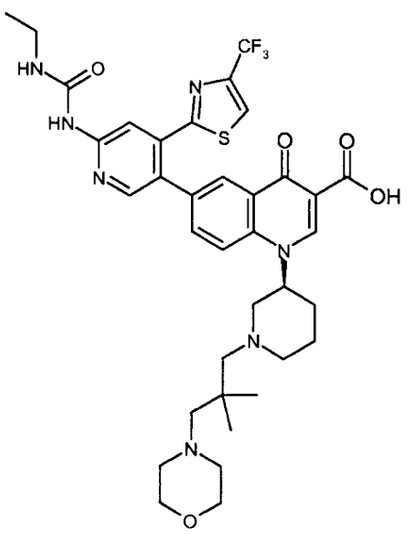
Ex	Compound	Data	SM
285	(R)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-(2-morpholinoethyl)piperidin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ES) $(M+H)^+$: 700 for $C_{33}H_{36}F_3N_7O_5S$ ^1H NMR (300 MHz, *DMSO- d_6*) δ 14.97 (br. s., 1 H), 9.74 (br. s., 1 H), 9.49 (s, 1 H), 8.52 (s, 1 H), 8.35 (br. s., 2 H), 8.22 (s, 1 H), 8.12 (d, *J*=9.04 Hz, 1 H), 7.86 (d, *J*=9.04 Hz, 1 H), 7.61 (br. s., 1 H), 5.04 (br. s., 1 H), 3.53 (br. s., 4 H), 3.07 - 3.27 (m, 3 H), 2.94 (d, *J*=10.55 Hz, 1 H), 2.66 (br. s., 1 H), 2.38 (br. s., 4 H), 1.97 (br. s., 2 H), 1.65 (br. s., 2 H), 1.11 (t, *J*=7.16 Hz, 3 H), 0.96 (t, 1 H).	Example 266
286	(R)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(piperidin-3-yl)-1,4-dihydroquinoline-3-carboxylic acid 	MS (ES) $(M+H)^+$: 657 for $C_{32}H_{35}F_3N_6O_4S$ ^1H NMR (300 MHz, *DMSO- d_6*) δ 10.17 (br. s., 1 H), 9.51 (s, 1 H), 8.97 (s, 1 H), 8.41 - 8.59 (m, 2 H), 8.29 - 8.39 (m, 2 H), 8.23 (s, 1 H), 7.97 (d, *J*=9.04 Hz, 1 H), 7.62 (br. s., 1 H), 6.00 (br. s., 1 H), 3.58 - 3.79 (m, 5 H), 3.12 - 3.28 (m, 5 H), 3.01 - 3.10 (m, 2 H), 2.33 - 2.42 (m, 2 H), 2.18 - 2.27 (m, 2 H), 2.08 (d, *J*=8.29 Hz, 2 H), 1.03 - 1.26 (m, 6 H).	Example 263

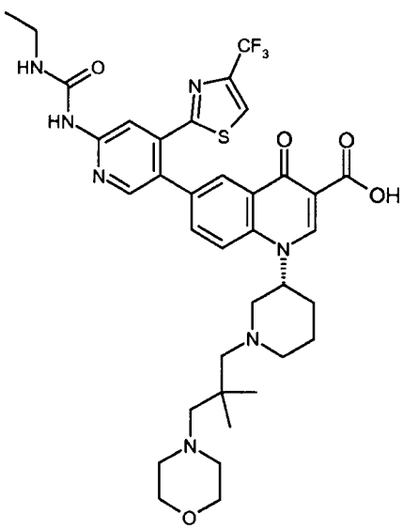
Examples 287-292

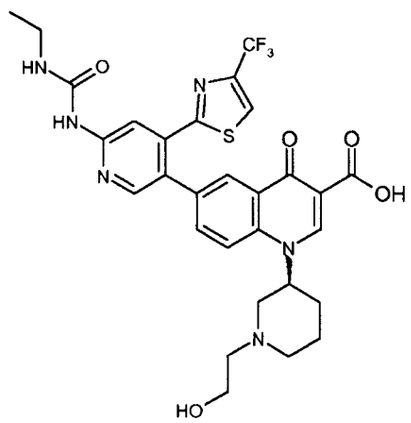
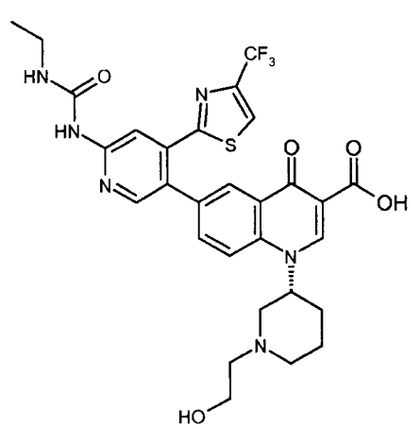
The following compounds were prepared according to the procedure described in Example 276 and purified by a Gilson HPLC on a C18 column using acetonitrile/water/TFA to yield the TFA salts.

Ex	Compound	Data	SM
287	(S)-ethyl 1-(1-(2-(diethylamino)ethyl)piperidin-3-yl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid trifluoroacetate 	MS (ES) $(M+H)^+$: 686 for $C_{33}H_{38}F_3N_7O_4S$ ^1H NMR (300 MHz, *DMSO- d_6*) δ 9.49 (s, 2 H), 8.55 (s, 1 H), 8.37 (s, 2 H), 8.10 - 8.26 (m, 2 H), 7.89 (d, *J*=8.29 Hz, 1 H), 7.59 (br. s., 1 H), 5.07 (br. s., 1 H), 3.21 (q, *J*=6.78 Hz, 8 H), 3.04 (none, 1 H), 2.73 (br. s., 3 H), 2.08 (br. s., 2 H), 1.74 (br. s., 2 H), 1.22 (t, *J*=7.16 Hz, 6 H), 1.12 (t, *J*=7.16 Hz, 3 H).	Example 275

Ex	Compound	Data	SM
288	(S)-ethyl 1-(1-(2-(diethylamino)ethyl)piperidin-3-yl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid trifluoroacetate 	MS (ES) $(M+H)^+$: 686 for $C_{33}H_{38}F_3N_7O_4S$ ^1H NMR (300 MHz, *DMSO- d_6*) δ 9.49 (s, 2 H), 8.55 (s, 1 H), 8.37 (s, 2 H), 8.23 (s, 1 H), 8.17 (d, *J*=9.04 Hz, 1 H), 7.89 (d, *J*=9.04 Hz, 1 H), 7.59 (br. s., 1 H), 5.07 (br. s., 1 H), 3.56 (br. s., 7 H), 3.09 - 3.31 (m, 8 H), 2.92 - 3.11 (m, 1 H), 2.73 (br. s., 2 H), 2.06 (br. s., 2 H), 1.74 (br. s., 1 H), 1.22 (t, *J*=7.16 Hz, 6 H), 1.12 (t, *J*=7.16 Hz, 4 H).	Example 274

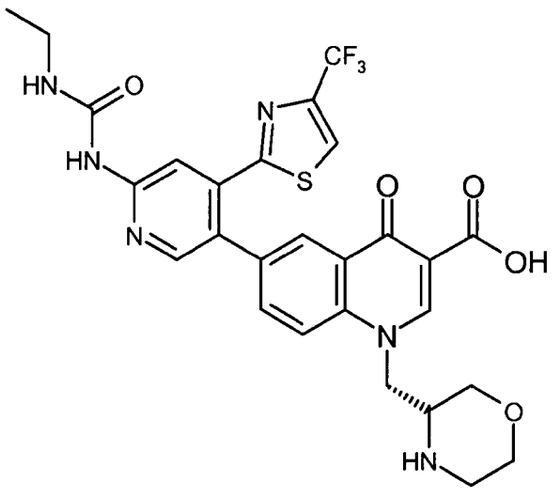
Ex	Compound	Data	SM
289	(S)-1-(1-(2,2-dimethyl-3-morpholinopropyl)piperidin-3-yl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ES) $(M+H)^+$: 742 for $C_{36}H_{42}F_3N_7O_5S$ ^1H NMR (300 MHz, *DMSO- d_6*) δ 9.51 (br. s., 2 H), 8.51 (s, 1 H), 8.35 (br. s., 2 H), 8.22 (s, 1 H), 8.12 (d, *J*=9.04 Hz, 1 H), 7.83 (d, *J*=7.54 Hz, 1 H), 7.63 (br. s., 1 H), 5.05 (br. s., 1 H), 3.50 (br. s., 4 H), 3.18 - 3.25 (m, 1 H), 2.94 (br. s., 2 H), 2.60 (d, *J*=18.84 Hz, 2 H), 2.40 (br. s., 4 H), 2.08 - 2.25 (m, 4 H), 2.02 (br. s., 1 H), 1.88 - 1.96 (m, 1 H), 1.72 (br. s., 2 H), 1.22 (s, 2 H), 1.11 (t, *J*=6.78 Hz, 3 H), 0.85 (s, 6 H).	Example 268

Ex	Compound	Data	SM
290	(R)-1-(1-(2,2-dimethyl-3-morpholinopropyl)piperidin-3-yl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ES) $(M+H)^+$: 742 for $C_{36}H_{42}F_3N_7O_5S$ ^1H NMR (300 MHz, *DMSO- d_6*) δ 9.49 (br. s., 2 H), 8.51 (s, 1 H), 8.35 (br. s., 2 H), 8.22 (s, 1 H), 8.11 (d, *J*=8.29 Hz, 1 H), 7.83 (d, *J*=7.54 Hz, 1 H), 7.62 (br. s., 1 H), 5.04 (br. s., 1 H), 3.51 (br. s., 4 H), 3.22 (d, *J*=6.78 Hz, 2 H), 2.94 (br. s., 2 H), 2.41 (br. s., 5 H), 1.99 - 2.26 (m, 6 H), 1.90 (br. s., 1 H), 1.73 (br. s., 2 H), 1.11 (t, *J*=6.78 Hz, 3 H), 0.85 (br. s., 6 H).	Example 269

Ex	Compound	Data	SM
291	(S)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-(2-hydroxyethyl)piperidin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ES) $(M+H)^+$: 631 for $C_{29}H_{29}F_3N_6O_5S$ ^{1}H NMR (300 MHz, *DMSO- d_6*) δ 9.77 (br. s., 1 H), 9.47 (s, 1 H), 8.51 (s, 1 H), 8.35 (d, *J*=3.77 Hz, 2 H), 8.22 (s, 1 H), 8.14 (d, *J*=9.80 Hz, 1 H), 7.86 (d, *J*=7.54 Hz, 1 H), 7.60 (br. s., 1 H), 5.04 (br. s., 1 H), 4.45 (t, *J*=4.90 Hz, 1 H), 3.62 (q, *J*=5.53 Hz, 2 H), 3.17 - 3.25 (m, 2 H), 3.05 - 3.13 (m, 1 H), 2.98 (br. s., 1 H), 2.72 (br. s., 1 H), 1.97 (br. s., 2 H), 1.65 (br. s., 2 H), 1.11 (t, *J*=6.78 Hz, 3 H).	Example 270
292	(R)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-(2-hydroxyethyl)piperidin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ES) $(M+H)^+$: 631 for $C_{29}H_{29}F_3N_6O_5S$ ^{1}H NMR (300 MHz, *DMSO- d_6*) δ 15.04 (s, 1 H), 9.78 (br. s., 1 H), 9.47 (s, 1 H), 8.52 (s, 1 H), 8.36 (br. s., 2 H), 8.23 (s, 1 H), 8.16 (br. s., 1 H), 7.87 (d, *J*=10.55 Hz, 1 H), 7.60 (br. s., 1 H), 5.04 (br. s., 1 H), 4.45 (br. s., 1 H), 3.61 (br. s., 2 H), 3.18 - 3.26 (m, 2 H), 2.99 (br. s., 2 H), 2.72 (br. s., 1 H), 1.98 (br. s., 2 H), 1.66 (br. s., 2 H), 1.11 (t, *J*=6.78 Hz, 3 H).	Example 271

Example 293

(R)-tert-butyl 3-((3-(ethoxycarbonyl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxoquinolin-1(4H)-yl)methyl)morpholine-4-carboxylic acid



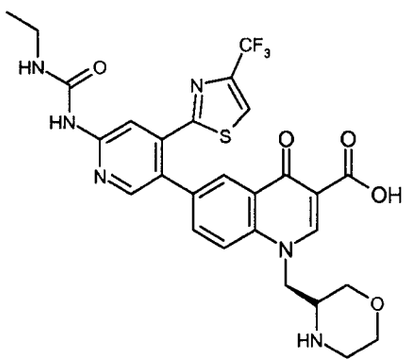
(R)-tert-butyl 3-((3-(ethoxycarbonyl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxoquinolin-1(4H)-yl)methyl)morpholine-4-carboxylate (Example 254, 0.150 g, 0.20 mmol) was suspended in MeOH (6 mL) in a microwave vessel (CEM). THF (3.00 mL) was added. A 2.0 M aq solution of LiOH (0.381 mL, 0.76 mmol) was added. The microwave vessel was heated in the microwave at 100 °C for 15 min. After cooling to room temperature solvent was removed *in vacuo* and residue was taken up in dichloromethane (2ml) and 4N HCl in dioxane (1ml) was added. The mixture was stirred at room temperature for 1 h, then diluted with water (3 ml) and neutralized with saturate $NaHCO_3$. The mixture was extracted with DCM three times, and the combined organic layers were dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by flash column chromatography on silica gel using (dichloromethane-methanol) to give (R)-tert-butyl 3-((3-(ethoxycarbonyl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxoquinolin-1(4H)-yl)methyl)morpholine-4-carboxylic acid (0.042g, 36%).
MS (ES) $(M+H)^+$: 603 for $C_{27}H_{25}F_3N_6O_5S$. NMR:

^1H NMR (300 MHz, *DMSO-d_6*) δ

15.06 (br. s., 1 H), 9.48 (s, 1 H), 8.93 (s, 1 H), 8.52 (s, 1 H), 8.34 (d, *J*=17.33 Hz, 2 H), 8.10 - 8.24 (m, 2 H), 7.83 (d, *J*=7.54 Hz, 1 H), 7.60 (br. s., 1 H), 4.65 (d, *J*=10.55 Hz, 1 H), 4.33 (dd, *J*=14.69, 8.67 Hz, 1 H), 3.86 (d, *J*=9.04 Hz, 1 H), 3.55 - 3.66 (m, 1 H), 3.34 - 3.44 (m, 1 H), 3.21 (t, *J*=6.40 Hz, 3 H), 3.05 (br. s., 1 H), 2.68 - 2.86 (m, 1 H), 1.11 (t, *J*=7.16 Hz, 3 H).

Example 294

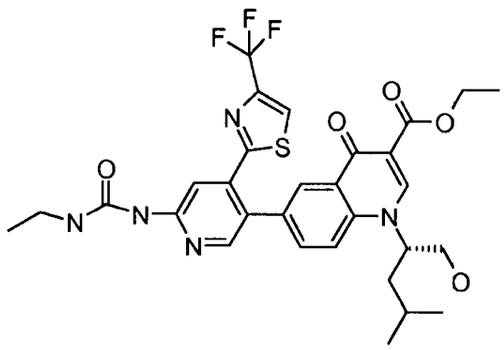
The following Examples were prepared by the procedure described in Example 293 from the starting materials (SM) indicated.

Ex	Compound	Data	SM
294	(S)-tert-butyl 3-((3-(ethoxycarbonyl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxoquinolin-1(4H)-yl)methyl)morpholine-4-carboxylic acid 	MS (ES) $(M+H)^+$: 603 for $C_{27}H_{25}F_3N_6O_5S$. ^1H NMR (300 MHz, *DMSO-d6*) δ 15.07 (br. s., 1 H), 9.47 (s, 1 H), 8.94 (s, 1 H), 8.52 (s, 1 H), 8.37 (s, 1 H), 8.29 - 8.35 (m, 2 H), 8.13 - 8.24 (m, 2 H), 7.83 (d, *J*=7.54 Hz, 1 H), 7.60 (br. s., 1 H), 4.63 (br. s., 1 H), 4.34 (dd, *J*=13.56, 9.04 Hz, 1 H), 3.86 (d, *J*=9.04 Hz, 1 H), 3.53 - 3.73 (m, 2 H), 3.37 - 3.52 (m, 1 H), 3.21 (t, *J*=6.40 Hz, 3 H), 3.05 (br. s., 1 H), 2.77 (t, *J*=12.43 Hz, 1 H), 1.11 (t, *J*=7.16 Hz, 3 H).	Example 255

Another potential method for preparation of the Examples described above is listed below for Example 119.

Example 119

(S)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-hydroxy-4-methylpentan-2-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate



Ethyl 3-(dimethylamino)-2-(5-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-2-fluorobenzoyl)acrylate (0.150 g, 0.26 mmol, Intermediate 125) and (S)-2-amino-4-methylpentan-1-ol (0.033 ml, 0.26 mmol) were taken up in THF (2 ml). The mixture was placed in an oil bath and heated to 60°C for 2 h. Potassium carbonate (0.107 g, 0.78 mmol) was added followed by DMF (1 ml) and the mixture was stirred at 60°C overnight. Reaction was cooled to room temperature and concentrated *in vacuo*. The residue was then diluted with water (0.5 mL) and cooled to 0°C. 1N HCl was added drop wise until pH~4. A light yellow solid was collected by filtration, washed with water, and dried in vacuum oven overnight at 50°C to give (S)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-hydroxy-4-methylpentan-2-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (0.072 g, 44 %) as a yellow solid.

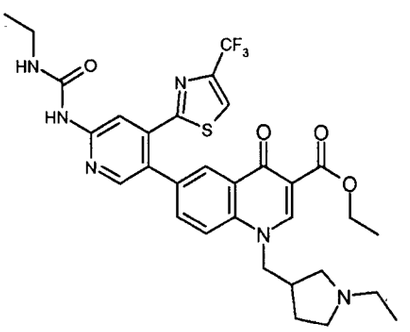
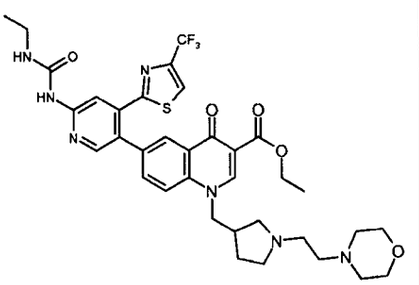
MS (ES) $(M+H)^+$: 632 for $C_{30}H_{32}F_3N_5O_5S$.

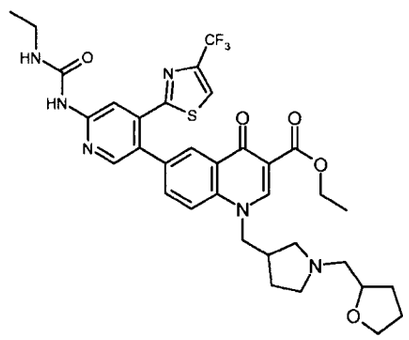
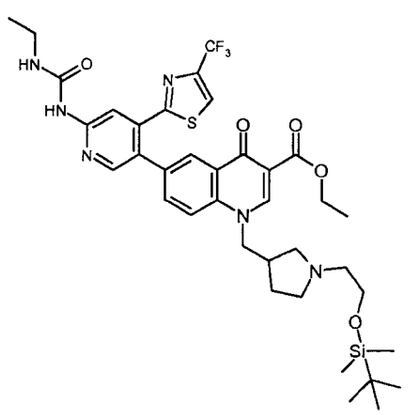
Examples 295-304

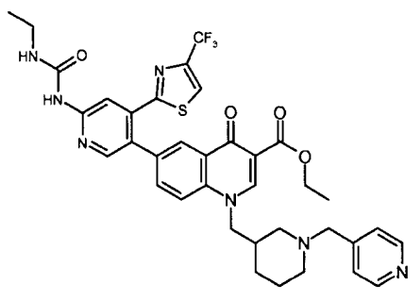
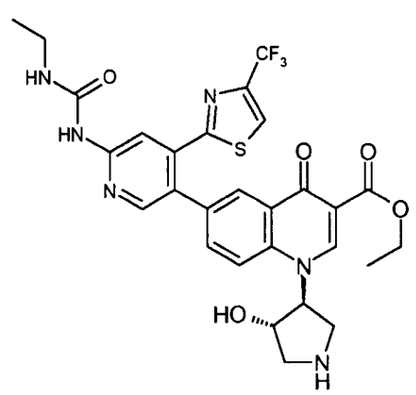
The following Examples were prepared according to the general procedure described below.

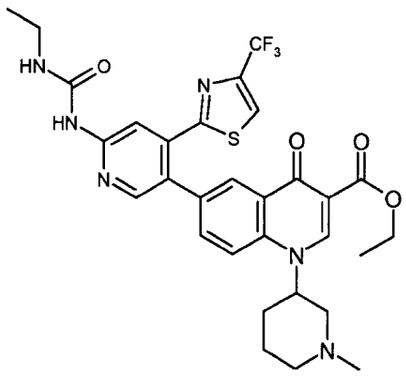
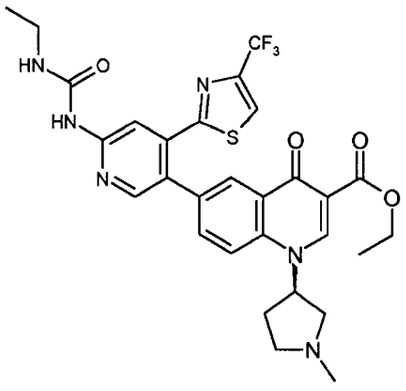
General Procedure

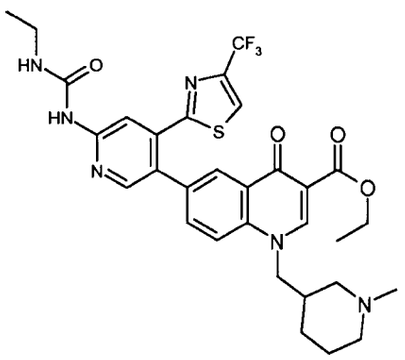
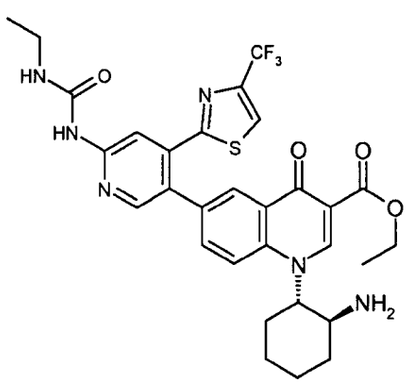
To a slurry of 6-(3-ethylureido)-4-(4-trifluoromethylthiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 17, 202 mg, 0.56 mmol), the appropriate dihydroquinoline (0.50 mmol) and trans dichlorobis(triphenylphosphine)palladium (II) (33 mg, 0.047 mmol) in 1,4-dioxane (8 mL) was added a solution of potassium carbonate (130 mg, 0.94 mmol) in water (2 mL). The reaction was stirred for 1.5 h at 70°C. The reaction was cooled to room temperature, and ethyl acetate (8 mL) was added to help separate the layers. The water was removed, and the organic phase was washed with water (3 mL). The reaction was then concentrated and the material was either chromatographed on a 4g Analogix column using 0-10% methanol in dichloromethane or triturated with ethanol for purification.

Ex	Compound	Data	SM
295	ethyl 1-((1-ethylpyrrolidin-3-yl)methyl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 643.2 (MH^+) for $C_{31}H_{33}F_3N_6O_4S$ ^1H NMR (300 MHz, DMSO-d_6): 1.22-1.35 (m, 6H), 1.42 (t, 3H), 3.40-3.52 (m, 2 H), 4.09 (q, 2H), 4.41 (q, 2 H), 7.27-7.41 (m, 5H), 7.61 (s, 1 H), 7.72 (m, 2H), 8.29 (s, 1H), 8.46 (s, 1H), 8.52-8.61 (m, 2H), 9.04 (bs, 1H)	Intermediate 17 and Intermediate 127
296	ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-((1-(2-morpholinoethyl)pyrrolidin-3-yl)methyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 728.1 (MH^+) for $C_{35}H_{40}F_3N_7O_5S$	Intermediate 17 and Intermediate 128

Ex	Compound	Data	SM
297	ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-((1-((tetrahydrofuran-2-yl)methyl)pyrrolidin-3-yl)methyl)-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 699.3 (MH^+) for $C_{34}H_{37}F_3N_6O_5S$ ^1H NMR (300 MHz, DMSO-d_6): 1.11 (t, 3H), 1.28 (t, 3H), 1.69 (m, 1H), 1.75-2.81 (bm, 10H) 3.09-3.26 (m, 2 H), 4.19 (q, 2H), 4.36 (d, 2 H), 7.52-7.68 (m, 3H), 7.94 (d, 1 H), 8.18 (s, 1H), 8.24 (s, 1H), 8.29 (s, 1H), 8.47 (s, 1H), 8.65 (dd, 1H), 9.41 (bs, 1H)	Intermediate 17 and Intermediate 129
298	ethyl 1-((1-(2-(tert-butyldimethylsilyloxy)ethyl)pyrrolidin-3-yl)methyl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 773.4 ($M+H^+$) for $C_{37}H_{47}F_3N_6O_5SSi$	Intermediate 17 and Intermediate 130

Ex	Compound	Data	SM
299	ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(1-(pyridin-4-ylmethyl)piperidin-3-yl)-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 706.2 (MH^+) for $C_{35}H_{34}F_3N_7O_4S$	Intermediate 17 and Intermediate 133
300	*Trans*-ethyl 1-(1-(tert-butoxycarbonyl)-4-hydroxypyrrolidin-3-yl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 717.3 (MH^+) for $C_{33}H_{35}F_3N_6O_7S$	Intermediate 17 and Intermediate 138

Ex	Compound	Data	SM
301	ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-methylpiperidin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 629.1 (MH^+) for $C_{30}H_{31}F_3N_6O_4S$	Intermediate 17 and Intermediate 134
302	(S)-ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-methylpyrrolidin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 615.0 (MH^+) for $C_{29}H_{29}F_3N_6O_4S$	Intermediate 17 and Intermediate 137

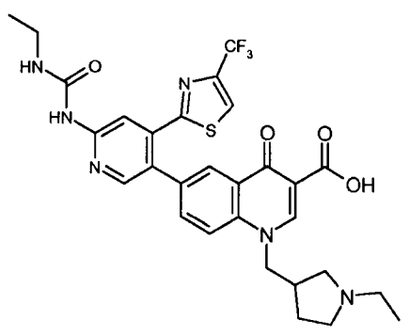
Ex	Compound	Data	SM
303	ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-((1-methylpiperidin-3-yl)methyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 643.1 (MH^+) for $C_{31}H_{33}F_3N_6O_4S$	Intermediate 17 and Intermediate 139
304	ethyl 1-((1S,2S)-2-aminocyclohexyl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 572.1 (MH^+) for $C_{30}H_{31}F_3N_6O_4S$	Intermediate 17 and Intermediate 140

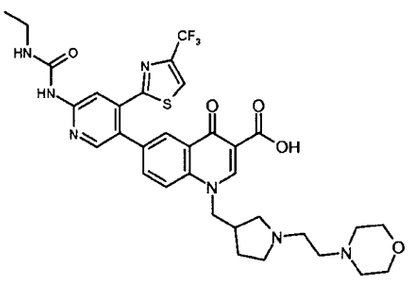
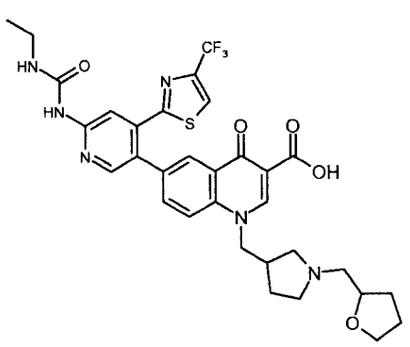
Examples 305-314

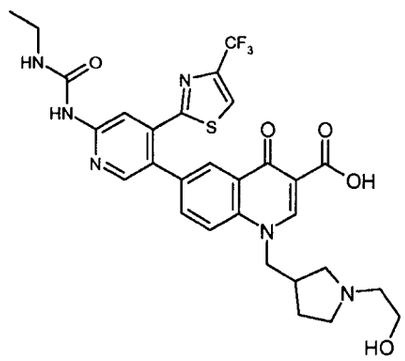
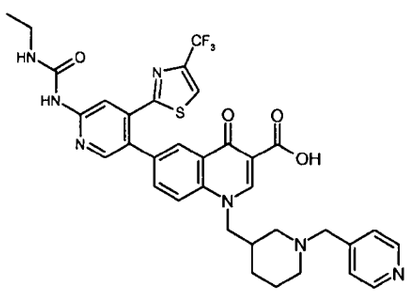
The following Examples were prepared according to the general procedure described below.

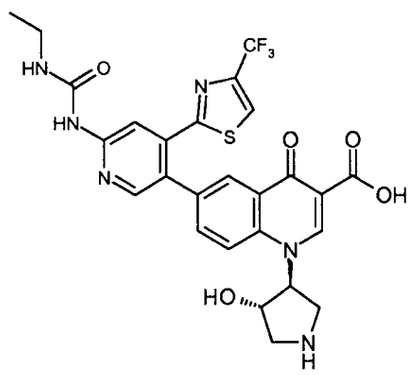
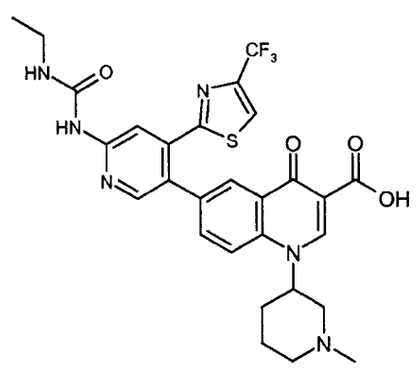
General Procedure

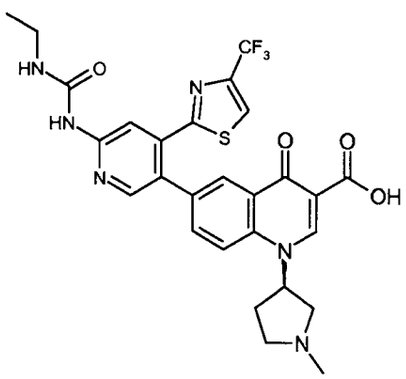
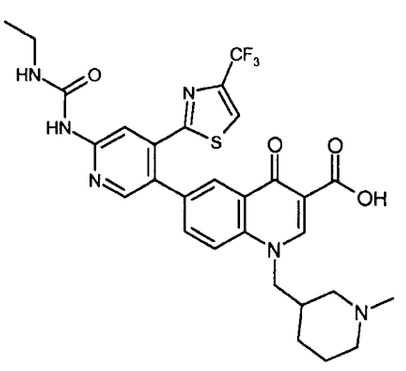
The ethyl ester (~110 mg) was dissolved in methanol (3 mL) and tetrahydrofuran (3 mL). To this solution was added 1N sodium hydroxide (3 mL) and the reaction was stirred at room temperature for 3 h. The solution was concentrated to remove the organics. Water (3 mL) was added and the aqueous layer was washed with methyl tert-butyl ether (3 mL). The aqueous phase was filtered then acidified to pH~3 with 1N hydrochloric acid. For compounds Example 308 and Example 310 the aqueous phase was taken to pH 1 and stirred for 3 h to remove the protecting groups then basified back to pH~3 with 1N sodium hydroxide. The acids were extracted with 1:1 ethyl acetate: tetrahydrofuran (3×, 5 mL each). The organic layers were combined, dried over sodium sulfate, and the solvent removed *in vacuo*.

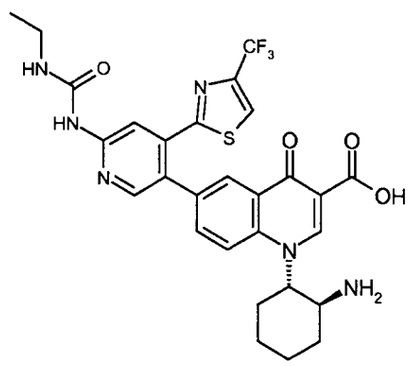
Ex	Compound	Data	SM
305	1-((1-ethylpyrrolidin-3-yl)methyl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 615.3 (MH^+) for $C_{29}H_{29}F_3N_6O_4S$ ^1H NMR (300 MHz, DMSO-d_6): 1.12 (t, 3H), 1.21 (t, 3H), 1.60-2.20 (m, 2H), 2.80-3.25 (m, 4H), 3.18-3.25 (m, 2H), 4.73 (brs, 1H), 7.62 (t, 1H), 7.87 (d, 1H), 8.19-8.24 (m, 2H), 8.32 (d, 1H), 8.36 (s, 1H), 8.54 (s, 1H), 9.13 (s, 1H), 9.50 (s, 1H)	Example 295

Ex	Compound	Data	SM
306	6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-((1-(2-morpholinoethyl)pyrrolidin-3-yl)methyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 700.2 (MH^+) for $C_{33}H_{36}F_3N_7O_5S$ ^1H NMR (300 MHz, DMSO-d_6): 1.12 (t, 3H), 1.80 (bs, 1H), 2.06 (bs, 1H), 2.38-2.50 (bm, 2H), 2.60-2.70 (bm, 2H), 2.80-3.00 (bm, 1H), 3.18-3.25 (bm, 4H), 3.50-3.62 (bm, 4H), 4.75 (bd, 2H), 7.63 (bt, 1H), 7.89 (dd, 1H), 8.23-8.26 (m, 2H), 8.32 (d, 1H), 8.37 (s, 1H), 8.55 (d, 1H), 9.14 (s, 1H), 9.53 (s, 1H)	Example 296
307	6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-((1-((tetrahydrofuran-2-yl)methyl)pyrrolidin-3-yl)methyl)-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 671.4 (MH^+) for $C_{32}H_{33}F_3N_6O_5S$ ^1H NMR (300 MHz, CD_3OD): 1.21 (t, 3H), 1.41-1.58 (bm, 1H), 1.62-1.79 (bm, 1H), 1.80-1.92 (bm, 2H), 1.93-2.10 (bm, 2H), 2.62-2.85 (bm, 4H), 2.80-3.00 (bm, 1H), 3.01-3.13 (bm, 1H), 3.31-3.37 (m, 2H), 3.63-3.75 (m, 1H), 3.78-3.89 (bm, 1H), 3.96-4.10 (bm, 1H), 4.53 (bd, 2H), 7.72 (d, 1H), 7.83 (s, 1H), 8.04 (d, 2H), 8.17 (s, 1H), 8.31 (d, 1H), 8.37 (s, 1H), 8.97 (d, 1H)	Example 297

Ex	Compound	Data	SM
308	6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-((1-(2-hydroxyethyl)pyrrolidin-3-yl)methyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid hydrochloride 	MS (ESP): 631.2 (MH^+) for $C_{29}H_{29}F_3N_6O_5S$ ^{1}H NMR (300 MHz, DMSO-d_6): 1.11 (t, 3H), 1.56-1.65 (bs, 1H), 1.83-2.03 (bs, 1H), 2.60-3.20 (bm, 6H), 3.18-3.24 (m, 3H), 3.55-3.62 (m, 2H), 4.65 (bd, 2H), 7.51-7.63 (m, 2H), 7.86 (dd, 1H), 8.20 (d, 1H), 8.22 (s, 2H), 8.32 (d, 1H), 8.38 (s, 1H), 8.54 (s, 1H), 9.11 (s, 1H), 9.52 (s, 1H)	Example 298
309	6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(1-(pyridin-4-ylmethyl)piperidin-3-yl)-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 678.3 (MH^+) for $C_{33}H_{30}F_3N_7O_4S$ ^{1}H NMR (300 MHz, DMSO-d_6): 1.11 (t, 3H), 1.80-2.40 (bm, 4H), 3.21-3.27 (m, 3H), 5.00-5.50 (bs, 1H), 7.63 (t, 1H), 7.90-7.94 (bm, 2H), 8.24 (s, 1H), 8.32-8.34 (m, 2H), 8.54 (d, 1H), 8.74 (bm, 2H), 9.52 (s, 1H)	Example 299

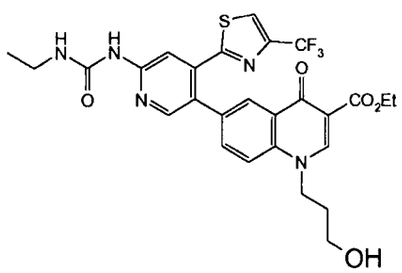
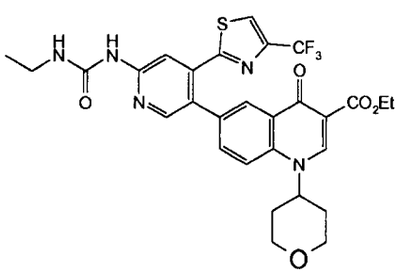
Ex	Compound	Data	SM
310	trans 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(4-hydroxypyrrolidin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 589.2 (MH^+) for $C_{26}H_{23}F_3N_6O_5S$ ^{1}H NMR (300 MHz, DMSO-d_6): 1.11 (t, 3H), 3.16-3.22 (m, 3H), 3.58-3.77 (m, 2H), 3.85-4.05 (m, 1H), 4.83 (q, 1H), 5.62 (q, 1H), 7.60-7.71 (m, 1H), 7.96 (dd, 1H), 8.24-8.36 (m, 4H), 8.54 (d, 1H), 9.08 (s, 1H), 9.52-9.56 (m, 2H), 9.79 (bs, 1H)	Example 300
311	6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-methylpiperidin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 601.2 (MH^+) for $C_{28}H_{27}F_3N_6O_4S$ ^{1}H NMR (300 MHz, DMSO-d_6): 1.11 (t, 3H), 2.07-2.20 (m, 2H), 2.21-2.48 (m, 2H), 2.79 (d, 3H), 3.02-3.20 (m, 1H), 3.21-3.27 (m, 3H), 3.49-3.71 (m, 2H), 5.51 (t, 1H), 7.66 (t, 1H), 7.97 (dd, 1H), 8.25 (d, 1H), 8.32-8.34 (m, 2H), 8.47 (d, 1H), 8.54 (d, 1H), 8.96 (s, H), 9.52 (s, 1H), 11.28 (bs, 1H)	Example 301

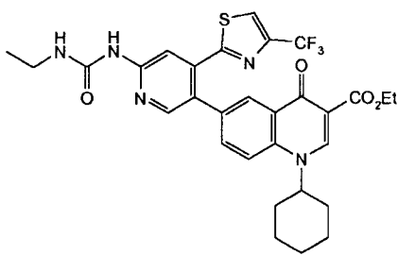
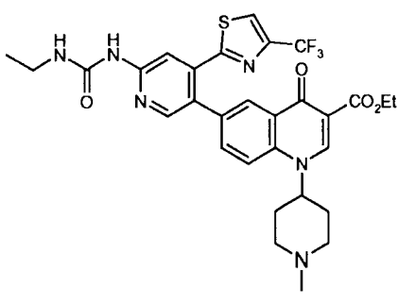
Ex	Compound	Data	SM
312	(S)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-methylpyrrolidin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 587.1 (MH^+) for $C_{22}H_{25}F_3N_6O_4S$ ^1H NMR (300 MHz, DMSO-d_6): 1.12 (t, 3H), 2.60-3.00 (bm, 2H), 2.94 (bs, 3H), 3.20-4.2 (bm, 4H), 5.6-6.0 (bm, 1H), 7.64 (t, 1H), 7.95 (dd, 1H), 8.10-8.24 (m, 2H), 8.34 (d, 1H), 8.37 (s, 1H), 8.56 (d, 1H), 9.06 (bs, 1H), 9.53 (s, 1H), 10.70-11.15 (bm, 1H)	Example 302
313	6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-((1-methylpiperidin-3-yl)methyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 615.3 (MH^+) for $C_{29}H_{29}F_3N_6O_4S$ ^1H NMR (300 MHz, DMSO-d_6): 1.11 (t, 4H), 1.40-1.90 (bm, 2H), 3.21-3.27 (m, 3H), 4.55 (bm, 4H), 7.64 (t, 1H), 7.86 (bd, 1H), 8.14 (d, 1H), 8.24 (s, 1H), 8.32 (d, 1H), 8.36 (s, 1H), 8.53 (d, 1H), 9.03 (s, 1H), 9.50 (s, 1H)	Example 303

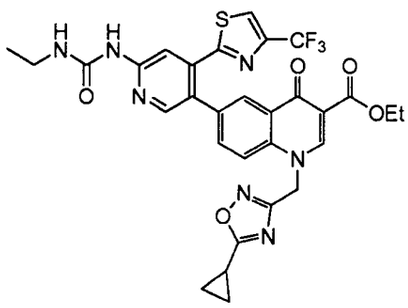
Ex	Compound	Data	SM
314	1-((1S,2S)-2-aminocyclohexyl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 601.2 (MH^+) for $C_{28}H_{27}F_3N_6O_4S$ ^1H NMR (300 MHz, CD_3OD): 1.20 (t, 3H), 1.58-1.80 (bm, 2H), 1.80-2.03 (bm, 4H), 2.10-2.22 (bm, 1H), 2.49-2.61 (bm, 1H), 3.20-3.40 (bm, 2H), 3.92-4.10 (bm, 1H), 5.00-5.20 (bm, 1H), 7.71 (d, 1H), 7.77 (s, 1H), 8.15 (s, 1H), 8.10-8.30 (bs, 1H), 8.22 (s, 1H), 8.30 (s, 1H), 8.36 (s, 1H), 9.00 (bs, 1H)	Example 304

Examples 315-319

The following Examples were prepared according to the general procedure described for Examples 295-304 from the indicated starting materials.

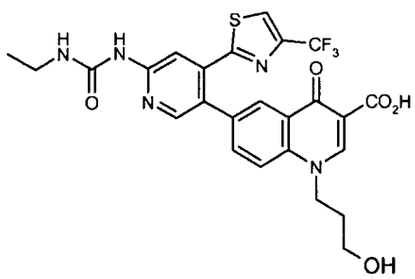
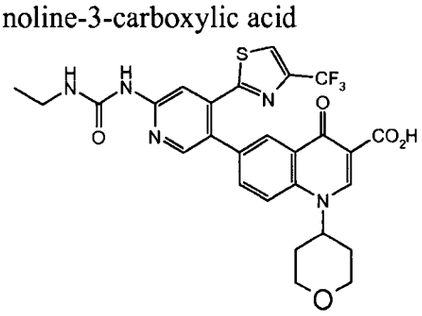
Ex	Compound	Data	SM
315	Ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(3-hydroxypropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 590 (M+1) for $C_{27}H_{26}F_3N_5O_5S$ ^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, J=7.20 Hz, 3H); 1.28 (t, J=7.07 Hz, 3H); 1.87 - 1.98 (m, 2H); 3.15 - 3.27 (m, 2H); 3.48 (q, J=5.56 Hz, 2H); 4.23 (q, J=6.99 Hz, 2H); 4.45 (t, J=6.95 Hz, 2H); 4.76 (t, J=4.67 Hz, 1H); 7.63 (t, J=5.05 Hz, 1H); 7.71 (dd, J=8.72, 2.15 Hz, 1H); 7.89 (d, J=8.84 Hz, 1H); 8.15 (d, J=2.27 Hz, 1H); 8.23 (s, 1H); 8.32 (s, 1H); 8.48 (s, 1H); 8.69 (s, 1H); 9.44 (s, 1H)	Intermediate 17 and Intermediate 141
316	Ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl) thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(tetrahydro-2H-pyran-4-yl)-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 616.18 (M+1) for $C_{29}H_{28}F_3N_5O_5S$	Intermediate 17 and Intermediate 142

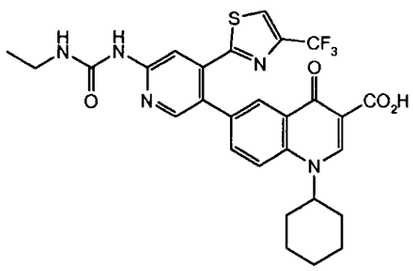
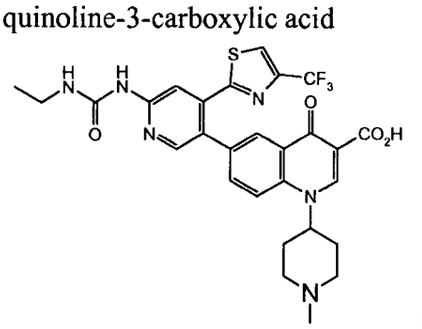
Ex	Compound	Data	SM
317	Ethyl 1-cyclohexyl -6-(6-(3-ethylureido)-4-(4-(trifluoromethyl) thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 614.17 (M+1) for $C_{30}H_{30}F_3N_5O_4S$ ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.11 (t, *J*=7.07 Hz, 3H); 1.21 - 1.39 (m, 4H); 1.51 - 1.95 (m, 7H); 1.98 - 2.13 (m, 2H); 3.14 - 3.26 (m, 2H); 4.24 (q, *J*=6.99 Hz, 2H); 4.59 - 4.80 (m, 1H); 7.58 - 7.67 (m, 1H); 7.69 (dd, *J*=8.84, 2.27 Hz, 1H); 8.07 (d, *J*=9.09 Hz, 1H); 8.19 (d, *J*=2.27 Hz, 1H); 8.23 (s, 1H); 8.31 (s, 1H); 8.48 (s, 1H); 8.64 (s, 1H); 9.44 (s, 1H)	Intermediate 17 and Intermediate 143
318	Ethyl 6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl) Pyridin-3-yl)-1-(1-methyl piperidin-4-yl)-4-oxo-1,4-dihydro quinoline-3-carboxylate 	MS (ESP): 629.23 (M+1) for $C_{30}H_{31}F_3N_6O_4S$ ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.10 (t, *J*=7.20 Hz, 3H); 1.28 (t, *J*=7.07 Hz, 3H); 1.92 - 2.10 (m, 4H); 2.17 - 2.33 (m, 5H); 2.85 - 3.00 (m, 2H); 3.13 - 3.27 (m, 2H); 4.23 (q, *J*=7.07 Hz, 2H); 4.62 - 4.79 (m, 1H); 7.58 - 7.67 (m, 1 H); 7.70 (dd, *J*=8.84, 2.27 Hz, 1H); 8.08 (d, *J*=9.09 Hz, 1H); 8.18 (d, *J*=2.27 Hz, 1H); 8.22 (s, 1H); 8.31 (s, 1H); 8.48 (s, 1H); 8.61 (s, 1H); 9.44 (s, 1H)	Intermediate 17 and Intermediate 144

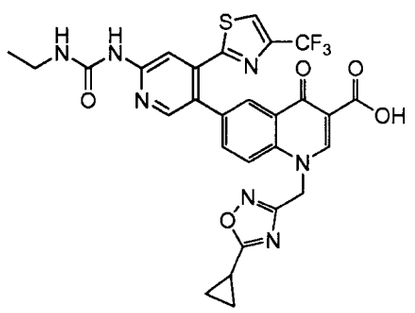
Ex	Compound	Data	SM
319	Ethyl 1-((5-cyclopropyl-1,2,4-oxadiazol-3-yl)methyl)-6-(6-(3-ethylureido) -4-(4-(trifluoro methyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 654.14 (M+1) for $C_{30}H_{26}F_3N_7O_5S$ ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.00 - 1.16 (m, 5H); 1.18 - 1.37 (m, 5H); 2.22 - 2.43 (m, 1H); 3.21 (dq, *J*=6.95, 6.69 Hz, 2H); 4.25 (q, *J*=7.07 Hz, 2H); 5.86 (s, 2H); 7.54 - 7.78 (m, 3H); 8.13 (s, 1H); 8.20 (s, 1H); 8.31 (s, 1H); 8.49 (s, 1H); 8.89 (s, 1H); 9.43 (s, 1H)	Intermediate 17 and Intermediate 145

Examples 320-324

The following Examples were prepared according to the procedure described for Example 293 from the indicated startin material.

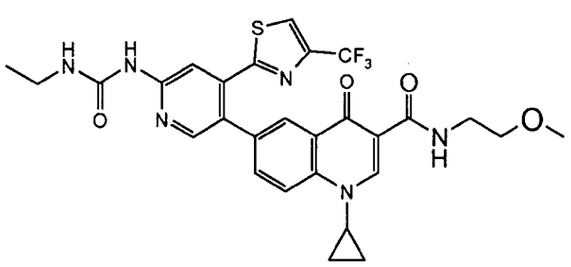
Ex	Compound	Data	SM
320	6-(6-(3-Ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl) pyridin-3-yl)-1-(3-hydroxy propyl)-4-oxo-1,4-dihydro quinoline-3-carboxylic acid 	MS (ESP): 562 (M+1) for $C_{25}H_{22}F_3N_5O_5S$ ^{1}H-NMR (400 MHz, DMSO-d$_6$) δ: 1.11 (t, *J*=7.20 Hz, 3H); 1.90 - 2.04 (m, 2H); 3.13 - 3.29 (m, *J*=6.95, 6.69, 6.57, 6.57 Hz, 2H); 3.48 (q, *J*=5.39 Hz, 2H); 4.65 (t, *J*=6.82 Hz, 2H); 4.77 (t, *J*=4.80 Hz, 1H); 7.60 (br. s., 1H); 7.87 (dd, *J*=8.72, 1.89 Hz, 1H); 8.09 (d, *J*=8.84 Hz, 1H); 8.22 (s, 1H); 8.31 (d, *J*=1.77 Hz, 1H); 8.37 (s, 1H); 8.51 (s, 1H); 9.04 (s, 1H); 9.48 (s, 1H); 15.07 (s, 1H)	Example 315
321	6-(6-(3-Ethylureido)-4-(4-(trifluoromethyl) thiazol-2-yl)pyridin-3-yl)-4-oxo-1-(tetrahydro-2H-pyran-4-yl)-1,4dihydroquinoline-3-carboxylic acid 	MS (ESP): 588.09 (M+1) for $C_{27}H_{24}F_3N_5O_5S$ ^{1}H-NMR (400 MHz, DMSO-d$_6$) δ: 1.11 (t, *J*=7.20 Hz, 3H); 1.96 - 2.20 (m, 4H); 3.15 - 3.27 (m, 2H); 3.60 - 3.77 (m, 2H); 3.96 - 4.09 (m, 2H); 5.16 (br. s., 1H); 7.64 (br. s., 1H); 7.83 (br. s., 1H); 8.23 (s, 1H); 8.35 (br. s., 2H); 8.49 (br. s., 1H); 8.90 (br. s., 1H); 9.48 (s, 1H); 15.02 (br. s., 1H)	Example 316

Ex	Compound	Data	SM
322	1-Cyclohexyl-6-(6-(3-ethylureido)-4-(4-(trifluoro methyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 586.36 (M+1) for $C_{28}H_{26}F_3N_5O_4S$ ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.11 (t, *J*=7.20 Hz, 3H) 1.27 - 1.41 (m, 1H) 1.55 - 1.76 (m, 3H); 1.80 - 1.97 (m, 4H); 2.02 - 2.14 (m, 2H); 3.14 - 3.28 (m, 2H); 4.83 - 4.99 (m, 1H); 7.62 (d, 1H); 7.86 (d, *J*=9.60 Hz, 1H); 8.23 (s, 1H); 8.25 - 8.31 (m, 1H); 8.33 - 8.38 (m, 2H); 8.51 (s, 1H); 8.92 (s, 1H); 9.48 (s, 1H)	Example 317
323	6-(6-(3-Ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-1-(1-methyl piperidin-4-yl)-4-oxo-1,4-dihydro quinoline-3-carboxylic acid 	MS (ESP): 601.22 (M+1) for $C_{28}H_{27}F_3N_6O_4S$ ^{1}H-NMR (400 MHz, DMSO-d6) δ: 1.11 (t, *J*=7.07 Hz, 3H); 2.00 - 2.17 (m, 4H); 2.19 - 2.38 (m, 5H); 2.87 - 3.05 (m, 2H); 3.14 - 3.27 (m, 2H); 4.78 - 4.98 (m, 1H); 7.61 (br. s., 1H); 7.86 (dd, *J*=8.97, 1.89 Hz, 1H); 8.23 (s, 1 H); 8.28 (d, *J*=9.35 Hz, 1H); 8.32 - 8.40 (m, 2H); 8.51 (s, 1H); 8.85 (s, 1H); 9.48 (s, 1H); 15.01 (br. s., 1H)	Example 318

Ex	Compound	Data	SM
324	1-((5-Cyclopropyl -1,2,4-oxadiazol-3-yl)methyl)-6-(6-(3-ethylureido) -4-(4-(trifluoro methyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 	MS (ESP): 626.03 (M+) for $C_{28}H_{22}F_3N_7O_5S$ ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 0.97 - 1.17 (m, 5H); 1.18 - 1.33 (m, 2H); 2.18 - 2.42 (m, J=8.34, 8.34, 4.42, 4.17 Hz, 1H); 3.11 - 3.27 (m, 2H); 6.06 (s, 2H) 7.57 (br. s., 1H); 7.77 - 7.86 (m, 1H); 7.86 - 7.96 (m, 1H); 8.17 - 8.26 (m, 1H); 8.24 - 8.33 (m, 1H); 8.36 (s, 1H); 8.52 (s, 1H); 9.27 (s, 1H); 9.46 (s, 1H); 14.82 (s, 1H)	Example 319

Example 325

1-Cyclopropyl-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-N-(2-methoxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide



To a solution of 1-cyclopropyl-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 20, 80 mg, 0.15 mmol) in DMF (3 mL) was added HATU (112 mg, 0.29 mmol), DIEA (0.051 mL, 0.29 mmol) followed by 2-methoxyethanamine (22.11 mg, 0.29 mmol). After 1 h stirring, LC-MS shows completion of reaction. DMF removed under vaccuum, and the residue was purified by ISCO column using MeOH-CH_2Cl_2 (0-20%) to give white solid (47.3 mg, 53.5%).

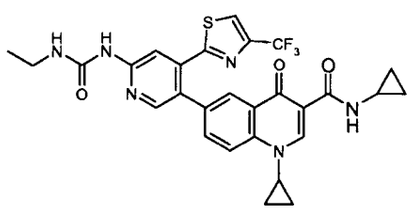
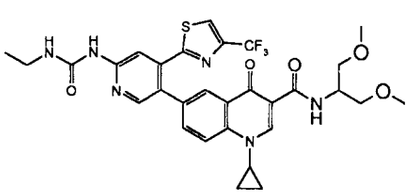
MS (ESP): 601.22 (M+1) for $C_{28}H_{27}F_3N_6O_4S$

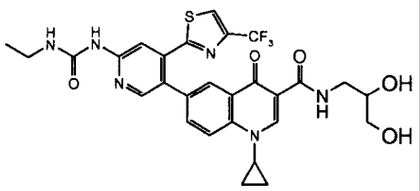
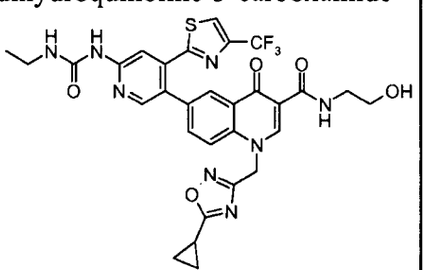
^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.11 (t, J=7.07 Hz, 3H); 1.20 - 1.37 (m, 4H); 3.15 - 3.25 (m, 2H); 3.40 - 3.54 (m, 4H); 3.73 - 3.85 (m, 1H); 7.56 - 7.67 (m, 1H); 7.80 (dd, J=8.84, 2.27

Hz, 1H); 8.14 - 8.29 (m, 3H); 8.33 (s, 1H); 8.48 (s, 1H); 8.75 (s, 1H); 9.45 (s, 1H); 9.74 - 9.99 (m, 1H).

Examples 326-329

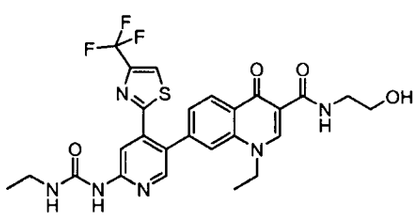
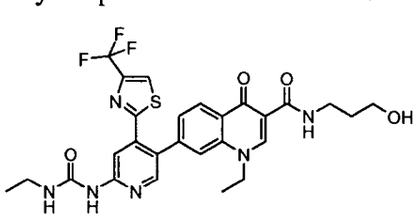
The following Examples were prepared according to the procedure described for Example 325 from the indicated starting materials.

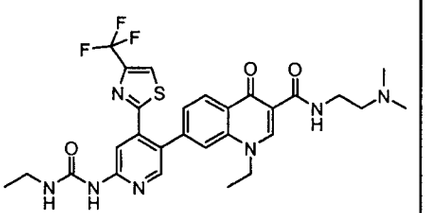
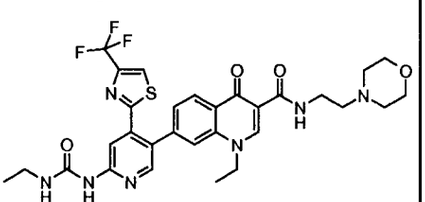
Ex	Compound	Data	SM
326	N,1-Dicycloprop yl-6-(6-(3-ethyl ureido)-4-(4-(trifluoromethyl) thiazol-2-yl)pyridin-3-yl) -4-oxo-1,4-dihydroquino line-3-carboxamide 	MS (ESP): 583.20 (M+1) for $C_{28}H_{25}F_3N_6O_3S$ ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 0.45 - 0.58 (m, 2H); 0.65 - 0.80 (m, 2H); 1.03 - 1.17 (m, 5H); 1.24 - 1.38 (m, 2H); 2.78 - 2.92 (m, 1H); 3.15 - 3.27 (m, 2H); 3.71 - 3.87 (m, 1H); 7.62 (br. s., 1H); 7.81 (dd, *J*=8.72, 2.15 Hz, 1H); 8.21 (s, 1H); 8.22 - 8.26 (m, 1H); 8.31 (s, 1H); 8.49 (s, 1H); 8.75 (s, 1H); 9.45 (s, 1H); 9.82 (d, 1H)	Example 20 and cyclopropyl-amine
327	1-Cyclopropyl-N-(1,3-dimethoxy propan-2-yl)-6-(6-(3-ethylureido) -4-(4-(trifluoro methyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 645.27 (M+1) for $C_{30}H_{31}F_3N_6O_5S$ ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.03 - 1.19 (m, 5H); 1.25 - 1.39 (m, 2H); 3.15 - 3.26 (m, 2H); 3.28 (s, 6H); 3.36 - 3.50 (m, 4H); 3.73 - 3.86 (m, 1H); 4.22 - 4.33 (m, 1H); 7.62 (br. s., 1H); 7.80 (dd, *J*=8.97, 1.89 Hz, 1H); 8.22 (d, *J*=8.84 Hz, 1H); 8.26 (s, 2H); 8.32 (s, 1H); 8.48 (s, 1 H); 8.75 (s, 1H); 9.45 (s, 1 H); 9.99 (d, *J*=8.34 Hz, 1H);	Example 20 and 1,3-dimethoxy-2-amino-propane

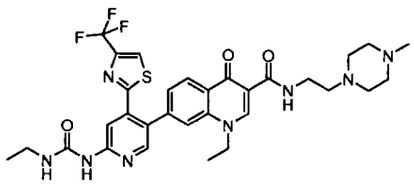
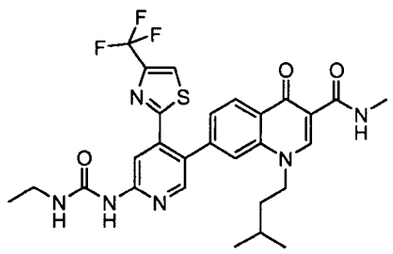
Ex	Compound	Data	SM
328	1-Cyclopropyl-N-(2,3-dihydroxy propyl)-6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxamide 	MS (ESP): 617.19 (M+1) for $C_{28}H_{27}F_3N_6O_5S$ ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 0.97 - 1.21 (m, 5H); 1.24 - 1.43 (m, 2H); 3.11 - 3.47 (m, 5H); 3.47 - 3.65 (m, 2H); 3.69 - 3.91 (m, 1H); 4.63 (t, *J*=5.68 Hz, 1H); 4.91 (d, 1H); 7.63 (br. s., 1H); 7.80 (dd, *J*=8.72, 1.89 Hz, 1H); 8.13 - 8.29 (m, 3H); 8.32 (s, 1H); 8.48 (s, 1H); 8.75 (s, 1H); 9.45 (s, 1H); 9.93 (br. s., 1H)	Example 20 and 2,3-dihydroxy-propanamine
329	1-((5-Cyclopropyl-1,2,4-oxadiazol-3-yl)methyl)-6-(6-(3-ethylureido) -4-(4-(trifluoro methyl)thiazol-2-yl)pyridin-3-yl)-N-(2-hydroxy ethyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide 	MS(ESP): 669.11 (M+1) for $C_{30}H_{27}F_3N_8O_5S$ ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 0.99 - 1.15 (m, 5H); 1.17 - 1.27 (m, J=7.64, 4.04, 3.76, 3.76 Hz, 2H); 2.26 - 2.39 (m, 1H); 3.21 (quin, J=6.76 Hz, 2H); 3.35 - 3.47 (m, 2H); 3.53 (q, J=5.39 Hz, 2H); 4.80 (t, J=5.05 Hz, 1H); 5.97 (s, 2H); 7.60 (br. s., 1H); 7.67 - 7.76 (m, 1H); 7.80 (d, 1H); 8.18 - 8.27 (m, 2H); 8.33 (s, 1H); 8.49 (s, 1H); 9.06 (s, 1H); 9.44 (s, 1H); 9.90 (t, 1H)	Example 324 2-hydroxy-ethanamine

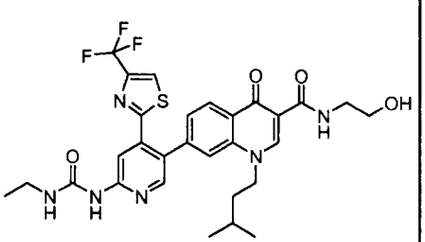
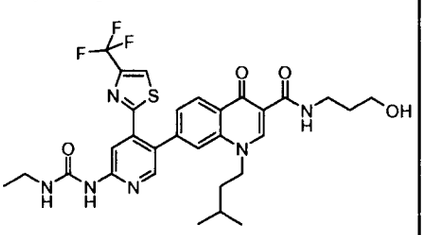
Examples 330-379

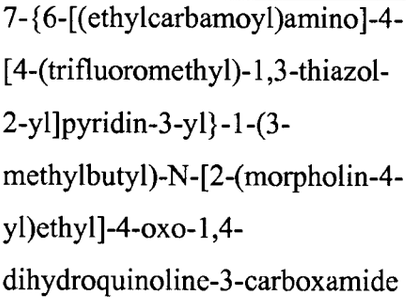
The following Examples were prepared according to the procedure described for Example 33 from the indicated starting materials.

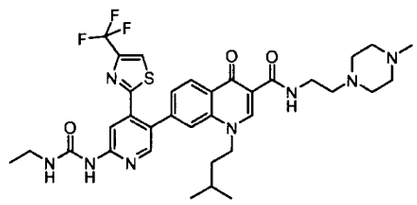
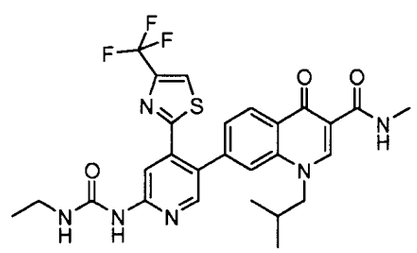
Ex	Compound	Data	SM
330	1-Ethyl-7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-N-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 1.08 (t, 3H), 1.15 (t, 3H), 3.21 (q, 2H), 3.41 (t, 2H), 3.56 (t, 2H), 4.41 (q, 2H), 4.80 (s, 1H), 7.42 (d, 1H), 7.61 (s, 1H), 7.86 (s, 1H), 8.22 (s, 1H), 8.34 (m, 2H), 8.48 (s, 1H), 8.88 (s, 1H), 9.46 (s, 1H), 10.06 (s, 1H). LC-MS: m/z 575.2 (M+H)	Example 42 and 3-aminoethanol
331	1-Ethyl-7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-N-(3-hydroxypropyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 1.08 (t, 3H), 1.15 (t, 3H), 1.64 (m, 2H), 3.21 (q, 2H), 3.38 (q, 2H), 3.44 (q, 2H), 4.21 (m, 3H), 7.39 (d, 1H), 7.58 (s, 1H), 7.84 (s, 1H), 8.21 (s, 1H), 8.37 (m, 2H), 8.43 (s, 1H), 8.84 (s, 1H), 9.42 (s, 1H), 9.98 (t, 1H). LC-MS: m/z 589.3 (M+H)	Example 42 and 3-amino-propanol

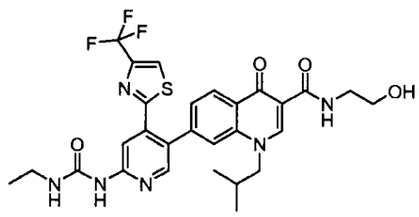
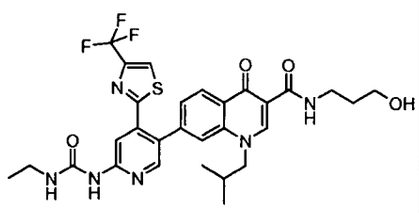
Ex	Compound	Data	SM
332	N-[2-(dimethylamino)ethyl]-1-ethyl-7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-4-oxo-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 1.08 (t, 3H), 1.14 (t, 3H), 2.78 (s, 5H), 3.21 (m, 4H), 3.67 (d, 2H), 4.23 (q, 2H), 7.42 (d, 1H), 7.56 (m, 2H), 7.92 (s, 1H), 8.21 (s, 1H), 8.35 (d, 1H), 8.42 (s, 1H), 8.52 (s, 1H), 8.91 (s, 1H), 9.48 (s, 1H), 10.16 (t, 1H). LC-MS: m/z 602.3 (M+H)	Example 42 2-(N,N-dimethyl-amino)-ethanamine
333	1-Ethyl-7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-N-[2-(morpholin-4-yl)ethyl]-4-oxo-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 1.08 (t, 3H), 1.14 (t, 3H), 3.18 (m, 4H), 3.61 (m, 6H), 4.02 (m, 2H), 4.22 (q, 2H), 7.42 (d, 1H), 7.58 (s, 1H), 7.86 (s, 1H), 8.21 (s, 1H), 8.38 (m, 2H), 8.51 (s, 1H), 8.91 (s, 1H), 9.42 (s, 1H), 9.44 (s, 1H), 10.18 (s, 1H). LC-MS: m/z 644.2 (M+H)	Example 42 and 2-morpholino-ethylamine

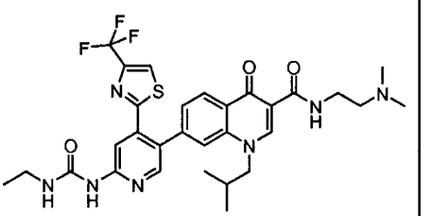
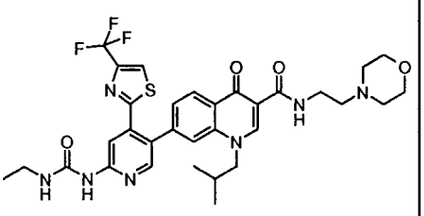
Ex	Compound	Data	SM
334	1-Ethyl-7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-N-[2-(4-methylpiperazin-1-yl)ethyl]-4-oxo-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 1.08 (q, 3H), 1.12 (t, 3H), 2.19 (m, 4H), 2.28 (m, 7H), 3.21 (q, 2H), 3.42 (d, 2H), 4.22 (d, 2H), 7.22 (m, 7H), 7.84 (s, 1H), 8.21 (s, 1H), 8.37 (m, 3H), 8.82 (s, 1H), 9.46 (s, 1H), 9.96 (s, 1H). LC-MS: m/z 657.4 (M+H)	Example 42 and 2-(4-methyl-piperazino)-ethanamine
335	7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-N-methyl-1-(3-methylbutyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 0.85 (d, 6H), 1.14 (t, 3H), 1.38 (d, 2H), 1.54 (m, 1H), 2.86 (d, 3H), 3.19 (q, 2H), 4.21 (s, 1H), 7.52 (d, 1H), 7.60 (s, 1H), 7.79 (s, 1H), 8.24 (s, 1H), 8.41 (d, 2H), 8.51 (s, 1H), 8.86 (s, 1H), 9.48 (s, 1H), 9.78 (d, 1H). LC-MS: m/z 587.4 (M+H)	Example 63 and methylamine

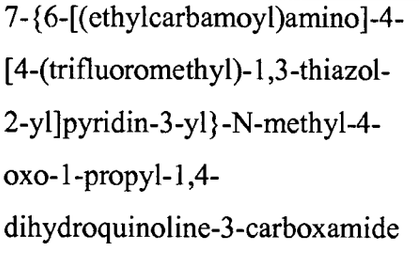
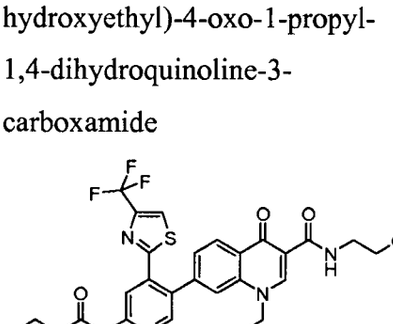
Ex	Compound	Data	SM
336	7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-N-(2-hydroxyethyl)-1-(3-methylbutyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 0.84 (d, 6H), 1.15 (t, 3H), 1.41 (q, 2H), 1.52 (m, 1H), 3.21 (q, 4H), 3.42 (d, 2H), 3.58 (q, 2H), 4.42 (t, 2H), 4.82 (s, 1H), 7.48 (d, 1H), 7.58 (s, 1H), 7.78 (s, 1H), 8.24 (s, 1H), 8.39 (d, 2H), 8.48 (s, 1H), 8.84 (s,1H), 9.42 (s,1H), 10.06 (s, 1H) LC-MS: m/z 617.3 (M+H)	Example 63 and ethanolamine
337	7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-N-(3-hydroxypropyl)-1-(3-methylbutyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 0.84 (d, 6H), 1.15 (t, 3H), 1.38 (t, 2H), 1.52 (m, 1H), 1.68 (q, 2H), 3.20 (q, 2H), 3.39 (t, 2H), 3.45 (t, 2H), 4.38 (t, 2H), 4.49 (s, 1H), 7.46 (d, 1H), 7.58 (s, 1H), 7.78 (s, 1H), 8.24 (s, 1H), 8.39 (d, 2H), 8.49 (s,1H), 8.85 (s,1H), 9.43 (s, 1H), 9.96 (s, 1H) LC-MS: m/z 631.3 (M+H)	Example 63 and 3-amino-propanol

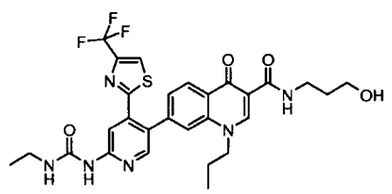
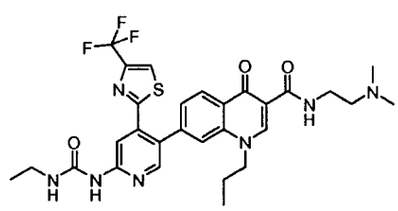
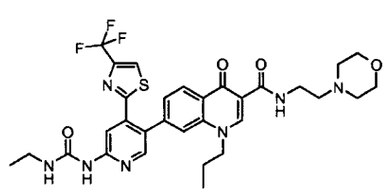
Ex	Compound	Data	SM
338	N-[2-(dimethylamino)ethyl]-7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-1-(3-methylbutyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 0.82 (d, 6H), 1.12 (t, 3H), 1.39 (q, 2H), 1.48 (m, 1H), 2.29 (s, 6H), 2.44 (s, 2H), 3.21 (q, 2H), 3.44 (t, 2H), 4.41 (t, 2H), 7.45 (d, 1H), 7. 6 (s, 1H), 7.80 (s, 1H), 8.22 (s, 1H), 8.41 (d, 2H), 8.52 (s, 1H), 8.85 (s,1H), 9.48 (s, 1H), 10.0 (t, 1H) LC-MS: m/z 643.74 (M+H)	Example 63 and 2-(N,N-dimethyl-amino)-ethanamine
339	7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-1-(3-methylbutyl)-N-[2-(morpholin-4-yl)ethyl]-4-oxo-1,4-dihydroquinoline-3-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6): δ 0.84 (d, 6H), 1.14 (t, 3H), 1.38 (d, 2H), 1.54 (m, 1H), 3.21 (q, 4H), 3.60 (m, 6H), 3.96 (s, 2H), 4.40 (s, 2H), 7.52 (d, 2H), 7.79 (s, 1H), 8.22 (s, 1H), 8.39 (d, 2H), 8.54 (s, 1H), 8.88 (s, 1H), 9.44 (s, 1H), 10.18 (s,1H). LC-MS: m/z 686.3 (M+H)	Example 63 and 2-morpholino-ethanamine

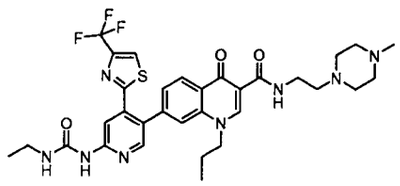
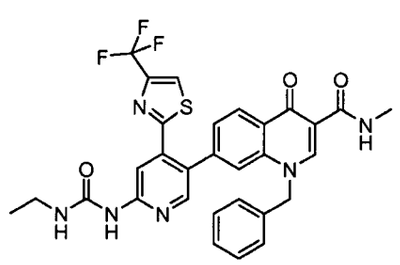
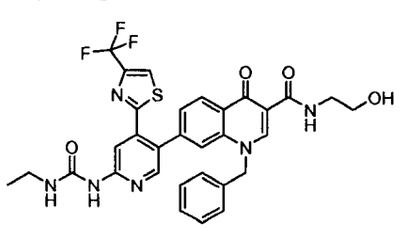
Ex	Compound	Data	SM
340	7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-1-(3-methylbutyl)-N-[2-(4-methylpiperazin-1-yl)ethyl]-4-oxo-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 0.89 (d, 6H), 1.08 (t, 3H), 1.38 (m, 4H), 2.19 (s, 4H), 2.26 (m, 5H), 3.21 (m, 3H), 3.42 (m, 3H), 4.40 (s, 2H), 7.21 (m, 8H), 7.64 (m, 3H), 7.79 (s, 1H), 8.21 (s, 1H), 8.38 (s, 1H), 8.54 (s, 1H), 8.81 (s, 1H), 9.43 (s, 1H), 9.95 (s, 1H). LC-MS: m/z 699.9 (M+H)	Example 63 and 2-(4-methyl-piperazino)-ethanamine
341	7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-N-methyl-1-(2-methylpropyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 0.73 - 0.75 (d, 6H), 1.11 (t, 3H), 1.63 (m, 1H), 2.86 - 2.89 (m, 3H), 3.19 (t, 2H), 4.21 - 4.23 (d, 2H), 7.51 - 7.54 (m, 1H), 7.60 (m, 1H), 7.78 (s, 1H), 8.18 (s, 1H), 8.39 (t, 2H), 8.51 (s, 1H), 8.80 (s, 1H), 9.48 (s, 1H), 9.78 - 9.79 (m, 1H). LC-MS: m/z 573.3 (M+H)	Example 64 and methylamine

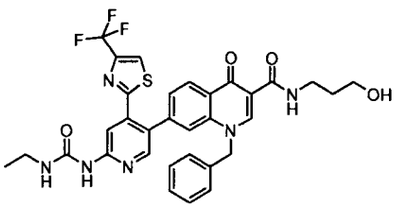
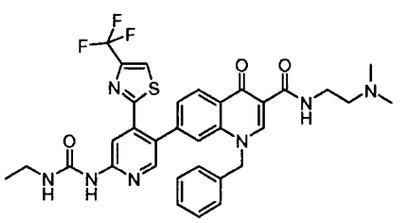
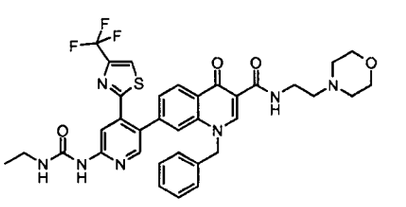
Ex	Compound	Data	SM
342	7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-N-(2-hydroxyethyl)-1-(2-methylpropyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 0.75 (d, 6H), 1.11 (t, 3H), 1.63 (m, 1H), 3.21 (m, 2H), 3.41 (m, 2H), 3.54 (m, 2H), 4.22 (d, 2H), 4.81 (t, 1H), 7.52 (d, 1H), 7.60 (br s, 1H), 7.78 (s, 1H), 8.18 (s, 1H), 8.38 - 8.40 (m, 2H), 8.52 (s, 1H), 8.81 (s, 1H), 9.48 (s, 1H), 10.05 (t, 1H). LC-MS: m/z 603.3 (M+H)	Example 64 and ethanolamine
343	7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-N-(3-hydroxypropyl)-1-(2-methylpropyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 0.74 - 0.75 (m, 6H), 1.11 (t, 3H), 1.65-1.71 (m, 3H), 3.17-3.24 (m, 2H), 3.37-3.49 (m, 2H), 3.49-3.51 (m, 2H), 4.20-4.22 (m, 2H), 4.51 (br s, 1H), 7.34-7.45 (m, 2H), 7.78 (s, 1H), 8.18 (s, 1H), 8.37-8.39 (m, 2H), 8.50 (s, 1H), 8.79 (s, 1H), 9.48 (s, 1H), 9.95 (s, 1H). LC-MS: m/z 617.2 (M+H)	Example 64 and 3-amino-propanol

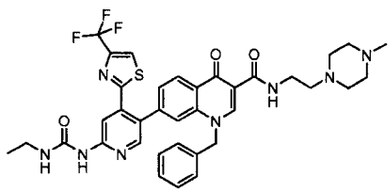
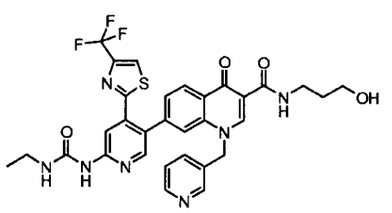
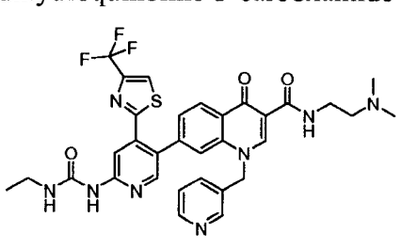
Ex	Compound	Data	SM
344	N-[2-(dimethylamino)ethyl]-7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-1-(2-methylpropyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 0.75 (d, 6H), 1.11 (t, 3H), 1.61 (m, 1H), 2.76 (br s, 6H), 3.19 (m, 4H), 3.68 (m, 2H), 4.22 (d, 2H), 7.51 (m, 2H), 7.82 (s, 1H), 8.11 (s, 1H), 8.31 - 8.42 (m, 2H), 8.55 (s, 1H), 8.87 (s, 1H), 9.41 (s, 1H), 10.12 (t, 1H). LC-MS: m/z 630.4 (M+H)	Example 64 and 2-(N,N-dimethyl-amino)-ethanamine
345	7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-1-(2-methylpropyl)-N-[2-(morpholin-4-yl)ethyl]-4-oxo-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 0.75 (d, 6H), 1.12 (m, 4H), 1.64 (m, 2H), 2.47 (m, 4H), 3.24 (m, 2H), 3.49 (m, 2H), 3.61 (m, 4H), 4.22 (d, 2H), 7.53 (m, 1H), 7.61 (t, 1H), 7.78 (s, 1H), 8.18 (s, 1H), 8.40 (m, 2H), 8.52 (s, 1H), 8.79 (s, 1H), 9.49 (s, 1H), 10.02 (t, 1H). LC-MS: m/z 672.3 (M+H)	Example 64 and 2-morpholino-ethanamine

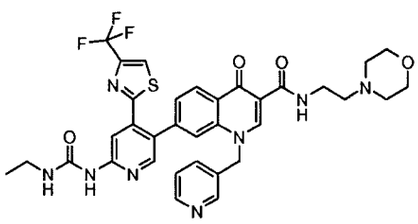
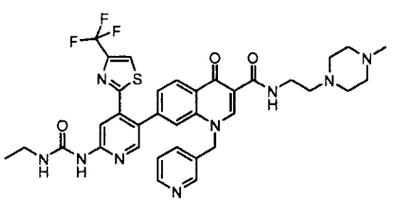
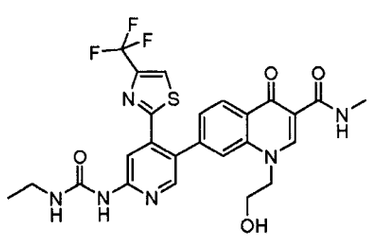
Ex	Compound	Data	SM
346	7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-N-[2-(4-methylpiperazin-1-yl)ethyl]-1-(2-methylpropyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, CD_3OD): δ 0.91 (d, 6H), 1.12 (t, 3H), 1.82 (m, 1H), 2.18 (s, 3H), 2.65 (m, 8H), 3.19 (q, 2H), 3.59 (q, 2H), 4.18 (d, 2H), 7.54 (d, 1H), 7.69 (s, 1H), 7.81 (s, 1H), 8.22 (s, 1H), 8.40 (s, 1H), 8.51 (d, 1H), 8.79 (s, 1H). LC-MS: m/z 685.3 (M+H)	Example 65 and 2-(4-methyl-piperazino)-ethanamine
347	7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-N-methyl-4-oxo-1-propyl-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 0.78 (t, 3H), 1.11 (t, 3H), 1.52 (m, 2H), 2.87 (m, 3H), 3.19 (m, 2H), 4.31 (t, 2H), 7.41 (d, 1H), 7.62 (br s, 1H), 7.82 (s, 1H), 8.21 (s, 1H), 8.36 - 8.39 (m, 2H), 8.49 (s, 1H), 8.87 (s, 1H), 9.42 (s, 1H), 9.79 - 9.78 (m, 1H). LC-MS: m/z 559.3 (M+H)	Example 65 and methylamine
348	7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-N-(2-hydroxyethyl)-4-oxo-1-propyl-1,4-dihydroquinoline-3-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6): δ 0.78 (t, 3H), 1.10 (t, 3H), 1.50-1.55 (m, 2H), 3.19-3.22 (m, 2H), 3.40-3.42 (m, 2H), 3.52-3.53 (m, 2H), 4.37 (m, 2H), 4.81 (br s, 1H), 7.47-7.51 (m, 1H), 7.71 (br s, 1H), 7.84 (s, 1H), 8.22 (m, 1H), 8.36-8.39 (m, 2H), 8.49 (s, 1H), 8.84 (s, 1H), 9.58 (s, 1H), 10.03 (s, 1H). LC-MS: m/z 589.19 (M+H)	Example 65 and ethanolamine

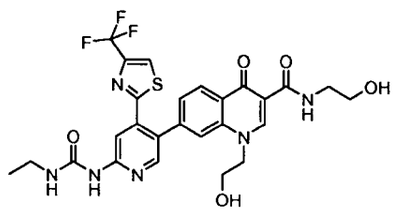
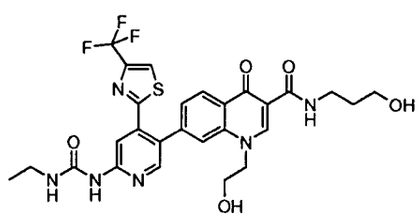
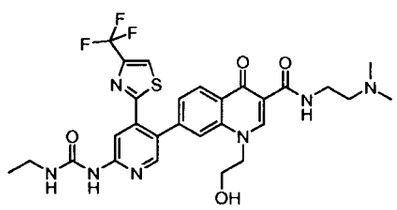
Ex	Compound	Data	SM
349	7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-N-(3-hydroxypropyl)-4-oxo-1-propyl-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 0.78 (t, 3H), 1.11 (t, 3H), 1.50 - 1.55 (m, 2H), 1.66 - 1.69 (m, 2H), 3.21 (t, 2H), 3.41 (m, 2H), 3.47-3.51 (m, 2H), 4.37 (t, 2H), 4.55 (t, 1H), 7.47-7.49 (d, 1H), 7.61 (br s, 1H), 7.85 (s, 1H), 8.20 (s, 1H), 8.36-8.39 (m, 2H), 8.49 (s, 1H), 8.83 (s, 1H), 9.48 (s, 1H), 9.91 (t, 1H). LC-MS: m/z 603.3 (M+H)	Example 65 and 3-amino-propanol
350	N-[2-(dimethylamino)ethyl]-7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-4-oxo-1-propyl-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 0.782 (t, 3H), 1.09 (t, 3H), 1.49-1.55 (m, 2H), 2.20 (s, 6H), 2.41 (t, 2H), 3.18-3.24 (m, 2H), 3.42-3.45 (m, 2H), 4.37 (t, 2H), 7.31 (m, 1H), 7.61 (m, 1H), 7.84 (s, 1H), 8.21 (s, 1H), 8.36-8.40 (m, 2H), 8.49 (s, 1H), 8.84 (s, 1H), 9.48 (s, 1H), 9.91 (t, 1H). LC-MS: m/z 616 (M+H)	Example 65 and 2-(N,N-dimethyl-amino)-ethanamine
351	7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-N-[2-(morpholin-4-yl)ethyl]-4-oxo-1-propyl-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 0.782 (t, 3H), 1.11 (t, 3H), 1.50-1.55 (m, 2H), 2.43 - 2.41 (m, 4H), 3.18 -3.22 (m, 2H), 3.44-3.49 (m, 3H), 3.59-3.61 (m, 5H), 4.37 (t, 2H), 7.46-7.49 (d, 1H), 7.61 (br s, 1H), 7.85 (s, 1H), 8.20 (s, 1H), 8.36-8.40 (m, 2H), 8.49 (s, 1H), 8.84 (s, 1H), 9.48 (s, 1H), 10.07 (t, 1H). LC-MS: m/z 658.3 (M+H)	Example 65 and 2-morpholino-ethanamine

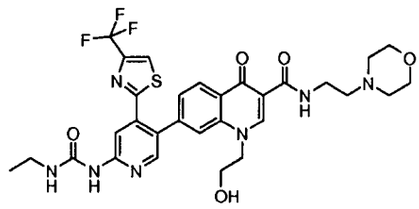
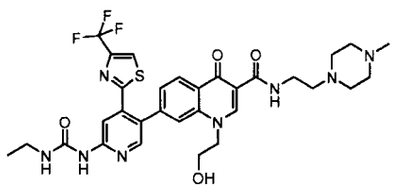
Ex	Compound	Data	SM
352	7-{6-[(Ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-N-[2-(4-methylpiperazin-1-yl)ethyl]-4-oxo-1-propyl-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, CD_3OD): δ 0.92 (q, 3H), 1.11 (q, 3H), 1.64 (q, 2H), 2.38 (s, 3H), 2.61 (m, 8H), 3.14 (q, 2H), 3.59 (t, 2H), 4.29 (t, 2H), 7.48 (d, 1H), 7.78 (s, 1H), 7.84 (s, 1H), 8.21 (s, 1H), 8.41 (s, 1H), 8.42 (d, 1H), 8.83 (s, 1H). LC-MS: m/z 671.4 (M+H)	Example 65 and 2-(4-methylpiperazino)-ethanamine
353	1-Benzyl-7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-N-methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 1.10 (t, 3H), 2.88-2.89 (m, 3H), 3.16-3.23 (m, 2H), 5.74 (s, 2H), 7.10-7.08 (m, 2H), 7.19-7.25 (m, 3H), 7.40-7.42 (m, 1H), 7.51-7.53 (br s, 1H), 7.79 (s, 1H), 8.16 (s, 1H), 8.22 (s, 1H), 8.32 (s, 1H), 8.37-8.38 (s, 1H), 9.07 (s,1H). 9.42 (s,1H). 9.75-9.77 (m,1H). LC-MS: m/z 607.3 (M+H)	Example 66 and methylamine
354	1-Benzyl-7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-N-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 1.1 (t, 3H), 3.16-3.23 (m, 2H), 3.41-3.45 (m, 2H), 3.53-3.57 (m, 2H), 5.74 (s, 1H), 7.08-7.10 (m, 2H), 7.19-7.42 (m, 1H), 7.51-7.25 (m, 3H), 7.40-7.42 (m, 1H), 7.53 (br s, 1H), 7.79 (s, 1H), 8.17 (s, 1H), 8.22 (s, 1H), 8.32 (s,1H). 8.36-8.38 (s,1H). 9.07 (s,1H). 9.42 (s,1H). 10.02 (m,1H). LC-MS: m/z 637.3 (M+H)	Example 66 and ethanolamine

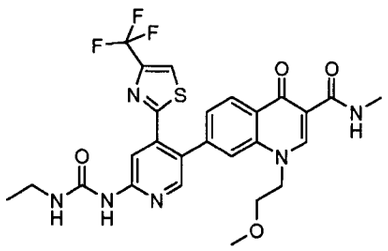
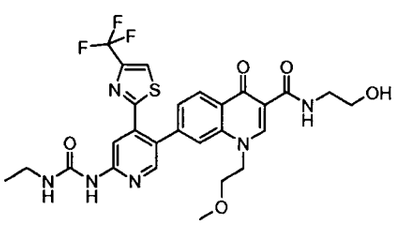
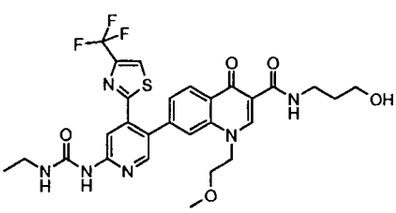
Ex	Compound	Data	SM
355	1-Benzyl-7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-N-(3-hydroxypropyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 1.08-1.11 (t, 3H), 1.66-1.73 (m, 2H), 3.16-3.23 (m, 2H), 3.39-3.51 (m, 2H), 3.48-3.53 (m, 2H), 4.54 (t, 1H), 7.08-7.10 (m, 2H), 7.19-7.25 (m, 3H), 7.40-7.42 (m, 1H), 7.51-7.53 (br s, 1H), 7.79 (s, 1H), 8.17 (s, 1H), 8.23 (s, 1H), 8.32-8.38 (m,2H). 9.06 (s,1H). 9.42 (s,1H). 9.94 (t,1H). LC-MS: m/z 651.3 (M+H)	Example 66 and 3-amino-propanol
356	1-Benzyl-N-[2-(dimethylamino)ethyl]-7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-4-oxo-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 1.09 (t, 3H), 3.21 (s, 6H), 2.43 (m, 2H), 3.16-3.29 (m, 2H), 3.43-3.47 (m, 2H), 5.73 (s, 2H), 7.08-7.10 (m, 2H), 7.19-7.25 (m, 3H), 7.40-7.42 (m, 1H), 7.52 (br s, 1H), 7.78 (s, 1H), 8.17 (s, 1H), 8.22 (s, 1H), 8.33-8.38 (m,2H). 9.65 (s,1H). 9.42 (s,1H). 9.95 (m,1H). LC-MS: m/z 664.4 (M+H)	Example 66 and 2-(N,N-dimethyl-amino)-ethanamine
357	1-Benzyl-7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-N-[2-(morpholin-4-yl)ethyl]-4-oxo-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 1.10 (t, 3H), 2.32 (m, 4H), 3.20 (q, 2H), 3.48 (d, 2H), 3.61 (s, 4H), 5.74 (s, 2H), 7.10 (d, 2H), 7.21 (d, 3H), 7.39 (d, 1H), 7.41 (s, 1H), 7.79 (s, 1H), 8.17 (d, 2H), 8.32 (m, 2H), 9.06 (s, 1H), 9.43 (s, 1H), 9.99 (s, 1H). LC-MS: m/z 706.3 (M+H)	Example 66 and 2-morpholino-ethanamine

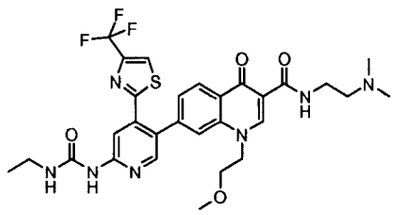
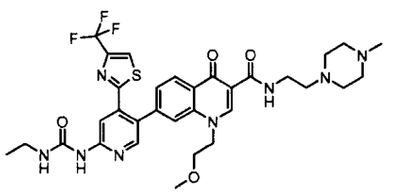
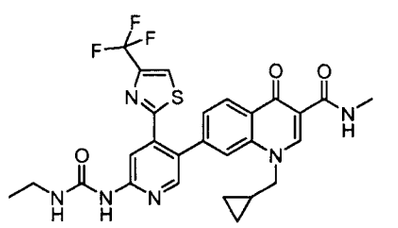
Ex	Compound	Data	SM
358	1-Benzyl-7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-N-[2-(4-methylpiperazin-1-yl)ethyl]-4-oxo-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 1.09 (t, 3H), 2.16 (s, 3H), 2.31 – 2.34 (m, 4H), 3.16 – 3.23 (m, 2H), 3.44 – 3.48 (q, 2H), 5.73 (s, 2H), 7.08 – 7.10 (m, 2H), 7.19 – 7.24 (m, 2H), 7.39 – 7.41 (d, 1H), 7.53 (m, 1H), 7.79 (s, 1H), 8.17 (s, 1H), 8.23 (s, 1H), 8.31 (s, 1H), 8.37 – 8.39 (d, 1H), 9.05 (s, 1H), 9.43 (s, 1H), 9.94 – 9.96 (t, 1H). LC-MS: m/z 719.89 (M+H)	Example 66 and 2-(4-methylpiperazino)-ethanamine
359	7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-N-(3-hydroxypropyl)-4-oxo-1-(pyridin-3-ylmethyl)-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 1.10 (t, 3H), 1.70 (m, 2H), 3.21 (q, 2H), 3.40 (m, 5H), 4.57 (s, 1H), 5.80 (s, 2H), 7.22 (m, 1H), 7.42 (d, 2H), 7.58 (s, 1H), 7.84 (s, 1H), 8.19 (d, 2H), 8.33 (m, 4H), 9.12 (s, 1H), 9.46 (s, 1H), 9.93 (t, 1H). LC-MS: m/z 652 (M+H)	Example 67 and 3-amino-propanol
360	N-[2-(dimethylamino)ethyl]-7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-4-oxo-1-(pyridin-3-ylmethyl)-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, CD_3OD): δ 1.19 (t, 3H), 2.69 (s, 6H), 3.73 (q, 2H), 5.73 (s, 2H), 7.31 (m, 9H), 7.69 (s, 1H), 7.86 (s, 1H), 8.04 (s, 1H), 8.20 (s, 1H), 8.40 (m, 2H), 8.48 (d, 1H), 9.08 (s, 1H). LC-MS: m/z 665.4 (M+H)	Example 67 and 2-(N,N-dimethyl-amino)-ethanamine

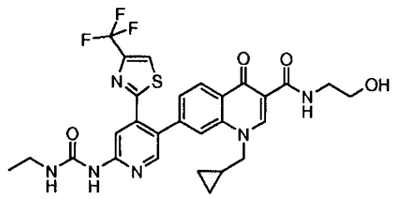
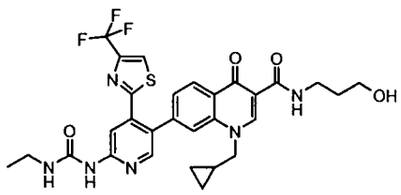
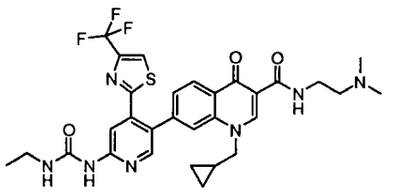
Ex	Compound	Data	SM
361	7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-N-[2-(morpholin-4-yl)ethyl]-4-oxo-1-(pyridin-3-ylmethyl)-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 1.08 (t, 3H), 2.33 (m, 6H), 3.18 (q, 2H), 3.48 (d, 2H), 3.61 (s, 4H), 5.80 (s, 2H), 7.22 (m, 2H), 7.36 (m, 4H), 7.56 (s, 2H), 7.84 (s, 1H), 8.19 (d, 2H), 8.40 (m, 4H), 9.11 (s, 1H), 9.45 (s, 1H), 9.99 (s, 1H). LC-MS: m/z 707.4 (M+H)	Example 67 and 2-morpholino-ethanamine
362	7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-N-[2-(4-methylpiperazin-1-yl)ethyl]-4-oxo-1-(pyridin-3-ylmethyl)-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, CD_3OD): δ 1.19 (t, 3H), 2.46 (s, 2H), 2.68 (m, 4H), 2.76 (m, 4H), 3.60 (q, 2H), 5.74 (s, 2H), 7.30 (m, 8H), 7.69 (s, 1H), 7.86 (s, 1H), 8.03 (s, 1H), 8.20 (s, 1H), 8.41 (s, 2H), 8.49 (d, 1H), 9.08 (s, 1H). LC-MS: m/z 720.45 (M+H)	Example 67 and 2-(4-methylpiperazino)-ethnamine
363	7-{6-[(Ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-1-(2-hydroxyethyl)-N-methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 1.09 – 1.12 (t, 3H), 2.86 – 2.87 (m, 3H), 3.19 – 3.22 (m, 2H), 3.59 – 3.60 (m, 2H), 4.49 (br s, 1H), 4.95 – 4.98 (t, 1H), 7.39 – 7.41 (d, 1H), 7.63 (br s, 1H), 7.98 (s, 1H), 8.24 (s, 1H), 8.34 – 8.37 (m, 2H), 8.48 (s, 1H), 8.87 (s, 1H), 9.48 (s, 1H), 9.79 – 9.80 (d, 1H). LC-MS: m/z 561.3 (M+H)	Example 68 and methylamine

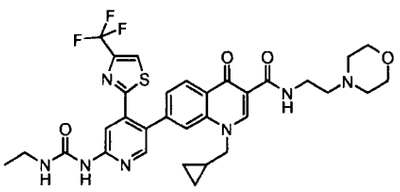
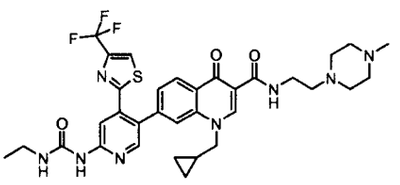
Ex	Compound	Data	SM
364	7-{6-[(Ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-N,1-bis(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 1.11(t, 3H), 3.19-3.22 (m, 2H), 3.40-3.42 (m, 2H), 3.52-3.60 (m, 4H), 4.83 (t, 1H), 4.97 (t, 1H), 7.40-7.42 (d, 1H), 7.6 (br s, 1H), 7.97 (s, 1H), 8.24 (s, 1H), 8.33-8.38 (m,2H). 8.4 (s,1H). 8.78 (s, 1H), 9.48 (s,1H). 10.06 (s,1H). LC-MS: m/z 591.3 (M+H)	Example 68 and ethanolamine
365	7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-1-(2-hydroxyethyl)-N-(3-hydroxypropyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 1.12(t, 3H), 1.7 (m, 2H), 3.21-3.22 (m, 2H), 3.40-3.42 (m, 2H), 3.49-3.52 (m, 2H), 3.6 (br s, 2H), 4.49 (br s, 2H), 4.54-4.57 (t, 1H), 4.9 (t, 1H), 7.4-7.42 (d, 1H). 7.6 (br s,1H). 7.9 (s, 1H), 8.24 (s,1H). 8.33-8.37 (m, 2H) 8.48 (s, 1H), 8.78 (s, 1H), 9.48 (s, 1H), 9.98 (t,1H). LC-MS: m/z 605.2 (M+H)	Example 68 and 3-amino-propanol
366	N-[2-(dimethylamino)ethyl]-7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 1.10 (t, 3H), 2.67 – 2.73 (m, 6H), 3.21 (m, 4H), 3.60 – 3.66 (m, 4H), 4.50 (s, 1H), 4.98 (t, 1H), 7.41 – 7.43 (m, 1H), 7.59 (br s, 2H), 7.99 (s, 1H), 8.24 (s, 1H), 8.34 – 8.38 (m, 1H), 8.50 (s, 1H), 8.79 (s, 1H), 9.49 (s, 1H), 10.12 (br s, 1H). LC-MS: m/z 618.2 (M+H)	Example 68 and 2-(N,N-dimethyl-amino)-ethanamine

Ex	Compound	Data	SM
367	7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-1-(2-hydroxyethyl)-N-[2-(morpholin-4-yl)ethyl]-4-oxo-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 1.11 (br s, 3H), 2.43 (m, 4H), 3.21 (br s, 3H), 3.46-3.60 (m, 9H), 7.39-7.41 (s, 1H), 7.61 (br s, 1H), 7.91 (s, 1H), 8.24 (s, 1H), 8.34-8.37 (m, 3H), 8.77 (s, 1H), 9.48 (s, 1H), 10.11 (br s, 1H). LC-MS: m/z 660.2 (M+H)	Example 68 and 2-morpholino-ethanamine
368	7-{6-[(Ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-1-(2-hydroxyethyl)-N-[2-(4-methylpiperazin-1-yl)ethyl]-4-oxo-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, CD_3OD): δ 1.21 (t, 3H), 2.45 (s, 3H), 2.67 (m, 8H), 3.59 (s, 2H), 3.79 (s, 2H), 4.49 (s, 2H), 7.43 (d, 1H), 7.88 (s, 2H), 8.16 (s, 1H), 8.41 (m, 2H), 8.86 (s, 1H). LC-MS: m/z 673.3 (M+H)	Example 68 and 2-(4-methylpiperazino)-ethanamine

Ex	Compound	Data	SM
369	7-{6-[(Ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-1-(2-methoxyethyl)-N-methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 1.12 (t, 3H), 2.83 (s, 3H), 3.18 (m, 5H), 3.46 (s, 2H), 4.59 (s, 2H), 7.41 (d, 1H), 7.58 (s, 1H), 7.95 (s, 1H), 8.22 (s, 1H), 8.34 (d, 2H), 8.48 (s, 1H), 8.78 (s, 1H), 9.42 (s, 1H), 9.76 (s,1H). LC-MS: m/z 575.3 (M+H)	Example 69 and methylamine
370	7-{6-[(Ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-N-(2-hydroxyethyl)-1-(2-methoxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 1.12 (t, 3H), 3.18 (s, 3H), 3.19 (m, 2H), 5.45 (m, 6H), 4.58 (s, 2H), 4.69 (s, 1H), 7.41 (d, 1H), 7.56 (s, 1H), 7.91 (s, 1H), 8.21 (s, 1H), 8.38 (m, 2H), 8.44 (s, 1H), 8.79 (s, 1H), 9.39 (s, 1H), 9.99 (s, 1H). LC-MS: m/z 605.3 (M+H)	Example 69 and ethanolamine
371	7-{6-[(Ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-N-(3-hydroxypropyl)-1-(2-methoxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 1.11 (t, 3H), 1.65 (s, 2H), 3.18 (s, 3H), 3.39 (m, 6H), 4.22 (s, 2H), 4.58 (s, 1H), 7.38 (m, 2H), 7.92 (s, 1H), 8.22 (s, 1H), 8.38 (m, 3H), 8.78 (s, 1H), 9.38 (s, 1H), 9.98 (s, 1H). LC-MS: m/z 619.3 (M+H)	Example 69 and 3-amino-propanol

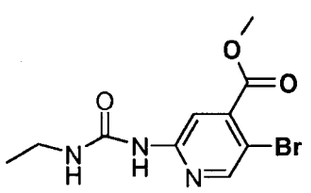
Ex	Compound	Data	SM
372	N-[2-(dimethylamino)ethyl]-7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-1-(2-methoxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 1.11 (t, 3H), 2.45 (s, 6H), 2.96 (s, 2H), 3.18 (s, 3H), 3.21 (q, 2H), 3.46 (s, 2H), 3.62 (s, 2H), 4.58 (s, 2H), 7.38 (m, 2H), 7.94 (s, 1H), 8.22 (s, 1H), 8.35 (m, 2H), 8.45 (s, 1H), 8.78 (s, 1H), 9.40 (s, 1H), 10.02 (s, 1H). LC-MS: m/z 632.3 (M+H)	Example 69 and 2-(N,N-dimethyl-amino)-ethanamine
373	7-{6-[(Ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-1-(2-methoxyethyl)-N-[2-(4-methylpiperazin-1-yl)ethyl]-4-oxo-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, CD_3OD): δ 1.12 (t, 3H), 2.78 (s, 2H), 2.86 (s, 3H), 3.21 (s, 3H), 3.38 (m, 4H), 3.59 (s, 4H), 4.58 (s, 2H), 7.26 (s, 1H), 7.84 (s, 2H), 8.21 (s, 1H), 8.38 (m, 2H), 8.82 (s, 1H). LC-MS: m/z 687.30 (M+H)	Example 69 and 2-(4-methylpiperazino)-ethanamine
374	1-(Cyclopropylmethyl)-7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-N-methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 0.39 (dd, 4H), 1.02 (m, 4H), 2.82 (d, 3H), 3.21 (q, 2H), 4.38 (d, 2H), 7.41 (m, 3H), 7.61 (s, 2H), 7.99 (s, 1H), 8.21 (s, 1H), 8.36 (m, 3H), 8.88 (s, 1H), 9.48 (s, 1H), 9.79 (s, 1H). LC-MS: m/z 571.4 (M+H)	Example 70 and methylamine

Ex	Compound	Data	SM
375	1-(Cyclopropylmethyl)-7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-N-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 0.38 (d, 4H), 1.05 (m, 1H), 1.16 (t, 3H), 3.21 (t, 2H), 3.39 (t, 2H), 3.51 (t, 2H), 4.29 (d, 2H), 4.81 (t, 1H), 7.48 (d, 1H), 7.61 (s, 1H), 7.98 (s, 1H), 8.24 (s, 1H), 8.38 (m, 2H), 8.48 (s, 1H), 8.91 (s, 1H), 9.48 (s, 1H), 10.4 (s, 1H). LC-MS: m/z 601.2 (M+H)	Example 70 and ethanolamine
376	1-(Cyclopropylmethyl)-7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-N-(3-hydroxypropyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 0.38 (d, 4H), 1.04 (m, 4H), 164 (s, 2H), 3.21 (q, 2H), 3.41 (dd, 4H), 4.28 (m, 2H), 4.52 (s, 1H), 7.44 (d, 1H), 7.51 (s, 1H), 7.96 (s, 1H), 8.21 (s, 1H), 8.36 (m, 3H), 8.86 (s, 1H), 9.46 (s, 1H), 9.94 (s, 1H) LC-MS: m/z 615.2 (M+H)	Example 70 and 3-amino-propanol
377	1-(Cyclopropylmethyl)-N-[2-(dimethylamino)ethyl]-7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-4-oxo-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 0.38 (d, 4H), 0.94 (s, 1H), 1.14 (t, 3H), 2.68 (s, 2H), 2.96 (d, 3H), 3.18 (m, 4H), 3.46 (m, 10H), 4.18 (d, 2H), 6.98 (s, 2H), 7.38 (d, 1H), 7.61 (s, 1H), 7.94 (d, 1H), 8.22 (s, 1H), 8.26 - 8.54 (m, 5H), 9.48 (s, 1H). LC-MS: m/z 628.3 (M+H)	Example 70 and 2-(N,N-dimethyl-amino)-ethanamine

Ex	Compound	Data	SM
378	1-(Cyclopropylmethyl)-7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-N-[2-(morpholin-4-yl)ethyl]-4-oxo-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 0.38 (d, 4H), 0.94 (s, 1H), 1.14 (t, 3H), 3.19 (s, 3H), 3.49 (q, 2H), 3.60 (s, 3H), 4.31 (t, 2H), 7.43 (d, 1H), 7.58 (s, 1H), 7.98 (s, 1H), 8.21 (s, 1H), 8.38 (m, 2H), 8.48 (s, 1H), 8.90 (s, 1H), 9.48 (s, 1H), 10.06 (s, 1H). LC-MS: m/z 670.2 (M+H)	Example 70 and 2-morpholino-ethanamine
379	1-(Cyclopropylmethyl)-7-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-N-[2-(4-methylpiperazin-1-yl)ethyl]-4-oxo-1,4-dihydroquinoline-3-carboxamide 	^{1}H NMR (400 MHz, DMSO-d_6): δ 0.37 – 0.43 (m, 4H), 1.01 (m, 1H), 1.11 (t, 3H), 2.24 – 2.33 (m, 4H), 3.18 – 3.24 (m, 3H), 3.43 – 3.36 (m, 2H), 4.30 – 4.32 (d, 2H), 7.46 – 7.48 (d, 1H), 7.61 (br s, 1H), 7.97 (s, 1H), 8.21 (s, 1H), 8.36 – 8.48 (m, 3H), 8.88 (s, 1H), 9.49 (s, 1H), 9.97 – 9.99 (t, 1H).	Example 70 and 2-(4-methylpiperazino)-ethanamine

Intermediate 1

Methyl 5-bromo-2-(3-ethylureido)isonicotinate



A solution of methyl 2-amino-5-bromoisonicotinate (50g, 216.5 mmol) in chloroform (500mL) was placed into a sealed tube. Ethyl isocyanate (51 mL, 649.4 mmol) was then added in two parts over the course of 6 hours. The sealed tube was insulated and heated at 40°C for 3 d. The reaction mixture was then cooled to room temperature, concentrated under reduced pressure, and extracted with ethyl acetate (3 L) and water (1 L). The ethyl acetate

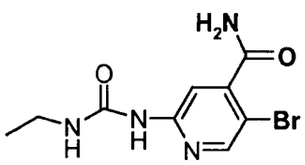
layer was then dried with sodium sulfate, filtered, and concentrated under reduced pressure to yield 68.4 g of a pale yellow solid (96%).

MS (ESP): 302 ($M+H^+$) for $C_{10}H_{12}BrN_3O_3$

^1H NMR ($CDCl_3$): δ 1.22 (t, 3H), 3.41 (q, 2H), 7.22 (s, 1H), 7.30 (s, 1H), 8.38 (s, 1H), 8.70 (s, 1H), 9.42 (s, 1H)

Intermediate 2

5-Bromo-2-(3-ethylureido)isonicotinamide



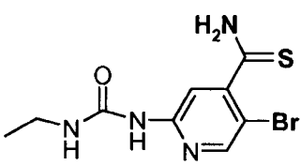
A solution of methyl 5-bromo-2-(3-ethylureido)isonicotinate (Intermediate 1, 56.22 g, 186.0 mmol) in 7N ammonia in methanol (1 L) was allowed to stir at room temperature in a sealed flask for 1 ½ d. The precipitate that formed was collected by filtration, rinsed with acetonitrile (500 mL), and then dried on the high vacuum pump overnight, yielding 50.8 g of a solid (95.1%).

MS (ESP): 287 ($M+H^+$) for $C_9H_{11}BrN_4O_2$

^1H NMR (DMSO-d_6): δ 1.1 (t, 3H), 3.18 (q, 2H), 7.40 (s, 1H), 7.60 (s, 1H), 7.80 (s, 1H), 8.1 (s, 1H), 8.38 (s, 1H), 9.39 (s, 1H)

Intermediate 3

5-Bromo-2-(3-ethylureido)pyridine-4-carbothioamide



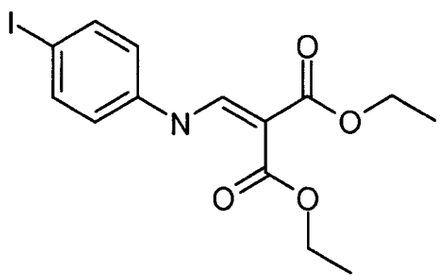
A solution of 5-bromo-2-(3-ethylureido)isonicotinamide (Intermediate 2, 52.17 g, 181.73 mmol), Lawesson's Reagent (73.50 g, 181.73 mmol), and tetrahydrofuran (840 mL) was prepared and stirred with heating at reflux overnight. After approximately 12 h, it was confirmed by LCMS that the reaction had gone to completion; therefore, stirring was stopped and a bright yellow precipitate was allowed to settle to ease filtration. The precipitate was then filtered and subsequently washed with 500 mL of additional tetrahydrofuran. The solid was then dried in the vacuum oven at 50°C for 30 min, yielding 51 g of a bright yellow solid (92.5%).

MS (ESP): 304 ($M+H^+$) for $C_9H_{11}BrN_4OS$

^1H NMR (DMSO-d_6): δ 1.1 (t, 3H), 3.18 (q, 2H), 7.38 (s, 1H), 7.50 (s, 1H), 8.28 (s, 1H), 9.25 (s, 1H), 9.80 (s, 1H), 10.28 (s, 1H)

Intermediate 4

Diethyl 2-((4-iodophenylamino)methylene)malonate

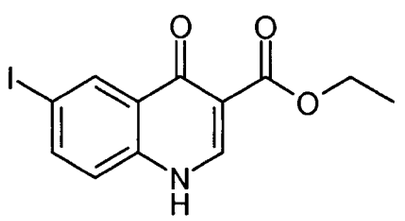


A mixture of ethoxymethylene malonic acid diethyl ester (20.1 mL, 0.10 mol) and 4-iodoaniline (22 g, 0.10 mole) in toluene (300 ml) was heated to reflux for 1 h. After this period of time, solvents were removed under vacuum, and the crude material was precipitated in methyl *tert*-butyl ether and the resulting white solid was filtered, and dried under vacuum to give 30 g product.

MS (ESP): 390 ($M+H^+$) for $C_{14}H_{16}INO_4$

Intermediate 5

Ethyl 6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate



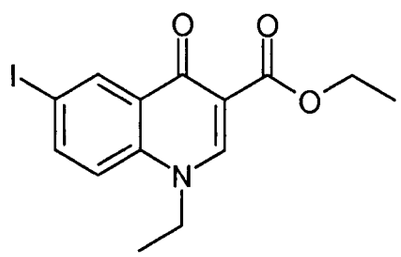
Method A: Diethyl 2-((4-iodophenylamino)methylene)malonate (Intermediate 4, 10 g, 25 mmol) was added to a round-bottom flask that was equipped with thermocouple and stirrer, then Eaton's reagent (26 ml) was added to the flask. The reaction mixture was stirred at 95°C for 6 h under nitrogen. After this period of time, the reaction mixture was cooled to 5°C and slowly transferred into an excess of saturated sodium carbonate solution (50 ml) that was cooled to 10°C. The precipitated solid was filtered, washed with water (~20 ml) and dried under vacuum to give product (80% yield).

Method B: Phenyl ether (70 ml) was heated with stirring to 240°C, then diethyl 2-((4-iodophenylamino)methylene)malonate (Intermediate 4, 10 g, 25 mmol) was gradually added and the resulting mixture was refluxed at 280°C for 1 hour. After cooling the reaction to room temperature, the resulting solid was collected by filtration, washed with methyl tert-butyl ether and dichloromethane to give a white solid (30% yield).

MS (ESP): 344 ($M+H^+$) for $C_{12}H_{10}INO_3$

Intermediate 6

Ethyl 1-ethyl-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate

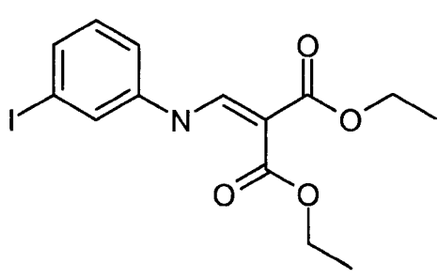


To ethyl 6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate (Intermediate 5, 5 g, 0.013 mol) in dimethylformamide (26 ml, 0.2M) were added potassium carbonate (4.50g, 0.033 mole) and ethyl bromide (5.71 g, 0.053 mole). The reaction was stirred at 90°C overnight then the solvent was removed *in vacuo*. The residue was taken up in ethyl acetate washed with water, brine, and dried over sodium sulfate. Solvents were removed under vacuum and the residue was purified by flash column chromatography on silica gel using (dichloromethane-ethyl acetate) to give the desired quinolone product (90%) and trace of O-alkylated impurity.

MS (ESP): 372 ($M+H^+$) for $C_{14}H_{14}INO_3$

Intermediate 7

Diethyl 2-((3-iodophenylamino)methylene)malonate



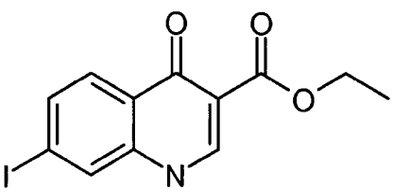
A mixture of ethoxymethylene malonic acid diethyl ester (13.72 g, 0.068 mol) and 3-iodoaniline (15 g, 0.068 mole) in toluene (230 ml) was refluxed for 1 h. After this period of time, solvents were

removed under vacuum, and the crude material was precipitated in methyl *tert*-butyl ether and the resulting white solid was filtered, and dried under vacuum (24.3 g, 93%).

MS (ESP): 390 ($M+H^+$) for $C_{14}H_{16}INO_4$

Intermediate 8

Ethyl 7-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate



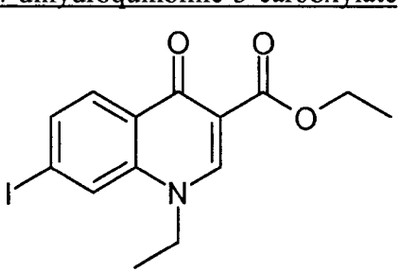
Method A: Diethyl 2-((3-iodophenylamino)methylene)malonate (Intermediate 7, 10 g, 25 mmol) was added to a round-bottom flask that was equipped with thermocouple and stirrer, then Eaton's reagent (26 ml) was added to the flask. The reaction mixture was stirred at 95°C for 6 h under nitrogen. After this period of time, the reaction mixture was cooled to 5°C and slowly transferred into an excess of saturated sodium carbonate solution (50 ml) that was cooled to 10°C. The precipitated solid was filtered, washed with water (~20 ml) and dried under vacuum to give product (80% yield).

Method B: Phenyl ether (70 ml) was heated with stirring to 240°C, then diethyl 2-((3-iodophenylamino)methylene)malonate (Intermediate 7, 10 g, 25 mmol) was gradually added and the resulting mixture was refluxed at 280°C for 1 hour. After cooling the reaction to room temperature, the resulting solid was collected by filtration, washed with methyl *tert*-butyl ether and dichloromethane to give a white solid (30% yield).

MS (ESP): 344 ($M+H^+$) for $C_{12}H_{10}INO_3$

Intermediate 9

Ethyl 1-ethyl-7-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate

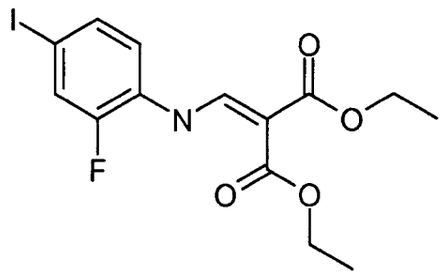


To ethyl 6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate (Intermediate 8, 5 g, 0.013 mol) in dimethylformamide (26 ml, c=0.2M) were added potassium carbonate (4.50g, 0.033 mole) and ethyl bromide (5.71 g, 0.053 mole). The reaction was stirred at 90°C overnight then the solvent was removed *in vacuo*. The residue was taken up in ethyl acetate washed with water, brine, and dried over sodium sulfate. Solvents were removed under vacuum and the crude was purified by flash column chromatography on silica gel using (dichloromethane-ethyl acetate) to give the desired quinolone (90%).

MS (ESP): 372 ($M+H^+$) for $C_{14}H_{14}INO_3$

Intermediate 10

2-((2-Fluoro-4-iodophenylamino)methylene)malonate



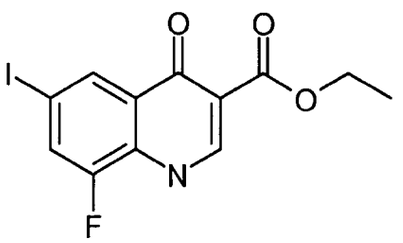
A solution of 2-fluoro-4-iodoaniline (15 g, 63.29 mmol) and diethyl ethoxymethylene malonate (41.05 g, 0.19 mol) in toluene (75 mL) was heated to reflux with a Dean-Stark condenser for 7 h. The mixture was cooled, concentrated and washed with methyl *tert*-butyl ether (500 ml). The methyl *tert*-butyl ether layer was then concentrated and the residue was washed with heptane (500 ml), yielding a white solid that precipitated out of the yellow solution. This solid was then collected, yielding 23.6 g (91%) of diethyl 2-((2-fluoro-4-iodophenylamino)methylene)malonate.

MS (ESP): 407 ($M+H^+$) for $C_{14}H_{15}FINO_4$

^1H NMR ($CDCl_3$): δ 1.40 (t, 6H), 4.30 (q, 4H), 7.03 (t, 1H), 7.51 (d, 1H), 8.42 (d, 1H), 11.02 (d, 1H).

Intermediate 11

Ethyl 8-fluoro-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate



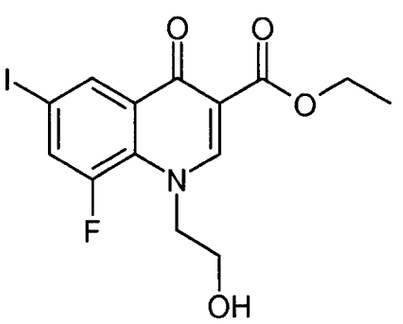
Diethyl 2-((2-fluoro-4-iodophenylamino)methylene)malonate (Intermediate 10, 13.45 g, 33.05 mmol) was placed in a 250 mL round bottom flask with Eaton's Reagent (55 mL, 0.29 mol) and aged while stirring at 90°C for 4-5 days. The reaction was then cooled to 5°C and was slowly quenched with saturated sodium carbonate solution (500 ml) at 10°C to form a clumpy brownish-yellow solid. The precipitate was vacuum filtered and washed with water (300 ml). The collected solid was dried under vacuum at 50°C for 16 h, resulting in 10.7 g (90%) of light tan solid.

MS (ESP): 362 ($M+H^+$) for $C_{12}H_9FINO_3$

^1H NMR ($CDCl_3$): δ 1.37 (t, 3H), 4.18 (q, 2H), 6.59 (d, 1H), 7.20 (d, 1H), 7.30 (d, 1H), 7.64 (d, 1H)

Intermediate 12

Ethyl 8-fluoro-1-(2-hydroxyethyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate

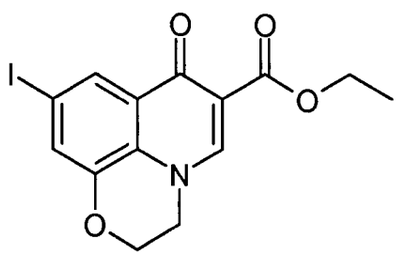


Ethyl 8-fluoro-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate (Intermediate 11, 7.22 g, 20 mmol) was dissolved in dimethylformamide (35 ml). Powdered potassium carbonate (8.28 g, 60 mmol) and 2-iodoethanol (11.3 ml, 145 mmol) were then added and the reaction mixture was allowed to stir at 90°C for 1 h. The reaction mixture was cooled to room temperature and poured into brine (300 ml) then water (50 ml) was added to dissolve the material. This

solution was extracted with 9:1 tetrahydrofuran:methyl *tert*-butyl ether (5 × 200 ml). The organic extracts were combined washed with brine (2 × 200 ml), dried over sodium sulfate, and concentrated under reduced pressure to give a dark yellow oil of ethyl 8-fluoro-1-(2-hydroxyethyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate that was carried on to the next reaction without any further purification. MS (ESP): 405 ($M+H^+$) for $C_{14}H_{13}FINO_4$

Intermediate 13

Ethyl 9-iodo-7-oxo-3,7-dihydro-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylate

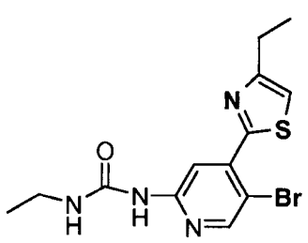


A solution of ethyl 8-fluoro-1-(2-hydroxyethyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate (Intermediate 12, 20 mmol) in DMF (30 mL) was treated with 1.8-diazabicyclo[5.4.0]undec-7-ene (5.6 ml, 40 mmol) and the reaction mixture was stirred at 100°C for 24 h. The solvent was then removed *in vacuo* and the residue was chromatographed on silica gel using 0-5% (0.2N ammonia in methanol) in dichloromethane to give 1.4g (18%) of ethyl 9-iodo-7-oxo-3,7-dihydro-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylate as a white solid.

MS (ESP): 386 ($M+H^+$) for $C_{14}H_{12}INO_4$

Intermediate 14

1-(5-Bromo-4-(4-ethylthiazol-2-yl)pyridin-2-yl)-3-ethylurea



5-Bromo-2-(3-ethylureido)pyridine-4-carbothioamide (Intermediate 3, 6.06g, 20 mmol) was suspended in acetonitrile (150 ml). 1-Bromobutan-2-one (30 mmol) was added and the reaction mixture was heated at reflux for 16 h. The reaction was cooled to 0°C and the

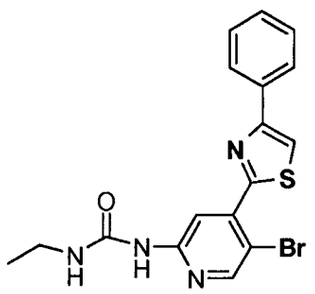
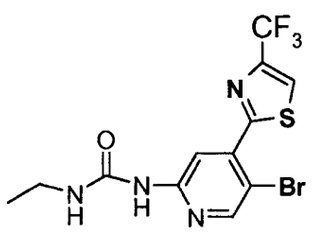
suspension was filtered. The solid was washed with acetonitrile (50 ml), collected, and dried in a vacuum oven at 50°C for 4 hours to give an off white solid.

MS (ESP): 356 (MH^+) for $C_{13}H_{15}BrN_4OS$

^1H NMR (d_6-DMSO): δ 0.91 (t, 3H), 1.28 (t, 3H), 3.83 (q, 2 H), 3.18 (q, 2H), 7.31 (bs, 1H), 7.66 (s, 1 H), 8.37 (s, 1H), 8.47 (s, 1H), 9.37 (s, 1H).

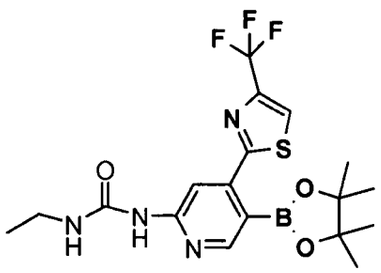
Intermediates 15-16

The following Intermediates were prepared by the procedure described for the preparation of Intermediate 14 from the starting materials (SM) indicated.

Int	Compound	Data	SM
15	1-(5-bromo-4-(4-phenylthiazol-2-yl)pyridin-2-yl)-3-ethylurea 	MS (ESP): 504 (MH^+) for $C_{17}H_{15}BrN_4OS$ ^1H NMR: 1.10 (t, 3H), 3.19 (q, 2 H), 7.24-7.40 (m, 2H), 7.41-7.50 (m, 2 H), 8.04 (d, 1H), 8.43-8.53 (m, 3H), 9.39 (s, 1H)	Intermediate 3 and 2-bromo-1-phenylethanone
16	1-(5-bromo-4-(4-trifluoromethylthiazol-2-yl)pyridin-2-yl)-3-ethylurea 	MS (ESP): 395 ($M+H^+$) for $C_{12}H_{10}BrF_3N_4OS$ ^1H NMR: 1.1 (t, 3H), 3.20 (q, 2H), 7.23 (s, 1H), 8.40 (s, 1H), 8.60 (s, 1H), 8.83 (s, 1H), 9.40 (s, 1H)	Intermediate 3 and 3-bromo-1,1,1,-trifluoro-acetone

Intermediate 17

1-Ethyl-3-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)urea



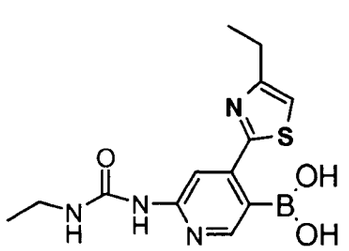
1-(5-Bromo-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea (Intermediate 16, 200 mg, 0.51 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (386 mg, 1.52 mmol), potassium acetate (149 mg, 1.52 mmol), and 1,1'-bis(diphenylphosphino)ferrocene-palladium dichloride (20.72 mg, 0.03 mmol) were taken in a microwave vial and degassed with argon. DMSO (4 mL) was added to the vial and the solution was heated at 90 °C for 5 h. The reaction mixture was partitioned between water and ethyl acetate. The layers were separated and the organic layer was back extracted three times with ethyl acetate. The organic layers were combined and washed with water and brine, then dried over magnesium sulfate and concentrated under reduced pressure to give a light brown solid that was a mixture of the title compound (35%), {6-{[(ethylamino)carbonyl]amino}-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}boronic acid (25 %) and *N*-ethyl-*N*'-{4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-2-yl}urea (25 %). The crude mixture was taken to the next step without further purification.

MS (ESP): 361 (MH^+) for $C_{12}H_{12}BF_3N_4O_3S$

^{1}H NMR (d_6-DMSO): δ 1.11 (t, 3H), 3.16-3.22 (q, 2 H), 7.71 (bt, 1H), 7.89 (d, 1 H), 8.16 (s, 1H), 8.28 (s, 1H), 8.63 (s, 1H), 9.26 (s, 1H).

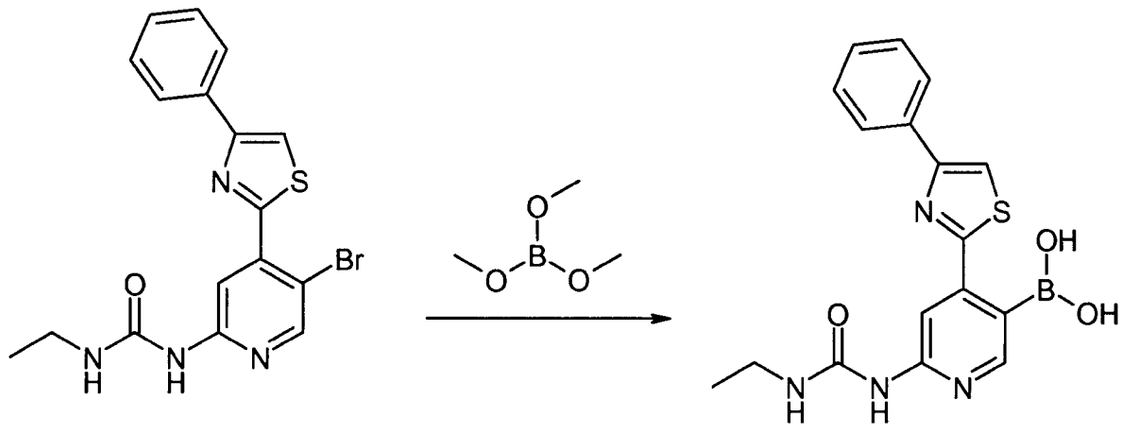
Intermediate 18

The following Intermediate was prepared by the procedure described in Intermediate 17 from the starting materials (SM) indicated.

Int	Compound	Data	SM
18	6-(3-ethylureido)-4-(4-ethylthiazol-2-yl)pyridin-3-ylboronic acid 	MS (ESP): 321 (MH^+) for $C_{13}H_{17}BN_4O_3S$ ^{1}H NMR (d_6-DMSO): δ 1.16 (t, 3H), 1.23 (t, 3H), 2.78 (q, 2H), 3.18-3.23 (m, 2 H), 7.48 (s, 1H), 7.78 (bt, 1 H), 7.91 (s, 1H), 8.26 (s, 1H), 9.40 (s, 1H)	Intermediate 14

Intermediate 19

6-(3-Ethylureido)-4-(4-phenylthiazol-2-yl)pyridin-3-ylboronic acid

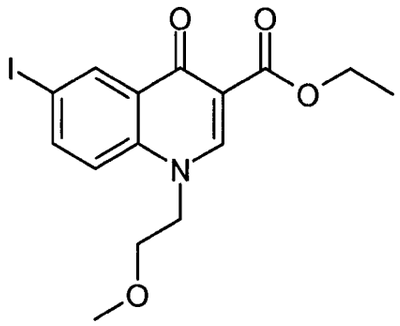


A solution of 1-(5-bromo-4-(4-phenylthiazol-2-yl)pyridin-2-yl)-3-ethylurea (2.97 g, 7.36 mmol, Intermediate 15) in THF (25 mL) was cooled to -78 °C. Isopropylmagnesium chloride (2.0M in THF; 8.84 mL, 17.67 mmol, Aldrich) was added slowly and the reaction was slowly warmed to -15 °C before being cooled back down to -78 °C. N-Butyllithium (2.5M in hexanes; 14.73 mL, 36.82 mmol, Aldrich) was then added and the reaction was stirred at -78 °C for 1 hour. Trimethyl borate (8.21 mL, 73.64 mmol, Aldrich) was added all at once and an exotherm was observed. Following the exotherm, the reaction mixture was allowed to warm to room temperature and stir for 3 h. The reaction mixture was then cooled to 0 °C and 20 mL of water was added slowly followed by 10 mL of 6N HCl. The reaction mixture was allowed to warm to room temperature and stir for 30 min. The reaction mixture was concentrated under reduced pressure to remove THF. The aqueous portion was diluted with 1N NaOH and diethylether. The impurities went into the ether layer (yellow) and the remaining white solid was filtered, washed with water and dried. The solid was then triturate with dilute acid (pH 4.5) to remove salts. The solid was dried overnight to yield product as a white solid (1.60g). MS (ES) $(M+H)^+$: 369 for $C_{17}H_{17}BN_4O_3S$

NMR: 1.10 (t, 3H), 3.20 (q, 2H), 7.37-7.51 (m, 3H), 7.79 (m, 1H), 7.93 (s, 1H), 8.06 (d, 2H), 8.28 (d, 2H), 9.30 (s, 1H).

Intemediate 20

Ethyl 6-iodo-1-(2-methoxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate



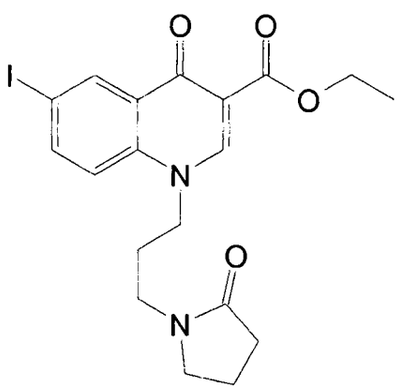
(Z)-Ethyl 3-(dimethylamino)-2-(2-fluoro-5-iodobenzoyl)acrylate (0.428 g, 1.09 mmol, Intermediate 24) and 2-methoxyethanamine (0.082 g, 1.09 mmol, Acros) were combined in DMF (3.0 mL). Potassium carbonate (0.151 g, 1.09 mmol, Fisher) was added and the reaction was heated in the microwave at 90 °C for 30 min. After 30 minutes, LC/MS indicated that the reaction was complete. The reaction mixture was cooled to room temperature and slowly poured into water. The resulting precipitate was filtered, washed with water and dried overnight to yield a white solid (0.277g).

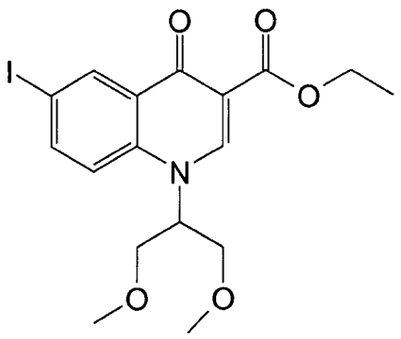
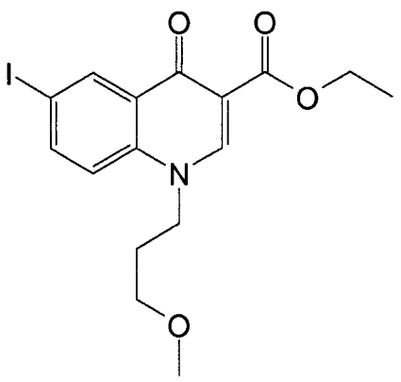
MS (ES) $(M+H)^+$: 402 for $C_{15}H_{16}INO_4$;

NMR: 1.28 (t, 3H), 3.21 (s, 3H), 3.65 (t, 2H), 4.21 (q, 2H), 4.55 (t, 2H), 7.68 (d, 1H), 8.04 (d, 1H), 8.50 (s, 1H), 8.60 (s, 1H).

Intermediates 21-23

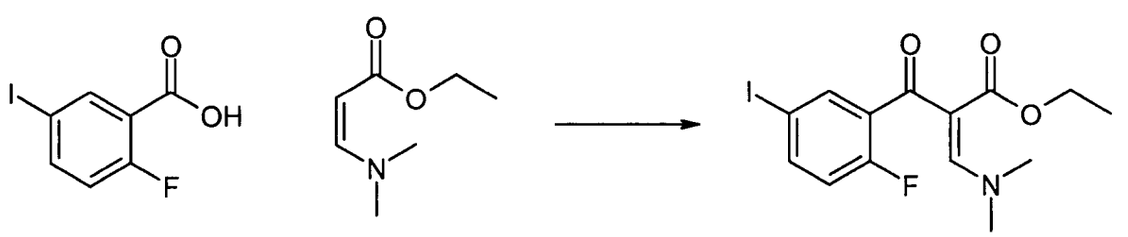
The following Intermediates were prepared by the procedure described in Intermediate 20 from the starting materials (SM) indicated.

Int	Compound	Data	SM
21	ethyl 6-iodo-4-oxo-1-(3-(2-oxopyrrolidin-1-yl)propyl)-1,4-dihydroquinoline-3-carboxylate 	MS (ES) $(M+H)^+$: 469 for $C_{19}H_{21}IN_2O_4$	Intermediate 24 and 1-(3-aminopropyl) pyrrolidin-2-one (Acros)

Int	Compound	Data	SM
22	ethyl 1-(1,3-dimethoxypropan-2-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ES) $(M+H)^+$: 446 for $C_{17}H_{20}INO_5$ NMR: 1.28 (t, 3H), 3.24 (s, 6H), 3.73-3.84 (m, 4H), 4.22 (q, 2H), 5.27 (q, 1H), 7.81 (d, 1H), 8.04 (d, 1H), 8.51 (s, 1H), 8.72 (s, 1H).	Intermediate 24 and 1,3-dimethoxy-propan-2-amine (Tyger)
23	ethyl 6-iodo-1-(3-methoxypropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ES) $(M+H)^+$: 416 for $C_{16}H_{18}INO_4$ NMR: 1.28 (t, J = 8 Hz, 3H), 1.97 (m, 2H), 3.34 (m, 5H), 4.21 (q, J = 8 Hz, 2H), 4.39 (m, 2H), 7.62 (d, J = 9 Hz, 1H), 8.06 (d, J = 9 Hz, 1H), 8.51 (s, 1H), 8.63 (s, 1H).	Intermediate 24 and 3-methoxyprop ylamine

Intermediate 24

(Z)-Ethyl 3-(dimethylamino)-2-(2-fluoro-5-iodobenzoyl)acrylate



2-Fluoro-5-iodobenzoic acid (5.20 g, 19.55 mmol, Aldrich) was suspended in thionyl chloride (1.427 mL, 19.55 mmol, Aldrich) and heated to reflux for 30 min. The reaction mixture was cooled to room temperature and concentrated under reduced pressure to a tan solid. The solid was dissolved in toluene (30 mL) and concentrated under reduced pressure again. To a

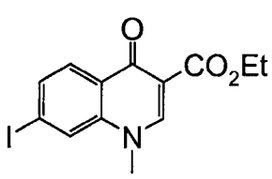
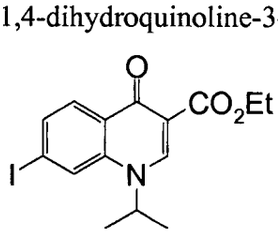
solution of the resulting solid (5.20 g, 19.55 mmol) in toluene (30 mL) was added triethylamine(2.72 mL, 19.55 mmol, Acros) and (Z)-ethyl 3-(dimethylamino)acrylate (3.64 mL, 25.41 mmol, Acros) and the reaction mixture was heated to 90 °C for 1 h. The reaction mixture was diluted with water and extracted three times with ethyl acetate. The combined organic extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure. Purification by Isco column (0%-100% ethyl acetate/dichloromethane) afforded the desired compound as a yellow solid (6.51g).

MS (ES) $(M+H)^+$: 392 for $C_{14}H_{15}FINO_3$

NMR: 0.88 (t, 3H), 2.78 (s, 3H), 3.33 (s, 3H), 3.85 (q, 2H), 7.03 (dd, 1H), 7.65 (dd, 1H), 7.77 (s, 2H).

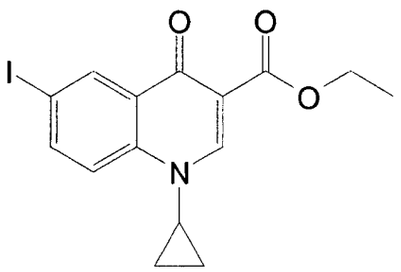
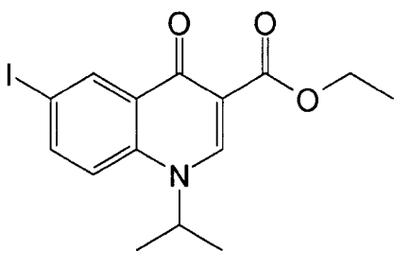
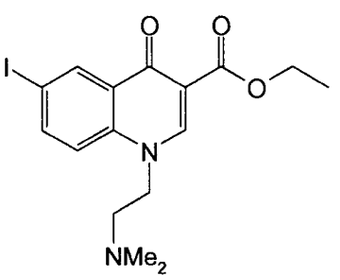
Intermediates 25-26

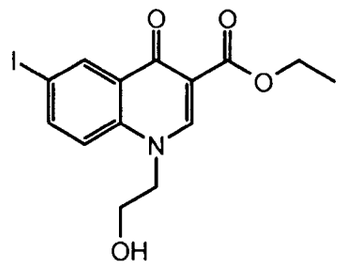
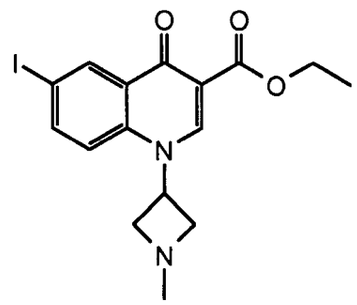
The following Intermediates were prepared by the procedure described in Intermediate 9 from the starting materials (SM) indicated.

Int	Compound	Data	SM
25	Ethyl 7-iodo-1-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 358 (M+1) for $C_{13}H_{12}INO_3$ ^{1}H-NMR (DMSO-d_6) δ: 1.28 (t, 3H); 3.90 (s, 3H); 4.22 (q, *J*=7.07 Hz, 2H); 7.83 (dd, 1H); 7.94 (d, *J*=8.59 Hz, 1H); 8.10 (s, 1H); 8.64 (s, 1H)	Intermediate 8 and iodomethane
26	Ethyl 7-iodo-1-isopropyl-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 386 (M+1) for $C_{15}H_{16}INO_3$ ^{1}H-NMR (DMSO-d_6): 1.29 (d, J=6.06 Hz, 6H); 1.36 (t, J=7.07 Hz, 3H); 4.39 (q, J=7.07 Hz, 2H); 4.58 - 4.70 (m, 1H); 7.96 (dd, 1H) 8.03 (d, 1H); 8.45 (d, J=1.26 Hz, 1H); 9.04 (s, 1H)	Intermediate 8 and 2-iodopropane

Intermediates 27-31

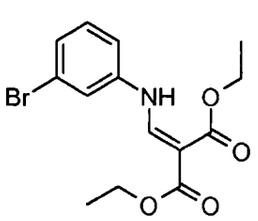
The following Intermediates were prepared by the procedure described in Intermediate 20 from the starting materials (SM) indicated.

Int	Compound	Data	SM
27	Ethyl 1-cyclopropyl-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 384 (M+1) for $C_{15}H_{14}INO_3$ ^{1}H-NMR (DMSO-d_6): 1.05 - 1.13 (m, 2H); 1.20 - 1.32 (m, 5H); 3.60 - 3.69 (m, 1H); 4.22 (q, *J*=7.07 Hz, 2H); 7.89 (d, *J*=8.84 Hz, 2H); 8.12 (dd, *J*=8.84, 2.02 Hz, 1H); 8.47 (d, *J*=2.02 Hz, 1H); 8.49 (s, 1H)	Intermediate 24 and cyclopropylamine
28	Ethyl 6-iodo-1-isopropyl-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 386 (M+1) for $C_{15}H_{16}INO_3$ ^{1}H-NMR (DMSO-d_6) : 1.29 (t, J=7.07 Hz, 3H): 1.49 (d, J=6.57 Hz, 6H): 4.23 (q, J=7.07Hz, 2H): 5.00 - 5.10 (m, 1H): 7.80 (d, J=9.35 Hz, 1H): 8.07 (dd, J=9.09, 2.27 Hz, 1 H) 8.53 (d, J=2.02 Hz, 1H): 8.61 (s, 1H)	Intermediate 24 and propan-2-amine
29	Ethyl 1-(2-(dimethylamino)ethyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 415 (M+1) for $C_{16}H_{19}IN_2O_3$ ^{1}H-NMR (DMSO-d_6) : 1.28 (t, *J*=7.20 Hz, 3H); 2.18 (s, 6H); 2.58 (t, *J*=5.94 Hz, 2H); 4.23 (q, *J*=7.24 Hz, 2H); 4.44 (t, *J*=5.81 Hz, 2H); 7.65 (d, *J*=8.84 Hz, 1H); 8.06 (dd, *J*=8.84, 2.27 Hz, 1H); 8.51 (d, *J*=2.02 Hz, 1H); 8.63 (s, 1H)	Intermediate 24 and 2-(N,N-dimethylamino)-ethanamine

Int	Compound	Data	SM
30	Ethyl 1-(2-hydroxyethyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 388 (M+1) for $C_{14}H_{14}INO_4$ ^{1}H-NMR (DMSO-d_6): 1.28 (t, J=7.06 Hz, 3H); 3.63 - 3.76 (m, 2H); 4.22 (q, J=6.97 Hz, 2H); 4.36 - 4.46 (m, 2H); 5.02 (t, J=5.46 Hz, 1H); 7.67 (d, J=9.04 Hz, 1H); 8.04 (dd, J=9.04, 1.88 Hz, 1H); 8.51 (d, J=1.88 Hz, 1H); 8.59 (s, 1H)	Intermediate 24 and 2-aminoethanol
31	Ethyl 6-iodo-1-(1-methylazetidin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 413 (M+1) for $C_{16}H_{17}IN_2O_3$ ^{1}H NMR (DMSO-d_6): 1.29 (t, J=7.06 Hz, 3H); 2.31 (s, 3H); 3.25 - 3.39 (m, 2H); 3.85 (t, 2H); 4.25 (q, J=7.03 Hz, 2H); 5.01 - 5.16 (m, 1H); 7.45 (d, J=8.85 Hz, 1H); 8.03 (dd, J=8.85, 2.07 Hz, 1H); 8.50 (d, J=2.07 Hz, 1H); 8.60 (s, 1H)	Intermediate 24 and 1-methylazetidin-3-amine

Intermediate 32

Diethyl {[(3-bromophenyl)amino]methylidene}propanedioate

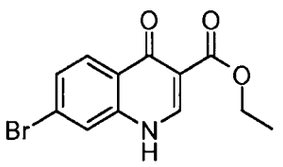


A mixture of 3-bromoaniline (10.0 g, 58.1 mmol) and diethyl (ethoxymethylidene)propanedioate (13.9 mL, 63.9 mmol) were heated to 110 °C for 1 h. After completion of the reaction, the reaction mixture was cooled to room temperature. The obtained solid was filtered and dried to afford 16.0 g 78% of diethyl {[(3-bromophenyl)amino]methylidene}propanedioate.

^{1}H NMR (400 MHz, $CDCl_3$): 1.37 (m, 6H), 4.25 (m, 4H), 7.05 (d, 1H), 7.25 (m, 2H), 8.44 (d, 1H), 10.95 (d, 1H).

Intermediate 33

Ethyl 7-bromo-4-oxo-1,4-dihydroquinoline-3-carboxylate

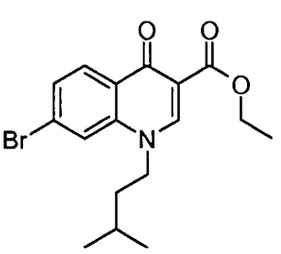


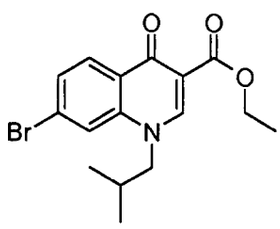
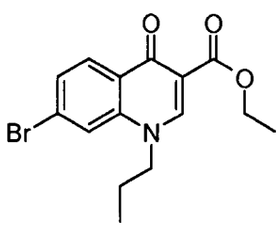
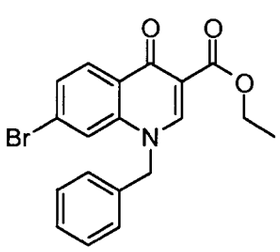
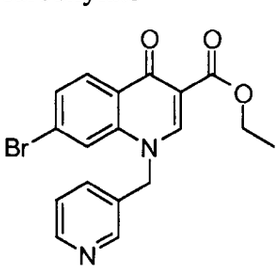
Dowtherm (50 mL) was taken in double neck round bottom flask (100 mL) and heated to 250 °C in sand bath. At this temperature diethyl {[(3-bromophenyl)amino]methylidene}propanedioate (Intermediate 32, 10.0 g, 29.2 mmol) was added and the reaction temperature was maintained for another 1 h at 250 °C. After completion of the reaction, the reaction mixture was cooled to room temperature, a white solid was collected by filtration and dried to yield 6.0 g (69.3%) ethyl 7-bromo-4-oxo-1,4-dihydroquinoline-3-carboxylate.

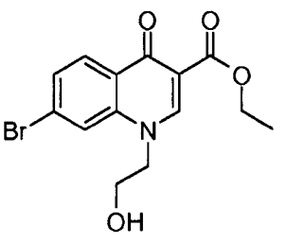
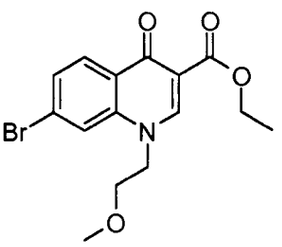
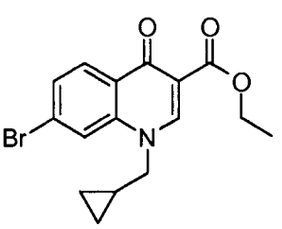
^{1}H NMR (400 MHz, DMSO-d_6): 1.07 (t, 3H), 1.22 (s, 12H), 3.16 (q, 2H), 7.29 (m, 1H), 7.31 (d, 2H), 7.61 (s, 1H), 7.88 (s, 1H), 8.31 (s, 1H), 8.65 (s, 1H), 9.44 (s, 1H).

Intermediates 34-41

The following Intermediates were prepared by the procedure described in Intermediate 9 from the starting materials (SM) indicated.

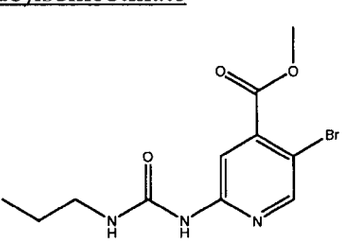
Int	Compound	Data	SM
34	Ethyl 7-bromo-1-(3-methylbutyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	^{1}H NMR (400 MHz, $CDCl_3$): 1.04 (d, 6H), 1.41 (t, 3H), 1.78 (q, 3H), 4.14 (q, 2H), 4.40 (q, 2H), 7.52 (s, 1H), 7.56 (d, 1H), 8.39 (s, 1H), 8.42 (d, 1H).	Intermediate 33 and 1-bromo-3-methylbutane

Int	Compound	Data	SM
35	Ethyl 7-bromo-1-(2-methylpropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	^{1}H NMR (400 MHz, $CDCl_3$): 1.02 (d, 6H), 1.39 (t, 3H), 2.27 (m, 1H), 3.93 (d, 2H), 4.41 (q, 2H), 4.53 (d, 2H), 8.40 (d, 2H).	Intermediate 33 and 1-bromo-2-methylpropane
36	Ethyl 7-bromo-4-oxo-1-propyl-1,4-dihydroquinoline-3-carboxylate 	^{1}H NMR (400 MHz, DMSO-d_6): 0.90 (t, 3H), 1.75 (q, 2H), 4.24 (q, 2H), 4.35 (q, 2H), 7.63 (d, 1H), 8.07 (s, 1H), 8.14 (d, 1H), 8.66 (s, 1H).	Intermediate 33 and 1-bromopropane
37	Ethyl 1-benzyl-7-bromo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	^{1}H NMR (400 MHz, DMSO-d_6): 1.24 (t, 3H), 2.83 (s, 1H), 4.22 (q, 2H), 4.57 (s, 1H), 5.67 (s, 2H), 7.22 (m, 2H), 7.33 (m, 2H), 7.56 (m, 2H), 7.85 (s, 1H), 8.12 (d, 1H), 8.86 (s, 1H).	Intermediate 33 and benzyl bromide
38	Ethyl 7-bromo-4-oxo-1-(pyridin-3-ylmethyl)-1,4-dihydroquinoline-3-carboxylate 	^{1}H NMR (400 MHz, DMSO-d_6): 1.29 (t, 3H), 4.25 (q, 2H), 5.74 (s, 2H), 7.37 (d, 1H), 7.61 (d, 2H), 7.91 (s, 1H), 8.14 (d, 1H), 8.42 (d, 1H), 8.58 (d, 1H), 8.91 (s, 1H).	Intermediate 33 and 3-(bromomethyl) pyridine

Int	Compound	Data	SM
39	Ethyl 7-bromo-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	^{1}H NMR (400 MHz, DMSO-d_6): 1.28 (t, 3H), 3.71 (d, 2H), 4.23 (q, 2H), 4.42 (s, 2H), 4.48 (s, 2H), 4.99 (m, 1H), 7.62 (d, 1H), 8.10 (s, 1H), 8.14 (d, 1H), 8.56 (s, 1H).	Intermediate 33 and 2-bromoethanol
40	Ethyl 7-bromo-1-(2-methoxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	^{1}H NMR (400 MHz, DMSO-d_6): 1.33 (t, 3H), 3.22 (s, 3H), 3.65 (m, 2H), 4.22 (q, 2H), 4.58 (m, 2H), 7.62 (d, 1H), 8.15 (m, 2H), 8.49 (s, 1H).	Intermediate 33 and 1-bromo-2-methoxy-ethane
41	Ethyl 7-bromo-1-(cyclopropylmethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	^{1}H NMR (400 MHz, $CDCl_3$): 0.48 (d, 2H), 0.79 (m, 2H), 1.39 (m, 1H), 1.42 (t, 3H), 3.98 (d, 2H), 4.42 (q, 2H), 7.53 (d, 1H), 7.65 (s, 1H), 8.40 (d, 1H), 8.54 (s, 1H).	Intermediate 33 and (bromomethyl) cyclopropyl

Intermediate 42

methyl 5-bromo-2-(3-propylureido)isonicotinate



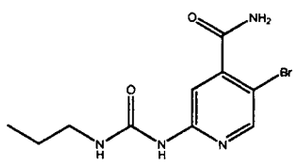
Methyl 2-amino-5-bromoisonicotinate (100 g, 433 mmol) was dissolved in chloroform (600 mL) and placed into a 1 L sealed tube. Propyl isocyanate (122.5 mL, 1.29 mol) was then added. The reactor was heated at 55°C for 72 h at which time the reaction was determined to be complete. The mixture was then cooled to room temperature, concentrated under reduced pressure, and the solid was dissolved in 2:1 ethyl acetate: tetrahydrofuran (3 L). This solution was washed with water (2 × 200 mL), and the water was back extracted with ethyl acetate (300 mL). The organic layers were then dried with sodium sulfate, filtered, and concentrated yielding 129g (95%) of methyl 5-bromo-2-(3-propylureido)isonicotinate as a dark yellow solid.

MS (ESP): 316.1 (MH^+) for $C_{11}H_{14}BrN_3O_3$

^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, 3H), 1.45 (m, 2H), 3.11 (m, 2H), 3.90 (s, 3H), 7.21 (bt, 1H), 8.02 (s, 1H), 8.46 (s, 1H), 9.40 (s, 1H)

Intermediate 43

5-bromo-2-(3-propylureido)isonicotinamide



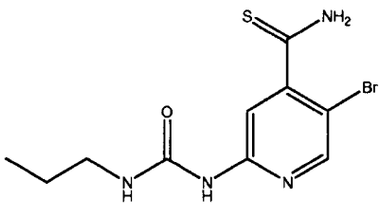
A solution of methyl 5-bromo-2-(3-propylureido)isonicotinate (Intermediate 42, 128 g, 405 mmol) and 7N ammonia in methanol (1 L) was allowed to stir at room temperature for 3 d. Stirring for the reaction was then stopped and the solids were allowed to settle. The precipitated was then vacuum filtered, rinsed with methanol (2 × 500 mL), and then dried on the high vacuum pump overnight, yielding 123 g (quant) of 5-bromo-2-(3-propylureido)isonicotinamide as a white solid.

MS (ESP): 301.1 (MH^+) for $C_{10}H_{13}BrN_4OS$

^1H NMR (300 MHz, DMSO-d_6): δ 0.88 (t, 3H), 1.46 (m, 2H), 3.18 (q, 2H), 7.41 (bs, 1H), 7.58 (s, 1H), 7.78 (bs, 1H), 8.08 (bs, 1H), 8.33 (s, 1H), 9.31 (s, 1H)

Intermediate 44

5-bromo-2-(3-propylureido)pyridine-4-carbothioamide



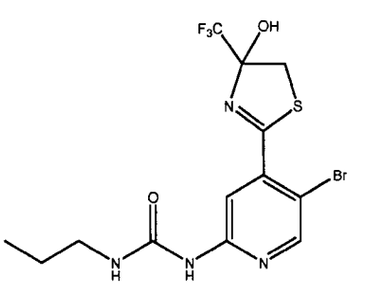
A suspended mixture of 5-bromo-2-(3-propylureido)isonicotinamide (Intermediate 43, 123 g, 407 mmol), Lawesson's Reagent (131.6 g, 326 mmol), and tetrahydrofuran (1.55 L) was stirred at 70°C for 18 h. Stirring was stopped and a bright yellow precipitate was allowed to settle. The precipitate was then vacuum filtered and washed with methyl tert-butyl ether (2 × 500 L). This solid was then dried in the vacuum oven at 50°C for 12 hours to give 50g of product solid. The mother liquor was concentrated and the residue was suspended in toluene (300 mL). The solid thus obtained was filtered and combined with the previous solid. The combined totaled 110g (85%) of 5-bromo-2-(3-propylureido)pyridine-4-carbothioamide as an off white solid

MS (ESP): 317.2 (MH^+) for $C_{10}H_{13}BrN_4OS$

^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, 3H), 1.42 (m, 2H), 3.13 (m, 2H), 7.38 (s, 1H), 7.50 (s, 1H), 8.28 (s, 1H), 9.25 (s, 1H), 9.80 (s, 1H), 10.28 (s, 1H)

Intermediate 45

1-(5-bromo-4-(4-hydroxy-4-(trifluoromethyl)-4,5-dihydrothiazol-2-yl)pyridin-2-yl)-3-propylurea



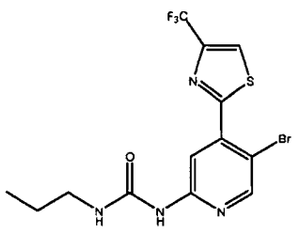
A suspension of 5-bromo-2-(3-propylureido)pyridine-4-carbothioamide (Intermediate 44, 100 g, 315 mmol), 3-bromo-1,1,1-trifluoroacetone (64 mL, 630 mmol) in acetonitrile (1.5 L) was heated at 80°C for 20 hours. The solution was then cooled down and was concentrated under reduced pressure. This gave an orange oil that was carried on without further purification.

MS (ESP): 426.9 (MH^+) for $C_{13}H_{14}BrF_3N_4O_2S$

^1H NMR (300 MHz, DMSO-d_6): δ 0.88(t, 3H), 1.48 (m, 2H), 3.11 (m, 2H), 3.62 (d, 1H), 3.92 (d, 1H), 7.30 (bs, 1H), 7.98 (s, 1H), 8.46 (s, 1H), 9.42 (s, 1H).

Intermediate 46

1-(5-bromo-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-propylurea



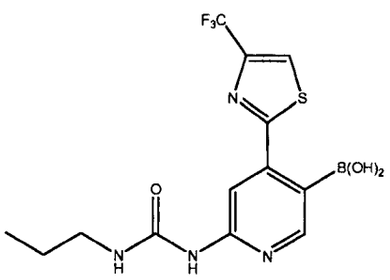
A solution of 1-(5-bromo-4-(4-hydroxy-4-(trifluoromethyl)-4,5-dihydrothiazol-2-yl)pyridin-2-yl)-3-propylurea (Intermediate 45, 315 mmol) and triethylamine (217 mL, 1.57 mol) in tetrahydrofuran (1.3 L) was prepared and stirred at room temperature. Methane sulfonyl chloride (61 mL, 787 mmol) was added dropwise over the course of 1 h. This mixture was stirred at 26°C for 4 h. Stirring was then stopped and the solids were filtered, washed with tetrahydrofuran (3 × 200 mL), and discarded. The combined tetrahydrofuran layers were concentrated to a viscous, yellow semi-solid which was then triturated with methanol (1L). The solid was filtered and washed with methanol (2 × 300 mL). The solid was then dried in the vacuum oven at 50°C for 12 h. This gave 99.4g (76%) of 1-(5-bromo-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-propylurea as an off-white solid.

MS (ESP): 409.1 (MH^+) for $C_{13}H_{12}BrF_3N_4OS$

^1H NMR (300 MHz, DMSO-d_6): δ 0.89 (t, 3H), 1.47 (m, 2H), 3.16 (m, 2H), 7.25 (s, 1H), 8.41 (s, 1H), 8.57 (s, 1H), 8.82 (s, 1H), 9.39 (s, 1H).

Intermediate 47

6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-ylboronic acid



A suspension of 1-(5-bromo-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-propylurea (Intermediate 46, 50 g, 123 mmol) in tetrahydrofuran (1.25 L) was prepared and stirred at -50°C. 2.0M isopropyl magnesium chloride in tetrahydrofuran (183 mL, 368 mmol) was added dropwise over 45 min so that the temperature never rose above -35°C. The reaction mixture was stirred for a further hour at -40°C then was cooled to -78°C. 2.5M n-Butyl

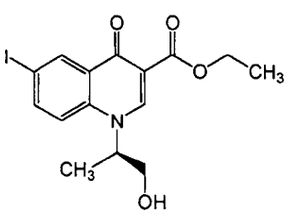
lithium in hexanes (295 mL, 735 mmol) was then added dropwise to the reaction solution over the course of 1 h so that the temperature never rose above -65°C. This mixture was then allowed to react at -78°C for 1.5 h. Boron methoxide (164 mL, 1.47 mol) was added in 1 portion and the cold bath was removed. The reaction was allowed to warm to room temperature and stirred for 1 h. 3N Hydrochloric acid (500 mL) was then added slowly to minimize foaming and the reaction was stirred at room temperature for 30 min so that all of the solids dissolved. The reaction was concentrated to remove the tetrahydrofuran and water (1L) was added. The solution was basified to pH 10 with 24% sodium hydroxide and the total volume was increased to 2L with water. The aqueous solution was extracted with methyl tert-butyl ether (3 × 650 mL). The layers were slow to separate. The organic layers were combined and extracted with 5% sodium hydroxide (100 mL). The aqueous phases were combined and acidified to pH 5.5 with 6N hydrochloric acid when a suspension formed. This suspension was extracted with 2:1 ethyl acetate: THF (5 × 400 mL) ensuring all solid dissolved in the organic phase. The organic phases were combined and back washed with water (1 L). The organics were concentrated and triturated with methyl tert-butyl ether (1 L). The solid obtained was dried in a vacuum oven at 50°C for 18 h. This gave 25 g (55%) of 6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-ylboronic acid as an off-white solid.

MS (ESP): 375.0 (MH^+) for $C_{13}H_{14}BF_3N_4O_3S$

^1H NMR (300 MHz, DMSO-d_6): δ 0.90 (t, 3H), 1.45-1.52 (m, 2H), 3.07-3.16 (m, 2H), 7.81 (bt, 1H), 7.91 (s, 1H), 8.20 (br, 2H), 8.31 (d, 1H), 8.65 (m, 1H), 9.32 (s, 1H).

Intermediate 48

ethyl 1-[(1*R*)-2-hydroxy-1-methylethyl]-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate



To a solution of ethyl 3-(dimethylamino)-2-(2-fluoro-5-iodobenzoyl)acrylate (Intermediate 24, 1 g, 2.56 mmol) dissolved in THF (10 mL) was added (*R*)-2-aminopropan-1-ol (300 mg, 2.56 mmol). The reaction mixture was stirred at 60 °C for 2 h. The reaction mixtrure was concentrated under reduced pressure, and the resulting residue was suspended in DMF (10

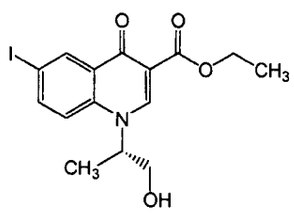
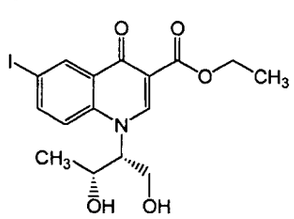
mL). Potassium carbonate was added (1.06 g, 7.67 mmol, 3 equiv.), and the reaction mixture was stirred at 70 °C for 18 h. The reaction mixture was cooled down to room temperature and quenched with 1 N HCl. The precipitate that formed was collected by filtration, washed with water and hexanes to provide (*R*)-ethyl 1-(1-hydroxypropan-2-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate (446 mg, 39 %).

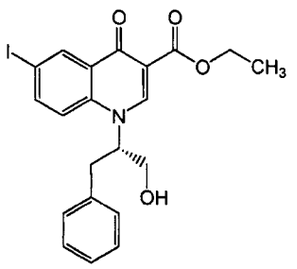
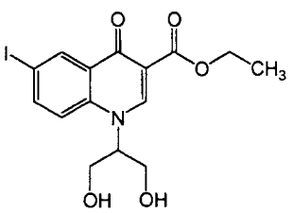
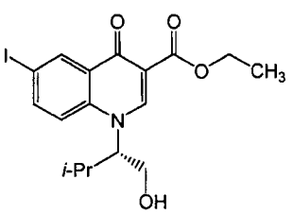
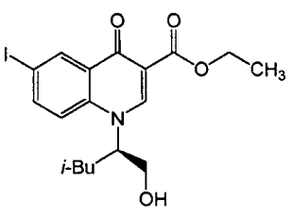
MS (ESP): 402 for $C_{15}H_{16}INO_4$.

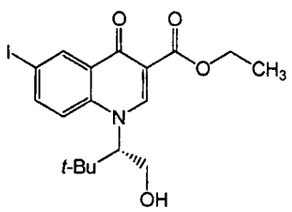
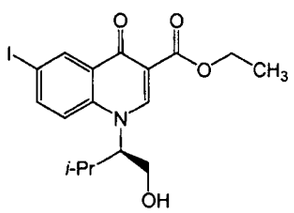
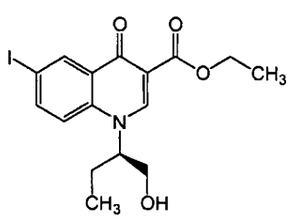
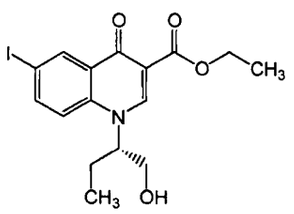
NMR (d_6-DMSO) δ 8.65 (s, 1H), 8.53 (d, 1H), 8.07 (dd, 1H), 7.82 (d, 1H), 5.23 (s, 1H), 5.05-4.98 (m, 1H), 4.27-4.2 (m, 2H), 3.74.

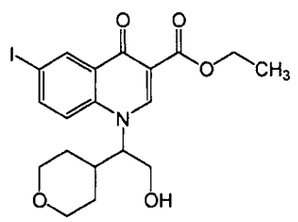
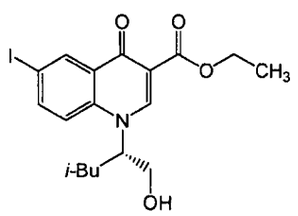
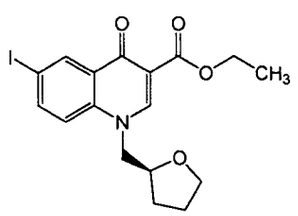
Intermediates 49-68

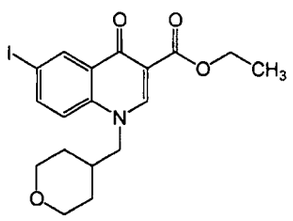
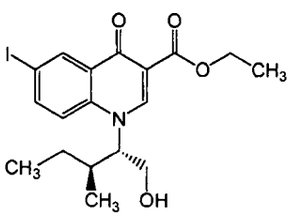
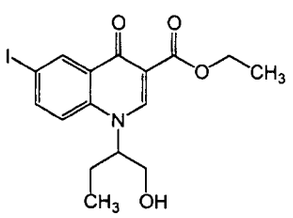
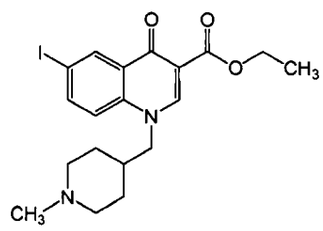
The following examples were prepared by the procedure described in Intermediate 48 from the indicated starting material.

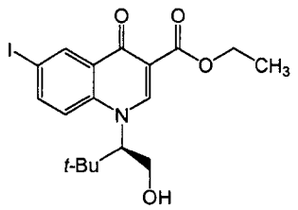
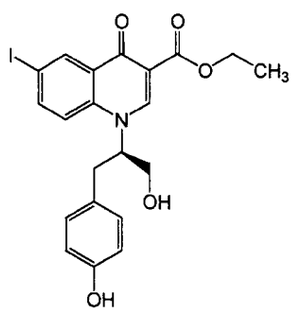
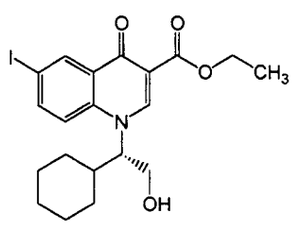
Int	Compound	Data	SM
49	(*S*)-ethyl 1-(1-hydroxypropan-2-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 402 for $C_{15}H_{16}INO_4$ NMR (d_6-DMSO) δ 8.65 (s, 1H), 8.54 (d, 1H), 8.07 (dd, 1H), 7.82 (d, 1H), 5.19 (s, 1H), 5.03-4.98 (m, 1H), 4.27-4.2 (m, 2H), 3.74 (d, 2H), 1.48 (d, 3H), 1.28 (t, 3H)	Intermediate 24 & (*S*)-2-aminopropan-1-ol
50	Ethyl 1-((2*R*,3*R*)-1,3-dihydroxybutan-2-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 432 for $C_{16}H_{16}INO_5$ NMR (d_6-DMSO) δ 8.88 (s, 1H), 8.52 (d, 1H), 8.03 (dd, 1H), 7.84 (d, 1H), 5.2 (s, 2H), 4.8-4.76 (m, 1H), 4.26-4.19 (m, 2H), 4.25-4.14 (m, 2H), 3.92-3.79 (m, 2H), 1.27 (t, 3H), 1.1 (d, 3H)	Intermediate 24 & (2*R*, 3*R*)-2-aminobutane-1,3-diol

Int	Compound	Data	SM
51	(*S*)-ethyl 1-(1-hydroxy-3-phenylpropan-2-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 478 for $C_{21}H_{20}INO_4$ NMR (d_6-DMSO) δ 8.7 (s, 1H), 8.44 (d, 1H), 7.98 (dd, 1H), 7.78 (d, 1H), 7.23-7.16 (m, 5H), 7.14-7.09 (m, 1H), 5.38-5.27 (m, 2H), 4.29-4.18 (m, 2H), 3.81 (d, 2H), 3.27-3.15 (m, 2H), 1.29 (t, 3H)	Intermediate 24 & (*S*)-2-amino-3-phenylpropan-1-ol
52	Ethyl 1-(1,3-dihydroxypropan-2-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 418 for $C_{15}H_{16I}NO_5$ NMR (d_6-DMSO) δ 8.65 (s, 1H), 8.53 (d, 1H), 8.07 (dd, 1H), 7.82 (d, 1H), 5.23 (s, 1H), 5.04-4.98 (m, 1H), 4.27-4.2 (m, 2H), 3.74 (d, 2H), 1.48 (d, 3H), 1.28 (t, 3H)	Intermediate 24 & 2-aminopropan-1,3-diol
53	(*S*)-ethyl 1-(1-hydroxy-3-methylbutan-2-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 430 for $C_{17}H_{20}INO_4$ NMR (d_6-DMSO) δ 8.69 (s, 1H), 8.53 (d, 1H), 8.04 (dd, 1H), 7.9 (d, 1H), 5.25-5.15 (m, 1H), 4.65-4.58 (m, 1H), 4.26-4.19 (m, 2H), 3.92-3.86 (m, 1H), 3.77-3.72 (m, 1H), 2.4-2.3 (m, 1H), 1.27 (t, 3H), 1.1 (d, 3H), 0.71 (d, 3H)	Intermediate 24 & (*S*)-2-amino-3-methylbutan-1-ol
54	(*R*)-ethyl 1-(1-hydroxy-4-methylpentan-2-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 444 for $C_{18}H_{22}INO_4$ NMR (d_6-DMSO) δ 8.6 (s, 1H), 8.53 (d, 1H), 8.07 (dd, 1H), 7.89 (d, 1H), 5.23 (s, 1H), 4.94 (s, 1H), 4.26-4.19 (m, 2H), 3.71 (d, 2H), 1.87-1.77 (m, 1H), 1.74-1.69 (m, 1H), 1.46-1.38 (m, 1H), 1.27 (t, 3H), 0.89 (d, 3H), 0.84 (t, 3H)	Intermediate 24 & (*R*)-2-amino-4-methylpentan-1-ol

Int	Compound	Data	SM
55	(*S*)-ethyl 1-(1-hydroxy-3,3-dimethylbutan-2-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 443 for $C_{18}H_{22}INO_4$ H^1NMR (d_6-DMSO) δ 8.62 (s, 1H), 8.53 (s, 1H), 8.01 (s, 1H), 5.07-4.99 (m, 1H), 4.92-4.85 (m, 1H), 4.26-4.20 (m, 2H), 4.02-3.95 (m, 2H), 1.28 (t, 3H), 0.95 (s, 9H)	Intermediate 24 & (*S*)-2-amino-3,3-dimethylbutan-1-ol
56	(*R*)-ethyl 1-(1-hydroxy-3-methylbutan-2-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 430 for $C_{17}H_{20}INO_4$ H^1NMR (d_6-DMSO) δ 8.69 (s, 1H), 8.53 (d, 1H), 8.04 (dd, 1H), 7.91 (t, 1H), 4.65-4.59 (m, 1H), 4.26-4.19 (m, 2H), 3.92-3.86 (m, 1H), 3.76-3.72 (m, 1H), 2.31-2.21 (m, 1H), 1.27 (t, 3H), 1.1 (d, 3H), 0.71 (d, 3H)	Intermediate 24 & (*R*)-2-amino-3-methylbutan-1-ol
57	(*R*)-ethyl 1-(1-hydroxy-3-methylbutan-2-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 416 for $C_{16}H_{18}INO_4$ NMR (d_6-DMSO) δ 8.62 (s, 1H), 8.53 (s, 1H), 8.03 (dd, 1H), 7.85 (d, 1H), 4.83 (s, 1H), 4.26-4.19 (m, 2H), 3.77-3.73 (m, 2H), 1.99-1.83 (m, 2H), 1.28 (t, 3H), 0.84 (t, 3H)	Intermediate 24 & (*R*)-2-aminobutan-1-ol
58	(*S*)-ethyl 1-(1-hydroxy-3-methylbutan-2-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 416 for $C_{16}H_{18}INO_4$ NMR (d_6-DMSO) δ 8.62 (s, 1H), 8.53 (s, 1H), 8.06 (d, 1H), 7.85 (d, 1H), 4.83 (s, 1H), 4.25-4.2 (m, 2H), 3.78-3.71 (m, 2H), 1.99-1.84 (m, 2H), 1.27 (t, 3H), 0.84 (t, 3H)	Intermediate 24 & (*S*)-2-aminobutan-1-ol

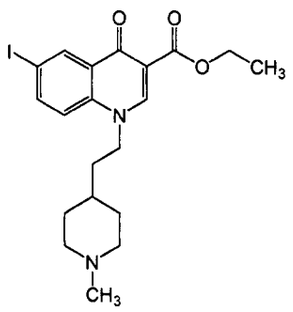
Int	Compound	Data	SM
59	Ethyl 1-(2-hydroxy-1-(tetrahydro-2H-pyran-4-yl)ethyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 472 for $C_{19}H_{22}INO_5$ [NMR (d_6-DMSO) δ 8.75 (s, 1H), 8.52 (s, 1H), 8.05 (d, 1H), 7.94 (d, 1H), 5.22-5.17 (m, 1H), 4.75 (s, 1H), 4.27-4.2 (m, 2H), 3.91-3.88 (m, 2H), 3.81-3.78 (m, 2H), 3.28-3.16 (m, 1H), 2.27-2.23 (m, 1H), 1.77-1.72 (m, 1H), 1.59-1.52 (m, 1H), 1.28 (t, 3H), 1.17 (t, 3H), 1.1-1.02 (1H)	Intermediate 24 & 2-amino-2-(tetrahydro-2H-pyran-4-yl)ethanol
60	(*S*)-ethyl 1-(1-hydroxy-3,3-dimethylbutan-2-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 444 for $C_{18}H_{22}INO_5$ H^1NMR (d_6-DMSO) δ 8.6 9 (s, 1H), 8.53 (d, 1H), 8.07 (dd, 1H), 7.89 (d, 1H), 4.95-4.91 (m, 1H), 4.26-4.19 (m, 2H), 3.71 (d, 2H), 1.86-1.8 (m, 1H), 1.75-1.72 (m, 1H), 1.46-1.39 (m, 1H), 1.27 (t, 3H), 0.89 (d, 3H), 0.84 (d, 3H)	Intermediate 24 & (*S*)-2-amino-4-methylpentan-1-ol
61	(*S*)-ethyl 6-iodo-4-oxo-1-((tetrahydrofuran-2-yl)methyl)-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 428 for $C_{17}H_{18}INO_4$ NMR (d_6-DMSO) δ 8.62 (s, 1H), 8.5 (d, 1H), 8.06 (dd, 1H), 7.74 (d, 1H), 4.6 (dd, 1H), 4.3-4.27 (m, 1H), 4.25-4.21 (m, 2H), 4.17-4.12 (m, 1H), 3.82-3.75 (m, 1H), 3.65-3.61 (m, 1H), 2.06-1.9 (m, 1H), 1.87-1.8 (m, 2H), 1.63-1.57 (m, 1H), 1.28 (t, 3H)	Intermediate 24 & (*S*)-(tetrahydrofuran-2-yl)methanamine

Int	Compound	Data	SM
62	Ethyl 6-iodo-4-oxo-1-((tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 442d for $C_{18}H_{20}INO_4$ NMR (d_6-DMSO) δ 8.66 (s, 1H), 8.51 (d, 1H), 8.07 (dd, 1H), 7.74 (d, 1H), 4.33-4.19 (m, 4H), 3.84 (d, 2H), 3.23-3.15 (m, 2H), 2.08-2.02 (m, 1H), 1.42-1.37 (m, 4H), 1.28 (t, 3H)	Intermediate 24 & (tetrahydro-2H-pyran-4-yl)methanamine
63	Ethyl 1-((2*S*,3*S*)-1,3-dihydroxypentan-2-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 444 for $C_{18}H_{22}INO_4$ H^1NMR (d_6-DMSO) δ 8.69 (S, 1H), 8.53 (d, 1H), 8.05 (d, 1H), 7.89 (d, 1H), 5.16-5.13 (m, 1H), 4.68 (s, 1H), 4.26-4.19 (m, 2H), 3.94-3.87 (m, 1H), 3.78-3.72 (m, 1H), 2.13-2.08 (m, 1H), 1.28 (t, 3H), 1.16-0.95 (m, 2H), 1.07 (d, 2H), 0.73 (t, 3H)	Intermediate 24 & (2*S*,3*S*)-2-amino-3-methylpentan-1-ol
64	Ethyl 1-(1-hydroxybutan-2-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 416 for $C_{16}H_{18}INO_4$ NMR (d_6-DMSO) δ 8.62 (s, 1H), 8.53 (s, 1H0, 8.06 (dd, 1H), 7.85 (d, 1H), 5.18-5.13 (m, 1H), 4.83 (s, 1H), 4.27-4.2 (m, 2H), 3.76-3.72 (m, 2H), 1.97-1.82 (m, 2H), 1.28 (t, 3H), 0.84 (t, 3H)	Intermediate 24 & 2-aminobutan-1-ol
65	Ethyl 6-iodo-1-((1-methylpiperidin-4-yl)methyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 455 for $C_{19}H_{23}IN_2O_3$ NMR (d_6-DMSO) δ 8.65 (s, 1H), 8.5 (d, 1H), 8.07 (dd, 1H), 7.71 (d, 1H), 4.27-4.19 (m, 2H), 2.74.2.7 (m, 2H), 2.09 (s, 3H), 1.72-1.66 (m, 3H), 1.45-1.42 (m, 2H), 1.28 (t, 3H)	Intermediate 24 & (1-methylpiperidin-4-yl)methanamine

Int	Compound	Data	SM
66	(*R*)-ethyl 1-(1-hydroxy-3,3-dimethylbutan-2-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 444 for $C_{18}H_{22}INO_4$ NMR (d_6-DMSO) δ 8.62 (s, 1H), 8.53 (s, 1H), 8.01 (s, 2H), 5.08-5.04 (m, 1H), 4.89-4.84 (m, 1H), 4.26-4.22 (m, 2H), 4.02-3.98 (m, 2H), 1.28 (t, 3H), 0.95 (s, 9H)	Intermediate 24 & (*R*)-2-amino-3,3-dimethylbutan-1-ol
67	(*R*)-ethyl 1-(1-hydroxy-3-(4-hydroxyphenyl)propan-2-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 494 for $C_{21}H_{20}INO_5$ NMR (d_6-DMSO) δ 8.64 (s, 1H), 8.45 (d, 1H), 7.99 (dd, 1H), 7.76 (d, 1H), 6.98 (d, 2H), 6.56 (d, 2H), 5.18 (s, 1H), 4.29-4.19 (m, 2H), 3.78 (d, 2H), 3.13-3.09 (m, 2H), 1.29 (t, 3H)	Intermediate 24 & (*R*)-4-(2-amino-3-hydroxypropyl)phenol
68	(*S*)-ethyl 1-(1-cyclohexyl-2-hydroxyethyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 470 for $C_{20}H_{24}INO_4$ NMR (d_6-DMSO) δ 8.71 (s, 1H), 8.53 (d, 1H), 8.04 (dd, 1H), 7.9 (t, 1H), 5.15 (s, 1H), 4.68 (s, 1H), 4.27-4.2 (m, 2H), 3.92-3.89 (m, 1H), 3.77-3.74 (m, 1H), 1.98-1.9 (m, 2H), 1.82-1.74 (m, 1H), 1.61-1.55 (m, 2H), 1.28 (t, 3H), 1.25-1.2 (m, 2H), 1.09-1.05 (m, 2H), 0.92-0.86 (m, 1H)	Intermediate 24 & (*S*)-2-amino-2-cyclohexylethanol

Intermediate 69

ethyl 6-iodo-1-[2-(1-methylpiperidin-4-yl)ethyl]-4-oxo-1,4-dihydroquinoline-3-carboxylate



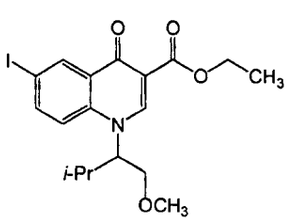
To a solution of ethyl 3-(dimethylamino)-2-(2-fluoro-5-iodobenzoyl)acrylate (Intermediate 24, 1 g, 2.56 mmol) dissolved in THF (5.5 mL) was added 2-(1-methylpiperidin-4-yl-ethanamine (0.406 mL, 2.56 mmol). The reaction mixture was stirred at 60 °C for 2 h. Potassium carbonate was added (1.06 g, 7.67 mmol), and the reaction was stirred for 18 h and cooled down to room temperature. The reaction was quenched with 1 N HCl and partitioned between dichloromethane (10 mL) and water (20 mL). The aqueous layer was extracted with dichloromethane (2x10 mL), and the organics were dried over sodium sulfate and concentrated to give ethyl 6-iodo-1-(2-(1-methylpiperidin-4-yl)ethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate as a light yellow solid (1.08 g, 90%).

MS (ESP): 469 for $C_{20}H_{25}IN_2O_4$.

NMR (d_6-DMSO) δ 8.7 (s, 1H), 8.5 (d, 1H), 8.089 (dd, 1H), 7.6 (d, 1H), 4.4-4.35 (m, 1H), 4.26-4.19 (m, 2H), 2.75-2.7 (m, 2H), 2.12 (s, 3H), 1.83-1.74 (m, 2H), 1.69-1.61 (m, 4H), 1.28 (t, 3H), 1.25-1.13 (m, 2H).

Intermediate 70

ethyl 6-iodo-1-[1-(methoxymethyl)-2-methylpropyl]-4-oxo-1,4-dihydroquinoline-3-carboxylate



To a solution of ethyl 3-(dimethylamino)-2-(2-fluoro-5-iodobenzoyl)acrylate (Intermediate 24, 1 g, 2.56 mmol) dissolved in THF (10 mL) was added 1-methoxy-3-methylbutan-2-amine hydrochloride (366 mg, 2.38 mmol) followed by potassium carbonate. The reaction mixture was stirred at 60 °C for 2 d. The reaction mixture was concentrated under reduced pressure and the residue was resuspended in DMF (10 mL). Potassium carbonate was added (978 mg,

7.08 mmol), and the reaction mixture was stirred at 70 °C for 2 h. The reaction mixture was cooled down to room temperature and quenched with 1 N HCl. The reaction mixture was partitioned between water (20 mL) and ethyl acetate (20 mL). The aqueous layer was extracted with ethyl acetate, and the organics were dried and concentrated to provide ethyl 6-iodo-1-(1-methoxy-3-methylbutan-2-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (623 mg, 60 %).

MS (ESP): 444 for $C_{18}H_{22}INO_4$.

NMR (d_6-DMSO) δ 8.69 (s, 1H), 8.53 (d, 1H), 8.05 (d, 1H), 7.94 (d, 1H), 4.83-4.78 (m, 1H), 4.26-4.2 (m, 2H), 3.9-3.74 (m, 1H), 3.71-3.68 (m, 1H), 3.46-3.4 (m, 1H), 2.3-2.26 (m, 1H), 1.28 (t, 3H), 1.11 (d, 3H), 0.92-0.85 (m, 2H), 0.71 (d, 3H).

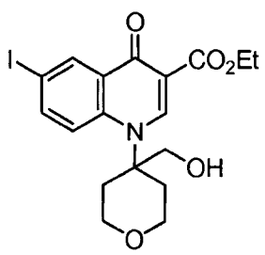
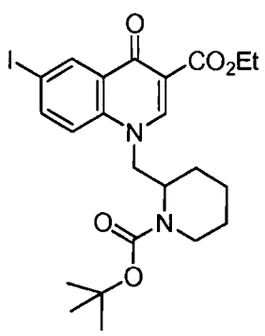
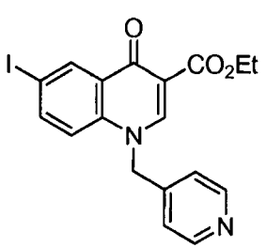
Intermediates 71-77

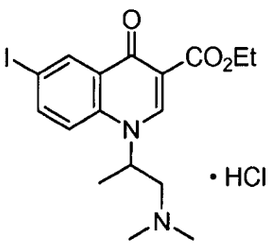
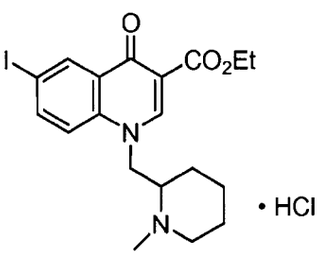
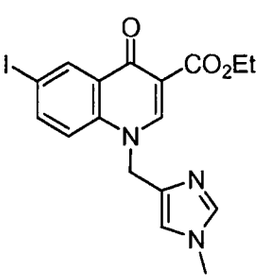
The following compounds were prepared according to either of the procedures described below from the starting materials indicated.

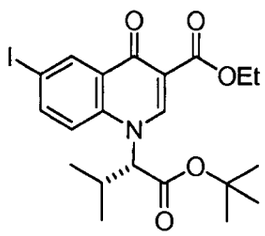
General Procedures

Procedure A: (Z)-Ethyl 3-(dimethylamino)-2-(2-fluoro-5-iodobenzoyl)acrylate (Intermediate 24, eq, 2.5 mmol) and the appropriate amine (1.1-1.2 eq) were diluted with THF (10 mL) and heated to 60 °C for 1 h. After cooling to RT, the mixture was conconcentrated *in vacuo*. Potassium carbonate (3 eq) and DMF (5 mL) were added and the mixture was then heated to 70 °C overnight. The mixture was cooled to 0 °C and acidified to approx. pH 4 with 1 N aq HCl. The resultant solid was collected and used without additional purification.

Procedure B: (Z)-Ethyl 3-(dimethylamino)-2-(2-fluoro-5-iodobenzoyl)acrylate (Intermediate 24, 1 eq, 2.5 mmol) and the appropriate amine hydrochloride salt (1.1-1.2 eq) were diluted with THF (10 mL). Potassium carbonate (1.2 eq) was added and the mixture was heated to 60 °C for 1 h. After cooling to room temperature, the mixture was concentrated *in vacuo*. Additional potassium carbonate (3 eq) and DMF (5 mL) were added and the mixture was then heated to 70 °C overnight. The mixture was cooled to 0 °C and acidified to approx. pH 4 with 1 N aq HCl. The resultant solid was collected and used without additional purification

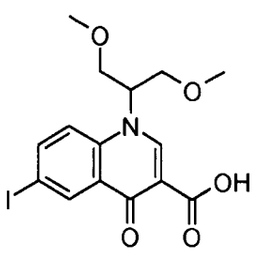
Int	Compound	Data	SM
71	ethyl 1-(4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 458 for $C_{18}H_{20}INO_5$ NMR ($DMSO-d_6$): δ8.71 (s, 1H); 8.57 (d, 1H); 8.05 (m, 1H); 7.94 (dd, 1H); 5.36 (br s, 1H); 4.23 (q, 2H); 4.17 (s, 2H); 3.68 (m, 4H); 2.35 (m, 4H); 1.27 (t, 3H).	(4-amino-tetrahydro-2H-pyran-4-yl)methanol
72	ethyl 1-((1-(tert-butoxycarbonyl)piperidin-2-yl)methyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 541 for $C_{23}H_{29}IN_2O_5$ ^1H NMR ($DMSO-d_6$): δ8.50 (d, 1H); 8.47 (s, 1H); 8.06 (d, 1H); 7.73 (d, 1H); 4.70 (m, 1H); 4.47 (m, 2H); 4.21 (m, 2H); 3.91 (m, 1H); 3.14 (m, 1H); 1.87 (m, 1H); 1.59 (m, 4H); 1.26 (m, 4H); 1.10 (br s, 3H); 0.75 (br s, 6H).	2-(Amino-methyl)-1-N-Boc-piperidine
73	ethyl 6-iodo-4-oxo-1-(pyridin-4-ylmethyl)-1,4-dihydroquinoline-3-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 435 for $C_{18}H_{15}IN_2O_3$ ^1H NMR ($DMSO-d_6$): δ8.92 (s, 1H); 8.51 (m, 3H); 7.95 (dd, 1H); 7.31 (d, 1H); 7.17 (m, 2H); 5.72 (s, 2H); 4.24 (q, 2H); 1.28 (t, 3H).	4-Aminomethyl pyridine

Int	Compound	Data	SM
74	ethyl 1-(1-(dimethylamino)propan-2-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate, hydrochloride salt 	LC/MS (ES^+)[$(M+H)^+$]: 429 for $C_{17}H_{21}IN_2O_3$ ^1H NMR (DMSO-d_6): δ10.23 (br s, 1H); 8.53 (s, 1H); 8.45 (d, 1H); 8.03 (m, 1H); 7.88 (m, 1H); 5.42 (br s, 1H); 4.17 (q, 2H); 3.72 (m, 1H); 3.59 (m, 1H); 2.70 (br s, 6H); 1.50 (m, 3H); 1.21 (t, 3H).	1-Dimethyl-amino-2-propylamine
75	ethyl 6-iodo-1-((1-methylpiperidin-2-yl)methyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate, hydrochloride salt 	LC/MS (ES^+)[$(M+H)^+$]: 455 for $C_{19}H_{23}IN_2O_3$	(1-Methyl-piperidin-2-yl)methan-amine
76	ethyl 6-iodo-1-((1-methyl-1H-imidazol-4-yl)methyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 438 for $C_{17}H_{16}IN_3O_3$ ^1H NMR (DMSO-d_6): δ8.82 (s, 1H); 8.47 (d, 1H); 8.00 (dd, 1H); 7.79 (d, 1H); 7.51 (s, 1H); 7.21 (s, 1H); 5.41 (s, 2H); 4.23 (q, 2H); 3.58 (s, 3H); 1.28 (t, 3H).	(1-Methyl-1H-imidazol-4-yl)methan-amine

Int	Compound	Data	SM
77	(S)-ethyl 1-(1-tert-butoxy-3-methyl-1-oxobutan-2-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 500 for $C_{21}H_{26}INO_5$ ^1H NMR (DMSO-d_6): δ8.66 (m, 1H); 8.53 (d, 1H); 8.10 (dd, 1H); 7.95 (m, 1H); 5.26 (d, 1H); 4.24 (q, 2H); 2.60 (m, 1H); 1.36 (br s, 9H); 1.28 (t, 3H); 1.15 (m, 3H); 0.78 (br s, 3H).	L-valine tert-butyl ester hydrochloride

Intermediate 78

1-(1,3-dimethoxypropan-2-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



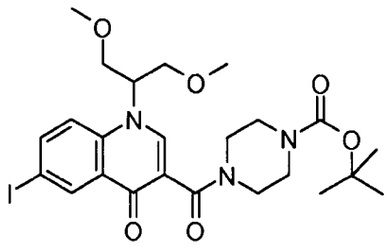
Ethyl 1-(1,3-dimethoxypropan-2-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate (Intermediate 22, 270 mg, 0.60 mmol) was dissolved in tetrahydrofuran (20 mL) and water (5 mL). Lithium hydroxide (56 mg, 2.42 mmol) was added and the mixture was stirred for 10 min at room temperature. The reaction mixture was then refluxed at 80 °C for 1 h. The reaction mixture was concentrated under reduced pressure and water (10 mL) was added. The pH was adjusted to 2 with hydrochloric acid (2N) and the solid that precipitated was collected by filtration and dried to afford 185 mg (75%) of 1-(1,3-dimethoxypropan-2-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

^1H NMR (400 MHz, DMSO-d_6): δ 3.22 (s, 6H), 3.62 (q, 2H), 3.72 (q, 2H), 4.68 (m, 1H), 7.81 (d, 1H), 8.14 (d, 1H), 8.78 (s, 1H), 9.14 (s, 1H).

LC-MS: m/z 417.8 (M+H).

Intermediate 79

Tert-butyl 4-{[1-(1,3-dimethoxypropan-2-yl)-6-iodo-4-oxo-1,4-dihydroquinolin-3-yl]carbonyl}piperazine-1-carboxylate



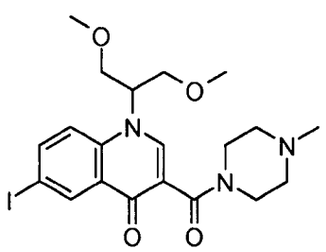
To a solution of 1-(1,3-dimethoxypropan-2-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Intermediate 78, 500 mg, 1.12 mmol) and tert-butyl piperazine-1-carboxylate (312 mg, 1.67 mmol) in dichloromethane (50 mL) was added hydroxybenzotriazole (HOBT) (183 mg, 1.12 mmol) and N-methyl morpholine (484 mg, 4.79 mmol). The reaction mixture was stirred for 1 h at room temperature and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI HCl) (390.mg, 2.15 mmol) was added. The resulting reaction mixture was stirred for room temperature overnight. The reaction mixture was quenched with dilute hydrochloric acid (2N, 30 mL) and the layers were separated. The organic layer was washed with saturated sodium bicarbonate solution (40 mL), water (60 mL) and finally with brine successively and dried over anhydrous sodium sulphate, filtered, concentrated under vacuum to afford tert-butyl 4-{[1-(1,3-dimethoxypropan-2-yl)-6-iodo-4-oxo-1,4-dihydroquinolin-3-yl]carbonyl}piperazine-1-carboxylate 400 mg (57%) as thick oil.

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.40 (s, 9H), 3.08 – 3.28 (m, 12H), 3.22 – 3.72 (m, 8H), 3.79 (m, 1H), 4.52 (m, 1H), 7.82 (d, 1H), 8.08 (d, 1H), 8.78 (2s, 2H).

MASS (APCI +ve Scan): m/z 586.1 (M+H).

Intermediate 80

1-(1,3-dimethoxypropan-2-yl)-6-iodo-3-[(4-methylpiperazin-1-yl)carbonyl]quinolin-4(1H)-one



To a solution of 1-(1,3-dimethoxypropan-2-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Intermediate 78, 300 mg, 0.72 mmol) and 1-methylpiperazine (100 mg, 1.00 mmol) in dichloromethane (50 mL) was added hydroxybenzotriazole (HOBT) (110 mg, 0.72 mmol) and N-methylmorpholine (290 mg, 2.87 mmol). The reaction mixture was stirred for 1

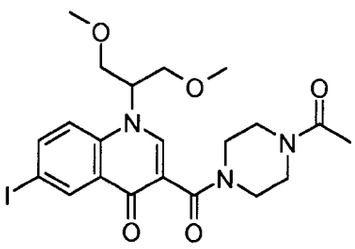
h at room temperature and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC HCl) (234 mg, 1.29 mmol) was added. The resulting reaction mixture was stirred at room temperature over night. The reaction mixture was quenched with 2N hydrochloric acid (30 mL) and the layers were separated. The organic layer was washed with saturated sodium bicarbonate solution (40 mL), water (60 mL) and finally with brine successively and dried over anhydrous sodium sulphate, filtered and concentrated under vacuum to afford 1-(1,3-dimethoxypropan-2-yl)-6-iodo-3-[(4-methylpiperazin-1-yl) carbonyl] quinolin-4(1H)-one 300 mg (80%) as thick oil.

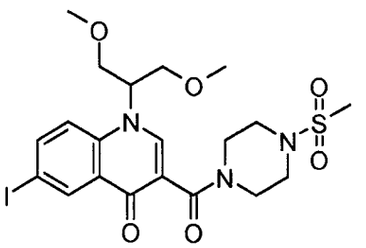
^{1}H NMR (400 MHz, DMSO-d_6): δ 2.17 (s, 2H), 2.21 (s, 3H), 3.21 – 3.46 (m, 4H), 3.16 – 3.31 (s, 6H), 3.41 – 3.72 (m, 5H), 3.85 (s, 1H), 4.57 (m, 1H), 7.81 (d, 1H), 8.07 (d, 1H), 8.74 (2s, 2H).

MASS (APCI +ve Scan): m/z 500 (M+H).

Intermediates 81-82

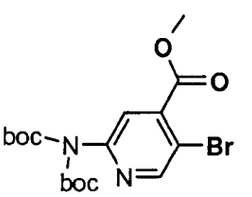
The following compounds were prepared according to the procedure described for Intermediate 80 from the starting material listed in the table.

Int	Compound	Data	SM
81	3-[(4-acetylpiperazin-1-yl)carbonyl]-1-(1,3-dimethoxypropan-2-yl)-6-iodoquinolin-4(1H)-one 	^{1}H NMR (400 MHz, DMSO-d_6): δ 1.96 – 2.20 (m, 3H), 2.10 (s, 3H), 2.35 (m, 3H), 3.18 – 3.30 (m, 6H), 3.79 (m, 1H), 4.56 (m, 1H), 7.82 (d, 1H), 8.09 (d, 1H), 8.78 (m, 2H). MASS (APCI +ve Scan): m/z 528.1 (M+H)	Intermediate 78 and 3-(4-acetyl)piperazine

Int	Compound	Data	SM
82	1-(1,3-dimethoxypropan-2-yl)-6-iodo-3-{[4-(methylsulfonyl)piperazin-1-yl]carbonyl}quinolin-4(1H)-one 	^{1}H NMR (400 MHz, DMSO-d_6): δ 2.97 (s, 3H), 3.11 – 3.40 (m, 14H), 3.45 (m, 1H), 3.56 (m, 4H), 4.04 (m, 1H), 4.53 (m, 1H), 7.81 (d, 1H), 8.12 (d, 1H), 8.78 (br s, 2H). MASS (APCI +ve Scan): m/z 564.0 (M+H)	Intermediate 78 and 3-(4-methane-sulfonyl)pip-erazine

Intermediate 83

Methyl 2-(bis(tert-butoxycarbonyl)amino)-5-bromoisonicotinate



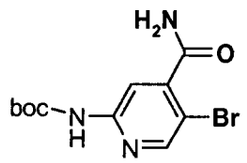
To a 5 L round bottom flask was charged methyl 2-amino-5-bromoisonicotinate (200 g, 866 mmol) and *tert*-butanol (3000 mL). The reaction mixture was kept at 30°C, then 4-dimethylaminopyridine (DMAP, 6.3 g, 52 mmol) and di-*tert*-butyl dicarbonate (566 g, 2.6 mol) were added, the resulting mixture was slowly heated to 60°C for 2 h. The reaction mixture was concentrated under reduced pressure to one-fourth volume. A yellow needle-like solid precipitated which was collected by filtration and washed by ethanol. After drying under vacuum overnight at 25°C, the first crop was obtained as 282 g pale yellow needle-like solid.

MS (ESP): 277.1 ($M+H^+$-Boc-tBu) for $C_{17}H_{23}BrN_2O_6$

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.5 (s, 18H), 4.0 (s, 32H), 7.7 (s, 1H), 8.7 (s, 1H).

Intermediate 84

tert-butyl 5-bromo-4-carbamoylpyridin-2-ylcarbamate



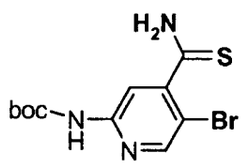
A solution of methyl 2-(bis(tert-butoxycarbonyl)amino)-5-bromoisonicotinate (Intermediate 83, 100 g, 232 mmol) in 7 N ammonia in methanol (600 mL) was allowed to stir at 50°C in a 1 L sealed tube overnight. The resulting mixture was evaporated to dryness and the crude product was directly used for the next step without further purification.

MS (ESP): 339.9 ($M+Na^+$) for $C_{11}H_{14}BrN_3O_3$

^1H NMR (300 MHz, dmso-d_6): δ 1.47 (s, 9H), 7.82 (d, 2H), 8.07 (s, 1H), 8.41 (d, 1H), 10.2 (s, 1H).

Intermediate 85

tert-butyl 5-bromo-4-carbamothioylpyridin-2-ylcarbamate



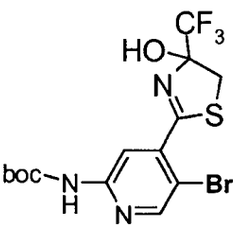
The crude tert-butyl 5-bromo-4-carbamoylpyridin-2-ylcarbamate (Intermediate 84, 232 mmol) was treated with Lawesson's Reagent (94 g, 232 mmol, 1 eq) and tetrahydrofuran (700 mL), the resulting mixture was heated at reflux for 1 h, then it was allowed to stir at room temperature over the weekend. The mixture was concentrated to dryness *in vacuo* and toluene (~300 mL) was added. A bright yellow solid precipitated formed which was collected by filtration and washed with toluene, then dried in the vacuum oven at 50°C for 4 h, yielding 75 g of a bright yellow solid (97%).

MS (ESP): 354.2 ($M+Na^+$) for $C_{11}H_{14}BrN_3O_2S$

^1H NMR (300 MHz, $CDCl_3$): δ 1.53 (s, 9H), 7.03 (br, 1H), 7.61 (br, 1H), 7.74 (br, 1H), 8.2 (s, 1H), 8.35 (s, 1H).

Intermediate 86

tert-butyl 5-bromo-4-(4-hydroxy-4-(trifluoromethyl)-4,5-dihydrothiazol-2-yl)pyridin-2-ylcarbamate



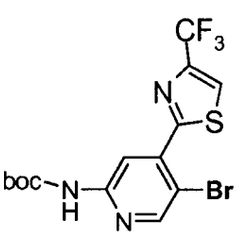
To a 2 L round bottom flask was charged tert-butyl 5-bromo-4-carbamothioylpyridin-2-ylcarbamate (Intermediate 85, 50 g, 151 mmol) in tetrahydrofuran (800 mL), then solid sodium bicarbonate (25.4 g, 302 mmol) was added followed by 1,1,1-trifluoro-3-bromoacetone (31 mL, 290 mmol). The resulting mixture (yellow suspension) was allowed to stir at room temperature overnight. The white suspension was filtered and the solid was washed with water (2.2~2.5 L). The white solid was dried under vacuum to give 56.8g of white powder (85%)

MS (ESP): 386.0 (M-*t*-Bu) for $C_{14}H_{15}BrF_3N_3O_3S$

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.6 (s, 9 H), 3.3 (br, 2H), 3.6 (d, 1H), 3.9 (d, 1H), 8.2 (s, 1H), 8.5 (s, 1H).

Intermediate 87

tert-butyl 5-bromo-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-ylcarbamate



To a 2L round bottom flask was charged tert-butyl 5-bromo-4-(4-hydroxy-4-(trifluoromethyl)-4,5-dihydrothiazol-2-yl)pyridin-2-ylcarbamate (Intermediate 86, 56.8 g, 128 mmol) and dimethoxyethane (800 mL). The reaction mixture was chilled in an ice-water bath, then trifluoroacetic anhydride (69 mL, 514mmol) and 2,6-lutidine (133 mL, 1.15 mol) were added simultaneously over 1h. An orange/yellow solution which resulted was allowed to stir in the ice-water bath for 30 min, then the solution was warmed to room temperature. The orange solution was concentrated under reduced pressure to dryness, and the resulting

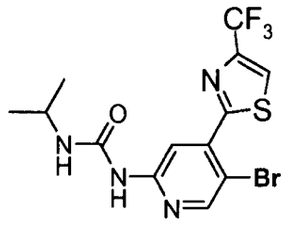
residue was triturated with methanol. The solid was collected by filtration and washed with more methanol, dried under vacuum overnight, yielding 49 g of white solid.

MS (ESP): 368.0 (M-*t*-Bu) for $C_{14}H_{13}BrF_3N_3O_2S$

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.6 (s, 9H), 8.0 (s, 1H), 8.2 (br, 1H), 8.55 (s, 1H), 8.65 (s, 1H).

Intermediate 88

1-(5-bromo-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-isopropylurea

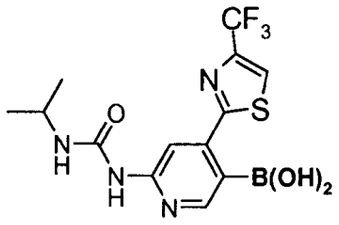


A mixture of tert-butyl 5-bromo-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-ylcarbamate (Intermediate 87, 25 g, 59 mmol), isopropyl amine (250 mL) and acetonitrile (100 mL) was heated at 130°C in a Parr Bomb apparatus for 50 h (~150 PSI). The reaction mixture was cooled to room temperature and the reaction filtered through Celite, and the filtrate was washed with tetrahydrofuran (~300 mL). The solvents were evaporated and the residue was triturated with methanol (200 mL), filtered and the solid was dried to give 14.6 g of product.

MS (ESP): 410 (MH^+) for $C_{13}H_{12}BrF_3N_4OS$.

Intermediate 89

6-(3-isopropylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-ylboronic acid



A suspension of 1-(5-bromo-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-isopropylurea (Intermediate 88, 14.6 g, 35.7 mmol) in tetrahydrofuran (400 mL) was prepared and stirred at -50°C. 2.0M Isopropyl magnesium chloride in tetrahydrofuran (53.6 mL, 107 mmol) was added dropwise over 45 min so that the temperature never rose above -35°C. The reaction mixture was stirred for 1 h at -40°C then was cooled to -78°C. 2.5M n-Butyl lithium in hexanes (85.8 mL, 215mmol) was then added dropwise to the reaction solution so that the temperature never rose above -65°C. This reaction mixture was then allowed to react at -78°C

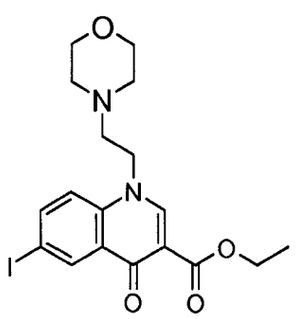
for 1.5 h. Boron methoxide (44 mL, 394 mmol) was added in 1 portion and the cold bath was removed. The reaction mixture was allowed to warm to room temperature and stir for 1 h. 3N Hydrochloric acid (500 mL) was then added slowly to minimize foaming and the reaction was stirred at room temperature for 30 min. The reaction mixture was concentrated under high vacuum to remove the tetrahydrofuran and water (1L). The solution was basified to pH 10 with 24% sodium hydroxide and the total volume was increased to 2L with water. The aqueous solution was extracted with methyl tert-butyl ether (3 × 300 mL). The organic layers were combined and extracted with 5% sodium hydroxide (100 mL). The aqueous phases were combined and acidified to pH 5.5 with 6 N hydrochloric acid when a suspension formed. This suspension was extracted with 2:1 ethyl acetate: THF (5 × 400 mL). The organic phases were combined and back washed with water (1 L). The organics were concentrated and triturated with methyl tert-butyl ether (1 L). The solid obtained was dried in a vacuum oven at 50°C to give 10.4 g of product.

MS (ESP): 375.0 (MH^+) for $C_{13}H_{14}BF_3N_4O_3S$

^1H NMR (300 MHz, DMSO-d_6): δ 1.24 (d, 6H), 3.98 (m, 1H), 7.80 (bt, 1H), 7.91 (s, 1H), 8.20 (br, 2H), 8.31 (d, 1H), 8.63 (m, 1H), 9.32 (s, 1H).

Intermediate 90

ethyl 6-iodo-1-(2-morpholinoethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate



2-Morpholinoethanamine (0.88 g, 6.7 mmol) was added to the stock solution of (Z)-ethyl 3-(dimethylamino)-2-(3-iodobenzoyl)acrylate (Intermediate 24, 0.38M, 18 mL, 7 mmol) and the mixture was heated at 40°C for 3 h. The solvent was removed *in vacuo* and the resulting residue was dried in a vacuum oven for 1.5 h. The residue was then dissolved in dimethyl formamide (5 mL) and potassium carbonate powder (1.2 g, 10 mmol) was added. The reaction was heated at 70°C for a further 3 h then cooled to room temperature. The crude reaction mixture was placed into a fridge for a 3 h. The solid precipitate that formed was

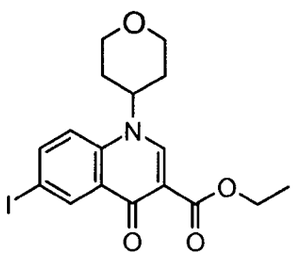
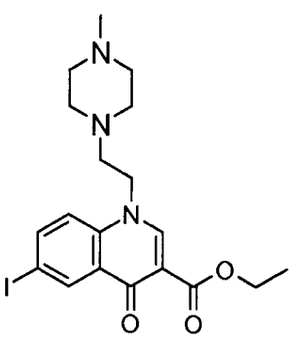
collected by filtration, washed with a small amount of dimethylformamide, followed by water, then dried under high vacuum.

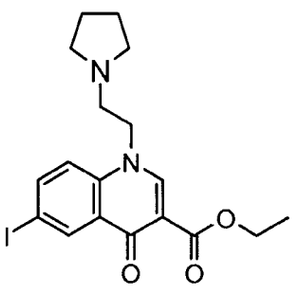
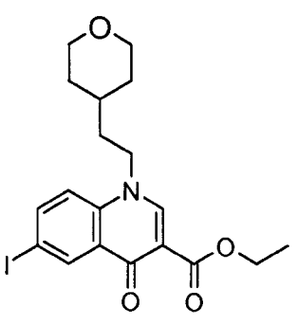
MS (ESP): 457 ($M+H^+$) for $C_{18}H_{21}IN_2O_4$

^{1}H NMR (300 MHz, DMSO-d_6): δ 1.28 (t, 3H), 2.42 (brs, 4H), 2.61 (brs, 2H), 3.50 (br, 4H), 4.23 (q, 2H), 4.46 (br, 2H), 7.67 (d, 1H), 8.05, (d, 1H), 8.50 (s, 1H), 8.64 (s, 1H).

Intermediates 91-94

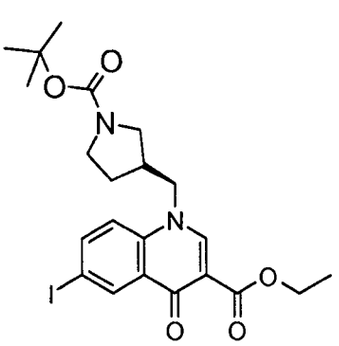
The following compounds were prepared according to the procedure described for Intermediate 90 from the starting materials indicated.

Int	Compound	Data	SM
91	ethyl 6-iodo-4-oxo-1-(tetrahydro-2H-pyran-4-yl)-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 428.1 ($M+H^+$) for $C_{17}H_{18}INO_4$ ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.29 (t, 3H), 2.00 (brs, 4H), 3.64 (m, 2H), 4.00 (d, 2H), 4.23 (q, 2H), 4.95 (m, 1H), 7.92 (d, 1H), 8.06 (d, 1H), 8.53 (s, 1H), 8.60 (s, 1H)	Intermediate 24 and tetrahydro-2*H*-pyran-4-amine
92	ethyl 6-iodo-1-(2-(4-methylpiperazin-1-yl)ethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 470.1 ($M+H^+$) for $C_{19}H_{24}IN_3O_3$ ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.29 (t, 3H), 2.10 (s, 3H), 2.22 (br, 4H), 2.41 (br, 4H), 2.60 (t, 2H), 4.22 (q, 2H), 4.43 (t, 2H), 7.66 (d, 1H), 8.03 (d, 1H), 8.50 (s, 1H), 8.59 (s, 1H).	Intermediate 24 and 2-(4-methyl-piperazino)-ethanamine

Int	Compound	Data	SM
93	ethyl 6-iodo-4-oxo-1-(2-(pyrrolidin-1-yl)ethyl)-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 441.1 ($M+H^+$) for $C_{18}H_{21}IN_2O_3$ ^1H NMR (300 MHz, dmso-d_6): δ 1.28 (t, 3H), 1.65 (br, 4H), 2.48 (m, 4H), 2.75 (br, 2H), 4.20 (q, 2H), 4.45 (m, 2H), 7.64 (d, 1H), 8.04 (d, 1H), 8.63 (s, 1H), 8.65 (s, 1H)	Intermediate 24 and 2-pyrrolidino-ethanamine
94	ethyl 6-iodo-4-oxo-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 456.1 ($M+H^+$) for $C_{19}H_{22}INO_4$ ^1H NMR (300 MHz, $CDCl_3$): δ 1.22 (m, 1H), 1.28 (t, 3H), 1.67 (m, 4H), 3.27 (t, 2H), 3.34 (m, 2H), 3.84 (d, 2H), 4.22 (q, 2H), 4.40 (m, 2H), 7.59 (d, 1H), 8.08 (d, 1H), 8.50 (s, 1H), 8.72 (s, 1H)	Intermediate 24 and 2-(tetrahydro-2*H*-pyran-4-yl)-ethanamine

Intermediate 95

(R)-ethyl 1-((1-(tert-butoxycarbonyl)pyrrolidin-3-yl)methyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate



(R)-3-(Aminomethyl)-1-N-Boc-pyrrolidine (994 mg, 4.86 mmol) was added to the stock solution of (Z)-ethyl 3-(dimethylamino)-2-(3-iodobenzoyl)acrylate (Intermediate 24, 0.34M,

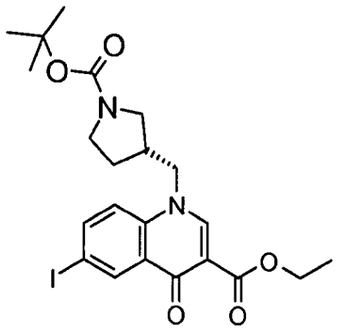
13 mL, 4.42 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* and the residue was dried in a vacuum oven for 1.5 h. The resulting residue was then dissolved in dimethylformamide (8 mL) and potassium carbonate powder (670 mg, 4.86 mmol) was added. The reaction mixturwe was heated at 60°C for overnight then cooled to room temperature. Water (50 mL) was added and the suspension was extracted with ethyl acetate (3 × 50 mL). The organic layers were dried over sodium sulfate, and the solvent was removed *in vacuo* to give quantitative (R)-ethyl 1-((1-(tert-butoxycarbonyl)pyrrolidin-3-yl)methyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate as a brown sticky solid.

MS (ESP): 527.1 ($M+H^+$) for $C_{22}H_{27}IN_2O_5$

^1H NMR (300 MHz, DMSO-d_6): δ 1.42 (t, 3H), 1.46 (s, 9H), 1.71 (m, 1H), 2.02 (bm, 1H), 2.78 (bs, 1H), 3.12 (bs, 1H), 3.25-3.62 (bm, 3H), 3.96-4.40 (bm, 2H), 4.42 (q, 2H), 7.19 (d, 1H), 7.92 (dd, 1H), 8.40 (s, 1H), 8.83 (s, 1H).

Intermediate 96

(S)-ethyl 1-((1-(tert-butoxycarbonyl)pyrrolidin-3-yl)methyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate



(S)-3-(Aminomethyl)-1-N-Boc-pyrrolidine (994 mg, 4.86 mmol) was added to the stock solution of (Z)-ethyl 3-(dimethylamino)-2-(3-iodobenzoyl)acrylate (Intermediate 24, 0.34M, 13 mL, 4.42 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* and the residue was dried in a vacuum oven for 1.5 h. The resulting residue was then dissolved in dimethylformamide (8 mL) and potassium carbonate powder (670 mg, 4.86 mmol) was added. The reaction mixture was heated at 60°C for overnight then cooled to room temperature. Water (50 mL) was added and the suspension was extracted with ethyl acetate (3 × 50 mL). The organic layers were dried over sodium sulfate, and the solvent was removed *in vacuo* to give quantitative (S)-ethyl 1-((1-(tert-

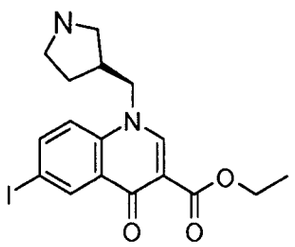
butoxycarbonyl)pyrrolidin-3-yl)methyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate as a brown sticky solid.

MS (ESP): 527.1 ($M+H^+$) for $C_{22}H_{27}IN_2O_5$

^1H NMR (300 MHz, DMSO-d_6): δ 1.42 (t, 3H), 1.46 (s, 9H), 1.71 (m, 1H), 2.02 (bm, 1H), 2.78 (bs, 1H), 3.12 (bs, 1H), 3.25-3.62 (bm, 3H), 3.96-4.40 (bm, 2H), 4.42 (q, 2H), 7.19 (d, 1H), 7.92 (dd, 1H), 8.40 (s, 1H), 8.83 (s, 1H).

Intermediate 97

(R)-ethyl 6-iodo-4-oxo-1-(pyrrolidin-3-ylmethyl)-1,4-dihydroquinoline-3-carboxylate hydrochloride

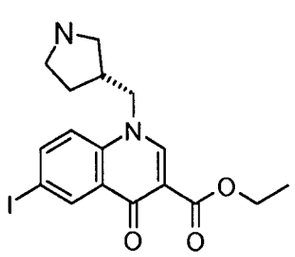


The crude (R)-ethyl 1-((1-(tert-butoxycarbonyl)pyrrolidin-3-yl)methyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate (Intermediate 95, ~4.4 mmol) was dissolved in 1,4-dioxane (20 mL) and 4.0M hydrogen chloride in 1,4-dioxane (20 mL) was added. The reaction mixture was stirred at room temperature for 1 h, and the solvent was removed *in vacuo*. The solid was then dried in a vacuum oven at 40°C for 18 h to give 2.3 g (quant. yield) of (R)-ethyl 6-iodo-4-oxo-1-(pyrrolidin-3-ylmethyl)-1,4-dihydroquinoline-3-carboxylate hydrochloride as a yellow solid.

MS (ESP): 427.1 ($M+H^+$) for $C_{17}H_{19}IN_2O_3$

Intermediate 98

(S)-ethyl 6-iodo-4-oxo-1-(pyrrolidin-3-ylmethyl)-1,4-dihydroquinoline-3-carboxylate hydrochloride

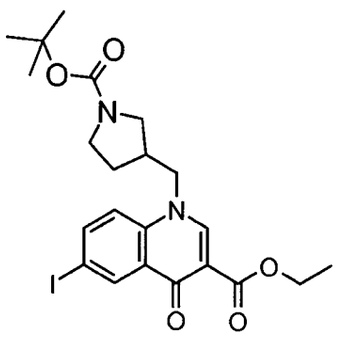


The crude (S)-ethyl 1-((1-(tert-butoxycarbonyl)pyrrolidin-3-yl)methyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate (Intermediate 96, ~4.4 mmol) was dissolved in 1,4-dioxane (20 mL) and 4.0M hydrogen chloride in 1,4-dioxane (20 mL) was added. The reaction mixture was stirred at room temperature for 1 h, and the solvent was removed *in vacuo*. The solid was then dried in a vacuum oven at 40°C for 18 h to give 2.3 g (quant. yield) of (S)-ethyl 6-iodo-4-oxo-1-(pyrrolidin-3-ylmethyl)-1,4-dihydroquinoline-3-carboxylate hydrochloride as a yellow solid.

MS (ESP): 427.1 ($M+H^+$) for $C_{17}H_{19}IN_2O_3$

Intermediate 99

ethyl 1-((1-(tert-butoxycarbonyl)pyrrolidin-3-yl)methyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate



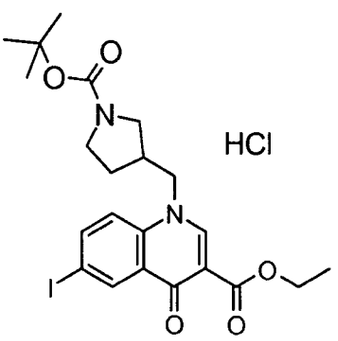
3-(Aminomethyl)-1-N-Boc-pyrrolidine (2.5 g, 12.5 mmol) was added to the stock solution of (Z)-ethyl 3-(dimethylamino)-2-(3-iodobenzoyl)acrylate (Intermediate 24, 0.34M, 34 mL, 11.3 mmol). The reaction mixture was heated at 50°C for 3 h. The solvent was removed *in vacuo* and the resulting residue was dried in a vacuum oven for 1.5 h. The residue was then dissolved in dimethylformamide (20 mL) and potassium carbonate powder (2.2 g, 15.8 mmol) was added. The reaction mixture was heated at 70°C for 3 h then cooled to room temperature. Water (100 mL) was added and the suspension was extracted with 1:1 ethyl acetate: methyl tert-butyl ether (3 × 50 mL). The organic layers were dried over sodium sulfate, and the solvent was removed *in vacuo*. The residue was suspended in methyl tert-butyl ether (20 mL) and stirred at 40°C for 1 h. The suspension was filtered and the solid dried to give 4.15g (70% yield) of ethyl 1-((1-(tert-butoxycarbonyl)pyrrolidin-3-yl)methyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate as a yellowish powder.

MS (ESP): 527.1 ($M+H^+$) for $C_{22}H_{27}IN_2O_5$

^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 1.42 (t, 3H), 1.46 (s, 9H), 1.71 (m, 1H), 2.02 (bm, 1H), 2.78 (bs, 1H), 3.12 (bs, 1H), 3.25-3.62 (bm, 3H), 3.96-4.40 (bm, 2H), 4.42 (q, 2H), 7.19 (d, 1H), 7.92 (dd, 1H), 8.40 (s, 1H), 8.83 (s, 1H)

Intermediate 100

ethyl 6-iodo-4-oxo-1-(pyrrolidin-3-ylmethyl)-1,4-dihydroquinoline-3-carboxylate hydrochloride

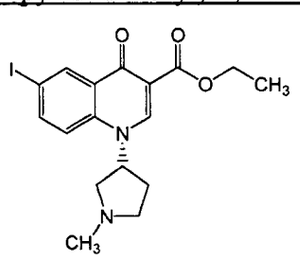


Ethyl 1-((1-(tert-butoxycarbonyl)pyrrolidin-3-yl)methyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate (Intermediate 99, 3.0 g, 5.7 mmol) was dissolved in 1,4-dioxane (15 mL) and 4.0M hydrogen chloride in 1,4-dioxane (10 mL) was added. The reaction was stirred at 23°C for 3 hours, and the solvent was removed *in vacuo*. The solid was then dried in a vacuum oven at 50°C for 18 h to give 2.61 (quant. yield) of ethyl 6-iodo-4-oxo-1-(pyrrolidin-3-ylmethyl)-1,4-dihydroquinoline-3-carboxylate hydrochloride as a yellow solid.

MS (ESP): 427.1 ($M+H^+$) for $C_{17}H_{19}IN_2O_3$

Intermediate 101

(*R*)-ethyl 6-iodo-4-oxo-1-(1-methyl-pyrrolidin-3-yl)-1,4-dihydroquinoline-3-carboxylate



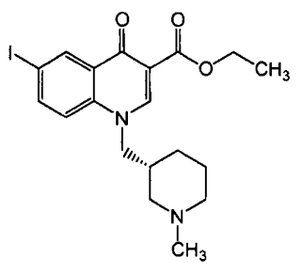
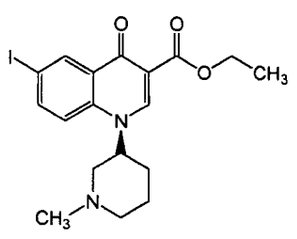
To a solution of (*R*)-ethyl 6-iodo-4-oxo-1-(pyrrolidin-3-yl)-1,4-dihydroquinoline-3-carboxylate (Intermediate 110, 282 mg, 0.68 mmol, 1 equiv.) in THF (7 mL) was added iodomethane (0.0471 mL, 0.75 mmol, 1.1 equiv.) followed by potassium carbonate (378 mg, 2.74 mmol, 4 equiv.). This was stirred at 60 °C for 1 d. The reaction mixture was cooled to room temperature and partitioned between ethyl acetate (10 mL) and water (10 mL). The

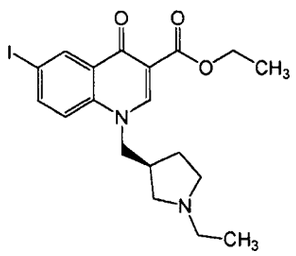
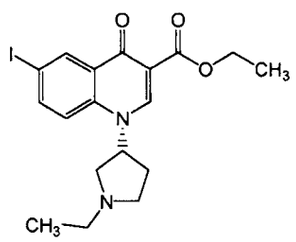
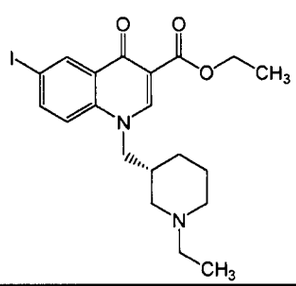
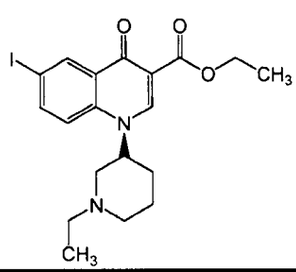
aqueous layer was extracted with ethyl acetate (2 x 10 mL), and the organics were concentrated to provide (*R*)-ethyl 6-iodo-1-(1-methylpyrrolidin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate as a light yellow solid (282 mg, >99 %).

NMR (d_6-DMSO) δ 8.97 (s, 1H), 8.51 (s, 1H), 8.13 (dd, 1H), 7.86 (d, 1H), 5.46-4.38 (m, 1H), 4.28-4.18 (m, 2H), 3.59-3.54 (m, 1H), 3.24-3.1 (m, 3H), 2.6-2.54 (m, 2H), 2.36 (s, 3H), 2.26-2.14 (m, 2H), 1.28 (t, 3H).

Intermediates 102-107

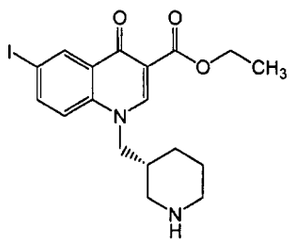
The following Intermediates were prepared according to the procedure described for Intermediate 101 from the indicated starting materials.

Int	Compound	Data	SM
102	(*R*)-ethyl 6-iodo-1-((1-methylpiperidin-3-yl)methyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	Calcd for $C_{19}H_{23}IN_2O_3$ [M + H]$^+$: 454.96	Iodomethane and Intermediate 108
103	(*R*)-ethyl 6-iodo-1-(1-methylpiperidin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	Calcd for $C_{18}H_{21}IN_2O_3$ [M + H]$^+$: 440.91	Iodomethane & Intermediate 111

Int	Compound	Data	SM
104	(*S*)-ethyl 1-((1-ethylpyrrolidin-3-yl)methyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	Calcd for $C_{19}H_{23}IN_2O_3$ [M + H]$^+$: 455.01	Iodoethane & Intermediate 109
105	(*R*)-ethyl 1-(1-ethylpyrrolidin-3-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	Calcd for $C_{18}H_{21}IN_2O_3$ [M + H]$^+$: 441.0	Iodoethane & Intermediate 110
106	(*R*)-ethyl 1-((1-ethylpiperidin-3-yl)methyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	Calcd for $C_{20}H_{25}IN_2O_3$ [M + H]$^+$: 469.11	Iodoethane & Intermediate 108
107	(*R*)-ethyl 1-(1-ethylpiperidin-3-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	Calcd for $C_{19}H_{23}IN_2O_3$ [M + H]$^+$: 454.66	Iodoethane & Intermediate 111

Intermediate 108

(*S*)-ethyl 1-(1-piperidin-3-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate

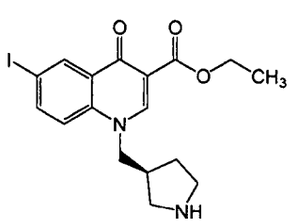


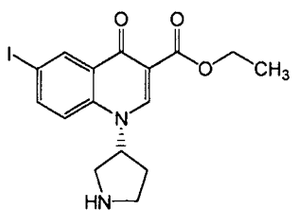
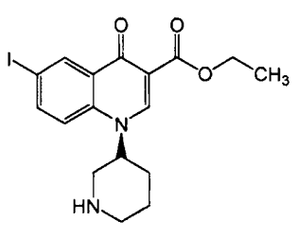
To a solution of (*S*)-ethyl 1-((1-(*tert*-butoxycarbonyl)piperidin-3-yl)methyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate (Intermediate 112, 2.47 g, 4.57 mmol, 1 equiv.) in dichloromethane (18 mL) was added 4 N hydrogen chloride (4.57 mL, 18.28 mmol, 4 equiv.). This was stirred at room temperature for 12 h. The precipitate was washed with diethyl ether and dried to provide (*R*)-ethyl 6-iodo-4-oxo-1-(piperidin-3-ylmethyl)-1,4-dihydroquinoline-3-carboxylate as a light yellow solid (2.1 g, >99 %).

Calcd for $C_{18}H_{21}IN_2O_3$ $[M + H]^+$: 440.95.

Intermediates 109-111

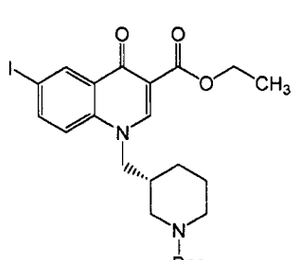
The following Intermediates were prepared according to the procedures described for Intermediate 108 from the indicated starting materials.

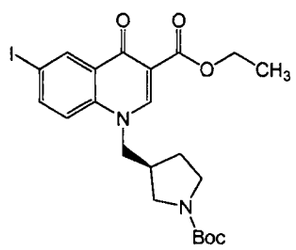
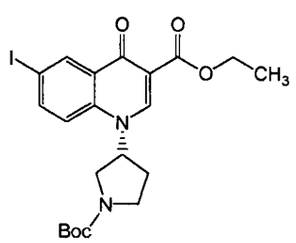
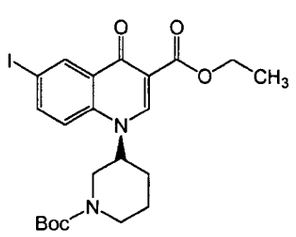
Int	Compound	Data	SM
109	(*S*)-ethyl 6-iodo-4-oxo-1-(pyrrolidin-3-ylmethyl)-1,4-dihydroquinoline-3-carboxylate 	Calcd for $C_{17}H_{19}IN_2O_3$ $[M + H]^+$: 426.94	Intermediate 113

Int	Compound	Data	SM
110	(*R*)-ethyl 6-iodo-4-oxo-1-(pyrrolidin-3-yl)-1,4-dihydroquinoline-3-carboxylate 	Calcd for $C_{16}H_{17}IN_2O_3$ [M + H]$^+$: 412.92	Intermediate 114
111	(*S*)-ethyl 6-iodo-4-oxo-1-(piperidin-3-yl)-1,4-dihydroquinoline-3-carboxylate 	Calcd for $C_{17}H_{19}IN_2O_3$ [M + H]$^+$: 426.95	Intermediate 115

Intermediates 112-115

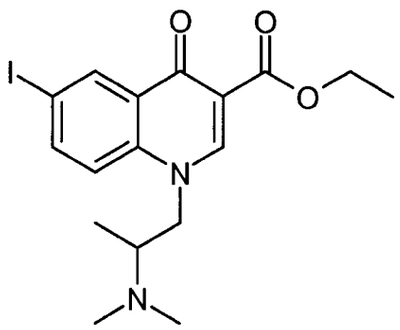
The following Intermediates were prepared according to the procedure described for Intermediate 96 from the starting materials indicated.

Int	Compound	Data	SM
112	(*S*)-ethyl 1-((1-(*tert*-butoxycarbonyl)piperidin-3-yl)methyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	Calcd for $C_{23}H_{29}IN_2O_5$ [M + H]$^+$: 541.07	(*S*)-*tert*-butyl 3-(aminomethyl)piperidine-1-carboxylate & Intermediate 24

Int	Compound	Data	SM
113	(*R*)-ethyl 1-((1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)methyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	Calcd for $C_{22}H_{27}IN_2O_5$ [M + H]$^+$: 527.03	(*R*)-*tert*-butyl 3-aminomethyl pyrrolidine-1-carboxylate & Intermediate 24
114	(*R*)-ethyl 1-(1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	Calcd for $C_{21}H_{25}IN_2O_5$ [M + H]$^+$: 512.99	(*R*)-*tert*-butyl 3-amino-pyrrolidine-1-carboxylate & Intermediate 24
115	(*S*)-ethyl 1-(1-(*tert*-butoxycarbonyl)piperidin-3-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	Calcd for $C_{22}H_{27}IN_2O_5$ [M + H]$^+$: 527.01	(*S*)-*tert*-butyl 3-amino-piperidine-1-carboxylate & Intermediate 24

Intemediate 116

Ethyl 1-(2-(dimethylamino)propyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate



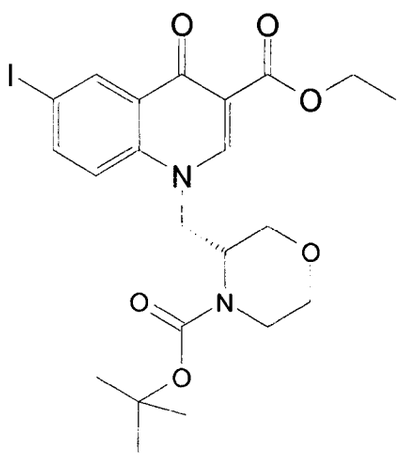
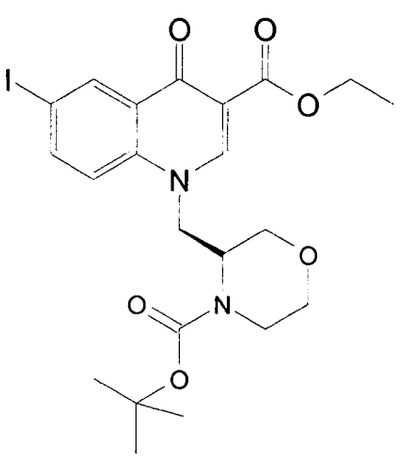
(Z)-Ethyl 3-(dimethylamino)-2-(2-fluoro-5-iodobenzoyl)acrylate (0.500 g, 1.28 mmol, Intermediate 24), N2,N2-dimethylpropane-1,2-diamine hydrochloride (0.177 g, 1.28 mmol), and potassium carbonate (0.194 g, 1.41 mmol) were combined in THF (10.0 mL). The reaction was heated at 60 °C for 2 hrs. After 2 h, DMF(5.0 mL) was added followed by potassium carbonate (0.530 g, 3.83 mmol). The reaction was heated at 90 °C for 6h. The reaction mixture was cooled to 0°C and 1N HCl was slowly added until pH was around 4. The resulting precipitate was filtered, washed with water and dried overnight to yield a light yellow solid (0.428g).

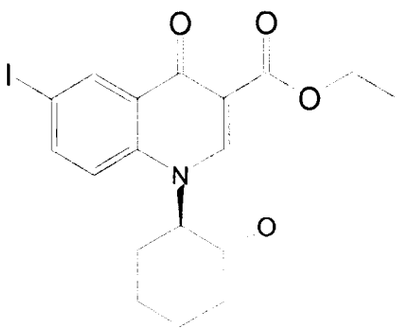
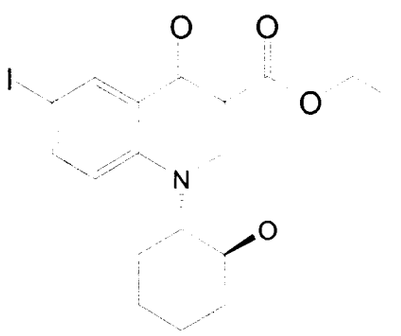
MS (ES) $(M+H)^+$: 429 for $C_{17}H_{21}IN_2O_3$;

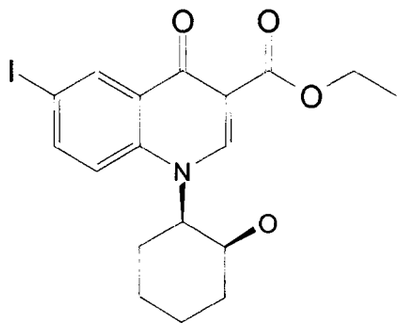
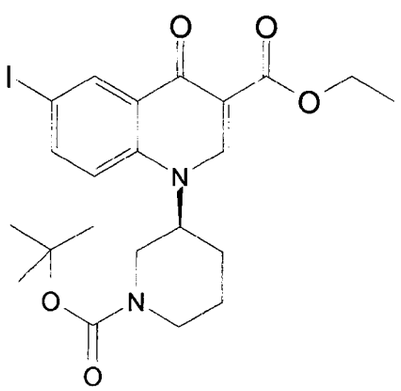
NMR: 10.99 (br. s., 1 H), 8.73 (br. s., 1 H), 8.51 (s, 1 H), 8.07 (dd, *J*=8.67, 1.88 Hz, 1 H), 7.83 - 7.97 (m, 1 H), 4.92 (d, *J*=12.06 Hz, 1 H), 4.59 (t, *J*=11.30 Hz, 1 H), 4.24 (q, *J*=7.54 Hz, 2 H), 3.70 - 3.89 (m, 1 H), 2.68 - 2.86 (m, 6 H), 1.29 (t, *J*=7.16 Hz, 4 H), 1.15 (d, *J*=3.77 Hz, 3 H).

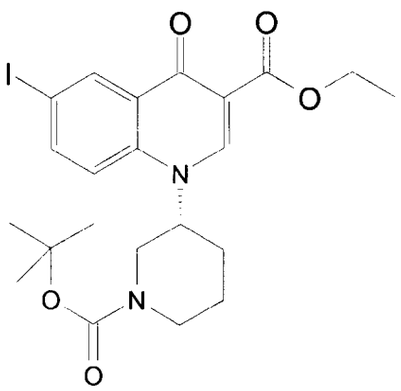
Intermediates 117-123

The following Intermediates were prepared by the procedure described in Intermediate 116 from the starting materials (SM) indicated.

Int	Compound	Data	SM
117	(R)-tert-butyl 3-((3-(ethoxycarbonyl)-6-iodo-4-oxoquinolin-1(4H)-yl)methyl)morpholine-4-carboxylate 	MS (ES) $(M+H)^+$: 543 for $C_{22}H_{27}IN_2O_6$ NMR: 8.45 - 8.56 (m, 2 H), 8.06 (d, *J*=7.54 Hz, 1 H), 7.79 (d, *J*=9.04 Hz, 1 H), 4.56 - 4.76 (m, 2 H), 4.20 (d, *J*=7.54 Hz, 3 H), 3.94 - 4.06 (m, 1 H), 3.74 - 3.92 (m, 2 H), 3.44 - 3.68 (m, 2 H), 1.21 - 1.43 (m, 4 H), 1.12 (s, 3 H), 0.77 (s, 6 H).	Intermediate 24 and (R)-tert-butyl 3-(aminomethyl)-morpholine-4-carboxylate
118	(S)-tert-butyl 3-((3-(ethoxycarbonyl)-6-iodo-4-oxoquinolin-1(4H)-yl)methyl)morpholine-4-carboxylate 	MS (ES) $(M+H)^+$: 543 for $C_{22}H_{27}IN_2O_6$ NMR: 8.42 - 8.56 (m, 2 H), 8.06 (d, *J*=8.29 Hz, 1 H), 7.79 (d, *J*=8.29 Hz, 1 H), 4.53 - 4.79 (m, 2 H), 4.20 (d, *J*=6.78 Hz, 3 H), 3.94 - 4.09 (m, 1 H), 3.72 - 3.94 (m, 2 H), 3.45 - 3.70 (m, 2 H), 1.19 - 1.43 (m, 4 H), 1.12 (s, 3 H), 0.77 (s, 6H).	Intermediate 24 and (S)-tert-butyl 3-(aminomethyl)-morpholine-4-carboxylate

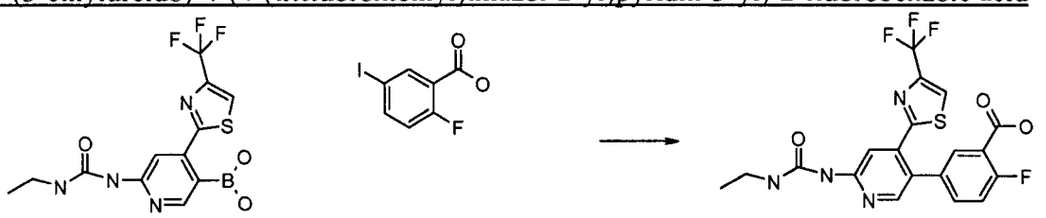
Int	Compound	Data	SM
119	ethyl 1-((1R,2R)-2-hydroxycyclohexyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ES) $(M+H)^+$: 442 for $C_{18}H_{20}INO_4$ NMR: 8.62 (s, 1 H), 8.52 (s, 1 H), 8.03 (d, *J*=9.04 Hz, 1 H), 7.84 - 7.93 (m, 1 H), 5.10 (d, *J*=4.52 Hz, 1 H), 4.51 (t, *J*=8.67 Hz, 1 H), 4.24 (q, *J*=6.78 Hz, 2 H), 3.87 (d, *J*=4.52 Hz, 1 H), 1.86 - 2.09 (m, 2 H), 1.71 (br. s., 3 H), 1.41 - 1.60 (m, 3 H), 1.29 (t, *J*=7.16 Hz, 3 H).	Intermediate 24 and (1R,2R)-2-aminocyclo-hexanol hydrochloride
120	ethyl 1-((1S,2S)-2-hydroxycyclohexyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ES) $(M+H)^+$: 442 for $C_{18}H_{20}INO_4$	Intermediate 24 and (1S,2S)-2-aminocyclo-hexanol hydrochloride

Int	Compound	Data	SM
121	ethyl 1-(*cis*-2-hydroxycyclohexyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ES) $(M+H)^+$: 442 for $C_{18}H_{20}INO_4$ NMR: 1.21 - 1.35 (m, 3 H), 1.39 - 1.67 (m, 3 H), 1.67 - 1.95 (m, 4 H), 2.15 - 2.31 (m, 1 H), 3.94 (br. s., 1 H), 4.24 (q, *J*=6.78 Hz, 2 H), 4.72 - 4.85 (m, 1 H), 5.12 (d, *J*=5.27 Hz, 1 H), 7.83 (d, *J*=9.04 Hz, 1 H), 8.05 (dd, *J*=9.04, 2.26 Hz, 1 H), 8.55 (d, *J*=2.26 Hz, 1 H), 8.64 (s, 1 H).	Intermediate 24 and *cis*-2-aminocyclo-hexanol hydrochloride
122	(S)-ethyl 1-(1-(tert-butoxycarbonyl)piperidin-3-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ES) $(M+H)^+$: 527 for $C_{22}H_{27}IN_2O_5$	Intermediate 24 and (S)-tert-butyl 3-amino-piperidine-1-carboxylate

Int	Compound	Data	SM
123	(R)-ethyl 1-(1-(tert-butoxycarbonyl)piperidin-3-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ES) $(M+H)^+$: 527 for $C_{22}H_{27}IN_2O_5$	Intermediate 24 and (R)-tert-butyl 3-amino-piperidine-1-carboxylate

Intermediate 124

5-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-2-fluorobenzoic acid



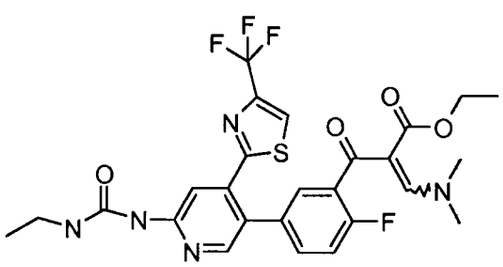
6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 17, 0.261 g, 0.72 mmol, Intermediate 17) and 2-fluoro-5-iodobenzoic acid (0.175 g, 0.66 mmol, aldrich) were combined in dioxane (1ml). A solution of cesium carbonate (0.364 g, 1.12 mmol) in water (0.658 ml) was added followed by tetrakis(triphenylphosine) palladium(0)(0.076 g, 0.07 mmol, strem) and additional dioxane (2.63 ml). The flask was placed in an oil bath preheated to 100 °C and was heated for 1h., then cooled to 0°C and 1 N HCl was added until the pH was ~3. EtOAc (5ml) was added and a solid crashed out and was collected by filtration and washed with EtOAc, then dried to give a grey solid 5-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-2-fluorobenzoic acid (0.180 g, 60.2 %).

MS (ES) $(M+H)^+$: 455 for $C_{19}H_{14}F_4N_4O_3S$ NMR:

^{1}H NMR (300 MHz, *DMSO-d_6*) δ 13.38 (br. s., 1 H), 9.43 (s, 1 H), 8.53 (s, 1 H), 8.28 (s, 1 H), 8.21 (s, 1 H), 7.76 (d, *J*=6.78 Hz, 1 H), 7.59 (d, *J*=3.77 Hz, 2 H), 7.35 - 7.47 (m, 1 H), 3.18 - 3.25 (m, 2 H), 1.10 (t, *J*=7.16 Hz, 3 H).

Intermediate 125

ethyl 3-(dimethylamino)-2-(5-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-2-fluorobenzoyl)acrylate

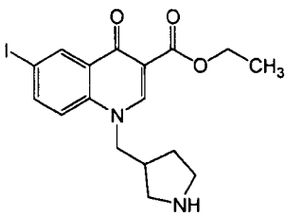


5-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-2-fluorobenzoic acid (0.180 g, 0.40 mmol, Intermediate 124) was suspended in toluene (3 mL). Thionyl chloride (0.145 mL, 1.98 mmol, Aldrich) and 1drop of DMF were added and the mixture was heated to 45°C for 15 min. After cooling to room temperature, the mixture was concentrated *in vacuo*, and toluene was added, then the mixture was concentrated *in vacuo* again to give a dark yellow residue. After drying under high vacuum overnight the oil turned into a dark yellow film. This film was taken up in THF (2 mL). In separate flask ethyl 3-(dimethylamino)acrylate (0.074 g, 0.51 mmol, Acros) and triethylamine (0.082 mL, 0.59 mmol, Acros) were dissolved in THF (5ml). The solution of the acid chloride in THF (2ml) was added dropwise to acrylate solution, then the flask was placed in an oil bath preheated to 72 °C and stirred for 1 h. After cooling to room temperature, the mixture was diluted with EtOAc(10 mL) and water (10 mL). The layers were seperated and the organic layer was washed with 1 N HCl, twice with water, once with brine, then dry over Na_2SO_4, filter and concentrated *in vacuo* to give crude product as an orange oil.

MS (ES) $(M+H)^+$: 580 for $C_{26}H_{25}F_4N_5O_4S$.

Intermediate 126

ethyl 6-iodo-4-oxo-1-(pyrrolidin-3-ylmethyl)-1,4-dihydroquinoline-3-carboxylate hydrochloride

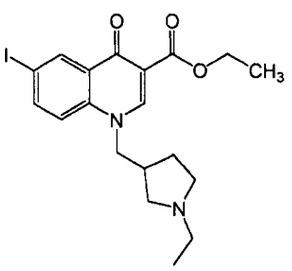


Ethyl 1-((1-(tert-butoxycarbonyl)pyrrolidin-3-yl)methyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate (Intermediate 100, 3.0 g, 5.7 mmol) was dissolved in 1,4-dioxane (15 mL) and 4.0M hydrogen chloride in 1,4-dioxane (10 mL) was added. The reaction was stirred at 23°C for 3 h, and the solvent was removed *in vacuo*. The solid was then dried in a vacuum oven at 50°C for 18 h to give 2.61 (quant. yield) of ethyl 6-iodo-4-oxo-1-(pyrrolidin-3-ylmethyl)-1,4-dihydroquinoline-3-carboxylate hydrochloride as a yellow solid.

MS (ESP): 427.1 ($M+H^+$) for $C_{17}H_{19}IN_2O_3$

Intemediate 127

ethyl 1-((1-ethylpyrrolidin-3-yl)methyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate

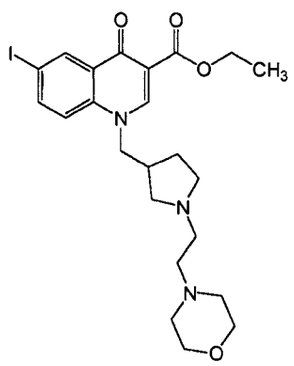


Ethyl 6-iodo-4-oxo-1-(pyrrolidin-3-ylmethyl)-1,4-dihydroquinoline-3-carboxylate hydrochloride (Intermediate 126, 500 mg, 1.08 mmol) was suspended in methanol (15 mL) then acetaldehyde (300 µl, 5.4 mmol) and sodium cyanoborohydride (612 mg, 9.7 mmol) were added. The reaction was stirred at 23°C for 16 h. The volume of the reaction was reduced by half and water (25 mL) was added. The suspension was extracted with 2:1 ethyl acetate: tetrahydrofuran (3 × 10 mL). The organic phases were combined, dried over sodium sulfate, and the solvent was removed *in vacuo*. The residue was passed through a plug of silica gel (2g) eluting with 10% methanol in dichloromethane to remove any remaining borohydride. The solid was then dried in a vacuum oven at 50°C for 18 h to give 378 mg (77% yield) of ethyl 1-((1-ethylpyrrolidin-3-yl)methyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate as an off white solid.

MS (ESP): 455.1 ($M+H^+$) for $C_{18}H_{21}IN_2O_3$

Intermediate 128

ethyl 6-iodo-1-((1-(2-morpholinoethyl)pyrrolidin-3-yl)methyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate

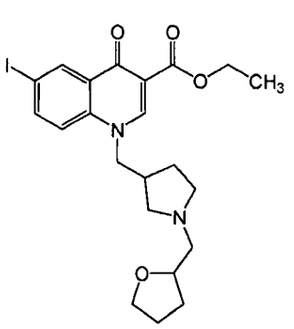


Ethyl 6-iodo-4-oxo-1-(pyrrolidin-3-ylmethyl)-1,4-dihydroquinoline-3-carboxylate hydrochloride (Intermediate 127, 500 mg, 1.08 mmol) was suspended in methanol (15 mL) then morpholine-4-ylacetaldehyde monohydrate hydrochloride (1 g, 5.4 mmol) and sodium cyanoborohydride (612 mg, 9.7 mmol) were added. The reaction was stirred at 23°C for 16 h. The volume of the reaction was reduced by half and water (25 mL) was added. The suspension was extracted with 2:1 ethyl acetate: tetrahydrofuran (3 × 10 mL). The organic phases were combined, dried over sodium sulfate, and the solvent was removed *in vacuo*. The residue was passed through a plug of silica gel (2g) eluting with 10% methanol in dichloromethane to remove any remaining borohydride. The solid was then dried in a vacuum oven at 50°C for 18 h to give 225 mg (38% yield) of ethyl 6-iodo-1-((1-(2-morpholinoethyl)pyrrolidin-3-yl)methyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate as an off white solid.

MS (ESP): 540.0 ($M+H^+$) for $C_{23}H_{30}IN_3O_4$

Intermediate 129

ethyl 6-iodo-4-oxo-1-((1-((tetrahydrofuran-2-yl)methyl)pyrrolidin-3-yl)methyl)-1,4-dihydroquinoline-3-carboxylate



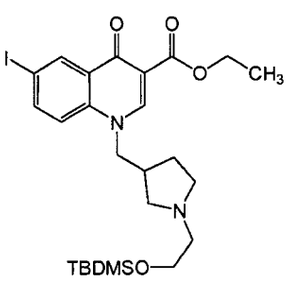
Ethyl 6-iodo-4-oxo-1-(pyrrolidin-3-ylmethyl)-1,4-dihydroquinoline-3-carboxylate hydrochloride (Intermediate 126, 500 mg, 1.08 mmol) was suspended in dimethyl formamide (3 mL) then tetrahydrofurfuryl chloride (1 mL) and potassium carbonate powder (400 mg, 22.2 mmol) were added. The reaction was stirred at 70°C for 36 h. Water (15 mL) was added and the suspension was extracted with ethyl acetate (3 × 10 mL). The organic phases were combined, dried over sodium sulfate, and the solvent was removed *in vacuo*. The residue was chromatographed on a 4g Analogix column using 0-10% methanol in dichloromethane. The solid was then dried in a vacuum oven at 50°C for 18 h to give 181 mg (32% yield) of ethyl 6-iodo-4-oxo-1-((1-((tetrahydrofuran-2-yl)methyl)pyrrolidin-3-yl)methyl)-1,4-dihydroquinoline-3-carboxylate as an off white solid.

MS (ESP): 511.1 ($M+H^+$) for $C_{22}H_{27}IN_2O_4$

^1H NMR (300 MHz, $CDCl_3$): δ 1.38 (t, 3H), 1.42-1.61 (m, 2H), 1.81-2.08 (m, 4H), 2.38-2.81 (m, 6H), 2.84-2.96 (m, 1H), 3.71-4.28 (m, 6H), 4.38 (q, 2H), 7.28(dd, 1H), 7.93 (dd, 1H), 8.49 (s, 1H), 8.83 (d, 1H).

Intermediate 130

ethyl 1-((1-(2-(tert-butyldimethylsilyloxy)ethyl)pyrrolidin-3-yl)methyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate



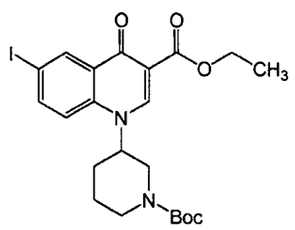
Ethyl 6-iodo-4-oxo-1-(pyrrolidin-3-ylmethyl)-1,4-dihydroquinoline-3-carboxylate hydrochloride (Intermediate 126, 500 mg, 1.08 mmol) was suspended in methanol (15 mL) then (tert-butyldimethylsilyloxy)acetaldehyde (1 mL, 5.4 mmol) and sodium cyanoborohydride (612 mg, 9.7 mmol) were added. The reaction was stirred at 23°C for 16 h. The volume of the reaction was reduced by half and water (25 mL) was added. The suspension was extracted with 2:1 ethyl acetate: tetrahydrofuran (3×, 10 mL). The organic phases were combined, dried over sodium sulfate, and the solvent was removed *in vacuo*. The residue was chromatographed on a 4g Analogix column eluting with 0-10% methanol in dichloromethane. The solid was then dried in a vacuum oven at 50°C for 18 h to give 253 mg

(39% yield) of ethyl 1-((1-(2-(tert-butyldimethylsilyloxy)ethyl)pyrrolidin-3-yl)methyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate as an off white solid.

MS (ESP): 585.2 ($M+H^+$) for $C_{25}H_{28}IN_2O_4Si$

Intermediate 131

ethyl 1-(1-(tert-butoxycarbonyl)piperidin-3-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate



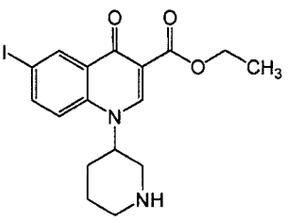
3-Amino-1-N-Boc-piperidine (2.5 g, 12.5 mmol) was added to the solution of (Z)-ethyl 3-(dimethylamino)-2-(3-iodobenzoyl)acrylate (Intermediate 24, 0.34M, 34 mL, 11.3 mmol) and heated at 50°C for 3 h. The solvent was removed *in vacuo* and the residue was dried in a vacuum oven for 1.5 h. The residue was then dissolved in dimethyl formamide (20 mL) and potassium carbonate powder (2.2 g, 15.8 mmol) was added. The reaction was heated at 70°C for 3 h then cooled to room temperature. Water (100 mL) was added and the suspension was extracted with 1:1 ethyl acetate : methyl tert-butyl ether (3×, 50 mL). The organic layers were dried over sodium sulfate, and the solvent was removed *in vacuo*. The residue was suspended in methyl tert-butyl ether (20 mL) and stirred at 40°C for 1 h. The suspension was filtered and the solid dried to give 4.93g (82% yield) of ethyl 1-(1-(tert-butoxycarbonyl)piperidin-3-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate as a yellowish powder.

MS (ESP): 527.1 ($M+H^+$) for $C_{22}H_{27}IN_2O_5$

^1H NMR (300 MHz, DMSO-d_6): δ 1.24 (t, 3H), 1.45 (s, 9H), 1.61-1.90(bm, 4H), 2.18 (bs, 2H), 2.94 (bs, 1H), 3.20 (bs, 1H), 3.83 (bd, 1H), 4.08 (bd, 1H), 4.23 (q, 2H), 4.62 (bs, 1H), 7.77 (bd, 1H), 8.08 (d, 1H), 8.52 (d, 1H), 8.61 (s, 1H).

Intermediate 132

ethyl 6-iodo-4-oxo-1-(piperidin-3-yl)-1,4-dihydroquinoline-3-carboxylate hydrochloride

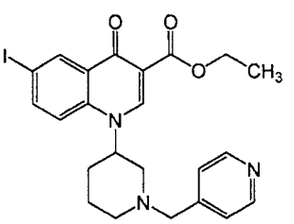


Ethyl 1-((1-(tert-butoxycarbonyl)pyrrolidin-3-yl)methyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate (Intermediate 131, 3.0 g, 5.7 mmol) was dissolved in 1,4-dioxane (15 mL) and 4.0M hydrogen chloride in 1,4-dioxane (10 mL) was added. The reaction was stirred at 23°C for 3 h, and the solvent was removed *in vacuo*. The solid was then dried in a vacuum oven at 50°C for 18 h to give 2.64g (quant. yield) of ethyl 6-iodo-4-oxo-1-(piperidin-3-yl)-1,4-dihydroquinoline-3-carboxylate hydrochloride as a yellow solid.

MS (ESP): 427.0 ($M+H^+$) for $C_{22}H_{27}IN_2O_5$

Intermediate 133

ethyl 6-iodo-4-oxo-1-(1-(pyridin-4-ylmethyl)piperidin-3-yl)-1,4-dihydroquinoline-3-carboxylate

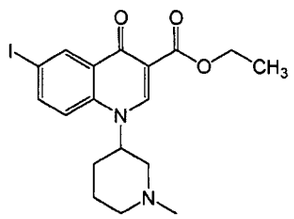


Ethyl 6-iodo-4-oxo-1-(piperidin-3-yl)-1,4-dihydroquinoline-3-carboxylate hydrochloride (Intemediate 132, 500 mg, 1.08 mmol) was suspended in methanol (15 mL) then 4-pyridinecarboxaldehyde (520 µl, 5.4 mmol) and sodium cyanoborohydride (612 mg, 9.7 mmol) were added. The reaction was stirred at 23°C for 16 h. The volume of the reaction was reduced by half and water (25 mL) was added. The suspension was extracted with 2:1 ethyl acetate: tetrahydrofuran (3×, 10 mL). The organic phases were combined, dried over sodium sulfate, and the solvent was removed *in vacuo*. The residue was passed through a plug of silica gel (2g) eluting with 10% methanol in dichloromethane to remove any remaining borohydride. The solid was then dried in a vacuum oven at 50°C for 18 h to give 460 mg (82% yield) of ethyl 6-iodo-4-oxo-1-(1-(pyridin-4-ylmethyl)piperidin-3-yl)-1,4-dihydroquinoline-3-carboxylate as an off white solid.

MS (ESP): 706.2 ($M+H^+$) for $C_{12}H_{10}BrF_3N_4OS$.

Intermediate 134

ethyl 6-iodo-1-(1-methylpiperidin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate

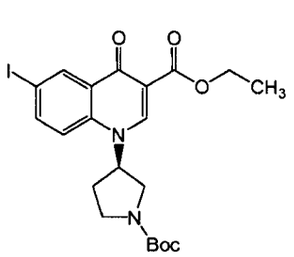


Ethyl 6-iodo-4-oxo-1-(piperidin-3-yl)-1,4-dihydroquinoline-3-carboxylate hydrochloride (Intermediate 132, 500 mg, 1.08 mmol) was suspended in methanol (15 mL) then 37% formaldehyde in water (405 µl, 5.4 mmol) and sodium cyanoborohydride (612 mg, 9.7 mmol) were added. The reaction was stirred at 23°C for 16 h. The volume of the reaction was reduced by half and water (25 mL) was added. The suspension was extracted with 2:1 ethyl acetate: tetrahydrofuran (3 × 10 mL). The organic phases were combined, dried over sodium sulfate, and the solvent was removed *in vacuo*. The residue was passed through a plug of silica gel (2g) eluting with 10% methanol in dichloromethane to remove any remaining borohydride. The solid was then dried in a vacuum oven at 50°C for 18 h to give 386 mg (81% yield) of ethyl 6-iodo-1-(1-methylpiperidin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate as an off white solid.

MS (ESP): 441.0 ($M+H^+$) for $C_{18}H_{21}IN_2O_3$

Intermediate 135

(S)-ethyl 1-(1-(tert-butoxycarbonyl)pyrrolidin-3-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate



(S)-3-Amino-1-N-Boc-pyrrolidine (1 g, 5.36 mmol) was added to the solution of (Z)-ethyl 3-(dimethylamino)-2-(3-iodobenzoyl)acrylate (Intermediate 24, 0.34M, 14.3 mL, 4.88 mmol) and heated at 50°C for 3 h. The solvent was removed *in vacuo* and the residue was dried in a vacuum oven for 1.5 h. The residue was then dissolved in dimethyl formamide (8 mL) and

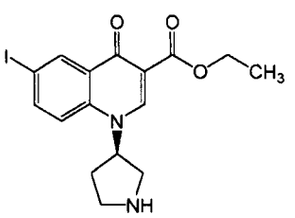
potassium carbonate powder (1.0 g, 6.83 mmol) was added. The reaction was heated at 70°C for 3 h then cooled to room temperature. Water (40 mL) was added and the suspension was extracted with 1:1 ethyl acetate : methyl tert-butyl ether (3×, 30 mL). The organic layers were dried over sodium sulfate, and the solvent was removed *in vacuo*. The residue was suspended in methyl tert-butyl ether (20 mL) and stirred at 40°C for 1 hour. The suspension was filtered and the solid dried to give 1.76g (71% yield) of (R)-ethyl 1-(1-(tert-butoxycarbonyl)pyrrolidin-3-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate as a yellowish powder.

MS (ESP): 513.0 ($M+H^+$) for $C_{21}H_{25}IN_2O_5$

^1H NMR (300 MHz, DMSO-d_6): δ 1.23 (t, 3H), 1.42 (s, 9H), 2.22 (bs, 2H), 2.48 (bs, 2H), 3.40 (bd, 2H), 3.73 (bm, 2H), 4.18 (q, 2H), 5.31 (bs, 1H), 7.78 (d, 1H), 8.07 (dd, 1H), 8.41 (bd, 1H), 8.52 (s, 1H).

Intermediate 136

(S)-ethyl 6-iodo-4-oxo-1-(pyrrolidin-3-yl)-1,4-dihydroquinoline-3-carboxylate hydrochloride

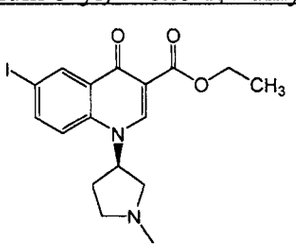


(S)-Ethyl 1-(1-(tert-butoxycarbonyl)pyrrolidin-3-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate (1.2 g, 1.08 mmol) was dissolved in 1,4-dioxane (10 mL) and 4.0M hydrogen chloride in 1,4-dioxane (4 mL) was added. The reaction was stirred at 23°C for 3 hours, and the solvent was removed *in vacuo*. The solid was then dried in a vacuum oven at 50°C for 18 hours to give 1.03g (quant. yield) of (R)-ethyl 6-iodo-4-oxo-1-(pyrrolidin-3-yl)-1,4-dihydroquinoline-3-carboxylate hydrochloride as a yellow solid.

MS (ESP): 412.9 ($M+H^+$) for $C_{16}H_{17}IN_2O_3$

Intermediate 137

(S)-ethyl 6-iodo-1-(1-methylpyrrolidin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate

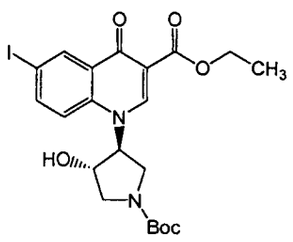


(S)-Ethyl 6-iodo-4-oxo-1-(pyrrolidin-3-yl)-1,4-dihydroquinoline-3-carboxylate hydrochloride (Intermediate 136, 484 mg, 1.08 mmol) was suspended in methanol (15 mL) then 37% formaldehyde in water (405 µl, 5.4 mmol) and sodium cyanoborohydride (612 mg, 9.7 mmol) were added. The reaction was stirred at 23°C for 16 h. The volume of the reaction was reduced by half and water (25 mL) was added. The suspension was extracted with 2:1 ethyl acetate: tetrahydrofuran (3×, 10 mL). The organic phases were combined, dried over sodium sulfate, and the solvent was removed *in vacuo*. The residue was passed through a plug of silica gel (2g) eluting with 10% methanol in dichloromethane to remove any remaining borohydride. The solid was then dried in a vacuum oven at 50°C for 18 h to give 379 mg (82% yield) of (S)-ethyl 6-iodo-1-(1-methylpyrrolidin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate as an off white solid.

MS (ESP): 426.9 ($M+H^+$) for $C_{17}H_{19}IN_2O_3$

Intermediate 138

Trans-ethyl 1-(1-(tert-butoxycarbonyl)-4-hydroxypyrrolidin-3-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate

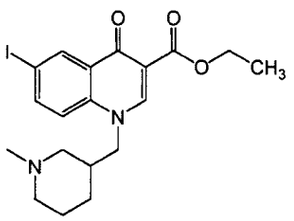


Trans-tert-butyl 3-amino-4-hydroxypyrrolidine-1-carboxylate (500 mg, 2.47 mmol) was added to the solution of (Z)-ethyl 3-(dimethylamino)-2-(3-iodobenzoyl)acrylate (Intermediate 24, 0.34M, 6.7 mL, 2.25 mmol) and the mixture was heated at 50°C for 3 hour. The solvent was removed *in vacuo* and the residue was dried in a vacuum oven for 1.5 hours. The residue was then dissolved in dimethyl formamide (5 mL) and potassium carbonate powder (435 mg, 3.15 mmol) was added. The reaction was heated at 70°C for 3 h then cooled to room temperature. Water (30 mL) was added and the suspension was extracted with 1:1 ethyl acetate : methyl tert-butyl ether (3 × 50 mL). The organic layers were dried over sodium sulfate, and the solvent was removed *in vacuo*. The residue was suspended in methyl tert-butyl ether (20 mL) and stirred at 40°C for 1 h. The suspension was filtered and the solid dried to give 751 mg (64% yield) of racemic *trans*-ethyl 1-(1-(tert-butoxycarbonyl)-4-hydroxypyrrolidin-3-yl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate as a yellowish powder.

MS (ESP): 528.9 ($M+H^+$) for $C_{21}H_{25}IN_2O_6$

Intermediate 139

ethyl 6-iodo-1-((1-methylpiperidin-3-yl)methyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate



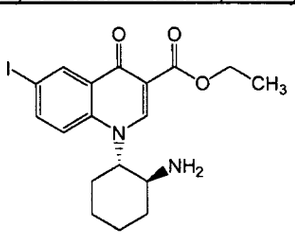
1-(1-Methylpiperidine-3-yl)methanamine (500 mg, 3.9 mmol) was added to the solution of (Z)-ethyl 3-(dimethylamino)-2-(3-iodobenzoyl)acrylate (Intermediate 24, 0.34M, 10.4 mL, 2.25 mmol) and the mixture was heated at 50°C for 3 h. The solvent was removed *in vacuo* and the residue was dried in a vacuum oven for 1.5 h. The residue was then dissolved in dimethyl formamide (7 mL) and potassium carbonate powder (695 mg, 5.1 mmol) was added. The reaction was heated at 70°C for 3 h then cooled to room temperature. Water (30 mL) was added and the suspension was extracted with 1:1 ethyl acetate : methyl tert-butyl ether (3 × 50 mL). The organic layers were dried over sodium sulfate, and the solvent was removed *in vacuo*. The residue was suspended in methyl *tert*-butyl ether (20 mL) and stirred at 40°C for 1 h. The suspension was filtered and the solid dried to give 1.12 mg (69% yield) of ethyl 6-iodo-1-((1-methylpiperidin-3-yl)methyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate as a yellowish powder.

MS (ESP): 455.2 ($M+H^+$) for $C_{19}H_{23}IN_2O_3$

^1H NMR (300 MHz, DMSO-d_6): δ 1.12 (m, 1H), 1.28 (t, 3H), 1.29-1.60 (m, 2H), 1.68 (m, 1H), 1.79 (m, 1H), 1.98-2.19 (m, 2H), 2.17 (s, 3H), 2.20-2.42 (m, 2H), 3.38 (m, 1H), 4.26(q, 2H), 4.20-4.41 (m, 2H), 7.69 (d, 1H), 8.05 (dd, 1H), 8.52 (d, 1H), 8.63 (s, 1H).

Intermediate 140

ethyl 1-((1S,2S)-2-aminocyclohexyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate



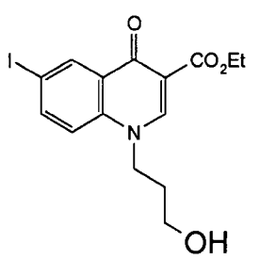
(1S,2S)-(+)-1,2-Diaminocyclohexane (500 mg, 4.3 mmol) was added to the solution of (Z)-ethyl 3-(dimethylamino)-2-(3-iodobenzoyl)acrylate (Intermediate 24, 0.34M, 11.7 mL, 3.9

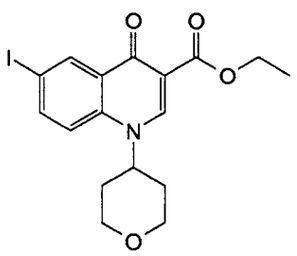
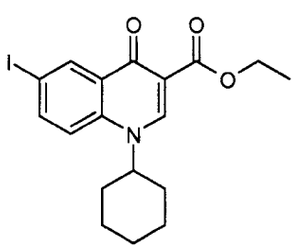
mmol) and the mixture was heated at 50°C for 3 h. The solvent was removed *in vacuo* and the residue was dried in a vacuum oven for 1.5 h. The residue was then dissolved in dimethyl formamide (7 mL) and potassium carbonate powder (753 mg, 5.5 mmol) was added. The reaction was heated at 70°C for 3 h then cooled to room temperature. Water (30 mL) was added and the suspension was extracted with 1:1 ethyl acetate : methyl tert-butyl ether (3 × 50 mL). The organic layers were dried over sodium sulfate, and the solvent was removed *in vacuo*. The residue was suspended in methyl tert-butyl ether (20 mL) and stirred at 40°C for 1 h. The suspension was filtered and the solid dried to give 724mg (42% yield) of ethyl 1-((1S,2S)-2-aminocyclohexyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate as a yellowish powder that was contaminated with about 40% bis dihydroquinoline. This material was used as is in the coupling step.

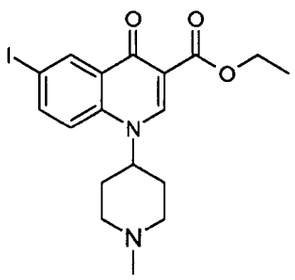
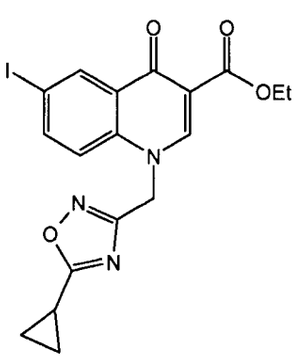
MS (ESP): 441.0 ($M+H^+$) for $C_{18}H_{21}IN_2O_3$

Intermediates 141-145

The following Intermediates were prepared according to the procedure described for Intermediate 140 from the indicated starting materials.

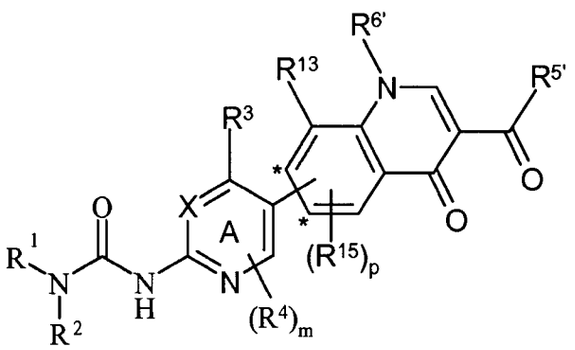
Int	Compound	Data	SM
141	Ethyl 1-(3-hydroxypropyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 402 (M+1) for $C_{15}H_{16}INO_4$ ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.28 (t, *J*=7.07 Hz, 3H); 1.79 - 1.97 (m, 2H); 3.44 (q, *J*=5.64 Hz, 2H); 4.22 (q, *J*=7.07 Hz, 2H); 4.39 (t, *J*=7.07 Hz, 2H); 4.72 (t, *J*=4.93, Hz, 1H); 7.65 (d, *J*=9.09 Hz, 1H); 8.07 (dd, *J*=8.97, 2.15 Hz, 1H); 8.50 (d, *J*=2.27 Hz, 1H); 8.66 (s, 1H).	Intermediate 24 and 3-aminopropan-1ol

Int	Compound	Data	SM
142	Ethyl 6-iodo-4-oxo-1-(tetrahydro-2H-pyran-4-yl)-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 427.98 (M+) for $C_{17}H_{18}INO_4$ ^{1}H-NMR (400 MHz, CHLOROFORM-d) δ: 1.43 (t, *J*=7.07 Hz, 3H); 2.06 - 2.24 (m, 4H); 3.68 (td, *J*=11.56, 2.15 Hz, 2H); 4.24 (dd, *J*=11.49, 3.66 Hz, 2H); 4.42 (q, *J*=7.16 Hz, 2H); 4.61 - 4.73 (m, 1H); 7.39 (d, *J*=8.84 Hz, 1H); 7.96 (dd, *J*=8.97, 2.15 Hz, 1H); 8.66 (s, 1H); 8.88 (d, *J*=2.02 Hz, 1H).	Intermediate 24 and tetrahydro-2H-pyran-4-amine
143	Ethyl 1-cyclohexyl-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 426.03 (M+1) for $C_{18}H_{20}INO_3$ ^{1}H-NMR (400 MHz, CHLOROFORM-d) δ: 1.43 (t, J=7.20 Hz, 3H); 1.50 - 1.64 (m, 2H); 1.71 - 1.94 (m, 4H); 2.00 - 2.11 (m, 2H); 2.13 - 2.22 (m, 2H); 4.31 - 4.48 (m, 3H); 7.34 (d, J=9.09 Hz, 1H); 7.96 (dd, J=8.97, 2.15 Hz, 1H); 8.68 (s, 1H); 8.89 (d, J=2.02 Hz, 1H).	Intermediate 24 and cyclohexylamine

Int	Compound	Data	SM
144	Ethyl 6-iodo-1-(1-methylpiperidin-4-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 441.13 (M+1) for $C_{18}H_{21}IN_2O_3$ ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.28 (t, *J*=7.07 Hz, 3H); 1.90 - 2.04 (m, 4H); 2.16 - 2.30 (m, 5H); 2.85 - 2.99 (m, 2H); 4.22 (q, *J*=7.07 Hz, 2H); 4.54 - 4.71 (m, 1H); 7.84 (d, *J*=9.35 Hz, 1H); 8.06 (dd, *J*=9.09, 2.27 Hz, 1H); 8.52 (d, *J*=2.27 Hz, 1H); 8.58 (s, 1H).	Intermediate 24 and 1-methylpiperidin-4-amine
145	Ethyl 1-((5-cyclopropyl-1,2,4-oxadiazol-3-yl)methyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate 	MS (ESP): 465.95 (M+) for $C_{18}H_{16}IN_3O_4$ ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.02 - 1.10 (m, 2H); 1.17- 1.26 (m, 2H); 1.29 (t, *J*=7.07 Hz, 3H); 2.26 - 2.38 (m, 1H); 4.24 (q, *J*=7.07 Hz, 2H); 5.81 (s, 2H); 7.48 (d, *J*=9.09 Hz, 1H); 8.00 - 8.08 (m, 1H); 8.49 (d, *J*=2.27 Hz, 1H); 8.87 (s, 1H).	Intermediate 24 and 5-cyclopropyl-1,2,4-oxadiazol-3-yl methylamine

Claims

1. A compound of formula **(I')**:



(I')

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is attached to one of the carbon atoms indicated by "*";

X is N, CH or CR^4;

$\mathbf{R^1}$ is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{3-6}cycloalkyl; wherein R^1 may be optionally substituted on carbon by one or more R^7;

$\mathbf{R^2}$ is selected from hydrogen or C_{1-6}alkyl; wherein said C_{1-6}alkyl may be optionally substituted by one or more groups independently selected from halo, cyano, hydroxy, nitro and amino;

or $\mathbf{R^1}$ **and** $\mathbf{R^2}$ **together** with the nitrogen to which they are attached form a heterocyclyl; wherein said heterocyclyl may be optionally substituted on one or more carbon atoms with one or more R^8; and wherein if said heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^9;

$\mathbf{R^3}$ is a C_{3-14}carbocyclyl or a heterocyclyl; wherein the carbocyclyl or heterocyclyl may be optionally substituted on one or more carbon atoms by one or more R^{10}; and wherein if said heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{11};

$\mathbf{R^4}$ and $\mathbf{R^{15}}$, for each occurrence, are independently selected from the group consisting of halo, nitro, cyano, hydroxy, amino, mercapto, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-}

$_{6}$alkoxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, and C_{1-6}alkylsulfanyl; wherein R^4, R^{13}, and R^{15} independently of each other may be optionally substituted on one or more carbon by one or more one or more R^{12};

$R^{5'}$ is –OH, a C_{1-6}alkoxy, C_{3-14}cycloalkoxy, or -NR^aR^b; wherein the C_{1-6}alkoxy group may be optionally substituted on one or more carbon atoms with one or more, independently selected R^{14}; and wherein R^a and R^b are each independently, hydrogen, a C_{1-6}alkyl, or a C_{3-14}carbocycle, or R^a and R^b, together with the nitrogen to which they are attached form a heterocycle, wherein R^a and R^b may be optionally substituted on one or more carbon atoms with one or more, independently selected R^{14}; and wherein if said heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{22};

$R^{6'}$, for each occurrence, is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}alkylsulfanyl, carboxy, carbamoyl, N-(C_{1-6}alkyl)carbamoyl, N,N-(C_{1-6}alkyl)$_2$carbamoyl, C_{3-14}carbocyclyl-L-, and heterocyclyl-L-; wherein R^6 is optionally substituted on one or more carbon atoms with one or more R^{16}; and wherein if said heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from $R^{17'}$;

R^{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, hydroxy, amino, mercapto, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, and C_{1-6}alkylsulfanyl; wherein R^{13} may be optionally substituted on one or more carbon by one or more one or more R^{16}; or

$R^{6'}$ and R^{13} together with the intervening ring atoms may form a fused heterocyclyl, wherein the fused heterocyclyl may be optionally substituted on one or more carbon atoms with one or more independently selected R^{16}; and wherein if said fused heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said fused heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from $R^{17'}$;

m is 0 or1;

p is 0, 1, or 2;

L, for each occurrence, is independently a direct bond or a C_{1-6}alkylene;

R^7, R^8, R^{10}, R^{12}, R^{14} and R^{16} are substituents on carbon which, for each occurrence, are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$- wherein a is 0, 1 or 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, C_{3-6}carbocyclyl or heterocyclyl; wherein R^7, R^8, R^{10}, R^{12}, R^{14} and R^{16} independently of each other may be optionally substituted on one or more carbon by one or more R^{19}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{20}; and wherein if said heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups;

R^9, R^{11}, and R^{20}, for each occurrence, are independently selected from C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl; wherein R^9, R^{11}, and R^{20} independently of each other may be optionally substituted on carbon by one or more R^{23};

$R^{17'}$, for each occurrence, is independently selected from C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl, phenylsulphonyl, C_{3-14}carbocyclyl-L-, and heterocyclyl-L-; wherein each $R^{17'}$, independently, may be optionally substituted on carbon by one or more R^{24}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{25}; and wherein if said heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups;

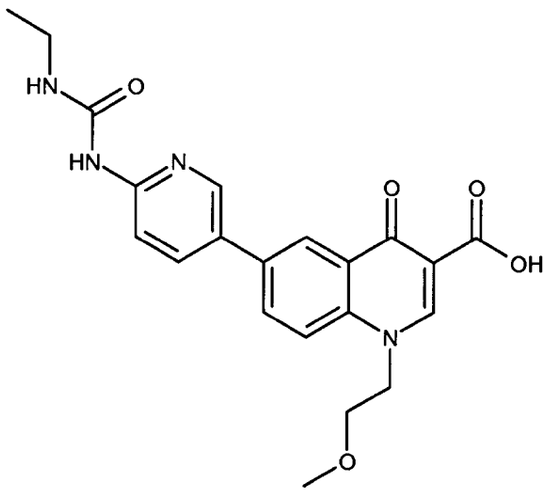
R^{22}, for each occurrence is independently selected from C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{1-6}alkoxycarbonyl, carbamoyl, N,N-(C_{1-6}alkyl)$_2$sulfamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and

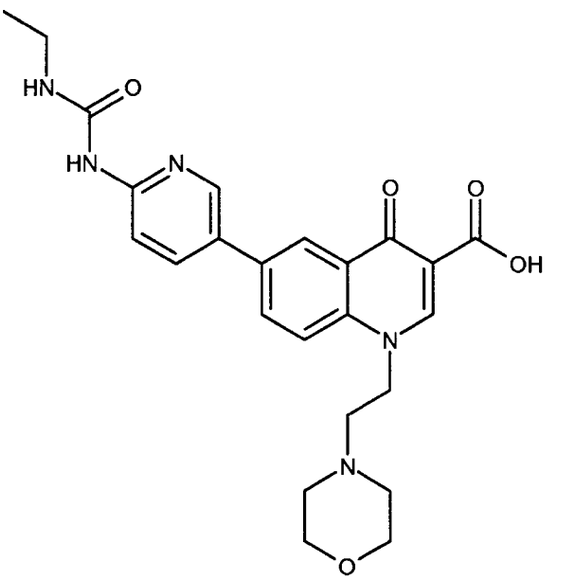
phenylsulphonyl; wherein R^{22} for each occurrence may be independently optionally substituted on carbon by one or more R^{23};

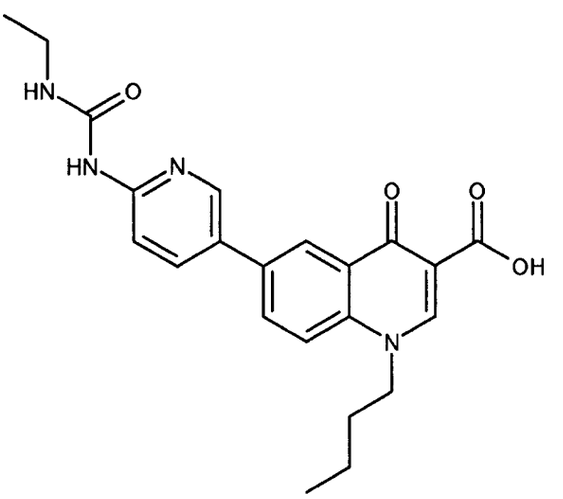
R^{19} and R^{23}, for each occurrence, are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{1-6}alkoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

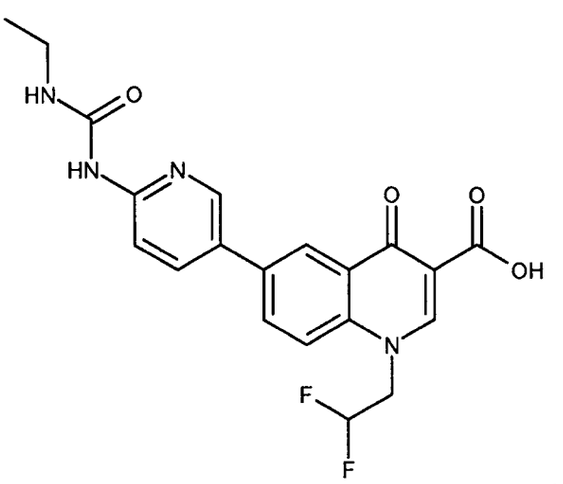
R^{24}, for each occurrence, are independently selected from halo, nitro, cyano, hydroxy, oxo, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{1-6}alkoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl; and

R^{25}, for each occurrence is independently selected from a C_{1-6}alkyl, provided that the compound is not one of the following compounds:

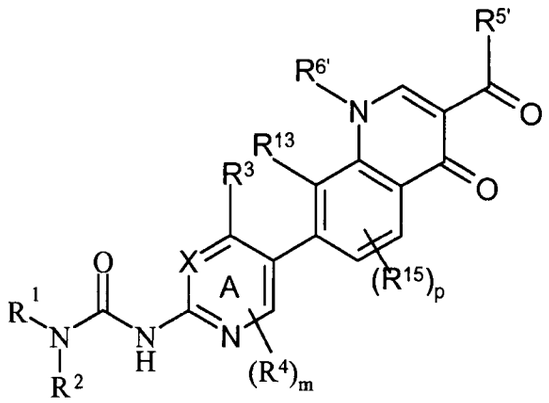








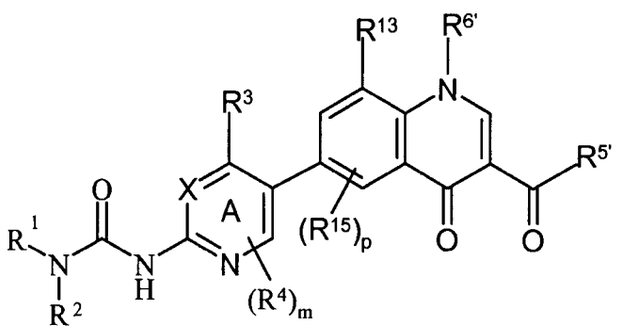
2. The compound of Claim 1, wherein the compound is represented by formula **(Ia')**:



(Ia')

or a pharmaceutically acceptable salts thereof.

3. The compound of Claim 1, wherein the compound is represented by formula **(Ib)**:



(Ib)

or a pharmaceutically acceptable salts thereof.

4. The compound of Claim 1, 2, or 3, wherein X is CH.

5. The compound of Claim 1, 2, or 3, wherein X is N.

6. The compound of any one of the preceding claims, wherein R^1 is a C_{1-6}alkyl.

7. The compound of Claim 6, wherein R^1 is ethyl.

8. The compound of any one of the preceding claims, wherein R^2 is hydrogen.

9. The compound of any one of the preceding claims, wherein R^3 is a 5- or 6-membered heteroaryl; wherein the heteroaryl may be optionally substituted on one or more carbon atoms by one or more R^{10}; and wherein if said heteroaryl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heteroaryl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{11}.

10. The compound of Claim 9, wherein R^3 is 4-trifluouromethyl-thiazole-2-yl, 4-ethyl-thiazole-2-yl, or 4-phenyl-thiazole-2-yl.

11. The compound of any one of the preceding claims, wherein $R^{5'}$ is selected from the group consisting of –OH, ethoxy, N-methylamino, and N-ethylamino.

12. The compound of any one of the preceding claims, wherein $R^{6'}$ is a C_{1-6}alkyl which is substituted on one or more carbon atoms with one or more independently selected R^{16}.

13. The compound of Claim 12, wherein R^{16}, for each occurrence, is independently selected from the group consisting of –OH, fluoro, N-methylamino, N,N-dimethylamino, methoxy, ethoxy, methylsulfanyl, methylsulfonyl, piperidinyl, piperazinyl, morpholinyl, pyrrolidinyl, 2-oxopyrrolidinyl, pyrrolyl, imidazolyl, triazolyl, phenyl which may be optionally substituted with one or more halo, isoxazolyl, pyridinyl, and cyclopropyl.

14. The compound of any one of Claims 1-11, wherein $R^{6'}$ is hydrogen.

15. The compound of any one of Claims 1-11, wherein $R^{6'}$ is C_{1-6}alkyl or a C_{3-6}cycloalkyl.

16. The compound of any one of Claims 1-11, wherein $R^{6'}$ is a non-aromatic heterocyclyl having 3 to 6 ring atoms; wherein said heterocyclyl is optionally substituted on one or more carbon atoms with one or more R^{16}; and wherein if said heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{17}.

17. The compound of any one of Claims 1-11, wherein R^{13} and $R^{6'}$ together with the intervening ring atoms for a 5- or 6-membered fused heterocyclyl.

18. The compound of any one of Claims 1-11, wherein $R^{6'}$ is selected from the group consisting of methyl, ethyl, propan-1-yl, propan-2-yl, 1-hydroxy-4-methyl-pentan-2-yl, 2-methyl-propan-1-yl, 3-methyl-butan-1-yl, 2-hydroxyethyl, 2-methoxyethyl, cyclopropyl, cyclopropylmethyl, benzyl, pyridin-3-ylmethyl, 3-methoxypropan-1-yl, 2-(N,N-dimethyl)-ethyl, 3-(2-oxopyrrolidin-1-yl)-propan-1-yl, 1,3-dimethoxy-propan-2-yl, and 1-methyl-azetidine-3-yl.

19. The compound of any one of Claims 1-16 or Claim 18, wherein R^{13} is hydrogen.

20. The compound of any one of the preceding claims wherein m is 0.

21. The compound of any one of the preceding claims wherein p is 0.

22. The compound of any one of the preceding claims wherein p is 1.

23. A pharmaceutical composition comprising a compound of any one of Claims 1-22, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient or carrier.

24. A method of inhibiting bacterial DNA gyrase and/or bacterial topoisomerase IV in a warm-blooded animal in need of such treatment, comprising administering to the animal an effective amount of a compound of any one of Claims 1-22, or a pharmaceutically acceptable salt thereof.

25. A method of producing an antibacterial effect in a warm-blooded animal in need of such treatment, comprising administering to the animal an effective amount of a compound of any one of Claims 1-22, or a pharmaceutically acceptable salt thereof.

26. A method of treating a bacterial infection in a warm-blooded animal in need thereof, comprising administering to the animal an effective amount of a compound of any one of Claims 1-22, or a pharmaceutically acceptable salt thereof.

27. The method of Claim 26, wherein the bacterial infection is selected from the group consisting of community-acquired pneumoniae, hospital-acquired pneumoniae, skin and skin structure infections, acute exacerbation of chronic bronchitis, acute sinusitis, acute otitis media, catheter-related sepsis, febrile neutropenia, osteomyelitis, endocarditis, urinary tract infections and infections caused by drug resistant bacteria such as Penicillin-resistant Streptococcus pneumoniae, methicillin-resistant Staphylococcus aureus, methicillin-resistant Staphylococcus epidermidis and Vancomycin-Resistant Enterococci.

28. The method of any one of Claims 24 through 27, wherein the warm-blooded animal is a human.

29. The use of a compound of any one of Claims 1-22, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use in the production of an antibacterial effect in a warm-blooded animal.

30. The use of a compound of any one of Claims 1-22, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use in inhibition of bacterial DNA gyrase and/or topoisomerase IV in a warm-blooded animal.

31. The use of a compound of any one of Claims 1-22, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use the treatment of a bacterial infection in a warm-blooded animal.

32. The use of Claim 31, wherein the bacterial infection is selected from the group consisting of community-acquired pneumoniae, hospital-acquired pneumoniae, skin and skin structure infections, acute exacerbation of chronic bronchitis, acute sinusitis, acute otitis media, catheter-related sepsis, febrile neutropenia, osteomyelitis, endocarditis, urinary tract infections, Penicillin-resistant Streptococcus pneumoniae, methicillin-resistant Staphylococcus aureus, methicillin-resistant Staphylococcus epidermidis and Vancomycin-Resistant Enterococci.

33. The use of any one of Claims 29 through 32, wherein the warm-blooded animal is a human.

34. A compound of any one of Claims 1-22, or a pharmaceutically acceptable salt thereof, for use in production of an anti-bacterial effect in a warm-blooded animal.

35. A compound of any one of Claims 1-22, or a pharmaceutically acceptable salt thereof, for use in inhibition of bacterial DNA gyrase and/or topoisomerase IV in a warm-blooded animal.

36. A compound of any one of Claims 1-22, or a pharmaceutically acceptable salt thereof, for use in the treatment of a bacterial infection in a warm-blooded animal.

37. A compound of any one of Claims 1-22, or a pharmaceutically acceptable salt thereof, for use in the treatment of community-acquired pneumoniae, hospital-acquired pneumoniae, skin and skin structure infections, acute exacerbation of chronic bronchitis, acute sinusitis, acute otitis media, catheter-related sepsis, febrile neutropenia, osteomyelitis, endocarditis, urinary tract infections, Penicillin-resistant Streptococcus pneumoniae, methicillin-resistant Staphylococcus aureus, methicillin-resistant Staphylococcus epidermidis or Vancomycin-Resistant Enterococci.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2009/050611

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D417/14 C07D498/06 A61P31/04 A61K31/4709 A61K31/4738

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, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2006/092599 A (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; BASARAB GREG [US]; GRAVE) 8 September 2006 (2006-09-08) cited in the application claim 1	1
A	WO 2007/071965 A (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; BASARAB GREGORY [US]; NI) 28 June 2007 (2007-06-28) cited in the application claim 1	1
P,X	WO 2008/068470 A (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; BASARAB GREGORY STEVEN [) 12 June 2008 (2008-06-12) claims 1,20 pages 64-67; examples 42-49	1-37

☐ 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
10 July 2009	22/07/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Duval, Eric

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2009/050611

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006092599 A	08-09-2006	CN 101171247 A	30-04-2008
		EP 1861393 A2	05-12-2007
		JP 2008531671 T	14-08-2008
		US 2008269214 A1	30-10-2008
WO 2007071965 A	28-06-2007	AU 2006328196 A1	28-06-2007
		CA 2633563 A1	28-06-2007
		CN 101389627 A	18-03-2009
		EP 1991545 A2	19-11-2008
		JP 2009520785 T	28-05-2009
		KR 20080080211 A	02-09-2008
		US 2008312211 A1	18-12-2008
WO 2008068470 A	12-06-2008	AR 064130 A1	11-03-2009
		CL 34702007 A1	22-08-2008
		US 2008132546 A1	05-06-2008
		UY 30759 A1	31-07-2008

DERIVADOS DE UREA HETEROCÍCLICOS Y MÉTODOS DE USO DE LOS MISMOS-332

Campo de la invención

La presenten invención se refiere a compuestos que demuestran actividad antibacteriana, a procedimientos para su preparación, a composiciones farmacéuticas que los contienen como ingrediente activo, a su uso como medicamentos y a su uso en la fabricación de medicamentos para uso en el tratamiento de infecciones bacterianas en animales de sangre caliente, tales como los seres humanos. En particular, esta invención se refiere a compuestos útiles para el tratamiento de infecciones bacterianas en animales de sangre caliente tales como los seres humanos; más particularmente, al uso de estos compuestos en la fabricación de medicamentos para uso en el tratamiento de infecciones bacterianas en animales de sangre caliente tales como los seres humanos.

Antecedentes de la invención

La comunidad microbiológica internacional continúa expresando una gran preocupación porque la evolución de la resistencia a antibióticos podría dar como resultado cepas frente a las cuales los agentes antibacterianos actualmente disponibles serán ineficaces. En general, los patógenos bacterianos se pueden clasificar como patógenos Gram-positivos o Gram-negativos. Se considera que los compuestos antibióticos con actividad eficaz frente a patógenos tanto Gram-positivos como Gram-negativos generalmente tienen un espectro amplio de actividad. Los compuestos de la presente invención se consideran principalmente eficaces frente a patógenos tanto Gram-positivos como frente a ciertos patógenos Gram-negativos.

Los patógenos Gram-positivos, por ejemplo estafilococos, enterococos, estreptococos y micobacterias, son particularmente importantes debido al desarrollo de cepas resistentes que son difíciles tanto de tratar como de erradicar del medio hospitalario una vez asentados. Los ejemplos de tales cepas son *Staphylococcus aureus* resistente a meticilina (MRSA), estafilococos negativos a la coagulasa resistentes a meticilina (MRCNS), *Streptococcus pneumoniae* resistente a penicilina, y *Enterococcus faecium* con multirresistente.

El antibiótico clínicamente eficaz preferido para el tratamiento de último recurso de tales patógenos Gram-positivos resistentes es vancomicina. La vancomicina es un glicopéptido, y está asociada con diversas toxicidades, incluyendo nefrotoxicidad. Además, y

lo más importante, también está apareciendo una resistencia antibacteriana a vancomicina y a otros glicopéptidos. Esta resistencia está creciendo a un ritmo constante, haciendo a estos agentes cada vez menos eficaces en el tratamiento de patógenos Gram-positivos. Ahora también está creciendo la aparición de resistencia con respecto a agentes tales como β-lactamas, quinolonas y macrólidos, usados para el tratamiento de las infecciones de las vías respiratorias superiores, también causadas por ciertas cepas Gram-negativas, incluyendo *H. influenzae* y *M. catarrhalis*.

En consecuencia, a fin de superar la amenaza de organismos resistentes a múltiples fármacos ampliamente extendidos, existe una necesidad continua de desarrollar nuevos antibióticos, particularmente aquellos con un nuevo mecanismo de acción y/o que contienen nuevos grupos farmacóforos.

La ácido dexosirribonucleico (ADN) girasa es un miembro de la familia de tipo II de topoisomerasas que controla el estado topológico del ADN en las células (Champoux, J. J.; 2001. Ann. Rev. Biochem. 70: 369-413). Las topoisomerasas de tipo II usan la energía libre de la hidrólisis del trifosfato de adenosina (ATP) para alterar la topología del ADN, introduciendo rupturas transitorias en la cadena doble en el ADN, catalizando el paso de la cadena a través de la ruptura, y volviendo a unir 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 superhélices negativas en el ADN. La enzima consta de dos subunidades, codificadas por *gyrA* y *gyrB*, formando un complejo tetrámero A_2B_2. La subunidad A de la girasa (GyrA) está implicada en la ruptura y reunificación del ADN, y contiene un resto de tirosina conservado que forma el enlace covalente transitorio al ADN durante el paso de la cadena. La subunidad B (GyrB) cataliza la hidrólisis de ATP e interactúa con la subunidad A para traducir la energía libre de la hidrólisis al cambio conformacional en la enzima, que permite el paso de cadena y la reunificación del ADN.

Otra topoisomerasa de tipo II conservada y esencial en las bacterias, denominada topoisomerasa IV, es responsable principalmente de separar los cromosomas bacterianos circulares cerrados enlazados, producidos en la replicación. Esta enzima está estrechamente relacionada con la ADN girasa, y tiene una estructura tetrámera similar, formada por subunidades homólogas a GyrA y a GyrB. La identidad de secuencia global entre la girasa y la topoisomerasa IV, en diferentes especies bacterianas, es elevada. Por lo tanto, los compuestos dirigidos contra topoisomerasas de tipo II bacterianas tienen el potencial para

inhibir dos dianas en las células, la ADN girasa y la topoisomerasa IV, como es el caso para antibacterianos quinolónicos existentes (Maxwell, A. 1997, Trends Microbiol. 5: 102-109).

La ADN girasa es una diana bien aceptada de los antibacterianos, incluyendo las quinolonas y las cumarinas. Las quinolonas (*por ejemplo*, la ciprofloxacina) son antibacterianos de amplio espectro que inhiben la actividad de la enzima en la ruptura y reunificación del ADN, y atrapan la subunidad de GyrA complejada covalentemente con ADN (Drlica, K., y X. Zhao, 1997, Microbiol. Molec. Biol.. Rev. 61: 377-392). Los miembros de esta clase de antibacterianos también inhiben topoisomerasa IV y, como resultado, la diana principal de estos compuestos varía entre las especies. Aunque las quinolonas son antibacterianos exitosos, la resistencia, generada principalmente por mutaciones en la diana (ADN girasa y topoisomerasa IV), se está convirtiendo en un problema creciente en varios organismos, incluyendo *S aureus* y *Streptococcus pneumoniae* (Hooper, D. C., 2002, The Lancet Infectious Diseases 2: 530-538). Además, las quinolonas, como clase química, tienen efectos secundarios tóxicos, incluyendo artropatía, lo que evita su uso en niños (Lipsky, B. A. y Baker, C. A., 1999, Clin. Infect. Dis. 28: 352-364). Además, se ha citado la potencial cardiotoxicidad, según se predice mediante prolongación del intervalo de QT_c, como un problema de toxicidad de las quinilonas.

Hay varios productos naturales conocidos, inhibidores de la ADN girasa, que compiten con el ATP por la unión a la subunidad GyrB (Maxwell, A. y Lawson, D.M. 2003, Curr. Topics in Med. Chem. 3: 283-303). Las cumarinas son productos naturales aislados de *Streptomyces spp.*, cuyos ejemplos son novobiocina, clorobiocina y cumermicina A1. Aunque estos compuestos son potentes inhibidores de la ADN girasa, su utilidad terapéutica está limitada debido a toxicidad en eucariotas y a la mala penetración en bacterias Gram-negativas (Maxwell, A. 1997, Trends Microbiol. 5: 102-109). Otra clase de compuestos de productos naturales que se dirigen contra la subunidad GyrB son las ciclotialidinas, que se aíslan 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 muestra actividad sólo frente a algunas especies eubacterianas (Nakada, N, 1993, *Antimicrob. Agents Chemother.* 37: 2656-2661).

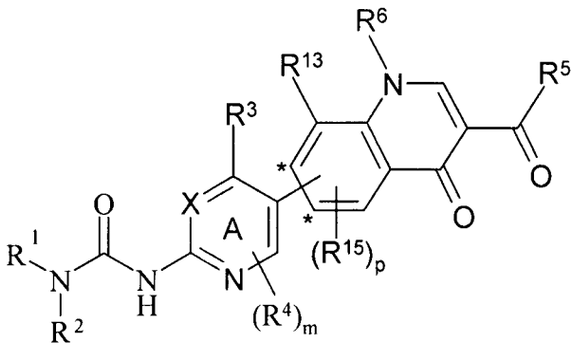
En la técnica se conocen inhibidores sintéticos que se dirigen contra la subunidad B de la ADN girasa y topoisomerasa IV. Por ejemplo, en la Solicitud de patente número WO 99/35155 se describen compuestos que contienen cumarina; en la Solicitud de patente WO 02/060879 se describen compuestos heteroaromáticos 5,6-bicíclicos; y en la Solicitud de

patente WO 01/52845 (patente de los Estados Unidos US6.608.087) se describen compuestos pirazólicos. AstraZeneca también ha publicado algunas Solicitudes que describen compuestos antibacterianos: WO2005/026149, WO2006/087544, WO2006/087548, WO2006/087543, WO2006/092599, WO2006/092608, y WO2007/071965.

Sumario de la invención

Se ha descubierto una nueva clase de compuestos que son útiles para inhibir ADN girasa y/o topoisomerasa IV.

En una realización, según la presente invención, se proporciona un compuesto de fórmula **(I)**:



(I)

o una sal farmacéuticamente aceptable del mismo, en la que:

El anillo A está unido a uno de los átomos de carbono indicados por "*";

X es N, CH o CR^4;

R^1 se selecciona de alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6} o cicloalquilo C_{3-6}; en la que R^1 puede estar opcionalmente sustituido en el carbono con uno o más R^7;

R^2 se selecciona de hidrógeno o alquilo C_{1-6}; en el que dicho alquilo C_{1-6} puede estar opcionalmente sustituido con uno o más grupos seleccionados independientemente de halo, ciano, hidroxi, nitro y amino;

o **R^1 y R^2**, junto con el nitrógeno al que están unidos, forman un heterociclilo; en la que dicho heterociclilo puede estar opcionalmente sustituido en uno o más átomos de carbono con uno o más R^8; y en la que, si dicho heterociclilo contiene un resto =N- o –S-, ese nitrógeno puede estar opcionalmente sustituido con un grupo oxo, y ese azufre puede estar opcionalmente sustituido con uno o dos grupos oxo; y en la que, si dicho heterociclilo contiene un resto -NH-, ese nitrógeno puede estar opcionalmente sustituido con un grupo seleccionado de R^9;

R^3 es un carbociclilo C_{3-14} o un heterociclilo; en la que el carbociclilo or heterociclilo puede estar opcionalmente sustituido en uno o más átomos de carbono con uno o más R^{10}; y en la que, si dicho heterociclilo contiene un resto =N- o –S-, ese nitrógeno puede estar opcionalmente sustituido con un grupo oxo, y ese azufre puede estar opcionalmente sustituido con uno o dos grupos oxo; y en la que, si dicho heterociclilo contiene un resto -NH-, ese nitrógeno puede estar opcionalmente sustituido con un grupo seleccionado de R^{11};

R^4 y **R^{15}**, para cada caso, se seleccionan independientemente del grupo que consiste en halo, nitro, ciano, hidroxi, amino, mercapto, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, alcoxi C_{1-6}, *N*-(alquil C_{1-6})amino, *N,N*-(alquil C_{1-6})$_2$amino, y alquil C_{1-6}-sulfanilo; en la que R^4, R^{13}, y R^{15}, independientemente entre sí, pueden estar opcionalmente sustituidos en uno o más carbonos con uno o más R^{12};

R^5 es –OH, -NH_2, un alcoxi C_{1-6}, un *N*-(alquil C_{1-6})amino, o *N,N*-(alquil C_{1-6})$_2$amino; en la que el alcoxi C_{1-6}, un *N*-(alquil C_{1-6})amino, o *N,N*-(alquil C_{1-6})$_2$amino pueden estar opcionalmente sustituidos en uno o más átomos de carbono con uno o más R^{14}, seleccionados independientemente;

R^6, para cada caso, se selecciona independientemente del grupo que consiste en hidrógeno, alquilo C_{1-6}, alquil C_{1-6}-sulfanilo, carboxi, carbamoilo, N-(alquil C_{1-6})carbamoilo, N,N-(alquil C_{1-6})$_2$carbamoilo, carbociclilo C_{3-14}, y heterociclilo; en la que R^6 está opcionalmente sustituido en uno o más átomos de carbono con uno o más R^{16}; y en la que, si dicho heterociclilo contiene un resto =N- o –S-, ese nitrógeno puede estar opcionalmente sustituido con un grupo oxo, y ese azufre puede estar opcionalmente sustituido con uno o dos grupos oxo; y en la que, si dicho heterociclilo contiene un resto -NH-, ese nitrógeno puede estar opcionalmente sustituido con un grupo seleccionado de R^{17};

R^{13} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, hidroxi, amino, mercapto, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, alcoxi C_{1-6}, *N*-(alquil C_{1-6})amino, *N,N*-(alquil C_{1-6})$_2$amino, y alquil C_{1-6}-sulfanilo; en la que R^{13} puede estar opcionalmente sustituido en uno o más carbonos con uno o más R^{16}; o

R^6 y R^{13}, junto con los átomos anulares que intervienen, pueden formar un heterociclilo condensado, en la que el heterociclilo condensado puede estar opcionalmente sustituido en uno o más átomos de carbono con uno o más R^{16}, seleccionados independientemente; y en la que, si dicho heterociclilo condensado contiene un resto =N- o –S-, ese nitrógeno puede estar opcionalmente sustituido con un grupo oxo, y ese azufre puede estar opcionalmente sustituido con uno o dos grupos oxo; y en la que, si dicho heterociclilo

condensado contiene un resto -NH-, ese nitrógeno puede estar opcionalmente sustituido con un grupo seleccionado de R^{17};

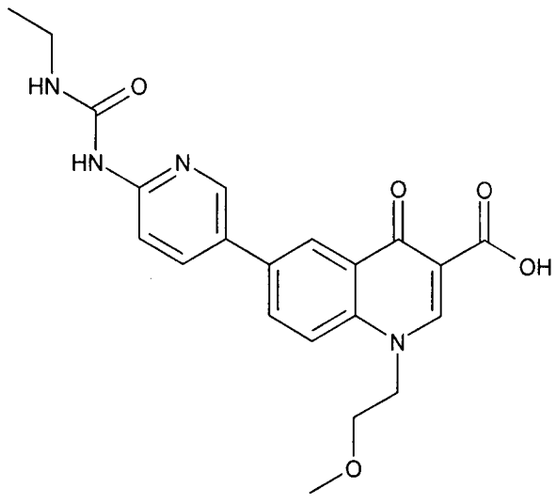
m es 0 ó 1;

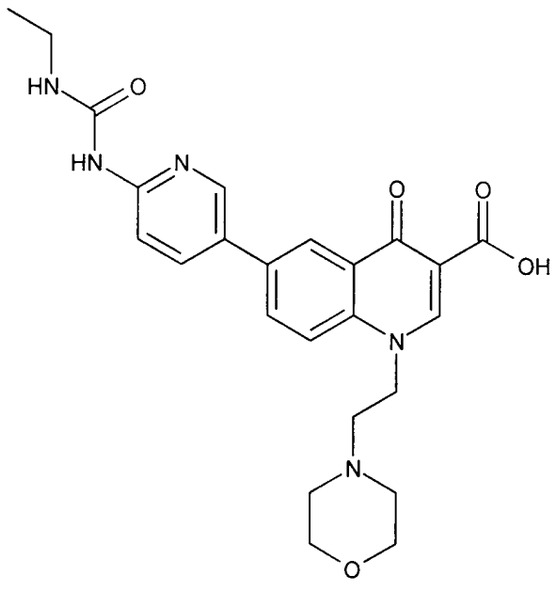
p es 0, 1, ó 2;

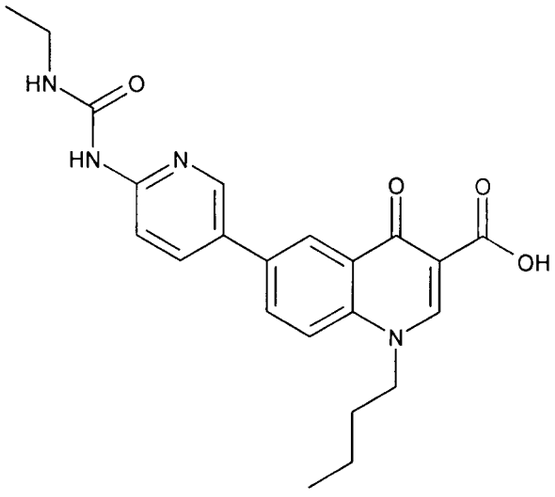
R^7, R^8, R^{10}, R^{12}, R^{14} y R^{16} son sustituyentes en el carbono que, para cada caso, se seleccionan independientemente de halo, nitro, ciano, hidroxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, alcoxi C_{1-6}, alcanoilo C_{1-6}, alcanoil C_{1-6}-oxi, *N*-(alquil C_{1-6})amino, *N,N*-(alquil C_{1-6})$_2$amino, alcanoil C_{1-6}-amino, *N*-(alquil C_{1-6})carbamoilo, *N,N*-(alquil C_{1-6})$_2$carbamoilo, alquil C_{1-6}-$S(O)_a$-, en el que a es 0, 1 ó 2, alcoxi C_{1-6}-carbonilo, alcoxi C_{1-6}-carbonilamino, *N*-(alquil C_{1-6})sulfamoilo, *N,N*-(alquil C_{1-6})$_2$sulfamoilo, alquil C_{1-6}-sulfonilamino, carbociclilo C_{3-6} o heterociclilo; en la que R^7, R^8, R^{10}, R^{12}, R^{14} y R^{16}, independientemente entre sí, pueden estar opcionalmente sustituidos en uno o más carbonos con uno o más R^{19}; y en la que, si dicho heterociclilo contiene un resto -NH-, ese nitrógeno puede estar opcionalmente sustituido con un grupo seleccionado de R^{20}; y en la que, si dicho heterociclilo contiene un resto =N- o –S-, ese nitrógeno puede estar opcionalmente sustituido con un grupo oxo, y ese azufre puede estar opcionalmente sustituido con uno o dos grupos oxo

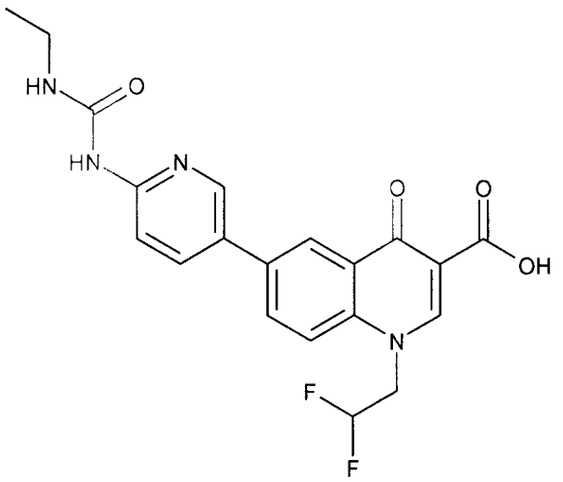
R^9, R^{11}, R^{17} y R^{20}, para cada caso, se seleccionan independientemente de alquilo C_{1-6}, cicloalquilo C_{3-6}, alcanoilo C_{1-6}, alquil C_{1-6}-sulfonilo, alcoxi C_{1-6}-carbonilo, carbamoilo, *N*-(alquil C_{1-6})carbamoilo, *N,N*-(alquil C_{1-6})carbamoilo, bencilo, benciloxicarbonilo, benzoilo y fenilsulfonilo; en la que R^9, R^{11}, R^{17}, y R^{20}, independientemente entre sí, pueden estar opcionalmente sustituidos en el carbono con uno o más R^{23}; y

R^{19} y R^{23}, para cado caso, se seleccionan independientemente de halo, nitro, ciano, hidroxi, trifluorometoxi, trifluorometilo, amino, carboxi, carbamoilo, mercapto, sulfamoilo, alquilo C_{1-6}, alcoxi C_{1-6}, acetilo, acetoxi, metilamino, etilamino, dimetilamino, dietilamino, *N*-metil-*N*-etilamino, acetilamino, *N*-metilcarbamoilo, *N*-etilcarbamoilo, *N,N*-dimetilcarbamoilo, *N,N*-dietilcarbamoilo, *N*-metil-*N*-etilcarbamoilo, metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo, etilsulfonilo, metoxicarbonilo, etoxicarbonilo, *N*-metilsulfamoilo, *N*-etilsulfamoilo, *N,N*-dimetilsulfamoilo, *N,N*-dietilsulfamoilo o *N*-metil-*N*-etilsulfamoilo, con la condición de que el compuesto no sea uno de los siguientes compuestos:

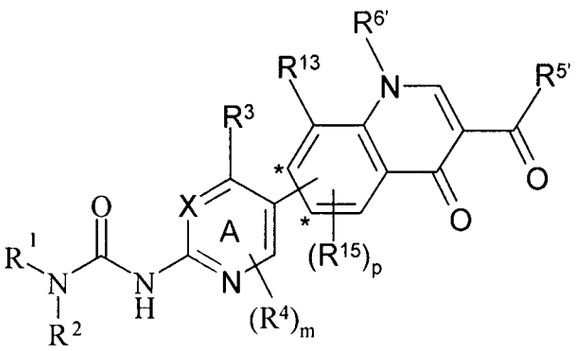








En otra realización, la invención proporciona un compuesto de fórmula **(I')**:



(I')

o una sal farmacéuticamente aceptable del mismo, en la que:

El anillo A está unido a uno de los átomos de carbono indicados por "*";

X es N, CH o CR^4;

R^1 se selecciona de alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6} o cicloalquilo C_{3-6}; en la que R^1 puede estar opcionalmente sustituido en el carbono con uno o más R^7;

R^2 se selecciona de hidrógeno o alquilo C_{1-6}; en la que dicho alquilo C_{1-6} puede estar opcionalmente sustituido con uno o más grupos seleccionados independientemente de halo, ciano, hidroxi, nitro y amino;

o **R^1 y** R^2, junto con el nitrógeno al que están unidos, forman un heterociclilo; en la que dicho heterociclilo puede estar opcionalmente sustituido en uno o más átomos de carbono con uno o más R^8; y en la que, si dicho heterociclilo contiene un resto =N- o –S-, ese nitrógeno puede estar opcionalmente sustituido con un grupo oxo, y ese azufre puede estar opcionalmente sustituido con uno o dos grupos oxo; y en la que, si dicho heterociclilo contiene un resto -NH-, ese nitrógeno puede estar opcionalmente sustituido con un grupo seleccionado de R^9;

R^3 es un carbociclilo C_{3-14} o un heterociclilo; en la que el carbociclilo o heterociclilo puede estar opcionalmente sustituido en uno o más átomos de carbono con uno o más R^{10}; y en la que, si dicho heterociclilo contiene un resto =N- o –S-, ese nitrógeno puede estar opcionalmente sustituido con un grupo oxo, y ese azufre puede estar opcionalmente sustituido con uno o dos grupos oxo; y en la que, si dicho heterociclilo contiene un resto -NH-, ese nitrógeno puede estar opcionalmente sustituido con un grupo seleccionado de R^{11};

R^4 y **R^{15}**, para cada caso, se seleccionan independientemente del grupo que consiste en halo, nitro, ciano, hidroxi, amino, mercapto, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, alcoxi C_{1-6}, *N*-(alquil C_{1-6})amino, *N,N*-(alquil C_{1-6})$_2$amino, y alquil C_{1-6}-sulfanilo; en la que R^4, R^{13} y R^{15}, independientemente entre sí, pueden estar opcionalmente sustituidos en uno o más carbonos con uno o más R^{12};

$R^{5'}$ es –OH, un alcoxi C_{1-6}, cicloalcoxi C_{3-14}, o $-NR^aR^b$; en la que el grupo alcoxi C_{1-6} puede estar opcionalmente sustituido en uno o más átomos de carbono con uno o más R^{14}, seleccionados independientemente; y en la que R^a y R^b son cada uno independientemente hidrógeno, un alquilo C_{1-6}, o un carbociclo C_{3-14}, o R^a y R^b, junto con el nitrógeno al que están unidos, forman un heterociclo, en el que R^a y R^b pueden estar opcionalmente sustituidos en uno o más átomos de carbono con uno o más R^{14}, seleccionados independientemente; y en la que, si dicho heterociclilo contiene un resto =N- o –S-, ese nitrógeno puede estar opcionalmente sustituido con un grupo oxo, y ese azufre puede estar opcionalmente sustituido con uno o dos grupos oxo; y en la que, si dicho heterociclilo contiene un resto -NH-, ese nitrógeno puede estar opcionalmente sustituido con un grupo seleccionado de R^{22};

$R^{6'}$, para cada caso, se selecciona independientemente del grupo que consiste en hidrógeno, alquilo C_{1-6}, alquil C_{1-6}-sulfanilo, carboxi, carbamoilo, N-(alquil C_{1-6})carbamoilo, N,N-(alquil C_{1-6})$_2$carbamoilo, carbociclilo C_{3-14}-L-, y heterociclilo-L-; en la que R^6 está opcionalmente sustituido en uno o más átomos de carbono con uno o más R^{16}; y en la que, si dicho heterociclilo contiene un resto =N- o –S-, ese nitrógeno puede estar opcionalmente sustituido con un grupo oxo, y ese azufre puede estar opcionalmente sustituido con uno o dos grupos oxo; y en la que, si dicho heterociclilo contiene un resto -NH-, ese nitrógeno puede estar opcionalmente sustituido con un grupo seleccionado de $R^{17'}$;

R^{13} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, hidroxi, amino, mercapto, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, alcoxi C_{1-6}, *N*-(alquil C_{1-6})amino, *N,N*-(alquil C_{1-6})$_2$amino, y alquil C_{1-6}-sulfanilo; en la que R^{13} puede estar opcionalmente sustituido en uno o más carbonos con uno o más R^{16}; o

$R^{6'}$ y R^{13}, junto con los átomos anulares que intervienen, pueden formar un heterociclilo condensado, en la que el heterociclilo condensado puede estar opcionalmente sustituido en uno o más átomos de carbono con uno o más R^{16}, seleccionados independientemente; y en la que, si dicho heterociclilo condensado contiene un resto =N- o –S-, ese nitrógeno puede estar opcionalmente sustituido con un grupo oxo, y ese azufre puede estar opcionalmente sustituido con uno o dos grupos oxo; y en la que, si dicho heterociclilo condensado contiene un resto -NH-, ese nitrógeno puede estar opcionalmente sustituido con un grupo seleccionado de $R^{17'}$;

m es 0 ó 1;

p es 0, 1, ó 2;

L, para cada caso, es independientemente un enlace directo o un alquileno C_{1-6};

R^7, R^8, R^{10}, R^{12}, R^{14} y R^{16} son sustituyentes en el carbono que, para cada caso, se seleccionan independientemente de halo, nitro, ciano, hidroxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, alcoxi C_{1-6}, alcanoilo C_{1-6}, alcanoil C_{1-6}-oxi, *N*-(alquil C_{1-6})amino, *N,N*-(alquil C_{1-6})$_2$amino, alcanoil C_{1-6}-amino, *N*-(alquil C_{1-6})carbamoilo, *N,N*-(alquil C_{1-6})$_2$carbamoilo, alquil C_{1-6}-$S(O)_a$-, en el que a es 0, 1 ó 2, alcoxi C_{1-6}-carbonilo, alcoxi C_{1-6}-carbonilamino, *N*-(alquil C_{1-6})sulfamoilo, *N,N*-(alquil C_{1-6})$_2$sulfamoilo, alquil C_{1-6}-sulfonilamino, carbociclilo C_{3-6} o heterociclilo; en la que R^7, R^8, R^{10}, R^{12}, R^{14} y R^{16}, independientemente entre sí, pueden estar opcionalmente sustituidos en uno o más carbonos con uno o más R^{19}; y en la que, si dicho heterociclilo contiene un resto -NH-, ese nitrógeno puede estar opcionalmente sustituido con un grupo seleccionado de R^{20}; y en la que, si dicho heterociclilo contiene un resto =N- o –S-, ese nitrógeno puede estar opcionalmente sustituido con un grupo oxo, y ese azufre puede estar opcionalmente sustituido con uno o dos grupos oxo;

R^9, R^{11}, y R^{20}, para cada caso, se seleccionan independientemente de alquilo C_{1-6}, cicloalquilo C_{3-6}, alcanoilo C_{1-6}, alquil C_{1-6}-sulfonilo, alcoxi C_{1-6}-carbonilo, carbamoilo, *N*-(alquil C_{1-6})carbamoilo, *N,N*-(alquil C_{1-6})$_2$carbamoilo, bencilo, benciloxicarbonilo, benzoilo y fenilsulfonilo; en la que R^9, R^{11}, y R^{20}, independientemente entre sí, pueden estar opcionalmente sustituidos en el carbono con uno o más R^{23};

$R^{17'}$, para cada caso, se selecciona independientemente de alquilo C_{1-6}, cicloalquilo C_{3-6}, alcanoilo C_{1-6}, alquil C_{1-6}-sulfonilo, alcoxi C_{1-6}-carbonilo, carbamoilo, *N*-(alquil C_{1-6})carbamoilo, *N,N*-(alquil C_{1-6})carbamoilo, bencilo, benciloxicarbonilo, benzoilo, fenilsulfonilo, carbociclilo C_{3-14}-L-, y heterociclilo-L-; en la que cada $R^{17'}$,

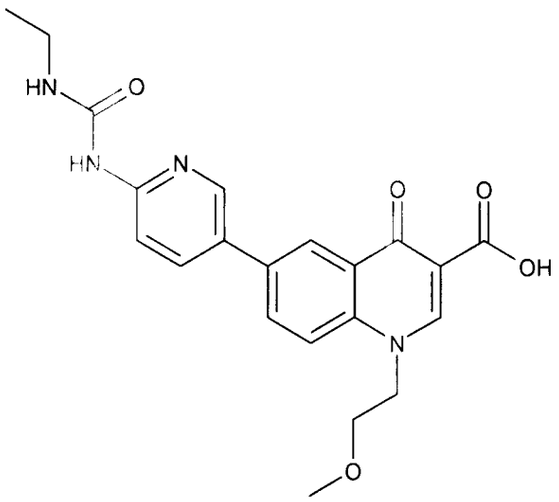
independientemente, puede estar opcionalmente sustituido en el carbono con uno o más R^{24}; y en la que, si dicho heterociclilo contiene un resto -NH-, ese nitrógeno puede estar opcionalmente sustituido con un grupo seleccionado de R^{25}; y en la que, si dicho heterociclilo contiene un resto =N- o –S-, ese nitrógeno puede estar opcionalmente sustituido con un grupo oxo, y ese azufre puede estar opcionalmente sustituido con uno o dos grupos oxo;

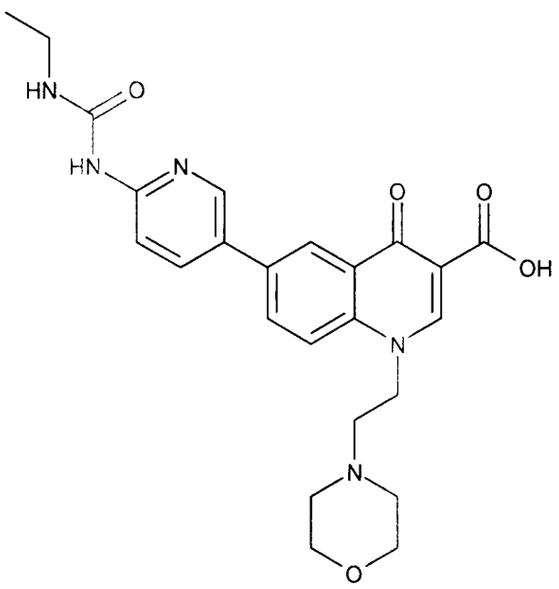
R^{22}, para cada caso, se selecciona independientemente de alquilo C_{1-6}, cicloalquilo C_{3-6}, alcanoilo C_{1-6}, alquil C_{1-6}-sulfonilo, alcoxi C_{1-6}-carbonilo, carbamoilo, N,N-(alquil C_{1-6})$_2$sulfamoilo, *N*-(alquil C_{1-6})carbamoilo, *N,N*-(alquil C_{1-6})$_2$carbamoilo, bencilo, benciloxicarbonilo, benzoilo y fenilsulfonilo; en la que R^{22}, para cada caso, puede estar independientemente sustituido de forma opcional en el carbono con uno o más R^{23};

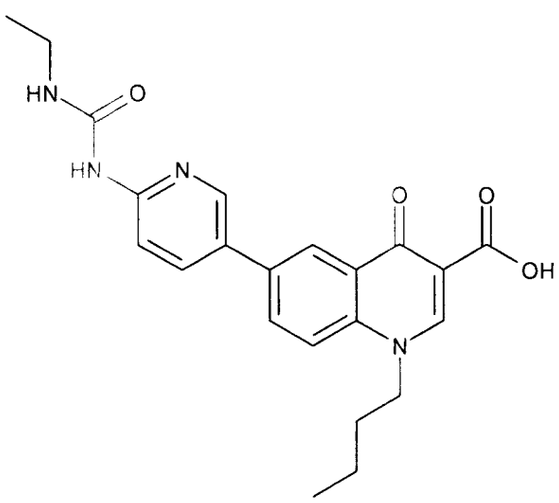
R^{19} y R^{23}, para cada caso, se seleccionan independientemente de halo, nitro, ciano, hidroxi, trifluorometoxi, trifluorometilo, amino, carboxi, carbamoilo, mercapto, sulfamoilo, alquilo C_{1-6}, alcoxi C_{1-6}, acetilo, acetoxi, metilamino, etilamino, dimetilamino, dietilamino, *N*-metil-*N*-etilamino, acetilamino, *N*-metilcarbamoilo, *N*-etilcarbamoilo, *N,N*-dimetilcarbamoilo, *N,N*-dietilcarbamoilo, *N*-metil-*N*-etilcarbamoilo, metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo, etilsulfonilo, metoxicarbonilo, etoxicarbonilo, *N*-metilsulfamoilo, *N*-etilsulfamoilo, *N,N*-dimetilsulfamoilo, *N,N*-dietilsulfamoilo o *N*-metil-*N*-etilsulfamoilo;

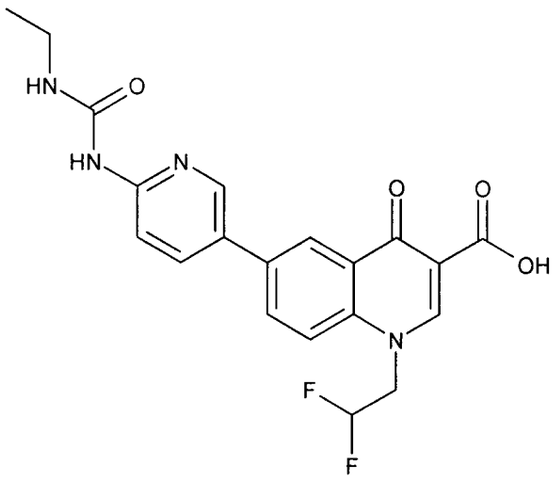
R^{24}, para cada caso, se seleccionan independientemente de halo, nitro, ciano, hidroxi, oxo, trifluorometoxi, trifluorometilo, amino, carboxi, carbamoilo, mercapto, sulfamoilo, alquilo C_{1-6}, alcoxi C_{1-6}, acetilo, acetoxi, metilamino, etilamino, dimetilamino, dietilamino, *N*-metil-*N*-etilamino, acetilamino, *N*-metilcarbamoilo, *N*-etilcarbamoilo, *N,N*-dimetilcarbamoilo, *N,N*-dietilcarbamoilo, *N*-metil-*N*-etilcarbamoilo, metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo, etilsulfonilo, metoxicarbonilo, etoxicarbonilo, *N*-metilsulfamoilo, *N*-etilsulfamoilo, *N,N*-dimetilsulfamoilo, *N,N*-dietilsulfamoilo o *N*-metil-*N*-etilsulfamoilo; y

R^{25}, para cada caso, se selecciona independientemente de un alquilo C_{1-6}, con la condición de que el compuesto no sea uno de los siguientes compuestos:









En otra realización, la invención proporciona composiciones farmacéuticas que comprenden un compuesto representado por la fórmula **(I)** o **(I')**, o una sal farmacéuticamente aceptable del mismo, y un excipiente o vehículo farmacéuticamente aceptable.

En otra realización, la invención proporciona un método para inhibir ADN girasa bacteriana y/o topoisomerasa IV bacteriana en un animal de sangre caliente que necesite de tal tratamiento, que comprende administrar al animal una cantidad eficaz de un compuesto representado por la fórmula **(I)** o **(I')**, o una sal farmacéuticamente aceptable del mismo. En una realización particular, el animal de sangre caliente es un ser humano.

En otra realización, la invención proporciona un método para producir un efecto antibacteriano en un animal de sangre caliente que necesite de tal tratamiento, que comprende administrar al animal una cantidad eficaz de un compuesto representado por la fórmula **(I)** o **(I')**, o una sal farmacéuticamente aceptable del mismo. En una realización particular, el animal de sangre caliente es un ser humano.

En otra realización, la invención proporciona un método para tratar una infección bacteriana en un animal de sangre caliente que lo necesite, que comprende administrar al animal una cantidad eficaz de un compuesto representado por la fórmula **(I)** o **(I')**, o una sal farmacéuticamente aceptable del mismo. En una realización particular, el animal de sangre caliente es un ser humano. En una realización, la infección bacteriana se selecciona del grupo que consiste en neumonía adquirida en la comunidad, neumonía adquirida en el hospital, infecciones de la piel y de la estructura de la piel, exacerbación aguda de bronquitis crónica, sinusitis aguda, otitis media aguda, septicemia relacionada con cateterismo, neutropenia febril, osteomielitis, endocarditis, infecciones del aparato urinario e infecciones provocadas por bacterias resistentes a fármacos tales como Streptococcus pneumoniae resistente a penicilina,

Staphylococcus aureus resistente a meticilina, Staphylococcus epidermidis resistente a meticilina y enterococos resistentes a vancomicina. En una realización particular, el animal de sangre caliente es un ser humano.

En otra realización, la invención proporciona el uso de un compuesto representado por la fórmula **(I)** o **(I')**, o una sal farmacéuticamente aceptable del mismo, para la fabricación de un medicamento para uso en la producción de un efecto antibacteriano en un animal de sangre caliente. En una realización particular, el animal de sangre caliente es un ser humano.

En otra realización, la invención proporciona el uso de un compuesto representado por la fórmula **(I)** o **(I')**, o una sal farmacéuticamente aceptable del mismo, para la fabricación de un medicamento para uso en la inhibición de ADN girasa y/o topoisomerasa IV bacterianas en un animal de sangre caliente. En una realización particular, el animal de sangre caliente es un ser humano.

En otra realización, la invención proporciona el uso de un compuesto representado por la fórmula **(I)** o **(I')**, o una sal farmacéuticamente aceptable del mismo, para la fabricación de un medicamento para uso en el tratamiento de una infección bacteriana en un animal de sangre caliente. En una realización, la infección bacteriana se selecciona del grupo que consiste en neumonía adquirida en la comunidad, neumonía adquirida en un hospital, infecciones de la piel y de la estructura de la piel, exacerbación aguda de bronquitis crónica, sinusitis aguda, otitis media aguda, septicemia relacionada con cateterismo, neutropenia febril, osteomielitis, endocarditis, infecciones del aparato urinario, Streptococcus pneumoniae resistente a penicilina, Staphylococcus aureus resistente a meticilina, Staphylococcus epidermidis resistente a meticilina y enterococos resistentes a vancomicina. En una realización particular, el animal de sangre caliente es un ser humano.

En otra realización, la invención proporciona un compuesto representado por la fórmula **(I)** o **(I')**, o una sal farmacéuticamente aceptable del mismo, para uso en la producción de un efecto antibacteriano en un animal de sangre caliente.

En otra realización, la invención proporciona un compuesto representado por la fórmula **(I)** o **(I')**, o una sal farmacéuticamente aceptable del mismo, para uso en la inhibición de una ADN girasa y/o topoisomerasa IV bacterianas en un animal de sangre caliente.

En otra realización, la invención proporciona un compuesto representado por la fórmula **(I)** o **(I')**, o una sal farmacéuticamente aceptable del mismo, para uso en el tratamiento de una infección bacteriana en un animal de sangre caliente.

En otra realización, la invención proporciona un compuesto representado por la fórmula **(I)** o **(I')**, o una sal farmacéuticamente aceptable del mismo, para uso en el tratamiento de neumonía adquirida en la comunidad, neumonía adquirida en un hospital, infecciones de la piel y de la estructura de la piel, exacerbación aguda de bronquitis crónica, sinusitis aguda, otitis media aguda, septicemia relacionada con cateterismo, neutropenia febril, osteomielitis, endocarditis, infecciones del aparato urinario, Streptococcus pneumoniae resistente a penicilina, Staphylococcus aureus resistente a meticilina, Staphylococcus epidermidis resistente a meticilina o enterococos resistentes a vancomicina.

Descripción detallada de la invención

En esta memoria descriptiva, el término alquilo incluye grupos hidrocarbonados tanto de cadena lineal como de cadena ramificada, saturados. Por ejemplo "alquilo C_{1-6}" se refiere a un alquilo que tiene de 1 a 6 átomos de carbono, e incluye, por ejemplo, metilo, etilo, propilo, isopropilo y *t*-butilo. Sin embargo, las referencias a grupos alquilo individuales, tales como propilo, son específicas para la versión de cadena lineal solamente, excepto que se indique de otro modo (por ejemplo, isopropilo). Se aplica una convención análoga a otros términos genéricos.

Como se usa aquí, el término "alquileno" se refiere a un grupo alquilo que tiene dos puntos de unión. Los ejemplos de grupos alquileno incluyen metileno, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, y $-CH_2C(CH_3)_2CH_2-$.

Como se usa aquí, el término "halo" ser refiere a fluoro, cloro, bromo, y yodo.

Un "heterociclilo" es un anillo mono- o bicíclico, saturado, parcialmente saturado o insaturado, que contiene 4-14 átomos, de los cuales al menos un átomo se escoge de nitrógeno, azufre u oxígeno, que puede estar, excepto que se especifique de otro modo, enlazado mediante carbono o nitrógeno, en el que un grupo $-CH_2-$ se puede sustituir opcionalmente por un -C(O)-, y un nitrógeno anular se puede sustituir opcionalmente con un oxo para formar un N-óxido, y un azufre anular se puede sustituir opcionalmente con uno o dos grupos oxo para formar el o los S-óxido(s). En una realización de la invención, un "heterociclilo" es un anillo monocíclico saturado, parcialmente saturado o insaturado, que contiene 5 ó 6 átomos, de los cuales al menos un átomo se escoge de nitrógeno, azufre u oxígeno, que puede, excepto que se especifique de otro modo, estar enlazado mediante carbono o nitrógeno. En un aspecto adicional de la invención, un "heterociclilo" es un anillo monocíclico insaturado, enlazado mediante carbono, que contiene 5 ó 6 átomos, de los cuales

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al menos un átomo se escoge de nitrógeno, azufre u oxígeno. Los ejemplos y valores adecuados del término "heterociclilo" son morfolinilo, piperidilo, piridinilo, piranilo, pirrolilo, pirazolilo, isotiazolilo, indolilo, quinolinilo, tienilo, 1,3-benzodioxolilo, benzotiazolilo, tiadiazolilo, oxadiazolilo, piperazinilo, tiazolidinilo, pirrolidinilo, tiomorfolino, pirrolinilo, homopiperazinilo, 3,5-dioxapiperidinilo, tetrahidropiranilo, imidazolilo, 4,5-dihidro-oxazolilo, pirimidinilo, pirazinilo, piridazinilo, isoxazolilo, tiazolilo, 1*H*-tetrazolilo, 1*H*-triazolilo, *N*-metilpirrolilo, 4-piridona, quinolin-4(1*H*)-ona, piridin-2(1*H*)-ona, imidazo[1,2-a]piridinilo, 1-isoquinolona, 2-pirrolidona, 4-tiazolidona, quinoxalinilo, 5,6-dihidro[1,3]tiazolo[4,5-*d*]piridazinilo, *N*-óxido de piridina y *N*-óxido de quinolina. Los ejemplos adecuados de un "heterociclilo enlazado mediante nitrógeno" son morfolino, piperazin-1-ilo, piperidin-1-ilo e imidazol-1-ilo. En un aspecto adicional de la invención, un "heterociclilo" es un heteroarilo. El término "heteroarilo" se refiere a un heterociclilo insaturado y aromático. Los ejemplos y valores adecuados para grupos heteroarilo incluyen piridinilo, pirrolilo, pirazolilo, isotiazolilo, indolilo, quinolinilo, tienilo, benzotiazolilo, tiadiazolilo, oxadiazolilo, imidazolilo, pirimidinilo, pirazinilo, piridazinilo, isoxazolilo, tiazolilo, 1*H*-tetrazolilo, 1*H*-triazolilo, *N*-metilpirrolilo, quinolin-4(1*H*)-ona, piridin-2(1*H*)-ona, imidazo[1,2-a]piridinilo, 1-isoquinolona, quinoxalinilo, *N*-óxido de piridina y *N*-óxido de quinolina. En una realización particular, el heteroarilo es un heteroarilo de 5 ó 6 miembros, por ejemplo piridinilo, pirrolilo, pirazolilo, isotiazolilo, tienilo, tiadiazolilo, oxadiazolilo, imidazolilo, pirimidinilo, pirazinilo, piridazinilo, isoxazolilo, tiazolilo, 1*H*-tetrazolilo, 1*H*-triazolilo, *N*-metilpirrolilo, y *N*-óxido de piridina.

Un "carbociclilo" es un anillo de carbonos mono-, bi- o tricíclico, saturado, parcialmente saturado o insaturado, que contiene 3-14 átomos; en el que un grupo $-CH_2-$ se puede sustituir opcionalmente por un -C(O)-. En una realización, "carbociclilo" es un anillo monocíclico que contiene 5 ó 6 átomos, o un anillo bicíclico que contiene 9 ó 10 átomos. Ejemplos de carbociclilos incluyen ciclopropilo, ciclobutilo, 1-oxociclopentilo, ciclopentilo, ciclopentenilo, ciclohexilo, ciclohexenilo, fenilo, naftilo, tetralinilo, indanilo o 1-oxoindanilo. El término carbociclilo engloba tanto grupos cicloalquilo como arilo. El término cicloalquilo se refiere a un carbociclilo que está completamente saturado, por ejemplo ciclopropilo, ciclobutilo, ciclopentilo, y ciclohexilo. El término "arilo" se refiere a un carbociclilo que está completamente insaturado y es aromático. Un arilo C_{6-14} es un anillo de carbonos mono-, bi- o tricíclico, aromático, que contiene 6-14 átomos, por ejemplo fenilo o naftenilo.

Un ejemplo de "alcanoil C_{1-6}-oxi" es acetoxi. Ejemplos de "alcoxi C_{1-6}-carbonilo" son metoxicarbonilo, etoxicarbonilo, *n*- y *t*-butoxicarbonilo. Ejemplos de "alcoxi C_{1-6}-carbonilamino" son metoxicarbonilamino, etoxicarbonilamino, *n*- y *t*-butoxicarbonilamino. Ejemplos de "alcoxi C_{1-6}" son metoxi, etoxi y propoxi. Ejemplos de "alcanoil C_{1-6}-amino" son formamido, acetamido y propionilamino. Ejemplos de "alquil C_{1-6}-$S(O)_a$ en el que a es 0, 1, ó 2" son metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo y etilsulfonilo. Ejemplos de "alcanoilo C_{1-6}" son propionilo y acetilo. Ejemplos de "*N*-(alquil C_{1-6})amino" son metilamino y etilamino. Ejemplos de "*N,N*-(alquil C_{1-6})$_2$amino" son di-*N*-metilamino, di-(*N*-etil)amino y *N*-etil-*N*-metilamino. Ejemplos de "alquenilo C_{2-4}" son vinilo, alilo y 1-propenilo. Ejemplos de "alquinilo C_{2-4}" son etinilo, 1-propinilo y 2-propinilo. Ejemplos de "*N*-(alquil C_{1-6})sulfamoilo" son *N*-(metil)sulfamoilo y *N*-(etil)sulfamoilo. Ejemplos de "*N,N*-(alquil C_{1-6})$_2$sulfamoilo" son *N,N*-(dimetil)sulfamoilo y *N*-(metil)-*N*-(etil)sulfamoilo. Ejemplos de "*N*-(alquil C_{1-6})carbamoilo" son metilaminocarbonilo y etilaminocarbonilo. Ejemplos de "*N,N*-(alquil C_{1-6})$_2$carbamoilo" son dimetilaminocarbonilo y metiletilaminocarbonilo. Ejemplos de "*N*-(alcoxi C_{1-6})carbamoilo" son metoxiaminocarbonilo e isopropoxiaminocarbonilo. Ejemplos de "*N*-(alquil C_{1-6})-*N*-(alcoxi C_{1-6})carbamoilo" son *N*-metil-*N*-metoxiaminocarbonilo y *N*-metil-*N*-etoxiaminocarbonilo. Ejemplos de "cicloalquilo C_{3-6}" son ciclopropilo, ciclobutilo, ciclopropilo y ciclohexilo. Ejemplos de "alquil C_{1-6}-sulfonilamino" son metilsulfonilamino, isopropilsulfonilamino y *t*-butilsulfonilamino. Ejemplos de "alquil C_{1-6}-sulfonilaminocarbonilo" son metilsulfonilaminocarbonilo, isopropilsulfonilaminocarbonilo y *t*-butilsulfonilaminocarbonilo. Ejemplos de "alquil C_{1-6}-sulfonilo" son metilsulfonilo, isopropilsulfonilo y *t*-butilsulfonilo.

El término "fórmula **(I)**", excepto que se especifique de otro modo, se refiere a todas las realizaciones de la fórmula **(I)**, incluyendo, pero sin limitarse a, la fórmula **(Ia)**, la fórmula **(Ib)**, y la fórmula **(Ic)**.

El término "fórmula **(I')**", excepto que se especifique de otro modo, se refiere a todas las realizaciones de fórmula **(I')**, incluyendo, pero sin limitarse a, la fórmula **(Ia')**, la fórmula **(Ib')**, y la fórmula **(Ic')**.

Un compuesto de fórmula **(I)** o **(I')** puede formar sales ácidas o básicas estables, y en tales casos la administración de un compuesto como una sal puede ser apropiada, y las sales farmacéuticamente aceptables se pueden obtener mediante métodos convencionales, tales como los descritos más abajo.

Las sales farmacéuticamente aceptables adecuadas incluyen sales de adición de ácidos tales como metanosulfonato, tosilato, α-glicerofosfato, fumarato, hidrocloruro, citrato, maleato, tartrato y (menos preferiblemente) hidrobromuro. También son adecuadas las sales formadas con ácido fosfórico y sulfúrico. En otro aspecto, las sales adecuadas son sales de bases, tales como una sal de metal alcalino, por ejemplo sodio, una sal de metal alcalino-térreo, por ejemplo calcio o magnesio, una sal de amina orgánica, por ejemplo trietilamina, morfolina, *N*-metilpiperidina, *N*-etilpiperidina, procaína, dibencilamina, *N,N*-dibenciletilamina, tris-(2-hidroxietil)amina, *N*-metil-d-glucamina y aminoácidos tales como lisina. Puede haber más de un catión o anión, dependiendo del número de funciones cargadas y la valencia de los cationes o aniones. Una sal farmacéuticamente aceptable preferida es la sal sódica.

Sin embargo, para facilitar el aislamiento de la sal durante la preparación, se pueden preferir sales que son menos solubles en el disolvente elegido, ya sean farmacéuticamente aceptables o no.

En la presente invención se entenderá que un compuesto de la fórmula **(I)** o **(I')**, o una sal del mismo, puede mostrar el fenómeno de tautomería, y que los dibujos de las fórmulas en esta memoria descriptiva pueden representar sólo una de las posibles formas tautómeras. Se entenderá que la invención engloba cualquier forma tautómera que inhiba ADN girasa y/o topoisomerasa IV, y no estará limitada solamente a una cualquiera de las formas tautómeras utilizadas en los dibujos de las fórmulas. Los dibujos de las fórmulas en esta memoria descriptiva pueden representar sólo una de las posibles formas tautómeras, y se entenderá que la memoria descriptiva engloba todas las formas tautómeras posibles de los compuestos dibujados, no sólo aquellas formas que se han podido mostrar gráficamente aquí. Lo mismo se aplica a los nombres de los compuestos.

Los expertos en la técnica apreciarán que algunos compuestos de fórmula **(I)** o **(I')** contienen un átomo de carbono y/o de azufre asimétricamente sustituido, y en consecuencia pueden existir en, y ser aislados en, formas ópticamente activas y racémicas. Algunos compuestos pueden mostrar polimorfismo. Se entenderá que la presente invención engloba cualquier forma racémica, ópticamente activa, polimórfica o estereoisómera, o sus mezclas, forma la cual posee propiedades útiles inhibiendo ADN girasa y/o topoisomerasa IV, siendo bien conocido en la técnica cómo preparar formas ópticamente activas (por ejemplo, mediante resolución de la forma racémica mediante técnicas de recristalización, mediante síntesis a partir de materiales de partida ópticamente activos, mediante síntesis quiral, mediante

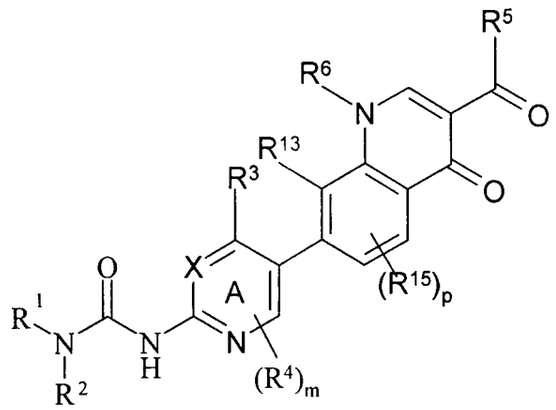
resolución enzimática, mediante biotransformación, o mediante separación cromatográfica usando una fase estacionaria quiral) y cómo determinar la eficacia para la inhibición de ADN girasa y/o topoisomerasa IV mediante los ensayos estándar descritos aquí más abajo.

A título de claridad, los compuestos de la invención incluyen todos los isótopos de los átomos presentes en la fórmula **(I)** o **(I')** y cualquiera de los ejemplos o realizaciones descritos aquí. Por ejemplo, H (o hidrógeno) representa cualquier forma isotópica de hidrógeno, incluyendo ^{1}H, ^{2}H (D), y ^{3}H (T); C representa cualquier forma isotópica de carbono, incluyendo ^{12}C, ^{13}C, y ^{14}C; O representa cualquier forma isotópica de oxígeno, incluyendo ^{16}O, ^{17}O y ^{18}O; N representa cualquier forma isotópica de nitrógeno, incluyendo ^{13}N, ^{14}N y ^{15}N; P representa cualquier forma isotópica de fósforo, incluyendo ^{31}P y ^{32}P; S representa cualquier forma isotópica de azufre, incluyendo ^{32}S y ^{35}S; F representa cualquier forma isotópica de flúor, incluyendo ^{19}F y ^{18}F; Cl representa cualquier forma isotópica de cloro, incluyendo ^{35}Cl, ^{37}Cl y ^{36}Cl; y similares. En una realización preferida, los compuestos representados mediante la fórmula **(I)** o **(I')** comprenden isómeros de los átomos en ellas en su abundancia natural. Sin embargo, en algunos casos, es deseable enriquecer uno o más átomos en un isótopo particular, que normalmente estaría presente en menor abundancia. Por ejemplo, ^{1}H normalmente estaría presente en una abundancia mayor de 99,98%; sin embargo, un compuesto de la invención se puede enriquecer en ^{2}H o ^{3}H en una o más posiciones en las que H esté presente. En realizaciones particulares de los compuestos de fórmula **(I)** o **(I')**, cuando, por ejemplo, el hidrógeno se enriquece en el isótopo de deuterio, el símbolo "D" se usa para representar el enriquecimiento en deuterio. En una realización, cuando un compuesto de la invención se enriquece en un isótopo radioactivo, por ejemplo ^{3}H y ^{14}C, puede ser útil en ensayos de distribución en tejidos de fármacos y/o sustratos. Se entenderá que la invención engloba todas las citadas formas isotópicas que inhiban ADN girasa y/o topoisomerasa IV.

También se entenderá que algunos compuestos de la fórmula **(I)** o **(I')**, y sus sales, pueden existir en formas solvatadas así como formas no solvatadas, tales como, por ejemplo, formas hidratadas. Se entenderá que la invención engloba tales formas solvatadas que inhiben ADN girasa y/o topoisomerasa IV.

A continuación se dan valores particulares y adecuados para ciertos sustituyentes y grupos citados en esta memoria descriptiva. Estos valores se pueden usar cuando sea apropiado con cualquiera de las definiciones y realizaciones descritas aquí anteriormente, o aquí en lo sucesivo. Para evitar dudas, cada especie señalada representa un aspecto particular e independiente de esta invención.

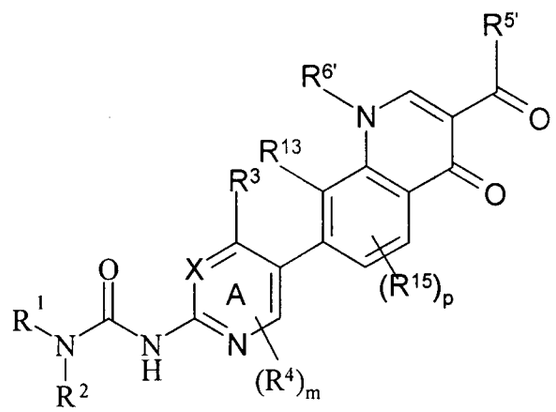
En una realización, los compuestos de la invención se representan mediante la fórmula **(Ia)**:



(Ia)

o sales farmacéuticamente aceptables del mismo, en la que X, R^1, R^2, R^3, R^4, R^5, R^6, R^{13}, R^{15}, m y p son como se definen para la fórmula **(I)**.

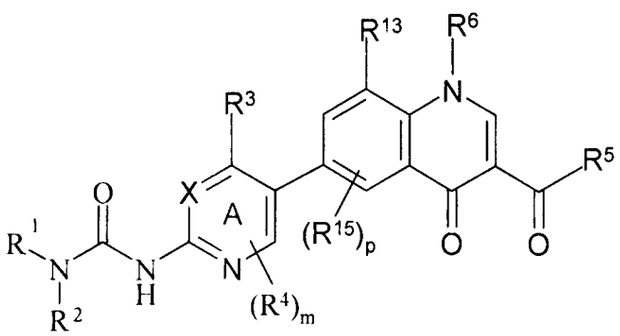
En otra realización, los compuestos de la invención se representan mediante la fórmula **(Ia')**:



(Ia')

o sales farmacéuticamente aceptables del mismo, en la que X, R^1, R^2, R^3, R^4, $R^{5'}$, $R^{6'}$, R^{13}, R^{15}, m y p son como se definen para la fórmula **(I')**.

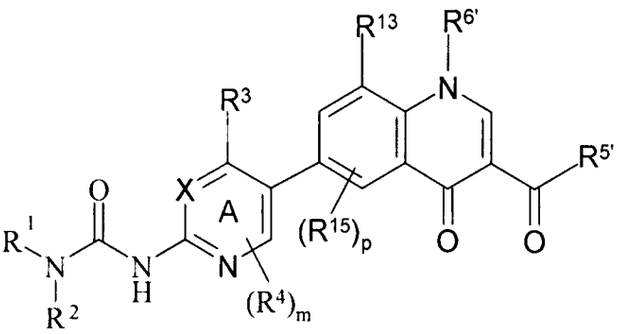
En otra realización, el compuesto está representado por la fórmula **(Ib)**:



(Ib)

o sales farmacéuticamente aceptables del mismo, en la que X, R^1, R^2, R^3, R^4, R^5, R^6, R^{13}, R^{15}, m y p son como se definen para la fórmula **(I)**.

En otra realización, el compuesto está representado por la fórmula **(Ib')**:



(Ib')

o sales farmacéuticamente aceptables del mismo, en la que X, R^1, R^2, R^3, R^4, $R^{5'}$, $R^{6'}$, R^{13}, R^{15}, m y p son como se definen para la fórmula **(I')**.

En otra realización, la invención proporciona unos compuestos representados por la fórmula **(I)** o **(I')** en las que X es CH.

En otra realización, la invención proporciona unos compuestos representados por la fórmula **(I)** o **(I')** en las que X es N.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I)** o **(I')** en la que X es CR^4, y R^4 es fluoro, cloro, bromo, yodo, un alquilo C_{1-4}, o un alcoxi C_{1-4}.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I)** o **(I')** en la que R^1 es un alquilo C_{1-6}. Por ejemplo, R^1 es metilo, etilo, propilo, isopropilo, butilo, isobutilo, *sec*-butilo, y *terc*-butilo. En una realización particular, R^1 es etilo.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I)** o **(I')** en la que R^2 es hidrógeno.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I)** o **(I')** en la que R^2 es un alquilo C_{1-6}. Por ejemplo, R^2 es metilo, etilo, propilo, isopropilo, butilo, isobutilo, *sec*-butilo, y *terc*-butilo.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I)** o **(I')** en la que R^3 es un heteroarilo de 5 miembros; y en la que el heteroarilo puede estar opcionalmente sustituido en uno o más átomos de carbono con uno o más R^{10}; y en la que, si dicho heteroarilo contiene un resto =N- o –S-, ese nitrógeno puede estar opcionalmente sustituido con un grupo oxo, y ese azufre puede estar opcionalmente sustituido con uno o dos grupos oxo; y en la que, si dicho heteroarilo contiene un resto -NH-, ese nitrógeno puede estar opcionalmente sustituido con un grupo seleccionado de R^{11}. En un aspecto de esta realización, R^{10} se selecciona del grupo que consiste en metilo, etilo, fenilo, trifluorometilo, y piridinilo. En otro aspecto de esta realización, R^{11} es metilo.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I)** o **(I')** en la que R^3 es un tiazolilo; y en la que el tiazolilo puede estar opcionalmente sustituido en el carbono con uno o más R^{10}; y en la que el =N- del tiazolilo puede estar opcionalmente sustituido con un grupo oxo; y en la que el –S- del tiazolilo puede estar opcionalmente sustituido con uno o dos grupos oxo. En un aspecto de esta realización, R^{10} se selecciona del grupo que consiste en metilo, etilo, fenilo, trifluorometilo, y piridinilo. En otro aspecto de esta realización, R^{11} es metilo.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I)** o **(I')** en la que R^3 es un 1,3,4-oxadiazolilo; y en la que el 1,3,4-oxadiazolilo puede estar opcionalmente sustituido en uno o más carbonos con uno o más R^{10}; y en la que cada =N- del 1,3,4-oxadiazolilo puede estar independientemente sustituido de forma opcional con un grupo oxo. En un aspecto de esta realización, R^{10} se selecciona del grupo que consiste en metilo, fenilo, trifluorometilo, y piridinilo. En otro aspecto de esta realización, R^{11} es metilo.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I)** o **(I')** en la que R^3 es a 1*H*-pirazolilo; y en la que el 1*H*-pirazolilo puede estar opcionalmente sustituido en uno o más carbonos con uno o más R^{10}; y en la que el =N- del 1*H*-pirazolilo puede estar opcionalmente sustituido con un grupo oxo; y en la que el resto -NH- del 1*H*-pirazolilo puede estar opcionalmente sustituido con un grupo seleccionado de R^{11}. En un aspecto de esta realización, R^{10} se selecciona del grupo que consiste en metilo, fenilo, trifluorometilo, y piridinilo. En otro aspecto de esta realización, R^{11} es metilo.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I)** o **(I')** en la que R^3 es 1,3-benzotiazolilo; y en la que el 1,3-benzotiazolilo puede estar opcionalmente sustituido en uno o más carbonos con uno o más R^{10}; y en la que el =N- del 1,3-benzotiazolilo puede estar opcionalmente sustituido con un grupo oxo; y en la que el –S- del 1,3-benzotiazolilo puede estar opcionalmente sustituido con uno o dos grupos oxo. En un aspecto de esta realización, R^{10} se selecciona del grupo que consiste en metilo, fenilo, trifluorometilo, y piridinilo. En otro aspecto de esta realización, R^{11} es metilo.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I)** o **(I')** en la que R^3 es un arilo C_{6-14} que puede estar opcionalmente sustituido en uno o más átomos de carbono con uno o más R^{10}.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I)** o **(I')** en la que R^3 es 4-trifluorometil-tiazol-2-ilo, 4-etil-tiazol-2-ilo, o 4-fenil-tiazol-2-ilo.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I)** en la que R^5 es –OH.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I')** en la que $R^{5'}$ es –OH.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I)** en la que R^5 es alcoxi C_{1-6}, en la que el grupo alcoxi C_{1-6} puede estar opcionalmente sustituido en uno o más átomos de carbono con uno o más R^{14}, seleccionados independientemente. En un aspecto de esta realización, R^{14}, para cada caso, se selecciona independientemente de hidroxi, N,N-(alquil C_{1-6})$_2$-amino, morfolinilo, alcoxi C_{1-6}, piperazinilo, y N-alquil-piperizinilo. En otro aspecto de esta realización, R^{14}, para cada caso, se selecciona independientemente de hidroxi, N,N-dimetilamino, morfolino, metoxi, piperazino, y N-metil-piperizino.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I)** en la que R^5 es alcoxi C_{1-6}.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I)** en la que R^5 es etoxi.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I')** en la que $R^{5'}$ es alcoxi C_{1-6}, en la que el grupo alcoxi C_{1-6} puede estar opcionalmente sustituido en uno o más átomos de carbono con uno o más R^{14}, seleccionados independientemente. En un aspecto de esta realización, R^{14}, para cada caso, se selecciona independientemente de hidroxi, N,N-(alquil C_{1-6})$_2$-amino, morfolinilo, alcoxi C_{1-6},

piperazinilo, y N-alquil-piperizinilo. En otro aspecto de esta realización, R^{14}, para cada caso, se selecciona independientemente de hidroxi, N,N-dimetilamino, morfolino, metoxi, piperazino, y N-metil-piperizino.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I')** en la que $R^{5'}$ es alcoxi C_{1-6}.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I')** en la que $R^{5'}$ es etoxi.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I)** en la que R^5 es amino, N-(alquil C_{1-6})amino o N,N-(alquil C_{1-6})$_2$amino, en la que cada grupo alquilo C_{1-6} puede estar independientemente sustituido de forma opcional en uno o más átomos de carbono con uno o más R^{14}, seleccionado independientemente. En un aspecto de esta realización, R^{14}, para cada caso, se selecciona independientemente de hidroxi, N,N-(alquil C_{1-6})$_2$-amino, morfolinilo, alcoxi C_{1-6}, piperazinilo, y N-alquil-piperizinilo. En otro aspecto de esta realización, R^{14}, para cada caso, se selecciona independientemente de hidroxi, N,N-dimetilamino, morfolino, metoxi, piperazino, y N-metil-piperizino.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I)** en la que R^5 es amino, N-(alquil C_{1-6})amino o N,N-(alquil C_{1-6})$_2$amino.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I')** en la que $R^{5'}$ es amino, N-(alquil C_{1-6})amino o N,N-(alquil C_{1-6})$_2$amino, en la que cada grupo alquilo C_{1-6} puede estar independientemente sustituido de forma opcional en uno o más átomos de carbono con uno o más R^{14}, seleccionados independientemente. En un aspecto de esta realización, R^{14}, para cada caso, se selecciona independientemente de hidroxi, N,N-(alquil C_{1-6})$_2$-amino, morfolinilo, alcoxi C_{1-6}, piperazinilo, y N-alquil-piperizinilo. En otro aspecto de esta realización, R^{14}, para cada caso, se selecciona independientemente de hidroxi, N,N-dimetilamino, morfolino, metoxi, piperazino, y N-metil-piperizino.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I')** en la que $R^{5'}$ es amino, N-(alquil C_{1-6})amino o N,N-(alquil C_{1-6})$_2$amino.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I)** en la que R^5 se selecciona del grupo que consiste en –OH, etoxi, N-metilamino, y N-etilamino.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I')** en la que $R^{5'}$ se selecciona del grupo que consiste en –OH, etoxi, N-metilamino, y N-etilamino.

En otra realización, la invención proporciona compuestos representados por la fórmula (I') en la que $R^{5'}$ es $-NR^aR^b$ y uno de R^a o R^b es un alquilo C_{1-6} y el otro es hidrógeno, en la que el alquilo C_{1-6} puede estar opcionalmente sustituido en uno o más átomos de carbono con uno o más R^{14}, seleccionados independientemente. En un aspecto de esta realización, R^{14}, para cada caso, se selecciona independientemente de hidroxi, N,N-(alquil $C_{1-6})_2$-amino, morfolinilo, alcoxi C_{1-6}, piperazinilo, y N-alquil-piperizinilo. En otro aspecto de esta realización, R^{14}, para cada caso, se selecciona independientemente de hidroxi, N,N-dimetilamino, morfolino, metoxi, piperazino, y N-metil-piperizino.

En otra realización, la invención proporciona compuestos representados por la fórmula (I') en la que $R^{5'}$ es $-NR^aR^b$ y uno de R^a o R^b es un cicloalquilo C_{3-6} y el otro es hidrógeno, en la que el cicloalquilo puede estar opcionalmente sustituido en uno o más átomos de carbono con uno o más R^{14}, seleccionados independientemente.

En otra realización, R5' es $-NR^aR^b$; en el que R^a y R^b, junto con el nitrógeno al que están unidos, forman un heterociclo, en el que R^a y R^b pueden estar opcionalmente sustituidos en uno o más átomos de carbono con uno o más R^{14}, seleccionados independientemente; y en el que, si dicho heterociclilo contiene un resto =N- o –S-, ese nitrógeno puede estar opcionalmente sustituido con un grupo oxo, y ese azufre puede estar opcionalmente sustituido con uno o dos grupos oxo; y en el que, si dicho heterociclilo contiene un resto -NH-, ese nitrógeno puede estar opcionalmente sustituido con un grupo seleccionado de R^{22}. En un aspecto de esta realización, R^{14}, para cada caso, se selecciona independientemente de hidroxi, N,N-(alquil $C_{1-6})_2$-amino, morfolinilo, alcoxi C_{1-6}, piperazinilo, y N-alquil-piperizinilo. En otro aspecto de esta realización, R^{14}, para cada caso, se selecciona independientemente de hidroxi, N,N-dimetilamino, morfolino, metoxi, piperazino, y N-metil-piperizino. En otro aspecto de esta realización, R^{22}, para cada caso, se selecciona independientemente de un alquilo C_{1-6}, alquil C_{1-6}-sulfonilo, N-(alquil C_{1-6})sulfamoilo, N,N-(alquil $C_{1-6})_2$sulfamoilo, y alcanoilo C_{1-6}. En otro aspecto de esta realización, R^{22}, para cada caso, se selecciona independientemente de metilo, metilsulfonilo, N,N-dimetilsulfamoilo, y acetilo.

En otra realización, la invención proporciona compuestos representados por la fórmula (I') en la que $R^{5'}$ se selecciona del grupo que consiste en metilamino, N-ciclopropilamino, N-(2-hidroxietil)-amino, N-(3-hidroxipropil)-amino, N-[2-(N,N-dimetilamino)-etil]-amino, N-(2-morfolinoetil)-amino, N-[1-(metoximetil)-2-metoxi-etil]-amino, N-[1-(hidroximetil)-2-hidroxi-etil]-amino, N-[2-(4-metil-piperazino)-etil]-amino, N-(2-piperazino-etil)-amino, 4-acetil-

piperazino, 4-metilsulfonil-piperazino, 4-(2-hidroxietil)-piperazino, y 4-(N,N-dimetilsulfamoil)-piperazino.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I)** en la que R^5 se selecciona del grupo que consiste en –OH, etoxi, metilamino, N-(2-hidroxietil)-amino, N-(3-hidroxipropil)-amino, N-[2-(N,N-dimetilamino)-etil]-amino, N-(2-morfolinoetil)-amino, N-[1-(metoximetil)-2-metoxi-etil]-amino, N-[1-(hidroximetil)-2-hidroxi-etil]-amino, N-[2-(4-metil-piperazino)-etil]-amino, y N-(2-piperazino-etil)-amino.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I')** en la que $R^{5'}$ se selecciona del grupo que consiste en metilamino, N-(2-hidroxietil)-amino, N-(3-hidroxipropil)-amino, N-[2-(N,N-dimetilamino)-etil]-amino, N-(2-morfolinoetil)-amino, N-[1-(metoximetil)-2-metoxi-etil]-amino, N-[1-(hidroximetil)-2-hidroxi-etil]-amino, N-[2-(4-metil-piperazino)-etil]-amino, y N-(2-piperazino-etil)-amino.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I')** en la que $R^{5'}$ se selecciona del grupo que consiste en 4-acetil-piperazino, 4-metilsulfonil-piperazino, 4-(2-hidroxietil)-piperazino, y 4-(N,N-dimetilsulfamoil)-piperazino.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I)** en la que R^6 es un alquilo C_{1-6} que está sustituido en uno o más átomos de carbono con uno o más R^{16}, seleccionados independientemente. En un aspecto de esta realización, R^{16}, para cada caso, se selecciona independientemente del grupo que consiste en –OH, fluoro, N-metilamino, N,N-dimetilamino, metoxi, etoxi, metilsulfanilo, metilsulfonilo, piperidinilo, piperazinilo, morfolinilo, pirrolidinilo, 2-oxopirrolidinilo, pirrolilo, imidazolilo, triazolilo, y fenilo que puede estar opcionalmente sustituido con uno o más halo, isoxazolilo, piridinilo, y ciclopropilo. En otro aspecto de esta realización, R^{16}, para cada caso, se selecciona independientemente de N,N-(alquil C_{1-6})$_2$amino, hidroxi, alcoxi C_{1-6}, y carboxi. En otro aspecto de esta realización, R^{16}, para cada caso, se selecciona independientemente de N,N-dimetilamino, hidroxi, metoxi, y carboxi.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I')** en la que $R^{6'}$ es un alquilo C_{1-6} que está sustituido en uno o más átomos carbono con uno o más R^{16}, seleccionados independientemente. En un aspecto de esta realización, R^{16}, para cada caso, se selecciona independientemente del grupo que consiste en –OH, carboxi, fluoro, N-metilamino, N,N-dimetilamino, metoxi, etoxi, metilsulfanilo, metilsulfonilo, ciclohexilo, piperidinilo, piperazinilo, morfolinilo, pirrolidinilo, 2-oxopirrolidinilo, pirrolilo, imidazolilo, triazolilo, y fenilo. En otro aspecto de esta realización, R^{16}, para cada caso, se selecciona

independientemente de N,N-(alquil C_{1-6})$_2$amino, hidroxi, alcoxi C_{1-6}, y carboxi. En otro aspecto de esta realización, R^{16}, para cada caso, se selecciona independientemente de N,N-dimetilamino, hidroxi, metoxi, y carboxi.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I')** en la que $R^{6'}$ es un carbociclo C_{3-6}-alquileno C_{1-6} que está opcionalmente sustituido en uno o más átomos de carbono con uno o más R^{16}.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I')** en la que $R^{6'}$ es un carbociclo C_{3-6}-alquileno C_{1-6}, no sustituido.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I')** en la que $R^{6'}$ es un ciclopropilmetilo o bencilo.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I')** en la que $R^{6'}$ es un heterociclilo-alquileno C_{1-6} que está opcionalmente sustituido en uno o más átomos de carbono con uno o más R^{16}; en la que, si dicho heterociclilo contiene un resto =N- o –S-, ese nitrógeno puede estar opcionalmente sustituido con un grupo oxo, y ese azufre puede estar opcionalmente sustituido con uno o dos grupos oxo; y en la que, si dicho heterociclilo contiene un resto -NH-, ese nitrógeno puede estar opcionalmente sustituido con un grupo seleccionado de $R^{17'}$. En un aspecto de esta realización, R^{16}, para cada caso, se selecciona independientemente de oxo, cicloalquilo C_{3-6}, N,N-(alquil C_{1-6})$_2$amino, hidroxi, alcoxi C_{1-6}, y carboxi. En otro aspecto de esta realización, R^{16}, para cada caso, se selecciona independientemente de oxo, ciclopropilo, N,N-dimetilamino, hidroxi, metoxi, y carboxi. En otro aspecto de esta realización, R^{16}, para cada caso, se selecciona independientemente de oxo y ciclopropilo. En otro aspecto de esta realización, $R^{17'}$, para cada caso, se selecciona independientemente de alquil C_{1-6}-sulfonil-alquilo (C_{1-6}), hidroxi-alquilo C_{1-6}, heterociclilo-alquileno (C_{1-6}), alquilo C_{1-6}, amino-alquilo C_{1-6}, N-(alquil C_{1-6})amino, y N,N-(alquil C_{1-6})$_2$amino. En otro aspecto de esta realización, $R^{17'}$, para cada caso, se selecciona independientemente de 2-(metilsulfonil)-etilo, 1-metil-pirrol-2-ilmetilo, 2,2-dimetil-propilo, 2-morfolino-etilo, 2-(N,N-dietilamino)-etilo, 3-morfolino-2,2-dimetil-propilo, 2-hidroxietilo, metilo, etilo, piridin-4-ilmetilo, y tetrahidrofuran-2-ilmetilo. En otro aspecto de esta realización, $R^{17'}$, para cada caso, se selecciona independientemente de un alquilo C_{1-6} o heterociclilo-alquileno C_{1-6}. En otro aspecto de esta realización, $R^{17'}$, para cada caso, se selecciona independientemente de metilo, etilo, tetrahidrofuran-metilo, 2-hidroxietilo, y 2-morfolino-etilo.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I)** en la que R^6 es un carbociclilo que está opcionalmente sustituido en uno o más átomos de carbono con uno o más R^{16}. En un aspecto de esta realización, R^{16}, para cada caso, se selecciona independientemente de oxo, cicloalquilo C_{3-6}, amino, N-(alquil C_{1-6})amino, N,N-(alquil C_{1-6})$_2$amino, hidroxi, alcoxi C_{1-6}, y carboxi. En otro aspecto de esta realización, R^{16}, para cada caso, se selecciona independientemente de oxo, ciclopropilo, amino, N,N-dimetilamino, hidroxi, metoxi, y carboxi. En otro aspecto de esta realización, R^{16}, para cada caso, se selecciona independientemente de hidroxi o amino.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I')** en la que $R^{6'}$ es un carbociclilo que está opcionalmente sustituido en uno o más átomos de carbono con uno o más R^{16}. En un aspecto de esta realización, R^{16}, para cada caso, se selecciona independientemente de oxo, cicloalquilo C_{3-6}, amino, N-(alquil C_{1-6})amino, N,N-(alquil C_{1-6})$_2$amino, hidroxi, alcoxi C_{1-6}, y carboxi. En otro aspecto de esta realización, R^{16}, para cada caso, se selecciona independientemente de oxo, ciclopropilo, amino, N,N-dimetilamino, hidroxi, metoxi, y carboxi. En otro aspecto de esta realización, R^{16}, para cada caso, se selecciona independientemente de hidroxi o amino.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I)** en la que R^6 es un heterociclilo que está opcionalmente sustituido en uno o más átomos de carbono con uno o más R^{16}; y en la que, si dicho heterociclilo contiene un resto =N- o –S-, ese nitrógeno puede estar opcionalmente sustituido con un grupo oxo, y ese azufre puede estar opcionalmente sustituido con uno o dos grupos oxo; y en la que, si dicho heterociclilo contiene un resto -NH-, ese nitrógeno puede estar opcionalmente sustituido con un grupo seleccionado de R^{17}. En un aspecto de esta realización, R^{16}, para cada caso, se selecciona independientemente de oxo, cicloalquilo C_{3-6}, amino, N-(alquil C_{1-6})amino, N,N-(alquil C_{1-6})$_2$amino, hidroxi, alcoxi C_{1-6}, y carboxi. En otro aspecto de esta realización, R^{16}, para cada caso, se selecciona independientemente de oxo, ciclopropilo, amino, N,N-dimetilamino, hidroxi, metoxi, y carboxi. En otro aspecto de esta realización, R^{16}, para cada caso, se selecciona independientemente de hidroxi o amino. En otro aspecto de esta realización, R^{17}, para cada caso, se selecciona independientemente de 2-(metilsulfonil)-etilo, 2,2-dimetil-propilo, 2-(N,N-dietilamino)-etilo, 2-hidroxietilo, metilo, y etilo. En otro aspecto de esta realización, R^{17}, para cada caso, se selecciona independientemente de un alquilo C_{1-6}. En otro aspecto de esta realización, R^{17}, para cada caso, se selecciona independientemente de metilo, etilo, y 2-hidroxietilo.

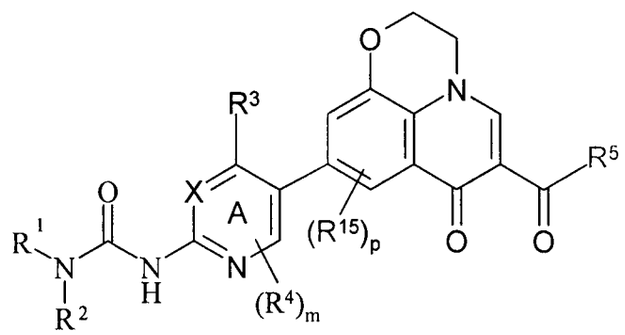
En otra realización, la invención proporciona compuestos representados por la fórmula **(I')** en la que $R^{6'}$ es un heterociclilo que está opcionalmente sustituido en uno o más átomos de carbono con uno o más R^{16}; y en la que, si dicho heterociclilo contiene un resto =N- o –S-, ese nitrógeno puede estar opcionalmente sustituido con un grupo oxo, y ese azufre puede estar opcionalmente sustituido con uno o dos grupos oxo; y en la que, si dicho heterociclilo contiene un resto -NH-, ese nitrógeno puede estar opcionalmente sustituido con un grupo seleccionado de $R^{17'}$. En un aspecto de esta realización, R^{16}, para cada caso, se selecciona independientemente de oxo, cicloalquilo C_{3-6}, amino, N-(alquil C_{1-6})amino, N,N-(alquil C_{1-6})$_2$amino, hidroxi, alcoxi C_{1-6}, y carboxi. En otro aspecto de esta realización, R^{16}, para cada caso, se selecciona independientemente de oxo, ciclopropilo, amino, N,N-dimetilamino, hidroxi, metoxi, y carboxi. En otro aspecto de esta realización, R^{16}, para cada caso, se selecciona independientemente de hidroxi o amino. En otro aspecto de esta realización, $R^{17'}$, para cada caso, se selecciona independientemente de alquil C_{1-6}-sulfonil-alquilo (C_{1-6}), hidroxi-alquilo C_{1-6}, heterociclilo-alquileno (C_{1-6}), alquilo C_{1-6}, amino-alquilo C_{1-6}, N-(alquil C_{1-6})amino, y N,N-(alquil C_{1-6})$_2$amino. En otro aspecto de esta realización, $R^{17'}$, para cada caso, se selecciona independientemente de 2-(metilsulfonil)-etilo, 1-metil-pirrol-2-ilmetilo, 2,2-dimetil-propilo, 2-morfolino-etilo, 2-(N,N-dietilamino)-etilo, 3-morfolino-2,2-dimetil-propilo, 2-hidroxietilo, metilo, etilo, piridin-4-ilmetilo, y tetrahidrofuran-2-ilmetilo. En otro aspecto de esta realización, $R^{17'}$, para cada caso, se selecciona independientemente de un alquilo C_{1-6} o heterociclilo-alqueno C_{1-6}. En otro aspecto de esta realización, $R^{17'}$, para cada caso, se selecciona independientemente de metilo, etilo, tetrahidrofuran-metilo, 2-hidroxietilo, y 2-morfolino-etilo.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I)** en la que R^6 es hidrógeno.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I)** en la que R^6 es alquilo C_{1-6} o un cicloalquilo C_{3-6}.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I)** en la que R^6 es heterociclilo no aromático que tiene 3 a 6 átomos anulares; en la que dicho heterociclilo está opcionalmente sustituido en uno o más átomos de carbono con uno o más R^{16}; y en la que, si dicho heterociclilo contiene un resto =N- o –S-, ese nitrógeno puede estar opcionalmente sustituido con un grupo oxo, y ese azufre puede estar opcionalmente sustituido con uno o dos grupos oxo; y en la que, si dicho heterociclilo contiene un resto -NH-, ese nitrógeno puede estar opcionalmente sustituido con un grupo seleccionado de R^{17}.

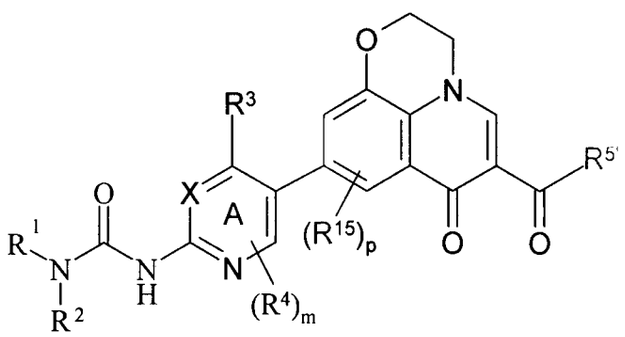
En otra realización, la invención proporciona compuestos representados por la fórmula **(I)** en la que R^{13} y R^6, junto con los átomos anulares que intervienen, forman un heterociclilo condensado de 5 ó 6 miembros. En un aspecto de esta realización, los compuestos de la invención están representados por la fórmula **(Ic)**:



(Ic)

o sales farmacéuticamente aceptables del mismo, en la que X, R^1, R^2, R^3, R^4, R^5, R^{15}, m y p son como se definen para la fórmula **(I)**.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I')** en la que R^{13} y $R^{6'}$, junto con los átomos anulares que intervienen, forman un heterociclilo condensado de 5 ó 6 miembros. En un aspecto de esta realización, los compuestos de la invención están representados por la fórmula **(Ic')**:



(Ic')

o sales farmacéuticamente aceptables del mismo, en la que X, R^1, R^2, R^3, R^4, $R^{5'}$, R^{15}, m y p son como se definen para la fórmula **(I')**.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I)** en la que R^6 se selecciona de hidrógeno, 2-(N,N-dimetilamino)-etilo, 1-metil-2-hidroxi-etilo, morfolin-3-ilmetilo, 2-(N,N-dimetilamino)-propilo, 2-hidroxiciclohexilo, 1-(2-mesil-etil)-piperidin-3-ilo, 1-(2,2-dimetil-propil)-piperidin-3-ilo, 1-[2-(N,N-dimetilamino)-etil]-piperidin-3-ilo, 2-hidroxietilo, etilo, 3-metoxipropilo, metilo, ciclopropilo, isopropilo, 3-metil-butilo, propilo, ciclopropilmetilo, 2-hidroxietilo, 1-metoximetil-2-metoxi-etilo, 1-metil-azetidin-3-ilo,

bencilo, 3-hidroxi-propilo, ciclohexilo, tetrahidro-2H-piran-4-ilo, 1-metil-piperidin-4-ilo, isobutilo, 2-metoxietilo, 1-metil-piperidin-4-ilmetilo, 1-etil-2-hidroxi-etilo, 1-hidroximetil-3-metil-butilo, 1-carboxi-2-metil-propilo, 1-metoximetil-2-metil-propilo, pirrolidin-1-iletilo, 1-hidroximetil-2-metil-butilo, piridin-3-ilmetilo, 2-metoxi-etilo, tetrahidro-2H-piran-4-ilmetilo, tetrahidrofuran-2-ilmetilo, 1-hidroximetil-2,2-dimetil-propilo, 5-ciclopropil-1,2,4-oxadiazol-3-ilo, 1-metil-imidazol-4-ilmetilo, piridin-4-ilmetilo, 1-hidroximeti-propilo, 4-metil-piperazin-1-iletilo, 1-metil-2-(N,N-dimetilamino)-etilo, 1-metil-piperidin-2-ilo, piperidin-2-ilo, 1-hidroximetil-2-metil-propilo, 1-hidroximetil-2-hidroxi-etilo, 1-hidroximetil-2-fenil-etilo, 1-hidroximetil-2-hidroxi-propilo, 1-etil-pirrolidin-3-ilo, 4-hidroxi-pirrolidin-3-ilo, 1-metil-pirrolidin-3-ilo, 1-hidroximetil-etilo, 1-(2-hidroxi-etil)-pirrolidin-3-ilmetilo, 2-amino-ciclohexilo, tetrahidro-2H-piran-4-iletilo, 1-ciclohexil-2-hidroxi-etilo, 1-hidroximetil-2-(4-hidroxifenil)-etilo, 1-(2-hidroxietil)-piperidin-3-ilo, pirrolidin-3-ilmetilo, piperidin-3-ilmetilo, piperidin-3-ilo, 1-etil-pirrolidin-3-ilo, 1-etil-piperidin-3-ilo, 1-metil-pirrolidin-3-ilo, y 1-etil-piperidin-3-ilmetilo.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I')** en la que $R^{6'}$ se selecciona de hidrógeno, 2-(N,N-dimetilamino)-etilo, 1-metil-2-hidroxi-etilo, morfolin-3-ilmetilo, 2-(N,N-dimetilamino)-propilo, 2-hidroxiciclohexilo, 1-(2-mesil-etil)-piperidin-3-ilo, 1-(1-metil-pirrol-2-ilmetil)-piperidin-3-ilo, 1-(2,2-dimetil-propil)-piperidin-3-ilo, 1-(2-morfolino-etil)-pirrolidin-3-ilmetilo, 1-(2-morfolinoetil)-piperidin-3-ilo, 1-[2-(N,N-dimetilamino)-etil]-piperidin-3-ilo, 1-(2,2-dimetil-3-morfolino-propil)-piperidin-3-ilo, 2-hidroxietilo, etilo, 3-metoxipropilo, metilo, ciclopropilo, 3-(2-oxo-pirrolidin-1-il)-propilo, isopropilo, 3-metil-butilo, propilo, ciclopropilmetilo, 2-hidroxietilo, 1-metoximetil-2-metoxi-etilo, 1-metil-azetidin-3-ilo, bencilo, 3-hidroxi-propilo, ciclohexilo, tetrahidro-2H-piran-4-ilo, 1-metil-piperidin-4-ilo, isobutilo, 2-metoxietilo, 1-metil-piperidin-4-ilmetilo, 1-etil-2-hidroxi-etilo, 1-hidroximetil-3-metil-butilo, 1-carboxi-2-metil-propilo, 1-metoximetil-2-metil-propilo, pirrolidin-1-iletilo, 1-hidroximetil-2-metil-butilo, piridin-3-ilmetilo, 2-metoxi-etilo, tetrahidro-2H-piran-4-ilmetilo, tetrahidrofuran-2-ilmetilo, 1-hidroximetil-2,2-dimetil-propilo, 5-ciclopropil-1,2,4-oxadiazol-3-ilo, 1-metil-imidazol-4-ilmetilo, piridin-4-ilmetilo, 1-hidroximeti-propilo, 4-metil-piperazin-1-iletilo, 1-metil-2-(N,N-dimetilamino)-etilo, 1-metil-piperidin-2-ilo, piperidin-2-ilo, 1-hidroximetil-2-metil-propilo, 1-hidroximetil-2-hidroxi-etilo, 1-hidroximetil-2-fenil-etilo, 1-hidroximetil-2-hidroxi-propilo, 1-etil-pirrolidin-3-ilo, 4-hidroxi-pirrolidin-3-ilo, 1-metil-pirrolidin-3-ilo, 1-hidroximetil-etilo, 1-(piridin-4-ilmetil)-piperidin-3-ilo, 1-(tetrahidrofuran-2-il)-pirrolidin-3-ilmetilo, 1-(2-hidroxi-etil)-pirrolidin-3-ilmetilo, 2-amino-

ciclohexilo, tetrahidro-2H-piran-4-iletilo, 1-ciclohexil-2-hidroxi-etilo, 1-hidroximetil-2-(4-hidroxifenil)-etilo, 1-(2-hidroxietil)-piperidin-3-ilo, pirrolidin-3-ilmetilo, piperidin-3-ilmetilo, piperidin-3-ilo, 1-etil-pirrolidin-3-ilo, 1-etil-piperidin-3-ilo, 1-metil-pirrolidin-3-ilo, 1-etil-piperidin-3-ilmetilo.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I)** en la que R^6 se selecciona del grupo que consiste en metilo, etilo, propan-1-ilo, propan-2-ilo, 2-metil-propan-1-ilo, 3-metil-butan-1-ilo, 2-hidroxietilo, 2-metoxietilo, ciclopropilo, ciclopropilmetilo, bencilo, piridin-3-ilmetilo, 3-metoxipropan-1-ilo, 2-(N,N-dimetil)-etilo, 3-(2-oxopirrolidin-1-il)-propan-1-ilo, 1,3-dimetoxi-propan-2-ilo, y 1-metil-azetidin-3-ilo.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I) o (I')** en la que R^{13} es hidrógeno.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I) o (I')** en la que m es 0.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I) o (I')** en la que m es 0 y X es CH.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I) o (I')** en la que m es 0 y X es N.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I) o (I')** en la que m es 1.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I) o (I')** en la que p es 0.

En otra realización, la invención proporciona compuestos representados por la fórmula **(I) o (I')** en la que p es 1.

En una realización particular, la presente invención proporciona compuestos que tienen una fórmula estructural **(I)** como se da a conocer anteriormente, en la que:

X es CH;

R^1 es alquilo C_{1-4};

R^2 es hidrógeno;

R^3 es un tiazolilo; en la que el tiazolilo puede estar opcionalmente sustituido en el carbono con uno o más R^{10};

R^5 es –OH, etoxi, N-metilamino, o N-etilamino;

R^6 es un alquilo C_{1-6} que está opcionalmente sustituido en uno o más átomos de carbono con uno o más R^{16};

R^{10} es trifluorometilo, etilo, o fenilo;

R^{13} es hidrógeno;

R^{16}, para cada caso, se selecciona independientemente del grupo que consiste en –OH, fluoro, N-metilamino, N,N-dimetilamino, metoxi, etoxi, metilsulfanilo, metilsulfonilo, piperidinilo, piperazinilo, morfolinilo, pirrolidinilo, 2-oxopirrolidinilo, pirrolilo, imidazolilo, triazolilo, fenilo que puede estar opcionalmente sustituido con uno o más halo, isoxazolilo, piridinilo, y ciclopropilo.

m es 0; y

p es 0.

En una realización particular, la presente invención proporciona compuestos que tienen una fórmula estructural **(I')** como se da a conocer anteriormente, en la que:

X es CH;

R^1 es alquilo C_{1-4};

R^2 es hidrógeno;

R^3 es un tiazolilo; en la que el tiazolilo puede estar opcionalmente sustituido en el carbono con uno o más R^{10};

$R^{5'}$ es –OH, etoxi, N-metilamino, o N-etilamino;

$R^{6'}$ es un alquilo C_{1-6} que está opcionalmente sustituido en uno o más átomos de carbono con uno o más R^{16};

R^{10} es trifluorometilo, etilo, o fenilo;

R^{13} es hidrógeno;

R^{16}, para cada caso, se selecciona independientemente del grupo que consiste en –OH, fluoro, N-metilamino, N,N-dimetilamino, metoxi, etoxi, metilsulfanilo, metilsulfonilo, piperidinilo, piperazinilo, morfolinilo, pirrolidinilo, 2-oxopirrolidinilo, pirrolilo, imidazolilo, triazolilo, fenilo que puede estar opcionalmente sustituido con uno o más halo, isoxazolilo, piridinilo, y ciclopropilo;

m es 0; y

p es 0.

En una realización particular, la presente invención proporciona compuestos que tienen una fórmula estructural **(I)** como se da a conocer anteriormente, en la que:

X es CH;

R^1 es etilo;

R^2 es hidrógeno;

R^3 es un tiazolilo; en la que el tiazolilo puede estar opcionalmente sustituido en el carbono con uno o más R^{10};

R^5 es –OH, etoxi, N-metilamino, o N-etilamino;

R^6 es un alquilo C_{1-6} que está opcionalmente sustituido en uno o más átomos de carbono con uno o más R^{16};

R^{10} es trifluorometilo;

R^{13} es hidrógeno;

R^{16}, para cada caso, se selecciona independientemente de –OH o alcoxi C_{1-6};

m es 0; y

p es 0.

En una realización particular, la presente invención proporciona unos compuestos que tienen una fórmula estructural **(I')** como se da a conocer anteriormente, en la que:

X es CH;

R^1 es etilo;

R^2 es hidrógeno;

R^3 es un tiazolilo; en la que el tiazolilo puede estar opcionalmente sustituido en el carbono con uno o más R^{10};

$R^{5'}$ es –OH, etoxi, N-metilamino, o N-etilamino;

$R^{6'}$ es un alquilo C_{1-6} que está opcionalmente sustituido en uno o más átomos de carbono con uno o más R^{16};

R^{10} es trifluorometilo;

R^{13} es hidrógeno;

R^{16}, para cada caso, se selecciona independientemente de –OH o alcoxi C_{1-6};

m es 0; y

p es 0.

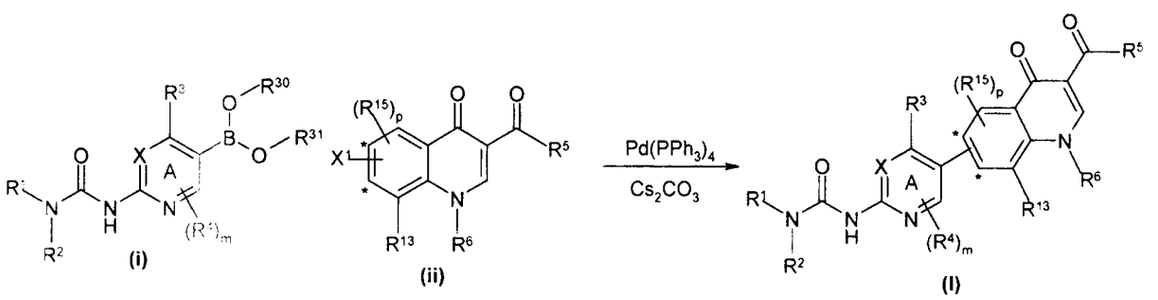
Compuestos particulares de la invención son los compuestos de los Ejemplos, y sus sales farmacéuticamente aceptables, cada uno de los cuales proporciona un aspecto adicional independiente de la invención.

En otra realización, la invención proporciona unas composiciones farmacéuticas que comprenden un excipiente o vehículo farmacéuticamente aceptable y un compuesto representando por la fórmula **(I) o (I')**, o una sal farmacéuticamente aceptable del mismo.

En un aspecto adicional, la presente invención proporciona un procedimiento para preparar un compuesto de fórmula **(I)** o **(I')**, o una sal farmacéuticamente aceptable del

mismo, en el que los grupos variables en los esquemas a continuación son como se definen en la fórmula **(I)** o (I'), excepto que se especifique de otro modo. En general, los compuestos de fórmula **(I)** se pueden preparar mediante una reacción de acoplamiento de Suzuki, catalizada por paladio, de un derivado de éster borónico o un derivado de ácido **(i)** o **(iv)** y un haloderivado **(ii)** o **(iii)**, como se muestra en los Esquemas I y II. Igualmente, los compuestos de fórmula **(I')** se pueden preparar mediante una reacción de acoplamiento de Suzuki, catalizada por paladio, de un derivado de éster borónico o un derivado de ácido **(i)** o **(iv')** y un haloderivado (ii') o **(iii)**, como se muestra en los Esquemas I' y II'. Típicamente, la reacción de acoplamiento se calienta y se lleva a cabo en presencia de una base, tal como Cs_2CO_3.

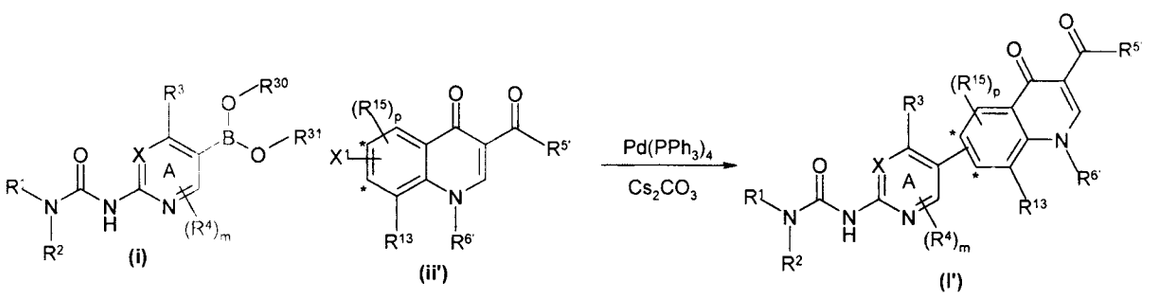
Esquema I



X^1 es un halo

R^{30} y R^{31} son cada uno independientemente hidrógeno, un grupo alquilo, o R^{30} y R^{31}, junto con –O-B-O-, pueden formar un éster borónico cíclico tal como 4,4,5,5,-tetrametil-1,3,2-dioxaborolan-2-ilo.

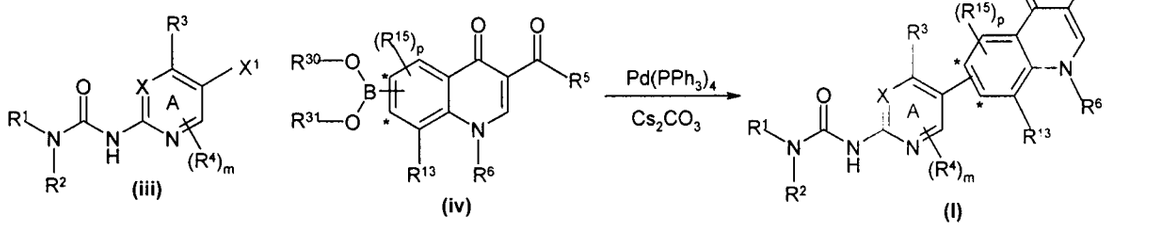
Esquema I'



X^1 es un halo

R^{30} y R^{31} son cada uno independientemente hidrógeno, un grupo alquilo, o R^{30} y R^{31}, junto con –O-B-O-, pueden formar un éster borónico cíclico tal como 4,4,5,5,-tetrametil-1,3,2-dioxaborolan-2-ilo.

Esquema II

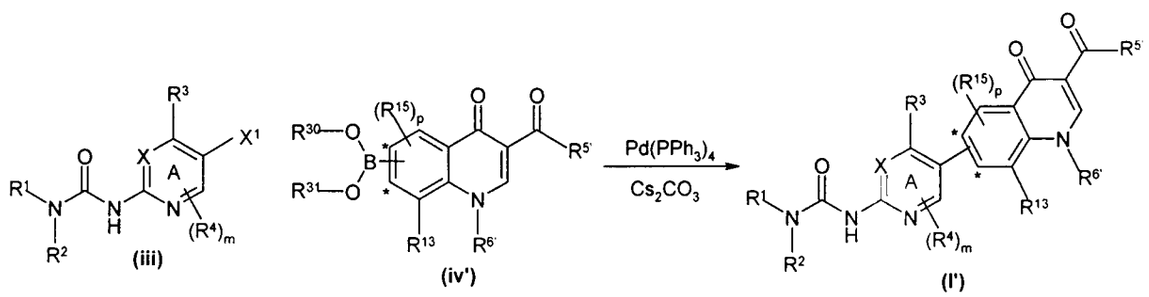


(iii) (iv) (I)

X^1 es un halo

R^{30} y R^{31} son cada uno independientemente hidrógeno, un grupo alquilo, o R^{30} y R^{31}, junto con –O-B-O-, pueden formar un éster borónico cíclico tal como 4,4,5,5,-tetrametil-1,3,2-dioxaborolan-2-ilo.

Esquema II'



(iii) (iv') (I')

X^1 es un halo

R^{30} y R^{31} son cada uno independientemente hidrógeno, un grupo alquilo, o R^{30} y R^{31}, junto con –O-B-O-, pueden formar un éster borónico cíclico tal como 4,4,5,5,-tetrametil-1,3,2-dioxaborolan-2-ilo.

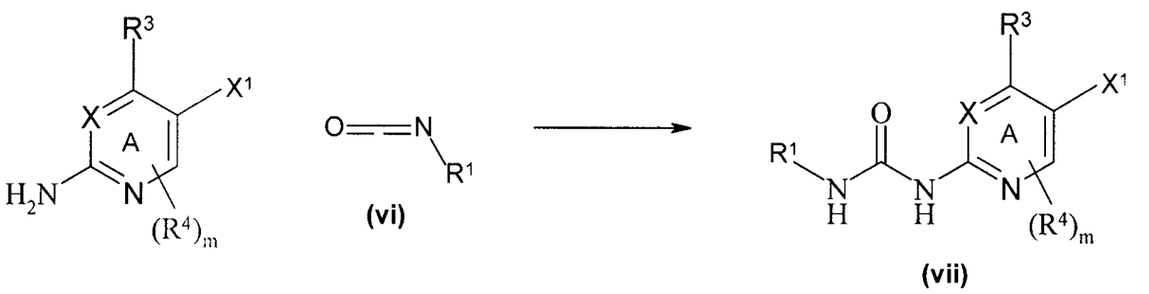
Los derivados de ésteres borónicos se pueden preparar calentando un haloderivado con un compuesto de diboro tal como 4,4,4',4',5,5,5',5'-octametil-2,2'-bi(1,3,2-dioxaborolano) en presencia de dicloruro de 1,1'-bis(difenilfosfino)ferroceno-paladio en un disolvente orgánico.

R^5 o $R^{5'}$ en el Intermediario **(ii)**, **(ii')**, **(iv)**, y **(iv')** es típicamente un grupo alcoxi, que es generalmente estable durante la reacción de acoplamiento de Suzuki. R^5 o $R^{5'}$ se puede convertir en un grupo –OH tras la reacción de acoplamiento tratando el producto con una base fuerte en un disolvente prótico tal como agua, un alcohol o una mezcla de un alcohol y un disolvente orgánico (por ejemplo THF/MeOH). R^5 o $R^{5'}$ se puede convertir en un amino, un N-alquilamino o un N,N-dialquilamino calentando el derivado de éster con un amino, un N-alquilamino o un N,N-dialquilamino puro o en un disolvente tal como un alcohol.

La porción de urea de los compuestos de la invención se puede preparar a partir de un derivado de isocianato, ya sea antes o después de la reacción de acoplamiento de Suzuki, a partir de un derivado de amina. Si la reacción de acoplamiento de Suzuki se lleva a cabo antes

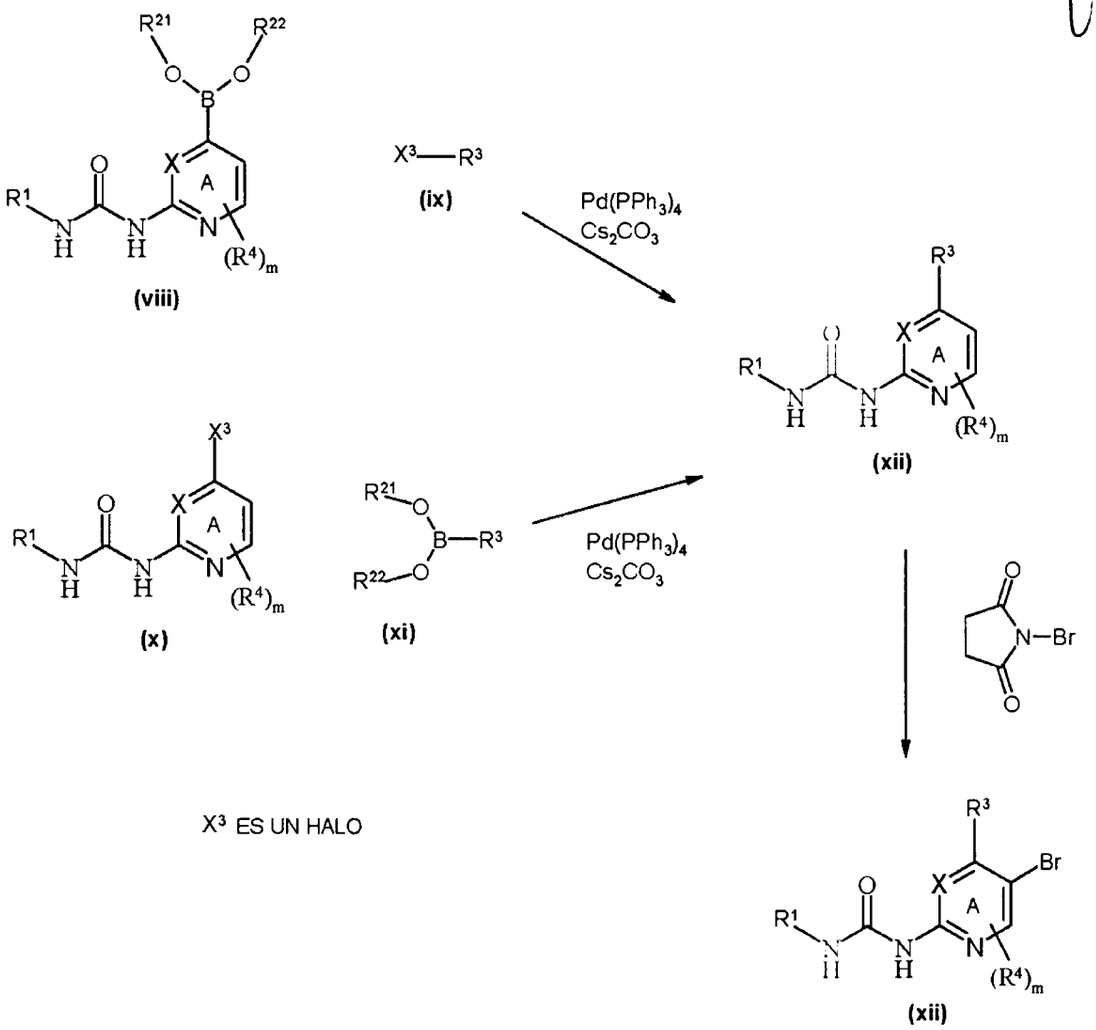
de la formación de la urea, la amina se protege con un grupo protector de amina. Cuando se forme el derivado de urea, típicamente se combina un derivado de isocianato **(vi)** con el derivado de amina **(v)** en un disolvente orgánico y se calienta, como se muestra en el Esquema III. El disolvente puede ser acuoso, orgánico, o una mezcla de un disolvente orgánico miscible acuoso y agua.

Esquema III



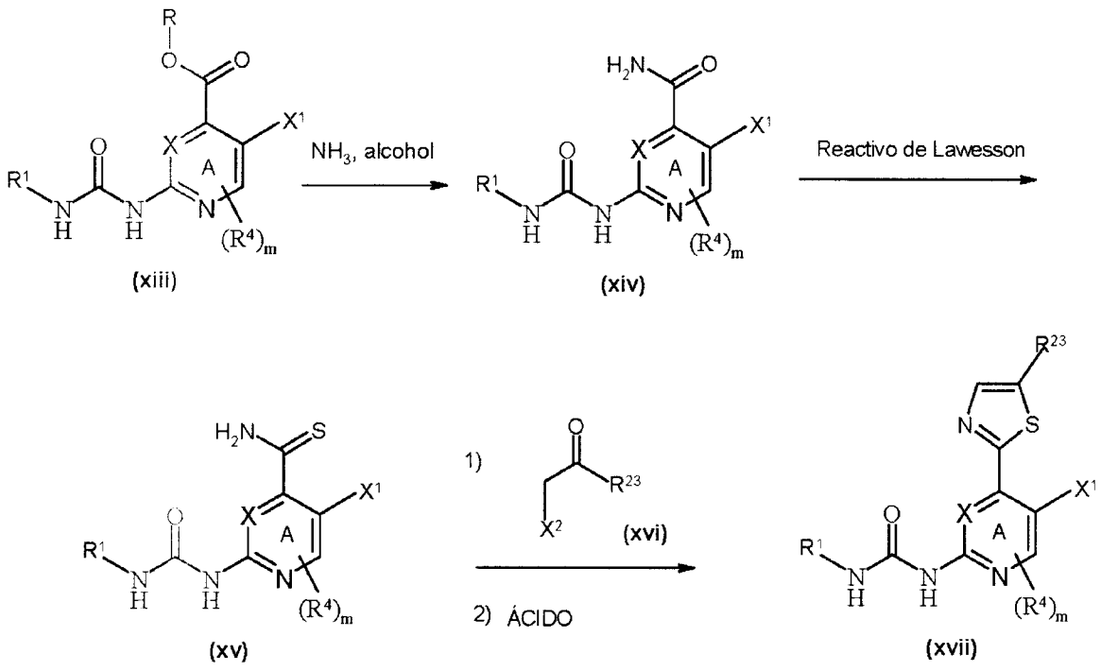
Cuando R^3 es un arilo o un heteroarilo, se puede usar una reacción de acoplamiento de Suzuki para unirlo a un anillo A como se muestra en el esquema IV. Aunque el Esquema IV muestra que la reacción de acoplamiento de R^3 se produce antes de la reacción de acoplamiento para enlazar el anillo A al anillo de 1,4-dihidroquinolina, las reacciones se podrían llevar a cabo en el orden alternativo. Cuando el grupo R^3 se une antes de la reacción de acoplamiento para unir el anillo de 1,4-dihidroquinolina, el anillo A se puede bromar calentándolo con 1-bromopirrolidin-2,5-diona, para formar un sustrato para la reacción de acoplamiento de Suzuki mostrada en el Esquema II.

Esquema IV



Como alternativa, cuando R^3 es un heterociclilo, se puede preparar a partir de un derivado de éster, ya sea antes o después del acoplamiento del anillo de 1,4-dihidroquinolina al anillo A. Por ejemplo, cuando R^3 es un grupo tiazolilo, un derivado de éster **(xiii)** se puede convertir en una amida **(xiv)** tratándolo con una disolución de amoníaco en un alcohol. El derivado de amida **(xiv)** se puede convertir entonces en una tioamida **(xv)** tratando la amida con el reactivo de Lawesson. La tioamida **(xv)** se calienta entonces con una α-halo-cetona o un α-halo-aldehído **(xvi)**, seguido del tratamiento con un ácido, tal como ácido tirfluoroacético, para formar el tiazol **(xvii)** (véase el Esquema V). Aunque el anillo de tiazol se prepara antes de la reacción de acoplamiento de Suzuki para unir el anillo de 1,4-dihidroquinolina en el Esquema V, también se podría preparar después de la reacción de acoplamiento del derivado de éster al anillo de 1,4-dihidroquinolina.

Esquema V



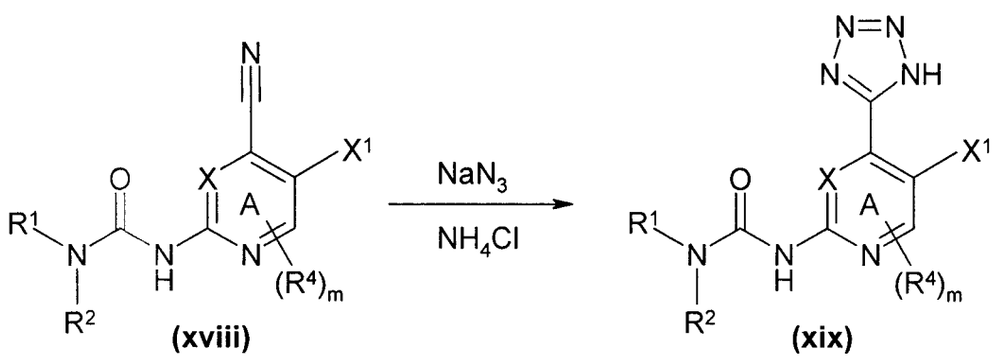
X^2 es un halo.

R es un alquilo.

R^{23} es hidrógeno, un alquilo opcionalmente sustituido, un carbociclilo o un heterociclilo.

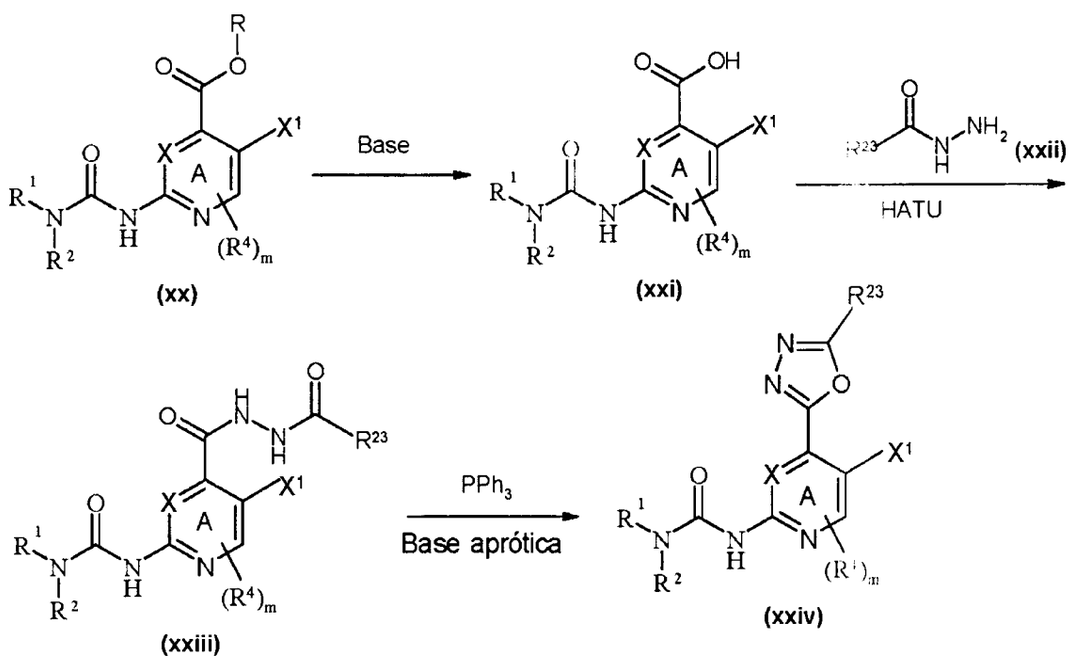
Cuando R^3 es tetrazolilo, se puede preparar calentando un cianoderivado con azida sódica y cloruro de amonio en un disolvente como se muestra en el Esquema VI. Un grupo R^3 tetrazolílico se puede preparar mediante la reacción mostrada en el Esquema VI, ya sea antes o después del acoplamiento del anillo de 1,4-dihidroquinolina al anillo A.

Esquema VI



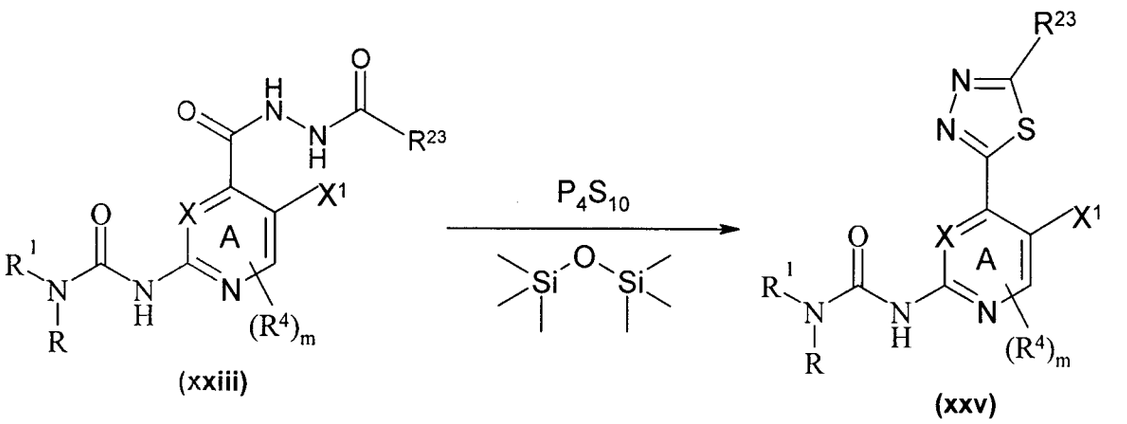
Cuando R^3 es un grupo 1,3,4-oxadiazolilo, se puede preparar a partir de un derivado de éster **(xx)** tratando el éster con una base en para formar un ácido carboxílico **(xxi)**. El ácido carboxílico **(xxi)** se acopla entonces a un derivado de hidrazida (xxii) en presencia del reactivo de acoplamiento de amidas HATU, para formar un derivado de dihidrazida **(xxiii)**. La dihidrazida **(xxiii)** se trata entonces con trifenilfosfina en un disolvente orgánico aprótico, en presencia de una cantidad en exceso de una base aprótica, para formar un compuesto en el que el grupo R^3 es 1,3,4-oxadiazolilo **(xxiv)** como se muestra en el Esquema VII. Un grupo R^3 1,3,4-oxadiazolílico se puede preparar mediante la reacción mostrada en el Esquema VII, ya sea antes o después del acoplamiento del anillo de 1,4-dihidroquinolina al anillo A.

Esquema VII



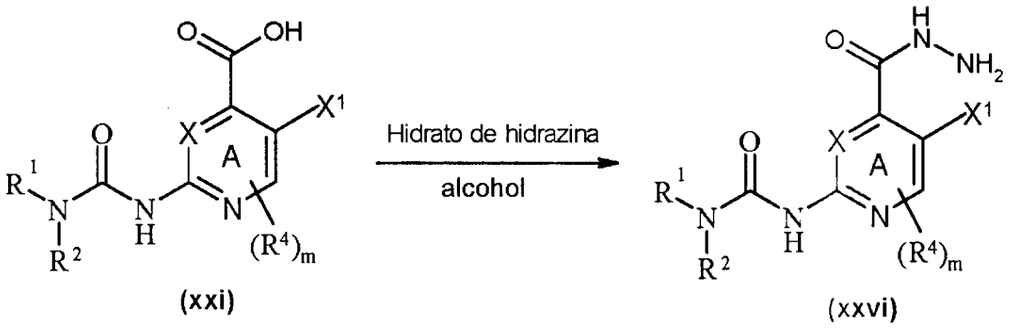
Cuando R^3 es un grupo 1,3,4-tiadiazolilo, se puede preparar a partir de un derivado de dihidrazida **(xxiii)** (véase el Esquema VII para la preparación de derivados de dihidrazida). El derivado de dihidrazida **(xxiii)** se calienta con pentasulfuro de fósforo y hexametildisiloxano en un disolvente orgánico para formar un compuesto que tiene un grupo R^3 1,3,4-tiadiazolílico **(xxv)** como se muestra en el Esquema VIII. Un grupo R^3 1,3,4-tiadiazolílico se puede preparar mediante la reacción mostrada en el Esquema VIII, ya sea antes o después del acoplamiento del anillo de 1,4-dihidroquinolina al anillo A.

Esquema VIII

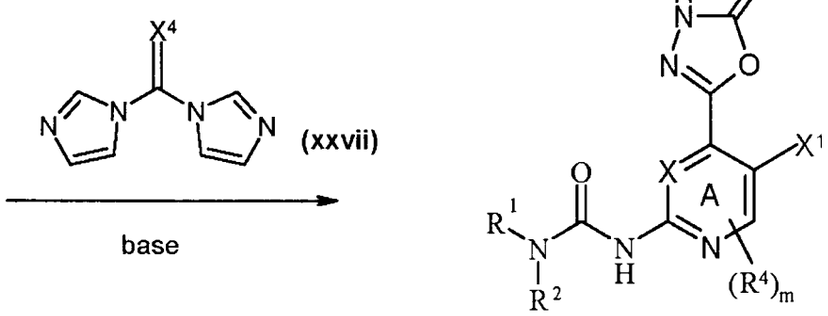


Cuando R^3 es un grupo 2-oxo-1,3,4-oxadiazolilo o un grupo 2-tioxo-1,3,4-oxadiazolilo, se puede preparar a partir de un ácido carboxílico **(xxi)** (véase el Esquema VII para la preparación del derivado de ácido carboxílico). El derivado de ácido carboxílico **(xxi)** se calienta con hidrato de hidrazina en un alcohol, para formar un derivado de hidrazida **(xxvi)**. El derivado de hidrazida **(xxvi)** se hace reaccionar entonces con carbonildiimidazol o di(1-H-imidazol-2-il)metanotiona **(xxvii)** en presencia de una base aprótica en un disolvente aprótico para formar un compuesto que tiene un grupo R^3 2-oxo-1,3,4-oxadiazolílico o 2-tioxo-1,3,4-oxadiazolílico **(xxviii)** como se muestra en el Esquema IX. Un grupo R^3 2-oxo-1,3,4-oxadiazolílico o 2-tioxo-1,3,4-oxadiazolílico se puede preparar mediante la reacción mostrada en el Esquema IX, ya sea antes o después del acoplamiento del anillo de 1,4-dihidroquinolina al anillo A.

Esquema IX



(xxi) (xxvi)



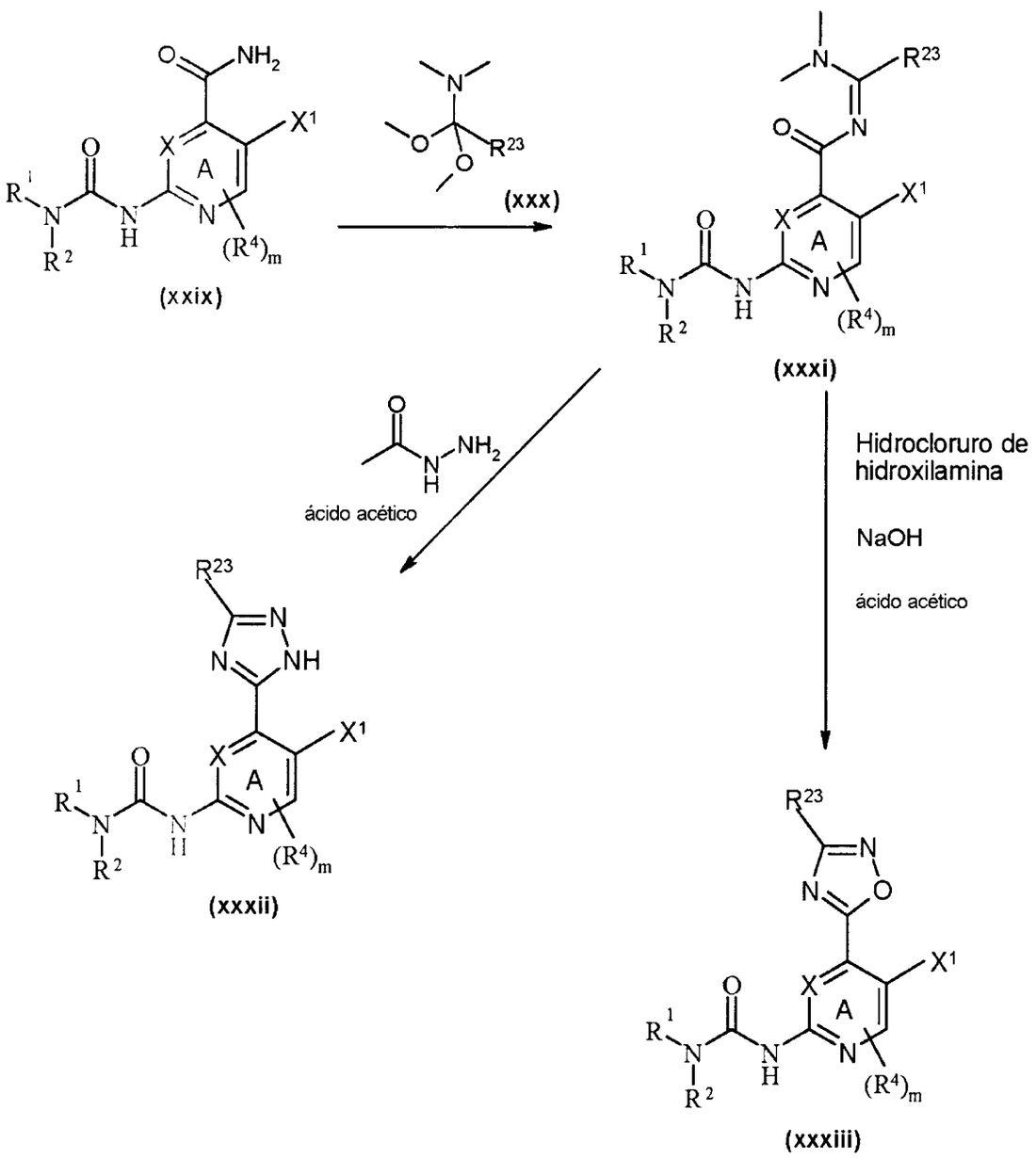
(xxviii)

X^4 es O o S.

Cuando R^3 es un grupo 1,2,4-triazolilo, se puede preparar a partir de un derivado de amida **(xxix)**, calentándolo en 1-(N,N-dimetilamino)-1,1-dimetoxi-etano **(xxx)** para formar **(xxxi)**. El compuesto **(xxxi)** se calienta entonces con acetohidrazida en ácido acético para formar un compuesto que tiene un grupo R^3 1,2,4-triazolílico **(xxxii)** como se muestra en el Esquema X. Un grupo R^3 1,2,4-triazolílico se puede preparar mediante la reacción mostrada en el Esquema X, ya sea antes o después del acoplamiento del anillo de 1,4-dihidroquinolina al anillo A.

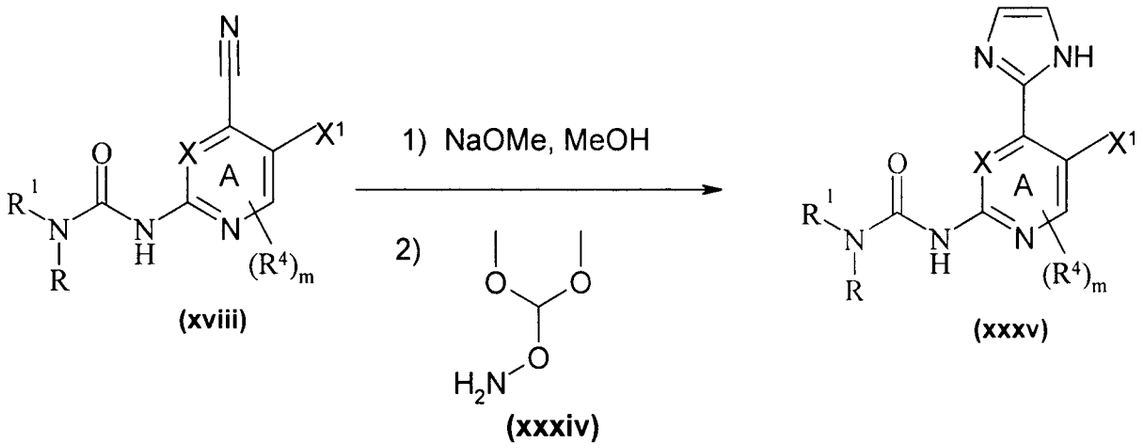
Cuando R^3 es un grupo 1,2,4-oxadiazolilo, se puede preparar a partir de **(xxxi)** calentando **(xxxi)** con hidrocloruro de hidroxilamina en una disolución de hidróxido sódico en ácido acético al 70% en dioxano, para formar un compuesto en el que R^3 es un grupo 1,2,4-oxadiazolílico **(xxxiii)**, como se muestra en el Esquema X. Un grupo R^3 1,2,4-oxadiazolílico se puede preparar mediante la reacción mostrada en el Esquema X, ya sea antes o después del acoplamiento del anillo de 1,4-dihidroquinolina al anillo A.

Esquema X



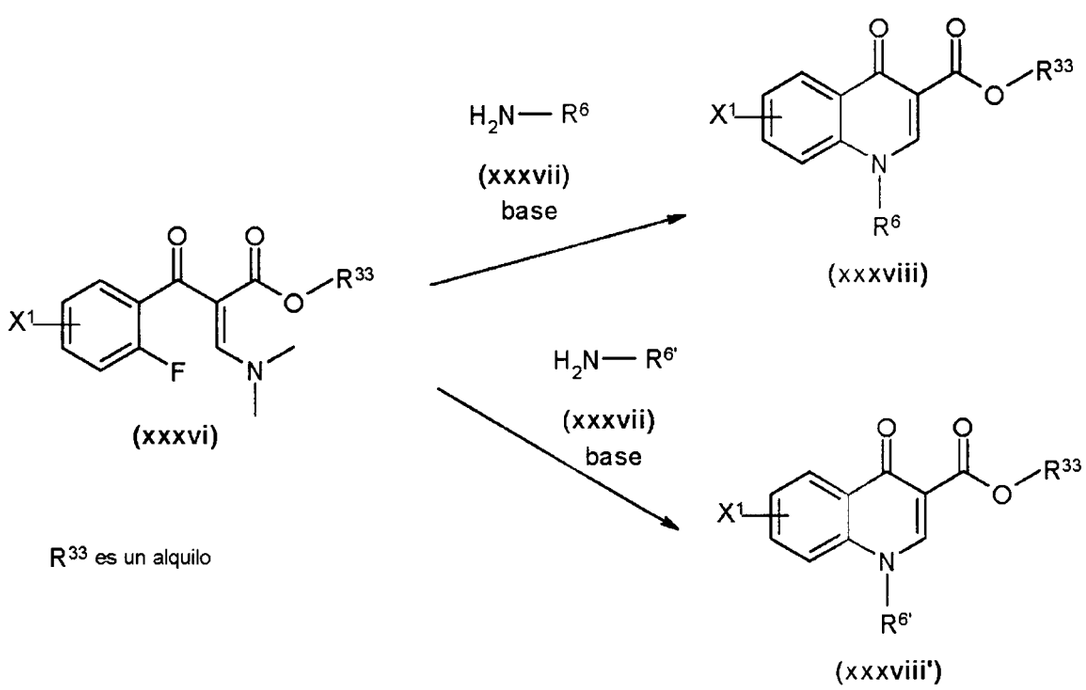
Cuando R^3 es un grupo imidazolilo, se puede preparar a partir de un cianoderivado **(xvii)**, agitando el cianoderivado **(xvii)** a temperatura ambiente en una disolución de metóxido sódico en metanol durante varias horas. Entonces se añade a la disolución 1,1-dimetoxi-2-aminoetano **(xxxiv)**, y se calienta para dar un compuesto en el que R^3 es un grupo imidazolilo **(xxxv)**, como se muestra en el Esquema XI. Un grupo R^3 imidazolílico se puede preparar mediante la reacción mostrada en el Esquema XI, ya sea antes o después del acoplamiento del anillo de 1,4-dihidroquinolina al anillo A.

Esquema XI



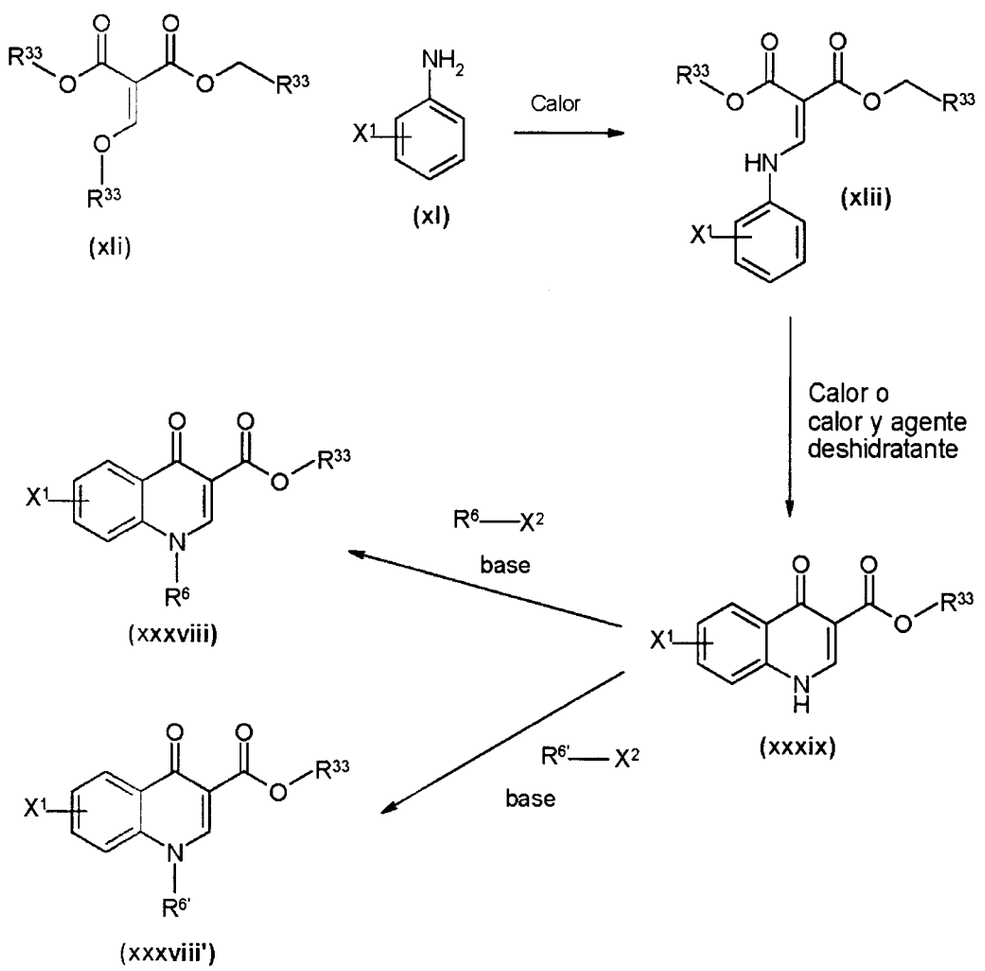
El derivado 1,4-dihidroquinolínico **(xxxviii)** se puede preparar a partir de (Z)-3-(dimetilamino)-2-(2-fluoro-5-halobenzoil)acrilato de alquilo o de un (Z)-3-(dimetilamino)-2-(2-fluoro-4-halobenzoil)acrilato de alquilo **(xxxvi)**, calentándolo con una amina primaria **(xxxvii)** en presencia de una base, como se muestra en el Esquema XII.

Esquema XII



R^{33} es un alquilo

Como alternativa, el derivado 1,4-dihidroquinolínico **(xxxix)** se puede preparar calentando una anilina **(xl)** en presencia de un (alcoximetiliden)propanodioato de dialquilo **(xli)**, para formar el Intermediario **(xlii)**. El Intermediario (lxii) se puede calentar en un disolvente hasta alrededor de 200°C a 300°C, o se puede calentar a una temperatura inferior (por ejemplo, alrededor de 80°C-120°C) en presencia de un reactivo deshidratante tal como el reactivo de Eaton, para dar el derivado 1,4-dihidroquinolínico **(xxxix).** El derivado 1,4-dihidroquinolínico **(xxxix)** se puede convertir en el derivado 1,4-dihidroquinolínico **(xxxviii)** calentándolo con un haluro de alquilo en presencia de una base tal como carbonato potásico.



La formación de una sal farmacéuticamente aceptable está dentro de la pericia de un químico orgánico normal usando técnicas estándar.

Se apreciará que algunos de los diversos sustituyentes del anillo en los compuestos de la presente invención se pueden introducir mediante reacciones de sustitución aromática estándar, o se pueden generar mediante modificaciones de grupos funcionales convencionales, ya sea antes o inmediatamente después de los procedimientos mencionados anteriormente, y,

como tales, se incluyen en el aspecto del procedimiento de la invención. Los reactivos usados para introducir tales sustituyentes del anillo están comercialmente disponibles o se obtienen mediante procedimientos conocidos en la técnica.

La introducción de sustituyentes en un anillo puede convertir un compuesto de la fórmula **(I)** en otro compuesto de la fórmula **(I)**. Igualmente, la introducción de sustituyentes en un anillo puede convertir un compuesto de la fórmula **(I')** en otro compuesto de la fórmula **(I')**. Tales reacciones y modificaciones incluyen, por ejemplo, la introducción de un sustituyente por medio de una reacción de sustitución aromática, la reducción de sustituyentes, la alquilación de sustituyentes, la oxidación de sustituyentes, la esterificación de sustituyentes, la amidación de sustituyentes, la formación de anillos heteroarílicos. Los reactivos y condiciones de reacción para tales procedimientos son bien conocidos en la técnica química. Ejemplos particulares de reacciones de sustitución aromática incluyen la introducción de alcóxidos, reacciones de diazotación seguidas de la introducción del grupo tiol, del grupo alcohol, del grupo halógeno. Los ejemplos de modificaciones incluyen la oxidación de alquiltio a alquilsulfinilo o alquilsufonilo.

El químico orgánico experto será capaz de usar y adaptar la información contenida y referida en las referencias anteriores, y en los Ejemplos que se acompañan allí, y también en los Ejemplos aquí, para obtener materiales de partida necesarios y productos. Si no están comercialmente disponibles, los materiales de partida necesarios para los procedimientos, tales como los descritos anteriormente, se pueden obtener mediante procedimientos que se seleccionan de técnicas de química orgánica estándar, técnicas las cuales son análogas a la síntesis de compuestos conocidos, estructuralmente similares, o técnicas las cuales son análogas al procedimiento descrito anteriormente o a los procedimientos descritos en los Ejemplos. Es de señalar que muchos de los materiales de partida para los métodos sintéticos como se describen anteriormente están comercialmente disponibles y/o se dan a conocer ampliamente en la bibliografía científica, o se podrían obtener a partir de compuestos comercialmente disponibles usando adaptaciones de procedimientos dados a conocer en la bibliografía científica. Se dirige adicionalmente al lector a Advanced Organic Chemistry, 4ª edición, de Jerry March, publicado por John Wiley & Sons 1992, para una guía general sobre condiciones de reacción y reactivos.

También se apreciará que, en algunas de las reacciones mencionadas aquí, puede ser necesario/deseable proteger cualesquiera grupos sensibles en los compuestos. Los casos en los que es necesaria o deseable la protección son conocidos por los expertos en la técnica, como

lo son los métodos adecuados para tal protección. Se pueden usar grupos protectores convencionales según la práctica estándar (para una ilustración, véase T.W. Greene, Protective Groups in Organic Synthesis, John Wiley y Sons, 1991).

Los ejemplos de un grupo protector adecuado para un grupo hidroxi es, por ejemplo, un grupo acilo, por ejemplo un grupo alcanoilo, tal como acetilo, un grupo aroilo, por ejemplo benzoilo, un grupo sililo, tal como trimetilsililo, o un grupo arilmetilo, por ejemplo bencilo. Las condiciones de desprotección para los grupos protectores anteriores necesariamente variarán con la elección del grupo protector. De este modo, por ejemplo, un grupo acilo, tal como un grupo alcanoilo o aroilo, se puede eliminar, por ejemplo, mediante hidrólisis con una base adecuada, tal como un hidróxido de metal alcalino, por ejemplo hidróxido de litio o de sodio. Como alternativa, un grupo sililo, tal como trimetilsililo, se puede eliminar, por ejemplo, mediante fluoruro o mediante un ácido acuoso; o un grupo arilmetilo, tal como un grupo bencilo, se puede eliminar, por ejemplo, mediante hidrogenación en presencia de un catalizador tal como paladio sobre carbón.

Un grupo protector adecuado para un grupo amino es, por ejemplo, un grupo acilo, por ejemplo un grupo alcanoilo tal como acetilo, un grupo alcoxicarbonilo, por ejemplo un grupo metoxicarbonilo, etoxicarbonilo o *t*-butoxicarbonilo, un grupo arilmetoxicarbonilo, por ejemplo benciloxicarbonilo, o un grupo aroilo, por ejemplo benzoilo. Las condiciones de desprotección para los grupos protectores anteriores variarán necesariamente con la elección del grupo protector. De este modo, por ejemplo, un grupo acilo, tal como un grupo alcanoilo o alcoxicarbonilo, o un grupo aroilo, se puede eliminar, por ejemplo, mediante hidrólisis con una base adecuada, tal como un hidróxido de metal alcalino, por ejemplo hidróxido de litio o de sodio. Como alternativa, un grupo acilo, tal como un grupo *t*-butoxicarbonilo, se puede eliminar, por ejemplo, mediante tratamiento con un ácido adecuado, tal como ácido clorhídrico, sulfúrico o fosfórico, o ácido trifluoroacétio, y un grupo arilmetoxicarbonilo, tal como un grupo benciloxicarbonilo, se puede eliminar, por ejemplo, mediante hidrogenación sobre un catalizador, tal como paladio sobre carbón, o mediante tratamiento con un ácido de Lewis, por ejemplo tris(trifluoroacetato) de boro. Un grupo protector alternativo adecuado para un grupo amino primario es, por ejemplo, un grupo ftaloilo, que se puede eliminar mediante tratamiento con una alquilamina, por ejemplo dimetilaminopropilamina o 2-hidroxietilamina, o con hidrazina.

Un grupo protector adecuado para un grupo carboxi es, por ejemplo, un grupo esterificante, por ejemplo un grupo metilo o un grupo etilo, que se puede eliminar, por

ejemplo, mediante hidrólisis con una base, tal como hidróxido de sodio, o por ejemplo un grupo *t*-butilo, que se puede eliminar, por ejemplo, mediante tratamiento con un ácido, por ejemplo un ácido orgánico tal como ácido trifluoroacético, o por ejemplo un grupo bencilo, que se puede eliminar, por ejemplo, mediante hidrogenación sobre un catalizador, tal como paladio sobre carbón, o por ejemplo un grupo alilo, que se puede eliminar, por ejemplo, mediante el uso de un catalizador de paladio, tal como acetato de paladio.

Los grupos protectores se pueden eliminar en cualquier etapa conveniente en la síntesis usando técnicas convencionales bien conocidas en la técnica química, o se pueden eliminar durante una etapa de reacción o tratamiento posterior.

Cuando se requiere una forma ópticamente activa de un compuesto de la invención, se puede obtener llevando a cabo uno de los procedimientos anteriores usando un material de partida ópticamente activo (formado, por ejemplo, mediante inducción asimétrica de una etapa de reacción adecuada), o mediante resolución de una forma racémica del compuesto o Intermediario usando un procedimiento estándar, o mediante separación cromatográfica de diasterioisómeros (cuando se produzcan). También pueden ser útiles para la preparación de compuestos y/o Intermediarios ópticamente activos las técnicas enzimáticas.

De forma similar, cuando se requiere un regioisómero puro de un compuesto de la invención, se puede obtener llevando a cabo uno de los procedimientos anteriores usando un regioisómero puro como material de partida, o mediante resolución de una mezcla de los regioisómeros o Intermediarios usando un procedimiento estándar.

Métodos de ensayo de la potencia enzimática

Actividad de Inhibición de ATPasa de GyrB de *E.coli*: Los compuestos se pueden ensayar para determinar la inhibición de la actividad de ATPasa de GyrB de *E. coli* usando un ensayo de detección de fosfato a base de molibdato de amonio/verde de malaquita (Lanzetta, P. A., L. J. Alvarez, P. S. Reinach, y O. A. Candia, 1979, 100:95-97). Los ensayos se pueden realizar en placas de múltiples pocillos en reacciones de 30 µl que contienen: 50 mM de tampón de Hepes, pH 7,5, 75 mM de acetato de amonio, 8,0 mM de cloruro de magnesio, 0,5 mM de ácido etilendiaminotetraacético, 5% de glicerol, 1 mM de 1,4-ditio-DL-treitol, 200 nM de seroalbúmina bovina, 1,6 µg/ml de ADN de esperma de salmón cortado, 400 pM de GyrA de *E. coli*, 400 pM de GyrB de *E. coli*, 250 µM de ATP, y compuesto en dimetilsulfóxido. Las reacciones se pueden paralizar con 30 µl de reactivo de detección de molibdato de amonio/verde de malaquita, que contiene 1,2 mM de hidrocloruro de verde de malaquita, 8,5

mM de molibdato de amonio tetrahidratado, y 1 M de ácido clorhídrico. Las placas se pueden leer en un lector de placas de absorbancia a 650 nm, y los valores de la inhibición en porcentaje se calculan usando reacciones que contienen dimetilsulfóxido (2%) como inhibición del 0%, y reacciones que contienen EDTA (2,4 μM) como controles de inhibición del 100%. Se puede determinar una medida de la IC_{50} de la potencia del compuesto para cada compuesto a partir de reacciones realizadas en presencia de 10 concentraciones diferentes de compuestos.

Actividad de Inhibición de ATPasa de Topoisomerasa IV de *E.coli*: Los compuestos se pueden ensayar para determinar la inhibición de la actividad de ATPasa de topoisomerasa IV de *E. coli* como se describe anteriormente para la GyrB de *E. coli*, excepto que las reacciones de 30 μl contenían lo siguiente: 20 mM de tampón de TRIS, pH 8, 50 mM de acetato de amonio, 8 mM de cloruro de magnesio, 5% de glicerol, 5 mM de 1,4-ditio-DL-treitol, 0,005% de Brij-35, 5 μg/ml de ADN de esperma de salmón cortado, 500 pM de ParC de *E. coli*, 500 pM de ParE de *E. coli*, 160 μM de ATP, y compuesto en dimetilsulfóxido. Se puede determinar una medida de la IC_{50} de la potencia del compuesto para cada compuesto a partir de reacciones realizadas en presencia de 10 concentraciones diferentes de compuestos.

Muchos de los compuestos de la invención se evaluaron en un ensayo sustancialmente similar a los ensayos descritos anteriormente para medir la inhibición de ATPasa de GyrB de *E.coli* y la ATPasa de Topoisomerasa IV de *E. coli*, y tuvieron valores de IC_{50} <200μM en uno o en ambos ensayos.

Actividad de Inhibición de ATPasa de GyrB de *S.aureus*: Los compuestos se pueden ensayar para determinar la inhibición de la actividad de ATPasa de GyrB de *S. aureus* usando un ensayo de detección de fosfato a base de molibdato de amonio/verde de malaquita (Lanzetta, P. A., L. J. Alvarez, P. S. Reinach, y O. A. Candia, 1979, 100:95-97). Los ensayos se pueden realizar en placas de múltiples pocillos en reacciones de 30 μl que contienen: 50 mM de tampón de Hepes, pH 7,5, 75 mM de acetato de amonio, 8,0 mM de cloruro de magnesio, 0,5 mM de ácido etilendiaminotetraacético, 5% de glicerol, 1,0 mM de 1,4-ditio-DL-treitol, 200 nM de seroalbúmina bovina, 1,0 μg/ml de ADN de esperma de salmón cortado, 250 pM de GyrA de *E. coli*, 250 pM de GyrB de *S. aureus*, 250 μM de ATP, y compuesto en dimetilsulfóxido. Las reacciones se pueden paralizar con 30 μl de reactivo de detección de molibdato de amonio/verde de malaquita, que contiene 1,2 mM de hidrocloruro de verde de

malaquita, 8,5 mM de molibdato de amonio tetrahidratado, y 1 M de ácido clorhídrico. Las placas se pueden leer en un lector de placas de absorbancia a 650 nm, y los valores de la inhibición en porcentaje se pueden calcular usando reacciones que contienen dimetilsulfóxido (2%) como inhibición del 0%, y reacciones que contienen EDTA (2,4 μM) como controles de inhibición del 100%. Se puede determinar una medida de la IC_{50} de la potencia del compuesto para cada compuesto a partir de reacciones realizadas en presencia de 10 concentraciones diferentes de compuestos.

Los compuestos en la tabla a continuación se evaluaron en un ensayo sustancialmente similar al ensayo descrito anteriormente para medir la inhibición de ATPasa de GyrB de *S. aureus*, y se encontró que la tienen un porcentaje de inhibición de ATPasa de GyrB de *S. aureus* a 1 μM como se muestra en la tabla. Si un compuesto se evaluó más de una vez, en la tabla se muestra un valor del porcentaje de inhibición para cada evaluación.

Ejemplo	% de inhibición	Ejemplo	% de inhibición	Ejemplo	% de inhibición
1	100 104	128	92	255	Sin datos
2	100	129	93	256	Sin datos
3	Sin datos	130	101	257	Sin datos
4	98	131	Sin datos	258	Sin datos
5	Sin datos	132	Sin datos	259	Sin datos
6	Sin datos	133	Sin datos	260	Sin datos
7	100	134	Sin datos	261	Sin datos
8	Sin datos	135	Sin datos	262	Sin datos
9	106	136	Sin datos	263	Sin datos
10	99	137	Sin datos	264	Sin datos
11	102	138	Sin datos	265	Sin datos
12	93	139	Sin datos	266	Sin datos
13	98	140	95	267	Sin datos
14	Sin datos	141	97	268	Sin datos
15	101	142	97	269	Sin datos
16	101	143	95	270	Sin datos

17	103	144	94	271	Sin datos
18	98	145	92	272	Sin datos
19	98	146	Sin datos	273	Sin datos
20	96	147	102	274	Sin datos
21	98	148	93	275	Sin datos
22	99	149	93	276	106
23	101	150	Sin datos	277	103
24	99	151	Sin datos	278	101
			95		
25	99	152	106	279	103
26		153	105	280	103
27	99	154	107	281	106
28	97	155	94	282	105
29	Sin datos	156	105	283	102
30	95	157	103	284	107
31	Sin datos	158	106	285	105
32	98	159	105	286	102
	97				
33	109	160	103	287	100
34	100	161	101	288	99
35	Sin datos	162	106	289	103
36	64	163	106	290	100
37	96	164	107	291	107
38	99	165	109	292	102
39	101	166	104	293	106
40	Sin datos	167	109	294	109
41	105	168	102	295	Sin datos
42	113	169	105	296	Sin datos
43	Sin datos	170	102	297	Sin datos
44	98	171	112	298	Sin datos
45	Sin datos	172	107	299	Sin datos
46	Sin datos	173	Sin datos	300	Sin datos

47	Sin datos	174	Sin datos	301	Sin datos
48	106	175	Sin datos	302	Sin datos
49	Sin datos	176	Sin datos	302	Sin datos
50	Sin datos	177	Sin datos	304	Sin datos
51	Sin datos	178	Sin datos	305	103
52	Sin datos	179	Sin datos	306	105 100 102
53	Sin datos	180	Sin datos	307	105
54	Sin datos	181	Sin datos	308	111
55	Sin datos	182	Sin datos	309	109
56	Sin datos	183	Sin datos	310	106
57	Sin datos	184	Sin datos	311	100
58	Sin datos	185	Sin datos	312	105
59	Sin datos	186	Sin datos	313	103
60	Sin datos	187	Sin datos	314	114
61	Sin datos	188	Sin datos	315	Sin datos
62	Sin datos	189	100	316	Sin datos
63	Sin datos	190	Sin datos	317	Sin datos
64	Sin datos	191	94	318	Sin datos
65	Sin datos	192	92	319	Sin datos
66	Sin datos	193	93	320	98
67	Sin datos	194	93	321	100
68	Sin datos	195	98	322	96
69	Sin datos	196	97	323	106
70	Sin datos	197	116	324	Sin datos
71	107	198	108	325	96
72	103	199	103	326	97
73	105	200	111	327	100
74	103	201	Sin datos	328	109
75	102	202	103	329	97
76	110	203	87	330	109

77	110	204	Sin datos	331	109
78	102	205	94	332	109
79	97	206	92	333	106
80	96	207	93	334	95
81	96	208	97	335	107
82	111	209	Sin datos	336	109
83	96	210	93	337	106
84	95	211	97	338	99
85	96	212	94	339	109
86	98	213	94	340	93
87	96	214	118	341	99
88	90	215	120	342	99
89	91	216	109	343	98
90	97	217	105	344	95
91	Sin datos	218	97	345	98
92	Sin datos	219	86	346	87
93	95	220	97	347	100
94	95	221	72	348	98
95	109	222	106	349	108
96	95	223	98	350	96
97	Sin datos	224	96	351	95
98	Sin datos	225	95	352	88
99	Sin datos	226	94	353	99
100	Sin datos	227	91	354	98
101	Sin datos	228	104	355	87
102	Sin datos	229	106	356	85
103	Sin datos	230	102	357	87
104	Sin datos	231	Sin datos	358	95
105	Sin datos	232	98	359	92
106	Sin datos	233	Sin datos	360	Sin datos
107	Sin datos	234	Sin datos	361	97
108	Sin datos	235	Sin datos	362	94

109	Sin datos	236	Sin datos	363	95
110	Sin datos	237	103	364	97
111	Sin datos	238	97	365	99
112	Sin datos	239	Sin datos	366	99
113	Sin datos	240	Sin datos	367	100
114	Sin datos	241	105 100 102	368	87
115	Sin datos	242	104	369	97
116	Sin datos	243	116	370	98
117	Sin datos	244	111	371	98
118	Sin datos	245	105	372	98
119	Sin datos	246	104	373	94
120	Sin datos	247	115	374	86
121	Sin datos	248	103	375	99
122	95	249	113	376	108
123	95	250	112	377	106
124	87	251	113	378	107
125	93	252	105	379	97
126	117	253	Sin datos	380	Sin datos
127	117	254	Sin datos		

Métodos de ensayo de la susceptibilidad bacteriana

Los compuestos se pueden ensayar para determinar la actividad antimicrobiana ensayando la susceptibilidad en medios líquidos. Los compuestos se disolvieron en dimetilsulfóxido, y se ensayaron en diluciones de 10 veces en los ensayos de susceptibilidad. Los organismos usados en el ensayo se hicieron crecer toda la noche en medio de agar adecuado, y después se suspendieron en un medio líquido apropiado para el crecimiento del organismo. La suspensión puede ser una 0,5 McFarland, y se puede hacer una dilución adicional de 1 en 10 en el mismo medio líquido, para preparar la suspensión final de organismo en 100 µl. Las placas se incubaron en condiciones apropiadas a 37°C durante 24 h,

antes de la lectura. La Concentración Inhibidora Mínima (MIC) se puede determinar como la concentración de fármaco más baja capaz de reducir el crecimiento un 80% o más.

En un ensayo comparable al anterior, el Ejemplo 9 tuvo una MIC de 0,02 μM frente a *Streptococcus pneumoniae*.

Según una característica adicional de la invención, se proporciona un compuesto de la fórmula **(I) o (I')**. o una sal farmacéuticamente aceptable del mismo, para uso en un método de tratamiento del cuerpo humano o animal, mediante terapia.

En una realización, la invención proporciona un método para tratar una infección bacteriana en un animal, tal como un ser humano, que comprende administrar al animal o ser humano una cantidad eficaz de un compuesto de una cualquiera de las fórmulas **(I)** o **(I')**, o una sal farmacéuticamente aceptable del mismo.

Se ha encontrado que los compuestos de la presente invención inhiben la ADN girasa y / o topoisomerasa IV bacterianas, y por lo tanto son de interés por sus efectos antibacterianos. En un aspecto de la invención, los compuestos de la invención inhiben la ADN girasa bacteriana, y por lo tanto son de interés por sus efectos antibacterianos. En un aspecto de la invención, los compuestos de la invención inhiben la topoisomerasa IV bacteriana, y por lo tanto son de interés por sus efectos antibacterianos. En un aspecto de la invención, los compuestos de la invención inhiben tanto ADN girasa como topoisomerasa IV, y por lo tanto son de interés por sus efectos antibacterianos. De este modo, los compuestos de la invención son útiles para tratar o prevenir infecciones bacterianas.

En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Acinetobacter baumanii*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Acinetobacter haemolyticus*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Acinetobacter junii*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Acinetobacter johnsonii*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Acinetobacter lwoffi*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Bacteroides bivius*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Bacteroides fragilis*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Burkholderia cepacia*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a

una infección provocada por *Campylobacter jejuni*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Chlamydia pneumoniae*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Chlamydia urealyticus*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Chlamydophila pneumoniae*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Clostridium difficile*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Enterobacter aerogenes*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Enterobacter cloacae*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Enterococcus faecalis*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Enterococcus faecium*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Escherichia coli*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Gardnerella vaginalis*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Haemophilus parainfluenzae*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Haemophilus influenzae*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Helicobacter pylori*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Klebsiella pneumoniae*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Legionella pneumophila*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Staphylococcus aureus* resistente a meticilina. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Staphylococcus aureus* susceptible a meticilina. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Moraxella catarrhalis*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Morganella morganii*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Mycoplasma pneumoniae*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Neisseria gonorrhoeae*. En un aspecto de

la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Streptococcus pneumoniae* resistente a penicilina. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Streptococcus pneumoniae* susceptible a penicilina. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Peptostreptococcus magnus*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Peptostreptococcus micros*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Peptostreptococcus anaerobius*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Peptostreptococcus asaccharolyticus*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Peptostreptococcus prevotii*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Peptostreptococcus tetradius*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Peptostreptococcus vaginalis*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Proteus mirabilis*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Pseudomonas aeruginosa*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Staphylococcus aureus* resistente a quinolonas. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Staphylococcus epidermis* resistente aquinolonas. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Salmonella typhi*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Salmonella paratyphi*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Salmonella enteritidis*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Salmonella typhimurium*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Serratia marcescens*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Staphylococcus aureus*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Staphylococcus epidermidis*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección

provocada por *Staphylococcus saprophyticus*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Streptococcus agalactiae*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Streptococcus pneumoniae*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Streptococcus pyogenes*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Stenotrophomonas maltophilia*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Ureaplasma urealyticum*. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Enterococcus faecium* resistente a vancomicina. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Enterococcus faecalis* resistente a vancomicina. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Staphylococcus aureus* resistente a vancomicina. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por *Staphylococcus epidermis* resistente a vancomicina. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por Mycobacterium tuberculosis. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por Clostridium perfringens. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por Klebsiella oxitoca. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por Neisseria miningitidis. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por Fusobacterium spp. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por Peptococcus spp. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por Proteus vulgaris. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por Staphylococcus negativa a la coagulasa (incluyendo Staphylococcus lugdunensis, Staphylococcus capitis, Staphylococcus hominis, y Staphylococcus saprophyticus).

En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por Acinetobacter spp. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por Bacteroides spp.

En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por Burkholderia spp. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por Campylobacter spp. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por Chlamydia spp. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por Chlamydophila spp. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por Clostridium spp. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por Enterobacter spp. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por Enterococcus spp. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por Escherichia spp. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por Gardnerella spp. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por Haemophilus spp. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por Helicobacter spp. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por Klebsiella spp. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por Legionella spp. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por Moraxella spp. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por Morganella spp. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por Mycoplasma spp. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por Neisseria spp. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por Peptostreptococcus spp. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por Proteus spp. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por Pseudomonas spp. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por Salmonella spp. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por Serratia spp. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por Staphylococcus spp. En un

aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por Streptoccocus spp. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por Stenotrophomonas spp. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por Ureaplasma spp. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por microorganismos aerobios. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por microorganismos anaerobios estrictos. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por microorganismos anaerobios facultativos. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por bacterias gram-positivas. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por bacterias gram-negativas. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por bacterias gram-variables. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por patógenos respiratorios atípicos. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por microorganismos entéricos. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por Shigella spp. En un aspecto de la invención, una "infección" o "infección bacteriana" se refiere a una infección provocada por Citrobacter.

En un aspecto de la invención, "infección" o "infección bacteriana" se refiere a una infección ginecológica. En un aspecto de la invención, "infección" o "infección bacteriana" se refiere a una infección del aparato respiratorio (RTI). En un aspecto de la invención, "infección" o "infección bacteriana" se refiere a una enfermedad transmitida sexualmente. En un aspecto de la invención, "infección" o "infección bacteriana" se refiere a una infección del aparato urinario. En un aspecto de la invención, "infección" o "infección bacteriana" se refiere a exacerbación aguda de la bronquitis crónica (ACEB). En un aspecto de la invención, "infección" o "infección bacteriana" se refiere a otitis media aguda. En un aspecto de la invención, "infección" o "infección bacteriana" se refiere a sinusitis aguda. En un aspecto de la invención, "infección" o "infección bacteriana" se refiere a una infección provocada por bacterias resistentes a fármacos. En un aspecto de la invención, "infección" o "infección bacteriana" se refiere a septicemia relacionada con cateterismo. En un aspecto de la invención, "infección" o "infección bacteriana" se refiere a chancroide. En un aspecto de la

invención, "infección" o "infección bacteriana" se refiere a clamidiasis. En un aspecto de la invención, "infección" o "infección bacteriana" se refiere a neumonía adquirida en la comunidad (CAP). En un aspecto de la invención, "infección" o "infección bacteriana" se refiere a infección complicada de la piel y de la estructura de la piel. En un aspecto de la invención, "infección" o "infección bacteriana" se refiere a infección no complicada de la piel y de la estructura de la piel. En un aspecto de la invención, "infección" o "infección bacteriana" se refiere a endocarditis. En un aspecto de la invención, "infección" o "infección bacteriana" se refiere a neutropenia febril. En un aspecto de la invención, "infección" o "infección bacteriana" se refiere a cervicitis gonocócica. En un aspecto de la invención, "infección" o "infección bacteriana" se refiere a uretritis gonocócica. En un aspecto de la invención, "infección" o "infección bacteriana" se refiere a neumonía adquirida en un hospital (HAP). En un aspecto de la invención, "infección" o "infección bacteriana" se refiere a osteomielitis. En un aspecto de la invención, "infección" o "infección bacteriana" se refiere a septicemia. En un aspecto de la invención, "infección" o "infección bacteriana" se refiere a sífilis. En un aspecto de la invención, "infección" o "infección bacteriana" se refiere a neumonía asociada con ventiladores. En un aspecto de la invención, "infección" o "infección bacteriana" se refiere a infecciones intraabdominales. En un aspecto de la invención, "infección" o "infección bacteriana" se refiere a gonorrea. En un aspecto de la invención, "infección" o "infección bacteriana" se refiere a meningitis. En un aspecto de la invención, "infección" o "infección bacteriana" se refiere a tétano. En un aspecto de la invención, "infección" o "infección bacteriana" se refiere a tuberculosis.

En una realización, es de esperar que los compuestos de la presente invención serán útiles para tratar infecciones bacterianas, incluyendo, pero sin limitarse a, neumonía adquirida en la comunidad, neumonía adquirida en el hospital, infecciones de la piel y de la estructura de la piel, exacerbación aguda de bronquitis crónica, sinusitis aguda, otitis media aguda, septicemia relacionada con cateterismo, neutropenia febril, osteomielitis, endocarditis, infecciones del aparato urinario e infecciones provocadas por bacterias resistentes a fármacos tales como Streptococcus pneumoniae resistente a penicilina, Staphylococcus aureus resistente a meticilina, Staphylococcus epidermidis resistente a meticilina y enterococos resistentes a vancomicina.

Según una característica adicional de la presente invención, se proporciona un método para producir un efecto antibacteriano en un animal de sangre caliente, tal como el hombre,

que necesite de tal tratamiento, que comprende administrar a dicho animal una cantidad eficaz de un compuesto de la presente invención, o una sal farmacéuticamente aceptable del mismo.

Según una característica adicional de la presente invención, se proporciona un método para inhibir la ADN girasa y / o topoisomerasa IV bacterianas en un animal de sangre caliente, tal como un ser humano, que necesite de tal tratamiento, que comprende administrar a dicho animal una cantidad eficaz de un compuesto de fórmula **(I)** o **(I')**, o una sal farmacéuticamente aceptable del mismo como se define aquí anteriormente.

Según una característica adicional de la presente invención, se proporciona un método para tratar una infección bacteriana en un animal de sangre caliente, tal como un ser humano, que necesite de tal tratamiento, que comprende administrar a dicho animal una cantidad eficaz de un compuesto de fórmula **(I)** o **(I')**, o una sal farmacéuticamente aceptable del mismo como se define aquí anteriormente.

Según una característica adicional de la invención, se proporciona un método para tratar una infección bacteriana, seleccionada de neumonía adquirida en la comunidad, neumonía adquirida en el hospital, infecciones de la piel y de la estructura de la piel, exacerbación aguda de bronquitis crónica, sinusitis aguda, otitis media aguda, septicemia relacionada con cateterismo, neutropenia febril, osteomielitis, endocarditis, infecciones del aparato urinario e infecciones provocadas por bacterias resistentes a fármacos tales como Streptococcus pneumoniae resistente a penicilina, Staphylococcus aureus resistente a meticilina, Staphylococcus epidermidis resistente a meticilina y enterococos resistentes a vancomicina, en un animal de sangre caliente, tal como un ser humano, que necesite de tal tratamiento, que comprende administrar a dicho animal una cantidad eficaz de un compuesto de fórmula **(I)** o **(I')**, o una sal farmacéuticamente aceptable del mismo como se define aquí anteriormente.

Una característica adicional de la presente invención es un compuesto de fórmula **(I)** o **(I')**, y sales farmacéuticamente aceptables del mismo, para uso como un medicamento. De forma adecuada, el medicamento es un agente antibacteriano.

Según un aspecto adicional de la invención, se proporciona el uso de un compuesto de fórmula **(I)** o **(I')**, o una sal farmacéuticamente aceptable del mismo, en la fabricación de un medicamento para uso en la producción de un efecto antibacteriano en un animal de sangre caliente, tal como un ser humano.

Según un aspecto adicional de la invención, se proporciona el uso de un compuesto de fórmula **(I)** o **(I')**, o una sal farmacéuticamente aceptable del mismo, en la fabricación de un

medicamento para uso en la inhibición de ADN girasa y /o topoisomerasa IV bacterianas en un animal de sangre caliente, tal como un ser humano.

De este modo, según un aspecto adicional de la invención, se proporciona el uso de un compuesto de fórmula **(I)** o **(I')**, o una sal farmacéuticamente aceptable del mismo, en la fabricación de un medicamento para uso en el tratamiento de una infección bacteriana en un animal de sangre caliente, tal como un ser humano.

De este modo, según un aspecto adicional de la invención, se proporciona el uso de un compuesto de fórmula **(I)** o **(I')**, o una sal farmacéuticamente aceptable del mismo, en la fabricación de un medicamento para uso en el tratamiento de una infección bacteriana, seleccionada de neumonía adquirida en la comunidad, neumonía adquirida en el hospital, infecciones de la piel y de la estructura de la piel, exacerbación aguda de bronquitis crónica, sinusitis aguda, otitis media aguda, septicemia relacionada con cateterismo, neutropenia febril, osteomielitis, endocarditis, infecciones del aparato urinario e infecciones provocadas por bacterias resistentes a fármacos tales como Streptococcus pneumoniae resistente a penicilina, Staphylococcus aureus resistente a meticilina, Staphylococcus epidermidis resistente a meticilina y enterococos resistentes a vancomicina, en un animal de sangre caliente, tal como un ser humano.

Según un aspecto adicional de la invención, se proporciona un compuesto de fórmula **(I)** o **(I')**, o una sal farmacéuticamente aceptable del mismo, para uso en la producción de un efecto antibacteriano en un animal de sangre caliente, tal como un ser humano.

Según un aspecto adicional de la invención, se proporciona un compuesto de fórmula **(I)** o **(I')**, o una sal farmacéuticamente aceptable del mismo, para uso en la inhibición de ADN girasa y / o topoisomerasa IV bacterianas en un animal de sangre caliente, tal como un ser humano.

De este modo, según un aspecto adicional de la invención, se proporciona un compuesto de fórmula **(I)** o **(I')**, o una sal farmacéuticamente aceptable del mismo, para uso en el tratamiento de una infección bacteriana en un animal de sangre caliente, tal como un ser humano.

De este modo, según un aspecto adicional de la invención, se proporciona un compuesto de fórmula **(I)** o **(I')**, o una sal farmacéuticamente aceptable del mismo, para uso en el tratamiento de una infección bacteriana, seleccionada de neumonía adquirida en la comunidad, neumonía adquirida en el hospital, infecciones de la piel y de la estructura de la piel, exacerbación aguda de bronquitis crónica, sinusitis aguda, otitis media aguda, septicemia

relacionada con cateterismo, neutropenia febril, osteomielitis, endocarditis, infecciones del aparato urinario e infecciones provocadas por bacterias resistentes a fármacos tales como Streptococcus pneumoniae resistente a penicilina, Staphylococcus aureus resistente a meticilina, Staphylococcus epidermidis resistente a meticilina y enterococos resistentes a vancomicina, en un animal de sangre caliente, tal como un ser humano.

A fin de usar un compuesto de la fórmula **(I)** o **(I')**, o una sal farmacéuticamente aceptable del mismo (en lo sucesivo en esta sección que se refiere a composición farmacéutica, "un compuesto de esta invención") para el tratamiento terapéutico (incluyendo el profiláctico) de mamíferos, incluyendo seres humanos, en particular en el tratamiento de una infección, normalmente se formula según la práctica farmacéutica estándar como una composición farmacéutica.

Por lo tanto, en otro aspecto, la presente invención proporciona una composición farmacéutica que comprende un compuesto de la fórmula **(I) o (I')**, o una sal farmacéuticamente aceptable del mismo, y un diluyente o vehículo farmacéuticamente aceptable.

Según un aspecto adicional de la invención, se proporciona una composición farmacéutica que comprende un compuesto de fórmula **(I)** o **(I')**, como se define aquí anteriormente, o una sal farmacéuticamente aceptable del mismo, en asociación con un excipiente o vehículo farmacéuticamente aceptable para uso en la producción de un efecto antibacteriano en un animal de sangre caliente, tal como un ser humano.

Según un aspecto adicional de la invención, se proporciona una composición farmacéutica que comprende un compuesto de fórmula **(I)** o **(I')**, como se define aquí anteriormente, o una sal farmacéuticamente aceptable del mismo, en asociación con un excipiente o vehículo farmacéuticamente aceptable para uso en la inhibición de ADN girasa y / o topoisomerasa IV bacterianas en un animal de sangre caliente, tal como un ser humano.

Según un aspecto adicional de la invención, se proporciona una composición farmacéutica que comprende un compuesto de fórmula **(I)** o **(I')**, como se define aquí anteriormente, o una sal farmacéuticamente aceptable del mismo, en asociación con un excipiente o vehículo farmacéuticamente aceptable para uso en el tratamiento de una infección bacteriana en un animal de sangre caliente, tal como un ser humano.

Según un aspecto adicional de la invención, se proporciona una composición farmacéutica que comprende un compuesto de fórmula **(I)** o **(I')**, como se define aquí anteriormente, o una sal farmacéuticamente aceptable del mismo, en asociación con un

excipiente o vehículo farmacéuticamente aceptable para uso en el tratamiento de una infección bacteriana, seleccionada de neumonía adquirida en la comunidad, neumonía adquirida en el hospital, infecciones de la piel y de la estructura de la piel, exacerbación aguda de bronquitis crónica, sinusitis aguda, otitis media aguda, septicemia relacionada con cateterismo, neutropenia febril, osteomielitis, endocarditis, infecciones del aparato urinario e infecciones provocadas por bacterias resistentes a fármacos tales como Streptococcus pneumoniae resistente a penicilina, Staphylococcus aureus resistente a meticilina, Staphylococcus epidermidis resistente a meticilina y enterococos resistentes a vancomicina, en un animal de sangre caliente, tal como un ser humano.

Las composiciones de la invención pueden estar en una forma adecuada para uso oral (por ejemplo, como comprimidos, tabletas, cápsulas duras o blandas, suspensiones acuosas u oleosas, emulsiones, polvos o gránulos dispersables, jarabes o elixires), para uso tópico (por ejemplo, como cremas, ungüentos, geles, o suspensiones o disoluciones acuosas u oleosas), para administración mediante inhalación (por ejemplo, como un polvo finamente dividido o un aerosol líquido), para administración por insuflación (por ejemplo, como un polvo finamente dividido) o para administración parenteral (por ejemplo, como una disolución acuosa u oleosa estéril para dosificación intravenosa, subcutánea, intramuscular, o como un supositorio para dosificación rectal).

Las composiciones de la invención se pueden obtener mediante procedimientos convencionales usando excipientes farmacéuticos convencionales, bien conocidos en la técnica. De este modo, las composiciones destinadas a uso oral pueden contener, por ejemplo, uno o más agentes colorantes, edulcorantes, saborizantes y/o conservantes.

Los excipientes adecuados farmacéuticamente aceptables para una formulación en comprimidos incluyen, por ejemplo, diluyentes inertes tales como lactosa, carbonato de sodio, fosfato de calcio o carbonato de calcio, agentes granulantes y disgregantes tales como almidón de maíz o ácido algínico; agentes aglutinantes tales como almidón; agentes lubricantes tales como estearato de magnesio, ácido esteárico o talco; agentes conservantes tales como p-hidroxibenzoato de etilo o de propilo, y antioxidantes, tales como ácido ascórbico. Las formulaciones en comprimidos pueden estar recubiertas o no recubiertas, ya sea para modificar su desintegración y la absorción subsiguiente del ingrediente activo en el tubo digestivo, o para mejorar su estabilidad y/o aspecto, usando en cualquier caso agentes de revestimiento convencionales y procedimientos bien conocidos en la técnica.

Las composiciones para uso oral pueden estar en forma de cápsulas de gelatina duras, en las que el ingrediente activo se mezcla con un diluyente sólido inerte, por ejemplo carbonato de calcio, fosfato de calcio o caolín; o como cápsulas de gelatina blandas, en las que el ingrediente activo se mezcla con agua o un aceite, tal como aceite de cacahuete, parafina líquida, o aceite de oliva.

Las suspensiones acuosas generalmente contienen el ingrediente activo en forma de polvo fino, junto con uno o más agentes de suspensión, tales como carboximetilcelulosa sódica, metilcelulosa, hidroxipropilmetilcelulosa, alginato sódico, polivinilpirrolidona, goma de tragacanto y goma arábiga; agentes dispersantes o humectantes, tales como lecitina o productos de condensación de un óxido de alquileno con ácidos grasos (por ejemplo estearato de polioxietileno), o productos de condensación de óxido de etileno con alcoholes alifáticos de cadena larga, por ejemplo heptadecaetilenoxicetanol, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos con un hexitol, tales como monooleato de polioxietilensorbitol, o productos de condensación de óxido de etileno con alcoholes alifáticos de cadena larga, por ejemplo heptadecaetilenoxicetanol, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos con un hexitol, tales como monooleato de polioxietilensorbitol, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos con anhídridos de hexitol, por ejemplo monooleato de polietilensorbitán. Las suspensiones acuosas también pueden contener uno o más agentes conservantes (tales como p-hidroxibenzoato de etilo o de propilo), antioxidantes (tales como ácido ascórbico), agentes colorantes, agentes aromatizantes, y/o agentes edulcorantes (tales como sacarosa, sacarina o aspartamo).

Las suspensiones oleosas se pueden formular suspendiendo el ingrediente activo en un aceite vegetal (tal como aceite de cacahuete, 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. Se pueden añadir agentes edulcorantes, tales como los expuestos anteriormente, y agentes aromatizantes, para proporcionar una preparación oral de sabor agradable. Estas composiciones se pueden conservar mediante adición de un antioxidante, tal como ácido ascórbico.

Los polvos y gránulos dispersables, adecuados para la preparación de una suspensión acuosa mediante adición de agua, generalmente contienen el ingrediente activo junto con un agente dispersante o humectante, un agente de suspensión, y uno o más conservantes. Los

agentes dispersantes o humectantes y los agentes de suspensión adecuados se ejemplifican mediante los ya mencionados anteriormente. También pueden estar presentes excipientes adicionales tales como agentes edulcorantes, aromatizantes 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 cacahuete, o un aceite mineral, tal como por ejemplo parafina líquida, o una mezcla de cualquiera de estos. Los agentes emulsionantes adecuados pueden ser, por ejemplo, gomas de origen natural, tales como goma arábiga o goma de tragacanto, fosfátidos de origen natural, tales como haba de soja, lecitina, y ésteres o ésteres parciales derivados de ácidos grasos con anhídridos de hexitol (por ejemplo monooleato de sorbitán), y productos de condensación de los mencionados ésteres parciales con óxido de etileno, tales como monooleato de polioxietilensorbitán. Las emulsiones también pueden contener agentes edulcorantes, aromatizantes y conservantes.

Los jarabes y elixires se pueden formular con agentes edulcorantes, tales como glicerol, propilenglicol, sorbitol, aspartamo o sacarosa, y también pueden contener un agente emoliente, un conservante, un aromatizante y/o un colorante.

Las composiciones farmacéuticas también pueden estar en forma de una suspensión acuosa u oleosa estéril inyectable, que se puede formular según procedimientos conocidos usando uno o más de los agentes dispersantes o humectantes y agentes de suspensión apropiados, que se han mencionado anteriormente. Una preparación inyectable estéril también puede ser una disolución o suspensión inyectable estéril en un diluyente o disolvente no tóxico, parenteralmente aceptable, por ejemplo una disolución en 1,3-butanodiol.

Las composiciones para la administración mediante inhalación pueden estar en forma de un aerosol a presión convencional, montado para administrar el ingrediente activo ya sea como un aerosol que contiene un sólido finamente dividido o como gotitas líquidas. Se pueden usar propelentes convencionales de aerosoles, tales como hidrocarburos fluorados volátiles o hidrocarburos, y el dispositivo de aerosol se monta convenientemente para suministrar una cantidad medida de ingrediente activo.

Para una información adicional sobre la formulación, refiérase el lector al Capítulo 25.2 en el Volumen 5 de Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board). Pergamon Press 1990.

La cantidad de ingrediente activo que se combina con uno o más excipientes para producir una forma de dosificación individual variará necesariamente dependiendo del

hospedante tratado y de la vía particular de administración. Por ejemplo, una formulación destinada a la administración oral a seres humanos generalmente contendrá, por ejemplo, de 0,5 mg a 2 g de agente activo, formulado con una cantidad apropiada y conveniente de excipientes, que puede variar de alrededor de 5 hasta alrededor de 98 por ciento en peso de la composición total. Las formas unitarias de dosificación generalmente contendrán alrededor de 1 mg hasta alrededor de 500 mg de un ingrediente activo. Para una información adicional sobre vías de administración y regímenes de dosificación, refiérase el lector al Capítulo 25.3 en el Volumen 5 de Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

Los compuestos de la invención descritos aquí se pueden aplicar como una terapia individual, o pueden implicar, además de un compuesto de la invención, una o más sustancias y/o tratamientos. Tal tratamiento conjunto se puede lograr por medio de la administración simultánea, secuencial o separada de los componentes individuales del tratamiento. Cuando la administración es secuencial o separada, el retraso en la administración del segundo componente no debería de ser tal que se perdiese el efecto beneficioso de la combinación. Las clases y sustancias adecuadas se pueden seleccionar de una o más de las siguientes:

i) otros agentes antibacterianos, por ejemplo macrólidos, por ejemplo eritromicina, azitromicina o claritromicina; quinolonas, por ejemplo ciprofloxacina o levofloxacina; β-lactamas, por ejemplo penicilinas, por ejemplo amoxicilina o piperacilina; cefalosporinas, por ejemplo ceftriaxona o ceftazidima; carbapenems, por ejemplo meropenem o imipenem etc; aminoglicósidos, por ejemplo gentamicina o tobramicina; u oxazolidinonas; y/o

ii) agentes antiinfecciosos por ejemplo, un triazol antifúngico por ejemplo o amfotericina; y/o

iii) compuestos terapéuticos proteínicos biológicos, por ejemplo anticuerpos, citocinas, productos proteínicos que incrementan el efecto bactericida/permeabilidad (BPI); y/o

iv) inhibidores de la bomba de eflujo.

Por lo tanto, en un aspecto adicional de la invención se proporciona un compuesto de la fórmula **(I)** o **(I')**, o una sal farmacéuticamente aceptable del mismo, y un agente quimioterapéutico seleccionado de:

i) uno o más agentes antibacterianos adicionales; y/o

ii) uno o más agentes antiinfecciosos; y/o

iii) compuestos terapéuticos proteínicos biológicos, por ejemplo anticuerpos, citocinas, productos proteínicos que incrementan el efecto bactericida/permeabilidad (BPI); y/o

iv) uno o más inhibidores de la bomba de eflujo.

En otra realización, la invención se refiere a un método para tratar una infección bacteriana en un animal, tal como un ser humano, que comprende administrar al animal una cantidad eficaz de un compuesto de fórmula **(I)** o **(I')**, o una sal farmacéuticamente aceptable del mismo, y un agente quimioterapéutico seleccionado de:

i) uno o más agentes antibacterianos adicionales; y/o

ii) uno o más agentes antiinfecciosos; y/o

iii) compuestos terapéuticos proteínicos biológicos, por ejemplo anticuerpos, citocinas, productos proteínicos que incrementan el efecto bactericida/permeabilidad (BPI); y/o

iv) uno o más inhibidores de la bomba de eflujo.

Como se ha expuesto anteriormente, el tamaño de la dosis requerida para el tratamiento terapéutico o profiláctico de una enfermedad particular variará necesariamente dependiendo del hospedante tratado, de la vía de administración, de la gravedad de la enfermedad que se esté tratando, y de si se administra o no un agente quimioterapéutico adicional en combinación con un compuesto de la invención. Preferiblemente, se emplea una dosis diaria en el intervalo de 1-50 mg/kg. Sin embargo, la dosis diaria variará necesariamente dependiendo del hospedante tratado, de la vía particular de administración, de la gravedad de la enfermedad que se esté tratando, y de si se administra o no un agente quimioterapéutico adicional en combinación con un compuesto de la invención. En consecuencia, la dosis óptima se puede determinar por el médico que trata a cualquier paciente particular.

Como se señala anteriormente, una realización de la presente invención se dirige al tratamiento o prevención de enfermedades provocadas por infecciones bacterianas, en las que la bacteria comprende una enzima GyrB ATPasa o topoisomerasa IV ATPasa. "Tratar un sujeto que padece una enfermedad provocada por una infección bacteriana" incluye lograr, parcial o sustancialmente, uno o más de lo siguiente: reducir o aliviar la progresión, gravedad y/o duración de la infección, detener la expansión de la infección, aliviar o mejorar un síntoma clínico o indicador asociado con la infección (tal como componentes de tejidos o del suero), y prevenir la reaparición de la infección.

Como se usa aquí, la expresión "prevenir una infección bacteriana" se refiere a reducir el riesgo de adquirir la infección, o reducir o inhibir la recurrencia de la infección. En una realización preferida, un compuesto de la invención se administra como una medida preventiva a un paciente, preferiblemente un ser humano, antes de que se lleve a cabo un procedimiento quirúrgico sobre el paciente, para prevenir la infección.

Como se usa aquí, la expresión "cantidad eficaz" referida a una cantidad de un compuesto de esta invención para tratar o prevenir una infección bacteriana es una cantidad que es suficiente para prevenir el comienzo de una infección, reducir o aliviar la gravedad, duración, o progresión, de una infección, prevenir el avance de una infección, provocar la regresión de una infección, prevenir la recurrencia, desarrollo, comienzo o progresión de un síntoma asociado con una infección, o potenciar o mejorar el efecto (o efectos) profiláctico(s) o terapéutico(s) de otra terapia.

Además de su uso en medicina terapéutica, los compuestos de la fórmula **(I)**, y sus sales farmacéuticamente aceptables, son útiles también como herramientas farmacológicas en el desarrollo y la estandarización de sistemas de ensayo *in vitro* e *in vivo* para la evaluación de los efectos de los inhibidores de ADN girasa y / o topoisomerasa IV en animales de laboratorio, tales como gatos, perros, conejos, monos, ratas y ratones, como parte de la investigación para la búsqueda de nuevos agentes terapéuticos.

En lo anterior también se aplican otras características de composición farmacéutica, de procedimiento, de método, de uso y de fabricación de medicamento, las realizaciones alternativas y particulares de los compuestos de la invención descritos aquí.

Ejemplo

La invención se ilustra ahora, pero no se limita, mediante los siguientes Ejemplos, en los que, excepto que se establezca de otro modo:

(i) las evaporaciones se llevaron a cabo mediante evaporación giratoria *a vacío*, y los procedimientos de tratamiento se llevaron a cabo después de la eliminación de residuos sólidos mediante filtración;

(ii) las operaciones se llevaron a cabo generalmente a temperatura ambiente, esto es, típicamente en el intervalo de 18-26°C y sin la exclusión de aire, excepto que se establezca de otro modo, o excepto que la persona experta trabajase de otro modo en una atmósfera inerte;

(iii) se usó cromatografía en columna (mediante el procedimiento ultrarrápido) para purificar los compuestos, y se realizó en sílice Kieselgel de Merck (Art. 9385), excepto que se establezca de otro modo;

(iv) los rendimientos se dan con fines ilustrativos solamente, y no son necesariamente los máximos obtenibles;

la estructura de los productos finales de la invención se confirmó generalmente mediante técnicas de RMN y de espectro de masas; se dan los espectros de resonancia magnética de protón, y se determinaron generalmente en DMSO-d_6, excepto que se establezca de otro modo, usando un espectrómetro Bruker DRX-300 que funciona a una potencia de campo de 300 MHz. Los desplazamientos químicos se dan en partes por millón, campo abajo de tetrametilsilano como patrón interno (escala δ), y de este modo se muestran las multiplicidades de los picos: s, singlete; d, doblete; AB o dd, doblete de doblete; dt, doblete de tripletes; dm, doblete de multipletes, t, triplete; m, multiplete; br, ancho; los datos espectrales de masas mediante bombardeo con átomos rápidos (FAB) se obtuvieron generalmente usando un espectrómetro Platform (suministrado por Micromass) que funciona en modo de electropulverización, y, cuando sea apropiado, se recogieron los datos de iones positivos o los datos de iones negativos, o usando un LC/MSD Agilent serie 1100, equipado con Sedex 75ELSD, que funciona en modo de ionización química a presión atmosférica, y, cuando sea apropiado, se recogieron los datos de iones positivos o los datos de iones negativos; los espectros de masas se llevaron a cabo con una energía electrónica de 70 electrón-voltios en el modo de ionización química (CI) usando una sonda de exposición directa; cuando se indica, la ionización se efectuó mediante impacto con electrones (EI), bombardeo con átomos rápidos (FAB) o electropulverización (ESP); se dan los valores para m/z; generalmente, sólo se dan a conocer los iones que indican la masa progenitora;

(vi) cada Intermediario se purificó al estándar requerido para la etapa subsiguiente, y se caracterizó con suficiente detalle para confirmar que la estructura asignada era la correcta; la pureza se determinó mediante cromatografía de líquidos a altas presiones, cromatografía de capa fina, o RMN; y la identidad se determinó mediante espectroscopía de infrarrojos (IR), espectroscopía de masas o espectroscopía de RMN, según sea apropiado;

(vii) se pueden usar las siguientes abreviaturas:

ACN es acetonitrilo;

$CDCl_3$ es cloroformo deuterado;

DBU es 1,8-diazabiciclo[5.4.0]undec-7-eno;

DCM es diclorometano;

DIEA es diisopropiletilamina;

DMF es *N,N*-dimetilformamida;

DMSO es dimetilsulfóxido;

EDC es 1-etil-3-(3-dimetilaminopropil)carbodiimida;

EtOAc es acetato de etilo;

EtOH es etanol;

HATU es N-óxido de hexafluorofosfato de N-[(dimetilamino)-1H,2,3-triazolo[4,5-b-]piridin-1-ilmetilen]-N-metilmetanaminio;

HOBT es 1-hidroxibenzotriazol;

MeOH es metanol;

MS es espectroscopía de masas;

RT o rt es temperatura ambiente;

SM es material de partida;

TFA es ácido trifluoroacético;

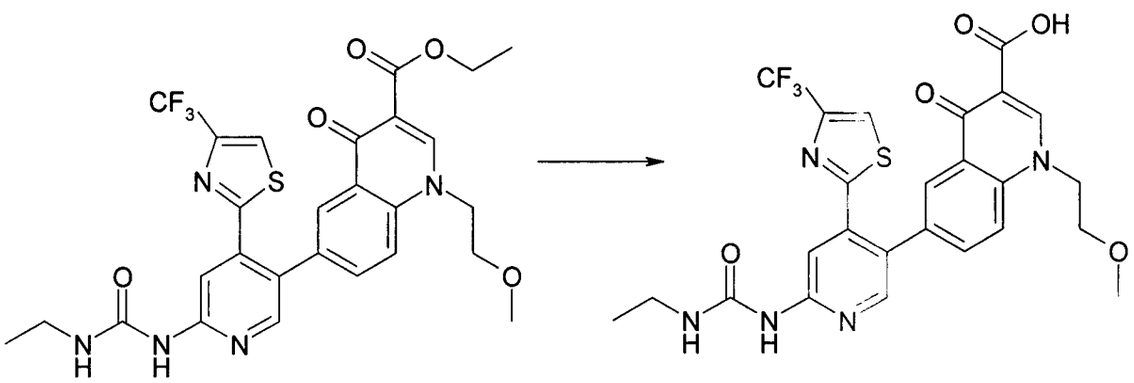
TFAA es anhídrido trifluoroacético;

THF es tetrahidrofurano; y

(viii) las temperaturas se dan como °C.

Ejemplo 1

Ácido 6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(2-metoxietil)-4-oxo-1,4-dihidroquinolin-3-carboxílico



6-(6-(3-Etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(2-metoxietil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo (Ejemplo 51, 0,090 g, 0,15 mmoles) y LiOH (0,092 ml,

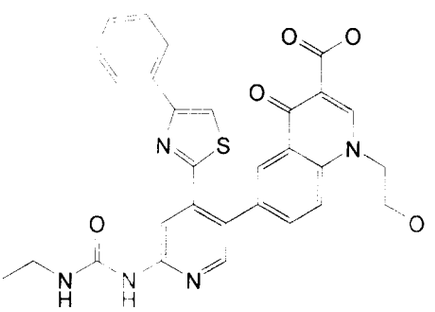
0,18 mmoles) se combinaron en MeOH (1 ml)/THF (1 ml) y se calentaron hasta 100 °C en el microondas durante 15 min. La mezcla de reacción se enfrió hasta la temperatura ambiente, se diluyó con agua (1.000 ml) y se calentó hasta que el compuesto se disolvió. La disolución resultante se filtró, y el filtrado se concentró entonces a presión reducida para eliminar el metanol. Se añadió HCl (1 N), y el precipitado resultante se recogió mediante filtración, se lavó con agua y se secó toda la noche para producir un sólido blanco (0,063 g).

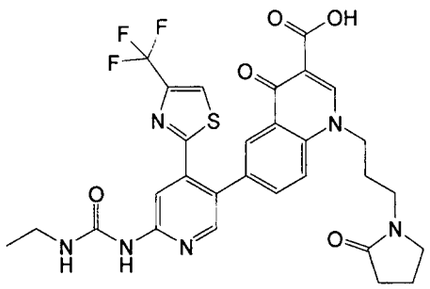
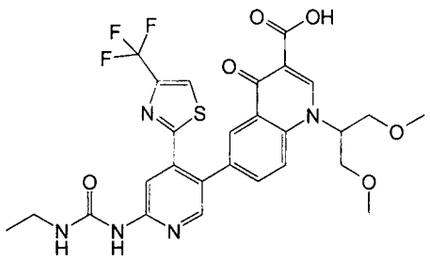
MS (ES) $(M+H)^+$: 562 para $C_{25}H_{22}F_3N_5O_5S$;

RMN: 1,11 (t, 3H), 3,19-3,23 (m, 5H), 3,71 (d, 2H), 4,81 (q, 2H), 7,60 (dd, 1H), 7,86 (d, 1H), 8,12 (d, 1H), 8,22 (s, 1H), 8,31 (s, 1H), 8,38 (s, 1H), 8,52 (s, 1H), 8,96 (s, 1H), 8,49 (s, 1H).

Ejemplos 2-4

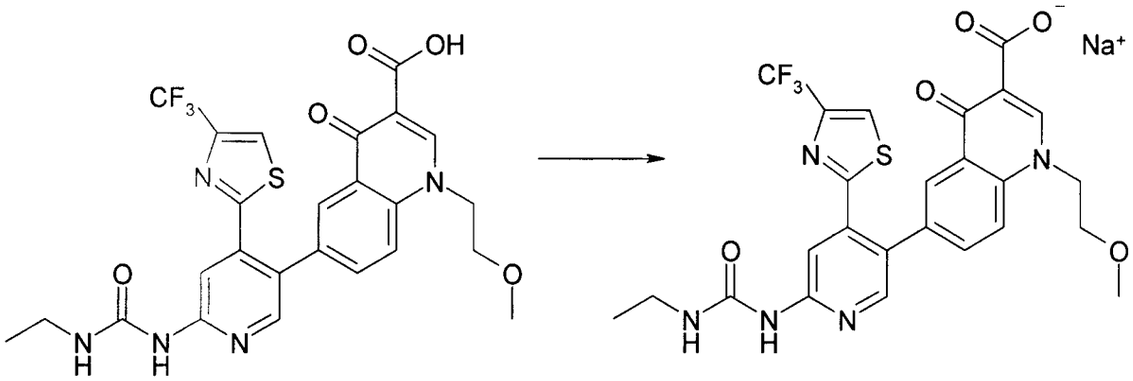
Los siguientes Ejemplos se prepararon mediante el procedimiento descrito en el Ejemplo 1 a partir de los materiales de partida (SM) indicados.

Ej.	Compuesto	Datos	SM
2	Ácido 6-(6-(3-etilureido)-4-(4-feniltiazol-2-il)piridin-3-il)-1-(2-metoxietil)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ES) $(M+H)^+$: 570 para $C_{30}H_{27}N_5O_5S$ RMN: 1,12 (t, 3H), 3,18-3,21 (m, 5H), 3,69 (t, 2H), 4,63 (q, 2H), 7,31-7,39 (m, 3H), 7,75-7,83 (m, 4H), 7,88 (d, 1H), 8,14 (s, 1H), 8,29 (s, 3H), 8,81 (s, 1H), 9,47 (s, 1H).	Ejemplo 52

Ej.	Compuesto	Datos	SM
3	Ácido 6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-(3-(2-oxopirrolidin-1-il)propil)-1,4-dihidroquinolin-3-carboxílico 	MS (ES) $(M+H)^+$: 629 para $C_{29}H_{27}F_3N_6O_5S$	Ejemplo 53
4	Ácido 1-(1,3-dimetoxipropan-2-il)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ES) $(M+H)^+$: 606 para $C_{27}H_{26}F_3N_5O_6S$	Ejemplo 54

Ejemplo 5

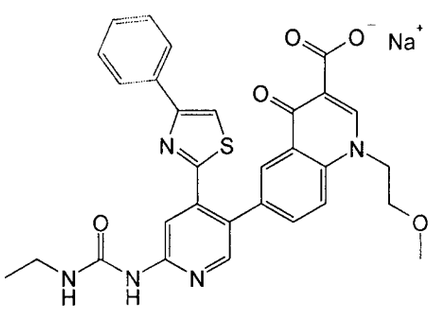
6-(6-(3-Etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(2-metoxietil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de sodio

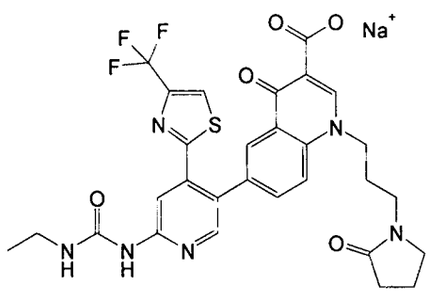
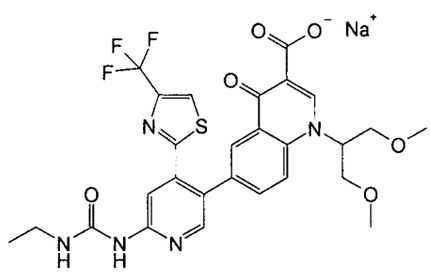


Se suspendió ácido 6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(2-metoxietil)-4-oxo-1,4-dihidroquinolin-3-carboxílico (0,032 g, 0,06 mmoles, Ejemplo 1) en MeOH (1,0 ml)/THF (1,0 ml). Se añadió NaOH 1N (0,057 ml, 0,06 mmoles). Una vez en disolución, la mezcla de reacción se concentró a presión reducida y se secó durante varias horas para producir un sólido blanco (0,030 g).

Ejemplos 6-8

Los siguientes Ejemplos se prepararon mediante el procedimiento descrito en el Ejemplo 5 a partir de los materiales de partida (SM) indicados.

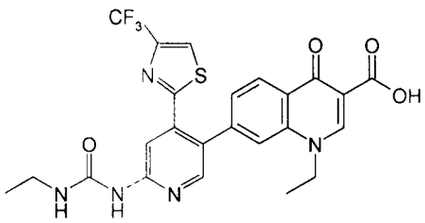
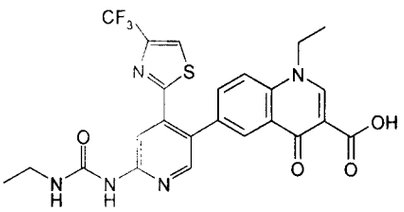
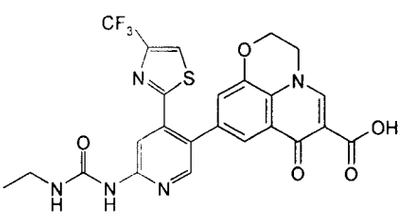
Ej.	**Compuesto**	**Datos**	**SM**
6	6-(6-(3-etilureido)-4-(4-feniltiazol-2-il)piridin-3-il)-1-(2-metoxietil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de sodio 	MS (ES) $(M+H)^+$: 570 para $C_{30}H_{27}N_5O_5S[Na+]$ RMN: 1,12 (t, 3H), 3,18-3,21 (m, 5H), 3,69 (t, 2H), 4,60 (q, 2H), 7,31-7,39 (m, 3H), 7,75-7,83 (m, 4H), 7,88 (d, 1H), 8,14 (s, 1H), 8,29 (s, 3H), 8,81 (s, 1H), 9,49 (s, 1H).	Ejemplo 2

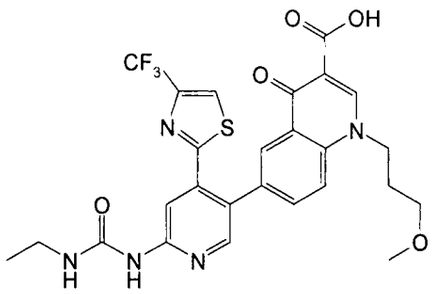
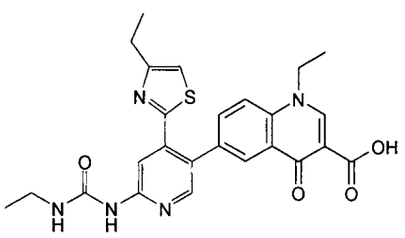
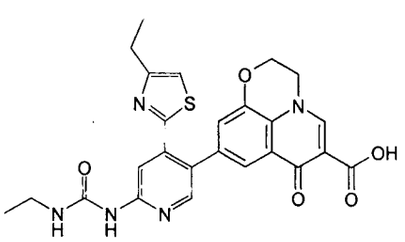
Ej.	Compuesto	Datos	SM
7	Sal sódica del ácido 6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-(3-(2-oxopirrolidin-1-il)propil)-1,4-dihidroquinolin-3-carboxílico 	MS (ES) $(M+H)^+$: 629 para $C_{29}H_{27}F_3N_6O_5S$ [Na+] RMN: 1,11 (t, 3H), 1,94 (m, 5H), 2,22 (t, 3H), 3,31-3,36 (m, 4H), 4,35 (q, 2H), 7,60 (d, 1H), 7,80 (d, 1H), 8,20 (m, 1H), 8,25 (s, 1H), 8,32 (s, 1H), 8,38 (s, 1H), 8,44 (s, 1H), 8,66 (s, 1H), 10,18 (s, 1H).	Ejemplo 3
8	Sal sódica del ácido 1-(1,3-dimetoxipropan-2-il)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ES) $(M+H)^+$: 570 para $C_{27}H_{26}F_3N_5O_6S \cdot$[Na+]	Ejemplo 4

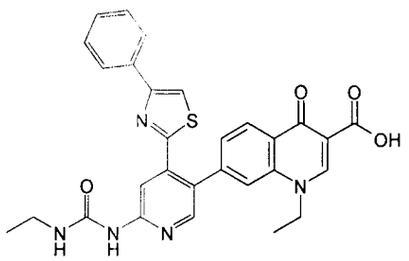
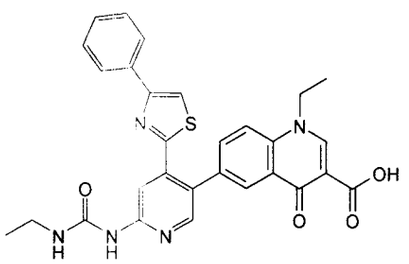
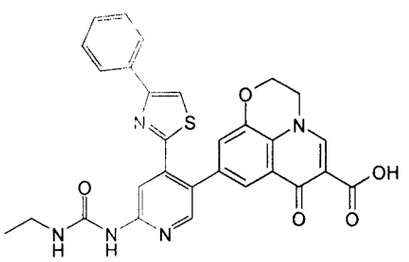
Ejemplos 9-32

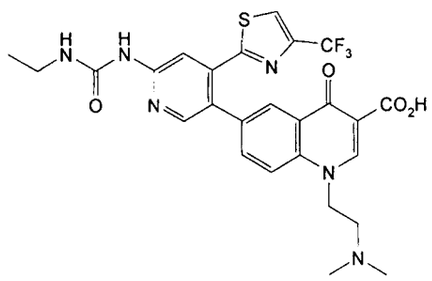
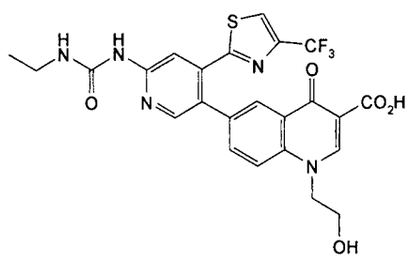
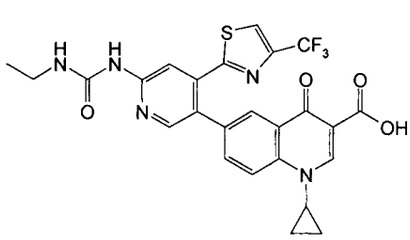
Los siguientes Ejemplos se prepararon mediante el procedimiento descrito en el Ejemplo 1 a partir de los materiales de partida (SM) indicados.

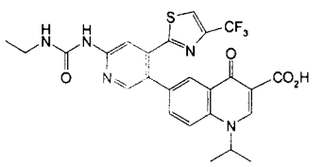
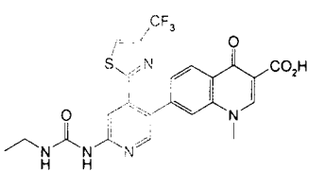
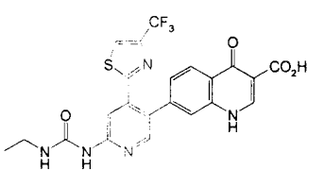
Ej.	Compuesto	Datos	SM

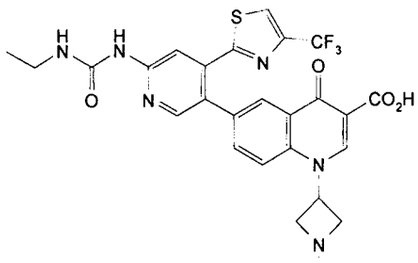
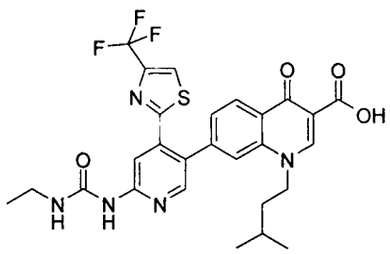
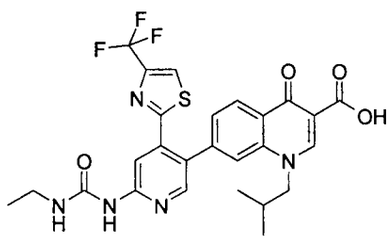
Ej.	Compuesto	Datos	SM
9	Ácido 1-etil-7-(6-(3-etilureido)-4-(4-trifluorometiltiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 532 (MH^+) para $C_{24}H_{20}F_3N_5O_4S$ RMN ^1H (d_6-DMSO): δ 1,11 (t, 3H), 1,24 (t, 3H), 3,21 (m, 2H), 4,58 (q, 2H), 7,56-7,61 (m, 2H), 8,07 (d, 1H), 8,24 (s, 1H), 8,38-8,42 (m, 2H), 8,51 (d, 1H), 9,09 (s, 1H), 9,55 (s, 1H)	Ejemplo 42
10	Ácido 1-etil-6-(6-(3-etilureido)-4-(4-trifluorometiltiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 532 (MH^+) para $C_{24}H_{20}F_3N_5O_4S$ RMN ^1H (d_6-DMSO): δ 1,11 (t, 3H), 1,40 (t, 3H), 3,20 (m, 2H), 4,64 (q, 2H), 7,63 (bt, 1H), 7,85 (d, 1H), 8,11 (d, 1H), 8,23 (s, 1H), 8,32 (d, 1H), 8,37 (s, 1H), 8,51 (d, 1H), 9,11 (s, 1H), 9,51 (s, 1H)	Ejemplo 45
11	Ácido 9-(6-(3-etilureido)-4-(4-trifluorometiltiazol-2-il)piridin-3-il)-7-oxo-3,7-dihidro-2H-[1,4]oxazino[2,3,4-ij]quinolin-6-carboxílico 	MS (ESP): 546 (MH^+) para $C_{24}H_{18}F_3N_5O_5S$ RMN ^1H (d_6-DMSO): δ 1,11 (t, 3H), 3,17-3,24 (m, 2H), 4,51-4,69 (m, 4H), 7,45 (d, 1H), 7,62 (bt, 1H), 7,80 (d, 1H), 8,22 (s, 1H), 8,32 (s, 1H), 8,53 (d, 1H), 8,99 (s, 1H), 9,48 (s, 1H).	Ejemplo 48

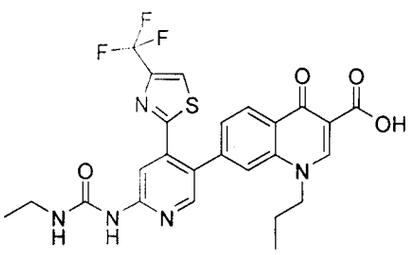
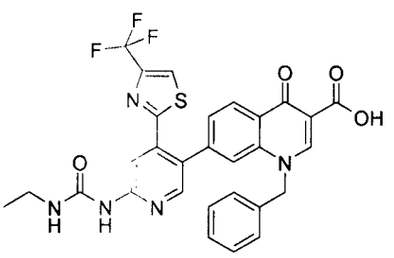
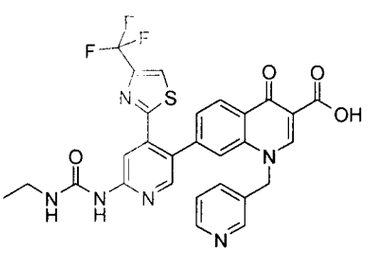
Ej.	Compuesto	Datos	SM
12	Ácido 6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(3-metoxipropil)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 576 (MH^+) para $C_{26}H_{24}F_3N_5O_5S$ RMN ^1H (300 MHz, DMSO-d6) δ 1,11 t, J = 7 Hz, 3H), 2,05 (m, 2H), 3,18 (m, 4H), 3,20 (s, 3H), 4,65 (m, 2H), 7,61 (m, 1H), 7,88 (m, 1H), 8,05 (m, 1H), 8,22 (s, 1H), 8,34 (m, 1H), 8,37 (s, 1H), 8,52 (s, 1H), 9,02 (s, 1H), 9,49 (s, 1H), 15,06 (br s, 1H).	Ejemplo 55
13	Ácido 1-etil-6-(6-(3-etilureido)-4-(4-etiltiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 492 (MH^+) para $C_{25}H_{25}N_5O_4S$ RMN ^1H (d_6-DMSO): δ 1,02-1,14 (m, 6H), 1,43 (t, 3H), 2,64 (q, 2H), 3,23 (m, 2H), 4,63 (q, 2H), 7,35 (s, 1H), 7,72 (bt, 1H), 7,82 (d, 1H), 8,07 (d, 1H), 8,13 (s, 1H), 8,26-8,30 (m, 2H), 9,10 (s, 1H), 9,43 (s, 1H)	Ejemplo 46
14	Ácido 9-(6-(3-etilureido)-4-(4-etiltiazol-2-il)piridin-3-il)-7-oxo-3,7-dihidro-2H-[1,4]oxazino[2,3,4-ij]quinolin-6-carboxílico 	MS (ESP): 506 (MH^+) para $C_{25}H_{23}N_5O_5S$ RMN ^1H (d_6-DMSO): δ 1,11 (t, 6H), 2,67 (q, 2H), 3,21 (m, 2H), 4,58 (m, 4H), 7,37 (m, 2H), 7,73 (bt, 1H), 7,76 (d, 1H), 8,12 (s, 1H), 8,26 (s, 1H), 8,98 (s, 1H), 9,42 (s, 1H)	Ejemplo 49

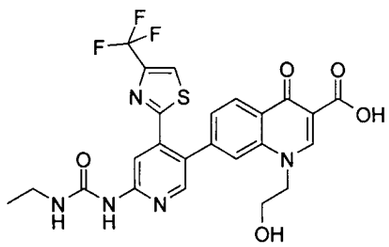
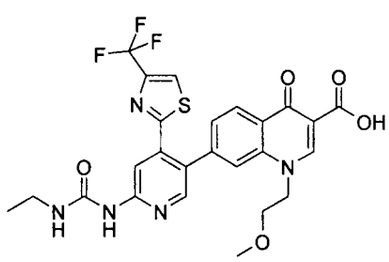
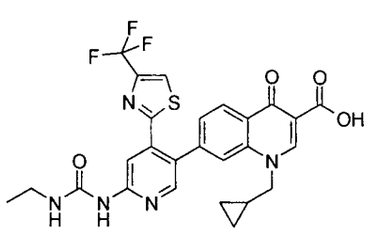
Ej.	Compuesto	Datos	SM
15	Ácido 1-etil-7-(6-(3-etilureido)-4-(4-feniltiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 540 (MH^+) para $C_{29}H_{25}N_5O_4S$ RMN ^1H (d_6-DMSO): δ 1,08-1,27 (m, 6H), 3,15-3,24 (m, 2H), 4,58 (bq, 2H), 7,26-7,35 (m, 3H), 7,59 (d, 1H), 7,61-7,70 (m, 3H), 8,08 (s, 1H), 8,18 (s, 1H), 8,27 (s, 1H), 8,35-8,41 (m, 2H), 9,08 (s, 1H), 9,51 (s, 1H)	Ejemplo 44
16	Ácido 1-etil-6-(6-(3-etilureido)-4-(4-feniltiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 540 (MH^+) para $C_{29}H_{25}N_5O_4S$ RMN ^1H (d_6-DMSO): δ 1,12 (t, 3H), 1,41 (t, 3H), 3,16-3,28 (m, 2H), 4,60 (bq, 2H), 7,31-7,39 (m, 3H), 7,71-7,81 (m, 4H), 8,05 (d, 1H), 8,17 (s, 1H), 8,29-8,36 (m, 2H), 9,05 (s, 1H), 9,61 (br s, 1H)	Ejemplo 47
17	Ácido 9-(6-(3-etilureido)-4-(4-feniltiazol-2-il)piridin-3-il)-7-oxo-3,7-dihidro-2H-[1,4]oxazino[2,3,4-ij]quinolin-6-carboxílico 	MS (ESP): 554 (MH^+) para $C_{29}H_{23}N_5O_5S$ RMN ^1H (d_6-DMSO): δ 1,09 (t, 3H), 3,19-3,26 (m, 2H), 4,59 (m, 4H), 7,34-7,38 (m, 3H), 7,43 (d, 1H), 7,70 (bt, 1H), 7,80 (d, 1H), 7,83 (d, 1H), 7,87 (d, 1H), 8,18 (s, 1H), 8,26 (s, 1H), 8,29 (s, 1H), 8,99 (s, 1H), 9,45 (s, 1H)	Ejemplo 50

Ej.	Compuesto	Datos	SM
18	Ácido 1-(2-(dimetilamino)etil)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 575 (M+1) para $C_{26}H_{25}F_3N_6O_4S$ RMN ^{1}H (DMSO-d_6): 1,11 (t, *J*=7,20 Hz, 3H); 2,87 (br. s., 6H); 3,13 - 3,28 (m, 2H); 3,57 (br. s., 2H); 5,01 (br. s., 2H); 7,64 (br. s., 1H); 7,92 (dd, *J*=8,72, 1,64 Hz, 1H); 8,14 - 8,28 (m, 2H); 8,28 - 8,41 (m, 2H); 8,54 (s, 1H); 9,17 (s, 1H); 9,51 (s, 1H); 10,74 (br. s., 1H); 14,91 (br. s., 1H)	Ejemplo 56
19	Ácido 6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(2-hidroxietil)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 548 (M+1) para $C_{24}H_{20}F_3N_5O_5S$ RMN ^{1}H (DMSO-d_6) δ: 1,11 (t, *J*=7,20 Hz, 3H); 3,15 - 3,28 (m, 2H); 3,73 - 3,83 (m, 2H); 4,59 - 4,72 (m, 2H); 5,10 (t, *J*=5,56 Hz, 1H); 7,62 (br. s., 1H); 7,86 (dd, *J*=8,97, 2,15 Hz, 1H); 8,13 (d, *J*=8,84 Hz, 1 H); 8,23 (s, 1H); 8,33 (d, *J*=2,27 Hz, 1H); 8,37 (s, 1 H); 8,52 (s, 1H); 8,94 (s, 1 H)	Ejemplo 57
20	Ácido 1-ciclopropil-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 544 (M+1) para $C_{25}H_{20}F_3N_5O_4S$ RMN ^{1}H (DMSO-d_6): 1,11 (t, *J*=7,20 Hz, 3H); 1,16 - 1,25 (m, 2H); 1,29 - 1,38 (m, 2H); 3,15 - 3,28 (m, 2H); 3,83 - 3,93 (m, 2H); 7,56 - 7,66 (m, 1H); 7,92 (dd, *J*=8,84, 2,02 Hz, 1 H); 8,23 (s, 1H); 8,27 - 8,39 (m, 2H); 8,52 (s, 1H); 8,80 (s, 1H); 9,48 (s, 1H)	Ejemplo 58

Ej.	Compuesto	Datos	SM
21	Ácido 6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-isopropil-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 546 (M+1) para $C_{25}H_{22}F_3N_5O_4S$ RMN ^{1}H (DMSO-d_6): 1,11 (t, J=7,20 Hz, 3H); 1,54 (d, J=5,81 Hz, 6H); 3,14 - 3,26 (m, 2H); 5,10 - 5,29 (m, 1H); 7,51 - 7,82 (m, 2H); 8,09 (br. s., 1H); 8,25 (s, 1H); 8,28 - 8,39 (m, 2H); 8,45 (br. s., 1H); 8,95 (s, 1H); 9,46 (s, 1H)	Ejemplo 59
22	Ácido 7-(6-(3-etilureido)-4(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-metil-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 518 (M+1) $C_{23}H_{18}F_3N_5O_4S$ RMN ^{1}H (DMSO-d_6): 1,11 (t, J=7,20 Hz, 3H); 3,15 - 3,26 (m, 2H); 4,08 (s, 3H); 7,51 (d, J=7,83 Hz, 1H); 7,55 - 7,63 (m, 1H); 8,04 (s, 1 H); 8,24 (s, 1H); 8,34 (d, J=8,34 Hz, 1H); 8,45 (s, 1 H); 8,53 (s, 1H); 9,08 (s, 1 H); 9,53 (s, 1H); 15,18 (s, 1H)	Ejemplo 60
23	Ácido 7-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 504 (M+1) $C_{22}H_{16}F_3N_5O_4S$ RMN ^{1}H (DMSO-d_6): 1,11 (t, J=7,07 Hz, 3H); 3,09 - 3,28 (m, 2H); 7,50 (d, J=8,34 Hz, 1H); 7,53 - 7,64 (m, 1H); 7,76 (s, 1H); 8,24 (s, 1H); 8,30 (d, J=8,34 Hz, 1H); 8,37 (s, 1H); 8,52 (s, 1H); 8,89 - 9,00 (m, 1H); 9,51 (s, 1H); 13,43 (br. s., 1H)	Ejemplo 61

Ej.	Compuesto	Datos	SM
24	Ácido 6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-metilazetidin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 573 (M+1) para $C_{26}H_{23}F_3N_6O_4S$ RMN ^{1}H (DMSO-d_6): 1,11 (t, J=7,07 Hz, 3H); 2,33 (s, 3H); 3,14 - 3,27 (m, 2H); 3,35 - 3,46 (m, 2H); 3,90 (t, J=6,69 Hz, 2H); 5,19 - 5,33 (m, 1H); 7,64 - 7,92 (m, 3H); 8,23 - 8,40 (m, 3H); 8,49 (s, 1H); 8,87 (s, 1H); 9,80 (br s, 1H)	Ejemplo 62
25	Ácido 7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-1-(3-metilbutil)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	RMN ^{1}H (400 MHz, DMSO-d_6): 0,83 (d, 6H), 1,13 (t, 3H), 1,44 (q, 2H), 1,55 (m, 1H), 3,21 (q, 2H), 4,52 (t, 2H), 7,56 (m, 1H), 7,63 (d, 1H), 7,93 (s, 1H), 8,25 (s, 1H), 8,40 (s, 1H), 8,43 (d, 1H), 8,51 (s, 1H), 9,06 (s, 1H), 9,48 (s, 1H).	Ejemplo 63
26	Ácido 7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-1-(2-metilpropil)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	RMN ^{1}H (400 MHz, DMSO-d_6): 0,75 (d, 6H), 1,13 (t, 3H), 1,64 (m, 1H), 3,21 (q, 2H), 4,33 (d, 2H), 7,59 (m, 4H), 7,94 (s, 1H), 8,19 (s, 1H), 8,40 (s, 1H), 8,43 (d, 1H), 8,53 (s, 1H), 9,00 (s, 1H), 9,49 (s, 1H).	Ejemplo 64

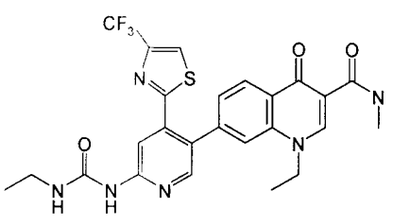
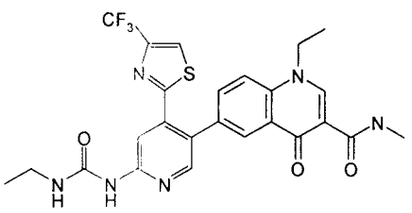
Ej.	Compuesto	Datos	SM
27	Ácido 7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-4-oxo-1-propil-1,4-dihidroquinolin-3-carboxílico 	RMN ^{1}H (400 MHz, DMSO-d_6): 0,79 (t, 3H), 1,11 (t, 3H), 1,55 (q, 2H), 3,21 (q, 2H), 4,48 (t, 2H), 7,60 (m, 2H), 8,00 (s, 1H), 8,21 (s, 1H), 8,41 (t, 2H), 8,51 (s, 1H), 9,06 (s, 1H), 9,49 (s, 1H).	Ejemplo 65
28	Ácido 1-bencil-7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-4-oxo-1,4-dihidroquinolin-3-carboxílico 	RMN ^{1}H (400 MHz, DMSO-d_6): 1,10 (t, 3H), 3,20 (q, 2H), 5,84 (s, 2H), 7,15 (t, 2H), 7,23 (m, 3H), 7,53 (d, 2H), 7,92 (s, 1H), 8,15 (s, 1H), 8,24 (s, 1H), 8,34 (s, 1H), 8,41 (d, 1H), 9,29 (s, 1H), 9,48 (s, 1H).	Ejemplo 66
29	Ácido 7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-4-oxo-1-(piridin-3-ilmetil)-1,4-dihidroquinolin-3-carboxílico 	RMN ^{1}H (400 MHz, DMSO-d_6): 0,85 (m, 3H), 1,10 (t, 3H), 3,19 (q, 2H), 5,92 (s, 2H), 7,39 (m, 1H), 7,54 (m, 2H), 7,67 (d, 1H), 7,96 (s, 1H), 8,17 (s, 1H), 8,25 (s, 1H), 8,36 (s, 1H), 8,41 (d, 1H), 8,50 (d, 1H), 8,57 (br s, 1H), 9,34 (s, 1H), 9,50 (s, 1H).	Ejemplo 67

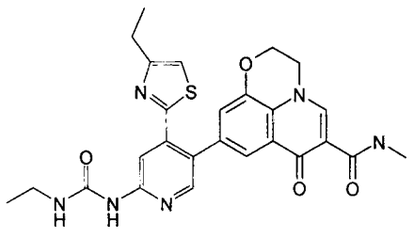
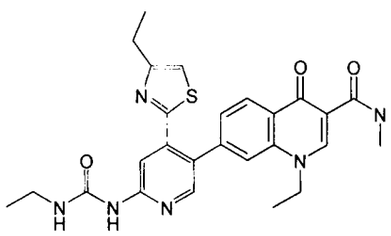
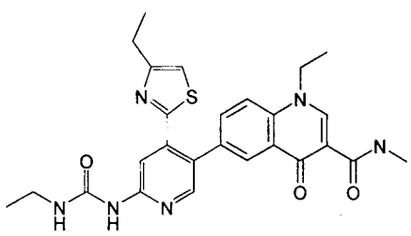
Ej.	Compuesto	Datos	SM
30	Ácido 7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-1-(2-hidroxietil)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	RMN ^{1}H (400 MHz, DMSO-d_6): 1,11 (t, 3H), 3,22 (q, 2H), 3,61 (q, 2H), 4,62 (s, 2H), 5,02 (s, 1H), 7,51 (d, 1H), 7,63 (s, 1H), 8,14 (s, 1H), 8,26 (s, 1H), 8,41 (d, 2H), 8,51 (s, 1H), 8,91 (s, 1H), 9,56 (s, 1H).	Ejemplo 68
31	Ácido 7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-1-(2-metoxietil)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	RMN ^{1}H (400 MHz, DMSO-d_6): 1,11 (t, 3H), 3,21 (m, 5H), 3,50 (t, 2H), 4,75 (m, 2H), 7,58 (d, 2H), 8,12 (s, 1H), 8,24 (s, 1H), 8,40 (m, 2H), 8,52 (s, 1H), 8,92 (s, 1H), 9,49 (s, 1H).	Ejemplo 69
32	Ácido 1-(ciclopropilmetil)-7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-4-oxo-1,4-dihidroquinolin-3-carboxílico 	RMN ^{1}H (400 MHz, DMSO-d_6): 0,44 (m, 4H), 1,09 (m, 1H), 1,11 (t, 3H), 3,22 (m, 3H), 4,42 (d, 2H), 7,61 (m, 2H), 8,13 (s, 1H), 8,21 (s, 1H), 8,40(s, 1H), 8,42 (s, 1H), 9,08 (s, 1H), 9,50 (s, 1H).	Ejemplo 70

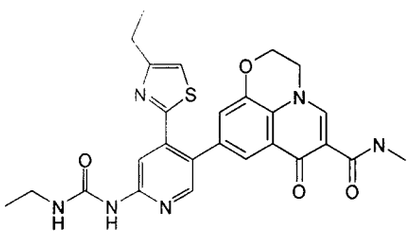
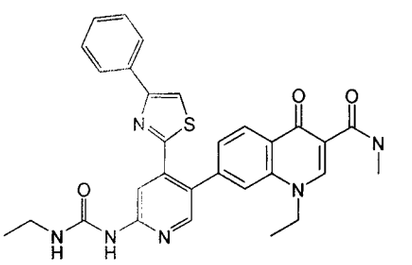
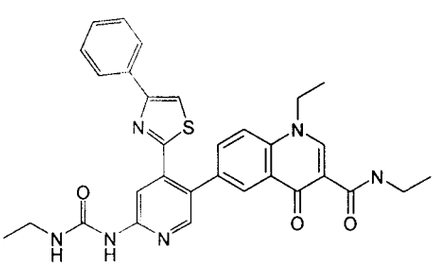
Ejemplos 33-41

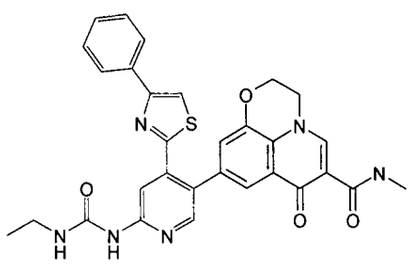
Los siguientes compuestos se sintetizaron mediante el procedimiento general descrito a continuación.

El material de partida del éster etílico (SM) (0,09 mmoles) se suspendió en metilamina al 33% en etanol (3,5 ml). La suspensión resultante se calentó a 90°C en un microondas durante 1,5 h. Cuando la reacción estuvo terminada, la disolución se enfrió hasta la temperatura ambiente, y se añadió metil-terc-butiléter (4 ml). La mezcla de reacción se dejó reposar durante 1 h, y después se filtró. El sólido se lavó con metil-*terc*-butiléter (4 ml), y se secó en un horno de vacío a 50°C durante 4 horas.

Ej.	Compuesto	Datos	SM
33	1-etil-7-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-N-metil-4-oxo-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 545,1 (MH^+) para $C_{25}H_{23}F_3N_6O_3S$ RMN ^1H (d_6-DMSO): 1,11 (t, 3H), 1,24 (t, 3H), 3,21 (m, 2H), 4,58 (q, 2H), 7,45 (dd, 1H), 7,62 (br t, 1H), 7,91 (d, 1H), 8,22 (d, 1H), 8,34-8,40 (m, 2H), 8,48 (d, 1H), 8,89 (s, 1H), 9,50 (s, 1H), 9,78 (m, 1H)	Ejemplo 42
34	1-etil-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-N-metil-4-oxo-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 545,1 (MH^+) para $C_{25}H_{23}F_3N_6O_3S$ RMN ^1H (d_6-DMSO): 1,11 (t, 3H), 1,40 (t, 3H), 2,85 (d, 3H), 3,20 (m, 2H), 4,54 (q, 2H), 7,64 (br t, 1H), 7,68 (dd, 1H), 7,98 (d, 1H), 8,23-8,26 (m, 2H), 8,34 (d, 1H), 8,48 (d, 1H), 8,92 (s, 1H), 9,46 (s, 1H), 9,73 (d, 1H)	Ejemplo 45

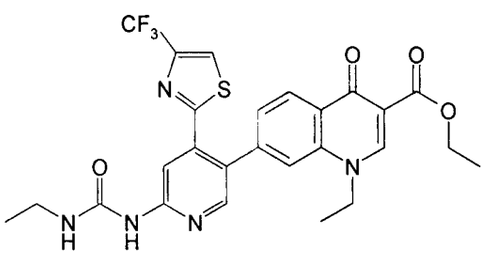
Ej.	Compuesto	Datos	SM
35	N-metil-9-(6-(3-etilureido)-4-(4-trifluorometiltiazol-2-il)piridin-3-il)-7-oxo-3,7-dihidro-2H-[1,4]oxazino[2,3,4-ij]quinolin-6-carboxamida 	MS (ESP): 559,2 (MH^+) para $C_{25}H_{21}F_3N_6O_4S$ RMN ^1H (d_6-DMSO): 1,11 (t, 3H), 2,49 (d, 3H), 3,19-3,28 (m, 2H), 4,51-4,58 (br s, 4H), 7,32 (d, 1H), 7,63 (br t, 1H), 7,73 (d, 1H), 8,22 (s, 1H), 8,29 (s, 1H), 8,50 (d, 1H), 8,79 (s, 1H), 9,45 (s, 1H), 9,72 (d, 1H)	Ejemplo 48
36	1-etil-7-(4-(4-etiltiazol-2-il)-6-(3-etilureido)piridin-3-il)-N-metil-4-oxo-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 505,2 (MH^+) para $C_{26}H_{28}N_6O_3S$ RMN ^1H (d_6-DMSO): 1,00-1,16 (m, 9H), 2,64 (q, 2H), 2,87 (d, 3H), 3,24 (q, 2H), 4,46 (q, 2H), 7,34 (s, 1H), 7,39 (d, 1H), 7,73 (m, 1H), 7,82 (s, 1H), 8,11 (s, 1H), 8,33-8,36 (m, 2H), 8,87 (s, 1H), 9,44 (s, 1H), 9,80 (d, 1H)	Ejemplo 43
37	1-etil-6-(4-(4-etiltiazol-2-il)-6-(3-etilureido)piridin-3-il)-N-metil-4-oxo-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 505,2 (MH^+) $C_{26}H_{28}N_6O_3S$ RMN ^1H (d_6-DMSO): 1,00-1,14 (m, 6H), 1,40 (t, 3H), 2,65 (q, 2H), 2,85 (d, 3H), 3,21 (m, 2H), 4,53 (q, 2H), 7,33 (s, 1H), 7,68-7,72 (m, 2H), 7,93 (d, 1H), 8,13 (s, 1H), 8,21 (d, 1H), 8,26 (s, 2H), 8,90 (s, 1H), 9,43 (s, 1H), 9,76 (m, 1H)	Ejemplo 46

Ej.	Compuesto	Datos	SM
38	9-(4-(4-etiltiazol-2-il)-6-(3-etilureido)piridin-3-il)-N-metil-7-oxo-3,7-dihidro-2H-[1,4]oxazino[2,3,4-ij]quinolin-6-carboxamida 	MS (ESP): 518,3 (MH^+) para $C_{26}H_{26}N_6O_4S$ RMN ^1H (d_6-DMSO): 1,06-1,16 (m, 6H), 2,50 (q, 2H), 2,85 (d, 3H), 3,16-3,22 (m, 2H), 4,52 (br s, 4H), 7,24 (d, 1H), 7,33 (s, 1H), 7,70 (d, 1H), 7,76 (br t, 1H), 8,12 (s, 1H), 8,23 (s, 1H), 8,78 (s, 1H), 9,40 (s, 1H), 9,74 (m, 1H)	Ejemplo 49
39	1-etil-7-(6-(3-etilureido)-4-(4-feniltiazol-2-il)piridin-3-il)-N-metil-4-oxo-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 553,2 (MH^+) para $C_{30}H_{28}N_6O_3S$ RMN ^1H (d_6-DMSO): 1,08-1,22 (m, 6H), 2,87 (d, 3H), 3,15-3,24 (m, 2H), 4,47 (br q, 2H), 7,26-7,42 (m, 3H), 7,47 (d, 1H), 7,72-7,76 (m, 3H), 7,93 (s, 1H), 8,16 (s, 1H), 8,26 (s, 1H), 8,33-8,37 (m, 2H), 8,88 (s, 1H), 9,48 (s, 1H), 9,81 (m, 1H)	Ejemplo 44
40	1-etil-6-(6-(3-etilureido)-4-(4-feniltiazol-2-il)piridin-3-il)-N-metil-4-oxo-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 553,2 (MH^+) para $C_{30}H_{28}N_6O_3S$ RMN ^1H (d_6-DMSO): 1,12 (t, 3H), 1,41 (t, 3H), 3,16-3,28 (m, 2H), 4,60 (br q, 2H), 7,31-7,39 (m, 3H), 7,71-7,81 (m, 4H), 8,05 (d, 1H), 8,17 (s, 1H), 8,29-8,36 (m, 2H), 9,05 (s, 1H), 9,61 (br s, 1H)	Ejemplo 47

Ej.	Compuesto	Datos	SM
41	9-(6-(3-etilureido)-4-(4-feniltiazol-2-il)piridin-3-il)-N-metil-7-oxo-3,7-dihidro-2H-[1,4]oxazino[2,3,4-ij]quinolin-6-carboxamida 	MS (ESP): 567,3 (MH^+) para $C_{30}H_{26}N_6O_4S$ RMN ^1H (d_6-DMSO): 1,12 (t, 3H), 2,84 (d, 3H), 3,16-3,28 (m, 2H), 4,53 (br s, 4H), 7,35-7,44 (m, 4H), 7,77-7,85 (m, 4H), 8,17 (s, 1H), 8,26 (m, 2H), 8,79 (s, 1H), 9,47 (s, 1H), 9,75 (m, 1H)	Ejemplo 50

Ejemplo 42

1-Etil-7-(6-(3-etilureido)-4-(4-trifluorometiltiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo



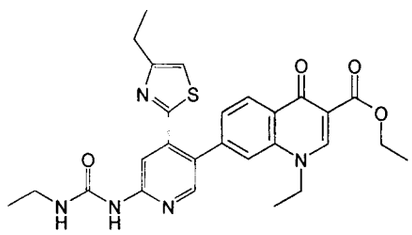
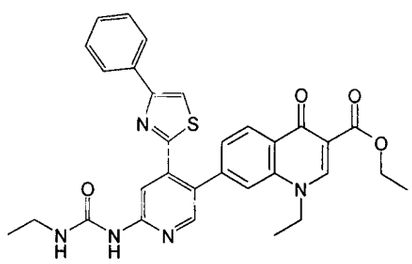
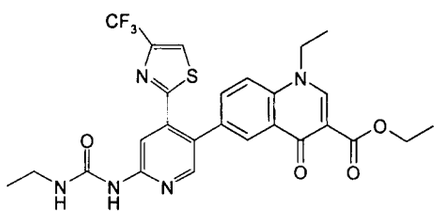
A una suspensión de ácido 6-(3-etilureido)-4-(4-trifluorometiltiazol-2-il)piridin-3-ilborónico (Intermediario 17, 330 mg, 0,91 mmoles), 1-etil-7-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo (Intermediario 9, 281 mg, 0,75 mmoles) y trans-diclorobis(trifenilfosfina)paladio (II) (53 mg, 0,075 mmoles) en 1,4-dioxano (8 ml) se añadió una disolución de carbonato de potasio (210 mg, 1,52 mmoles) en agua (3 ml). La reacción se agitó durante 1,5 horas a 70°C. La reacción se enfrió hasta la temperatura ambiente, y se añadió acetato de etilo (8 ml) para ayudar a separar las capas. Se eliminó el agua, y la fase orgánica se lavó con agua (3 ml). Entonces la reacción se concentró, y se añadió etanol (5 ml). La suspensión se filtró, y el sólido se lavó con metil-*terc*-butiléter (2 × 5 ml). El sólido se secó en un horno de vacío a 50°C durante 4 horas para dar 195 mg (60%) de 1-etil-7-(6-(3-etilureido)-4-(4-trifluorometiltiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo como un sólido blanquecino.

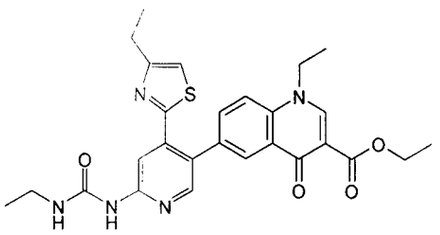
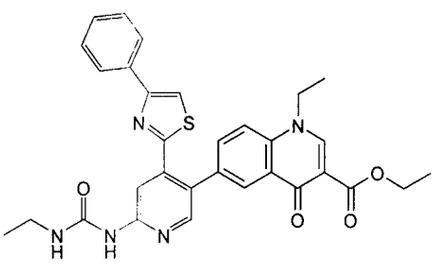
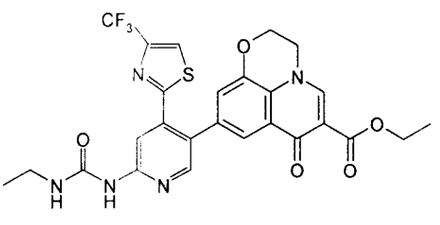
MS (ESP): 560 (MH^+) para $C_{26}H_{24}F_3N_5O_4S$

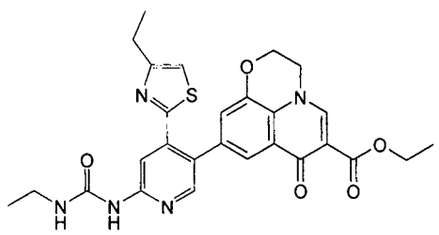
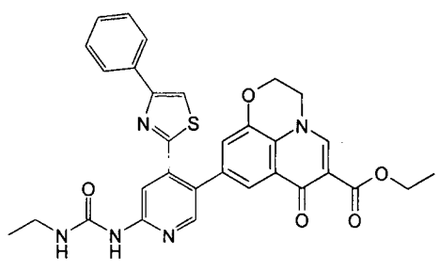
RMN ^1H ($CDCl_3$): δ 1,24 (m, 3H), 1,28 9 (m, 6H), 3,50 (m, 2H), 4,20 (m, 2H), 4,42 (m, 2H), 7,34 (m, 2H), 7,53 (s, 1H), 7,72 (s, 1H), 8,29 (s, 1H), 8,53 (s, 1H) 8,59 (m, 1H), 9,03 (m, 1H).

Ejemplos 43-50

Los siguientes Ejemplos se prepararon mediante el procedimiento descrito en el Ejemplo 42 a partir de los materiales de partida (SM) indicados.

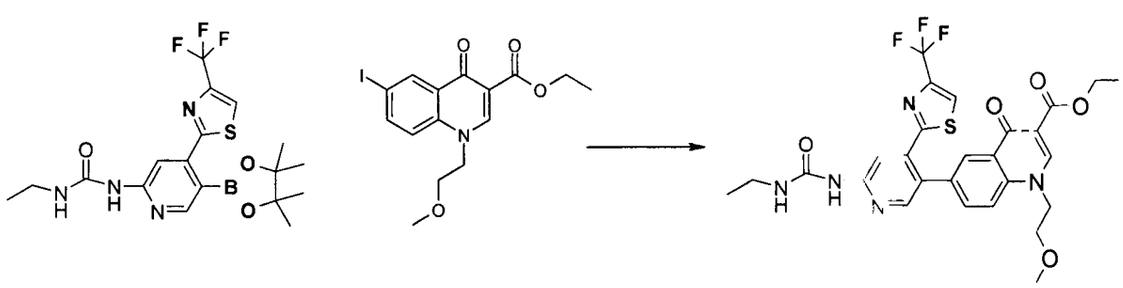
Ej.	Compuesto	Datos	SM
43	1-etil-7-(6-(3-etilureido)-4-(4-etiltiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 520,2 (MH^+) para $C_{27}H_{29}N_5O_4S$	Intermediario18 e Intermediario 9
44	1-etil-7-(6-(3-etilureido)-4-(4-feniltiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 568,2 (MH^+) para $C_{31}H_{29}N_5O_4S$ RMN ^1H ($CDCl_3$): δ 1,22-1,35 (m, 6H), 1,42 (t, 3H), 3,40-3,52 (m, 2 H), 4,09 (q, 2H), 4,41 (q, 2 H), 7,27-7,41 (m, 5H), 7,61 (s, 1 H), 7,72 (m, 2H), 8,29 (s, 1H), 8,46 (s, 1H), 8,52-8,61 (m, 2H), 9,04 (br s, 1H)	Intermediario19 e Intermediario 9
45	1-etil-6-(6-(3-etilureido)-4-(4-trifluorometiltiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 560,1 (MH^+) para $C_{26}H_{24}F_3N_5O_4S$ RMN ^1H (d_6-DMSO): δ 1,12 (t, 3H), 1,26 (t, 3H), 1,39 (t, 3 H), 3,15-3,21 (m, 2 H), 4,24 (q, 3H), 4,44 (q, 2H), 7,64 (bt, 1H), 7,71 (d, 1H), 7,91 (d, 1 H), 8,18 (d, 1H), 8,23 (s, 1H), 8,33 (s, 1H), 8,42 (s, 1H), 8,72 (s, 1H), 9,42 (s, 1H)	Intermediario 17 e Intermediario 6

Ej.	Compuesto	Datos	SM
46	1-etil-6-(6-(3-etilureido)-4-(4-etiltiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 520,1 (MH^+) para $C_{27}H_{29}N_5O_4S$ RMN ^1H (d_6-DMSO): δ 1,10 (m, 6H), 1,28 (t, 3H), 1,37 (t, 3 H), 2,68 (q, 2H), 3,14-3,21 (m, 2 H), 4,22 (q, 3H), 4,45 (q, 2H), 7,35 (s, 1H), 7,66 (d, 1H), 7,79 (bt, 1H), 7,84 (d, 1H), 8,15 (d, 1 H), 8,23 (s, 1H), 8,74 (s, 1H), 9,41 (s, 1H)	Intermediario18 e Intermediario 6
47	1-etil-6-(6-(3-etilureido)-4-(4-feniltiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 568,2 (MH^+) para $C_{31}H_{29}N_5O_4S$ RMN ^1H (d_6-DMSO): δ 1,11 (t, 3H), 1,28 (t, 3H), 1,35 (t, 3H), 3,18-3,23 (m, 2 H), 4,19 (q, 2H), 4,46 (q, 2 H), 7,28-7,41 (m, 4H), 62-7,80 (m, 5 H), 7,85 (d, 1H), 8,14 (d, 1H), 8,19 (d, 1H), 8,24 (m, 2H), 8,75 (s, 1H), 9,41 (bs, 1H)	Intermediario19 e Intermediario 6
48	9-(6-(3-etilureido)-4-(4-trifluorometiltiazol-2-il)piridin-3-il)-7-oxo-3,7-dihidro-2H-[1,4]oxazino[2,3,4-ij]quinolin-6-carboxilato de etilo 	MS (ESP): 574,2 (MH^+) para $C_{26}H_{22}F_3N_5O_3S$ RMN ^1H (d_6-DMSO): δ 1,11 (t, 3H), 1,28 (t, 3H), 3,18-3,22 (m, 2H), 4,23 (q, 2H), 4,45 (m, 2H), 4,51 (m, 2H), 7,28 (s, 1H), 7,63-7,70 (m, 2H), 8,22 (s, 1H), 8,28 (s, 1H), 8,51 (s, 1H), 8,62 (s, 1H), 9,44 (s, 1H)	Intermediario 17 e Intermediario 13

Ej.	Compuesto	Datos	SM
49	9-(6-(3-etilureido)-4-(4-etiltiazol-2-il)piridin-3-il)-7-oxo-3,7-dihidro-2H-[1,4]oxazino[2,3,4-ij]quinolin-6-carboxilato de etilo 	MS (ESP): 534,1 (MH^+) para $C_{27}H_{27}N_5O_5S$	Intermediario18 e Intermediario 13
50	9-(6-(3-etilureido)-4-(4-feniltiazol-2-il)piridin-3-il)-7-oxo-3,7-dihidro-2H-[1,4]oxazino[2,3,4-ij]quinolin-6-carboxilato de etilo 	MS (ESP): 581,9 (MH^+) para $C_{31}H_{27}N_5O_5S$ RMN ^1H (d_6-DMSO): δ 1,08-1,18 (m, 6H), 1,27 (t, 3H), 3,17-3,24 (m, 2 H), 4,22 (q, 2H), 4,44 (m, 4 H), 7,23-7,55 (m, 5H), 7,71-7,82 (m, 2 H), 8,00-8,29 (m, 2H), 8,61 (m, 1H), 9,51 (bs, 1H)	Intermediario19 e Intermediario 13

Ejemplo 51

6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(2-metoxietil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo



1-Etil-3-(5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-4-(4-(trifluorometil)tiazol-2-il)piridin-2-il)urea (0,171 g, 0,39 mmoles, Intermediario 17), 6-yodo-1-(2-metoxietil)-4-oxo-1,4-

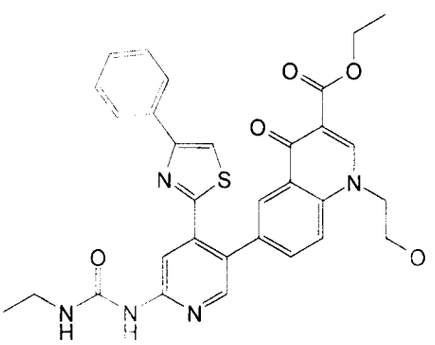
dihidroquinolin-3-carboxilato de etilo (0,155 g, 0,39 mmoles, Intermediario 20), carbonato de cesio (0,214 g, 0,66 mmoles, Aldrich) y tris(dibencilidenacetona)paladio (0) (0,035 g, 0,04 mmoles, Aldrich) o tetraquis(trifenilfosfina)paladio (0) (5% en moles, Strem) se combinaron en dioxano (2 ml)/agua (0 ml) y se calentó hasta 100 °C. La mezcla de reacción se agitó durante 1 h. La mezcla de reacción se enfrió hasta la temperatura ambiente, y después se colocó en un baño de hielo. El precipitado resultante se recogió mediante filtración y se secó a vacío para proporcionar el producto deseado (0,090 g).

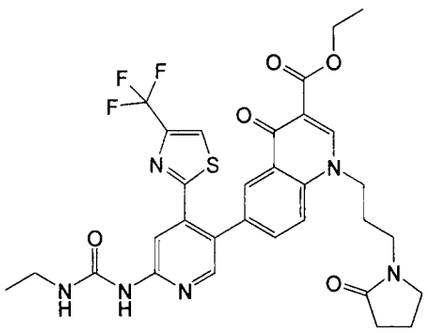
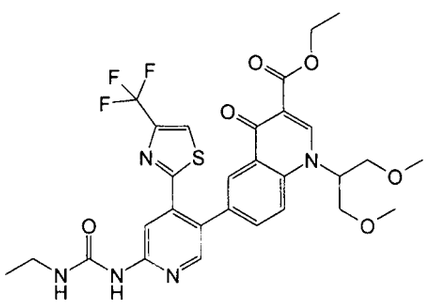
MS (ES) $(M+H)^+$: 590 para $C_{27}H_{26}F_3N_5O_5S$;

RMN: 1,11 (t, 3H), 1,28 (t, 3H), 3,24 (m, 5H), 3,66 (d, 2H), 4,24 (q, 2H), 4,61 (q, 2H), 7,70 (m, 2H), 7,91 (d, 1H), 8,14 (s, 1H), 8,22 (s, 1H), 8,33 (s, 1H), 8,49 (s, 1H), 8,62 (s, 1H), 9,46 (s, 1H).

Ejemplos 52-54

Los siguientes Ejemplos se prepararon mediante el procedimiento descrito en el Ejemplo 51 a partir de los materiales de partida (SM) indicados.

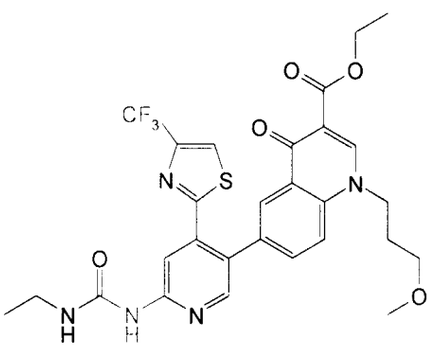
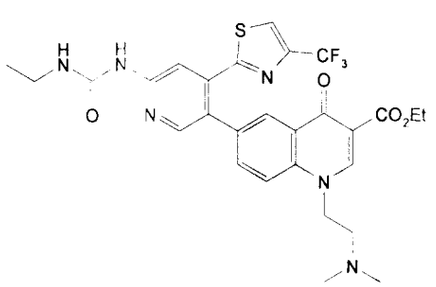
Ej.	Compuesto	Datos	SM
52	6-(6-(3-etilureido)-4-(4-feniltiazol-2-il)piridin-3-il)-1-(2-metoxietil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ES) $(M+H)^+$: 598 para $C_{32}H_{31}N_5O_5S$ RMN: 1,12 (t, 3H), 1,28 (t, 3H), 3,18-3,22 (m, 5H), 3,66 (d, 2H), 4,22 (q, 2H), 4,61 (q, 2H), 7,32-7,38 (m, 3H), 7,70-7,77 (m, 4H), 7,89 (d, 1H), 8,16 (s, 1H), 8,20 (s, 1H), 8,26 (d, 1H), 8,62 (s, 1H), 9,44 (s, 1H).	Intermediario19 e Intermediario 20

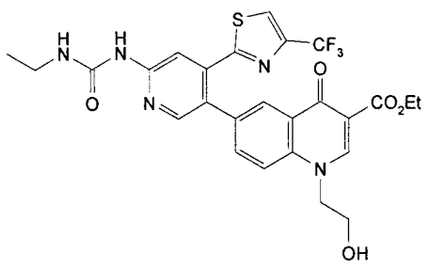
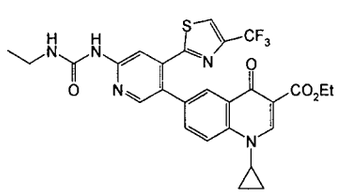
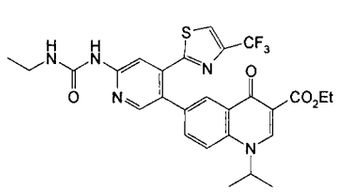
Ej.	Compuesto	Datos	SM
53	6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-(3-(2-oxopirrolidin-1-il)propil)-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ES) $(M+H)^+$: 657 para $C_{31}H_{31}F_3N_6O_5S$ RMN: 1,11 (t, 3H), 1,29 (t, 3H), 2,22 (m, 4H), 2,73 (d, 1H), 3,31 (s, 6H), 4,22 (q, 2H), 4,39 (q, 2H), 7,70 (s, 1H), 7,73 (d, 1H), 7,87 (d, 1H), 8,15 (s, 1H), 8,23 (s, 1H), 8,33 (s, 1H), 8,49 (s, 1H), 8,75 (s, 1H), 9,49 (s, 1H).	Intermediario 17 e Intermediario 21
54	1-(1,3-dimetoxipropan-2-il)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ES) $(M+H)^+$: 634 para $C_{29}H_{30}F_3N_5O_6S$	Intermediario 17 e Intermediario 22

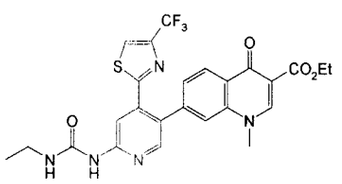
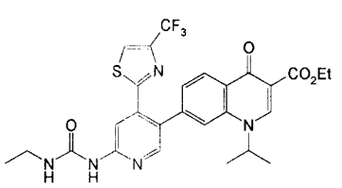
Ejemplos 55-61

Los siguientes Ejemplos se prepararon mediante el procedimiento descrito en el Ejemplo 51 a partir de los materiales de partida (SM) indicados.

Ej.	Compuesto	Datos	SM

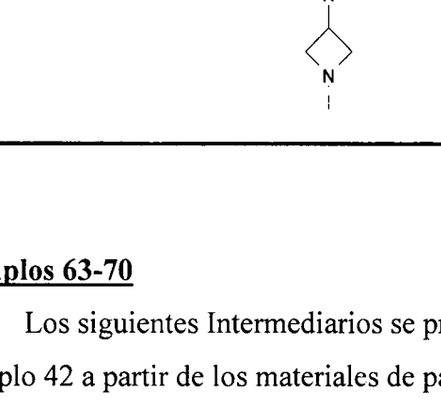
Ej.	Compuesto	Datos	SM
55	6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(3-metoxipropil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ES) $(M+H)^+$: 604 para $C_{28}H_{28}F_3N_5O_5S$	Intermediario 17 e Intermediario 23
56	1-(2-(dimetilamino)etil)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 603 (M+1) para $C_{28}H_{29}F_3N_6O_4S$ RMN ^{1}H (DMSO-d_6) 1,11 (t, J=7,07 Hz, 3H); 1,29 (t, J=7,07 Hz, 3H); 2,21 (br. s., 6H); 2,57 - 2,69 (m, 2H); 3,16 - 3,27 (m, 2H); 4,24 (q, J=7,07 Hz, 2H); 4,51 (br. s., 2H); 7,59 - 7,66 (m, 1H); 7,69 (dd, J=8,59, 2,02 Hz, 1H); 7,88 (d, J=9,09 Hz, 1H); 8,15 (d, J=2,02 Hz, 1H); 8,22 (s, 1H); 8,33 (s, 1H); 8,51 (s, 1H); 8,66 (s, 1H); 9,45 (s, 1H)	Intermediario 17 e Intermediario 29

Ej.	Compuesto	Datos	SM
57	6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(2-hidroxietil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 576 (M+1) para $C_{26}H_{24}F_3N_5O_5S$ RMN ^{1}H (DMSO-d_6) : 1,11 (t, J=7,20 Hz, 3H); 1,28 (t, J=7,07 Hz, 3H); 3,16 - 3,26 (m, 2H); 3,71 - 3,78 (m, 2H); 4,24 (q, J=7,07 Hz, 2H); 4,41 - 4,51 (m, 2H); 5,07 (t, J=5,43 Hz, 1H); 7,60 - 7,67(m, 1H); 7,69 (dd, J=8,84, 2,27 Hz, 1H); 7,91 (d, J=8,84 Hz, 1 H); 8,16 (d, J=2,27 Hz, 1H); 8,23 (s, 1H); 8,31 (s, 1H); 8,49 (s, 1H); 8,61 (s, 1H); 9,45 (s, 1 H)	Intermediario 17 e Intermediario 30
58	1-ciclopropil-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 572 (M+1) para $C_{27}H_{24}F_3N_5O_4S$	Intermediario 17 e Intermediario 27
59	6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-isopropil-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 574 (M+1) para $C_{27}H_{26}F_3N_5O_4S$	Intermediario 17 e Intermediario 28

Ej.	Compuesto	Datos	SM
60	7-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-metil-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 546 (M+1) para $C_{25}H_{22}F_3N_5O_4S$	Intermediario 17 e Intermediario 25
61	7-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-isopropil-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 574 (M+1) para $C_{27}H_{26}F_3N_5O_4S$	Intermediario 17 e Intermediario 26

Ejemplo 62

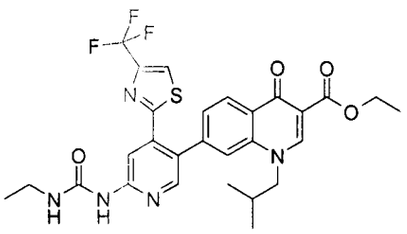
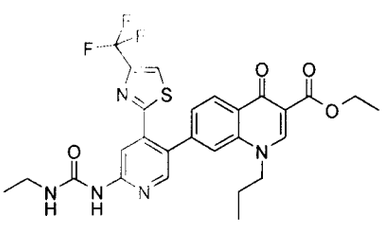
El siguiente Intermediario se preparó mediante el procedimiento descrito en el Ejemplo 51 a partir de los materiales de partida (SM) indicados.

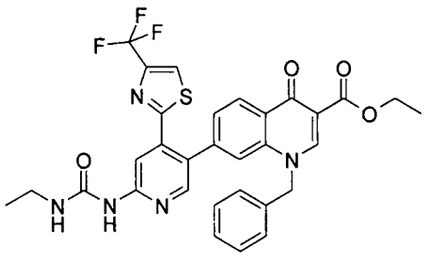
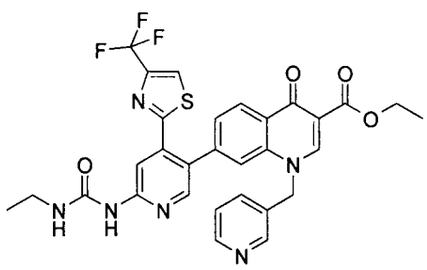
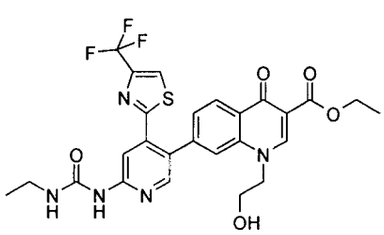
Ej.	Compuesto	Datos	SM
62	6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-metilazetidin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 601 (M+1) para $C_{28}H_{27}F_3N_6O_4S$	Intermediario 17 e Intermediario 31

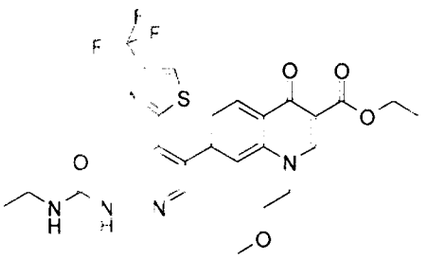
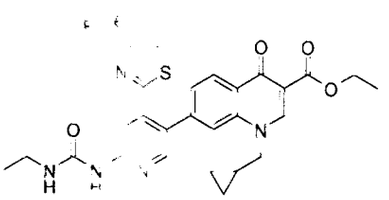
Ejemplos 63-70

Los siguientes Intermediarios se prepararon mediante el procedimiento descrito en el Ejemplo 42 a partir de los materiales de partida (SM) indicados.

Ej.	Compuesto	Datos	SM
63	7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-1-(3-metilbutil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo	RMN ^{1}H (400 MHz, DMSO-d_6): 0,91 (d, 6H), 1,12 (t, 3H), 1,31 (t, 3H), 1,39 (d, 2H), 1,56 (m, 1H), 3,21 (q, 2H), 4,21 (q, 2H), 4,31 (t, 2H), 7,48 (d, 1H), 7,58 (t, 2H), 7,68 (s, 1H), 8,24 (s, 1H), 8,30 (d, 1H), 8,38 (s, 1H), 8,51 (s, 1H), 8,68 (s, 1H).	Intermediario 17 e Intermediario 34

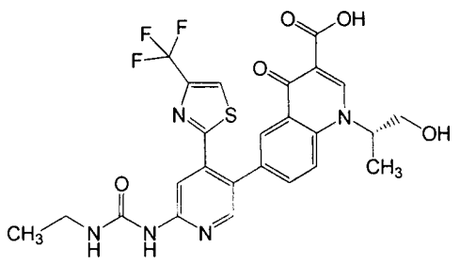
Ej.	Compuesto	Datos	SM
64	7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-1-(2-metilpropil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	RMN ^{1}H (400 MHz, DMSO-d_6): 0,78 (d, 6H), 1,15 (t, 3H), 1,32 (t, 3H), 1,61 (m, 1H), 3,38 (q, 2H), 4,12 (d, 2H), 4,36 (q, 2H), 7,48 (d, 1H), 7,61 (d, 2H), 7,71 (s, 1H), 8,18 (s, 1H), 8,31 (d, 1H), 8,39 (s, 1H), 8,52 (s, 1H), 8,64 (s, 1H), 9,52 (s, 1H).	Intermediario 17 e Intermediario 35
65	7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-4-oxo-1-propil-1,4-dihidroquinolin-3-carboxilato de etilo 	RMN ^{1}H (400 MHz, DMSO-d_6): 0,91 (t, 3H), 1,16 (t, 3H), 1,56 (m, 2H), 3,21 (q, 2H), 3,34 (s, 2H), 4,26 (q, 2H), 7,41 (d, 1H), 7,60 (s, 1H), 7,78 (s, 1H), 8,21 (s, 1H), 8,28 (d, 1H), 8,52 (s, 2H), 8,68 (s, 1H), 9,42 (s, 1H).	Intermediario 17 e Intermediario 36

Ej.	Compuesto	Datos	SM
66	1-bencil-7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	RMN ^{1}H (400 MHz, DMSO-d_6): 1,10 (t, 3H), 1,31 (t, 3H), 3,21 (q, 2H), 4,24 (q, 2H), 5,63 (s, 1H), 7,14 (d, 2H), 7,22 (d, 3H), 7,36 (d, 1H), 7,56 (s, 1H), 7,77 (s, 1H), 8,14 (s, 1H), 8,24 (s, 1H), 8,31 (s, 2H), 8,89 (s, 1H), 9,41 (s, 1H).	Intermediario 17 e Intermediario 37
67	7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-4-oxo-1-(piridin-3-ilmetil)-1,4-dihidroquinolin-3-carboxilato de etilo 	RMN ^{1}H (400 MHz, DMSO-d_6): 1,08 (t, 3H), 1,36 (t, 3H), 3,21 (q, 2H), 4,21 (q, 2H), 5,68 (s, 2H), 7,38 (d, 2H), 7,61 (d, 2H), 7,71 (s, 1H), 8,18 (s, 1H), 8,22 (s, 1H), 8,31 (d, 1H), 8,34 (s, 1H), 8,51 (s, 2H).	Intermediario 17 e Intermediario38
68	7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-1-(2-hidroxietil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 1,16 (t, 3H), 1,29 (t, 3H), 3,21 (t, 2H), 3,61 (t, 2H), 4,21 (q, 2H), 4,41 (s, 2H), 5,01 (s, 1H), 7,26 (s, 1H), 7,38 (d, 2H), 7,65 (s, 1H), 7,89 (s, 1H), 8,26 (d, 2H), 8,36 (s, 1H), 8,48 (s, 1H), 8,58 (s, 1H), 9,52 (s, 1H).	Intermediario 17 e Intermediario 39

Ej.	Compuesto	Datos	SM
69	7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-1-(2-metoxietil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	RMN ^{1}H (400 MHz, DMSO-d_6): 1,14 (t, 3H), 1,32 (t, 3H), 3,11 (s, 3H), 3,30 (s, 2H), 3,46 (s, 1H), 4,21 (q, 2H), 4,58 (s, 2H), 7,41 (d, 1H), 7,64 (s, 1H), 7,86 (s, 1H), 8,24 (d, 2H), 8,38 (s, 1H), 8,50 (s, 1H), 8,58 (s, 1H).	Intermediario 17 e Intermediario 40
70	1-(ciclopropilmetil)-7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	RMN ^{1}H (400 MHz, DMSO-d_6): 0,38 (m, 4H), 0,98 (m, 1H), 1,10 (t, 3H), 1,29 (t, 3H), 3,19 (q, 2H), 4,29 (q, 2H), 7,40 (d, 1H), 7,61 (s, 1H), 7,91 (s, 1H), 8,21 (s, 1H),. 8,23 (d, 1H), 8,38 (s, 1H), 8,48 (s, 1H), 8,71 (s, 1H), 9,42 (s, 1H).	Intermediario 17 e Intermediario 41

Ejemplo 71

Ácido (*S*)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-hidroxipropan-2-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico



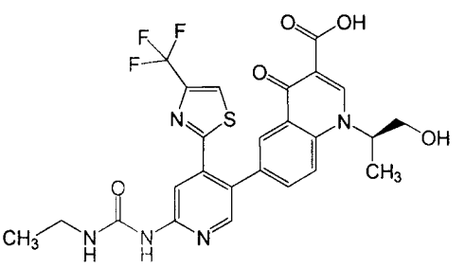
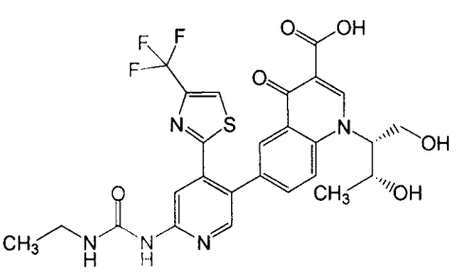
A una disolución de (*S*)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-hidroxipropan-2-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo (Ejemplo 97, 200 mg, 0,34 mmoles, 1 equiv.) en tetrahidrofurano (1 ml) y metanol (1 ml) se añadió hidróxido de litio 2 M (0,339 ml). La mezcla se agitó en el microondas a 100 °C durante 15 min. La mezcla de reacción se enfrió hasta la temperatura ambiente y se diluyó con agua. Se añadió HCl 1 N hasta que se alcanzó un pH de 3-4. La mezcla de reacción se repartió entre acetato de etilo (5 ml) y agua (5 ml). La capa acuosa se extrajo con acetato de etilo (2x5 ml), y los orgánicos se lavaron con salmuera (10 ml), se secaron sobre sulfato de sodio, y se concentraron a presión reducida. Se purificó vía HPLC de fase inversa (columna C18, gradiente 0-95% de acetonitrilo/agua) y se concentró a presión reducida para proporcionar ácido (*S*)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-hidroxipropan-2-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico como un sólido amarillo claro (92 mg, 48%).

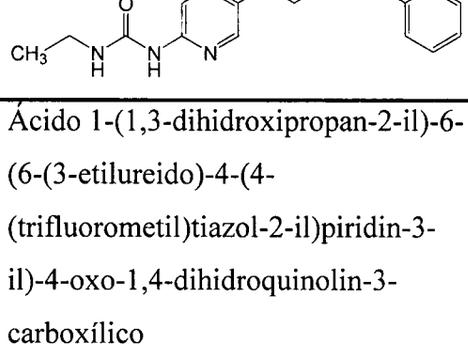
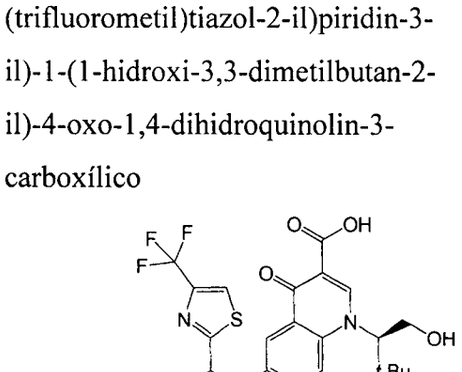
MS (ESP) $[M + H]^+$: 562 para $C_{25}H_{22}F_3N_5O_5S$.

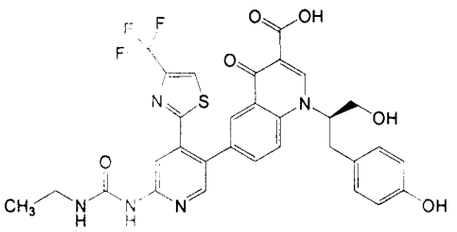
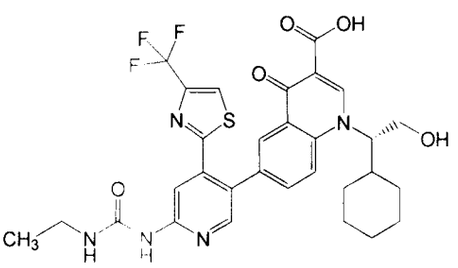
RMN ^1H (d_6-DMSO) δ 14,98 (s, 1H), 9,53 (s, 1H), 8,93 (s, 1H), 8,51 (s, 1H), 8,36 (s, 1H), 8,34 (d, 1H), 8,25 (d, 1H), 8,23 (s, 1H), 7,87-7,83 (dd, 1H), 7,65 (t, 1H), 5,28 (s, 2H), 3,81 (s, 2H), 3,25-3,16 (m, 3H), 1,56 (d, 3H), 1,11 (t, 3H).

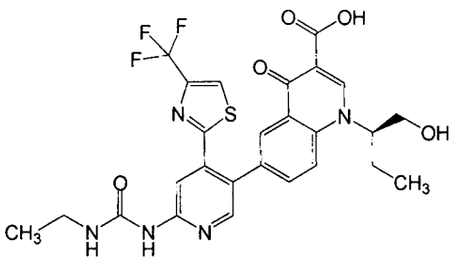
Ejemplos 72-79

Los siguientes Ejemplos se prepararon mediante el procedimiento descrito en el Ejemplo 71 a partir del material de partida indicado.

Ej.	Compuesto	Datos	SM
72	Ácido (*R*)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-hidroxipropan-2-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 562 (M + 1) para $C_{25}H_{22}F_3N_5O_5S$ RMN (d_6-DMSO) δ 15,09 (s, 1H), 9,51 (s, 1H), 8,94 (s, 1H), 8,51 (s, 1H), 8,36 (d, 2H), 8,24 (s, 2H), 7,87 (d, 1H), 7,65 (s, 1H), 5,3 (s, 2H), 3,82 (s, 2H), 3,21 (m, 3H), 1,56 (d, 3H), 1,11 (t, 3H)	Ejemplo 98
73	Ácido 1-((2*R*,3*R*)-1,3-dihidroxibutan-2-il)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 592 (M + 1) para $C_{26}H_{24}F_3N_5O_6S$ RMN (d_6-DMSO) δ 15,1 (s, 1H), 9,48 (s, 1H), 9,12 (s, 1H), 8,53 (s, 1H), 8,38, (s, 1H), 8,33 (d, 1H), 8,29 (d, 1H), 8,22 (s, 1H), 7,84 (dd, 1H), 7,61 (t, 1H), 5,3-5,1 (m, 2H), 4,26 (t, 1H), 4,04-3,97 (m, 1H), 3,87 (d, 1H), 3,23-3,17 (m, 2), 1,14 (d, 3H), 1,11 (t, 3H)	Ejemplo 99

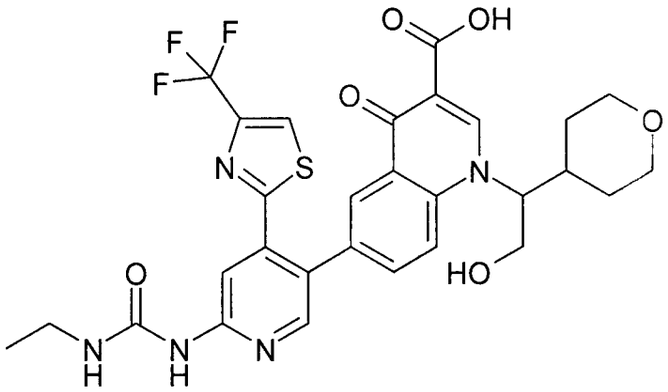
Ej.	Compuesto	Datos	SM
74	Ácido (*S*)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-hidroxi-3-fenilpropan-2-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 638 (M + 1) para $C_{31}H_{26}F_3N_5O_5S$ RMN (d_6-DMSO) δ 14,47 (s, 1H), 9,47 (s, 1H), 9,05 (s, 1H), 8,58 (s, 1H), 8,32 (s, 1H), 8,24 (d, 1H), 8,22 (s, 1H), 8,19 (d, 1H), 7,77 (dd, 1H), 7,6 (t, 1H), 7,2-7,15 (m, 5H), 5,55 (s, 1H), 5,36 (t, 1H), 3,99-3,82 (m, 2H), 3,22-3,16 (m, 2H), 1,11 (t, 3H)	Ejemplo 109
75	Ácido 1-(1,3-dihidroxipropan-2-il)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 578 (M + 1) para $C_{25}H_{22}F_3N_5O_6S$ RMN (d_6-DMSO) δ 9,5 (s, 1H), 8,96 (s, 1H), 8,51 (d, 1H), 8,36 (s, 1H), 8,35 (d, 1H), 8,26 (d, 1H), 8,23 (s, 1H), 7,87 (dd, 1H), 7,63 (t, 1H), 5,28-5,19 (m, 2H), 3,99-3,84 (m, 4H), 3,25-3,16 (2H), 1,11 (t, 3H)	Ejemplo 100
76	Ácido (*R*)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-hidroxi-3,3-dimetilbutan-2-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico	MS (ESP): 604 (M + 1) para $C_{28}H_{28}F_3N_5O_5S$ RMN (d_6-DMSO) δ 9,59 (s, 1H), 8,87 (s, 1H), 8,55 (s, 1H), 8,47 (d, 1H), 8,39 (s, 1H), 8,33 (d, 1H), 8,23 (s, 1H), 7,8 (dd, 1H), 7,67 (t, 1H), 5,21-5,17 (m, 1H), 4,16-4,03 (m, 2H), 3,25-3,16 (m, 2H), 1,11 (t, 3H), 0,97 (s, 9H)	Ejemplo 108

Ej.	Compuesto	Datos	SM
77	Ácido (*R*)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-hidroxi-3-(4-hidroxifenil)propan-2-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 604 (M + 1) para $C_{31}H_{26}F_3N_5O_6S$ RMN (d_6-DMSO) δ 14,99 (s, 1H), 9,46 (s, 1H), 89,25 (s, 1H), 9,01 (s, 1H), 8,51 (s, 1H), 8,32 (s, 1H), 8,24 (s, 1H), 8,19 (d, 1H), 7,79 (d, 1H), 7,6 (t, 1H), 6,98 (d, 2H), 6,56 (d, 2H), 5,51-5,44 (m 1H), 5,33 (t, 1H), 3,99-3,79 (m, 2H), 3,26-3,09 (m, 3H), 1,11 (t, 3H), 0,07 (s, 1H)	Ejemplo 117
78	Ácido (*S*)-1-(1-ciclohexil-2-hidroxietil)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 630 (M + 1) para $C_{30}H_{30}F_3N_5O_5S$ RMN (d_6-DMSO) δ 15,03 (s, 1H), 9,48 (s, 1H), 9,01 (s, 1H), 8,54 (s, 1H), 8,39 (s, 1H), 8,34 (d, 1H), 8,32 (d, 1H), 8,2 (s, 1H), 7,82 (dd, 1H), 7,59 (t, 1H), 5,27 (t, 1H), 5,02-4,95 (m, 1H), 4,07-3,97 (m, 1H), 3,81-3,75 (m, 1H), 3,26-3,18 (m, 2H), 2,15-2,01 (m, 1H), 1,97-1,9 (m 1H), 1,81-1,73 (m, 1H), 1,61-1,55 (m , 2H), 1,3-1,17 (m, 2H), 1,11 (t, 3H)	Ejemplo 118

Ej.	Compuesto	Datos	SM
79	Ácido (*R*)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-hidroxibutan-2-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 576 (M + 1) para $C_{26}H_{24}F_3N_5O_5S$ RMN (d_6-DMSO) δ 15,1 (s, 1H), 9,48 (s, 1H), 8,93 (s, 1H), 8,53 (s, 1H), 8,38 (s, 1H), 8,34 (d, 1H), 8,3 (d, 1H), 8,22 (s, 1H), 7,86 (dd, 1H), 7,6 (t, 1H), 5,13 (m, 2H), 3,92-3,84 (m, 2H), 3,26-3,17 (m, 2H), 2,06-1,92 (m, 2H), 1,11 (t, 3H), 0,89 (t, 3H)	Ejemplo 102

Ejemplo 80

Ácido 6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(2-hidroxi-1-(tetrahidro-2H-piran-4-il)etil)-4-oxo-1,4-dihidroquinolin-3-carboxílico



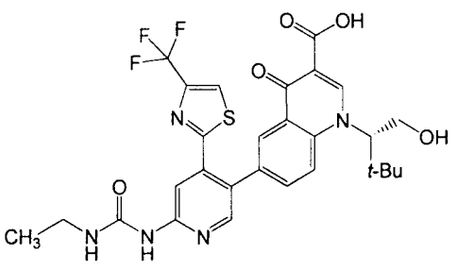
A una disolución de 6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(2-hidroxi-1-(tetrahidro-2H-piran-4-il)etil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo (Ejemplo 103, 107 mg, 0,16 mmoles, 1 equiv.) en tetrahidrofurano (1 ml) y metanol (1 ml) se añadió hidróxido de litio 2 M (0,162 ml, 0,32 mmoles). La mezcla de reacción se calentó hasta 100 °C durante 15 min en un microondas. La mezcla de reacción se enfrió hasta la temperatura ambiente, y se diluyó con agua. La mezcla de reacción se filtró, y el filtrado se secó. La purificación vía HPLC de fase inversa (C18, gradiente 0-95% de acetonitrilo/agua) y la concentración a presión reducida proporcionó ácido 6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(2-hidroxi-1-(tetrahidro-2H-piran-4-il)etil)-4-oxo-1,4-dihidroquinolin-3-carboxílico como un sólido amarillo claro (26,5 mg, 26%).

MS (ESP): 632 (M + 1) para $C_{29}H_{28}F_3N_5O_6S$.

RMN (d_6-DMSO) δ 15,03 (s, 1H), 9,39 (s, 1H), 8,98 (s, 1H), 8,46 (s, 1H), 8,32 (s, 1H), 8,29 (d, 1H), 8,25 (d, 1H), 8,13 (s, 1H), 7,76 (dd, 1H), 7,51 (t, 1H), 4,97 (m, 1H), 3,98 (dd, 1H), 3,83 (dd, 1H), 3,73-3,63 (3H), 3,19-3,10 (m, 2H), 2,31-2,2 (m, 1H), 1,73-1,68 (m, 1H), 1,59-1,5 (m, 1H), 1,16-1,09 (m, 1H), 1,04 (t, 3H), 1,0-0,94 (m, 1H).

Ejemplo 81

Ácido 6-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-1-[(1*S*)-1-(hidroximetil)-2,2-dimetilpropil]-4-oxo-1,4-dihidroquinolin-3-carboxílico



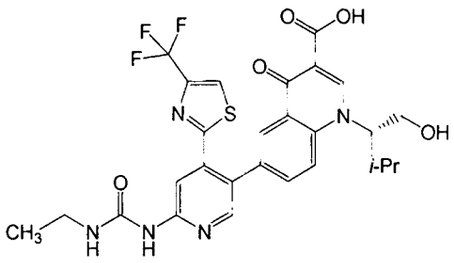
A una disolución de (*S*)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-hidroxi-3,3-dimetilbutan-2-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo (Ejemplo 104, 212,7 mg, 0,34 mmoles) en tetrahidrofurano (1 ml) y metanol (1 ml) se añadió hidróxido de litio 2 M (0,253 ml, 0,51 mmoles). La mezcla de reacción se calentó a 100 °C durante 15 min en un reactor de microondas. La mezcla de reacción se enfrió hasta la temperatura ambiente y se diluyó con agua. Se añadió HCl 1 N hasta que se alcanzó un pH de 3-4. El precipitado que se formó se recogió mediante filtración, se lavó con agua y hexanos. La purificación vía cromatografía en columna (sílice, cloruro de metileno/metanol 95:5) proporcionó ácido (*S*)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-hidroxi-3,3-dimetilbutan-2-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico como un sólido amarillo claro (72,3 mg, 35%).

MS (ESP): 604 (M + 1) para $C_{28}H_{28}F_3N_5O_5S$.

RMN (d_6-DMSO) δ 15,01 (s, 1H), 9,4 (s, 1H), 8,78 (s, 1H), 8,46 (s, 1H), 8,37 (d, 1H), 8,31 (s, 1H), 8,25 (d, 1H), 8,11 (s, 1H), 7,72 (dd, 1H), 7,5 (t, 1H), 5,12-5,08 (m, 1H), 4,09-3,96 (m, 2H), 3,17-3,08 (m, 2H), 1,02 (t, 3H), 0,89 (s, 9H).

Ejemplo 82

Ácido 6-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-1-[(1*S*)-1-(hidroximetil)-2-metilpropil]-4-oxo-1,4-dihidroquinolin-3-carboxílico



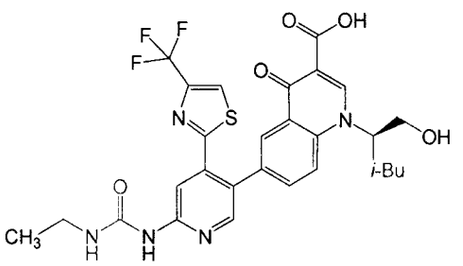
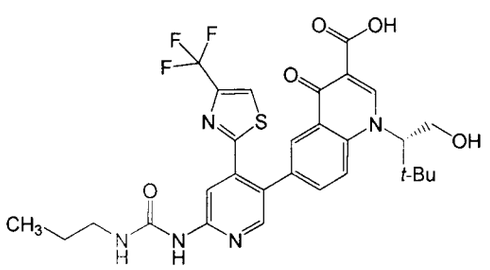
A una disolución de (*S*)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-hidroxi-3-metilbutan-2-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo (Ejemplo 110, 213 mg, 0,35 mmoles) en tetrahidrofurano (1 ml) y metanol (1 ml) se añadió hidróxido de litio 2 M (0,259 ml, 0,52 mmoles). La mezcla de reacción se calentó a 100 °C durante 15 min en un reactor de microondas. La mezcla de reacción se enfrió hasta la temperatura ambiente, se diluyó con agua, y se trató con HCl 1 N hasta pH 3-4. El precipitado que se formó se recogió mediante filtración, se lavó con agua y hexanos. La purificación vía HPLC de fase inversa (C18, gradiente 0-95% de acetonitrilo/agua) proporcionó ácido (*S*)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-hidroxi-3-metilbutan-2-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico como un sólido amarillo claro (146,4 mg, 72%).

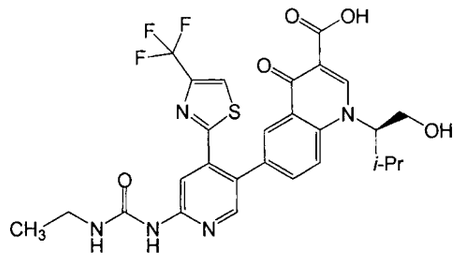
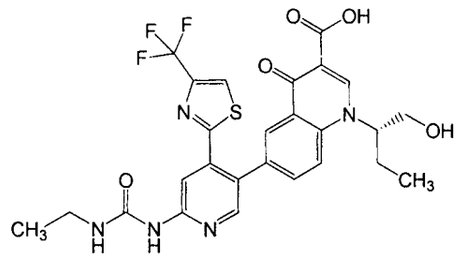
MS (ESP): 590 para $C_{27}H_{26}F_3N_5O_5S$.

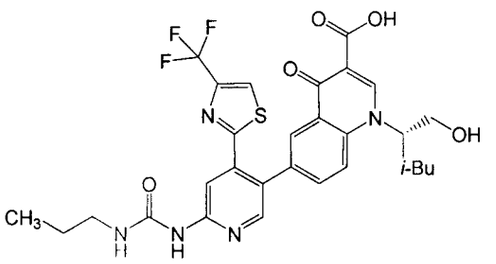
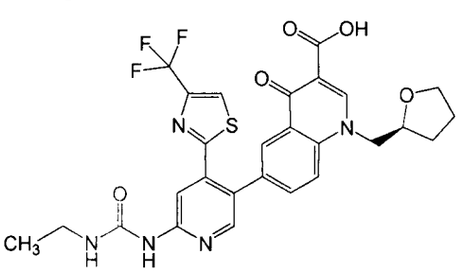
RMN (d_6-DMSO) δ 14,98 (s, 1H), 9,5 (s, 1H), 9,0 (s, 1H), 8,53 (s, 1H), 8,39 (s, 1H), 8,33 (d, 1H), 8,21 (s, 1H), 7,83 (dd, 1H), 7,62 (t, 1H), 5,26 (s, 1H), 4,92 (s, 1H), 4,0 (d, 1H), 3,81 (d, 1H), 3,22-3,19 (m, 2H), 2,38 (m, 1H), 1,11 (t, 3H), 1,09 (d, 3H), 0,74 (d, 3H).

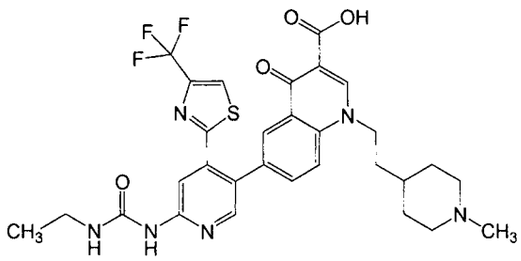
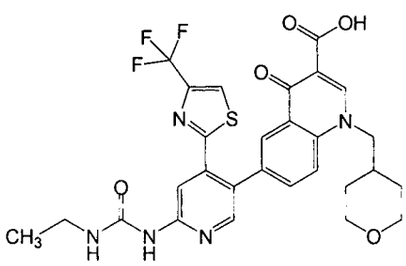
Ejemplos 83-95

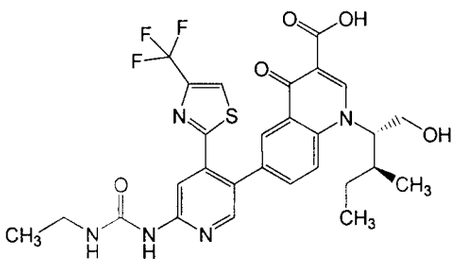
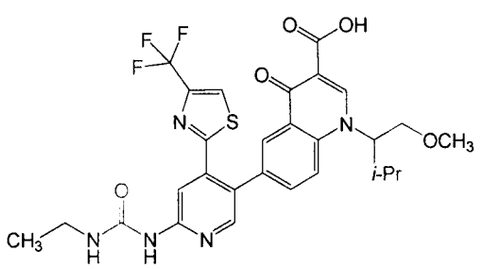
Los siguientes Ejemplos se prepararon mediante el procedimiento descrito en el Ejemplo 83 a partir del material de partida indicado.

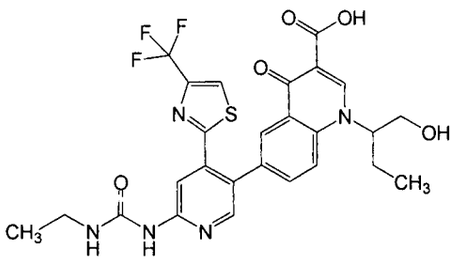
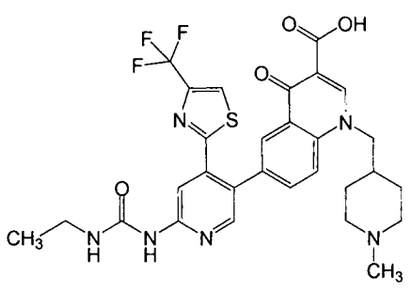
Ej.	Compuesto	Datos	SM
83	Ácido (*S*)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-hidroxi-4-metilpentan-2-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 604 para $C_{28}H_{28}F_3N_5O_5S$ RMN (d_6-DMSO) δ 14,88 (s, 1H), 9,53 (s, 1H), 8,9 (s, 1H), 8,54 (s, 1H), 8,39 (s, 1H), 8,34 (d, 1H), 8,32 (d, 1H), 8,22 (s, 1H), 7,85 (dd, 1H), 7,63 (t, 1H), 5,24 (s, 2H), 3,83-3,73 (m, 2H), 3,22-3,17 (m, 3H), 1,97-1,81 (m, 2H), 1,48-1,4 (m, 1H), 1,11 (t, 3H), 0,92 (d, 3H), 0,86 (d, 3H)	Ejemplo 111
84	Ácido (*S*)-1-(1-hidroxi-3,3-dimetilbutan-2-il)-4-oxo-6-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 618 para $C_{29}H_{30}F_3N_5O_5S$ RMN (d_6-DMSO) δ 15,09 (s, 1H), 9,48 (s, 1H0, 8,91 (s, 1H), 8,54 (s, 1H), 8,39 (s, 1H), 8,34 (d, 1H), 8,3 (s, 1H), 8,22 (s, 1H), 7,87 (dd, 1H), 7,65 (t, 1H), 5,26-5,23 (m, 2H), 3,85-3,73 (m, 2H), 3,19-3,12 (m, 2H), 1,55-1,42 (m, 2H), 0,92 (t, 3H), 0,91 (s, 9H)	Ejemplo 101

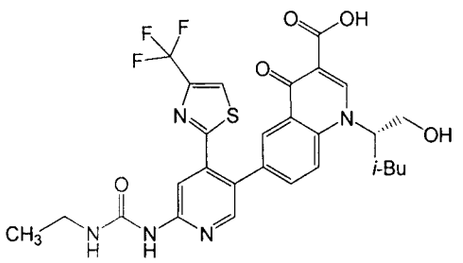
Ej.	Compuesto	Datos	SM
85	Ácido (*R*)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-hidroxi-3-metilbutan-2-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 590 para $C_{27}H_{26}F_3N_5O_5S$ RMN ^1H (d_6-DMSO) δ 9,56 (s, 1H), 8,99 (s, 1H), 8,53 (s, 1H), 8,39 (s, 1H) 8,33 (d, 1H), 8,3 (s, 1H), 8,22 (s, 1H), 7,82 (dd, 1H), 7,67 (t, 1H), 4,91 (s, 1H), 4,04-3,98 (m, 1H), 3,8 (d, 1H), 3,25-3,16 (m, 2H), 2,42-2,35 (m, 1H), 1,11 (t, 3H), 1,09 (d, 3H), 0,73 (d, 3H)	Ejemplo 112
86	Ácido (*S*)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-hidroxibutan-2-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 576 para $C_{30}H_{24}F_3N_5O_5S$ RMN (d_6-DMSO) δ 15,08 (s, 1H), 9,48 (s, 1H), 8,93 (s, 1H), 8,53 (s, 1H), 8,38 (s, 1H) 8,34 (d, 1H), 8,3 (d, 1H), 8,22 (s, 1H), 7,86 (dd, 1H), 7,6 (t, 1H), 5,13 (m, 2H), 3,89-3,75 (m, 2H), 3,26-3,17 (m, 2H), 2,09-1,92 (m, 2H), 1,11 (t, 3H), 0,89 (t, 3H)	Ejemplo 113

Ej.	Compuesto	Datos	SM
87	Ácido (*S*)-1-(1-hidroxi-4-metilpentan-2-il)-4-oxo-6-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 618 para $C_{29}H_{30}F_3N_5O_5S$ RMN ^1H (d_6-DMSO) δ 14,61 (s, 1H), 9,04 (s, 1H), 8,47 (s, 1H), 8,1 (s, 1H), 7,96 (s, 1H), 7,9 (s, 1H), 7,89 (d, 1H), 7,78 (s, 1H), 7,42 (dd, 1H), 7,2 (t, 1H), 4,79 (m, 1H), 3,3 (m, 2H), 2,74-2,69 (m, 2H), 1,54-1,47 (m, 1H), 1,44-1,39 (m, 1H), 1,1-,79 (m, 3H), 0,48 (t, 3H), 0,47 (d, 3H), 0,43 (d, 3H)	Ejemplo 114
88	Ácido (*S*)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-((tetrahidrofuran-2-il)metil)-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 588 para $C_{27}H_{24}F_3N_5O_5S$ RMN ^1H (d_6-DMSO) δ 15,06 (s, 1H), 9,48 (s, 1H), 8,98 (s, 1H), 8,51 (s, 1H), 8,37 (s, 1H), 8,32 (d, 1H), 8,23 (s, 1H), 8,19 (d, 1H), 7,86 (dd, 1H), 7,61 (t, 1H), 4,88 (d, 1h), 4,55-4,46 (m, 1H), 4,21-4,16 (m, 1H), 3,86-3,78 (m, 1H), 3,78-3,62 (m, 1H), 3,24-3,18 (m, 2H), 2,11-2,07 (m, 1H), 1,94-1,87 (m, 1H), 1,87-1,81 (m, 1H), 1,67-1,61 (m 1H), 1,11 (t, 3H)	Ejemplo 105

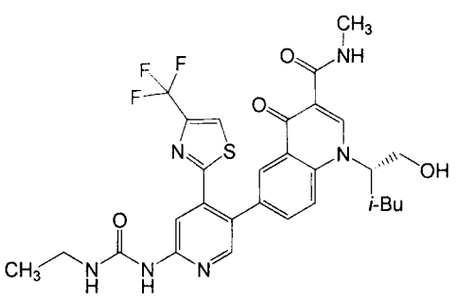
Ej.	Compuesto	Datos	SM
89	Ácido 6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(2-(1-metilpiperidin-4-il)etil)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 629 para $C_{30}H_{31}F_3N_6O_4S$ RMN (d_6-DMSO) δ 15,02 (s, 1H), 9,44 (s, 1H), 9,1 (s, 1H), 8,49 (s, 1H), 8,33 (s, 1H), 8,28 (d, 1H), 8,18 (s, 1H), 8,02 (s, 1H), 7,83 (dd, 1H), 7,54 (t, 1H), 4,62-4,55 (m, 2H), 3,21-3,12 (m, 2H), 2,93-2,81 (m, 2H), 2,72 (d, 3H), 1,95 (d, 2H), 1,77-1,69 (m, 3H), 1,37-1,25(m, 2H), 1,07 (t, 3H)	Ejemplo 106
90	Ácido 6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-((tetrahidro-2H-piran-4-il)metil)-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 602 para $C_{28}H_{26}F_3N_5O_5S$ RMN (d_6-DMSO) δ 15,08 (s, 1H), 9,48 (s, 1H), 9,06 (s, 1H), 8,54 (s, 1H), 8,39 (s, 1H), 8,31 (d, 1H), 8,21 (s, 1H), 8,17 (d, 1H), 7,84 (dd, 1H), 7,59 (t, 1H), 4,54 (dd, 2H), 3,86 (dd, 2H), 3,26-3,14 (m, 4H), 2,15-2,04 (m, 1H), 1,47-1,3 (m, 4H), 1,11 (t, 3H)	Ejemplo 107

Ej.	Compuesto	Datos	SM
91	Ácido 1-((2*S*,3*S*)-1,3-dihidroxipentan-2-il)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 604 para $C_{28}H_{28}F_3N_5O_5S$ RMN (d_6-DMSO) δ 15,03 (s, 1H), 9,52 (s, 1H), 8,97 (s, 1H), 8,59 (s, 1H), 8,38 (s, 1H), 8,32 (d, 1H), 8,26 (d, 1H), 8,21 (s, 1H), 7,8 (m, 1H), 7,64 (t, 1H), 5,3-5,2 (m, 1H), 5,0-4,86 (m, 1H), 4,14-3,95 (m, 1H), 3,85-3,72 (m, 1H), 3,24-3,16 (m, 2H), 2,23-2,11 (m, 1H), 1,11 (t, 3H), 0,76-0,7 (m, 2H), 0,06 (t, 3H)	Ejemplo 115
92	Ácido 6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-metoxi-3-metilbutan-2-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 604 para $C_{28}H_{28}F_3N_5O_5S$ RMN ^{1}H (d_6-DMSO) δ 15,06 (s, 1H), 9,48 (s, 1H), 8,98 (s, 1H), 8,55 (s, 1H), 8,4 (s, 1H), 8,37 (d, 1H), 8,32 (s, 1H), 8,2 (s, 1H), 7,83 (dd, 1H), 7,59 (t, 1H), 5,19-5,05 (m, 1H), 4,06-3,93 (m, 1H), 3,8-3,73 (m, 1H), 3,63-3,59 (m, 1H), 3,3-3,23 (m, 2H), 3,24 (s, 3H), 1,81-1,73 (m, 1H), 1,11 (t, 3H), 1,09 (d, 3H), 0,72 (d, 3H)	Ejemplo 116

Ej.	Compuesto	Datos	SM
93	Ácido 6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-hidroxibutan-2-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 576 para $C_{26}H_{24}F_3N_5O_5S$ RMN (d_6-DMSO) δ 15,13 (s, 1H), 9,48 (s, 1H), 8,93 (s, 1H), 8,53 (s, 1H), 8,38 (s, 1H), 8,34 (s, 1H), 8,3 (d, 1H), 8,21 (d, 1H), 8,21 (d, 1H), 7,86 (dd, 1H), 7,61 (t, 1H), 5,28-2,21 (m, 1H), 5,17-5,06 (m, 1H), 3,95-3,88 (m, 1H), 3,8-3,75 (m, 1H), 3,26-3,19 (m, 2H), 2,09-1,88 (m, 2H), 1,11 (t, 3H), 0,89 (t, 3H)	Ejemplo 120
94	Ácido 6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-((1-metilpiperidin-4-il)metil)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 615 para $C_{29}H_{29}F_3N_6O_4S$ RMN (d_6-DMSO) δ 9,53 (s, 1H), 8,82 (s, 1H), 8,46 (s, 1H), 8,34 (s, 1H), 8,26 (s, 1H), 8,25 (s, 1H), 7,95 (dd, 1H), 7,72 (t, 1H), 7,65 (d, 1H), 4,35-4,3 (m, 2H), 3,26-3,18 (m, 2H), 2,76-2,71 (m, 2H), 2,1 (s, 3H), 1,75-1,67 (m, 2H), 1,48-1,4 (m, 2H), 1,37-1,31 (m, 2H), 1,25-1,22 (m, 1H), 1,1 (t, 3H)	Ejemplo 121

Ej.	Compuesto	Datos	SM
95	Ácido (*S*)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-hidroxi-4-metilpentan-2-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 604 para $C_{28}H_{28}F_3N_5O_5S$ RMN (d_6-DMSO) δ 15,08 (s, 1H), 9,47 (s, 1H), 8,89 (s, 1H), 8,53 (s, 1H), 8,37 (s, 1H), 8,32 (d, 1H), 8,2 (s, 1H), 7,85 (dd, 1H), 7,58 (t, 1H), 5,23 (s, 2H), 3,84-3,75 (m, 2H), 3,24-3,17 (m, 2H), 1,92-1,82 (m, 2H), 1,48-1,42 (m, 1H), 1,09 (t, 3H), 0,91 (d, 3H), 0,85 (d, 3H)	Ejemplo 119

Ejemplo 96



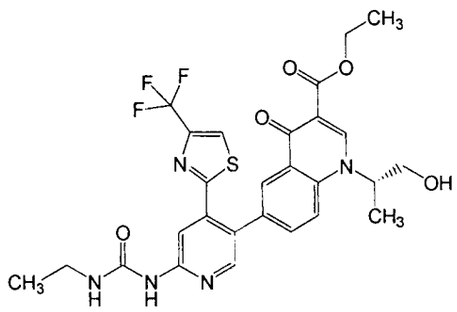
Una disolución de (*S*)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-hidroxi-4-metilpentan-2-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo (Ejemplo 119, 280 mg, 0,44 mmoles) en disolución al 33% en peso de metilamina en etanol absoluto (4 ml, 32,13 mmoles) se calentó en el microondas a 80 °C durante 30 min. La mezcla de reacción se concentró a presión reducida. La purificación vía cromatografía en columna (sílice, cloruro de metileno/metanol 95:5) dio (*S*)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-hidroxi-4-metilpentan-2-il)-N-metil-4-oxo-1,4-dihidroquinolin-3-carboxamida como un sólido amarillo claro (219,2 mg, 80 %).

MS (ESP): 617 para $C_{29}H_{31}F_3N_6O_4S$.

RMN (d_6-DMSO) δ 9,75-9,7 (m, 1H), 9,46 (s, 1H), 8,86 (s, 1H), 8,52 (s, 1H), 8,36 (s, 1H), 8,27 (d, 1H), 8,21 (s, 1H), 8,19 (d, 1H), 7,75 (dd, 1H), 7,62 (t, 1H), 5,19 (t, 1H), 5,12 (s, 1H), 3,79-3,7 (m, 2H), 3,25-3,17 (m, 2H), 2,86 (d, 3H), 1,96-1,85 (m, 1H), 1,85-1,74 (m, 1H), 1,48-1,34 (m, 1H), 1,11 (t, 3H), 0,91 (d, 3H), 0,85 (d, 3H).

Ejemplo 97

6-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-1-[(1*S*)-2-hidroxi-1-metiletil]-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo



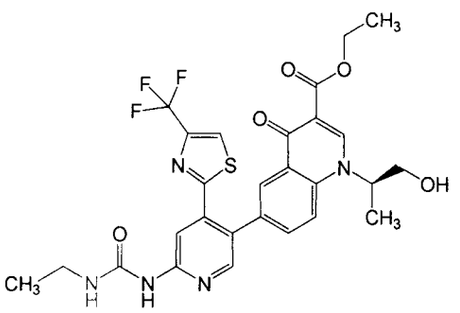
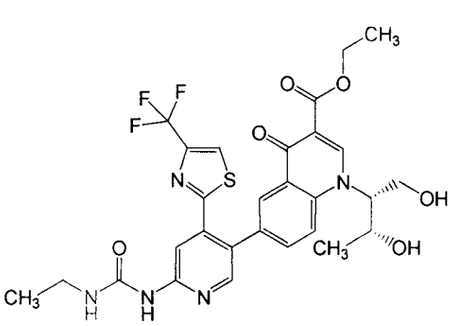
A una disolución de acetato de paladio (II) (28,0 mg, 0,12 mmoles, 0,1 equiv.) y 1,1'-bis(di-*t*-butilfosfino)ferroceno (59,1 mg, 0,12 mmoles, 0,1 equiv.) en acetonitrilo (3 ml) se añadió (*S*)-1-(1-hidroxipropan-2-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo (Intermediario 49, 500 mg, 1,25 mmoles), seguido de ácido 6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-ilborónico (Intermediario 17, 453 mg, 1,26 mmoles) y una disolución de carbonato de potasio (258 mg, 1,87 mmoles, 1,5 equiv.) en agua (1 ml). La mezcla de reacción se agitó a 60 °C durante 2 h, se enfrió hasta la temperatura ambiente, y se diluyó con agua (2 ml). El precipitado que se formó se recogió mediante filtración, se lavó con agua y hexanos, y se secó para proporcionar (*S*)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-hidroxipropan-2-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo como un sólido gris (583 mg, 79%).

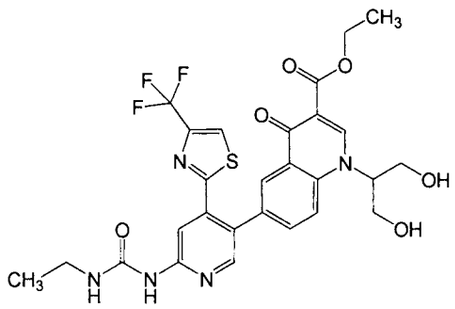
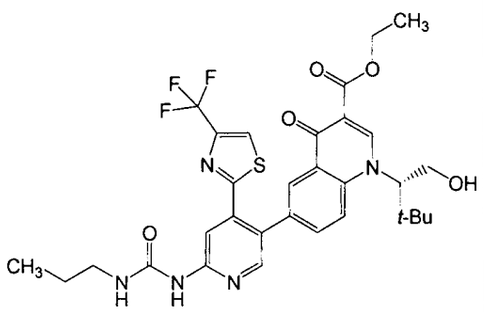
MS (ESP): 590 para $C_{27}H_{26}F_3N_5O_5S$.

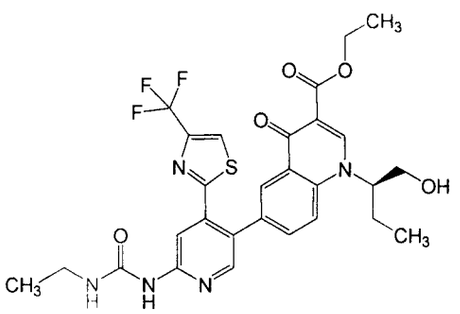
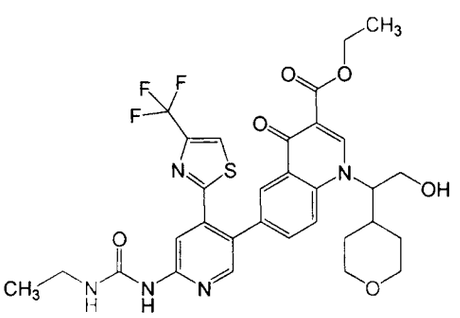
RMN (d_6-DMSO) δ 9,47 (s, 1H), 8,68 (s, 1H), 8,49 (s, 1H), 8,31 (s, 1H), 8,24 (s, 1H), 8,19 (d, 1h), 8,106 (d, 1H), 7,72 (dd, 1H), 7,66 (t, 1H), 5,26 (s, 1H), 5,11-5,06 (m, 1H), 4,28 (m, 2H), 3,79 (d, 2H), 3,25-3,17 (m, 2H), 1,51 (d, 3H), 1,29 (t, 3H), 1,11 (t, 3H).

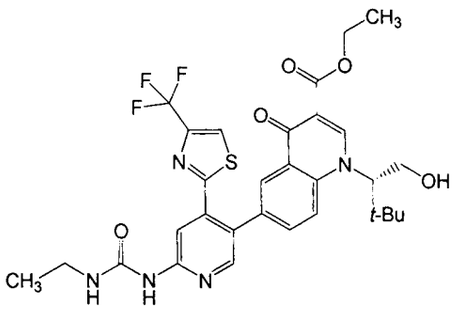
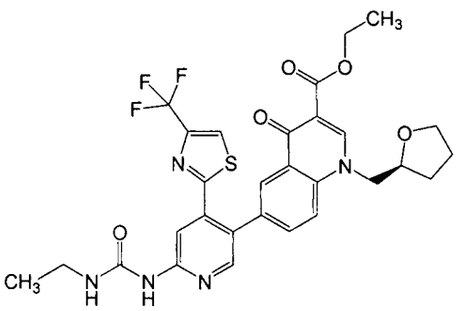
Ejemplos 98-108

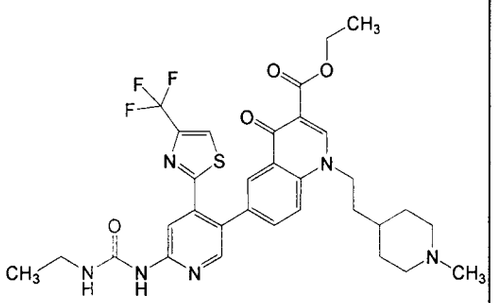
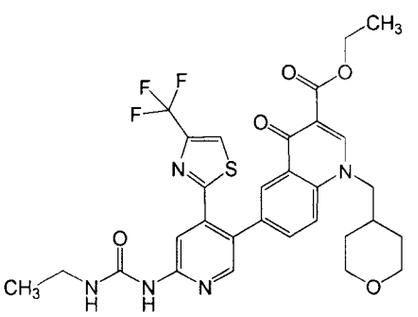
Los siguientes Ejemplos se prepararon mediante el procedimiento descrito en el Ejemplo 97 a partir del material de partida indicado.

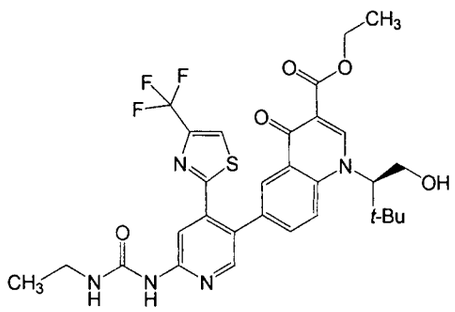
Ej.	Compuesto	Datos	SM
98	(*R*)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-hidroxipropan-2-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 590 para $C_{27}H_{26}F_3N_5O_5S$ RMN (d_6-DMSO) δ 9,48 (s, 1H), 8,68 (s, 1H), 8,49 (s, 1H), 8,31 (s, 1H),l 8,24 (s, 1h), 8,19 (d, 1H), 8,06 (d, 1H), 7,71 (dd, 2H), 5,35-5,25 (m, 1H), 5,11-5,06 (m, 1H), 4,28-4,21 (m, 2H), 3,79 (d, 2H), 3,25-3,19 (m, 2H), 1,51 (d, 3H), 1,29 (t, 3H), 1,11 (t, 3H)	Intermediario 48 e Intermediario 17
99	1-((2*R*,3*R*)-1,3-dihidroxibutan-2-il)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 620 para $C_{28}H_{28}F_3N_5O_6S$ RMN (d_6-DMSO) δ 9,47 (s, 1H), 8,89 (s, 1H), 8,51 (s, 1H), 8,32 (s, 1H), 8,23 (s, 1H), 8,17 (s, 1H), 8,07 (d, 1H), 7,7-7,65 (m, 2H), 5,22 (s, 1H), 4,87 (s, 1H), 4,25-4,22 (m, 3H), 3,97-3,82 (m, 2H), 3,25-3,18 (m, 2H), 1,28 (t, 3H), 1,13 (d, 3H), 1,11 (t, 3H)	Intermediario 50 e Intermediario 17

Ej.	Compuesto	Datos	SM
100	1-(1,3-dihidroxipropan-2-il)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 606 para $C_{27}H_{26}F_3N_5O_6S$ RMN (d_6-DMSO) δ 9,47 (s, 1H), 8,72 (s, 1H), 8,49 (s, 1H), 8,31(s, 1H), 8,24 (s, 1H), 8,19 (d, 1H0, 8,13 (s, 1H), 7,71 (dd, 1H), 5,3 (s, 1H), 4,54-4,36 (m, 2H), 4,25-4,14 (m, 2H), 4,04-3,86 (m, 2H), 3,24-3,14 (m, 4H), 1,27 (t, 3H), 1,11 (t, 3H)	Intermediario 52 e Intermediario 17
101	(*S*)-6-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-hidroxi-3,3-dimetilbutan-2-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 646 para $C_{31}H_{34}F_3N_5O_5S$	Intermediario 55 e Intermediario 47

Ej.	Compuesto	Datos	SM
102	(*R*)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-hidroxibutan-2-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 604 para $C_{28}H_{28}F_3N_5O_5S$ RMN (d_6-DMSO) δ 9,45 (s, 1H), 8,66 (s, 1H), 8,51 (s, 1H), 8,33 (s, 1H), 8,22 (s, 1H), 8,19 (d, 1H), 8,06 (d, 1H), 7,7-7,65 (m, 2H), 5,23-5,18 (m, 1H), 4,91 (s, 1H), 4,28-4,21 (m, 2H), 3,85-3,73 (m, 2H), 3,25-3,17 (m, 2H), 2,0-1,9 (m, 2H), 1,28 (t, 3H), 1,11 (t, 3H), 0,89 (t, 3H)	Intermediario 57 e Intermediario 17
103	6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(2-hidroxi-1-(tetrahidro-2H-piran-4-il)etil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 660 para $C_{31}H_{32}F_3N_5O_6S$ RMN (d_6-DMSO) δ 9,44 (s, 1H), 8,79 (s, 1H), 8,53 (s, 1H), 8,35 (s, 1H), 8,22 (s, 1H), 8,19 (d, 1H), 8,15 (d, 1H), 7,68-7,6 (m, 2H), 5,27-5,23 (m, 1H), 4,83 (s, 1H), 4,29-4,22 (m, 2H), 4,0-3,92 (m, 2H), 3,81-3,75 (m, 2H), 3,25-3,2 (m, 2H), 2,3-2,25 (m, 1H), 1,83-1,76 (m, 2H), 1,3 (t, 3H), 1,23-1,17 (m, 2H), 1,13 (t, 3H)	Intermediario 59 e Intermediario 17

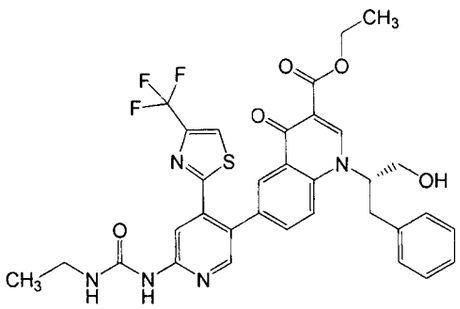
Ej.	Compuesto	Datos	SM
104	(*S*)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-hidroxi-3,3-dimetilbutan-2-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 632 para $C_{30}H_{32}F_3N_5O_5S$ RMN (d_6-DMSO) δ 9,45 (s, 1H), 8,65 (s, 1H), 8,53 (s, 1H), 8,34 (s, 1H), 8,21-8,17 (m, 3H), 7,63 (d, 2H), 5,12-5,09 (m, 1H), 4,97-4,92 (m, 1H), 4,29-4,2 (m, 2H), 4,05-4,0 (m, 2H), 3,26-3,18 (m, 2H), 1,28 (t, 3H), 1,11 (t, 3H), 0,97 (s, 9H)	Intermediario 55 e Intermediario 17
105	(*S*)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-((tetrahidrofuran-2-il)metil)-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 616 para $C_{29}H_{28}F_3N_5O_5S$ RMN (d_6-DMSO) δ 9,45 (s, 1H), 8,63 (s, 1H), 8,49 (s, 1H), 8,32 (s, 1H), 8,23 (s, 1H), 8,15 (d, 1H), 7,98 (d, 1H), 7,7 (dd, 1H), 7,67 (t, 1H), 4,67 (d, 1H), 4,35-4,3 (m, 1H), 4,27-4,21 (m, 2H), 4,2-4,18 (m, 1H), 3,83-3,79 (m, 1H), 3,67-3,62 (m, 1H), 3,25-3,19 (m, 2H), 2,1-2,04 (m, 1H), 1,92-1,8 (m, 2H), 1,64-1,55 (m, 2H), 1,28 (t, 3H), 1,11 (t, 3H)	Intermediario 61 e Intermediario 17

Ej.	Compuesto	Datos	SM
106	6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(2-(1-metilpiperidin-4-il)etil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 657 para $C_{32}H_{35}F_3N_6O_4S$ RMN (d_6-DMSO) δ 9,45 (s, 1H), 8,72 (s, 1H), 8,49 (s, 1H), 8,32 (s, 1H), 8,22 (s, 1H), 8,14 (s, 1H), 7,84 (d, 1H), 7,7 (dd, 1H), 7,62 (t, 1H), 4,48-4,4 (m, 1H), 4,27-4,19 (m, 2H), 3,25-3,19 (m, 2H), 2,82-2,72 (m, 2H), 2,15 (s, 3H), 1,86-1,82 (m, 2H), 1,75-1,68 (m, 2H), 1,28 (t, 3H), 1,11 (t, 3H)	Intermediario 69 e Intermediario 17
107	6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-((tetrahidro-2H-piran-4-il)metil)-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 630 para $C_{30}H_{30}F_3N_5O_5S$ RMN (d_6-DMSO) δ 9,45 (s, 1H), 8,68 (s, 1H), 8,51 (s, 1H), 8,33 (s, 1H), 8,21 (s, 1H), 8,14 (s, 1H), 7,96 (d, 1H), 7,68 (dd, 1H), 7,62 (t, 1H), 4,34 (d, 1H), 4,24-4,2 (m, 2H), 3,86 (d, 2H), 3,24-3,17 (m, 4H), 2,1-2,06 (m, 1H), 1,46-1,42 (m, 4H), 1,28 (t, 3H), 1,11 (t, 3H)	Intermediario 62 e Intermediario 17

Ej.	Compuesto	Datos	SM
108	(*R*)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-hidroxi-3,3-dimetilbutan-2-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 632 para $C_{30}H_{32}F_3N_5O_5S$	Intermediario 66 e Intermediario 17

Ejemplo 109

1-[(1*S*)-1-bencil-2-hidroxietil]-6-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo



A una disolución de acetato de paladio (II) (23,52 mg, 0,10 mmoles, 0,1 equiv.) y 1,1'-bis(di-*t*-butilfosfino)ferroceno (49,7 mg, 0,10 mmoles, 0,1 equiv.) en acetonitrilo (3 ml) se añadió (*S*)-1-(1-hidroxi-3-fenilpropan-2-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo (Intermediario 51, 500 mg, 1,05 mmoles), seguido de ácido 6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-ilborónico (Intermediario 17, 381 mg, 1,06 mmoles) y una disolución de carbonato de potasio (217 mg, 1,57 mmoles) en agua (1 ml). La mezcla de reacción se agitó a 60 °C durante 2 h, se enfrió hasta la temperatura ambiente, y se diluyó con agua (2 ml). La mezcla de reacción se repartió entre agua (10 ml) y acetato de etilo (10 ml). La capa acuosa se extrajo con acetato de etilo (2x10 ml), y los orgánicos se secaron sobre

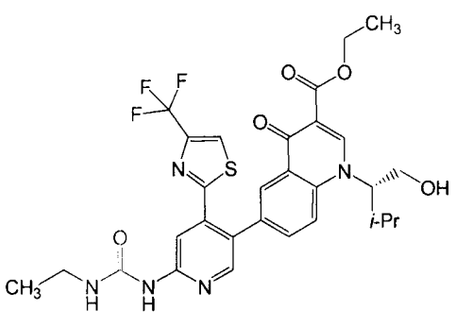
sulfato de sodio y se concentraron para proporcionar (*S*)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-hidroxi-3-fenilpropan-2-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo como un sólido gris (619 mg, 89%).

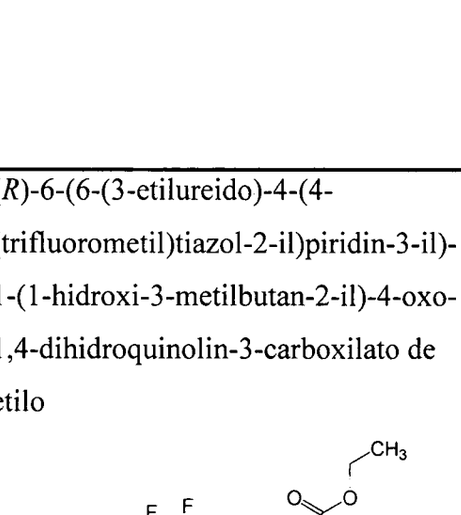
MS (ESP): 620 para $C_{28}H_{28}F_3N_5O_6S$.

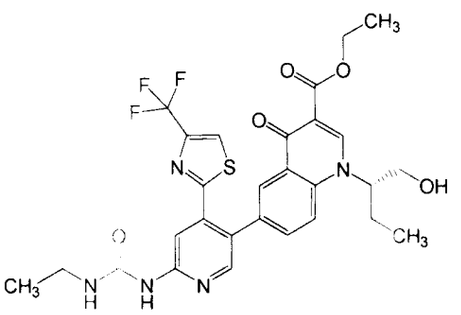
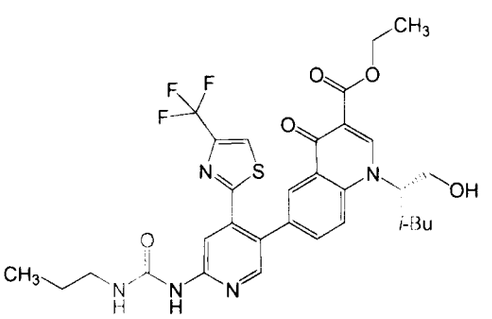
RMN (d_6-DMSO) δ 9,43 (s, 1H), 8,75 (s, 1H), 8,56 (s, 1H), 8,26 (s, 1H), 8,22 (s, 1H), 8,08 (d, 1H), 7,97 (d, 1H), 7,64-7,56 (m, 2H), 5,35-5,29 (m, 2H), 4,29-4,19 (m, 2H), 3,85 (s, 2H), 3,25-3,16 (m, 3H), 1,3 (t, 3H), 1,1 (t, 3H).

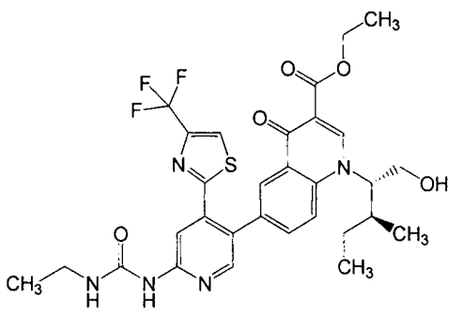
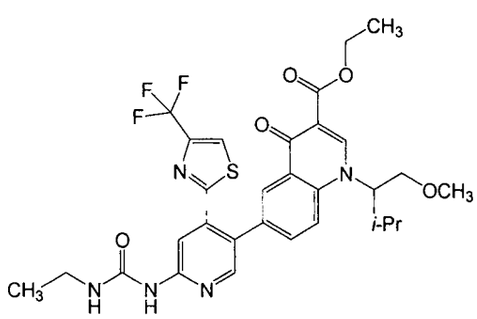
Ejemplos 110-119

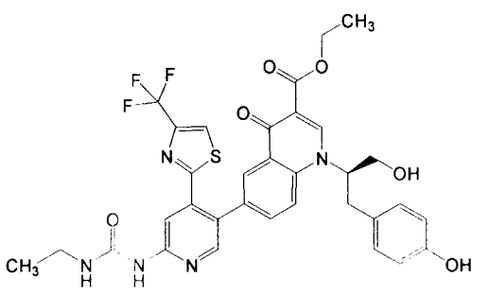
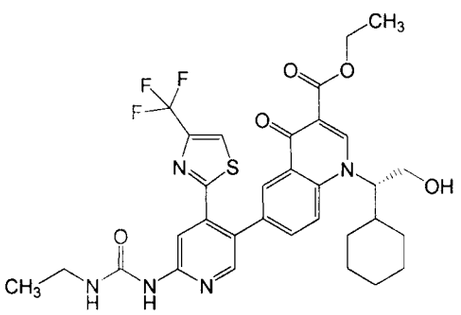
Los siguientes Ejemplos se prepararon mediante el procedimiento descrito en el Ejemplo 109 a partir del material de partida indicado.

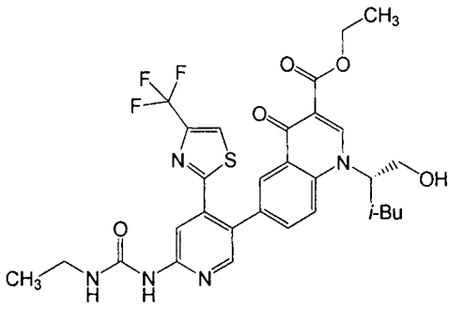
Ej.	Compuesto	Datos	SM
110	(*S*)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-hidroxi-3-metilbutan-2-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 618 para $C_{29}H_{30}F_3N_5O_5S$ RMN (d_6-DMSO) δ 9,44 (s, 1H), 8,72 (s, 1H), 8,51 (s, 1H), 8,33 (s, 1H), 8,2 (s, 1H), 8,17 (d, 1H), 8,11 (d, 1H), 7,62 (t, 2H), 5,22-5,17 (m, 1H), 4,68 (s, 1H), 4,27-4,2 (m, 2H), 3,95-3,91 (m, 1H), 3,8-3,74 (m, 1H), 3,24-3,15 (m 4H), 2,4-2,3 (m, 1H), 1,27 (t, 3H), 1,1 (t, 3H), 1,08 (d, 3H), 0,75 (d, 3H)	Intermediario 53 e Intermediario 17

Ej.	Compuesto	Datos	SM
111	(*R*)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-hidroxi-4-metilpentan-2-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 632 para $C_{30}H_{32}F_3N_5O_5S$ RMN (d_6-DMSO) δ 9,45 (s, 1H), 8,64 (s, 1H), 8,52 (s, 1H), 8,33 (s, 1H), 8,21 (s, 1H), 8,17 (d, 1H), 8,14 (d, 1H), 7,64 (t, 1H), 7,47 (dd, 1H), 5,19 (t, 1H), 5,02 (s, 1H), 4,27-4,2 (m, 3H), 3,76-3,72 (m, 2H), 3,25-3,15 (m, 4H), 1,9-1,78 (m, 1H), 1,76-1,72 (m, 1H), 1,56-1,45 (m, 2H), 1,28 (t, 3H), 1,11 (t, 3H), 0,92 (d, 3H), 0,86 (d, 3H)	Intermediario 54 e Intermediario 17
112	(*R*)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-hidroxi-3-metilbutan-2-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo	MS (ESP): 618 para $C_{29}H_{30}F_3N_5O_5S$ RMN (d_6-DMSO) δ 9,45 (s, 1H), 8,73 (s, 1H), 8,51 (s, 1H), 8,34 (s, 1H), 8,21 (s, 1H), 8,17 (d, 1H), 8,12 (d, 1H), 7,63 (t, 2H), 5,22-5,17 (m, 1H), 4,7 (s, 1H), 4,27-4,2 (m, 2H), 3,98-3,91 (m, 1H), 3,81-3,76 (m, 1H), 3,25-3,15 (m, 2H), 2,34-3,27 (m, 1H), 1,28 (t, 3H), 1,11 (t, 3H), 1,08 (d, 3H), 0,75 (d, 3H)	Intermediario 56 e Intermediario 17

Ej.	Compuesto	Datos	SM
113	(*S*)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-hidroxibutan-2-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 604 para $C_{28}H_{28}F_3N_5O_5S$ RMN (d_6-DMSO) δ 9,45 (s, 1H), 8,66 (s, 1H), 8,51 (s, 1H), 8,33 (s, 1H), 8,22 (s, 1H), 8,18 (d, 1H), 8,08 (d, 1H), 7,69 (dd, 1H), 7,66 (t, 1H), 5,23-5,18 (m, 1H), 4,91 (s, 1H), 4,27-4,2 (m, 2H), 3,83-3,75 (m, 2H), 3,25-3,17 (m, 2H), 2,07-1,9 (m, 2H), 1,28 (t, 3H), 1,11 (t, 3H), 0,88 (t, 3H)	Intermediario 58 e Intermediario 17
114	(*S*)-1-(1-hidroxi-3,3-dimetilbutan-2-il)-4-oxo-6-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 646 para $C_{31}H_{34}F_3N_5O_5S$ RMN (d_6-DMSO) δ 9,44 (s, 1H), 8,64 (s, 1H), 8,52 (s, 1H), 8,33 (s, 1H), 8,22 (s, 1H), 8,17 (d, 1H), 8,1 (d, 1H), 7,7-7,66 (m, 2H), 5,22-5,18 (m, 1H), 5,02 (s, 1H), 4,27-4,2 (m, 2H), 3,76-3,73 (m, 2H), 3,18-3,12 (m, 2H), 1,99-94 (m, 1H), 1,93-1,88 (s, 1H), 1,54-1,44 (m, 2H), 1,28 (t, 3H), 0,92 (d, 3H), 0,9 (s, 9H), 0,88 (d, 3H)	Intermediario 60 e Intermediario 47

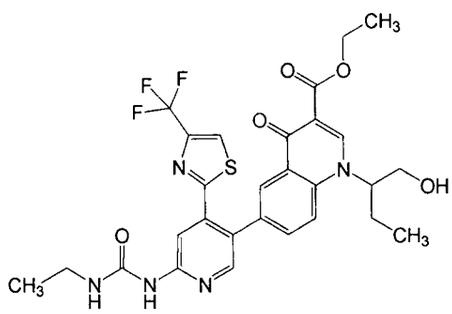
Ej.	Compuesto	Datos	SM
115	1-((2*S*,3*S*)-1,3-dihidroxipentan-2-il)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 632 para $C_{30}H_{32}F_3N_5O_5S$ RMN (d_6-DMSO) δ 9,45 (s, 1H), 8,72 (s, 1H), 8,52 (s, 1H), 8,34 (s, 1H), 8,2 (d, 1H), 8,09 (d, 1H), 7,68-7,60 (m, 2H), 5,2-5,17 (m, 1H), 4,76 (s, 1H), 4,27-4,2 (m, 2H), 4,01-3,94 (m, 1H), 3,8-3,75 (m, 1H), 3,24-3,16 (m, 2H), 2,13 (s, 1H), 1,27 (t, 3H), 1,11 (t, 3H), 0,77-0,73 (m, 4H)	Intermediario 63 e Intermediario 17
116	6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-metoxi-3-metilbutan-2-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 632 para $C_{30}H_{32}F_3N_5O_5S$ RMN (d_6-DMSO) δ 9,45 (s, 1H), 8,71 (s, 1H), 8,52 (s, 1H), 8,35 (s, 1H), 8,2-8,12 (m, 3H), 7,65-7,62 (m, 2H), 4,89 (s, 1H), 4,27-4,2 (m, 2H), 3,91 (s, 1H0, 3,74-3,71 (m, 1H), 3,26-3,21 (m, 2H), 3,25 (s, 3H), 2,3-2,27 (m, 2H), 1,28 (t, 3H), 1,11 (t, 3H), 0,75 (d, 3H)	Intermediario 70 e Intermediario 17

Ej.	Compuesto	Datos	SM
117	(*R*)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-hidroxi-3-(4-hidroxifenil)propan-2-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 682 para $C_{33}H_{30}F_3N_5O_6S$	Intermediario 67 e Intermediario 17
118	(*S*)-1-(1-ciclohexil-2-hidroxietil)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 658 para $C_{32}H_{34}F_3N_5O_5S$	Intermediario 68 e Intermediario 17

Ej.	Compuesto	Datos	SM
119	(*S*)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-hidroxi-4-metilpentan-2-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 632 para $C_{30}H_{32}F_3N_5O_5S$ RMN (d_6-DMSO) δ 9,45 (s, 1H), 8,64 (s, 1H), 8,52 (s, 1H), 8,33 (s, 1H), 8,21 (s, 1H), 8,18 (d, 1H), 8,1 (d, 1H), 7,69-7,61 (m, 2H), 5,21-5,18 (m, 1H), 5,02 (s, 1H), 4,27-4,21 (m, 2H), 3,78-3,71 (m, 2H), 3,25-3,17 (m, 2H), 1,92-1,84 (m, 1H), 1,78-1,74 (m, 1H), 1,49-1,42 (m, 1H), 1,28 (t, 3H), 1,11 (t, 3H), 0,92 (d, 3H), 0,86 (d, 3H)	Intermediario 60 e Intermediario 17

Ejemplo 120

6-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-1-[1-(hidroximetil)propil]-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo



A una suspensión de 1-(1-hidroxibutan-2-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo (Intermediario 64, 282 mg, 0,78 mmoles) y ácido 6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-ilborónico (Intermediario 17, 350 mg, 0,84 mmoles) en 1,4-dioxano (3 ml) se añadió una disolución de carbonato de cesio (467 mg, 1,43 mmoles) en agua (1 ml), seguido de tetraquis(trifenilfosfino)paladio(0) (48,7 mg, 0,04 mmoles). La mezcla de reacción se agitó a 100 °C durante 2 h, se enfrió hasta la temperatura ambiente, y se

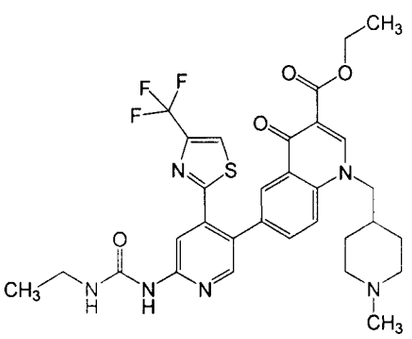
diluyó con agua (2 ml). El precipitado que se formó se recogió mediante filtración, se lavó con agua y hexanos. La purificación vía cromatografía en columna (sílice, cloruro de metileno/metanol 95:5) proporcionó 6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-hidroxibutan-2-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo como un sólido amarillo/naranja (136 mg, 27%).

MS (ESP): 604 para $C_{28}H_{28}F_3N_5O_5S$.

RMN (d_6-DMSO) δ 9,44 (s, 1H), 8,66 (s, 1H), 8,5 (s, 1H), 8,32 (s, 1H), 8,22 (s, 1H), 8,18 (d, 1H), 8,08 (d, 1H), 7,69-7,65 (m, 2H), 5,23-5,18 (m, 1H), 4,9 (s, 1H), 4,27-4,2 (m, 2H), 3,82-3,76 (m, 2H), 3,26-3,16 (m, 2H), 2,0-1,93 (m, 2H), 1,28 (t, 3H), 1,11 (t, 3H), 0,88 (t, 3H).

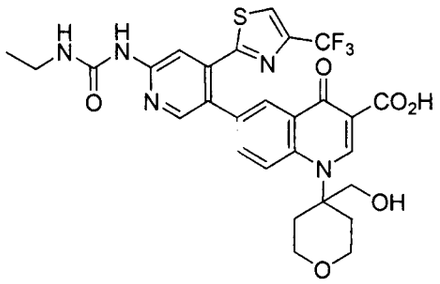
Ejemplo 121

El siguiente ejemplo se preparó mediante el procedimiento descrito en el Ejemplo 120 con el material de partida indicado.

Ej.	Compuesto	Datos	SM
121	6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-((1-metilpiperidin-4-il)metil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 643 para $C_{31}H_{33}F_3N_6O_4S$ RMN (d_6-DMSO) δ 9,47 (s, 1H), 8,72 (s, 1H), 8,5 (s, 1H), 8,23 (s, 1H), 8,31 (s, 1H), 8,15 (d, 1H), 7,97 (d, 1H), 7,72 (dd, 1H), 7,66 (t, 1H), 4,4-4,36 (m, 1H), 4,26-4,21 (m, 2H), 3,39-3,35 (m, 2H), 3,25-3,19 (m, 2H), 2,85-2,8 (m, 2H), 2,69 (d, 3H), 1,8-1,76 (m, 2H), 1,63-1,5 (m, 2H), 1,28 (t, 3H), 1,11 (t, 3H)	Intermediario 65 e Intermediario 17

Ejemplo 122

Ácido 6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(4-(hidroximetil)tetrahidro-2*H*-piran-4-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico



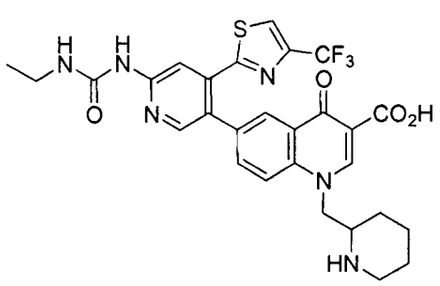
6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(4-(hidroximetil)tetrahidro-2*H*-piran-4-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo (Ejemplo 132, 0,225 g, 0,35 mmoles) se diluyó con MeOH:THF 2:1 (3 ml). Se añadió una disolución acuosa 2 M de LiOH (0,35 ml, 0,7 mmoles), y la mezcla de reacción se calentó en el microondas hasta 100 °C durante 15 min. La mezcla se concentró *a vacío* y se acidificó hasta aprox. pH 3 con HCl 1 N ac. El sólido resultante se recogió y purificó mediante cromatografía en columna (sílice, cloruro de metileno/metanol 95:5) seguido de purification mediante HPLC de fase inversa (C18, gradiente 0-95% de acetonitrilo/agua).

LC/MS (ES^+)[$(M+H)^+$]: 618 para $C_{28}H_{26}F_3N_5O_6S$

RMN ^1H (DMSO-d_6): δ14,93 (br s, 1H); 9,52 (s, 1H); 8,96 (s, 1H); 8,55 (s, 1H); 8,49 (m, 1H); 8,37 (m, 2H); 8,22 (s, 1H); 7,73 (m, 1H); 7,63 (m, 1H); 5,48 (t, 1H); 4,29 (m, 2H); 3,75 (m, 4 H); 3,21 (m, 2H); 2,54 –2,32 (br m, 4 H); 1,11 (t, 3H).

Ejemplo 123

Ácido 6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-(piperidin-2-ilmetil)-1,4-dihidroquinolin-3-carboxílico



Una disolución de ácido 1-((1-(terc-butoxicarbonil)piperidin-2-il)metil)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico (Ejemplo 138, 0,888 g, 1,27 mmoles) en THF (10 ml) y anisol (0,208 ml, 1,90 mmoles) se enfrió hasta 0 °C. Se añadió gota a gota una disolución 4 M de HCl en dioxano (9,5 ml, 38 mmoles). Después

de que la adición estuviese terminada, se retiró el baño de hielo, y la reacción se agitó a temperatura ambiente durante 1,5 h. Se añadieron 40 ml adicionales de HCl 4 M en dioxanos, y la mezcla de reacción se agitó durante 5 días. El volumen de la mezcla de reacción se redujo entonces a dos tercios, *a vacío*. Se añadió éter dietílico (15 ml) a la mezcla de reacción en N_2, y se agitó durante 1 h. El sólido resultante se recogió y enjuagó con éter. La purificación se llevó a cabo mediante HPLC de fase inversa (C18, gradiente 0-95% de acetonitrilo/agua) para proporcionar el producto deseado.

LC/MS (ES^+)[$(M+H)^+$]: 601 para $C_{28}H_{27}F_3N_6O_4S$

RMN ^1H (DMSO-d_6): δ9,48 (s, 1H); 8,94 (s, 1H); 8,53 (s, 1H); 8,37 (s, 1H); 8,31 (d, 1H); 8,21 (s, 1H); 8,13 (d, 1H); 7,82 (dd, 1H); 7,60 (m, 1H); 4,60 (dd, 1H); 4,34 (m, 1H); 3,21 (m, 2H); 2,86 (m, 2H); 2,30 (m, 1H); 1,73 (m, 2H); 1,47 (m, 1H); 1,27 (m, 2H); 1,11 (m, 1H); 1,11 (t, 3H).

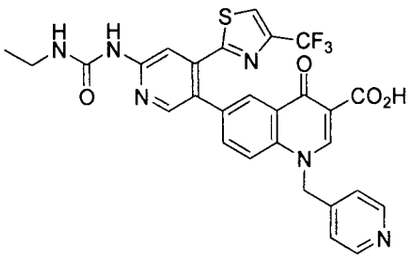
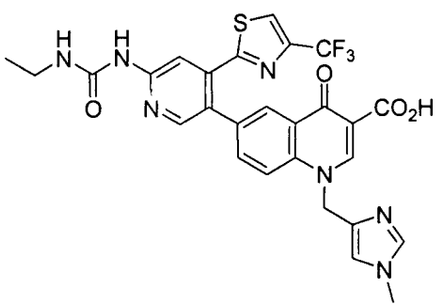
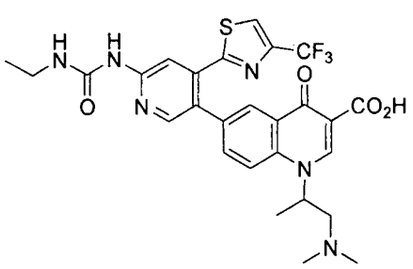
Ejemplos 124-127

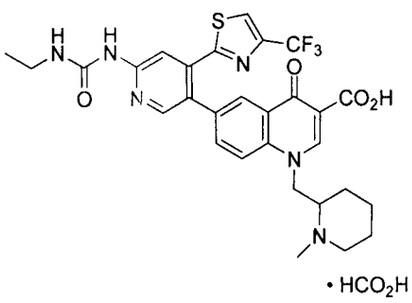
Procedimientos Generales

Los siguientes compuestos se prepararon mediante cualquiera de los procedimientos descritos más abajo a partir de los materiales de partida indicados en la tabla.

Procedimiento A: El éster etílico apropiado (1 eq) se diluyó con MeOH:THF 2:1. Se añadió una disolución ac. 2 M de LiOH (2 eq), y la mezcla de reacción se calentó en el microondas hasta 100 °C durante 15 min. La mezcla se concentró *a vacío*, y después se diluyó con CH_2Cl_2 y se enfrió hasta 0 °C. La mezcla se acidificó hasta aproximadamente pH 4 con HCl 1 N ac. Las capas se separaron, y la capa orgánica se concentró *a vacío*. La purificación se llevó a cabo mediante cromatografía en columna (sílice, cloruro de metileno/metanol 95:5) para proporcionar el producto deseado.

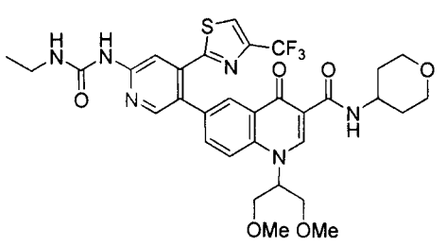
Procedimiento B: El éster etílico apropiado (1 eq) se diluyó con MeOH:THF 2:1. Se añadió una disolución ac. 2 M de LiOH (2 eq), y la mezcla de reacción se calentó en el microondas hasta 100 °C durante 15 min. La mezcla se enfrió hasta 0 °C, se acidificó con HCl 1 N ac y se concentró *a vacío*. La purificación se llevó a cabo mediante HPLC de fase inversa (C18, gradiente 0-95% de acetonitrilo/agua) para proporcionar el producto deseado.

Ej.	Compuesto	Datos	SM
124	Ácido 6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-(piridin-4-ilmetil)-1,4-dihidroquinolin-3-carboxílico 	LC/MS (ES^+)[$(M+H)^+$]:595 para $C_{28}H_{21}F_3N_6O_4S$ RMN ^1H (DMSO-d_6): δ14,96 (s, 1H); 9,46 (s, 1H); 9,33 (s, 1H); 8,53 (m, 3H); 8,33 (m, 2H); 8,19 (s, 1H); 7,74 (s, 2H); 7,57 (m, 1H); 7,22 (m, 2H); 5,97 (s, 2H); 3,20 (m, 2H); 1,10 (t, 3H).	Ejemplo 133
125	Ácido 6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-((1-metil-1H-imidazol-4-il)metil)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	LC/MS (ES^+)[$(M+H)^+$]: 598 para $C_{27}H_{22}F_3N_7O_4S$ RMN ^1H (DMSO-d_6): δ15,04 (br s, 1H); 9,48 (s, 1H); 9,19 (s, 1H); 8,49 (s, 1H); 8,33 (s, 1H); 8,27 (m, 2H); 8,21 (s, 1H); 7,82 (m, 1H); 7,61 (m, 1H); 7,54 (s, 1H); 7,31 (s, 1H); 5,66 (s, 2H); 3,59 (s, 3H); 3,20 (m, 2H); 1,10 (t, 3H).	Ejemplo 136
126	Ácido 1-(1-(dimetilamino)propan-2-il)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	LC/MS (ES^+)[$(M+H)^+$]: 589 para $C_{27}H_{27}F_3N_6O_4S$ RMN ^1H (DMSO-d_6): δ15,07 (s, 1H); 9,47 (s, 1H); 8,88 (s, 1H); 8,53 (s, 1H); 8,39 (s, 1H); 8,34 (d, 1H); 8,29 (d, 1H); 8,22 (s, 1H); 7,84 (m, 1H); 7,59 (m, 1H); 5,35 (br s, 1H); 3,22 (m, 2H); 3,10 (m, 1H); 2,62 (m, 1H); 2,14 (br s, 6H); 1,54 (m, 3H); 1,11 (t, 3H).	Ejemplo 134

127	Ácido 6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-((1-metilpiperidin-2-il)metil)-4-oxo-1,4-dihidroquinolin-3-carboxílico, sal del ácido fórmico 	LC/MS (ES^+)[$(M+H)^+$]: 615 para $C_{29}H_{29}F_3N_6O_4S$ RMN ^1H (DMSO-d_6): δ15,00 (br s, 1H); 9,46 (s, 1H); 9,01 (s, 1H); 8,53 (s, 1H); 8,39 (s, 1H); 8,30 (d, 1H); 8,21 (s, 1H); 8,14 (s, 1H); 8,05 (d, 1H); 7,84 (dd, 1H); 7,57 (m, 1H); 5,02 (m, 1H); 4,47 (m, 1H): 3,22 (m, 2H): 2,95 (m, 1H); 2,57 (m, 2H); 2,42 (s, 3H); 2,18 (m, 1H); 1,62 (m, 1H); 1,47 (m, 2H); 1,21 (m, 2H); 1,11 (t, 3H).	Ejemplo 135

Ejemplo 128

1-(1,3-dimetoxipropan-2-il)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-N-(tetrahidro-2H-piran-4-il)-1,4-dihidroquinolin-3-carboxamida

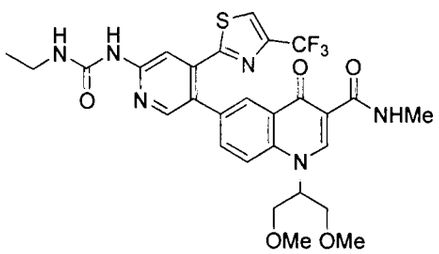


Se suspendió ácido 1-(1,3-dimetoxipropan-2-il)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico (Ejemplo 4, 0,112 g, 0,18 mmoles) en DMF (1 ml). Se añadió hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (HATU) (0,105 g, 0,28 mmoles), seguido de diisopropiletilamina (0,193 ml, 1,11 mmoles). La mezcla de reacción se agitó durante 15 min a RT. Se añadió hidrocloruro de 4-aminotetrahidropirano (0,038 g, 0,28 mmoles) en una porción, y la mezcla se agitó a RT durante 2 días. Se añadió agua, y el sólido resultante se purificó mediante cromatografía en columna (sílice, cloruro de metileno/metanol 95:5) para proporcionar el producto como un sólido. El sólido se purificó adicionalmente mediante trituración con CH_2Cl_2 y hexanos. LC/MS (ES^+)[$(M+H)^+$]: 689 para $C_{32}H_{35}F_3N_6O_6S$

RMN ^{1}H (DMSO-d_6): δ9,99 (m, 1H); 9,46 (s, 1H); 8,93 (s, 1H); 8,50 (s, 1H); 8,32 (d, 2H); 8,24 (s, 1H); 8,15 (d, 1H); 7,73 (m, 1H); 7,61 (m, 1H); 5,45 (br s, 1H); 3,92 (m, 7H); 3,45 (m, 2H); 3,25 (m, 8H); 1,87 (m, 2H); 1,50 (m, 2H); 1,11 (t, 3H).

Ejemplo 129

1-(1,3-dimetoxipropan-2-il)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-N-metil-4-oxo-1,4-dihidroquinolin-3-carboxamida



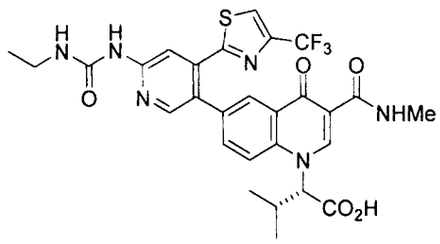
Se suspendió ácido 1-(1,3-dimetoxipropan-2-il)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico (Ejemplo 4, 0,112 g, 0,18 mmoles) en DMF (1 ml). Se añadió hexafluorofosfato de O-(7-Azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (HATU) (0,105 g, 0,28 mmoles), seguido de diisopropiletilamina (0,097 ml, 0,55 mmoles). La mezcla de reacción se agitó durante 15 min a RT. Se añadió una disolución 2,0 M de metilamina en THF (0,2 ml, 0,40 mmoles), y la mezcla se agitó a RT durante 2 d. Se añadió agua, y el precipitado sólido se purificó mediante cromatografía en columna (sílice, cloruro de metileno/metanol 95:5). El sólido se purificó adicionalmente mediante trituración con CH_2Cl_2 y hexanos.

LC/MS (ES^+)[$(M+H)^+$]: 619 para $C_{28}H_{29}F_3N_6O_5S$

RMN ^{1}H (DMSO-d_6): δ9,69 (m, 1H); 9,46 (s, 1H); 8,92 (s, 1H); 8,50 (s, 1H); 8,29 (m, 3H); 8,14 (d, 1H); 7,74 (m, 1H); 7,63 (m, 1H); 5,44 (br s, 1H); 3,84 (m, 4H); 3,25 (m, 8H); 2,86 (m, 3H); 1,11 (t, 3H).

Ejemplo 130

Ácido (S)-2-(6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-3-(metilcarbamoil)-4-oxoquinolin-1(4*H*)-il)-3-metilbutanoico



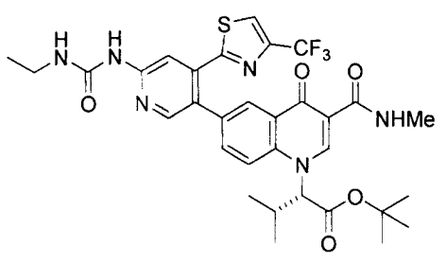
Se diluyó (S)-2-(6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-3-(metilcarbamoil)-4-oxoquinolin-1(4H)-il)-3-metilbutanoato de *terc*-butilo (Ejemplo 131, 0,079 g, 0,12 mmoles) con CH_2Cl_2 (4 ml). Se añadió trietilsilano (0,047 ml, 0,29 mmoles), seguido inmediatamente de la adición de ácido trifluoroacético (0,118 ml, 1,53 mmoles). La disolución se agitó a RT toda la noche. Se añadieron 26 eq adicionales de TFA (0,24 ml) y 5 eq de trietilsilano (0,1 ml), y la mezcla se agitó durante 2 d. La mezcla se concentró *a vacío*, después se diluyó con éter y se concentró *a vacío* nuevamente. Se añadió éter al residuo, y el sólido resultante se recogió y se lavó con éter. El sólido se purificó mediante trituración con EtOAc.

LC/MS (ES^+)[$(M+H)^+$]: 617 para $C_{28}H_{27}F_3N_6O_5S$

RMN ^1H (DMSO-d_6): δ9,64 (s, 1H); 9,46 (s, 1H); 8,91 (s, 1H); 8,50 (s, 1H); 8,36 (s, 1H); 8,23 (m, 2H); 7,76 (m, 1H); 7,62 (s, 1H); 5,43 (s, 1H); 3,21 (m, 3H); 2,86 (m, 3H); 1,13 (m, 6H); 0,81 (br s, 3H).

Ejemplo 131

2-(6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-3-(metilcarbamoil)-4-oxoquinolin-1(4*H*)-il)-3-metilbutanoato de (S)-terc-butilo



Una disolución de (S)-1-(1-*terc*-butoxi-3-metil-1-oxobutan-2-il)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo (Ejemplo 137, 0,100 g, 0,15 mmoles) en disolución al 33% en peso de metilamina en etanol absoluto (3 ml, 24,1 mmoles) se calentó en el microondas hasta 80 °C durante 15 min. La

mezcla se concentró *a vacío* y se purificó mediante cromatografía en columna (sílice, cloruro de metileno/metanol 95:5) para proporcionar el producto deseado.

LC/MS (ES^+)[$(M+H)^+$]: 673 para $C_{32}H_{35}F_3N_6O_5S$

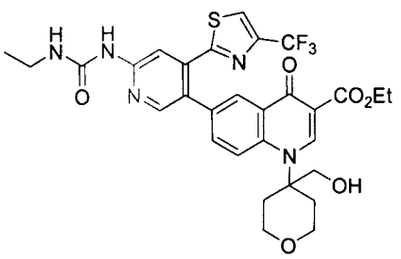
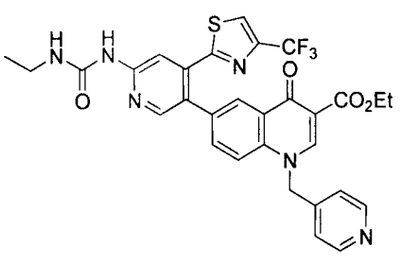
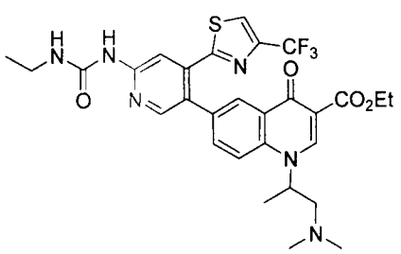
RMN ^1H (DMSO-d_6): δ9,62 (m, 1H); 9,46 (s, 1H); 8,90 (br s, 1H); 8,53 (s, 1H); 8,37 (s, 1H); 8,25 (d, 1H); 8,18 (s, 1H); 7,75 (m, 1H); 7,60 (m, 2H); 5,43 (m, 1H); 3,21 (m, 2H); 2,86 (d, 3H); 2,59 (m, 1H); 1,36 (br s, 9H); 1,17 (br s, 3H); 1,11 (t, 3H); 0,82 (br s, 3H).

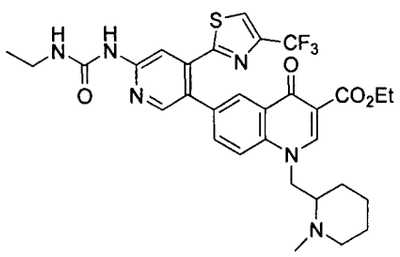
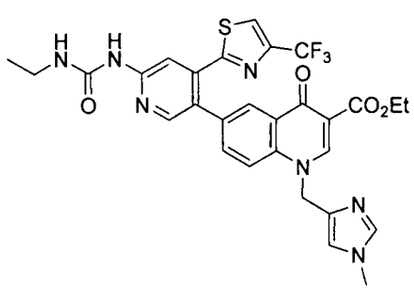
Ejemplos 132-137

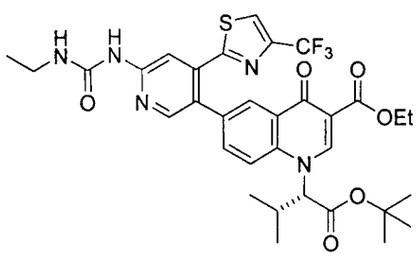
Los siguientes compuestos se sintetizaron mediante cualquiera de los procedimientos descritos más abajo a partir del material de partida en la tabla.

Procedimiento A: Se combinaron ácido 6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-ilborónico (Intermediario 17) (1 eq) y el yoduro de arilo apropiado (1 eq), y se diluyeron con dioxano. Se añadió una disolución de Cs_2CO_3 (1,7 eq) en agua (se usó una relación 4:1 de dioxano a agua en la reacción). Se añadió tetraquis(trifenilfosfina)paladio(0) (0,1 eq), y la mezcla de reacción se calentó a 100 °C. Tras enfriar hasta RT, se añadió agua, y se recogió el sólido resultante. En algunos casos, la purification se llevó a cabo mediante cromatografía en columna.

Procedimiento B: Se combinaron ácido 6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-ilborónico (Intermediario 17) (1 eq) y el yoduro de arilo apropiado (1 eq) , y se diluyeron con dioxano. Se añadió una disolución de Cs_2CO_3 (3 eq) en agua (se usó una relación 4:1 de dioxano a agua en la reacción). Se añadió tetraquis(trifenilfosfina)paladio(0) (0,1 eq), y la mezcla de reacción se calentó a 100 °C. Tras enfriar hasta RT, se añadió agua, y se recogió el sólido resultante. El sólido se purificó mediante cromatografía en columna.

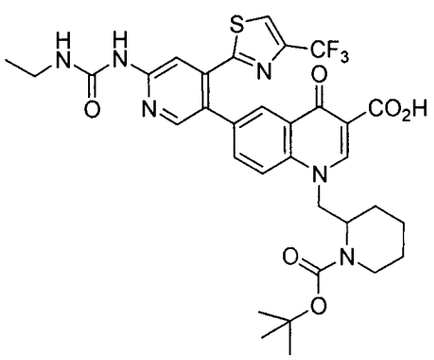
Ej.	Compuesto	Datos	SM
132	6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(4-(hidroximetil)tetrahidro-2H-piran-4-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	LC/MS (ES^+)[$(M+H)^+$]: 646 para $C_{30}H_{30}F_3N_5O_6S$	Intermediario 71
133	6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-(piridin-4-ilmetil)-1,4-dihidroquinolin-3-carboxilato de etilo 	LC/MS (ES^+)[$(M+H)^+$]: 623 para $C_{30}H_{25}F_3N_6O_4S$	Intermediario 73
134	1-(1-(dimetilamino)propan-2-il)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	LC/MS (ES^+)[$(M+H)^+$]: 617 para $C_{29}H_{31}F_3N_6O_4S$ RMN ^1H (DMSO-d_6): δ9,45 (s, 1H); 8,58 (s, 1H); 8,51 (d, 1H); 8,33 (s, 1H); 8,22 (s, 1H); 8,18 (d, 1H); 8,09 (d, 1H); 7,67 (dd, 1H); 7,63 (m, 1H); 5,12 (m, 1H); 4,22 (m, 2H); 3,21 (m, 2H); 2,99 (m, 1H); 2,57 (m, 1H); 2,15 (br s, 6H); 1,44 (d, 3H); 1,28 (t, 3H); 1,11 (t, 3H).	Intermediario 74

135	6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-((1-metilpiperidin-2-il)metil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	LC/MS (ES^+)[$(M+H)^+$]: 643 para $C_{31}H_{33}F_3N_6O_4S$ RMN ^1H (DMSO-d_6): δ9,45 (s, 1H); 8,68 (s, 1H); 8,51 (d, 1H); 8,34 (s, 1H); 8,21 (s, 1H); 8,14 (d, 1H); 7,84 (d, 1H); 7,68 (dd, 1H); 7,61 (m, 1H); 4,86 (m, 1H); 4,23 (q, 2H); 4,22 (m, 1H); 3,21 (m, 2H); 2,85 (m, 1H); 2,45 (m, 1H); 2,38 (s, 3H); 2,10 (m, 1H); 1,63 (m, 1H); 1,46 (m, 2H); 1,28 (t, 3H); 1,26 (m, 2H); 1,11 (t, 3H); 1,11 (m, 1H).	Intermediario 75
136	6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-((1-metil-1H-imidazol-4-il)metil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	LC/MS (ES^+)[$(M+H)^+$]: 626 para $C_{29}H_{26}F_3N_7O_4S$	Intermediario 76

137	(S)-1-(1-terc-butoxi-3-metil-1-oxobutan-2-il)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	LC/MS (ES^+)[$(M+H)^+$]: 688 para $C_{33}H_{36}F_3N_5O_6S$ RMN ^1H (DMSO-d_6): δ9,46 (s, 1H); 8,70 (br m , 1H); 8,53 (s, 1H); 8,35 (m, 1H); 8,17 (m, 2H); 7,64 (m, 3H); 5,32 (m, 1H); 4,25 (q, 2H); 3,21 (m, 2H); 2,59 (m, 1H); 1,37 (br s, 9H); 1,28 (t, 3H); 1,17 (br s, 3H); 1,11 (t, 3H); 0,83 (br s, 3H).	Intermediario 77

Ejemplo 138

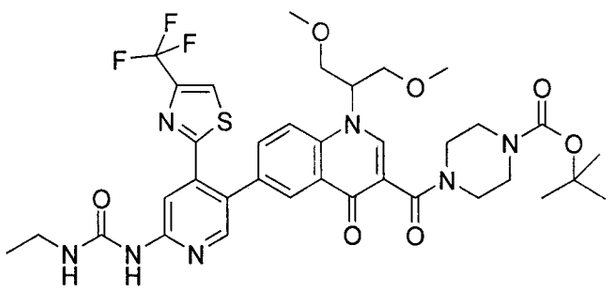
Ácido 1-((1-(terc-butoxicarbonil)piperidin-2-il)metil)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico



Se combinaron ácido 6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-ilborónico (Intermediario 17, 0,448 g, 1,24 mmoles) y 1-((1-(terc-butoxicarbonil)piperidin-2-il)metil)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo (Intermediario 72, 0,672 g, 1,24 mmoles), y se diluyeron con dioxano (6 ml). Se añadió una disolución de Cs_2CO_3 (0,689 g, 2,11 mmoles) en agua (1,5 ml). Se añadió tetraquis(trifenilfosfina)paladio(0) (0,144 g, 0,12 mmoles). La mezcla se calentó a 100 °C toda la noche. Tras enfriar hasta RT, se añadieron agua y MeOH, y la mezcla se concentró *a vacío*. El residuo se acidificó con HCl 1 N ac, y después se secó en un liofilizador. El sólido resultante se diluyó con EtOAc y agua, y las capas se separaron. La capa orgánica se lavó con agua, salmuera, se secó sobre Na_2SO_4 y se concentró *a vacío* para dar el compuesto del título, que se usó sin purificación adicional.
LC/MS (ES^+)[$(M+H)^+$]: 701 para $C_{33}H_{35}F_3N_6O_6S$

Ejemplo 139

4-{[1-(1,3-dimetoxipropan-2-il)-6-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-4-oxo-1,4-dihidroquinolin-3-il]carbonil}piperazin-1-carboxilato de terc-butilo



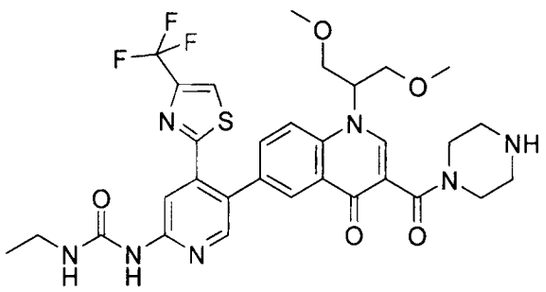
Una disolución de 4-{[1-(1,3-dimetoxipropan-2-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-il]carbonil}piperazin-1-carboxilato de terc-butilo (Intermediario 79, 400 mg, 0,68 mmoles) en dimetilformamida (15 ml) se purgó con gas argón, y después se añadió tetraquis(trifenilfosfina)paladio (69,25 mg, 0,06 mmoles) seguido de 1-etil-3-{5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-2-il}urea (Intermediario 17, 360 mg, 0,82 mmoles). La mezcla se agitó a temperatura ambiente, y se añadió carbonato de sodio (217 mg, 2,05 mmoles), que se disolvió en una cantidad mínima de agua, y la mezcla de reacción se calentó hasta 95 °C durante 3 h. Tras completar la reacción, la mezcla de reacción se enfrió hasta la temperatura ambiente, se filtró a través de celita, y el filtrado se vertió en agua (200 ml) y se agitó durante 30 min. El sólido obtenido se filtró y se secó para dar el compuesto bruto. El bruto se purificó mediante cromatografía en columna, eluyendo con un gradiente de 30% de acetato de etilo / éter de petróleo hasta 60% de acetato de etilo / éter de petróleo, para dar 260 mg (49%) de 4-{[1-(1,3-dimetoxipropan-2-il)-6-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-4-oxo-1,4-dihidroquinolin-3-il]carbonil}piperazin-1-carboxilato de terc-butilo.

RMN ^{1}H (400 MHz, DMSO-d_6): δ 1,13 (t, 3H), 1,41 (s, 9H), 3,02 (s, 3H), 3,18 – 3,29 (m, 8H), 3,31 – 3,72 (m, 8H), 3,79 (m, 1H), 4,48 (m, 1H), 7,63 (d, 1H), 7,74 (d, 1H), 8,06 (d, 1H), 8,37 (2s, 2H), 8,39 (s, 1H), 8,47 (s, 1H), 8,75 (s, 1H), 9,47 (s, 1H).

Masas (Barrido APCI +ve): m/z 774 (M+H).

Ejemplo 140

1-{5-[1-(1,3-dimetoxipropan-2-il)-4-oxo-3-(piperazin-1-ilcarbonil)-1,4-dihidroquinolin-6-il]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-2-il}-3-etilurea



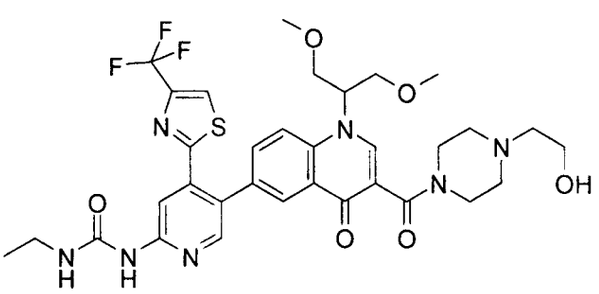
Se disolvió 4-{[1-(1,3-dimetoxipropan-2-il)-6-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-4-oxo-1,4-dihidroquinolin-3-il]carbonil}piperazin-1-carboxilato de terc-butilo (Ejemplo 139, 260 mg, 0,33 mmoles) en diclorometano (15 ml). Se añadió ácido trifluoroacético (195 mg, 1,68 mmoles) a la mezcla, y se agitó durante 30 h a temperatura ambiente. La mezcla de reacción se concentró, y el pH se ajustó hasta 8 con disolución saturada de bicarbonato de sodio para dar un compuesto sólido que se filtró y se secó para dar 160 mg (72%) de 1-{5-[1-(1,3-dimetoxipropan-2-il)-4-oxo-3-(piperazin-1-ilcarbonil)-1,4-dihidroquinolin-6-il]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-2-il}-3-etilurea.

RMN ^{1}H (400 MHz, DMSO-d_6): δ 1,13 (t, 3H), 2,4-2-82 (m, 3H), 3,02 (s, 3H), 3,18 – 3,29 (m, 7H), 3,31 – 3,72 (m, 8H), 3,79 (m, 1H), 4,48 (m, 1H), 7,63 (d, 1H), 7,74 (d, 1H), 8,06 (d, 1H), 8,37 (2s, 2H), 8,39 (s, 1H), 8,47 (s, 1H), 8,75 (s, 1H), 9,47 (s, 1H).

LC-MS: m/z 674 (M+H).

Ejemplo 141

1-{5-[1-(1,3-dimetoxipropan-2-il)-3-{[4-(2-hidroxietil)piperazin-1-il]carbonil}-4-oxo-1,4-dihidroquinolin-6-il]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-2-il}-3-etilurea



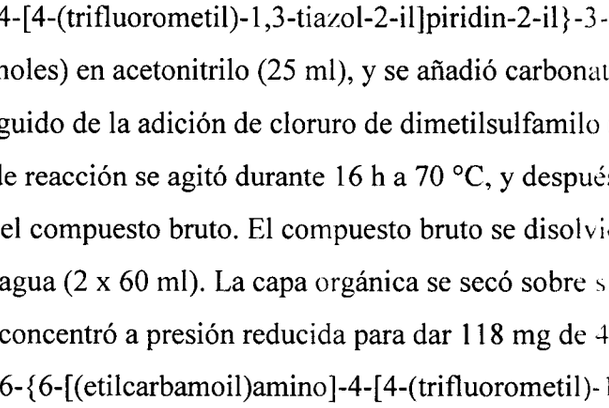
Se disolvió 1-{5-[1-(1,3-dimetoxipropan-2-il)-4-oxo-3-(piperazin-1-ilcarbonil)-1,4-dihidroquinolin-6-il]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-2-il}-3-etilurea (Ejemplo 140, 180 mg, 0,267 mmoles) en acetonitrilo (15 ml). Se añadió carbonato de potasio (73,7 mg,

0,53 mmoles), seguido de la adición de 2-bromoetanol (40 mg, 0,32 mmoles), y la mezcla se calentó hasta 55 °C durante 16 h. La mezcla de reacción se filtró, y el filtrado se concentró y se secó para dar el compuesto bruto. El bruto se disolvió en agua (10 ml), y el pH se ajustó hasta 2. La disolución acuosa se lavó con acetato de etilo, después se basificó hasta pH~8 con disolución saturada de bicarbonato de sodio, y después se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio anhidro, se filtró y se concentró a presión reducida para dar 65 mg (34%) de 1-{5-[1-(1,3-dimetoxipropan-2-il)-3-{[4-(2-hidroxietil)piperazin-1-il]carbonil}-4-oxo-1,4-dihidroquinolin-6-il]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-2-il}-3-etilurea como un sólido blanquecino.

RMN ^{1}H (400 MHz, DMSO-d_6): δ 1,09 (t, 3H), 2,41 – 2,44 (m, 5H), 2,66 (m, 1H), 3,04 (s, 3H), 3,21 – 3,24 (m, 7H), 3,49 – 3,60 (m, 7H), 3,77 (br s, 1H), 4,39 (t, 1H), 4,53 (t, 1H), 7,60 (s, 1H), 7,70 (d, 1H), 8,03 (d, 1H), 8,26 (s, 2H), 8,43 (d, 2H), 8,70 (s, 1H), 9,44 (s, 1H).
LC-MS: m/z 718,5 (M+H).

Ejemplo 142

4-{[1-(1,3-dimetoxipropan-2-il)-6-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-4-oxo-1,4-dihidroquinolin-3-il]carbonil}-N,N-dimetilpiperazin-1-sulfonamida

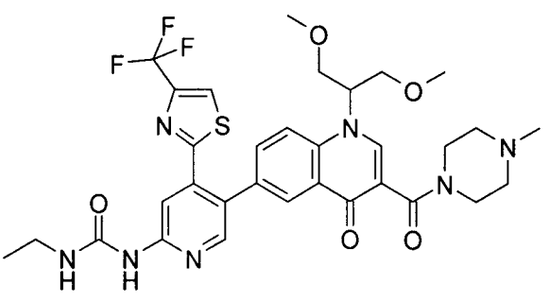


Se disolvió 1-{5-[1-(1,3-dimetoxipropan-2-il)-4-oxo-3-(piperazin-1-ilcarbonil)-1,4-dihidroquinolin-6-il]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-2-il}-3-etilurea (Ejemplo 140, 250 mg, 0,37 mmoles) en acetonitrilo (25 ml), y se añadió carbonato de potasio (204,7 mg, 1,48 mmoles), seguido de la adición de cloruro de dimetilsulfamilo (133 mg, 0,92 mmoles). La mezcla de reacción se agitó durante 16 h a 70 °C, y después se filtró. El filtrado se concentró para dar el compuesto bruto. El compuesto bruto se disolvió en acetato de etilo (60 ml) y se lavó con agua (2 x 60 ml). La capa orgánica se secó sobre sulfato de sodio anhidro, se filtró y se concentró a presión reducida para dar 118 mg de 4-{[1-(1,3-dimetoxipropan-2-il)-6-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-4-oxo-1,4-dihidroquinolin-3-il]carbonil}-N,N-dimetilpiperazin-1-sulfonamida.

RMN ^{1}H (400 MHz, DMSO-d_6): δ 1,07 – 1,13 (m, 4H), 2,74 – 2,78 (m, 6H), 3,04 (s, 3H), 3,13 – 3,20 (m, 1H), 3,25 – 3,37 (m, 6H), 3,42 (m, 3H), 3,51 (d, 3H), 3,68 – 3,69 (br d, 1H), 3,85 (br d, 1H), 4,47 – 4,50 (t, 1H), 7,59 (s, 1H), 7,69 – 7,72 (d, 1H), 8,04 – 8,08 (m, 1H), LC-MS: m/z 781 (M+H).

Ejemplo 143

1-(5-{1-(1,3-dimetoxipropan-2-il)-3-[(4-metilpiperazin-1-il)carbonil]-4-oxo-1,4-dihidroquinolin-6-il}-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-2-il)-3-etilurea



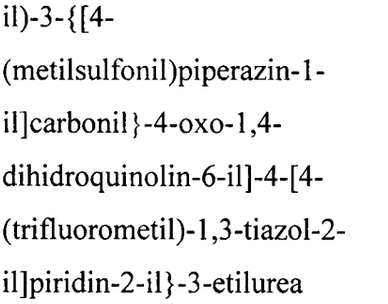
Se preparó una disolución de 1-(1,3-dimetoxipropan-2-il)-6-yodo-3-[(4-metilpiperazin-1-il)carbonil]quinolin-4(1H)-ona (Intermediario 80, 300 mg, 0,6012 mmoles) en dimetilformamida (10 ml). La disolución se purgó con gas argón, y se añadió tetraquis(trifenilfosfina)paladio (69,25 mg, 0,060 mmoles) seguido de 1-etil-3-{5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-2-il}urea (Intermediario 17, 398 mg, 0,90mmoles), y la mezcla se agitó a temperatura ambiente. Se disolvió carbonato de sodio (125 mg, 1,18 mmoles) en una cantidad mínima de agua, y la disolución se añadió a la mezcla de reacción. La mezcla de reacción se calentó hasta 95 °C durante 3 h. Tras completar la reacción, la mezcla de reacción se enfrió hasta la temperatura ambiente, se filtró a través de celita, y el filtrado se vertió en agua (200 ml) y se agitó durante ½ h. El sólido obtenido se filtró y se secó para obtener un producto bruto que se purificó mediante cromatografía en columna, eluyendo con un gradiente de 100% de acetato de etilo hasta 55 de metanol / acetato de etilo, para dar 150 mg (48%) de 1-(5-{1-(1,3-dimetoxipropan-2-il)-3-[(4-metilpiperazin-1-il)carbonil]-4-oxo-1,4-dihidroquinolin-6-il}-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-2-il)-3-etilurea.

RMN ^{1}H (400 MHz, DMSO-d_6): δ 1,14 (t, 3H), 2,22 (s, 4H), 2,34 (d, 2H), 2,37 (d, 2H), 3,04 (s, 3H), 3,18 – 3,33 (m, 7H), 3,42 (m, 1H), 3,44 – 3,56(m, 4H), 4,83 (s, 1H), 4,51 (m, 1H), 7,64 (d, 1H), 7,72 (d, 1H), 8,06 (d, 1H), 8,28 (d, 2H), 8,37 (s, 1H), 8,46 (s, 1H), 8,72 (s, 1H), 9,48 (s, 1H).

LC-MS: m/z 688,5 (M+H) a 98,23%

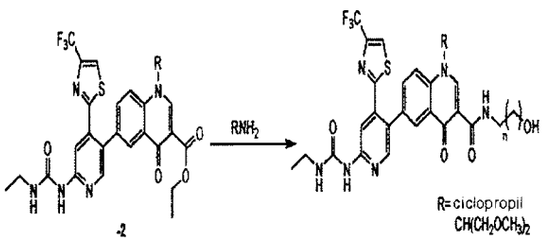
Ejemplos 144-145

Los siguientes compuestos se prepararon según el procedimiento descrito para el Ejemplo 143 a partir de los materiales de partida indicados en la tabla.

Ej.	Compuesto	Datos	SM
144	1-(5-{3-[(4-acetilpiperazin-1-il)carbonil]-1-(1,3-dimetoxipropan-2-il)-4-oxo-1,4-dihidroquinolin-6-il}-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-2-il)-3-etilurea 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 1,14 (t, 3H), 2,19 (d, 3H), 3,05 (s, 3H), 3,11 – 3,33 (m, 6H), 3,38 (m, 2H), 3,32 – 3,84 (m, 8H), 4,52 (m, 1H), 7,63 (d, 1H), 7,74 (d, 1H), 8,06 (d, 1H), 8,21 (s, 1H), 8,24 (d, 1H), 8,37 (s, 1H), 8,46 (s, 1H), 8,77 (d, 1H), 9,48 (s, 1H). LC-MS: m/z 716,5 (M+H) .	Intermediario 81 e Intermediario 17
145	1-{5-[1-(1,3-dimetoxipropan-2-il)-3-{[4-(metilsulfonil)piperazin-1-il]carbonil}-4-oxo-1,4-dihidroquinolin-6-il]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-2-il}-3-etilurea	RMN ^{1}H (400 MHz, DMSO-d_6): δ 1,14 (t, 3H), 2,92 (s, 3H), 3,06 (s, 3H), 3,11 – 3,24 (m, 6H), 3,33 - 3,46 (m, 4H), 3,52 (m, 3H), 3,64 (m, 1H), 4,04 (m, 1H), 4,48 (m, 1H), 7,62 (d, 1H), 7,74 (d, 1H), 8,06 (d, 1H), 8,26 (s, 1H), 8,32 (s, 1H), 8,38 (s, 3H), 8,46 (s, 1H), 8,76 (s, 1H), 9,46 (s, 1H). LC-MS: m/z 752 (M+H).	Intermediario 82 e Intermediario 17

Ejemplo 146

1-ciclopropil-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-N-(2-hidroxietil)-4-oxo-1,4-dihidroquinolin-3-carboxamida



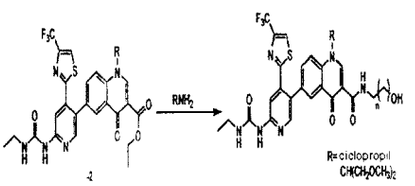
Una suspensión de 1-ciclopropil-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-N-(2-hidroxietil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo (Ejemplo 58, 50 mg, 0,09 mmoles) en etanolamina (0,5 ml) se calentó hasta 100°C en un microondas durante 30 min. La mezcla de reacción se enfrió hasta la temperatura ambiente. El precipitado que se formó se aisló mediante filtración y se lavó con metil-terc-butiléter y agua, y después se secó para dar 20 mg de un sólido blanco.

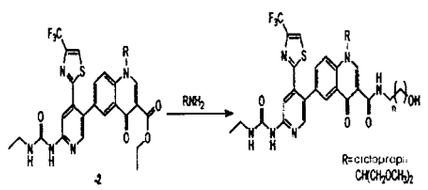
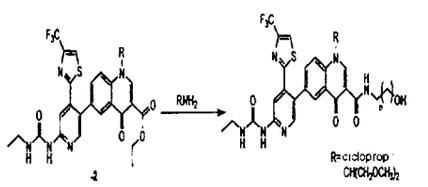
MS (ESP): 587 (MH^+) para $C_{27}H_{25}F_3N_6O_4S$

RMN ^1H (300 MHz, DMSO-d_6): δ 1,11 (m, 4H), 1,32 (m, 3H), 3,21 (q, 2H), 3,42 (q, 2H), 3,50 (q, 2H), 3,79 (brs, 1H), 4,82 (t, 1H), 7,65 (t, 1H), 7,79 (d, 1H), 8,20 (s, 1H), 8,25 (m, 2H), 8,32 (s, 1H), 8,48 (s, 1H), 8,75 (s, 1H), 9,47 (s, 1H), 9,91 (s, 1H).

Ejemplos 147-149

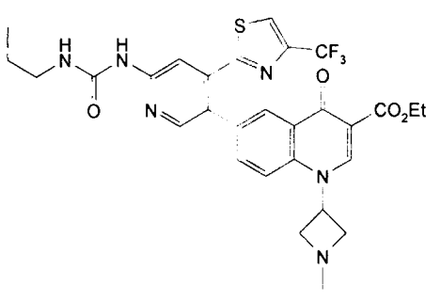
Los siguientes compuestos se prepararon según el procedimiento descrito para el Ejemplo 146 a partir de los materiales de partida indicados.

Ej.	Compuesto	Datos	SM
147	1-ciclopropil-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-N-(3-hidroxipropil)-4-oxo-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 601 (MH^+) para $C_{28}H_{27}F_3N_6O_4S$ RMN ^1H (300 MHz, CD_3OD): δ 1,23 (m, 4H), 1,38 (m, 3H), 1,83 (m, 2H), 3,34 (q, 2H), 3,53 (q, 2H), 3,65 (q, 2H), 3,76 (brs, 1H), 7,77 (d, 1H), 7,89 (s, 1H), 8,14 (s, 1H), 8,25 (d, 1H), 8,35 (s, 1H), 8,36 (s, 1H), 8,9 (s, 1H).	Ejemplo 59 y propanol-amina

148	1-(1,3-dimetoxipropan-2-il)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-N-(2-hidroxietil)-4-oxo-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 649 (MH^+) para $C_{30}H_{31}F_3N_6O_5S$ RMN ^1H (300 MHz, CD_3OD): δ 1,19 (t, 3H), 3,55 (brs, 2H), 3,71 (brs, 2H), 3,86 (brs 2H), 3,95 (brs, 2H), 5,34 (brs, 1H), 7,67 (d, 1H), 7,85 (s, 1H), 7,99 (d, 1H), 8,12 (s, 1H), 8,32 (s, 1H), 8,39 (s, 1H), 9,06 (s, 1H)	Ejemplo 54 y etanolamina
149	1-(1,3-dimetoxipropan-2-il)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-N-(3-hidroxipropil)-4-oxo-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 663,3 (MH^+) para $C_{31}H_{35}F_3N_6O_8S$ RMN ^1H (300 MHz, DMSO-d_6): δ 1,11 (t, 3H), 1,62-1,71 (m, 2H), 3,16-3,33 (m, 2H), 3,26 (s, 6H), 3,40-3,51 (m, 2H), 3,77-3,82 (m, 2H), 3,84-3,93 (m, 2H), 4,56, (t, 1H), 5,46 (m, 1H), 7,64 (bt, 1H), 7,73 (dd, 1H), 8,14 (d, 1H), 8,23 (s, 1H), 8,29 (d, 1H), 8,35 (s, 1H), 8,51 (d, 1H), 8,92 (s, 1H), 9,49 (s, 1H), 9,89 (bt, 1H)	Ejemplo 54 y propanol-amina

Ejemplo 150

1-(1-metilazetidin-3-il)-4-oxo-6-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1,4-dihidroquinolin-3-carboxilato de etilo

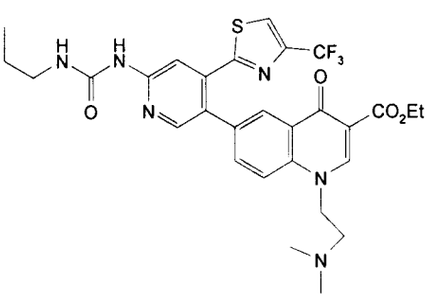


Una suspensión de 6-yodo-1-(1-metilazetidin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo (Intermediario 31, 500 mg, 1,21 mmoles) en dimetoxietano (9,7 ml) en un vial se agitó con calor para obtener una disolución. La disolución se enfrió hasta 30 °C, y se añadió trans-diclorobis(trifenilfosfina)paladio (II) (111 mg, 0,16 mmoles). La mezcla se agitó durante ~10 min a temperatura ambiente, después se añadió ácido 6-(3-propilureido)-4-(4-trifluorometiltiazol-2-il)piridin-3-ilborónico (Intermediario 47, 1,3 eq) a la mezcla, seguido de una disolución acuosa de bicarbonato de sodio (252 mg en 2,4 ml de agua), y el vial se cerró herméticamente. La mezcla se agitó a 75°C durante 1 h, y después se enfrió hasta 0 °C. El sólido que se formó se aisló mediante filtración, se lavó con una pequeña cantidad de dimetoxietano, y después metil-terc-butiléter, para dar 735 mg de un sólido amarillo, que se usó sin purificación adicional.

MS (ESP): 615 (MH^+) para $C_{29}H_{29}F_3N_6O_4S$

Ejemplo 151

1-(1-metilazetidin-3-il)-4-oxo-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1,4-dihidroquinolin-3-carboxilato de etilo

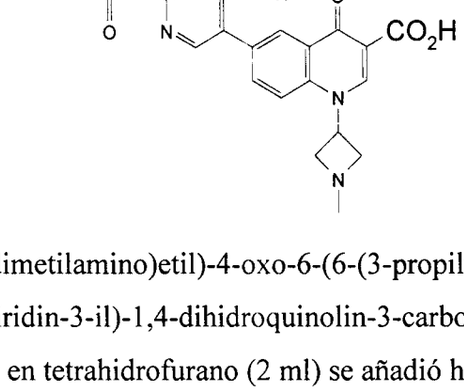


El siguiente compuesto se preparó según el procedimiento descrito para el Ejemplo 150 a partir del Intermediario 29 e Intermediario 47.

MS (ESP): 617 (MH^+) para $C_{29}H_{31}F_3N_6O_4S$.

Ejemplo 152

Ácido 1-(2-(dimetilamino)etil)-4-oxo-6-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1,4-dihidroquinolin-3-carboxílico



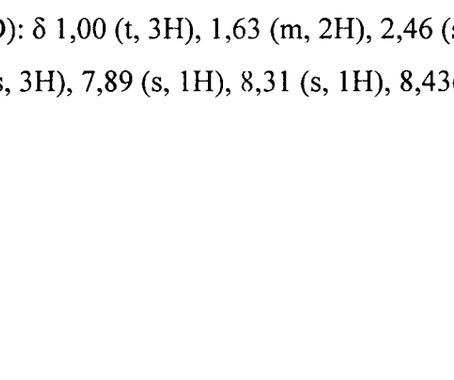
A una disolución de 1-(2-(dimetilamino)etil)-4-oxo-6-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1,4-dihidroquinolin-3-carboxilato de etilo (Ejemplo 150, 100 mg, 0,16 mmoles) en tetrahidrofurano (2 ml) se añadió hidróxido de litio (1 M, 650 µl), y la mezcla se agitó durante 1 h a temperatura ambiente. Los orgánicos se eliminaron en una corriente de nitrógeno, y el precipitado que se formó se aisló mediante filtración, se lavó con agua (1 ml), y se secó en un horno de vacío toda la noche a 40 °C para dar 70 mg de un sólido amarillento.

MS (ESP): 589 (MH^+) para $C_{27}H_{27}F_3N_6O_4S$.

RMN ^1H (300 MHz, CD_3OD): δ 1,11 (t, 3H), 1,63 (m, 3H), 2,32 (s, 6H), 2,87 (q, 2H), 4,50 (q, 2H), 4,39 (t, 2H), 7,65 (d, 1H), 7,82 (d, 1H), 7,87(s, 1H), 8,33 (s, 1H), 8,44 (s, 1H), 8,78 (s, 1H)

Ejemplo 153

Ácido 1-(1-metilazetidin-3-il)-4-oxo-6-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1,4-dihidroquinolin-3-carboxílico



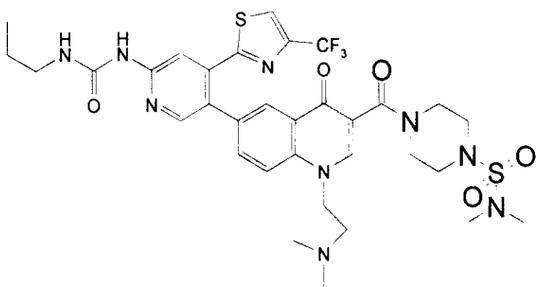
El siguiente compuesto se preparó según el procedimiento descrito para el Ejemplo 152 usando el Ejemplo 151 como el material de partida.

MS (ESP): 587 (MH^+) para $C_{27}H_{24}F_3N_6NaO_4S$.

RMN ^1H (300 MHz, CD_3OD): δ 1,00 (t, 3H), 1,63 (m, 2H), 2,46 (s, 3H), 3,51 (m, 2H), 4,09 (t, 2H), 5,17 (m, 1H), 7,60 (s, 3H), 7,89 (s, 1H), 8,31 (s, 1H), 8,43(s, 1H), 8,66 (s, 1H).

Ejemplo 154

4-(1-(2-(dimetilamino)etil)-4-oxo-6-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1,4-dihidroquinolin-3-carbonil)-N,N-dimetilpiperazin-1-sulfonamida



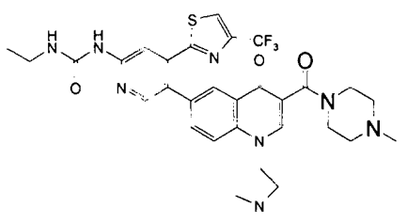
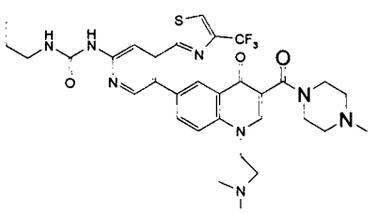
A una disolución de ácido 1-(2-(dimetilamino)etil)-4-oxo-6-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1,4-dihidroquinolin-3-carboxílico (Ejemplo 153, 80 mg, 0,14 mmoles) en dimetilformamida (0,5 ml) se añadió HATU (78,4 mg, 0,20 mmoles), y después diisopropiletilamina (95,2 ul, 0,55 mmoles). A esto le siguió N,N-dimetilpiperazin-1-sulfonamida (52,7 mg, 0,27 mmoles), y la reacción se agitó a temperatura ambiente durante 1 h. El disolvente se eliminó a presión reducida, y el residuo se purificó mediante HPLC prep (agua-metanol-0,1% de ácido fórmico).

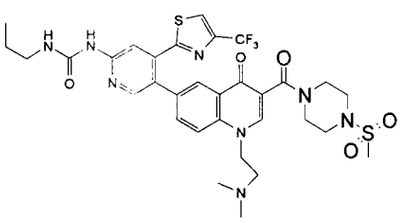
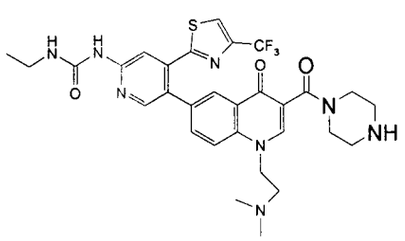
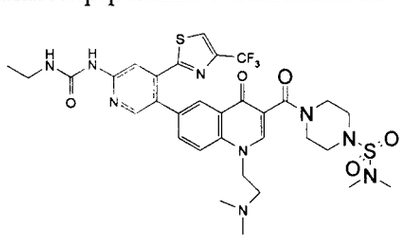
MS (ESP): 764,4 (MH^+) para $C_{34}H_{42}F_3N_9O_7S_2$

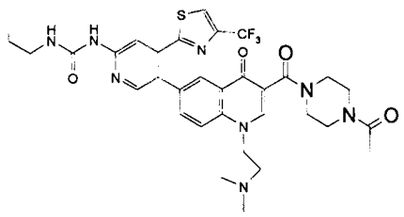
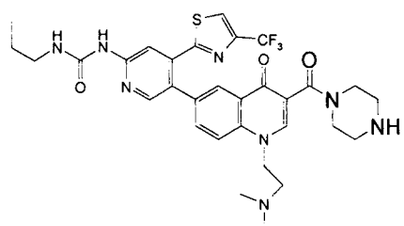
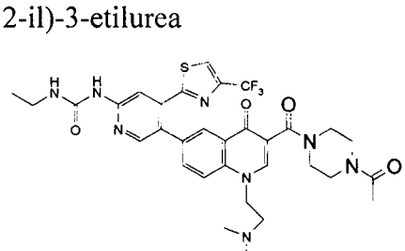
RMN ^1H (300 MHz, CD_3OD): δ 0,99 (t, 3H), 1,63 (m, 2H), 2,43 (s, 6H), 2,85 (s, 6H), 2,92 (t, 2H), 3,32 (brs, 6H), 3,47 (brs, 2H), 3,81 (brs, 2H), 4,55 (t, 2H), 7,67 (d, 1H), 7,84 (s, 1H), 7,87 (d, 1H), 8,18 (s, 1H), 8,29 (s, 1H), 8,32 (s, 2H).

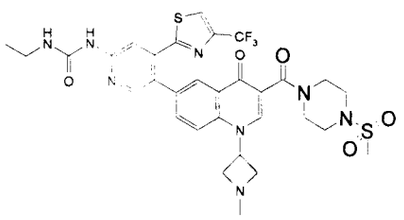
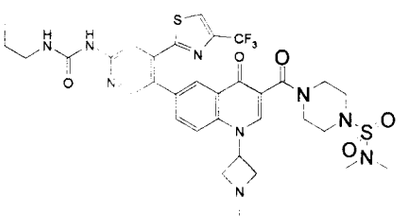
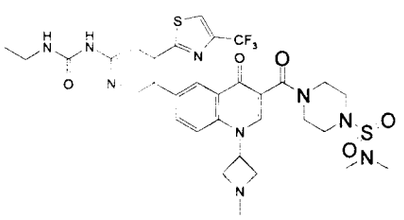
Ejemplos 155-172

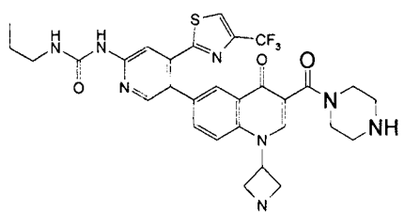
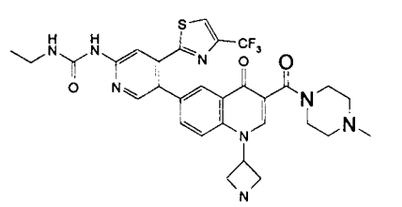
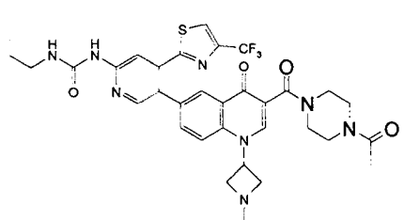
Los siguientes compuestos se prepararon según el procedimiento descrito para el Ejemplo 154 a partir de los materiales de partida indicados en la tabla.

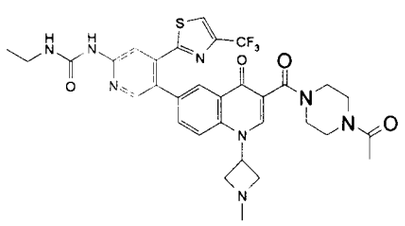
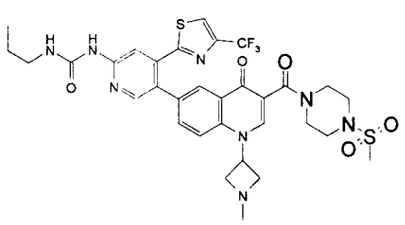
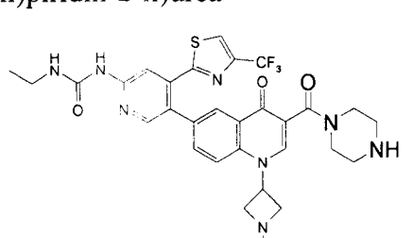
Ej.	Compuesto	Datos	SM
155	1-(5-(1-(2-(dimetilamino)etil)-3-(4-metilpiperazin-1-carbonil)-4-oxo-1,4-dihidroquinolin-6-il)-4-(4-(trifluorometil)tiazol-2-il)piridin-2-il)-3-etilurea 	MS (ESP): 657 (MH^+) para $C_{32}H_{37}F_3N_8O_5S$ RMN ^1H (300 MHz, CD_3OD): δ 1,22 (t, 3H), 2,44 (s, 6H), 2,62 (s, 3H), 2,93 (brs, 6H), 3,34 (q, 2H), 3,54 (brs, 2H), 3,89 (brs, 2H), 4,55 (t, 2H), 7,70 (d, 1H), 7,85 (s, 1H), 7,88 (d, 1H), 8,19 (s, 1H), 8,28 (s, 1H), 8,32 (s, 1H), 8,35 (s, 1H)	Ejemplo 18 y 4-metil-piperazina
156	1-(5-(1-(2-(dimetilamino)etil)-3-(4-metilpiperazin-1-carbonil)-4-oxo-1,4-dihidroquinolin-6-il)-4-(4-(trifluorometil)tiazol-2-il)piridin-2-il)-3-propilurea 	MS (ESP): 671 (MH^+) para $C_{32}H_{37}F_3N_8O_3S$ RMN ^1H (300 MHz, CD_3OD): δ 0,99 (t, 3H), 1,64 (m, 2H), 2,32 (s, 6H), 2,54 (brs, 4H), 2,77 (t, 2H), 3,45 (brs, 2H), 3,79 (brs, 2H), 4,49 (brs, 2H), 7,70 (d, 1H), 7,85 (m, 2H), 8,18 (s, 1H), 8,25 (s, 1H), 8,32 (s, 1H), 8,35 (s, 1H)	Ejemplo 153 y 4-metil-piperzina

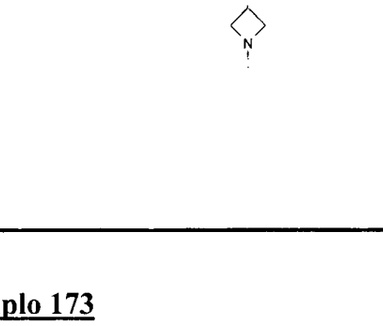
157	1-(5-(1-(2-(dimetilamino)etil)-3-(4-(metilsulfonil)piperazin-1-carbonil)-4-oxo-1,4-dihidroquinolin-6-il)-4-(4-(trifluorometil)tiazol-2-il)piridin-2-il)-3-propilurea 	MS (ESP): 735 (MH^+) para $C_{33}H_{39}F_3N_8O_7S_2$ RMN ^1H (300 MHz, CD_3OD): δ 1,02 (t, 3H), 1,63 (m, 2H), 2,49 (s, 6H), 2,87 (s, 3H), 3,01 (t, 2H), 3,52 (brs, 2H), 3,86 (brs, 2H), 4,59 (t, 2H), 7,70 (d, 1H), 7,85 (m, 2H), 8,19 (s, 1H), 8,28 (s, 1H), 8,32 (d, 1H), 8,35 (s, 1H)	Ejemplo 153 y 4-metil-sulfonil-piperazina
158	1-(5-(1-(2-(dimetilamino)etil)-4-oxo-3-(piperazin-1-carbonil)-1,4-dihidroquinolin-6-il)-4-(4-(trifluorometil)tiazol-2-il)piridin-2-il)-3-etilurea 	MS (ESP): 643 (MH^+) para $C_{31}H_{35}F_3N_8O_5S$ RMN ^1H (300 MHz, CD_3OD): δ 1,22 (t, 3H), 3,04 (s, 6H), 3,31 (m, 8), 3,68 (m, 4H), 4,0 (brs, 2H), 7,80 (d, 1H), 7,90 (s, 1H), 7,96 (d, 1H), 8,22 (s, 1H), 8,34 (s, 1H), 8,35 (s, 1H), 8,46 (s, 1H)	Ejemplo 18 y piperazina
159	4-(1-(2-(dimetilamino)etil)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carbonil)-N,N-dimetilpiperazin-1-sulfonamida 	MS (ESP): 750 (MH^+) para $C_{33}H_{40}F_3N_9O_7S_2$ RMN ^1H (300 MHz, CD_3OD): δ 1,22 (t, 3H), 2,40 (s, 6H), 2,84 (s, 6H), 2,86 (t, 2H), 3,36 (m, 6H), 3,47 (brs, 2H), 3,82 (brs, 2H), 4,53 (t, 2H), 7,72 (d, 1H), 7,85 (s, 2H), 7,87 (d, 1H), 8,19 (s, 1H), 8,29 (s, 1H), 8,32 (s, 1H), 8,35 (s, 1H)	Ejemplo 18 y N,N-dimetil-piperazin-1-sulfonamida

160	1-(5-(3-(4-acetilpiperazin-1-carbonil)-1-(2-(dimetilamino)etil)-4-oxo-1,4-dihidroquinolin-6-il)-4-(4-(trifluorometil)tiazol-2-il)piridin-2-il)-3-propilurea 	MS (ESP): 699 (MH^+) para $C_{34}H_{39}F_3N_8O_6S$ RMN ^1H (300 MHz, CD_3OD): δ 0,99 (t, 3H), 1,61 (m, 2H), 2,15 (br s, 3H), 2,34 (s, 6H), 2,80 (t, 2H), 3,66 (brm, 8H), 4,51 (t, 2H), 7,68 (d, 1H), 7,85 (s, 2H), 7,88 (d, 1H), 8,19 (s, 1H), 8,28 (s, 1H), 8,32 (s, 1H), 8,36 (s, 1H)	Ejemplo 153 y 4-acetil-piperazina
161	1-(5-(1-(2-(dimetilamino)etil)-4-oxo-3-(piperazin-1-carbonil)-1,4-dihidroquinolin-6-il)-4-(4-(trifluorometil)tiazol-2-il)piridin-2-il)-3-propilurea 	MS (ESP): 657 (MH^+) para $C_{31}H_{36}ClF_3N_8O_3S$ RMN ^1H (300 MHz, CD_3OD): δ 0,99 (t, 3H), 1,62 (m, 2H), 3,05 (s, 6H), 3,31 (m, 4H), 3,72 (m, 6H), 3,99 (brs, 2H), 7,86 (d, 1H), 8,08 (s, 1H), 8,11 (d, 1H), 8,32 (s, 1H), 8,34 (s, 1H), 8,45 (s, 1H), 8,51 (1H).	Ejemplo 153 y piperazina
162	1-(5-(3-(4-acetilpiperazin-1-carbonil)-1-(2-(dimetilamino)etil)-4-oxo-1,4-dihidroquinolin-6-il)-4-(4-(trifluorometil)tiazol-2-il)piridin-2-il)-3-etilurea 	MS (ESP): 685 (MH^+) para $C_{32}H_{35}F_3N_8O_4S$ RMN ^1H (300 MHz, CD_3OD): δ 1,20 (t, 3H), 2,11&2,15 (s, 3H), 2,36 (s, 6H), 2,83 (t, 2H), 3,39 (q, 2H), 3,65 (m, 8H), 4,54 (t, 2H), 7,69 (d, 1H), 7,85 (s, 1H), 7,88 (d, 1H), 8,19 (s, 1H), 8,29 (s, 1H), 8,32 (s, 1H), 8,36 (s, 1H)	Ejemplo 18 y 4-acetil-piperazina

163	1-etil-3-(5-(1-(1-metilazetidin-3-il)-3-(4-(metilsulfonil)piperazin-1-carbonil)-4-oxo-1,4-dihidroquinolin-6-il)-4-(4-(trifluorometil)tiazol-2-il)piridin-2-il)urea 	MS (ESP): 719 (MH^+) para $C_{32}H_{35}F_3N_8O_7S_2$ RMN ^1H (300 MHz, CD_3OD): δ 1,22 (t, 3H), 2,57 (s, 3H), 2,87 (s, 3H), 3,32 (m, 6H), 3,52 (brs, 2H), 3,73 (t, 2H), 3,88 (brs, 2H), 4,18 (t, 2H), 5,31 (m, 1H), 7,65 (d, 1H), 7,68 (d, 1H), 7,85 (s, 1H), 8,19 (s, 1H), 8,22 (brs, 1H), 8,32 (s, 1H), 8,34 (s, 2H)	Ejemplo 24 y 4-(metil-sulfonil)-piperazina
164	N,N-dimetil-4-(1-(1-metilazetidin-3-il)-4-oxo-6-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1,4-dihidroquinolin-3-carbonil)piperazin-1-sulfonamida 	MS (ESP): 762 (MH^+) para $C_{34}H_{40}F_3N_9O_7S_2$ RMN ^1H (300 MHz, CD_3OD): δ 0,99 (t, 3H), 1,61 (m, 2H), 2,54 (s, 3H), 2,84 (s, 6H), 3,35 (brs, 6H), 3,47 (brs, 2H), 3,67 (brs, 2H), 3,84 (brs, 2H), 4,16 (t, 2H), 5,29 (brs, 1H), 7,66 (d, 1H), 7,69 (d, 1H), 7,84 (s, 1H), 8,18 (s, 1H), 8,33 (m, 3H).	Ejemplo 152 y N,N-dimetilpiperazin-1-sulfonamida
165	4-(6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-metilazetidin-3-il)-4-oxo-1,4-dihidroquinolin-3-carbonil)-N,N-dimetilpiperazin-1-sulfonamida 	MS (ESP): 748 (MH^+)) para $C_{33}H_{38}F_3N_9O_7S_2$ RMN 1H (300 MHz, CD_3OD): δ 1,22 (t, 3H), 2,59 (s, 3H), 2,84 (s, 6H), 3,31 (m, 6H), 3,47 (brs, 2H), 3,84 (m, 4H), 4,22 (t, 2H), 5,33 (m, 1H), 7,62 (d, 1H), 7,68 (d, 1H), 7,84 (s, 1H), 8,19 (s, 2H), 8,35 (m, 3H).	Ejemplo 24 y N,N-dimetil-piperazin-1-sulfonamida

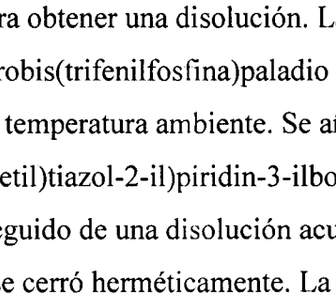
166	1-(5-(1-(1-metilazetidin-3-il)-4-oxo-3-(piperazin-1-carbonil)-1,4-dihidroquinolin-6-il)-4-(4-(trifluorometil)tiazol-2-il)piridin-2-il)-3-propilurea 	MS (ESP): 655 (MH^+) para $C_{31}H_{34}ClF_3N_8O_3S$ RMN ^1H (300 MHz, CD_3OD): δ 0,99 (t, 3H), 1,62 (m, 2H), 3,12 & 3,18 (s, 3H), 3,36 (brs, 4H), 3,72 (m, 4H), 4,01 (br, 2H), 4,89 (m, 2H), 5,01 (m, 2H), 5,86 & 6,0 (brs, 1H), 7,68 (d, 1H), 7,81 (d, 1H), 8,02 (s, 1H), 8,31 (s, 1H), 8,33 (s, 1H), 8,40 & 8,61 (s, 1H), 8,43 (s, 1H).	Ejemplo 152 y piperazina
167	1-etil-3-(5-(1-(1-metilazetidin-3-il)-3-(4-metilpiperazin-1-carbonil)-4-oxo-1,4-dihidroquinolin-6-il)-4-(4-(trifluorometil)tiazol-2-il)piridin-2-il)urea 	MS (ESP): 655 (MH^+) para $C_{32}H_{35}F_3N_8O_5S$ RMN ^1H (300 MHz, CD_3OD): δ 1,22 (t, 3H), 2,33 (s, 3H), 2,46 (s, 3H), 2,50 (brs, 4H), 3,31 (q, 2H), 3,44 (brs, 2H), 3,51 (t, 2H), 3,80 (brs, 2H), 4,05 (t, 2H), 5,21 (m, 1H), 7,66 (d, 1H), 7,67 (d, 1H), 7,85 (s, 2H), 8,17 (s, 1H), 8,32 (m, 2H), 8,34 (s, 1H).	Ejemplo 24 y 4-metil-piperazina
168	1-(5-(3-(4-acetilpiperazin-1-carbonil)-1-(1-metilazetidin-3-il)-4-oxo-1,4-dihidroquinolin-6-il)-4-(4-(trifluorometil)tiazol-2-il)piridin-2-il)-3-propilurea 	MS (ESP): 697 (MH^+) para $C_{33}H_{35}F_3N_8O_4S$ RMN ^1H (300 MHz, CD_3OD): δ 0,99 (t, 3H), 1,61 (m, 2H), 2,11 & 2,16 (s, 3H), 2,47 (s, 3H), 3,52 (m, 7H), 4,07 (t, 2H), 5,23 (m, 1H), 7,67 (d, 1H), 7,69 (d, 1H), 7,85 (s, 2H), 8,19 (s, 1H), 8,35 (m, 3H).	Ejemplo 152 y 4-acetil-piperazina

169	1-(5-(3-(4-acetilpiperazin-1-carbonil)-1-(1-metilazetidin-3-il)-4-oxo-1,4-dihidroquinolin-6-il)-4-(4-(trifluorometil)tiazol-2-il)piridin-2-il)-3-etilurea 	MS (ESP): 683 (MH^+) para $C_{33}H_{35}F_3N_8O_6S$ RMN ^1H (300 MHz, CD_3OD): δ 1,22 (t, 3H), 2,11 & 2,16 (s, 3H), 2,63 (s, 3H), 3,31 (m, 2H), 3,67 (brm, 8H), 3,81 (m, 2H), 4,25 (t, 2H), 5,36 (m, 1H), 7,64 (d, 1H), 7,69 (d, 1H), 7,85 (s, 2H), 8,18 (s, 1H), 8,34 (m, 3H).	Ejemplo 24 y 4-acetil-piperazina
170	1-(5-(1-(1-metilazetidin-3-il)-3-(4-(metilsulfonil)piperazin-1-carbonil)-4-oxo-1,4-dihidroquinolin-6-il)-4-(4-(trifluorometil)tiazol-2-il)piridin-2-il)-3-propilurea 	MS (ESP): 733 (MH^+) para $C_{33}H_{37}F_3N_8O_7S_2$ RMN ^1H (300 MHz, CD_3OD): δ 0,99 (t, 3H), 1,61 (m, 2H), 2,57 (s, 3H), 2,88 (s, 3H), 3,52 (brs, 2H), 3,74 (t, 2H), 3,88 (brs, 2H), 4,19 (t, 2H), 5,31 (m, 1H), 7,65 (d, 1H), 7,69 (d, 1H), 7,85 (s, 2H), 8,19 (s, 1H), 8,35 (m, 3H).	Ejemplo 152 y 4-(metil-sulfonil)-piperazina
171	1-etil-3-(5-(1-(1-metilazetidin-3-il)-4-oxo-3-(piperazin-1-carbonil)-1,4-dihidroquinolin-6-il)-4-(4-(trifluorometil)tiazol-2-il)piridin-2-il)urea 	MS (ESP): 641,1 (MH^+) para $C_{30}H_{32}ClF_3N_8O_3S$ RMN ^1H (300 MHz, CD_3OD): δ 1,22 (t, 3H), 3,12 & 3,18 (s, 3H), 3,39 (m, 4H), 3,67 (m, 4H), 4,02 (brs, 2H), 4,80 (m, 2H), 4,99 (m, 2H), 5,75 & 6,0 (brs, 1H), 7,71 (d, 1H), 7,86 (d, 1H), 8,07 (s, 1H), 8,33 (s, 2H), 8,41 y 8,64 (s, 1H), 8,45 (s, 1H).	Ejemplo 24 y piperazina

172	1-(5-(1-(1-metilazetidin-3-il)-3-(4-metilpiperazin-1-carbonil)-4-oxo-1,4-dihidroquinolin-6-il)-4-(4-(trifluorometil)tiazol-2-il)piridin-2-il)-3-propilurea 	MS (ESP): 669,3 (MH^+) para $C_{33}H_{37}F_3N_8O_5S_2$ RMN ^1H (300 MHz, CD_3OD): δ 1,02 (t, 3H), 1,64 (m, 2H), 2,52 (s, 3H), 2,54 (s, 3H), 2,81 (brs, 4H), 3,53 (brs, 2H), 3,66 (t, 2H), 3,87 (brs, 2H), 4,12 (t, 2H), 5,27 (m, 1H), 7,65 (d, 1H), 7,68 (d, 1H), 7,85 (s, 1H), 8,17 (s, 1H), 8,29 (brs, 1H), 8,32 (s, 1H), 8,34 (s, 1H)	Ejemplo 152 y 4-metil-piperazina

Ejemplo 173

1-(2-(dimetilamino)etil)-6-(6-(3-isopropilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo

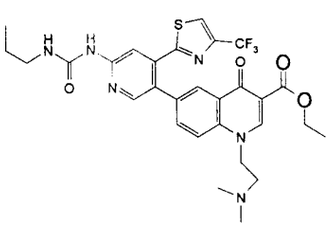
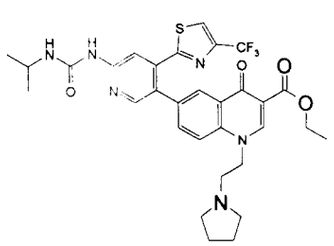


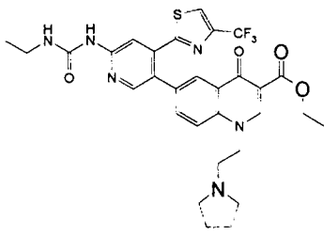
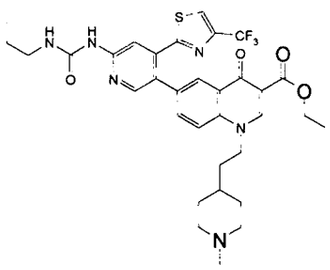
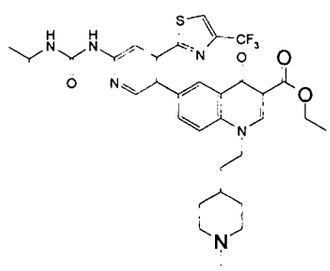
Una suspensión de 1-(2-(dimetilamino)etil)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo (Intermediario 29, 250 mg, 0,60 mmoles) en dimetoxietano (4,8 ml) en un vial de microondas se agitó con calor para obtener una disolución. La disolución se enfrió entonces hasta 30°C, se añadió trans-diclorobis(trifenilfosfina)paladio (II) (55 mg, 0,08 mmoles), y la mezcla se agitó durante 10 min a temperatura ambiente. Se añadió ácido 6-(3-isopropilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-ilborónico (Intermediario 89, 294 mg, 0,79 mmoles) a la mezcla, seguido de una disolución acuosa de bicarbonato de sodio (163 mg en 1,2 ml de agua), y el vial se cerró herméticamente. La mezcla se agitó a 65 °C durante 30 min en un bloque calefactor, y después se enfrió hasta la temperatura ambiente. La mezcla de reacción bruta se colocó en un refrigerador durante 2 h. El precipitado sólido que se formó se recogió mediante filtración, se lavó con una pequeña cantidad de dimetoxietano, metil-terc-butiléter y se secó para dar ~270 mg de un sólido amarillento.

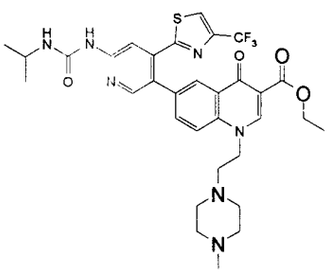
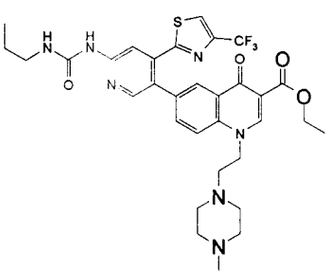
MS (ESP): 634 ($M+H^+$) para $C_{29}H_{30}F_3N_5O_6S$.

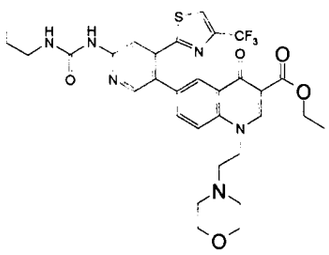
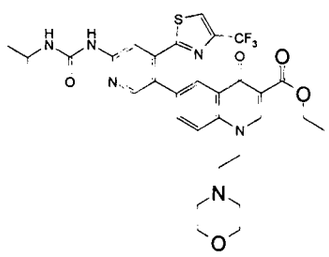
Ejemplos 174-188

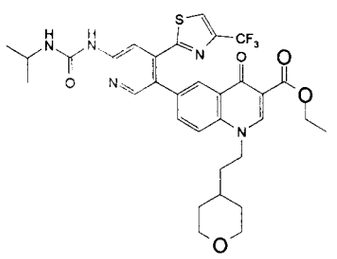
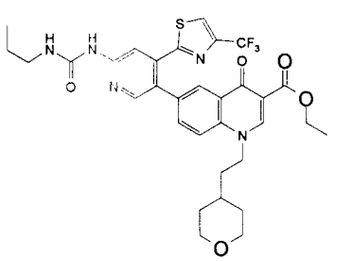
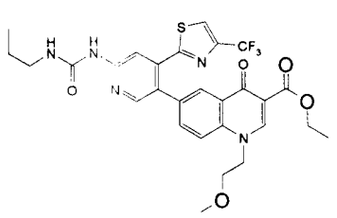
Los siguientes compuestos se prepararon según el procedimiento descrito para el Ejemplo 173 a partir del material de partida indicado.

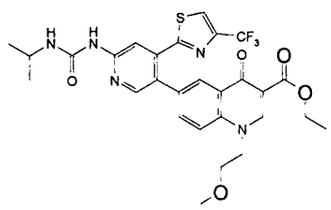
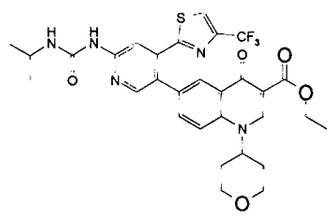
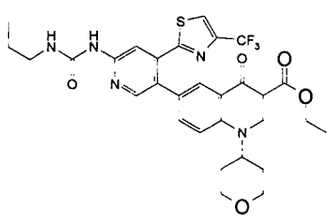
Ej.	Compuesto	Datos	SM
174	1-(2-(dimetilamino)etil)-4-oxo-6-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 634 ($M+H^+$) para $C_{29}H_{30}F_3N_5O_6S$	Intermediario 29 e Intermediario 47
175	6-(6-(3-isopropilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-(2-(pirrolidin-1-il)etil)-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 643,2 ($M+H^+$) para $C_{31}H_{33}F_3N_6O_4S$	Intermediario 89 e Intermediario 93

176	4-oxo-6-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(2-(pirrolidin-1-il)etil)-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 643,2 ($M+H^+$) para $C_{31}H_{33}F_3N_6O_4S$	Intermediario 47 e Intermediario 93
177	1-(2-(1-metilpiperidin-4-il)etil)-4-oxo-6-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 671,1 ($M+H^+$) para $C_{33}H_{37}F_3N_6O_4S$	Intermediario 47 e Intermediario 69
178	6-(6-(3-isopropilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(2-(1-metilpiperidin-4-il)etil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 671,1 ($M+H^+$) para $C_{33}H_{37}F_3N_6O_4S$	Intermediario 89 e Intermediario 69

179	6-(6-(3-isopropilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(2-(4-metilpiperazin-1-il)etil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 673 ($M+H^+$) para $C_{32}H_{36}F_3N_7O_4S$	Intermediario 89 e Intermediario 92
180	1-(2-(4-metilpiperazin-1-il)etil)-4-oxo-6-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 673 ($M+H^+$) para $C_{32}H_{36}F_3N_7O_4S$	Intermediario 47 e Intermediario 92

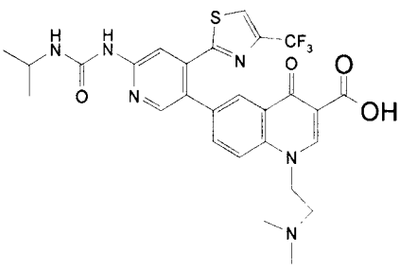
181	1-(2-morfolinoetil)-4-oxo-6-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 660,1 ($M+H^+$) para $C_{31}H_{33}F_3N_6O_5S$	Intermediario 47 e Intermediario 90
182	6-(6-(3-isopropilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(2-morfolinoetil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 660,1 ($M+H^+$) para $C_{31}H_{33}F_3N_6O_5S$	Intermediario 89 e Intermediario 90

183	6-(6-(3-isopropilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-(2-(tetrahidro-2H-piran-4-il)etil)-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 659 ($M+H^+$) para $C_{32}H_{34}F_3N_5O_5S$	Intermediario 89 e Intermediario 94
184	4-oxo-6-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(2-(tetrahidro-2H-piran-4-il)etil)-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 659 ($M+H^+$) para $C_{32}H_{34}F_3N_5O_5S$	Intermediario 47 e Intermediario 94
185	1-(2-metoxietil)-4-oxo-6-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 604,6 ($M+H^+$) para $C_{28}H_{28}F_3N_5O_5S$	Intermediario 47 e Intermediario 20

186	6-(6-(3-isopropilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(2-metoxietil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 604,6 ($M+H^+$) para $C_{28}H_{28}F_3N_5O_5S$	Intermediario 89 e Intermediario 20
187	6-(6-(3-isopropilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-(tetrahidro-2H-piran-4-il)-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 631 ($M+H^+$) para $C_{30}H_{30}F_3N_5O_5S$	Intermediario 89 e Intermediario 91
188	4-oxo-6-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(tetrahidro-2H-piran-4-il)-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 631 ($M+H^+$) para $C_{30}H_{30}F_3N_5O_5S$	Intermediario 47 e Intermediario 91

Ejemplo 189

1-(2-(dimetilamino)etil)-7-(6-(3-isopropilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato



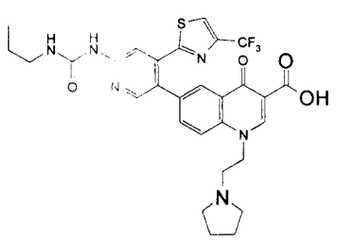
Una disolución de 1-(2-(dimetilamino)etil)-6-(6-(3-isopropilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo (Ejemplo 173, 100 mg, 0,16 mmoles) se disolvió en tetrahidrofurano (4 ml) y se trató con hidróxido de litio 1M (1 ml), y la mezcla se agitó a temperatura ambiente durante 24 h. La mezcla de reacción se concentró a presión reducida, se diluyó con agua, y se acidificó hasta pH 4 con HCl 1 N. El sólido que se formó se recogió mediante filtración y se lavó con acetato de etilo para dar 60 mg de producto después de secar.

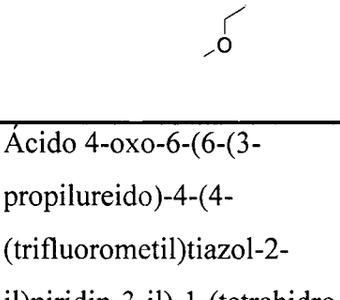
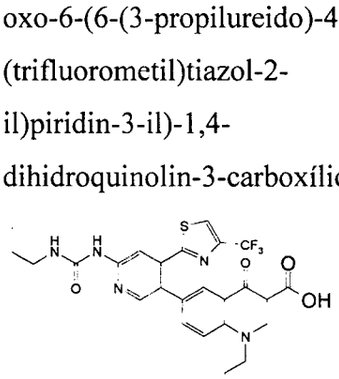
MS (ESP): 589,2 ($M+H^+$) para $C_{27}H_{26}F_3N_6NaO_4S$.

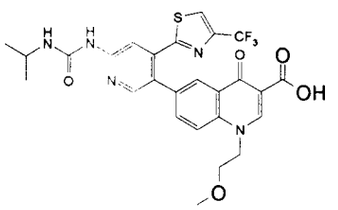
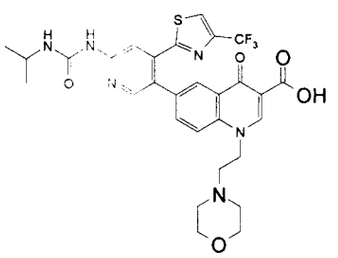
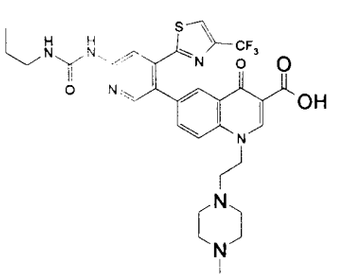
RMN ^1H (300 MHz, DMSO-d_6): δ 1,07 (d, 6H), 2,19 (s, 6H), 2,58 (t, 2H), 3,35-3,80 (m, 1H), 4,38 (t, 2H), 7,41 (d, 1H), 7,67 (d, 1H), 8,02-8,05 (m, 2H), 8,14 (d, 1H), 8,39 (s, 1H), 8,54 (d, 1H)

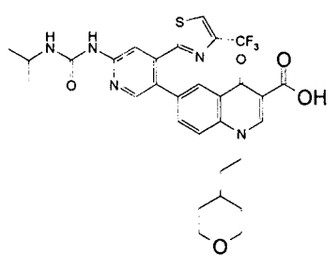
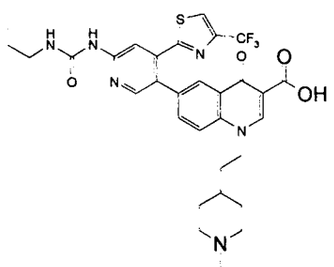
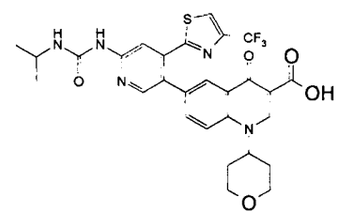
Ejemplos 190-202

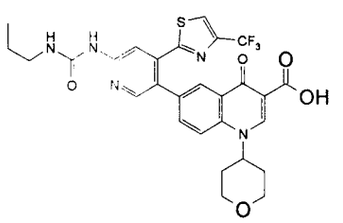
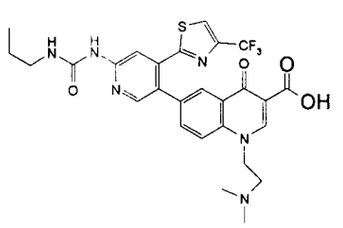
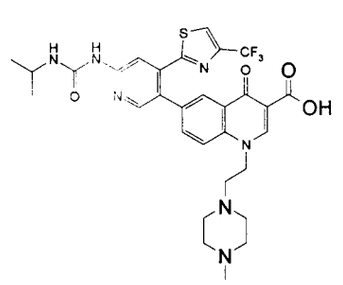
Los siguientes compuestos se prepararon según el procedimiento descrito para el Ejemplo 189 a partir de los materiales de partida indicados en la tabla.

Ej.	Compuesto	Datos	SM
190	Ácido 4-oxo-6-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(2-(pirrolidin-1-il)etil)-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 614 ($M+H^+$) para $C_{29}H_{29}F_3N_6O_4S$ RMN ^1H (300 MHz, CD_3OD): δ 0,99 (t, 3H), 1,63 (m, 2H), 1,81 (m, 4H), 2,63 (m, 4H), 2,97 (m, 2H), 4,51 (m, 2H), 7,68 (d, 1H), 7,85 (d, 1H), 7,87 (s, 1H), 8,15 (s, 1H), 8,33 (s, 1H), 8,43 (s, 1H), 8,77 (s, 1H)	Ejemplo 176

191	Ácido 1-(2-metoxietil)-4-oxo-6-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 576 ($M+H^+$) para $C_{26}H_{23}F_3N_5NaO_5S$ RMN ^1H (300 MHz, DMSO-d_6): δ 0,90 (t, 3H), 1,50 (m, 2H), 3,15 (s, 2H), 3,23 (s, 3H), 3,69 (brs, 2H), 4,61 (brs, 2H), 7,66 (d, 1H), 7,82 (s, 1H), 7,92 (d, 1H), 8,25 (s, 1H), 8,28 (s, 1H), 8,32 (s, 1H), 8,45 (s, 1H), 8,78 (s, 1H), 9,61(s, 1H).	Ejemplo 185
192	Ácido 4-oxo-6-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(tetrahidro-2H-piran-4-il)-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 603 ($M+H^+$) para $C_{28}H_{25}F_3N_5NaO_5S$ RMN ^1H (300 MHz, DMSO-d_6): δ 0,90 (t, 3H), 1,50 (m, 2H), 2,02 (m, 4H), 3,13 (m, 2H), 3,64 (m, 2H), 4,02 (m, 2H), 5,05 (brs, 1H), 7,62 (d, 1H), 7,80 (brs, 1H), 8,19 (d, 1H), 8,28 (s, 1H), 8,31 (s, 1H), 8,44 (s, 2H), 8,94 (s, 1H), 9,5 (s, 1H)	Ejemplo 184
193	Ácido 1-(2-morfolinoetil)-4-oxo-6-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1,4-dihidroquinolin-3-carboxílico	MS (ESP): 631 ($M+H^+$) para $C_{29}H_{28}F_3LiN_6O_5S$ RMN ^1H (300 MHz, DMSO-d_6): δ 0,90 (t, 3H), 1,49 (m, 2H), 2,49 (brs, 4H), 2,73 (m, 2H), 3,16 (m, 2H), 3,46 (m, 2H), 4,52 (brs, 2H), 7,61 (d, 1H), 7,75 (brs, 1H), 7,90 (d, 1H), 8,25 (s, 2H), 8,31 (s, 1H), 8,44 (s, 1H), 8,78 (s, 1H), 9,53 (s, 1H), 9,46 (s, 1H)	Ejemplo 181

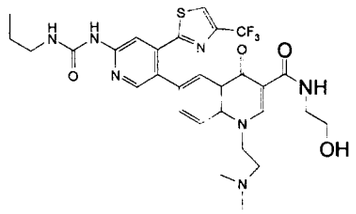
194	Ácido 6-(6-(3-isopropilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(2-metoxietil)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 576 ($M+H^+$) para $C_{26}H_{24}F_3N_5O_5S$ RMN ^1H (300 MHz, CD_3OD): δ 1,24 (d, 6H), 3,81 (t, 2H), 3,99 (m, 1H), 4,71 (t, 2H), 7,78 (d, 1H), 7,90 (s, 1H), 8,00 (d, 1H), 8,18 (s, 1H), 8,37 (s, 1H), 8,42 (s, 1H), 8,89 (s, 1H)	Ejemplo 186
195	Ácido 6-(6-(3-isopropilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(2-morfolinoetil)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 631 ($M+H^+$) para $C_{29}H_{29}F_3N_6O_5S$ RMN ^1H (300 MHz, CD_3OD): δ 1,24 (d, 6H), 3,4 (brs, 2H), 3,63 (brs, 2H), 3,99 (brs, 5H), 4,97 (brs (2H), 7,86 (d, 1H), 7,90 (s, 1H), 8,03 (d, 1H), 8,21 (s, 2H), 8,34 (s, 1H), 8,41 (s, 1H), 9,04 (s, 1H).	Ejemplo 182
196	Ácido 1-(2-(4-metilpiperazin-1-il)etil)-4-oxo-7-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 644,1 ($M+H^+$) para $C_{30}H_{32}F_3N_7O_4S$ RMN ^1H (300 MHz, DMSO-d_6): δ 0,91 (t, 3H), 1,50 (m, 2H), 2,10 (s, 3H), 2,22-2,73 (m, 10H), 3,16 (q, 2H), 4,69 (t, 2H), 7,65 (s, 1H), 7,85 (dd, 1H), 8,11 (d, 1H), 8,22 (s, 1H), 8,28 (s, 1H), 8,30 (d, 1H), 8,39 (s, 1H), 8,52 (d, 1H), 8,92 (d, 1H), 9,48 (s, 1H)	Ejemplo 180

197	7-(6-(3-isopropilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-(2-(tetrahidro-2H-piran-4-il)etil)-1,4-dihidroquinolin-3-carboxilato 	MS (ESP): 630,3 ($M+H^+$) para $C_{30}H_{29}F_3N_5NaO_5S$ RMN ^1H (300 MHz, CD_3OD): δ 1,25 (d, 6H), 1,35-1,40 (m, 2H), 1,71-1,87 (m, 4H), 3,43 (t, 2H), 3,72 (m, 1H), 3,90-4,05 (m, 3H), 4,40 (t, 2H), 7,55-7,65 (m, 3H), 7,77 (d, 1H), 7,92 (s, 1H), 8,14 (d, 1H), 8,33 (s, 1H), 8,41 (d, 1H), 8,51 (s, 1H)	Ejemplo 183
198	Ácido 1-(2-(1-metilpiperidin-4-il)etil)-4-oxo-6-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 643 ($M+H^+$) para $C_{31}H_{33}F_3N_6O_4S$ RMN ^1H (300 MHz, CD_3OD): δ 0,99 (t, 3H), 1,37 (m, 2H), 1,63 (m, 2H), 1,84 (m, 3H), 2,03 (t, 2H), 2,25 (s, 3H), 2,99 (m, 2H), 4,40 (t, 2H), 7,61 (d, 1H), 7,76 (d, 1H), 7,90 (s, 1H), 8,32 (s, 1H), 8,44 (s, 1H), 8,61 (s, 1H)	Ejemplo 177
199	Ácido 6-(6-(3-isopropilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-(tetrahidro-2H-piran-4-il)-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 602 ($M+H^+$) para $C_{28}H_{26}F_3N_5O_5S$ RMN ^1H (300 MHz, CD_3OD): δ 1,26 (d, 6H), 2,16 (m, 4H), 3,75 (m, 2H), 3,99 (m, 1H), 4,15 (m, 2H), 5,15 (brs, 1H), 7,82 (d, 1H), 7,90 (s, 1H), 8,18 (s, 1H), 8,22 (d, 1H), 8,38 (s, 1H), 8,47 (s, 1H), 9,01 (s, 1H).	Ejemplo 187

200	Ácido 4-oxo-6-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(2-(tetrahidro-2H-piran-4-il)etil)-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 630 ($M+H^+$) para $C_{30}H_{30}F_3N_5O_5S$ RMN ^1H (300 MHz, CD_3OD): δ 0,99 (t, 3H), 1,38 (m, 2H), 1,71 (m, 7H), 3,43 (m, 2H), 3,92 (m, 1H), 4,40 (m, 2H), 7,60 (d, 1H), 7,75 (d, 1H), 7,90 (s, 1H), 8,30 (s, 1H), 8,43 (s, 1H), 8,54 (s, 1H), 8,59 (s, 1H).	Ejemplo 188
201	Ácido 6-(6-(3-isopropilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(2-(1-metilpiperidin-4-il)etil)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 589,2 ($M+H^+$) para $C_{27}H_{27}F_3N_6O_4S$ RMN ^1H (300 MHz, CD_3OD): δ 1,00 (t, 3H), 1,88 (m, 2H), 2,34 (s, 6H), 2,79 (t, 2H), 4,46 (t, 2H), 7,62 (d, 1H), 7,79 (d, 1H), 7,89 (s, 1H), 8,14 (s, 1H), 8,34 (s, 1H), 8,43 (s, 1H), 8,55 (s, 1H).	Ejemplo 174
202	Ácido 6-(6-(3-isopropilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(2-(1-metilpiperidin-4-il)etil)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 643,2 ($M+H^+$) para $C_{31}H_{33}F_3N_6O_4S$ RMN ^1H (300 MHz, CD_3OD): δ 1,25 (d, 6H), 1,52 (m, 2H), 1,93 (m, 3H), 2,13 (brd, 2H), 2,87 (s, 3H), 3,02 (m, 2H), 3,53 (m, 2H), 4,02 (m, 1H), 4,60 (t, 2H), 7,81 (d, 1H), 7,92 (s, 1H), 7,96 (d, 1H), 8,21 (s, 1H), 8,38 (s, 1H), 8,43 (s, 1H), 9,00 (s, 1H).	Ejemplo 179

Ejemplo 203

1-(2-(dimetilamino)etil)-N-(2-hidroxietil)-4-oxo-6-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1,4-dihidroquinolin-3-carboxamida



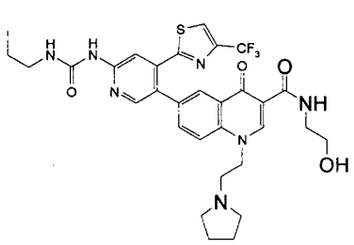
Una suspensión de 1-(2-(dimetilamino)etil)-4-oxo-6-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1,4-dihidroquinolin-3-carboxilato de etilo (Ejemplo 174, 50 mg, 0,09 mmoles) en etanolamina (0,5 ml) se calentó hasta 85-90°C durante 3 h. La mezcla de reacción se enfrió hasta la temperatura ambiente, y el precipitado que se formó se aisló mediante filtración y se lavó con acetonitrilo y agua, y después se secó toda la noche a alto vacío.

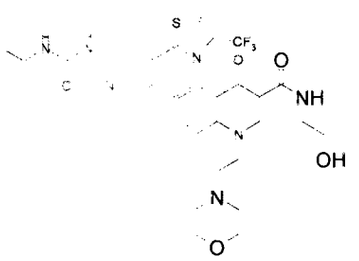
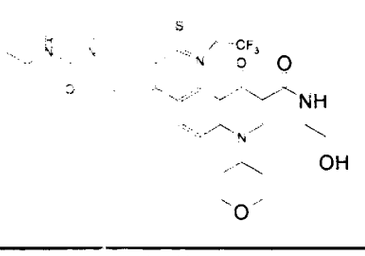
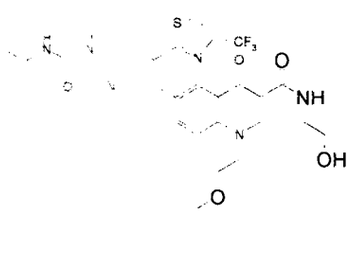
MS (ESP): 589 ($M+H^+$) para $C_{29}H_{32}F_3N_7O_4S$

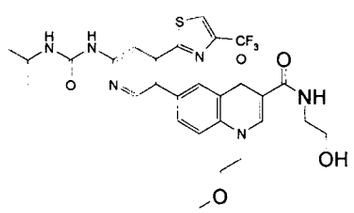
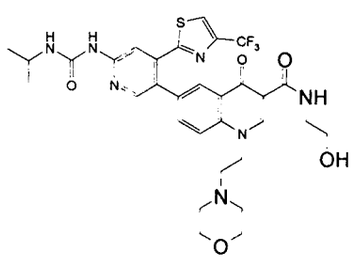
RMN ^1H (300 MHz, CD_3OD): δ 1,00 (t, 3H), 1,64 (m, 2H), 2,33 (s, 6H), 2,78 (t, 2H), 3,37 (q, 2H), 3,66 (m, 2H), 3,83 (brs, 2H), 4,37 (t, 2H), 7,60 (m, 4H), 8,01 (s, 1H), 8,24 (s, 1H), 8,59 (s, 1H), 8,84 (s, 1H), 9,1 (brs, 1H), 10,25 (brs, 1H).

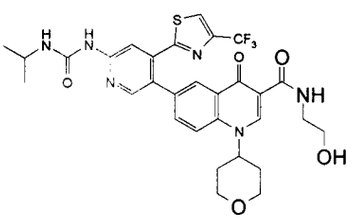
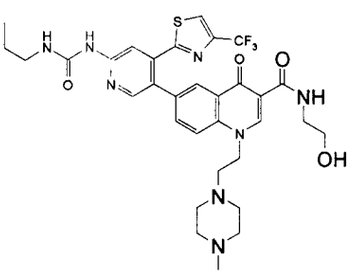
Ejemplos 204-232

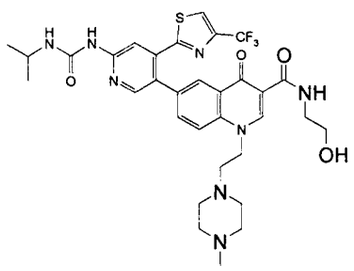
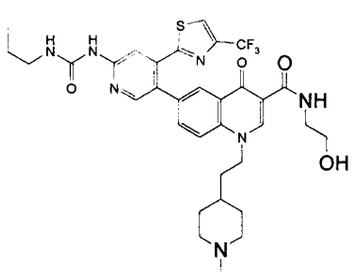
Los siguientes compuestos se prepararon según el procedimiento descrito para el Ejemplo 203 a partir de los materiales de partida indicados en la tabla.

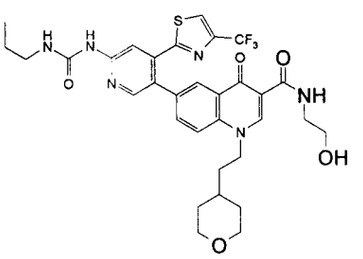
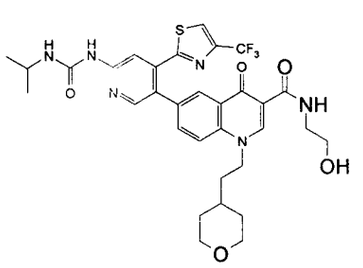
Ej.	Compuesto	Datos	SM
204	N-(2-hidroxietil)-4-oxo-6-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(2-(pirrolidin-1-il)etil)-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 658 ($M+H^+$) para $C_{31}H_{34}F_3N_7O_4S$ RMN ^1H (300 MHz, CD_3OD): δ 1,00 (t, 3H), 1,62 (m, 2H), 1,80 (m, 4H), 2,62 (m, 4H), 2,98 (m, 2H), 3,56 (m, 2H), 3,72 (m, 2H), 4,59 (m, 2H) 7,73 (d, 1H), 7,86 (s, 1H), 7,89 (d, 1H), 8,15 (s, 1H), 8,35 (s, 1H), 8,39 (s, 1H), 8,88 (s, 1H)	Ejemplo 176 y etanolamina

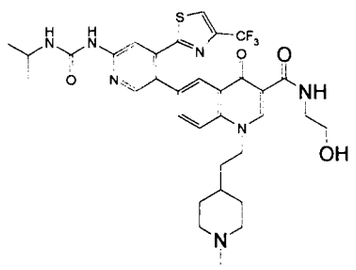
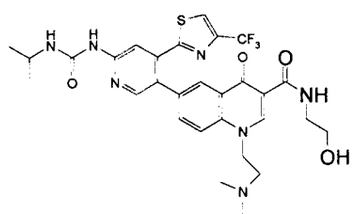
205	N-(2-hidroxietil)-1-(2-morfolinoetil)-4-oxo-6-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 675 ($M+H^+$) para $C_{31}H_{34}F_3N_7O_5S$ RMN ^1H (300 MHz, CD_3OD): δ 0,90 (t, 3H), 1,49 (m, 2H), 2,4 (brs, 4H), 2,67 (m, 2H), 3,16 (m, 2H), 3,41 (m, 2H), 3,50 (brs, 6H), 4,60 (brs, 2H), 7,70 (s, 1H), 7,73 (d, 1H), 7,96 (d, 1H), 8,23 (s, 1H), 8,25 (s, 1H), 8,34 (s, 1H), 8,48 (s, 1H), 8,84 (s, 1H), 9,46 (s, 1H), 9,97 (s, 1H)	Ejemplo 181 y etanolamina
206	N-(2-hidroxietil)-4-oxo-6-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(tetrahidro-2H-piran-4-il)-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 645 ($M+H^+$) para $C_{30}H_{31}F_3N_6O_5S$ RMN ^1H (300 MHz, CD_3OD): δ 0,99 (t, 3H), 2,18 (m, 4H), 3,55 (m, 2H), 3,74 (m, 4H), 4,17 (m, 2H), 5,10 (m, 1H), 7,72 (d, 1H), 7,86 (s, 1H), 8,09 (d, 1H), 8,14 (s, 1H), 8,34 (s, 1H), 8,42 (s, 1H), 8,99 (s, 1H)	Ejemplo 188 y etanolamina
207	N-(2-hidroxietil)-1-(2-metoxietil)-4-oxo-6-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 619 ($M+H^+$) para $C_{29}H_{31}F_3N_6O_7S$ RMN ^1H (300 MHz, dmso-d_6): δ 0,91 (t, 3H), 1,49 (m, 2H), 3,16 (q, 2H), 3,23 (s, 3H), 3,40 (m, 2H), 3,50 (m, 2H), 3,69 (m, 2H), 4,70 (brs, 2H), 4,82 (t, 1H), 7,67 (t, 1H), 7,72 (d, 1H), 7,99 (d, 1H), 8,26 (s, 1H), 8,24 (s, 1H), 8,34 (s, 1H), 8,79 (s, 1H), 9,47 (s, 1H), 9,98 (t, 1H)	Ejemplo 185 y etanolamina

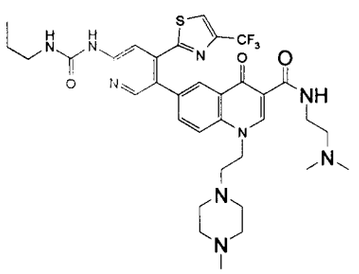
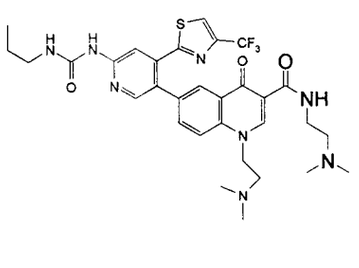
208	N-(2-hidroxietil)-6-(6-(3-isopropilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(2-metoxietil)-4-oxo-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 619 ($M+H^+$) para $C_{28}H_{29}F_3N_6O_5S$ RMN ^1H (300 MHz, DMSO-d_6): δ 1,15(d, 6H), 3,34(s, 3H), 3,41 (m, 2H), 3,51 (m, 2H), 3,69 (m, 3H), 3,83 (m, 1H), 4,70 (brs, 2H), 4,82 (t, 1H), 7,71 (d, 1H), 7,74 (d, 1H), 8,02 (d, 1H), 8,26 (s, 1H), 8,28 (s, 1H), 8,35 (s, 1H), 8,49 (s, 1H), 8,80 (s, 1H), 9,34 (s, 1H), 9,98 (t, 1H)	Ejemplo 186 y etanolamina
209	N-(2-hidroxietil)-6-(6-(3-isopropilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(2-morfolinoetil)-4-oxo-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 674 ($M+H^+$) para $C_{31}H_{34}F_3N_7O_5S$ RMN ^1H (300 MHz, dmso-d_6): δ 1,15 (d, 6H), 2,44 (brs, 4H), 2,67 (brs, 2H), 3,42 (m, 2H), 3,53 (brs, 6H), 3,82 (m, 1H), 4,61 (brs,2H), 4,82 (t, 1H), 7,48 (d, 1H), 7,73 (d, 1H), 7,98 (d, 1H), 8,25 (s, 1H), 8,27 (s, 1H), 8,35 (s, 1H), 8,49 (s, 1H), 8,84 (s, 1H), 9,46 (s, 1H), 9,97 (s, 1H)	Ejemplo 182 y etanolamina

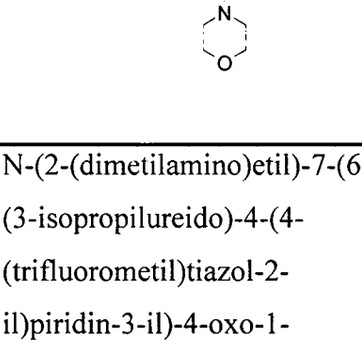
210	N-(2-hidroxietil)-6-(6-(3-isopropilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-(tetrahidro-2H-piran-4-il)-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 645 ($M+H^+$) para $C_{30}H_{31}F_3N_6O_5S$ RMN ^1H (300 MHz, CD_3OD): δ 1,22 (d, 6H), 2,18 (m, 4H), 2,72 (m, 1H), 3,57 (t, 2H), 3,72 (m, 4H), 3,99 (m, 1H), 4,14 (m, 2H), 5,10 (m, 1H), 7,73 (d, 1H), 7,91 (s, 1H), 8,10 (d, 1H), 8,14 (s, 1H), 8,35 (s, 1H), 8,43 (s, 1H), 9,00 (s, 1H)	Ejemplo 187 y etanolamina
211	N-(2-hidroxietil)-1-(2-(4-metilpiperazin-1-il)etil)-4-oxo-7-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 687,3 ($M+H^+$) para $C_{32}H_{37}F_3N_8O_4S$ RMN ^1H (300 MHz, dmso-d_6): δ 0,91 (t, 3H), 1,46-1,53 (m, 2H), 2,09 (s, br, 3H), 2,14-2,45 (m, 5H), 2,66 (t, 2H), 3,16 (q, 2H), 3,37-3,40 (m, 4H), 3,51 (q, 3H), 4,60 (t, br, 2H), 4,83 (t, 1H), 7,68-7,74 (m, 2H), 7,97 (d, 1H), 8,23 (s, 1H), 8,25 (d, 1H), 8,35 (s, 1H), 8,50 (t, 1H), 8,82 (d, 1H), 9,47 (s, 1H), 9,99 (t, 1H)	Ejemplo 180 y etanolamina

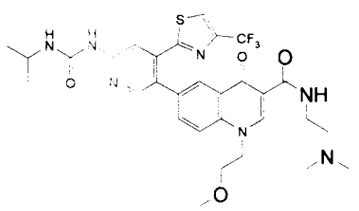
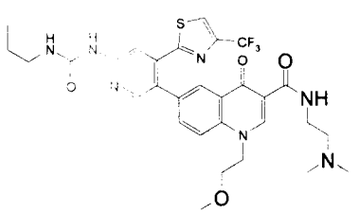
212	N-(2-hidroxietil)-6-(4-(3-isopropilureido)-2-(4-(trifluorometil)tiazol-2-il)fenil)-1-(2-(4-metilpiperazin-1-il)etil)-4-oxo-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 687 ($M+H^+$) para $C_{33}H_{37}F_3N_8O_4S$ RMN ^1H (300 MHz, dmso-d_6): δ 1,17 (d, 6H), 2,10 (s, 3H), 2,43 (brs, 2H), 2,49 (brs, 2H), 2,66 (brs, 2H), 3,31 (m, 2H), 3,52 (m, 2H), 3,85 (m, 1H), 4,58 (m, 2H), 4,58 (t, 1H), 7,43 (d, 1H), 7,69 (d, 1H), 7,69 (d, 1H), 7,94 (d, 1H), 8,24 (s, 1H), 8,26 (s, 1H), 8,34 (s, 1H), 8,48 (s, 1H), 9,91 (s, 1H), 9,99 (t, 1H)	Ejemplo 179 y etanolamina
213	N-(2-hidroxietil)-1-(2-(1-metilpiperidin-4-il)etil)-4-oxo-6-(4-(3-propilureido)-2-(4-(trifluorometil)tiazol-2-il)fenil)-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 686 ($M+H^+$) para $C_{33}H_{38}F_3N_7O_4S$ RMN ^1H (300 MHz, dmso-d_6): δ 0,91 (t, 3H), 1,23 (m, 3H), 1,59 (m, 2H), 1,76 (m, 4H), 2,12 (s, 3H), 2,75 (m, 2H), 3,18 (m, 2H), 3,37 (m, 1H), 3,50 (m, 2H), 4,49 (brs, 2H), 4,80 (brs, 1H), 7,72 (d, 1H), 7,89 (d, 1H), 7,69 (d, 1H), 7,82 (s, 2H), 8,31 (s, 1H), 8,48 (s, 1H), 8,89 (s, 1H), 9,53 (s, 1H), 9,95 (t, 1H)	Ejemplo 177 y etanolamina

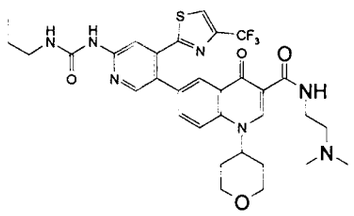
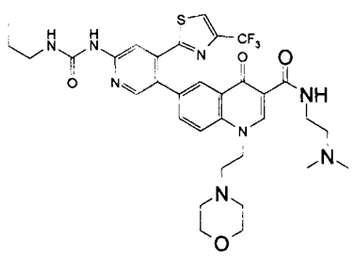
214	N-(2-hidroxietil)-4-oxo-6-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(2-(tetrahidro-2H-piran-4-il)etil)-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 673 ($M+H^+$) para $C_{32}H_{35}F_3N_6O_5S$ RMN ^1H (300 MHz, dmso-d_6): δ 0,90 (t, 3H), 1,27 (m, 2H), 1,48 (m, 2H), 1,64 (m, 4H), 2,92 (m, 1H), 3,24 (m, 2H), 3. 28 (m, 2H), 3,39 (m, 2H), 3,86 (m, 2H), 4,51 (t, 2H), 4,81 (s, 1H), 7,75 (d, 1H), 7,93 (d, 1H), 8,25 (s, 2H), 8,34 (s, 1H), 8,49 (s, 2H), 8,91 (s, 1H), 9,57 (s, 1H), 9,98 (t, 1H)	Ejemplo 184 y etanolamina
215	N-(2-hidroxietil)-7-(6-(3-isopropilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-(2-(tetrahidro-2H-piran-4-il)etil)-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 673,2 ($M+H^+$) para $C_{32}H_{35}F_3N_6O_5S$ RMN ^1H (300 MHz, dmso-d_6): δ 1,15 (d, 6H), 1,23-1,35 (m, 3H), 1,64-1,79 (m, 6H), 3,05-3,12 (m, 2H), 3,49-3,53 (m, 2H), 3,83-3,87 (m, 3H), 4,54 (br, 2H), 4,64 (t, 1H), 4,80 (t, 1H), 7,45 (dd, 1H), 7,74 (dd, 1H), 7,92 (d, 1H), 8,25 (d, 1H), 8,27 (d, 1H), 8,34 (d, 1H), 8,49 (d, 1H), 8,91 (s, 1H), 9,32 (s, 1H), 9,98 (t, 1H)	Ejemplo 183 y etanolamina

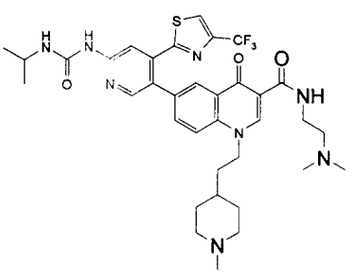
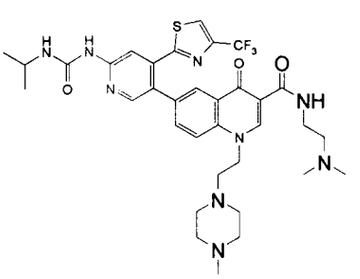
216	N-(2-hidroxietil)-6-(6-(3-isopropilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(2-(1-metilpiperidin-4-il)etil)-4-oxo-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 686 ($M+H^+$) para $C_{33}H_{38}F_3N_7O_4S$ RMN ^1H (300 MHz, dmso-d_6): δ 1,20 (d, 3H), 1,24 (m, 2H), 1,68 (m, 3H), 1,83 (m, 2H), 2,08 (s, 3H), 2,75 (brs, 2H), 3,41 (m, 2H), 3,50 (m, 2H), 3,83 (m, 1H), 4,53 (t, 2H), 4,81 (t, 1H), 7,46 (d, 1H), 7,76 (d, 1H), 7,89 (d, 1H), 8,25 (s, 1H), 8,27 (s, 1H), 8,34 (s, 1H), 8,49 (s, 1H), 8,89 (s, 1H), 9,32 (s, 1H), 9,98 (t, 1H)	Ejemplo 178 y etanolamina
217	1-(2-(dimetilamino)etil)-N-(2-hidroxietil)-7-(6-(3-isopropilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 632,1 ($M+H^+$) para $C_{29}H_{32}F_3N_7O_4S$ RMN ^1H (300 MHz, dmso-d_6): δ 1,15 (d, 6H), 2,19 (s, 6H), 2,62 (t, 2H), 3,40 (q, 2H), 3,43-3,51 (m, 2H), 3,81-3,88 (m, 1H), 4,59 (t, br, 2H), 4,81 (br, 1H), 7,46 (d, 1H), 7,72 (dd, 1H), 7,95 (d, 1H), 8,25 (d, 1H), 8,27 (s, 1H), 8,34 (d, 1H), 8,49 (d, 1H), 8,82 (s, 1H), 9,33 (s, 1H), 9,99 (t, 1H)	Ejemplo 173 y etanolamina

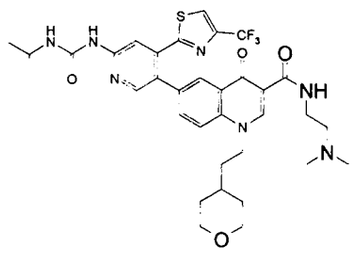
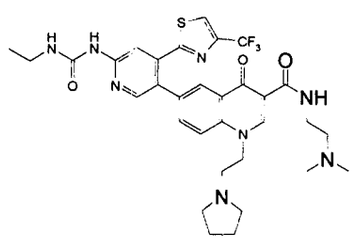
218	N-(2-(dimetilamino)etil)-1-(2-(4-metilpiperazin-1-il)etil)-4-oxo-7-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 714,3 ($M+H^+$) para $C_{34}H_{42}F_3N_9O_3S$ RMN ^1H (300 MHz, dmso-d_6): δ 0,91 (t, 3H), 1,47-1,54 (m, 2H), 2,11 (s, 3H), 2,18 (s, 6H), 2,19-2,38 (m, 2H), 2,40-2,50 (m, 4H), 2,66 (t, 2H), 3,15 (q, 2H), 3,42 (q, 2H), 4,58 (t, 2H), 7,66-7,72 (m, 2H), 7,96 (d, 1H), 8,24 (s, 1H), 8,27 (d, 1H), 8,34 (d, 1H), 8,49 (d, 1H), 8,80 (s, 1H), 9,44 (s, 1H), 9,92 (t, 1H)	Ejemplo 180 y N^1,N^1-dimetil-etano-1,2-diamina
219	N,1-bis(2-(dimetilamino)etil)-4-oxo-6-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 659 ($M+H^+$) para $C_{31}H_{37}F_3N_8O_3S$ RMN ^1H (300 MHz, dmso-d_6): δ 0,91 (t, 3H), 1,51 (m, 2H), 2,17 (s, 6H), 2,39 (t, 2H), 2,61 (brs, 2H), 3,16 (m, 2H), 3,42 (m, 2H), 4,57 (t, 2H), 7,69 (s, 1H), 7,71 (d, 1H), 7,96 (d, 1H), 8,24 (s, 1H), 8,27 (s, 1H), 8,33 (s, 1H), 8,48 (s, 1H), 8,80 (s, 1H), 9,4 (s, 1H), 9,93 (brs, 1H)	Ejemplo 174 y N^1,N^1-dimetil-etano-1,2-diamina

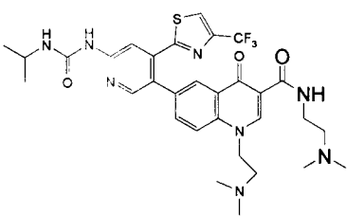
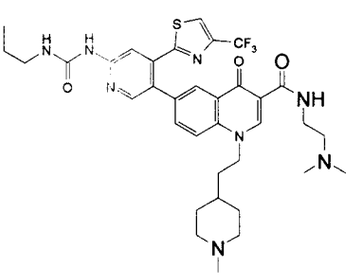
220	N-(2-(dimetilamino)etil)-7-(6-(3-isopropilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(2-morfolinoetil)-4-oxo-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 701,4 ($M+H^+$) para $C_{33}H_{39}F_3N_8O_4S$ RMN ^1H (300 MHz, dmso-d_6): δ 1,15 (d, 6H), 2,12 (d, 1H), 2,18 (s, 6H), 2,27 (t, 1H), 2,37-2,51 (m, 8H), 2,65 (t, 1H), 2,73 (t, 1H), 3,42 (q, 1H), 3,50 (t, 2H), 3,8 (q, 1H), 4,60 (t, 1H), 7,45 (d, 1H), 7,70 (dd, 1H), 7,96 (d, 1H), 8,27 (m, 2H), 8,34 (s, 1H), 8,48 (d, 1H), 8,83 (s, 1H), 9,34 (s, 1H), 9,91 (m, 1H)	Ejemplo 182 y N^1,N^1-dimetil-etano-1,2-diamina
221	N-(2-(dimetilamino)etil)-7-(6-(3-isopropilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-(tetrahidro-2H-piran-4-il)-1,4-dihidroquinolin-3-carboxamida	MS (ESP): 672,3 ($M+H^+$) para $C_{32}H_{36}F_3N_7O_4S$ RMN ^1H (300 MHz, dmso-d_6): δ 1,15 (d, 6H), 2,03-2,16 (m, 4H), 2,16 (s, 6H), 3,60-3,70 (m, 1H), 3,80-3,90 (m, 1H), 4,0-4,1 (m, 1H), 5,05-5,10 (m, 1H), 7,50 (d, 1H), 7,72 (dd, 1H), 8,20-8,32 (m, 3H), 8,46 (s, 1H), 8,84 (s, 1H), 9,32 (d, 1H), 9,88 (m, 1H)	Ejemplo 187 and N^1,N^1-dimetil-etano-1,2-diamina

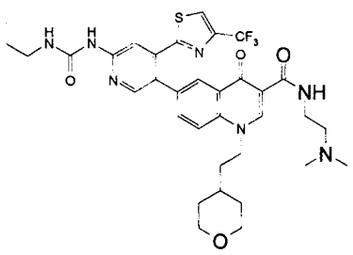
222	N-(2-(dimetilamino)etil)-7-(6-(3-isopropilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(2-metoxietil)-4-oxo-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 646,2 ($M+H^+$) para $C_{30}H_{34}F_3N_7O_4S$ RMN ^1H (300 MHz, $CDCl_3$): δ 1,29 (d, 6H), 2,32 (s, 6H), 2,56 (t, 2H), 3,34 (s, 3H), 3,60 (q, 2H), 3,80 (t, 2H), 4,11 (q, 1H), 4,46 (t, 2H), 7,22 (d, 1H), 7,42 (s, 1H), 7,51-7,61 (m, 2H), 7,68 (s, 1H), 8,28 (s, 1H), 8,57 (d, 1H), 8,84 (s, 1H), 8,91 (d, 1H), 10,02 (br, 1H)	Ejemplo 186 y N^1,N^1-dimetil-etano-1,2-diamina
223	N-(2-(dimetilamino)etil)-1-(2-metoxietil)-4-oxo-7-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 646,2 ($M+H^+$) para $C_{30}H_{34}F_3N_7O_4S$ RMN ^1H (300 MHz, $CDCl_3$): δ 1,01 (t, 3H), 1,67 (q, 2H), 2,18 (s, 6H), 2,32 (t, 2H), 3,34 (s, 3H), 3,39 (q, 2H), 3,60 (q, 2H), 3,80 (t, 2H), 4,46 (t, 2H), 7,44 (s, 1H), 7,48 (s, 1H), 7,52-7,61 (m, 2H), 7,68 (d, 1H), 8,27 (s, 1H), 8,57 (d, 1H), 8,85 (s, 1H), 9,11 (br, 1H), 10,02 (br, 1H)	Ejemplo 185 y N^1,N^1-dimetil-etano-1,2-diamina

224	N-(2-(dimetilamino)etil)-4-oxo-7-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(tetrahidro-2H-piran-4-il)-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 672,3 ($M+H^+$) para $C_{32}H_{36}F_3N_7O_4S$ RMN ^1H (300 MHz, $CDCl_3$): δ 1,01 (t, 3H), 1,67 (q, 2H), 2,10-2,30 (m, 4H), 2,31 (s, 6H), 2,56 (t, 2H), 3,41 (q, 2H), 3,57-3,70 (m, 4H), 4,25 (dd, 2H), 4,73 (m, 1H), 7,44 (s, 1H), 7,50 (s, 1H), 7,54-7,66 (m, 2H), 7,68 (d, 1H), 8,27 (d, 1H), 8,62 (d, 1H), 9,03 (s, 1H), 9,09 (br, 1H), 10,01 (t, br, 1H)	Ejemplo 188 y N^1,N^1-dimetil-etano-1,2-diamina
225	N-(2-(dimetilamino)etil)-1-(2-morfolinoetil)-4-oxo-7-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 701,4 ($M+H^+$) para $C_{33}H_{39}F_3N_8O_4S$ RMN ^1H (300 MHz, $CDCl_3$): δ 1,01 (t, 3H), 1,64 (q, 2H), 2,32 (s, 6H), 2,52-2,56 (m, 6H), 2,81 (t, 2H), 3,38 (q, 2H), 3,59-3,70 (m, 6H), 4,37 (t, 2H), 7,40 (s, 1H), 7,55 (d, 2H), 7,69 (s, 1H), 8,27 (s, 1H), 8,58 (s, 1H), 8,82 (s, 1H), 9,05 (br, 1H), 10,01 (br, 1H)	Ejemplo 181 y N^1,N^1-dimetil-etano-1,2-diamina

226	N-(2-(dimetilamino)etil)-6-(4-(3-isopropilureido)-2-(4-(trifluorometil)tiazol-2-il)fenil)-1-(2-(1-metilpiperidin-4-il)etil)-4-oxo-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 686 ($M+H^+$) para $C_{35}H_{43}F_3N_8O_3S$ RMN ^1H (300 MHz, dmso-d_6): δ 1,17 (d, 6H), 1,23 (m, 3H), 1,72 (m, 4H), 1,80 (m, 2H), 2,12 (s, 3H), 2,17 (s, 6H), 2,39 (t, 2H), 2,71 (m, 2H), 3,41 (m, 2H), 3,85 (m, 1H), 4,52 (brs, 1H), 7,45 (d, 1H), 7,73 (d, 1H), 7,89 (d, 1H), 8,27 (s, 2H), 8,34 (s, 1H), 8,48 (s, 1H), 8,89 (s, 1H), 9,33 (s, 1H), 9,92 (t, 1H)	Ejemplo 178 y N^1,N^1-dimetil-etano-1,2-diamina
227	N-(2-(dimetilamino)etil)-6-(6-(3-isopropilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(2-(4-metilpiperazin-1-il)etil)-4-oxo-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 714 ($M+H^+$) para $C_{34}H_{42}F_3N_9O_3S$ RMN ^1H (300 MHz, dmso-d_6): δ 1,14 (d, 6H), 2,12 (s, 3H), 2,18 (s, 6H), 2,27 (brs, 2H), 2,36 (m, 6H), 2,66 (t, 2H), 3,41 (m, 2H), 3,87 (m, 1H), 4,58 (t, 2H), 7,48 (d, 1H), 7,71 (d, 1H), 7,97 (d, 1H), 8,26 (s, 2H), 8,34 (s, 1H), 8,48 (s, 1H), 8,80 (s, 1H), 9,34 (s, 1H), 9,92 (t, 1H)	Ejemplo 179 y N^1,N^1-dimetil-etano-1,2-diamina

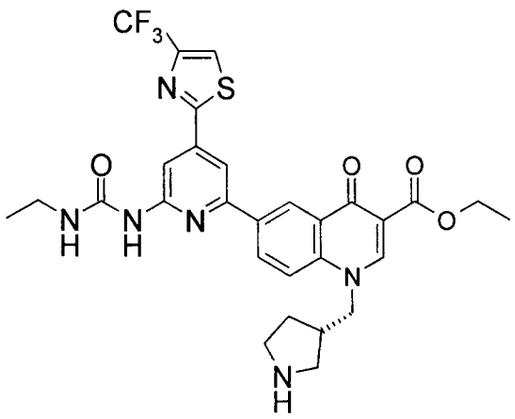
228	N-(2-(dimetilamino)etil)-7-(6-(3-isopropilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-(2-(tetrahidro-2H-piran-4-il)etil)-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 700,2 ($M+H^+$) para $C_{34}H_{40}F_3N_7O_4S$ RMN ^1H (300 MHz, dmso-d_6): δ 1,15 (d, 6H), 1,23-1,35 (m, 3H), 1,64-1,79 (m, 6H), 2,22 (s, 6H), 3,20-3,40 (m, 2H), 3,43-3,53 (m, 2H), 3,83-3,87 (m, 3H), 4,54 (br, 2H), 7,45 (d, 1H), 7,73 (dd, 1H), 7,91 (d, 1H), 8,27 (d, 2H), 8,34 (d, 1H), 8,49 (d, 1H), 8,91 (s, 1H), 9,32 (s, 1H), 9,94 (t, 1H)	Ejemplo 183 y N^1,N^1-dimetil-etano-1,2-diamina
229	N-(2-(dimetilamino)etil)-4-oxo-7-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(2-(pirrolidin-1-il)etil)-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 685,2 ($M+H^+$) para $C_{34}H_{41}F_3N_8O_5S$ RMN ^1H (300 MHz, dmso-d_6): δ 0,83-0,88 (m, 2H), 0,91 (t, 3H), 1,47-1,54 (m, 2H), 1,65 (br, 4H), 2,18 (s, 6H), 2,39 (t, 2H), 2,82 (t, 2H), 3,15 (q, 2H), 3,34-3,50 (m, 4H), 4,60 (t, 2H), 7,67-7,73 (m, 2H), 7,95 (d, 1H), 8,24 (s, 1H), 8,27 (d, 1H), 8,35 (s, 1H), 8,48 (d, 1H), 8,82 (s, 1H), 9,46 (s, 1H), 9,92 (t, 1H)	Ejemplo 176 y N^1,N^1-dimetil-etano-1,2-diamina

230	N,1-bis(2-(dimetilamino)etil)-7-(6-(3-isopropilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 659,4 ($M+H^+$) para $C_{31}H_{37}F_3N_8O_3S$ RMN ^1H (300 MHz, dmso-d_6): δ 1,16 (d, 6H), 2,19 (s, 6H), 2,21 (s, 6H), 2,44 (t, 2H), 2,62 (t, 2H), 3,43 (q, 2H), 3,80-3,86 (m, 1H), 4,58 (t, br, 2H), 7,44 (d, 1H), 7,71 (dd, 1H), 7,95 (d, 1H), 8,27 (d, 2H), 8,35 (d, 1H), 8,49 (d, 1H), 8,81 (s, 1H), 9,32 (s, 1H), 9,95 (t, 1H)	Ejemplo 173 y N^1,N^1-dimetil-etano-1,2-diamina
231	N-(2-(dimetilamino)etil)-1-(2-(1-metilpiperidin-4-il)etil)-4-oxo-6-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 713 ($M+H^+$) para $C_{36}H_{45}F_3N_8O_5S$ RMN ^1H (300 MHz, dmso-d_6): δ 0,91 (t, 3H), 1,25 (brs, 4H), 1,51 (m, 2H), 1,72 (m, 3H), 1,89 (t, 2H), 2,40 (t, 2H), 2,80 (m, 2H), 2,50 (s, 9H), 3,16 (q, 2H), 3,43 (m, 2H), 4,52 (t, 2H), 7,67 (t, 1H), 7,74 (d, 1H), 7,89 (d, 1H), 8,24 (s, 1H), 8,27 (s, 1H), 8,34 (s, 1H), 8,48 (s, 1H), 8,89 (s, 1H), 9,45 (s, 1H), 9,92 (s, 1H)	Ejemplo 177 y N^1,N^1-dimetil-etano-1,2-diamina

232	N-(2-(dimetilamino)etil)-4-oxo-6-(6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(2-(tetrahidro-2H-piran-4-il)etil)-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 700 ($M+H^+$) para $C_{35}H_{42}F_3N_7O_6S$ RMN ^1H (300 MHz, CD_3OD): δ 1,00 (t, 3H), 1,36 (m, 2H), 1,59 (m, 2H), 1,64 (m, 3H), 1,84 (m, 2H), 2,60 (s, 6H), 2,93 (t, 2H), 3,43 (t, 2H), 3. 68 (t, 2H), 3,97 (m, 2H), 4,53 (t, 2H), 7,75 (d, 1H), 7,87 (s, 1H), 7,90 (d, 1H), 8,17 (s, 1H), 8,35 (s, 1H), 8,39 (s, 1H), 8,51 (brs, 1H), 8,89 (s, 1H)	Ejemplo 184 y N^1,N^1-dimetil-etano-1,2-diamina

Ejemplo 233

(R)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-(pirrolidin-3-ilmetil)-1,4-dihidroquinolin-3-carboxilato de etilo



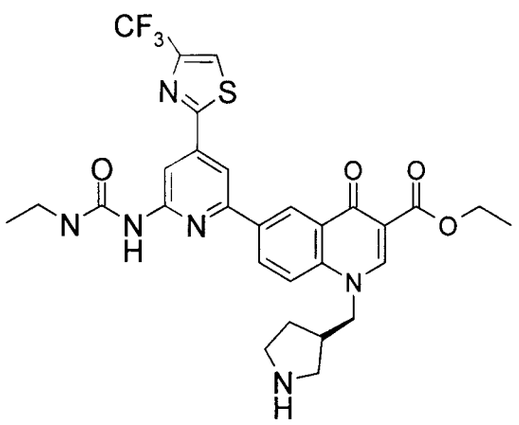
Un vial se cargó con hidrocloruro de (R)-6-yodo-4-oxo-1-(pirrolidin-3-ilmetil)-1,4-dihidroquinolin-3-carboxilato de etilo (Intermediario 97, 1,0 g, 2,16 mmoles), ácido 6-(3-etilureido)-4-(4-trifluorometiltiazol-2-il)piridin-3-ilborónico (Intermediario 17, 940 mg, 2,61 mmoles) y bicarbonato de sodio (730 mg, 8,65 mmoles) en dimetoxietano (10 ml) y agua (2 ml). La mezcla de reacción se purgó con N_2 durante alrededor de 5 min, y después se añadió trans-diclorobis(trifenilfosfina)paladio (II) (160 mg, 0,228 mmoles). La mezcla de reacción se calentó durante 3 h a 80-85°C, después se enfrió hasta la temperatura ambiente y se añadió agua (10 ml). El sólido precipitado se recogió mediante filtración para dar (R)-6-(6-(3-

etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-(pirrolidin-3-ilmetil)-1,4-dihidroquinolin-3-carboxilato de etilo (1,1 g, 82,7%) como un sólido marrón claro después de secar a vacío a 40°C toda la noche.

MS (ESP): 615,3 ($M+H^+$) para $C_{29}H_{29}F_3N_6O_4S$.

Ejemplo 234

(S)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-(pirrolidin-3-ilmetil)-1,4-dihidroquinolin-3-carboxilato de etilo

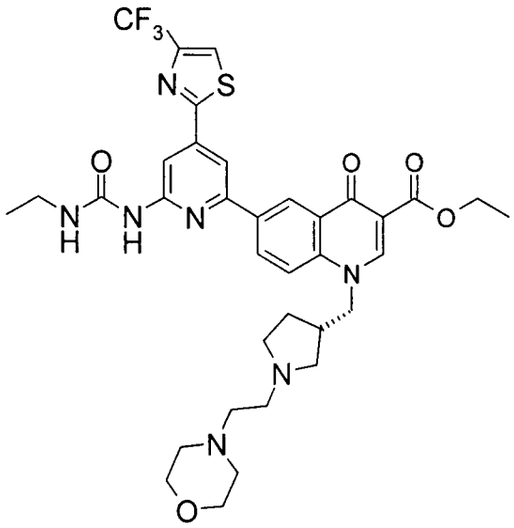


Un vial se cargó con hidrocloruro de (S)-6-yodo-4-oxo-1-(pirrolidin-3-ilmetil)-1,4-dihidroquinolin-3-carboxilato de etilo (Intermediario 98, 1,0 g, 2,16 mmoles), ácido 6-(3-etilureido)-4-(4-trifluorometiltiazol-2-il)piridin-3-ilborónico (Intermediario 17, 940 mg, 2,61 mmoles) y bicarbonato de sodio (730 mg, 8,65 mmoles) en dimetoxietano (10 ml) y agua (2 ml). La mezcla de reacción se purgó mediante N_2 durante alrededor de 5 min, y después se añadió trans-diclorobis(trifenilfosfina)paladio (II) (160 mg, 0,228 mmoles). La reacción se calentó durante 1 hora a 80-85°C, después se enfrió hasta la temperatura ambiente y se añadió agua (10 ml). El precipitado que se formó se recogió mediante filtración para dar (S)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-(pirrolidin-3-ilmetil)-1,4-dihidroquinolin-3-carboxilato de etilo (1,16 g, 87,2%) como un sólido marrón claro después de secar a vacío a 40°C toda la noche.

MS (ESP): 615,3 ($M+H^+$) para $C_{29}H_{29}F_3N_6O_4S$.

Ejemplo 235

(R)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-((1-(2-morfolinoetil)pirrolidin-3-il)metil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo

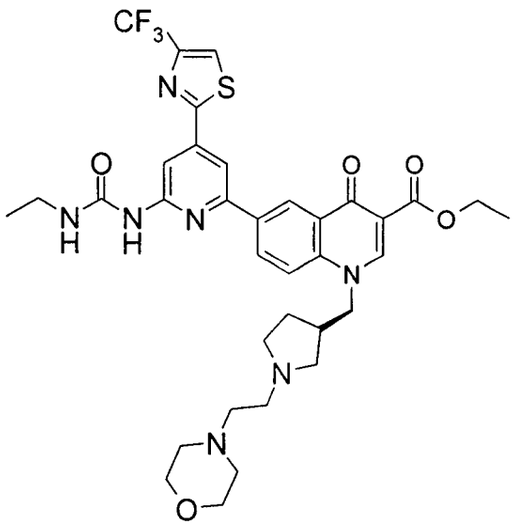


Un vial se cargó con (R)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-(pirrolidin-3-ilmetil)-1,4-dihidroquinolin-3-carboxilato de etilo (Ejemplo 233, 700 mg, 1,14 mmoles) e hidrocloruro de monohidrato de morfolin-4-il-acetaldehído (250 mg, 1,37 mmoles) en metanol (10 ml). Se añadieron perlas de cianoborohidruro de MP (730 mg, 1,71 mmoles), y la mezcla resultante se dejó agitar a temperatura ambiente toda la noche. La mezcla de reacción se filtró, y las perlas se lavaron con más metanol. El filtrado se concentró a presión reducida y se purificó mediante Analogix SF15-24 g en un sistema de diclorometano/ metanol para dar un sólido amarillo claro (320 mg, 38,6%).

MS (ESP): 728,1 (MH^+) para $C_{35}H_{40}F_3N_7O_5S$.

Ejemplo 236

(S)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-((1-(2-morfolinoetil)pirrolidin-3-il)metil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo

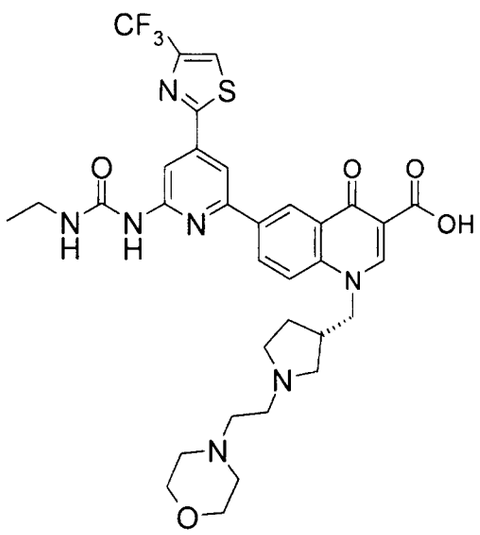


Un vial se cargó con (S)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-(pirrolidin-3-ilmetil)-1,4-dihidroquinolin-3-carboxilato de etilo (Ejemplo 234, 800 mg, 1,3 mmoles) e hidrocloruro de monohidrato de morfolin-4-il-acetaldehído (270 mg, 1,47 mmoles) en metanol (10 ml). Se añadieron perlas de cianoborohidruro de MP (850 mg, 2,0 mmoles), y la mezcla resultante se dejó agitar a temperatura ambiente toda la noche. La mezcla se filtró, y las perlas se lavaron con más metanol. El filtrado se concentró, y se purificó mediante Analogix SF15-24 g en un sistema DCM/ metanol para dar un sólido amarillo claro (380 mg, 45,8%).

MS (ESP): 728,1 (MH^+) para $C_{35}H_{40}F_3N_7O_5S$

Ejemplo 237

Ácido (R)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-((1-(2-morfolinoetil)pirrolidin-3-il)metil)-4-oxo-1,4-dihidroquinolin-3-carboxílico



Se disolvió (R)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-((1-(2-morfolinoetil)pirrolidin-3-il)metil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo (Ejemplo 235, 320 mg) en metanol (3 ml) y tetrahidrofurano (3 ml). A esta disolución se añadió hidróxido de sodio al 24% en peso (1 ml), y la mezcla de reacción se agitó a temperatura ambiente toda la noche. La mezcla de reacción se concentró entonces para eliminar los disolventes orgánicos. Se añadió agua (10 ml), y la capa acuosa se acidificó hasta pH 6~7 con ácido clorhídrico 1N. La disolución se centrifugó para ayudar a aislar el sólido que precipitó, y el precipitado se lavó con agua fría una vez para dar un sólido amarillo claro (260 mg, 86,9%) después de secar.

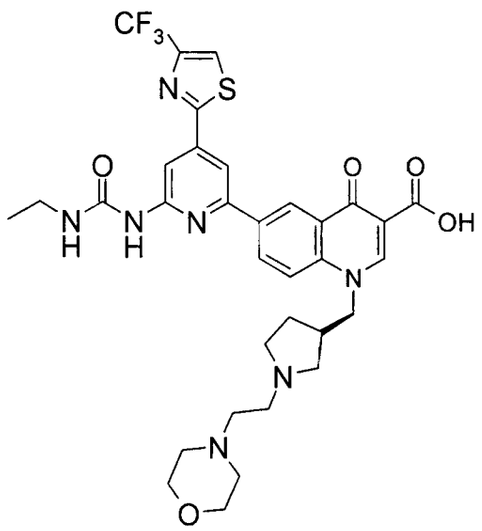
MS (ESP): 700,2 (MH^+) para $C_{33}H_{36}F_3N_7O_5S$

RMN ^{1}H (300 MHz, DMSO-d_6):1,11 (t, 3H), 2,38-2,50 (bm, 4H), 3,18-3,25 (bm, 8H), 3,50-3,62 (bm, 6H), 4,13 (br, 1H), 4,75 (br, 2H), 7,67 (bt, 1H), 7,86 (dd, 1H), 8,23-8,25 (b, 1H), 8,25 (s, 1H), 8,31 (d, 1H), 8,37 (s, 1H), 8,54 (s, 1H), 9,11 (s, 1H), 9,55 (s, 1H)

Espectro de RMN ^{19}F (DMSO-d_6) -62,79

Ejemplo 238

Ácido (S)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-((1-(2-morfolinoetil)pirrolidin-3-il)metil)-4-oxo-1,4-dihidroquinolin-3-carboxílico



Se disolvió (S)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-((1-(2-morfolinoetil)pirrolidin-3-il)metil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo (Ejemplo 236, 380 mg) en metanol (3 ml) y tetrahidrofurano (3 ml). A esta disolución se añadió hidróxido de sodio al 24% en peso (1 ml), y la reacción se agitó a temperatura ambiente toda la noche. La disolución se concentró entonces para eliminar los disolventes orgánicos. Se añadió agua (10 ml), y la capa acuosa se acidificó con cuidado hasta pH 6~7 con ácido clorhídrico 1N. La disolución se centrifugó para ayudar a aislar el sólido que precipitó, el cual se lavó con agua fría una vez para dar un sólido amarillo claro (300 mg, 82,1%) después de secar.

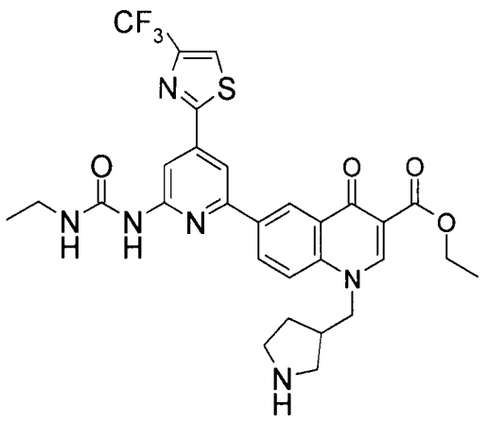
MS (ESP): 700,2 (MH^+) para $C_{33}H_{36}F_3N_7O_5S$

RMN ^{1}H (300 MHz, CD_3OD): 1,23 (m, 3H), 1,99-2,1 (br, 1H), 2,25-2,4 (br, 2H), 3,2-3,3 (m, 4H), 3,30-3,5 (m, 6H), 3,6-3,7 (m, 4H), 3,9-4,0 (m, 4H), 4,70-4,8 (br, 2H), 7,85 (d, 1H), 7,88 (s, 1H), 8,11 (d, 1H), 8,22 (s, 1H), 8,37 (s, 1H), 8,46 (d, 1H), 9,09 (s, 1H)

Espectro de RMN ^{19}F (CD_3OD) -65,78.

Ejemplo 239

6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-(pirrolidin-3-ilmetil)-1,4-dihidroquinolin-3-carboxilato de etilo

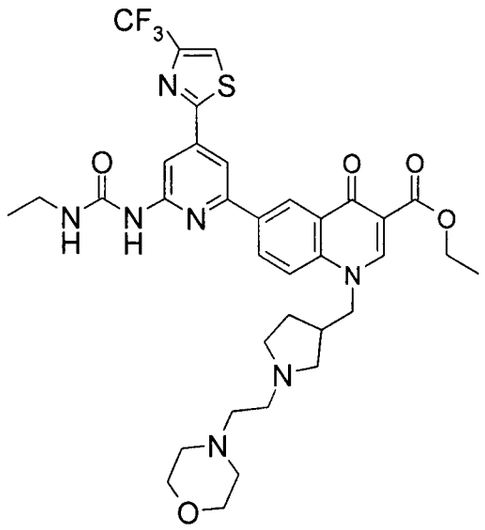


Un vial largo se cargó con hidrocloruro de 6-yodo-4-oxo-1-(pirrolidin-3-ilmetil)-1,4-dihidroquinolin-3-carboxilato de etilo (Intermediario 126, 1,5 g, 3,24 mmoles), ácido 6-(3-etilureido)-4-(4-trifluorometiltiazol-2-il)piridin-3-ilborónico (Intermediario 17, 1,41 g, 3,9 mmoles) y bicarbonato de sodio (1,1 g, 12,9 mmoles) en dimetoxietano (10 ml) y agua (2 ml). La mezcla de reacción se purgó mediante N_2 durante alrededor de 5 minutos, y después se añadió trans-diclorobis(trifenilfosfina)paladio (II) (228 mg, 0,324 mmoles). La reacción se agitó durante 1 h a 75°C. La mezcla de reacción se enfrió hasta la temperatura ambiente, y se añadió agua (10 ml). Precipitó un sólido, y se recogió para dar 6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-(pirrolidin-3-ilmetil)-1,4-dihidroquinolin-3-carboxilato de etilo (1,6 g, 80,4%) como un sólido marrón claro después de secar en un horno de vacío a 40°C toda la noche.

MS (ESP): 615,0 ($M+H^+$) para $C_{29}H_{29}F_3N_6O_4S$.

Ejemplo 240

6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-((1-(2-morfolinoetil)pirrolidin-3-il)metil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo

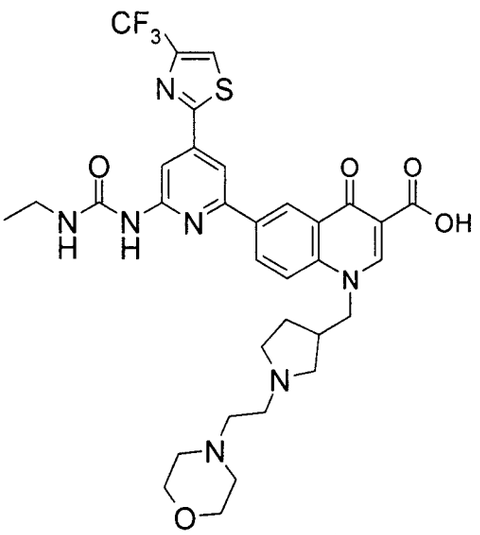


Un vial se cargó con 6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-(pirrolidin-3-ilmetil)-1,4-dihidroquinolin-3-carboxilato de etilo (Ejemplo 239, 700 mg, 1,14 mmoles), hidrocloruro de monohidrato de morfolin-4-il-acetaldehído (260 mg, 1,39 mmoles) y metanol (10 ml). Se añadieron perlas de cianoborohidruro de MP (730 mg, 1,71 mmoles), y la mezcla resultante se dejó agitar a temperatura ambiente toda la noche. La reacción se llegó a terminar basándose en LC. La mezcla se filtró y las perlas se lavaron con metanol. El filtrado se concentró a presión reducida, y se purificó mediante una columna Analogix SF15-24 g, eluyendo con un sistema diclorometano/ metanol, para dar un sólido amarillo claro (310 mg, 37,4%).

MS (ESP): 728,1 (MH^+) para $C_{35}H_{40}F_3N_7O_5S$.

Ejemplo 241

Ácido 6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-((1-(2-morfolinoetil)pirrolidin-3-il)metil)-4-oxo-1,4-dihidroquinolin-3-carboxílico



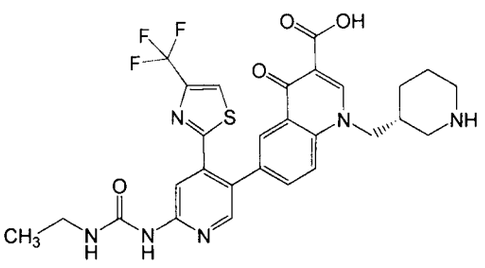
Se disolvió 6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-((1-(2-morfolinoetil)pirrolidin-3-il)metil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo (Ejemplo 240, 340 mg) en metanol (3 ml) y tetrahidrofurano (3 ml). A esta disolución se añadió hidróxido de sodio al 24% en peso (1 ml), y la mezcla de reacción se agitó a temperatura ambiente durante 3 h. La disolución se concentró a presión reducida para eliminar los orgánicos. Se añadió agua (7 ml), y la capa acuosa se acidificó con cuidado hasta pH~3 con ácido clorhídrico 1N. Precipitó un sólido, y la mezcla se centrifugó para ayudar a recoger el sólido, el cual se lavó entonces con agua fría una vez, y se secó para dar un sólido amarillo claro (270 mg, 81,2%).

MS (ESP): 700,2 (MH^+) para $C_{33}H_{36}F_3N_7O_5S$

RMN ^1H (CD_3OD): 1,23 (m, 3H), 1,99-2,1 (br, 1H), 2,25-2,4 (br, 2H), 3,3-3,4 (m, 6H), 3,45-3,6 (m, 4H), 3,7-3,8 (m, 4H), 3,9-4,0 (m, 4H), 4,85-4,9 (br, 2H), 7,85 (d, 1H), 7,90 (s, 1H), 8,12 (d, 1H), 8,23 (s, 1H), 8,37 (s, 1H), 8,47 (s, 1H), 9,11 (s, 1H).

Ejemplo 242

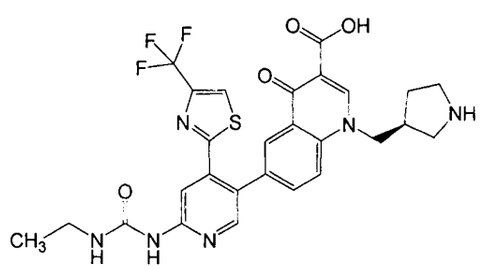
Ácido (*R*)-1-((1-piperidin-3-il)metil)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico

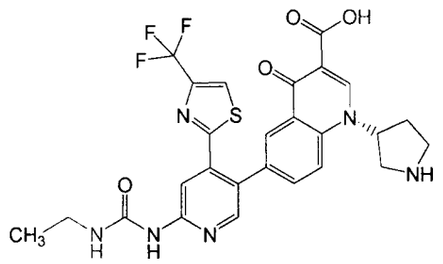
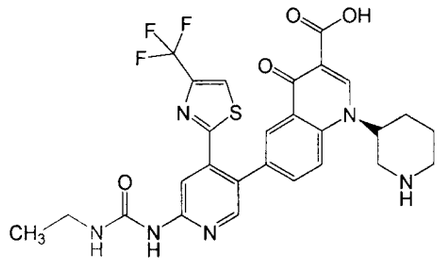
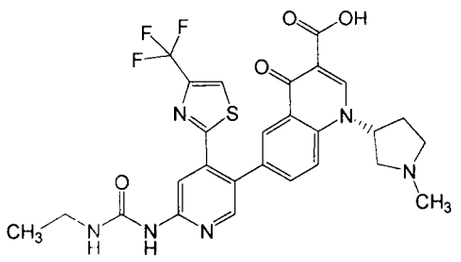


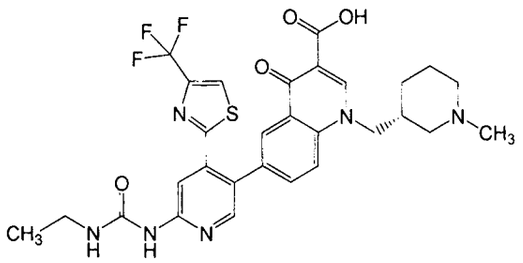
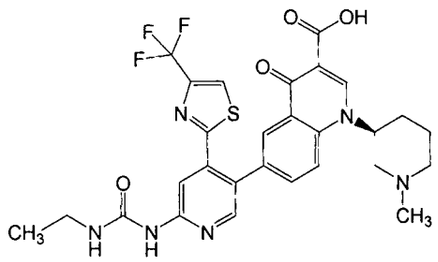
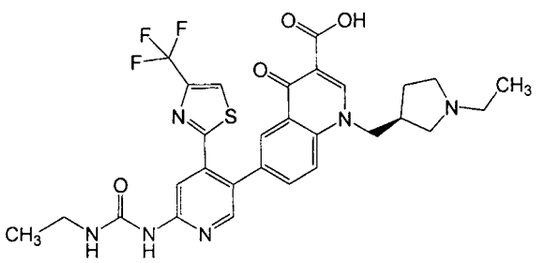
A una disolución de (*R*)-6-yodo-4-oxo-1-(piperidin-3-ilmetil)-1,4-dihidroquinolin-3-carboxilato de etilo (Intermediario 108, 200 mg, 0,42 mmoles, 1 equiv.) y ácido 6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-ilborónico (Intermediario 17, 151 mg, 0,42 mmoles, 1 equiv.) en 1,4-dioxano (4,5 ml) se añadió tetraquis(trifenilfosfina)paladio(0) (48,5 mg, 0,04 mmoles, 0,1 equiv.), seguido de una disolución de carbonato de cesio (205 mg, 0,63 mmoles, 1,5 equiv.) en agua (1,5 ml). Ésta se agitó a 100 °C durante 2 h. Entonces se añadió hidróxido de litio 2 M (0,629 ml, 1,26 mmoles, 3 equiv.), y la mezcla se agitó a 100 °C durante 12 h. La mezcla de reacción se diluyó con agua, y el precipitado que se formó se recogió mediante filtración, se lavó con agua y hexanos y se secó a vacío. La purificación vía HPLC de fase inversa (C18, gradiente 0-95% de acteonitirilo/agua) dio ácido (*R*)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-(piperidin-3-ilmetil)-1,4-dihidroquinolin-3-carboxílico como un sólido amarillo claro (92,5 mg, 36 %).
Calc. para $C_{28}H_{27}F_3N_6O_4S$ $[M + H]^+$: 601,06.

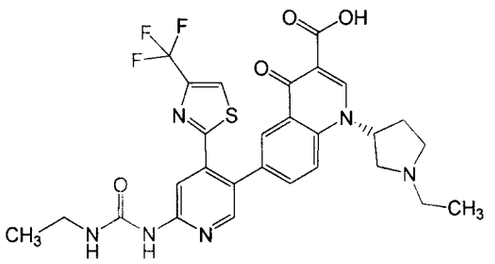
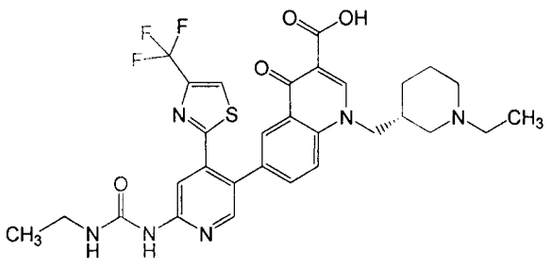
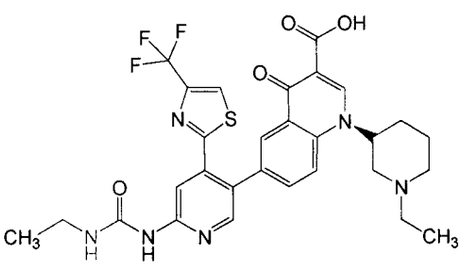
Ejemplos 243-252

Los siguientes Ejemplos se prepararon según el procedimiento descrito en el Ejemplo 242 a partir de los materiales de partida indicados.

Ej.	Compuesto	Datos	SM
243	Ácido (*S*)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-(pirrolidin-3-ilmetil)-1,4-dihidroquinolin-3-carboxílico 	Calc. para $C_{27}H_{25}F_3N_6O_4S$ $[M + H]^+$: 587,02	Intermediario 109 e Intermediario 17

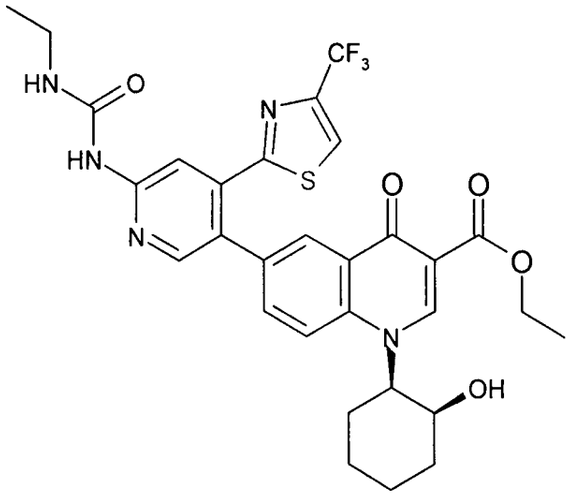
Ej.	Compuesto	Datos	SM
244	Ácido (*R*)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-(pirrolidin-3-il)-1,4-dihidroquinolin-3-carboxílico 	Calc. para $C_{26}H_{23}F_3N_6O_4S$ $[M + H]^+$: 573,01	Intermediario 110 e Intermediario 17
245	Ácido (*S*)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-(piperidin-3-il)-1,4-dihidroquinolin-3-carboxílico 	Calc. para $C_{27}H_{25}F_3N_6O_4S$ $[M + H]^+$: 587,02	Intermediario 111 e Intermediario 17
246	Ácido (*R*)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-metilpirrolidin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	Calc. para $C_{27}H_{25}F_3N_6O_4S$ $[M + H]^+$: 587,02	Intermediario 101 e Intermediario 17

Ej.	Compuesto	Datos	SM
247	Ácido (*R*)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-((1-metilpiperidin-3-il)metil)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	Calc. para $C_{29}H_{29}F_3N_6O_4S$ [M + H]$^+$: 615,02	Intermediario 102 e Intermediario 17
248	Ácido (*S*)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-metilpiperidin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	Calc. para $C_{28}H_{27}F_3N_6O_4S$ [M + H]$^+$: 601,04	Intermediario 103 e Intermediario 17
249	Ácido (*S*)-1-((1-etilpirrolidin-3-il)metil)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	Calc. para $C_{29}H_{29}F_3N_6O_4S$ [M + H]$^+$: 615,04	Intermediario 104 e Intermediario 17

Ej.	Compuesto	Datos	SM
250	Ácido (*R*)-1-(1-etilpirrolidin-3-il)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	Calc. para $C_{28}H_{27}F_3N_6O_4S$ [M + H]$^+$: 615,04	Intermediario 105 e Intermediario 17
251	Ácido (*R*)-1-((1-etilpiperidin-3-il)metil)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	Calc. para $C_{30}H_{31}F_3N_6O_4S$ [M + H]$^+$: 629,06	Intermediario 106 e Intermediario 17
252	Ácido (*R*)-1-(1-etilpiperidin-3-il)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	Calc. para $C_{29}H_{29}F_3N_6O_4S$ [M + H]$^+$: 615,04	Intermediario 107 e Intermediario 17

Ejemplo 253

6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(*cis*-2-hidroxiciclohexil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo

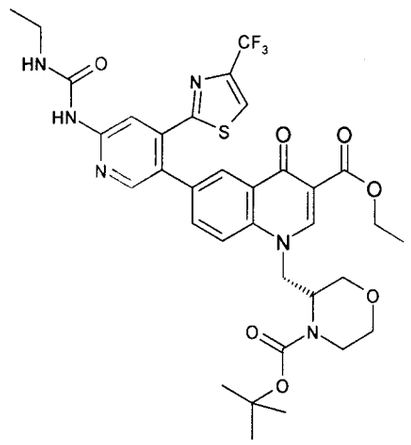
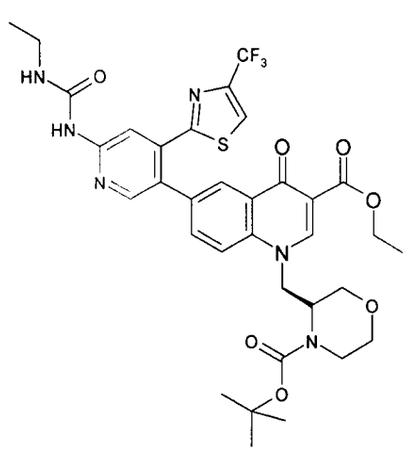


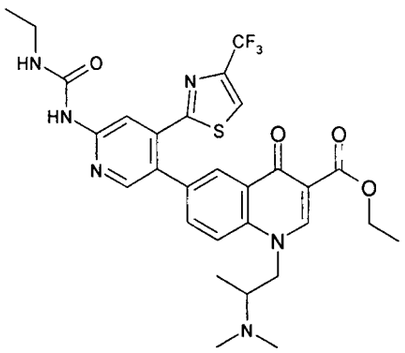
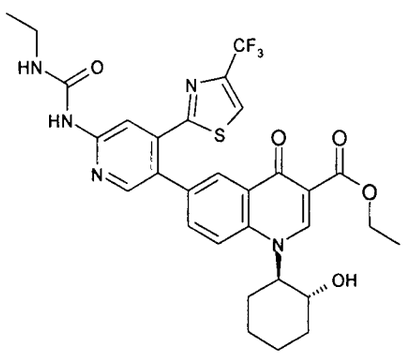
Se disolvieron acetato de paladio (II) (0,027 g, 0.12 mmoles) y 1,1'-bis(di-t-butilfosfino)ferroceno (0,058 g, 0,12 mmoles) en 1 ml de acetonitrilo. Se añadieron 1-(*cis*-2-hidroxiciclohexil)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo (Intermediario 121, 0,539 g, 1,22 mmoles) y ácido 6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-ilborónico (Intermediario 17, 0,444 g, 1,23 mmoles), junto con 2 ml adicionales de acetonitrilo. Se disolvió carbonato de potasio (0,253 g, 1,83 mmoles) en agua (1,333 ml), y después se añadió a la mezcla. La reacción se agitó a 100°C durante 30 min, después se enfrió hasta la temperatura ambiente y se paralizó con agua (2 ml). El precipitado se separó por filtración y se lavó con agua, acetato de etilo y hexanos, después se secó en un horno de vacío a 50°C durante 18 h para dar 0,606g (78%) de 6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(cis-2-hidroxiciclohexil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo como un sólido marrón claro.

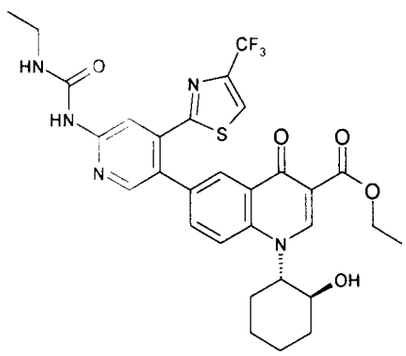
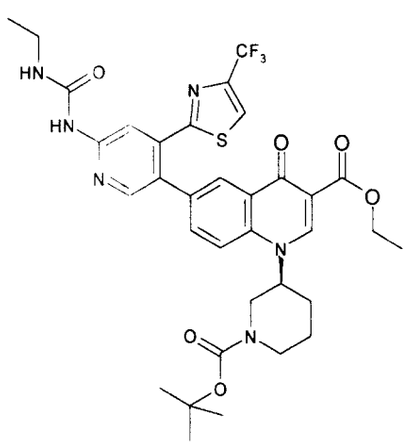
MS (ES) $(M+H)^+$: 630 para $C_{30}H_{30}F_3N_5O_5S$.

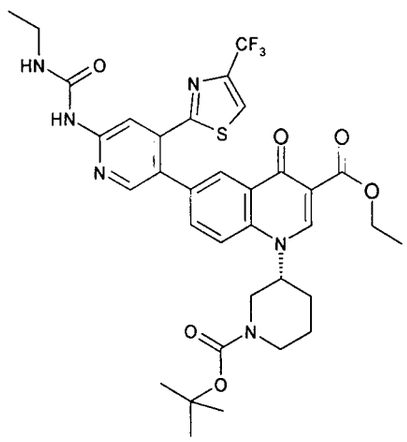
Ejemplos 254-260

Los siguientes Ejemplos se prepararon mediante el procedimiento descrito en el Ejemplo 253 a partir de los materiales de partida (SM) indicados.

Ej.	Compuesto	Datos	SM
254	(R)-3-((3-(etoxicarbonil)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxoquinolin-1(4H)-il)metil)morfolin-4-carboxilato de terc-butilo 	MS (ES) $(M+H)^+$: 731 para $C_{34}H_{37}F_3N_6O_7S$ RMN: (300 MHz, *DMSO-d_6*) δ 9,45 (br. s., 1 H), 8,53 (s, 2 H), 8,31 - 8,44 (m, 1 H), 8,15 - 8,26 (m, 2 H), 7,97 - 8,14 (m, 1 H), 7,61 - 7,75 (m, 2 H), 4,61 - 4,81 (m, 2 H), 4,14 - 4,32 (m, 2 H), 3,96 - 4,06 (m, 1 H), 3,60 - 3,94 (m, 2 H), 3,49 - 3,60 (m, 1 H), 3,38 (d, *J*=7,54 Hz, 2 H), 3,15 - 3,27 (m, 2 H), 1,21 - 1,33 (m, 4 H), 1,05 - 1,20 (m, 6 H), 0,79 - 0,90 (m, 6 H).	Intermediario 17 e Intermediario 117
255	(S)-3-((3-(etoxicarbonil)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxoquinolin-1(4H)-il)metil)morfolin-4-carboxilato de terc-butilo 	MS (ES) $(M+H)^+$: 731 para $C_{34}H_{37}F_3N_6O_7S$ RMN: (300 MHz, *DMSO-d_6*) δ 9,46 (br. s., 1 H), 8,53 (s, 1 H), 8,32 - 8,45 (m, 1 H), 8,15 - 8,27 (m, 2 H), 7,98 - 8,14 (m, 1 H), 7,61 - 7,75 (m, 2 H), 4,64 - 4,76 (m, 2 H), 4,15 - 4,33 (m, 3 H), 3,95 - 4,14 (m, 2 H), 3,73 - 3,95 (m, 2 H), 3,36 - 3,61 (m, 2 H), 3,10 - 3,29 (m, 2 H), 1,21 - 1,34 (m, 4 H), 1,03 - 1,20 (m, 6 H), 0,76 - 0,90 (m, 6 H).	Intermediario 17 e Intermediario 118

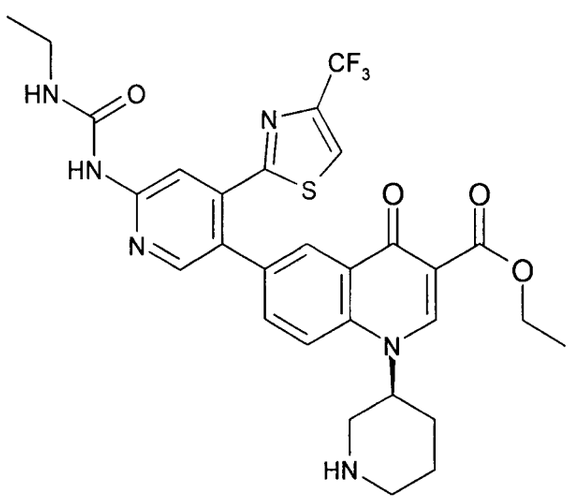
Ej.	Compuesto	Datos	SM
256	1-(2-(dimetilamino)propil)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ES) $(M+H)^+$: 617 para $C_{29}H_{31}F_3N_6O_4S$ RMN: (300 MHz, *DMSO-d*$_6$) δ 9,44 (s, 1 H), 8,56 (s, 1 H), 8,51 (s, 1 H), 8,33 (s, 1 H), 8,22 (s, 1 H), 8,14 (d, *J*=2,26 Hz, 1 H), 7,86 (d, *J*=9,04 Hz, 1 H), 7,58 - 7,68 (m, 2 H), 4,17 - 4,42 (m, 4 H), 3,15 - 3,27 (m, 2 H), 2,92 - 3,05 (m, 1 H), 2,16 (s, 5 H), 1,28 (t, *J*=6,78 Hz, 3 H), 1,11(t, *J*=7,16 Hz, 3 H), 0,96 (d, 3 H).	Intermediario 17 e Intermediario 116
257	6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-((1R,2R)-2-hidroxiciclohexil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ES) $(M+H)^+$: 630 para $C_{30}H_{30}F_3N_5O_5S$ RMN: (300 MHz, *DMSO-d*$_6$) δ 9,43 (s, 1 H), 8,59 - 8,70 (m, 1 H), 8,46 - 8,55 (m, 1 H), 8,31 (s, 1 H), 8,05 - 8,25 (m, 3 H), 7,56 - 7,74 (m, 2H), 5,15 (d, *J*=5,27 Hz, 1 H), 4,50 - 4,69 (m, 1 H), 4,25 (q, *J*=6,78 Hz, 2 H), 3,94 (br. s., 1 H), 3,38 (q, *J*=7,28 Hz, 1 H), 3,21 (dq, *J*=6,78, 6,53 Hz, 2H), 1,89 - 2,11 (m, 1 H), 1,73 (d, *J*=9,04 Hz, 2 H), 1,39 - 1,63 (m, 3 H), 1,29 (t, *J*=7,16 Hz, 3 H), 1,10 (q, *J*=6,78 Hz, 4 H).	Intermediario 17 e Intermediario 119

Ej.	Compuesto	Datos	SM
258	6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-((1R,2R)-2-hidroxiciclohexil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ES) $(M+H)^+$: 630 para $C_{30}H_{30}F_3N_5O_5S$ RMN: (300 MHz, *DMSO-d_6*) δ 9,43 (s, 1 H), 8,65 (s, 1 H), 8,48 (s, 1 H), 8,29 - 8,38 (m, 1 H), 8,04 - 8,26 (m, 2 H), 7,60 - 7,71 (m, 1 H), 5,15 (d, *J*=5,27 Hz, 1 H), 4,59 (br. s., 1 H), 4,25 (q, *J*=6,78 Hz, 1 H), 4,08 (q, *J*=5,27 Hz, 1 H), 3,86 - 3,98 (m, 1 H), 3,15 - 3,26 (m, 6 H), 1,99 (s, 2 H), 1,71 (br. s., 2 H), 1,48 (d, *J*=9,80 Hz, 2 H), 1,29 (t, *J*=7,16 Hz, 2 H), 1,03 - 1,18 (m, 3 H).	Intermediario 17 e Intermediario 120
259	(S)-1-(1-(terc-butoxicarbonil)piperidin-3-il)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ES) $(M+H)^+$: 630 para $C_{34}H_{37}F_3N_6O_6S$	Intermediario 17 e Intermediario 122

Ej.	Compuesto	Datos	SM
260	(R)-1-(1-(terc-butoxicarbonil)piperidin-3-il)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ES) $(M+H)^+$: 630 para $C_{34}H_{37}F_3N_6O_6S$	Intermediario 17 e Intermediario 123

Ejemplo 261

(S)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-(piperidin-3-il)-1,4-dihidroquinolin-3-carboxilato de etilo



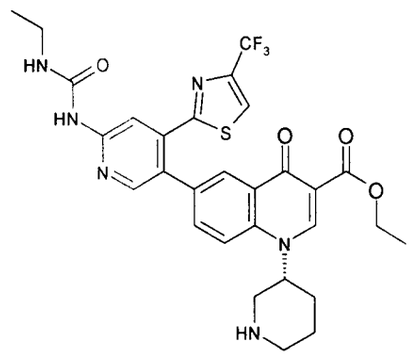
Se recogió (S)-1-(1-(*terc-but*oxicarbonil)piperidin-3-il)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo (Ejemplo 259, 5,00 g, 7,00 mmoles) en diclorometano (10 ml) y se añadió HCl 4M en dioxano (0,486 ml, 13,99 mmoles) mientras se agitaba a RTdurante 1h. El disolvente se

eliminó a vacío, y el residuo se recogió nuevamente en metanol y agua. La reacción se neutralizó usando $NaHCO_3$ y se recogió un precipitado, se lavó con éter y se secó a alto vacío toda la noche para dar (S)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-(piperidin-3-il)-1,4-dihidroquinolin-3-carboxilato de etilo (3,10 g, 72,1 %).

MS (ES) $(M+H)^+$: 615 para $C_{29}H_{29}F_3N_6O_4S$.

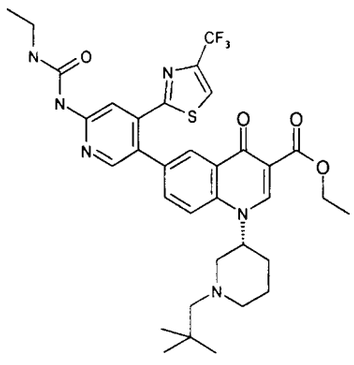
Ejemplo 262

El siguiente ejemplo se preparó mediante el procedimiento descrito en el Ejemplo 261 a partir de los materiales de partida (SM) indicados.

Int.	Compuesto	Datos	SM
262	(R)-1-(1-(terc-butoxicarbonil)piperidin-3-il)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ES) $(M+H)^+$: 615 para $C_{29}H_{29}F_3N_6O_4S$	Ejemplo 260

Ejemplo 263

(R)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-(piperidin-3-il)-1,4-dihidroquinolin-3-carboxilato de etilo

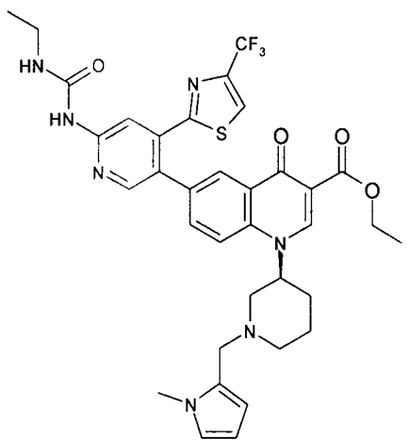
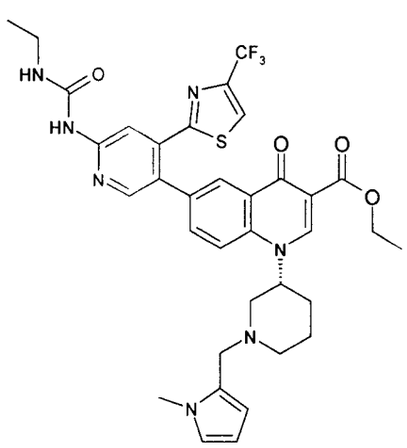


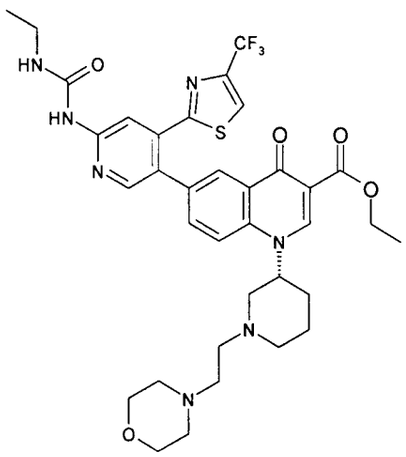
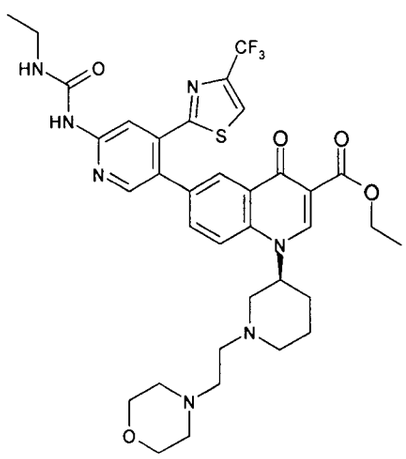
Se recogió (R)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-(piperidin-3-il)-1,4-dihidroquinolin-3-carboxilato de etilo (Ejemplo 262, 0,150 g, 0,24 mmoles) en diclorometano (5 ml), y se añadió pivalaldehído (0,030 ml, 0,27 mmoles) y se agitó a RT durante 15 min. Se añadió triacetoxiborohidruro de sodio (0,078 g, 0,37 mmoles), y la reacción se agitó a 60°C durante 18 h. La reacción se paralizó entonces con $NaHCO_3$, y se extrajo 3 veces con DCM. Los orgánicos se combinaron y se secaron sobre Na_2SO_4, y después el disolvente se eliminó *a vacío*. El residuo se purificó mediante cromatografía ultrarrápida en columna sobre gel de sílice, usando (diclorometano-metanol), para dar (R)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-(piperidin-3-il)-1,4-dihidroquinolin-3-carboxilato de etilo (0,060 g, 38%).

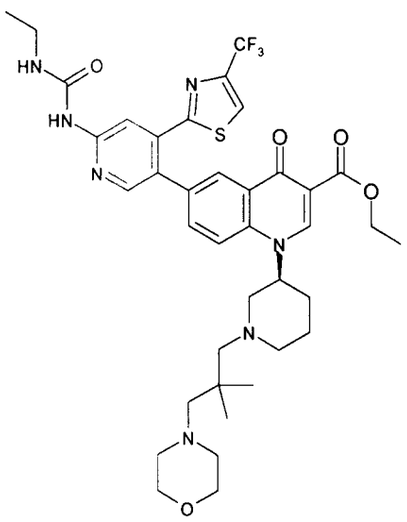
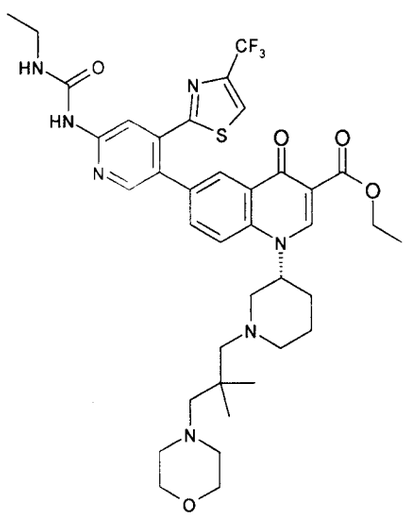
MS (ES) $(M+H)^+$: 685 para $C_{34}H_{39}F_3N_6O_4S$

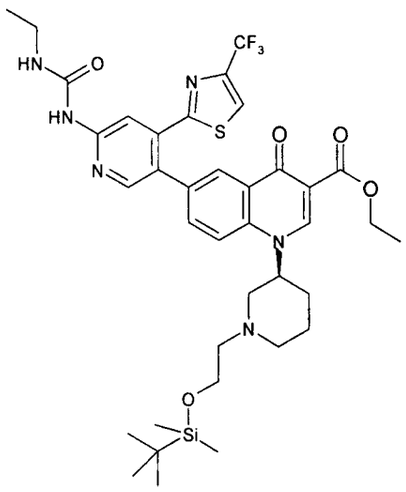
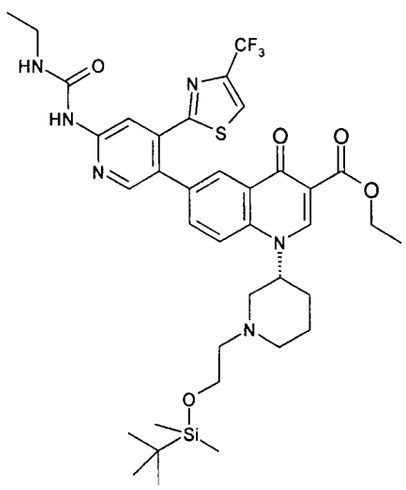
Ejemplos 264-272

Los siguientes Ejemplos se prepararon mediante el procedimiento descrito en el Ejemplo 263 a partir de los materiales de partida (SM) indicados.

Ej.	Compuesto	Datos	SM
264	(S)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-((1-metil-1H-pirrol-2-il)metil)piperidin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ES) $(M+H)^+$: 708 para $C_{35}H_{36}F_3N_7O_4S$	Ejemplo 261 y 1-metil-1H-pirrol-2-carbaldehído
265	(R)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-((1-metil-1H-pirrol-2-il)metil)piperidin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ES) $(M+H)^+$: 708 para $C_{35}H_{36}F_3N_7O_4S$	Ejemplo 262 y 1-metil-1H-pirrol-2-carbaldehído

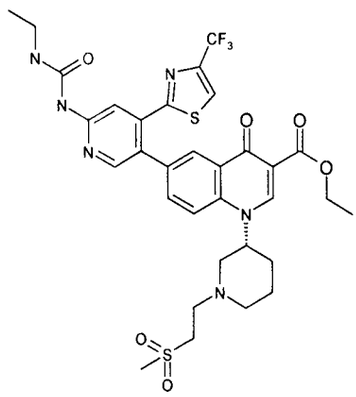
266	(R)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-(2-morfolinoetil)piperidin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ES) $(M+H)^+$: 728 para $C_{35}H_{40}F_3N_7O_5S$	Ejemplo 262 y 2,2,2-trifluoro-acetato de 2-morfolino-acetaldehído
267	(S)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-(2-morfolinoetil)piperidin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ES) $(M+H)^+$: 728 para $C_{35}H_{40}F_3N_7O_5S$	Ejemplo 261 y 2,2,2-trifluoro-acetato de 2-morfolino-acetaldehído

268	(S)-1-(1-(2,2-dimetil-3-morfolinopropil)piperidin-3-il)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ES) $(M+H)^+$: 770 para $C_{38}H_{46}F_3N_7O_5S$	Ejemplo 261 y 2,2-dimetil-3-morfolino-propanal
269	(R)-1-(1-(2,2-dimetil-3-morfolinopropil)piperidin-3-il)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ES) $(M+H)^+$: 770 para $C_{38}H_{46}F_3N_7O_5S$	Ejemplo 262 y 2,2-dimetil-3-morfolino-propanal

270	(S)-1-(1-(2-(terc-butildimetilsilyloxi)etil)piperidin-3-il)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ES) $(M+H)^+$: 773 para $C_{37}H_{47}F_3N_6O_5SSi$	Ejemplo 261 y 2-(terc-butil-dimetilsililoxi)acet-aldehído
271	(R)-1-(1-(2-(terc-butildimetilsilyloxi)etil)piperidin-3-il)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ES) $(M+H)^+$: 773 para $C_{37}H_{47}F_3N_6O_5SSi$	Ejemplo 262 y 2-(terc-butil-dimetilsililoxi)acet-aldehído

Ejemplo 272

(R)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-(2-(metilsulfonil)etil)piperidin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo

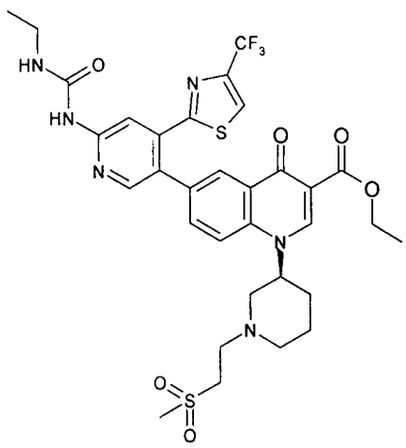


Se recogió (R)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-(piperidin-3-il)-1,4-dihidroquinolin-3-carboxilato de etilo (Ejemplo 262, 0,150 g, 0,24 mmoles) en isopropanol (2 ml), y se añadió metilvinilsulfona (0,026 ml, 0,29 mmoles). La mezcla de reacción se agitó a 100 °C durante 18 h en una vasija cerrada herméticamente, después se enfrió hasta la temperatura ambiente y el disolvente se eliminó *a vacío* y se cargó directamente sobre sílice. La purificación mediante cromatografía ultrarrápida en columna sobre gel de sílice, usando (diclorometano-metanol), dio (R)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-(2-(metilsulfonil)etil)piperidin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo (0,110 g, 62,5 %).

MS (ES) $(M+H)^+$:721 para $C_{32}H_{35}F_3N_6O_6S_2$

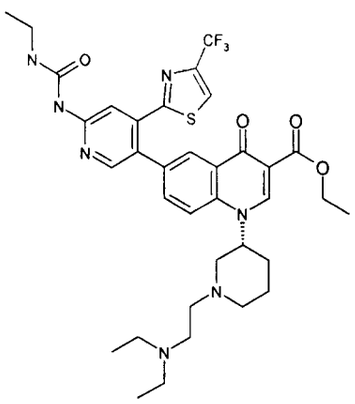
Ejemplo 273

El siguiente ejemplo se preparó según el procedimiento descrito en el Ejemplo 272 a partir de los materiales de partida indicados.

Int.	Compuesto	Datos	SM
273	(S)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-(2-(metilsulfonil)etil)piperidin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ES) $(M+H)^+$: 721 para $C_{32}H_{35}F_3N_6O_6S_2$	Ejemplo 261 y metilvinilsulfona

Ejemplo 274

(R)-1-(1-(2-(dietilamino)etil)piperidin-3-il)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo



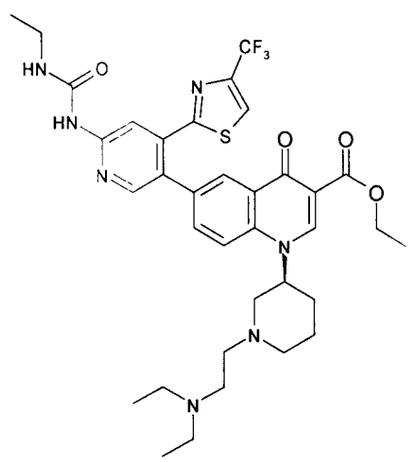
Se recogió (R)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-(piperidin-3-il)-1,4-dihidroquinolin-3-carboxilato de etilo (Ejemplo 262, 0,100 g, 0,16 mmoles) en DMF (2 ml), y se añadieron K_2CO_3 (0,112 g, 0,81 mmoles) e hidrocloruro de 2-cloro-N,N-dietiletanamina (0,031 g, 0,18 mmoles). La mezcla se calentó hasta 100 °C toda la noche, y después la reacción se enfrió hasta la temperatura ambiente y se diluyó con EtOAc.

La capa orgánica se lavó con salmuera dos veces y con agua dos veces, después el disolvente se eliminó *a vacío* y el residuo se purificó mediante cromatografía ultrarrápida en columna sobre gel de sílice, usando (diclorometano-metanol), para dar (R)-1-(1-(2-(dietilamino)etil)piperidin-3-il)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo (0,020 g, 17 %).

MS (ES) $(M+H)^+$: 714 para $C_{35}H_{42}F_3N_7O_4S$

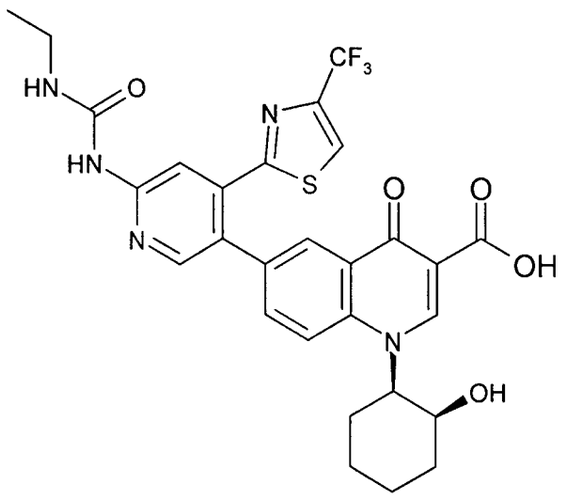
Ejemplo 275

El siguiente ejemplo se preparó según el procedimiento descrito para el Ejemplo 274 a partir del material de partida indicado.

Ej.	Compuesto	Datos	SM
275	(S)-1-(1-(2-(dietilamino)etil)piperidin-3-il)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ES) $(M+H)^+$: 714 para $C_{35}H_{42}F_3N_7O_4S$	Ejemplo 261 e hidrocloruro de 2-cloro-N,N-dietil-etanamina

Ejemplo 276

Ácido 6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(*cis*-2-hidroxiciclohexil)-4-oxo-1,4-dihidroquinolin-3-carboxílico



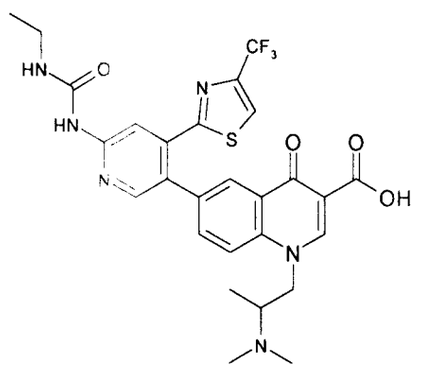
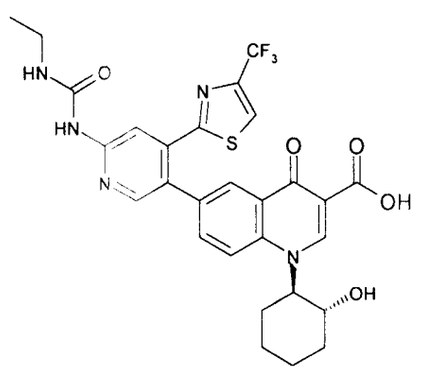
Se suspendió 6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(*cis*-2-hidroxiciclohexil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo (Ejemplo 253, 0,240 g, 0,38 mmoles) en MeOH (6 ml) en una vasija de microondas (CEM). Se añadió THF (3,00 ml). Se añadió una disolución ac. 2,0 M de LiOH (0,381 ml, 0,76 mmoles). La vasija de microondas se calentó en el microondas a 100 °C durante 15 min. Tras enfriar hasta la temperatura ambiente, el disolvente se eliminó *a vacío* para dar un residuo que se purificó mediante cromatografía ultrarrápida en columna sobre gel de sílice, usando (diclorometano-metanol), para dar ácido 6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(*cis*-2-hidroxiciclohexil)-4-oxo-1,4-dihidroquinolin-3-carboxílico (0,113g, 49%).

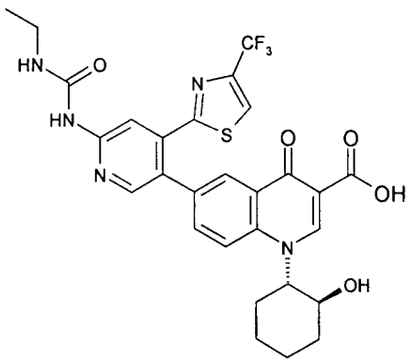
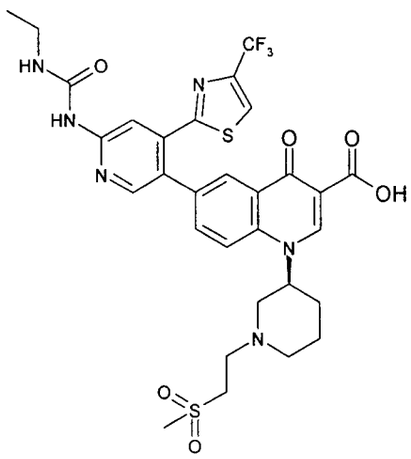
MS (ES) $(M+H)^+$: 602 para $C_{28}H_{26}F_3N_5O_5S$.

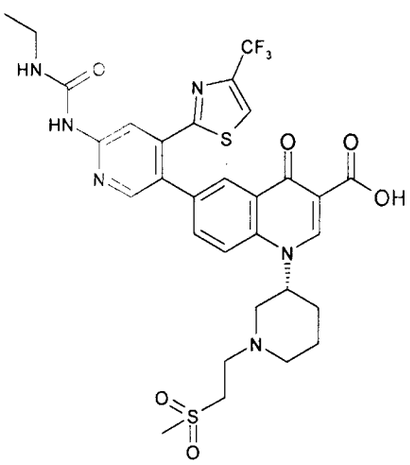
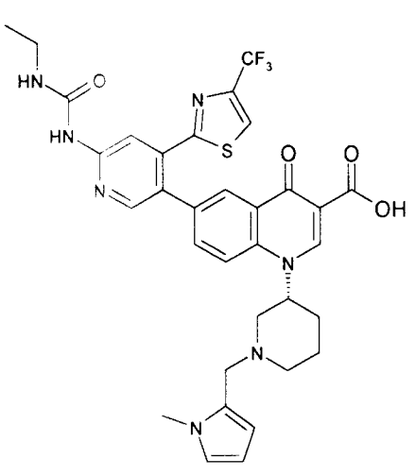
RMN ^1H (300 MHz, *DMSO-d*$_6$) δ 15,10 (s, 1 H), 9,48 (s, 1 H), 8,87 (s, 1 H), 8,53 (s, 1 H), 8,36 (s, 2 H), 8,29 (d, *J*=9,80 Hz, 1 H), 8,22 (s, 1 H), 7,85 (d, *J*=7,54 Hz, 1 H), 7,57 - 7,65 (m, 1 H), 5,20 (d, *J*=4,52 Hz, 1 H), 5,09 (d, *J*=10,55 Hz, 1 H), 3,96 (br. s., 1 H), 3,15 - 3,27 (m, 2 H), 2,29 (d, *J*=11,30 Hz, 1 H), 1,74 - 1,96 (m, 4 H), 1,62 (d, *J*=7,54 Hz, 2 H), 1,48 (d, 1 H), 1,11 (t, *J*=7,16 Hz, 3 H).

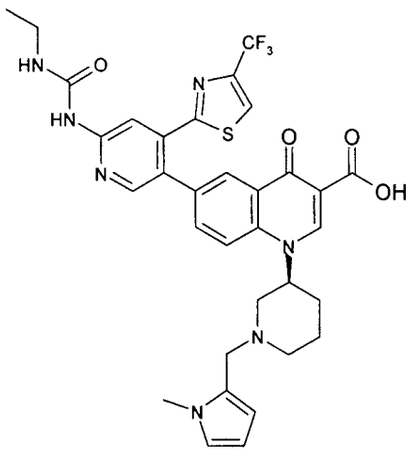
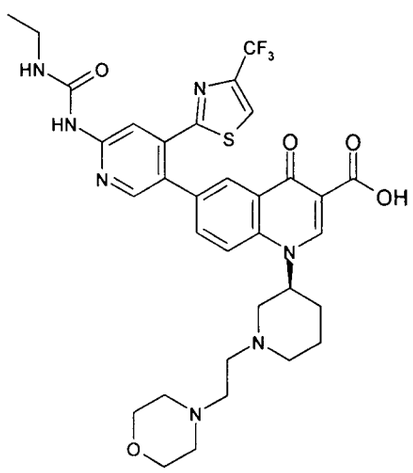
Ejemplos 277-286

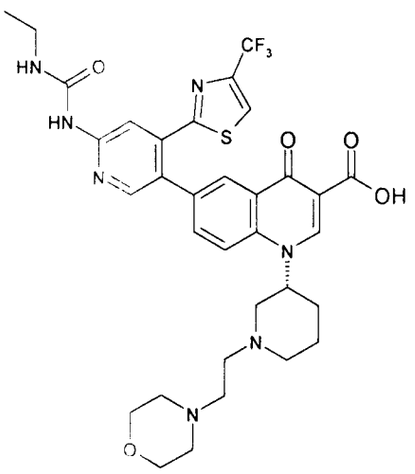
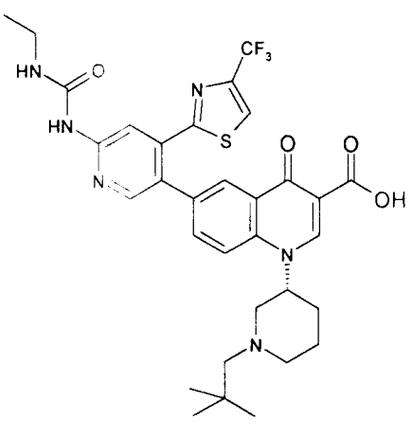
Los siguientes Ejemplos se prepararon según el procedimiento descrito para el Ejemplo 276 a partir de los materiales de partida indicados.

Ej.	Compuesto	Datos	SM
277	Ácido 1-(2-(dimetilamino)propil)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ES) $(M+H)^+$: 589 para $C_{27}H_{27}F_3N_6O_4S$ RMN ^1H (300 MHz, *DMSO-d_6*) δ 14,87 (br. s., 1 H), 10,57 (br. s., 1 H), 9,48 (s, 1 H), 9,16 (s, 1 H), 8,55 (s, 1 H), 8,34 (d, *J*=12,81 Hz, 2 H), 8,23 (s, 2 H), 7,89 (d, *J*=8,29 Hz, 1 H), 7,60 (br. s., 1 H), 5,06 (br. s., 1 H), 4,86 (d, *J*=11,30 Hz, 1 H), 3,93 (br. s., 1 H), 3,17 - 3,25 (m, 1 H), 2,84 (br. s., 6 H), 1,05 - 1,26 (m, 6 H).	Ejemplo 256
278	Ácido 6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-((1R,2R)-2-hidroxiciclohexil)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ES) $(M+H)^+$: 602 para $C_{28}H_{26}F_3N_5O_5S$ RMN ^1H (300 MHz, *DMSO-d_6*) δ 15,15 (s, 1 H), 9,47 (s, 1 H), 8,98 (s, 1 H), 8,51 (s, 1 H), 8,35 (d, *J*=9,80 Hz, 3 H), 8,22 (s, 1 H), 7,85 (d, *J*=10,55 Hz, 1 H), 7,61 (t, *J*=4,90 Hz, 1 H), 5,21 (d, *J*=5,27 Hz, 1 H), 4,80 (t, *J*=9,04 Hz, 1 H), 4,00 - 4,11 (m, 1 H), 3,15 - 3,27 (m, 2 H), 2,01 (d, *J*=14,32 Hz, 2 H), 1,80 - 1,94 (m, 1 H), 1,72 (br. s., 2 H), 1,45 - 1,64 (m, 3 H), 1,11 (t, *J*=7,16 Hz, 3 H).	Ejemplo 257

279	Ácido 6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-((1S,2S)-2-hidroxiciclohexil)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ES) $(M+H)^+$: 602 para $C_{28}H_{26}F_3N_5O_5S$ RMN ^1H (300 MHz, *DMSO-d_6*) δ 15,15 (s, 1 H), 9,47 (s, 1 H), 8,98 (s, 1 H), 8,51 (s, 1 H), 8,35 (d, *J*=9,80 Hz, 3 H), 8,22 (s, 1 H), 7,85 (dd, *J*=9,04, 2,26 Hz, 1 H), 7,61 (t, *J*=5,27 Hz, 1 H), 5,21 (d, *J*=5,27 Hz, 1 H), 4,75 - 4,85 (m, 1 H), 4,04 - 4,13 (m, 2 H), 3,23 (d, *J*=6,78 Hz, 1 H), 2,02 (d, *J*=13,56 Hz, 2 H), 1,85 (d, *J*=11,30 Hz, 1 H), 1,72 (br. s., 2 H), 1,44 - 1,64 (m, 3 H), 1,11 (t, *J*=7,16 Hz, 3 H).	Ejemplo 258
280	Ácido (S)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-(2-(metilsulfonil)etil)piperidin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ES) $(M+H)^+$: 693 para $C_{30}H_{31}F_3N_6O_5S_2$ RMN ^1H (300 MHz, *DMSO-d_6*) δ 15,01 (br. s., 1 H), 9,48 (s, 1 H), 9,40 (br. s., 1 H), 8,52 (s, 1 H), 8,36 (br. s., 2 H), 8,13 - 8,28 (m, 2 H), 7,88 (d, *J*=9,04 Hz, 1 H), 7,60 (d, *J*=5,27 Hz, 1 H), 5,03 (br. s., 1 H), 3,28 - 3,45 (m, 3 H), 3,14 - 3,28 (m, 3 H), 2,99 - 3,12 (m, 3 H), 2,87 (t, *J*=6,78 Hz, 3 H), 2,70 (d, *J*=15,82 Hz, 1 H), 1,90 - 2,14 (m, 2 H), 1,72 (br. s., 2 H), 1,11 (t, *J*=6,78 Hz, 3 H).	Ejemplo 273

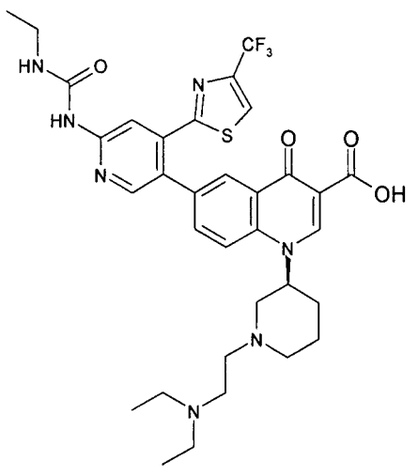
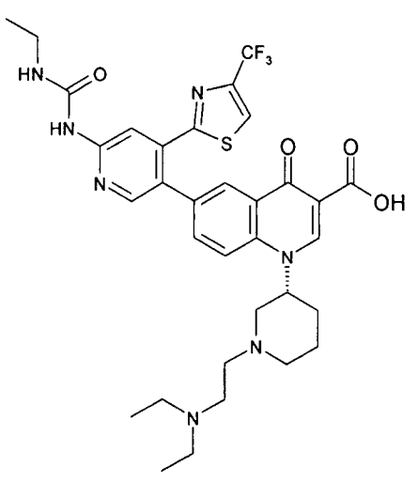
281	Ácido (R)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-(2-(metilsulfonil)etil)piperidin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ES) $(M+H)^+$: 693 para $C_{30}H_{31}F_3N_6O_5S_2$ RMN ^1H (300 MHz, *DMSO-d*$_6$) δ 14,99 (br. s., 1 H), 9,48 (s, 1 H), 9,30 - 9,45 (m, 1 H), 8,53 (s, 1 H), 8,35 (br. s., 2 H), 8,23 (s, 2 H), 7,91 (br. s., 1 H), 7,55 - 7,69 (m, 1 H), 5,04 (br. s., 1 H), 3,21 (dq, *J*=6,78, 6,53 Hz, 3 H), 3,06 (br. s., 5 H), 2,87 (br. s., 2 H), 2,72 (br. s., 1 H), 2,06 (br. s., 3 H), 1,72 (d, *J*=7,54 Hz, 2 H), 1,11 (t, *J*=7,16 Hz, 3 H).	Ejemplo 272
282	Ácido (R)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-((1-metil-1H-pirrol-2-il)metil)piperidin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ES) $(M+H)^+$: 680 para $C_{33}H_{32}F_3N_7O_4S$ RMN ^1H (300 MHz, *DMSO- d*$_6$) δ 15,04 (br. s., 1 H), 9,55 (br. s., 2 H), 8,50 (s, 1 H), 8,34 (br. s., 2 H), 8,24 (s, 1 H), 8,08 (d, *J*=9,04 Hz, 1 H), 7,82 (d, *J*=8,29 Hz, 1 H), 7,66 (br. s., 1 H), 6,67 (br. s., 1 H), 5,96 (br. s., 1 H), 5,86 (br. s., 1 H), 5,08 (br. s., 1 H), 3,68 (s, 3 H), 3,57 (d, *J*=13,56 Hz, 1 H), 3,43 (d, *J*=13,56 Hz, 1 H), 3,12 - 3,25 (m, 2 H), 2,92 - 3,07 (m, 1 H), 2,89 (br. s., 1 H), 2,38 (br. s., 1 H), 1,96 (d, *J*=15,82 Hz, 2 H), 1,66 (br. s., 2 H), 1,19 - 1,39 (m, 1 H), 1,11 (t, *J*=7,16 Hz, 3 H).	Ejemplo 265

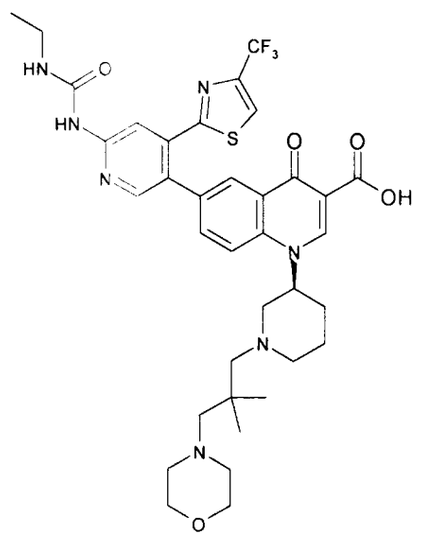
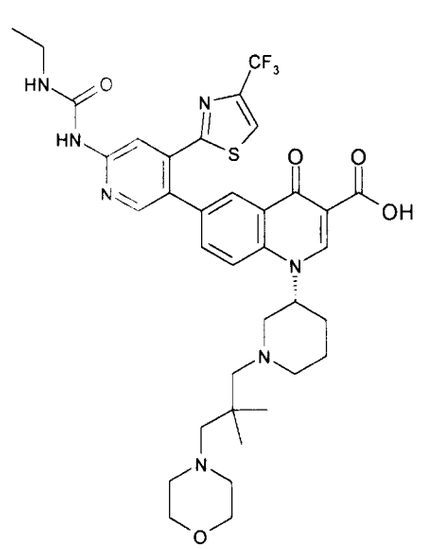
283	Ácido (R)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-((1-metil-1H-pirrol-2-il)metil)piperidin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ES) $(M+H)^+$: 680 para $C_{33}H_{32}F_3N_7O_4S$ RMN ^1H (300 MHz, *DMSO- d_6*) δ 14,89 (br. s., 1 H), 10,60 (br. s., 1 H), 9,49 (s, 1 H), 8,97 (s, 1 H), 8,55 (s, 2 H), 8,35 (br. s., 3 H), 8,24 (s, 1 H), 7,97 (d, *J*=9,04 Hz, 1 H), 7,62 (br. s., 1 H), 6,88 (br. s., 1 H), 6,33 (br. s., 1 H), 6,04 (br. s., 1 H), 4,37 (br. s., 2 H), 3,70 (s, 5 H), 3,48 - 3,57 (m, 1 H), 3,22 (ddd, 3 H), 1,99 - 2,34 (m, 3 H), 1,12 (t, *J*=7,16 Hz, 3 H).	Ejemplo 264
284	Ácido (S)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-(2-morfolinoetil)piperidin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ES) $(M+H)^+$: 700 para $C_{33}H_{36}F_3N_7O_5S$ RMN ^1H (300 MHz, *DMSO- d_6*) δ 15,01 (br. s., 1 H), 9,75 (br. s., 1 H), 9,48 (s, 1 H), 8,52 (s, 1 H), 8,35 (br. s., 2 H), 8,22 (s, 1 H), 8,12 (d, *J*=9,04 Hz, 1 H), 7,86 (d, *J*=8,29 Hz, 1 H), 7,61 (br. s., 1 H), 5,04 (br. s., 1 H), 3,53 (d, *J*=4,52 Hz, 4 H), 3,06 - 3,26 (m, 3 H), 2,94 (d, *J*=9,80 Hz, 1 H), 2,66 (br. s., 1 H), 2,38 (br. s., 4 H), 1,98 (br. s., 2 H), 1,65 (br. s., 2 H), 1,11 (t, *J*=7,16 Hz, 3 H), 0,96 (t, *J*=6,78 Hz, 1 H).	Ejemplo 267

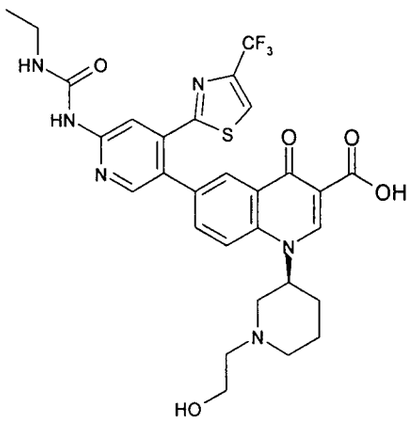
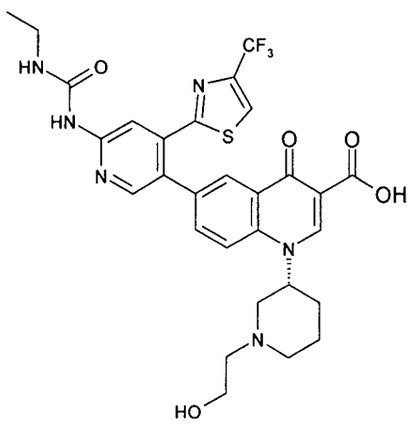
285	Ácido (R)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-(2-morfolinoetil)piperidin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ES) $(M+H)^+$: 700 para $C_{33}H_{36}F_3N_7O_5S$ RMN ^1H (300 MHz, *DMSO- d_6*) δ 14,97 (br. s., 1 H), 9,74 (br. s., 1 H), 9,49 (s, 1 H), 8,52 (s, 1 H), 8,35 (br. s., 2 H), 8,22 (s, 1 H), 8,12 (d, *J*=9,04 Hz, 1 H), 7,86 (d, *J*=9,04 Hz, 1 H), 7,61 (br. s., 1 H), 5,04 (br. s., 1 H), 3,53 (br. s., 4 H), 3,07 - 3,27 (m, 3 H), 2,94 (d, *J*=10,55 Hz, 1 H), 2,66 (br. s., 1 H), 2,38 (br. s., 4 H), 1,97 (br. s., 2 H), 1,65 (br. s., 2 H), 1,11 (t, *J*=7,16 Hz, 3 H), 0,96 (t, 1 H).	Ejemplo 266
286	Ácido (R)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-(piperidin-3-il)-1,4-dihidroquinolin-3-carboxílico 	MS (ES) $(M+H)^+$: 657 para $C_{32}H_{35}F_3N_6O_4S$ RMN ^1H (300 MHz, *DMSO- d_6*) δ 10,17 (br. s., 1 H), 9,51 (s, 1 H), 8,97 (s, 1 H), 8,41 - 8,59 (m, 2 H), 8,29 - 8,39 (m, 2 H), 8,23 (s, 1 H), 7,97 (d, *J*=9,04 Hz, 1 H), 7,62 (br. s., 1 H), 6,00 (br. s., 1 H), 3,58 - 3,79 (m, 5 H), 3,12 - 3,28 (m, 5 H), 3,01 - 3,10 (m, 2 H), 2,33 - 2,42 (m, 2 H), 2,18 - 2,27 (m, 2 H), 2,08 (d, *J*=8,29 Hz, 2 H), 1,03 - 1,26 (m, 6 H).	Ejemplo 263

Ejemplos 287-292

Los siguientes compuestos se prepararon según el procedimiento descrito en el Ejemplo 276, y se purificaron mediante una HPLC de Gilson en una columna C18 usando acetonitrilo/agua/TFA para producir las sales de TFA.

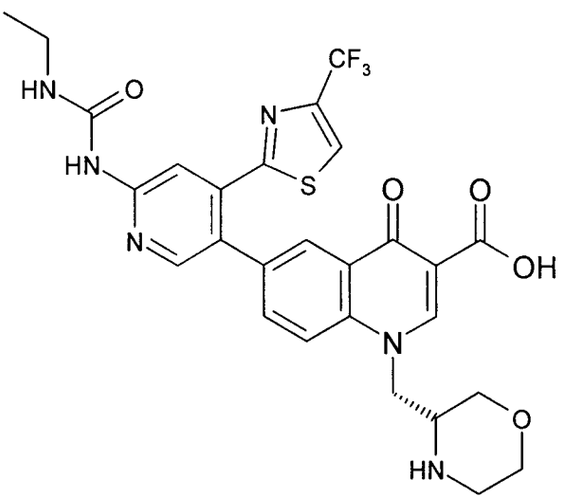
Ej.	Compuesto	Datos	SM
287	Ácido (S)-1-(1-(2-(dietilamino)etil)piperidin-3-il)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ES) $(M+H)^+$: 686 para $C_{33}H_{38}F_3N_7O_4S$ RMN ^1H (300 MHz, *DMSO- d_6*) δ 9,49 (s, 2 H), 8,55 (s, 1 H), 8,37 (s, 2 H), 8,10 - 8,26 (m, 2 H), 7,89 (d, *J*=8,29 Hz, 1 H), 7,59 (br. s., 1 H), 5,07 (br. s., 1 H), 3,21 (q, *J*=6,78 Hz, 8 H), 3,04 (ninguno, 1 H), 2,73 (br. s., 3 H), 2,08 (br. s., 2 H), 1,74 (br. s., 2 H), 1,22 (t, *J*=7,16 Hz, 6 H), 1,12 (t, *J*=7,16 Hz, 3 H).	Ejemplo 275
288	Ácido (S)-1-(1-(2-(dietilamino)etil)piperidin-3-il)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ES) $(M+H)^+$: 686 para $C_{33}H_{38}F_3N_7O_4S$ RMN ^1H (300 MHz, *DMSO- d_6*) δ 9,49 (s, 2 H), 8,55 (s, 1 H), 8,37 (s, 2 H), 8,23 (s, 1 H), 8,17 (d, *J*=9,04 Hz, 1 H), 7,89 (d, *J*=9,04 Hz, 1 H), 7,59 (br. s., 1 H), 5,07 (br. s., 1 H), 3,56 (br. s., 7 H), 3,09 - 3,31 (m, 8 H), 2,92 - 3,11 (m, 1 H), 2,73 (br. s., 2 H), 2,06 (br. s., 2 H), 1,74 (br. s., 1 H), 1,22 (t, *J*=7,16 Hz, 6 H), 1,12 (t, *J*=7,16 Hz, 4 H).	Ejemplo 274

289	Ácido (S)-1-(1-(2,2-dimetil-3-morfolinopropil)piperidin-3-il)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ES) $(M+H)^+$: 742 para $C_{36}H_{42}F_3N_7O_5S$ RMN ^1H (300 MHz, *DMSO- d_6*) δ 9,51 (br. s., 2 H), 8,51 (s, 1 H), 8,35 (br. s., 2 H), 8,22 (s, 1 H), 8,12 (d, *J*=9,04 Hz, 1 H), 7,83 (d, *J*=7,54 Hz, 1 H), 7,63 (br. s., 1 H), 5,05 (br. s., 1 H), 3,50 (br. s., 4 H), 3,18 - 3,25 (m, 1 H), 2,94 (br. s., 2 H), 2,60 (d, *J*=18,84 Hz, 2 H), 2,40 (br. s., 4 H), 2,08 - 2,25 (m, 4 H), 2,02 (br. s., 1 H), 1,88 - 1,96 (m, 1 H), 1,72 (br. s., 2 H), 1,22 (s, 2 H), 1,11 (t, *J*=6,78 Hz, 3 H), 0,85 (s, 6 H).	Ejemplo 268
290	Ácido (R)-1-(1-(2,2-dimetil-3-morfolinopropil)piperidin-3-il)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ES) $(M+H)^+$: 742 para $C_{36}H_{42}F_3N_7O_5S$ RMN ^1H (300 MHz, *DMSO- d_6*) δ 9,49 (br. s., 2 H), 8,51 (s, 1 H), 8,35 (br. s., 2 H), 8,22 (s, 1 H), 8,11 (d, *J*=8,29 Hz, 1 H), 7,83 (d, *J*=7,54 Hz, 1 H), 7,62 (br. s., 1 H), 5,04 (br. s., 1 H), 3,51 (br. s., 4 H), 3,22 (d, *J*=6,78 Hz, 2 H), 2,94 (br. s., 2 H), 2,41 (br. s., 5 H), 1,99 - 2,26 (m, 6 H), 1,90 (br. s., 1 H), 1,73 (br. s., 2 H), 1,11 (t, *J*=6,78 Hz, 3 H), 0,85 (br. s., 6 H).	Ejemplo 269

291	Ácido (S)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-(2-hidroxietil)piperidin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ES) $(M+H)^+$: 631 para $C_{29}H_{29}F_3N_6O_5S$ RMN ^1H (300 MHz, *DMSO- d_6*) δ 9,77 (br. s., 1 H), 9,47 (s, 1 H), 8,51 (s, 1 H), 8,35 (d, *J*=3,77 Hz, 2 H), 8,22 (s, 1 H), 8,14 (d, *J*=9,80 Hz, 1 H), 7,86 (d, *J*=7,54 Hz, 1 H), 7,60 (br. s., 1 H), 5,04 (br. s., 1 H), 4,45 (t, *J*=4,90 Hz, 1 H), 3,62 (q, *J*=5,53 Hz, 2 H), 3,17 - 3,25 (m, 2 H), 3,05 - 3,13 (m, 1 H), 2,98 (br. s., 1 H), 2,72 (br. s., 1 H), 1,97 (br. s., 2 H), 1,65 (br. s., 2 H), 1,11 (t, *J*=6,78 Hz, 3 H).	Ejemplo 270
292	Ácido (R)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-(2-hidroxietil)piperidin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ES) $(M+H)^+$: 631 para $C_{29}H_{29}F_3N_6O_5S$ RMN ^1H (300 MHz, *DMSO- d_6*) δ 15,04 (s, 1 H), 9,78 (br. s., 1 H), 9,47 (s, 1 H), 8,52 (s, 1 H), 8,36 (br. s., 2 H), 8,23 (s, 1 H), 8,16 (br. s., 1 H), 7,87 (d, *J*=10,55 Hz, 1 H), 7,60 (br. s., 1 H), 5,04 (br. s., 1 H), 4,45 (br. s., 1 H), 3,61 (br. s., 2 H), 3,18 - 3,26 (m, 2 H), 2,99 (br. s., 2 H), 2,72 (br. s., 1 H), 1,98 (br. s., 2 H), 1,66 (br. s., 2 H), 1,11 (t, *J*=6,78 Hz, 3 H).	Ejemplo 271

Ejemplo 293

Ácido 3-((3-(etoxicarbonil)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxoquinolin-1(4H)-il)metil)morfolin-4-carboxílico



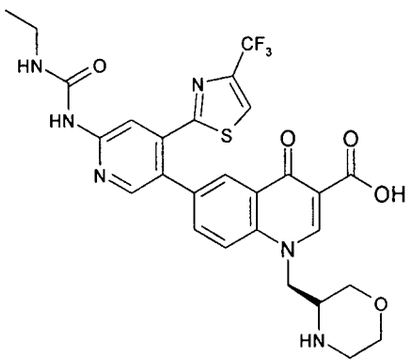
Se suspendió (R)-3-((3-(etoxicarbonil)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxoquinolin-1(4H)-il)metil)morfolin-4-carboxilato de terc-butilo (Ejemplo 254, 0,150 g, 0,20 mmoles) en MeOH (6 ml) en una vasija de microondas (CEM). Se añadió THF (3,00 ml). Se añadió una disolución ac. 2,0 M de LiOH (0,381 ml, 0,76 mmoles). La vasija de microondas se calentó en el microondas a 100 °C durante 15 min. Tras enfriar hasta la temperatura ambiente, el disolvente se eliminó *a vacío*, y el residuo se recogió en diclorometano (2 ml), y se añadió HCl 4N en dioxano (1 ml). La mezcla se agitó a temperatura ambiente durante 1 h, después se diluyó con agua (3 ml) y se neutralizó con $NaHCO_3$ saturado. La mezcla se extrajo tres veces con DCM, y las capas orgánicas combinadas se secaron sobre Na_2SO_4 y se filtraron. El filtrado se concentró *a vacío*, y el residuo se purificó mediante cromatografía ultrarrápida en columna sobre gel de sílice, usando (diclorometano-metanol), para dar ácido (R)-3-((3-(etoxicarbonil)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxoquinolin-1(4H)-il)metil)morfolin-4-carboxílico (0,042 g, 36%).

MS (ES) $(M+H)^+$: 603 para $C_{27}H_{25}F_3N_6O_5S$. RMN:

RMN ^1H (300 MHz, *DMSO-d_6*) δ 15,06 (br. s., 1 H), 9,48 (s, 1 H), 8,93 (s, 1 H), 8,52 (s, 1 H), 8,34 (d, *J*=17,33 Hz, 2 H), 8,10 - 8,24 (m, 2 H), 7,83 (d, *J*=7,54 Hz, 1 H), 7,60 (br. s., 1 H), 4,65 (d, *J*=10,55 Hz, 1 H), 4,33 (dd, *J*=14,69, 8,67 Hz, 1 H), 3,86 (d, *J*=9,04 Hz, 1 H), 3,55 - 3,66 (m, 1 H), 3,34 - 3,44 (m, 1 H), 3,21 (t, *J*=6,40 Hz, 3 H), 3,05 (br. s., 1 H), 2,68 - 2,86 (m, 1 H), 1,11 (t, *J*=7,16 Hz, 3 H).

Ejemplo 294

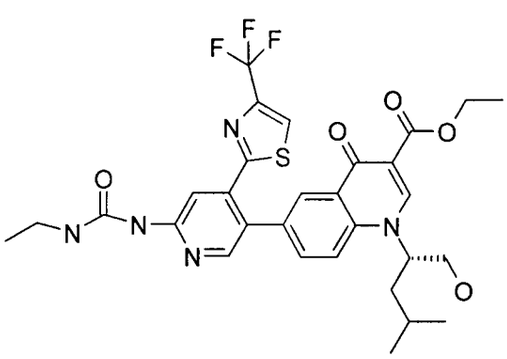
Los siguientes Ejemplos se prepararon mediante el procedimiento descrito en el Ejemplo 293 a partir de los materiales de partida (SM) indicados.

Ej.	Compuesto	Datos	SM
294	Ácido (S)-3-((3-(etoxicarbonil)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxoquinolin-1(4H)-il)metil)morfolin-4-carboxílico 	MS (ES) $(M+H)^+$: 603 para $C_{27}H_{25}F_3N_6O_5S$. RMN ^1H (300 MHz, *DMSO-d_6*) δ 15,07 (br. s., 1 H), 9,47 (s, 1 H), 8,94 (s, 1 H), 8,52 (s, 1 H), 8,37 (s, 1 H), 8,29 - 8,35 (m, 2 H), 8,13 - 8,24 (m, 2 H), 7,83 (d, *J*=7,54 Hz, 1 H), 7,60 (br. s., 1 H), 4,63 (br. s., 1 H), 4,34 (dd, *J*=13,56, 9,04 Hz, 1 H), 3,86 (d, *J*=9,04 Hz, 1 H), 3,53 - 3,73 (m, 2 H), 3,37 - 3,52 (m, 1 H), 3,21 (t, *J*=6,40 Hz, 3 H), 3,05 (br. s., 1 H), 2,77 (t, *J*=12,43 Hz, 1 H), 1,11 (t, *J*=7,16 Hz, 3 H).	Ejemplo 255

Más abajo se da para el Ejemplo 119 otro método potencial para la preparación de los Ejemplos descritos anteriormente.

Ejemplo 119

6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-hidroxi-4-metilpentan-2-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de (S)-etilo



Se recogieron 3-(dimetilamino)-2-(5-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-2-fluorobenzoil)acrilato de etilo (0,150 g, 0,26 mmoles, Intermediario 125) y (S)-2-amino-4-metilpentan-1-ol (0,033 ml, 0,26 mmoles) en THF (2 ml). La mezcla se colocó en un baño de aceite, y se calentó hasta 60°C durante 2 h. Se añadió carbonato de potasio (0,107 g, 0,78 mmoles), seguido de DMF (1 ml), y la mezcla se agitó a 60°C toda la noche. La reacción se enfrió hasta la temperatura ambiente y se concentró *a vacío*. El residuo se diluyó entonces con agua (0,5 ml) y se enfrió hasta 0°C. Se añadió gota a gota HCl 1N hasta pH~4. Se recogió un sólido amarillo claro mediante filtración, se lavó con agua, y se secó en un horno de vacío toda la noche a 50°C para dar (S)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-hidroxi-4-metilpentan-2-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo (0,072 g, 44 %) como un sólido amarillo.

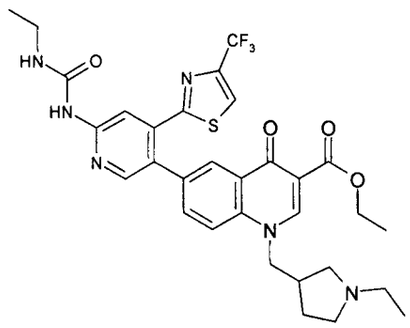
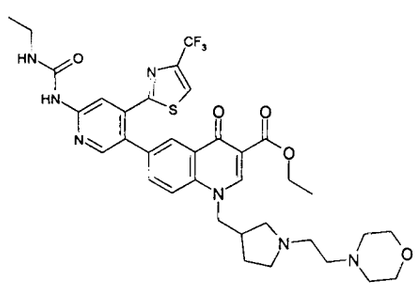
MS (ES) $(M+H)^+$: 632 para $C_{30}H_{32}F_3N_5O_5S$.

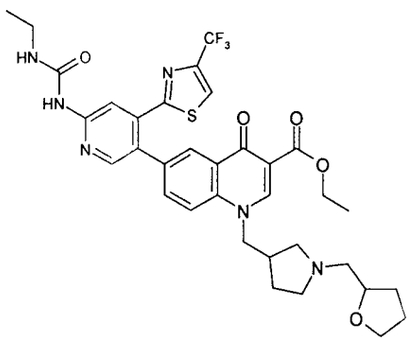
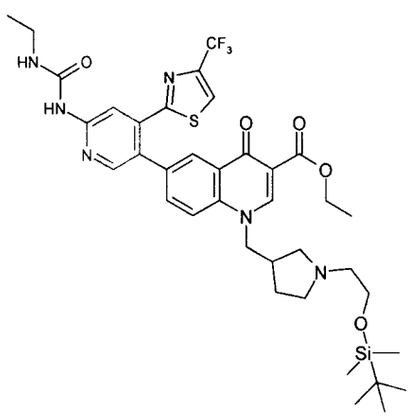
Ejemplos 295-304

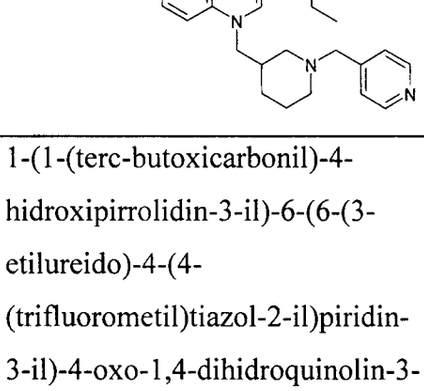
Los siguientes Ejemplos se prepararon según el procedimiento general descrito más abajo.

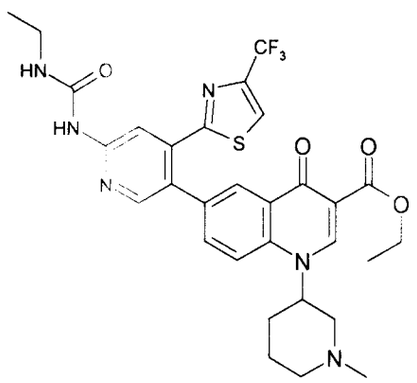
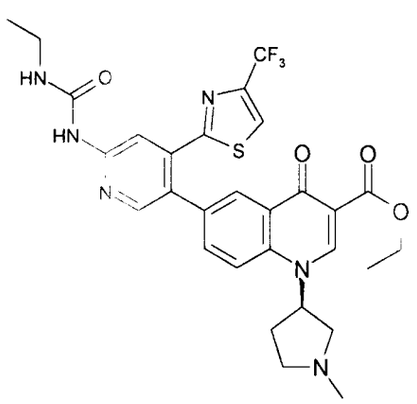
Procedimiento General

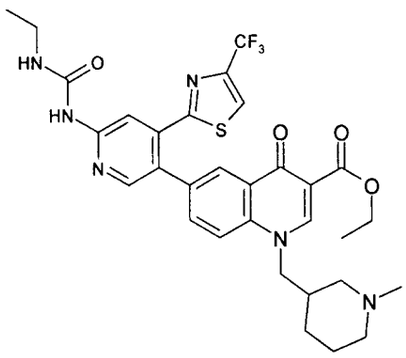
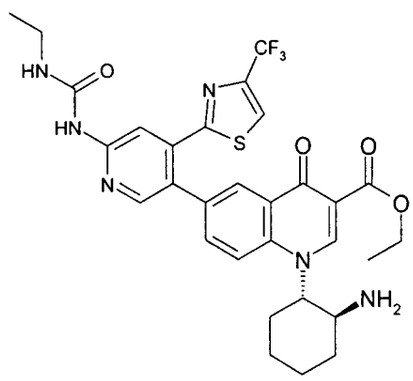
A una suspensión de ácido 6-(3-etilureido)-4-(4-trifluorometiltiazol-2-il)piridin-3-ilborónico (Intermediario 17, 202 mg, 0,56 mmoles), la dihidroquinolina apropiada (0,50 mmoles) y trans-diclorobis(trifenilfosfina)paladio (II) (33 mg, 0,047 mmoles) en 1,4-dioxano (8 ml) se añadió una disolución de carbonato de potasio (130 mg, 0,94 mmoles) en agua (2 ml). La reacción se agitó durante 1,5 h a 70°C. La reacción se enfrió hasta la temperatura ambiente, y se añadió acetato de etilo (8 ml) para ayudar a separar las capas. Se eliminó el agua, y la fase orgánica se lavó con agua (3 ml). La reacción se concentró entonces, y el material se cromatografió en una columna de 4g Analogix, usando 0-10% de metanol en diclorometano, o se trituró con etanol para purification.

Ej.	Compuesto	Datos	SM
295	1-((1-etilpirrolidin-3-il)metil)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 643,2 (MH^+) para $C_{31}H_{33}F_3N_6O_4S$ RMN ^1H (300 MHz, DMSO-d_6): 1,22-1,35 (m, 6H), 1,42 (t, 3H), 3,40-3,52 (m, 2 H), 4,09 (q, 2H), 4,41 (q, 2 H), 7,27-7,41 (m, 5H), 7,61 (s, 1 H), 7,72 (m, 2H), 8,29 (s, 1H), 8,46 (s, 1H), 8,52-8,61 (m, 2H), 9,04 (bs, 1H)	Intermediario 17 e Intermediario 127
296	6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-((1-(2-morfolinoetil)pirrolidin-3-il)metil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 728,1 (MH^+) para $C_{35}H_{40}F_3N_7O_5S$	Intermediario 17 e Intermediario 128

297	6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-((1-((tetrahidrofuran-2-il)metil)pirrolidin-3-il)metil)-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 699,3 (MH^+) para $C_{34}H_{37}F_3N_6O_5S$ RMN ^1H (300 MHz, DMSO-d_6): 1,11 (t, 3H), 1,28 (t, 3H), 1,69 (m, 1H), 1,75-2,81 (bm, 10H) 3,09-3,26 (m, 2 H), 4,19 (q, 2H), 4,36 (d, 2 H), 7,52-7,68 (m, 3H), 7,94 (d, 1 H), 8,18 (s, 1H), 8,24 (s, 1H), 8,29 (s, 1H), 8,47 (s, 1H), 8,65 (dd, 1H), 9,41 (bs, 1H)	Intermediario 17 e Intermediario 129
298	1-((1-(2-(terc-butildimetilsilyloxi)etil)pirrolidin-3-il)metil)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 773,4 ($M+H^+$) para $C_{37}H_{47}F_3N_6O_5SSi$	Intermediario 17 e Intermediario 130

299	6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-(1-(piridin-4-ilmetil)piperidin-3-il)-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 706,2 (MH^+) para $C_{35}H_{34}F_3N_7O_4S$	Intermediario 17 e Intermediario 133
300	1-(1-(terc-butoxicarbonil)-4-hidroxipirrolidin-3-il)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de *trans*-etilo	MS (ESP): 717,3 (MH^+) para $C_{33}H_{35}F_3N_6O_7S$	Intermediario 17 e Intermediario 138

301	6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-metilpiperidin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 629,1 (MH^+) para $C_{30}H_{31}F_3N_6O_4S$	Intermediario 17 e Intermediario 134
302	(S)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-metilpirrolidin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 615,0 (MH^+) para $C_{29}H_{29}F_3N_6O_4S$	Intermediario 17 e Intermediario 137

303	6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-((1-metilpiperidin-3-il)metil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 643,1 (MH^+) para $C_{31}H_{33}F_3N_6O_4S$	Intermediario 17 e Intermediario 139
304	1-((1S,2S)-2-aminociclohexil)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 572,1 (MH^+) para $C_{30}H_{31}F_3N_6O_4S$	Intermediario 17 e Intermediario 140

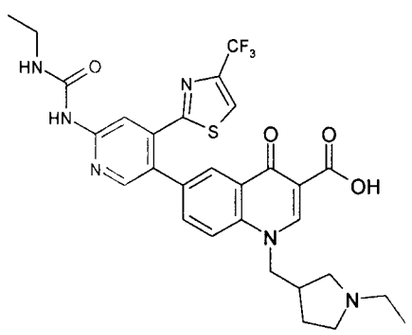
Ejemplos 305-314

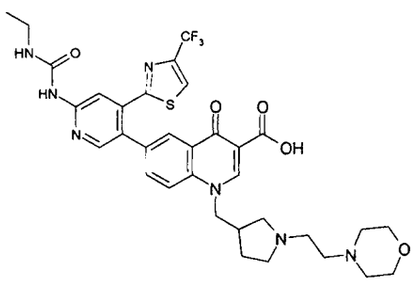
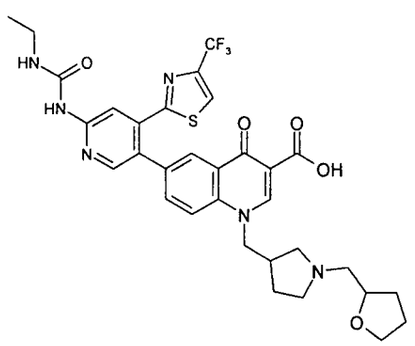
Los siguientes Ejemplos se prepararon según el procedimiento general descrito más abajo.

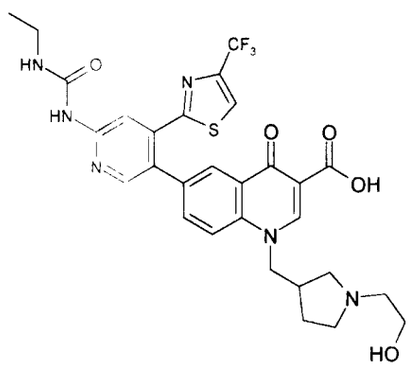
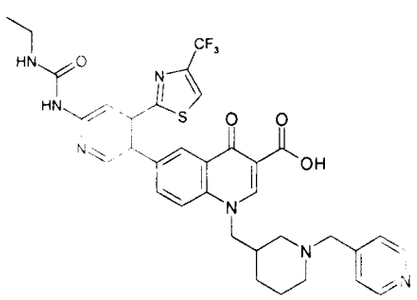
Procedimiento General

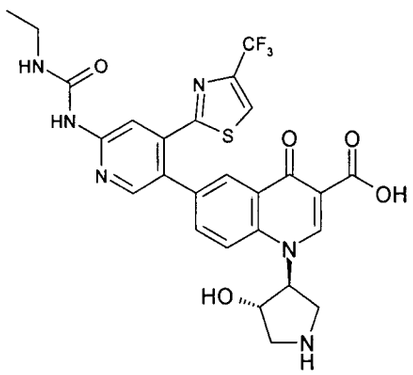
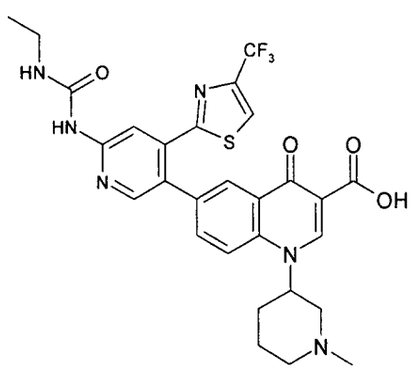
El éster etílico (~110 mg) se disolvió en metanol (3 ml) y tetrahidrofurano (3 ml). A esta disolución se añadió hidróxido de sodio 1N (3 ml), y la reacción se agitó a temperatura

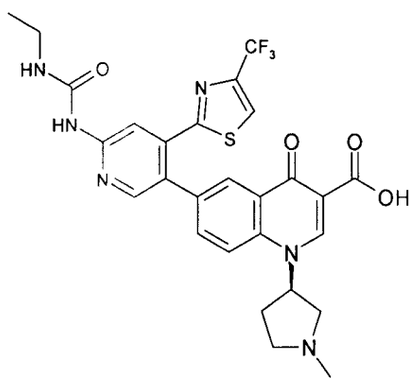
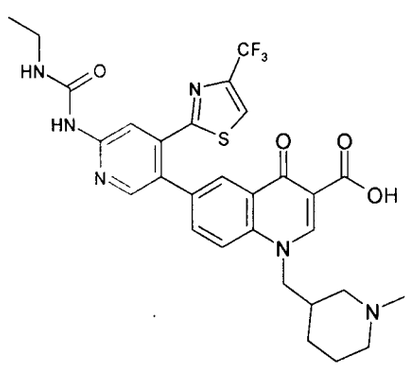
ambiente durante 3 h. La disolución se concentró para eliminar los orgánicos. Se añadió agua (3 ml), y la capa acuosa se lavó con metil-terc-butiléter (3 ml). La fase acuosa se filtró, y después se acidificó hasta pH~3 con ácido clorhídrico 1N. Para los compuestos del Ejemplo 308 y del Ejemplo 310, la fase acuosa se llevó hasta pH 1 y se agitó durante 3 h para eliminar los grupos protectores, y después se basificó nuevamente hasta pH~3 con hidróxido de sodio 1N. Los ácidos se extrajeron con acetato de etilo: tetrahidrofurano 1:1 (3× 5 ml cada vez). Las capas orgánicas se combinaron, se secaron sobre sulfato de sodio, y el disolvente se eliminó *a vacío*.

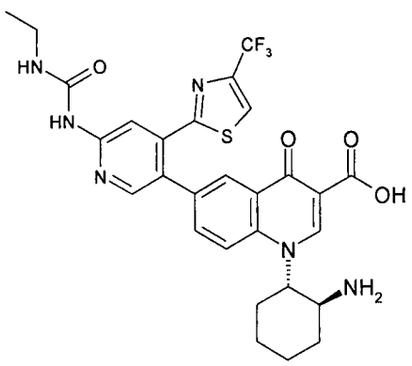
Ej.	Compuesto	Datos	SM
305	Ácido 1-((1-etilpirrolidin-3-il)metil)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 615,3 (MH^+) para $C_{29}H_{29}F_3N_6O_4S$ RMN ^1H (300 MHz, DMSO-d_6): 1,12 (t, 3H), 1,21 (t, 3H), 1,60-2,20 (m, 2H), 2,80-3,25 (m, 4H), 3,18-3,25 (m, 2H), 4,73 (brs, 1H), 7,62 (t, 1H), 7,87 (d, 1H), 8,19-8,24 (m, 2H), 8,32 (d, 1H), 8,36 (s, 1H), 8,54 (s, 1H), 9,13 (s, 1H), 9,50 (s, 1H)	Ejemplo 295

306	Ácido 6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-((1-(2-morfolinoetil)pirrolidin-3-il)metil)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 700,2 (MH^+) para $C_{33}H_{36}F_3N_7O_5S$ RMN ^1H (300 MHz, DMSO-d_6): 1,12 (t, 3H), 1,80 (bs, 1H), 2,06 (bs, 1H), 2,38-2,50 (bm, 2H), 2,60-2,70 (bm, 2H), 2,80-3,00 (bm, 1H), 3,18-3,25 (bm, 4H), 3,50-3,62 (bm, 4H), 4,75 (bd, 2H), 7,63 (bt, 1H), 7,89 (dd, 1H), 8,23-8,26 (m, 2H), 8,32 (d, 1H), 8,37 (s, 1H), 8,55 (d, 1H), 9,14 (s, 1H), 9,53 (s, 1H)	Ejemplo 296
307	Ácido 6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-((1-((tetrahidrofuran-2-il)metil)pirrolidin-3-il)metil)-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 671,4 (MH^+) para $C_{32}H_{33}F_3N_6O_5S$ RMN ^1H (300 MHz, CD_3OD): 1,21 (t, 3H), 1,41-1,58 (bm, 1H), 1,62-1,79 (bm, 1H), 1,80-1,92 (bm, 2H), 1,93-2,10 (bm, 2H), 2,62-2,85 (bm, 4H), 2,80-3,00 (bm, 1H), 3,01-3,13 (bm, 1H), 3,31-3,37 (m, 2H), 3,63-3,75 (m, 1H), 3,78-3,89 (bm, 1H), 3,96-4,10 (bm, 1H), 4,53 (bd, 2H), 7,72 (d, 1H), 7,83 (s, 1H), 8,04 (d, 2H), 8,17 (s, 1H), 8,31 (d, 1H), 8,37 (s, 1H), 8,97 (d, 1H)	Ejemplo 297

308	Hidrocloruro del ácido 6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-((1-(2-hidroxietil)pirrolidin-3-il)metil)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 631,2 (MH^+) para $C_{29}H_{29}F_3N_6O_5S$ RMN ^1H (300 MHz, DMSO-d_6): 1,11 (t, 3H), 1,56-1,65 (bs, 1H), 1,83-2,03 (bs, 1H), 2,60-3,20 (bm, 6H), 3,18-3,24 (m, 3H), 3,55-3,62 (m, 2H), 4,65 (bd, 2H), 7,51-7,63 (m, 2H), 7,86 (dd, 1H), 8,20 (d, 1H), 8,22 (s, 2H), 8,32 (d, 1H), 8,38 (s, 1H), 8,54 (s, 1H), 9,11 (s, 1H), 9,52 (s, 1H)	Ejemplo 298
309	Ácido 6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-(1-(piridin-4-ilmetil)piperidin-3-il)-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 678,3 (MH^+) para $C_{33}H_{30}F_3N_7O_4S$ RMN ^1H (300 MHz, DMSO-d_6): 1,11 (t, 3H), 1,80-2,40 (bm, 4H), 3,21-3,27 (m, 3H), 5,00-5,50 (bs, 1H), 7,63 (t, 1H), 7,90-7,94 (bm, 2H), 8,24 (s, 1H), 8,32-8,34 (m, 2H), 8,54 (d, 1H), 8,74 (bm, 2H), 9,52 (s, 1H)	Ejemplo 299

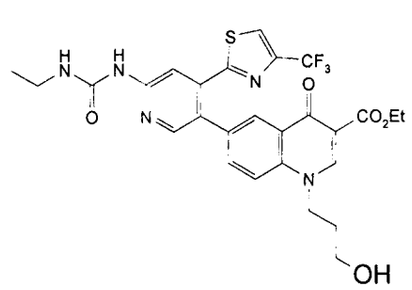
310	Ácido trans-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(4-hidroxipirrolidin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 589,2 (MH^+) para $C_{26}H_{23}F_3N_6O_5S$ RMN ^1H (300 MHz, DMSO-d_6): 1,11 (t, 3H), 3,16-3,22 (m, 3H), 3,58-3,77 (m, 2H), 3,85-4,05 (m, 1H), 4,83 (q, 1H), 5,62 (q, 1H), 7,60-7,71 (m, 1H), 7,96 (dd, 1H), 8,24-8,36 (m, 4H), 8,54 (d, 1H), 9,08 (s, 1H), 9,52-9,56 (m, 2H), 9,79 (bs, 1H)	Ejemplo 300
311	Ácido 6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-metilpiperidin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 601,2 (MH^+) para $C_{28}H_{27}F_3N_6O_4S$ RMN ^1H (300 MHz, DMSO-d_6): 1,11 (t, 3H), 2,07-2,20 (m, 2H), 2,21-2,48 (m, 2H), 2,79 (d, 3H), 3,02-3,20 (m, 1H), 3,21-3,27 (m, 3H), 3,49-3,71 (m, 2H), 5,51 (t, 1H), 7,66 (t, 1H), 7,97 (dd, 1H), 8,25 (d, 1H), 8,32-8,34 (m, 2H), 8,47 (d, 1H), 8,54 (d, 1H), 8,96 (s, H), 9,52 (s, 1H), 11,28 (bs, 1H)	Ejemplo 301

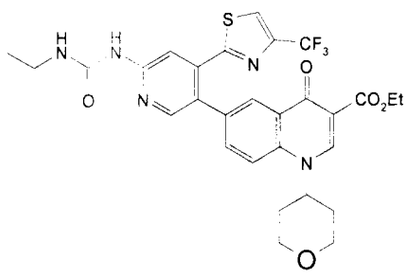
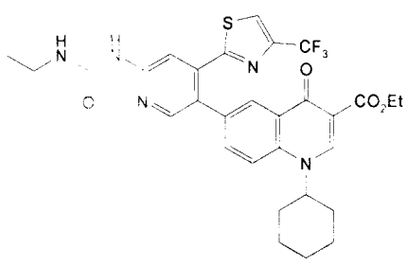
312	Ácido (S)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-metilpirrolidin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 587,1 (MH^+) para $C_{22}H_{25}F_3N_6O_4S$ RMN ^1H (300 MHz, DMSO-d_6): 1,12 (t, 3H), 2,60-3,00 (bm, 2H), 2,94 (bs, 3H), 3,20-4,2 (bm, 4H), 5,6-6,0 (bm, 1H), 7,64 (t, 1H), 7,95 (dd, 1H), 8,10-8,24 (m, 2H), 8,34 (d, 1H), 8,37 (s, 1H), 8,56 (d, 1H), 9,06 (bs, 1H), 9,53 (s, 1H), 10,70-11,15 (bm, 1H)	Ejemplo 302
313	Ácido 6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-((1-metilpiperidin-3-il)metil)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 615,3 (MH^+) para $C_{29}H_{29}F_3N_6O_4S$ RMN ^1H (300 MHz, DMSO-d_6): 1,11 (t, 4H), 1,40-1,90 (bm, 2H), 3,21-3,27 (m, 3H), 4,55 (bm, 4H), 7,64 (t, 1H), 7,86 (bd, 1H), 8,14 (d, 1H), 8,24 (s, 1H), 8,32 (d, 1H), 8,36 (s, 1H), 8,53 (d, 1H), 9,03 (s, 1H), 9,50 (s, 1H)	Ejemplo 303

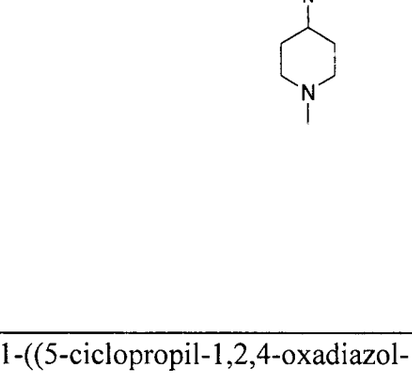
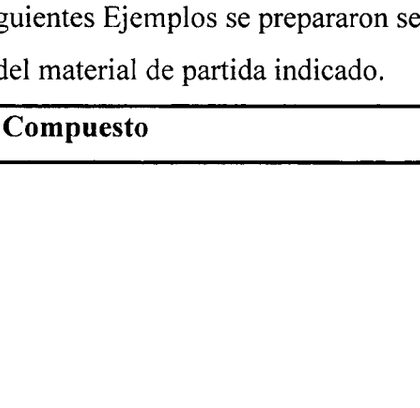
314	Ácido 1-((1S,2S)-2-aminociclohexil)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 601,2 (MH^+) para $C_{28}H_{27}F_3N_6O_4S$ RMN ^1H (300 MHz, CD_3OD): 1,20 (t, 3H), 1,58-1,80 (bm, 2H), 1,80-2,03 (bm, 4H), 2,10-2,22 (bm, 1H), 2,49-2,61 (bm, 1H), 3,20-3,40 (bm, 2H), 3,92-4,10 (bm, 1H), 5,00-5,20 (bm, 1H), 7,71 (d, 1H), 7,77 (s, 1H), 8,15 (s, 1H), 8,10-8,30 (bs, 1H), 8,22 (s, 1H), 8,30 (s, 1H), 8,36 (s, 1H), 9,00 (bs, 1H)	Ejemplo 304

Ejemplos 315-319

Los siguientes Ejemplos se prepararon según el procedimiento general descrito para los Ejemplos 295-304 a partir de los materiales de partida indicados.

Ej.	Compuesto	Datos	SM
315	6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(3-hidroxipropil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 590 (M+1) para $C_{27}H_{26}F_3N_5O_5S$ RMN ^1H (DMSO-d_6) δ: 1,11 (t, J=7,20 Hz, 3H); 1,28 (t, J=7,07 Hz, 3H); 1,87 - 1,98 (m, 2H); 3,15 - 3,27 (m, 2H); 3,48 (q, J=5,56 Hz, 2H); 4,23 (q, J=6,99 Hz, 2H); 4,45 (t, J=6,95 Hz, 2H); 4,76 (t, J=4,67 Hz, 1H); 7,63 (t, J=5,05 Hz, 1H); 7,71 (dd, J=8,72, 2,15 Hz, 1H); 7,89 (d, J=8,84 Hz, 1H); 8,15 (d, J=2,27 Hz, 1H); 8,23 (s, 1H); 8,32 (s, 1H); 8,48 (s, 1H); 8,69 (s, 1H); 9,44 (s, 1H)	Intermediario 17 e Intermediario 141

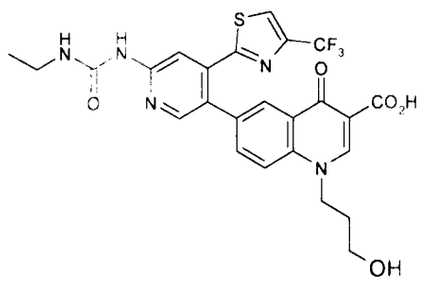
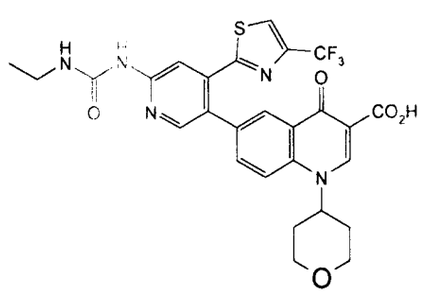
316	6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1-(tetrahidro-2H-piran-4-il)-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 616,18 (M+1) para $C_{29}H_{28}F_3N_5O_5S$	Intermediario 17 e Intermediario 142
317	1-ciclohexil-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 614,17 (M+1) para $C_{30}H_{30}F_3N_5O_4S$ RMN ^{1}H (400 MHz, DMSO-d_6) δ: 1,11 (t, *J*=7,07 Hz, 3H); 1,21 - 1,39 (m, 4H); 1,51 - 1,95 (m, 7H); 1,98 - 2,13 (m, 2H); 3,14 - 3,26 (m, 2H); 4,24 (q, *J*=6,99 Hz, 2H); 4,59 - 4,80 (m, 1H); 7,58 - 7,67 (m, 1H); 7,69 (dd, *J*=8,84, 2,27 Hz, 1H); 8,07 (d, *J*=9,09 Hz, 1H); 8,19 (d, *J*=2,27 Hz, 1H); 8,23 (s, 1H); 8,31 (s, 1H); 8,48 (s, 1H); 8,64 (s, 1H); 9,44 (s, 1H)	Intermediario 17 e Intermediario 143

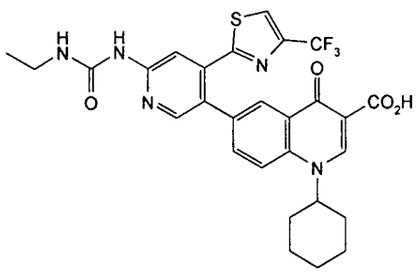
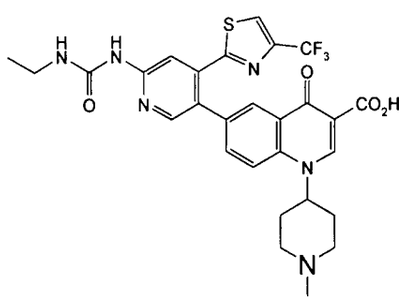
318	6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)Piridin-3-il)-1-(1-metilpiperidin-4-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 629,23 (M+1) para $C_{30}H_{31}F_3N_6O_4S$ RMN ^{1}H (400 MHz, DMSO-d_6) δ: 1,10 (t, *J*=7,20 Hz, 3H); 1,28 (t, *J*=7,07 Hz, 3H); 1,92 - 2,10 (m, 4H); 2,17 - 2,33 (m, 5H); 2,85 - 3,00 (m, 2H); 3,13 - 3,27 (m, 2H); 4,23 (q, *J*=7,07 Hz, 2H); 4,62 - 4,79 (m, 1H); 7,58 - 7,67 (m, 1H); 7,70 (dd, *J*=8,84, 2,27 Hz, 1H); 8,08 (d, *J*=9,09 Hz, 1H); 8,18 (d, *J*=2,27 Hz, 1H); 8,22 (s, 1H); 8,31 (s, 1H); 8,48 (s, 1H); 8,61 (s, 1H); 9,44 (s, 1H)	Intermediario 17 e Intermediario 144
319	1-((5-ciclopropil-1,2,4-oxadiazol-3-il)metil)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 654,14 (M+1) para $C_{30}H_{26}F_3N_7O_5S$ RMN ^{1}H (400 MHz, DMSO-d_6) δ: 1,00 - 1,16 (m, 5H); 1,18 - 1,37 (m, 5H); 2,22 - 2,43 (m, 1H); 3,21 (dq, *J*=6,95, 6,69 Hz, 2H); 4,25 (q, *J*=7,07 Hz, 2H); 5,86 (s, 2H); 7,54 - 7,78 (m, 3H); 8,13 (s, 1H); 8,20 (s, 1H); 8,31 (s, 1H); 8,49 (s, 1H); 8,89 (s, 1H); 9,43 (s, 1H)	Intermediario 17 e Intermediario 145

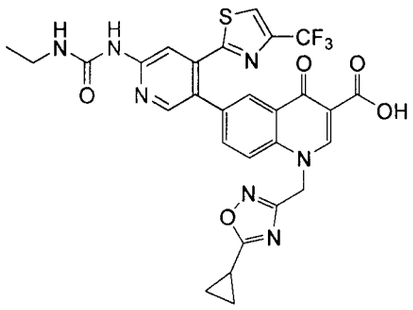
Ejemplos 320-324

Los siguientes Ejemplos se prepararon según el procedimiento descrito para el Ejemplo 293 a partir del material de partida indicado.

Ej.	Compuesto	Datos	SM

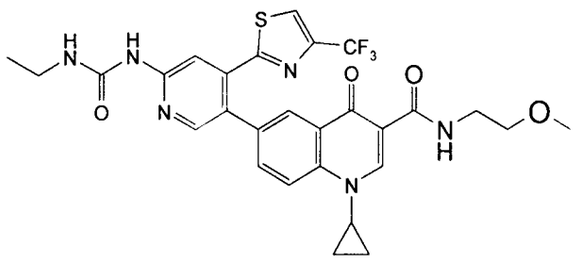
320	Ácido 6-(6-(3-etilureido)-4-(4-(trifluorometill)tiazol-2-il)piridin-3-il)-1-(3-hidroxipropil)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 562 (M+1) para $C_{25}H_{22}F_3N_5O_5S$ RMN ^{1}H (400 MHz, DMSO-d_6) δ: 1,11 (t, *J*=7,20 Hz, 3H); 1,90 - 2,04 (m, 2H); 3,13 - 3,29 (m, *J*=6,95, 6,69, 6,57, 6,57 Hz, 2H); 3,48 (q, *J*=5,39 Hz, 2H); 4,65 (t, *J*=6,82 Hz, 2H); 4,77 (t, *J*=4,80 Hz, 1H); 7,60 (br. s., 1H); 7,87 (dd, *J*=8,72, 1,89 Hz, 1H); 8,09 (d, *J*=8,84 Hz, 1H); 8,22 (s, 1H); 8,31 (d, *J*=1,77 Hz, 1H); 8,37 (s, 1H); 8,51 (s, 1H); 9,04 (s, 1H); 9,48 (s, 1H); 15,07 (s, 1H)	Ejemplo 315
321	Ácido 6-(6-(3-etilureido)-4-(4-(trifluorometil) tiazol-2-il)piridin-3-il)-4-oxo-1-(tetrahidro-2H-piran-4-il)-1,4dihidroquinolin-3-carboxílico 	MS (ESP): 588,09 (M+1) para $C_{27}H_{24}F_3N_5O_5S$ RMN ^{1}H (400 MHz, DMSO-d_6) δ: 1,11 (t, *J*=7,20 Hz, 3H); 1,96 - 2,20 (m, 4H); 3,15 - 3,27 (m, 2H); 3,60 - 3,77 (m, 2H); 3,96 - 4,09 (m, 2H); 5,16 (br. s., 1H); 7,64 (br. s., 1H); 7,83 (br. s., 1H); 8,23 (s, 1H); 8,35 (br. s., 2H); 8,49 (br. s., 1H); 8,90 (br. s., 1H); 9,48 (s, 1H); 15,02 (br. s., 1H)	Ejemplo 316

322	Ácido 1-ciclohexil-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 586,36 (M+1) para $C_{28}H_{26}F_3N_5O_4S$ RMN ^{1}H (400 MHz, DMSO-d_6) δ: 1,11 (t, *J*=7,20 Hz, 3H) 1,27 - 1,41 (m, 1H) 1,55 - 1,76 (m, 3H); 1,80 - 1,97 (m, 4H); 2,02 - 2,14 (m, 2H); 3,14 - 3,28 (m, 2H); 4,83 - 4,99 (m, 1H); 7,62 (d, 1H); 7,86 (d, *J*=9,60 Hz, 1H); 8,23 (s, 1H); 8,25 - 8,31 (m, 1H); 8,33 - 8,38 (m, 2H); 8,51 (s, 1H); 8,92 (s, 1H); 9,48 (s, 1H)	Ejemplo 317
323	Ácido 6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-1-(1-metilpiperidin-4-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 601,22 (M+1) para $C_{28}H_{27}F_3N_6O_4S$ RMN ^{1}H (400 MHz, DMSO-d6) δ: 1,11 (t, *J*=7,07 Hz, 3H); 2,00 - 2,17 (m, 4H); 2,19 - 2,38 (m, 5H); 2,87 - 3,05 (m, 2H); 3,14 - 3,27 (m, 2H); 4,78 - 4,98 (m, 1H); 7,61 (br. s., 1H); 7,86 (dd, *J*=8,97, 1,89 Hz, 1H); 8,23 (s, 1 H); 8,28 (d, *J*=9,35 Hz, 1H); 8,32 - 8,40 (m, 2H); 8,51 (s, 1H); 8,85 (s, 1H); 9,48 (s, 1H); 15,01 (br. s., 1H)	Ejemplo 318

324	Ácido 1-((5-ciclopropil-1,2,4-oxadiazol-3-il)metil)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico 	MS (ESP): 626,03 (M+) para $C_{28}H_{22}F_3N_7O_5S$ RMN ^{1}H (400 MHz, DMSO-d_6) δ: 0,97 - 1,17 (m, 5H); 1,18 - 1,33 (m, 2H); 2,18 - 2,42 (m, J=8,34, 8,34, 4,42, 4,17 Hz, 1H); 3,11 - 3,27 (m, 2H); 6,06 (s, 2H) 7,57 (br. s., 1H); 7,77 - 7,86 (m, 1H); 7,86 - 7,96 (m, 1H); 8,17 - 8,26 (m, 1H); 8,24 - 8,33 (m, 1H); 8,36 (s, 1H); 8,52 (s, 1H); 9,27 (s, 1H); 9,46 (s, 1H); 14,82 (s, 1H)	Ejemplo 319

Ejemplo 325

1-Ciclopropil-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-N-(2-metoxietil)-4-oxo-1,4-dihidroquinolin-3-carboxamida



A una disolución de ácido 1-ciclopropil-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxílico (Ejemplo 20, 80 mg, 0,15 mmoles) en DMF (3 ml) se añadió HATU (112 mg, 0,29 mmoles), DIEA (0,051 ml, 0,29 mmoles), seguido de 2-metoxietanamina (22,11 mg, 0,29 mmoles). Después de agitar 1 h, la espectroscopia LC-MS muestra que la reacción estaba terminada. La DMF se eliminó a vacío, y el residuo se purificó mediante columna ISCO, usando MeOH-CH_2Cl_2 (0-20%), para dar un sólido blanco (47,3 mg, 53,5%).

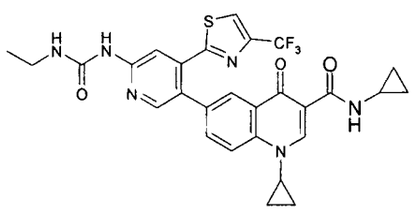
MS (ESP): 601,22 (M+1) para $C_{28}H_{27}F_3N_6O_4S$

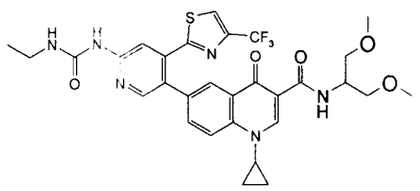
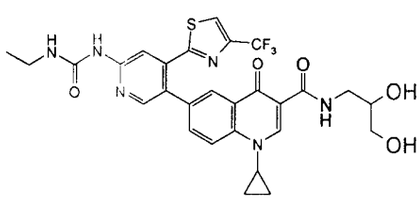
RMN ^{1}H (400 MHz, DMSO-d_6) δ: 1,11 (t, J=7,07 Hz, 3H); 1,20 - 1,37 (m, 4H); 3,15 - 3,25 (m, 2H); 3,40 - 3,54 (m, 4H); 3,73 - 3,85 (m, 1H); 7,56 - 7,67 (m, 1H); 7,80 (dd, J=8,84, 2,27

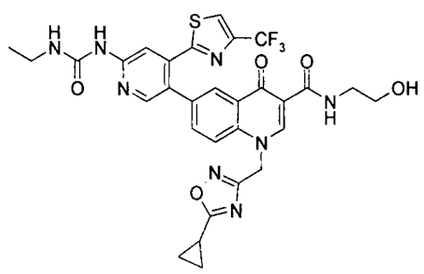
Hz, 1H); 8,14 - 8,29 (m, 3H); 8,33 (s, 1H); 8,48 (s, 1H); 8,75 (s, 1H); 9,45 (s, 1H); 9,74 - 9,99 (m, 1H).

Ejemplos 326-329

Los siguientes Ejemplos se prepararon según el procedimiento descrito para el Ejemplo 325 a partir de los materiales de partida indicados.

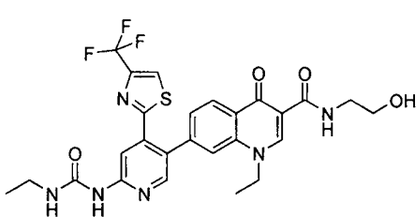
Ej.	Compuesto	Datos	SM
326	N,1-Diciclopropil-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 583,20 (M+1) para $C_{28}H_{25}F_3N_6O_3S$ RMN ^{1}H (400 MHz, DMSO-d_6) δ: 0,45 - 0,58 (m, 2H); 0,65 - 0,80 (m, 2H); 1,03 - 1,17 (m, 5H); 1,24 - 1,38 (m, 2H); 2,78 - 2,92 (m, 1H); 3,15 - 3,27 (m, 2H); 3,71 - 3,87 (m, 1H); 7,62 (br. s., 1H); 7,81 (dd, *J*=8,72, 2,15 Hz, 1H); 8,21 (s, 1H); 8,22 - 8,26 (m, 1H); 8,31 (s, 1H); 8,49 (s, 1H); 8,75 (s, 1H); 9,45 (s, 1H); 9,82 (d, 1H)	Ejemplo 20 y ciclopropil-amina

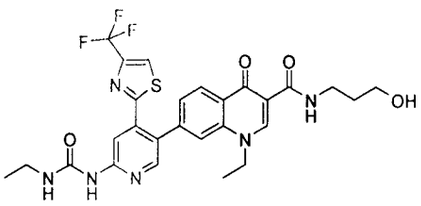
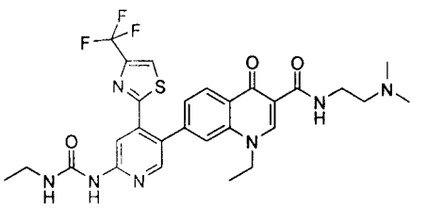
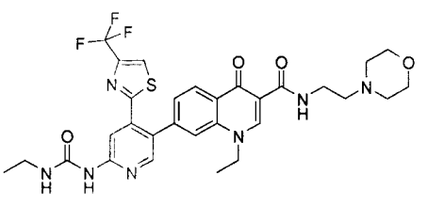
327	1-Ciclopropil-N-(1,3-dimetoxipropan-2-il)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 645,27 (M+1) para $C_{30}H_{31}F_3N_6O_5S$ RMN ^{1}H (400 MHz, DMSO-d_6) δ: 1,03 - 1,19 (m, 5H); 1,25 - 1,39 (m, 2H); 3,15 - 3,26 (m, 2H); 3,28 (s, 6H); 3,36 - 3,50 (m, 4H); 3,73 - 3,86 (m, 1H); 4,22 - 4,33 (m, 1H); 7,62 (br. s., 1H); 7,80 (dd, *J*=8,97, 1,89 Hz, 1H); 8,22 (d, *J*=8,84 Hz, 1H); 8,26 (s, 2H); 8,32 (s, 1H); 8,48 (s, 1 H); 8,75 (s, 1H); 9,45 (s, 1 H); 9,99 (d, *J*=8,34 Hz, 1H);	Ejemplo 20 y 1,3-dimetoxi-2-amino-propano
328	1-Ciclopropil-N-(2,3-dihidroxipropil)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxamida 	MS (ESP): 617,19 (M+1) para $C_{28}H_{27}F_3N_6O_5S$ RMN ^{1}H-RMN (400 MHz, DMSO-d_6) δ: 0,97 - 1,21 (m, 5H); 1,24 - 1,43 (m, 2H); 3,11 - 3,47 (m, 5H); 3,47 - 3,65 (m, 2H); 3,69 - 3,91 (m, 1H); 4,63 (t, *J*=5,68 Hz, 1H); 4,91 (d, 1H); 7,63 (br. s., 1H); 7,80 (dd, *J*=8,72, 1,89 Hz, 1H); 8,13 - 8,29 (m, 3H); 8,32 (s, 1H); 8,48 (s, 1H); 8,75 (s, 1H); 9,45 (s, 1H); 9,93 (br. s., 1H)	Ejemplo 20 y 2,3-dihidroxi-propanamina

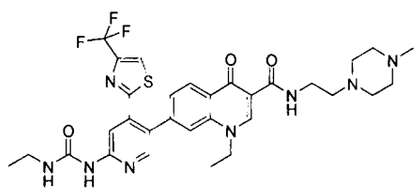
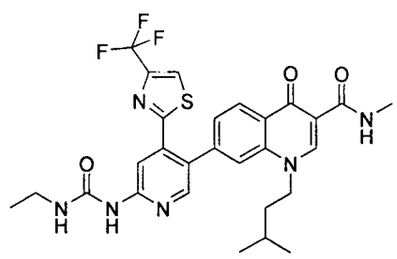
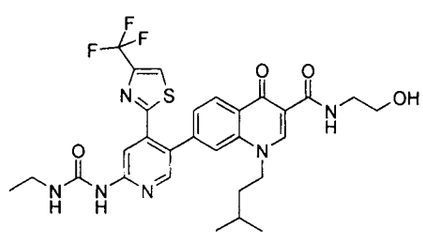
329	1-((5-Ciclopropil-1,2,4-oxadiazol-3-il)metil)-6-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-N-(2-hidroxietil)-4-oxo-1,4-dihidroquinolin-3-carboxamida 	MS(ESP): 669,11 (M+1) para $C_{30}H_{27}F_3N_8O_5S$ RMN ^{1}H (400 MHz, DMSO-d_6) δ: 0,99 - 1,15 (m, 5H); 1,17 - 1,27 (m, J=7,64, 4,04, 3,76, 3,76 Hz, 2H); 2,26 - 2,39 (m, 1H); 3,21 (quin, J=6,76 Hz, 2H); 3,35 - 3,47 (m, 2H); 3,53 (q, J=5,39 Hz, 2H); 4,80 (t, J=5,05 Hz, 1H); 5,97 (s, 2H); 7,60 (br. s., 1H); 7,67 - 7,76 (m, 1H); 7,80 (d, 1H); 8,18 - 8,27 (m, 2H); 8,33 (s, 1H); 8,49 (s, 1H); 9,06 (s, 1H); 9,44 (s, 1H); 9,90 (t, 1H)	Ejemplo 324 e 2-hidroxi-etanamina

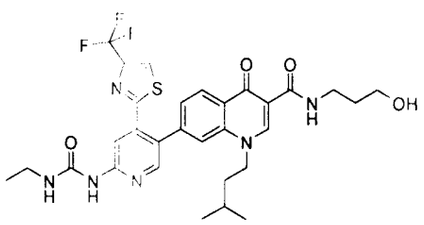
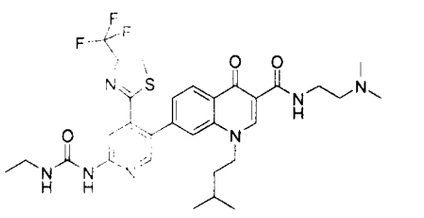
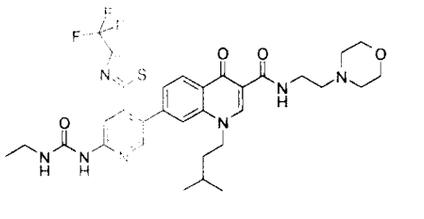
Ejemplos 330-379

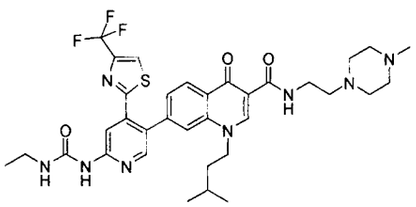
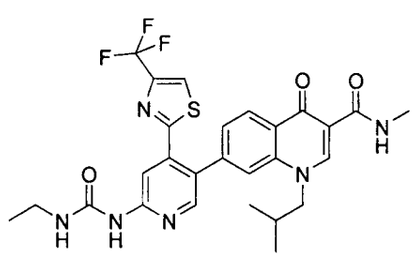
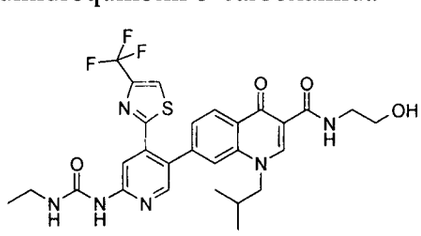
Los siguientes Ejemplos se prepararon según el procedimiento descrito para el Ejemplo 33 a partir de los materiales de partida indicados.

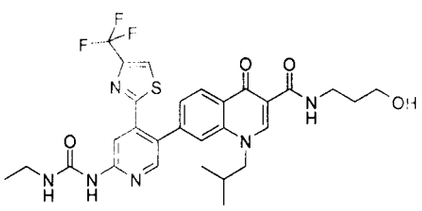
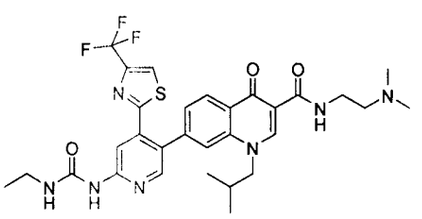
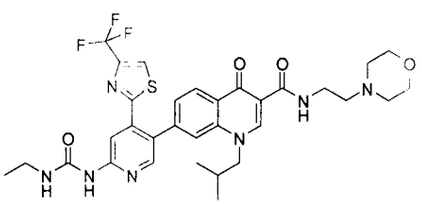
Ej.	Compuesto	Datos	SM
330	1-Etil-7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-N-(2-hidroxietil)-4-oxo-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 1,08 (t, 3H), 1,15 (t, 3H), 3,21 (q, 2H), 3,41 (t, 2H), 3,56 (t, 2H), 4,41 (q, 2H), 4,80 (s, 1H), 7,42 (d, 1H), 7,61 (s, 1H), 7,86 (s, 1H), 8,22 (s, 1H), 8,34 (m, 2H), 8,48 (s, 1H), 8,88 (s, 1H), 9,46 (s, 1H), 10,06 (s, 1H). LC-MS: m/z 575,2 (M+H)	Ejemplo 42 y 3-amino-etanol

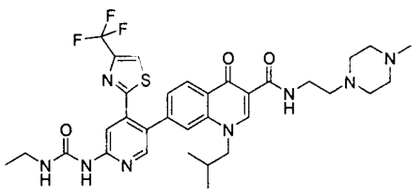
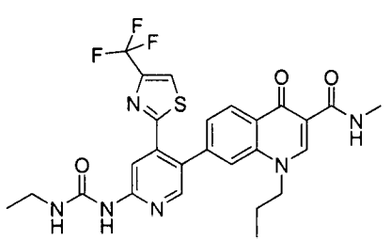
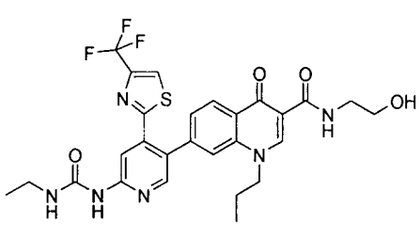
331	1-Etil-7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-N-(3-hidroxipropil)-4-oxo-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 1,08 (t, 3H), 1,15 (t, 3H), 1,64 (m, 2H), 3,21 (q, 2H), 3,38 (q, 2H), 3,44 (q, 2H), 4,21 (m, 3H), 7,39 (d, 1H), 7,58 (s, 1H), 7,84 (s, 1H), 8,21 (s, 1H), 8,37 (m, 2H), 8,43 (s, 1H), 8,84 (s, 1H), 9,42 (s, 1H), 9,98 (t, 1H). LC-MS: m/z 589,3 (M+H)	Ejemplo 42 y 3-amino-propanol
332	N-[2-(dimetilamino)etil]-1-etil-7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-4-oxo-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 1,08 (t, 3H), 1,14 (t, 3H), 2,78 (s, 5H), 3,21 (m, 4H), 3,67 (d, 2H), 4,23 (q, 2H), 7,42 (d, 1H), 7,56 (m, 2H), 7,92 (s, 1H), 8,21 (s, 1H), 8,35 (d, 1H), 8,42 (s, 1H), 8,52 (s, 1H), 8,91 (s, 1H), 9,48 (s, 1H), 10,16 (t, 1H). LC-MS: m/z 602,3 (M+H)	Ejemplo 42 y 2-(N,N-dimetil-amino)-etanamina
333	1-Etil-7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-N-[2-(morfolin-4-il)etil]-4-oxo-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 1,08 (t, 3H), 1,14 (t, 3H), 3,18 (m, 4H), 3,61 (m, 6H), 4,02 (m, 2H), 4,22 (q, 2H), 7,42 (d, 1H), 7,58 (s, 1H), 7,86 (s, 1H), 8,21 (s, 1H), 8,38 (m, 2H), 8,51 (s, 1H), 8,91 (s, 1H), 9,42 (s, 1H), 9,44 (s, 1H), 10,18 (s, 1H). LC-MS: m/z 644,2 (M+H)	Ejemplo 42 y 2-morfolino-etilamina

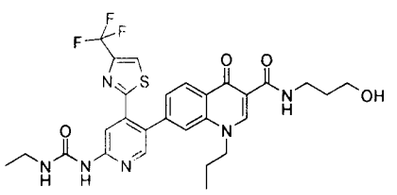
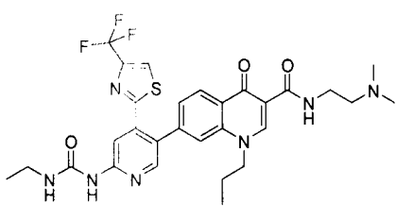
334	1-Etil-7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-N-[2-(4-metilpiperazin-1-il)etil]-4-oxo-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 1,08 (q, 3H), 1,12 (t, 3H), 2,19 (m, 4H), 2,28 (m, 7H), 3,21 (q, 2H), 3,42 (d, 2H), 4,22 (d, 2H), 7,22 (m, 7H), 7,84 (s, 1H), 8,21 (s, 1H), 8,37 (m, 3H), 8,82 (s, 1H), 9,46 (s, 1H), 9,96 (s, 1H). LC-MS: m/z 657,4 (M+H)	Ejemplo 42 y 2-(4-metil-piperazino)-etanamina
335	7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-N-metil-1-(3-metilbutil)-4-oxo-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 0,85 (d, 6H), 1,14 (t, 3H), 1,38 (d, 2H), 1,54 (m, 1H), 2,86 (d, 3H), 3,19 (q, 2H), 4,21 (s, 1H), 7,52 (d, 1H), 7,60 (s, 1H), 7,79 (s, 1H), 8,24 (s, 1H), 8,41 (d, 2H), 8,51 (s, 1H), 8,86 (s, 1H), 9,48 (s, 1H), 9,78 (d, 1H). LC-MS: m/z 587,4 (M+H)	Ejemplo 63 y metilamina
336	7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-N-(2-hidroxietil)-1-(3-metilbutil)-4-oxo-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 0,84 (d, 6H), 1,15 (t, 3H), 1,41 (q, 2H), 1,52 (m, 1H), 3,21 (q, 4H), 3,42 (d, 2H), 3,58 (q, 2H), 4,42 (t, 2H), 4,82 (s, 1H), 7,48 (d, 1H), 7,58 (s, 1H), 7,78 (s, 1H), 8,24 (s, 1H), 8,39 (d, 2H), 8,48 (s, 1H), 8,84 (s, 1H), 9,42 (s, 1H), 10,06 (s, 1H) LC-MS: m/z 617,3 (M+H)	Ejemplo 63 y etanolamina

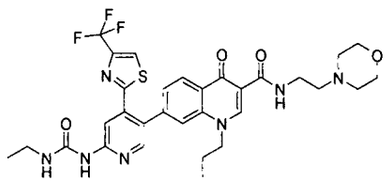
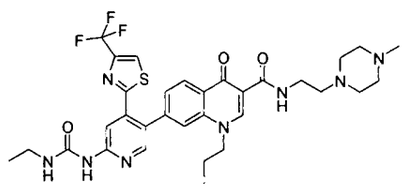
337	7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-N-(3-hidroxipropil)-1-(3-metilbutil)-4-oxo-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 0,84 (d, 6H), 1,15 (t, 3H), 1,38 (t, 2H), 1,52 (m, 1H), 1,68 (q, 2H), 3,20 (q, 2H), 3,39 (t, 2H), 3,45 (t, 2H), 4,38 (t, 2H), 4,49 (s, 1H), 7,46 (d, 1H), 7,58 (s, 1H), 7,78 (s, 1H), 8,24 (s, 1H), 8,39 (d, 2H), 8,49 (s, 1H), 8,85 (s, 1H), 9,43 (s, 1H), 9,96 (s, 1H) LC-MS: m/z 631,3 (M+H)	Ejemplo 63 y 3-amino-propanol
338	N-[2-(dimetilamino)etil]-7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-1-(3-metilbutil)-4-oxo-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 0,82 (d, 6H), 1,12 (t, 3H), 1,39 (q, 2H), 1,48 (m, 1H), 2,29 (s, 6H), 2,44 (s, 2H), 3,21 (q, 2H), 3,44 (t, 2H), 4,41 (t, 2H), 7,45 (d, 1H), 7. 6 (s, 1H), 7,80 (s, 1H), 8,22 (s, 1H), 8,41 (d, 2H), 8,52 (s, 1H), 8,85 (s, 1H), 9,48 (s, 1H), 10,0 (t, 1H) LC-MS: m/z 643,74 (M+H)	Ejemplo 63 y 2-(N,N-dimetil-amino)-etanamina
339	7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-1-(3-metilbutil)-N-[2-(morfolin-4-il)etil]-4-oxo-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 0,84 (d, 6H), 1,14 (t, 3H), 1,38 (d, 2H), 1,54 (m, 1H), 3,21 (q, 4H), 3,60 (m, 6H), 3,96 (s, 2H), 4,40 (s, 2H), 7,52 (d, 2H), 7,79 (s, 1H), 8,22 (s, 1H), 8,39 (d, 2H), 8,54 (s, 1H), 8,88 (s, 1H), 9,44 (s, 1H), 10,18 (s, 1H). LC-MS: m/z 686,3 (M+H)	Ejemplo 63 y 2-morfolino-etanamina

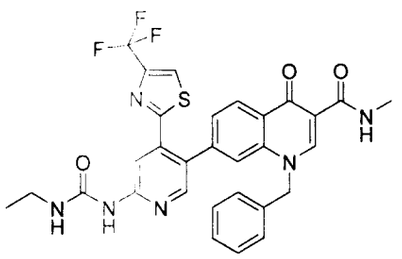
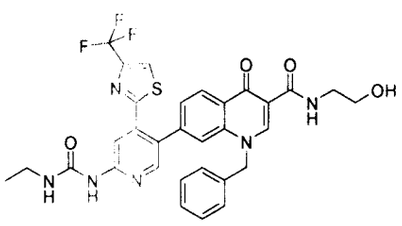
340	7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-1-(3-metilbutil)-N-[2-(4-metilpiperazin-1-il)etil]-4-oxo-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 0,89 (d, 6H), 1,08 (t, 3H), 1,38 (m, 4H), 2,19 (s, 4H), 2,26 (m, 5H), 3,21 (m, 3H), 3,42 (m, 3H), 4,40 (s, 2H), 7,21 (m, 8H), 7,64 (m, 3H), 7,79 (s, 1H), 8,21 (s, 1H), 8,38 (s, 1H), 8,54 (s, 1H), 8,81 (s, 1H), 9,43 (s, 1H), 9,95 (s, 1H). LC-MS: m/z 699,9 (M+H)	Ejemplo 63 y 2-(4-metil-piperazino)-etanamina
341	7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-N-metil-1-(2-metilpropil)-4-oxo-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 0,73 - 0,75 (d, 6H), 1,11 (t, 3H), 1,63 (m, 1H), 2,86 - 2,89 (m, 3H), 3,19 (t, 2H), 4,21 - 4,23 (d, 2H), 7,51 - 7,54 (m, 1H), 7,60 (m, 1H), 7,78 (s, 1H), 8,18 (s, 1H), 8,39 (t, 2H), 8,51 (s, 1H), 8,80 (s, 1H), 9,48 (s, 1H), 9,78 - 9,79 (m, 1H). LC-MS: m/z 573,3 (M+H)	Ejemplo 64 y metilamina
342	7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-N-(2-hidroxietil)-1-(2-metilpropil)-4-oxo-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 0,75 (d, 6H), 1,11 (t, 3H), 1,63 (m, 1H), 3,21 (m, 2H), 3,41 (m, 2H), 3,54 (m, 2H), 4,22 (d, 2H), 4,81 (t, 1H), 7,52 (d, 1H), 7,60 (br s, 1H), 7,78 (s, 1H), 8,18 (s, 1H), 8,38 - 8,40 (m, 2H), 8,52 (s, 1H), 8,81 (s, 1H), 9,48 (s, 1H), 10,05 (t, 1H). LC-MS: m/z 603,3 (M+H)	Ejemplo 64 y etanolamina

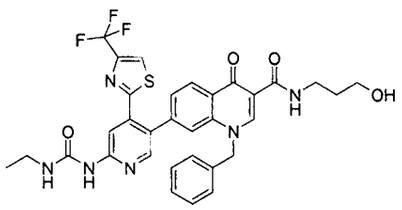
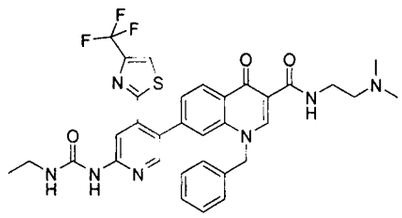
343	7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-N-(3-hidroxipropil)-1-(2-metilpropil)-4-oxo-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 0,74 - 0,75 (m, 6H), 1,11 (t, 3H), 1,65-1,71 (m, 3H), 3,17-3,24 (m, 2H), 3,37-3,49 (m, 2H), 3,49-3,51 (m, 2H), 4,20-4,22 (m, 2H), 4,51 (br s, 1H), 7,34-7,45 (m, 2H), 7,78 (s, 1H), 8,18 (s, 1H), 8,37-8,39 (m, 2H), 8,50 (s, 1H), 8,79 (s, 1H), 9,48 (s, 1H), 9,95 (s, 1H). LC-MS: m/z 617,2 (M+H)	Ejemplo 64 y 3-amino-propanol
344	N-[2-(dimetilamino)etil]-7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-1-(2-metilpropil)-4-oxo-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 0,75 (d, 6H), 1,11 (t, 3H), 1,61 (m, 1H), 2,76 (br s, 6H), 3,19 (m, 4H), 3,68 (m, 2H), 4,22 (d, 2H), 7,51 (m, 2H), 7,82 (s, 1H), 8,11 (s, 1H), 8,31 - 8,42 (m, 2H), 8,55 (s, 1H), 8,87 (s, 1H), 9,41 (s, 1H), 10,12 (t, 1H). LC-MS: m/z 630,4 (M+H)	Ejemplo 64 y 2-(N,N-dimetil-amino)-etanamina
345	7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-1-(2-metilpropil)-N-[2-(morfolin-4-il)etil]-4-oxo-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 0,75 (d, 6H), 1,12 (m, 4H), 1,64 (m, 2H), 2,47 (m, 4H), 3,24 (m, 2H), 3,49 (m, 2H), 3,61 (m, 4H), 4,22 (d, 2H), 7,53 (m, 1H), 7,61 (t, 1H), 7,78 (s, 1H), 8,18 (s, 1H), 8,40 (m, 2H), 8,52 (s, 1H), 8,79 (s, 1H), 9,49 (s, 1H), 10,02 (t, 1H). LC-MS: m/z 672,3 (M+H)	Ejemplo 64 y 2-morfolino-etanamina

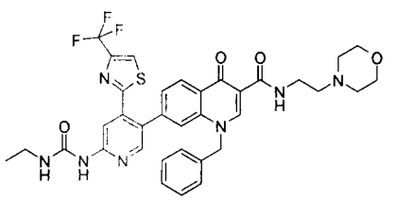
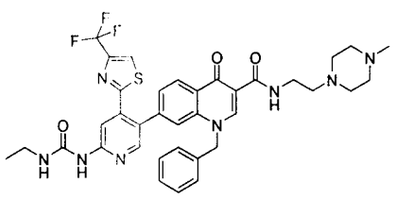
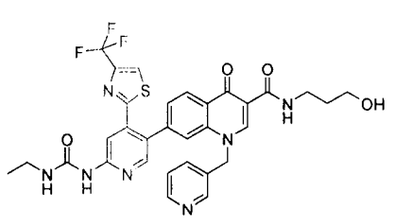
346	7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-N-[2-(4-metilpiperazin-1-il)etil]-1-(2-metilpropil)-4-oxo-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, CD_3OD): δ 0,91 (d, 6H), 1,12 (t, 3H), 1,82 (m, 1H), 2,18 (s, 3H), 2,65 (m, 8H), 3,19 (q, 2H), 3,59 (q, 2H), 4,18 (d, 2H), 7,54 (d, 1H), 7,69 (s, 1H), 7,81 (s, 1H), 8,22 (s, 1H), 8,40 (s, 1H), 8,51 (d, 1H), 8,79 (s, 1H). LC-MS: m/z 685,3 (M+H)	Ejemplo 65 y 2-(4-metil-piperazino)-etanamina
347	7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-N-metil-4-oxo-1-propil-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 0,78 (t, 3H), 1,11 (t, 3H), 1,52 (m, 2H), 2,87 (m, 3H), 3,19 (m, 2H), 4,31 (t, 2H), 7,41 (d, 1H), 7,62 (br s, 1H), 7,82 (s, 1H), 8,21 (s, 1H), 8,36 - 8,39 (m, 2H), 8,49 (s, 1H), 8,87 (s, 1H), 9,42 (s, 1H), 9,79 - 9,78 (m, 1H). LC-MS: m/z 559,3 (M+H)	Ejemplo 65 y metilamina
348	7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-N-(2-hidroxietil)-4-oxo-1-propil-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 0,78 (t, 3H), 1,10 (t, 3H), 1,50-1,55 (m, 2H), 3,19-3,22 (m, 2H), 3,40-3,42 (m, 2H), 3,52-3,53 (m, 2H), 4,37 (m, 2H), 4,81 (br s, 1H), 7,47-7,51 (m, 1H), 7,71 (br s, 1H), 7,84 (s, 1H), 8,22 (m, 1H), 8,36-8,39 (m, 2H), 8,49 (s, 1H), 8,84 (s, 1H), 9,58 (s, 1H), 10,03 (s, 1H). LC-MS: m/z 589,19 (M+H)	Ejemplo 65 y etanolamina

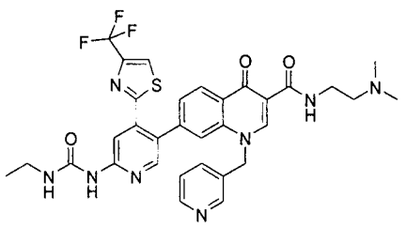
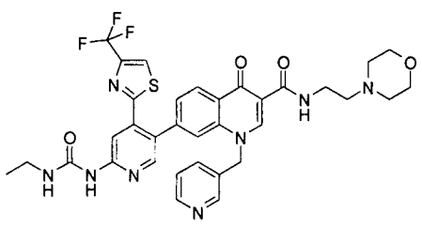
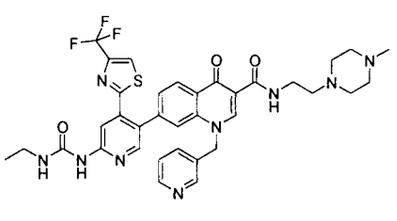
349	7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-N-(3-hidroxipropil)-4-oxo-1-propil-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 0,78 (t, 3H), 1,11 (t, 3H), 1,50 - 1,55 (m, 2H), 1,66 - 1,69 (m, 2H), 3,21 (t, 2H), 3,41 (m, 2H), 3,47-3,51 (m, 2H), 4,37 (t, 2H), 4,55 (t, 1H), 7,47-7,49 (d, 1H), 7,61 (br s, 1H), 7,85 (s, 1H), 8,20 (s, 1H), 8,36-8,39 (m, 2H), 8,49 (s, 1H), 8,83 (s, 1H), 9,48 (s, 1H), 9,91 (t, 1H). LC-MS: m/z 603,3 (M+H)	Ejemplo 65 y 3-amino-propanol
350	N-[2-(dimetilamino)etil]-7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-4-oxo-1-propil-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 0,782 (t, 3H), 1,09 (t, 3H), 1,49-1,55 (m, 2H), 2,20 (s, 6H), 2,41 (t, 2H), 3,18-3,24 (m, 2H), 3,42-3,45 (m, 2H), 4,37 (t, 2H), 7,31 (m, 1H), 7,61 (m, 1H), 7,84 (s, 1H), 8,21 (s, 1H), 8,36-8,40 (m, 2H), 8,49 (s, 1H), 8,84 (s, 1H), 9,48 (s, 1H), 9,91 (t, 1H). LC-MS: m/z 616 (M+H)	Ejemplo 65 y 2-(N,N-dimetil-amino)-etanamina

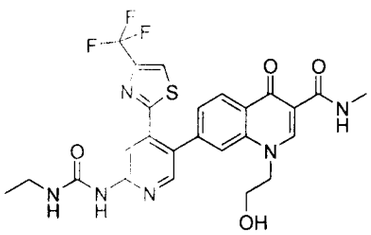
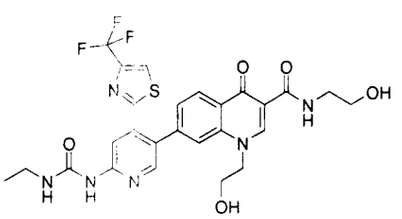
351	7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-N-[2-(morfolin-4-il)etil]-4-oxo-1-propil-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 0,782 (t, 3H), 1,11 (t, 3H), 1,50-1,55 (m, 2H), 2,43 - 2,41 (m, 4H), 3,18 -3,22 (m, 2H), 3,44-3,49 (m, 3H), 3,59-3,61 (m, 5H), 4,37 (t, 2H), 7,46-7,49 (d, 1H), 7,61 (br s, 1H), 7,85 (s, 1H), 8,20 (s, 1H), 8,36-8,40 (m, 2H), 8,49 (s, 1H), 8,84 (s, 1H), 9,48 (s, 1H), 10,07 (t, 1H). LC-MS: m/z 658,3 (M+H)	Ejemplo 65 y 2-morfolino-etanamina
352	7-{6-[(Etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-N-[2-(4-metilpiperazin-1-il)etil]-4-oxo-1-propil-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, CD_3OD): δ 0,92 (q, 3H), 1,11 (q, 3H), 1,64 (q, 2H), 2,38 (s, 3H), 2,61 (m, 8H), 3,14 (q, 2H), 3,59 (t, 2H), 4,29 (t, 2H), 7,48 (d, 1H), 7,78 (s, 1H), 7,84 (s, 1H), 8,21 (s, 1H), 8,41 (s, 1H), 8,42 (d, 1H), 8,83 (s, 1H). LC-MS: m/z 671,4 (M+H)	Ejemplo 65 y 2-(4-metilpiperazino)-etanamina

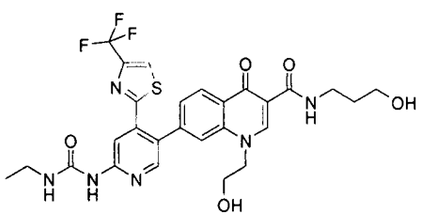
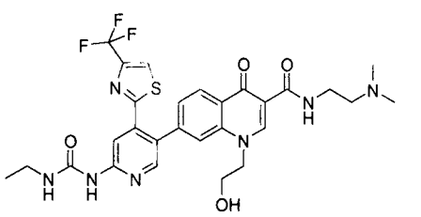
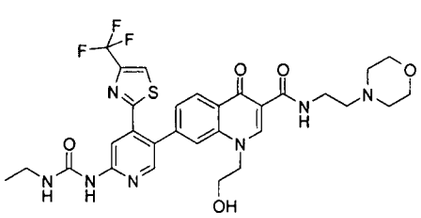
353	1-Bencil-7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-N-metil-4-oxo-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 1,10 (t, 3H), 2,88-2,89 (m, 3H), 3,16-3,23 (m, 2H), 5,74 (s, 2H), 7,10-7,08 (m, 2H), 7,19-7,25 (m, 3H), 7,40-7,42 (m, 1H), 7,51-7,53 (br s, 1H), 7,79 (s, 1H), 8,16 (s, 1H), 8,22 (s, 1H), 8,32 (s, 1H), 8,37-8,38 (s, 1H), 9,07 (s, 1H), 9,42 (s, 1H), 9,75-9,77 (m, 1H). LC-MS: m/z 607,3 (M+H)	Ejemplo 66 y metilamina
354	1-Bencil-7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-N-(2-hidroxietil)-4-oxo-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 1,1 (t, 3H), 3,16-3,23 (m, 2H), 3,41-3,45 (m, 2H), 3,53-3,57 (m, 2H), 5,74 (s, 1H), 7,08-7,10 (m, 2H), 7,19-7,42 (m, 1H), 7,51-7,25 (m, 3H), 7,40-7,42 (m, 1H), 7,53 (br s, 1H), 7,79 (s, 1H), 8,17 (s, 1H), 8,22 (s, 1H), 8,32 (s, 1H), 8,36-8,38 (s, 1H), 9,07 (s, 1H), 9,42 (s, 1H), 10,02 (m, 1H). LC-MS: m/z 637,3 (M+H)	Ejemplo 66 y etanolamina

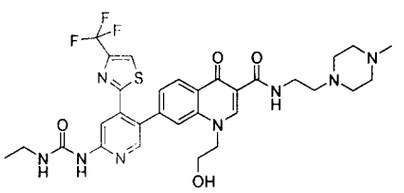
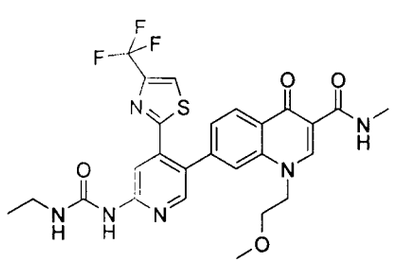
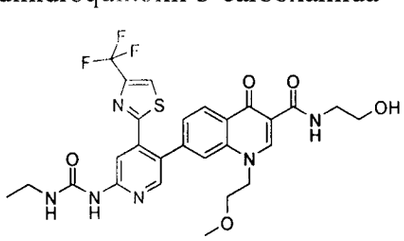
355	1-Bencil-7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-N-(3-hidroxipropil)-4-oxo-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 1,08-1,11 (t, 3H), 1,66-1,73 (m, 2H), 3,16-3,23 (m, 2H), 3,39-3,51 (m, 2H), 3,48-3,53 (m, 2H), 4,54 (t, 1H), 7,08-7,10 (m, 2H), 7,19-7,25 (m, 3H), 7,40-7,42 (m, 1H), 7,51-7,53 (br s, 1H), 7,79 (s, 1H), 8,17 (s, 1H), 8,23 (s, 1H), 8,32-8,38 (m,2H), 9,06 (s, 1H), 9,42 (s, 1H), 9,94 (t, 1H). LC-MS: m/z 651,3 (M+H)	Ejemplo 66 y 3-amino-propanol
356	1-Bencil-N-[2-(dimetilamino)etil]-7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-4-oxo-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 1,09 (t, 3H), 3,21 (s, 6H), 2,43 (m, 2H), 3,16-3,29 (m, 2H), 3,43-3,47 (m, 2H), 5,73 (s, 2H), 7,08-7,10 (m, 2H), 7,19-7,25 (m, 3H), 7,40-7,42 (m, 1H), 7,52 (br s, 1H), 7,78 (s, 1H), 8,17 (s, 1H), 8,22 (s, 1H), 8,33-8,38 (m,2H), 9,65 (s, 1H), 9,42 (s, 1H), 9,95 (m, 1H). LC-MS: m/z 664,4 (M+H)	Ejemplo 66 y 2-(N,N-dimetil-amino)-etanamina

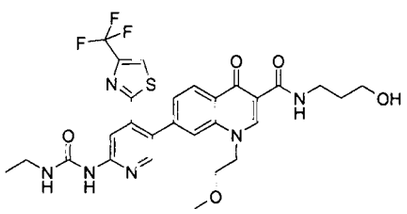
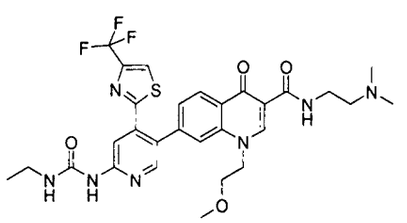
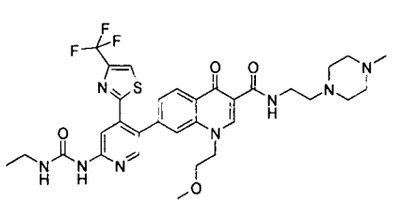
357	1-Bencil-7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-N-[2-(morfolin-4-il)etil]-4-oxo-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 1,10 (t, 3H), 2,32 (m, 4H), 3,20 (q, 2H), 3,48 (d, 2H), 3,61 (s, 4H), 5,74 (s, 2H), 7,10 (d, 2H), 7,21 (d, 3H), 7,39 (d, 1H), 7,41 (s, 1H), 7,79 (s, 1H), 8,17 (d, 2H), 8,32 (m, 2H), 9,06 (s, 1H), 9,43 (s, 1H), 9,99 (s, 1H). LC-MS: m/z 706,3 (M+H)	Ejemplo 66 y 2-morfolino-etanamina
358	1-Bencil-7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-N-[2-(4-metilpiperazin-1-il)etil]-4-oxo-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 1,09 (t, 3H), 2,16 (s, 3H), 2,31 – 2,34 (m, 4H), 3,16 – 3,23 (m, 2H), 3,44 – 3,48 (q, 2H), 5,73 (s, 2H), 7,08 – 7,10 (m, 2H), 7,19 – 7,24 (m, 2H), 7,39 – 7,41 (d, 1H), 7,53 (m, 1H), 7,79 (s, 1H), 8,17 (s, 1H), 8,23 (s, 1H), 8,31 (s, 1H), 8,37 – 8,39 (d, 1H), 9,05 (s, 1H), 9,43 (s, 1H), 9,94 – 9,96 (t, 1H). LC-MS: m/z 719,89 (M+H)	Ejemplo 66 y 2-(4-metilpiperazino)-etanamina
359	7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-N-(3-hidroxipropil)-4-oxo-1-(piridin-3-ilmetil)-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 1,10 (t, 3H), 1,70 (m, 2H), 3,21 (q, 2H), 3,40 (m, 5H), 4,57 (s, 1H), 5,80 (s, 2H), 7,22 (m, 1H), 7,42 (d, 2H), 7,58 (s, 1H), 7,84 (s, 1H), 8,19 (d, 2H), 8,33 (m, 4H), 9,12 (s, 1H), 9,46 (s, 1H), 9,93 (t, 1H). LC-MS: m/z 652 (M+H)	Ejemplo 67 y 3-amino-propanol

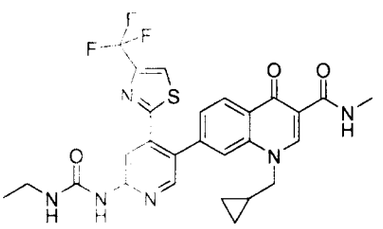
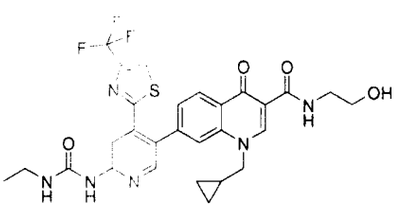
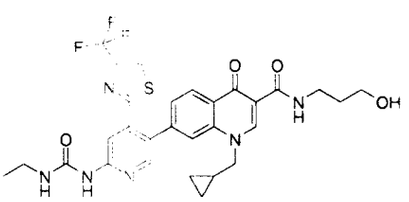
360	N-[2-(dimetilamino)etil]-7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-4-oxo-1-(piridin-3-ilmetil)-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, CD_3OD): δ 1,19 (t, 3H), 2,69 (s, 6H), 3,73 (q, 2H), 5,73 (s, 2H), 7.31 (m, 9H), 7,69 (s, 1H), 7,86 (s, 1H), 8,04 (s, 1H), 8,20 (s, 1H), 8,40 (m, 2H), 8,48 (d, 1H), 9,08 (s, 1H). LC-MS: m/z 665,4 (M+H)	Ejemplo 67 y 2-(N,N-dimetil-amino)-etanamina
361	7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-N-[2-(morfolin-4-il)etil]-4-oxo-1-(piridin-3-ilmetil)-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 1,08 (t, 3H), 2,33 (m, 6H), 3,18 (q, 2H), 3,48 (d, 2H), 3,61 (s, 4H), 5,80 (s, 2H), 7,22 (m, 2H), 7,36 (m, 4H), 7,56 (s, 2H), 7,84 (s, 1H), 8,19 (d, 2H), 8,40 (m, 4H), 9,11 (s, 1H), 9,45 (s, 1H), 9,99 (s, 1H). LC-MS: m/z 707,4 (M+H)	Ejemplo 67 y 2-morfolino-etanamina
362	7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-N-[2-(4-metilpiperazin-1-il)etil]-4-oxo-1-(piridin-3-ilmetil)-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, CD_3OD): δ 1,19 (t, 3H), 2,46 (s, 2H), 2,68 (m, 4H), 2,76 (m, 4H), 3,60 (q, 2H), 5,74 (s, 2H), 7.30 (m, 8H), 7,69 (s, 1H), 7,86 (s, 1H), 8,03 (s, 1H), 8,20 (s, 1H), 8,41 (s, 2H), 8,49 (d, 1H), 9.08 (s, 1H). LC-MS: m/z 720,45 (M+H)	Ejemplo 67 y 2-(4-metilpiperazino)-etanamina

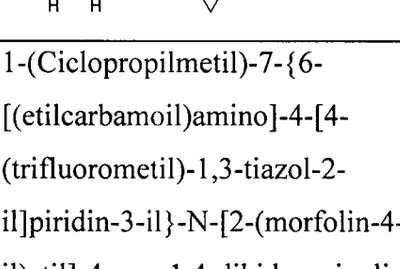
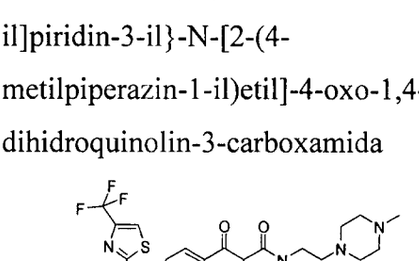
363	7-{6-[(Etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-1-(2-hidroxietil)-N-metil-4-oxo-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 1,09 – 1,12 (t, 3H), 2,86 – 2,87 (m, 3H), 3,19 – 3,22 (m, 2H), 3,59 – 3,60 (m, 2H), 4,49 (br s, 1H), 4,95 – 4,98 (t, 1H), 7,39 – 7,41 (d, 1H), 7,63 (br s, 1H), 7,98 (s, 1H), 8,24 (s, 1H), 8,34 – 8,37 (m, 2H), 8,48 (s, 1H), 8,87 (s, 1H), 9,48 (s, 1H), 9,79 – 9,80 (d, 1H). LC-MS: m/z 561,3 (M+H)	Ejemplo 68 y metilamina
364	7-{6-[(Etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-N,1-bis(2-hidroxietil)-4-oxo-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 1,11(t, 3H), 3,19-3,22 (m, 2H), 3,40-3,42 (m, 2H), 3,52-3,60 (m, 4H), 4,83 (t, 1H), 4,97 (t, 1H), 7,40-7,42 (d, 1H), 7,6 (br s, 1H), 7,97 (s, 1H), 8,24 (s, 1H), 8,33-8,38 (m, 2H), 8,4 (s, 1H), 8,78 (s, 1H), 9,48 (s, 1H), 10,06 (s, 1H). LC-MS: m/z 591,3 (M+H)	Ejemplo 68 y etanolamina

365	7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-1-(2-hidroxietil)-N-(3-hidroxipropil)-4-oxo-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 1,12(t, 3H), 1,7 (m, 2H), 3,21-3,22 (m, 2H), 3,40-3,42 (m, 2H), 3,49-3,52 (m, 2H), 3,6 (br s, 2H), 4,49 (br s, 2H), 4,54-4,57 (t, 1H), 4,9 (t, 1H), 7,4-7,42 (d, 1H), 7,6 (br s, 1H), 7,9 (s, 1H), 8,24 (s, 1H), 8,33-8,37 (m, 2H) 8,48 (s, 1H), 8,78 (s, 1H), 9,48 (s, 1H), 9,98 (t, 1H). LC-MS: m/z 605,2 (M+H)	Ejemplo 68 y 3-amino-propanol
366	N-[2-(dimetilamino)etil]-7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-1-(2-hidroxietil)-4-oxo-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 1,10 (t, 3H), 2,67 – 2,73 (m, 6H), 3,21 (m, 4H), 3,60 – 3,66 (m, 4H), 4,50 (s, 1H), 4,98 (t, 1H), 7,41 – 7,43 (m, 1H), 7,59 (br s, 2H), 7,99 (s. 1H), 8,24 (s, 1H), 8,34 – 8,38 (m, 1H), 8,50 (s, 1H), 8,79 (s, 1H), 9,49 (s, 1H), 10,12 (br s, 1H). LC-MS: m/z 618,2 (M+H)	Ejemplo 68 y 2-(N,N-dimetil-amino)-etanamina
367	7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-1-(2-hidroxietil)-N-[2-(morfolin-4-il)etil]-4-oxo-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 1,11 (br s, 3H), 2,43 (m, 4H), 3,21 (br s, 3H), 3,46-3,60 (m, 9H), 7,39-7,41 (s, 1H), 7,61 (br s, 1H), 7,91 (s, 1H), 8,24 (s, 1H), 8,34-8,37 (m, 3H), 8,77 (s, 1H), 9,48 (s, 1H), 10,11 (br s, 1H). LC-MS: m/z 660,2 (M+H)	Ejemplo 68 y 2-morfolino-etanamina

368	7-{6-[(Etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-1-(2-hidroxietil)-N-[2-(4-metilpiperazin-1-il)etil]-4-oxo-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, CD_3OD): δ 1,21 (t, 3H), 2,45 (s, 3H), 2,67 (m, 8H), 3,59 (s, 2H), 3,79 (s, 2H), 4,49 (s, 2H), 7,43 (d, 1H), 7,88 (s, 2H), 8,16 (s, 1H), 8,41 (m, 2H), 8,86 (s, 1H). LC-MS: m/z 673,3 (M+H)	Ejemplo 68 y 2-(4-metilpiperazino)-etanamina
369	7-{6-[(Etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-1-(2-metoxietil)-N-metil-4-oxo-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 1,12 (t, 3H), 2,83 (s, 3H), 3,18 (m, 5H), 3,46 (s, 2H), 4,59 (s, 2H), 7,41 (d, 1H), 7,58 (s, 1H), 7,95 (s, 1H), 8,22 (s, 1H), 8,34 (d, 2H), 8,48 (s, 1H), 8,78 (s, 1H), 9,42 (s, 1H), 9,76 (s, 1H). LC-MS: m/z 575,3 (M+H)	Ejemplo 69 y metilamina
370	7-{6-[(Etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-N-(2-hidroxietil)-1-(2-metoxietil)-4-oxo-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 1,12 (t, 3H), 3,18 (s, 3H), 3,19 (m, 2H), 5,45 (m, 6H), 4,58 (s, 2H), 4,69 (s, 1H), 7,41 (d, 1H), 7,56 (s, 1H), 7,91 (s, 1H), 8,21 (s, 1H), 8,38 (m, 2H), 8,44 (s, 1H), 8,79 (s, 1H), 9,39 (s, 1H), 9,99 (s, 1H). LC-MS: m/z 605,3 (M+H)	Ejemplo 69 y etanolamina

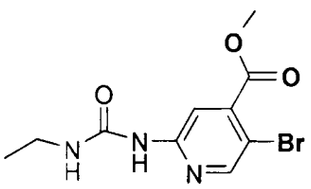
371	7-{6-[(Etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-N-(3-hidroxipropil)-1-(2-metoxietil)-4-oxo-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 1,11 (t, 3H), 1,65 (s, 2H), 3,18 (s, 3H), 3,39 (m, 6H), 4,22 (s, 2H), 4,58 (s, 1H), 7,38 (m, 2H), 7,92 (s, 1H), 8,22 (s, 1H), 8,38 (m, 3H), 8,78 (s, 1H), 9,38 (s, 1H), 9,98 (s, 1H). LC-MS: m/z 619,3 (M+H)	Ejemplo 69 y 3-amino-propanol
372	N-[2-(dimetilamino)etil]-7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-1-(2-metoxietil)-4-oxo-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 1,11 (t, 3H), 2,45 (s, 6H), 2,96 (s, 2H), 3,18 (s, 3H), 3,21 (q, 2H), 3,46 (s, 2H), 3,62 (s, 2H), 4,58 (s, 2H), 7,38 (m, 2H), 7,94 (s, 1H), 8,22 (s, 1H), 8,35 (m, 2H), 8,45 (s, 1H), 8,78 (s, 1H), 9,40 (s, 1H), 10,02 (s, 1H). LC-MS: m/z 632,3 (M+H)	Ejemplo 69 y 2-(N,N-dimetil-amino)-etanamina
373	7-{6-[(Etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-1-(2-metoxietil)-N-[2-(4-metilpiperazin-1-il)etil]-4-oxo-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, CD_3OD): δ 1,12 (t, 3H), 2,78 (s, 2H), 2,86 (s, 3H), 3,21 (s, 3H), 3,38 (m, 4H), 3,59 (s, 4H), 4,58 (s, 2H), 7,26 (s, 1H), 7,84 (s, 2H), 8,21 (s, 1H), 8,38 (m, 2H), 8,82 (s, 1H). LC-MS: m/z 687,30 (M+H)	Ejemplo 69 y 2-(4-metilpiperazino)-etanamina

374	1-(Ciclopropilmetil)-7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-N-metil-4-oxo-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 0,39 (dd, 4H), 1,02 (m, 4H), 2,82 (d, 3H), 3,21 (q, 2H), 4,38 (d, 2H), 7,41 (m, 3H), 7,61 (s, 2H), 7,99 (s, 1H), 8,21 (s, 1H), 8,36 (m, 3H), 8,88 (s, 1H), 9,48 (s, 1H), 9,79 (s, 1H). LC-MS: m/z 571,4 (M+H)	Ejemplo 70 y metilamina
375	1-(Ciclopropilmetil)-7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-N-(2-hidroxietil)-4-oxo-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 0,38 (d, 4H), 1,05 (m, 1H), 1,16 (t, 3H), 3,21 (t, 2H), 3,39 (t, 2H), 3,51 (t, 2H), 4,29 (d, 2H), 4,81 (t, 1H), 7,48 (d, 1H), 7,61 (s, 1H), 7,98 (s, 1H), 8,24 (s, 1H), 8,38 (m, 2H), 8,48 (s, 1H), 8,91 (s, 1H), 9,48 (s, 1H), 10,4 (s, 1H). LC-MS: m/z 601,2 (M+H)	Ejemplo 70 y etanolamina
376	1-(Ciclopropilmetil)-7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-N-(3-hidroxipropil)-4-oxo-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 0,38 (d, 4H), 1,04 (m, 4H), 164 (s, 2H), 3,21 (q, 2H), 3,41 (dd, 4H), 4,28 (m, 2H), 4,52 (s, 1H), 7,44 (d, 1H), 7,51 (s, 1H), 7,96 (s, 1H), 8,21 (s, 1H), 8,36 (m, 3H), 8,86 (s, 1H), 9,46 (s, 1H), 9,94 (s, 1H) LC-MS: m/z 615,2 (M+H)	Ejemplo 70 y 3-amino-propanol

377	1-(Ciclopropilmetil)-N-[2-(dimetilamino)etil]-7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-4-oxo-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 0,38 (d, 4H), 0,94 (s, 1H), 1,14 (t, 3H), 2,68 (s, 2H), 2,96 (d, 3H), 3,18 (m, 4H), 3,46 (m, 10H), 4,18 (d, 2H), 6,98 (s, 2H), 7,38 (d, 1H), 7,61 (s, 1H), 7,94 (d, 1H), 8,22 (s, 1H), 8,26 - 8,54 (m, 5H), 9,48 (s, 1H). LC-MS: m/z 628,3 (M+H)	Ejemplo 70 y 2-(N,N-dimetil-amino)-etanamina
378	1-(Ciclopropilmetil)-7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-N-[2-(morfolin-4-il)etil]-4-oxo-1,4-dihidroquinolin-3-carboxamida 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 0,38 (d, 4H), 0,94 (s, 1H), 1,14 (t, 3H), 3,19 (s, 3H), 3,49 (q, 2H), 3,60 (s, 3H), 4,31 (t, 2H), 7,43 (d, 1H), 7,58 (s, 1H), 7,98 (s, 1H), 8,21 (s, 1H), 8,38 (m, 2H), 8,48 (s, 1H), 8,90 (s, 1H), 9,48 (s, 1H), 10,06 (s, 1H). LC-MS: m/z 670,2 (M+H)	Ejemplo 70 y 2-morfolino-etanamina
379	1-(Ciclopropilmetil)-7-{6-[(etilcarbamoil)amino]-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}-N-[2-(4-metilpiperazin-1-il)etil]-4-oxo-1,4-dihidroquinolin-3-carboxamida	RMN ^{1}H (400 MHz, DMSO-d_6): δ 0,37 – 0,43 (m, 4H), 1,01 (m, 1H), 1,11 (t, 3H), 2,24 – 2,33 (m, 4H), 3,18 – 3,24 (m, 3H), 3,43 – 3,36 (m, 2H), 4,30 – 4,32 (d, 2H), 7,46 – 7,48 (d, 1H), 7,61 (br s, 1H), 7,97 (s, 1H), 8,21 (s, 1H), 8,36 – 8,48 (m, 3H), 8,88 (s, 1H), 9,49 (s, 1H), 9,97 – 9,99 (t, 1H).	Ejemplo 70 y 2-(4-metilpiperazino)-etanamina

Intermediario 1

5-bromo-2-(3-etilureido)isonicotinato de metilo



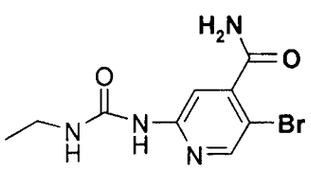
Una disolución de 2-amino-5-bromoisonicotinato de metilo (50g, 216,5 mmoles) en cloroformo (500ml) se colocó en un tubo cerrado herméticamente. Entonces se añadió isocianato de etilo (51 ml, 649,4 mmoles) en dos partes, en el transcurso de 6 horas. El tubo cerrado herméticamente se aisló y se calentó a 40°C durante 3 d. La mezcla de reacción se enfrió entonces hasta la temperatura ambiente, se concentró a presión reducida y se extrajo con acetato de etilo (3 l) y agua (1 l). La capa de acetato de etilo se secó entonces con sulfato de sodio, se filtró, y se concentró a presión reducida para producir 68,4 g de un sólido amarillo pálido (96%).

MS (ESP): 302 ($M+H^+$) para $C_{10}H_{12}BrN_3O_3$

RMN ^1H ($CDCl_3$): δ 1,22 (t, 3H), 3,41 (q, 2H), 7,22 (s, 1H), 7,30 (s, 1H), 8,38 (s, 1H), 8,70 (s, 1H), 9,42 (s, 1H)

Intermediario 2

5-Bromo-2-(3-etilureido)isonicotinamida



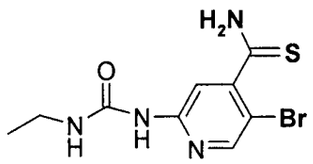
Una disolución de 5-bromo-2-(3-etilureido)isonicotinato de metilo (Intermediario 1, 56,22 g, 186,0 mmoles) en amoníaco 7N en metanol (1 l) se dejó agitar a temperatura ambiente en un matraz cerrado herméticamente, durante 1 ½ d. El precipitado que se formó se recogió mediante filtración, se enjuagó con acetonitrilo (500 ml), y entonces se secó en la bomba a alto vacío toda la noche, produciendo 50,8 g de un sólido (95,1%).

MS (ESP): 287 ($M+H^+$) para $C_9H_{11}BrN_4O_2$

RMN ^1H (DMSO-d_6): δ 1,1 (t, 3H), 3,18 (q, 2H), 7,40 (s, 1H), 7,60 (s, 1H), 7,80 (s, 1H), 8,1 (s, 1H), 8,38 (s, 1H), 9,39 (s, 1H)

Intermediario 3

5-Bromo-2-(3-etilureido)piridin-4-carbotioamida



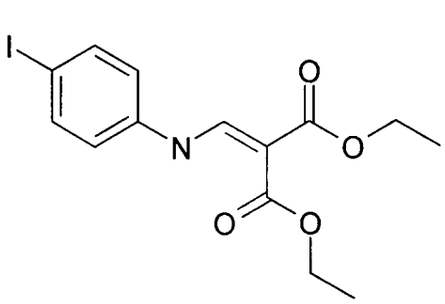
Una disolución de 5-bromo-2-(3-etilureido)isonicotinamida (Intermediario 2, 52,17 g, 181,73 mmoles), el reactivo de Lawesson (73,50 g, 181,73 mmoles) y tetrahidrofurano (840 ml) se preparó y se agitó con calentamiento a reflujo toda la noche. Después de aproximadamente 12 h, mediante LCMS se confirmó que la reacción estaba terminada; por lo tanto, se detuvo la agitación y se dejó que sedimentase un precipitado amarillo brillante, para facilitar la filtración. El precipitado se filtró entonces y se lavó subsiguientemente con 500 ml de tetrahidrofurano adicional. El sólido se secó entonces en el horno de vacío a 50°C durante 30 min, produciendo 51 g de un sólido amarillo brillante (92,5%).

MS (ESP): 304 ($M+H^+$) para $C_9H_{11}BrN_4OS$

RMN ^1H (DMSO-d_6): δ 1,1 (t, 3H), 3,18 (q, 2H), 7,38 (s, 1H), 7,50 (s, 1H), 8,28 (s, 1H), 9,25 (s, 1H), 9,80 (s, 1H), 10,28 (s, 1H)

Intermediario 4

2-((4-yodofenilamino)metilen)malonato de dietilo

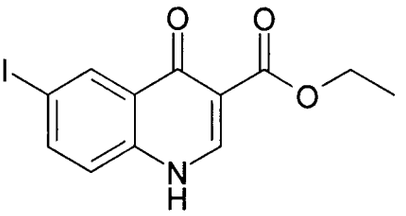


Una mezcla de éster dietílico del ácido etoximetilenmalónico (20,1 ml, 0,10 moles) y 4-yodoanilina (22 g, 0,10 moles) en tolueno (300 ml) se calentó a reflujo durante 1 h. Después de este período de tiempo, los disolventes se eliminaron a vacío, y el material bruto precipitó en metil-terc-butiléter, y el sólido blanco resultante se filtró y se secó a vacío para dar 30 g de producto.

MS (ESP): 390 ($M+H^+$) para $C_{14}H_{16}INO_4$

Intermediario 5

6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo



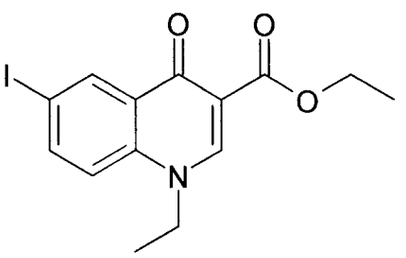
Método A: Se añadió 2-((4-yodofenilamino)metilen)malonato de dietilo (Intermediario 4, 10 g, 25 mmoles) a un matraz de fondo redondo que estaba equipado con un termopar y un agitador, y entonces se añadió el reactivo de Eaton (26 ml) al matraz. La mezcla de reacción se agitó a 95°C durante 6 h en nitrógeno. Después de este período de tiempo, la mezcla de reacción se enfrió hasta 5°C y se transfirió lentamente a un exceso de disolución saturada de carbonato de sodio (50 ml), que se enfrió hasta 10°C. El sólido precipitado se filtró, se lavó con agua (~20 ml) y se secó a vacío para dar el producto (80% de rendimiento).

Método B: Se calentó éter fenílico (70 ml) con agitación hasta 240°C, después se añadió gradualmente 2-((4-yodofenilamino)metilen)malonato de dietilo (Intermediario 4, 10 g, 25 mmoles), y la mezcla resultante se puso a reflujo a 280°C durante 1 hora. Tras enfriar la reacción hasta la temperatura ambiente, el sólido resultante se recogió mediante filtración, se lavó con metil-terc-butiléter y diclorometano para dar un sólido blanco (30% de rendimiento).

MS (ESP): 344 ($M+H^+$) para $C_{12}H_{10}INO_3$

Intermediario 6

1-etil-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo



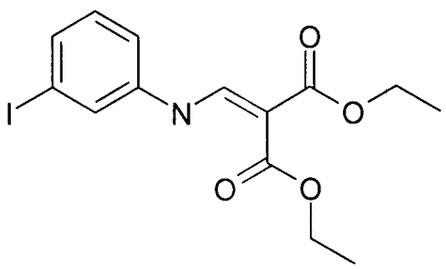
A 6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo (Intermediario 5, 5 g, 0,013 mol) en dimetilformamida (26 ml, 0,2M) se añadieron carbonato de potasio (4,50g, 0,033 moles) y bromuro de etilo (5,71 g, 0,053 moles). La reacción se agitó a 90°C toda la noche, y después el disolvente se eliminó *a vacío*. El residuo se recogió en acetato de etilo, se lavó con agua,

con salmuera, y se secó sobre sulfato de sodio. Los disolventes se eliminaron a vacío, y el residuo se purificó mediante cromatografía ultrarrápida en columna sobre gel de sílice, usando (diclorometano-acetato de etilo), para dar el producto quinolónico deseado (90%) y trazas de impureza O-alquilada.

MS (ESP): 372 ($M+H^+$) para $C_{14}H_{14}INO_3$

Intermediario 7

2-((3-yodofenilamino)metilen)malonato de dietilo

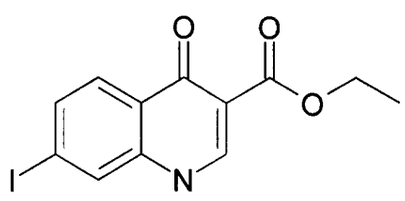


Una mezcla de éster dietílico del ácido etoximetilenmalónico (13,72 g, 0,068 mol) y 3-yodoanilina (15 g, 0,068 moles) en tolueno (230 ml) se puso a reflujo durante 1 h. Después de este período de tiempo, los disolventes se eliminaron a vacío, y el material bruto precipitó en metil-terc-butiléter, y el sólido blanco resultante se filtró y se secó a vacío (24,3 g, 93%).

MS (ESP): 390 ($M+H^+$) para $C_{14}H_{16}INO_4$

Intermediario 8

7-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo



Método A: Se añadió 2-((3-yodofenilamino)metilen)malonato de dietilo (Intermediario 7, 10 g, 25 mmoles) a un matraz de fondo redondo que estaba equipado con un termopar y un agitador, y entonces se añadió el reactivo de Eaton (26 ml) al matraz. La mezcla de reacción se agitó a 95°C durante 6 h en nitrógeno. Después de este período de tiempo, la mezcla de reacción se enfrió hasta 5°C y se transfirió lentamente a un exceso de disolución saturada de

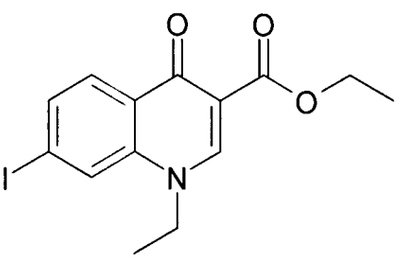
carbonato de sodio (50 ml) que se enfrió hasta 10°C. El sólido precipitado se filtró, se lavó con agua (~20 ml) y se secó a vacío para dar el producto (80% de rendimiento).

Método B: Se calentó éter fenílico (70 ml) con agitación hasta 240°C, después se añadió gradualmente 2-((3-yodofenilamino)metilen)malonato de dietilo (Intermediario 7, 10 g, 25 mmoles), y la mezcla resultante se puso a reflujo a 280°C durante 1 hora. Tras enfriar la reacción hasta la temperatura ambiente, el sólido resultante se recogió mediante filtración, se lavó con metil-terc-butiléter y diclorometano para dar un sólido blanco (30% de rendimiento).

MS (ESP): 344 ($M+H^+$) para $C_{12}H_{10}INO_3$

Intermediario 9

1-etil-7-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo

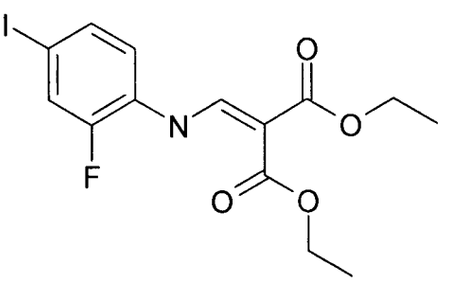


A 6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo (Intermediario 8, 5 g, 0,013 mol) en dimetilformamida (26 ml, c=0,2M) se añadieron carbonato de potasio (4,50g, 0,033 moles) y bromuro de etilo (5,71 g, 0,053 moles). La reacción se agitó a 90°C toda la noche, y después el disolvente se eliminó *a vacío*. El residuo se recogió en acetato de etilo, se lavó con agua, con salmuera, y se secó sobre sulfato de sodio. Los disolventes se eliminaron a vacío, y el bruto se purificó mediante cromatografía ultrarrápida en columna sobre gel de sílice, usando (diclorometano-acetato de etilo), para dar la quinolona deseada (90%).

MS (ESP): 372 ($M+H^+$) para $C_{14}H_{14}INO_3$

Intermediario 10

2-((2-Fluoro-4-yodofenilamino)metilen)malonato



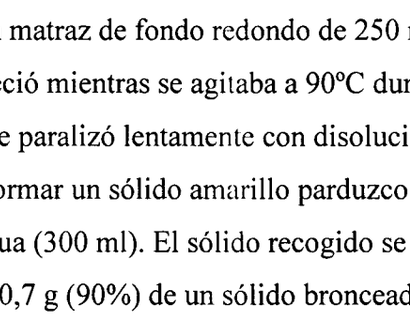
Una disolución de 2-fluoro-4-yodoanilina (15 g, 63,29 mmoles) y etoximetilenmalonato de dietilo (41,05 g, 0,19 moles) en tolueno (75 ml) se calentó a reflujo con un condensador Dean-Stark durante 7 h. La mezcla se enfrió, se concentró y se lavó con metil-terc-butiléter (500 ml). La capa de metil-terc-butiléter se concentró entonces, y el residuo se lavó con heptano (500 ml), produciendo un sólido blanco que precipitó de la disolución amarilla. Este sólido se recogió entonces, produciendo 23,6 g (91%) de 2-((2-fluoro-4-yodofenilamino)metilen)malonato de dietilo.

MS (ESP): 407 ($M+H^+$) para $C_{14}H_{15}FINO_4$

RMN ^1H ($CDCl_3$): δ 1,40 (t, 6H), 4,30 (q, 4H), 7,03 (t, 1H), 7,51 (d, 1H), 8,42 (d, 1H), 11,02 (d, 1H).

Intermediario 11

8-fluoro-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo



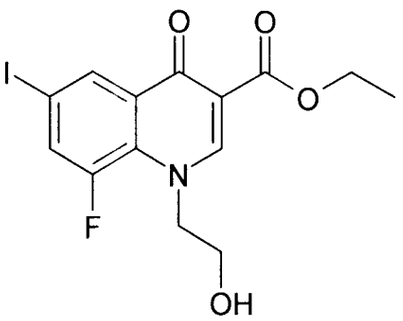
Se colocó 2-((2-fluoro-4-yodofenilamino)metilen)malonato de dietilo (Intermediario 10, 13,45 g, 33,05 mmoles) en un matraz de fondo redondo de 250 ml con el reactivo de Eaton (55 ml, 0,29 mol), y se envejeció mientras se agitaba a 90°C durante 4-5 días. La reacción se enfrió entonces hasta 5°C, y se paralizó lentamente con disolución saturada de carbonato de sodio (500 ml) a 10°C, para formar un sólido amarillo parduzco grumoso. El precipitado se filtró a vació y se lavó con agua (300 ml). El sólido recogido se secó a vacío a 50°C durante 16 h, dando como resultado 10,7 g (90%) de un sólido bronceado claro.

MS (ESP): 362 ($M+H^+$) para $C_{12}H_9FINO_3$

RMN ^1H ($CDCl_3$): δ 1,37 (t, 3H), 4,18 (q, 2H), 6,59 (d, 1H), 7,20 (d, 1H), 7,30 (d, 1H), 7,64 (d, 1H)

Intermediario 12

8-fluoro-1-(2-hidroxietil)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo

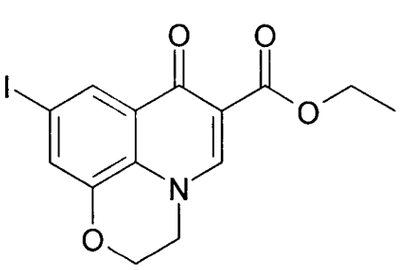


Se disolvió 8-fluoro-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo (Intermediario 11, 7,22 g, 20 mmoles) en dimetilformamida (35 ml). Entonces se añadió carbonato de potasio en polvo (8,28 g, 60 mmoles) y 2-yodoetanol (11,3 ml, 145 mmoles), y la mezcla de reacción se dejó agitar a 90°C durante 1 h. La mezcla de reacción se enfrió hasta la temperatura ambiente y se vertió en salmuera (300 ml), y después se añadió agua (50 ml) para disolver el material. Esta disolución se extrajo con tetrahidrofurano:metil-terc-butiléter 9:1 (5 × 200 ml). Los extractos orgánicos se combinaron, se lavaron con salmuera (2 × 200 ml), se secaron sobre sulfato de sodio, y se concentraron a presión reducida para dar un aceite amarillo oscuro de 8-fluoro-1-(2-hidroxietil)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo, que se llevó a la siguiente reacción sin ninguna purificación adicional.

MS (ESP): 405 ($M+H^+$) para $C_{14}H_{13}FINO_4$

Intermediario 13

9-yodo-7-oxo-3,7-dihidro-2H-[1,4]oxazino[2,3,4-ij]quinolin-6-carboxilato de etilo

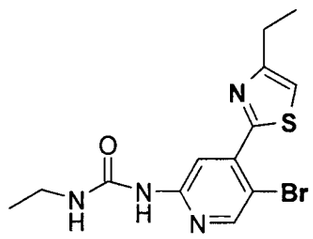


Una disolución de 8-fluoro-1-(2-hidroxietil)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo (Intermediario 12, 20 mmoles) en DMF (30 ml) se trató con 1,8-diazabiciclo[5,4,0]undec-7-eno (5,6 ml, 40 mmoles), y la mezcla de reacción se agitó a 100°C durante 24 h. El disolvente se eliminó entonces *a vacío*, y el residuo se cromatografió sobre gel de sílice, usando 0-5% de (amoníaco 0,2N en metanol) en diclorometano, para dar 1,4g (18%) de 9-yodo-7-oxo-3,7-dihidro-2H-[1,4]oxazino[2,3,4-ij]quinolin-6-carboxilato de etilo como un sólido blanco.

MS (ESP): 386 ($M+H^+$) para $C_{14}H_{12}INO_4$

Intermediario 14

1-(5-Bromo-4-(4-etiltiazol-2-il)piridin-2-il)-3-etilurea



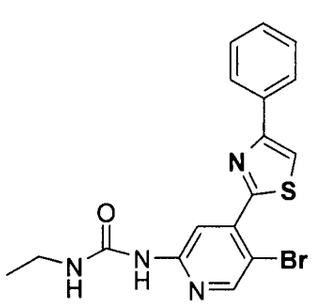
Se suspendió 5-bromo-2-(3-etilureido)piridin-4-carbotioamida (Intermediario 3, 6,06g, 20 mmoles) en acetonitrilo (150 ml). Se añadió 1-bromobutan-2-ona (30 mmoles), y la mezcla de reacción se calentó a reflujo durante 16 h. La reacción se enfrió hasta 0°C, y la suspensión se filtró. El sólido se lavó con acetonitrilo (50 ml), se recogió, y se secó en un horno de vacío a 50°C durante 4 horas para dar un sólido blanquecino.

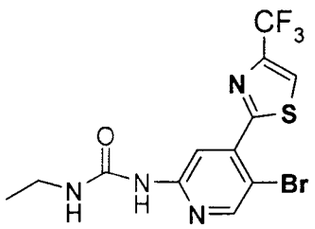
MS (ESP): 356 (MH^+) para $C_{13}H_{15}BrN_4OS$

RMN ^1H (d_6-DMSO): δ 0,91 (t, 3H), 1,28 (t, 3H), 3,83 (q, 2 H), 3,18 (q, 2H), 7,31 (bs, 1H), 7,66 (s, 1 H), 8,37 (s, 1H), 8,47 (s, 1H), 9,37 (s, 1H).

Intermediarios 15-16

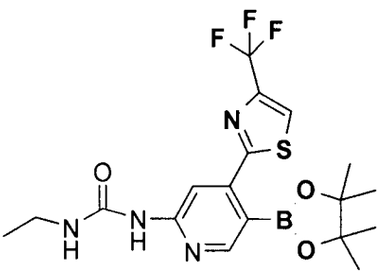
Los siguientes Intermediarios se prepararon mediante el procedimiento descrito para la preparación del Intermediario 14 a partir de los materiales de partida (SM) indicados.

Int.	Compuesto	Datos	SM
15	1-(5-bromo-4-(4-feniltiazol-2-il)piridin-2-il)-3-etilurea 	MS (ESP): 504 (MH^+) para $C_{17}H_{15}BrN_4OS$ RMN ^1H: 1,10 (t, 3H), 3,19 (q, 2 H), 7,24-7,40 (m, 2H), 7,41-7,50 (m, 2 H), 8,04 (d, 1H), 8,43-8,53 (m, 3H), 9,39 (s, 1H)	Intermediario 3 y 2-bromo-1-feniletanona

Int.	Compuesto	Datos	SM
16	1-(5-bromo-4-(4-trifluorometiltiazol-2-il)piridin-2-il)-3-etilurea 	MS (ESP): 395 ($M+H^+$) para $C_{12}H_{10}BrF_3N_4OS$ RMN ^1H: 1,1 (t, 3H), 3,20 (q, 2H), 7,23 (s, 1H), 8,40 (s, 1H), 8,60 (s, 1H), 8,83 (s, 1H), 9,40 (s, 1H)	Intermediario 3 y 3-bromo-1,1,1,-trifluoro-acetona

Intermediario 17

1-Etil-3-(5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-4-(4-(trifluorometil)tiazol-2-il)piridin-2-il)urea



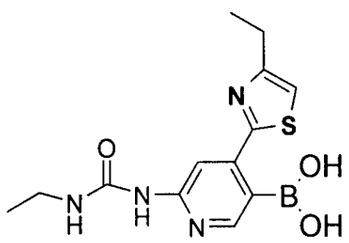
1-(5-Bromo-4-(4-(trifluorometil)tiazol-2-il)piridin-2-il)-3-etilurea (Intermediario 16, 200 mg, 0,51 mmoles), 4,4,4',4',5,5,5',5'-octametil-2,2'-bi(1,3,2-dioxaborolano) (386 mg, 1,52 mmoles), acetato de potasio (149 mg, 1,52 mmoles), y dicloruro de 1,1'-bis(difenilfosfino)ferroceno-paladio (20,72 mg, 0,03 mmoles) se recogieron en un vial de microondas, y se desgasificó con argón. Se añadió DMSO (4 ml) al vial, y la disolución se calentó a 90 °C durante 5 h. La mezcla de reacción se repartió entre agua y acetato de etilo. Las capas se separaron, y la capa orgánica se extrajo nuevamente tres veces con acetato de etilo. Las capas orgánicas se combinaron y se lavaron con agua y salmuera, después se secaron sobre sulfato de magnesio y se concentraron a presión reducida para dar un sólido marrón claro, que era una mezcla del compuesto del título (35%), ácido {6-{[(etilamino)carbonil]amino}-4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-3-il}borónico (25 %) y *N*-etil-*N'*-{4-[4-(trifluorometil)-1,3-tiazol-2-il]piridin-2-il}urea (25 %). La mezcla bruta se llevó a la siguiente etapa sin purificación adicional.

MS (ESP): 361 (MH^+) para $C_{12}H_{12}BF_3N_4O_3S$

RMN ^{1}H (d_6-DMSO): δ 1,11 (t, 3H), 3,16-3,22 (q, 2 H), 7,71 (bt, 1H), 7,89 (d, 1 H), 8,16 (s, 1H), 8,28 (s, 1H), 8,63 (s, 1H), 9,26 (s, 1H).

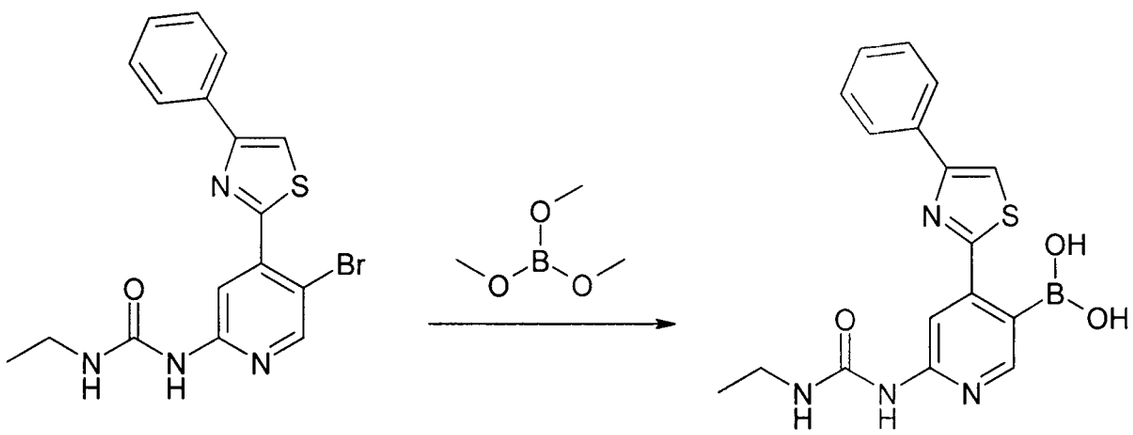
Intermediario 18

Los siguientes Intermediario se prepararon mediante el procedimiento descrito en el Intermediario 17 a partir de los materiales de partida (SM) indicados.

Int.	Compuesto	Datos	SM
18	Ácido 6-(3-etilureido)-4-(4-etiltiazol-2-il)piridin-3-ilborónico 	MS (ESP): 321 (MH^+) para $C_{13}H_{17}BN_4O_3S$ RMN ^{1}H (d_6-DMSO): δ 1,16 (t, 3H), 1,23 (t, 3H), 2,78 (q, 2H), 3,18-3,23 (m, 2 H), 7,48 (s, 1H), 7,78 (bt, 1 H), 7,91 (s, 1H), 8,26 (s, 1H), 9,40 (s, 1H)	Intermediario 14

Intermediario 19

Ácido 6-(3-etilureido)-4-(4-feniltiazol-2-il)piridin-3-ilborónico



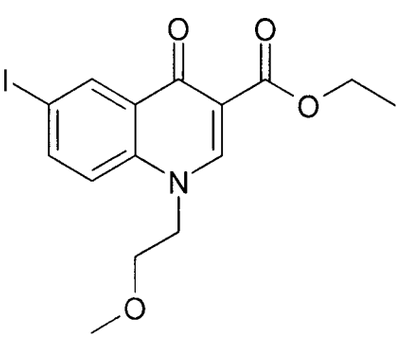
Una disolución de 1-(5-bromo-4-(4-feniltiazol-2-il)piridin-2-il)-3-etilurea (2,97 g, 7,36 mmoles, Intermediario 15) en THF (25 ml) se enfrió hasta -78 °C. Se añadió lentamente cloruro de isopropilmagnesio (2,0M en THF; 8,84 ml, 17,67 mmoles, Aldrich), y la reacción se calentó lentamente hasta -15 °C antes de enfriarla nuevamente hasta -78 °C. Entonces se añadió n-butil-litio (2,5M en hexanos; 14,73 ml, 36,82 mmoles, Aldrich), y la reacción se

agitó a -78 °C durante 1 hora. Se añadió de una sola vez borato de trimetilo (8,21 ml, 73,64 mmoles, Aldrich) y se observó exotermia. Tras la exotermia, la mezcla de reacción se dejó calentar hasta la temperatura ambiente y se dejó agitar durante 3 h. La mezcla de reacción se enfrió entonces hasta 0 °C, y se añadieron lentamente 20 ml de agua, seguido de 10 ml de HCl 6N. La mezcla de reacción se dejó calentar hasta la temperatura ambiente y se dejó agitar durante 30 min. La mezcla de reacción se concentró a presión reducida para eliminar THF. La porción acuosa se diluyó con NaOH 1N y éter dietílico. La impurezas se eliminaron en la capa de éter (amarilla), y el sólido blanco que queda se filtró, se lavó con agua y se secó. El sólido se trituró entonces con ácido diluido (pH 4,5) para eliminar sales. El sólido se secó toda la noche para producir producto como un sólido blanco (1,60 g). MS (ES) $(M+H)^+$: 369 para $C_{17}H_{17}BN_4O_3S$

RMN: 1,10 (t, 3H), 3,20 (q, 2H), 7,37-7,51 (m, 3H), 7,79 (m, 1H), 7,93 (s, 1H), 8,06 (d, 2H), 8,28 (d, 2H), 9,30 (s, 1H).

Intermediario 20

6-yodo-1-(2-metoxietil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo



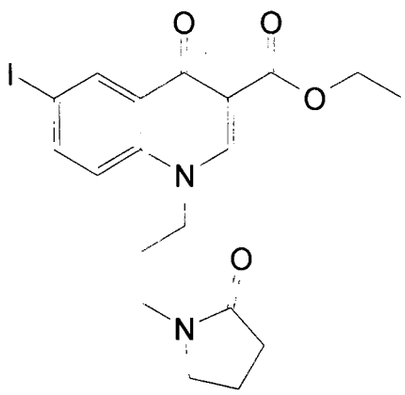
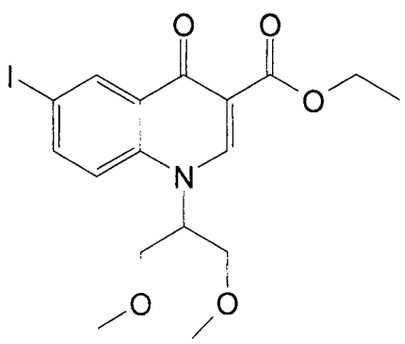
(Z)-3-(dimetilamino)-2-(2-fluoro-5-yodobenzoil)acrilato de etilo (0,428 g, 1,09 mmoles, Intermediario 24) y 2-metoxietanamina (0,082 g, 1,09 mmoles, Acros) se combinaron en DMF (3,0 ml). Se añadió carbonato de potasio (0,151 g, 1,09 mmoles, Fisher), y la reacción se calentó en el microondas a 90 °C durante 30 min. Después de 30 minutos, la LC/MS indicó que la reacción estaba terminada. La mezcla de reacción se enfrió hasta la temperatura ambiente, y se vertió lentamente en agua. El precipitado resultante se filtró, se lavó con agua y se secó toda la noche para producir un sólido blanco (0,277 g).

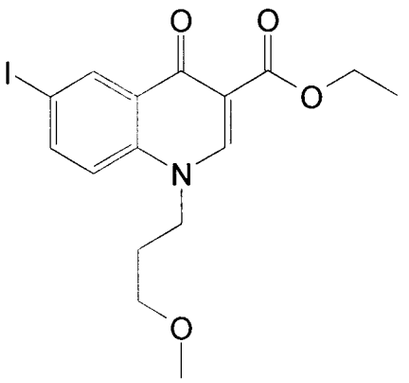
MS (ES) $(M+H)^+$: 402 para $C_{15}H_{16}INO_4$;

RMN: 1,28 (t, 3H), 3,21 (s, 3H), 3,65 (t, 2H), 4,21 (q, 2H), 4,55 (t, 2H), 7,68 (d, 1H), 8,04 (d, 1H), 8,50 (s, 1H), 8,60 (s, 1H).

Intermediarios 21-23

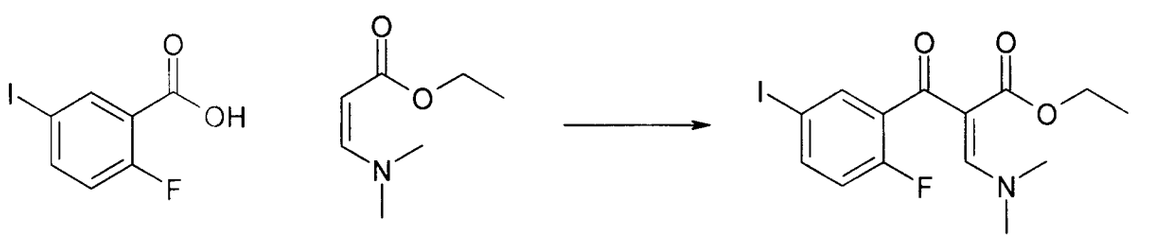
Los siguientes Intermediarios se prepararon mediante el procedimiento descrito en el Intermediario 20 a partir de los materiales de partida (SM) indicados.

Int.	Compuesto	Datos	SM
21	6-yodo-4-oxo-1-(3-(2-oxopirrolidin-1-il)propil)-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ES) $(M+H)^+$: 469 para $C_{19}H_{21}IN_2O_4$	Intermediario 24 y 1-(3-aminopropil)pirrolidin-2-ona (Acros)
22	1-(1,3-dimetoxipropan-2-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ES) $(M+H)^+$: 446 para $C_{17}H_{20}INO_5$ RMN: 1,28 (t, 3H), 3,24 (s, 6H), 3,73-3,84 (m, 4H), 4,22 (q, 2H), 5,27 (q, 1H), 7,81 (d, 1H), 8,04 (d, 1H), 8,51 (s, 1H), 8,72 (s, 1H).	Intermediario 24 y 1,3-dimetoxi-propan-2-amina (Tyger)

Int.	Compuesto	Datos	SM
23	6-yodo-1-(3-metoxipropil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ES) $(M+H)^+$: 416 para $C_{16}H_{18}INO_4$ RMN: 1,28 (t, J = 8 Hz, 3H), 1,97 (m, 2H), 3,34 (m, 5H), 4,21 (q, J = 8 Hz, 2H), 4,39 (m, 2H), 7,62 (d, J = 9 Hz, 1H), 8,06 (d, J = 9 Hz, 1H), 8,51 (s, 1H), 8,63 (s, 1H).	Intermediario 24 y 3-metoxipropilamina

Intermediario 24

3-(dimetilamino)-2-(2-fluoro-5-yodobenzoil)acrilato de (Z)-etilo

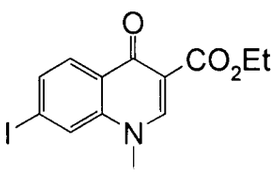
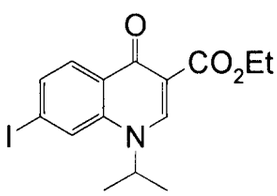


El ácido 2-fluoro-5-yodobenzoico (5,20 g, 19,55 mmoles, Aldrich) se suspendió en cloruro de tionilo (1,427 ml, 19,55 mmoles, Aldrich), y se calentó a reflujo durante 30 min. La mezcla de reacción se enfrió hasta la temperatura ambiente, y se concentró a presión reducida hasta un sólido bronceado. El sólido se disolvió en tolueno (30 ml), y se concentró a presión reducida nuevamente. A una disolución del sólido resultante (5,20 g, 19,55 mmoles) en tolueno (30 ml) se añadió trietilamina (2,72 ml, 19,55 mmoles, Acros) y (Z)-3-(dimetilamino)acrilato de etilo (3,64 ml, 25,41 mmoles, Acros), y la mezcla de reacción se calentó hasta 90 °C durante 1 h. La mezcla de reacción se diluyó con agua y se extrajo tres veces con acetato de etilo. Los extractos orgánicos combinados se secaron sobre sulfato de magnesio, se filtraron y se concentraron a presión reducida. La purificación mediante columna Isco (0%-100% de acetato de etilo/diclorometano) dio el compuesto deseado como un sólido amarillo (6,51 g). MS (ES) $(M+H)^+$: 392 para $C_{14}H_{15}FINO_3$

RMN: 0,88 (t, 3H), 2,78 (s, 3H), 3,33 (s, 3H), 3,85 (q, 2H), 7,03 (dd, 1H), 7,65 (dd, 1H), 7,77 (s, 2H).

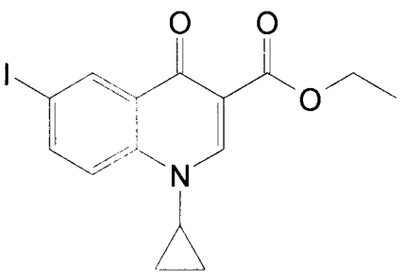
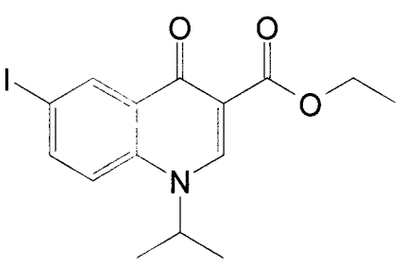
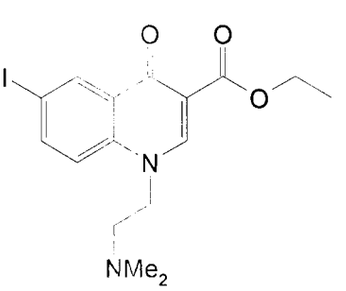
Intermediarios 25-26

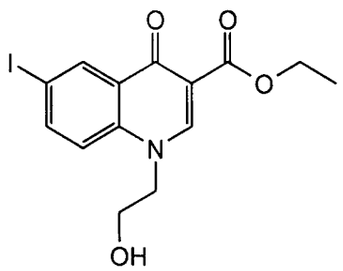
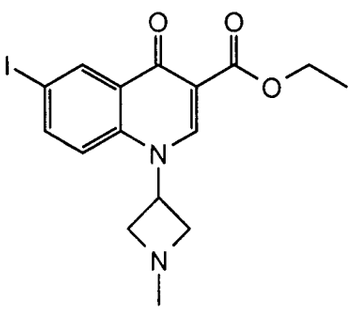
Los siguientes Intermediarios se prepararon mediante el procedimiento descrito en el Intermediario 9 a partir de los materiales de partida (SM) indicados.

Int.	Compuesto	Datos	SM
25	7-yodo-1-metil-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 358 (M+1) para $C_{13}H_{12}INO_3$ RMN ^{1}H (DMSO-d_6) δ: 1,28 (t, 3H); 3,90 (s, 3H); 4,22 (q, *J*=7,07 Hz, 2H); 7,83 (dd, 1H); 7,94 (d, *J*=8,59 Hz, 1H); 8,10 (s, 1H); 8,64 (s, 1H)	Intermediario 8 y yodometano
26	7-yodo-1-isopropil-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 386 (M+1) para $C_{15}H_{16}INO_3$ RMN ^{1}H (DMSO-d_6): 1,29 (d, J=6,06 Hz, 6H); 1,36 (t, J=7,07 Hz, 3H); 4,39 (q, J=7,07 Hz, 2H); 4,58 - 4,70 (m, 1H); 7,96 (dd, 1H) 8,03 (d, 1H); 8,45 (d, J=1,26 Hz, 1H); 9,04 (s, 1H)	Intermediario 8 y 2-yodopropano

Intermediarios 27-31

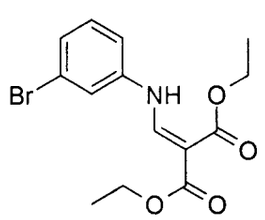
Los siguientes Intermediarios se prepararon mediante el procedimiento descrito en el Intermediario 20 a partir de los materiales de partida (SM) indicados.

Int.	Compuesto	Datos	SM
27	1-ciclopropil-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 384 (M+1) para $C_{15}H_{14}INO_3$ RMN ^1H (DMSO-d_6): 1,05 - 1,13 (m, 2H); 1,20 - 1,32 (m, 5H); 3,60 - 3,69 (m, 1H); 4,22 (q, *J*=7,07 Hz, 2H); 7,89 (d, *J*=8,84 Hz, 2H); 8,12 (dd, *J*=8,84, 2,02 Hz, 1H); 8,47 (d, *J*=2,02 Hz, 1H); 8,49 (s, 1H)	Intermediario 24 y ciclopropilamina
28	6-yodo-1-isopropil-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 386 (M+1) para $C_{15}H_{16}INO_3$ RMN ^1H (DMSO-d_6): 1,29 (t, J=7,07 Hz, 3H): 1,49 (d, J=6,57 Hz, 6H): 4,23 (q, J=7,07Hz, 2H): 5,00 - 5,10 (m, 1H): 7,80 (d, J=9,35 Hz, 1H): 8,07 (dd, J=9,09, 2,27 Hz, 1 H) 8,53 (d, J=2,02 Hz, 1H): 8,61 (s, 1H)	Intermediario 24 y propan-2-amina
29	1-(2-(dimetilamino)etil)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 415 (M+1) para $C_{16}H_{19}IN_2O_3$ RMN ^1H (DMSO-d_6) : 1,28 (t, *J*=7,20 Hz, 3H); 2,18 (s, 6H); 2,58 (t, *J*=5,94 Hz, 2H); 4,23 (q, *J*=7,24 Hz, 2H); 4,44 (t, *J*=5,81 Hz, 2H); 7,65 (d, *J*=8,84 Hz, 1H); 8,06 (dd, *J*=8,84, 2,27 Hz, 1H); 8,51 (d, *J*=2,02 Hz, 1H); 8,63 (s, 1H)	Intermediario 24 y 2-(N,N-dimetilamino) etanamina

Int.	Compuesto	Datos	SM
30	1-(2-hidroxietil)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 388 (M+1) para $C_{14}H_{14}INO_4$ RMN ^{1}H (DMSO-d_6): 1,28 (t, J=7,06 Hz, 3H); 3,63 - 3,76 (m, 2H); 4,22 (q, J=6,97 Hz, 2H); 4,36 - 4,46 (m, 2H); 5,02 (t, J=5,46 Hz, 1H); 7,67 (d, J=9,04 Hz, 1H); 8,04 (dd, J=9,04, 1,88 Hz, 1H); 8,51 (d, J=1,88 Hz, 1H); 8,59 (s, 1H)	Intermediario 24 y 2-aminoetanol
31	6-yodo-1-(1-metilazetidin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 413 (M+1) para $C_{16}H_{17}IN_2O_3$ RMN ^{1}H (DMSO-d_6): 1,29 (t, J=7,06 Hz, 3H); 2,31 (s, 3H); 3,25 - 3,39 (m, 2H); 3,85 (t, 2H); 4,25 (q, J=7,03 Hz, 2H); 5,01 - 5,16 (m, 1H); 7,45 (d, J=8,85 Hz, 1H); 8,03 (dd, J=8,85, 2,07 Hz, 1H); 8,50 (d, J=2,07 Hz, 1H); 8,60 (s, 1H)	Intermediario 24 y 1-metilazetidin-3-amina

Intermediario 32

{[(3-bromofenil)amino]metiliden}propanodioato de dietilo

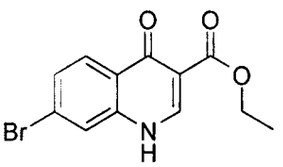


Una mezcla de 3-bromoanilina (10,0 g, 58,1 mmoles) y (etoximetiliden)propanodioato de dietilo (13,9 ml, 63,9 mmoles) se calentó hasta 110 °C durante 1 h. Tras completar la reacción, la mezcla de reacción se enfrió hasta la temperatura ambiente. El sólido obtenido se filtró y se secó para dar 16,0 g 78% de {[(3-bromofenil)amino]metiliden}propanodioato de dietilo.

RMN ^{1}H (400 MHz, $CDCl_3$): 1,37 (m, 6H), 4,25 (m, 4H), 7,05 (d, 1H), 7,25 (m, 2H), 8,44 (d, 1H), 10,95 (d, 1H).

Intermediario 33

7-bromo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo

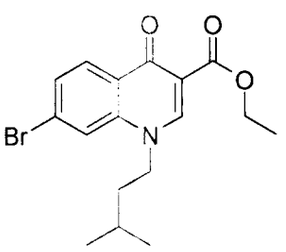


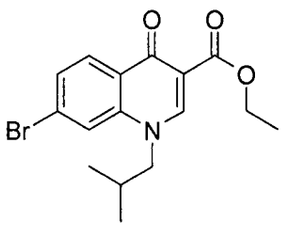
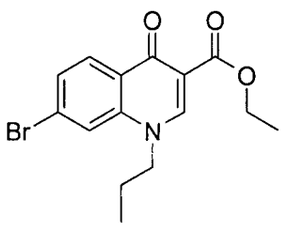
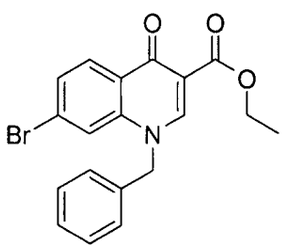
Se recogió Dowtherm (50 ml) en un matraz de fondo redondo de dos bocas (100 ml) y se calentó hasta 250 °C en un baño de arena. A esta temperatura se añadió {[(3-bromofenil)amino]metiliden}propanodioato de dietilo (Intermediario 32, 10,0 g, 29,2 mmoles), y la temperatura de la reacción se mantuvo otra 1 h a 250 °C. Tras completar la reacción, la mezcla de reacción se enfrió hasta la temperatura ambiente, se recogió un sólido blanco mediante filtración y se secó para producir 6,0 g (69,3%) de 7-bromo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo.

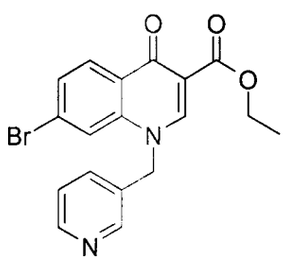
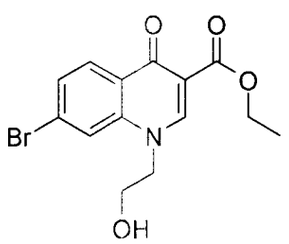
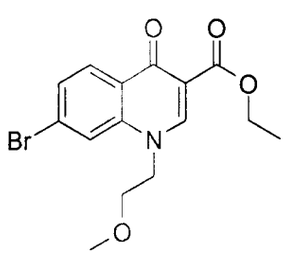
RMN ^{1}H (400 MHz, DMSO-d_6): 1,07 (t, 3H), 1,22 (s, 12H), 3,16 (q, 2H), 7,29 (m, 1H), 7,31 (d, 2H), 7,61 (s, 1H), 7,88 (s, 1H), 8,31 (s, 1H), 8,65 (s, 1H), 9,44 (s, 1H).

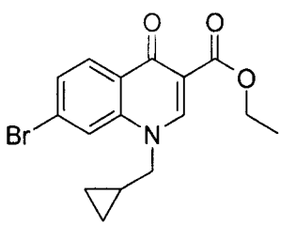
Intermediarios 34-41

Los siguientes Intermediarios se prepararon mediante el procedimiento descrito en el Intermediario 9 a partir de los materiales de partida (SM) indicados.

Int.	Compuesto	Datos	SM
34	7-bromo-1-(3-metilbutil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	RMN ^{1}H (400 MHz, $CDCl_3$): 1,04 (d, 6H), 1,41 (t, 3H), 1,78 (q, 3H), 4,14 (q, 2H), 4,40 (q, 2H), 7,52 (s, 1H), 7,56 (d, 1H), 8,39 (s, 1H), 8,42 (d, 1H).	Intermediario 33 y 1-bromo-3-metilbutano

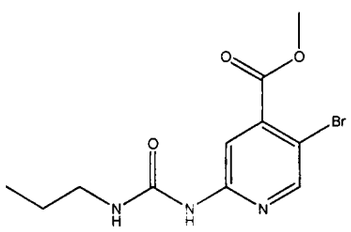
Int.	Compuesto	Datos	SM
35	7-bromo-1-(2-metilpropil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	RMN ^{1}H (400 MHz, $CDCl_3$): 1,02 (d, 6H), 1,39 (t, 3H), 2,27 (m, 1H), 3,93 (d, 2H), 4,41 (q, 2H), 4,53 (d, 2H), 8,40 (d, 2H).	Intermediario 33 y 1-bromo-2-metilpropano
36	7-bromo-4-oxo-1-propil-1,4-dihidroquinolin-3-carboxilato de etilo 	RMN ^{1}H (400 MHz, DMSO-d_6): 0,90 (t, 3H), 1,75 (q, 2H), 4,24 (q, 2H), 4,35 (q, 2H), 7,63 (d, 1H), 8,07 (s, 1H), 8,14 (d, 1H), 8,66 (s, 1H).	Intermediario 33 y 1-bromopropano
37	1-bencil-7-bromo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	RMN ^{1}H (400 MHz, DMSO-d_6): 1,24 (t, 3H), 2,83 (s, 1H), 4,22 (q, 2H), 4,57 (s, 1H), 5,67 (s, 2H), 7,22 (m, 2H), 7,33 (m, 2H), 7,56 (m, 2H), 7,85 (s, 1H), 8,12 (d, 1H), 8,86 (s, 1H).	Intermediario 33 y bromuro de bencilo

Int.	Compuesto	Datos	SM
38	7-bromo-4-oxo-1-(piridin-3-ilmetil)-1,4-dihidroquinolin-3-carboxilato de etilo 	RMN ^{1}H (400 MHz, DMSO-d_6): 1,29 (t, 3H), 4,25 (q, 2H), 5,74 (s, 2H), 7,37 (d, 1H), 7,61 (d, 2H), 7,91 (s, 1H), 8,14 (d, 1H), 8,42 (d, 1H), 8,58 (d, 1H), 8,91 (s, 1H).	Intermediario 33 y 3-(bromometil)piridina
39	7-bromo-1-(2-hidroxietil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	RMN ^{1}H (400 MHz, DMSO-d_6): 1,28 (t, 3H), 3,71 (d, 2H), 4,23 (q, 2H), 4,42 (s, 2H), 4,48 (s, 2H), 4,99 (m, 1H), 7,62 (d, 1H), 8,10 (s, 1H), 8,14 (d, 1H), 8,56 (s, 1H).	Intermediario 33 y 2-bromoetanol
40	7-bromo-1-(2-metoxietil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	RMN ^{1}H (400 MHz, DMSO-d_6): 1,33 (t, 3H), 3,22 (s, 3H), 3,65 (m, 2H), 4,22 (q, 2H), 4,58 (m, 2H), 7,62 (d, 1H), 8,15 (m, 2H), 8,49 (s, 1H).	Intermediario 33 y 1-bromo-2-metoxi-etano

Int.	Compuesto	Datos	SM
41	7-bromo-1-(ciclopropilmetil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	RMN ^{1}H (400 MHz, $CDCl_3$): 0,48 (d, 2H), 0,79 (m, 2H), 1,39 (m, 1H), 1,42 (t, 3H), 3,98 (d, 2H), 4,42 (q, 2H), 7,53 (d, 1H), 7,65 (s, 1H), 8,40 (d, 1H), 8,54 (s, 1H).	Intermediario 33 y (bromometil)ciclopropilo

Intermediario 42

5-bromo-2-(3-propilureido)isonicotinato de metilo



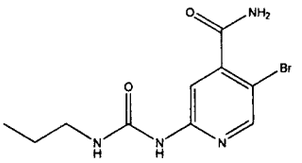
Se disolvió 2-amino-5-bromoisonicotinato de metilo (100 g, 433 mmoles) en cloroformo (600 ml) y se colocó en un tubo cerrado herméticamente de 1 l. Entonces se añadió isocianato de propilo (122,5 ml, 1,29 moles). El reactor se calentó a 55°C durante 72 h, en cuyo momento se determinó que la reacción estaba terminada. La mezcla se enfrió entonces hasta la temperatura ambiente, se concentró a presión reducida, y el sólido se disolvió en acetato de etilo: tetrahidrofurano 2:1 (3 l). Esta disolución se lavó con agua (2 × 200 ml), y el agua se volvió a extraer con acetato de etilo (300 ml). Las capas orgánicas se secaron entonces con sulfato de sodio, se filtraron, y se concentraron, produciendo 129g (95%) de 5-bromo-2-(3-propilureido)isonicotinato de metilo como un sólido amarillo oscuro.

MS (ESP): 316,1 (MH^+) para $C_{11}H_{14}BrN_3O_3$

RMN ^{1}H (300 MHz, $CDCl_3$): δ 0,88 (t, 3H), 1,45 (m, 2H), 3,11 (m, 2H), 3,90 (s, 3H), 7,21 (bt, 1H), 8,02 (s, 1H), 8,46 (s, 1H), 9,40 (s, 1H)

Intermediario 43

5-bromo-2-(3-propilureido)isonicotinamida



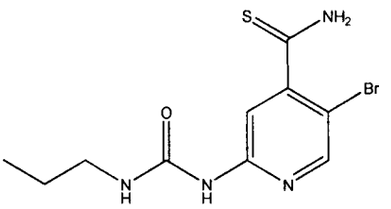
Una disolución de 5-bromo-2-(3-propilureido)isonicotinato de metilo (Intermediario 42, 128 g, 405 mmoles) y amoníaco 7N en metanol (1 l) se dejó agitar a temperatura ambiente durante 3 d. Después se detuvo la agitación de la reacción, y los sólidos se dejaron sedimentar. El precipitado se filtró entonces a vacío, se enjuagó con metanol (2 × 500 ml), y después se secó en la bomba de alto vacío toda la noche, produciendo 123 g (cuant.) de 5-bromo-2-(3-propilureido)isonicotinamida como un sólido blanco.

MS (ESP): 301,1 (MH^+) para $C_{10}H_{13}BrN_4OS$

RMN ^1H (300 MHz, DMSO-d_6): δ 0,88 (t, 3H), 1,46 (m, 2H), 3,18 (q, 2H), 7,41 (bs, 1H), 7,58 (s, 1H), 7,78 (bs, 1H), 8,08 (bs, 1H), 8,33 (s, 1H), 9,31 (s, 1H)

Intermediario 44

5-bromo-2-(3-propilureido)piridin-4-carbotioamida



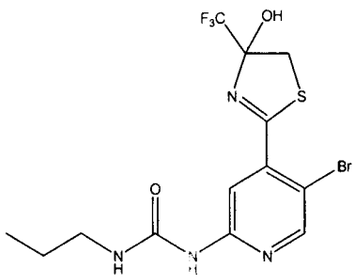
Una mezcla suspendida de 5-bromo-2-(3-propilureido)isonicotinamida (Intermediario 43, 123 g, 407 mmoles), el reactivo de Lawesson (131,6 g, 326 mmoles) y tetrahidrofurano (1,55 l) se agitó a 70°C durante 18 h. La agitación se detuvo, y se dejó sedimentar un precipitado amarillo brillante. El precipitado se filtró entonces a vacío y se lavó con metil-terc-butiléter (2 × 500 l). Este sólido se secó entonces en el horno de vacío a 50°C durante 12 horas para dar 50 g de producto sólido. El licor madre se concentró, y el residuo se suspendió en tolueno (300 ml). El sólido así obtenido se filtró y se combinó con el sólido previo. Lo combinado sumó 110 g (85%) de 5-bromo-2-(3-propilureido)piridin-4-carbotioamida como un sólido blanquecino.

MS (ESP): 317,2 (MH^+) para $C_{10}H_{13}BrN_4OS$

RMN ^1H (300 MHz, $CDCl_3$): δ 0,88 (t, 3H), 1,42 (m, 2H), 3,13 (m, 2H), 7,38 (s, 1H), 7,50 (s, 1H), 8,28 (s, 1H), 9,25 (s, 1H), 9,80 (s, 1H), 10,28 (s, 1H)

Intermediario 45

1-(5-bromo-4-(4-hidroxi-4-(trifluorometil)-4,5-dihidrotiazol-2-il)piridin-2-il)-3-propilurea



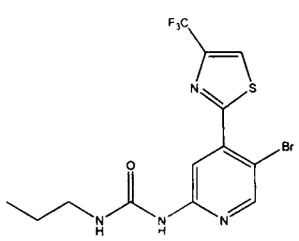
Una suspensión de 5-bromo-2-(3-propilureido)piridin-4-carbotioamida (Intermediario 44, 100 g, 315 mmoles), 3-bromo-1,1,1-trifluoroacetona (64 ml, 630 mmoles) en acetonitrilo (1,5 l) se calentó a 80°C durante 20 horas. La disolución se enfrió entonces y se concentró a presión reducida. Esto dio un aceite naranja que se llevó a la siguiente reacción sin purificación adicional.

MS (ESP): 426,9 (MH^+) para $C_{13}H_{14}BrF_3N_4O_2S$

RMN ^1H (300 MHz, DMSO-d_6): δ 0,88(t, 3H), 1,48 (m, 2H), 3,11 (m, 2H), 3,62 (d, 1H), 3,92 (d, 1H), 7,30 (bs, 1H), 7,98 (s, 1H), 8,46 (s, 1H), 9,42 (s, 1H).

Intermediario 46

1-(5-bromo-4-(4-(trifluorometil)tiazol-2-il)piridin-2-il)-3-propilurea



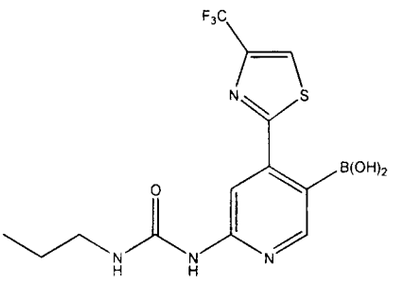
Una disolución de 1-(5-bromo-4-(4-hidroxi-4-(trifluorometil)-4,5-dihidrotiazol-2-il)piridin-2-il)-3-propilurea (Intermediario 45, 315 mmoles) y trietilamina (217 ml, 1,57 moles) en tetrahidrofurano (1,3 l) se preparó y se agitó a temperatura ambiente. Se añadió gota a gota cloruro de metanosulfonilo (61 ml, 787 mmoles) en el transcurso de 1 h. Esta mezcla se agitó a 26°C durante 4 h. Entonces la agitación se detuvo, y los sólidos se filtraron, se lavaron con tetrahidrofurano (3 × 200 ml), y se desecharon. Las capas tetrahidrofuránicas combinadas se concentraron hasta un semisólido amarillo viscoso, que entonces se trituró con metanol (1 l). El sólido se filtró y se lavó con metanol (2 × 300 ml). El sólido se secó entonces en el horno de vacío a 50°C durante 12 h. Esto dio 99,4g (76%) de 1-(5-bromo-4-(4-(trifluorometil)tiazol-2-il)piridin-2-il)-3-propilurea como un sólido blanquecino.

MS (ESP): 409,1 (MH^+) para $C_{13}H_{12}BrF_3N_4OS$

RMN ^1H (300 MHz, DMSO-d_6): δ 0,89 (t, 3H), 1,47 (m, 2H), 3,16 (m, 2H), 7,25 (s, 1H), 8,41 (s, 1H), 8,57 (s, 1H), 8,82 (s, 1H), 9,39 (s, 1H).

Intermediario 47

Ácido 6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-ilborónico



Una suspensión de 1-(5-bromo-4-(4-(trifluorometil)tiazol-2-il)piridin-2-il)-3-propilurea (Intermediario 46, 50 g, 123 mmoles) en tetrahidrofurano (1,25 l) se preparó y se agitó a -50°C. Se añadió gota a gota cloruro de isopropilmagnesio 2,0M en tetrahidrofurano (183 ml, 368 mmoles) durante 45 min, de forma que la temperatura nunca subió por encima de -35°C. La mezcla de reacción se agitó otra hora más a -40°C, y después se enfrió hasta -78°C. Entonces se añadió gota a gota n-butil-litio 2,5M en hexanos (295 ml, 735 mmoles) a la disolución de la reacción en el transcurso de 1 h, de forma que la temperatura nunca subió por encima de -65°C. Esta mezcla se dejó reaccionar entonces a -78°C durante 1,5 h. Se añadió metóxido de boro (164 ml, 1,47 moles) en 1 porción, y se eliminó el baño de frío. La reacción se dejó calentar hasta la temperatura ambiente, y se agitó durante 1 h. Entonces se añadió lentamente ácido clorhídrico 3N (500 ml), para minimizar la espumación, y la reacción se agitó a temperatura ambiente durante 30 min de forma que todos los sólidos se disolvieran. La reacción se concentró para eliminar el tetrahidrofurano, y se añadió agua (1 l). La disolución se basificó hasta pH 10 con hidróxido de sodio al 24%, y el volumen total se incrementó hasta 2 l con agua. La disolución acuosa se extrajo con metil-terc-butiléter (3 × 650 ml). Las capas se separaron lentamente. Las capas orgánicas se combinaron y se extrajeron con hidróxido de sodio al 5% (100 ml). Las fases acuosas se combinaron y se acidificaron hasta pH 5,5 con ácido clorhídrico 6N, momento en el que se formó una suspensión. Esta suspensión se extrajo con acetato de etilo: THF 2:1 (5 × 400 ml), asegurando que todo el sólido se disolvió en la fase orgánica. Las fases orgánicas se combinaron y se lavaron nuevamente con agua (1 l). Los orgánicos se concentraron y se trituraron con metil-terc-butiléter (1 l). El sólido obtenido se

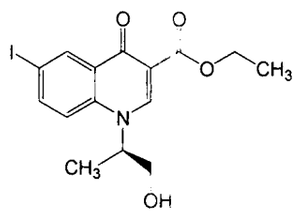
secó en un horno de vacío a 50°C durante 18 h. Esto dio 25 g (55%) de ácido 6-(3-propilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-ilborónico como un sólido blanquecino.

MS (ESP): 375,0 (MH^+) para $C_{13}H_{14}BF_3N_4O_3S$

RMN ^1H (300 MHz, DMSO-d_6): δ 0,90 (t, 3H), 1,45-1,52 (m, 2H), 3,07-3,16 (m, 2H), 7,81 (bt, 1H), 7,91 (s, 1H), 8,20 (br, 2H), 8,31 (d, 1H), 8,65 (m, 1H), 9,32 (s, 1H).

Intermediario 48

1-[(1*R*)-2-hidroxi-1-metiletil]-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo



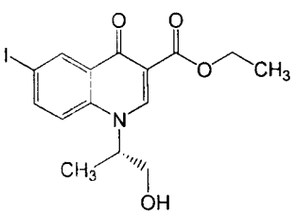
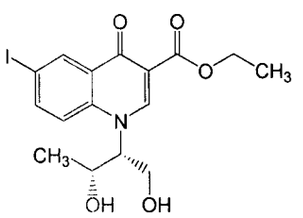
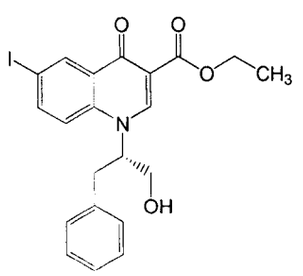
A una disolución de 3-(dimetilamino)-2-(2-fluoro-5-yodobenzoil)acrilato de etilo (Intermediario 24, 1 g, 2,56 mmoles) disuelto en THF (10 ml) se añadió (*R*)-2-aminopropan-1-ol (300 mg, 2,56 mmoles). La mezcla de reacción se agitó a 60 °C durante 2 h. La mezcla de reacción se concentró a presión reducida, y el residuo resultante se suspendió en DMF (10 ml). Se añadió carbonato de potasio (1,06 g, 7,67 mmoles, 3 equiv.), y la mezcla de reacción se agitó a 70 °C durante 18 h. La mezcla de reacción se enfrió hasta la temperatura ambiente, y se paralizó con HCl 1 N. El precipitado que se formó se recogió mediante filtración, se lavó con agua y hexanos para proporcionar (*R*)-1-(1-hidroxipropan-2-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo (446 mg, 39 %).

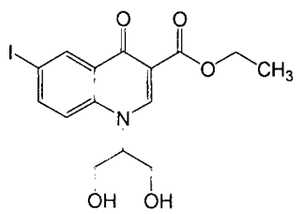
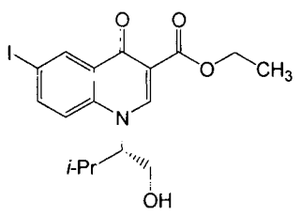
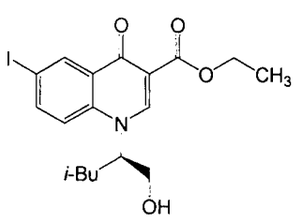
MS (ESP): 402 para $C_{15}H_{16}INO_4$.

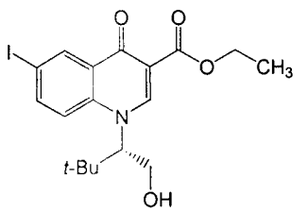
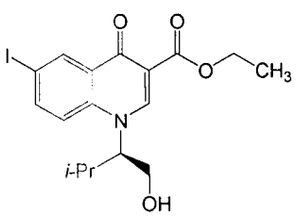
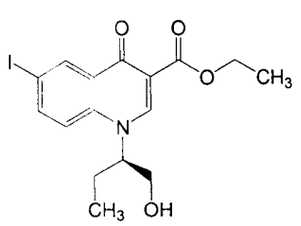
RMN (d_6-DMSO) δ 8,65 (s, 1H), 8,53 (d, 1H), 8,07 (dd, 1H), 7,82 (d, 1H), 5,23 (s, 1H), 5,05-4,98 (m, 1H), 4,27-4,2 (m, 2H), 3,74.

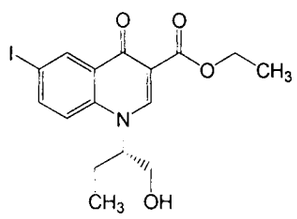
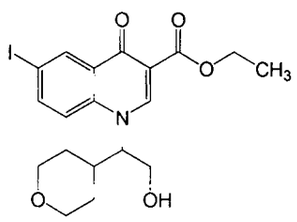
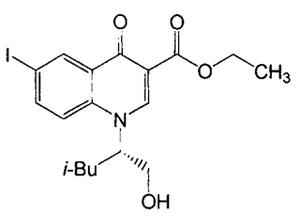
Intermediarios 49-68

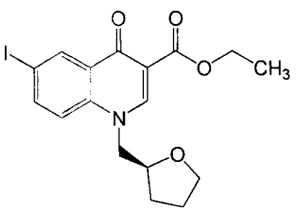
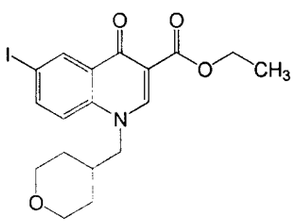
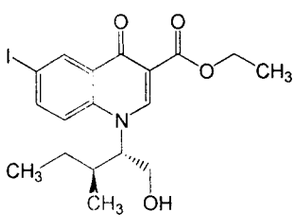
Los siguientes Ejemplos se prepararon mediante el procedimiento descrito en el Intermediario 48 a partir del material de partida indicado.

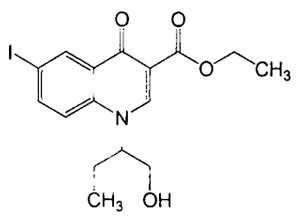
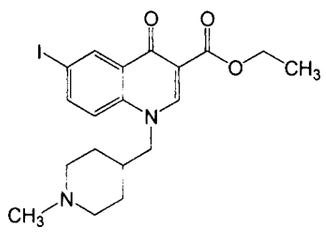
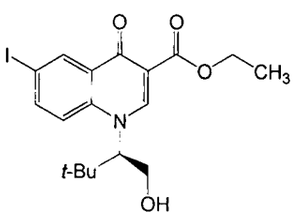
Int.	Compuesto	Datos	SM
49	(*S*)-1-(1-hidroxipropan-2-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 402 para $C_{15}H_{16}INO_4$ RMN (d_6-DMSO) δ 8,65 (s, 1H), 8,54 (d, 1H), 8,07 (dd, 1H), 7,82 (d, 1H), 5,19 (s, 1H), 5,03-4,98 (m, 1H), 4,27-4,2 (m, 2H), 3,74 (d, 2H), 1,48 (d, 3H), 1,28 (t, 3H)	Intermediario 24 y (*S*)-2-aminopropan-1-ol
50	1-((2*R*,3*R*)-1,3-dihidroxibutan-2-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 432 para $C_{16}H_{16}INO_5$ RMN (d_6-DMSO) δ 8,88 (s, 1H), 8,52 (d, 1H), 8,03 (dd, 1H), 7,84 (d, 1H), 5,2 (s, 2H), 4,8-4,76 (m, 1H), 4,26-4,19 (m, 2H), 4,25-4,14 (m, 2H), 3,92-3,79 (m, 2H), 1,27 (t, 3H), 1,1 (d, 3H)	Intermediario 24 y (2*R*,3*R*)-2-aminobutano-1,3-diol
51	(*S*)-1-(1-hidroxi-3-fenilpropan-2-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 478 para $C_{21}H_{20}INO_4$ RMN (d_6-DMSO) δ 8,7 (s, 1H), 8,44 (d, 1H), 7,98 (dd, 1H), 7,78 (d, 1H), 7,23-7,16 (m, 5H), 7,14-7,09 (m, 1H), 5,38-5,27 (m, 2H), 4,29-4,18 (m, 2H), 3,81 (d, 2H), 3,27-3,15 (m, 2H), 1,29 (t, 3H)	Intermediario 24 y (*S*)-2-amino-3-fenilpropan-1-ol

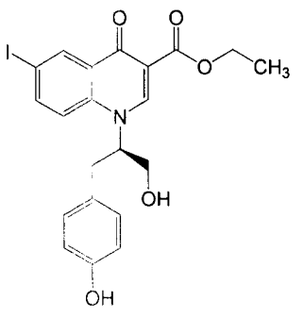
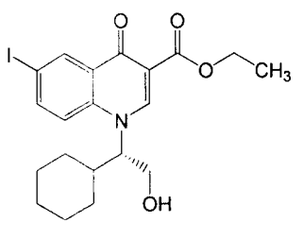
Int.	Compuesto	Datos	SM
52	1-(1,3-dihidroxipropan-2-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 418 para $C_{15}H_{16}INO_5$ RMN (d_6-DMSO) δ 8,65 (s, 1H), 8,53 (d, 1H), 8,07 (dd, 1H), 7,82 (d, 1H), 5,23 (s, 1H), 5,04-4,98 (m, 1H), 4,27-4,2 (m, 2H), 3,74 (d, 2H), 1,48 (d, 3H), 1,28 (t, 3H)	Intermediario 24 y 2-aminopropan-1,3-diol
53	(*S*)-1-(1-hidroxi-3-metilbutan-2-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 430 para $C_{17}H_{20}INO_4$ RMN (d_6-DMSO) δ 8,69 (s, 1H), 8,53 (d, 1H), 8,04 (dd, 1H), 7,9 (d, 1H), 5,25-5,15 (m, 1H), 4,65-4,58 (m, 1H), 4,26-4,19 (m, 2H), 3,92-3,86 (m, 1H), 3,77-3,72 (m, 1H), 2,4-2,3 (m, 1H), 1,27 (t, 3H), 1,1 (d, 3H), 0,71 (d, 3H)	Intermediario 24 y (*S*)-2-amino-3-metilbutan-1-ol
54	(*R*)-1-(1-hidroxi-4-metilpentan-2-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 444 para $C_{18}H_{22}INO_4$ RMN (d_6-DMSO) δ 8,6 (s, 1H), 8,53 (d, 1H), 8,07 (dd, 1H), 7,89 (d, 1H), 5,23 (s, 1H), 4,94 (s, 1H), 4,26-4,19 (m, 2H), 3,71 (d, 2H), 1,87-1,77 (m, 1H), 1,74-1,69 (m, 1H), 1,46-1,38 (m, 1H), 1,27 (t, 3H), 0,89 (d, 3H), 0,84 (t, 3H)	Intermediario 24 y (*R*)-2-amino-4-metilpentan-1-ol

Int.	Compuesto	Datos	SM
55	(*S*)-1-(1-hidroxi-3,3-dimetilbutan-2-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 443 para $C_{18}H_{22}INO_4$ RMN 1H (d_6-DMSO) δ 8,62 (s, 1H), 8,53 (s, 1H), 8,01 (s, 1H), 5,07-4,99 (m, 1H), 4,92-4,85 (m, 1H), 4,26-4,20 (m, 2H), 4,02-3,95 (m, 2H), 1,28 (t, 3H), 0,95 (s, 9H)	Intermediario 24 y (*S*)-2-amino-3,3-dimetilbutan-1-ol
56	(*R*)-1-(1-hidroxi-3-metilbutan-2-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 430 para $C_{17}H_{20}INO_4$ RMN 1H (d_6-DMSO) δ 8,69 (s, 1H), 8,53 (d, 1H), 8,04 (dd, 1H), 7,91 (t, 1H), 4,65-4,59 (m, 1H), 4,26-4,19 (m, 2H), 3,92-3,86 (m, 1H), 3,76-3,72 (m, 1H), 2,31-2,21 (m, 1H), 1,27 (t, 3H), 1,1 (d, 3H), 0,71 (d, 3H)	Intermediario 24 y (*R*)-2-amino-3-metilbutan-1-ol
57	(*R*)-1-(1-hidroxi-3-metilbutan-2-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 416 para $C_{16}H_{18}INO_4$ RMN (d_6-DMSO) δ 8,62 (s, 1H), 8,53 (s, 1H), 8,03 (dd, 1H), 7,85 (d, 1H), 4,83 (s, 1H), 4,26-4,19 (m, 2H), 3,77-3,73 (m, 2H), 1,99-1,83 (m, 2H), 1,28 (t, 3H), 0,84 (t, 3H)	Intermediario 24 y (*R*)-2-aminobutan-1-ol

Int.	Compuesto	Datos	SM
58	(*S*)-1-(1-hidroxi-3-metilbutan-2-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 416 para $C_{16}H_{18}INO_4$ RMN (d_6-DMSO) δ 8,62 (s, 1H), 8,53 (s, 1H), 8,06 (d, 1H), 7,85 (d, 1H), 4,83 (s, 1H), 4,25-4,2 (m, 2H), 3,78-3,71 (m, 2H), 1,99-1,84 (m, 2H), 1,27 (t, 3H), 0,84 (t, 3H)	Intermediario 24 y (*S*)-2-aminobutan-1-ol
59	1-(2-hidroxi-1-(tetrahidro-2H-piran-4-il)etil)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 472 para $C_{19}H_{22}INO_5$ [RMN (d_6-DMSO) δ 8,75 (s, 1H), 8,52 (s, 1H), 8,05 (d, 1H), 7,94 (d, 1H), 5,22-5,17 (m, 1H), 4,75 (s, 1H), 4,27-4,2 (m, 2H), 3,91-3,88 (m, 2H), 3,81-3,78 (m, 2H), 3,28-3,16 (m, 1H), 2,27-2,23 (m, 1H), 1,77-1,72 (m, 1H), 1,59-1,52 (m, 1H), 1,28 (t, 3H), 1,17 (t, 3H), 1,1-1,02 (1H)	Intermediario 24 y 2-amino-2-(tetrahidro-2H-piran-4-il)etanol
60	(*S*)-1-(1-hidroxi-3,3-dimetilbutan-2-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 444 para $C_{18}H_{22}INO_5$ RMN 1H (d_6-DMSO) δ 8,69 (s, 1H), 8,53 (d, 1H), 8,07 (dd, 1H), 7,89 (d, 1H), 4,95-4,91 (m, 1H), 4,26-4,19 (m, 2H), 3,71 (d, 2H), 1,86-1,8 (m, 1H), 1,75-1,72 (m, 1H), 1,46-1,39 (m, 1H), 1,27 (t, 3H), 0,89 (d, 3H), 0,84 (d, 3H)	Intermediario 24 y (*S*)-2-amino-4-metilpentan-1-ol

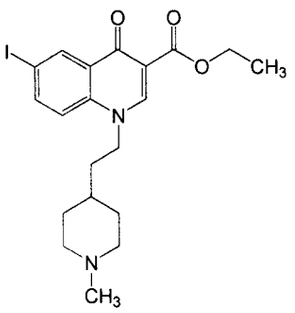
Int.	Compuesto	Datos	SM
61	(*S*)-6-yodo-4-oxo-1-((tetrahidrofuran-2-il)metil)-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 428 para $C_{17}H_{18}INO_4$ RMN (d_6-DMSO) δ 8,62 (s, 1H), 8,5 (d, 1H), 8,06 (dd, 1H), 7,74 (d, 1H), 4,6 (dd, 1H), 4,3-4,27 (m, 1H), 4,25-4,21 (m, 2H), 4,17-4,12 (m, 1H), 3,82-3,75 (m, 1H), 3,65-3,61 (m, 1H), 2,06-1,9 (m, 1H), 1,87-1,8 (m, 2H), 1,63-1,57 (m, 1H), 1,28 (t, 3H)	Intermediario 24 y (*S*)-(tetrahidrofuran-2-il)metanamina
62	6-yodo-4-oxo-1-((tetrahidro-2H-piran-4-il)metil)-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 442d para $C_{18}H_{20}INO_4$ RMN (d_6-DMSO) δ 8,66 (s, 1H), 8,51 (d, 1H), 8,07 (dd, 1H), 7,74 (d, 1H), 4,33-4,19 (m, 4H), 3,84 (d, 2H), 3,23-3,15 (m, 2H), 2,08-2,02 (m, 1H), 1,42-1,37 (m, 4H), 1,28 (t, 3H)	Intermediario 24 y (tetrahidro-2H-piran-4-il)metanamina
63	1-((2*S*,3*S*)-1,3-dihidroxipentan-2-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 444 para $C_{18}H_{22}INO_4$ RMN ^{1}H (d_6-DMSO) δ 8,69 (S, 1H), 8,53 (d, 1H), 8,05 (d, 1H), 7,89 (d, 1H), 5,16-5,13 (m, 1H), 4,68 (s, 1H), 4,26-4,19 (m, 2H), 3,94-3,87 (m, 1H), 3,78-3,72 (m, 1H), 2,13-2,08 (m, 1H), 1,28 (t, 3H), 1,16-0,95 (m, 2H), 1,07 (d, 2H), 0,73 (t, 3H)	Intermediario 24 y (2*S*,3*S*)-2-amino-3-metilpentan-1-ol

Int.	Compuesto	Datos	SM
64	1-(1-hidroxibutan-2-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 416 para $C_{16}H_{18}INO_4$ RMN (d_6-DMSO) δ 8,62 (s, 1H), 8,53 (s, 1H0, 8,06 (dd, 1H), 7,85 (d, 1H), 5,18-5,13 (m, 1H), 4,83 (s, 1H), 4,27-4,2 (m, 2H), 3,76-3,72 (m, 2H), 1,97-1,82 (m, 2H), 1,28 (t, 3H), 0,84 (t, 3H)	Intermediario 24 y 2-aminobutan-1-ol
65	6-yodo-1-((1-metilpiperidin-4-il)metil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 455 para $C_{19}H_{23}IN_2O_3$ RMN (d_6-DMSO) δ 8,65 (s, 1H), 8,5 (d, 1H), 8,07 (dd, 1H), 7,71 (d, 1H), 4,27-4,19 (m, 2H), 2,74,2,7 (m, 2H), 2,09 (s, 3H), 1,72-1,66 (m, 3H), 1,45-1,42 (m, 2H), 1,28 (t, 3H)	Intermediario 24 y (1-metilpiperidin-4-il)metanamina
66	(*R*)-1-(1-hidroxi-3,3-dimetilbutan-2-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 444 para $C_{18}H_{22}INO_4$ RMN (d_6-DMSO) δ 8,62 (s, 1H), 8,53 (s, 1H), 8,01 (s, 2H), 5,08-5,04 (m, 1H), 4,89-4,84 (m, 1H), 4,26-4,22 (m, 2H), 4,02-3,98 (m, 2H), 1,28 (t, 3H), 0,95 (s, 9H)	Intermediario 24 y (*R*)-2-amino-3,3-dimetilbutan-1-ol

Int.	Compuesto	Datos	SM
67	(*R*)-1-(1-hidroxi-3-(4-hidroxifenil)propan-2-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 494 para $C_{21}H_{20}INO_5$ RMN (d_6-DMSO) δ 8,64 (s, 1H), 8,45 (d, 1H), 7,99 (dd, 1H), 7,76 (d, 1H), 6,98 (d, 2H), 6,56 (d, 2H), 5,18 (s, 1H), 4,29-4,19 (m, 2H), 3,78 (d, 2H), 3,13-3,09 (m, 2H), 1,29 (t, 3H)	Intermediario 24 y (*R*)-4-(2-amino-3-hidroxipropil)fenol
68	(*S*)-1-(1-ciclohexil-2-hidroxietil)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 470 para $C_{20}H_{24}INO_4$ RMN (d_6-DMSO) δ 8,71 (s, 1H), 8,53 (d, 1H), 8,04 (dd, 1H), 7,9 (t, 1H), 5,15 (s, 1H), 4,68 (s, 1H), 4,27-4,2 (m, 2H), 3,92-3,89 (m, 1H), 3,77-3,74 (m, 1H), 1,98-1,9 (m, 2H), 1,82-1,74 (m, 1H), 1,61-1,55 (m, 2H), 1,28 (t, 3H), 1,25-1,2 (m, 2H), 1,09-1,05 (m, 2H), 0,92-0,86 (m, 1H)	Intermediario 24 y (*S*)-2-amino-2-ciclohexil-etanol

Intermediario 69

6-yodo-1-[2-(1-metilpiperidin-4-il)etil]-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo



5

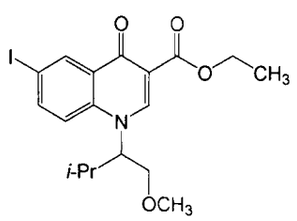
A una disolución de 3-(dimetilamino)-2-(2-fluoro-5-yodobenzoil)acrilato de etilo (Intermediario 24, 1 g, 2,56 mmoles) disuelto en THF (5,5 ml) se añadió 2-(1-metilpiperidin-4-il-etanamina (0,406 ml, 2,56 mmoles). La mezcla de reacción se agitó a 60 °C durante 2 h. Se añadió carbonato de potasio (1,06 g, 7,67 mmoles), y la reacción se agitó durante 18 h y se enfrió hasta la temperatura ambiente. La reacción se paralizó con HCl 1 N, y se repartió entre diclorometano (10 ml) y agua (20 ml). La capa acuosa se extrajo con diclorometano (2x10 ml), y los orgánicos se secaron sobre sulfato de sodio y se concentraron para dar 6-yodo-1-(2-(1-metilpiperidin-4-il)etil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo como un sólido amarillo claro (1,08 g, 90%).

MS (ESP): 469 para $C_{20}H_{25}IN_2O_4$.

RMN (d_6-DMSO) δ 8,7 (s, 1H), 8,5 (d, 1H), 8,089 (dd, 1H), 7,6 (d, 1H), 4,4-4,35 (m, 1H), 4,26-4,19 (m, 2H), 2,75-2,7 (m, 2H), 2,12 (s, 3H), 1,83-1,74 (m, 2H), 1,69-1,61 (m, 4H), 1,28 (t, 3H), 1,25-1,13 (m, 2H).

Intermediario 70

6-yodo-1-[1-(metoximetil)-2-metilpropil]-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo



A una disolución de 3-(dimetilamino)-2-(2-fluoro-5-yodobenzoil)acrilato de etilo (Intermediario 24, 1 g, 2,56 mmoles) disuelto en THF (10 ml) se añadió hidrocloruro de 1-metoxi-3-metilbutan-2-amina (366 mg, 2,38 mmoles), seguido de carbonato de potasio. La mezcla de reacción se agitó a 60 °C durante 2 d. La mezcla de reacción se concentró a presión reducida, y el residuo se resuspendió en DMF (10 ml). Se añadió carbonato de potasio (978 mg, 7,08 mmoles), y la mezcla de reacción se agitó a 70 °C durante 2 h. La mezcla de reacción se enfrió hasta la temperatura ambiente, y se paralizó con HCl 1 N. La mezcla de reacción se repartió entre agua (20 ml) y acetato de etilo (20 ml). La capa acuosa se extrajo con acetato de etilo, y los orgánicos se secaron y se concentraron para proporcionar 6-yodo-1-(1-metoxi-3-metilbutan-2-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo (623 mg, 60 %).

MS (ESP): 444 para $C_{18}H_{22}INO_4$.

RMN (d_6-DMSO) δ 8,69 (s, 1H), 8,53 (d, 1H), 8,05 (d, 1H), 7,94 (d, 1H), 4,83-4,78 (m, 1H), 4,26-4,2 (m, 2H), 3,9-3,74 (m, 1H), 3,71-3,68 (m, 1H), 3,46-3,4 (m, 1H), 2,3-2,26 (m, 1H), 1,28 (t, 3H), 1,11 (d, 3H), 0,92-0,85 (m, 2H), 0,71 (d, 3H).

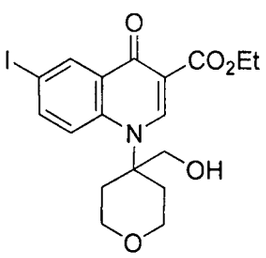
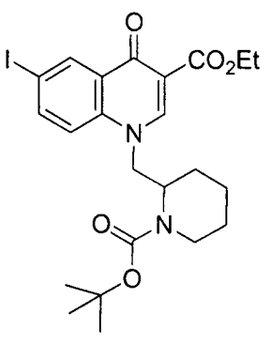
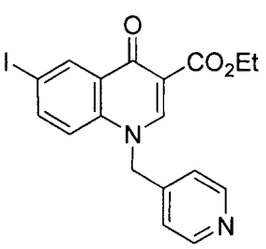
Intermediarios 71-77

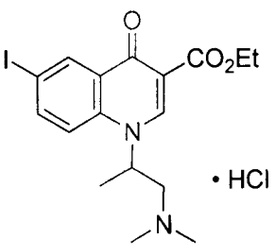
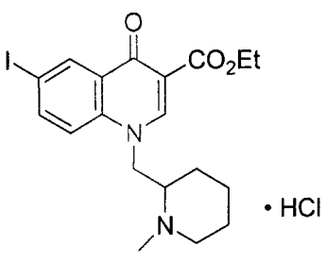
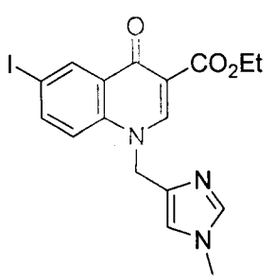
Los siguientes compuestos se prepararon según cualquiera de los procedimientos descritos más abajo a partir de los materiales de partida indicados.

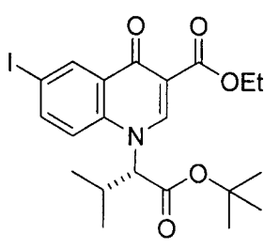
Procedimientos Generales

Procedimiento A: (Z)-3-(dimetilamino)-2-(2-fluoro-5-yodobenzoil)acrilato de etilo (Intermediario 24, eq, 2,5 mmoles) y la amina apropiada (1,1-1,2 eq) se diluyeron con THF (10 ml) y se calentaron hasta 60 °C durante 1 h. Tras enfriar hasta RT, la mezcla se concentró *a vacío*. Se añadieron carbonato de potasio (3 eq) y DMF (5 ml), y la mezcla se calentó entonces hasta 70 °C toda la noche. La mezcla se enfrió hasta 0 °C y se acidificó hasta aprox. pH 4 con HCl 1 N ac. El sólido resultante se recogió y se usó sin purificación adicional.

Procedimiento B: (Z)-3-(dimetilamino)-2-(2-fluoro-5-yodobenzoil)acrilato de etilo (Intermediario 24, 1 eq, 2,5 mmoles) y la sal de hidrocloruro de la amina apropiada (1,1-1,2 eq) se diluyeron con THF (10 ml). Se añadió carbonato de potasio (1,2 eq), y la mezcla se calentó hasta 60 °C durante 1 h. Tras enfriar hasta la temperatura ambiente, la mezcla se concentró *a vacío*. Se añadieron carbonato de potasio adicional (3 eq) y DMF (5 ml), y la mezcla se calentó entonces hasta 70 °C toda la noche. La mezcla se enfrió hasta 0 °C, y se acidificó hasta aprox. pH 4 con HCl 1 N ac. El sólido resultante se recogió y se usó sin purificación adicional.

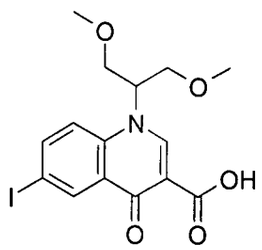
Int.	Compuesto	Datos	SM
71	1-(4-(hidroximetil)tetrahidro-2H-piran-4-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	LC/MS (ES^+)[$(M+H)^+$]: 458 para $C_{18}H_{20}INO_5$ RMN (DMSO-d_6): δ8,71 (s, 1H); 8,57 (d, 1H); 8,05 (m, 1H); 7,94 (dd, 1H); 5,36 (br s, 1H); 4,23 (q, 2H); 4,17 (s, 2H); 3,68 (m, 4H); 2,35 (m, 4H); 1,27 (t, 3H).	(4-amino-tetrahidro-2H-piran-4-il)metanol
72	1-((1-(terc-butoxicarbonil)piperidin-2-il)metil)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	LC/MS (ES^+)[$(M+H)^+$]: 541 para $C_{23}H_{29}IN_2O_5$ RMN ^1H (DMSO-d_6): δ8,50 (d, 1H); 8,47 (s, 1H); 8,06 (d, 1H); 7,73 (d, 1H); 4,70 (m, 1H); 4,47 (m, 2H); 4,21 (m, 2H); 3,91 (m, 1H); 3,14 (m, 1H); 1,87 (m, 1H); 1,59 (m, 4H); 1,26 (m, 4H); 1,10 (br s, 3H); 0,75 (br s, 6H).	2-(Amino-metil)-1-N-Boc-piperidina
73	6-yodo-4-oxo-1-(piridin-4-ilmetil)-1,4-dihidroquinolin-3-carboxilato de etilo 	LC/MS (ES^+)[$(M+H)^+$]: 435 para $C_{18}H_{15}IN_2O_3$ RMN H (DMSO-d_6): δ8,92 (s, 1H); 8,51 (m, 3H); 7,95 (dd, 1H); 7,31 (d, 1H); 7,17 (m, 2H); 5,72 (s, 2H); 4,24 (q, 2H); 1,28 (t, 3H).	4-Aminometil-piridina

Int.	Compuesto	Datos	SM
74	Sal de hidrocloruro del 1-(1-(dimetilamino)propan-2-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	LC/MS (ES^+)[$(M+H)^+$]: 429 para $C_{17}H_{21}IN_2O_3$ RMN ^1H (DMSO-d_6): δ10,23 (br s, 1H); 8,53 (s, 1H); 8,45 (d, 1H); 8,03 (m, 1H); 7,88 (m, 1H); 5,42 (br s, 1H); 4,17 (q, 2H); 3,72 (m, 1H); 3,59 (m, 1H); 2,70 (br s, 6H); 1,50 (m, 3H); 1,21 (t, 3H).	1-Dimetil-amino-2-propilamina
75	Sal de hidrocloruro del 6-yodo-1-((1-metilpiperidin-2-il)metil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	LC/MS (ES^+)[$(M+H)^+$]: 455 para $C_{19}H_{23}IN_2O_3$	(1-Metil-piperidin-2-il)metan-amina
76	6-yodo-1-((1-metil-1H-imidazol-4-il)metil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	LC/MS (ES^+)[$(M+H)^+$]: 438 para $C_{17}H_{16}IN_3O_3$ RMN ^1H (DMSO-d_6): δ8,82 (s, 1H); 8,47 (d, 1H); 8,00 (dd, 1H); 7,79 (d, 1H); 7,51 (s, 1H); 7,21 (s, 1H); 5,41 (s, 2H); 4,23 (q, 2H); 3,58 (s. 3H); 1,28 (t, 3H).	(1-Metil-1H-imidazol-4-il)metan-amina

Int.	Compuesto	Datos	SM
77	(S)-1-(1-terc-butoxi-3-metil-1-oxobutan-2-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	LC/MS (ES^+)[$(M+H)^+$]: 500 para $C_{21}H_{26}INO_5$ RMN ^1H (DMSO-d_6): δ8,66 (m, 1H); 8,53 (d, 1H); 8,10 (dd, 1H); 7,95 (m, 1H); 5,26 (d, 1H); 4,24 (q, 2H); 2,60 (m, 1H); 1,36 (br s, 9H); 1,28 (t, 3H); 1,15 (m, 3H); 0,78 (br s, 3H).	Hidrocloruro del éster terc-butílico de L-valina

Intermediario 78

Ácido 1-(1,3-dimetoxipropan-2-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxílico



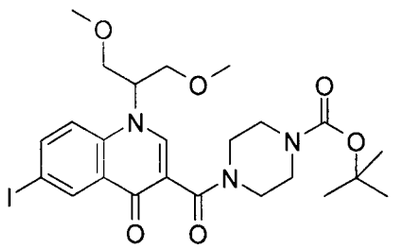
Se disolvió 1-(1,3-dimetoxipropan-2-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo (Intermediario 22, 270 mg, 0,60 mmoles) en tetrahidrofurano (20 ml) y agua (5 ml). Se añadió hidróxido de litio (56 mg, 2,42 mmoles), y la mezcla se agitó durante 10 min a temperatura ambiente. La mezcla de reacción se puso entonces a reflujo a 80 °C durante 1 h. La mezcla de reacción se concentró a presión reducida, y se añadió agua (10 ml). El pH se ajustó hasta 2 con ácido clorhídrico (2N), y el sólido que precipitó se recogió mediante filtración y se secó para dar 185 mg (75%) de ácido 1-(1,3-dimetoxipropan-2-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxílico.

RMN ^1H (400 MHz, DMSO-d_6): δ 3,22 (s, 6H), 3,62 (q, 2H), 3,72 (q, 2H), 4,68 (m, 1H), 7,81 (d, 1H), 8,14 (d, 1H), 8,78 (s, 1H), 9,14 (s, 1H).

LC-MS: m/z 417,8 (M+H).

Intermediario 79

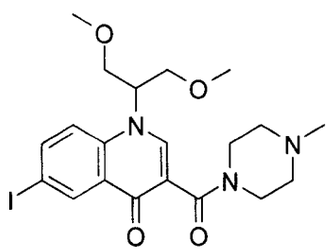
4-{[1-(1,3-dimetoxipropan-2-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-il]carbonil}piperazin-1-carboxilato de terc-butilo



A una disolución de ácido 1-(1,3-dimetoxipropan-2-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxílico (Intermediario 78, 500 mg, 1,12 mmoles) y piperazin-1-carboxilato de terc-butilo (312 mg, 1,67 mmoles) en diclorometano (50 ml) se añadió hidroxibenzotriazol (HOBT) (183 mg, 1,12 mmoles) y N-metilmorfolina (484 mg, 4,79 mmoles). La mezcla de reacción se agitó durante 1 h a temperatura ambiente, y se añadió hidrocloruro de 1-etil-3-(3-dimetilaminopropil)carbodiimida (EDCI HCl) (390 mg, 2,15 mmoles). La mezcla de reacción resultante se agitó a temperatura ambiente toda la noche. La mezcla de reacción se paralizó con ácido clorhídrico diluido (2N, 30 ml), y las capas se separaron. La capa orgánica se lavó con disolución saturada de bicarbonato de sodio (40 ml), con agua (60 ml) y finalmente con salmuera, sucesivamente, y se secó sobre sulfato de sodio anhidro, se filtró, se concentró a vacío para dar 4-{[1-(1,3-dimetoxipropan-2-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-il]carbonil}piperazin-1-carboxilato de terc-butilo 400 mg (57%) como un aceite espeso.
RMN ^{1}H (400 MHz, DMSO-d_6): δ 1,40 (s, 9H), 3,08 – 3,28 (m, 12H), 3,22 – 3,72 (m, 8H), 3,79 (m, 1H), 4,52 (m, 1H), 7,82 (d, 1H), 8,08 (d, 1H), 8,78 (2s, 2H).
MASS (APCI +ve Scan): m/z 586,1 (M+H).

Intermediario 80

1-(1,3-dimetoxipropan-2-il)-6-yodo-3-[(4-metilpiperazin-1-il)carbonil]quinolin-4(1H)-ona



A una disolución de ácido 1-(1,3-dimetoxipropan-2-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxílico (Intermediario 78, 300 mg, 0,72 mmoles) y 1-metilpiperazina (100 mg, 1,00 mmoles) en diclorometano (50 ml) se añadió hidroxibenzotriazol (HOBT) (110 mg, 0,72 mmoles) y N-metilmorfolina (290 mg, 2,87 mmoles). La mezcla de reacción se agitó durante 1 h a temperatura ambiente, y se añadió hidrocloruro de 1-etil-3-(3-

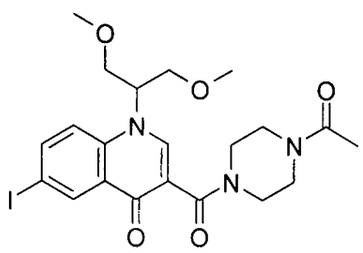
dimetilaminopropil)carbodiimida (EDC HCl) (234 mg, 1,29 mmoles). La mezcla de reacción resultante se agitó a temperatura ambiente toda la noche. La mezcla de reacción se paralizó con ácido clorhídrico 2N (30 ml), y las capas se separaron. La capa orgánica se lavó con disolución saturada de bicarbonato de sodio (40 ml), con agua (60 ml) y finalmente con salmuera, sucesivamente, y se secó sobre sulfato de sodio anhidro, se filtró y se concentró a vacío para dar 1-(1,3-dimetoxipropan-2-il)-6-yodo-3-[(4-metilpiperazin-1-il)carbonil]quinolin-4(1H)-ona 300 mg (80%) como un aceite espeso.

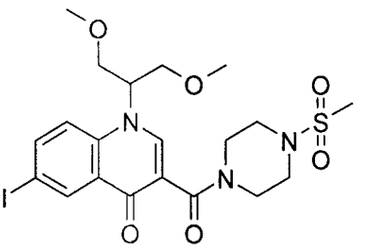
RMN ^{1}H (400 MHz, DMSO-d_6): δ 2,17 (s, 2H), 2,21 (s, 3H), 3,21 – 3,46 (m, 4H), 3,16 – 3,31 (s, 6H), 3,41 – 3,72 (m, 5H), 3,85 (s, 1H), 4,57 (m, 1H), 7,81 (d, 1H), 8,07 (d, 1H), 8,74 (2s, 2H).

MASS (Barrido APCI +ve): m/z 500 (M+H).

Intermediarios 81-82

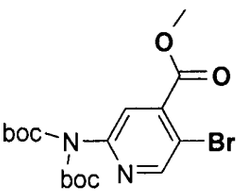
Los siguientes compuestos se prepararon según el procedimiento descrito para el Intermediario 80 a partir del material de partida dado a conocer en la tabla.

Int.	Compuesto	Datos	SM
81	3-[(4-acetilpiperazin-1-il)carbonil]-1-(1,3-dimetoxipropan-2-il)-6-yodoquinolin-4(1H)-ona 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 1,96 – 2,20 (m, 3H), 2,10 (s, 3H), 2,35 (m, 3H), 3,18 – 3,30 (m, 6H), 3,79 (m, 1H), 4,56 (m, 1H), 7,82 (d, 1H), 8,09 (d, 1H), 8,78 (m, 2H). MASS (Barrido APCI +ve): m/z 528,1 (M+H)	Intermediario 78 y 3-(4-acetil)-piperazina

Int.	Compuesto	Datos	SM
82	1-(1,3-dimetoxipropan-2-il)-6-yodo-3-{[4-(metilsulfonil)piperazin-1-il]carbonil}quinolin-4(1H)-ona 	RMN ^{1}H (400 MHz, DMSO-d_6): δ 2,97 (s, 3H), 3,11 – 3,40 (m, 14H), 3,45 (m, 1H), 3,56 (m, 4H), 4,04 (m, 1H), 4,53 (m, 1H), 7,81 (d, 1H), 8,12 (d, 1H), 8,78 (br s, 2H). MASS (Barrido APCI +ve): m/z 564,0 (M+H)	Intermediario 78 y 3-(4-metanosulfonil)-piperazina

Intermediario 83

2-(bis(terc-butoxicarbonil)amino)-5-bromoisonicotinato de metilo



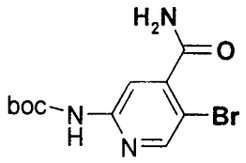
A un matraz de fondo redondo de 5 l se cargó 2-amino-5-bromoisonicotinato de metilo (200 g, 866 mmoles) y *terc*-butanol (3000 ml). La mezcla de reacción se mantuvo a 30°C, después se añadieron 4-dimetilaminopiridina (DMAP, 6,3 g, 52 mmoles) y bicarbonato de di-*terc*-butilo (566 g, 2,6 moles), y la mezcla resultante se calentó lentamente hasta 60°C durante 2 h. La mezcla de reacción se concentró a presión reducida hasta un cuarto del volumen. Precipitó un sólido amarillo similar a agujas, el cual se recogió mediante filtración y se lavó con etanol. Después de secar a vacío toda la noche a 25°C se obtuvo la primera cosecha 282 g de un sólido amarillo pálido similar a agujas.

MS (ESP): 277,1 ($M+H^+$-Boc-tBu) para $C_{17}H_{23}BrN_2O_6$

RMN ^{1}H (300 MHz, $CDCl_3$): δ 1,5 (s, 18H), 4,0 (s, 32H), 7,7 (s, 1H), 8,7 (s, 1H).

Intermediario 84

5-bromo-4-carbamoilpiridin-2-ilcarbamato de terc-butilo



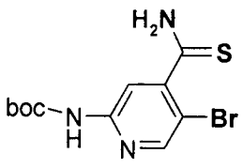
Una disolución de 2-(bis(terc-butoxicarbonil)amino)-5-bromoisonicotinato de metilo (Intermediario 83, 100 g, 232 mmoles) en amoníaco 7 N en metanol (600 ml) se dejó agitar toda la noche a 50°C en un tubo cerrado herméticamente de 1 l. La mezcla resultante se evaporó hasta sequedad, y el producto bruto se usó directamente para la siguiente etapa sin purificación adicional.

MS (ESP): 339,9 ($M+Na^+$) para $C_{11}H_{14}BrN_3O_3$

RMN ^1H (300 MHz, dmso-d_6): δ 1,47 (s, 9H), 7,82 (d, 2H), 8,07 (s, 1H), 8,41 (d, 1H), 10,2 (s, 1H).

Intermediario 85

5-bromo-4-carbamotioylpiridin-2-ilcarbamatp de terc-butilo



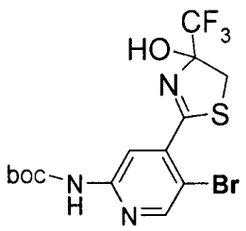
El 5-bromo-4-carbamoilpiridin-2-ilcarbamato de terc-butilo bruto (Intermediario 84, 232 mmoles) se trató con el reactivo de Lawesson (94 g, 232 mmoles, 1 eq) y tetrahidrofurano (700 ml), la mezcla resultante se calentó a reflujo durante 1 h, y después se dejó agitar a temperatura ambiente a lo largo del fin de semana. La mezcla se concentró hasta sequedad *a vacío*, y se añadió tolueno (~300 ml). Se formó un sólido amarillo brillante precipitado, el cual se recogió mediante filtración y se lavó con tolueno, y después se secó en el horno de vacío a 50°C durante 4 h, produciendo 75 g de un sólido amarillo brillante (97%).

MS (ESP): 354,2 ($M+Na^+$) para $C_{11}H_{14}BrN_3O_2S$

RMN ^1H (300 MHz, $CDCl_3$): δ 1,53 (s, 9H), 7,03 (br, 1H), 7,61 (br, 1H), 7,74 (br, 1H), 8,2 (s, 1H), 8,35 (s, 1H).

Intermediario 86

5-bromo-4-(4-hidroxi-4-(trifluorometil)-4,5-dihidrotiazol-2-il)piridin-2-ilcarbamato de terc-butilo



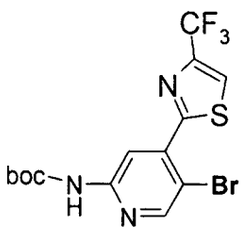
A un matraz de fondo redondo de 2 l se cargó 5-bromo-4-carbamotioilpiridin-2-ilcarbamato de terc-butilo (Intermediario 85, 50 g, 151 mmoles) en tetrahidrofurano (800 ml), y después se añadió bicarbonato de sodio sólido (25,4 g, 302 mmoles), seguido de 1,1,1-trifluoro-3-bromoacetona (31 ml, 290 mmoles). La mezcla resultante (suspensión amarilla) se dejó agitar a temperatura ambiente toda la noche. La suspensión blanca se filtró, y el sólido se lavó con agua (2,2~2,5 l). El sólido blanco se secó a vacío para dar 56,8 g de un polvo blanco (85%).

MS (ESP): 386,0 (M-*t*-Bu) para $C_{14}H_{15}BrF_3N_3O_3S$

RMN ^{1}H (300 MHz, $CDCl_3$): δ 1,6 (s, 9 H), 3,3 (br, 2H), 3,6 (d, 1H), 3,9 (d, 1H), 8,2 (s, 1H), 8,5 (s, 1H).

Intermediario 87

5-bromo-4-(4-(trifluorometil)tiazol-2-il)piridin-2-ilcarbamato de terc-butilo



A un matraz de fondo redondo de 2 l se cargó 5-bromo-4-(4-hidroxi-4-(trifluorometil)-4,5-dihidrotiazol-2-il)piridin-2-ilcarbamato de terc-butilo (Intermediario 86, 56,8 g, 128 mmoles) y dimetoxietano (800 ml). La mezcla de reacción se enfrió en un baño de hielo y agua, y después se añadieron simultáneamente durante 1h anhídrido trifluoroacético (69 ml, 514 mmoles) y 2,6-lutidina (133 ml, 1,15 moles). La disolución naranja/amarilla resultante se dejó agitar en el baño de hielo y agua durante 30 min, y después la disolución se calentó hasta la temperatura ambiente. La disolución naranja se concentró a presión reducida hasta sequedad, y el residuo resultante se trituró con metanol. El sólido se recogió mediante filtración, y se lavó con más metanol, se secó a vacío toda la noche, produciendo 49 g de un sólido blanco.

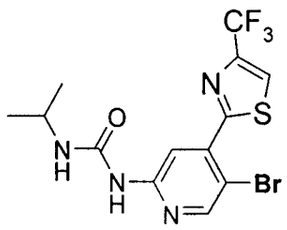
MS (ESP): 368,0 (M-*t*-Bu) para $C_{14}H_{13}BrF_3N_3O_2S$

RMN ^{1}H (300 MHz, $CDCl_3$): δ 1,6 (s, 9H), 8,0 (s, 1H), 8,2 (br, 1H), 8,55 (s, 1H), 8,65 (s,

1H).

Intermediario 88

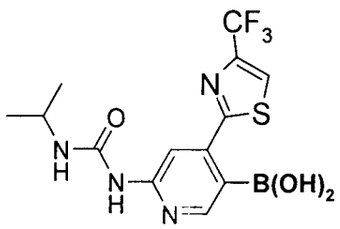
1-(5-bromo-4-(4-(trifluorometil)tiazol-2-il)piridin-2-il)-3-isopropilurea



Una mezcla de 5-bromo-4-(4-(trifluorometil)tiazol-2-il)piridin-2-ilcarbamato de terc-butilo (Intermediario 87, 25 g, 59 mmoles), isopropilamina (250 ml) y acetonitrilo (100 ml) se calentó a 130°C en un aparato de bomba de Parr durante 50 h (~150 PSI). La mezcla de reacción se enfrió hasta la temperatura ambiente, y la reacción se filtró a través de celita, y el filtrado se lavó con tetrahidrofurano (~300 ml). Los disolventes se evaporaron, y el residuo se trituró con metanol (200 ml), se filtró, y el sólido se secó para dar 14,6 g de producto.
MS (ESP): 410 (MH^+) para $C_{13}H_{12}BrF_3N_4OS$.

Intermediario 89

Ácido 6-(3-isopropilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-ilborónico



Una suspensión de 1-(5-bromo-4-(4-(trifluorometil)tiazol-2-il)piridin-2-il)-3-isopropilurea (Intermediario 88, 14,6 g, 35,7 mmoles) en tetrahidrofurano (400 ml) se preparó y se agitó a -50°C. Se añadió gota a gota cloruro de isopropilmagnesio 2,0M en tetrahidrofurano (53,6 ml, 107 mmoles) durante 45 min, de forma que la temperatura nunca subió por encima de -35°C. La mezcla de reacción se agitó durante 1 h a -40°C, y después se enfrió hasta -78°C. Entonces se añadió gota a gota n-butil-litio 2,5M en hexanos (85,8 ml, 215mmoles) a la disolución de la reacción, de forma que la temperatura nunca subió por encima de -65°C. Esta mezcla de reacción se dejó reaccionar entonces a -78°C durante 1,5 h. Se añadió metóxido de boro (44 ml, 394 mmoles) en 1 porción, y se eliminó el baño de frío. La mezcla de reacción se dejó calentar hasta la temperatura ambiente, y se agitó durante 1 h. Entonces se añadió lentamente

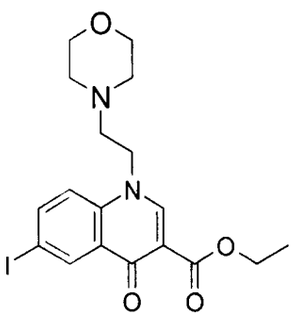
ácido clorhídrico 3N (500 ml), para minimizar la espumación, y la reacción se agitó a temperatura ambiente durante 30 min. La mezcla de reacción se concentró a alto vacío para eliminar el tetrahidrofurano, y agua (1 l). La disolución se basificó hasta pH 10 con hidróxido de sodio al 24%, y el volumen total se incrementó hasta 2 l con agua. La disolución acuosa se extrajo con metil-terc-butiléter (3 × 300 ml). Las capas orgánicas se combinaron y se extrajeron con hidróxido de sodio al 5% (100 ml). Las fases acuosas se combinaron y se acidificaron hasta pH 5,5 con ácido clorhídrico 6 N, momento en el que se formó una suspensión. Esta suspensión se extrajo con acetato de etilo: THF 2:1 (5 × 400 ml). Las fases orgánicas se combinaron y se lavaron nuevamente con agua (1 l). Los orgánicos se concentraron y se trituraron con metil-terc-butiléter (1 l). El sólido obtenido se secó en un horno de vacío a 50°C para dar 10,4 g de producto.

MS (ESP): 375,0 (MH^+) para $C_{13}H_{14}BF_3N_4O_3S$

RMN ^1H (300 MHz, DMSO-d_6): δ 1,24 (d, 6H), 3,98 (m, 1H), 7,80 (bt, 1H), 7,91 (s, 1H), 8,20 (br, 2H), 8,31 (d, 1H), 8,63 (m, 1H), 9,32 (s, 1H).

Intermediario 90

6-yodo-1-(2-morfolinoetil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo



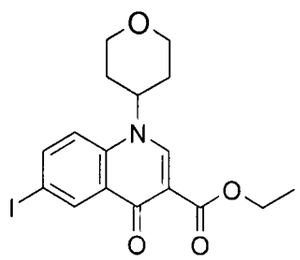
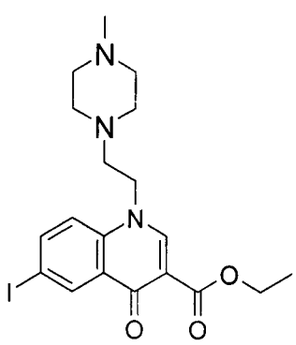
Se añadió 2-morfolinoetanamina (0,88 g, 6,7 mmoles) a la disolución madre de (Z)-3-(dimetilamino)-2-(3-yodobenzoil)acrilato de etilo (Intermediario 24, 0,38M, 18 ml, 7 mmoles), y la mezcla se calentó a 40°C durante 3 h. El disolvente se eliminó *a vacío*, y el residuo resultante se secó en un horno de vacío durante 1,5 h. El residuo se disolvió entonces en dimetilformamida (5 ml), y se añadió polvo de carbonato de potasio (1,2 g, 10 mmoles). La reacción se calentó a 70°C otras 3 h, y después se enfrió hasta la temperatura ambiente. La mezcla de reacción bruta se colocó en un refrigerador durante 3 h. El precipitado sólido que se formó se recogió mediante filtración, se lavó con una pequeña cantidad de dimetilformamida, seguido de agua, y después se secó a alto vacío.

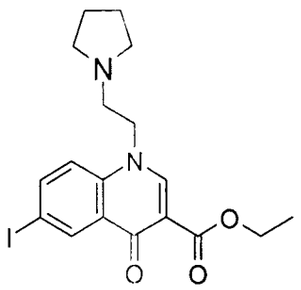
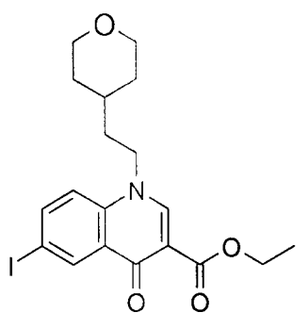
MS (ESP): 457 ($M+H^+$) para $C_{18}H_{21}IN_2O_4$

RMN ^{1}H (300 MHz, DMSO-d_6): δ 1,28 (t, 3H), 2,42 (brs, 4H), 2,61 (brs, 2H), 3,50 (br, 4H), 4,23 (q, 2H), 4,46 (br, 2H), 7,67 (d, 1H), 8,05, (d, 1H), 8,50 (s, 1H), 8,64 (s, 1H).

Intermediarios 91-94

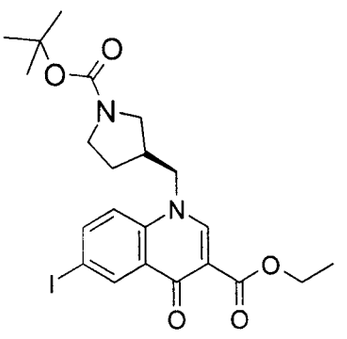
Los siguientes compuestos se prepararon según el procedimiento descrito para el Intermediario 90 a partir de los materiales de partida indicados.

Int.	Compuesto	Datos	SM
91	6-yodo-4-oxo-1-(tetrahidro-2H-piran-4-il)-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 428,1 ($M+H^+$) para $C_{17}H_{18}INO_4$ RMN ^{1}H (300 MHz, DMSO-d_6): δ 1,29 (t, 3H), 2,00 (brs, 4H), 3,64 (m, 2H), 4,00 (d, 2H), 4,23 (q, 2H), 4,95 (m, 1H), 7,92 (d, 1H), 8,06 (d, 1H), 8,53 (s, 1H), 8,60 (s, 1H)	Intermediario 24 y tetrahidro-2*H*-piran-4-amina
92	6-yodo-1-(2-(4-metilpiperazin-1-il)etil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 470,1 ($M+H^+$) para $C_{19}H_{24}IN_3O_3$ RMN ^{1}H (300 MHz, DMSO-d_6): δ 1,29 (t, 3H), 2,10 (s, 3H), 2,22 (br, 4H), 2,41 (br, 4H), 2,60 (t, 2H), 4,22 (q, 2H), 4,43 (t, 2H), 7,66 (d, 1H), 8,03 (d, 1H), 8,50 (s, 1H), 8,59 (s, 1H).	Intermediario 24 y 2-(4-metil-piperazino)-etanamina

Int.	Compuesto	Datos	SM
93	6-yodo-4-oxo-1-(2-(pirrolidin-1-il)etil)-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 441,1 ($M+H^+$) para $C_{18}H_{21}IN_2O_3$ RMN ^1H (300 MHz, dmso-d_6): δ 1,28 (t, 3H), 1,65 (br, 4H), 2,48 (m, 4H), 2,75 (br, 2H), 4,20 (q, 2H), 4,45 (m, 2H), 7,64 (d, 1H), 8,04 (d, 1H), 8,63 (s, 1H), 8,65 (s, 1H)	Intermediario 24 y 2-pirrolidino-etanamina
94	6-yodo-4-oxo-1-(2-(tetrahidro-2H-piran-4-il)etil)-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 456,1 ($M+H^+$) para $C_{19}H_{22}INO_4$ RMN ^1H (300 MHz, $CDCl_3$): δ 1,22 (m, 1H), 1,28 (t, 3H), 1,67 (m, 4H), 3,27 (t, 2H), 3,34 (m, 2H), 3,84 (d, 2H), 4,22 (q, 2H), 4,40 (m, 2H), 7,59 (d, 1H), 8,08 (d, 1H), 8,50 (s, 1H), 8,72 (s, 1H)	Intermediario 24 y 2-(tetrahidro-2*H*-piran-4-il)-etanamina

Intermediario 95

(R)-1-((1-(terc-butoxicarbonil)pirrolidin-3-il)metil)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo



Se añadió (R)-3-(aminometil)-1-N-Boc-pirrolidina (994 mg, 4,86 mmoles) a la disolución madre de (Z)-3-(dimetilamino)-2-(3-yodobenzoil)acrilato de etilo (Intermediario 24, 0,34M,

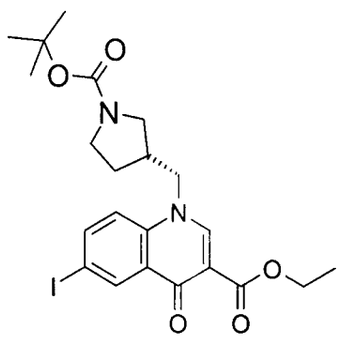
13 ml, 4,42 mmoles). La mezcla de reacción se agitó a temperatura ambiente toda la noche. El disolvente se eliminó *a vacío*, y el residuo se secó en un horno de vacío durante 1,5 h. El residuo resultante se disolvió entonces en dimetilformamida (8 ml), y se añadió polvo de carbonato de potasio (670 mg, 4,86 mmoles). La mezcla de reacción se calentó a 60°C toda la noche, y después se enfrió hasta la temperatura ambiente. Se añadió agua (50 ml), y la suspensión se extrajo con acetato de etilo (3 × 50 ml). Las capas orgánicas se secaron sobre sulfato de sodio, y el disolvente se eliminó *a vacío* para dar (R)-1-((1-(terc-butoxicarbonil)pirrolidin-3-il)metil)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo cuantitativo como un sólido marrón pegajoso.

MS (ESP): 527,1 ($M+H^+$) para $C_{22}H_{27}IN_2O_5$

RMN ^1H (300 MHz, DMSO-d_6): δ 1,42 (t, 3H), 1,46 (s, 9H), 1,71 (m, 1H), 2,02 (bm, 1H), 2,78 (bs, 1H), 3,12 (bs, 1H), 3,25-3,62 (bm, 3H), 3,96-4,40 (bm, 2H), 4,42 (q, 2H), 7,19 (d, 1H), 7,92 (dd, 1H), 8,40 (s, 1H), 8,83 (s, 1H).

Intermediario 96

(S)-1-((1-(terc-butoxicarbonil)pirrolidin-3-il)metil)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo



Se añadió (S)-3-(aminometil)-1-N-Boc-pirrolidina (994 mg, 4,86 mmoles) a la disolución madre de (Z)-3-(dimetilamino)-2-(3-yodobenzoil)acrilato de etilo (Intermediario 24, 0,34M, 13 ml, 4,42 mmoles). La mezcla de reacción se agitó a temperatura ambiente toda la noche. El disolvente se eliminó *a vacío*, y el residuo se secó en un horno de vacío durante 1,5 h. El residuo resultante se disolvió entonces en dimetilformamida (8 ml), y se añadió polvo de carbonato de potasio (670 mg, 4,86 mmoles). La mezcla de reacción se calentó a 60°C toda la noche, y después se enfrió hasta la temperatura ambiente. Se añadió agua (50 ml), y la suspensión se extrajo con acetato de etilo (3 × 50 ml). Las capas orgánicas se secaron sobre sulfato de sodio, y el disolvente se eliminó *a vacío* para dar (S)-1-((1-(terc-

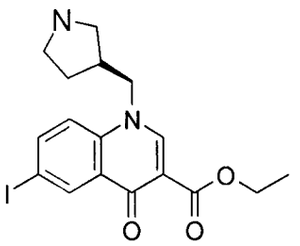
butoxicarbonil)pirrolidin-3-il)metil)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo cuantitativo como un sólido marrón pegajoso.

MS (ESP): 527,1 ($M+H^+$) para $C_{22}H_{27}IN_2O_5$

RMN ^1H (300 MHz, DMSO-d_6): δ 1,42 (t, 3H), 1,46 (s, 9H), 1,71 (m, 1H), 2,02 (bm, 1H), 2,78 (bs, 1H), 3,12 (bs, 1H), 3,25-3,62 (bm, 3H), 3,96-4,40 (bm, 2H), 4,42 (q, 2H), 7,19 (d, 1H), 7,92 (dd, 1H), 8,40 (s, 1H), 8,83 (s, 1H).

Intermediario 97

Hidrocloruro de (R)-6-yodo-4-oxo-1-(pirrolidin-3-ilmetil)-1,4-dihidroquinolin-3-carboxilato de etilo

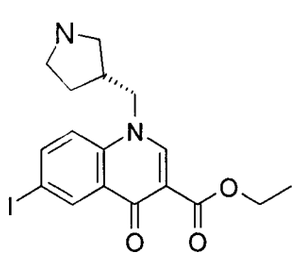


El (R)-1-((1-(terc-butoxicarbonil)pirrolidin-3-il)metil)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo bruto (Intermediario 95, ~4,4 mmoles) se disolvió en 1,4-dioxano (20 ml), y se añadió cloruro de hidrógeno 4,0M en 1,4-dioxano (20 ml). La mezcla de reacción se agitó a temperatura ambiente durante 1 h, y el disolvente se eliminó *a vacío*. El sólido se secó entonces en un horno de vacío a 40°C durante 18 h para dar 2,3 g (rendimiento cuant.) de hidrocloruro de (R)-6-yodo-4-oxo-1-(pirrolidin-3-ilmetil)-1,4-dihidroquinolin-3-carboxilato de etilo como un sólido amarillo.

MS (ESP): 427,1 ($M+H^+$) para $C_{17}H_{19}IN_2O_3$

Intermediario 98

Hidrocloruro de (S)-6-yodo-4-oxo-1-(pirrolidin-3-ilmetil)-1,4-dihidroquinolin-3-carboxilato de etilo



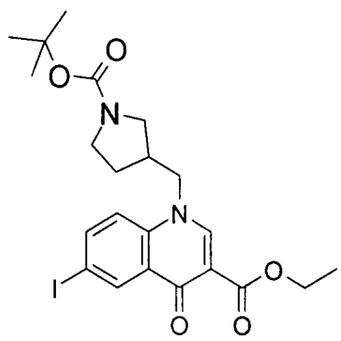
El (S)-1-((1-(terc-butoxicarbonil)pirrolidin-3-il)metil)-6-yodo-4-oxo-1,4-dihidroquinolin-3-

carboxilato de etilo bruto (Intermediario 96, ~4,4 mmoles) se disolvió en 1,4-dioxano (20 ml), y se añadió cloruro de hidrógeno 4,0M en 1,4-dioxano (20 ml). La mezcla de reacción se agitó a temperatura ambiente durante 1 h, y el disolvente se eliminó *a vacío*. El sólido se secó entonces en un horno de vacío a 40°C durante 18 h para dar 2,3 g (rendimiento cuant.) de hidrocloruro de (S)-6-yodo-4-oxo-1-(pirrolidin-3-ilmetil)-1,4-dihidroquinolin-3-carboxilato de etilo como un sólido amarillo.

MS (ESP): 427,1 ($M+H^+$) para $C_{17}H_{19}IN_2O_3$

Intermediario 99

1-((1-(terc-butoxicarbonil)pirrolidin-3-il)metil)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo



Se añadió 3-(aminometil)-1-N-Boc-pirrolidina (2,5 g, 12,5 mmoles) a la disolución madre de (Z)-3-(dimetilamino)-2-(3-yodobenzoil)acrilato de etilo (Intermediario 24, 0,34M, 34 ml, 11,3 mmoles). La mezcla de reacción se calentó a 50°C durante 3 h. El disolvente se eliminó *a vacío*, y el residuo resultante se secó en un horno de vacío durante 1,5 h. El residuo se disolvió entonces en dimetilformamida (20 ml), y se añadió polvo de carbonato de potasio (2,2 g, 15,8 mmoles). La mezcla de reacción se calentó a 70°C durante 3 h, y después se enfrió hasta la temperatura ambiente. Se añadió agua (100 ml), y la suspensión se extrajo con acetato de etilo: metil-terc-butiléter 1:1 (3 × 50 ml). Las capas orgánicas se secaron sobre sulfato de sodio, y el disolvente se eliminó *a vacío*. El residuo se suspendió en metil-terc-butiléter (20 ml) y se agitó a 40°C durante 1 h. La suspensión se filtró, y el sólido se secó para dar 4,15g (70% de rendimiento) de 1-((1-(terc-butoxicarbonil)pirrolidin-3-il)metil)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo como un polvo amarillento.

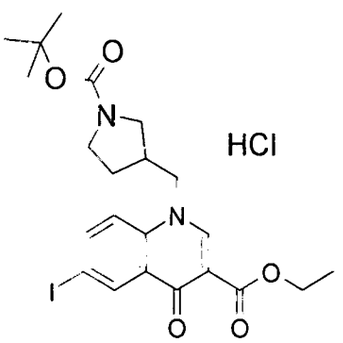
MS (ESP): 527,1 ($M+H^+$) para $C_{22}H_{27}IN_2O_5$

RMN ^1H (300 MHz, DMSO-d_6): δ ppm 1,42 (t, 3H), 1,46 (s, 9H), 1,71 (m, 1H), 2,02 (bm, 1H), 2,78 (bs, 1H), 3,12 (bs, 1H), 3,25-3,62 (bm, 3H), 3,96-4,40 (bm, 2H), 4,42 (q, 2H), 7,19

(d, 1H), 7,92 (dd, 1H), 8,40 (s, 1H), 8,83 (s, 1H)

Intermediario 100

Hidrocloruro de 6-yodo-4-oxo-1-(pirrolidin-3-ilmetil)-1,4-dihidroquinolin-3-carboxilato de etilo

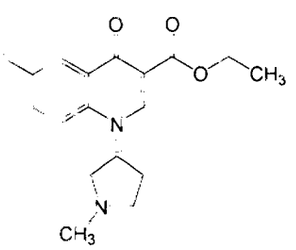


Se disolvió 1-((*R*)-(terc-butoxicarbonil)pirrolidin-3-il)metil)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo (Intermediario 99, 3,0 g, 5,7 mmoles) en 1,4-dioxano (15 ml), y se añadió cloruro de hidrógeno 4,0M en 1,4-dioxano (10 ml). La reacción se agitó a 23 °C durante 3 horas, y el disolvente se eliminó *a vacío*. El sólido se secó entonces en un horno de vacío a 50°C durante 18 h para dar 2,61 (rendimiento cuant.) de hidrocloruro de 6-yodo-4-oxo-1-(pirrolidin-3-ilmetil)-1,4-dihidroquinolin-3-carboxilato de etilo como un sólido amarillo.

MS (ESP): 427,1 ($M+H^+$) para $C_{17}H_{19}IN_2O_3$

Intermediario 101

(*R*)-6-yodo-4-oxo-1-(1-metil-pirrolidin-3-il)-1,4-dihidroquinolin-3-carboxilato de etilo



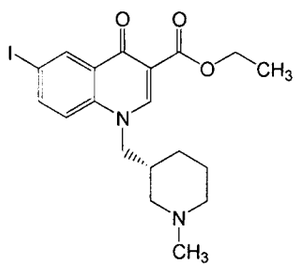
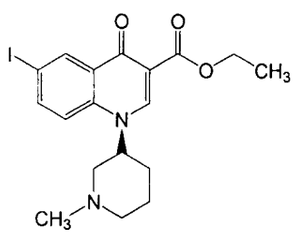
A una disolución de (*R*)-6-yodo-4-oxo-1-(pirrolidin-3-il)-1,4-dihidroquinolin-3-carboxilato de etilo (Intermediario 110, 282 mg, 0,68 mmoles, 1 equiv.) en THF (7 ml) se añadió yodometano (0,047 ml, 0,75 mmol, 1,1 equiv.), seguido de carbonato de potasio (378 mg, 2,74 mmoles, 4 equiv.). Esto se agitó a 60 °C durante 1 d. La mezcla de reacción se enfrió hasta la temperatura ambiente, y se repartió entre acetato de etilo (10 ml) y agua (10 ml). La capa acuosa se extrajo con acetato de etilo (2 x 10 ml), y los orgánicos se concentraron para

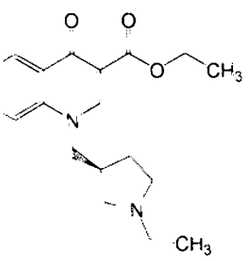
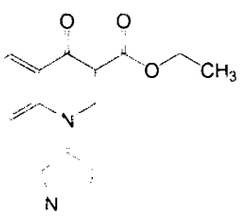
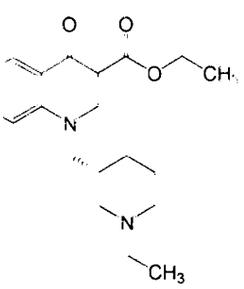
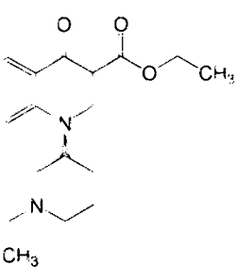
proporcionar (*R*)-6-yodo-1-(1-metilpirrolidin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo como un sólido amarillo claro (282 mg, >99 %).

RMN (d_6-DMSO) δ 8,97 (s, 1H), 8,51 (s, 1H), 8,13 (dd, 1H), 7,86 (d, 1H), 5,46-4,38 (m, 1H), 4,28-4,18 (m, 2H), 3,59-3,54 (m, 1H), 3,24-3,1 (m, 3H), 2,6-2,54 (m, 2H), 2,36 (s, 3H), 2,26-2,14 (m, 2H), 1,28 (t, 3H).

Intermediarios 102-107

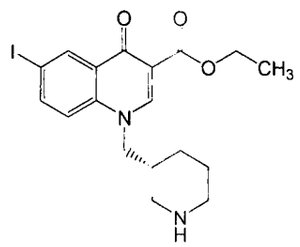
Los siguientes Intermediarios se prepararon según el procedimiento descrito para el Intermediario 101 a partir de los materiales de partida indicados.

Int.	Compuesto	Datos	SM
102	(*R*)-6-yodo-1-((1-metilpiperidin-3-il)metil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	Calc. para $C_{19}H_{23}IN_2O_3$ [M + H]$^+$: 454,96	Yodometano e Intermediario 108
103	(*R*)-6-yodo-1-(1-metilpiperidin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	Calc. para $C_{18}H_{21}IN_2O_3$ [M + H]$^+$: 440,91	Yodometano e Intermediario 111

Int.	Compuesto	Datos	SM
104	(*S*)-1-((1-etilpirrolidin-3-il)metil) 6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	Calc. para $C_{19}H_{23}IN_2O_3$ [M + H]$^+$: 455,01	Yodoetano e Intermediario 109
105	(*R*)-1-(1-etilpirrolidin-3-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	Calc. para $C_{18}H_{21}IN_2O_3$ [M + H]$^+$: 441,0	Yodoetano e Intermediario 110
106	(*R*)-1-((1-etil)piperidin-3-il)metil)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	Calc. para $C_{20}H_{25}IN_2O_3$ [M + H]$^+$: 469,11	Yodoetano e Intermediario 108
107	(*R*)-1-(1-etil)piperidin-3-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	Calc. para $C_{19}H_{23}IN_2O_3$ [M + H]$^+$: 454,66	Yodoetano e Intermediario 111

Intermediario 108

(*S*)-1-(1-piperidin-3-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo

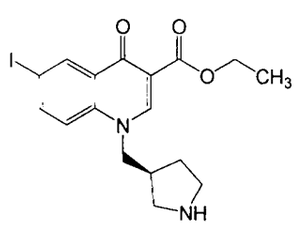


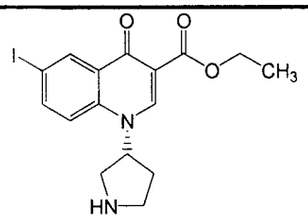
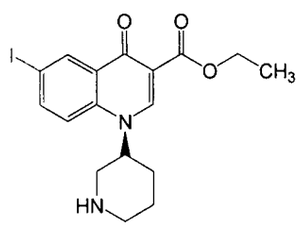
A una disolución de (*S*)-1-((1-(*terc*-butoxicarbonil)piperidin-3-il)metil)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo (Intermediario 112, 2,47 g, 4,57 mmoles, 1 equiv.) en diclorometano (18 ml) se añadió cloruro de hidrógeno 4 N (4,57 ml, 18,28 mmoles, 4 equiv.). Esto se agitó a temperatura ambiente durante 12 h. El precipitado se lavó con éter dietílico y se secó para proporcionar (*R*)-6-yodo-4-oxo-1-(piperidin-3-ilmetil)-1,4-dihidroquinolin-3-carboxilato de etilo como un sólido amarillo claro (2,1 g, >99 %).

Calc. para $C_{18}H_{21}IN_2O_3$ $[M + H]^+$: 440,95.

Intermediarios 109-111

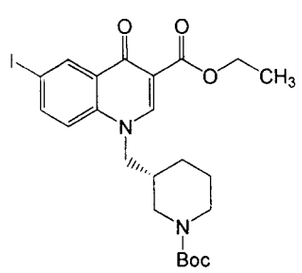
Los siguientes Intermediarios se prepararon según los procedimientos descritos para el Intermediario 108 a partir de los materiales de partida indicados.

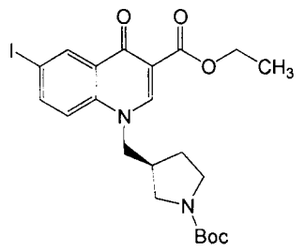
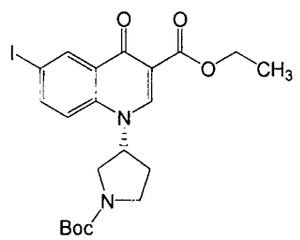
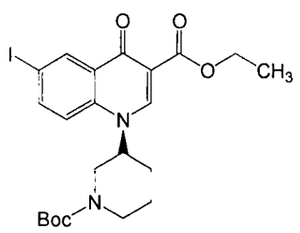
Int.	Compuesto	Datos	SM
109	(*S*)-6-yodo-4-oxo-1-(pirrolidin-3-ilmetil)-1,4-dihidroquinolin-3-carboxilato de etilo 	Calc. para $C_{17}H_{19}IN_2O_3$ $[M + H]^+$: 426,94	Intermediario 113
110	(*R*)-6-yodo-4-oxo-1-(pirrolidin-3-il)-1,4-dihidroquinolin-3-carboxilato de etilo	Calc. para $C_{16}H_{17}IN_2O_3$ $[M + H]^+$: 412,92	Intermediario 114

Int.	Compuesto	Datos	SM
			
111	(*S*)-6-yodo-4-oxo-1-(piperidin-3-il)-1,4-dihidroquinolin-3-carboxilato de etilo 	Calc. para $C_{17}H_{19}IN_2O_3$ [M + H]$^+$: 426,95	Intermediario 115

Intermediarios 112-115

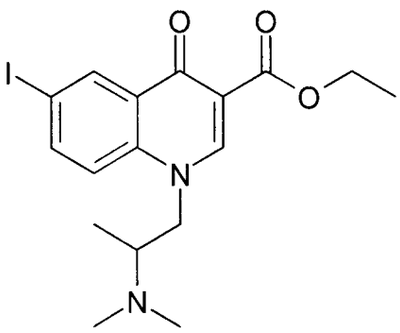
Los siguientes Intermediarios se prepararon según el procedimiento descrito para el Intermediario 96 a partir de los materiales de partida indicados.

Int.	Compuesto	Datos	SM
112	(*S*)-1-((1-(*terc-but*oxicarbonil)piperidin-3-il)metil)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	Calc. para $C_{23}H_{29}IN_2O_5$ [M + H]$^+$: 541,07	3-(aminometil)-piperidin-1-carboxilato de (*S*)-*terc*-butilo e Intermediario 24

Int.	Compuesto	Datos	SM
113	(*R*)-1-((1-(*terc-but*oxicarbonil)pirrolidin-3-il)metil)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	Calc. para $C_{22}H_{27}IN_2O_5$ $[M + H]^+$: 527,03	3-aminometil-pirrolidin-1-carboxilato de (*R*)-*terc*-butilo e Intermediario 24
114	(*R*)-1-(1-(*terc-but*oxicarbonil)pirrolidin-3-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	Calc. para $C_{21}H_{25}IN_2O_5$ $[M + H]^+$: 512,99	3-amino-pirrolidin-1-carboxilato de (*R*)-*terc*-butilo e Intermediario 24
115	(*S*)-1-(1-(*terc-but*oxicarbonil)piperidin-3-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	Calc. para $C_{22}H_{27}IN_2O_5$ $[M + H]^+$: 527,01	3-amino-piperidin-1-carboxilato de (*S*)-*terc*-butilo e Intermediario 24

Intermediario 116

1-(2-(dimetilamino)propil)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo



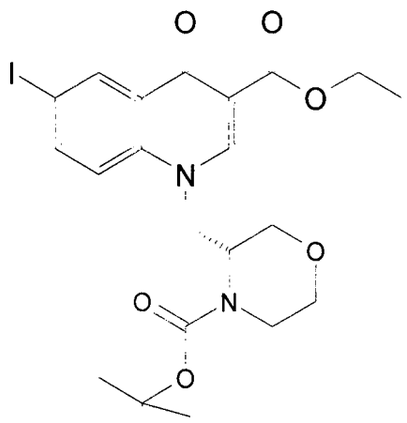
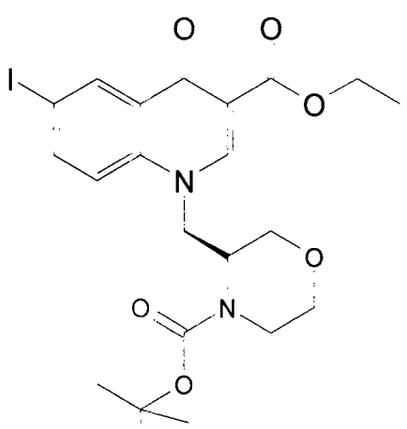
Se combinaron (*Z*)-3-(dimetilamino)-2-(2-fluoro-5-yodobenzoil)acrilato de etilo (0,500 g, 1,28 mmoles, Intermediario 24), hidrocloruro de N2,N2-dimetilpropan-1,2-diamina (0,177 g, 1,28 mmoles), y carbonato de potasio (0,194 g, 1,41 mmoles) en THF (10,0 ml). La reacción se calentó a 60 °C durante 2 h. Después de 2 h, se añadió DMF (5,0 ml), seguido de carbonato de potasio (0,530 g, 3,83 mmoles). La reacción se calentó a 90 °C durante 6h. La mezcla de reacción se enfrió hasta 0°C, y se añadió lentamente HCl 1N hasta que el pH fue alrededor de 4. El precipitado resultante se filtró, se lavó con agua y se secó toda la noche para producir un sólido amarillo claro (0,428g).

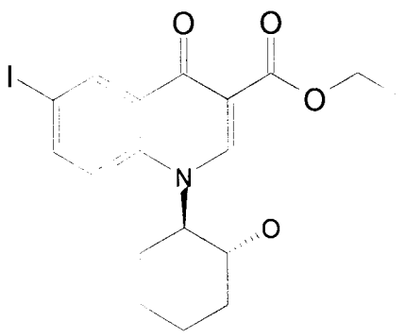
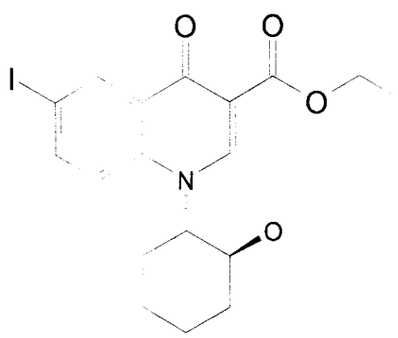
MS (ES) $(M+H)^+$: 429 para $C_{17}H_{21}IN_2O_3$;

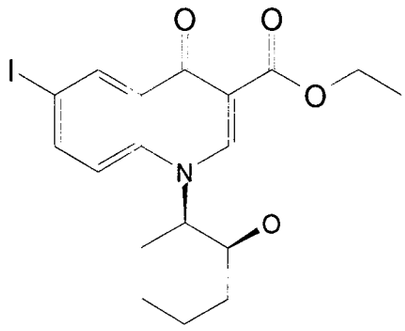
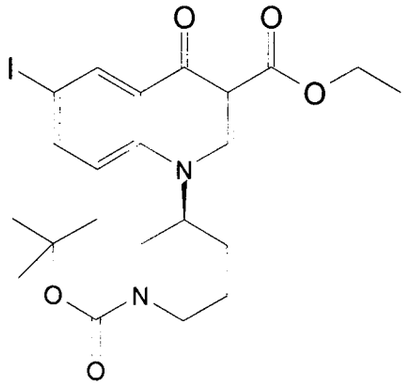
RMN: 10,99 (br. s., 1 H), 8,73 (br. s., 1 H), 8,51 (s, 1 H), 8,07 (dd, *J*=8,67, 1,88 Hz, 1 H), 7,83 - 7,97 (m, 1 H), 4,92 (d, *J*=12,06 Hz, 1 H), 4,59 (t, *J*=11,30 Hz, 1 H), 4,24 (q, *J*=7,54 Hz, 2 H), 3,70 - 3,89 (m, 1 H), 2,68 - 2,86 (m, 6 H), 1,29 (t, *J*=7,16 Hz, 4 H), 1,15 (d, *J*=3,77 Hz, 3 H).

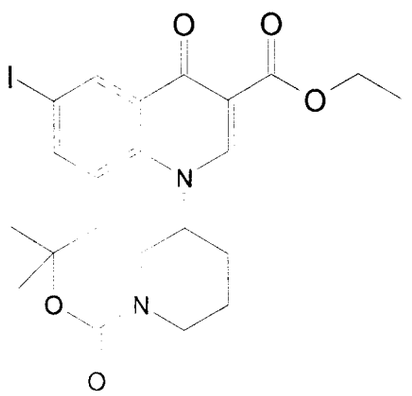
Intermediarios 117-123

Los siguientes Intermediarios se prepararon mediante el procedimiento descrito en el Intermediario 116 a partir de los materiales de partida (SM) indicados.

Int.	Compuesto	Datos	SM
117	(R)-3-((3-(etoxicarbonil)-6-yodo-4-oxoquinolin-1(4H)-il)metil)morfolin-4-carboxilato de terc-butilo 	MS (ES) $(M+H)^+$: 543 para $C_{22}H_{27}IN_2O_6$ RMN: 8,45 - 8,56 (m, 2 H), 8,06 (d, *J*=7,54 Hz, 1 H), 7,79 (d, *J*=9,04 Hz, 1 H), 4,56 - 4,76 (m, 2 H), 4,20 (d, *J*=7,54 Hz, 3 H), 3,94 - 4,06 (m, 1 H), 3,74 - 3,92 (m, 2 H), 3,44 - 3,68 (m, 2 H), 1,21 - 1,43 (m, 4 H), 1,12 (s, 3 H), 0,77 (s, 6 H).	Intermediario 24 y (R)-3-(aminometil)-morfolin-4-carboxilato de terc-butilo
118	(S)-3-((3-(etoxicarbonil)-6-yodo-4-oxoquinolin-1(4H)-il)metil)morfolin-4-carboxilato de terc-butilo 	MS (ES) $(M+H)^+$: 543 para $C_{22}H_{27}IN_2O_6$ RMN: 8,42 - 8,56 (m, 2 H), 8,06 (d, *J*=8,29 Hz, 1 H), 7,79 (d, *J*=8,29 Hz, 1 H), 4,53 - 4,79 (m, 2 H), 4,20 (d,*J*=6,78 Hz, 3 H), 3,94 - 4,09 (m, 1 H), 3,72 - 3,94 (m, 2 H), 3,45 - 3,70 (m, 2 H), 1,19 - 1,43 (m, 4 H), 1,12 (s, 3 H), 0,77 (s, 6H).	Intermediario 24 y (S)-3-(aminometil)-morfolin-4-carboxilato de terc-butilo

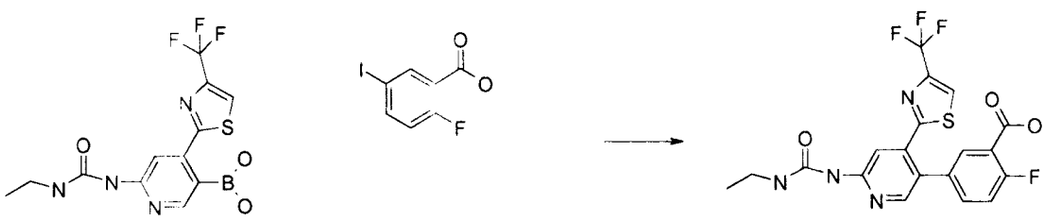
Int.	Compuesto	Datos	SM
119	1-((1R,2R)-2-hidroxiciclohexil)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ES) $(M+H)^+$: 442 para $C_{18}H_{20}INO_4$ RMN: 8,62 (s, 1 H), 8,52 (s, 1 H), 8,03 (d, *J*=9,04 Hz, 1 H), 7,84 - 7,93 (m, 1 H), 5,10 (d, *J*=4,52 Hz, 1 H), 4,51 (t, *J*=8,67 Hz, 1 H), 4,24 (q, *J*=6,78 Hz, 2 H), 3,87 (d, *J*=4,52 Hz, 1 H), 1,86 - 2,09 (m, 2 H), 1,71 (br. s., 3 H), 1,41 - 1,60 (m, 3 H), 1,29 (t, *J*=7,16 Hz, 3 H).	Intermediario 24 e hidrocloruro de (1R,2R)-2-amino-ciclohexanol
120	1-((1S,2S)-2-hidroxiciclohexil)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ES) $(M+H)^+$: 442 para $C_{18}H_{20}INO_4$	Intermediario 24 e hidrocloruro de (1S,2S)-2-aminociclo-hexanol

Int.	Compuesto	Datos	SM
121	1-(*cis*-2-hidroxiciclohexil)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ES) $(M+H)^+$: 442 para $C_{18}H_{20}INO_4$ RMN: 1,21 - 1,35 (m, 3 H), 1,39 - 1,67 (m, 3 H), 1,67 - 1,95 (m, 4 H), 2,15 - 2,31 (m, 1 H), 3,94 (br. s., 1 H), 4,24 (q, *J*=6,78 Hz, 2 H), 4,72 - 4,85 (m, 1 H), 5,12 (d, *J*=5,27 Hz, 1 H), 7,83 (d, *J*=9,04 Hz, 1 H), 8,05 (dd, *J*=9,04, 2,26 Hz, 1 H), 8,55 (d, *J*=2,26 Hz, 1 H), 8,64 (s, 1 H).	Intermediario 24 e hidrocloruro de *cis*-2-aminociclo-hexanol
122	(S)-1-(1-(terc-butoxicarbonil)piperidin-3-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ES) $(M+H)^+$: 527 para $C_{22}H_{27}IN_2O_5$	Intermediario 24 y (S)-3-amino-piperidin-1-carboxilato de terc-butilo

Int.	Compuesto	Datos	SM
123	(R)-1-(1-(terc-butoxicarbonil)piperidin-3-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ES) $(M+H)^+$: 527 para $C_{22}H_{27}IN_2O_5$	Intermediario 24 y (R)-3-amino-piperidin-1-carboxilato de terc-butilo

Intermediario 124

Ácido 5-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-2-fluorobenzoico



Se combinaron ácido 6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-ilborónico (Intermediario 17, 0,261 g, 0,72 mmoles, Intermediario 17) y ácido 2-fluoro-5-yodobenzoico (0,175 g, 0,66 mmoles, Aldrich) en dioxano (1 ml). Se añadió una disolución de carbonato de cesio (0,364 g, 1,12 mmoles) en agua (0.658 ml), seguido de tetraquis(trifenilfosfina)paladio (0) (0,076 g, 0,07 mmoles, strem) y dioxanos adicional (2,63 ml). El matraz se colocó en un baño de aceite precalentado hasta 100 °C, y se calentó durante 1h., después se enfrió hasta 0°C y se añadió HCl 1 N hasta que el pH fue ~3. Se añadió EtOAc (5ml), y apareció un sólido y se recogió mediante filtración y se lavó con EtOAc, y después se secó para dar un sólido gris ácido 5-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-2-fluorobenzoico (0.180 g, 60,2 %).

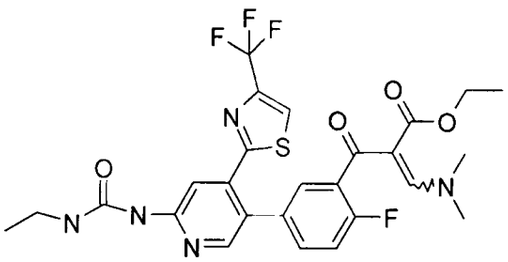
MS (ES) $(M+H)^+$: 455 para $C_{19}H_{14}F_4N_4O_3S$ RMN:

RMN ^1H (300 MHz, *DMSO-d_6*) δ 13,38 (br. s., 1 H), 9,43 (s, 1 H), 8,53 (s, 1 H), 8,28 (s, 1 H),

8,21 (s, 1 H), 7,76 (d, *J*=6,78 Hz, 1 H), 7,59 (d, *J*=3,77 Hz, 2 H), 7,35 - 7,47 (m, 1 H), 3,18 - 3,25 (m, 2 H), 1,10 (t, *J*=7,16 Hz, 3 H).

Intermediario 125

3-(dimetilamino)-2-(5-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-2-fluorobenzoil)acrilato de etilo

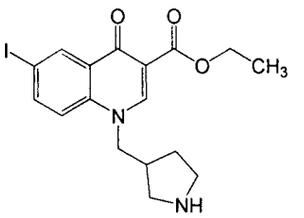


Se suspendió ácido 5-(6-(3-etilureido)-4-(4-(trifluorometil)tiazol-2-il)piridin-3-il)-2-fluorobenzoico (0,180 g, 0,40 mmoles, Intermediario 124) en tolueno (3 ml). Se añadieron cloruro de tionilo (0,145 ml, 1,98 mmoles, Aldrich) y 1 gota de DMF, y la mezcla se calentó hasta 45°C durante 15 min. Tras enfriar hasta la temperatura ambiente, la mezcla se concentró *a vacío* y se añadió tolueno, y después la mezcla se concentró *a vacío* nuevamente para dar un residuo amarillo oscuro. Después de secar a alto vacío toda la noche, el aceite se convirtió en una película amarilla oscura. Esta película se recogió en THF (2 ml). En un matraz separado, se disolvieron 3-(dimetilamino)acrilato de etilo (0,074 g, 0,51 mmoles, Acros) y trietilamina (0,082 ml, 0,59 mmoles, Acros) en THF (5 ml). Se añadió gota a gota la disolución del cloruro de ácido en THF (2ml) a la disolución de acrilato, y después el matraz se colocó en un baño de aceite precalentado hasta 72 °C y se agitó durante 1 h. Tras enfriar hasta la temperatura ambiente, la mezcla se diluyó con EtOAc (10 ml) y agua (10 ml). Las capas se separaron, y la capa orgánica se lavó con HCl 1 N, dos veces con agua, una vez con salmuera, y entonces se secó sobre Na_2SO_4, se filtró y se concentró *a vacío* para dar el producto bruto como un aceite naranja.

MS (ES) $(M+H)^+$: 580 para $C_{26}H_{25}F_4N_5O_4S$.

Intermediario 126

Hidrocloruro de 6-yodo-4-oxo-1-(pirrolidin-3-ilmetil)-1,4-dihidroquinolin-3-carboxilato de etilo

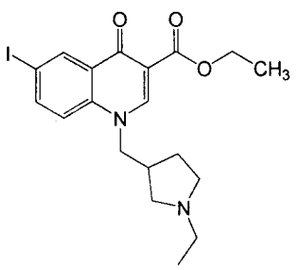


Se disolvió 1-((1-(terc-butoxicarbonil)pirrolidin-3-il)metil)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo (Intermediario 100, 3,0 g, 5,7 mmoles) en 1,4-dioxano (15 ml), y se añadió cloruro de hidrógeno 4,0M en 1,4-dioxano (10 ml). La reacción se agitó a 23°C durante 3 h, y el disolvente se eliminó *a vacío*. El sólido se secó entonces en un horno de vacío a 50°C durante 18 h para dar 2,61 (rendimiento cuant.) de hidrocloruro de 6-yodo-4-oxo-1-(pirrolidin-3-ilmetil)-1,4-dihidroquinolin-3-carboxilato de etilo como un sólido amarillo.

MS (ESP): 427,1 ($M+H^+$) para $C_{17}H_{19}IN_2O_3$

Intermediario 127

1-((1-etilpirrolidin-3-il)metil)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo

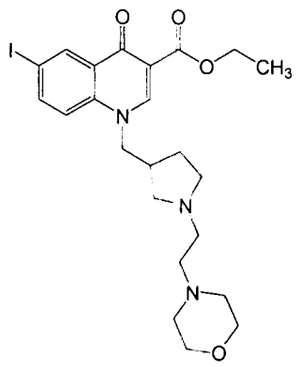


Se suspendió hidrocloruro de 6-yodo-4-oxo-1-(pirrolidin-3-ilmetil)-1,4-dihidroquinolin-3-carboxilato de etilo (Intermediario 126, 500 mg, 1,08 mmoles) en metanol (15 ml), y después se añadieron acetaldehído (300 µl, 5,4 mmoles) y cianoborohidruro de sodio (612 mg, 9,7 mmoles). La reacción se agitó a 23°C durante 16 h. El volumen de la reacción se redujo a la mitad, y se añadió agua (25 ml). La suspensión se extrajo con acetato de etilo: tetrahidrofurano 2:1 (3 × 10 ml). Las fases orgánicas se combinaron, se secaron sobre sulfato de sodio, y el disolvente se eliminó *a vacío*. El residuo se hizo pasar a través de un tapón de gel de sílice (2 g), eluyendo con 10% de metanol en diclorometano para eliminar cualquier borohidruro que quede. El sólido se secó entonces en un horno de vacío a 50°C durante 18 h para dar 378 mg (77% de rendimiento) de 1-((1-etilpirrolidin-3-il)metil)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo como un sólido blanquecino.

MS (ESP): 455,1 ($M+H^+$) para $C_{18}H_{21}IN_2O_3$

Intermediario 128

6-yodo-1-((1-(2-morfolinoetil)pirrolidin-3-il)metil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo

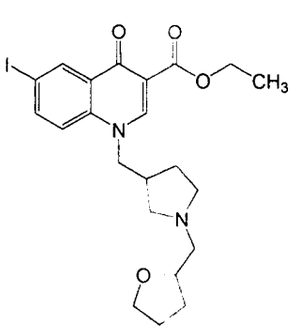


Se suspendió hidrocloruro de 6-yodo-4-oxo-1-(pirrolidin-3-ilmetil)-1,4-dihidroquinolin-3-carboxilato de etilo (Intermediario 127, 500 mg, 1,08 mmoles) en metanol (15 ml), y después se añadieron hidrocloruro de monohidrato de morfolin-4-ilacetaldehído (1 g, 5,4 mmoles) y cianoborohidruro de sodio (612 mg, 9,7 mmoles). La reacción se agitó a 23°C durante 16 h. El volumen de la reacción se redujo a la mitad, y se añadió agua (25 ml). La suspensión se extrajo con acetato de etilo: tetrahidrofurano 2:1 (3 × 10 ml). Las fases orgánicas se combinaron, se secaron sobre sulfato de sodio, y el disolvente se eliminó *a vacío*. El residuo se hizo pasar a través de un tapón de gel de sílice (2 g), eluyendo con 10% de metanol en diclorometano para eliminar cualquier borohidruro que quede. El sólido se secó entonces en un horno de vacío a 50°C durante 18 h para dar 225 mg (38% de rendimiento) de 6-yodo-1-((1-(2-morfolinoetil)pirrolidin-3-il)metil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo como un sólido blanquecino.

MS (ESP): 540,0 ($M+H^+$) para $C_{23}H_{30}IN_3O_4$

Intermediario 129

6-yodo-4-oxo-1-((1-((tetrahidrofuran-2-il)metil)pirrolidin-3-il)metil)-1,4-dihidroquinolin-3-carboxilato de etilo



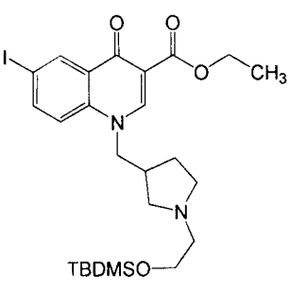
Se suspendió hidrocloruro de 6-yodo-4-oxo-1-(pirrolidin-3-ilmetil)-1,4-dihidroquinolin-3-carboxilato de etilo (Intermediario 126, 500 mg, 1,08 mmoles) en dimetilformamida (3 ml), y después se añadieron cloruro de tetrahidrofurfurilo (1 ml) y polvo de carbonato de potasio (400 mg, 22,2 mmoles). La reacción se agitó a 70°C durante 36 h. Se añadió agua (15 ml), y la suspensión se extrajo con acetato de etilo (3 × 10 ml). Las fases orgánicas se combinaron, se secaron sobre sulfato de sodio, y el disolvente se eliminó *a vacío*. El residuo se cromatografió en una columna de 4 g Analogix, usando 0-10% de metanol en diclorometano. El sólido se secó entonces en un horno de vacío a 50°C durante 18 h para dar 181 mg (32% de rendimiento) de 6-yodo-4-oxo-1-((1-((tetrahidrofuran-2-il)metil)pirrolidin-3-il)metil)-1,4-dihidroquinolin-3-carboxilato de etilo como un sólido blanquecino.

MS (ESP): 511,1 ($M+H^+$) para $C_{22}H_{27}IN_2O_4$

RMN ^1H (300 MHz, $CDCl_3$): δ 1,38 (t, 3H), 1,42-1,61 (m, 2H), 1,81-2,08 (m, 4H), 2,38-2,81 (m, 6H), 2,84-2,96 (m, 1H), 3,71-4,28 (m, 6H), 4,38 (q, 2H), 7,28(dd, 1H), 7,93 (dd, 1H), 8,49 (s, 1H), 8,83 (d, 1H).

Intermediario 130

1-((1-(2-(terc-butildimetilsilyloxi)etil)pirrolidin-3-il)metil)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo



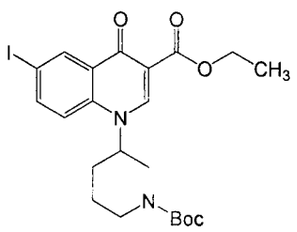
Se suspendió hidrocloruro de 6-yodo-4-oxo-1-(pirrolidin-3-ilmetil)-1,4-dihidroquinolin-3-carboxilato de etilo (Intermediario 126, 500 mg, 1,08 mmoles) en metanol (15 ml), y después se añadieron (terc-butildimetilsililoxi)acetaldehído (1 ml, 5,4 mmoles) y cianoborohidruro de sodio (612 mg, 9,7 mmoles). La reacción se agitó a 23°C durante 16 h. El volumen de la reacción se redujo a la mitad, y se añadió agua (25 ml). La suspensión se extrajo con acetato de etilo: tetrahidrofurano 2:1 (3× 10 ml). Las fases orgánicas se combinaron, se secaron sobre sulfato de sodio, y el disolvente se eliminó *a vacío*. El residuo se cromatografió en una columna de 4 g Analogix, eluyendo con 0-10% de metanol en diclorometano. El sólido se secó entonces en un horno de vacío a 50°C durante 18 h para dar 253 mg (39% de rendimiento) de 1-((1-(2-(terc-butildimetilsililoxi)etil)pirrolidin-3-il)metil)-6-yodo-4-oxo-1,4-

dihidroquinolin-3-carboxilato de etilo como un sólido blanquecino.

MS (ESP): 585,2 ($M+H^+$) para $C_{25}H_{28}IN_2O_4Si$

Intermediario 131

1-(1-(terc-butoxicarbonil)piperidin-3-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo



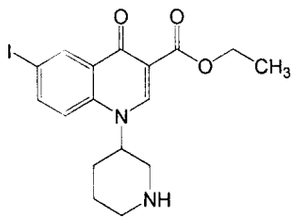
Se añadió 3-amino-1-N-Boc-piperidina (2,5 g, 12,5 mmoles) a la disolución de (Z)-3-(dimetilamino)-2-(3-yodobenzoil)acrilato de etilo (Intermediario 24, 0,34M, 34 ml, 11,3 mmoles), y se calentó hasta 50°C durante 3 h. El disolvente se eliminó *a vacío*, y el residuo se secó en un horno de vacío durante 1,5 h. El residuo se disolvió entonces en dimetilformamida (20 ml), y se añadió polvo de carbonato de potasio (2,2 g, 15,8 mmoles). La reacción se calentó a 70°C durante 3 h, y después se enfrió hasta la temperatura ambiente. Se añadió agua (100 ml), y la suspensión se extrajo con acetato de etilo : metil-terc-butiléter 1:1 (3×, 50 ml). Las capas orgánicas se secaron sobre sulfato de sodio, y el disolvente se eliminó *a vacío*. El residuo se suspendió en metil-terc-butiléter (20 ml), y se agitó a 40°C durante 1 h. La suspensión se filtró, y el sólido se secó para dar 4,93 g (82% de rendimiento) de 1-(1-(terc-butoxicarbonil)piperidin-3-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo como un polvo amarillento.

MS (ESP): 527,1 ($M+H^+$) para $C_{22}H_{27}IN_2O_5$

RMN ^1H (300 MHz, DMSO-d_6): δ 1,24 (t, 3H), 1,45 (s, 9H), 1,61-1,90(bm, 4H), 2,18 (bs, 2H), 2,94 (bs, 1H), 3,20 (bs, 1H), 3,83 (bd, 1H), 4,08 (bd, 1H), 4,23 (q, 2H), 4,62 (bs, 1H), 7,77 (bd, 1H), 8,08 (d, 1H), 8,52 (d, 1H), 8,61 (s, 1H).

Intermediario 132

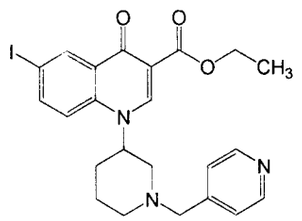
Hidrocloruro de 6-yodo-4-oxo-1-(piperidin-3-il)-1,4-dihidroquinolin-3-carboxilato de etilo



Se disolvió 1-((1-(terc-butoxicarbonil)pirrolidin-3-il)metil)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo (Intermediario 131, 3,0 g, 5,7 mmoles) en 1,4-dioxano (15 ml), y se añadió cloruro de hidrógeno 4,0M en 1,4-dioxano (10 ml). La reacción se agitó a 23°C durante 3 h. y el disolvente se eliminó *a vacío*. El sólido se secó entonces en un horno de vacío a 50°C durante 18 h para dar 2,64g (rendimiento cuant.) de hidrocloruro de 6-yodo-4-oxo-1-(piperidin-3-il)-1,4-dihidroquinolin-3-carboxilato de etilo como un sólido amarillo.
MS (ESP): 427,0 ($M+H^+$) para $C_{22}H_{27}IN_2O_5$

Intermediario 133

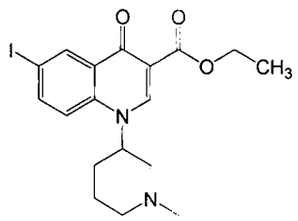
6-yodo-4-oxo-1-(1-(piridin-4-ilmetil)piperidin-3-il)-1,4-dihidroquinolin-3-carboxilato de etilo



Se suspendió hidrocloruro de 6-yodo-4-oxo-1-(piperidin-3-il)-1,4-dihidroquinolin-3-carboxilato de etilo (Intermediario 132, 500 mg, 1,08 mmoles) en metanol (15 ml), y después se añadieron 4-piridincarboxaldehído (520 µl, 5,4 mmoles) y cianoborohidruro de sodio (612 mg, 9,7 mmoles). La reacción se agitó a 23°C durante 16 h. El volumen de la reacción se redujo a la mitad, y se añadió agua (25 ml). La suspensión se extrajo con acetato de etilo: tetrahidrofurano 2:1 (3× 10 ml). Las fases orgánicas se combinaron, se secaron sobre sulfato de sodio, y el disolvente se eliminó *a vacío*. El residuo se hizo pasar a través de un tapón de gel de sílice (2 g), eluyendo con 10% de metanol en diclorometano para eliminar cualquier borohidruro que quede. El sólido se secó entonces en un horno de vacío a 50°C durante 18 h para dar 460 mg (82% de rendimiento) de 6-yodo-4-oxo-1-(1-(piridin-4-ilmetil)piperidin-3-il)-1,4-dihidroquinolin-3-carboxilato de etilo como un sólido blanquecino.
MS (ESP): 706,2 ($M+H^+$) para $C_{12}H_{10}BrF_3N_4OS$.

Intermediario 134

6-yodo-1-(1-metilpiperidin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo

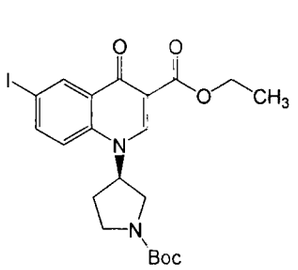


Se suspendió hidrocloruro de 6-yodo-4-oxo-1-(piperidin-3-il)-1,4-dihidroquinolin-3-carboxilato de etilo (Intermediario 132, 500 mg, 1,08 mmoles) en metanol (15 ml), y después se añadieron formaldehído al 37% en agua (405 µl, 5,4 mmoles) y cianoborohidruro de sodio (612 mg, 9,7 mmoles). La reacción se agitó a 23°C durante 16 h. El volumen de la reacción se redujo a la mitad, y se añadió agua (25 ml). La suspensión se extrajo con acetato de etilo: tetrahidrofurano 2:1 (3 × 10 ml). Las fases orgánicas se combinaron, se secaron sobre sulfato de sodio, y el disolvente se eliminó *a vacío*. El residuo se hizo pasar a través de un tapón de gel de sílice (2 g), eluyendo con 10% de metanol en diclorometano para eliminar cualquier borohidruro que quede. El sólido se secó entonces en un horno de vacío a 50°C durante 18 h para dar 386 mg (81% de rendimiento) de 6-yodo-1-(1-metilpiperidin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo como un sólido blanquecino.

MS (ESP): 441,0 ($M+H^+$) para $C_{18}H_{21}IN_2O_3$

Intermediario 135

(S)-1-(1-(terc-butoxicarbonil)pirrolidin-3-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo



Se añadió (S)-3-amino-1-N-Boc-pirrolidina (1 g, 5,36 mmoles) a la disolución of (Z)-3-(dimetilamino)-2-(3-yodobenzoil)acrilato de etilo (Intermediario 24, 0,34M, 14,3 ml, 4,88 mmoles), y se calentó a 50°C durante 3 h. El disolvente se eliminó *a vacío*, y el residuo se secó en un horno de vacío durante 1,5 h. El residuo se disolvió entonces en dimetilformamida (8 ml), y se añadió polvo de carbonato de potasio (1,0 g, 6,83 mmoles). La reacción se calentó a 70°C durante 3 h, y después se enfrió hasta la temperatura ambiente. Se añadió agua (40 ml), y la suspensión se extrajo con acetato de etilo : metil-terc-butiléter 1:1 (3× 30 ml). Las capas orgánicas se secaron sobre sulfato de sodio, y el disolvente se eliminó *a vacío*. El residuo se

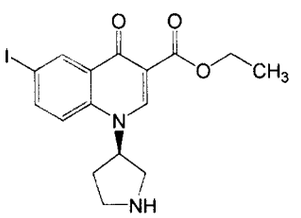
suspendió en metil-terc-butiléter (20 ml), y se agitó a 40°C durante 1 hora. La suspensión se filtró, y el sólido se secó para dar 1,76 g (71% de rendimiento) de (R)-1-(1-(terc-butoxicarbonil)pirrolidin-3-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo como un polvo amarillento.

MS (ESP): 513,0 ($M+H^+$) para $C_{21}H_{25}IN_2O_5$

RMN ^1H (300 MHz, DMSO-d_6): δ 1,23 (t, 3H), 1,42 (s, 9H), 2,22 (bs, 2H), 2,48 (bs, 2H), 3,40 (bd, 2H), 3,73 (bm, 2H), 4,18 (q, 2H), 5,31 (bs, 1H), 7,78 (d, 1H), 8,07 (dd, 1H), 8,41 (bd, 1H), 8,52 (s, 1H).

Intermediario 136

Hidrocloruro de (S)-6-yodo-4-oxo-1-(pirrolidin-3-il)-1,4-dihidroquinolin-3-carboxilato de etilo

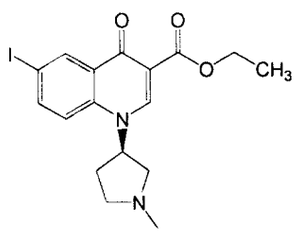


Se disolvió (S)-1-(1-(terc-butoxicarbonil)pirrolidin-3-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo (1,2 g, 1,08 mmoles) en 1,4-dioxano (10 ml), y se añadió cloruro de hidrógeno 4,0M en 1,4-dioxano (4 ml). La reacción se agitó a 23°C durante 3 horas, y el disolvente se eliminó *a vacío*. El sólido se secó entonces en un horno de vacío a 50°C durante 18 horas para dar 1,03g (rendimiento cuant.) de hidrocloruro de (R)-6-yodo-4-oxo-1-(pirrolidin-3-il)-1,4-dihidroquinolin-3-carboxilato de etilo como un sólido amarillo.

MS (ESP): 412,9 ($M+H^+$) para $C_{16}H_{17}IN_2O_3$

Intermediario 137

(S)-6-yodo-1-(1-metilpirrolidin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo



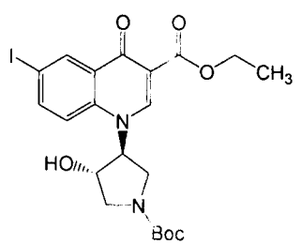
Se suspendió hidrocloruro de (S)-6-yodo-4-oxo-1-(pirrolidin-3-il)-1,4-dihidroquinolin-3-carboxilato de etilo (Intermediario 136, 484 mg, 1,08 mmoles) en metanol (15 ml), y después se añadieron formaldehído al 37% en agua (405 µl, 5,4 mmoles) y cianoborohidruro de sodio

(612 mg, 9,7 mmoles). La reacción se agitó a 23°C durante 16 h. El volumen de la reacción se redujo a la mitad, y se añadió agua (25 ml). La suspensión se extrajo con acetato de etilo: tetrahidrofurano 2:1 (3 × 10 ml). Las fases orgánicas se combinaron, se secaron sobre sulfato de sodio, y el disolvente se eliminó *a vacío*. El residuo se hizo pasar a través de un tapón de gel de sílice (2 g), eluyendo con 10% de metanol en diclorometano para eliminar cualquier borohidruro que quede. El sólido se secó entonces en un horno de vacío a 50°C durante 18 h para dar 379 mg (82% de rendimiento) de (S)-6-yodo-1-(1-metilpirrolidin-3-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo como un sólido blanquecino.

MS (ESP): 426,9 ($M+H^+$) para $C_{17}H_{19}IN_2O_3$

Intermediario 138

trans-1-(1-(terc-butoxicarbonil)-4-hidroxipirrolidin-3-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo

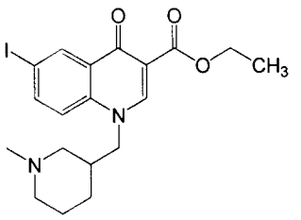


Se añadió *trans*-3-amino-4-hidroxipirrolidin-1-carboxilato de *terc*-butilo (500 mg, 2,47 mmoles) a la disolución de (Z)-3-(dimetilamino)-2-(3-yodobenzoil)acrilato de etilo (Intermediario 24, 0,34M, 6,7 ml, 2,25 mmoles), y la mezcla se calentó a 50°C durante 3 hora. El disolvente se eliminó *a vacío*, y el residuo se secó en un horno de vacío durante 1,5 horas. El residuo se disolvió entonces en dimetilformamida (5 ml), y se añadió polvo de carbonato de potasio (435 mg, 3,15 mmoles). La reacción se calentó a 70°C durante 3 h, y después se enfrió hasta la temperatura ambiente. Se añadió agua (30 ml), y la suspensión se extrajo con acetato de etilo : metil-terc-butiléter 1:1 (3 × 50 ml). Las capas orgánicas se secaron sobre sulfato de sodio, y el disolvente se eliminó *a vacío*. El residuo se suspendió en metil-terc-butiléter (20 ml) y se agitó a 40°C durante 1 h. La suspensión se filtró, y el sólido se secó para dar 751 mg (64% de rendimiento) de *trans*-1-(1-(terc-butoxicarbonil)-4-hidroxipirrolidin-3-il)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo racémico como un polvo amarillento.

MS (ESP): 528,9 ($M+H^+$) para $C_{21}H_{25}IN_2O_6$

Intermediario 139

6-yodo-1-((1-metilpiperidin-3-il)metil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo



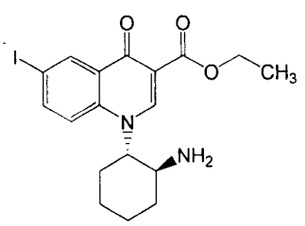
Se añadió 1-(1-metilpiperidin-3-il)metanamina (500 mg, 3,9 mmoles) a la disolución de (Z)-3-(dimetilamino)-2-(3-yodobenzoil)acrilato de etilo (Intermediario 24, 0,34M, 10,4 ml, 2,25 mmoles), y la mezcla se calentó a 50°C durante 3 h. El disolvente se eliminó *a vacío*, y el residuo se secó en un horno de vacío durante 1,5 h. El residuo se disolvió entonces en dimetilformamida (7 ml), y se añadió polvo de carbonato de potasio (695 mg, 5,1 mmoles). La reacción se calentó a 70°C durante 3 h, y después se enfrió hasta la temperatura ambiente. Se añadió agua (30 ml), y la suspensión se extrajo con acetato de etilo : metil-terc-butiléter 1:1 (3 × 50 ml). Las capas orgánicas se secaron sobre sulfato de sodio, y el disolvente se eliminó *a vacío*. El residuo se suspendió en metil-terc-butiléter (20 ml) y se agitó a 40°C durante 1 h. La suspensión se filtró, y el sólido se secó para dar 1,12 mg (69% de rendimiento) de 6-yodo-1-((1-metilpiperidin-3-il)metil)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo como un polvo amarillento.

MS (ESP): 455,2 ($M+H^+$) para $C_{19}H_{23}IN_2O_3$

RMN ^1H (300 MHz, DMSO-d_6): δ 1,12 (m, 1H), 1,28 (t, 3H), 1,29-1,60 (m, 2H), 1,68 (m, 1H), 1,79 (m, 1H), 1,98-2,19 (m, 2H), 2,17 (s, 3H), 2,20-2,42 (m, 2H), 3,38 (m, 1H), 4,26(q, 2H), 4,20-4,41 (m, 2H), 7,69 (d, 1H), 8,05 (dd, 1H), 8,52 (d, 1H), 8,63 (s, 1H).

Intermediario 140

1-((1S,2S)-2-aminociclohexil)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo

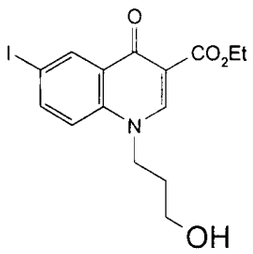


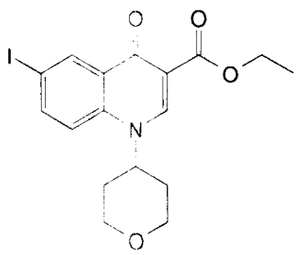
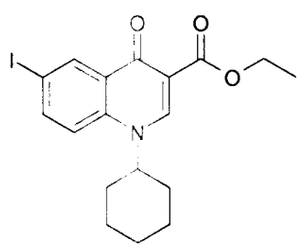
Se añadió (1S,2S)-(+)-1,2-diaminociclohexano (500 mg, 4,3 mmoles) a la disolución de (Z)-3-(dimetilamino)-2-(3-yodobenzoil)acrilato de etilo (Intermediario 24, 0,34M, 11,7 ml, 3,9 mmoles), y la mezcla se calentó a 50°C durante 3 h. El disolvente se eliminó *a vacío*, y el residuo se secó en un horno de vacío durante 1,5 h. El residuo se disolvió entonces en dimetilformamida (7 ml), y se añadió polvo de carbonato de potasio (753 mg, 5,5 mmoles).

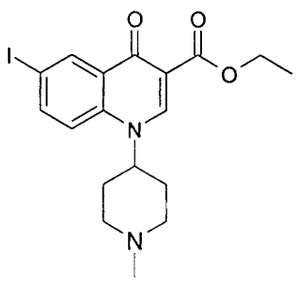
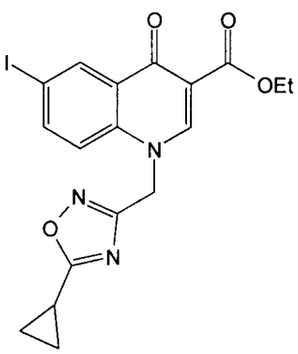
La reacción se calentó a 70°C durante 3 h, y después se enfrió hasta la temperatura ambiente. Se añadió agua (30 ml), y la suspensión se extrajo con acetato de etilo : metil-terc-butiléter 1:1 (3 × 50 ml). Las capas orgánicas se secaron sobre sulfato de sodio, y el disolvente se eliminó *a vacío*. El residuo se suspendió en metil-terc-butiléter (20 ml) y se agitó a 40°C durante 1 h. La suspensión se filtró, y el sólido se secó para dar 724 mg (42% de rendimiento) de 1-((1S,2S)-2-aminociclohexil)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo como un polvo amarillento que estaba contaminado con alrededor de 40% de bisdihidroquinolina. Este material se usó como tal en la etapa de acoplamiento.
MS (ESP): 441,0 ($M+H^+$) para $C_{18}H_{21}IN_2O_3$

Intermediarios 141-145

Los siguientes Intermediarios se prepararon según el procedimiento descrito para el Intermediario 140 a partir de los materiales de partida indicados.

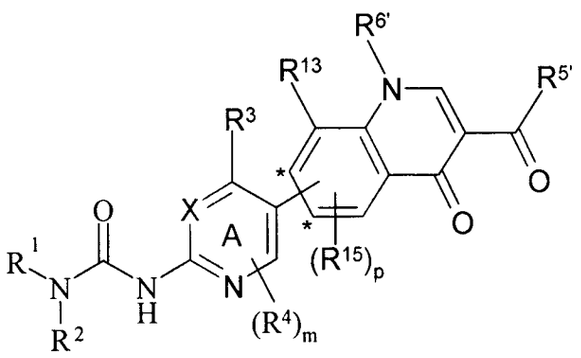
Int.	Compuesto	Datos	SM
141	1-(3-hidroxipropil)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 402 (M+1) para $C_{15}H_{16}INO_4$ RMN ^{1}H (400 MHz, DMSO-d_6) δ: 1,28 (t, *J*=7,07 Hz, 3H); 1,79 - 1,97 (m, 2H); 3,44 (q, *J*=5,64 Hz, 2H); 4,22 (q, *J*=7,07 Hz, 2H); 4,39 (t, *J*=7,07 Hz, 2H); 4,72 (t, *J*=4,93, Hz, 1H); 7,65 (d, *J*=9,09 Hz, 1H); 8,07 (dd, *J*=8,97, 2,15 Hz, 1H); 8,50 (d, *J*=2,27 Hz, 1H); 8,66 (s, 1H).	Intermediario 24 y 3-aminopropan-1-ol

Int.	Compuesto	Datos	SM
142	6-yodo-4-oxo-1-(tetrahidro-2H-piran-4-il)-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 427,98 (M+) para $C_{17}H_{18}INO_4$ RMN ^1H (400 MHz, CLOROFORMO-d) δ: 1,43 (t, *J*=7,07 Hz, 3H); 2,06 - 2,24 (m, 4H); 3,68 (td, *J*=11,56, 2,15 Hz, 2H); 4,24 (dd, *J*=11,49, 3,66 Hz, 2H); 4,42 (q, *J*=7,16 Hz, 2H); 4,61 - 4,73 (m, 1H); 7,39 (d, *J*=8,84 Hz, 1H); 7,96 (dd, *J*=8,97, 2,15 Hz, 1H); 8,66 (s, 1H); 8,88 (d, *J*=2,02 Hz, 1H).	Intermediario 24 y tetrahidro-2H-piran-4-amina
143	1-ciclohexil-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 426,03 (M+1) para $C_{18}H_{20}INO_3$ RMN ^1H (400 MHz, CLOROFORMO-d) δ: 1,43 (t, J=7,20 Hz, 3H); 1,50 - 1,64 (m, 2H); 1,71 - 1,94 (m, 4H); 2,00 - 2,11 (m, 2H); 2,13 - 2,22 (m, 2H); 4,31 - 4,48 (m, 3H); 7,34 (d, J=9,09 Hz, 1H); 7,96 (dd, J=8,97, 2,15 Hz, 1H); 8,68 (s, 1H); 8,89 (d, J=2,02 Hz, 1H).	Intermediario 24 y ciclohexilamina

Int.	Compuesto	Datos	SM
144	6-yodo-1-(1-metilpiperidin-4-il)-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 441,13 (M+1) para $C_{18}H_{21}IN_2O_3$ RMN ^{1}H (400 MHz, DMSO-d_6) δ: 1,28 (t, *J*=7,07 Hz, 3H); 1,90 - 2,04 (m, 4H); 2,16 - 2,30 (m, 5H); 2,85 - 2,99 (m, 2H); 4,22 (q, *J*=7,07 Hz, 2H); 4,54 - 4,71 (m, 1H); 7,84 (d, *J*=9,35 Hz, 1H); 8,06 (dd, *J*=9,09, 2,27 Hz, 1H); 8,52 (d, *J*=2,27 Hz, 1H); 8,58 (s, 1H).	Intermediario 24 y 1-metilpiperidin-4-amina
145	1-((5-ciclopropil-1,2,4-oxadiazol-3-il)metil)-6-yodo-4-oxo-1,4-dihidroquinolin-3-carboxilato de etilo 	MS (ESP): 465,95 (M+) para $C_{18}H_{16}IN_3O_4$ RMN ^{1}H-RMN (400 MHz, DMSO-d_6) δ: 1,02 - 1,10 (m, 2H); 1,17- 1,26 (m, 2H); 1,29 (t, *J*=7,07 Hz, 3H); 2,26 - 2,38 (m, 1H); 4,24 (q, *J*=7,07 Hz, 2H); 5,81 (s, 2H); 7,48 (d, *J*=9,09 Hz, 1H); 8,00 - 8,08 (m, 1H); 8,49 (d, *J*=2,27 Hz, 1H); 8,87 (s, 1H).	Intermediario 24 y 5-ciclopropil-1,2,4-oxadiazol-3-ilmetilamina

Reivindicaciones

1. Un compuesto de fórmula **(I')**:



(I')

o una sal farmacéuticamente aceptable del mismo, en la que:

El anillo A está unido a uno de los átomos de carbono indicados por "*";

X es N, CH o CR^4;

R^1 se selecciona de alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6} o cicloalquilo C_{3-6}; en la que R^1 puede estar opcionalmente sustituido en el carbono con uno o más R^7;

R^2 se selecciona de hidrógeno o alquilo C_{1-6}; en la que dicho alquilo C_{1-6} puede estar opcionalmente sustituido con uno o más grupos seleccionados independientemente de halo, ciano, hidroxi, nitro y amino;

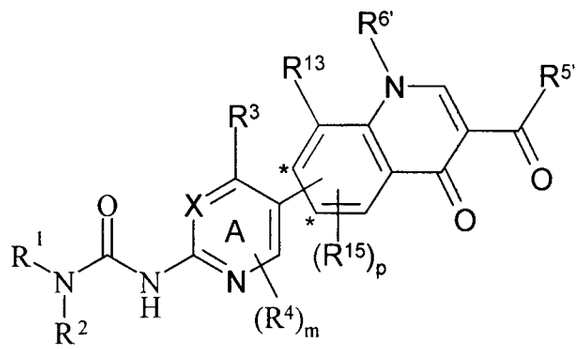
o **R^1 y R^2**, junto con el nitrógeno al que están unidos, forman un heterociclilo; en la que dicho heterociclilo puede estar opcionalmente sustituido en uno o más átomos de carbono con uno o más R^8; y en la que, si dicho heterociclilo contiene un resto =N- o –S-, ese nitrógeno puede estar opcionalmente sustituido con un grupo oxo, y ese azufre puede estar opcionalmente sustituido con uno o dos grupos oxo; y en la que, si dicho heterociclilo contiene un resto -NH-, ese nitrógeno puede estar opcionalmente sustituido con un grupo seleccionado de R^9;

R^3 es un carbociclilo C_{3-14} o a heterociclilo; en la que el carbociclilo o heterociclilo puede estar opcionalmente sustituido en uno o más átomos de carbono con uno o más R^{10}; y en la que, si dicho heterociclilo contiene un resto =N- o –S-, ese nitrógeno puede estar opcionalmente sustituido con un grupo oxo, y ese azufre puede estar opcionalmente sustituido con uno o dos grupos oxo; y en la que, si dicho heterociclilo contiene un resto -NH-, ese nitrógeno puede estar opcionalmente sustituido con un grupo seleccionado de R^{11};

R^4 y **R^{15}**, para cada caso, se seleccionan independientemente del grupo que consiste en

Reivindicaciones

1. Un compuesto de fórmula **(I')**:



(I')

o una sal farmacéuticamente aceptable del mismo, en la que:

El anillo A está unido a uno de los átomos de carbono indicados por "*";

X es N, CH o CR^4;

$\mathbf{R^1}$ se selecciona de alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6} o cicloalquilo C_{3-6}; en la que R^1 puede estar opcionalmente sustituido en el carbono con uno o más R^7;

$\mathbf{R^2}$ se selecciona de hidrógeno o alquilo C_{1-6}; en la que dicho alquilo C_{1-6} puede estar opcionalmente sustituido con uno o más grupos seleccionados independientemente de halo, ciano, hidroxi, nitro y amino;

o $\mathbf{R^1}$ y $\mathbf{R^2}$, junto con el nitrógeno al que están unidos, forman un heterociclilo; en la que dicho heterociclilo puede estar opcionalmente sustituido en uno o más átomos de carbono con uno o más R^8; y en la que, si dicho heterociclilo contiene un resto =N- o –S-, ese nitrógeno puede estar opcionalmente sustituido con un grupo oxo, y ese azufre puede estar opcionalmente sustituido con uno o dos grupos oxo; y en la que, si dicho heterociclilo contiene un resto -NH-, ese nitrógeno puede estar opcionalmente sustituido con un grupo seleccionado de R^9;

$\mathbf{R^3}$ es un carbociclilo C_{3-14} o a heterociclilo; en la que el carbociclilo o heterociclilo puede estar opcionalmente sustituido en uno o más átomos de carbono con uno o más R^{10}; y en la que, si dicho heterociclilo contiene un resto =N- o –S-, ese nitrógeno puede estar opcionalmente sustituido con un grupo oxo, y ese azufre puede estar opcionalmente sustituido con uno o dos grupos oxo; y en la que, si dicho heterociclilo contiene un resto -NH-, ese nitrógeno puede estar opcionalmente sustituido con un grupo seleccionado de R^{11};

$\mathbf{R^4}$ y $\mathbf{R^{15}}$, para cada caso, se seleccionan independientemente del grupo que consiste en

halo, nitro, ciano, hidroxi, amino, mercapto, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, alcoxi C_{1-6}, *N*-(alquil C_{1-6})amino, *N,N*-(alquil C_{1-6})$_2$amino, y alquil C_{1-6}-sulfanilo; en la que R^4, R^{13}, y R^{15}, independientemente entre sí, pueden estar opcionalmente sustituidos en uno o más carbonos con uno o más R^{12};

$R^{5'}$ es –OH, un alcoxi C_{1-6}, cicloalcoxi C_{3-14}, o -NR^aR^b; en la que el grupo alcoxi C_{1-6} puede estar opcionalmente sustituido en uno o más átomos de carbono con uno o más R^{14}, seleccionados independientemente; y en la que R^a y R^b son cada uno independientemente hidrógeno, un alquilo C_{1-6}, o un carbociclo C_{3-14}, o R^a y R^b, junto con el nitrógeno al que están unidos, forman un heterociclo, en el que R^a y R^b pueden estar opcionalmente sustituidos en uno o más átomos de carbono con uno o más R^{14}, seleccionados independientemente; y en la que, si dicho heterociclilo contiene un resto =N- o –S-, ese nitrógeno puede estar opcionalmente sustituido con un grupo oxo, y ese azufre puede estar opcionalmente sustituido con uno o dos grupos oxo; y en la que, si dicho heterociclilo contiene un resto -NH-, ese nitrógeno puede estar opcionalmente sustituido con un grupo seleccionado de R^{22};

$R^{6'}$, para cada caso, se selecciona independientemente del grupo que consiste en hidrógeno, alquilo C_{1-6}, alquil C_{1-6}-sulfanilo, carboxi, carbamoilo, N-(alquil C_{1-6})carbamoilo, N,N-(alquil C_{1-6})$_2$carbamoilo, carbociclil C_{3-14}-L-, y heterociclil-L-; en la que R^6 está opcionalmente sustituido en uno o más átomos de carbono con uno o más R^{16}; y en la que, si dicho heterociclilo contiene un resto =N- o –S-, ese nitrógeno puede estar opcionalmente sustituido con un grupo oxo, y ese azufre puede estar opcionalmente sustituido con uno o dos grupos oxo; y en la que, si dicho heterociclilo contiene un resto -NH-, ese nitrógeno puede estar opcionalmente sustituido con un grupo seleccionado de $R^{17'}$;

R^{13} se selecciona del grupo que consiste en hidrógeno, halo, nitro, ciano, hidroxi, amino, mercapto, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, alcoxi C_{1-6}, *N*-(alquil C_{1-6})amino, *N,N*-(alquil C_{1-6})$_2$amino, y alquil C_{1-6}-sulfanilo; en la que R^{13} puede estar opcionalmente sustituido en uno o más carbonos con uno o más R^{16}; o

$R^{6'}$ y R^{13}, junto con los átomos anulares que intervienen, pueden formar un heterociclilo condensado, en la que el heterociclilo condensado puede estar opcionalmente sustituido en uno o más átomos de carbono con uno o más R^{16}, seleccionados independientemente; y en la que, si dicho heterociclilo condensado contiene un resto =N- o –S-, ese nitrógeno puede estar opcionalmente sustituido con un grupo oxo, y ese azufre puede estar opcionalmente sustituido con uno o dos grupos oxo; y en la que, si dicho heterociclilo condensado contiene un resto -NH-, ese nitrógeno puede estar opcionalmente sustituido con

un grupo seleccionado de R^{17};

m es 0 ó 1;

p es 0, 1, ó 2;

L, para cada caso, es independientemente un enlace directo o un alquileno C_{1-6};

R^7, R^8, R^{10}, R^{12}, R^{14} y R^{16} son sustituyentes en el carbono que, para cada caso, se seleccionan independientemente de halo, nitro, ciano, hidroxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, alcoxi C_{1-6}, alcanoilo C_{1-6}, alcanoil C_{1-6}-oxi, *N*-(alquil C_{1-6})amino, *N,N*-(alquil C_{1-6})$_2$amino, alcanoil C_{1-6}-amino, *N*-(alquil C_{1-6})carbamoilo, *N,N*-(alquil C_{1-6})$_2$carbamoilo, alquil C_{1-6}-$S(O)_a$- en el que a es 0, 1 ó 2, alcoxi C_{1-6}-carbonilo, alcoxi C_{1-6}-carbonilamino, *N*-(alquil C_{1-6})sulfamoilo, *N,N*-(alquil C_{1-6})$_2$sulfamoilo, alquil C_{1-6}-sulfonilamino, carbociclilo C_{3-6} o heterociclilo; en la que R^7, R^8, R^{10}, R^{12}, R^{14} y R^{16}, independientemente entre sí, pueden estar opcionalmente sustituidos en uno o más carbonos con uno o más R^{19}; y en la que, si dicho heterociclilo contiene un resto -NH-, ese nitrógeno puede estar opcionalmente sustituido con un grupo seleccionado de R^{20}; y en la que, si dicho heterociclilo contiene un resto =N- o –S-, ese nitrógeno puede estar opcionalmente sustituido con un grupo oxo, y ese azufre puede estar opcionalmente sustituido con uno o dos grupos oxo;

R^9, R^{11}, y R^{20}, para cada caso, se seleccionan independientemente de alquilo C_{1-6}, cicloalquilo C_{3-6}, alcanoilo C_{1-6}, alquil C_{1-6}-sulfonilo, alcoxi C_{1-6}-carbonilo, carbamoilo, *N*-(alquil C_{1-6})carbamoilo, *N,N*-(alquil C_{1-6})$_2$carbamoilo, bencilo, benciloxicarbonilo, benzoilo y fenilsulfonilo; en la que R^9, R^{11}, y R^{20}, independientemente entre sí, pueden estar opcionalmente sustituidos en el carbono con uno o más R^{23};

$R^{17'}$, para cada caso, se selecciona independientemente de alquilo C_{1-6}, cicloalquilo C_{3-6}, alcanoilo C_{1-6}, alquil C_{1-6}-sulfonilo, alcoxi C_{1-6}carbonilo, carbamoilo, *N*-(alquil C_{1-6})carbamoilo, *N,N*-(alquil C_{1-6})carbamoilo, bencilo, benciloxicarbonilo, benzoilo, fenilsulfonilo, carbociclil C_{3-14}-L-, y heterociclilo-L-; en la que cada $R^{17'}$, independientemente, puede estar opcionalmente sustituido en el carbono con uno o más R^{24}; y en la que, si dicho heterociclilo contiene un resto -NH-, ese nitrógeno puede estar opcionalmente sustituido con un grupo seleccionado de R^{25}; y en la que, si dicho heterociclilo contiene un resto =N- o –S-, ese nitrógeno puede estar opcionalmente sustituido con un grupo oxo, y ese azufre puede estar opcionalmente sustituido con uno o dos grupos oxo;

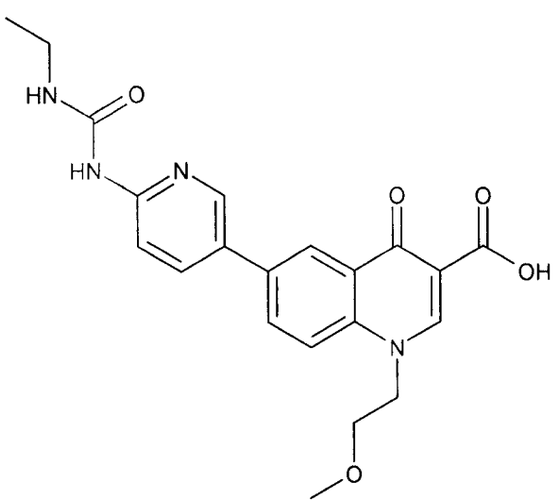
R^{22}, para cada caso, se selecciona independientemente de alquilo C_{1-6}, cicloalquilo C_{3-6}, alcanoilo C_{1-6}, alquil C_{1-6}-sulfonilo, alcoxi C_{1-6}-carbonilo, carbamoilo, N,N-(alquil C_{1-}

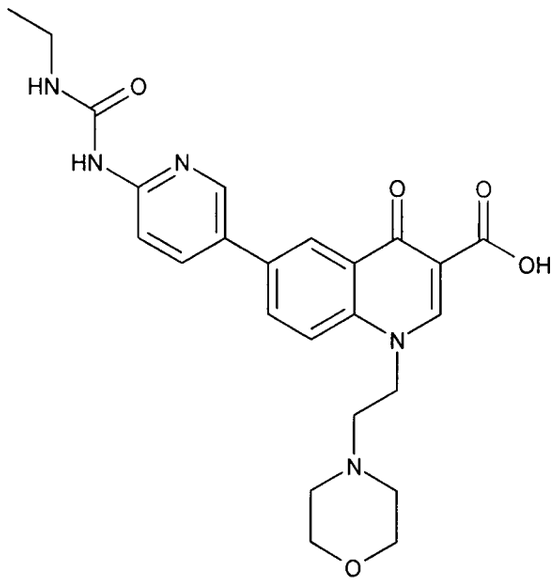
$_{6})_2$sulfamoilo, *N*-(alquil C_{1-6})carbamoilo, *N,N*-(alquil $C_{1-6})_2$carbamoilo, bencilo, benciloxicarbonilo, benzoilo y fenilsulfonilo; en la que R^{22}, para cada caso, puede estar independientemente sustituido de forma opcional en el carbono con uno o más R^{23};

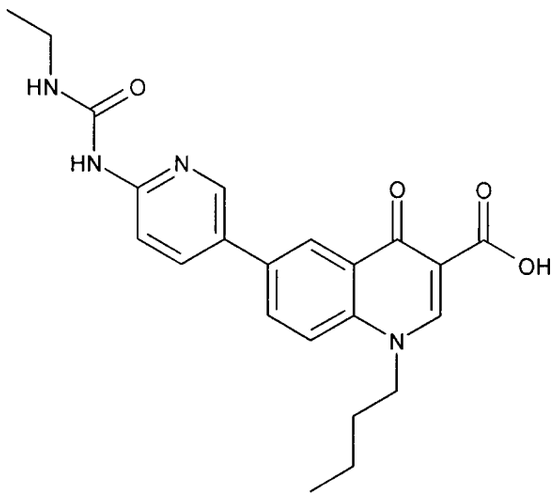
R^{19} y R^{23}, para cada caso, se seleccionan independientemente de halo, nitro, ciano, hidroxi, trifluorometoxi, trifluorometilo, amino, carboxi, carbamoilo, mercapto, sulfamoilo, alquilo C_{1-6}, alcoxi C_{1-6}, acetilo, acetoxi, metilamino, etilamino, dimetilamino, dietilamino, *N*-metil-*N*-etilamino, acetilamino, *N*-metilcarbamoilo, *N*-etilcarbamoilo, *N,N*-dimetilcarbamoilo, *N,N*-dietilcarbamoilo, *N*-metil-*N*-etilcarbamoilo, metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo, etilsulfonilo, metoxicarbonilo, etoxicarbonilo, *N*-metilsulfamoilo, *N*-etilsulfamoilo, *N,N*-dimetilsulfamoilo, *N,N*-dietilsulfamoilo o *N*-metil-*N*-etilsulfamoilo;

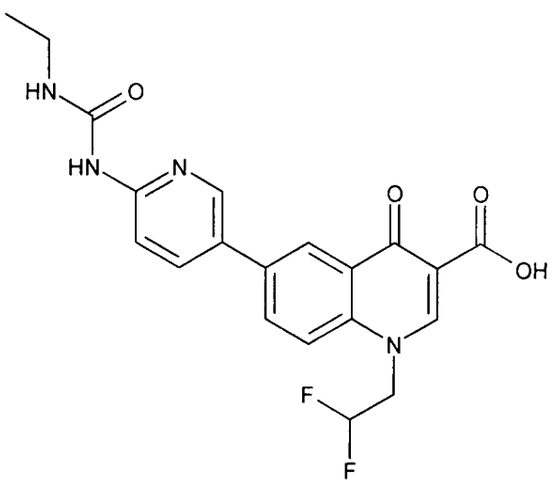
R^{24}, para cada caso, se selecciona independientemente de halo, nitro, ciano, hidroxi, oxo, trifluorometoxi, trifluorometilo, amino, carboxi, carbamoilo, mercapto, sulfamoilo, alquilo C_{1-6}, alcoxi C_{1-6}, acetilo, acetoxi, metilamino, etilamino, dimetilamino, dietilamino, *N*-metil-*N*-etilamino, acetilamino, *N*-metilcarbamoilo, *N*-etilcarbamoilo, *N,N*-dimetilcarbamoilo, *N,N*-dietilcarbamoilo, *N*-metil-*N*-etilcarbamoilo, metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo, etilsulfonilo, metoxicarbonilo, etoxicarbonilo, *N*-metilsulfamoilo, *N*-etilsulfamoilo, *N,N*-dimetilsulfamoilo, *N,N*-dietilsulfamoilo o *N*-metil-*N*-etilsulfamoilo; y

R^{25}, para cada caso, se selecciona independientemente de un alquilo C_{1-6}, con la condición de que el compuesto no sea uno de los siguientes compuestos:



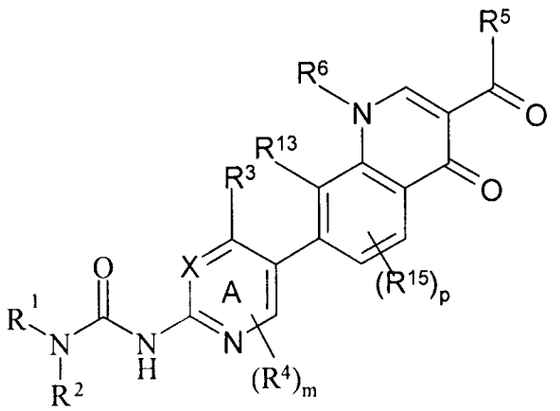






5

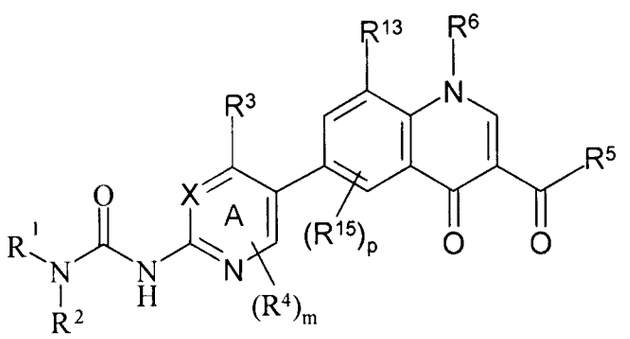
2. El compuesto según la reivindicación 1, en el que el compuesto está representado por la fórmula **(Ia)**:



(Ia)

o sales farmacéuticamente aceptables del mismo.

3. El compuesto según la reivindicación 1, en el que el compuesto está representado por la fórmula **(Ib)**:



(Ib)

o sales farmacéuticamente aceptables del mismo.

4. El compuesto según la reivindicación 1, 2, ó 3, en el que X es CH.

5. El compuesto según la reivindicación 1, 2, ó 3, en el que X es N.

6. El compuesto según cualquiera de las reivindicaciones anteriores, en el que R^1 es un alquilo C_{1-6}.

7. El compuesto según la reivindicación 6, en el que R^1 es etilo.

8. El compuesto según cualquiera de las reivindicaciones anteriores, en el que R^2 es hidrógeno.

9. El compuesto según cualquiera de las reivindicaciones anteriores, en el que R^3 es un heteroarilo de 5 ó 6 miembros; en el que el heteroarilo puede estar opcionalmente sustituido en uno o más átomos de carbono con uno o más R^{10}; y en el que, si dicho heteroarilo contiene un resto =N- o –S-, ese nitrógeno puede estar opcionalmente sustituido con un grupo oxo, y ese azufre puede estar opcionalmente sustituido con uno o dos grupos oxo; y en el que, si dicho heteroarilo contiene un resto -NH-, ese nitrógeno puede estar opcionalmente sustituido con un grupo seleccionado de R^{11}.

10. El compuesto según la reivindicación 9, en el que R^3 es 4-trifluorometil-tiazol-2-ilo, 4-etil-tiazol-2-ilo, o 4-fenil-tiazol-2-ilo.

11. El compuesto según cualquiera de las reivindicaciones anteriores, en el que R^5 se selecciona del grupo que consiste en –OH, etoxi, N-metilamino, y N-etilamino.

12. El compuesto según cualquiera de las reivindicaciones anteriores, en el que R^6 es un alquilo C_{1-6} que está sustituido en uno o más átomos carbono con uno o más R^{16}, seleccionados independientemente.

13. El compuesto según la reivindicación 12, en el que R^{16}, para cada caso, se selecciona independientemente del grupo que consiste en –OH, fluoro, N-metilamino, N,N-dimetilamino, metoxi, etoxi, metilsulfanilo, metilsulfonilo, piperidinilo, piperazinilo, morfolinilo, pirrolidinilo, 2-oxopirrolidinilo, pirrolilo, imidazolilo, triazolilo, fenilo que puede estar opcionalmente sustituido con uno o más halo, isoxazolilo, piridinilo, y ciclopropilo.

14. El compuesto según cualquiera de las reivindicaciones 1-11, en el que R^6 es hidrógeno.

15. El compuesto según cualquiera de las reivindicaciones 1-11, en el que R^6 es alquilo C_{1-6} o un cicloalquilo C_{3-6}.

16. El compuesto según cualquiera de las reivindicaciones 1-11, en el que R^6 es un

heterociclilo no aromático que tiene 3 a 6 átomos anulares; en el que dicho heterociclilo está opcionalmente sustituido en uno o más átomos de carbono con uno o más R^{16}; y en el que, si dicho heterociclilo contiene un resto =N- o –S-, ese nitrógeno puede estar opcionalmente sustituido con un grupo oxo, y ese azufre puede estar opcionalmente sustituido con uno o dos grupos oxo; y en el que, si dicho heterociclilo contiene un resto -NH-, ese nitrógeno puede estar opcionalmente sustituido con un grupo seleccionado de R^{17}.

17. El compuesto según cualquiera de las reivindicaciones 1-11, en el que R^{13} y R^6 junto con los átomos anulares que intervienen forman un heterociclilo condensado de 5 ó 6 miembros.

18. El compuesto según cualquiera de las reivindicaciones 1-11, en el que R^6 se selecciona del grupo que consiste en metilo, etilo, propan-1-ilo, propan-2-ilo, 2-metil-propan-1-ilo, 3-metil-butan-1-ilo, 2-hidroxietilo, 2-metoxietilo, ciclopropilo, ciclopropilmetilo, bencilo, piridin-3-ilmetilo, 3-metoxipropan-1-ilo, 2-(N,N-dimetil)-etilo, 3-(2-oxopirrolidin-1-il)-propan-1-ilo, 1,3-dimetoxi-propan-2-ilo, y 1-metil-azetidin-3-ilo.

19. El compuesto según cualquiera de las reivindicaciones 1-16 o la reivindicación 18, en el que R^{13} es hidrógeno.

20. El compuesto según cualquiera de las reivindicaciones anteriores, en el que m es 0.

21. El compuesto según cualquiera de las reivindicaciones anteriores, en el que p es 0.

22. El compuesto según cualquiera de las reivindicaciones anteriores, en el que p es 1.

23. Una composición farmacéutica que comprende un compuesto según cualquiera de las reivindicaciones 1-22, o una sal farmacéuticamente aceptable del mismo, y un excipiente o vehículo farmacéuticamente aceptable.

24. Un método para inhibir ADN girasa bacteriana y/o topoisomerasa IV bacteriana en un animal de sangre caliente que necesite de tal tratamiento, que comprende administrar al animal una cantidad eficaz de un compuesto según cualquiera de las reivindicaciones 1-22, o una sal

farmacéuticamente aceptable del mismo.

25. Un método para producir un efecto antibacteriano en un animal de sangre caliente que necesite de tal tratamiento, que comprende administrar al animal una cantidad eficaz de un compuesto según cualquiera de las reivindicaciones 1-22, o una sal farmacéuticamente aceptable del mismo.

26. Un método para tratar una infección bacteriana en un animal de sangre caliente que lo necesite, que comprende administrar al animal una cantidad eficaz de un compuesto según cualquiera de las reivindicaciones 1-22, o una sal farmacéuticamente aceptable del mismo.

27. El método según la reivindicación 26, en el que la infección bacteriana se selecciona del grupo que consiste en neumonía adquirida en la comunidad, neumonía adquirida en el hospital, infecciones de la piel y de la estructura de la piel, exacerbación aguda de bronquitis crónica, sinusitis aguda, otitis media aguda, septicemia relacionada con cateterismo, neutropenia febril, osteomielitis, endocarditis, infecciones del aparato urinario e infecciones provocadas por bacterias resistentes a fármacos tales como Streptococcus pneumoniae resistente a penicilina, Staphylococcus aureus resistente a meticilina, Staphylococcus epidermidis resistente a meticilina y enterococos resistentes a vancomicina.

28. El método según cualquiera de las reivindicaciones 24 a 27, en el que el animal de sangre caliente es un ser humano.

29. El uso de un compuesto según las reivindicaciones 1-22, o una sal farmacéuticamente aceptable del mismo, para la fabricación de un medicamento para uso en la producción de un efecto antibacteriano en un animal de sangre caliente.

30. El uso de un compuesto según las reivindicaciones 1-22, o una sal farmacéuticamente aceptable del mismo, para la fabricación de un medicamento para uso en la inhibición de ADN girasa y/o topoisomerasa IV bacterianas en un animal de sangre caliente.

31. El uso de un compuesto según las reivindicaciones 1-22, o una sal farmacéuticamente aceptable del mismo, para la fabricación de un medicamento para uso en el tratamiento de una

infección bacteriana en un animal de sangre caliente.

32. El uso según la reivindicación 31, en el que la infección bacteriana se selecciona del grupo que consiste en neumonía adquirida en la comunidad, neumonía adquirida en un hospital, infecciones de la piel y de la estructura de la piel, exacerbación aguda de bronquitis crónica, sinusitis aguda, otitis media aguda, septicemia relacionada con cateterismo, neutropenia febril, osteomielitis, endocarditis, infecciones del aparato urinario, Streptococcus pneumoniae resistente a penicilina, Staphylococcus aureus resistente a meticilina, Staphylococcus epidermidis resistente a meticilina y enterococos resistentes a vancomicina.

33. El uso según cualquiera de las reivindicaciones 29 a 32, en el que el animal de sangre caliente es un ser humano.

34. Un compuesto según cualquiera de las reivindicaciones 1-22, o una sal farmacéuticamente aceptable del mismo, para uso en la producción de un efecto antibacteriano en un animal de sangre caliente.

35. Un compuesto según cualquiera de las reivindicaciones 1-22, o una sal farmacéuticamente aceptable del mismo, para uso en la inhibición de ADN girasa y/o topoisomerasa IV bacterianas en un animal de sangre caliente.

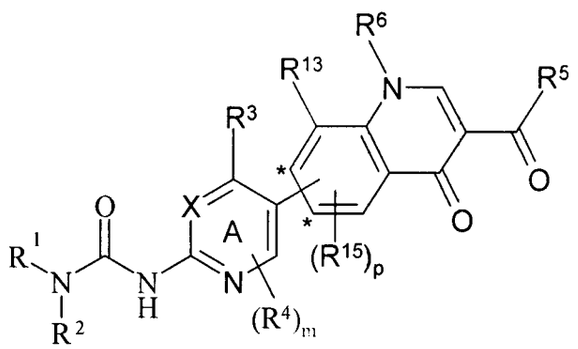
36. Un compuesto según cualquiera de las reivindicaciones 1-22, o una sal farmacéuticamente aceptable del mismo, para uso en el tratamiento de una infección bacteriana en un animal de sangre caliente.

37. Un compuesto según cualquiera de las reivindicaciones 1-22, o una sal farmacéuticamente aceptable del mismo, para uso en el tratamiento de neumonía adquirida en la comunidad, neumonía adquirida en un hospital, infecciones de la piel y de la estructura de la piel, exacerbación aguda de bronquitis crónica, sinusitis aguda, otitis media aguda, septicemia relacionada con cateterismo, neutropenia febril, osteomielitis, endocarditis, infecciones del aparato urinario, Streptococcus pneumoniae resistente a penicilina, Staphylococcus aureus resistente a meticilina, Staphylococcus epidermidis resistente a meticilina y enterococos resistentes a vancomicina.

RESUMEN

Compuestos Químicos

Se describen compuestos de fórmula **(I)** y sus sales farmacéuticamente aceptables. También se describen procedimientos para su preparación, composiciones farmacéuticas que los contienen, su uso como medicamentos y su uso en el tratamiento de infecciones bacterianas.



(I)

PATENT COOPERATION TREATY

PCT/GB2009/050611

ADVANCE E-MAIL

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

ASTRAZENECA INTELLECTUAL PROPERTY
AstraZeneca AB
S-151 85 Södertälje
SUÈDE

Date of mailing *(day/month/year)*
28 August 2009 (28.08.2009)

Applicant's or agent's file reference
103332-1P WO

IMPORTANT NOTIFICATION

International application No.
PCT/GB2009/050611

International filing date *(day/month/year)*
03 June 2009 (03.06.2009)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	E-mail address	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address	State of Nationality	State of Residence
CHOY, Allison, Laura AstraZeneca R&D Boston 35 Gatehouse Drive Waltham, MA 02451 United States of America	US	US
	Telephone No.	
	Facsimile No.	
	E-mail address ☐ Notifications by e-mail authorized	

3. Further observations, if necessary:
The person identified in Box 2 should be added to the record as applicant for the United States of America only and inventor for all designated States.

4. A copy of this notification has been sent to:

☐ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☐ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 87 40

Authorized officer
Martin Jean-Luc
e-mail pt01.pct@wipo.int
Telephone No. +41 22 338 74 01

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2009/050611	03.06.2009	04.06.2008

International Patent Classification (IPC) or both national classification and IPC
INV. C07D417/14 C07D498/06 A61P31/04 A61K31/4709 A61K31/4738

Applicant
ASTRAZENECA AB

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	see form PCT/ISA/210	Duval, Eric Telephone No. +31 70 340-9518

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2009/050611

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2009/050611

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-37
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-37
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-37
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

   and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

   see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Methods of treatment

Claims 24-28 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) / 67.1(iv) PCT. The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

2. Prior art

Reference is made to the following documents:

D1: WO 2006/092599 A (ASTRAZENECA AB [SE]) 8 September 2006 (2006-09-08) cited in the application

D2: WO 2007/071965 A (ASTRAZENECA AB [SE]) 28 June 2007 (2007-06-28) cited in the application

3. Novelty

D1 discloses (cf. claim 1) pyrrole derivatives as antibacterial agents.

D2 discloses (cf. claim 1) fused pyrrole derivatives as antibacterial agents.

Neither D1 nor D2 show any pyridinyl urea derivative comprising a quinoline unit. The subject-matter of claims 1-37 is thus novel.

4. Inventive step

The document D1 is regarded as being the closest prior art to the subject-matter of claim 1.

The compounds of claim 1 differ from those of D1 by their structure, e.g. the presence of the pyridine, urea and quinoline units.

The problem to be solved by the present invention may be regarded as the provision of further compounds for the treatment of bacterial infections.

This problem is solved by the present compounds, as demonstrated in the description (pages 49-53).

The solution proposed in claim 1 of the present application can be considered as involving an inventive step (Article 33(3) PCT) because the present compounds are structurally unrelated to those of the prior art D1 and D2. The skilled person does not find any incentive in the prior art to consider the present structures.

Re Item VI
Certain documents cited

The following document, showing the antibacterial activity of a genus of compounds encompassing the present ureas, is relevant for the assessment of inventive step. The priority of this conflicting application has however not been verified.

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO2008/068470	12/06/2008	03/12/2007	04/12/2006

Re Item VIII
Certain observations on the international application

The application does not meet the requirements of Article 6 PCT, because claim 1 is not clear.

None of the compounds of the proviso of claim 1 fall within the scope of formula (I'), since none of said compounds bears a cyclic substituent R^3 on the pyridine moiety. This inconsistency leads to a lack of clarity.